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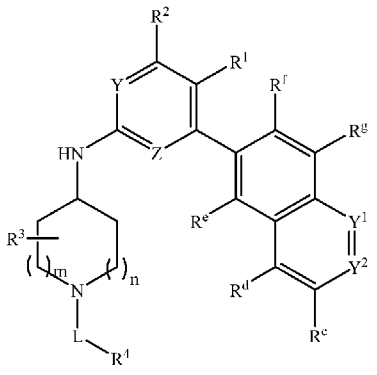
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(54) Title: CDK INHIBITORS



(I)

(57) Abstract: The present invention provides compounds of formula (I) and pharmaceutically acceptable salts thereof as cyclin-dependent kinase inhibitors (one or more of CDK1, CDK2, CDK4, and CDK6), methods of preparing them, and pharmaceutic al compositions containing them. The compounds of the present invention are useful in the treatment, prevention and/or amelioration of diseases or disorders associated with one or more of CDK1, CDK2, CDK4, and CDK6.

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CDK INHIBITORS

[01] This application claims the benefit of Indian Patent Applications having No. 202141000378 filed on January 05, 2021, and 202141044661 filed on October 01, 2021, which are hereby incorporated by reference.

FIELD OF THE INVENTION

[02] The present invention provides compounds of formula **(I)** which are cyclin-dependent kinase (one or more of CDK1, CDK2, CDK4, and CDK6) inhibitors (such as inhibitors of CDK2 and/or CDK 4/6), methods of preparing them, pharmaceutical compositions containing them, and methods of treatment, prevention and/or amelioration of diseases or disorders involving one or more of CDK1, CDK2, CDK4, and CDK6.

BACKGROUND OF THE INVENTION

[03] Cyclin-dependent kinases (CDKs) are serine/threonine kinases whose activity depends on a regulatory subunit-a cyclin. Based on the sequence of the kinase domain, CDKs belong to the CMGC group of kinases (named for the initials of some members), along with mitogen-activated protein kinases (MAPKs), glycogen synthase kinase-3 beta (Gsk3β), members of the dual-specificity tyrosine-regulated kinase (DYRK) family and CDK-like kinases. In related kinases such as MAPKs, substrate specificity is conferred by docking sites separated from the catalytic site, whereas CDKs are characterized by dependency on separate protein subunits that provide additional sequences required for enzymatic activity. To aid nomenclature and analysis of CDKs, proteins belonging to this family have been renamed as Cdk1 through to Cdk20.

[04] CDKs were first discovered by genetic and biochemical studies in model organisms such as yeasts and frogs. This work established the importance of CDKs in promoting transitions through the cell cycle. In addition, these studies showed that the catalytic subunit, the CDK, must associate with a regulatory subunit, the cyclin, whose protein levels are subject to regulation during the cell cycle (this oscillation lent these regulators their cyclin name). Since these pioneer studies conducted in the 1980s, the importance of CDKs acting as a major eukaryotic protein kinase family involved in the integration of extracellular and intracellular signals to modulate gene transcription and cell division has been clearly established.

[05] The number of CDKs increased during evolution and was marked by a greater expansion of the cell-cycle related group. Fungi contain 6 to 8 CDKs and 9 to 15 cyclins, whereas flies and echinodermata contain 11CDKs and 14 cyclins, and human cells have 20 CDKs and 29 cyclins. Evolutionary studies suggest that CDKs fall into eight subfamilies represented by Cdk1, Cdk4 and Cdk5 (from the yeast cell-cycle-related CDKs), and Cdk7, Cdk8, Cdk9, Cdk11 and Cdk20 (functioning as transcriptional CDKs). (Marcos Malumbres, *Genome Biology, 2014, 15:122)*.

[06] Cyclin-dependent kinase 1 (CDK1) is the major protein kinase that drives cells into normal mitosis. CDK1 is activated by binding to B-type cyclins (mainly cyclin B1), which then phosphorylates substrates critical for entry into mitosis. Destruction of cyclin B1 provides a mechanism to rapidly inactivate CDK1 and allow the cell to exit mitosis (R.Y.C. Poon, *in Encyclopedia of Cell Biology, 2016*). CDK1 is present throughout the cell cycle. In contrast, cyclin B1 accumulates and forms a complex with CDK1 after entering S phase. The complex is kept inactive before mitosis by MYT1 and WEE1 through phosphorylation of $CDK1^{Thr14/Tyr15}$. At the end of G2 phase, the stockpile of inactive cyclin B1–CDK1 is activated abruptly by members of the CDC25 phosphatase family. Cyclin B1–CDK1 catalyzes its own activation by simultaneously stimulating CDC25 activation and WEE1 inactivation (Lindqvist et al., *2009, JCB (2009), 185 (2): 193-202*). This bistable system is believed to be kick-started by PLK1, initiating the activation of CDC25 and inactivation of WEE1/MYT1 (Van Vugt and Medema, *Oncogene*, vol. 24, pages 2844–2859 (2005)). The activation of PLK1 in turn requires phosphorylation of $PLK1^{Thr210}$ by Aurora A, an event that is assisted by Bora. Binding of Bora to PLK1 is stimulated by cyclin B1–CDK1-dependent phosphorylation, creating yet another positive feedback loop in the activation of CDK1.

[07] CDK1 is a major cell cycle regulator. In yeast, cell cycle progression is controlled by a single CDK, known as Cdc28 of Saccharomyces cerevisiae and Cdc2 of Schizosaccharomyces pombe, and this binds to specific Cyclins at different stages of the cell cycle. By genetic studies on mice, the systematic knockout of Cdks of the mouse germline has shown that Cdk2, Cdk4, and Cdk6 are not essential for the cell cycle of most cell types. Only elimination of Cdk1 causes cell cycle arrest and embryonic lethality at the two-cell stage. CDK1 activity controls both M phase entry and exit. In G2/M transition, CDK1-Cyclin B1 activation leads to phosphorylation of various proteins that control chromosome condensation, nuclear envelope breakdown, and spindle assembly. At the onset of anaphase, CDK1-Cyclin B1 is involved in this event by

controlling the activity of separase, which is a protease that cleaves cohesion complexes that hold sister chromatids together. The regulation of CDK1 activity is controlled at multiple levels, such as binding with its regulatory subunits (Cyclin A and B), interactions with Cyclin-dependent kinase inhibitors (CKIs), and phosphorylation and dephosphorylation of specific residues by the activating kinase CAK (CDK activating kinase) or by several inhibitor kinases including Wee1 and Myt1 or phosphatase Cdc25. See also Brown *et al, Nat Commun.*, 6, 6769 (2015).

[08] CDK2 overexpression is associated with abnormal cell cycle regulation, and CDK2 /Cyclin E is involved in the regulation of cell cycle G1 to S phase. At the end of the G1 phase, the CDK2 /Cyclin E complex can also catalyze the phosphorylation of Rb, thereby promoting the progression of the cell cycle from the G1 phase to the S phase; in the S phase, the CDK2 /cyclin A complex can promote the DNA replication process. Asghar *et al., Nat. Rev. Drug. Discov.*, 2015;14(2):130-146. Cyclin E corresponding to CDK2 is commonly seen in tumors. The amplification and overexpression of Cyclin E1 are related to the poor prognosis of ovarian cancer, gastric cancer, and breast cancer. Nakayama *et al., Cancer*, 2010, 116:2621-34; Etemadmoghadam *et al., Clin cancer res,* 2013, 19:5960-71; Au-Yeung *et al., Clin. Cancer Res.* 2017, 30:297-303; Ooi et al., *Hum Pathol.*, 2017, 61:58-67; Noske *et al., Oncotarget*, 2017, 8:14794-14805. Cyclin E2 overexpression is associated with breast cancer resistance to endocrine therapy and inhibits CDK2 cells that are resistant to tamoxifen. Caldon *et al.*, *Mol Cancer Ther.*, 2012, 11:1488-99; Herrera-Abreu *et al., Cancer Res.*, 2016, 76:2301-2313. Cyclin E amplification is also related to trastuzumab resistance in HER2-positive breast cancer. Scaltriti *et al., Proc Natl Acad Sci.* 2011, 108:3761-6. The presumption that D-type cyclins might allosterically regulate a novel CDK was validated by the discovery of CDK4, which was revealed to physically bind to, and be enzymatically activated by, any of the three D-type cyclins. A related cyclin D–dependent kinase, CDK6, with similar properties was identified 2 years later. Although CDKs 1 and 2, in complexes with cyclins E, A, and B, drive cell cycle progression through S phase and M phase (mitosis), the cyclin D–dependent CDKs act during G 1 phase to propel quiescent cells that have entered the cell cycle, or proliferating cells that have completed mitosis, toward S phase. Unlike CDKs 1 and 2 that phosphorylate many hundreds of cellular protein substrates, CDK4 is a surprisingly fastidious enzyme that has a restricted propensity to phosphorylate the retinoblastoma protein (RB1, hereafter RB) and two other RB-family proteins [RB2 (p130), RBL1 (p107)], but very few other substrates.

[09] *RB* is a canonical tumor-suppressor gene in retinoblastoma and in many other cancers as well. The RB protein undergoes periodic phosphorylation as cells traverse the division cycle. RB is dephosphorylated as cells exit mitosis, and the hypophosphorylated form detected in G 1 phase becomes hyperphosphorylated (inactivated) in late G1 and remains so throughout progression through S phase to mitosis. The role of hypophosphorylated (active) RB to restrict proliferation and act as a potent tumor-suppressor gene was highlighted by studies indicating that RB's growth-suppressive function could be inactivated by its binding to DNA tumor virus oncoproteins (human papillomavirus E7, adenovirus E1A, and SV40 T antigen). In mammalian cells stimulated by mitogens to enter the division cycle from a quiescent state (G0), CDK4/6-mediated RB phosphorylation was first detected in mid-G 1 phase after induction of cyclin D but prior to activation of cyclin E– and A–dependent CDK2. Together, these results implied that the role of CDK4/6 was to phosphorylate RB, priming it for inactivation by other CDKs later in G1, and releasing E2F transcription factors from RB constraint to allow their coordinate induction of a suite of genes whose activities are jointly required for initiation of S phase. Sherr *et al., Cancer Discovery,* April 2016, 6(4):353-367CD-15-0894.

[10] CDK4 (INK4)-retinoblastoma (Rb) pathway regulates cellular proliferation by controlling the G1 (pre-DNA synthesis) to S (DNA synthesis) cell cycle checkpoint. Dysregulation of the cyclin D-CDK4/6-INK4-Rb pathway is frequently observed in cancer and contributes to cell cycle progression and continued growth. CDK4/6 mediates the transition from G1 to S phase by associating with D-type cyclins and regulating the phosphorylation state of Rb. Unphosphorylated Rb binds and represses the function of E2 family (E2F) transcription factors; upon phosphorylation, Rb dissociates from E2F transcription factors, freeing them to be able to participate in DNA replication and cell division. Increased cyclin D-CDK4/6 activity, which promotes phosphorylation of Rb, can occur through several mechanisms, including overexpression of D-type cyclins, mutation or amplification of CDK4/6, or loss of cyclin D-CDK4/6 negative regulators such as p16INK4A, and ultimately leads to cancer cell growth. Thus, the development of selective CDK4/6 inhibitors offers a novel therapeutic approach for patients with advanced cancer. Hamilton *et al., Cancer Treatment Reviews*, 45 (2016) 129–138.

[11] Cyclin-dependent kinase 4 (CDK4) and closely related CDK6 play key roles in mammalian cell proliferation, where they help to drive the progression of cells into the DNA synthetic (S) phase of the cell-division cycle. Unlike CDKs 1 and 2, which act later in the cell

cycle in response to periodic oscillations of cyclins E, A, and B to coordinate DNA replication with mitosis, the enzymatic activities of CDK4 and CDK6 in the first gap phase (G1) of the cycle are governed by D-type cyclins expressed in response to various extracellular signals, including stimulatory mitogens, inhibitory cytokines, differentiation inducers, cell–cell contacts, and other spatial cues. The three D-type cyclins (D1, D2, and D3) are differentially expressed, alone or in combination, in distinct cell lineages, where they assemble with CDK4 and CDK6 to form enzymatically active holoenzyme complexes. An understanding of how the three different D-type cyclins act as environmental sensors in responding dynamically to extracellular cues in various cell types helps to explain how CDK4/6 activities are differentially regulated and predicts the basis of functional interactions between mitogen signaling pathways and CDK4/6 activity in both normal and cancer cells. More than two decades after discovery of CDK4 and CDK6, drugs inhibiting their activities are now demonstrating significant efficacy in cancer treatment.

[12] The CDK4/6 inhibitors act at the G1-to-S cell cycle checkpoint. This checkpoint is tightly controlled by the D-type cyclins and CDK4 and CDK6. When CDK4 and CDK6 are activated by D-type cyclins, they phosphorylate the retinoblastoma-associated protein (pRb). This releases pRb's suppression of the E2F transcription factor family and ultimately allows the cell to proceed through the cell cycle and divide. In HR+ breast cancer, cyclin D overexpression is common and loss of pRb is rare, making the G1-to-S checkpoint an ideal therapeutic target. The CDK4/6 inhibitors prevent progression through this checkpoint, leading to cell cycle arrest.

[13] Despite the availability of many therapies, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (HR+/HER2−) advanced breast cancer is rarely curable. The current treatment paradigm for HR+/HER2− advanced breast cancer involves sequencing endocrine therapy, targeted therapy, and/or chemotherapy to prolong patients' lives, delay disease progression, and minimize cancer-related symptoms. The cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors are rapidly transforming this treatment landscape. There are currently three CDK4/6 inhibitors that have been approved by the U.S. Food and Drug Administration: Palbociclib, Ribociclib, and Abemaciclib.

[14] The CDK4/6 inhibitors as a class are generally well tolerated. The most common class-wide adverse effects include nausea, diarrhea, fatigue, neutropenia, leukopenia, anemia, and thrombocytopenia. Palbociclib and Ribociclib most commonly cause neutropenia, while

diarrhea is the unique gastrointestinal (GI) toxicity that is associated with abemaciclib, perhaps because of its greater affinity for CDK4 over CDK6. Shah et al., *Oncology (Williston Park)*, 2018 May 15; 32(5): 216–222.

[15] The U.S. Food and Drug Administration (FDA) is warning that Ibrance (palbociclib), Kisqali (ribociclib), and Verzenio (abemaciclib) used to treat some patients with advanced breast cancers may cause rare but severe inflammation of the lungs. *See* USFDA, Drugs Safety Communications, dated Sep 13th, 2019, titled "FDA warns about rare severe lung inflammation-Ibrance, Kisqali and Verzeni breast cancer".

[16] Patent literature related to CDK inhibitors includes and are not limited to International Publication Nos. WO 2000/064900, WO 2000/035908, WO 2004/031158, WO 2004/046130, WO 2004/101549, WO 2005/111019, WO 2006/105386, WO 2006/040050, WO 2006/040036, WO 2006/002828, WO 2006/040052, WO 2018/033815, WO 2020/223558, WO 2020/205560, WO 2020/180959, WO 2020/168197, WO 2020/157652, WO 2020/223469, WO 2021/072232, WO 2021/030537, WO 2021/170076, WO 2021/073593, WO 2019/161224, WO 2019/148161, WO 2019/170055, WO 2019/222521, WO 2019/035008, WO 2018/106870, WO 2018/108167, WO 2018/113771, WO 2018/045957, WO 2018/081211, WO 2018/081204, WO 2017/020065, WO 2017/114512, WO 2017/177836, WO 2017/177837, WO 2017/114351, WO 2017/133701, WO 2017/193872, WO 2017/041535, WO 2017/054484, WO 2016/058501, WO 2016/141881, WO 2016/194831, WO 2016/014904, WO 2016/015597, WO 2015/101293, WO 2015/180642, WO 2014/183520, WO 2011/101417, WO 2011/101409, WO 2010/132725, WO 2009/061345, WO 2006/008874, WO 2002/002550, WO 2021/030623, WO 2019/161224 each of which is incorporated herein by reference in its entirety for all purposes. The CDK 2/4/6 inhibitor PF-06873600 (WO 2018/033815) developed by Pfizer has selectivity for CDK 2/4/6 isoforms.

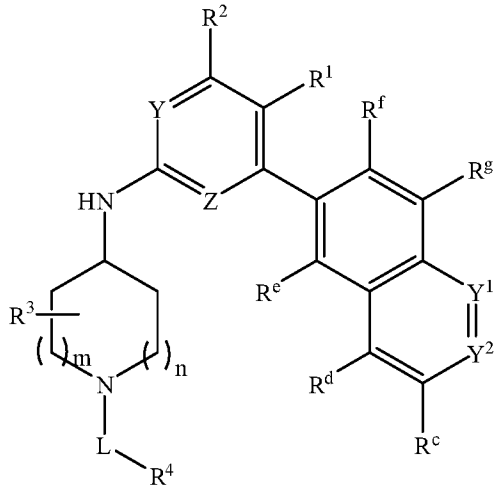
[17] There remains an unmet need for CDK inhibitors having activity on CDK1, CDK2 and/or CDK4/6 (such as on CDK2 and/or CDK4/6) for the treatment of various diseases and disorders associated with cell proliferation such as cancer.

SUMMARY OF INVENTION

[18] The present invention relates to compounds of formula **(I)**, methods for their preparation, pharmaceutical compositions containing them, and methods of treatment with them. In particular, the compounds of formula **(I)** and their pharmaceutically acceptable salts

thereof are useful in the treatment, prevention and/or amelioration of diseases or disorders associated with CDK1, CDK2 and/or CDK4/6.

[19] In one aspect, the present invention relates to a compound of formula **(I)**:



(I)

or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof,

wherein

Y^1 is selected from CR^a and N;

Y^2 is selected from CR^b and N; with the proviso that at least one of Y^1 and Y^2 is N;

R^a, R^b, R^c, R^d, R^e, R^f, and R^g are independently selected from hydrogen, halogen, hydroxy, amino, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminoalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-C(O)OR^j$, and $-C(O)NR^ZR^Z$;

Y is selected from CR^h and N;

Z is selected from CR^i and N; with the proviso that at least one of Y and Z is N;

R^h, R^i, and R^j are independently selected from hydrogen, halogen, substituted or unsubstituted alkyl, and substituted or unsubstituted haloalkyl;

R^1 and R^2 are independently selected from hydrogen, halogen, hydroxy, amino, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heterocyclylalkyl;

L is selected from -S-, -S(O)-, -SO_2-, and –S(=NH)O-;

R^3 is selected from hydrogen, hydroxy, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkoxy, substituted or unsubstituted haloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heterocyclylalkyl;

R^4 is selected from hydrogen, hydroxy, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkoxy, substituted or unsubstituted haloalkyl, substituted or unsubstituted aminoalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, -NR^zR^z, -$NR^zC(=O)NR^zR^z$, -$NR^zS(=O)R^z$, -$NR^zS(=O)_2R^z$, -$NR^zC(=O)OR^z$, -$NR^zC(=O)R^z$, -$NR^xC(=S)R^y$. -$NR^zC(=S)NR^zR^z$, -$CR^xR^yC(=O)R^z$, and -$CR^xR^yC(=S)R^z$;

each occurrence of R^z is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocyclyl, substituted heterocyclylalkyl, and substituted or unsubstituted amino; or any two of R^z when bound to a common atom may be joined to form a (i) substituted or unsubstituted, saturated or unsaturated 3-14 membered ring, which may optionally include one or more heteroatoms which may be the

same or different and are selected from O, NR^{za} and S; or (ii) an oxo (=O), thio (=S), or imino ($=NR^{za}$) group;

R^{za}, R^{x}, and R^{y} at each occurrence are independently selected from hydrogen, halo, hydroxy, amino, alkoxy, C_{1-5} alkyl, C_{3-7} cycloalkyl, C_{5-7} aryl, C_{5-7} heteroaryl, and C_{3-7} heterocycloalkyl;

m is an integer selected from 0, 1, and 2; and

n is an integer selected from 0, 1, and 2.

[20] These compounds are useful in the treatment, prevention and/or amelioration of diseases or disorders involving one or more of CDK1, CDK2, CDK4, and CDK6. In one embodiment, the compound inhibits CDK2 and therefore is useful in the treatment, prevention and/or amelioration of diseases or disorders involving CDK2. In another embodiment, the compound selectively inhibits CDK2 over CDK1, CDK4, and CDK6, and is useful in the treatment, prevention and/or amelioration of diseases or disorders involving CDK2.

[21] In yet another embodiment, the compounds described herein, including the compounds having formula **(I)** and their pharmaceutically acceptable salts, are useful in the treatment, prevention and/or amelioration of diseases or disorders involving CDK2 and/or CDK4/6.

[22] Yet another aspect relates to methods for preparation of compounds having formula **(I)** and their pharmaceutically acceptable salts, as well as tautomers thereof, prodrugs thereof, N-oxides thereof, stereoisomers thereof, pharmaceutically acceptable esters thereof, and pharmaceutically acceptable salts thereof.

[23] Yet another aspect relates to a method of inhibiting one or more of CDK1, CDK2, CDK4, and CDK6 by administering a compound of the invention. One embodiment is a method of selectively inhibiting CDK2 over CDK1, CDK4 and CDK6 by administering a compound of the invention.

[24] In certain embodiments, the present invention provides a compound having formula **(I)**, wherein Y^1 is N.

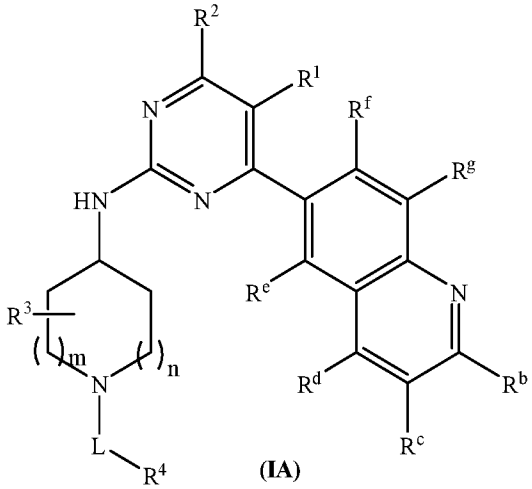
[25] In certain embodiments, Y^2 is CR^b. wherein R^b is hydrogen, hydroxy, haloalkyl, and C_{1-6} alkyl.

[26] In certain embodiments, Y is N.

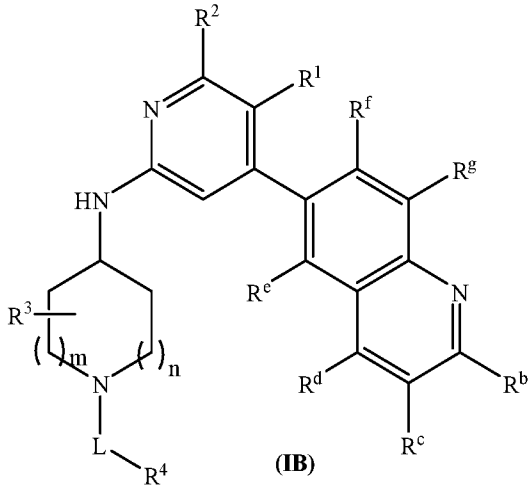
[27] In certain embodiments, Z is CR^i and R^i is hydrogen.

[28] In certain embodiments, Z is N.

[29] In certain embodiments the present invention provides a compound having formula **(IA)** or **(IB)**,



(IA)



(IB)

or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof.

[30] In certain embodiments of a compound having the formula **(I)**, **(IA)**, or **(IB)**, R^1 is hydrogen, substituted or unsubstitued alkyl, halogen, hydroxy, or amine.

[31] In certain embodiments of a compound having the formula **(I)**, **(IA)**, or **(IB)**, R^1 is substituted or unsubstitued $-C_{(1-6)}$alkyl, or halogen.

[32] In certain embodiments of a compound having the formula **(I)**, **(IA)**, or **(IB)**, R^1 is methyl, fluorine, or chlorine.

[33] In certain embodiments of a compound having the formula **(I)**, **(IA)**, or **(IB)**, R^2 is hydrogen.

[34] In certain embodiments of a compound having the formula **(I)**, **(IA)**, or **(IB)**, R^3 is hydrogen or hydroxy.

[35] In certain embodiments of a compound having the formula **(I)**, **(IA)**, or **(IB)**, L is $-SO_2-$

.

[36] In certain embodiments of a compound having the formula **(I)**, **(IA)**, or **(IB)**, R^4 is selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aminoalkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and $-NR^zR^z$.

[37] In certain embodiments of a compound having the formula **(I)**, **(IA)**, or **(IB)**, R^4 is $-C_{1-3}$alkyl, $-C_{2-3}$alkenyl, $-CF_3$, $-CHF_2$, $-N(CH_3)_2$, $-NH(C_2H_5)$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CH_2OH$, cyclopropyl, 4-fluorophenyl, or pyridyl.

[38] In certain embodiments of a compound having the formula **(I)**, **(IA)**, or **(IB)**, R^4 is $-C_{1-3}$alkyl, $-C_{2-3}$alkenyl, $-CF_3$, $-CHF_2$, $-N(CH_3)_2$, $-NH(C_2H_5)$, $-CH_2CH_2N(CH_3)_2$, or $-CH_2CH_2OH$.

[39] In certain embodiments of a compound having the formula **(I)**, **(IA)**, or **(IB)**, R^4 is cyclopropyl, 4-fluorophenyl, or pyridyl.

[40] In certain embodiments of a compound having the formula **(I)**, **(IA)**, or **(IB)**, integer "m" is 0, 1, or 2.

[41] In certain embodiments of a compound having the formula **(I)**, **(IA)**, or **(IB)**, integer "n" is 0, or 1.

[42] In certain embodiments of a compound having the formula **(I)**, **(IA)**, or **(IB)**, R^c, R^d, R^e, R^f and R^g are independently selected from hydrogen, cyano, halogen, hydroxy, substituted or unsubstitued alkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted haloalkyl, $-C(O)NR^ZR^Z$, and $-C(O)OR^j$.

[43] In certain embodiments of a compound having the formula **(I)**, **(IA)**, or **(IB)**, R^c is hydrogen.

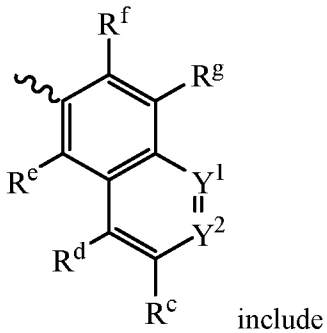
[44] In certain embodiments of a compound having the formula **(I)**, **(IA)**, or **(IB)**, R^d is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted aminoalkyl, cyano, $-C(O)OR^j$. or $-C(O)NR^zR^z$.

[45] In certain embodiments of a compound having the formula **(I)**, **(IA)**, or **(IB)**, R^d is isopropyl, propan-2-ol, 1-hydroxyethyl, $-CH_2OH$, CN, -C(O)OH, $-C(O)OCH_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, -C(O)NH-Boc, $-CH(NH_2)CH_3$, $-CH(NH_2)CH_2CH_3$, -CH(NH-Boc)CH_3, or -CH(NH-Boc)CH_2CH_3.

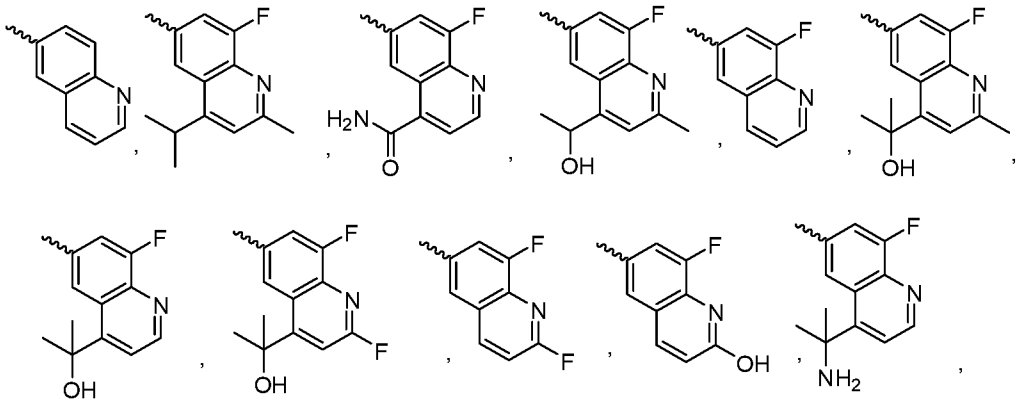
[46] In certain embodiments of a compound having the formula **(I)**, **(IA)**, or **(IB)**, R^e and R^f are hydrogen.

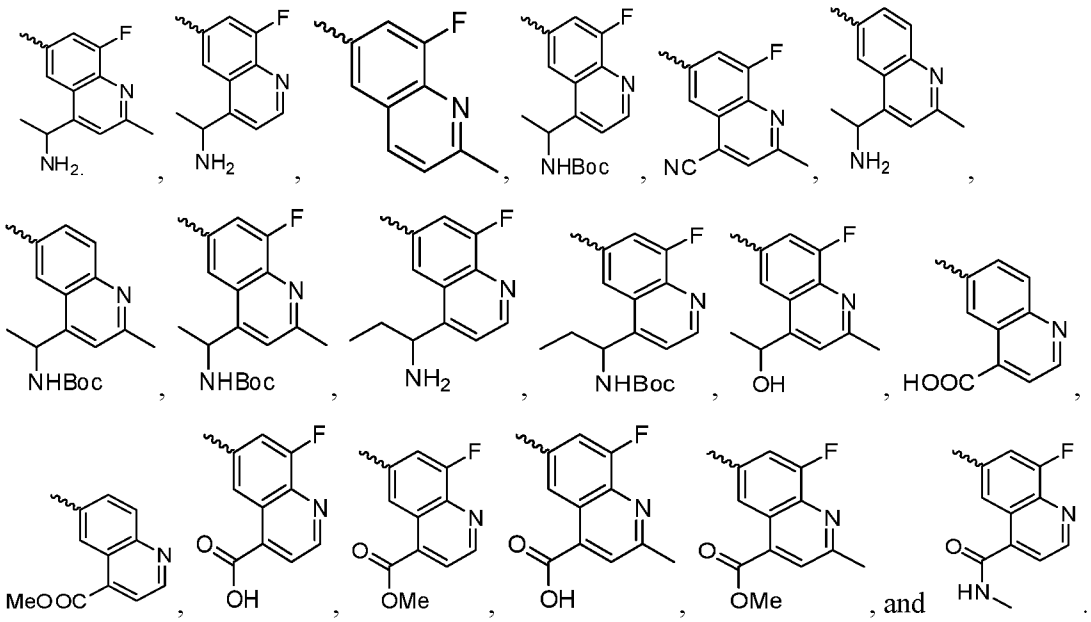
[47] In certain embodiments of a compound having the formula **(I)**, **(IA)**, or **(IB)**, R^g is hydrogen or halogen.

[48] Illustrative examples of the optionally substituted moiety



include





[49] Representative compounds of the present invention include those specified below and pharmaceutically acceptable salts thereof. The present invention should not be construed to be limited to them:

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine hydrochloride,

5-Fluoro-4-(8-fluoro-4-isopropyl-2-methylquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

2-(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)propan-2-ol,

N-(1-(Cyclopropylsulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(vinylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

N-(1-((2-(Dimethylamino)ethyl)sulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine,

N-(1-(ethylsulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine,

2-(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-4-yl)propan-2-ol,

2-((4-((5-Fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)ethan-1-ol,

4-((5-Fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-yl)amino)-N,N-dimethylpiperidine-1-sulfonamide,

N-Ethyl-4-((5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-yl)amino)piperidine-1-sulfonamide,

5-Fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)-4-(quinolin-6-yl)pyrimidin-2-amine,

5-Fluoro-N-(1-((4-fluorophenyl)sulfonyl)piperidin-4-yl)-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine,

2-(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)propan-2-ol dihydrochloride,

8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinoline-4-carboxamide,

1-(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)ethan-1-ol,

(±)-1-(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)ethan-1-ol,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(pyridin-3-ylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(pyridin-3-ylsulfonyl)piperidin-4-yl)pyrimidin-2-amine hydrochloride,

8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-N-methylquinoline-4-carboxamide,

8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-N-methylquinoline-4-carboxamide hydrochloride,

Methyl 8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinoline-4-carboxylate,

8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinoline-4-carboxylic acid,

Methyl 8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinoline-4-carboxylate,

8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinoline-4-carboxylic acid,

Methyl 6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinoline-4-carboxylate,

6-(5-Fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinoline-4-carboxylic acid,

5-Chloro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

5-Chloro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine hydrochloride,

(±)-1-(6-(5-Chloro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)ethan-1-ol,

(±)-4-((5-Fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-ol,

(±)-(3R,4R)-4-((5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-ol hydrochloride,

(±)-*Tert*-butyl (1-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)ethyl)carbamate,

(±)-4-(4-(1-Aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

(-)-4-(4-(1-Aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

(+)-4-(4-(1-Aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

(±)-*Tert*-butyl (1-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-4-yl)ethyl)carbamate,

(±)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

(-)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

(+)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

(±)-*Tert*-butyl (1-(6-(5-chloro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)ethyl)carbamate,

(±)-4-(4-(1-Aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-chloro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

(±)-*Tert*-butyl (1-(6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)ethyl)carbamate,

(±)-4-(4-(1-Aminoethyl)-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinoline-4-carbonitrile,

(±)-*Tert*-butyl (1-(6-(5-chloro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate,

(±)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-5-chloro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

5-Fluoro-4-(8-fluoro-2-methylquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

5-Fluoro-4-(8-fluoro-2-methylquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine hydrochloride,

(±)-*Tert*-butyl (1-(6-(2-((1-(ethylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate,

(±)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-N-(1-(ethylsulfonyl)piperidin-4-yl)-5-fluoropyrimidin-2-amine,

(±)-*Tert*-butyl (1-(6-(2-((1-(cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate,

4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-N-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-fluoropyrimidin-2-amine,

(±)-4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-N-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-fluoropyrimidin-2-amine,

(±)-4-(4-(1-aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine hydrochloride,

(±)-4-(4-(1-Aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine hemicitrate,

(±)-4-(4-(1-Aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine methanesulfonate,

(-)-4-(4-(1-Aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine hemicitrate,

(±)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine citrate,

(-)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine citrate,

(+)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine citrate,

(±)-Tert-butyl (1-(8-fluoro-6-(5-methyl-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-4-yl)ethyl)carbamate,

(±)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-5-methyl-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

(±)-1-(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-4-yl)ethan-1-ol,

(±)-1-(6-(2-((1-(Cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethanol,

2-(6-(2-((1-(Cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)propan-2-ol,

2-(6-(2-((1-(Cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)propan-2-ol,

(±)-*Tert*-butyl (1-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)propyl)carbamate,

(±)-4-(4-(1-Aminopropyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)pyrimidin-2-amine,

N-(1-((Difluoromethyl)sulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine,

2-(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyridin-4-yl)-2-methylquinolin-4-yl)propan-2-ol,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyridin-2-amine,

(±)-Tert-butyl (1-(8-fluoro-6-(5-fluoro-2-((1-((trifluoromethyl)sulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-4-yl)ethyl)carbamate,

(±)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)pyridin-2-amine,

(±)-*Tert*-butyl (1-(6-(2-((1-((difluoromethyl)sulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate,

(±)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-N-(1-((difluoromethyl)sulfonyl)piperidin-4-yl)-5-fluoropyrimidin-2-amine,

(±)-*Tert*-butyl (1-(6-(2-((1-(cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)propyl)carbamate,

(±)-4-(4-(1-Aminopropyl)-8-fluoro-2-methylquinolin-6-yl)-N-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-fluoropyrimidin-2-amine,

N-(1-(Ethylsulfonyl)azetidin-3-yl)-5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)azetidin-3-yl)pyrimidin-2-amine,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)pyrrolidin-3-yl)pyrimidin-2-amine,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-3-yl)pyrimidin-2-amine,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-3-yl)pyrimidin-2-amine hydrochloride,

6-(5-Fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-2-ol,

4-(2-chloroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

N-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine hydrochloride,

(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)methanol,

2-(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)propan-2-ol methane sulfonate,

2-(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)propan-2-ol 4-methylbenzenesulfonate,

1-(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)ethan-1-ol methanesulfonate,

2-(6-(2-((1-(Cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)propan-2-ol hydrochloride,

N-(1-((Difluoromethyl)sulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoro-4-isopropyl-2-methylquinolin-6-yl)pyrimidin-2-amine,

Tert-butyl (1-(6-(2-((1-(cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)ethyl)carbamate,

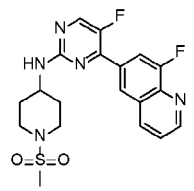
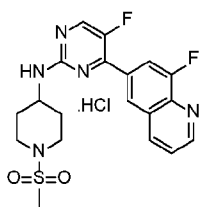
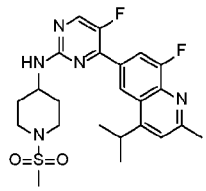
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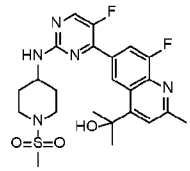
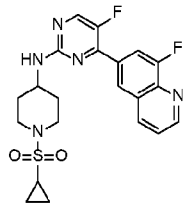
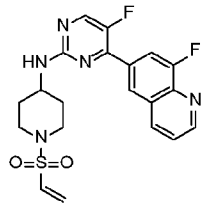
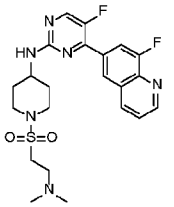
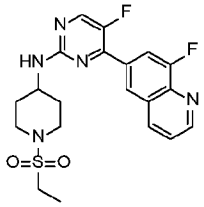
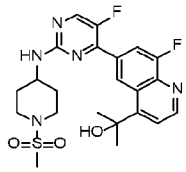
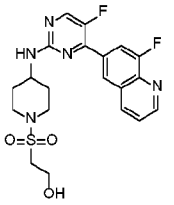
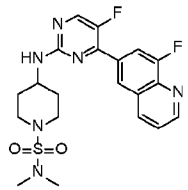
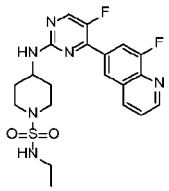
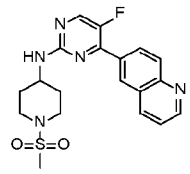
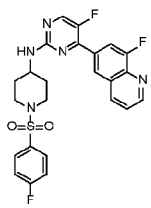
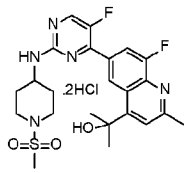
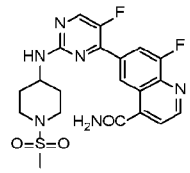
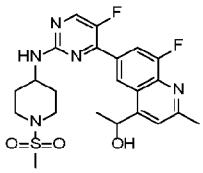
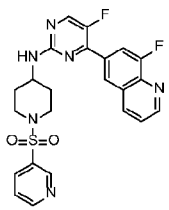
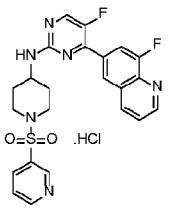
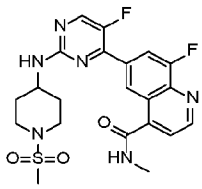
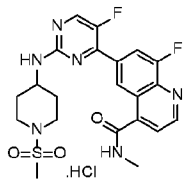
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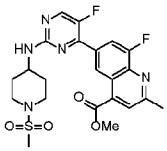
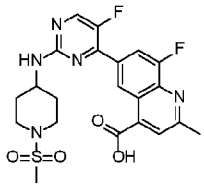
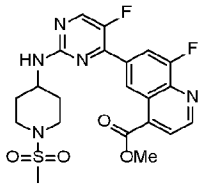
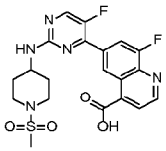
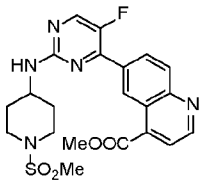
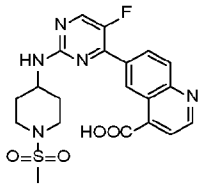
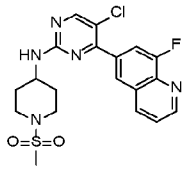
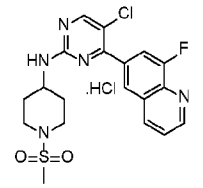
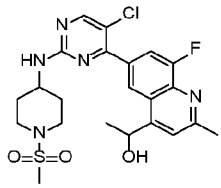
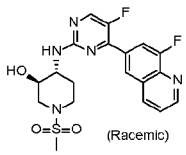
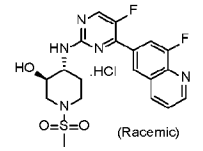
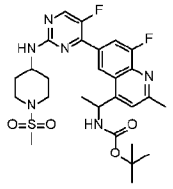
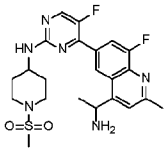
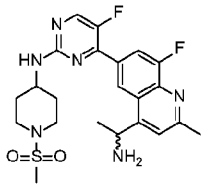
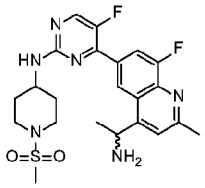
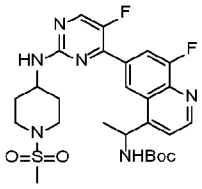
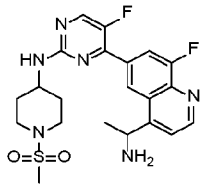
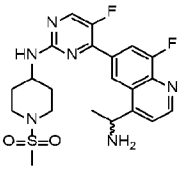
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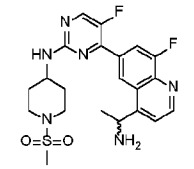
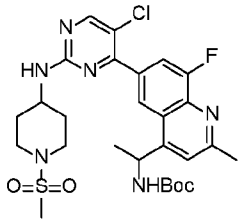
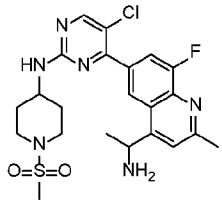
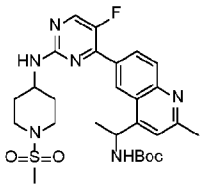
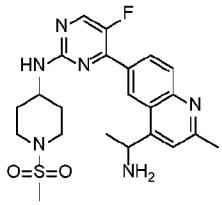
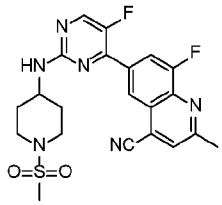
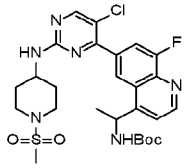
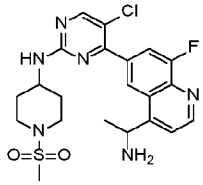
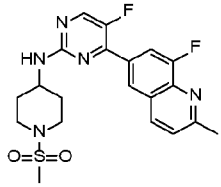
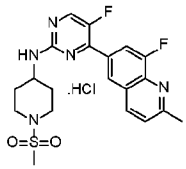
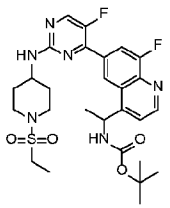
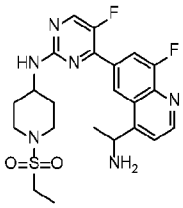
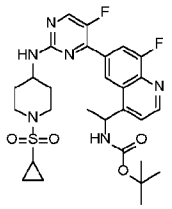
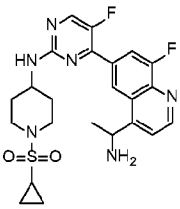
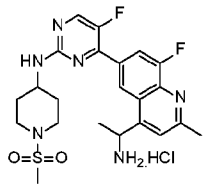
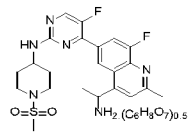
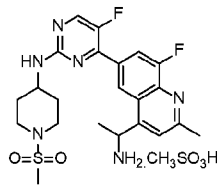
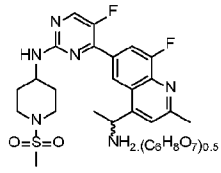
[50] Representative compounds of the present invention include those shown below and pharmaceutically acceptable salts thereof.

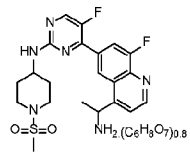
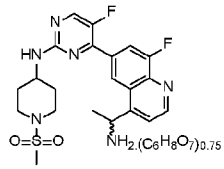
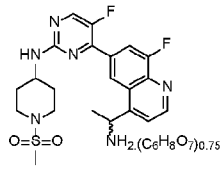
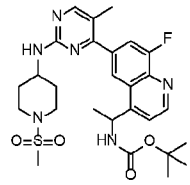
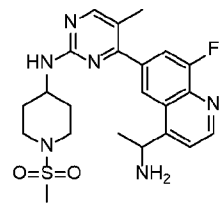
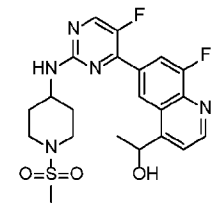
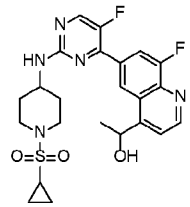
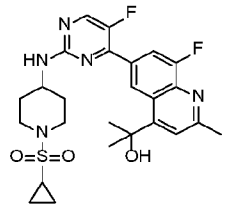
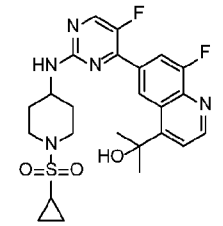
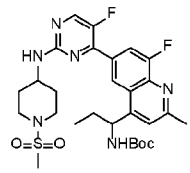
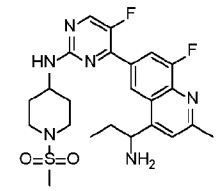
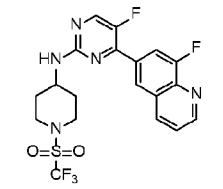
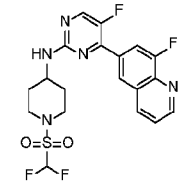
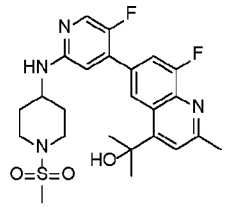
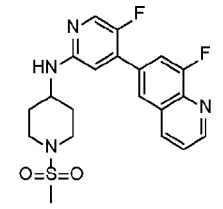
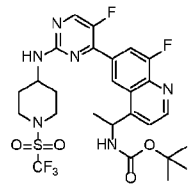
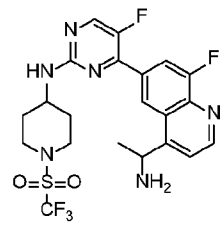
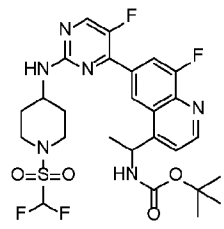
Table-1

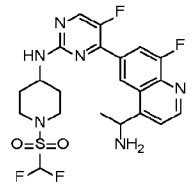
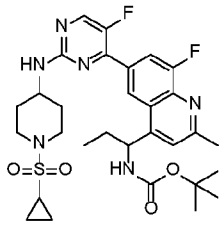
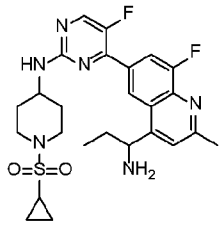
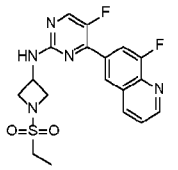
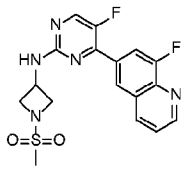
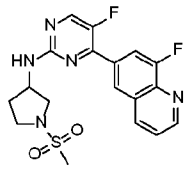
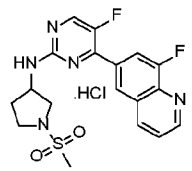
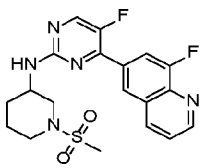
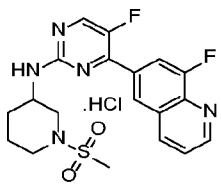
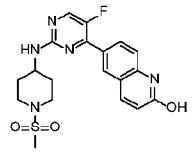
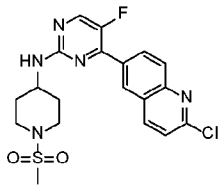
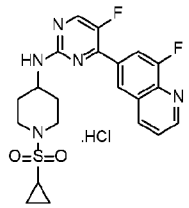
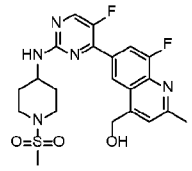
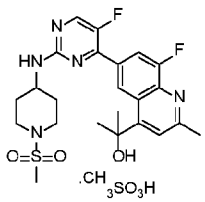
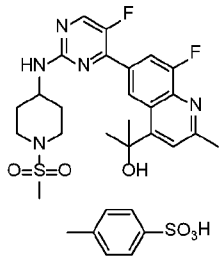
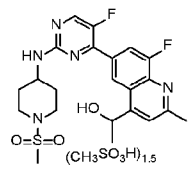
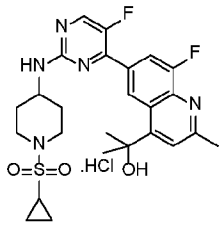
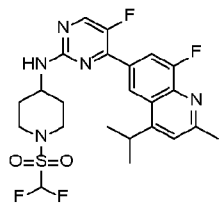
Ex.	Structure	Ex.	Structure	Ex.	Structure
1		2		3	

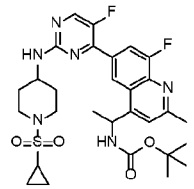
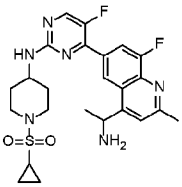
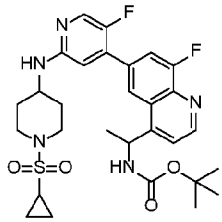
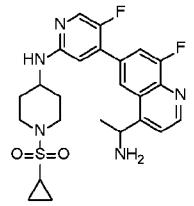
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4		5		6	
7		8		9	
10		11		12	
13		14		15	
16		17		18	
19		20		21	

Ex.	Structure	Ex.	Structure	Ex.	Structure
22		23		24	
25		26		27	
28		29		30	
31		32		33	
34		35		36	
37		38		39	

Ex.	Structure	Ex.	Structure	Ex.	Structure
40		41		42	
43		44		45	
46		47		48	
49		50		51	
52		53		54	
55		56		57	

Ex.	Structure	Ex.	Structure	Ex.	Structure
58		59		60	
61		62		63	
64		65		66	
67		68		69	
70		71		72	
73		74		75	

Ex.	Structure	Ex.	Structure	Ex.	Structure
76		77		78	
79		80		81	
82		83		84	
85		86		87	
88		89		90	
91		92		93	

Ex.	Structure	Ex.	Structure	Ex.	Structure
94		95		96	
97					

[51] Other representative compounds of the present invention include those listed below and pharmaceutically acceptable salts thereof.

Table-1A: Prophetic Examples

5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(oxetan-3-ylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(oxetan-3-ylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

4-(4-(1-aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-N-(1-(ethylsulfonyl)piperidin-4-yl)-5-fluoropyrimidin-2-amine,

N-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoro-4-(1-(methylamino)ethyl)quinolin-6-yl)pyrimidin-2-amine,

1-((1-(6-(2-((1-(cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethyl)amino)propan-2-ol,

N-(1-(6-(2-((1-(cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethyl)acetamide,

N-(1-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-4-yl)ethyl)acetamide,

N-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoro-4-(pyrrolidin-2-yl)quinolin-6-yl)pyrimidin-2-amine,

5-fluoro-4-(8-fluoro-4-(tetrahydrofuran-2-yl)quinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

4-(4-(1-aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyridin-2-amine,

4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyridin-2-amine,

N-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoro-4-(1-(methylamino)ethyl)quinolin-6-yl)pyridin-2-amine,

5-fluoro-4-(8-fluoro-4-(tetrahydrofuran-2-yl)quinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyridin-2-amine,

N-(1-((difluoromethyl)sulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoroquinolin-6-yl)pyridin-2-amine,

4-(4-(1-aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-N-(1-((difluoromethyl)sulfonyl)piperidin-4-yl)-5-fluoropyridin-2-amine,

4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-N-(1-((difluoromethyl)sulfonyl)piperidin-4-yl)-5-fluoropyridin-2-amine,

4-(4-(1-aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-N-(1-((difluoromethyl)sulfonyl)piperidin-4-yl)-5-fluoropyrimidin-2-amine,

2-(6-(2-((1-((difluoromethyl)sulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)propan-2-ol,

4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)-5-(trifluoromethyl)pyrimidin-2-amine,

4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)-5-(trifluoromethyl)pyrimidin-2-amine,

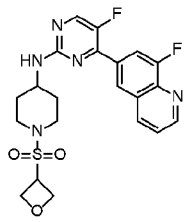
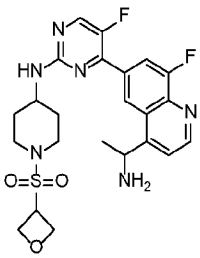
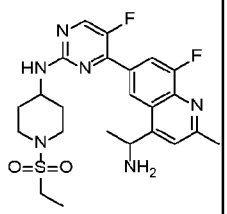
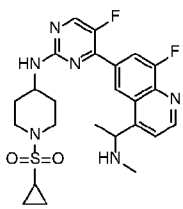
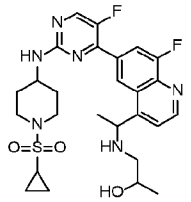
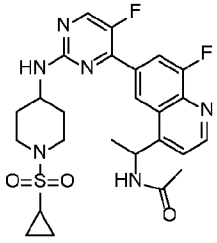
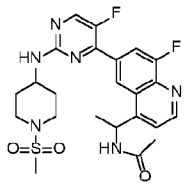
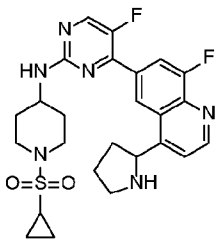
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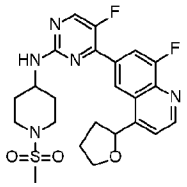
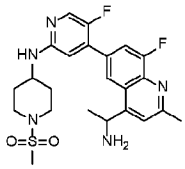
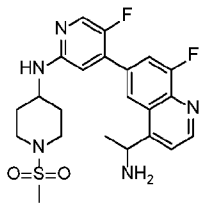
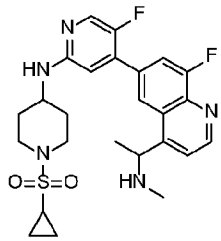
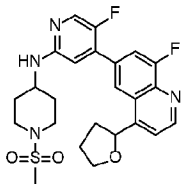
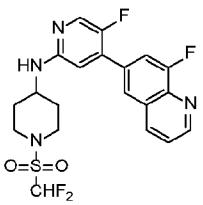
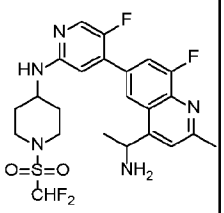
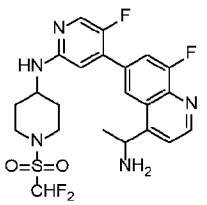
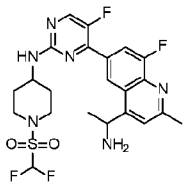
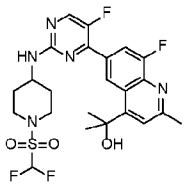
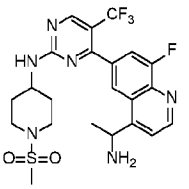
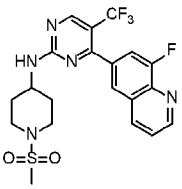
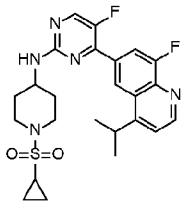
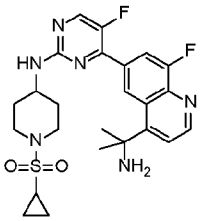
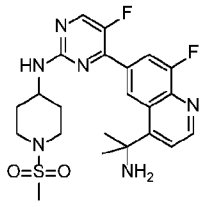
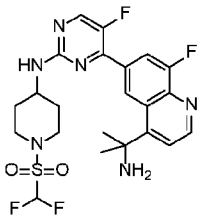
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4-(4-(2-aminopropan-2-yl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine, and

4-(4-(2-aminopropan-2-yl)-8-fluoroquinolin-6-yl)-N-(1-((difluoromethyl)sulfonyl)piperidin-4-yl)-5-fluoropyrimidin-2-amine.

[52] Other representative compounds of the present invention include those shown below and pharmaceutically acceptable salts thereof.

Ex.	Structure	Ex.	Structure	Ex.	Structure	Ex.	Structure
P1		P2		P3		P4	
P5		P6		P7		P8	

Ex.	Structure	Ex.	Structure	Ex.	Structure	Ex.	Structure
P9		P10		P11		P12	
P13		P14		P15		P16	
P17		P18		P19		P20	
P21		P22		P23		P24	

[53] Another aspect of the invention is a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier. The pharmaceutical composition may include one or more additional therapeutic agents.

[54] Yet another aspect of the present invention is a method for inhibiting one or more of CDK1, CDK2, CDK4 and CDK6 in a patient by administering to the patient an effective amount of at least one compound of the present invention such as a compound defined in formula **(I)**, **(IA)**, or **(IB)**. One embodiment is a method for inhibiting CDK2 and CDK 4/6 in

a patient by administering to the patient an effective amount of at least one compound of the present invention, such as a compound defined in formula **(I)**, **(IA)**, or **(IB)**.

[55] Another embodiment is a method for inhibiting CDK2 comprising administering at least one compound of the present invention. In one preferred embodiment, the compound exhibits greater inhibition of CDK2 than CDK1, CDK4 and/or CDK6 and therefore shows selectivity for CDK2.

[56] Yet another embodiment is a method for treating an inflammatory, autoimmune, or proliferative disease by administering to a patient in need of such treatment an effective amount of at least one compound of the present invention. In one embodiment, the compound of the present invention is administered in an effective amount to inhibit one or more of CDK1, CDK2, CDK4, and CDK6.

[57] Yet another embodiment is a method for treating a inflammatory, autoimmune or proliferative disease (e.g., via inhibition of one or more of CDK1, CDK2, CDK4, and CDK6) by administering to a patient in need of such treatment an effective amount of at least one compound of the present invention, in combination (simultaneously or sequentially) with at least one other anti-inflammatory, immunomodulator or anti-cancer agent. In one embodiment, the compound of the present invention inhibits one or more of CDK1, CDK2, CDK4, and CDK6. In another embodiment, the compound of the present invention inhibits CDK2 and/or CDK4/6. In another embodiment, the compound of the present invention predominantly inhibits CDK2 over CDK1, 4, and 6 (i.e., exhibits greater potency for CDK2 inhibition than for CDK1, 4, and 6).

[58] More particularly, the compounds of formula **(I)**, **(IA)** and **(IB)**, and pharmaceutically acceptable esters or salts thereof can be administered for the treatment, prevention and/or amelioration of diseases or disorders associated with a CDK enzyme selected from CDK1, CDK2, CDK4, CDK6, and any combination of any of the foregoing, such as the amelioration of diseases or disorders mediated by such a CDK enzyme, including, but not limited to, inflammatory diseases or disorders, autoimmune diseases or disorders, cancers, and other proliferative diseases or disorders.

[59] The compounds of the present invention are useful in the treatment of a variety of cancers, including, but not limited to:

- carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, including small cell lung cancer and carcinoma of the esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma;
- hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burkett's lymphoma;
- hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia;
- tumors of mesenchymal origin, including fibrosarcoma, and rhabdomyosarcoma;
- tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and schwannomas; and
- other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer, and Kaposi's sarcoma.

[60] The compounds of the present invention are useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of invasive cancer by either blocking the initiating mutagenic event or by blocking the progression of pre-malignant cells that have already suffered an insult or inhibiting tumor relapse. The compounds described herein are also useful in inhibiting tumor angiogenesis and metastasis. One embodiment of the invention is a method of inhibiting tumor angiogenesis or metastasis in a patient in need thereof by administering an effective amount of one or more compounds of the present invention.

[61] The compounds of the present invention are also useful in combination (administered together or sequentially) with known anti-cancer treatments, such as for example but not limited to radiation therapy or with cytostatic, cytotoxic or anticancer agents, such as for example, but not limited to, DNA interactive agents, such as cisplatin or doxorubicin; topoisomerase II inhibitors, such as etoposide; topoisomerase I inhibitors such as CPT-11 or topotecan; tubulin interacting agents, such as paclitaxel, docetaxel or the epothilones (for example ixabepilone), either naturally occurring or synthetic; hormonal agents, such as tamoxifen; thymidylate synthase inhibitors, such as 5-fluorouracil; anti-metabolites, such as methotrexate; other tyrosine kinase inhibitors such as Iressa and OSI-774; angiogenesis inhibitors; EGF inhibitors; VEGF inhibitors; HDAC inhibitors, SRC inhibitors; c-Kit inhibitors; Her1/2 inhibitors; monoclonal antibodies directed against growth factor receptors such as hercept (EGF) and herceptin (Her2); and other protein kinase modulators as well.

[62] The compounds of the present invention are also useful in combination (administered together or sequentially) with one or more steroidal, anti-inflammatory drugs, non-steroidal anti-inflammatory drugs (NSAIDs) or immune selective anti-inflammatory derivatives (ImSAIDs).

[63] In certain emdoiments, the present invention further provides a pharmaceutical composition comprising one or more compounds of the present invention (such as a compound having formula **(I)**, **(IA)**, or **(IB))** together with a pharmaceutically acceptable carrier. The pharmaceutical composition may further comprise one or more of the active ingredients identified above, such as other anti-cancer agents.

[64] In one embodiment, the pharmaceutical composition includes a therapeutically effective amount of one or more compounds of formula **(I)**, **(IA)**, or **(IB)**.

[65] Yet another embodiment is a method of treating cancer in a patient in need thereof by administering a therapeutically effective amount of a compound of the present invention. For example, the compounds of the present invention are effective for treating hematopoietic tumors of lymphoid lineage, leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, acute myelogenous leukemias, chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia. The compounds of the present invention are also effective for treating carcinoma of the bladder, carcinoma of the breast, carcinoma of the colon, carcinoma of the kidney, carcinoma of the liver, carcinoma of the lung, small cell lung cancer, esophageal cancer, gall bladder cancer, ovarian cancer, pancreatic cancer, stomach cancer, cervical cancer, thyroid cancer, prostate cancer, skin cancer, squamous cell carcinoma, tumors of mesenchymal origin, fibrosarcoma, rhabdomyosarcoma, tumors of the central and peripheral nervous system, astrocytoma, neuroblastoma, glioma, schwannoma, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

[66] Yet another embodiment is a method of treating leukemia in a patient in need thereof by administering a therapeutically effective amount of a compound of the present invention. For example, the compounds of the present invention are effective for treating carcinoma of the breast, ovarian cancer, carcinoma of the liver, carcinoma of the lung, small

cell lung cancer, esophageal cancer, gall bladder cancer, ovarian cancer, pancreatic cancer, or stomach cancer.

DETAILED DESCRIPTION OF THE INVENTION

[67] As used herein the following definitions shall apply unless otherwise indicated. Further many of the groups defined herein can be optionally substituted. The listing of substituents in the definition is exemplary and is not to be construed to limit the substituents defined elsewhere in the specification.

[68] Unless otherwise specified, the term "CDK4/6" refers to both CDK4 and CDK6. For instance, inhibition at "CDK4/6" refers to inhibition (to the same or different extent) at both CDK4 and CDK6.

[69] The term "alkyl", unless otherwise specified, refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to eight carbon atoms, and which is attached to the rest of the molecule by a single bond, e.g., methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, and 1,1-dimethylethyl (t-butyl). The term "C_{1-6}alkyl" refers to an alkyl group as defined above having up to 6 carbon atoms.

[70] The term "alkenyl", unless otherwise specified, refers to an aliphatic hydrocarbon group containing one or more carbon-carbon double bonds and which may be a straight or branched chain having about 2 to about 10 carbon atoms, e.g., ethenyl, 1-propenyl, 2-propenyl, iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, and 2-butenyl. The term "C_{2-6}alkenyl" refers to an alkenyl group as defined above having up to 6 carbon atoms.

[71] The term "alkynyl", unless otherwise specified, refers to a straight or branched chain hydrocarbyl radical having at least one carbon-carbon triple bond, and having in the range of 2 to up to 12 carbon atoms e.g., ethynyl, propynyl, and butnyl. The term "C_{2-6} alkynyl" refers to an alkynyl group as defined above having up to 6 carbon atoms.

[72] The term "alkoxy" unless otherwise specified, denotes an alkyl, cycloalkyl, or cycloalkylalkyl group as defined above attached via an oxygen linkage to the rest of the molecule. The term "substituted alkoxy" refers to an alkoxy group where the alkyl constituent is substituted (i.e., -O-(substituted alkyl). For example, "alkoxy" refers to the group -O-alkyl, including from 1 to 8 carbon atoms of a straight, branched, cyclic configuration and

combinations thereof attached to the parent structure through an oxygen atom. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, and cyclohexyloxy.

[73] The term "hydroxyalkyl" or "hydroxylalkyl" means alkyl substituted with one or more hydroxyl groups, wherein the alkyl groups are as defined above. Examples of "hydroxyalkyl" include but are not limited to hydroxymethyl, hydroxyethyl, hydroxypropyl, propan-2-ol and the like.

[74] The term "aminoalkyl" means alkyl substituted with one or more amine group(s), wherein the alkyl groups are as defined above. Examples of "aminoalkyl" include but are not limited to aminomethyl, aminoethyl, 2-aminopropyl, and the like.

[75] The term "cycloalkyl", unless otherwise specified, denotes a non-aromatic mono or multicyclic ring system of about 3 to 12 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Examples of multicyclic cycloalkyl groups include perhydronaphthyl, adamantyl and norbornyl groups, bridged cyclic groups, and sprirobicyclic groups, e.g., sprio (4,4) non-2-yl. The term "C_{3-6} cycloalkyl" refers to a cycloalkyl group as defined above having up to 6 carbon atoms.

[76] The term "cycloalkylalkyl", unless otherwise specified, refers to a cyclic ring-containing radical containing in the range of about 3 up to 8 carbon atoms directly attached to an alkyl group which is then attached to the main structure at any carbon from the alkyl group, such as cyclopropylmethyl, cyclobutylethyl, and cyclopentylethyl.

[77] The term "cycloalkenyl", unless otherwise specified, refers to cyclic ring-containing radicals containing in the range of about 3 up to 8 carbon atoms with at least one carbon-carbon double bond such as cyclopropenyl, cyclobutenyl, and cyclopentenyl. The term "cycloalkenylalkyl" refers to a cycloalkenyl group directly attached to an alkyl group which is then attached to the main structure at any carbon from the alkyl group.

[78] The term "aryl", unless otherwise specified, refers to aromatic radicals having in the range of 6 up to 20 carbon atoms such as phenyl, naphthyl, tetrahydronaphthyl, indanyl, and biphenyl.

[79] The term "arylalkyl", unless otherwise specified, refers to an aryl group as defined above directly bonded to an alkyl group as defined above, e.g., $-CH_2C_6H_5$ and $-C_2H_5C_6H_5$.

[80] The term "heterocyclic ring", unless otherwise specified, refers to a non-aromatic 3-to-15-member ring radical which consists of carbon atoms and at least one heteroatom selected from nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclic ring radical may be a mono-, bi-, tri- or tetracyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized. The heterocyclic ring radical may be attached to the main structure at any heteroatom or carbon atom.

[81] The term "heterocyclyl", unless otherwise specified, refers to a heterocylic ring radical as defined above. The heterocylcyl ring radical may be attached to the main structure at any heteroatom or carbon atom.

[82] The term "heterocyclylalkyl", unless otherwise specified, refers to a heterocylic ring radical as defined above directly bonded to an alkyl group. The heterocyclylalkyl radical may be attached to the main structure at any carbon atom in the alkyl group. Examples of such heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl.

[83] The term "heteroaryl", unless otherwise specified, refers to an optionally substituted 5-to-14-member aromatic ring having one or more heteroatoms selected from N, O, and S as ring atoms. The heteroaryl may be a mono-, bi- or tricyclic ring system. Examples of such "heterocyclic ring" or "heteroaryl" radicals include, but are not limited to, oxazolyl, thiazolyl, imidazolyl, pyrrolyl, furanyl, pyridinyl, pyrimidinyl, pyrazinyl, benzofuranyl, indolyl, benzothiazolyl, benzoxazolyl, carbazolyl, quinolyl, isoquinolyl, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofuranyl, carbazolyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, tetrazoyl, tetrahydroisoquinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, pyrrolidinyl, pyridazinyl, oxazolinyl, oxazolidinyl, triazolyl, indanyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl,

isothiazolidinyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, dioxaphospholanyl, oxadiazolyl, chromanyl, and isochromanyl. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom. The term "substituted heteroaryl" also includes ring systems substituted with one or more oxide substituents, such as pyridinyl N-oxides.

[84] The term "heteroarylalkyl", unless otherwise specified, refers to a heteroaryl ring radical as defined above directly bonded to an alkyl group. The heteroarylalkyl radical may be attached to the main structure at any carbon atom from alkyl group.

[85] The term "cyclic ring" refers to a cyclic ring containing 3 to 10 carbon atoms.

[86] The term "substituted" unless otherwise specified, refers to substitution with any one or any combination of the following substituents which may be the same or different and are independently selected from hydrogen, hydroxy, halogen, carboxyl, cyano, nitro, oxo (=O), thio (=S), substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted heterocyclylalkyl ring, substituted or unsubstituted guanidine, $-COOR^t$, $-C(O)R^v$, $-C(S)R^v$, $-C(O)NR^tR^u$, $-C(O)ONR^tR^u$, $-NR^tR^u$, $-NR^tCONR^uR^v$, $-N(R^t)SOR^u$, $-N(R^t)SO_2R^u$, $-(=N-N(R^t)R^u)$, $-NR^tC(O)OR^u$, $-NR^tR^u$, $-NR^tC(O)R^u-$, $-NR^tC(S)R^u$ $-NR^tC(S)NR^tR^u$, $-SONR^tR^u-$, $-SO_2NR^tR^u-$, $-OR^t$, $-OC(O)NR^uR^v$, $-OC(O)OR^u-$, $-OC(O)R^t$, $-OC(O)NR^tR^u$, $-R^tNR^uC(O)R^v$, $-R^tOR^u$, $-R^tC(O)OR^u$, $-R^tC(O)NR^uR^v$, $-R^tC(O)R^u$, $-R^tOC(O)R^u$, $-SR^t$, $-SOR^t$, $-SO_2R^t$, and $-ONO_2$, wherein R^t, R^u and R^v in each of the above groups can be hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, or substituted heterocyclylalkyl ring, or any two of R^t, R^u

and R^v may be joined to form a substituted or unsubstituted saturated or unsaturated 3-10 membered ring, which may optionally include heteroatoms which may be the same or different and are selected from O, NR^t (e.g., R^t can be hydrogen or C_{1-6} alkyl) or S. Substitution or the combinations of substituents envisioned by this invention are preferably those that result in the formation of a stable or chemically feasible compound. The term stable as used herein refers to the compounds or the structure that are not substantially altered when subjected to conditions to allow for their production, detection and preferably their recovery, purification, and incorporation into a pharmaceutical composition. The substituents in the aforementioned "substituted" groups cannot be further substituted.

[87] The term "halo", "halide", or, alternatively, "halogen" means fluoro, chloro, bromo or iodo. The terms "haloalkyl," "haloalkenyl," "haloalkynyl" and "haloalkoxy" include alkyl, alkenyl, alkynyl and alkoxy structures that are substituted with one or more halo groups or with combinations thereof. For example, the terms "fluoroalkyl" and "fluoroalkoxy" include haloalkyl and haloalkoxy groups, respectively, in which the halo is fluorine.

[88] The term "protecting group" or "PG" refers to a substituent that is employed to block or protect a particular functionality. Other functional groups on the compound may remain reactive. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino- protecting groups include, but are not limited to, acetyl, trifluoroacetyl, tert-butoxycarbonyl (Boc), benzyloxycarbonyl (CBz) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable hydroxy-protecting groups include, but are not limited to, acetyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Suitable carboxy-protecting groups include, but are not limited to, $-CH_2CH_2SO_2Ph$, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(p-toluenesulfonyl)ethyl, cyanoethyl, 2-(p-nitrophenylsulfenyl)ethyl, 2-(diphenylphosphino)-ethyl, and nitroethyl. For a general description of protecting groups and their use, T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

[89] Certain of the compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers,

including racemic mixtures, optically pure forms, and intermediate mixtures. More particularly non-limiting examples of intermediate mixtures include a mixture of isomers in a ratio of 10:90, 20:80, 30:70, 40:60, or 45:55, or, for instance, in any ratio between 5:95 to 45:55. Optically active (R)- and (S)- isomers can be prepared using chiral synthons or chiral reagents or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[90] The term "tautomers" refers to compounds, which are characterized by relatively easy interconversion of isomeric forms in equilibrium. These isomers are intended to be covered by this invention. "Tautomers" are structurally distinct isomers that interconvert by tautomerization. "Tautomerization" is a form of isomerization and includes prototropic or proton-shift tautomerization, which is considered a subset of acid-base chemistry. "Prototropic tautomerization" or "proton-shift tautomerization" involves the migration of a proton accompanied by changes in bond order, often the interchange of a single bond with an adjacent double bond. Where tautomerization is possible (e.g. in solution), a chemical equilibrium of tautomers can be reached. An example of tautomerization is keto-enol tautomerization. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. A specific example of phenol-keto tautomerization is the interconversion of pyridin-4-ol and pyridin-4(1H)-one tautomers.

[91] A "leaving group or atom" is any group or atom that will, under the reaction conditions, cleave from the starting material, thus promoting reaction at a specified site. Suitable examples of such groups unless otherwise specified are halogen atoms and mesyloxy, p-nitrobenzensulphonyloxy and tosyloxy groups.

[92] The term "prodrug" refers to a compound, which is an inactive precursor of a compound, converted into its active form in the body by normal metabolic processes. Prodrug design is discussed generally in Hardma, et al. (Eds.), Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th ed., pp. 11-16 (1996). A thorough discussion is provided in Higuchi, et al., Prodrugs as Novel Delivery Systems, Vol. 14, ASCD Symposium Series, and in Roche (ed.), Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press (1987). To illustrate, prodrugs can be converted into a pharmacologically active form through hydrolysis of, for example, an ester or amide linkage,

thereby introducing or exposing a functional group on the resultant product. The prodrugs can be designed to react with an endogenous compound to form a water-soluble conjugate that further enhances the pharmacological properties of the compound, for example, increased circulatory half-life. Alternatively, prodrugs can be designed to undergo covalent modification on a functional group with, for example, glucuronic acid, sulfate, glutathione, amino acids, or acetate. The resulting conjugate can be inactivated and excreted in the urine or rendered more potent than the parent compound. High molecular weight conjugates also can be excreted into the bile, subjected to enzymatic cleavage, and released back into circulation, thereby effectively increasing the biological half-life of the originally administered compound.

[93] The term "ester" refers to a compound, which is formed by reaction between an acid and an alcohol with elimination of water. An ester can be represented by the general formula RCOOR'.

[94] These prodrugs and esters are intended to be covered within the scope of this invention.

[95] Additionally, the instant invention also includes the compounds which differ only in the presence of one or more isotopically enriched atoms for example replacement of hydrogen with deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon.

[96] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[97] Pharmaceutically acceptable salts forming part of this invention include salts derived from inorganic bases such as Li, Na, K, Ca, Mg, Fe, Cu, Zn, and Mn; salts of organic bases such as N,N'-diacetylethylenediamine, glucamine, triethylamine, choline, hydroxide, dicyclohexylamine, metformin, benzylamine, trialkylamine, and thiamine; chiral bases such as alkylphenylamine, glycinol, and phenyl glycinol; salts of natural amino acids such as glycine, alanine, valine, leucine, isoleucine, norleucine, tyrosine, cystine, cysteine, methionine, proline, hydroxy proline, histidine, omithine, lysine, arginine, and serine; quaternary ammonium salts of the compounds of invention with alkyl halides, alkyl sulphates such as MeI and $(Me)_2SO_4$; non-natural amino acids such as D-isomers or substituted amino acids; guanidine; and

substituted guanidine wherein the substituents are selected from nitro, amino, alkyl, alkenyl, alkynyl, ammonium or substituted ammonium salts and aluminum salts.Salts may include acid addition salts where appropriate which are sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides (e.g., hydrochlorides), acetates, tartrates, maleates, citrates, fumarates, succinates, palmoates, methanesulphonates, benzoates, salicylates, benzenesulfonates, ascorbates, glycerophosphates, and ketoglutarates.

[98] When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary from, for example, between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") includes those embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, that "consist of" or "consist essentially of" the described features.

[99] The term "cell proliferation" refers to a phenomenon by which the cell number has changed because of division. This term also encompasses cell growth by which the cell morphology has changed (e.g., increased in size) consistent with a proliferative signal.

[100] The term "co-administration," "administered in combination with," and their grammatical equivalents, as used herein, encompasses administration of two or more agents to an animal so that both agents and/or their metabolites are present in the animal at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which both agents are present.

[101] The term "effective amount" or "therapeutically effective amount" refers to that amount of a compound described herein that is sufficient to show the intended application including but not limited to disease treatment, as defined below. The therapeutically effective amount may vary depending upon the intended application (*in vitro* or *in vivo*), or the subject and disease condition being treated, e.g., the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined

by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, e.g. reduction of platelet adhesion and/or cell migration. The specific dose will vary depending on the compounds chosen, the dosing regimen to be followed, whether it is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried. In one embodiment, the amount of compound administered ranges from about 0.1 mg to 5 g, from about 1 mg to 2.0 g, from about 100 mg to 1.5 g, from about 200 mg to 1.5 g, from about 400 mg to 1.5 g, and from about 400 mg to 1.0 g.

[102] As used herein, "treatment," "treating," or "ameliorating" are used interchangeably. These terms refer to an approach for obtaining beneficial or desired results including but not limited to therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient may still be afflicted with the underlying disorder. For prophylactic benefit, the compositions may be administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

[103] A "therapeutic effect," as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described above. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying, or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

[104] The term "subject" or “patient” refers to an animal, such as a mammal, for example a human. The methods described herein can be useful in both human therapeutics and veterinary applications (e.g., dogs, cats, cows, sheep, pigs, horses, goats, chickens, turkeys, ducks, and geese).

[105] In some embodiments, the patient is a mammal, and in some embodiments, the patient is human.

[106] "Radiation therapy" means exposing a patient, using routine methods and compositions known to the practitioner, to radiation emitters such as alpha-particle emitting radionuclides

(e.g., actinium and thorium radionuclides), low linear energy transfer (LET) radiation emitters (i.e. beta emitters), conversion electron emitters (e.g. strontium-89 and samarium- 153-EDTMP), or high-energy radiation, including without limitation x-rays, gamma rays, and neutrons.

[107] The term "pharmaceutically acceptable excipient" includes, but is not limited to, all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, one or more suitable diluents, fillers, salts, disintegrants, binders, lubricants, glidants, wetting agents, controlled release matrices, colorants/flavoring, carriers, buffers, stabilizers, solubilizers, and combinations thereof. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions of the invention is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

[108] The methods of the invention may be applied to cell populations *in vivo* or *ex vivo*. "*In vivo*" means within a living individual, as within an animal or human or in a subject's body. In this context, the methods of the invention may be used therapeutically or prophylactically in an individual."*Ex vivo*" or "*In vitro*" means outside of a living individual. Examples of ex vivo cell populations include in vitro cell cultures and biological samples including but not limited to fluid or tissue samples obtained from individuals. Such samples may be obtained by methods known in the art. Exemplary biological fluid samples include blood, cerebrospinal fluid, urine, and saliva. Exemplary tissue samples include tumors and biopsies thereof. In this context, the invention may be used for a variety of purposes, including therapeutic and experimental purposes. For example, the invention may be used ex vivo or in vitro to determine the optimal schedule and/or dosing of administration of a CDK inhibitor for a given indication, cell type, individual, and other parameters. Information gleaned from such use may be used for experimental or diagnostic purposes or in the clinic to set protocols for in vivo treatment. Other *ex vivo* uses for which the invention may be suited are described below or will become apparent to those skilled in the art.

PHARMACEUTICAL COMPOSITIONS

[109] The invention provides a pharmaceutical composition comprising one or more compounds of the present invention. The pharmaceutical composition may include one or more additional active ingredients as described herein. The one or more additional therapeutic agents

may be an anti-cancer agent, anti-inflammatory agent, immunosuppressive agent, steroid, non-steroidal anti-inflammatory agent, antihistamine, analgesic, or any combination of any of the foregoing. The pharmaceutical composition may be administered for any of the disorders described herein.

[110] The subject pharmaceutical compositions may be formulated to provide a therapeutically effective amount of a compound of the present invention as the active ingredient. The pharmaceutical compositions may contain a compound of the present invention as the active ingredient and one or more pharmaceutically acceptable carriers or excipients, such as inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants.

[111] The pharmaceutical compositions can be administered alone or in combination with one or more other agents, which are also typically administered in the form of pharmaceutical compositions. Where desired, the subject compounds and other agent(s) may be mixed into a preparation or both components may be formulated into separate preparations to use them in combination separately or at the same time.

[112] Preparations of various pharmaceutical compositions are known in the art., e.g., Anderson, Philip O.; Knoben, James E.; Troutman, William G, eds., Handbook of Clinical Drug Data, Tenth Edition, McGraw-Hill, 2002; Pratt and Taylor, eds., Principles of Drug Action, Third Edition, Churchill Livingston, New York, 1990; Katzung, ed., Basic and Clinical Pharmacology, Ninth Edition, McGraw Hill, 2003; Goodman and Gilman, eds., The Pharmacological Basis of Therapeutics, Tenth Edition, McGraw Hill, 2001; Remingtons Pharmaceutical Sciences, 20th Ed., Lippincott Williams & Wilkins., 2000; Martindale, The Extra Pharmacopoeia, Thirty-Second Edition (The Pharmaceutical Press, London, 1999), all of which are incorporated by reference herein in their entirety.

[113] The compounds or pharmaceutical composition of the present invention can be administered by any route that enables delivery of the compounds to the site of action, such as oral routes, intraduodenal routes, parenteral injection (including intravenous, intraarterial, subcutaneous, intramuscular, intravascular, intraperitoneal or infusion), topical administration (e.g. transdermal application), rectal administration, via local delivery by catheter or stent or through inhalation. The compounds can also be administered intraadiposally or intrathecally.

[114] The compositions can be administered in solid, semi-solid, liquid, or gaseous form, or may be in dried powder, such as lyophilized form. The pharmaceutical compositions can be packaged in forms convenient for delivery, including, for example, solid dosage forms such as capsules, sachets, cachets, gelatins, papers, tablets, capsules, suppositories, pellets, pills, troches, and lozenges. The type of packaging will generally depend on the desired route of administration. Implantable sustained release formulations are also contemplated, as are transdermal formulations.

METHOD OF TREATMENT

[115] The invention also provides methods of using the compounds or pharmaceutical compositions of the present invention to treat disease conditions, including, but not limited to, diseases associated with overexpression of one or more of CDK1, CDK2, CDK4 and CDK6.

[116] The treatment methods provided herein comprise administering to the subject a therapeutically effective amount of a compound of the invention. In one embodiment, the present invention provides a method of treating an inflammation disorder, including autoimmune diseases in a mammal. The method comprises administering to the mammal a therapeutically effective amount of a compound of the present invention.

[117] It will be appreciated that the treatment methods of the invention are useful in the fields of human medicine and veterinary medicine. Thus, the individual to be treated may be a mammal, preferably human, or another animal. For veterinary purposes, individuals include but are not limited to farm animals including cows, sheep, pigs, horses, and goats; companion animals such as dogs and cats; exotic and/or zoo animals; laboratory animals including mice, rats, rabbits, guinea pigs, and hamsters; and poultry such as chickens, turkeys, ducks, and geese.

[118] The invention also provides methods of using the compounds or pharmaceutical compositions of the present invention to treat disease conditions, including, but not limited to, diseases associated with overexpression of one or more of CDK1, CDK2, CDK4 and CDK6.

[119] The treatment methods provided herein comprise administering to the subject a therapeutically effective amount of a compound of the invention. In one embodiment, the present invention provides a method of treating an inflammation disorder, including autoimmune diseases in a mammal. The method comprises administering to the mammal a therapeutically effective amount of a compound of the present invention.

[120] It will be appreciated that the treatment methods of the invention are useful in the fields of human medicine and veterinary medicine. Thus, the individual to be treated may be a mammal, preferably human, or another animal. For veterinary purposes, individuals include but are not limited to farm animals including cows, sheep, pigs, horses, and goats; companion animals such as dogs and cats; exotic and/or zoo animals; laboratory animals including mice, rats, rabbits, guinea pigs, and hamsters; and poultry such as chickens, turkeys, ducks, and geese.

[121] The invention also relates to a method of treating a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof. In some embodiments, said method relates to the treatment of broad spectrum of tumors, including all solid tumors and hematological malignancies collectively referred to as cancer. Examples of such tumors include but are not limited to benign or malignant tumors of the brain, lung (in particular small-cell lung cancer and non-small cell lung cancer), squamous cell, bladder, gastric, pancreatic, breast, head and neck, renal, kidney, ureter, ovarian, prostate, colorectal, esophageal, testicular, gynecological (e.g., uterine sarcomas, carcinoma of the fallopian tubes, endometrial, cervix, vagina or vulva), thyroid, pancreatic, bone, skin, melanoma, uterine, ovarian, rectal, anal, colon, testicular, Hodgkin's disease, esophageal, small intestine, endocrine system (e.g., thyroid, parathyroid, or adrenal glands), sarcomas of soft tissues, urethra, penis, leukemia, lymphomas, neoplasms of the central nervous system, sarcomas, myeloma, biliary, liver, neurofibromatosis, acute myelogenous leukemia (AML), myelodysplastic syndromes (MDS), and Kaposi's sarcoma.

[122] The invention also relates to a method of treating the proliferative disease such as melanoma, lung cancer (including non-small cell lung cancer (NSCLC)), colorectal cancer (CRC), breast cancer, kidney cancer such as e.g., renal cell carcinoma (RCC), liver cancer, endometrial cancer, acute myelogenous leukemia (AML), myelodysplastic syndromes (MDS), thyroid cancer, particularly papillary thyroid cancer, pancreatic cancer, neurofibromatosis, or hepatocellular carcinoma.

[123] The invention also relates to a method of treating the proliferative disease such as solid tumor which includes melanoma, breast cancer, ovarian cancer, colorectal cancer, and generally gastrointestinal tract, cervix cancer, lung cancer (including small-cell lung cancer and non-small cell lung cancer), head and neck cancer, bladder cancer, prostate cancer, or Kaposi's sarcoma.

[124] In some embodiments, said method is for treating a disease selected from the group consisting of cancers mediated by one or more of CDK1, CDK2, CDK4 and CDK6 include, for example, solid tumors (e.g., breast cancer (e.g., ER+ breast cancer) and prostate cancer), leukemia (e.g., acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, hairy cell leukemia, and myeloid leukemia), lymphoma (e.g., Burkitt's lymphoma, cutaneous T-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), Hodgkin's lymphoma, mantel cell lymphoma, and non-Hodgkin's lymphoma (NHL)), adrenocortical cancer, AIDS-related cancer, anal cancer, astrocytoma, basal cell carcinoma, skin cancer (non-melanoma), bile duct cancer, bladder cancer, bone cancer (e.g., fibrosarcoma/osteosarcoma/malignant fibrous histiocytoma), brain tumor (e.g., cerebral astrocytoma, ependymoma, glioma, medulloblastoma, and supratentorial primitive neuroectodermal tumors (PNETs)), brainstem glioma, bronchial adenomas/carcinoids, carcinoid tumors, central nervous system neoplasms, cervical cancer, cholangiocarcinoma, chronic myeloproliferative disorder, colon cancer, endometrial cancer, esophageal cancer, melanoma (e.g., cutaneous or intraocular), gallbladder cancer, gastrointestinal cancer (e.g., colorectal, duodenal, and gastric (stomach) cancer), germ cell tumors, head and neck cancer, hepatocellular (liver) cancer, hypopharyngeal cancer, islet cell carcinoma, Kaposi's sarcoma, kidney (renal cell) cancer, laryngeal cancer, lip and oral cavity cancer, lung cancer (small cell and non-small cell), Merkel cell carcinoma, mesothelioma, endocrine cancer (e.g., multiple endocrine neoplasia syndrome), multiple myeloma/plasma cell neoplasm mycosis fungoides, myelodysplastic syndrome, myeloproliferative disorders, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, penile cancer, pituitary cancer, pleuropulmonary blastoma, rectal cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, Ewing sarcoma, soft tissue sarcoma, Sezary syndrome, squamous cell carcinoma, squamous neck cancer, synovial sarcoma, testicular cancer, thymoma, thymic carcinoma, thyroid cancer, transitional cell cancer, trophoblastic tumors, urethral cancer, uterine cancer, fallopian tube cancer, vaginal cancer, visual pathway and hypothalamic glioma, vulvar cancer, Waldenstrom's macroglobulinemia, and Wilms' tumor.

[125] The invention further provides methods of inhibiting a CDK enzyme selected from CDK1, CDK2, CDK4, CDK6, and any combination of any of the foregoing by contacting the CDK enzyme with an amount of a compound of the invention sufficient to inhibit the activity of the CDK enzyme.

[126] In some embodiments, the invention provides a method of inhibiting a CDK enzyme activity, where the CDK enzyme is selected from CDK1, CDK2, CDK4, CDK6, and any combination of any of the foregoing, by contacting the CDK enzyme with an amount of a compound of the invention sufficient to inhibit the activity of the CDK enzyme.

[127] In some embodiments, the invention provides a method of inhibiting a CDK enzyme activity, where the CDK enzyme is selected from CDK1, CDK2, CDK4, CDK6, and any combination of any of the foregoing. Such inhibition can take place in solution, in a cell expressing one or more CDKenzymes selected from CDK1, CDK2, CDK4, and CDK6, in a tissue comprising a cell expressing the CDK enzyme, or in an organism expressing the CDK enzyme. In some embodiments, the invention provides methods of inhibiting the CDK enzyme activity in an animal (including mammal such as humans) by contacting said animal with an amount of a compound of the invention sufficient to inhibit the activity of the CDK enzyme in said animal.

METHOD OF PREPARATION

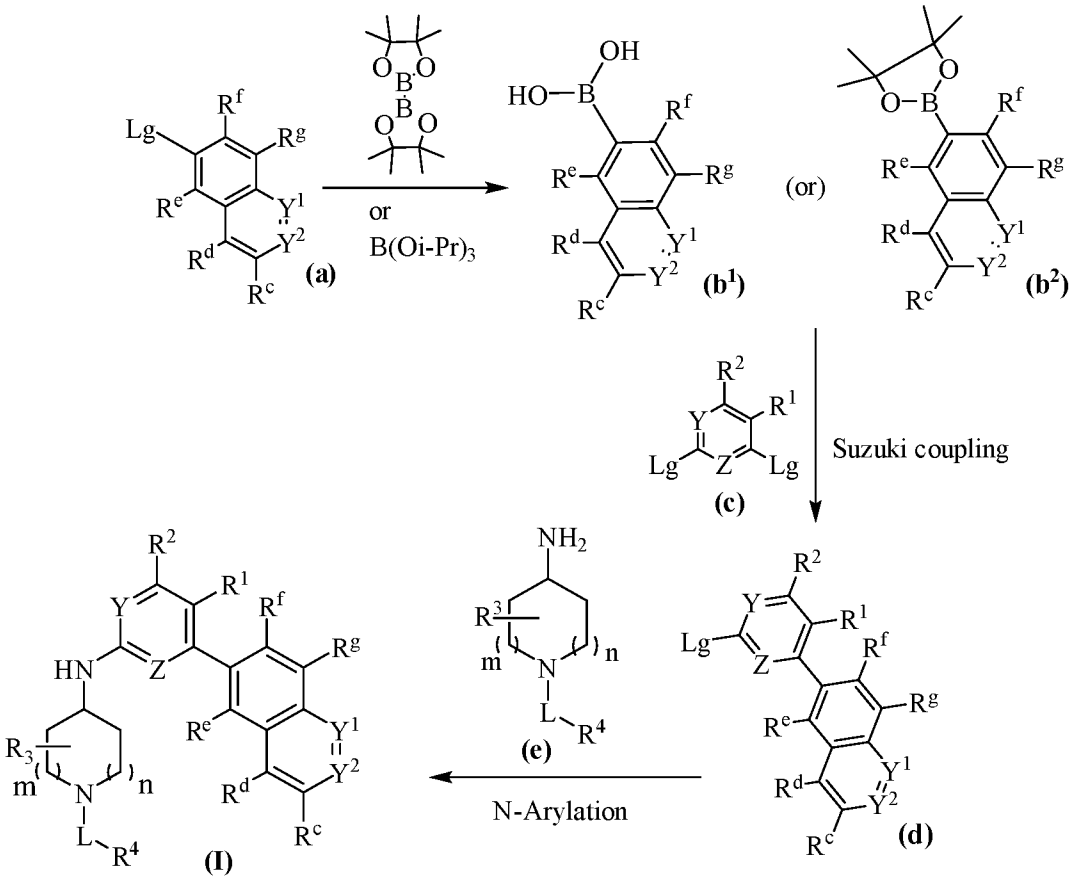
[128] Another aspect of the present invention relates to methods for preparation of compounds having formula **(I)** and their pharmaceutically acceptable salts.

[129] The following general methodologies provide processes for making the compounds of the present invention and are illustrative rather than limiting. Further modification of these methodologies and additionally new methods may also be devised to achieve and serve the purpose of the invention. Accordingly, there may be other embodiments which fall within the spirit and scope of the invention as defined by the specification hereto.

General Method of Preparation of Compounds of the Invention:

[130] A compound of formula **(I)** can be prepared by the process shown in Scheme-1 below.

Scheme-1:



[131] A compound of formula **(a)** (where Lg is a leaving group) can be converted to a compound of formula **(b^1)** or **(b^2)** by using triisopropylborate or bis(pinacolatodiboron), respectively. A compound of formula **(b^1)** or **(b^2)** can then be coupled with a compound of formula **(c)** (where each Lg moiety is a leaving group such as halogen) under Suzuki reaction conditions, for example, in the presence of a suitable base and a palladium catalyst such as $Pd(PPh_3)_4$, to form a compound of formula **(d)**. A compound of formula **(d)** can be N-arylated with a compound of formula **(e)**, for example, using suitable base such as sodium bicarbonate or using palladium catalysed N-arylation conditions to form a compound of formula **(I)**.

[132] This process is illustrated by Illustrations 1-6 below.

Illustration-1

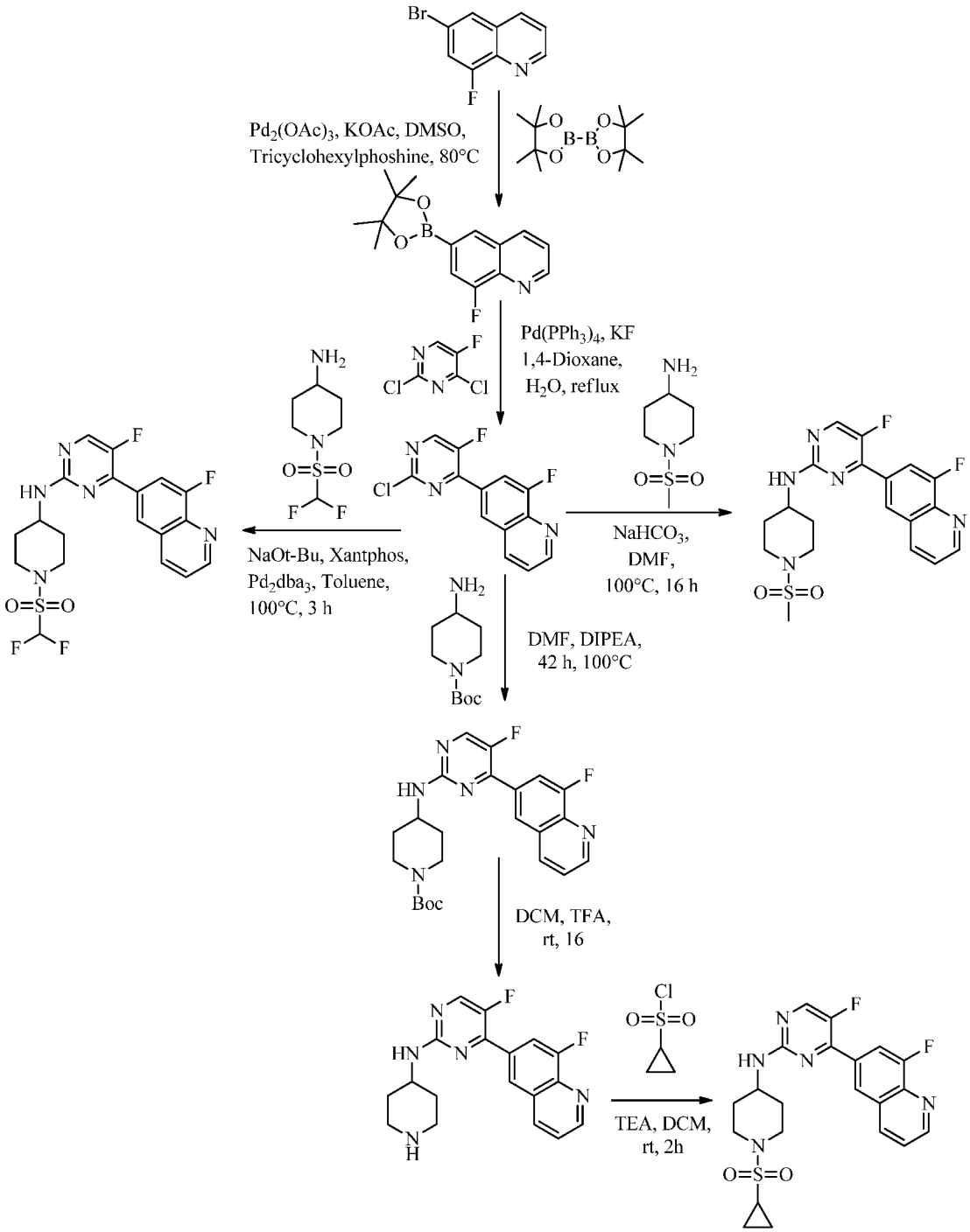


Illustration-2

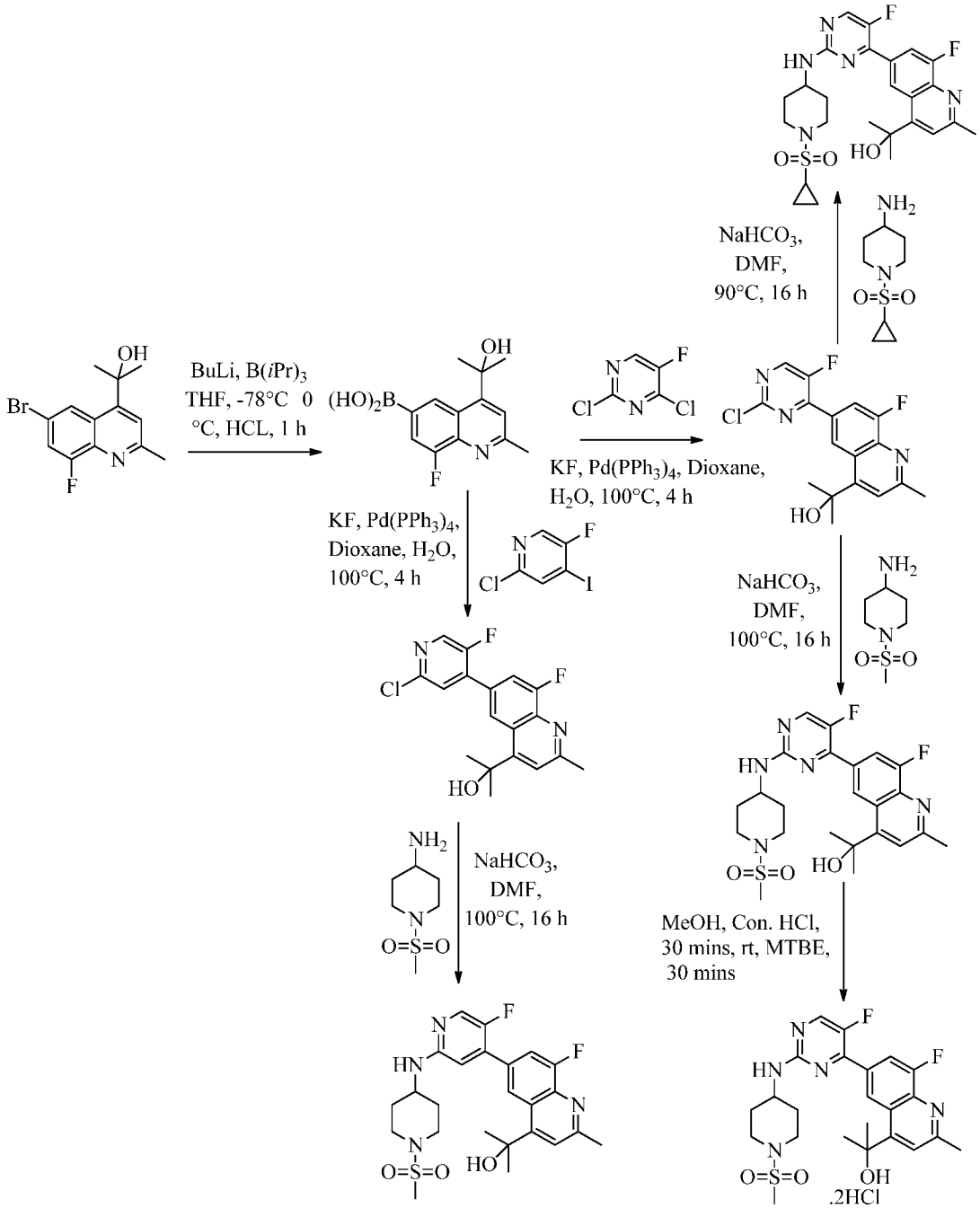


Illustration-3

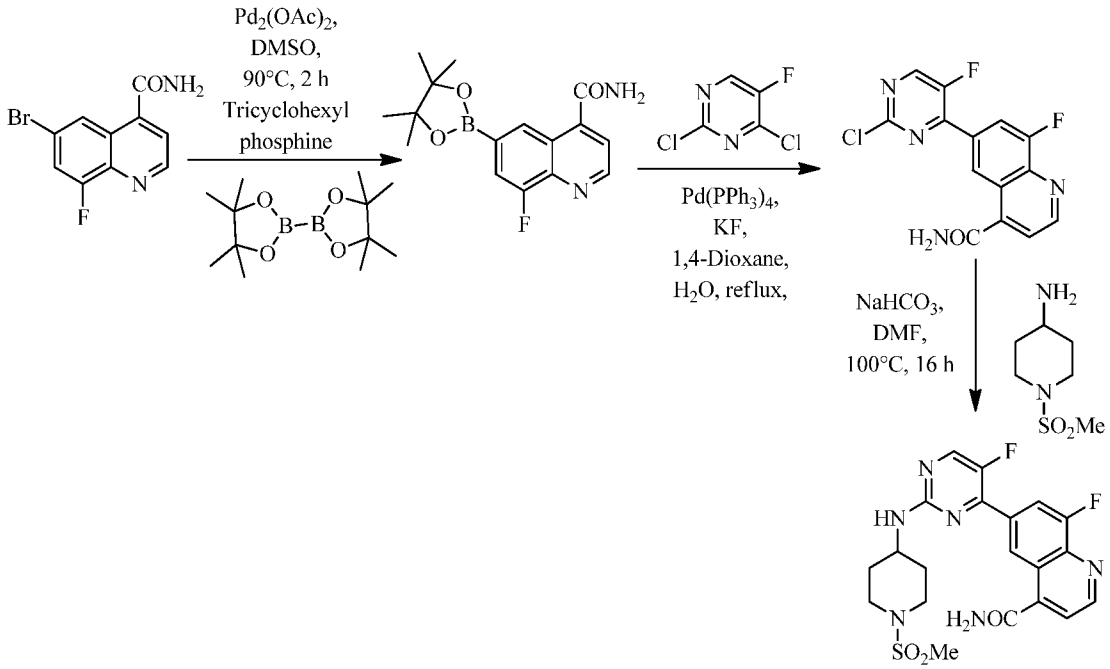


Illustration-4

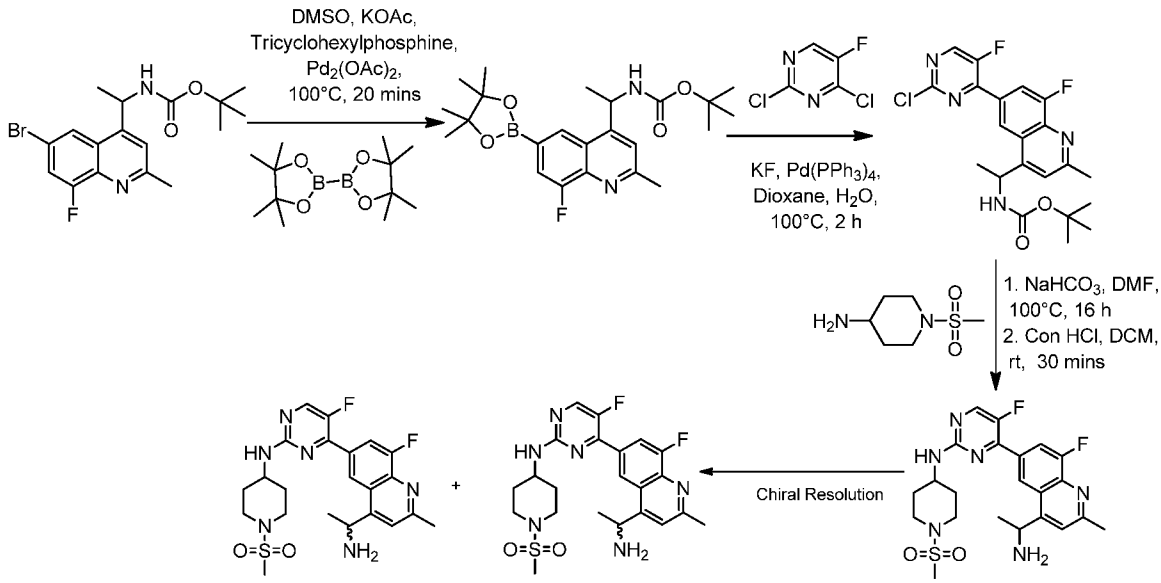


Illustration-5

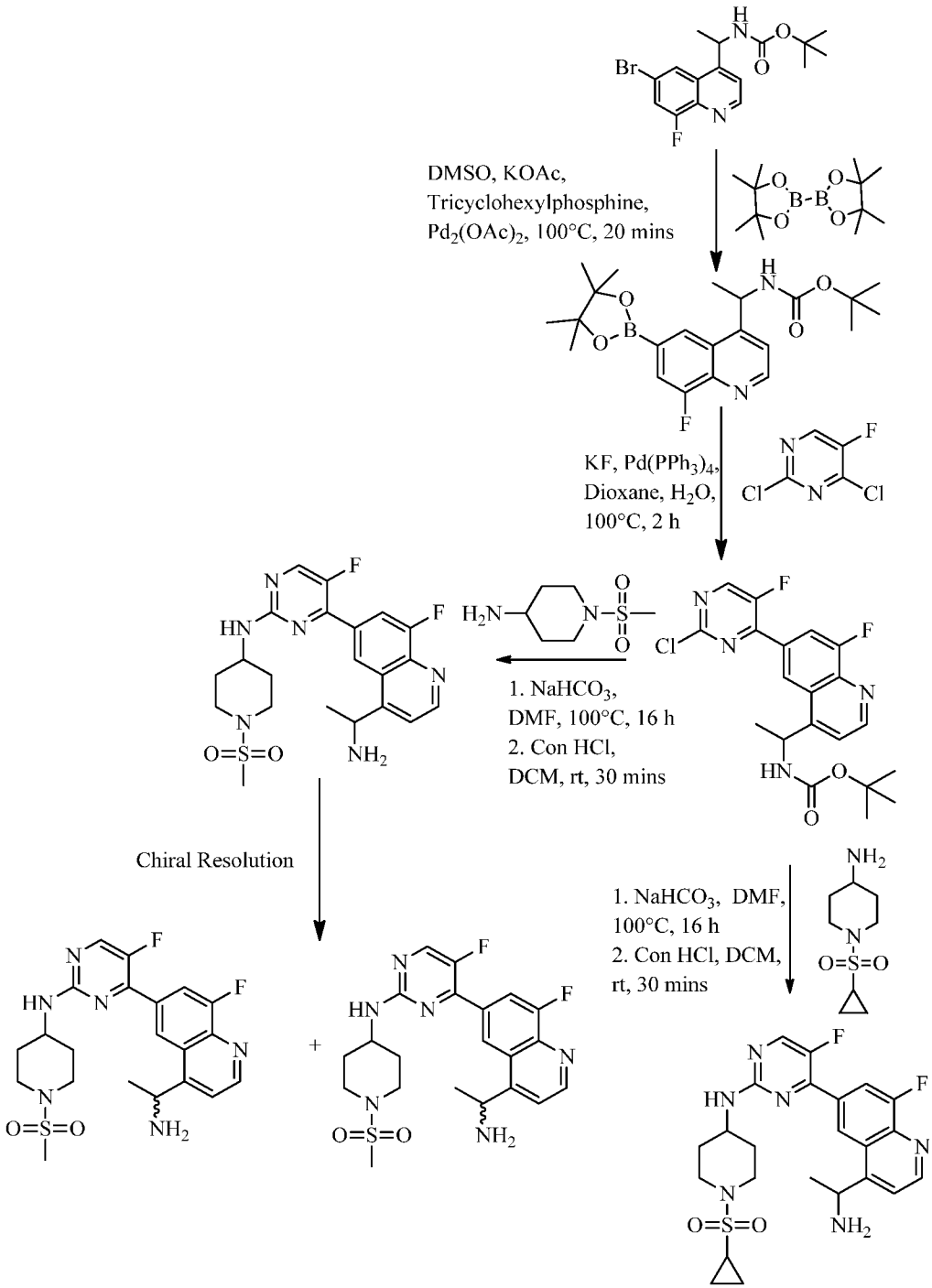
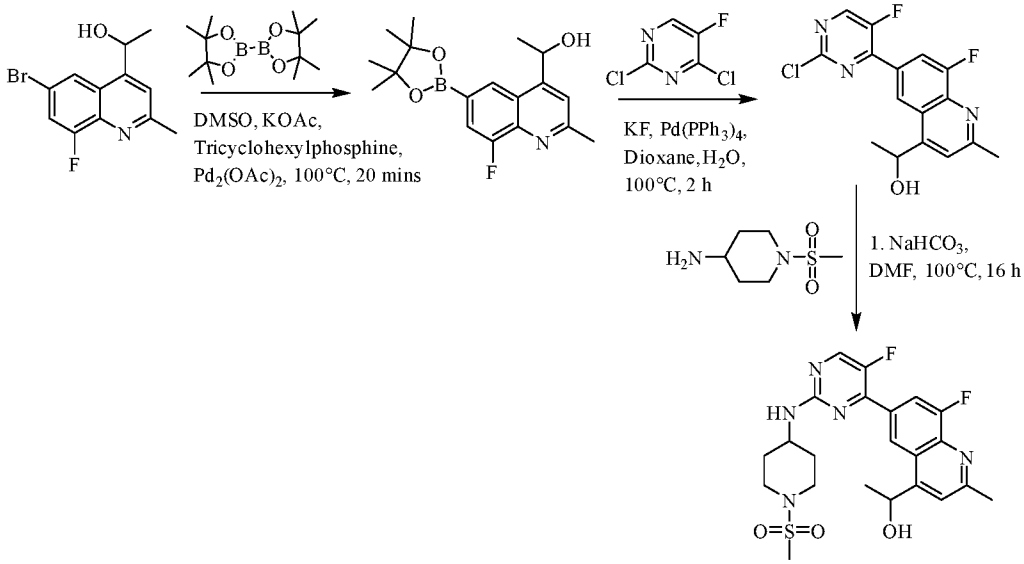
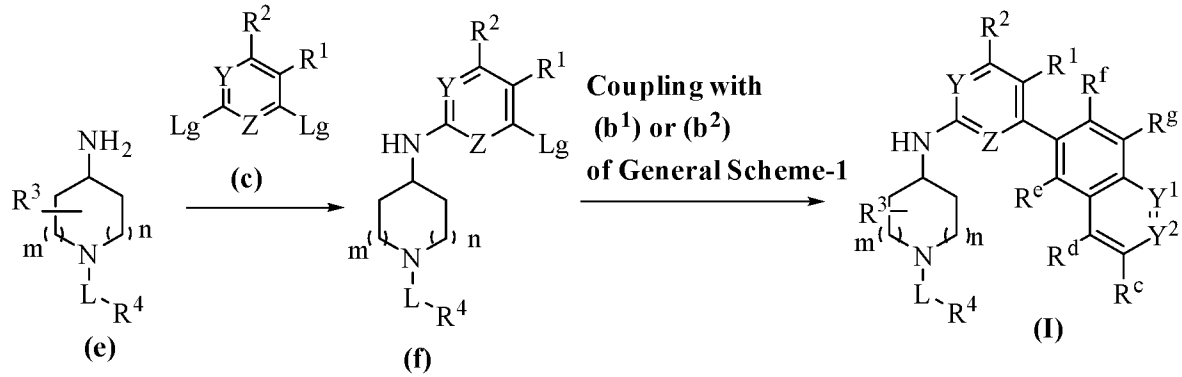


Illustration-6:



[133] A compound of formula **(I)** can be prepared by the process shown in Scheme-2 below.

Scheme-2:

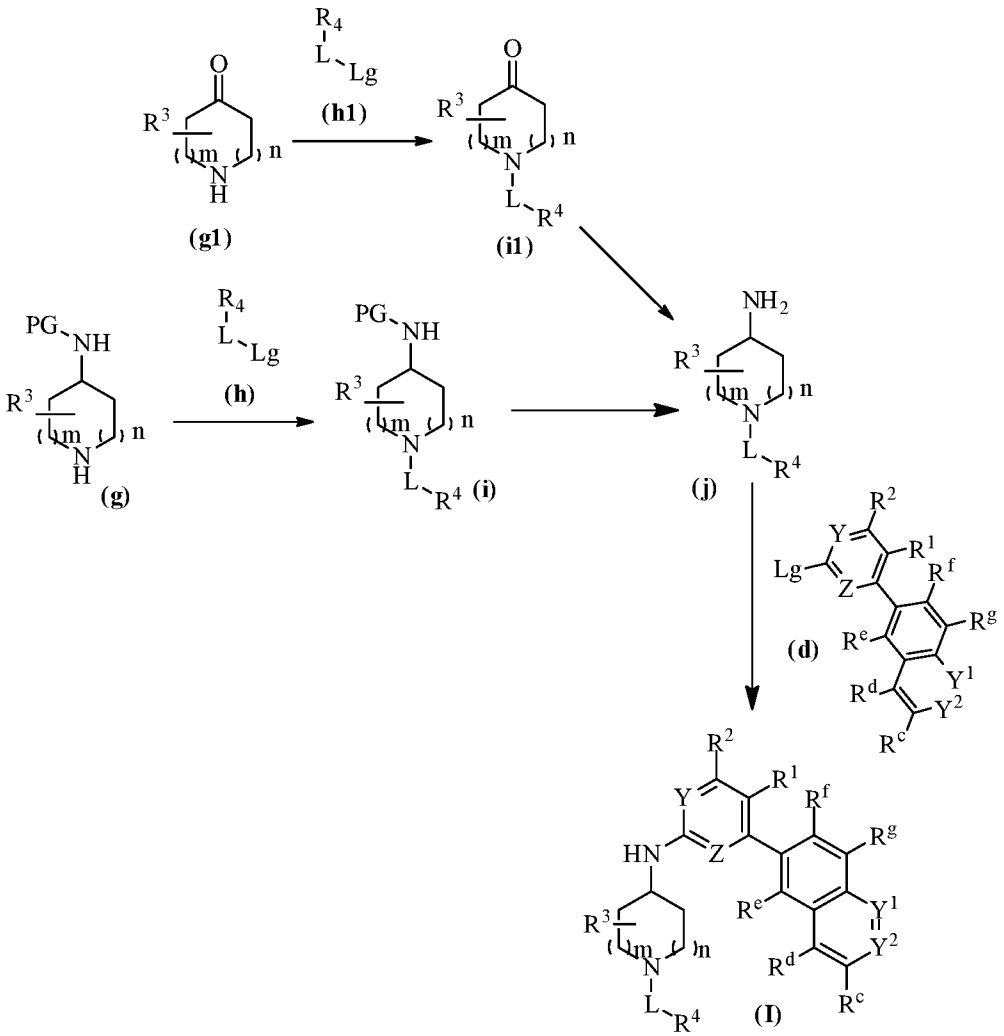


[134] A compound of formula **(e)** can be reacted with a compound of formula **(c)** in the presence of a base to give a compound of formula **(f)**. A compound of formula **(f)** can be coupled with a compound of formula **(b^1)** or **(b^2)** (prepared according to Scheme-1, where Lg

in compound (f) can be a halogen) under Suzuki reaction conditions, for example, in the presence of a suitable base and a palladium catalyst such as $Pd(PPh_3)_4$ to form a compound of formula **(I)**.

[135] A compound of formula **(I)** can be prepared by the process shown in Scheme-3 below.

Scheme-3



[136] A compound of formula **(g)** with protecting group PG can be reacted with a compound of formula **(h)** (where Lg is a leaving group) in the presence of a base, such as triethyl amine or N-ethyldiisopropyl amine, in a solvent, such as dichloromethane or N,N-dimethylformamide, to give a compound of formula **(i)**, which can be deprotected by removing

protecting group PG by hydrogenation in the presence of palladium on carbon to give a compound of formula **(j)**.

[137] Alternatively, a compound of formula **(g1)** can be reacted with a compound of formula **(h1)** in the presence of a base, such as aqueous sodium hydroxide solution in a solvent, such as THF, to give a compound of formula **(i1)**. The compound of formula **(i1)** can be reacted with ammonium acetate and ammonia in the presence of a palladium catalyst such as palladium on carbon in a solvent such as methanol to give a compound of formula **(j).**

[138] A compound of formula **(d)** can be coupled with a compound of formula **(j)** to form the compound of formula **(I)**. This reaction scheme is illustrated below in Illustrations 7 and 8.

Illustration 7:

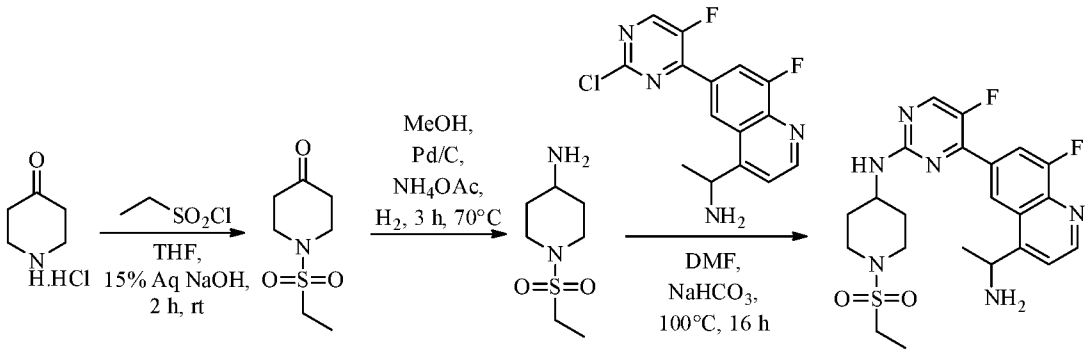
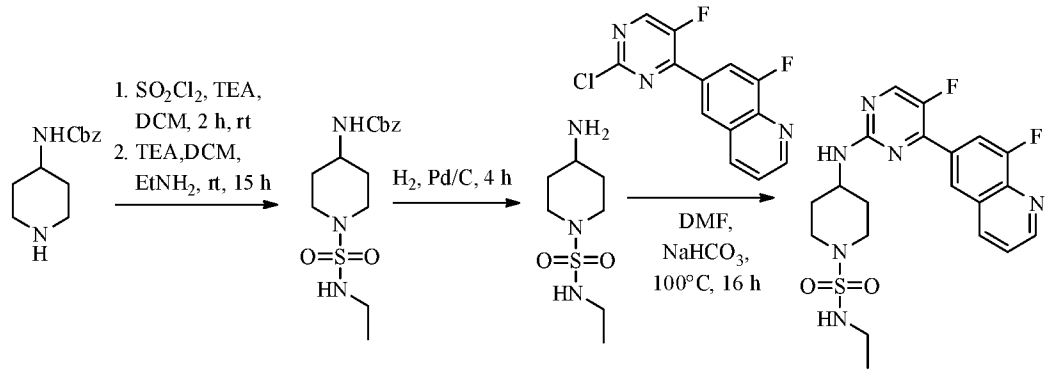
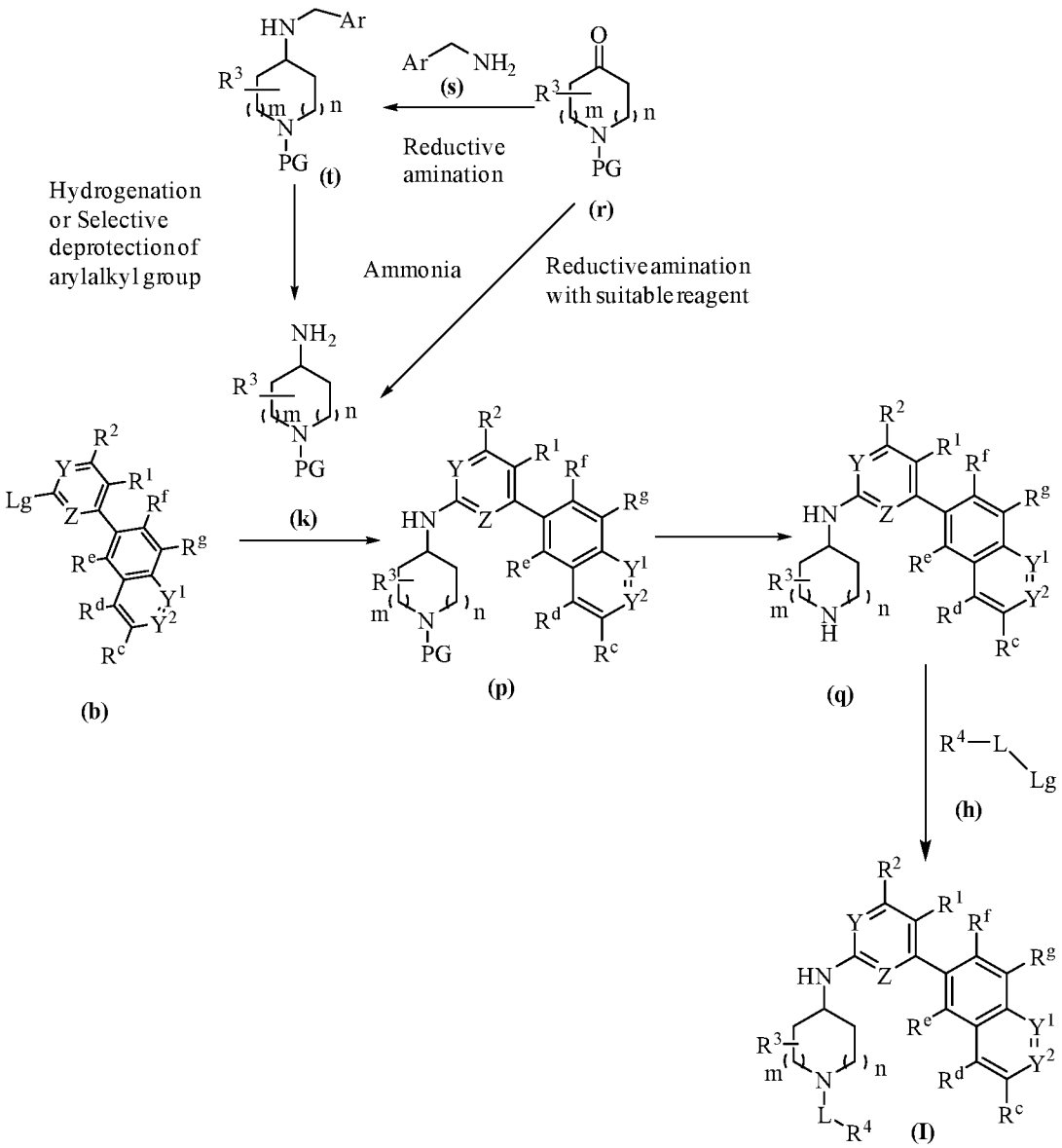


Illustration 8:



[139] A compound of formula **(I)** can be prepared by the process shown in Scheme-4 below.

Scheme-4

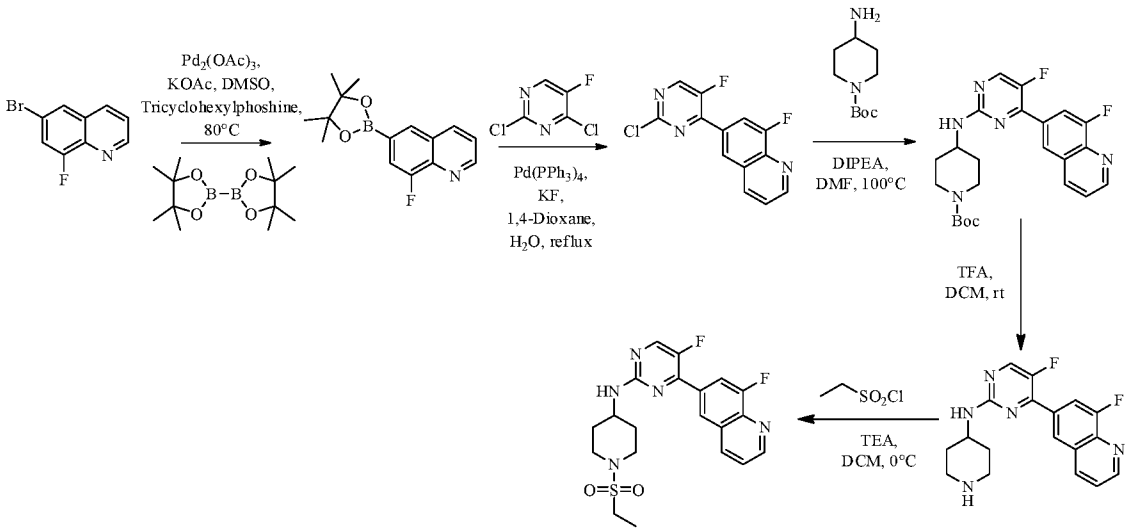


[140] A compound of formula **(r)** (where PG is a protective group such as Boc) undergoes reductive amination with an arylamine of formula **(s)** to give an amine of formula **(t)**. The amine of formula **(t)** can be hydrogenated or undergo selective deprotection of the arylalkyl group with a reducing agent such as palladium on carbon, to give the amine of formula **(k)**. Alternatively, the compound of formula **(r)** can undergo reductive amination with ammonia in the presence of a suitable reagent to give a compound of formula **(k)**.

[141] A compound of formula **(b)** can be coupled with a compound of formula **(k)** containing a protecting group PG (such as Boc) to form a compound of formula **(p)**. The protecting group in the compound of formula **(p)** can be removed by treatment with an acid such as

trifluoroacetic acid to yield a compound of formula **(q)**. The compound of formula **(q)** can be reacted with a compound of formula **(h)** having a leaving group Lg, in the presence of a base such as triethylamine or N-ethyldiisopropylamine, to give a compound of formula **(I)**. This reaction scheme is illustrated below in Illustration 9.

Illustration 9:



General Procedure-1: Preparation of Aryl boronic acid pinacol ester:

[142] To a solution of an arylbromide (1 eq.) in DMSO are added bis(pinacolatodiboron) (1.5 eq) and potassium acetate (3.0 eq). The mixture is degassed with nitrogen for 15 mins. Palladium acetate (0.11 eq) and tricyclohexyl phosphine (0.17 eq) are added and the mixture degassed for a further 15 min. and stirred at 80°C until starting material disappears as monitored by thin layer chromatography (TLC). After completion of the reaction, the reaction mixture is filtered on celite and the bed washed with ethyl acetate. Combined filtrate and washings are washed successively with brine and water and the organic layer dried on anhydrous sodium sulphate and distilled under vacuum to obtain the crude product which is purified by column chromatography.

General Procedure-2: Suzuki coupling reaction:

[143] To a solution of 2,4-dichloro-4-fluoropyrimidine (1 eq.) in dioxane and water (5:1) are added an arylboronicacid or an arylboronicacidpinacolester (1.3 eq), tetrakis(triphenylphosphine)palladium(0) (0.08 eq) and potassium fluoride (3.3 eq). The mixture is degassed with nitrogen for 30 min. and refluxed. After completion of the reaction as

indicated by TLC, the mixture is filtered through celite followed by work-up (H_2O/AcOEt) and purified to give the desired product.

General Procedure -3 for chiral separation of Racemic Examples:

[144] Chiral examples which are synthetically obtained in racemic form can be separated into the pure enantiomers by using following preparative chiral separation by suitable HPLC methods. By using the below methods selective racemic intermediates and compounds can be resolved into their enantiomerically pure forms.

Preparative Method-1:

Column	: CHIRALPAK IA, (250×30)mm, 5 micron
Mobile Phase	: MeOH/DCM/DEA (90/10/0.1 v/v/v)
Flow rate	: 40mL/min
Detection	: UV 260 nm
Temperature	: 25°C
Feed Conc.	: 10 mg/mL
Inj vol	: 12 mL (on column: 120 mg)
Runtime	: 15 min
Cycle time	: 10 min
Concentration	: 30°C

Preparative Method-2:

Column	: CHIRALPAK AD-H, (250 X 50) mm, 5 micron
Mobile Phase	: MeOH/CAN/DEA (70/30/0.1 v/v/v)
Flow rate	: 80mL/min
Detection	: UV 355 nm
Temperature	: 25°C

Feed Conc. : 10 mg/mL

Inj vol : 15 mL (on column: 150mg)

Run time : 18 min

Cycle time : 13 min

Concentration : 30°C

Preparative Method-3:

Column : CHIRALPAK AD-H, (250 X 50) mm, 5 micron

Mobile Phase : Hexanes/EtOH/MeOH/DEA (80/10/10/0.1 v/v/v/v)

Flow rate : 80mL/min

Detection : UV 355 nm

Temperature : 25°C

Feed Conc. : 50 mg/mL

Inj vol : 10 mL (on column: 300mg)

Run time : 18 min

Cycle time : 10 min

Concentration : 30°C

Analytical method 1:

Column : CHIRALPAK IA (250x4.6) mm, 5.0 µ

Mobile phase : MeOH/DEA (100/0.1 v/v)

Flow rate : 1.0 mL/min

Detection : UV 260 nm

Temperature : 25°C

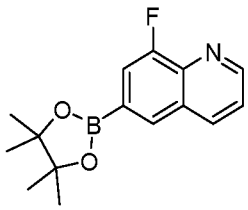
Analytical method 2:

Column	: CHIRALPAK AD-H (250x4.6) mm, 5.0 µm
Mobile phase	: MeOH/ACN/DEA (70/30/0.1 v/v/v)
Flow rate	: 1.0 mL/min
Detection	: UV 355 nm
Temperature	: 25°C

Analytical method 3:

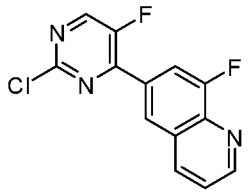
Column	: CHIRALPAK AD-H (250x4.6) mm, 5.0 µm
Mobile phase	: Hexanes/EtOH/MeOH/DEA (80/10/10/0.1 v/v/v/v)
Flow rate	: 1.0 mL/min
Detection	: UV 280 nm
Temperature	: 25°C

Intermediate 1: 8-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline



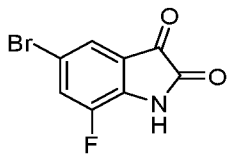
[145] Following the general procedure-1, the titled compound was synthesized from 6-bromo-8-fluoroquinoline (3.0 g, 13.27 mmol). After work up, the crude product was purified by column chromatography on 60-120 mesh silica gel using EtOAc and petroleum ether (20:80) as eluent to obtain the titled compound as a brown liquid (1.6 g). Yield: 44%. ^{1}H-NMR (δ ppm, $CDCl_3$, 400 MHz): 9.00 (dd, J 4.0, 1.6, 1H), 8.22 (br. d, J 8.4, 1H), 8.13 (s, 1H), 7.76 (d, J 9.8, 1H), 7.48 (dd, J 8.4, 4.4, 1H).

Intermediate 2: 6-(2-chloro-5-fluoropyrimidin-4-yl)-8-fluoroquinoline



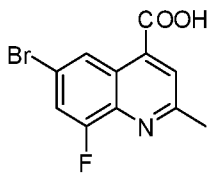
[146] Following the general procedure-2, the titled compound was synthesized from Intermediate 1 (1.5 g, 5.49 mmol) and 2,4-dichloro-4-fluoropyrimidine (917 mg, 5.49 mmol). After work up, crude product was purified by combi-flash using EtOAc and Petroleum ether (20:80) as eluent. Pure fractions from combi-flash were combined and distilled to obtain the titled compound as a brown solid (1.1 g). Yield: 80%. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 9.06-9.12 (m, 1H), 8.62 (d, J 2.8, 1H), 8.53 (s, 1H), 8.35 (d, J 8.4, 1H), 8.24 (d, J 11.6, 1H), 7.59 (dd, J 8.4, 4.0, 1H). MS (m/z): 277.8 (*M*+H)$^+$.

Intermediate 3: 5-bromo-7-fluoroindoline-2,3-dione



[147] 7-fluoroindoline-2,3-dione (50 g, 303 mmol) was dissolved in acetic acid (330 ml) and cooled to 0°C. Bromine (48.4 g, 303 mmol) was added dropwise to the stirred solution and stirred for 1 h at 0 to 5°C. After 1 h, the mixture was poured into ice cold water (500 ml). The solid precipitated was filtered, washed with water (100 ml) and dried in an oven to obtain the titled compound as a brick red solid (65 g). Yield: 88%. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 11.66 (s, 1H), 7.87 (dd, J = 9.6, 1.6, 1H), 7.56 (s, 1H). MS (m/z): 242.25 (*M*-H)$^-$.

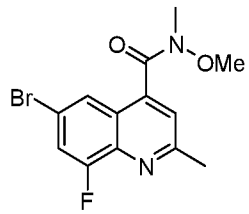
Intermediate 4: 6-bromo-8-fluoro-2-methylquinoline-4-carboxylic acid



[148] Intermediate 3 (65 g, 0.27 mol) was suspended in a solution of potassium hydroxide (103.4 g, 1.84 mol) in water (2.3 L) and acetone (260 ml) was added. This mixture was stirred at 50°C for 4 h. One more lot of acetone (260 ml) was added to the reaction mixture and stirred

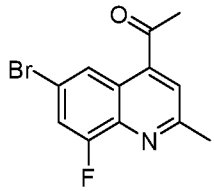
at 50°C for 16 h. The reaction mixture was cooled to rt and the pH was adjusted using 6N HCl to 3 (±0.5) when a solid was precipitated. The solid was filtered, washed with hot water (650 ml) and dried in an oven at 70°C for 15 h to obtain the titled compound as an off-white solid. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 14.14 (br. s, 1H), 8.72 (s, 1H), 8.00 (s, 1H), 7.90-7.96 (m, 1H), 2.72 (s, 3H). MS (m/z): 284.18 $(M+H)^+$.

Intermediate 5: 6-bromo-8-fluoro-N-methoxy-N,2-dimethylquinoline-4-carboxamide



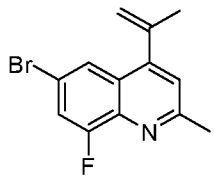
[149] Intermediate 4 (800 mg, 2.82 mmol) was dissolved in DCM (16 mL) and cooled to 0°C. To this mixture one drop of DMF was added followed by dropwise addition of oxalyl chloride (429 mg, 3.38 mmol). After complete addition of oxalyl chloride, the reaction mixture was allowed to warm up to rt and stirred for 2 h. Dichloromethane and oxalyl chloride were distilled out from the mixture and co-distilled with DCM (10mL) to obtain the residue of the acid chloride. Separately, N,O-dimethylhydroxylamine hydrochloride (275 mg, 2.82 mmol) was dissolved in DCM, cooled to 0°C, triethylamine (627 mg, 6.2 mmol) was added and stirred for 30 min. at 0 °C. To this mixture, a solution of the acid chloride described above in DCM (16 ml) was added slowly at 0°C. After complete addition, the reaction mixture was allowed to warm up to 25°C and stirred for 16 h. The reaction mixture was diluted with water and the layers separated. The aqueous layer was extracted with DCM (2*30 ml). Combined organic layers were washed successively with satd. Aq. $NaHCO_3$ solution (30 ml) and brine (30 ml). The organic layers were dried over sodium sulphate and the solvents distilled out to obtain the crude product. Purification by column chromatography on 60-120 mesh silica gel using EtOAc and petroleum ether (2:8) as eluent gave the titled compound as a yellow solid (500 mg). Yield: 54%. ^{1}H-NMR (δ ppm, $CDCl_3$, 400 MHz): 7.75 (br. s, 1H), 7.54 (dd, J 9.6, 1.6, 1H), 7.35 (s, 1H), 3.48 (br. s, 3H), 3.41 (br. s, 3H), 2.79 (s, 3H). MS (m/z): 327.18 $(M+H)^+$.

Intermediate 6: 1-(6-bromo-8-fluoro-2-methylquinolin-4-yl)ethan-1-one



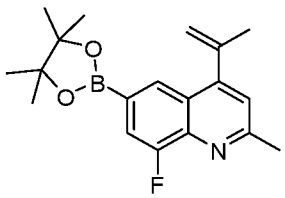
[150] Intermediate 5 (45 g, 137.4 mmol) was dissolved in THF (450 ml), cooled to 0°C and methylmagnesium chloride (3M in THF, 69 ml, 207 mmol) was added slowly. This mixture was stirred at rt for 2 h. The reaction mixture was quenched with aq. NH_4Cl solution and extracted with EtOAc. The organic layer was washed successively with water and brine solution, dried on anhydrous Na_2SO_4 and distilled to obtain the crude product. Purification by combi-flash using EtOAc and petroleum ether (12:88) as eluent gave the titled compound as a brown solid (27.4 g). Yield: 71%.^{1}H-NMR (δ ppm, $CDCl_3$, 400 MHz): 8.46 (br. s, 1H), 7.61 (s, 1H), 7.57 (dd, J 10.0, 2.0, 1H), 2.84 (s, 3H), 2.75 (s, 3H). MS (m/z): 282.18 $(M+H)^+$.

Intermediate 7: 6-bromo-8-fluoro-2-methyl-4-(prop-1-en-2-yl)quinoline



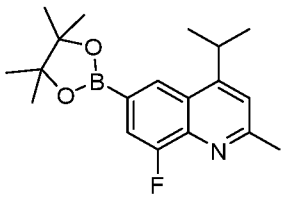
[151] Methyltriphenylphosphonium bromide (50.65 g, 0.142 mol) was dissolved in THF (50 ml), potassium *tert*-butoxide (15.91 g, 0.142 mol) was added and stirred at rt for 5 mins. A solution of the Intermediate 6 (20 g, 0.71 mol) in THF (100 ml) was added dropwise to this mixture over a period of 30 mins and stirred at rt for 8 h. The reaction was quenched with satd. aq. $NaHCO_3$ and extracted with EtOAc (2*500 ml). The Organic layer was washed successively with brine (2*250 ml) and water (250 ml), dried on anhydrous Na_2SO_4 and distilled to obtain the crude product. Purification by column chromatography on 60-120 mesh silica gel using EtOAc and petroleum ether (0.5:99.5) as eluent gave the titled compound as an off-white solid (5.7 g). Yield: 29%.^{1}H-NMR (δ ppm, $CDCl_3$, 400 MHz): 7.93 (s, 1H), 7.50 (dd, J 8.0, 1.6, 1H), 7.18 (s, 1H), 5.50 (s, 1H), 5.12 (s, 1H), 3.19 (s, 3H), 2.76 (s, 3H).

Intermediate 8: 8-fluoro-2-methyl-4-(prop-1-en-2-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline



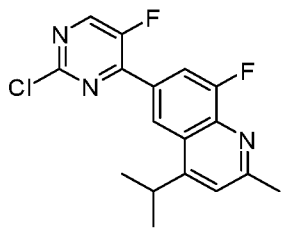
[152] Following the general procedure-1, the titled compound was synthesized from Intermediate 7 (1.0 g, 3.57 mmol). After work up, crude product was purified by combi-flash using EtOAc and petroleum ether (7:93) as eluent to obtain the titled compound as an off-white solid (500 mg). Yield: 43 %. ^{1}H-NMR (δ ppm, $CDCl_3$, 400 MHz): 8.22 (s, 1H), 7.72 (d, J 10.8, 1H), 7.16 (s, 1H), 5.50 (s, 1H), 5.14 (s, 1H), 2.78 (s, 3H), 2.22 (s, 3H), 1.37 (s, 12H).

Intermediate 9: 8-fluoro-4-isopropyl-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline



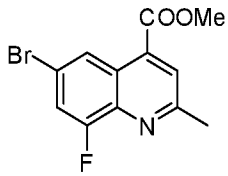
[153] Intermediate 8 (1.8 g, 5.5 mmol) was dissolved in MeOH (90 ml) and EtOH (90 ml). To this mixture 5% Pd/C (720 mg) was added and stirred in an autoclave reactor under 1 KG hydrogen atmosphere for 2 h. After 2 h, reaction mixture filtered on a cealite bed and bed washed with MeOH and DCM (1:9) (200 ml) mixture. Combined filtrates distilled to obtain a crude. Crude was purified by combi-flash using EtOAc and Petether (8:92) as eluent to obtain the titled compound as an off-white solid (1.35 g). Yield: 75%. ^{1}H-NMR (δ ppm, $CDCl_3$, 400 MHz): 8.29 (s, 1H), 7.70 (d, J 10.8, 1H), 7.25 (d, J 5.2, 1H), 3.81 (septet, J 6.4, 1H), 2.77 (s, 3H), 1.39 (s, 6H), 1.37 (s, 12 H).

Intermediate 10: 6-(2-chloro-5-fluoropyrimidin-4-yl)-8-fluoro-4-isopropyl-2-methylquinoline



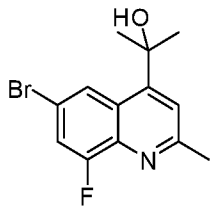
[154] Following the general procedure-2, the titled compound was synthesized from Intermediate 9 (1.3 g, 3.95 mmol) and 2,4-dichloro-4-fluoropyrimidine (791 mg, 4.74 mmol). After completion of the reaction, precipitated product in the reaction mass was filtered. Solid was dried under vacuum for 2 h to obtain the titled compound as an off-white solid (1.1 g). Yield: 83%. ^{1}H-NMR (δ ppm, $CDCl_3$, 400 MHz): 8.70 (s, 1H), 8.59 (d, J 2.8, 1H), 8.16 (d, J 12.4, 1H), 7.33 (s, 1H), 3.76 (septet, J 6.8, 1H), 2.81 (s, 3H), 1.43 (s, 6H).

Intermediate 11: Methyl 6-bromo-8-fluoro-2-methylquinoline-4-carboxylate



[155] Sulfuric acid (12 mL, 0.22 mmol) was added to a solution of intermediate 4 (36 g, 130 mmol) in methanol (360) and the mixture refluxed for 48 h. Methanol was removed by distillation and water (200 mL) was added to the residue and basified with satd. aq. $NaHCO_3$ solution. The solid was filtered, dissolved in methanol–dichloromethane mixture (1:9, 400 mL). The solution was washed with satd. aq. $NaHCO_3$ solution (3*100 mL), the organic layer dried over sodium sulfate and evaporated to give the title compound as a yellow solid (31.5 g). Yield: 83%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.61 (d, J 2.0, 1H), 8.0 (s, 1H), 7.96 (dd, J 10.0, 2.0, 1H), 3.98 (s, 3H), 2.73 (s, 3H). MS (m/z): 298.18 $(M+H)^+$.

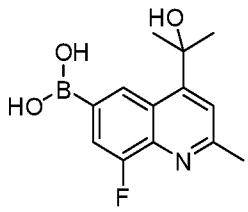
Intermediate 12: 2-(6-bromo-8-fluoro-2-methylquinolin-4-yl)propan-2-ol



[156] A 1M solution of methylmagnesium bromide in THF (290 mL, 290 mmol) was added slowly at 0 °C to a solution of 6-bromo-8-fluoro-2-methylquinoline-4-carboxylate (Intermediate 11, 17 g, 57 mmol) in THF (250 mL) and stirred at the same temperature for 2 h. Aq. satd. ammonium chloride solution (50 mL) was added to the mixture and extracted into ethyl acetate (2*50 mL). The organic layer was washed successively with water (50 mL) and brine (50 mL), dried over sodium sulfate and evaporated to give a residue that was purified by

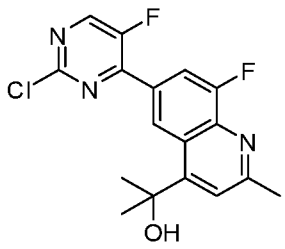
silica gel column chromatography on a combi-flash system, eluting with ethyl acetate-petether (15:85) to give the title compound as an off-white solid (11 g). Yield: 65%. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 8.89 (br. s, 1H), 7.78 (dd, J 10.0, 2.0, 1H), 7.50 (s, 1H), 5.66 (s, 1H), 2.65 (s, 3H), 1.64 (s, 6H). MS (m/z): 298.24 (*M*+H)$^+$.

Intermediate 13: (8-fluoro-4-(2-hydroxypropan-2-yl)-2-methylquinolin-6-yl)boronic acid



[157] Triisopropyl borate (8.1 mL, 35.0 mmol) was added dropwise at -78 °C to a solution of 2-(6-bromo-8-fluoro-2-methylquinolin-4-yl)propan-2-ol (Intermediate 85, 5.1 g, 17 mmol) in dry THF (176 mL) under nitrogen atmosphere. A 2.5M solution of *n*-BuLi in hexane (8.1 mL, 35 mmol) was added dropwise to the above mixture and stirred for 2 hrs at the same temperature. The mixture was brought up to RT and acidified with 2N HCl, stirred for 30 min., neutralised by the addition of aq. 10% NaOH, stirred for 20 min. and extracted into ethyl acetate (2*100 mL). The combined organic layers were washed successively with water (100 mL) and brine (100 mL), dried over sodium sulfate and concentrated. The residue was stirred with petroleum ether (10 mL) for 20 min. and the solid formed was filtered and dried. Off-white solid (3.0 g). Yield: 68%. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 8.85 (s, 1H), 8.30 (s, 2H), 7.74 (d, J 11.6, 1H), 7.32 (s, 1H), 5.48 (s, 1H), 2.65 (s, 3H), 1.69 (s, 6H). MS (m/z): 264.06 (*M*+H)$^+$.

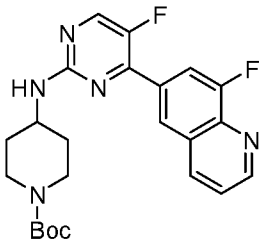
Intermediate 14: 2-(6-(2-chloro-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)propan-2-ol



[158] Following the general procedure-2, the titled compound was synthesized from Intermediate 86 (3.0 g, 11.4 mmol) and 2,4-dichloro-5-fluoropyrimidine (2.09 g, 12.5 mmol). After work up, crude product was purified by combi-flash using MeOH and DCM (1:99) as

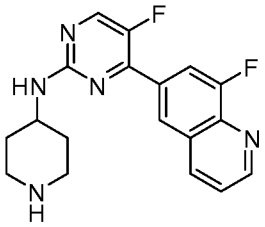
eluent to obtain the titled compound as a pale-yellow solid (2.5 g). Yield: 63%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.49 (s, 1H), 9.02 (d, J 3.2, 1H), 8.02 (d, J 11.6, 1H), 7.60 (s, 1H), 5.71 (s, 1H), 2.94 (s, 3H), 1.70 (s, 6H). MS (m/z): 350.30 (M+H)$^+$.

Intermediate 15: *Tert*-butyl 4-((5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[159] *Tert*-butyl 4-aminopiperidine-1-carboxylate (1 g, 5 mmol) and Intermediate 2 (1.52 g, 5.5 mmol) were suspended in DMF (10 ml). DIPEA (968 mg, 7.5 mmol) was added to this mixture and stirred for 42 h at 100°C. After 42 h, reaction mixture diluted with water (100 ml) and extracted with MeOH:DCM (1:9) (3*100 ml). Combined organic layers were evaporated to obtain crude. Crude product was purified by combi-flash using methanol and DCM (1:99) as eluent to obtain the titled compound as a pale-yellow solid (1.18 g). Yield: 54%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.03 (d, J 4.0, 1H), 8.63 (d, J 8, 1H), 8.52 (d, J 4, 1H), 8.48 (s, 1H), 8.12 (d, J 12, 1H), 7.72 (dd, J 8, 4, 1H), 7.41 (d, J 7.6, 1H), 3.98-3.82 (m, 3H), 3.00-2.80 (m, 2H), 1.88 (d, J 11.6, 2H), 1.94-1.84 (m, 2H), 1.39 (s, 9H), 1.38-1.35 (m, 2H). MS (m/z): 440.75 (M-H)$^-$.

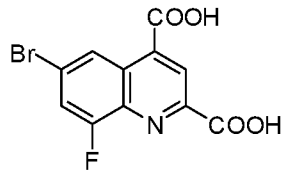
Intermediate 16: 5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(piperidin-4-yl)pyrimidin-2-amine



[160] *Tert*-butyl 4-((5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (Intermediate 15) (1.1 g, 2.5 mmol) was dissolved in DCM (11 ml). To this mixture trifluoroacetic acid (2.84 g, 25 mmol) was added and stirred at rt for 16 h. After 16 h, reaction mass quenched with aq saturated $NaHCO_3$ solution (100 ml). Aqueous layer extracted with

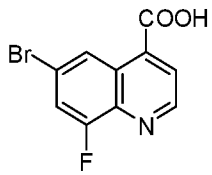
MeOH and DCM mixture (1:9) (4*70 ml). Combined organic layers were distilled to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (13:87) as eluent to obtain the titled compound as a pale-green solid (350 mg). Yield: 41%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.03 (d, J 4, 1H), 8.75 (bs, 1H), 8.63 (d, J 8.8, 1H), 8.56 (d, J 4, 1H), 8.50 (s, 1H), 8.15 (d, J 12, 1H), 7.73 (dd, J 8.8, 4, 1H), 7.64 (d, J 7.2, 1H), 4.10-4.00 (m, 1H), 3.35-3.25 (m, 2H), 3.10-2.98 (m, 2H), 2.13-2.03 (m, 2H), 1.80-1.68 (m, 2H). MS (m/z): 342.23 $(M+H)^+$.

Intermediate 17: 6-bromo-8-fluoroquinoline-2,4-dicarboxylic acid



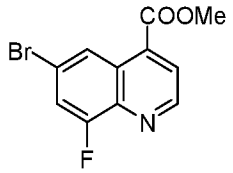
[161] Intermediate 3 (1 g, 4.10 mmol) was suspended in a solution of potassium hydroxide (10 g, 40.98 mmol) in water (360 ml) and sodium pyruvate (6.76 mg, 61.5 mmol) was added. This mixture was stirred at 50°C for 16 h. Reaction mixture cooled to 25°C and pH was adjusted to 3 (±0.5) using 6N HCl to obtain a solid. Solid was filtered and washed with water (200 ml) and dried in an oven at 70°C for 6 h to obtain the titled compound as a brown solid (8.2 g). Yield: 64%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 14.01 (bs, 2H), 8.89 (s, 1H), 8.57 (s, 1H), 8.11 (dd, J 10, 1.6, 1H). MS (m/z): 314.08 $(M+H)^+$.

Intermediate 18: 6-bromo-8-fluoroquinoline-4-carboxylic acid



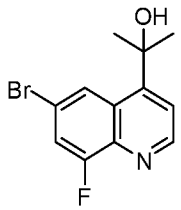
[162] Intermediate 17 (8 g, 25.5 mmol) was suspended in nitrobenzene (80 ml) and heated to 220°C for 5 h. After 5 h, reaction mixture cooled to rt and diluted with Petether (320 ml) to obtain a solid. This mixture was stirred for 1 h and filtered the solid. Solid was washed with Petether (80 ml). Solid was dried under vacuum for 1 h to obtain the titled compound as a pale-brown solid (6.1 g). Yield: 89%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 14.21 (s, 1H), 9.12 (d, J 4.4, 1H), 8.81 (s, 1H), 8.10 (d, J 4.4, 1H), 8.00 (dd, J 10, 2, 1H). MS (m/z): 270.16 $(M+H)^+$.

Intermediate 19: Methyl 6-bromo-8-fluoroquinoline-4-carboxylate



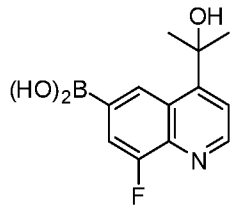
[163] Sulfuric acid (6 mL, 0.1 mmol) was added to a solution of Intermediate 18 (6 g, 22.2 mmol) in methanol (6 ml) and the mixture refluxed for 16 h. Methanol was removed by distillation and residue was dissolved in water (600 ml). Aqueous layer was extracted with EtOAc (3*300 ml) and washed the organic layer with satd. aq. $NaHCO_3$ solution (300 ml) followed by water (200 ml) and brine (200 ml). Organic layer distilled to obtain a crude. Crude product was purified by combi-flash using EtOAc and Petether (5:95) as eluent to obtain the title compound as a yellow solid (4.5 g). Yield: 71%. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 9.08 (d, J 4.4, 1H), 8.60 (t, J 1.6, 1H), 8.03 (d, J 4.4, 1H), 7.63 (dd, J 9.2, 2, 1H), 4.06 (s, 3H). MS (m/z): 284.15 $(M+H)^+$.

Intermediate 20: 2-(6-bromo-8-fluoroquinolin-4-yl)propan-2-ol



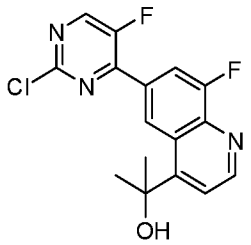
[164] A 2M solution of methylmagnesium bromide in THF (46 mL, 93 mmol) was added slowly at 0 °C to a solution of Intermediate 19 (3.3 g, 12 mmol) in THF (51.2 mL) and stirred at the same temperature for 2 h. Aq. satd. ammonium chloride solution (50 mL) was added to the mixture and extracted into ethyl acetate (200 mL). The organic layer was washed successively with water (100 mL) and brine (200 mL), dried over sodium sulfate and evaporated to give a residue that was purified by silica gel column chromatography on a combi-flash system, eluting with ethyl acetate and Petether (15:85) to give the title compound as an off-white solid (1.5 g). Yield: 46 %. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 8.98 (s, 1H), 8.89 (d, J 4.4, 1H), 7.86 (dd, J 10, 2, 1H), 7.61 (d, J 4.4, 1H), 5.72 (s,1 H), 1.65 (s, 6H). MS (m/z): 284.25 $(M+H)^+$.

Intermediate 21: (8-fluoro-4-(2-hydroxypropan-2-yl)quinolin-6-yl)boronic acid



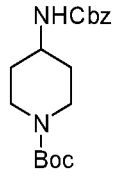
[165] Triisopropyl borate (8.1 mL, 35.0 mmol) was added dropwise at -78 °C to a solution of 2-(6-bromo-8-fluoro-2-methylquinolin-4-yl)propan-2-ol (Intermediate 20, 5.1 g, 17 mmol) in dry THF (176 mL) under nitrogen atmosphere. A 2.5M solution of *n*-BuLi in hexane (8.1 mL, 35 mmol) was added dropwise to the above mixture and stirred for 2 hrs at the same temperature. The mixture was brought up to RT and acidified with 2N HCl, stirred for 30 min., neutralised by the addition of aq. 10% NaOH, stirred for 20 min. and extracted into ethyl acetate (2*100 mL). The combined organic layers were washed successively with water (100 mL) and brine (100 mL), dried over sodium sulfate and concentrated. The residue was stirred with petroleum ether (10 mL) for 20 min. and the solid formed was filtered and dried. Off-white solid (3.0 g). Yield: 68%. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 8.94 (s, 1H), 8.86 (d, J 4.4, 1H), 8.37 (s, 2H), 7.80 (d, J 11.6, 1H), 7.67 (d, J 4.4, 1H), 5.54 (s, 1H), 1.70 (s, 6H). MS (m/z): 249.90 (*M*+H)$^+$.

Intermediate 22: 2-(6-(2-chloro-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)propan-2-ol



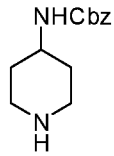
[166] Following the general procedure-2, the titled compound was synthesized from Intermediate 21 (400 mg, 1.61 mmol) and 2,4-dichloro-5-fluoropyrimidine (322 mg, 3.85 mmol). After work up, crude product was purified by combi-flash using EtOAc and Petether (1:1) as eluent to obtain the titled compound as an off-white solid (260 mg). Yield: 48%. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 9.55 (s, 1H), 9.04 (d, J 3.2, 1H), 8.99 (d, J 4.4, 1H), 8.06 (d, J 11.6, 1H), 7.72 (d, J 4.4, 1H), 5.78 (s, 1H), 1.71 (s, 6H). MS (m/z): 336.22 (*M*+H)$^+$.

Intermediate 23: *Tert*-butyl 4-(((benzyloxy)carbonyl)amino)piperidine-1-carboxylate



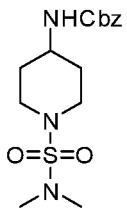
[167] *Tert*-butyl 4-aminopiperidine-1-carboxylate (1 g, 4.99 mmol) was dissolved in DCM (30 ml) and added DIPEA (2.6 ml, 14.88 mmol). This mixture stirred for 30 mins and cooled to 0°C. Benzylchloroformate was added to the above mixture and stirred at rt for 16 h. After 16 h, reaction mass quenched with aq. $NaHCO_3$ and separated organic layer. Aqueous layer extracted with DCM (2*100 ml) and combined organic layers were washed with brine (100 ml) and water (100 ml). Organic layer distilled to obtain crude product. Crude was purified by combi-flash using EtOAc and Petether (1:9) as eluent to afford the titled compound as a pale-yellow solid (1.1 g). Yield: 66%. ^{1}H-NMR (δ ppm, $CDCl_3$ 400 MHz): 7.40-7.30 (m, 5H), 5.09 (s, 2H), 4.65 (bs, 1H), 4.10-3.90 (m, 2H), 3.71-3.60 (m, 1H), 2.90-2.75 (m, 2H), 1.98-1.90 (m, 2H), 1.45 (s, 9H), 1.38-1.24 (m, 2H).

Intermediate 24: Benzyl piperidin-4-ylcarbamate



[168] Intermediate 23 (6 g, 18 mmol) was dissolved in DCM (60 ml) and trifluoracetic acid (13.8 ml, 179 mmol) was added. This mixture was stirred at rt for 3 h. After 3 h, reaction mixture was quenched with aq. $NaHCO_3$ solution to obtain a solid. Solid was filtered and triturated with Et_2O (20 ml). Filtered the solid and washed with Et_2O (20 ml). Solid was dried under vacuum to obtain the titled compound as a yellow solid (250 mg). Yield: 100%. ^{1}H-NMR (δ ppm, $CDCl_3$, 400 MHz): 7.40-7.30 (m, 5H), 5.09 (s, 2H), 4.69 (bs, 1H), 3.68-3.55 (m, 1H), 3.06 (d, J 9.2, 2H), 2.66 (t, J 11.6, 2H), 1.95 (d, J 11.2, 2H), 1.39-1.22 (m, 2H).

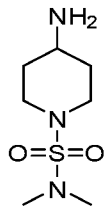
Intermediate 25: Benzyl (1-(N,N-dimethylsulfamoyl)piperidin-4-yl)carbamate



[169] Step-1: Intermediate 24 (3 g, 12.8 mmol) was dissolved in DCM (60 ml) and triethylamine (2.7 ml, 19.2 mmol) was added. This mixture was stirred at rt for 30 mins and cooled to 0°C. At 0°C, sulfuryl chloride (2.06 ml, 25.6 mmol) was added. This mixture was warmed to room temperature and stirred at rt for 2 h.

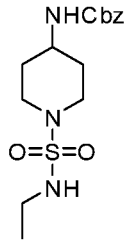
[170] Step-2: In a separate vessel N,N-dimethylamine hydrochloride (2.08 g, 25.6 mmol) was dissolved in DCM (41.6 ml) and triethylamine (10.7 ml, 76.02 mmol) was added. This mixture was cooled to 0°C and reaction mixture from Step-1 was added dropwise. Reaction mixture was warmed to room temperature stirred for 2 h. After 2 h, reaction mass quenched with water and separated organic layer. Aqueous layer extracted with DCM (2*70 ml). Combined organic layers were washed with aq. $NaHCO_3$ solution (3*100 ml) and water (100 ml). Organic layer distilled to obtain crude. Crude was purified by combi-flash using EtOAc and Petether (3:7) as eluent to afford the titled compound as a white solid (2 g). Yield: 46%.^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 7.40-7.28 (m, 5H), 4.99 (s, 2H), 3.52-3.42 (m, 3H), 2.97-2.87 (m, 2H), 2.71 (s, 6H), 1.82-1.72 (m, 2H), 1.44-1.32 (m, 2H).

Intermediate 26: 4-amino-N,N-dimethylpiperidine-1-sulfonamide



[171] Intermediate 25 (2 g, 5.85 mmol) was dissolved in THF (40 ml) and 5% Pd/C (2 g) was added. This mixture was taken in an autoclave and stirred at 5 Kg Hydrogen atmosphere for 3 h. After 3 h, reaction mixture filtered on a cealite bed and bed washed with MeOH:DCM (1:9) (400 ml) mixture. Combined filtrates were distilled to obtain a residue. Residue was dissolved in Et_2O (5 ml) and Petether (10 ml) was added slowly to obtain a solid. Solid was filtered and washed with Petether (5 ml). Solid was dried under vacuum to obtain the titled compound as an off-white solid (800 mg). Yield: 66%. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 3.51-3.43 (m, 2H), 3.18 (bs, 2H), 2.88-2.78 (m, 2H), 2.71 (s, 6H), 2.70-2.65 (m, 1H), 1.76-1.68 (m, 2H), 1.28-1.15 (m, 2H).

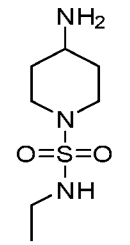
Intermediate 27: Benzyl (1-(N-ethylsulfamoyl)piperidin-4-yl)carbamate



[172] Step-1: Intermediate 24 (1.9 g, 8.1 mmol) was dissolved in DCM (38 ml) and triethylamine (1.7 ml, 12.16 mmol) was added. This mixture was stirred at rt for 30 mins and cooled to 0°C. At 0°C, sulfuryl chloride (1.3 ml, 16.2 mmol) was added. This mixture was warmed to room temperature and stirred at rt for 2 h.

[173] Step-2: In a separate vessel Ethylamine hydrochloride (1.32 g, 16.2 mmol) was dissolved in DCM (26.4 ml) and triethylamine (6.8 ml, 48.65 mmol) was added. This mixture was cooled to 0°C and reaction mixture from Step-1 was added dropwise. Reaction mixture was warmed to room temperature stirred for 2 h. After 2 h, reaction mass quenched with water (100 ml) and separated organic layer. Aqueous layer extracted with DCM (3*70 ml). Combined organic layers were washed with aq. $NaHCO_3$ solution (3*100 ml) and water (100 ml). Organic layer distilled to obtain crude. Crude was purified by combi-flash using EtOAc and Petether (3:7) as eluent to afford the titled compound as a white solid (400 mg). Yield: 24%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 7.40-7.28 (m, 6H), 7.12 (t, J 5.6, 1H), 4.99 (s, 2H), 3.48-3.38 (m, 3H), 2.88 (quintet, J 6, 2H), 2.88-2.78 (m, 2H), 1.84-1.75 (m, 2H), 1.45-1.33 (m, 2H), 1.03 (t, J 7.2, 3H). MS (m/z): 342.0 $(M+H)^+$.

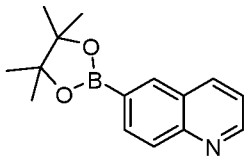
Intermediate 28: 4-amino-N-ethylpiperidine-1-sulfonamide



[174] Intermediate 27 (400 mg, 1.17 mmol) was dissolved in THF (20 ml) and 5% Pd/C (400 mg) was added. This mixture was taken in an autoclave and stirred at 5 Kg Hydrogen atmosphere for 3 h. After 3 h, reaction mixture filtered on a cealite bed and bed washed with MeOH:DCM (1:9) (200 ml) mixture. Combined filtrates were distilled to obtain a residue.

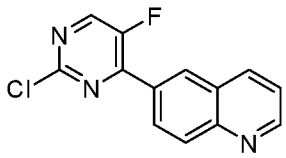
Residue was triturated in Et_2O (10 ml) to obtain a solid. Solid was filtered and dried under vacuum to obtain the titled compound as an off-white solid (210 mg). Yield: 86%. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 7.09 (bs, 1H), 3.46-3.30 (m, 3H), 2.91 (q, J 7.2, 2H), 2.72-2.63 (m, 2H), 1.79 -1.69 (m, 2H), 1.50 (bs, 2H), 1.30-1.18 (m, 2H), 1.06 (t, J 7.2, 3H).

Intermediate 29: 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline



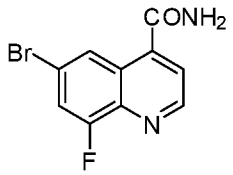
[175] Following the general procedure-1, the titled compound was synthesized from 6-Bromoquinoline (3.0 g, 14.42 mmol). After work up, the crude product was purified by column chromatography on 60-120 mesh silica gel using EtOAc and Petroleum ether (5:95) as eluent to obtain the titled compound as a brown liquid (3.2 g). Yield: 87%.^{1}H-NMR (δ ppm, $CDCl_3$, 400 MHz): 8.92-8.96 (m, 1H), 8.35 (s, 1H), 8.19 (dd, J 8.0, 1.2, 1H), 8.08 (br. s, 2H), 7.41 (dd, J 8.0, 4.0, 1H), 1.34 (s, 12H).

Intermediate 30: 6-(2-chloro-5-fluoropyrimidin-4-yl)quinoline



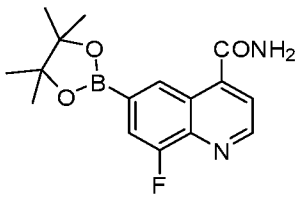
[176] Following the general procedure-2, the titled compound was synthesized from Intermediate 29 (3.0 g, 11.75 mmol) and 2,4-dichloro-5-fluoropyrimidine (1.96 g, 11.75 mmol). After work up, crude product was purified by combi-flash using EtOAc and Petroleum ether (21:79) as eluent to obtain the titled compound as a pale-yellow solid (1.7 g). Yield: 55%.^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 8.90-9.05 (m, 2H), 8.74 (s, 1H), 8.62 (d, J 8.4, 1H), 8.35 (d, J 8.8, 1H), 8.20 (d, J 9.2, 1H), 7.65 (dd, J 8.4, 4.4, 1H).

Intermediate 31: 6-bromo-8-fluoroquinoline-4-carboxamide



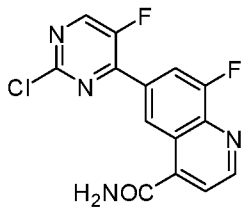
[177] Intermediate 18 (3.5 g, 12.96 mmol) was suspended in thionyl chloride (17 ml) and refluxed for 3 h. After 3 h, thionyl chloride was distilled out to obtain a residue. Residue was dissolved in dioxane (65 ml), cooled to 15°C and passed ammonia gas for 1 h. After 1 h, reaction mixture warmed to rt and continued stirring for additional 2 h. After 2h, reaction mixture diluted with water and extracted with EtOAc (3*70 ml). Combined organic layers were washed with water (100 ml). Organic layer distilled to obtain crude. Crude was triturated with diethyl ether (30 ml) to obtain a solid. Solid was filtered and washed with diethyl ether (30 ml). Solid was dried under vacuum to obtain the titled compound as a pale brown solid (3 g). Yield: 86 %. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 9.08 (d, J 4, 1H), 8.38 (s, 1H), 8.28 (d, J 1.2, 1H), 8.04 (s, 1H), 8.00 (dd, J 10, 1.2, 1H), 7.76 (d, J 4, 1H).

Intermediate 32: 8-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline-4-carboxamide



[178] Following the general procedure 1, the titled compound was synthesized from Intermediate 31 (2.9 g, 10.77 mmol). After work up, crude product was purified by combi-flash using MeOH and DCM (2.3:97.7) as eluent to obtain the titled compound as a brown solid (1.9 g). Yield: 56 %. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 9.06 (d, J 4, 1H), 8.36 (s, 1H), 8.32 (s, 1H), 7.99 (s, 1H), 7.69-7.63 (m, 2H), 1.33 (s, 12 H).

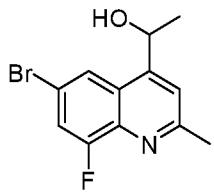
Intermediate 33: 6-(2-chloro-5-fluoropyrimidin-4-yl)-8-fluoroquinoline-4-carboxamide



[179] Following the general procedure-2, the titled compound was synthesized from Intermediate 32 (1.9 g, 6 mmol) and 2,4-dichloro-5-fluoropyrimidine (1.2 g, 7.21 mmol). After completion of reaction, reaction mixture cooled to rt to obtain a solid. Solid was filtered and washed with a mixture of Dioxane and water(1:1) (15 ml). Solid was further stirred with a

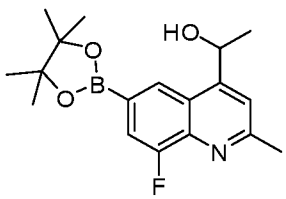
mixture of Diethyl ether and EtOAC (1:1) (20 ml) for 30 mins and filtered the solid. Solid was dried under vacuum to obtain the titled compound as a pink solid (1.5 g). Yield: 78 %. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 9.17 (d, J 4, 1H), 9.07 (d, J 2.8, 1H), 8.86 (s, 1H), 8.43 (s, 1H), 8.19 (d, J 12, 1H), 8.10 (s, 1H), 7.82 (d, J 4.4, 1H). MS (m/z): 321.19 (*M*+H)$^+$.

Intermediate 34: (±)-1-(6-bromo-8-fluoro-2-methylquinolin-4-yl)ethan-1-ol



[180] Intermediate 6 (2.7 g, 9.6 mmol) was dissolved in a mixture of MeOH (27 ml) and THF (27 ml). To this mixture $NaBH_4$ (2.12 g, 56.04 mmol) was added and refluxed this mixture for 3 h. After 3 h, reaction mixture cooled to rt and water (150 ml) was added. Aqueous layer extracted with EtOAc (3*80 ml). Combined organic layers were washed with water (100 ml) and brine (100 ml). Organic layer distilled under reduced pressure to obtain a solid. Solid was suspended in Petether (40 ml) and stirred for 30 mins. After 30 mins, filtered the solid and washed with Petether (20 ml). Solid was dried under vacuum to obtain the titled compound as an off-white solid (2.3 g). Yield: 77 %. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 8.20 (s, 1H), 7.82 (dd, J 10.4, 2, 1H), 7.61 (s, 1H), 5.65 (d, J 4.4, 1H), 5.43-5.35 (m, 1H), 2.66 (s, 3H), 1.43 (d, J 6.4, 3H). MS (m/z): 284.20 (*M*+H)$^+$.

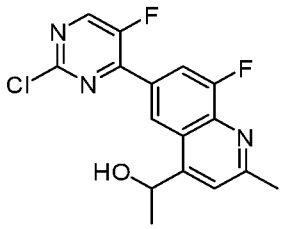
Intermediate 35: (±)-1-(8-fluoro-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-4-yl)ethan-1-ol



[181] Following the general procedure-1, the titled compound was synthesized from Intermediate 34 (2.3 g, 8.09 mmol). After work up, crude product was purified by combi-flash using EtOAc and Petether (35:65) as eluent to obtain the titled compound as an off-white solid (1 g). Yield: 39 %. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 8.27 (d, J 3.2, 1H), 7.61 (d, J 3.6,

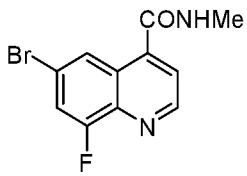
1H), 7.57 (dd, J 10.8, 3.2, 1H), 5.64 (d, J 3.6, 1H), 5.47-5.38 (m, 1H), 2.69 (s, 3H), 1.48 (d, J 6.4, 3H), 1.34 (s, 12 H). MS (m/z): 332.36 $(M+H)^+$.

Intermediate 36: (±)-1-(6-(2-Chloro-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)ethan-1-ol



[182] Following the general procedure-2, the titled compound was synthesized from Intermediate 35 (950 mg, 2.87 mmol) and 2,4-dichloro-5-fluoropyrimidine (580 mg, 3.44 mmol). After completion of reaction, reaction mixture cooled to rt and water (2.4 ml) was added to obtain a solid. This mixture was stirred and filtered the solid. Solid was washed with a mixture of Dioxane and water(1:1) (8 ml). Solid was further stirred with Diethyl ether (20 ml) for 30 mins and filtered the solid. Solid was dried under vacuum to obtain the titled compound as an off-white solid (670 mg). Yield: 70 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.05 (d, J 2.4, 1H), 8.69 (s, 1H), 8.04 (d, J 11.6, 1H), 7.69 (s, 1H), 5.71 (d, J 3.6, 1H), 5.49-5.40 (m, 1H), 2.73 (s, 3H), 1.52 (d, J 6.4, 3H). MS (m/z): 336.27 $(M+H)^+$.

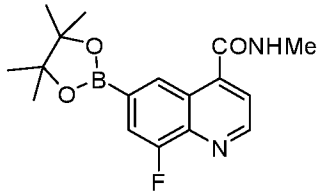
Intermediate 37: 6-bromo-8-fluoro-N-methylquinoline-4-carboxamide



[183] To a solution of Intermediate 18 (4 g, 15 mmol) in DMF (40 ml), HBTU (6.76 g, 17.8 mmol) and N-Ethyldiisopropylamine (7.74 ml, 44.4 mmol) were added. This mixture was stirred at 0°C for 15 mins in a sealed tube and 2M Methylamine (2.99 g, 96.3 mmol) was added. This mixture was stirred at rt for 2 h. Reaction mixture diluted with water and extracted with EtOAc (3*100 ml). Combined EtOAc layers were washed with water (100 ml) and brine (100 ml). EtOAc was evaporated to obtain crude solid (3.5 g), which was used in the next step without further purification. Yield: 83.5%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.06 (t, J

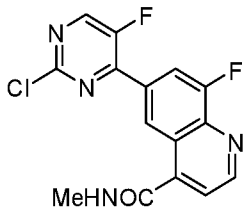
4.4, 1H), 8.84 (bs, 1H), 8.21 (d, J 1.2, 1H), 7.98 (d, J 10, 1H), 7.71 (d, J 4.4, 1H), 2.87 (d, J 4.4, 3H). MS (m/z): 283.19 $(M+H)^+$.

Intermediate 38: 8-fluoro-N-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline-4-carboxamide



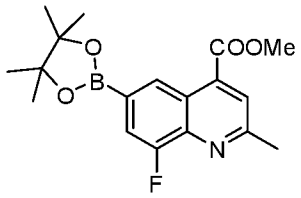
[184] Following the general procedure-1, the titled compound was synthesized from Intermediate 37 (2.5 g, 8.83 mmol). After work up, crude product was purified by combi-flash using MeOH and DCM (2:98) as eluent to obtain the titled compound as a grey solid (1.1 g). Yield: 38 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.08 (d, J 4.4, 1H), 8.83 (d, J 4.4, 1H), 8.35 (s, 1H), 7.70-7.62 (m, 2H), 2.89 (d, J 4.4, 3H), 1.36 (s, 12 H). MS (m/z): 331.33 $(M+H)^+$.

Intermediate 39: 6-(2-chloro-5-fluoropyrimidin-4-yl)-8-fluoro-N-methylquinoline-4-carboxamide



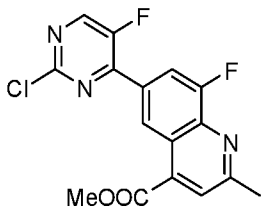
[185] Following the general procedure-2, the titled compound was synthesized from Intermediate 38 (1 g, 3.03 mmol) and 2,4-dichloro-5-fluoropyrimidine (607 mg, 3.6 mmol). After completion of reaction, reaction mixture cooled to rt to obtain a solid. Solid was filtered and washed with petether (500 ml). Solid was stirred with a mixture of diethyl ether and petether (1:1) (300 ml) for 30 mins. Solid was filtered and washed with petether and diethyl ether mixture (1:1) (200 ml). Solid was again co-distilled with toluene (20 ml) to obtain the titled compound as an off-white solid (600 mg). Yield: 59 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.17 (d, J 4.4, 1H), 9.07 (d, J 2.4, 1H), 8.93 (d, J 4.4, 1H), 8.80 (s, 1H), 8.18 (d, J 11.6, 1H), 7.80 (d, J 4, 1H), 2.90 (d, J 4, 3H). MS (m/z): 335.32 $(M+H)^+$.

Intermediate 40: Methyl 8-fluoro-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline-4-carboxylate



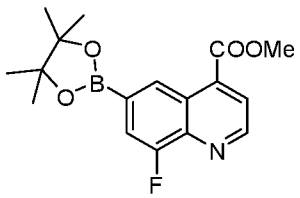
[186] Following the general procedure-1, the titled compound was synthesized from Intermediate 11 (5 g, 16.8 mmol). After work up, crude product was purified by combi-flash using EtOAc and petether (13:87) as eluent to obtain the titled compound as a brown solid (3.5 g). Yield: 60 %. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 8.75 (s, 1H), 7.96 (s, 1H), 7.65 (d, J 10.4, 1H), 3.99 (s, 3H), 2.76 (s, 3H), 1.34 (s, 12 H). MS (m/z): 346.35 (M+H).

Intermediate41: Methyl 6-(2-chloro-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinoline-4-carboxylate



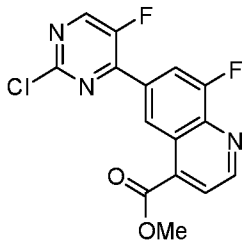
[187] Following the general procedure-2, the titled compound was synthesized from Intermediate 40 (3.5 g, 10.1 mmol) and 2,4-dichloro-5-fluoropyrimidine (2.03 g, 12.2 mmol). After completion of reaction, reaction mixture cooled to rt to obtain a solid. Solid was filtered and washed with petether (500 ml). Solid was stirred with diethylether (100 ml) for 30 mins. Solid was filtered and washed with diethyl ether (100 ml). Solid was again co-distilled with toluene (20 ml) for 30 mins to obtain the titled compound as an off-white solid (1.65 g). Yield: 47 %. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 9.25 (s, 1H), 9.07 (t, J 3.6, 1H), 8.17 (d, J 11.6, 1H), 8.10 (d, J 3.6, 1H), 4.01 (s, 3H), 2.80 (s, 3H).

Intermediate 42: Methyl 8-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline-4-carboxylate



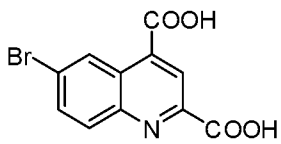
[188] Following the general procedure-1, the titled compound was synthesized from Intermediate 19 (3.1 g, 10.9 mmol). After work up, crude product was purified by combi-flash using EtOAc and Petether (20:80) as eluent to obtain the titled compound as a pale-red solid (3.4 g). Yield: 94 %. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 9.17 (d, J 4.4, 1H), 8.83 (s, 1H), 8.07 (d, J 4, 1H), 7.71 (d, J 10.4, 1H), 4.00 (s, 3H), 1.35 (s, 12 H). MS (m/z): 332.30 (*M*+H)$^+$.

Intermediate 43: Methyl 6-(2-chloro-5-fluoropyrimidin-4-yl)-8-fluoroquinoline-4-carboxylate



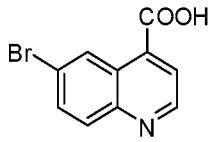
[189] Following the general procedure-2, the titled compound was synthesized from Intermediate 42 (3.4 g, 10.3 mmol) and 2,4-dichloro-5-fluoropyrimidine (2.06 g, 12.3 mmol). After completion of reaction, reaction mixture cooled to rt and stirred for 16 h to obtain a solid. Solid was filtered and washed with Dioxane: water mixture (1:1) (34 ml) and petether (100 ml). Solid was stirred with diethyl ether (30 ml) for 30 mins. Solid was filtered and washed with diethyl ether (200 ml). Solid was dried under vacuum to obtain the titled compound as a pink solid (2 g). Yield: 58 %. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz):9.29 (s, 1H), 9.24 (d, J 4.4, 1H), 9.08 (d, J 4.4, 1H), 8.21-8.16 (m, 2H), 4.02 (s, 3H). MS (m/z): 336.28 (*M*+H)$^+$.

Intermediate 44: 6-bromoquinoline-2,4-dicarboxylic acid



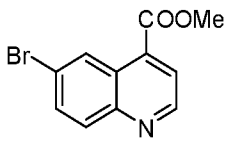
[190] 5-Bromoindolin-2,3-dione (20 g, 88.48 mmol) suspended in 33% aq. Potassium hydroxide (34.36 g, 612.3 mmol in 185 ml water). To this mixture 2-Oxopropanoic acid (13.6 g, 154.4 mmol) was added and stirred at 50°C for 16 h. After 16 h, reaction mixture cooled to rt and filtered the solid. Solid was washed with 33% aq. KOH solution (100 ml) and ethanol (100 ml). Solid was dissolved in water (100 ml) and pH adjusted to 2 using 6N HCl solution to obtain a solid. Solid was filtered and washed with water (100 ml). Solid was dried in hot air oven at 70°C for 16 h to obtain titled compound as an off-white solid (16.5 g). Yield: 63%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 14.03 (bs, 2H), 9.12 (d, J 5.2, 1H), 8.56 (d, J 6, 1H), 7.75 (d, J 6.8, 1H), 6.91 (s, 1H). MS (m/z): 296.06 $(M+H)^+$.

Intermediate 45: 6-bromoquinoline-4-carboxylic acid



[191] Intermediate 44 (16 g, 54 mmol) was suspended in nitrobenzene (160 ml). This heterogeneous mixture was stirred at 220°C for 5 h. After 5 h, reaction mixture cooled to rt and diluted with Petether (100 ml) to obtain a solid. This mixture was stirred at rt for 1 h. After 1 h, solid was filtered and washed with Petether (100 ml). Solid was dried under vacuum for 1 h to obtain titled compound as a pale-brown solid (12 g). Yield: 84%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 14.09 (bs, 1H), 9.09 (d, J 3.6, 1H), 9.01 (d, J 2, 1H), 8.07 (d, J 8.8, 1H), 8.02 (d, J 4, 1H), 7.99 (d, J 8.8, 1.6, 1H). MS (m/z): 252.15 $(M+H)^+$.

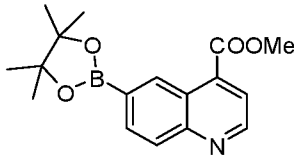
Intermediate 46: Methyl 6-bromoquinoline-4-carboxylate



[192] Intermediate 45 (13 g, 51.6 mmol) was suspended in MeOH (60 ml). To this mixture Con. H_2SO_4 (12.64 g, 128.9 mmol) was added and stirred at reflux for 16 h. After 16 h, reaction mixture cooled to rt and distilled out MeOH to obtain a residue. Residue was dissolved in DCM (500 ml) and washed with water (200 ml), aq. $NaHCO_3$ (300 ml) and brine (200 ml). Organic layer distilled to obtain a crude. Crude was purified by combi-flash using EtOAc and Petether (15:85) as eluent to obtain titled compound as an off-white solid (6 g). Yield: 44%. ^{1}H-NMR

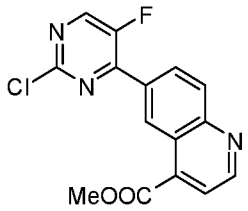
(δ ppm, DMSO-*d*6, 400 MHz): 9.11 (d, J 4.4, 1H), 8.88 (d, J 2.4,1H), 8.08 (d, J 9.2, 1H), 8.02 (d, J 4.4, 1H), 7.98 (dd, J 9.2, 2.4, 1H), 3.99 (s, 3H). MS (m/z): 266.16 $(M+H)^+$.

Intermediate 47: Methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline-4-carboxylate



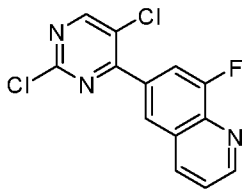
[193] Following the general procedure-1, the titled compound was synthesized from Intermediate 46 (5 g, 18.8 mmol). After work up, crude product was purified by combi-flash using EtOAc and Petether (10:90) as eluent to obtain the titled compound as a pale-red solid (3.5 g). Yield: 60 %. ^{1}H-NMR (δ ppm, DMSO-*d*6, 400 MHz): 9.10 (d, J 4.4, 1H), 9.01 (s, 1H), 8.10 (d, J 8.4, 1H), 8.02 (d, J 7.8, 1H), 7.96 (d, J 4.4, 1H), 3.99 (s, 3H), 1.34 (s, 12 H). MS (m/z): 314.32 $(M+H)^+$.

Intermediate 48: Methyl 6-(2-chloro-5-fluoropyrimidin-4-yl)quinoline-4-carboxylate



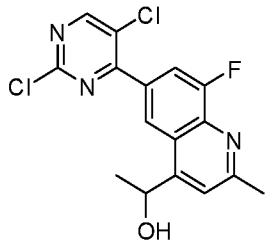
[194] Following the general procedure-2, the titled compound was synthesized from Intermediate 47 (3.3 g, 10.53 mmol) and 2,4-dichloro-5-fluoropyrimidine (2.06 g, 12.3 mmol). After completion of reaction, reaction mixture cooled to rt to obtain a solid. Solid was filtered and washed with Dioxane: water mixture (10 ml) and petether (100 ml). Solid was co-distilled with toluene (10 ml) at 65°C to obtain the titled compound as an off-white solid (1.8 g). Yield: 54 %. ^{1}H-NMR (δ ppm, DMSO-*d*6, 400 MHz): 9.46 (s, 1H), 9.19 (d, J 4.4, 1H), 9.05 (d, J 3.2, 1H), 8.42 (d, J 8.9, 1H), 8.30 (d, J 8.9, 1H), 8.07 (d, J 4.4, 1H), 4.00 (s, 3H). MS (m/z): 318.23 $(M+H)^+$.

Intermediate 49: 6-(2,5-dichloropyrimidin-4-yl)-8-fluoroquinoline



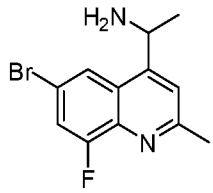
[195] Following the general procedure-2, the titled compound was synthesized from Intermediate 1 (3 g, 11 mmol) and 2,4,5-Trichloropyrimidine (2.42 g, 13.2 mmol). After completion of reaction, reaction mixture cooled to rt and diluted with DCM (300 ml). Reaction mixture filtered through cealite bed and bed was washed with DCM (200 ml) and water (200 ml). Separated organic and aqueous layers. Organic layer washed with water and brine. Organic layer was distilled to obtain a crude. Crude was purified by Combi-flash using EtOAc and Petether (5:95) as eluent to obtain the titled compound as an off-white solid (1.5 g). Yield: 46 %. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 9.12-9.08 (m, 2H), 8.67 (d, J 8.4, 1H), 8.41 (s, 1H), 8.00 (dd, J 11.6, 2.5, 1H), 7.77 (dd, J 8.4, 4.2, 1H). MS (m/z): 294.15 (*M*+H)$^+$.

Intermediate 50: (±)-1-(6-(2,5-dichloropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)ethan-1-ol



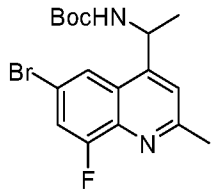
[196] Following the general procedure-2, the titled compound was synthesized from Intermediate 35 (2 g, 6 mmol) and 2,4,5-Trichloropyrimidine (1.33 g, 7.25 mmol). After completion of reaction, water (150 ml) was added to reaction mixture and extracted with DCM (3*100 ml). Organic layer washed with water (100 ml) and distilled to obtain crude. Crude was purified by combi-flash using EtOAc and petether (35:65) as eluent to obtain the titled compound as an off-white solid (1.2 g). Yield: 56 %. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz):9.08 (s, 1H), 8.51 (d, J 1, 1H), 7.88 (dd, J 11.5, 1.7, 1H), 7.69 (s, 1H), 5.72 (bs, 1H), 5.48-5.40 (m, 1H), 2.73 (s, 3H), 1.49 (d, J 6.5, 3H). MS (m/z): 352.23 (*M*+H)$^+$.

Intermediate 51: (±)-1-(6-bromo-8-fluoro-2-methylquinolin-4-yl)ethan-1-amine



[197] Intermediate 6 (200 g, 0.708 mol) was suspended in 2M methanolic ammonia (1.88 lt, 3.75 mol). To this mixture titanium(IV)isopropoxide (403 g, 1.42 mol) was added and stirred at rt for 16 h. After 16 h, reaction mixture cooled to 0°C and sodium borohydride (40.23 g, 1.06 mol) was added, warmed to rt and stirred at rt for 5 h. After 5 h, reaction mixture was quenched with Aq. ammonia (2 lt) and EtOAc (2 lt) to obtain a solid. Solid was filtered and washed the solid with EtOAc (10 lt). Combined filtrates were washed with water (3 lt) and brine (2.5 lt). Aqueous layer was extracted with EtOAc (8 lt). Combined EtOAc layers were distilled out to obtain a crude. Crude was co-distilled with (3*100 ml) toluene to obtain a solid. Solid was stirred with Diethyl ether (1 lt) and filtered the solid. Solid was dried under vacuum to obtain titled compound as a brown solid (120.5 g). Yield: 60%. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 8.22 (s, 1H), 7.81 (dd, J 10.4, 4, 1H), 7.73 (s, 1H), 4.76-4.70 (m, 1H), 2.66 (s, 3H), 2.09 (bs, 2H), 1.34 (d, J 6.8, 3H). MS (m/z): 283.17 (*M*+H)$^+$.

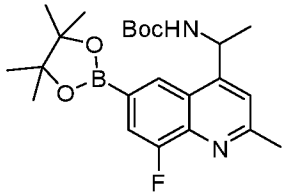
Intermediate 52: (±)-*Tert*-butyl (1-(6-bromo-8-fluoro-2-methylquinolin-4-yl)ethyl)carbamate



[198] Intermediate 51 (16 g, 56.5 mmol) dissolved in DCM (160 ml) and cooled to 0°C. To this solution, triethylamine (8.58 g, 84.76 mmol) was added. Bocanhydride (14.8 g, 67.8 mmol) was added to the reaction mixture and stirred at rt for 2 h. After 2h, reaction mixture diluted with water (900 ml) and separated the organic layer. Aqueous layer again extracted with a mixture of MeOH and DCM (1:9) (3*500 ml). Combined organic layers were washed with water (2*500 ml) and aq. Sodium bicarbonate (3*500 ml). Organic layer dried on anhydrous Na_2SO_4 and distilled to obtain titled compound as an off-white solid (20.8 g). Yield: 96%. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 8.22 (s, 1H), 7.86 (dd, J 10.4, 2, 1H), 7.71 (d, J 7.6, 1H),

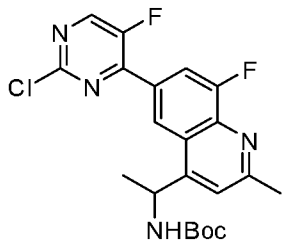
7.47 (s, 1H), 5.38-5.25 (m, 1H), 2.65 (s, 3H), 1.40 (d, J 7.2, 3H), 1.37 (s, 9H). MS (m/z): 383.18 $(M+H)^+$.

Intermediate 53: (±)-*Tert*-butyl (1-(8-fluoro-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-4-yl)ethyl)carbamate



[199] Following the general procedure-1, the titled compound was synthesized from Intermediate 52 (18 g, 47 mmol). After work up, crude product was purified by combi-flash using EtOAc and Petether (20:80) as eluent to obtain the titled compound as a pale-yellow solid (15.2 g). Yield: 75.2 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.22 (s, 1H), 7.74 (d, J 7.6, 1H), 7.58 (d, J 10.8, 1H), 7.50 (s, 1H), 5.42-5.30 (m, 1H), 2.68 (s, 3H), 1.41 (d, J 6.8, 3H), 1.37 (s, 12 H), 1.15 (s, 9H). MS (m/z): 431.30 $(M+H)^+$.

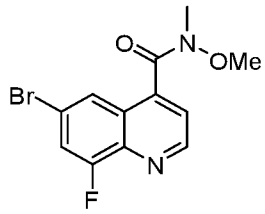
Intermediate 54: (±)-*Tert*-butyl (1-(6-(2-chloro-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)ethyl)carbamate



[200] Following the general procedure-2, the titled compound was synthesized from Intermediate 53 (15 g, 34.86 mmol) and 2,4-dichloro-5-fluoropyrimidine (6.98 g, 41.83 mmol). After completion of reaction, reaction mixture cooled to rt and stirred for 16 h to obtain a solid. Solid was filtered, washed with a mixture of dioxane and water (1:1) (50 ml) and Petether (100 ml). Solid was co-distilled with toluene (2*100 ml) at 65°C on rotavapor. Solid was stirred with a mixture of diethyl ether and Petether (1:1) (100 ml) for 30 mins. Solid was filtered and washed with Petether and diethyl ether mixture (1:1) (50 ml). Solid was dried under vacuum to obtain the titled compound as a white solid (10 g). Yield: 67 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400

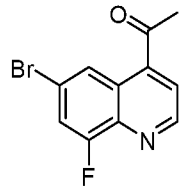
MHz): 9.07 (d, J 3.2, 1H), 8.62 (s, 1H), 8.06 (d, J 11.2, 1H), 7.79 (d, J 3.2, 1H), 7.58 (s, 1H), 5.42-5.30 (m, 1H), 2.73 (s, 3H), 1.46 (d, J 6.8, 3H), 1.37 (s, 9H). MS (m/z): 435.24 $(M+H)^+$.

Intermediate 55: 6-bromo-8-fluoro-N-methoxy-N-methylquinoline-4-carboxamide



[201] Intermediate 18 (3 g, 11.1 mmol), HATU (6.34 g, 16.7 mmol) and DIPEA (5.74 g, 44.4, mmol) were dissolved in DMF (30 ml). N,O-Dimethylhydroxylamine hydrochloride (2.17 g, 22.2 mmol) was added to the reaction mixture and stirred at rt for 16 h. After 16 h, reaction mixture diluted with water (150 ml) and extracted with EtOAc (3*70 ml). Combined organic layers were washed with aq. $NaHCO_3$ (3*100 ml) and brine (100 ml). Organic layer distilled to obtain crude. Crude was suspended in a mixture of diethylether and petether (1:1) (40 ml) and stirred for 30 mins to obtain solid. Solid was filtered and washed with Diethyl ether and Petether (1:1) (20 ml). Solid was dried under vacuum to obtain the titled compound as a pale-brown solid (2.5 g). Yield: 72%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.06 (d, J 4, 1H), 8.00 (dd, J 10, 1, 1H), 7.81 (t, J 1.6, 1H), 7.77 (d, J 4, 1H), 3.41 (bs, 6H). MS (m/z): 313.15 $(M+H)^+$.

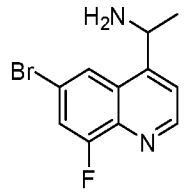
Intermediate 56: 1-(6-bromo-8-fluoroquinolin-4-yl)ethan-1-one



[202] Intermediate 55 (2.5 g, 7.98 mmol) was dissolved in THF (25 ml) and cooled to 0°C. Methylmagnesium chloride (3M in THF, 24.53 ml, 12 mmol) was added slowly. The mixture was stirred at rt for 3 h. The reaction mixture was quenched with aq. NH_4Cl solution. and extracted with EtOAc (2*25 ml). The organic layer was washed successively with water (25 ml) and brine solution (25 ml), dried on anhydrous Na_2SO_4 and distilled to obtain the crude product. Purification by combi-flash using EtOAc and petroleum ether (14:86) as eluent gave the titled compound as an off-white solid (900 mg). ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz):

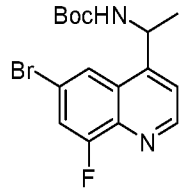
9.17 (d, J 4.4, 1H), 8.46 (s, 1H), 8.15 (d, J 4.4, 1H),8.01 (dd, J 10. 1.6, 1H), 2.76 (s, 3H). MS (m/z): 268.15 $(M+H)^+$.

Intermediate 57: (±)-1-(6-bromo-8-fluoroquinolin-4-yl)ethan-1-amine



[203] Intermediate 56 (900 mg, 3.4 mmol) was suspended in 2M Methanolic ammonia (8.4 ml, 17mol). To this mixture titanium (IV) isopropoxide (1.9 g, 6.7 mol) was added and stirred at rt for 16 h. After 16 h, reaction mixture cooled to 0°C and sodium borohydride (190 mg, 5.03 mol) was added, warmed to rt and stirred at rt for 5 h. After 5 h, reaction mixture was quenched with Aq. Ammonia (9 ml) and EtOAc (25 ml) to obtain a solid. Solid was filtered and washed the solid with EtOAc (25 ml). Combined filtrates were washed with water (100 ml) and brine (100 ml). Aqueous layer was extracted with EtOAc (2*30 ml). Combined EtOAc layers were distilled out to obtain a crude. Crude was purified by combi-flash using MeOH and DCM (3:97) as eluent to obtain titled compound as an off-white solid (500 mg). Yield: 55 %. ^{1}H-NMR (δ ppm, DMSO-*d6*, 400 MHz): 8.94 (d, J 4.4, 1H), 8.30 (s, 1H), 7.88 (dd, J 10, 1.6, 1H), 7.85 (d, J 4.4, 1H), 4.80-4.70 (m, 1H), 2.11 (s, 2H), 1.34 (d, J 6.8, 3H). MS (m/z): 269.16 $(M+H)^+$.

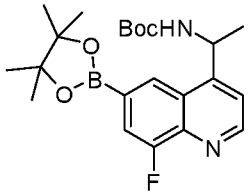
Intermediate 58: (±)-*Tert*-butyl (1-(6-bromo-8-fluoroquinolin-4-yl)ethyl)carbamate



[204] Intermediate 57 (2.1 g, 7.8 mmol) dissolved in DCM (21 ml) and cooled to 0°C. To this solution, triethylamine (1.18 g, 11.7 mmol) was added. Bocanhydride (2.04 g, 9.36 mmol) was added to this mixture and stirred at rt for 2 h. After 2h, reaction mixture diluted with water (100 ml) and separated the organic layer. Aqueous layer again extracted with DCM (3*70 ml). Combined organic layers were washed with water (100 ml) and aq. Sodium bicarbonate (3*100 ml). Organic layer dried on anhydrous Na_2SO_4 and distilled to obtain titled compound as an off-white solid (2.8 g). Yield: 97%. ^{1}H-NMR (δ ppm, DMSO-*d6*, 400 MHz): 8.96 (d, J 4.4, 1H),

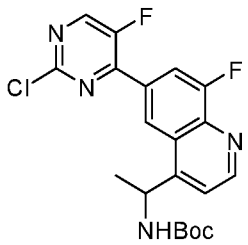
8.31 (s, 1H), 7.92 (dd, J 10, 1.6, 1H), 7.78 (d, J 7.6, 1H), 7.61 (d, J 4.4, 1H), 5.42-5.40 (m, 1H), 1.40 (d, J 6.8, 3H), 1.37 (s, 9H). MS (m/z): 369.12 $(M+H)^+$.

Intermediate 59: (±)-*Tert*-butyl (1-(8-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-4-yl)ethyl)carbamate



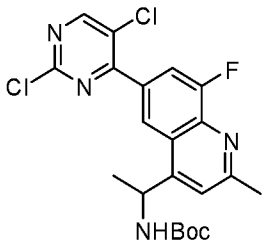
[205] Following the general procedure-1, the titled compound was synthesized from Intermediate 58 (2.8 g, 7.58 mmol). After work up, crude product was purified by combi-flash using EtOAc and Petether (23:77) as eluent to obtain the titled compound as a pale-yellow solid (1.7 g). Yield: 94 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.99 (d, J 4.4, 1H), 8.29 (s, 1H), 7.81 (d, J 7.6, 1H), 7.64 (d, J 7.2, 1H), 7.62 (s, 1H), 5.42-5.33 (m, 1H), 1.43 (d, J 6.8, 3H), 1.37 (s, 12 H), 1.35 (s, 9H). MS (m/z): 417.32 $(M+H)^+$.

Intermediate 60: (±)-*Tert*-butyl (1-(6-(2-chloro-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate



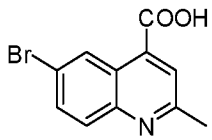
[206] Following the general procedure-2, the titled compound was synthesized from Intermediate 59 (1.7 g, 4.08 mmol) and 2,4-Dichloro-5-fluoropyrimidine (818 mg, 4.9 mmol). After completion of reaction, water (100 ml) was added to reaction mixture and extracted with DCM (3*70 ml). Organic layer washed with water (100 ml) and distilled to obtain crude. Crude was purified by combi-flash using EtOAc and Petether (27:63) as eluent to obtain the titled compound as an off-white solid (600 mg). Yield: 30 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.09 (d, J 3.2, 1H), 9.07 (d, J 4.4, 1H), 8.68 (s, 1H), 8.11 (d, J 11.2, 1H), 7.84 (d, J 7.6, 1H), 7.70 (d, J 4.4, 1H), 5.49-5.38 (m, 1H), 1.47 (d, J 7, 3H), 1.36 (s, 9H). MS (m/z): 421.11 $(M+H)^+$.

Intermediate 61: (±)-*Tert*-butyl (1-(6-(2,5-dichloropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)ethyl)carbamate



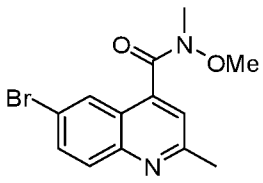
[207] Following the general procedure-2, the titled compound was synthesized from Intermediate 53 (2.5 g, 5.79 mmol) and 2,4,5-Trichloropyrimidine (1.27 g, 6.94 mmol). After completion of reaction, water (150 ml) was added to reaction mixture and extracted with DCM (3*100 ml). Organic layer washed with water (100 ml) and distilled to obtain crude. Crude was purified by combi-flash using EtOAc and Petether (35:65) as eluent to obtain the titled compound as an off-white solid (1.2 g). Yield: 46 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.09 (s, 1H), 8.46 (s, 1H), 7.92 (dd, J 11.3, 1.2, 1H), 7.76 (d, J 7.4, 1H), 7.55 (s, 1H), 5.40-5.31 (m, 1H), 3.34 (s, 3H), 1.44 (d, J 6.8, 3H), 1.34 (s, 9H). MS (m/z): 451.18 (M+H)$^+$.

Intermediate 62: 6-bromo-2-methylquinoline-4-carboxylic acid



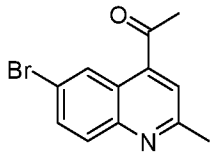
[208] 5-Bromoisatin (20 g, 88 mmol) was suspended in a solution of potassium hydroxide (34 g, 610 mmol) in water (782 ml) and acetone (74 ml) was added. This mixture was stirred at 50°C for 4 h. One more lot of acetone (74 ml) was added to the reaction mixture and stirred at 50°C for 17 h. The reaction mixture was cooled to rt and the pH adjusted using 6N HCl to 7 (±0.5) and filtered the reaction mass. Filtrate pH was adjusted to 2 (±0.5) using 6N HCl to obtain a solid. The solid was filtered, washed with hot water (200 ml) and dried in an oven at 70°C for 18 h to obtain the titled compound as a pale-yellow solid (16 g). Yield: 68%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 13.99 (bs, 1H), 8.90 (d, J 1.9, 1H), 7.96-7.88 (m, 3H), 2.69 (s, 3H). MS (m/z): 266.18 (M+H)$^+$.

Intermediate 63: 6-bromo-N-methoxy-N,2-dimethylquinoline-4-carboxamide



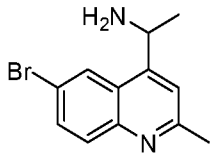
[209] Intermediate 62 (15 g, 56.4 mmol), HATU (32.15 g, 84.6 mmol) and DIPEA (29.14 g, 225.5 mmol) were dissolved in DMF (150 ml). N,O-Dimethylhydroxylamine hydrochloride (11 g, 112.7 mmol) was added to the reaction mixture and stirred at rt for 16 h. After 16 h, one more lot of N,O-Dimethylhydroxylamine hydrochloride (2.75 g, 28.18 mmol), HATU (10.72 g, 28.19 mmol) and DIPEA (14.57 g, 112.7 mmol) were added and stirred for 3 h at rt. After 3 h, reaction mixture diluted with water (800 ml) and extracted with EtOAc (2*300 ml). Combined organic layers were washed with water (2*225 ml), aq. $NaHCO_3$ (2*225 ml) and brine (300 ml). Organic layer distilled to obtain crude. Crude was suspended in a mixture of Diethyl ether and Petether (1:1) (150 ml) and stirred for 30 mins to obtain solid. Solid was filtered and washed with Diethyl ether and Petether (1:1) (50 ml) mixture. Solid was dried under vacuum to obtain the titled compound as a pale-brown solid (14.1 g). Yield: 81 %. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 7.99-7.80 (m, 3H), 7.55 (s, 1H), 3.33 (s, 3H), 2.68 (s, 3H), 2.49 (s, 3H). MS (m/z): 309.22 $(M+H)^+$.

Intermediate 64: 1-(6-bromo-2-methylquinolin-4-yl)ethan-1-one



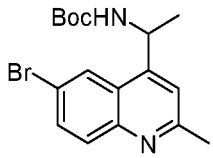
[210] Intermediate 63 (14 g, 45.3 mmol) was dissolved in THF (140 ml) and cooled to 0°C. Methylmagnesium chloride (3M in THF, 24.53 ml, 67.93 mmol) was added slowly. The mixture was stirred at rt for 2 h. The reaction mixture was quenched with aq. NH_4Cl solution and extracted with EtOAc (2*200 ml). The organic layer was washed successively with water (200 ml) and brine solution (200 ml), dried on anhydrous Na_2SO_4 and distilled to obtain the crude product. Crude was suspended in a mixture of Diethyl ether and Petether (1:1) (140 ml) and stirred for 1 h to obtain a solid. Solid was filtered and washed with Diethyl ether and Petether mixture (1:1) (70 ml). Solid was dried under vacuum to give the titled compound as a brown solid (9 g). ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 8.59 (d, J 2, 1H), 8.00-7.85 (m, 3H), 2.75 (s, 3H), 2.73 (s, 3H). MS (m/z): 264.19 $(M+H)^+$.

Intermediate 65: (±)-1-(6-bromo-2-methylquinolin-4-yl)ethan-1-amine



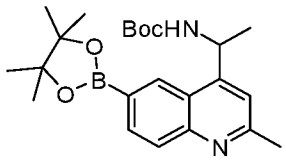
[211] Intermediate 64 (4 g, 15.1 mmol) was suspended in 2M Methanolic ammonia (40 ml, 80.3 mmol). To this mixture titanium (IV) isopropoxide (8.61 g, 30.3 mol) was added and stirred at rt for 70 h. After 70 h, reaction mixture cooled to 0°C and sodium borohydride (859 mg, 22.7 m mol) was added, warmed to rt and stirred at rt for 2 h. After 2 h, reaction mixture was quenched with Aq. Ammonia (40 ml) and EtOAc (40 ml) to obtain a solid. Solid was filtered and washed the solid with EtOAc (100 ml). Combined filtrates were washed with water (100 ml) and brine (100 ml). Aqueous layer was extracted with EtOAc (100 ml). Combined EtOAc layers were distilled out to obtain a crude. Crude was purified by combi-flash using MeOH and DCM (3:97) as eluent to obtain titled compound as a brown solid (2 g). Yield: 50 %. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 8.37 (d, J 2, 1H), 7.85 (d, J 8, 1H), 7.80 (dd, J 8.8, 2, 1H), 7.63 (s, 1H), 4.75-4.65 (m, 1H), 2.62 (s, 3H), 2.06 (s, 2H), 1.34 (d, J 6.4, 3H). MS (m/z): 265.16 (*M*+H)$^+$.

Intermediate 66: (±)-*Tert*-butyl (1-(6-bromo-2-methylquinolin-4-yl)ethyl)carbamate



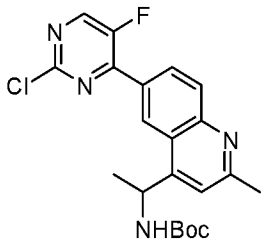
[212] Intermediate 65 (2 g, 7.5 mmol) dissolved in DCM (20 ml) and cooled to 0°C. To this solution, triethylamine (1.14 g, 11.3 mmol) was added. Bocanhydride (1.98 g, 9.05 mmol) was added to this mixture and stirred at rt for 2 h. After 2h, reaction mixture diluted with water (200 ml) and separated the organic layer. Aqueous layer again extracted with MeOH:DCM (1:9) mixture (3*200 ml). Combined organic layers were washed with water (2*200 ml) and aq. Sodium bicarbonate (3*200 ml). Organic layer dried on anhydrous Na_2SO_4 and distilled to obtain titled compound as an off-white solid (2.5 g). Yield: 91 %. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 8.36 (s, 1H), 7.92-7.80 (m, 2H), 7.68 (d, J 7.6, 1H), 7.39 (s, 1H), 5.38-5.27 (m, 1H), 2.63 (s, 3H), 1.41 (d, J 7.2, 3H), 1.37 (s, 9H). MS (m/z): 365.10 (*M*+H)$^+$.

Intermediate 67: (±)-*Tert*-butyl (1-(2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-4-yl)ethyl)carbamate



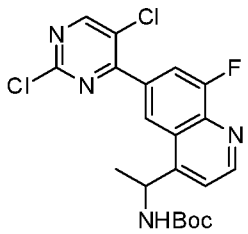
[213] Following the general procedure-1, the titled compound was synthesized from Intermediate 66 (2.5 g, 6.84 mmol). After work up, crude product was purified by combi-flash using EtOAc and Petether (2:8) as eluent to obtain the titled compound as a yellow solid (1.6 g). Yield: 57%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.41 (s, 1H), 7.91 (s, 2H), 7.74 (d, J 7.6, 1H), 7.41 (s, 1H), 5.45-5.38 (m, 1H), 2.64 (s, 3H), 1.41 (d, J 6.8, 3H), 1.40 (s, 9H), 1.38 (s, 12 H). MS (m/z): 413.29 (M+H)$^+$.

Intermediate 68: (±)-*Tert*-butyl (1-(6-(2-chloro-5-fluoropyrimidin-4-yl)-2-methylquinolin-4-yl)ethyl)carbamate



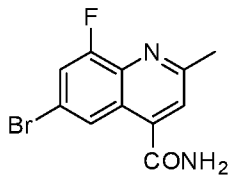
[214] Following the general procedure-2, the titled compound was synthesized from Intermediate 67 (1.5 g, 3.64 mmol) and 2,4-Dichloro-5-fluoropyrimidine (729 mg, 4.37 mmol). After completion of reaction, reaction mixture stirred at rt for 16 h to obtain a solid. Solid was filtered and washed with a mixture of water and dioxane (1:1) (20 ml). Solid was co-distilled with toluene (20 ml) and dried under vacuum to obtain the titled compound as pale-brown solid (700 mg). Yield: 46 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.41 (s, 1H), 7.91 (s, 2H), 7.74 (d, J 7.6, 1H), 7.41 (s, 1H), 5.45-5.38 (m, 1H), 2.64 (s, 3H), 1.41 (d, J 6.8, 3H), 1.40 (s, 9H), 1.38 (s, 9H). MS (m/z): 417.21 (M+H)$^+$.

Intermediate 69: (±)-*Tert*-butyl (1-(6-(2,5-dichloropyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate



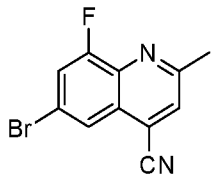
[215] Following the general procedure-2, the titled compound was synthesized from Intermediate 59 (3 g, 7.21 mmol) and 2,4,5-Trichloropyrimidine (1.59 g, 8.65 mmol). After completion of reaction, reaction mixture diluted with water (100 ml). Aqueous layer was extracted with DCM (3*100 ml). Combined organic layers were washed with water (100 ml). Organic layer distilled to obtain crude. Crude was purified by combi-flash using EtOAc and Petether (2:8) as eluent. Combined pure fractions from column were distilled to obtain the titled compound as an off-white solid (1.36 g). Yield: 43.2 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.11 (s, 1H), 9.06 (d, J 4.4, 1H), 8.52 (s, 1H), 7.97 (d, J 11.2, 1H), 7.84 (d, J 7.6, 1H), 7.68 (d, J 4.4, 1H), 5.45-5.38 (m, 1H), 1.45 (d, J 6.8, 3H), 1.34 (s, 9H). MS (m/z): 437.0 $(M+H)^+$.

Intermediate 70: 6-bromo-8-fluoro-2-methylquinoline-4-carboxamide



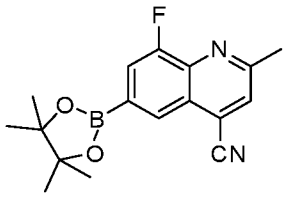
[216] Intermediate 4 (15 g, 52.8 mmol), HATU (30.12 g, 79.20 mmol) and DIPEA (27.6 ml, 158.4 mmol) were suspended in DMF (300 ml) and stirred for 15 mins. This mixture was cooled to 0°C and ammonia gas was passed for 1 h. Reaction mixture was warmed to 25°C and stirred at 25°C for 1 h. After 1 h, reaction mixture was quenched with water (500 ml) and organic layer was extracted with EtOAc (8* 250 ml). Combined organic layers were washed with aq. Sodium bicarbonate (2*500 ml) and brine (2*500 ml). Organic layer was distilled to obtain a crude solid. Diethyl ether and Petether (1:1) mixture (100 ml) added to crude solid and stirred for 30 mins. Filtered the solid and solid was washed with Diethyl ether and Petether (1:1) mixture (30 ml). Solid was dried under vacuum to obtain the titled compound as a brown solid (5.4 g). Yield: 36%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.33 (bs, 1H), 8.20 (s, 1H), 8.00 (bs, 1H), 7.93 (dd, J 10, 1.6, 1H), 7.66 (s, 1H), 2.71 (s, 3H). MS (m/z): 283.19 $(M+H)^+$.

Intermediate 71: 6-bromo-8-fluoro-2-methylquinoline-4-carbonitrile



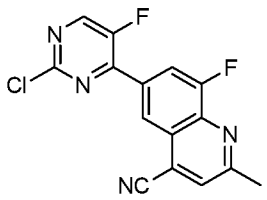
[217] Intermediate 70 (5.4 g, 19.1 mmol) was suspended in chloroform (54 ml). Triethylamine (13.3 ml, 95.4 mmol) was added to this mixture and cooled to 0°C. Trifluoroacetic anhydride (6.74 ml, 47.7 mmol) was added drop-wise to above mixture at 0°C. At this stage, reaction mixture was stirred at rt for 16 h. After 16 h, reaction mixture quenched with aq. Sodium bicarbonate solution (200 ml). Separated organic and aqueous layers. Aqueous layer was extracted with DCM (3*70 ml). Combined organic layers were washed with aq. Sodium bicarbonate solution (3*100 ml) and brine (100 ml). Organic layer was distilled under vacuum to obtain a crude. Diethyl ether and Petether mixture (1:9) (100 ml) was added to crude and stirred for 30 mins to obtain a solid. Solid was filtered and washed with Diethyl ether and Petether mixture (1:9) (50 ml). Solid was dried under vacuum to obtain the titled compound as a brown solid (4.8 g). Yield: 95.4%. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 8.25 (s, 1H), 8.10 (d, J 10, 1H), 8.00 (s, 1H), 2.73 (s, 3H). MS (m/z): 265.18 (*M*+H)$^+$.

Intermediate 72: 8-fluoro-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline-4-carbonitrile



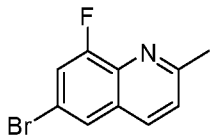
[218] Following the general procedure-1, the titled compound was synthesized from Intermediate 71 (4.3 g, 16.2 mmol). After work up, crude product was purified by combi-flash using EtOAc and Petether (8:92) as eluent to obtain the titled compound as a pale-yellow solid (3.2 g). Yield: 63%. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 8.23 (s, 1H), 8.15 (s, 1H), 7.77 (d, J 10.8, 1H), 2.77 (s, 3H), 1.36 (s, 12 H). MS (m/z): 313.31 (*M*+H)$^+$.

Intermediate 73: 6-(2-chloro-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinoline-4-carbonitrile



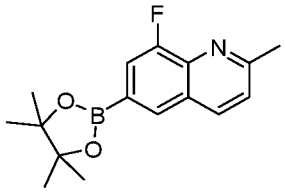
[219] Following the general procedure-2, the titled compound was synthesized from Intermediate 72 (1.75 g, 5.61 mmol) and 2,4-Dichloro-5-fluoropyrimidine (1.12 g, 6.73 mmol). After completion of reaction, reaction mixture stirred at rt for 16 h to obtain a solid. Solid was filtered and washed with a mixture of water and dioxane (1:1) (17.5 ml) and Petether (100 ml). Solid was co-distilled with toluene (100 ml). Solid was stirred with a mixture of Diethyl ether and Petether (1:1) (25 ml) for 30 mins. Solid was filtered and dried under vacuum to obtain the titled compound as an off-white solid (1.2 g). Yield: 67.6 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.11 (d, J 2.8, 1H), 8.54 (s, 1H), 8.33 (s, 1H), 8.26 (d, J 11.6, 1H), 2.80 (s, 3H). MS (m/z): 317.30 $(M+H)^+$.

Intermediate 74: 6-bromo-8-fluoro-2-methylquinoline



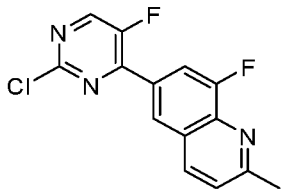
[220] Crotonaldehyde (612 mg, 8.74 mmol) was added to a mixture of 4-Bromo-2-fluoroaniline (2.00 g, 10.5 mmol) and aqueous 6N hydrochloric acid (42.1 ml) and stirred at RT for 1h. Toluene (11 ml) was added and the mixture heated at 110 °C for 17 h, cooled to RT and the layers were separated. The organic layer was extracted with aq. 6N HCl (50 ml). Combined aqueous layers were basified to pH 10-11 with aq. 10% sodium hydroxide solution and extracted into DCM (3*100 ml). Combined organic layers were washed successively with brine solution (100 ml) and water (100 ml), dried over sodium sulfate and concentrated. Purification of the residue by combi-flash chromatography system with petroleum ether – EtOAc (95:5) as the eluent gave the titled compound as a pale-yellow solid (1.2 g). Yield: 47%. ^{1}H-NMR (δ ppm, $CDCl_3$, 400 MHz):7.80 (dd, J 8.4, 1.2, 1H), 7.74 (s, 1H), 7.51 (dd, J 9.6, 1.6, 1H), 7.37 (d, J 8.4, 1H), 2.78 (s, 3H).

Intermediate 75: 8-fluoro-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline



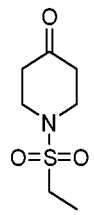
[221] Following the general procedure-1, the titled compound was synthesized from Intermediate 74 (1.0 g, 3.57 mmol). After work up, crude product was purified by combi-flash using EtOAc and petroleum ether (8:92) as eluent to obtain the titled compound as a pale-yellow solid (3.5 g). Yield: 60%. ^{1}H-NMR (δ ppm, $CDCl_3$, 400 MHz): 8.03-8.12 (m, 2H), 7.72 (d, J 11.2, 1H), 7.35 (d, J 8.4, 1H), 2.80 (s, 3H), 1.37 (s, 12H).

Intermediate 76: 6-(2-chloro-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinoline



[222] Following the general procedure-2, the titled compound was synthesized from Intermediate 75 (3.5 g, 12.19 mmol) and 2,4-dichloro-5-fluoropyrimidine (2.24 g, 13.41 mmol). After work up, crude product was purified by combi-flash using EtOAc and Petroleum ether (20:80) as eluent to obtain the titled compound as an off-white solid (2.5 g). Yield: 70%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.04 (d, J 3.2, 1H), 8.45-8.60 (m, 2H), 8.07 (d, J 12.0, 1H), 7.63 (d, J 8.4, 1H), 2.73 (s, 3H).

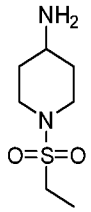
Intermediate 77: 1-(ethylsulfonyl)piperidin-4-one



[223] Piperidin-4-one monohydrate hydrochloride (5 g, 32.5 mmol) was dissolved in THF (50 ml). To this solution ethanesulfonylchloride (6.28 g, 48.8 mmol) was added dropwise. 15% aqueous sodium hydroxide solution (20 ml) was added to above mixture and stirred at rt for 2 h. After 2h, separated the organic and aqueous layers. Aqueous layer was extracted with THF

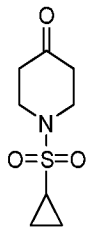
(3*50 ml). Combined THF layers were washed with brine (100 ml). Organic layer distilled under vacuum to obtain a crude. Crude was purified by Combi-flash using EtOAc and Petether (4:6) as eluent to afford the titled compound as an off-white solid (3.5 g). Yield: 56%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 3.53 (t, J 6.4, 4H), 3.15 (q, J 7.6, 2H), 2.43 (t, J 6.4, 4H), 1.22 (t, J 7.6, 3H). MS (m/z): 192.10 $(M+H)^+$.

Intermediate 78: 1-(ethylsulfonyl)piperidin-4-amine



[224] Intermediate 77 (1.5 g, 7.84 mmol), ammonium acetate (1.81 g, 2.35 mmol), MeOH (6 ml) and 2M ammonia in methanol (7 ml) were taken in an autoclave. 5% Palladium on carbon (300 mg) was added to this mixture and stirred at 70°C under 3 KG hydrogen atmosphere for 3 h. After 3 h, reaction mixture filtered through a cealite bed and bed was washed with a mixture of MeOH and DCM (1:9) (200 ml). Combined filtrates were evaporated to obtain a residue. Residue was dissolved in THF (50 ml) and washed with 15% aqueous Sodium hydroxide solution (10 ml). Separated the organic and aqueous layers. Aqueous layer was extracted with THF (3*50 ml). Combined organic layers were distilled to obtain a crude. Crude was purified by combi-flash using MeOH and DCM (1:9) as eluent to afford the titled compound as a colourless gummy liquid (800 mg). Yield: 50%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 3.55-3.49 (m, 2H), 3.23 (bs, 2H), 3.02 (q, J 7.6, 2H), 2.88-2.80 (m, 2H), 2.79-2.71 (m, 1H), 1.81-1.72 (m, 2H), 1.34-1.24 (m, 2H), 1.19 (t, J 7.6, 3H). MS (m/z): 193.12 $(M+H)^+$.

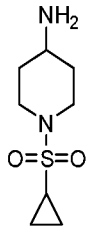
Intermediate 79: 1-(cyclopropylsulfonyl)piperidin-4-one



[225] Piperidin-4-one monohydrate hydrochloride (5 g, 32.5 mmol) was dissolved in THF (50 ml). To this cyclopropylsulfonyl chloride (6.9 g, 49.1 mmol) was added dropwise. 15% aqueous

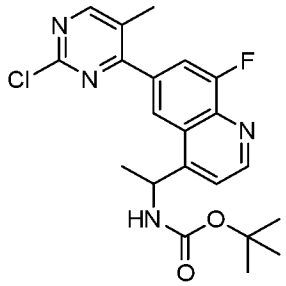
Sodium hydroxide solution (20 ml) was added to above mixture and stirred at rt for 2 h. After 2h, separated the organic and aqueous layers. Aqueous layer was extracted with THF (3*50 ml). Combined THF layers were washed with brine (100 ml). Organic layer distilled under vacuum to obtain a crude. Crude was purified by Combi-flash using EtOAc and Petether (4:6) as eluent to afford the titled compound as an off-white solid (3.7 g). Yield: 56%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 3.55 (t, J 6, 4H), 2.74-2.65 (m, 1H), 2.46 (t, J 6, 4H), 1.05-0.92 (m, 4H). MS (m/z): 204.15 $(M+H)^+$.

Intermediate 80: 1-(cyclopropylsulfonyl)piperidin-4-amine



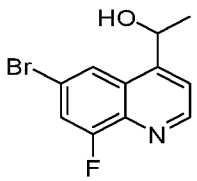
[226] Intermediate 79 (2 g, 9.83 mmol), ammonium acetate (2.27 g, 29.51 mmol), MeOH (8 ml) and 2M ammonia in Methanol (9 ml) were taken in an autoclave. 5% palladium on carbon (400 mg) was added to this mixture and stirred at 70°C under 3 KG hydrogen atmosphere for 3 h. After 3 h, reaction mixture filtered through a cealite bed and bed was washed with a mixture of MeOH and DCM (1:9) (200 ml). Combined filtrates were evaporated to obtain a residue. Residue was dissolved in THF (50 ml) and washed with 15% aqueous Sodium hydroxide solution (10 ml). Separated the organic and aqueous layers. Aqueous layer was extracted with THF (3*50 ml). Combined organic layers were distilled to obtain a crude. Crude was purified by combi-flash using MeOH and DCM (1:9) as eluent to afford the titled compound as a colourless gummy liquid (970 mg). Yield: 48 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 3.55-3.49 (m, 2H), 3.11 (bs, 2H), 2.88 (td, J 12, 2.8, 2H), 2.77-2.68 (m, 1H), 2.58-2.50 (m, 1H), 1.81-1.72 (m, 2H), 1.35-1.22 (m, 2H), 1.00-0.88 (m, 4H). MS (m/z): 205.13 $(M+H)^+$.

Intermediate 81: (±)-*Tert*-butyl (1-(6-(2-chloro-5-methylpyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate



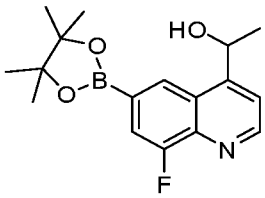
[227] Following the general procedure-2, the titled compound was synthesized from Intermediate 59 (3 g, 7.21 mmol) and 2,4-dichloro-5-methylpyrimidine (1.41 g, 8.65 mmol). After completion of reaction, water (100 ml) was added to reaction mixture and extracted with DCM (3*100 ml). Organic layer washed with water (100 ml) and distilled to obtain crude. Crude was purified by combi-flash using EtOAc and petether (35:65) as eluent to obtain the titled compound as an off-white solid (600 mg). Yield: 43 %. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 9.03 (d, J 4, 1H), 8.82 (s, 1H), 8.33 (s, 1H), 7.89 (d, J 11.2, 1H), 7.81 (d, J 7.2, 1H), 7.66 (d, J 4, 1H), 5.50-5.40 (m, 1H), 2.45 (s, 3H), 1.44 (d, J 7, 3H), 1.33 (s, 9H), MS (m/z): 417.0 (*M*+H)$^+$.

Intermediate 82: (±)-1-(6-bromo-8-fluoroquinolin-4-yl)ethanol



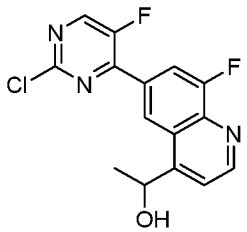
[228] Intermediate 56 (10 g, 37.3 mmol) was dissolved in a mixture of MeOH (100 ml) and THF (100 ml). To this mixture $NaBH_4$ (7.05 g, 186.5 mmol) was added and refluxed this mixture for 3 h. After 3 h, reaction mixture cooled to rt and water (500 ml) was added. Aqueous layer extracted with EtOAc (3*300 ml). Combined organic layers were washed with water (100 ml) and brine (100 ml). Organic layer distilled under reduced pressure to obtain a solid. Solid was suspended in diethyl ether (50 ml) and stirred for 30 mins. After 30 mins, filtered the solid and washed with diethyl ether (20 ml). Solid was dried under vacuum to obtain the titled compound as a yellow solid (9 g). Yield: 89 %. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 8.96 (d, J 4.4, 1H), 8.28 (s, 1H), 7.89 (d, J 10, 1H), 7.74 (d, J 4.4, 1H), 5.69 (d, J 4.4, 1H), 5.50-5.43 (m, 1H), 1.45 (d, J 6.4, 3H). MS (m/z): 270.21 (*M*+H)$^+$.

Intermediate 83: (±)-1-(8-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-4-yl)ethanol



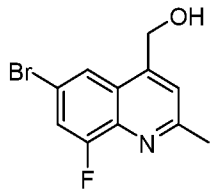
[229] Following the general procedure-1, the titled compound was synthesized from Intermediate 82 (3.6 g, 13.3 mmol). After work up, crude product was purified by combi-flash using EtOAc and Petether (35:65) as eluent to obtain the titled compound as an off-white solid (900 mg). Yield: 21 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.98 (d, J 4.8, 1H), 8.34 (s, 1H), 7.73 (d, J 4.8, 1H), 7.61 (d, J 10, 1H), 5.68 (d, J 4.8, 1H), 5.50-5.42 (m, 1H), 1.49 (d, J 6.4, 3H), 1.35 (s, 12H). MS (m/z): 318.40 $(M+H)^+$.

Intermediate 84: (±)-1-(6-(2-chloro-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethanol



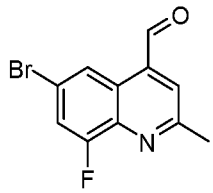
[230] Following the general procedure-2, the titled compound was synthesized from Intermediate 83 (900 mg, 2.84 mmol) and 2,4-dichloro-5-fluoropyrimidine (474 mg, 2.84 mmol). After completion of reaction, reaction mixture stirred at rt for 16 h to obtain a solid. Solid was filtered and washed with a mixture of dioxane and water (1:1) (17 ml) and Petether (100 ml). Solid was co-distilled with toluene at 65°C. Solid was suspended in diethyl ether (20 ml) and stirred for 30 mins. After 30 mins solid was filtered and washed with diethyl ether (20 ml). Solid was dried under vacuum to obtain the titled compound as an off-white solid (600 mg). Yield: 66 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.07 (d, J 3.2, 1H), 9.06 (d, J 4.4, 1H), 8.76 (s, 1H), 8.09 (d, J 11.6, 1H), 7.82 (d, J 4.4, 1H), 5.79 (d, J 4, 1H), 5.53-5.45 (m, 1H), 1.53 (d, J 6.4, 3H). MS (m/z): 322.25 $(M+H)^+$.

Intermediate 85: (6-bromo-8-fluoro-2-methylquinolin-4-yl)methanol



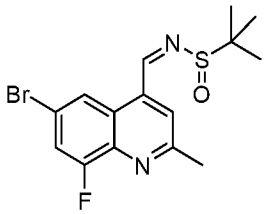
[231] A solution of methyl 6-bromo-8-fluoro-2-methylquinoline-4-carboxylate (Intermediate 11, 100g, 335 mmol) in ethanol (1.0 L) was cooled to 10°C and sodium borohydride (50.8, 1.34 mol) was added in portions over 45 min. and the mixture stirred at 60 °C for 90 min. The mixture was cooled to 25 °C, diluted with water (1.5 L) and stirred for 1 h. The solid formed was filtered, washed with water, and dried under vacuum for 5 h and then in a hot air oven at 70 °C for 17 h to give the title compound as an off-white solid (74 g). Yield: 82%. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 8.02 (t, J 1.6, 1H), 7.81 (dd, J 10.4, 2.0, 1H), 7.57 (s, 1H), 5.65 (t, J 5, 1H), 4.94 (d, J 4, 2H), 2.65 (s, 3H).

Intermediate 86: 6-bromo-8-fluoro-2-methylquinoline-4-carbaldehyde



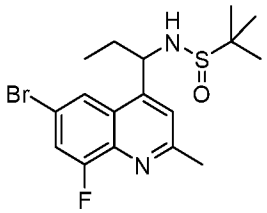
[232] Dimethyl sulfoxide (45.4 mL, 640 mmol) was added dropwise at -78°C to a solution of oxalyl chloride (36.55, 418 mmol) in dichloromethane (300 mL) over 30 min. and stirred for further 20 min. A solution of (6-bromo-8-fluoro-2-methylquinolin-4-yl)methanol (Intermediate 85, 60 g, 222.1 mmol) in dichloromethane (300 mL) was added to the above mixture at -78°C over 45 min. and stirred for further 30 min. Triethylamine (111 mL, 800 mmol) was added slowly to reaction mixture and stirred for 30 min. After adding water (500 mL), the mixture was warmed up to room temperature and extracted into dichloromethane (2*500 mL). Combined organic layers were washed successively with water (500 mL) and brine (500 mL), dried over sodium sulfate and concentrated. The residue was purified by silica gel chromatography on a combi-flash system using petroleum ether – EtOAc (90:10) as the eluent to give the product as an off-white solid (40 g). Yield: 67%. ^{1}H-NMR (δ ppm, $CDCl_3$, 400 MHz): 10.37 (s, 1H), 9.00 (s, 1H), 7.76 (s, 1H), 7.63 (dd, J 9.6, 2.0, 1H), 2.90 (s, 3H).

Intermediate 87: *N*-((6-bromo-8-fluoro-2-methylquinolin-4-yl)methylene)-2-methylpropane-2-sulfinamide



[233] Intermediate 86 (5 g, 18.7 mmol), *Tert*-butylsulfinamide (4.52 g, 37.3 mmol), titanium(IV)ethoxide (17 g, 74.6 mmol) and THF (15 ml) were mixed and refluxed at 80°C for 18 h. After 18 h, reaction mixture cooled to rt and diluted with water (500 ml). Aqueous layer extracted with EtOAc (500 ml). Organic layer was washed with water (500 ml) and brine solution (500 ml). Organic layer was dried on anhydrous Na_2SO_4 and distilled to obtain crude. Crude was purified by column chromatography on 60-120 mesh silica gel using EtOAc and Petether as eluent to obtain titled compound as an Off-white solid (5 g). Yield: 72%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.99 (t, J 2, 1H), 8.91 (s, 1H), 8.10 (s, 1H), 7.98 (d, J 10, 1H), 2.75 (s, 3H), 1.27 (s, 9H). MS (m/z): 370.96 $(M+H)^+$.

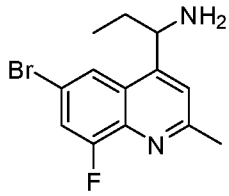
Intermediate 88: (±)-*N*-(1-(6-bromo-8-fluoro-2-methylquinolin-4-yl)propyl)-2-methylpropane-2-sulfinamide



[234] Intermediate 87 (5.5 g, 14.81 mmol) was suspended in THF and cooled to -78°C. 1M ethylmagnesiumbromide in THF (32.59 ml, 32.59 mmol) was added to above mixture at -78°C and stirred for 60 mins. After 60 mins, reaction mixture quenched with aq. NH_4Cl solution (100 ml). Aqueous layer was extracted with DCM (4*100 ml). Combined DCM layers were washed with brine solution (500 ml). Organic layer was dried on anhydrous Na_2SO_4 and distilled to obtain crude. Diethyl ether (50 ml) was added to above crude and stirred for 20 mins to obtain a solid. Solid was filtered and washed with diethyl ether (10 ml). Solid was dried under vacuum to obtain titled compound as a pale-yellow solid (4.3 g). Yield: 72%. ^{1}H-NMR (δ ppm, DMSO-

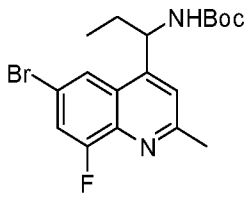
d_6, 400 MHz): 8.27 (s, 1H), 7.83 (dd, J 10, 2, 1H), 7.69 (s, 1H), 5.95 (d, J 8, 1H), 4.92-4.85 (m, 1H), 2.67 (s, 3H), 1.92-1.78 (m, 2H), 1.09 (s, 9H), 0.94 (t, J 7.2, 3H). MS (m/z): 401.35 $(M+H)^+$.

Intermediate 89: (±)-1-(6-bromo-8-fluoro-2-methylquinolin-4-yl)propan-1-amine



[235] Intermediate 88 (4.3 g, 10.7 mmol) was suspended in 4M HCl in MeOH (22.8 ml). This mixture was stirred at rt for 30 mins. After 30 mins, reaction mixture distilled to obtain a residue. Residue pH was adjusted to 8 using aq, $NaHCO_3$. Aqueous layer was extracted with DCM (2*200 ml). Organic layer was distilled to obtain a crude. Crude was purified by combi-flash using DCM and MeOH (97.5:2.5) as eluent to obtain titled compound as an off-white solid (2.5 g). Yield: 78 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.22 (s, 1H), 7.79 (d, J 10.4, 1H), 7.67 (s, 1H), 4.50-4.43 (m, 1H), 2.66 (s, 3H), 2.03 (s, 2H), 1.78-1.67 (m, 1H), 1.65-1.53 (m, 1H), 0.87 (t, J 7.2, 3H). MS (m/z): 297.29 $(M+H)^+$.

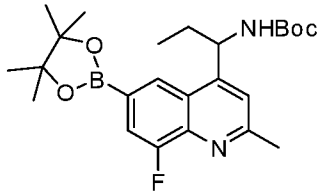
Intermediate 90: (±)-*Tert*-butyl (1-(6-bromo-8-fluoro-2-methylquinolin-4-yl)propyl)carbamate



[236] Intermediate 89 (2.45 g, 8.24 mmol) dissolved in DCM (25 ml) and cooled to 0°C. To this solution, triethylamine (1.72 ml, 12.4 mmol) was added. Bocanhydride (2.16 g, 9.89 mmol) was added to this mixture and stirred at rt for 2 h. After 2h, reaction mixture diluted with water (200 ml) and separated the organic layer. Aqueous layer again extracted with MeOH:DCM (1:9) mixture (2*100 ml). Combined organic layers were washed with water (100 ml) and aq. Sodium bicarbonate (3*100 ml). Organic layer dried on anhydrous Na_2SO_4 and distilled to obtain crude. Crude compound was suspended in Petether (25 ml) and stirred for 30 mins to obtain a solid. Solid was washed with Petether (10 ml) and dried under vacuum to obtain titled compound as an off-white solid (2.8 g). Yield: 85 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz):

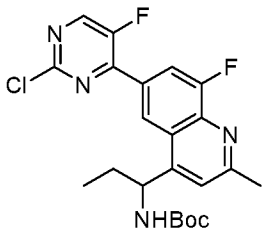
8.23 (s, 1H), 7.83 (dd, J 10, 2, 1H), 7.63 (d, J 8, 1H), 7.48 (s, 1H), 5.12-5.05 (m, 1H), 2.65 (s, 3H), 1.80-1.69 (m, 2H), 1.36 (s, 9H), 0.92 (t, J 7.2, 3H). MS (m/z): 397.27 $(M+H)^+$.

Intermediate 91: (±)-*Tert*-butyl (1-(8-fluoro-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-4-yl)propyl)carbamate



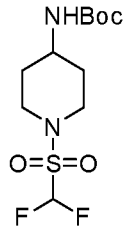
[237] Following the general procedure-1, the titled compound was synthesized from Intermediate 90 (3.0 g, 7.55 mmol). After work up, crude product was purified by combi-flash using EtOAc and petroleum ether (22:78) as eluent to obtain the titled compound as a pale-yellow solid (2.1 g). Yield: 63%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.23 (s, 1H), 7.68 (d, J 8.4, 1H), 7.58 (d, J 10.8, 1H), 7.51 (s, 1H), 5.24-5.15 (m, 1H), 2.68 (s, 3H), 1.79-1.70 (m, 2H), 1.37 (s, 9H), 1.34 (s, 12H), 0.91 (t, J 7.2, 3H). MS (m/z): 445.39 $(M+H)^+$.

Intermediate 92: (±)-*Tert*-butyl (1-(6-(2-chloro-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)propyl)carbamate



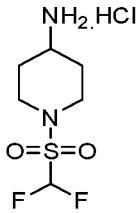
[238] Following the general procedure-2, the titled compound was synthesized from Intermediate 91 (2 g, 4.5 mmol) and 2,4-dichloro-5-fluoropyrimidine (902 mg, 5.4 mmol). After completion of reaction, reaction mixture stirred at rt for 16 h to obtain a solid. Solid was filtered and washed with a mixture of dioxane and water (1:1) (50 ml). Solid was co-distilled with toluene to obtain the titled compound as an Off-White solid (1 g). Yield: 49%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.06 (d, J 2.8,1H), 8.63 (s, 1H), 8.06 (d, J 11.6, 1H), 7.72 (d, J 8, 1H), 7.57 (s, 1H), 5.24-5.17 (m, 1H), 2.73 (s, 3H), 1.82-1.72 (m, 2H), 1.36 (s, 9H), 0.95 (t, J 7.2, 3H). MS (m/z): 449.36 $(M+H)^+$.

Intermediate 93: *Tert*-butyl (1-((difluoromethyl)sulfonyl)piperidin-4-yl)carbamate



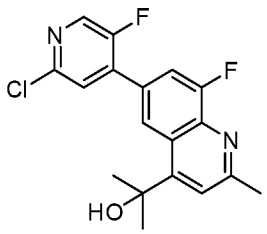
[239] *Tert*-butyl piperidin-4-ylcarbamate (3 g, 15 mmol) and Triethyl amine (5.22 mml. 37.4 mmol) were dissolved in DCM (30 ml). This mixture was cooled to 0°C and Difluoromethanesulfuonyl chloride (3.38 g, 22.5 mmol) was added. This mixture was stirred at rt for 5 h. After 5 h, reaction mixture quenched with water (50 ml). Separated the organic and aqueous layer. Aqueous layer extracted with DCM (3*30 ml). Combined DCM layers were washed with water (50 ml) and satd. Aq. $NaHCO_3$ (100 ml). Organic layer was distilled under vacuum to obtain a crude. Crude was purified by combi-flash using EtOAc and Petether (1:4) as eluent to afford the titled compound as an off-white solid (920 mg). Yield: 20%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 7.07 (t, J 52.4, 1H), 6.96 (s, 1H), 3.71-3.63 (m, 2H), 3.52-3.40 (m, 1H), 3.20-3.10 (m, 2H), 1.83-1.76 (m, 2H), 1.42-1.32 (m, 2H), 1.38 (s, 9H). MS (m/z): 215.15 ([*M*+H-Boc]$^+$).

Intermediate 94: 1-((difluoromethyl)sulfonyl)piperidin-4-amine hydrochloride



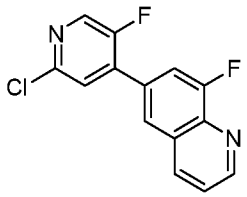
[240] Intermediate 93 (900 mg, 2.86 mmol) was suspended in 4M HCl in MeOH (9 ml) and stirred at 50°C for 2 h. After 2 h, reaction mixture was distilled to obtain a residue. Residue was co-distilled with toluene (2*10 ml) to obtain the titled compound as an off-white solid (560 mg). Yield: 78%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.30 (bs, 3H), 7.13 (t, J 52.8, 1H), 3.82-3.73 (m, 2H), 3.30-3.20 (m, 1H), 3.20-3.12 (m, 2H), 2.05-1.98 (m, 2H), 1.61-1.48 (m, 2H). MS (m/z): 215.08 ([*M*+H-HCl]$^+$).

Intermediate 95: 2-(6-(2-chloro-5-fluoropyridin-4-yl)-8-fluoro-2-methylquinolin-4-yl)propan-2-ol



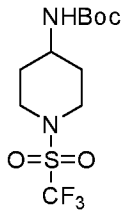
[241] Following the general procedure-2 using Sodium carbonate as a base, the titled compound was synthesized from Intermediate 13 (3.0 g, 11.4 mmol) and 2-chloro-5-fluoro-4-iodopyridine (1.17 g, 4.56 mmol). After work up, crude product was purified by combi-flash using EtOAc and petether (1:3) as eluent to obtain the titled compound as a pale-yellow solid (900 mg). Yield: 70%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.98 (s, 1H), 8.62 (d, J 2.4, 1H), 7.91 (d, J 5.6, 1H), 7.90 (d, J 12, 1H), 7.59 (s, 1H), 5.67 (s, 1H), 2.71 (s, 3H), 1.70 (s, 6H). MS (m/z): 349.34 ([*M*+H]$^+$).

Intermediate 96: 6-(2-chloro-5-fluoropyridin-4-yl)-8-fluoroquinoline



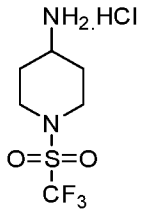
[242] Following the general procedure-2 using Sodium carbonate as a base, the titled compound was synthesized from Intermediate 1 (1.0 g, 3.66 mmol) and 2-chloro-5-fluoro-4-iodopyridine (1.04 g, 4.03 mmol). After work up, crude product was purified by combi-flash using EtOAc and petether (19:81) as eluent to obtain the titled compound as an off-white solid (510 mg). Yield: 50%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.06 (dd, J 4.4, 1.6, 1H), 8.64 (d, J 2, 1H), 8.57 (dt, J 8.4, 1.6, 1H), 8.26 (s, 1H), 8.12-7.95 (m, 2H), 7.75 (dd, J 8.4, 4, 1H). MS (m/z): 277.23 (*M*+H)$^+$.

Intermediate 97: *Tert*-butyl (1-((trifluoromethyl)sulfonyl)piperidin-4-yl)carbamate



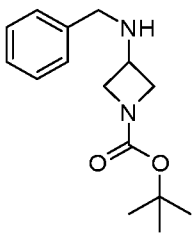
[243] tert-butyl piperidin-4-ylcarbamate (4 g, 20 mmol) dissolved in DCM (40 ml) and cooled to 0°C. Triethyl amine (4.18 ml, 30 mmol) was added and stirred at 0°C for 30 mins. After 30 mins, trifluoromethanesulfonyl chloride (5.05 g, 30 mmol) was added to above mixture dropwise. Reaction mixture stirred at 25°C for 2.5 h. After 2.5 h, reaction mixture diluted with water (100 ml). Separated the organic and aqueous layers. Aqueous layer was extracted with DCM (2*50 ml). Combined organic layers were washed with water (100 ml) and aq. $NaHCO_3$ (3*100 ml). Organic layer was dried on anhydrous Na_2SO_4 and distilled to obtain a crude. Crude was purified by combi-flash using EtOAc and petether (1:9) as eluent to afford the titled compound as an off-white solid (800 mg). Yield: 10%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 6.97 (d, J 7.2, 1H), 3.77-3.69 (m, 2H), 3.58-3.48 (m, 1H), 3.32-3.22 (m, 2H), 1.88-1.80 (m, 2H), 1.47-1.35 (m, 2H), 1.38 (s, 9H). MS (m/z): 233.18 (M+H-Boc)$^+$.

Intermediate 98: 1-((trifluoromethyl)sulfonyl)piperidin-4-amine hydrochloride



[244] Intermediate 97 (770 mg, 2.3 mmol) was suspended in 4M HCl in MeOH (15.4 ml) and stirred at 60°C for 2.5 h. After 2.5 h, reaction mixture was distilled to obtain a residue. Residue was co-distilled with toluene (2*10 ml) to obtain the titled compound as a pale-green solid (570 mg). Yield: 92 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.33 (bs, 3H), 3.90-3.80 (m, 2H), 3.35-3.22 (m, 2H), 2.10-2.03 (m, 2H), 1.65-1.52 (m, 2H). MS (m/z): 233.12 ([M+H-HCl]$^+$).

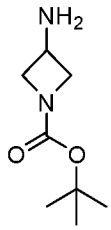
Intermediate 99: *Tert*-butyl 3-(benzylamino)azetidine-1-carboxylate



[245] *Tert*-butyl 3-oxoazetidine-1-carboxylate (10 g, 58.41 mmol) was dissolved in DCM (200 ml) and stirred for 10 mins. To this mixture, benzyl amine (6.88 g, 64.25 mmol) was added and stirred for 10 mins. Sodium triacetoxyborohydride (19.8 g, 93.45 mmol) was added to above

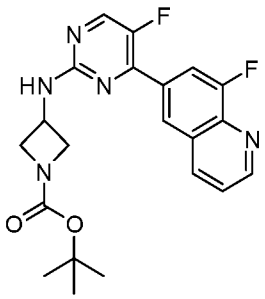
reaction mixture portion wise and stirred at rt for 16 h. After 16 h, reaction mixture quenched with aq. $NaHCO_3$ (200 ml) and separated organic layer. Aqueous layer extracted with DCM (2*100 ml). Combined organic layers were washed with water (3*100 ml) and aq. $NaHCO_3$ (3*100 ml). Organic layer distilled to obtain crude. Crude was purified by combi-flash using EtOAc and Petether (1:3) as eluent to afford the titled compound as a colourless liquid (9.5 g). Yield: 62%. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 7.32-7.26 (m, 4H), 7.24-7.19 (m, 1H), 3.90-3.73 (m, 2H), 3.58 (s, 2H), 3.55-3.40 (m, 3H), 2.85 (bs, 1H), 1.35 (s, 9H).

Intermediate 100: *Tert*-butyl 3-aminoazetidine-1-carboxylate



[246] Intermediate 99 (9.3 g, 35.4 mmol) was dissolved in MeOH (100 ml) and Pd/C (4.7 g) was added. This mixture was stirred in an autoclave at 6 Kg H_2 atmosphere for 16 h. After 16 h, reaction mixture filtered through cealite bed and bed was washed with MeOH and DCM (1:9) (750 ml). Combined filtrates were distilled to obtain a crude. Crude was purified by combi-flash using MeOH and DCM (3:97) as eluent to afford the titled compound as a black liquid (3.7 g). Yield: 61%. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 3.90 (t, J 7.2, 2H), 3.56 (quintet, J 7.2, 1H), 3.42 (t, J 7.2, 2H), 3.15 (s, 2H), 1.34 (s, 9H).

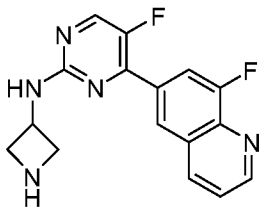
Intermediate 101: *Tert*-butyl 3-((5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-yl)amino)azetidine-1-carboxylate



[247] Intermediate 100 (1.86 g, 10.8 mmol) and intermediate 2 (3 g, 10.8 mmol) were suspended in DMF (18.6 ml). DIPEA (2.1 g, 16.2 mmol) was added to this mixture and stirred for 16 h at 100°C. After 16 h, reaction mixture diluted with water (200 ml) and extracted with

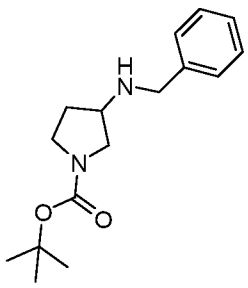
DCM (3*70 ml). Combined organic layers were washed with water (2*100 ml) and brine (100 ml). Organic layer evaporated to obtain crude. Crude product was purified by combi-flash using EtOAc and petether (35:65) as eluent to obtain the titled compound as a pale-yellow solid (1.5 g). Yield: 34%. M.P.: 186-188°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.05 (d, J 4.4, 1H), 8.65 (d, J 8.4, 1H), 8.57 (d, J 3.6, 1H), 8.52 (s, 1H), 8.15 (d, J 12, 1H), 8.06 (d, J 6, 1H), 7.73 (dd, J 8.4, 4.4, 1H), 4.6 (bs, 1H), 4.21-4.13 (m, 2H), 3.90-3.78 (m, 2H), 1.38 (s, 9H). MS (m/z): 414.17 $(M+H)^+$.

Intermediate 102: N-(azetidin-3-yl)-5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine



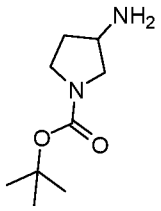
[248] Intermediate 101 (1.48 g, 3.58 mmol) was dissolved in DCM (15 ml). To this mixture trifluoroacetic acid (4.08 g, 35.8 mmol) was added and stirred at rt for 3 h. After 3 h, DCM was evaporated to obtain a residue. Residue was dissolved in water (40 ml) and extracted with DCM (4*30 ml). Aqueous layer pH adjusted to 14 using aq. Sodium hydroxide solution. Aqueous layer extracted with MeOH and DCM mixture (1:9) (15*70 ml). Combined organic layers were distilled to obtain crude. EtOAc and Petether mixture (3:7) (30 ml) was added to crude and stirred for 30 mins to obtain a solid. Solid was filtered and washed with a mixture of EtOAc and Petether (1:1) (20 ml) to obtain the titled compound as a pale brown solid (550 mg). Yield: 49 %. M.P.: 133-135°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.03 (d, J 3.6, 1H), 8.63 (d, J 8.4, 1H), 8.52 (d, J 3.6, 1H), 8.49 (bs, 1H), 8.14 (d, J 12, 1H), 7.71 (dd, J 8.4, 3.6, 1H), 3.53-3.40 (m, 2H), 3.39-3.25 (m, 4H), 3.21-3.15 (m, 1H). MS (m/z): 314.25 $(M+H)^+$.

Intermediate 103: *Tert*-butyl 3-(benzylamino)pyrrolidine-1-carboxylate



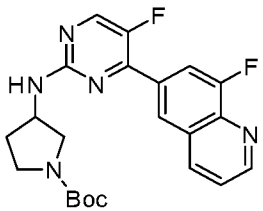
[249] *Tert*-butyl 3-oxopyrrolidine-1-carboxylate (10 g, 53.98 mmol) was dissolved in DCM (200 ml) and stirred for 10 mins. To this solution, benzyl amine (6.36 g, 59.37 mmol) was added and stirred for 10 mins. Sodium triacetoxyborohydride (18.3 g, 86.37 mmol) was added to reaction mixture portion wise and stirred at rt for 16 h. After 16 h, reaction mixture quenched with aq. $NaHCO_3$ (200 ml) and separated organic layer. Aqueous layer extracted with DCM (2*100 ml). Combined organic layers were washed with water (3*100 ml) and aq. $NaHCO_3$ (3*100 ml). Organic layer distilled to obtain crude. Crude was purified by combi-flash using EtOAc and Petether (1:3) as eluent to afford the titled compound as a pale-yellow liquid (9.5 g). Yield: 62 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 7.35-7.27 (m, 4H), 7.24-7.19 (m, 1H), 3.67 (s, 2H), 3.35-3.25 (m, 2H), 3.23-3.12 (m, 2H), 3.01 (dd, J 10.2, 4.4, 1H), 2.32-2.28 (m, 1H), 1.95-1.82 (m, 1H), 1.75-1.62 (m, 1H), 1.38 (s, 9H). MS (m/z): 276.97 $(M+H)^+$.

Intermediate 104: *Tert*-butyl 3-aminopyrrolidine-1-carboxylate



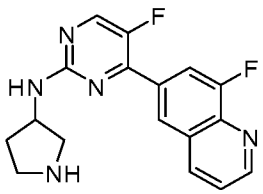
[250] Intermediate 103 (9.4 g, 34.01 mmol) was dissolved in MeOH (100 ml) and Pd/C (3.7 g) was added to this mixture. This mixture was stirred in an autoclave at 6 Kg H_2 atmosphere for 16 h. After 16 h, reaction mixture filtered through cealite bed and bed was washed with MeOH and DCM (1:9) (700 ml). Combined filtrates were distilled to obtain a crude. Crude was purified by combi-flash using MeOH and DCM (3:97) as eluent to afford the titled compound as a black liquid (4.9 g). Yield: 77 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 3.42-3.25 (m, 3H), 3.23-3.13 (m, 1H), 2.88-2.81 (m, 1H), 1.90-1.80 (m, 1H), 1.67 (bs, 2H), 1.57-1.47 (m, 1H), 1.38 (s, 9H).

Intermediate 105: *Tert*-butyl 3-((5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



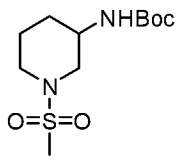
[251] Intermediate 104 (2 g, 10.8 mmol) and intermediate 2 (3 g, 10.8 mmol) were suspended in DMF (20 ml). DIPEA (2.1 g, 16.2 mmol) was added to this mixture and stirred for 16 h at 100°C. After 16 h, reaction mixture diluted with water (200 ml) and extracted with DCM (3*70 ml). Combined organic layers were washed with water (2*100 ml) and brine (100 ml). Organic layer evaporated to obtain crude. Crude product was purified by combi-flash using EtOAc and Petether (1:1) as eluent to obtain the titled compound as a pale-green solid (1.1 g). Yield: 24%. M.P.: 155-157°C. MS (m/z): 426.71 (M-H); calculated for [$C_{22}H_{23}F_2N_5O_2$- H]: 426.18.

Intermediate 106: 5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(pyrrolidin-3-yl)pyrimidin-2-amine



[252] Intermediate 105 (1.07 g, 2.50 mmol) was dissolved in DCM (11 ml). To this mixture trifluoroacetic acid (2.85 g, 25.0 mmol) was added and stirred at rt for 3 h. After 3 h, DCM was evaporated to obtain a residue. Residue was dissolved in water (40 ml) and extracted with DCM (4*30 ml). Aqueous layer pH adjusted to 14 using aq. Sodium hydroxide solution. Aqueous layer extracted with MeOH and DCM (1:9) (8*70 ml). Combined organic layers were distilled to obtain the titled compound as a pale-yellow solid (100 mg). Yield: 12 %. M.P.: 130-132°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.03 (d, J 4, 1H), 8.63 (d, J 8, 1H), 8.52 (d, J 2.8, 1H), 8.49 (s, 1H), 8.14 (d, J 12, 1H), 7.72 (dd, J 8, 4, 1H), 7.44 (d, J 6.8, 1H), 4.26 (bs, 1H), 3.05-2.95 (m, 1H), 2.94-2.86 (m, 1H), 2.80-2.70 (m, 1H), 2.70-2.62 (m, 1H), 2.05-1.94 (m, 1H), 1.71-1.59 (m, 1H). MS (m/z): 328.35 (M+H).

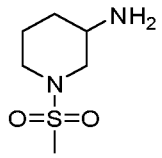
Intermediate 107: *Tert*-butyl (1-(methylsulfonyl)piperidin-3-yl)carbamate



[253] *Tert*-butyl piperidin-3-ylcarbamate (2 g, 9.99 mol) was dissolved in DCM (50 ml) and triethyl amine (1.52 g, 15 mmol) was added. This mixture was stirred at rt for 30 mins. After 30 mins, reaction mixture cooled to 0°C and methanesulfonyl chloride (2.17 g, 19 mmol) was

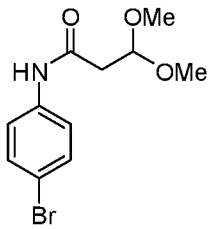
added. Reaction mixture was stirred at rt for 16 h. After 16 h, reaction mixture quenched with water ((200 ml) and separated the organic layer. Aqueous layer extracted with DCM (2*200 ml). Combined organic layers were washed with brine (100 ml). Organic layer distilled to obtain a solid. Solid was triturated with diethyl ether (50 ml). Solid was filtered and washed with diethyl ether (10 ml). Solid was dried under vacuum to obtain the titled compound as an off-white solid (2.5 g). Yield: 90 %. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 6.96 (d, J7.6, 1H), 3.51 (d, J 10.4, 1H), 3.40-3.33 (m, 1H), 2.84 (s, 3H), 2.68-2.58 (m, 1H), 2.40 (t, J 10.4, 1H), 1.80-1.70 (m, 2H), 1.55-1.41 (m, 1H), 1.38 (s, 9H), 1.34-1.20 (m, 2H). MS (m/z): 179.01 (*M*+H-Boc)$^+$.

Intermediate 108: 1-(methylsulfonyl)piperidin-3-amine



[254] Intermediate 107 (2.4 g, 8.6 mmol) was dissolved in DCM (24 ml) and trifluoroacetic acid (9.8 g, 86 mmol) was added. This mixture was stirred at rt for 4 h. After 4 h, reaction mixture distilled under vacuum to obtain a residue. Residue was basified with 10% aq. NaOH solution. Aqueous layer extracted with MeOH and DCM (1:9) (7*50 ml). Combined organic layers were distilled to obtain the titled compound as an off-white solid (700 mg). Yield: 46 %. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 3.47 (dd, J 11.2, 4, 1H), 3.37 (d, J 8, 2H), 2.82 (s, 3H), 2.71-2.56 (m, 2H), 2.35-2.26 (m, 1H), 1.81-1.68 (m, 2H), 1.58 (bs, 1H), 1.53-1.39 (m, 1H), 1.10-0.99 (m, 1H). MS (m/z): 179.00 (*M*+H)$^+$.

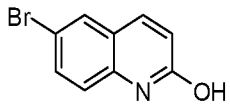
Intermediate 109: N-(4-bromophenyl)-3,3-dimethoxypropanamide



[255] 4-Bromoaniline (2 g, 11.6 mmol) was dissolved in THF (30 ml) and methyl 3,3-dimethoxypropanoate (2.07 g, 13.92 mmol) was added dropwise. This mixture was cooled to 0°C and Sodium bis(trimethylsilyl)amide (3.20 g, 17.4 mmol) was added dropwise. Reaction

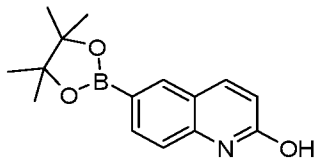
mixture was stirred at 0°C for 10 mins and at 20°C for 20 mins. Reaction mixture was warmed to rt and stirred at rt for 16 h. After 16 h, reaction mixture cooled to 0°C and added 20 % aq. Citric acid (60 ml). Separated the organic and aqueous layers. Aqueous layer was extracted with DCM (2*50 ml). Combined organic layers were washed with water (2*100 ml). Organic layer distilled to obtain a crude. Crude was triturated with diethyl ether (20 ml) and stirred for 20 mins to obtain a solid. Solid was filtered and dried under vacuum to obtain the titled compound as a brown solid (1.5 g). Yield: 45 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 10.10 (s, 1H), 7.56 (d, J 8.4, 2H), 7.47 (d, J 8.8, 2H), 4.77 (t, J 6.0, 1H), 3.26 (s, 6H), 2.62 (d, J 6.0, 2H). MS (m/z): 286.00 (M-H)$^-$.

Intermediate 110: 6-bromoquinolin-2-ol



[256] Intermediate 109 (5 g, 17.3 mmol) was dissolved in DCM (75 ml) and added cold Con. H_2SO_4 dropwise at 0°C. This mixture was stirred at 0°C for 10 mins and at rt for 1 hr. After 1 h, DCM was distilled out from reaction mixture to obtain a residue. Cold water was added to the residue to obtain a solid. Solid was filtered and dried under vacuum. Solid was suspended in acetonitrile (30 ml) and refluxed for 1 h. After 1 h, cooled to rt and filtered the solid. Solid was washed with acetonitrile (15 ml) and dried the solid under vacuum to obtain the titled compound as a brown solid (3.2 g). Yield: 83 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 11.88 (s, 1H), 7.93 (s, 1H), 7.89 (d, J 9.6, 1H), 7.66 (dd, J 8.4, 2, 1H), 7.27 (d, J 8.8, 1H), 6.56 (d, J 9.6, 1H). MS (m/z): 224.12 (M+H)$^+$.

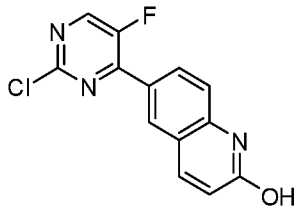
Intermediate 111: 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-2-ol



[257] Following the general procedure-1, the titled compound was synthesized from Intermediate 110 (2.0 g, 8.90 mmol). After work up, crude product was purified by combi-flash using MeOH and DCM (2.3:97.7) as eluent to obtain the titled compound as a brown solid (1.6 g). Yield: 66 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 11.87 (s, 1H), 8.00 (s, 1H), 7.98 (d, J

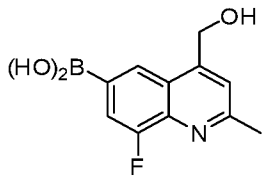
9.6, 1H), 7.73 (d, J , 1H), 7.27 (d, J 8.4, 1H), 6.49 (d, J 9.6, 1H), 1.29 (s, 12H). MS (m/z): 272.28 (M+H).

Intermediate 112: 6-(2-chloro-5-fluoropyrimidin-4-yl)quinolin-2-ol



[258] Following the general procedure-2, the titled compound was synthesized from Intermediate 111 (1.9 g, 6 mmol) and 2,4-dichloro-5-fluoropyrimidine (1.2 g, 7.21 mmol). After completion of reaction, reaction mixture cooled to rt to obtain a solid. Solid was filtered and washed with a mixture of dioxane and water (1:1) (10 ml). Solid was further stirred with Diethyl ether (20 ml) for 30 mins and filtered the solid. Solid was dried to obtain the titled compound as an off-white solid (1.4 g). Yield: 98 %. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 12.08 (s, 1H), 8.94 (d, J 3.2, 1H), 8.42 (s, 1H), 8.18 (d, J 8.4, 1H), 8.12 (d, J 9.6, 1H), 7.46 (d, J 8.8, 1H), 6.59 (d, J 9.6, 1H). MS (m/z): 276.21 (M+H).

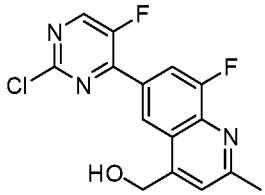
Intermediate 113: (8-fluoro-4-(hydroxymethyl)-2-methylquinolin-6-yl)boronicacid



[259] Triisopropyl borate (8 mL, 43.0 mmol) was added dropwise at -78 °C to a solution of Intermediate 85 (3.0 g, 10 mmol) in dry THF (215 mL) under nitrogen atmosphere. A 2.5M solution of *n*-BuLi in hexane (16.1 mL, 40.3 mmol) was added dropwise to the above mixture and stirred for 2 hrs at the same temperature. The mixture was brought up to RT and acidified with 2N HCl, stirred for 30 min., neutralised by the addition of aq. 10% NaOH, stirred for 20 min. and extracted with ethyl acetate (2*150 mL). The combined organic layers were washed successively with water (150 mL) and brine (150 mL), dried over sodium sulfate and concentrated. The residue was stirred with diethyl ether (30 mL) for 30 min. and the solid formed was filtered to obtain the titled compound as yellow solid (1.5 g). Yield: 60 %. ^{1}H-

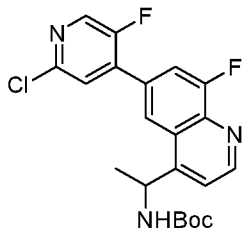
NMR (δ ppm, DMSO-d_6, 400 MHz): 8.30 (s, 2H), 8.24 (s, 1H), 7.76 (d, J 12, 1H), 7.55 (s, 1H), 5.61 (s, 1H), 5.03 (s, 2H), 2.68 (s, 3H). MS (m/z): 236.22 $(M+H)^+$.

Intermediate 114: (6-(2-chloro-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)methanol



[260] Following the general procedure-2, the titled compound was synthesized from Intermediate 113 (1.4 g, 5.96 mmol) and 2,4-dichloro-5-fluoropyrimidine (1.19 g, 7.15 mmol). After completion of reaction, reaction mixture cooled to rt and stirred for 16 h to obtain a solid. Solid was filtered and washed with Dioxane: water mixture (1:1) (50 ml). Solid was dried under vacuum to obtain the titled compound as an off-white solid (1 g). Yield: 52 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.07 (d, J 2.8, 1H), 8.53 (s, 1H), 8.06 (d, J 12, 1H), 7.66 (s, 1H), 5.74 (t, J 5.6, 1H), 5.06 (d, J 5.6, 2H), 3.34 (s, 3H). MS (m/z): 322.24 $(M+H)^+$.

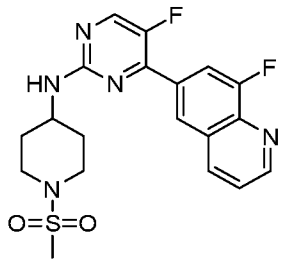
Intermediate 115: *Tert*-butyl (1-(6-(2-chloro-5-fluoropyridin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate



[261] Following the general procedure-2, the titled compound was synthesized from Intermediate 59 (900 mg, 2.2 mmol) and 2-chloro-5-fluoro-4-iodopyridine (610 mg, 2.4 mmol). After work up, crude product was purified by combi-flash using EtOAc and petether (1:3) as eluent to obtain the titled compound as a pale-yellow solid (900 mg). Yield: 70%.^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.02 (d, J 4.4, 1H), 8.63 (d, J 2, 1H), 8.40 (s, 1H), 8.00 (d, J 5.6, 1H), 7.96 (d, J 11.6, 1H), 7.79 (d, J 7.6, 1H), 7.56 (d, J 7.6, 1H), 5.55-5.46 (m, 1H), 1.45 (d, J 6.8, 3H), 1.35 (s, 9H). MS (m/z): 420.31 $(M+H)^+$.

Example 1

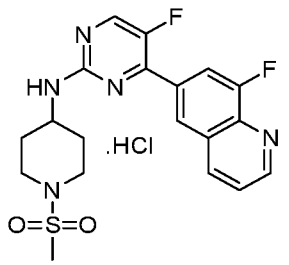
5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine



[262] 1-(methylsulfonyl)piperidin-4-amine (231 mg, 1.30 mmol) and sodium bicarbonate (166 mg, 1.98 mmol) were suspended in DMF (5 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 2 (300 mg, 1.08 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water and extracted with EtOAc. Organic layer evaporated to obtain crude. Crude product was purified by combi-flash using methanol and DCM (3:97) as eluent to obtain the titled compound as a pale-yellow solid (200 mg). Yield: 44 %. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 9.05 (d, J 2.8, 1H), 8.64 (d, J 8, 1H), 8.55 (d, J 3.6, 1H), 8.50 (s, 1H), 8.14 (d, J 12.4, 1H), 7.73 (dd, J 8, 3.6, 1H), 7.48 (d, J 7.6, 1H), 3.90 (bs, 1H), 3.55-3.51 (m, 2H), 2.98-2.85 (m, 2H), 2.89 (s, 3H), 2.08-1.98 (m, 2H), 1.64-1.51 (m, 2H). MS (m/z): 419.80 $(M+H)^+$.

Example 2

5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine hydrochloride

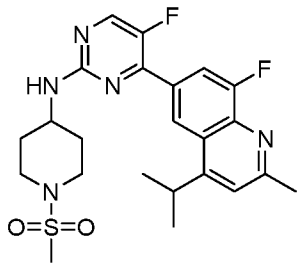


[263] 5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine (Example 1, 200 mg, 0.477 mmol) was dissolved in MeOH (4 ml) and Con. HCl (174 mg, 4.77 mmol) was added to obtain a clear solution. This mixture was stirred for 30 mins at

25°C. After 30 mins, MTBE (12 ml) was added to the above reaction to obtain a solid. This mixture was stirred for 1 h and filtered the solid. Solid was washed with MTBE (15 ml) and dried under vacuum to obtain the titled compound as a yellow solid. Yield: 65 %. M.P.: 196-198°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.04 (dd, J 4, 1.2, 1H), 8.64 (d, J 8.4, 1H), 8.54 (d, J 4, 1H), 8.49 (s, 1H), 8.14 (d, J 12, 1H), 7.73 (dd, J 8.4, 4, 1H), 7.48 (bs, 1H), 3.90 (m, 1H), 3.59-3.51 (m, 2H), 2.97-2.85 (m, 2H), 2.87 (s, 3H), 2.05-1.96 (m, 2H), 1.64-1.51 (m, 2H). MS (m/z): 420.36 $(M+H)^+$.

Example 3

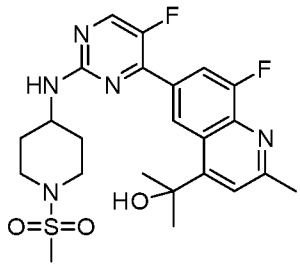
5-fluoro-4-(8-fluoro-4-isopropyl-2-methylquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine



[264] 1-(methylsulfonyl)piperidin-4-amine (64 mg, 0.36 mmol) and sodium bicarbonate (166 mg, 1.98 mmol) were suspended in DMF (5 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 10 (100 mg, 0.9 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water and extracted with EtOAc. Organic layer evaporated to obtain crude. Crude product was purified by combi-flash using methanol and DCM (1.3:98.7) as eluent to obtain the titled compound as a pale-yellow solid (23 mg). Yield: 16 %. M.P.: 200-202°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.59 (bs, 1H), 8.51 (d, J 4, 1H), 8.03 (d, J 11.6, 1H), 7.51 (s, 1H), 7.45 (d, J 7.6, 1H), 3.89 (bs, 1H), 3.70 (septet, J 6.8, 1H), 3.59-3.51 (m, 2H), 2.95-2.85 (m, 2H), 2.90 (s, 3H), 2.69 (s, 3H), 2.07-1.98 (m, 2H), 1.64-1.54 (m, 2H), 1.37 (d, J 6.8, 6H). MS (m/z): 476.51 $(M+H)^+$.

Example 4

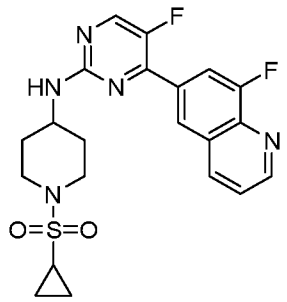
2-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)propan-2-ol



[265] 1-(methylsulfonyl)piperidin-4-amine (180 mg, 1.03 mmol) and sodium bicarbonate (160 mg, 1.97 mmol) were suspended in DMF (6 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 14 (300 mg, 0.86 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water and extracted with MeOH:DCM (1:9) (100 ml). Organic layer evaporated to obtain crude. Crude product was purified by combi-flash using methanol and DCM (2:98) as eluent to obtain the titled compound as an off-white solid (160 mg). Yield: 44 %. M.P.: 218-220°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.38 (bs, 1H), 8.50 (d, J 4, 1H), 8.01 (d, J 11.6, 1H), 7.58 (s, 1H), 7.41 (d, J 7.6, 1H), 5.64 (s, 1H), 3.95-3.83 (m, 1H), 3.60-3.52 (m, 2H), 2.95-2.85 (m, 2H), 2.88 (s, 3H), 2.70 (s, 3H), 2.07-1.98 (m, 2H), 1.70 (s, 6H), 1.63-1.53 (m, 2H). MS (m/z): 492.49 $(M+H)^+$.

Example 5

N-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine

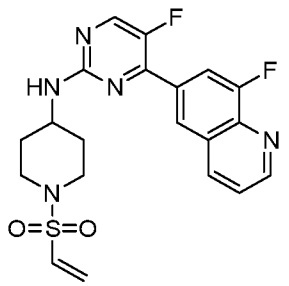


[266] 5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(piperidin-4-yl)pyrimidin-2-amine (Intermediate 16, 110 mg, 0.29 mmol) was dissolved in DCM (3 ml) and added TEA (48 mg, 0.44 mmol). This mixture was stirred at rt for 30 mins and cyclopropylsulfonyl chloride (77 mg, 0.55 mmol) was added and stirred at rt for 2 h. After 2 h, reaction mixture quenched with water and separated organic layer. Aqueous layer extracted with MeOH and DCM (1:9, 3*30 ml) and combined organic layers were distilled to obtain crude. Crude was purified by combi-flash

using MeOH and DCM (1.6:98.4) as eluent to afford the titled compound as a pale-green solid (60 mg). Yield: 42%. M.P.: 191-193°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.05 (d, J 4, 1H), 8.64 (d, J 8.4, 1H), 8.55 (d, J 4, 1H), 8.49 (s, 1H), 8.14 (d, J 12.4, 1H), 7.73 (dd, J 8.4, 4, 1H), 7.49 (d, J 7.6, 1H), 4.00-3.88 (m, 1H), 3.65-3.57 (m, 2 H), 3.08-2.98 (m, 2H), 2.63-2.55 (m, 1H), 2.05-1.97 (m, 2H), 1.65-1.53 (m, 2H), 1.05-0.90 (m, 4H). MS (m/z): 446.37 (M+H)$^+$.

Example 6

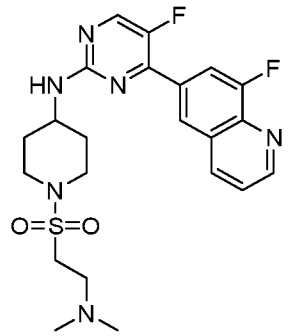
5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(vinylsulfonyl)piperidin-4-yl)pyrimidin-2-amine



[267] 5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(piperidin-4-yl)pyrimidin-2-amine (Intermediate 16, 400 mg, 1.2 mmol) was dissolved in DCM (12 ml) and added TEA (180 mg, 1.8 mmol). This mixture was stirred at rt for 30 mins and chloroethanesulfonyl chloride (290 mg, 1.8 mmol) was added and stirred at 0°C for 90 min. After 90 min, reaction mixture quenched with water and separated organic layer. Aqueous layer extracted with MeOH and DCM (1:9, 3*30 ml) and combined organic layers were distilled to obtain crude. Crude was purified by combi-flash using MeOH and DCM (2.2:97.8) as eluent to afford the titled compound as an off-white solid (120 mg). Yield: 23%. M.P.: 201-203°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.04 (d, J 4, 1H), 8.63 (d, J 8.4, 1H), 8.53 (d, J 4, 1H), 8.48 (s, 1H), 8.12 (d, 12.4, 1H), 7.72 (dd, J 8.4, 4, 1H), 7.48 (d, J 7.6, 1H), 6.82 (dd, J 16.8, 10, 1H), 6.15 (d, J 10, 1H), 6.12 (d, J 16.8, 1H), 3.88 (bs, 1H), 3.55-3.48 (m, 2H), 2.90-2.78 (m, 2H), 2.05-1.95 (m, 2H), 1.65-1.52 (m, 2H). MS (m/z): 432.33 (M+H)$^+$.

Example 7

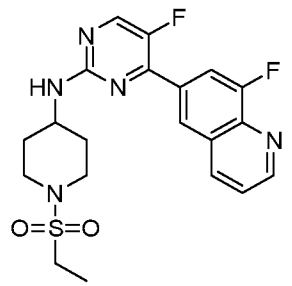
***N*-(1-((2-(dimethylamino)ethyl)sulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine**



[268] 5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(vinylsulfonyl)piperidin-4-yl)pyrimidin-2-amine (Example 6, 80 mg, 0.18 mmol) dissolved in THF (8 ml) and added Dimethylamine (40% in water) (0.3 ml, 1.48 mmol). This mixture was stirred in a sealed tube at rt for 16 h. After 16 h, reaction mixture diluted with water (50 ml) and extracted with MeOH and DCM mixture (1:9, 3*30 ml). Combined organic layers were washed with water (50 ml) and brine (50 ml). Organic layer distilled to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (5:95) as eluent to afford the titled compound as an off-white solid (29 mg). Yield: 33%. M.P.: 162-164°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.04 (d, J 4, 1H), 8.63 (d, J 8.4, 1H), 8.54 (d, J 3.2, 1H), 8.48 (s, 1H), 8.13 (d, J 12, 1H), 7.72 (dd, J 8.4, 4, 1H), 7.47 (d, J 7.6, 1H), 3.98-3.85 (m, 1H), 3.63-3.55 (m, 2H), 3.18 (t, J 6.8, 2H), 3.05-2.95 (m, 2H), 2.61 (t, J 6.8, 2H), 2.17 (s, 6H), 2.03-1.95 (m, 2H), 1.61-1.49 (m, 2H). MS (m/z): 475.41 (M-H)$^-$.

Example 8

N-(1-(ethylsulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine

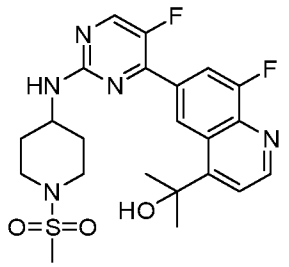


[269] 5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(piperidin-4-yl)pyrimidin-2-amine (Intermediate 16, 150 mg, 0.44 mmol) was dissolved in DCM (4.5 ml) and added TEA (67 mg, 0.66 mmol). This mixture was stirred at rt for 30 mins and ethanesulfonyl chloride (100 mg, 0.83 mmol) was added and stirred at 0°C for 90 min. After 90 min, reaction mixture quenched with water

and separated organic layer. Aqueous layer extracted with MeOH and DCM (1:9, 3*30 ml) and combined organic layers were distilled to obtain crude. Crude was purified by combi-flash using MeOH and DCM (2:98) as eluent to afford the titled compound as a pale-green solid (90 mg). Yield: 48%. M.P.: 203-205°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.04 (d, J 3.6, 1H), 8.63 (d, J 8.4, 1H), 8.54 (d, J 3.6, 1H), 8.48 (s, 1H), 8.13 (d, J 12, 1H), 7.72 (dd, J 8.4, 4, 1H), 7.48 (d, J 7.6, 1H), 3.92 (bs, 1H), 3.65-3.55 (m, 2H), 3.06 (q, J 7.2, 2H), 3.05-2.95 (m, 2H), 2.02-1.95 (m, 2H), 1.61-1.49 (m, 2H), 1.21 (t, J 7.6, 3H). MS (m/z): 434.41 (M+H)$^+$.

Example 9

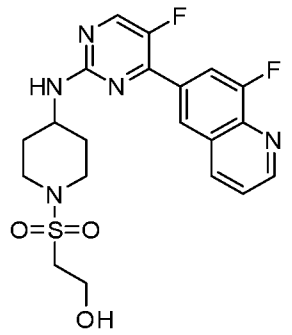
2-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-4-yl)propan-2-ol



[270] 1-(methylsulfonyl)piperidin-4-amine (159 mg, 0.894 mmol) and sodium bicarbonate (144 mg, 1.71 mmol) were suspended in DMF (6 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 22 (250 mg, 0.75 mmol) was added to the above mixture and stirred at 80°C for 16 h. Reaction mixture diluted with water and extracted with EtOAc. Organic layer evaporated to obtain crude. Crude product was purified by combi-flash using EtOAc and Petether (6:4) as eluent to obtain the titled compound as an off-white solid (45 mg). Yield: 13 %. M.P.: 227-229°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.45 (bs, 1H), 8.95 (d, J 4.4, 1H), 8.52 (d, J 3.6, 1H), 8.06 (d, J 12, 1H), 7.70 (d, J 4.4, 1H), 7.44 (d, J 7.6, 1H), 5.70 (s, 1H), 3.89 (bs, 1H), 3.55 (d, J 12, 2H), 2.90 (t, J 12, 2 H), 2.88 (s, 3H), 2.04 (d, J 12, 2H), 1.70 (s, 6H), 1.63-1.54 (m, 2H). MS (m/z): 478.39 (M+H)$^+$; calculated for [$C_{22}H_{25}F_2N_5O_3S$+H]: 478.53. HPLC Purity: 97.69%.

Example 10

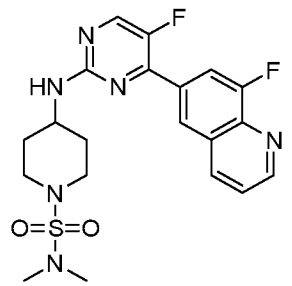
2-((4-((5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)ethan-1-ol



[271] 5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(vinylsulfonyl)piperidin-4-yl)pyrimidin-2-amine (Example 6, 180 mg, 0.42 mmol) dissolved in THF (18 ml) and tetrabutylammonium hydroxide (40% in water) (4.3 ml, 6.67 mmol) was added. This mixture was stirred at rt for 16 h. After 16 h, water (50 ml) was added to the reaction mixture and extracted with MeOH:DCM mixture (1:9) (3*30 ml). Combined organic layers were washed with water (50 ml) and distilled to obtain a crude. Crude was purified by combi-flash using MeOH and DCM (3:97) as eluent to afford the titled compound as a pale-green solid (90 mg). Yield: 48%. M.P.: 212-214°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.04 (d, J 2.8, 1H), 8.62 (d, J 8, 1H), 8.53 (d, J 3.6, 1H), 8.48 (s, 1H), 8.13 (d, J 11.6, 1H), 7.72 (dd, J 8.4, 4.4, 1H), 7.47 (d, J 8.4, 1H), 5.02 (t, J 5.6, 1H), 3.89 (bs, 1H), 3.76 (q, J 5.6, 2H), 3.61-3.52 (m, 2H), 3.19 (t, J 6.4, 2H), 3.04-2.95 (m, 2H), 2.02-1.92 (m, 2H), 1.61-1.48 (m, 2H). MS (m/z): 450.42 $(M+H)^+$.

Example 11

4-((5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-yl)amino)-N,N-dimethylpiperidine-1-sulfonamide

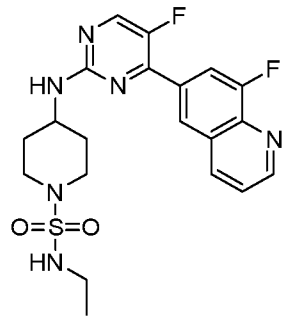


[272] Intermediate 26 (230 mg, 1.08 mmol) and Intermediate 2 (300 mg, 1.08 mmol) were suspended in DMF (3 ml). DIPEA (210 mg, 1.62 mmol) was added to this mixture and stirred for 16 h at 100°C. After 16 h, reaction mixture diluted with water (50 ml) and extracted with MeOH:DCM (1:9) (3*30 ml). Combined organic layers were evaporated to obtain crude.

Crude product was purified by combi-flash using EtOAc and Petether (1:1) as eluent to obtain the titled compound as a pale-green solid (90 mg). Yield: 18%. M.P.: 194-196°C. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 9.04 (s, 1H), 8.63 (d, J 7.6, 1H), 8.53 (s, 1H), 8.48 (s, 1H), 8.13 (d, J 12.4, 1H), 7.72 (dd, J 8, 4, 1H), 7.47 (d, J 6.4, 1H), 3.91 (bs, 1H), 3.63-3.52 (m, 2H), 3.09-2.98 (m, 2H), 2.75 (s, 6H), 2.00-1.90 (m, 2H), 1.61-1.47 (m, 2H). MS (m/z): 449.37 (*M*+H)$^+$.

Example 12

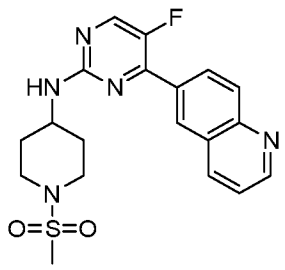
N-ethyl-4-((5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-yl)amino)piperidine-1-sulfonamide



[273] Intermediate 28 (150 mg, 0.72 mmol) and Intermediate 2 (200 mg, 0.72 mmol) were suspended in DMF (3 ml). DIPEA (140 mg, 1.08 mmol) was added to this mixture and stirred for 16 h at 100°C. After 16 h, reaction mixture diluted with water (50 ml) and extracted with MeOH:DCM (1:9) (3*30 ml). Combined organic layers were evaporated to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (1.6:98.4) as eluent to obtain the titled compound as a pale-green solid (34 mg). Yield: 10%. M.P.: 185-187°C. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 9.04 (d, J 4, 1H), 8.63 (d, J 8.4, 1H), 8.53 (d, J 3.2, 1H), 8.49 (s, 1H), 8.13 (d, J 12.4, 1H), 7.72 (dd, J 8.4, 4, 1H), 7.46 (d, J 7.2, 1H), 7.16 (t, J 5.6, 1H), 3.87 (bs, 1H), 3.55-3.48 (m, 2H), 2.97-2.90 (m, 2H), 2.86-2.80 (m, 2H), 2.02-1.90 (m, 2H), 1.62-1.50 (m, 2H), 1.06 (t, J 7.2, 3H). MS (m/z): 449.28 (*M*+H)$^+$.

Example 13

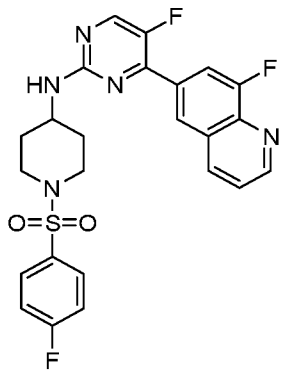
5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)-4-(quinolin-6-yl)pyrimidin-2-amine



[274] 1-(methylsulfonyl)piperidin-4-amine (247 mg, 1.39 mmol) and sodium bicarbonate (223 mg, 2.66 mmol) were suspended in DMF (6 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 30 (300 mg, 1.16 mmol) was added to the above mixture and stirred at 100°C for 16 h. After 16 h, reaction mixture diluted with water and extracted with MeOH and DCM (1:9) (3*30 ml). Combined organic layers were washed with water (3*50 ml) and brine (50 ml). Organic layer evaporated to obtain crude. Crude product was purified by combi-flash using EtOAc and Petether (3:1)) as eluent to obtain the titled compound as an off-white solid (65 mg). Yield: 14 %. M.P.: 220-222°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.00 (d, J 3.2, 1H), 8.62 (s, 1H), 8.55 (d, J 8, 1H), 8.53 (d, J 3.2, 1H), 8.34 (d, J 8.8, 1H), 8.16 (d, J 8.8, 1H), 7.62 (dd, J 8.4, 4.4, 1H), 7.44 (d, J 8, 1H), 3.92 (bs, 1H), 3.59-3.51 (m, 2H), 2.96-2.85 (m, 2H), 2.88 (s, 3H), 2.06-1.98 (m, 2H), 1.65-1.53 (m, 2H). MS (m/z): 402.36 $(M+H)^+$.

Example 14

5-fluoro-N-(1-((4-fluorophenyl)sulfonyl)piperidin-4-yl)-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine

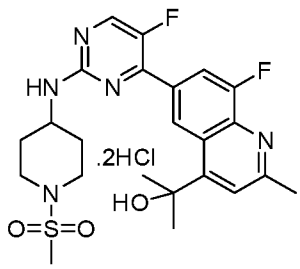


[275] 5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(piperidin-4-yl)pyrimidin-2-amine (Intermediate 16, 150 mg, 0.44 mmol) was dissolved in DCM (4.5 ml) and added TEA (89 mg, 0.88 mmol). This mixture was stirred at rt for 30 mins and 4-fluorobenzenesulfonylchloride (102 mg, 0.53 mmol) was added and stirred at rt for 15 mins. After 15 mins, reaction mixture quenched with

water and separated organic layer. Aqueous layer extracted with MeOH and DCM (1:9, 3*30 ml) and combined organic layers were washed with water (50 ml). Organic layer distilled to obtain crude. Crude was purified by combi-flash using MeOH and DCM (1.3:98.7) as eluent to afford the titled compound as a pale-green solid (120 mg). Yield: 60 %. M.P.: 218-220°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.05 (d, J 4, 1H), 8.62 (d, J 8, 1H), 8.51 (d, J 3.6, 1H), 8.47 (s, 1H), 8.11 (d, J 8, 1H), 7.85 (dd, J 8.8, 5.6, 2H), 7.73 (dd, J 8.4, 4.4, 1H), 7.51 (t, J 8.8, 2H), 7.45 (d, J 7.2, 1H), 3.80 (bs, 1H), 3.60-3.52 (m, 2H), 2.65-2.55 (m, 2H), 2.03-1.95 (m, 2H), 1.65-1.52 (m, 2H). MS (m/z): 500.40 (M+H)$^+$.

Example 15

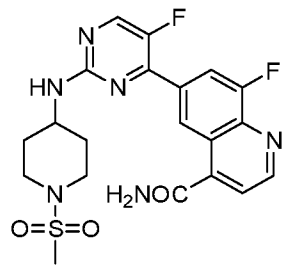
2-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)propan-2-ol dihydrochloride



[276] 2-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)propan-2-ol (Example 4, 150 mg, 0.305 mmol) was dissolved in MeOH (3 ml) and Con. HCl (111 mg, 3.05 mmol) was added to obtain a clear solution. This mixture was stirred for 30 mins at 25°C. After 30 mins, MTBE (9 ml) was added to the above reaction to obtain a solid. This mixture was stirred for 1 h and filtered the solid. Solid was washed with MTBE (10 ml) and dried under vacuum to obtain the titled compound as a yellow solid. Yield: 92 %. M.P.: 203-207°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.41 (bs, 1H), 8.51 (d, J 3.6, 1H), 8.01 (d, J 11.6, 1H), 7.66 (s, 1H), 7.45 (bs, 1H), 5.55 (bs, 1H), 3.95-3.83 (m, 1H), 3.60-3.52 (m, 2H), 2.95-2.85 (m, 2H), 2.88 (s, 3H), 2.74 (s, 3H), 2.08-1.99 (m, 2H), 1.71 (s, 6H), 1.63-1.53 (m, 2H). MS (m/z): 492.49 (M+H)$^+$.

Example 16

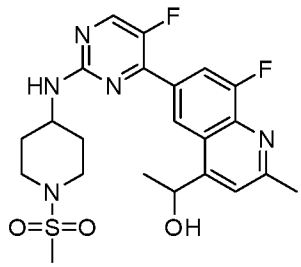
8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinoline-4-carboxamide



[277] 1-(methylsulfonyl)piperidin-4-amine (270 mg, 1.5 mmol) and sodium bicarbonate (260 mg, 2.87 mmol) were suspended in DMF (4 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 33 (400 mg, 1.25 mmol) was added to the above mixture and stirred at 100°C for 40 h. Reaction mixture diluted with water (50 ml) to obtain a solid. Solid was filtered and washed with water. Solid was purified by combi-flash using MeOH and DCM (4:96) as eluent to obtain the titled compound as a pale-yellow solid (40 mg). Yield: 7 %. M.P.: >275°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.10 (d, J 4, 1H), 8.77 (bs, 1H), 8.53 (d, J 3.2, 1H), 8.35 (s, 1H), 8.16 (d, J 12, 1H), 8.03 (s, 1H), 7.75 (d, J 4, 1H), 7.51 (d, J 7.2, 1H), 3.87 (bs, 1H), 3.60-3.51 (m, 2H), 2.94-2.85 (m, 2H), 2.88 (s, 3H), 2.08-1.98 (m, 2H), 1.65-1.52 (m, 2H). MS (m/z): 463.44 $(M+H)^+$.

Example 17

(±)-1-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)ethan-1-ol

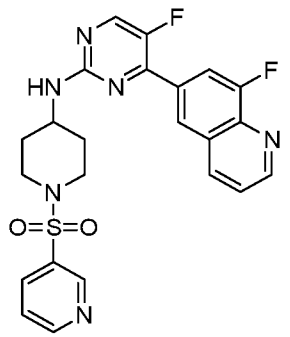


[278] 1-(methylsulfonyl)piperidin-4-amine (260 mg, 1.42 mmol) and sodium bicarbonate (230 mg, 2.74 mmol) were suspended in DMF (2.6 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 36 (400 mg, 1.19 mmol) was added to the above mixture and stirred at 100°C for 40 h. Reaction mixture diluted with water (50 ml) and extracted with MeOH:DCM (1:9) (3*30 ml). Combined organic layers were washed with water (2*50 ml) and brine (50 ml). Organic layer distilled under vacuum to obtain crude. Crude was purified by combi-flash using EtOAc and Petether (73:27) as eluent to obtain the titled compound as an off-white solid (170

mg). Yield: 30 %. M.P.: 208-210°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.62 (bs, 1H), 8.52 (d, J 3.6, 1H), 8.04 (d, J 12, 1H), 7.65 (s, 1H), 7.45 (d, J 7.6, 1H), 5.71 (d, J 3.6, 1H), 5.47-5.39 (m, 1H), 3.89 (m, 1H), 3.60-3.51 (m, 2H), 2.95-2.85 (m, 2H), 2.88 (s, 3H), 2.71 (s, 3H), 2.10-1.98 (m, 2H), 1.65-1.52 (m, 2H), 1.50 (d, J 6.4, 3H). MS (m/z): 478.51 $(M+H)^+$.

Example 18

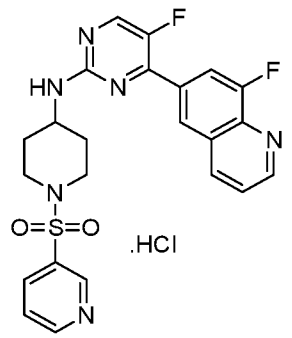
5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(pyridin-3-ylsulfonyl)piperidin-4-yl)pyrimidin-2-amine



[279] 5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(piperidin-4-yl)pyrimidin-2-amine (Intermediate 16, 200 mg, 0.58 mmol) was dissolved in DCM (4.5 ml) and added TEA (118 mg, 1.17 mmol). This mixture was stirred at rt for 30 mins and pyridine-3-sulfonyl chloride (156 mg, 0.87 mmol) was added and stirred at rt for 15 mins. After 15 mins, reaction mixture quenched with water and separated organic layer. Aqueous layer extracted with MeOH and DCM (1:9, 3*30 ml) and combined organic layers were washed with water (50 ml). Organic layer distilled to obtain crude. Crude was purified by combi-flash using MeOH and DCM (2.3:97.7) as eluent to afford the titled compound as a pale-green solid (85 mg). Yield: 30 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.60-9.20 (m, 1H), 8.94 (d, J 2, 1H), 8.91 (dd, J 4.8, 1.6, 1H), 8.61 (d, J 8.4, 1H), 8.50 (d, J 3.6, 1H), 8.46 (s, 1H), 8.19 (dd, J 4.8, 1.6, 1H), 8.11 (d, J 12, 1H), 7.75-7.68 (m, 2H), 7.45 (d, J 6.8, 1H), 3.83 (bs, 1H), 3.63-3.55 (m, 2H), 2.75-2.62 (m, 2H), 2.05-1.94 (m, 2H), 1.65-1.52 (m, 2H). MS (m/z): 483.40 $(M+H)^+$.

Example 19

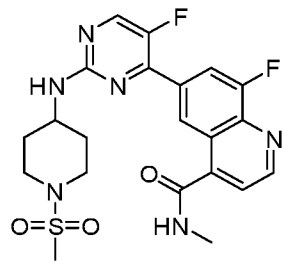
5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(pyridin-3-ylsulfonyl)piperidin-4-yl)pyrimidin-2-amine hydrochloride



[280] 5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(pyridin-3-ylsulfonyl)piperidin-4-yl)pyrimidin-2-amine (Example 18, 80 mg, 0.17 mmol) was dissolved in MeOH (1.6 ml) and Con. HCl (61 mg, 1.7 mmol) was added to obtain a clear solution. This mixture was stirred for 30 mins at 25°C. After 30 mins, MTBE (8 ml) was added to the above reaction to obtain a solid. This mixture was stirred for 1 h and filtered the solid. Solid was washed with MTBE (20 ml) and dried under vacuum to obtain the titled compound as a yellow solid (80 mg). Yield: 93 %. M.P.: 225-227°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.06 (d, J 3.2, 1H), 8.96 (d, J 2, 1H), 8.94 (d, J 4.4, 1H), 8.66 (d, J 8.4, 1H), 8.52 (d, J 3.6, 1H), 8.48 (s, 1H), 8.23 (d, J 8, 1H), 8.13 (d, J 12.4, 1H), 7.77-7.72 (m, 2H), 7.20 (bs, 1H), 3.84 (bs, 1H), 3.65-3.55 (m, 2H), 2.75-2.65 (m, 2H), 2.04-1.94 (m, 2H), 1.68-1.52 (m, 2H). MS (m/z): 483.43 $(M+H)^+$.

Example 20

8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-N-methylquinoline-4-carboxamide

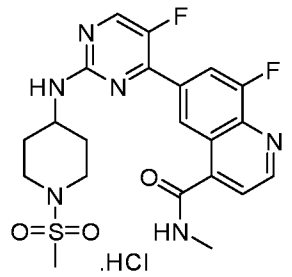


[281] 1-(methylsulfonyl)piperidin-4-amine (256 mg, 1.43 mmol) and sodium bicarbonate (231 mg, 2.75 mmol) were suspended in DMF (6.3 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 39 (400 mg, 1.2 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water and extracted with MeOH:DCM (1:9) (3*30 ml). Organic layer contains insoluble solid. Solid was filtered and dried under vacuum

to obtain the titled compound as a pale-yellow solid (210 mg). Yield: 37 %. M.P.: 276-278°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.12 (d, J 4.4, 1H), 8.89 (d, J 4.4, 1H), 8.77 (bs, 1H), 8.55 (d, J 3.2, 1H), 8.19 (d, J 12.4, 1H), 7.75 (d, J 4, 1H), 7.53 (d, J 6.8, 1H), 3.93-3.82 (m, 1H), 3.60-3.50 (m, 2H), 2.99-2.85 (m, 2H), 2.89 (s, 6H), 2.10-1.98 (m, 2H), 1.65-1.50 (m, 2H). MS (m/z): 475.49 (*M*-H)$^-$.

Example 21

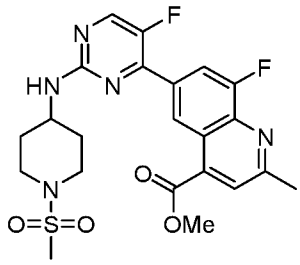
8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-N-methylquinoline-4-carboxamide hydrochloride



[282] 8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-N-methylquinoline-4-carboxamide (Example 20, 190 mg, 0.4 mmol) was dissolved in MeOH (3.8 ml) and Con. HCl (145 mg, 4 mmol) was added and stirred the heterogeneous mixture for 30 mins at 25°C. After 30 mins, MTBE (11.4 ml) was added to the above reaction mixture. This mixture was stirred for 1 h and filtered the solid. Solid was washed with MTBE (11.4 ml) and dried under vacuum to obtain the titled compound as a yellow solid (150 mg). Yield: 73 %. M.P.: 274-276°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.13 (d, J 4, 1H), 8.92 (d, J 4.8, 1H), 8.74 (bs, 1H), 8.55 (d, J 3.6, 1H), 8.19 (d, J 12, 1H), 7.76 (d, J 4, 1H), 7.54 (bs, 1H), 3.95-3.83 (m, 1H), 3.61-3.52 (m, 2H), 3.00-2.85 (m, 2H), 2.89 (s, 6H), 2.10-1.99 (m, 2H), 1.65-1.52 (m, 2H). MS (m/z): 475.54 (*M*-H-HCl)$^-$.

Example 22

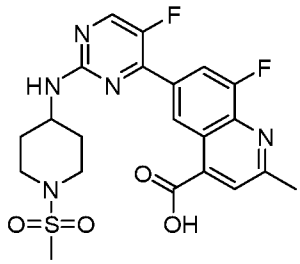
Methyl 8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinoline-4-carboxylate



[283] 1-(methylsulfonyl)piperidin-4-amine (920 mg, 5.1 mmol) and sodium bicarbonate (830 mg, 9.9 mmol) were suspended in DMF (40 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 41 (1.5 g, 4.3 mmol) was added to the above mixture and stirred at 100°C for 36 h. Reaction mixture diluted with water (300 ml) and extracted with MeOH:DCM (1:9) (3*200 ml). Combined organic layers were evaporated to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (2.4:97.6) as eluent to obtain the titled compound as a yellow solid (600 mg). Yield: 28 %. M.P.: 237-239°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.18 (bs, 1H), 8.54 (dd, J 4, 1.2, 1H), 8.16 (d, J 12, 1H), 8.04 (s, 1H), 7.48 (d, J 7.6, 1H), 4.00 (s, 3H), 3.95-3.86 (m, 1H), 3.61-3.53 (m, 2H), 2.99-2.90 (m, 2H), 2.83 (s, 3H), 2.78 (s, 3H), 2.10-1.99 (m, 2H), 1.65-1.53 (m, 2H). MS (m/z): 492.43 $(M+H)^+$.

Example 23

8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinoline-4-carboxylic acid

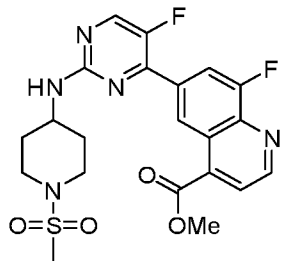


[284] Methyl 8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinoline-4-carboxylate (Example 22, 400 mg, 0.814 mmol) was suspended in a mixture of MeOH (2 ml) and THF (2 ml). To this mixture LiOH.H_2O (68.3 mg, 1.63 mmol) in water (2 ml) was added and stirred at rt for 36 h. After 36 h, reaction mixture diluted with water (20 ml) and acidified with Con HCl upto pH 4 (±0.5) to obtain a solid. Solid was filtered and washed with water (10 ml). Solid was dried under vacuum at 70°C for 8 h to obtain the titled compound as an off-white solid (330 mg). Yield: 85%. M.P.: >270°C. ^{1}H-NMR (δ ppm,

DMSO-d_6, 400 MHz): 9.14 (bs, 1H), 8.49 (d, J 3.2, 1H), 7.96 (d, J 12.4, 1H), 7.45 (s, 2H), 3.95-3.83 (m, 1H), 3.58-3.50 (m, 2H), 2.99-2.90 (m, 2H), 2.89 (s, 3H), 2.66 (s, 3H), 2.07-1.98 (m, 2H), 1.63-1.52 (m, 2H). MS (m/z): 478.41 $(M+H)^+$.

Example 24

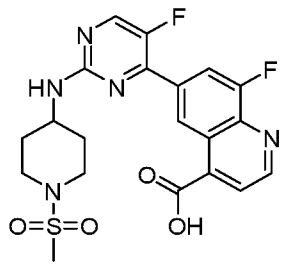
Methyl 8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinoline-4-carboxylate



[285] 1-(methylsulfonyl)piperidin-4-amine (956 mg, 5.4 mmol) and sodium bicarbonate (863 mg, 10.3 mmol) were suspended in DMF (9.6 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 43 (1.5 g, 4.5 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water (100 ml) to obtain a solid. Solid was filtered and washed with water. Solid purified by combi-flash using MeOH and DCM (1.7: 98.3) as eluent to afford the titled compound as a yellow solid (700 mg). Yield: 33 %. M.P.: 221-223°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.26 (bs, 1H), 9.21 (d, J 4.4, 1H), 8.56 (d, J 3.6, 1H), 8.22 (d, J 11.6, 1H), 8.15 (d, J 4.4, 1H), 7.51 (d, J 8, 1H), 4.01 (s, 3H), 3.95-3.86 (m, 1H), 3.61-3.53 (m, 2H), 2.99-2.85 (m, 2H), 2.89 (s, 3H), 2.10-2.00 (m, 2H), 1.65-1.52 (m, 2H). MS (m/z): 478.35 $(M+H)^+$.

Example 25

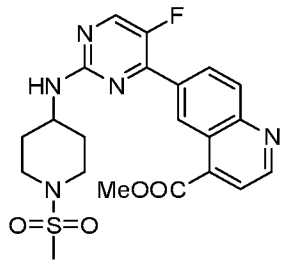
8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinoline-4-carboxylic acid



[286] Methyl 8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinoline-4-carboxylate (Example 24, 570 mg, 1.2 mmol) was suspended in a mixture of MeOH (3 ml) and THF (6 ml). To this mixture $LiOH.H_2O$ (250 mg, 6 mmol) in water (2 ml) was added and stirred at rt for 36 h. After 36 h, reaction mixture diluted with water (20 ml) and acidified with Con HCl upto pH 4 (±0.5) to obtain a solid. Solid was filtered and washed with water (10 ml). Solid was dried under vacuum at 70°C for 8 h to obtain the titled compound as an off-white solid (440 mg). Yield: 80 %. M.P.: 268-270°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 14.17 (bs, 1H), 9.31 (bs,1H), 9.17 (d, J 4.32, 1H), 8.54 (d, J 3.7, 1H), 8.18 (d, J 12, 1H), 8.11 (d, J 4.32, 1H), 7.49 (d, J 7.3, 1H), 3.95-3.83 (m, 1H), 3.60-3.52 (m, 2H), 2.95-2.82 (m, 2H), 2.88 (s, 3H), 2.08-1.98 (m, 2H), 1.65-1.52 (m, 2H). MS (m/z): 464.34 $(M+H)^+$.

Example 26

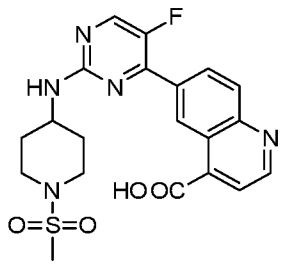
Methyl 6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinoline-4-carboxylate



[287] 1-(methylsulfonyl)piperidin-4-amine (1.2 g, 6.8 mmol) and sodium bicarbonate (1.1 g, 13 mmol) were suspended in DMF (40 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 48 (1.8 g, 5.7 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water (200 ml). Aqueous layer was extracted with ethyl acetate (2*200 ml). Organic layer was washed with water (4*200 ml) and brine (200 ml). Organic layer was distilled to obtain crude. Crude was purified by combi-flash using MeOH and DCM (1.8: 98.2) as eluent to afford the titled compound as a pale-yellow solid (400 mg). Yield: 15 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.42 (bs, 1H), 9.16 (dd, J 4.4, 1H), 8.54 (d, J 7.7, 1H), 8.43 (d, J 8.3, 1H), 8.27 (d, J 8.8, 1H), 8.05 (d, J 8.4, 1H), 7.48 (d, J 7.6, 1H), 4.01 (s, 3H), 3.96-3.88 (m, 1H), 3.61-3.54 (m, 2H), 2.99-2.90 (m, 2H), 2.89 (s, 3H) 2.10-2.00 (m, 2H), 1.66-1.54 (m, 2H). MS (m/z): 460.38 $(M+H)^+$.

Example 27

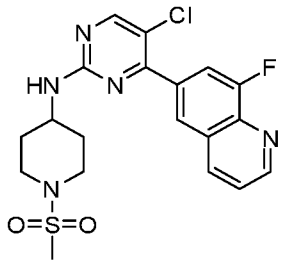
6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinoline-4-carboxylic acid



[288] Methyl 6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinoline-4-carboxylate (Example 26, 320 mg, 0.7 mmol) was suspended in a mixture of MeOH (4 ml) and THF (8 ml). To this mixture $LiOH.H_2O$ (146 mg, 3.5 mmol) in water (4ml) was added and stirred at rt for 16 h. After 16 h, reaction mixture diluted with water (20 ml) and acidified with Con HCl up to pH 2 (±0.5) to obtain a solid. Solid was filtered and washed with water (10 ml). Solid was dried under vacuum at 70°C for 8 h to obtain the titled compound as a pale-yellow solid (200 mg). Yield: 80 %. M.P.: >270°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 14.02 (bs, 1H), 9.46 (bs, 1H), 9.13 (d, J 4.4, 1H), 8.52 (d, J 3.7, 1H), 8.39 (d, J 8.6, 1H), 8.24 (d, J 8.9, 1H), 8.02 (d, J 4.4, 1H), 7.46 (d, J 7, 1H), 3.94-3.83 (m, 1H), 3.61-3.53 (m, 2H), 2.98-2.89 (m, 2H), 2.88 (s, 3H), 2.10-1.99 (m, 2H), 1.66-1.52 (m, 2H). MS (m/z): 446.42 $(M+H)^+$.

Example 28

5-chloro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine

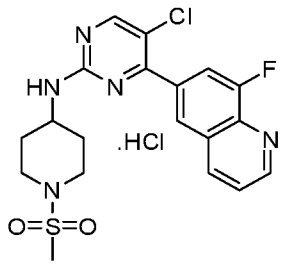


[289] 1-(methylsulfonyl)piperidin-4-amine (510 mg, 2.92 mmol) and sodium bicarbonate (460 mg, 5.5 mmol) were suspended in DMF (5.2 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 49 (1.1 g, 2.44 mmol) was added to the above mixture and stirred at 100°C

for 16 h. Reaction mixture diluted with water and extracted with MeOH:DCM (1:9) (3*70 ml). Organic layer was distilled to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (1.4:98.6) as eluent to obtain the titled compound as an off-white solid (650 mg). Yield: 45 %. M.P.: 146-148°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.05 (dd, J 4, 1.6, 1H), 8.61 (d, J 8.4, 1H), 8.52 (s, 1H), 8.29 (bs, 1H), 7.93 (d, J 11.6, 1H), 7.77 (bs, 1H), 7.73 (dd, J 8.4, 4.4, 1H), 3.95-3.86 (m, 1H), 3.58-3.50 (m, 2H), 2.93-2.87 (m, 2H), 2.86 (s, 3H), 2.04-1.95 (m, 2H), 1.65-1.52 (m, 2H). MS (m/z): 436.38 (M+H)$^+$.

Example 29

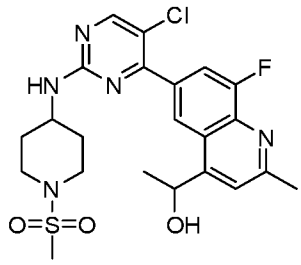
5-chloro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine hydrochloride



[290] 5-chloro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine (Example 28, 200 mg, 0.4 mmol) was dissolved in MeOH (4 ml) and Con. HCl (167 mg, 4.6 mmol) was added to obtain a clear solution. This mixture was stirred for 30 mins at 25°C. After 30 mins, MTBE (12 ml) was added to the above reaction mixture to obtain a solid. This mixture was stirred for 1 h and filtered the solid. Solid was washed with MTBE (12 ml) and dried under vacuum to obtain the titled compound as a yellow solid (160 mg). Yield: 73 %. M.P.: 215-218°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.06 (dd, J 4, 1.2, 1H), 8.62 (d, J 8.4, 1H), 8.52 (s, 1H), 8.30 (bs, 1H), 7.94 (d, J 11.6, 1H), 7.80 (bs, 1H), 7.74 (dd, J 8.4, 4.4, 1H), 3.95-3.86 (m, 1H), 3.58-3.49 (m, 2H), 2.93-2.88 (m, 2H), 2.87 (s, 3H), 2.06-1.94 (m, 2H), 1.65-1.52 (m, 2H). MS (m/z): 436.38 (M+H-HCl)$^-$.

Example 30

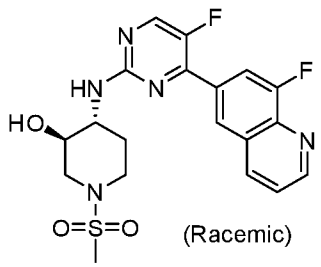
(±)-1-(6-(5-chloro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)ethan-1-ol



[291] 1-(methylsulfonyl)piperidin-4-amine (360 mg, 2.00 mmol) and sodium bicarbonate (330 mg, 3.9 mmol) were suspended in DMF (5.2 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 50 (600 mg, 1.7 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water and extracted with MeOH:DCM (1:9) (3*100 ml). Combined organic layers were distilled to obtain crude. Crude product was purified by combi-flash using EtOAc and Petether (8:2) as eluent to obtain the titled compound as an off-white solid (250 mg). Yield: 30 %. M.P.: 226-228°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.50 (s, 1H), 8.48-8.30 (m, 1H), 7.92-7.68 (m, 2H), 7.66 (s, 1H), 5.68 (s, 1H), 5.46-5.42 (m, 1H), 3.93-3.84 (m, 1H), 3.58-3.48 (m, 2H), 2.96-2.86 (m, 2H), 2.90 (s, 3H), 2.71 (s, 3H), 2.04-1.93 (m, 2H), 1.65-1.52 (m, 2H), 1.49 (d, J 6.4, 3H). MS (m/z): 494.38 (M+H)$^+$.

Example 31

(±)-4-((5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-ol

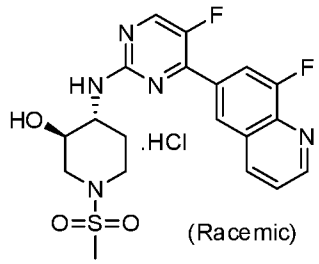


[292] (3R,4R)-4-amino-1-(methylsulfonyl)piperidin-3-ol (Racemic) (385 mg, 1.98 mmol) and sodium bicarbonate (277 mg, 3.3 mmol) were suspended in DMF (8.33 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 2 (00 mg, 1.8 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water and extracted with EtOAc (3*100 ml). Combined organic layers were distilled to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (1.7:98.3) as eluent to obtain the titled compound as an off-white solid (50 mg). Yield: 6.4 %. M.P.: 147-148°C. ^{1}H-NMR (δ ppm,

DMSO-d_6, 400 MHz): 9.04 (s, 1H), 8.64 (d, J 8, 1H), 8.54 (d, J 3.2, 1H), 8.50 (s, 1H), 8.15 (d, J 12, 1H), 7.74 (dd, J 8.4, 4, 1H), 7.37 (d, J 7.2, 1H), 5.23 (d, J 4, 1H), 3.90-3.76 (m, 1H), 3.70-3.55 (m, 2H), 3.51-3.43 (m, 1H), 2.99-2.85 (m, 1H), 2.91 (s, 3H), 2.75-2.61 (m, 1H), 2.15-2.03 (m, 1H), 1.60-1.48 (m, 1H). MS (m/z): 436.40 $(M+H)^+$.

Example 32

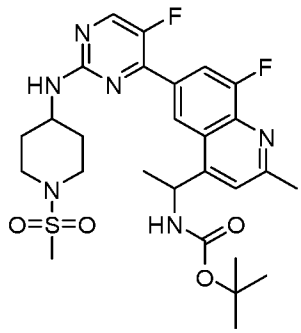
(±)-(3R,4R)-4-((5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-ol hydrochloride



[293] 4-((5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-ol (Example 31, 100 mg, 0.23 mmol) was dissolved in MeOH (2 ml) and Con. HCl (84 mg, 2.3 mmol) was added to obtain a clear solution. After few minutes precipitate formed in the reaction mixture. This heterogeneous mixture was stirred at 25°C for 30 mins. After 30 mins, MTBE (6 ml) was added to the above reaction mixture. This mixture was stirred for 1 h and filtered the solid. Solid was washed with MTBE (6 ml) and dried under vacuum to obtain the titled compound as a yellow solid (70 mg). Yield: 64 %. M.P.: 218-220°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.06 (dd, J 4.4, 1.6, 1H), 8.66 (d, J 8.4, 1H), 8.55 (d, J 3.6, 1H), 8.52 (s, 1H), 8.17 (d, J 12, 1H), 7.75 (dd, J 8.4, 4.4, 1H), 7.38 (bs, 1H), 5.52 (bs, 1H), 3.90-3.78 (m, 1H), 3.70-3.58 (m, 2H), 3.54-3.48 (m, 1H), 2.99-2.89 (m, 4H), 2.75-2.65 (m, 1H), 2.15-2.05 (m, 1H), 1.60-1.45 (m, 1H). MS (m/z): 436.35 $(M+H\text{-}HCl)^+$.

Example 33

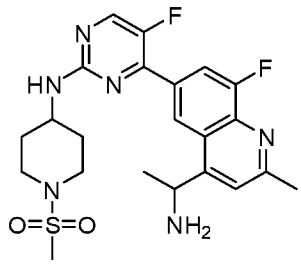
(±)-*Tert*-butyl (1-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)ethyl)carbamate



[294] 1-(methylsulfonyl)piperidin-4-amine (590 mg, 3.31 mmol) and sodium bicarbonate (533 mg, 6.35 mmol) were suspended in DMF (5.9 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 54 (1.2 g, 2.76 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water and extracted with MeOH:DCM (1:9) (3*70 ml). Organic layer was distilled to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (1.4:98.6) as eluent to obtain the titled compound as a white solid (650 mg). Yield: 41 %. M.P.: 173-175°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.57 (bs, 1H), 8.54 (d, J 3.6, 1H), 8.06 (d, J 11.6, 1H), 7.80 (d, J 7.2, 1H), 7.53 (s, 1H), 7.50 (d, J 5.6, 1H), 5.39-5.36 (m, 1H), 3.96-3.82 (m, 1H), 3.61-3.52 (m, 2H), 2.98-2.89 (m, 2H), 2.88 (s, 3H), 2.71 (s, 3H), 2.10-2.00 (m, 2H), 1.65-1.52 (m, 2H), 1.46 (d, J 6.8, 3H), 1.36 (s, 9H). MS (m/z): 577.40 $(M+H)^+$.

Example 34

(±)-4-(4-(1-aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine

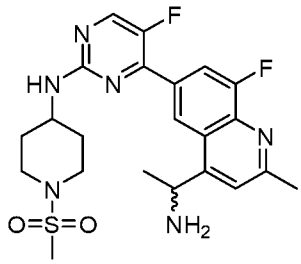


[295] (±)-*Tert*-butyl (1-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)ethyl)carbamate (Example: 33, 400 mg, 0.69 mmol) was dissolved in DCM (10 ml). To this mixture Con HCl (380 mg, 10 mmol) was added and stirred at rt for 3 h. After 3 h, DCM was evaporated to obtain a residue. Residue was

dissolved in water (40 ml) and extracted with DCM (3*20 ml). Aqueous layer pH adjusted to 8 using aq. Sodium bicarbonate solution. Aqueous layer extracted with MeOH and DCM (1:9) (3*70 ml). Combined organic layers were distilled to obtain a crude solid. Diethyl ether and Petether (1:1) mixture (40 ml) was added to the solid and stirred for 30 mins. Solid was filtered and washed with a mixture of Diethylether and pet-ether (1:1) (40 ml). Solid was dried under vacuum to obtain the titled compound as a white solid (230 mg). Yield: 70 %. M.P.: 182-184°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.65 (bs, 1H), 8.53 (d, J 4, 1H), 8.04 (d, J 12, 1H), 7.79 (s, 1H), 7.47 (d, J 7.6, 1H), 4.81-4.70 (m, 1H), 3.96-3.82 (m, 1H), 3.60-3.52 (m, 2H), 2.97-2.90 (m, 2H), 2.89 (s, 3H), 2.71 (s, 3H), 2.26 (bs, 2H, NH_2), 2.10-2.00 (m, 2H), 1.66-1.52 (m, 2H), 1.41 (d, J 6.4, 3H). MS (m/z): 477.44 (M+H)$^+$.

Example 35

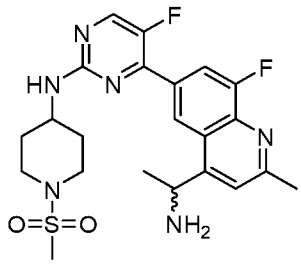
(-)-4-(4-(1-aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine



[296] Using the preparative methods reported in the General Procedure 3, the titled compound was resolved as a pure enantiomer from the racemic mixture of (±)-4-(4-(1-aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine (Example 34). Chiral HPLC Purity: 99.80, Retention time: 5.28 min. M.P.: 177-180°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.65 (bs, 1H), 8.53 (d, J 4, 1H), 8.04 (d, J 11.6, 1H), 7.79 (s, 1H), 7.46 (d, J 7.6, 1H), 4.80-4.74 (m, 1H), 3.96-3.85 (m, 1H), 3.60-3.52 (m, 2H), 2.97-2.91 (m, 2H), 2.89 (s, 3H), 2.71 (s, 3H), 2.17 (bs, 2H, NH_2), 2.09-2.00 (m, 2H), 1.65-1.54 (m, 2H), 1.41 (d, J 6.8, 3H). MS (m/z): 477.36 (M+H)$^+$. $[\alpha]_D^{25}$: -30.80° [MeOH: CHLOROFORM (1:1); c 1.0]..

Example 36

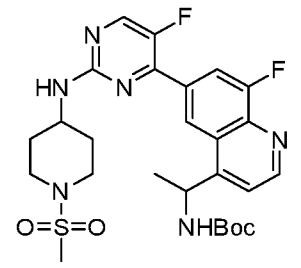
(+)-4-(4-(1-aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine



[297] Using the preparative methods reported in the General Procedure 3, the titled compound was resolved as a pure enantiomer from the racemic mixture of (±)-4-(4-(1-aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine (Example 34). Chiral HPLC Purity: 99.20, Retention time: 9.08 min. M.P.: 190-192°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.65 (bs, 1H), 8.53 (d, J 4, 1H), 8.04 (d, J 12, 1H), 7.79 (s, 1H), 7.47 (d, J 7.6, 1H), 4.81-4.74 (m, 1H), 3.95-3.85 (m, 1H), 3.61-3.53 (m, 2H), 2.97-2.90 (m, 2H), 2.89 (s, 3H), 2.71 (s, 3H), 2.14 (bs, 2H, NH_2), 2.09-2.00 (m, 2H), 1.66-1.55 (m, 2H), 1.41 (d, J 6.8, 3H). MS (m/z): 477.37 (M+H)$^+$. $[\alpha]_D^{25}$: +26.86° [MeOH: CHLOROFORM (1:1); *c* 1.0]. .

Example 37

(±)-*Tert*-butyl (1-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-4-yl)ethyl)carbamate

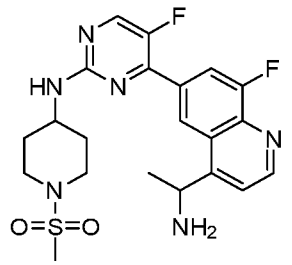


[298] 1-(methylsulfonyl)piperidin-4-amine (290 mg, 1.6 mmol) and sodium bicarbonate (260 mg, 3.1 mmol) were suspended in DMF (5.7 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 60 (570 mg, 1.4 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water and extracted with MeOH:DCM (1:9) (3*70 ml). Combined organic layers were distilled to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (1.8:98.2) as eluent to obtain the titled compound as an off-white solid (130 mg). Yield: 17 %. M.P.: 165-167°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.03 (d, J 3.6, 1H), 8.63 (bs, 1H), 8.56 (d, J 3.6, 1H), 8.12 (d, J 7.6, 1H), 7.87 (d, J 7.2, 1H), 7.66 (d,

J 4.4, 1H), 7.51 (bs, 1H), 5.49-5.40 (m, 1H), 3.96-3.88(m, 1H), 3.61-3.52 (m, 2H), 2.97-2.89 (m, 2H), 2.88 (s, 3H), 2.20-2.10 (m, 2H), 1.65-1.53 (m, 2H), 1.46 (d, J 6.8, 3H), 1.36 (s, 9H). MS (m/z): 563.25 $(M+H)^+$.

Example 38

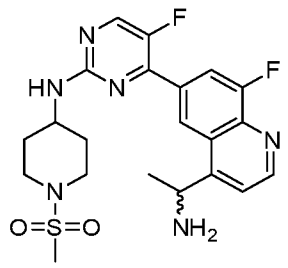
(±)-4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine



[299] (±)-*Tert*-butyl (1-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-4-yl)ethyl)carbamate (Example: 37, 100 mg, 0.18 mmol) was dissolved in DCM (10 ml). To this mixture Con HCl (970 mg, 27 mmol) was added and stirred at rt for 3 h. After 3 h, DCM was evaporated to obtain a residue. Residue was dissolved in water (30 ml) and extracted with DCM (3*20 ml). Aqueous layer pH adjusted to 8 using aq. Sodium bicarbonate solution. Aqueous layer extracted with MeOH and DCM (1:9) (6*40 ml). Combined organic layers were distilled to obtain a crude solid. Diethyl ether and Petether (1:1) mixture (10 ml) was added to the solid and stirred for 30 mins. Solid was filtered and washed with a mixture of Diethyl ether and Petether (1:1) (10 ml). Solid was dried under vacuum to obtain the titled compound as an off-white solid (60 mg). Yield: 70 %. M.P.: 197-199°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.00 (d, J 4.4, 1H), 8.72 (bs, 1H), 8.54 (d, J 4, 1H), 8.09 (d, J 12, 1H), 7.90 (d, J 4.4, 1H), 7.50 (d, J 7.6, 1H), 4.88-4.80 (m, 1H), 3.95-3.86 (m, 1H), 3.61-3.52 (m, 2H), 2.96-2.90 (m, 2H), 2.89 (s, 3H), 2.16 (bs, 2H, NH_2), 2.10-2.00 (m, 2H), 1.65-1.55 (m, 2H), 1.42 (d, J 6.8, 3H). MS (m/z): 463.33 $(M+H)^+$.

Example 39

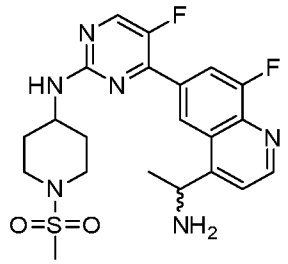
(-)-4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine



[300] Using the preparative methods reported in the General Procedure 3, the titled compound was resolved as a pure enantiomer from the racemic mixture of (±)-4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine (Example 38).Chiral HPLC Purity: 99.63, Retention time: 4.43 min. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.01 (d, J 4.4, 1H), 8.72 (bs, 1H), 8.54 (d, J 3.6, 1H), 8.09 (d, J 12, 1H), 7.90 (d, J 4.4, 1H), 7.48 (d, J 7.6, 1H), 4.86-4.79 (m, 1H), 3.95-3.85 (m, 1H), 3.61-3.53 (m, 2H), 2.96-2.90 (m, 2H), 2.89 (s, 3H), 2.17 (s, 2H, NH_2), 2.10-1.99 (m, 2H), 1.68-1.55 (m, 2H), 1.42 (d, J 6.8, 3H). MS (m/z): 462.85 $(M+H)^+$. $[\alpha]_D^{25}$: -27.39° [MeOH: CHLOROFORM (1:1); *c* 1.0]..

Example 40

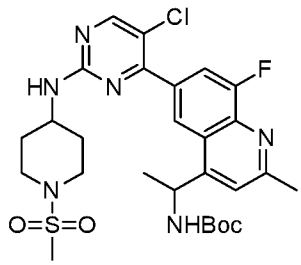
(+)-4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine



[301] Using the preparative methods reported in the General Procedure 3, the titled compound was resolved as a pure enantiomer from the racemic mixture of (±)-4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine (Example 38).Chiral HPLC Purity: 99.75, Retention time: 8.39 min. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.01 (d, J 4.4, 1H), 8.72 (bs, 1H), 8.54 (d, J 4, 1H), 8.09 (d, J 11.6, 1H), 7.90 (d, J 4.4, 1H), 7.48 (d, J 7.6, 1H), 4.89-4.80 (m, 1H), 3.96-3.85 (m, 1H), 3.61-3.52 (m, 2H), 2.97-2.90 (m, 2H), 2.89 (s, 3H), 2.16 (s, 2H, NH_2), 2.10-2.00 (m, 2H), 1.68-1.55 (m, 2H), 1.42 (d, J 6.8, 3H). MS (m/z): 462.83 $(M+H)^+$. $[\alpha]_D^{25}$: +27.55° [MeOH: CHLOROFORM (1:1); *c* 1.0]..

Example 41

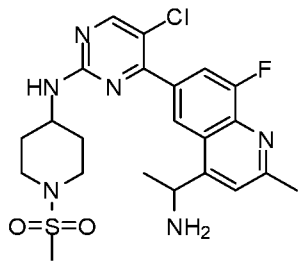
(±)-*Tert*-butyl (1-(6-(5-chloro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)ethyl)carbamate



[302] 1-(methylsulfonyl)piperidin-4-amine (521 mg, 2.92 mmol) and sodium bicarbonate (471 mg, 5.61 mmol) were suspended in DMF (5.2 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 61 (1.1 g, 2.44 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water and extracted with MeOH:DCM (1:9) (3*70 ml). Organic layer was distilled to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (1.4:98.6) as eluent to obtain the titled compound as an off-white solid (650 mg). Yield: 45 %. M.P.: 146-148°C. ^{1}H-NMR (δ ppm, DMSO-*d*$_6$, 400 MHz): 8.50 (s, 1H), 8.44-8.26 (m, 1H), 7.99-7.60 (m, 3H), 7.51 (s, 1H), 5.40-5.29 (m, 1H), 3.95-3.85 (m, 1H), 3.59-3.50 (m, 2H), 2.93-2.80 (m, 5H), 2.71 (s, 3H), 2.08-1.95 (m, 2H), 1.63-1.51 (m, 2H), 1.49-1.40 (m, 3H), 1.34 (s, 9H). MS (m/z): 593.38 (*M*+H)$^+$.

Example 42

(±)-4-(4-(1-aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-chloro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine

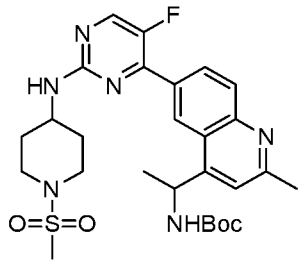


[303] (±)-*Tert*-butyl (1-(6-(5-chloro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)ethyl)carbamate (Example: 41, 400 mg, 0.67 mmol) was dissolved in DCM (10 ml). To this mixture Con HCl (370 mg, 10 mmol) was added and stirred

at rt for 3 h. After 3 h, DCM was evaporated to obtain a residue. Residue was dissolved in water (40 ml) and extracted with DCM (4*20 ml). Aqueous layer pH adjusted to 8 using aq. Sodium bicarbonate solution. Aqueous layer extracted with MeOH and DCM (1:9) (3*70 ml). Combined organic layers were distilled to obtain a crude solid. Diethyl ether and Petether (1:1) mixture (40 ml) was added to the solid and stirred for 30 mins. Solid was filtered and washed with a mixture of Diethyl ether and Petether (1:1) (40 ml). Solid was dried under vacuum to obtain the titled compound as a white solid (220 mg). Yield: 70 %. M.P.: 206-208°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.52-8.32 (m, 2H), 7.92-7.65 (m, 3H), 4.78-4.72 (m, 1H), 3.95-3.83 (m, 1H), 3.57-3.47 (m, 2H), 2.92-2.80 (m, 5H), 2.70 (s, 3H), 2.14 (s, 2H, NH_2), 2.05-1.93 (m, 2H), 1.64-1.50 (m, 2H), 1.39 (d, J 6.4, 3H). MS (m/z): 493.43 $(M+H)^+$.

Example 43

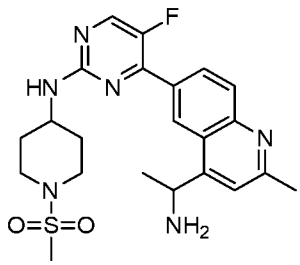
(±)-*Tert*-butyl (1-(6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)ethyl)carbamate



[304] 1-(methylsulfonyl)piperidin-4-amine (308 mg, 1.73 mmol) and sodium bicarbonate (278 mg, 3.31 mmol) were suspended in DMF (4.5 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 68 (600 mg, 1.44 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water and extracted with EtOAc (2*200 ml). Combined organic layers were distilled to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (1.4:98.6) as eluent to obtain the titled compound as a white solid (180 mg). Yield: 22.2 %. M.P.: 213-215°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.73 (bs, 1H), 8.51 (d, J 4, 1H), 8.26 (d, J 9.2, 1H), 8.07 (d, J 8.4, 1H), 7.78 (d, J 7.6, 1H), 7.49-7.42 (m, 2H), 5.49-5.40 (m, 1H), 3.96-3.88 (m, 1H), 3.60-3.52 (m, 2H), 2.97-2.89 (m, 2H), 2.88 (s, 3H), 2.67 (s, 3H), 2.10-2.00 (m, 2H), 1.65-1.52 (m, 2H), 1.45 (d, J 6.8, 3H), 1.36 (s, 9H). MS (m/z): 559.30 $(M+H)^+$.

Example 44

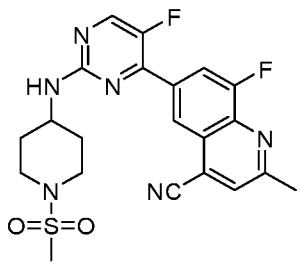
(±)-4-(4-(1-aminoethyl)-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine



[305] (±)-*Tert*-butyl (1-(6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)ethyl)carbamate (Example: 43, 150 mg, 0.27 mmol) was dissolved in DCM (10 ml). To this mixture Con HCl (147 mg, 4.03 mmol) was added and stirred at rt for 3 h. After 3 h, DCM was evaporated to obtain a residue. Residue was dissolved in water (40 ml) and extracted with DCM (3*20 ml). Aqueous layer pH adjusted to 8 using aq. Sodium bicarbonate solution. Aqueous layer extracted with MeOH and DCM (1:9) mixture (3*70 ml). Combined organic layers were distilled to obtain a crude solid. Diethyl ether and Petether (1:1) mixture (20 ml) was added to the solid and stirred for 30 mins. Solid was filtered and washed with a mixture of Diethyl ether and Petether (1:1) (10 ml). Solid was dried under vacuum to obtain the titled compound as an off-white solid (80 mg). Yield: 65 %. M.P.: 194-196°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.81 (bs, 1H), 8.50 (d, J 4, 1H), 8.25 (d, J 8.4, 1H), 8.05 (d, J 8.8, 1H), 7.68 (s, 1H), 7.43 (d, J 7.6, 1H), 4.85-4.77 (m, 1H), 3.95-3.85 (m, 1H), 3.61-3.52 (m, 2H), 2.94-2.85 (m, 2H), 2.89 (s, 3H), 2.68 (s, 3H), 2.15 (bs, 2H, NH_2), 2.10-2.00 (m, 2H), 1.65-1.55 (m, 2H), 1.41 (d, J 6.4, 3H). MS (m/z): 459.38 $(M+H)^+$.

Example 45

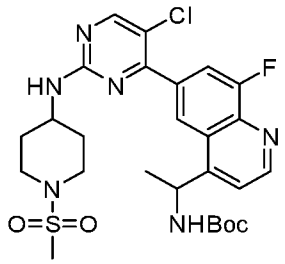
8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinoline-4-carbonitrile



[306] 1-(methylsulfonyl)piperidin-4-amine (777 mg, 4.36 mmol) and sodium bicarbonate (702 mg, 8.35 mmol) were suspended in DMF (7.8 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 73 (1.15 g, 3.63 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water and extracted with DCM and MeOH (9:1) mixture (3*30 ml). Combined organic layers were distilled to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (1:99) as eluent to obtain the titled compound as a yellow solid (420 mg). Yield: 25 %. M.P.: 239-241°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.60-8.48 (m, 2H), 8.27 (d, J 4.4, 1H), 8.26-8.20 (m, 1H), 7.57 (d, J 7.6, 1H), 3.95-3.85 (m, 1H), 3.62-3.54 (m, 2H), 2.99-2.90 (m, 2H), 2.89 (s, 3H), 2.78 (s, 3H), 2.10-2.00 (m, 2H), 1.65-1.54 (m, 2H). MS (m/z): 459.38 (M+H).

Example 46

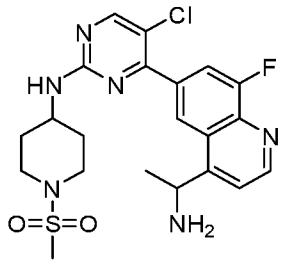
(±)-*Tert*-butyl (1-(6-(5-chloro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate



[307] 1-(methylsulfonyl)piperidin-4-amine (587 mg, 3.29 mmol) and sodium bicarbonate (530 mg, 6.31 mmol) were suspended in DMF (12.36 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 69 (1.2 g, 2.74 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water and extracted with EtOAc (2*200 ml). Combined organic layers were washed with water (100 ml) and brine (2*200 ml). Organic layer distilled to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (1:99) as eluent to obtain the titled compound as an Off-White solid (570 mg). Yield: 36 %. M.P.: 197-199°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.01 (d, J 4.4, 1H), 8.52 (s, 1H), 8.43-8.38 (m, 1H), 7.92 (bs, 1H), 7.84 (d, J 7.2, 1H), 7.74-7.68 (m, 1H), 7.64 (d, J 4.4, 1H), 5.43-5.35 (m, 1H), 3.94-3.86 (m, 1H), 3.60-3.50 (m, 2H), 2.93-2.80 (m, 5H), 2.10-1.95 (m, 2H), 1.65-1.55 (m, 2H), 1.45 (d, J 6.8, 3H), 1.34 (s, 9H). MS (m/z): 579.38 (M+H); calculated for [$C_{26}H_{32}ClFN_6O_4S$+H]: 579.19. HPLC Purity: 99.39%.

Example 47

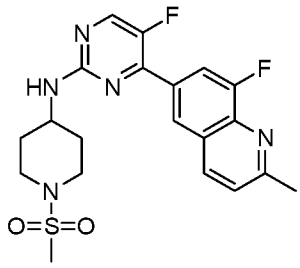
(±)-4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-5-chloro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine



[308] (±)-*Tert*-butyl (1-(6-(5-chloro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate (Example:46, 500 mg, 0.86 mmol) was dissolved in DCM (10 ml). To this mixture Con HCl (472 mg, 13 mmol) was added and stirred at rt for 30 min. After 30 mins, DCM was evaporated to obtain a residue. Residue was dissolved in water (50 ml) and extracted with DCM (5*25 ml). Aqueous layer pH adjusted to 8 using aq. Sodium bicarbonate solution. Aqueous layer extracted with MeOH and DCM (1:9) (3*100 ml). Combined organic layers were distilled to obtain a crude solid. Diethyl ether and Petether (1:1) mixture (20 ml) was added to the solid and stirred for 30 mins. Solid was filtered and washed with a mixture of Diethyl ether and Petether (1:1) (10 ml). Solid was dried under vacuum to obtain the titled compound as an off-white solid (300 mg). Yield: 72 %. M.P.: 201-202°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.00 (d, J 4.4, 1H), 8.56-8.42 (m, 2H), 7.95-7.85 (m, 2H), 7.73 (bs, 1H), 4.85-4.75 (m, 1H), 3.95-3.85 (m, 1H), 3.60-3.50 (m, 2H), 2.91-2.82 (m, 5H), 2.16 (s, 2H, NH_2), 2.05-1.94 (m, 2H), 1.65-1.55 (m, 2H), 1.41 (d, J 6.4, 3H). MS (m/z): 479.48 $(M+H)^+$.

Example 48

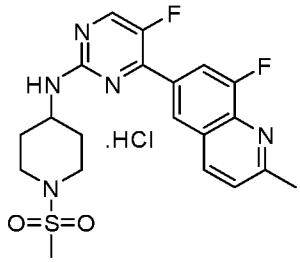
5-fluoro-4-(8-fluoro-2-methylquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine



[309] 1-(methylsulfonyl)piperidin-4-amine (367 mg, 2.06 mmol) and sodium bicarbonate (331 mg, 3.94 mmol) were suspended in DMF (5 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 76 (500 mg, 1.71 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water and extracted with EtOAc (3*100 ml). Combined organic layers were distilled to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (1:99) as eluent to obtain the titled compound as an Off-White solid (270 mg). Yield: 36 %. M.P.: 226-228°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.53 (d, J 4, 1H), 8.50 (d, J 8.8, 1H), 8.43 (s, 1H), 8.10 (d, J 12, 1H), 7.61 (d, J 8.8, 1H), 7.46 (d, J 7.6, 1H), 3.96-3.88 (m, 1H), 3.60-3.52 (m, 2H), 2.99-2.90 (m, 2H), 2.89 (s, 3H), 2.73 (s, 3H), 2.07-1.98 (m, 2H), 1.65-1.55 (m, 2H). MS (m/z): 434.41 $(M+H)^+$.

Example 49

5-fluoro-4-(8-fluoro-2-methylquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine hydrochloride

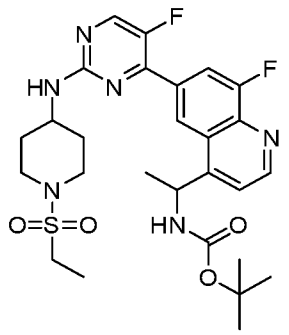


[310] 5-fluoro-4-(8-fluoro-2-methylquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine (Example 48, 190 mg, 0.4 mmol) was suspended in MeOH (3.8 ml) and Con. HCl (145 mg, 4 mmol) was added to obtain a clear solution. This mixture stirred for 30 mins at 25°C. After 30 mins, MTBE (12 ml) was added to the above reaction mixture to obtain a solid. This mixture was stirred for 1 h and filtered the solid. Solid was washed with MTBE (6 ml) and dried under vacuum to obtain the titled compound as a yellow solid (190 mg). Yield: 87 %. M.P.: 203-205°C.^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.56 (s, 1H), 8.54 (d, J 3.6,

1H), 8.46 (s, 1H), 8.12 (d, J 12, 1H), 7.65 (d, J 8.4, 1H), 7.46 (bs, NH), 3.98-3.88 (m, 1H), 3.60-3.52 (m, 2H), 2.98-2.90 (m, 2H), 2.89 (s, 3H), 2.75 (s, 3H), 2.07-1.96 (m, 2H), 1.65-1.53 (m, 2H). MS (m/z): 434.42 $(M$+H-HCl$)^+$.

Example 50

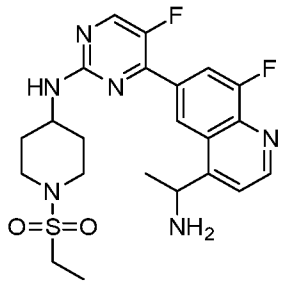
(±)-*Tert*-butyl (1-(6-(2-((1-(ethylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate



[311] Intermediate 78 (540 mg, 2.8 mmol) and sodium bicarbonate (390 mg, 4.6 mmol) were suspended in DMF (5.4 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 60 (850 mg, 2 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water and extracted with MeOH and DCM mixture (1:9) (3*50 ml). Combined organic layers were distilled to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (1.3:98.7) as eluent to obtain the titled compound as a white solid (500 mg). Yield: 43 %. M.P.: 200-202°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.03 (d, J 4.4, 1H), 8.64 (bs, 1H), 8.55 (d, J 3.6, 1H), 8.11 (d, J 11.6, 1H), 7.87 (d, J 7.2, 1H), 7.66 (d, J 4.4, 1H), 7.52 (d, J 6.4, 1H), 5.48-5.39 (m, 1H), 3.99-3.89 (m, 1H), 3.67-3.58 (m, 2H), 3.07 (q, J 7.6, 2H), 3.04-2.96 (m, 2H), 2.10-2.00 (m, 2H), 1.61-1.50 (m, 2H), 1.46 (d, J 7, 3H), 1.36 (s, 9H), 1.23 (t, J 7.6, 3H). MS (m/z): 577.46 $(M$+H$)^+$.

Example 51

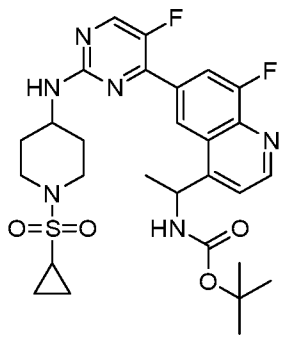
(±)-4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-N-(1-(ethylsulfonyl)piperidin-4-yl)-5-fluoropyrimidin-2-amine



[312] (±)-*Tert*-butyl (1-(6-(2-((1-(ethylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate (Example:50, 400 mg, 0.69 mmol) was dissolved in DCM (10 ml). To this mixture Con HCl (380 mg, 10.40 mmol) was added and stirred at rt for 30 min. After 30 mins, DCM was evaporated to obtain a residue. Residue was dissolved in water (30 ml) and extracted with DCM (3*30 ml). Aqueous layer pH adjusted to 8 using aq. Sodium bicarbonate solution. Aqueous layer extracted with MeOH and DCM mixture (1:9) (3*70 ml). Combined organic layers were distilled to obtain a crude solid. Diethyl ether (20 ml) was added to the solid and stirred for 30 mins. Solid was filtered and washed with Diethyl ether (20 ml). Solid was dried under vacuum to obtain the titled compound as an off-white solid (200 mg). Yield: 60 %. M.P.: 160-162°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.00 (d, J 4.4, 1H), 8.71 (bs, 1H), 8.54 (d, J 3.6, 1H), 8.09 (d, J 11.6, 1H), 7.90 (d, J 4.4, 1H), 7.48 (d, J 7.6, 1H), 4.89-4.80 (m, 1H), 3.97-3.88 (m, 1H), 3.66-3.58 (m, 2H), 3.08 (q, J 7.6, 2H), 3.06-2.96 (m, 2H), 2.18 (s, 2H, NH_2), 2.07-1.98 (m, 2H), 1.62-1.51 (m, 2H), 1.42 (d, J 6.8, 3H), 1.23 (t, J 7.6, 3H). MS (m/z): 477.53 $(M+H)^+$.

Example 52

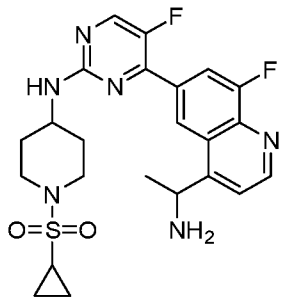
(±)-*Tert*-butyl (1-(6-(2-((1-(cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate



[313] Intermediate 80 (580 mg, 2.8 mmol) and sodium bicarbonate (390 mg, 4.6 mmol) were suspended in DMF (5.8 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 60 (850 mg, 2 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water and extracted with MeOH and DCM mixture (1:9) (3*50 ml). Combined organic layers were distilled to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (1.4:98.6) as eluent to obtain the titled compound as a white solid (400 mg). Yield: 33 %. M.P.: 221-223°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.02 (d, J 4.4, 1H), 8.65 (bs, 1H), 8.55 (d, J 3.6, 1H), 8.11 (d, J 11.6, 1H), 7.85 (d, J 7.2, 1H), 7.66 (d, J 4.4, 1H), 7.50 (d, J 6.8, 1H), 5.50-5.38 (m,1 H), 4.00-3.89 (m, 1H), 3.69-3.59 (m, 2H), 3.06-2.98 (m, 2H), 2.62-2.55 (m, 1H), 2.10-2.00 (m, 2H), 1.68-1.55 (m, 2H), 1.47 (d, J 6.8, 3H), 1.36 (s, 9H), 1.05-0.90 (m, 4H). MS (m/z): 589.37 $(M+H)^+$.

Example 53

(±)-4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-N-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-fluoropyrimidin-2-amine

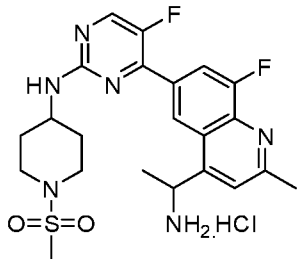


[314] (±)-*Tert*-butyl (1-(6-(2-((1-(cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate (Example: 52, 350 mg, 0.59 mmol) was dissolved in DCM (10 ml). To this mixture Con HCl (330 mg, 8.91 mmol) was added and stirred at rt for 30 min. After 30 mins, DCM was evaporated to obtain a residue. Residue was dissolved in water (30 ml) and extracted with DCM (3*30 ml). Aqueous layer pH adjusted to 8 using aq. Sodium bicarbonate solution. Aqueous layer extracted with MeOH and DCM mixture (1:9) (3*70 ml). Combined organic layers were distilled to obtain a crude solid. Diethyl ether (20 ml) was added to the solid and stirred for 30 mins. Solid was filtered and washed with Diethyl ether (20 ml). Solid was dried under vacuum to obtain the titled compound as an off-white solid (170 mg). Yield: 58 %. M.P.: 197-199°C.^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.01 (d, J 4.4, 1H), 8.72 (bs, 1H), 8.54 (d, J 3.6, 1H), 8.09 (d, J 11.6, 1H), 7.90 (d,

J 4.4, 1H), 7.48 (d, J 7.6, 1H), 4.89-4.80 (m, 1H), 3.97-3.88 (m, 1H), 3.70-3.60 (m, 2H), 3.10-2.98 (m, 2H), 2.63-2.55 (m, 1H), 2.20 (s, 2H, NH_2), 2.10-2.00 (m, 2H), 1.69-1.58 (m, 2H), 1.42 (d, J 6.4, 3H), 1.05-0.90 (m, 4H). MS (m/z): 489.47 $(M+H)^+$.

Example 54

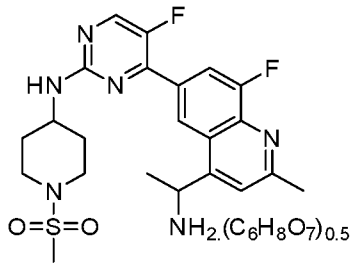
(±)-4-(4-(1-aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine hydrochloride



[315] (±)-4-(4-(1-Aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine (Example 34, 500 mg, 1.05 mmol) was suspended in MeOH (7 ml) and Con. HCl (383 mg, 10.5 mmol) was added by dissolving in MeOH (3 ml). Reaction mixture became clear solution after addition of Con HCl and stirred this solution for 30 mins at 25°C. After 30 mins, MTBE (11.4 ml) was added to the reaction mixture. This mixture was stirred for 1 h. MTBE was distilled out to obtain a residue. Residue was co-distilled with toluene (10 ml) to obtain a gummy solid. To this gummy Solid MTBE (30 ml) was added and stirred for 30 mins. MTBE was distilled out and n-Heptane (30 ml) was added and co-distilled under vacuum to obtain a solid. To this solid MTBE (30 ml) was added and stirred for 30 mins. Filtered the solid and dried under vacuum to obtain the titled compound as a brown solid (360 mg). Yield: 65 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.08 (bs, 3H), 8.57 (d, J 3.6, 1H), 8.53 (bs, 1H), 8.11 (d, J 11.6, 1H), 7.94 (s, 1H), 7.50 (bs, 1H), 5.20-5.10 (m, 1H), 3.98-3.88 (m, 1H), 3.60-3.51 (m, 2H), 3.00-2.91 (m, 2H), 2.90 (s, 3H), 2.75 (s, 3H), 2.09-1.99 (m, 2H), 1.67 (d, J 6.8, 3H), 1.63-1.52 (m, 2H). MS (m/z): 477.44 $(M+H-HCl)^+$.

Example 55

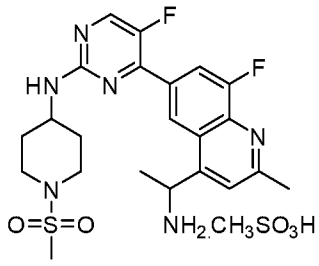
(±)4-(4-(1-aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine hemicitrate



[316] (±)-4-(4-(1-aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine (Example 34, 200 mg, 0.42 mmol) was suspended in MeOH (4 ml). Citric acid (81 mg, 0.42 mmol) dissolved in MeOH (1 ml) and added to the above suspension drop-wise. At this stage no clear solution observed and stirred the suspension at rt for 30 mins. MTBE (12 ml) was added to reaction mass and stirred for 60 mins to obtain more solid. Filtered the solid, washed with MTBE (10 ml) and dried under vacuum to obtain the titled compound as an off-white solid (190 mg). Yield: 78%. M.P.: ^{1}H-NMR (δ ppm, CD_3OD, 400 MHz): 8.62 (s, 1H), 8.37 (d, J 4, 1H), 8.19 (dd, J 12, 1.2, 1H), 7.68 (s, 1H), 5.29-5.20 (m, 1H), 4.03-3.95 (m, 1H), 3.76-3.69 (m, 2H), 3.04-2.94 (m, 2H), 2.87 (s, 3H), 2.81 (s, 3H), 2.76 (d, J 15.2, 1H, Citrate), 2.71 (d, J 15.2, 1H, Citrate), 2.21-2.12 (m, 2H), 1.71 (d, J 6.8, 3H), 1.78-1.65 (m, 2H). MS (m/z): 477.0 $[M+H-(C_6H_8O_7)_{0.5}]^+$.

Example 56

(±)-4-(4-(1-aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine methanesulfonate

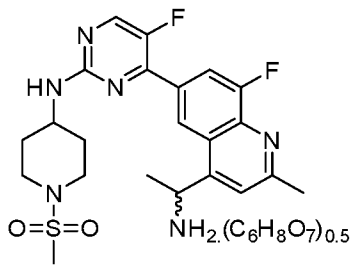


[317] (±)-4-(4-(1-aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine (Example34, 200 mg, 0.42 mmol) was suspended in MeOH (4 ml). Methanesulfonic acid (44.4 mg, 0.46 mmol) dissolved in MeOH (1 ml) and added to the above suspension drop-wise to obtain a clear solution. Reaction mixture stirred at rt for 30 mins. After 30 mins, MTBE (30 ml) was added to reaction mixture and stirred for 60 mins. Reaction mixture distilled under vacuum to obtain a residue. Residue was co-

distilled with toluene (10 ml) to obtain a gummy solid. MTBE (10 ml) was added to gummy solid and stirred for 30 mins to obtain a free solid. Solid was filtered and washed with MTBE (10 ml). Solid was dried under vacuum to obtain titled compound as a yellow solid (190 mg). Yield: 82%. M.P.: 192-195°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.64 (bs, 3H), 8.57 (s, 1H), 8.52 (s, 1H), 8.12 (d, J 11.6, 1H), 7.76 (s, 1H), 7.49 (bs, 1H), 5.35-5.24 (m, 1H), 3.98-3.85 (m, 1H), 3.62-3.52 (m, 2H), 3.00-2.85 (m, 5H), 2.77 (s, 3H, observed for CH_3SO_3H), 2.36 (s, 3H), 2.10-1.96 (m, 2H), 1.64 (d, J 6.4, 3H), 1.70-1.55 (m, 2H). MS (m/z): 477.0 (M+H-CH_3SO_3H)$^+$.

Example 57

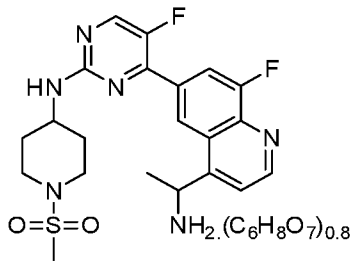
(-)-4-(4-(1-aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine hemicitrate



[318] (-)-4-(4-(1-aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine (Example 35, 3 g, 6.30 mmol) was suspended in MeOH (45 ml). Citric acid (1.21 g, 6.30 mmol) dissolved in MeOH (15 ml) and added to the above suspension drop-wise. At this stage no clear solution observed and stirred the suspension at rt for 30 mins. MTBE (180 ml) was added to reaction mass and stirred for 60 mins to obtain more solid. Filtered the solid and solid washed with MTBE (150 ml). Solid was dried under vacuum to obtain the titled compound as an off-white solid (2.86 g). Yield: 79%. M.P.: 225-228°C. ^{1}H-NMR (δ ppm, CD_3OD, 400 MHz): 8.63 (s, 1H), 8.37 (d, J 4, 1H), 8.19 (dd, J 12, 1.2, 1H), 7.68 (s, 1H), 5.22-5.15 (m, 1H), 4.03-3.95 (m, 1H), 3.76-3.69 (m, 2H), 3.04-2.96 (m, 2H), 2.87 (s, 3H), 2.81 (s, 3H), 2.79 (d, J 15.2, 1H, Citrate), 2.71 (d, J 15.2, 1H, Citrate) 2.20-2.13 (m, 2H), 1.78-1.66 (m, 2H), 1.68 (d, J 6.8, 3H). MS (m/z): 477.35 [M+H-$(C_6H_8O_7)_{0.5}$]$^+$.

Example 58

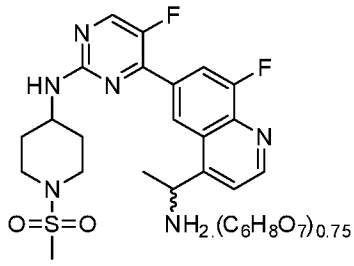
(±)-4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine citrate



[319] (±)-4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine (Example 38, 200 mg, 0.43 mmol) was suspended in MeOH (3 ml). Citric acid (83 mg, 0.43 mmol) dissolved in MeOH (1 ml) and added to the above suspension drop-wise. At this stage almost clear solution observed and the solution stirred at rt for 30 mins. MTBE (12 ml) was added to reaction mass and stirred for 60 mins to obtain a solid. Filtered the solid and solid washed with MTBE (10 ml). Solid was dried under vacuum at 55°C to obtain the titled compound as a yellow solid (154 mg). Yield: 54%. M.P.: 222-224°C. ^{1}H-NMR (δ ppm, CD_3OD, 400 MHz): 8.95 (d, J 4.8, 1H), 8.59 (s, 1H), 8.30 (d, J 4, 1H), 8.17 (dd, J 11.6, 1.2, 1H), 7.69 (d, J 4.8, 1H), 5.30-5.22 (m, 1H), 3.94-3.87 (m, 1H), 3.66-3.60 (m, 2H), 2.95-2.85 (m, 2H), 2.77 (s, 3H), 2.71 (d, J 15.6, 1.6H, Citrate), 2.62 (d, J 15.6, 1.6H, Citrate) 2.11-2.03 (m, 2H), 1.66 (d, J 6.8, 3H), 1.65-1.55 (m, 2H). MS (m/z): 463.48 $[M+H-(C_6H_8O_7)_{0.8}]^+$.

Example 59

(-)-4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine citrate

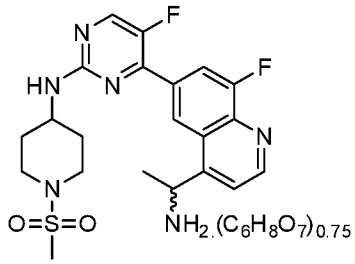


[320] (-)-4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine (Example 39, 2.5 g, 5.41 mmol) was

suspended in MeOH (37 ml). Citric acid (1.04 g, 5.41 mmol) dissolved in MeOH (13 ml) and added to the above suspension drop-wise. At this stage almost clear solution observed and the solution stirred at rt for 30 mins. MTBE (150 ml) was added to reaction mass and stirred for 60 mins to obtain a solid. Filtered the solid and solid washed with MTBE (100 ml) under nitrogen atmosphere. Solid was dried under vacuum at 55°C to obtain the titled compound as a yellow solid (2.85 g). Yield: 87 %. M.P.: 184-186°C. ^{1}H-NMR (δ ppm, CD_3OD, 400 MHz): 9.03 (d, J 4.4, 1H), 8.69 (s, 1H), 8.39 (d, J 4, 1H), 8.25 (d, J 11.6, 1H), 7.80 (d, J 4.4, 1H), 5.39-5.30 (m, 1H), 4.04-3.95 (m, 1H), 3.77-3.70 (m, 2H), 3.05-2.95 (m, 2H), 2.87 (s, 3H), 2.80 (d, J 15.6, 1.5H, Citrate), 2.72 (d, J 15.6, 1.5H, Citrate) 2.20-2.13 (m, 2H), 1.74 (d, J 6.8, 3H), 1.73-1.66 (m, 2H). MS (m/z): 463.41 $[M+H-(C_6H_8O_7)_{0.75}]^+$.

Example 60

(+)-4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine citrate

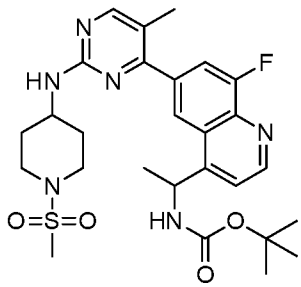


[321] (+)-4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine (Example 40, 2.5 g, 5.41 mmol) was suspended in MeOH (37 ml). Citric acid (1.14 g, 5.95 mmol) dissolved in MeOH (13 ml) and added to the above suspension drop-wise. At this stage almost clear solution observed and the solution stirred at rt for 30 mins. Reaction mixture refluxed for 1 h. Reaction mixture cooled to rt and MTBE (180 ml) was added to reaction mass and stirred for 60 mins to obtain solid. Filtered the solid and solid washed with MTBE (150 ml). Filtered solid was moisture sensitive. Solid was dissolved in a mixture of MeOH and DCM (1:9) (200 ml) and distilled to obtain a residue. Residue was co-distilled with MTBE to obtain a solid. Solid was dried under vacuum at 55°C. Solid was dried in vacuum oven at 55°C for 24 h to obtain the titled compound as a yellow solid (2.6 g). Yield: 79%. M.P.: 171-173°C. ^{1}H-NMR (δ ppm, CD_3OD, 400 MHz): 9.04 (d, J 4.4, 1H), 8.69 (s, 1H), 8.40 (d, J 3.6, 1H), 8.26 (d, J 11.6, 1H), 7.80 (d, J 4.4, 1H), 5.40-5.31 (m, 1H), 4.04-3.97 (m, 1H), 3.79-3.70 (m, 2H), 3.04-2.94 (m, 2H), 2.87 (s, 3H), 2.81 (d,

J 15.2, 1.5H, Citrate), 2.72 (d, J 15.2, 1.5H, Citrate) 2.20-2.13 (m, 2H), 1.75 (d, J 6.4, 3H), 1.75-1.65 (m, 2H). MS (m/z): 463.41 $[M+H-(C_6H_8O_7)_{0.75}]^+$.

Example 61

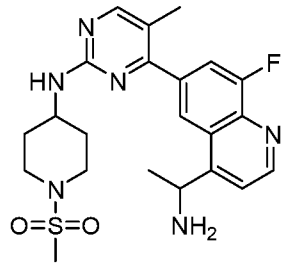
(±)-Tert-butyl (1-(8-fluoro-6-(5-methyl-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-4-yl)ethyl)carbamate



[322] 1-(methylsulfonyl)piperidin-4-amine (616 mg, 3.45 mmol) and sodium bicarbonate (556 mg, 6.62 mmol) were suspended in DMF (13 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 81 (1.2 g, 2.88 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water and extracted with EtOAc (2*100 ml). Combined organic layers were distilled to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (2.5:97.5) as eluent to obtain the titled compound as an Off-White solid (150 mg). Yield: 9.3 %. M.P.: 158-160°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.98 (d, J 4.4, 1H), 8.30 (s, 1H), 8.21 (s, 1H), 7.85-7.77 (m, 2H), 7.62 (d, J 4.4, 1H), 7.22-7.14 (m 1H), 5.45-5.37 (m, 1H), 3.97-3.85 (m 1H), 3.59-3.49 (m, 2H), 2.94-2.84 (m, 2H), 2.85 (s, 3H), 2.23 (s, 3H), 2.05-1.95 (m, 2H), 1.62-1.52 (m, 2H), 1.45 (d, J 6.8, 3H), 1.34 (s, 9H). MS (m/z): 559.27 $(M+H)^+$.

Example 62

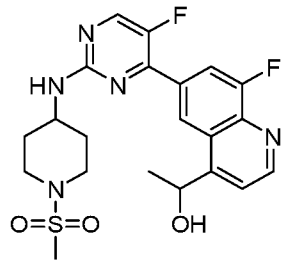
(±)-4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-5-methyl-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine



[323] Tert-butyl (1-(8-fluoro-6-(5-methyl-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-4-yl)ethyl)carbamate (Example: 61, 140 mg, 0.251 mmol) was dissolved in DCM (10 ml). To this mixture Con HCl (137 mg, 3.76 mmol) was added and stirred at rt for 30 mins. After 30 mins, DCM was evaporated to obtain a residue. Residue was dissolved in water (30 ml) and extracted with DCM (3*30 ml). Aqueous layer pH adjusted to 8 using aq. Sodium bicarbonate solution. Aqueous layer extracted with MeOH and DCM (1:9) mixture (3*70 ml). Combined organic layers were distilled to obtain a crude solid. Diethyl ether and Petether (1:1) mixture (20 ml) was added to the solid and stirred for 30 mins. Solid was filtered and washed with a mixture of Diethyl ether and Petether (1:1) (10 ml). Solid was dried under vacuum to obtain the titled compound as an off-white solid (50 mg). Yield: 43 %. M.P.: 176-178°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.97 (d, J 4.4, 1H), 8.30 (s, 1H), 8.27 (bs, 1H), 7.87 (d, J 4.4, 1H), 7.81 (d, J 11.6, 1H), 7.18 (d, J 7.2 1H), 4.89-4.80 (m, 1H), 3.95-3.85 (m, 1H), 3.58-3.49 (m, 2H), 2.92-2.82 (m, 2H), 2.86 (s, 3H), 2.24 (s, 3H), 2.12 (s, 2H, NH_2), 2.05-1.96 (m, 2H), 1.63-1.51 (m, 2H), 1.39 (d, J 6.8, 3H). MS (m/z): 459.27 (M+H)$^+$.

Example 63

(±)-1-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-4-yl)ethan-1-ol

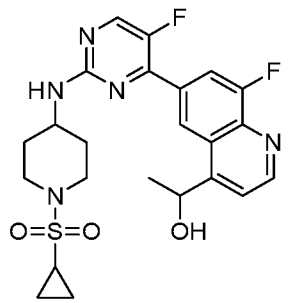


[324] 1-(methylsulfonyl)piperidin-4-amine (400 mg, 2.2 mmol) and sodium bicarbonate (360 mg, 4.3 mmol) were suspended in DMF (4 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 84 (600 mg, 1.9 mmol) was added to the above mixture and stirred at 100°C for

16 h. Reaction mixture diluted with water and extracted with MeOH and DCM mixture (1:9) (3*100 ml). Combined organic layers were washed with water (2*100 ml) and brine (100 ml). Organic layer distilled to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (1.8:98.2) as eluent to obtain the titled compound as an Off-White solid (250 mg). Yield: 29 %. M.P.: 197-199°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.02 (d, J 4.4, 1H), 8.69 (bs, 1H), 8.55 (d, J 3.6, 1H), 8.09 (d, J 11.6, 1H), 7.79 (d, J 4.4, 1H), 7.48 (d, J 7.6, 1H), 5.75 (d, J 4, 1H), 5.52-5.45 (m, 1H), 3.96-3.88 (m, 1H), 3.61-3.53 (m, 2H), 2.95-2.86 (m, 2H), 2.89 (s, 3H), 2.10-2.00 (m, 2H), 1.66-1.55 (m 2H), 1.51 (d, J 6.4, 3H). MS (m/z): 464.48 $(M+H)^+$.

Example 64

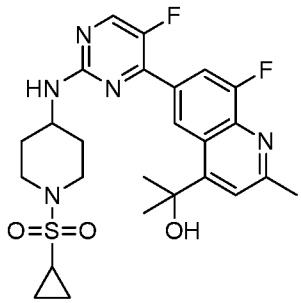
(±)-1-(6-(2-((1-(cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethanol



[325] Intermediate 80 (520 mg, 2.5 mmol) and sodium bicarbonate (350 mg, 4.1 mmol) were suspended in DMF (5.2 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 84 (580 mg, 1.8 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water and extracted with MeOH and DCM mixture (1:9) (3*50 ml). Combined organic layers were distilled to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (1.7:98.3) as eluent to obtain the titled compound as an Off-White solid (150 mg). Yield: 17 %. M.P.: 224-226°C.^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.02 (d, J 4.4, 1H), 8.70 (bs, 1H), 8.54 (d, J 3.6, 1H), 8.10 (d, J 12, 1H), 7.79 (d, J 4.4, 1H), 7.48 (d, J 7.6, 1H), 5.75 (d, J 4.4, 1H), 5.53-5.45 (m, 1H), 3.96-3.87 (m, 1H), 3.67-3.59 (m, 2H), 3.08-2.98 (m, 2H), 2.63-2.55 (m, 1H), 2.10-2.00 (m, 2H), 1.66-1.54 (m, 2H), 1.53 (d, J 6.4, 3H), 1.03-0.90 (m, 4H). MS (m/z): 490.54 $(M+H)^+$.

Example 65

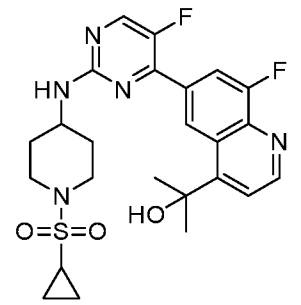
2-(6-(2-((1-(cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)propan-2-ol



[326] Intermediate 80 (340 mg, 1.67 mmol) and sodium bicarbonate (230 mg, 2.74 mmol) were suspended in DMF (5 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 14 (416 mg, 1.2 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water and extracted with MeOH and DCM mixture (1:9) (3*100 ml). Combined organic layers were distilled to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (1.7:98.3) as eluent to obtain the titled compound as an Off-White solid (300 mg). Yield: 48 %. M.P.: 204-206°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.40 (s, 1H), 8.51 (d, J 3.6, 1H), 8.03 (d, J 12, 1H), 7.59 (s, 1H), 7.41 (d, J 7.6, 1H), 5.64 (s, 1H), 3.96-3.88 (m, 1H), 3.67-3.59 (m, 2H), 3.07-2.98 (m, 2H), 2.71 (s, 3H), 2.63-2.55 (m, 1H), 2.10-2.00 (m, 2H), 1.72 (s, 6H), 1.65-1.53 (m, 2H), 1.03-0.90 (m, 4H). MS (m/z): 518.61 $(M+H)^+$.

Example 66

2-(6-(2-((1-(cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)propan-2-ol

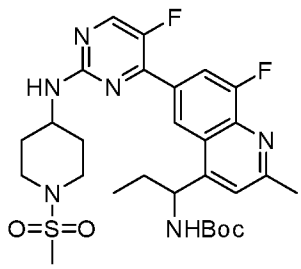


[327] Intermediate 80 (370 mg, 1.8 mmol) and sodium bicarbonate (290 mg, 3.4 mmol) were suspended in DMF (3.7 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 22 (416 mg, 1.2 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction

mixture diluted with water and extracted with MeOH and DCM mixture (1:9) (3*50 ml). Combined organic layers were distilled to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (2.8:97.2) as eluent to obtain the titled compound as an Off-White solid (300 mg). Yield: 40 %. M.P.: 204-206°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.47 (bs, 1H), 8.96 (d, J 4.4, 1H), 8.53 (d, J 3.6, 1H), 8.08 (d, J 12, 1H), 7.71 (d, J 4.4, 1H), 7.46 (d, J 4.4, 1H), 5.71 (s, 1H), 3.97-3.88 (M, 1H), 3.68-3.60 (m, 2H), 3.08-2.98 (m, 2H), 2.65-2.55 (m, 1H), 2.10-2.00 (m, 2H), 1.73 (s, 6H), 1.66-1.53 (m, 2H), 1.02-0.90 (m, 4H). MS (m/z): 504.51 $(M+H)^+$.

Example 67

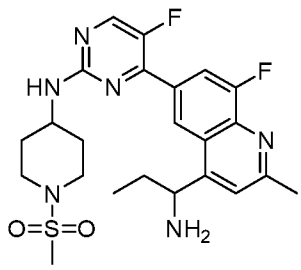
(±)-*Tert*-butyl (1-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)propyl)carbamate



[328] 1-(methylsulfonyl)piperidin-4-amine (600 mg, 1.34 mmol) and sodium bicarbonate (258 mg, 3.07 mmol) were suspended in DMF (12 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 92 (600 mg, 1.34 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water and extracted EtOAc (3*200 ml). Combined organic layers were distilled to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (1.7:98.3) as eluent to obtain the titled compound as an Off-White solid (240 mg). Yield: 30 %. M.P.: 209-211°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.59 (bs, 1H), 8.54 (d, J 4, 1H), 8.08 (d, J 12, 1H), 7.73 ((d, J 8, 1H), 7.54 (s, 1H), 7.47 (d, J 7.2, 1H), 5.25-5.18 (m, 1H), 3.98-3.88 (m, 1H), 3.60-3.53 (m, 1H), 2.98-2.86 (m, 2H), 2.88 (s, 3H), 2.71 (s, 3H), 2.10-2.00 (m, 2H), 1.82-1.80 (m, 2H), 1.68-1.53 (m, 2H), 1.36 (s, 9H), 0.96 (t, J 7.2, 3H). MS (m/z): 591.40 $(M+H)^+$.

Example 68

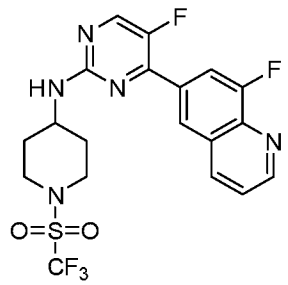
(±)-4-(4-(1-aminopropyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine



[329] (±)-*Tert*-butyl (1-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)propyl)carbamate (Example: 67, 200 mg, 0.339 mmol) was dissolved in DCM (10 ml). To this mixture Con HCl (185 mg, 5.08 mmol) was added and stirred at rt for 30 mins. After 30 mins, DCM was evaporated to obtain a residue. Residue was dissolved in water (50 ml) and extracted with DCM (5*50 ml). Aqueous layer pH adjusted to 8 using aq. Sodium bicarbonate solution. Aqueous layer extracted with MeOH and DCM (1:9) mixture (3*100 ml). Combined organic layers were distilled to obtain a crude solid. Diethyl ether and Petether (1:1) mixture (20 ml) was added to the solid and stirred for 30 mins. Solid was filtered and washed with a mixture of Diethyl ether and Petether (1:1) (10 ml). Solid was dried under vacuum to obtain the titled compound as an off-white solid (120 mg). Yield: 72 %. M.P.: 187-189°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.66 (bs, 1H), 8.52 (d, J 4, 1H), 8.05 (d, J 12, 1H), 7.74 (s, 1H), 7.45 (d, J 3.6, 1H), 4.58-4.51 (m, 1H), 3.96-3.85 (m, 1H), 3.60-3.53 (m, 2H), 2.98-2.85 (m, 2H), 2.89 (s, 3H), 2.71 9s, 3H), 2.26 (bs, 2H, NH_2), 2.08-2.00 (m, 2H), 1.88-1.75 (m, 1H), 1.70-1.52 (m, 3H), 0.90 (t, J 7.2, 3H). MS (m/z): 491.44 [M+H]; calculated for [$C_{23}H_{28}F_2N_6O_2S$+H]: 491.20.

Example 69

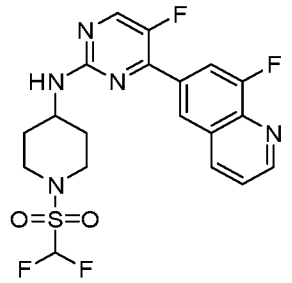
5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)pyrimidin-2-amine



[330] Intermediate 16 (100 mg, 0.293 mmol), Triethyl amine (29.6 mg, 0.293 mmol), N,N-dimethylaminopyridine (3.58 mg, 2.93 mmol) were dissolved in DCM (5 ml). This mixture was cooled to -40°C and triflic anhydride (82.6 mg, 0.293 mmol) was added. This mixture was stirred at -40°C for 1 h. After 1 h, reaction mixture warmed to 0°C and quenched with water. Reaction mixture basified with aq. $NaHCO_3$ upto pH 8 (±0.5). Aqueous layer extracted with DCM (3*100 ml). Organic layer distilled to obtain a crude. Crude was purified by combi-flash using MeOH and DCM (1.3:98.7) as eluent to afford the titled compound as an Off-White solid (45 mg). Yield: 32%. M.P.: 170-172°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.05 (dd, J 8.4, 1.6, 1H), 8.64 (d, J 8.4, 1H), 8.56 (d, J 4, 1H), 8.50 (s, 1H), 8.16 (d, J 12, 1H), 7.74 (d, J 8.4, 4, 1H), 7.54 (d, J 7.6, 1H), 4.14-4.04 (m, 1H), 3.88-3.80 (m, 2H), 3.48-3.39 (m, 2H), 2.10-2.03 (m, 2H), 1.66-1.53 (m, 2H). MS (m/z): 474.52 $(M+H)^+$.

Example 70

***N*-(1-((difluoromethyl)sulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine**

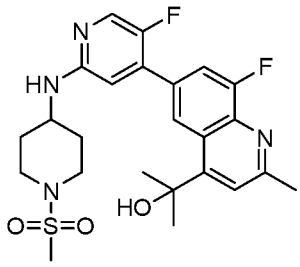


[331] Intermediate 94 (120 mg, 0.48 mmol), Intermediate 2 (100 mg, 0.36 mmol), Sodium *tert*-butoxide (86.5 mg, 0.48 mmol), and Xantphos (43.8 mg, 0.076 mmol) were suspended in toluene (10 ml) and degassed with Nitrogen for 15 mins. Tris(benzylideneacetone)palladium (0) (56.1 mg, 0.061 mmol) was added to above reaction mixture and again degassed with Nitrogen for 15 mins. Reaction mixture was stirred at 100°C for 3 h. After 3 h, reaction mixture was filtered on cealite bed. Cealite bed was washed with a mixture of DCM and MeOH (9:1) (100 ml). Combined filtrates were washed with water (50 ml) and brine (50 ml). Organic layer was distilled under vacuum to obtain a crude. Crude was purified by Combi-flash using MeOH and DCM (1:99) as eluent to obtain titled compound as a pale-yellow solid (30 mg). Yield: 18 %. M.P.: 186-188°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.05 (dd, J 4, 1.6, 1H), 8.64 (d, J 8.4, 1H), 8.55 (d, J 3.6, 1H), 8.50 (s, 1H), 8.16 (d, J 12.4, 1H), 7.73 (dd, J 8.4, 4, 1H), 7.53 (d,

J 7.6, 1H), 7.12 (t, J 52.8, 1H), 4.08-3.98 (m, 1H), 3.82-3.74 (m, 2H), 3.35-3.22 (m, 2H), 2.08-1.98 (m, 2H), 1.63-1.51 (m, 2H). MS (m/z): 456.54 $(M+H)^+$.

Example 71

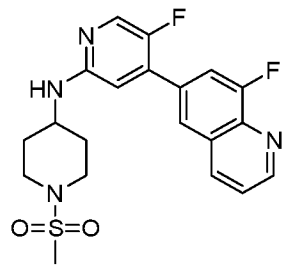
2-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyridin-4-yl)-2-methylquinolin-4-yl)propan-2-ol



[332] 1-(methylsulfonyl)piperidin-4-amine (310 mg, 1.1 mmol), Intermediate 95 (400 mg, 1.1 mmol), Sodium *tert*-butoxide (170 mg, 1.7 mmol), and Xantphos (140 mg, 0.24 mmol) were suspended in toluene (12 ml) and degassed with Nitrogen for 15 mins. Tris(benzylideneacetone)palladium (0) (180 mg, 0.19 mmol) was added to above reaction mixture and again degassed with Nitrogen for 15 mins. Reaction mixture was stirred at 110°C for 3 h. After 3 h, reaction mixture was filtered on cealite bed. Cealite bed was washed with a mixture of DCM and MeOH (9:1) (200 ml). Combined filtrates were washed with water and brine. Organic layer was distilled under vacuum to obtain a crude. Crude was purified by Combi-flash using MeOH and DCM (2.5:97.5) as eluent to obtain titled compound as a pale-yellow solid (140 mg). Yield: 25 %. M.P.: 228-230°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.85 (s, 1H), 8.09 (d, J 2.4, 1H), 7.68 (d, J 11.2, 1H), 7.56 (s, 1H), 6.74-6.65 (m, 2H), 5.64 (s, 1H), 3.90-3.80 (m, 1H), 3.58-3.49 (m, 2H), 2.98-2.85 (m, 2H), 2.88 (s, 3H), 2.70 (s, 3H), 2.09-2.00 (m, 2H), 1.70 (s, 6H), 1.55-1.43 (m, 2H). MS (m/z): 491.63 $(M+H)^+$.

Example 72

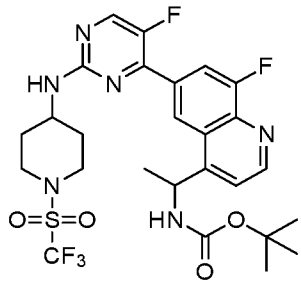
5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyridin-2-amine



[333] 1-(methylsulfonyl)piperidin-4-amine (150 mg, 0.87 mmol), Intermediate 96 (200 mg, 0.72 mmol), Sodium *tert*-butoxide (83 mg, 0.87 mmol), and BINAP (23 mg, 0.036 mmol) were suspended in toluene (10 ml) and degassed with Nitrogen for 15 mins. Tris(benzylideneacetone)palladium (0) (33 mg, 0.036 mmol) was added to above reaction mixture and again degassed with Nitrogen for 15 mins. Reaction mixture was stirred at 110°C for 48 h. After 48 h, reaction mixture was filtered on cealite bed. Cealite bed was washed with a mixture of DCM and MeOH (9:1) (100 ml). Combined filtrates were washed with water and brine. Organic layer was distilled under vacuum to obtain a crude. Crude was purified by Combi-flash using MeOH and DCM (1.7:98.3) as eluent to obtain titled compound as a pale-yellow solid (25 mg). Yield: 8.3 %. M.P.: 192-194°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.02 (dd, J 4.4, 1.6, 1H), 8.56 (d, J 4.4, 1H), 8.11 (d, J 2.8, 1H), 8.08 (s, 1H), 7.80 (d, J 11.6, 1H), 7.72 (dd, J 8.4, 4.4, 1H), 6.73 (d, J 5.2, 1H), 6.67 (d, J 7.6, 1H), 3.90-3.80 (m, 1H), 3.57-3.49 (m, 2H), 2.95-2.85 (m, 2H), 2.88 (s, 3H), 2.07-1.98 (m, 2H), 1.55-1.44 (m, 2H). MS (m/z): 418.12 $(M+H)^+$.

Example 73

(±)-Tert-butyl (1-(8-fluoro-6-(5-fluoro-2-((1-((trifluoromethyl)sulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-4-yl)ethyl)carbamate

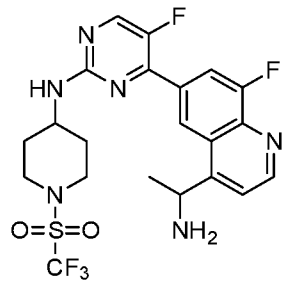


[334] Intermediate 98 (480 mg, 1.8 mmol), Intermediate 60 (500 mg, 1.2 mmol), Sodium *tert*-butoxide (290 mg, 3 mmol), and Xantphos (140 mg, 0.25 mmol) were suspended in toluene (15

ml) and degassed with Nitrogen for 15 mins. Tris(benzylideneacetone)palladium (0) (180 mg, 0.2 mmol) was added to above reaction mixture and again degassed with Nitrogen for 15 mins. Reaction mixture was stirred at 110°C for 3 h. After 3 h, reaction mixture was filtered on cealite bed. Cealite bed was washed with a mixture of DCM and MeOH (9:1) (100 ml). Combined filtrates were washed with water (100 ml) and brine (100 ml). Organic layer was distilled under vacuum to obtain a crude. Crude was purified by Combi-flash using MeOH and DCM (2:98) as eluent to obtain titled compound as a pale-brown solid (160 mg). Yield: 22 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.03 (d, J 4.4, 1H), 8.65 (bs, 1H), 8.56 (d, J 3.6, 1H), 8.12 (d, J 11.6, 1H), 8.85 (d, J 7.6, 1H), 7.67 (d, J 4.4, 1H), 7.57 (d, J 7.2, 1H), 5.50-5.40 (m, 1H), 4.14-4.05 (m, 1H), 3.89-3.79 (m, 2H), 3.45-3.36 (m, 2H), 2.13-2.03 (m, 2H), 1.65-1.53 (m, 2H), 1.46 (d, J 7.2, 3H), 1.35 (s, 9H). MS (m/z): 617.41 (M+H)$^+$.

Example 74

(±)-4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)pyridin-2-amine

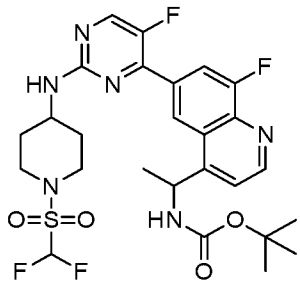


[335] (±)-Tert-butyl (1-(8-fluoro-6-(5-fluoro-2-((1-((trifluoromethyl)sulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-4-yl)ethyl)carbamate (Example: 73, 140 mg, 0.23 mmol) was dissolved in DCM (15 ml). To this mixture Con HCl (120 mg, 3.4 mmol) was added and stirred at rt for 30 mins. After 30 mins, DCM was evaporated to obtain a residue. Residue was dissolved in water (25 ml) and DCM (25 ml) and stirred for 30 mins to obtain a solid. Solid was filtered and washed with DCM (15 ml). Solid was dissolved in a mixture of MeOH and DCM (1:9) (100 ml) and washed with aq. $NaHCO_3$ solution (70 ml). Separated the organic and aqueous layers. Aqueous layer extracted with MeOH and DCM (1:9) mixture (2*70 ml). Combined organic layers were distilled to obtain a crude solid. Petether (10 ml) was added to crude solid and stirred for 30 mins. Solid was filtered and washed with Petether (10 ml). Solid was dried under vacuum to obtain the titled compound as an off-white solid (50 mg). Yield: 40 %. M.P.: 153-155°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.01 (d, J 4, 1H), 8.71 (bs, 1H),

8.55 (d, J 2.8, 1H), 8.10 (d, J 11.6, 1H), 7.90 (d, J 4, 1H), 7.55 (d, J 6.4, 1H), 4.88-4.79 (m, 1H), 4.12-4.04 (m, 1H), 3.90-3.79 (m, 2H), 3.46-3.33 (m, 2H), 2.28 (bs, 2H, NH_2), 2.12-2.03 (m, 2H), 1.68-1.55 (m, 2H), 1.42 (d, J 6.4, 3H). MS (m/z):517.52 $(M+H)^+$.

Example 75

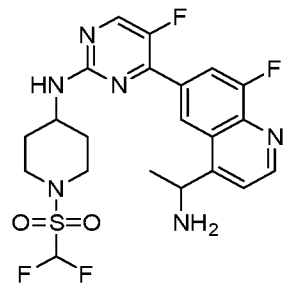
(±)-*Tert*-butyl (1-(6-(2-((1-((difluoromethyl)sulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate



[336] Intermediate 94 (447 mg, 1.78 mmol), Intermediate 60 (500 mg, 1.2 mmol), Sodium *tert*-butoxide (285 mg, 2.97 mmol), and Xantphos (144 mg, 0.25 mmol) were suspended in toluene (15 ml) and degassed with Nitrogen for 15 mins. Tris(benzylideneacetone)palladium (0) (185 mg, 0.2 mmol) was added to above reaction mixture and again degassed with Nitrogen for 15 mins. Reaction mixture was stirred at 100°C for 3 h. After 3 h, reaction mixture was filtered on cealite bed. Cealite bed was washed with a mixture of DCM and MeOH (9:1) (200 ml). Combined filtrates were washed with water (200 ml) and brine (200 ml). Organic layer was distilled under vacuum to obtain a crude. Crude was purified by Combi-flash using MeOH and DCM (2:98) as eluent to obtain titled compound as a brown solid (270 mg). Yield: 38 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.02 (d, J 4.4, 1H), 8.65 (bs, 1H), 8.55 (d, J 3.6, 1H), 8.12 (d, J 11.6, 1H), 7.85 (d, J 7.2, 1H), 7.66 (d, J 4, 1H), 7.55 (d, J 7.2, 1H), 7.12 (t, J 52.8, 1H), 4.08-3.98 (m, 1H), 3.82-3.74 (m, 2H), 3.31-3.22 (m, 2H), 2.10-2.00 (m, 2H), 1.62-1.52 (m, 2H), 1.46 (d, J 7.2, 3H), 1.35 (s, 9H). MS (m/z):599.42 $(M+H)^+$.

Example 76

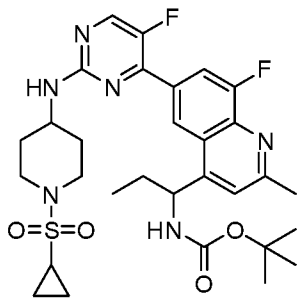
(±)-4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-N-(1-((difluoromethyl)sulfonyl)piperidin-4-yl)-5-fluoropyrimidin-2-amine



[337] (±)-*Tert*-butyl (1-(6-(2-((1-((difluoromethyl)sulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate (Example: 75, 250 mg, 0.418 mmol) was dissolved in DCM (10 ml). To this mixture Con HCl (228 mg, 6.26 mmol) was added and stirred at rt for 30 mins. After 30 mins, DCM was evaporated to obtain a residue. Residue was dissolved in water (25 ml) and DCM (25 ml) and stirred for 30 mins to obtain a solid. Solid was filtered and washed with DCM (15 ml). Solid was dissolved in a mixture of MeOH and DCM (1:9) (100 ml) and washed with aq. $NaHCO_3$ solution (70 ml). Separated the organic and aqueous layers. Aqueous layer extracted with MeOH and DCM (2:8) mixture (2*100 ml). Combined organic layers were distilled to obtain a crude solid. Diethyl ether (20 ml) was added to crude solid and stirred for 30 mins. Solid was filtered and washed with Diethyl ether (10 ml). Solid was dried under vacuum to obtain the titled compound as an off-white solid (180 mg). Yield: 86 %. M.P.: 186-188°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.01 (d, J 4.4, 1H), 8.71 (bs, 1H), 8.54 (d, J 3.6, 1H), 8.10 (d, J 12, 1H), 7.90 (d, J 4.4, 1H), 7.53 (d, J 7.2, 1H), 7.12 (t, J 52.4, 1H), 4.86-4.79 (m, 1H), 4.05-3.96 (m, 1H), 3.72-3.64 (m, 2H), 3.31 (s, 3H), 3.32-3.22 (m, 2H), 2.20 (s, 2H), 2.10-2.00 (m, 2H), 1.62-1.51 (m, 2H), 1.42 (d, J 6.4, 3H). MS (m/z): 499.45 $(M+H)^+$.

Example 77

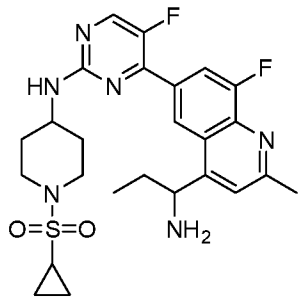
(±)-*Tert*-butyl (1-(6-(2-((1-(cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)propyl)carbamate



[338] Intermediate 80 (218 mg, 1.07 mmol) and sodium bicarbonate (172 mg, 2.05 mmol) were suspended in DMF (5 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 92 (400 mg, 0.89 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water and extracted EtOAc (3*100 ml). Combined organic layers were distilled to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (1.4:98.6) as eluent to obtain the titled compound as an Off-White solid (170 mg). Yield: 31 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.60 (bs, 1H), 8.53 (d, J 3.6, 1H), 8.08 (d, J 12, 1H), 7.73 (d, J 7.6, 1H), 7.54 (s, 1H), 7.47 (d, J 7.6, 1H), 5.25-5.15 (m, 1H), 4.00-3.90 (m, 1H), 3.68-3.58 (m, 2H), 3.08-2.97 (m, 2H), 2.71 (s, 3H), 2.61-2.54 (m, 1H), 2.10-2.00 (m, 2H), 1.83-1.74 (m, 2H), 1.67-1.52 (m, 2H), 1.36 (s, 9H), 1.05-0.90 (m, 7H). MS (m/z): 617.56 (M+H)$^+$.

Example 78

(±)-4-(4-(1-aminopropyl)-8-fluoro-2-methylquinolin-6-yl)-N-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-fluoropyrimidin-2-amine

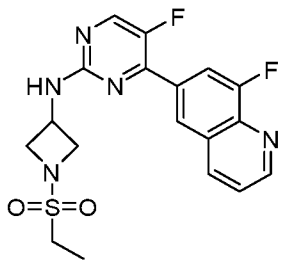


[339] (±)-*Tert*-butyl (1-(6-(2-((1-(cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)propyl)carbamate (Example: 77, 150 mg, 0.243 mmol) was dissolved in DCM (8 ml). To this mixture Con HCl (133 mg, 3.65 mmol) was added and stirred at rt for 30 mins. After 30 mins, DCM was evaporated to obtain a residue. Residue was dissolved in water (25 ml) and washed with DCM (5*50 ml). Aqueous layer was basified with aq. $NaHCO_3$ (50 ml) upto pH 8 (±0.5). Aqueous layer was extracted with MeOH and DCM mixture (1:9) (3*100 ml). Combined organic layers were distilled to obtain a crude solid. Diethyl ether (20 ml) was added to crude solid and stirred for 30 mins. After 30 mins, filtered the solid and washed with Diethyl ether (10 ml). Solid was dried under vacuum to obtain the titled compound as an off-white solid (110 mg).Yield: 87 %. M.P.: 177-179°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.66 (bs, 1H), 8.52 (d, J 4, 1H), 8.06 (d, J 12, 1H), 7.74 (s, 1H), 7.45 (d, J 8. 1H), 4.57 (t, J 6, 1H), 3.99-3.88 (m, 1H), 3.67-3.58 (m, 2H), 3.08-2.96 (m,

2H), 2.71 (s, 3H), 2.65-2.55 (m, 1H), 2.08-1.99 (m, 2H), 1.86-1.75 (m, 1H), 1.72-1.53 (m, 3H), 1.05-0.95 (m, 2H), 0.95-0.86 (m, 2H), 0.90 (t, J 7.2, 3H). MS (m/z): 517.56 $(M+H)^+$.

Example 79

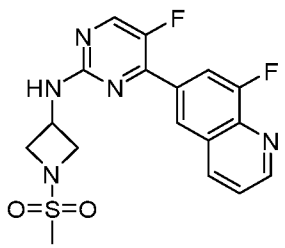
N-(1-(ethylsulfonyl)azetidin-3-yl)-5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine



[340] Intermediate 102 (200 mg, 0.64 mmol) was dissolved in DCM (6 ml) and added TEA (129 mg, 1.27 mmol). This mixture was stirred at rt for 90 mins. Reaction mixture cooled to 0°C and ethanesulfonyl chloride (157 mg, 1.22 mmol) was added. Stirred the reaction mixture at 0°C for 90 min. After 90 min, reaction mixture quenched with water (50 ml) and separated organic layer. Aqueous layer extracted with MeOH and DCM (1:9, 3*30 ml) and combined organic layers were distilled to obtain crude. Crude was purified by combi-flash using MeOH and DCM (1.8:98.2) as eluent to afford the titled compound as a white solid (90 mg). Yield: 35%. M.P.: 193-195°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.05 (d, J 4, 1H), 8.66 (d, J 8.4, 1H), 8.06 (d, J 3.6, 1H), 8.53 (s, 1H), 8.20-8.11 (m, 2H), 7.75 (dd, J 8.4, 4, 1H), 4.69 (bs, 1H), 4.15 (t, J 7.6, 2H), 3.94 (t, J 7.2, 2H), 3.19 (q, J 7.6, 2H), 1.25 (t, J 7.2, 3H). MS (m/z): 406.32 $(M+H)^+$.

Example 80

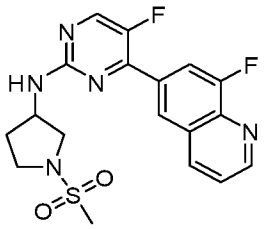
5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)azetidin-3-yl)pyrimidin-2-amine



[341] Intermediate 102 (200 mg, 0.64 mmol) was dissolved in DCM (6 ml) and added TEA (97 mg, 0.96 mmol). This mixture was stirred at rt for 90 mins and cooled to 0°C. Methanesulfonyl chloride (157 mg, 1.22 mmol) was added and stirred at 0°C for 90 min. After 90 min, reaction mixture quenched with water (50 ml) and separated organic layer. Aqueous layer extracted with MeOH and DCM (1:9, 3*30 ml) and combined organic layers were distilled to obtain crude. Crude was purified by combi-flash using MeOH and DCM (1.7:98.3) as eluent to afford the titled compound as an off-white white solid (40 mg). Yield: 16 %. M.P.: 220-222°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.06 (d, J 2.8, 1H), 8.67 (d, J 8, 1H), 8.61 (d, J 2.8, 1H), 8.53 (s, 1H), 8.16 (d, J 12, 1H), 8.13 (d, J 5.6, 1H), 7.75 (dd, J 8, 3.6, 1H), 4.70 (bs, 1H), 4.25-4.12 (m, 2H), 3.92 (t, J 6.8, 2H), 3.06 (s, 3H). MS (m/z): 392.30 (M+H)$^+$.

Example 81

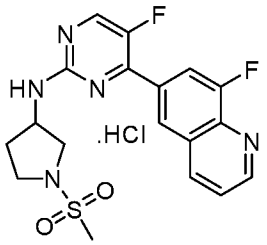
5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)pyrrolidin-3-yl)pyrimidin-2-amine



[342] Intermediate 106 (100 mg, 0.30 mmol) was dissolved in DCM (6 ml) and added TEA (70 mg, 0.69 mmol). This mixture was stirred at rt for 90 mins and cooled to 0°C. Methanesulfonyl chloride (78 mg, 0.68 mmol) was added and stirred at 0°C for 90 min. After 90 min, reaction mixture quenched with water (50 ml) and separated organic layer. Aqueous layer extracted with MeOH and DCM (1:9, 3*30 ml) and combined organic layers were distilled to obtain crude. Crude was purified by combi-flash using MeOH and DCM (1.7:98.3) as eluent to afford the titled compound as an off-white white solid (50 mg). Yield: 41 %. M.P.: 186-188°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.04 (d, J 4, 1H), 8.63 (d, J 8, 1H), 8.57 (d, J 3.6, 1H), 8.50 (s, 1H), 8.14 (d, J 12, 1H), 7.78-7.70(m, 2H), 4.50-4.42 (m, 1H), 3.66-3.56 (m, 1H), 3.50-3.42 (m, 1H), 3.39-3.32 (m, 1H), 3.25-3.18 (m, 1H), 2.90 (s, 3H), 2.28-2.18 (m, 1H), 2.05-1.94 (m, 1H). MS (m/z): 406.1 (M+H)$^+$.

Example 82

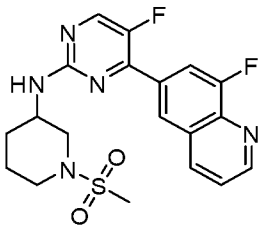
5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride



[343] 5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)pyrrolidin-3-yl)pyrimidin-2-amine (Example 81, 50 mg, 0.12 mmol) was dissolved in MeOH (1 ml) and Con. HCl (45 mg, 1.2 mmol) was added to obtain a clear solution. This mixture was stirred for 30 mins at 25°C. After 30 mins, MTBE (5 ml) was added to the above reaction to obtain a solid. This mixture was stirred for 1 h and filtered the solid. Solid was washed with MTBE (15 ml) and dried under vacuum to obtain the titled compound as a yellow solid (37 mg). Yield: 68 %. M.P.: 196-198°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.05 (d, J 3.2, 1H), 8.65 (d, J 8.4, 1H), 8.58 (d, J 3.6, 1H), 8.51 (s, 1H), 8.16 (d, J 12, 1H), 7.74 (dd, J 8.4, 4, 1H), 6.06 (bs, 1H), 4.45 (bs, 1H), 3.64-3.56 (m, 1H), 3.50-3.42 (m, 1H), 3.38-3.30 (m, 1H), 3.25-3.18 (m, 1H), 2.91 (s, 3H), 2.28-2.18 (m, 1H), 2.03-1.95 (m, 1H). MS (m/z): 406.41 (M+H-HCl)$^+$.

Example 83

5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-3-yl)pyrimidin-2-amine

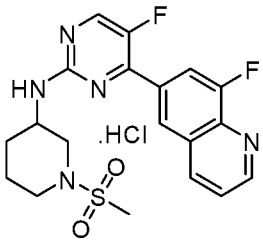


[344] Intermediate 108 (231 mg, 1.3 mmol) and sodium bicarbonate (209 mg, 2.49 mmol) were suspended in DMF (6 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 2 (300 mg, 1.08 mmol) was added to the above mixture and stirred at 100°C for 40 h. Reaction mixture diluted with water (50 ml) to obtain a solid. Solid was filtered and washed with water and MeOH:DCM (1:9) (200 ml) mixture. Solid was dried under vacuum to obtain the titled

compound as an off-white solid (140 mg). Yield: 31 %. M.P.: 245-247°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.07 (d, J 4, 1H), 8.63 (d, J 8.4, 1H), 8.59 (d, J 3.2, 1H), 8.56 (s, 1H), 8.18 (d, J 12, 1H), 7.75 (dd, J 8, 4, 1H), 7.53 (d, J 6.4, 1H), 4.15 (bs, 1H), 3.95-3.82 (m, 1H), 3.57-3.48 (m, 1H), 2.91 (s, 3H), 2.82-2.75 (m, 1H), 2.60-2.50 (m, 1H), 2.01-1.83 (m, 2H), 1.72-1.49 (m, 2H). MS (m/z): 420.0 $(M+H)^+$.

Example 84

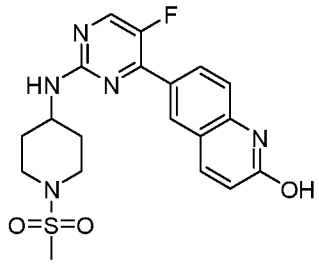
5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-3-yl)pyrimidin-2-amine hydrochloride



[345] 5-fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-3-yl)pyrimidin-2-amine (Example 83, 120 mg, 0.28 mmol) was dissolved in MeOH (2.4 ml) and Con. HCl (100 mg, 28 mmol) was added to obtain a clear solution. This mixture was stirred for 30 mins at 25°C. After 30 mins, MTBE (12 ml) was added to the above reaction to obtain a solid. This mixture was stirred for 1 h and filtered the solid. Solid was washed with MTBE (20 ml) and dried under vacuum to obtain the titled compound as a yellow solid (100 mg). Yield: 78 %. M.P.: 237-239°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.05 (d, J 4, 1H), 8.63 (d, J 8.4, 1H), 8.57 (d, J 3.6, 2H), 8.54 (s, 1H), 8.15 (d, J 12, 1H), 7.74 (dd, J 8, 4, 1H), 7.51 (bs, 1H), 4.15 (bs, 1H), 3.92-3.82 (m, 1H), 3.54-3.43 (m, 1H), 2.88 (s, 3H), 2.80-2.72 (m, 1H), 2.57-2.47 (m, 1H), 1.99-1.80 (m, 1H), 1.79-1.70 (m, 1H), 1.70-1.48 (m, 2H). MS (m/z): 420.40 $(M+H\text{-}HCl)^+$.

Example 85

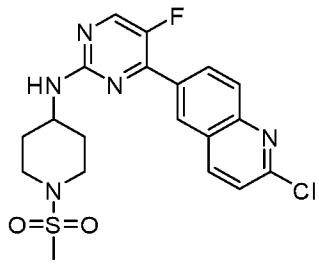
6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-2-ol



[346] 1-(methylsulfonyl)piperidin-4-amine (776 mg, 4.35 mmol) and sodium bicarbonate (701 mg, 8.34 mmol) were suspended in DMF (20 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 112 (1 g, 3.63 mmol) was added to the above mixture and stirred at 100°C for 48 h. Reaction mixture diluted with water (50 ml) to obtain a solid. Solid was filtered and washed with water. Solid was purified by combi-flash using MeOH and DCM (7:93) as eluent to obtain the titled compound as an off-white solid (275 mg). Yield: 17 %. M.P.: 252-255°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 12.01 (s, 1H), 8.45 (d, J 3.2, 1H), 8.32 (s, 1H), 8.16 (d, J 8, 1H), 8.05 (d, J 9.6, 1H), 7.44 (d, J 8.4, 4, 1H), 7.34 (d, J 7.6, 1H), 6.58 (d, J 9.6, 1H), 3.95-3.85 (m, 1H), 3.60-3.52 (m, 2H), 2.96-2.90 (m, 2H), 2.89 (s, 3H), 2.07-1.98 (m, 2H), 1.65-1.52 (m, 2H). MS (m/z): 416.63 (M-H)$^-$.

Example 86

4-(2-chloroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine

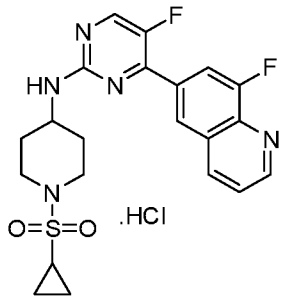


[347] 6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-2-ol (Example 85, 200 mg, 0.46 mmol) was suspended in toluene (4 ml) and $POCl_3$ (2.5 ml) was added. This mixture was stirred at 120°C for 8 h. After 8 h, reaction mixture cooled to rt and poured into ice cold water to obtain a solid. Solid was filtered and washed with water. Solid dried to obtain the titled compound as a pale brown solid (170 mg). Yield: 81 %. M.P.: 221-223°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.66 (s, 1H), 8.63 (d, J 8.8, 1H), 8.52 (d, J 3.6, 1H), 8.39 (d, J 8, 1H), 8.10 (d, J 8.8, 1H), 7.68 (d, J 8.8, 1H), 7.45 (d, J 5.2, 1H), 3.95-3.85 (m,

1H), 3.58-3.50 (m, 2H), 2.95-2.88 (m, 2H), 2.87 (s, 3H), 2.05-1.97 (m, 2H), 1.64-1.51 (m, 2H). MS (m/z): 436.34 $(M+H)^+$.

Example 87

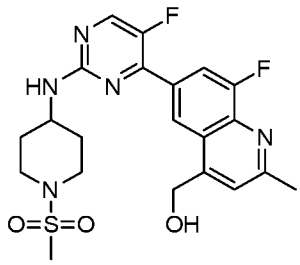
N-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine hydrochloride



[348] N-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine (Example 5, 200 mg, 0.44 mmol) was dissolved in MeOH (4 ml) was added aq. 35% hydrochloric acid (163 mg, 4.4 mmol) by dissolving in MeOH (1 ml). The resulting clear solution was stirred for 30 min. After 30 mins, diluted with methyl *tert*-butyl ether (20 mL) and stirred for 1 h to obtain a solid. Filtered the solid and dried the solid under vacuum at 55°C on rotavapor to obtain the titled compound as a pale-yellow solid (190 mg).^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.06 (dd, J 4.4, 1.6, 1H), 8.67 (d, J 8.8, 1H), 8.55 (d, J 3.6, 1H), 8.51 (s, 1H), 8.16 (d, J 12, 1H), 7.75 (dd, J 8.8, 4.4, 1H), 7.63 (bs, -NH), 4.00-3.90 (m, 1H), 3.65-3.58 (m, 2H), 3.08-2.98 (m, 2H), 2.64-2.56 (m, 1H), 2.06-1.98 (m, 2H), 1.66-1.53 (m, 2H), 1.03-0.90 (m, 4H). MS (m/z): 446.51 $(M+H\text{-}HCl)^+$.

Example 88

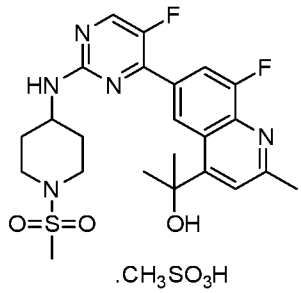
(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)methanol



[349] 1-(methylsulfonyl)piperidin-4-amine (266 mg, 1.5 mmol) and sodium bicarbonate (240 mg, 2.86 mmol) were suspended in DMF (8.3 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 114 (400 mg, 1.24 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water (100 ml). Aqueous layer extracted with a mixture of DCM and MeOH (1:9) 3*50 ml). Combined organic layers were washed with water (100 ml) and brine (2*50 ml). Organic layer distilled to obtain a crude. Crude was purified by Combi-flash using DCM and MeOH (97:3) as eluent. Combined pure fractions from column were distilled to obtain the titled compound as a pale-yellow solid (65 mg). Yield: 10 %. M.P.: 216-218°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.52 (d, J 3.6, 1H), 8.46 (s, 1H), 8.05 (d, J 12, 1H), 7.62 (s, 1H), 7.46 (d, J 7.2, 1H), 5.70 (t, J 5.2, 1H), 5.03 (d, J 5.2, 2H), 3.95-3.85 (m, 1H), 3.56 (d, J 11.6, 2H), 2.98-2.88 (m, 2H), 2.89 (s, 3H), 2.72 (s, 3H), 2.08-1.98 (m, 2H), 1.65-1.52 (m, 2H). MS (m/z): 464.47 $(M+H)^+$.

Example 89

2-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)propan-2-ol methane sulfonate

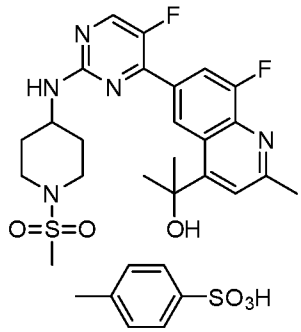


[350] 1-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)ethan-1-ol (Example 4, 250 mg, 0.5 mmol) was dissolved in MeOH (2.5 ml). Methanesulfoninc acid (64 mg, 0.66 mmol) was added to this reaction mixture. This heterogeneous mixture was stirred at rt for 30 mins. After 30 mins, MTBE (12.5 ml) was added to the above reaction mixture. This mixture was stirred for 30 min and filtered the solid. Solid was washed with MTBE (25 ml) and dried under vacuum at 55°C for 30 mins to obtain the titled compound as a yellow solid (270 mg). Yield: 90 %. M.P.: 197-199°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.42 (bs, 1H), 8.52 (d, J 3.2, 1H), 8.08 (d, J 12.4, 1H), 7.67 (s, 1H), 7.46 (bs, 1H), 5.60 (bs, -OH and Quinolinium-H), 3.96-3.88 (m, 1H), 3.60-3.52 (m, 2H), 2.95-2.85

(m, 2H), 2.89 (s, 3H), 2.75 (s, 3H), 2.36 (s, 3H), 2.08-2.00 (m, 2H), 1.72 (s, 6H), 1.65-1.55 (m, 2H). MS (m/z): 492.48 $[(M+H)-CH_3SO_3H]^+$.

Example 90

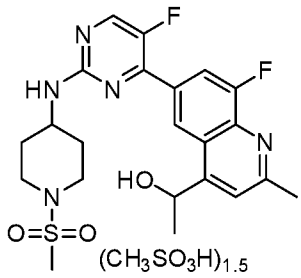
2-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)propan-2-ol 4-methylbenzenesulfonate



[351] 1-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)ethan-1-ol (Example 4, 250 mg, 0.51 mmol) was dissolved in MeOH (2.5 ml). p-Toluenesulfonic acid monohydrate (88 mg, 0.51 mmol) was added to this reaction mixture. This heterogeneous mixture was stirred at rt for 30 mins. After 30 mins, MTBE (12.5 ml) was added to the above reaction mixture. This mixture was stirred for 30 min and filtered the solid. Solid was washed with MTBE (25 ml) and dried under vacuum at 55°C for 30 mins to obtain the titled compound as a yellow solid (280 mg). Yield: 84 %. M.P.: 208-210°C. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.41 (bs, 1H), 8.52 (d, J 3.6, 1H), 8.07 (d, J 11.6, 1H), 7.64 (s, 1H), 7.47 (d, J 7.6, 3H), 7.11 (d, J 7.6, 2H), 5.35 (bs, -OH and Quinolinium-H), 3.96-3.86 (m, 1H), 3.56 (d, J 12, 2H), 2.96-2.85 (m, 2H), 2.89 (s, 3H), 2.74 (s, 3H), 2.28 (s, 3H), 2.08-1.99 (m, 2H), 1.72 (s, 6H), 1.65-1.53 (m, 2H). MS (m/z): 492.47 $[(M+H)-C_7H_8O_3S]^+$.

Example 91

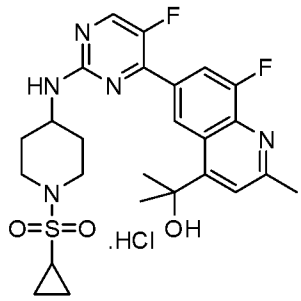
(±)-1-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)ethan-1-ol methanesulfonate



[352] (±)-1-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)ethan-1-ol (Example 17, 250 mg, 0.52 mmol) was dissolved in acetone (2 ml). Methane sulfonic acid (50 mg, 0.52 mmol) dissolved in acetone (0.1 ml) and added to the above mixture. Heterogeneous reaction mixture stirred for 30 mins at 25°C. MTBE (12.5 ml) was added to the reaction mixture to obtain solid and stirred at 25°C for 1 h. After 1 h, solid was filtered and washed with MTBE (20 ml). Solid was dried under vacuum at 55°C for 30 mins to obtain titled compound as a yellow solid. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.65 (bs, 1H), 8.54 (d, J 3.6, 1H), 8.10 (d, J 11.8, 1H), 7.74 (s, 1H), 7.50 (bs, 1H), 5.55-5.47 (m, 1H), 5.45 (bs, 1H), 3.95-3.88 (m, 1H), 3.61-3.52 (m, 2H), 2.96-2.85 (m, 2H), 2.89 (s, 3H), 2.76 (s, 3H), 2.37 (s, 4.5H), 2.10-2.00 (m, 2H), 1.67-1.54 (m, 2H), 1.52 (d, J 6.5, 3H). MS (m/z): 478.43 $[(M+H)-(CH_3SO_3H)_{1.5}]^+$.

Example 92

2-(6-(2-((1-(cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)propan-2-ol hydrochloride

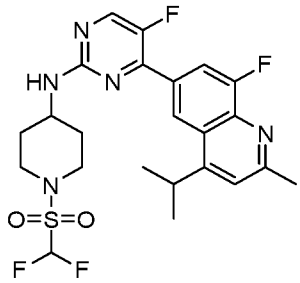


[353] 2-(6-(2-((1-(cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)propan-2-ol (Example 65, 200 mg, 0.4 mmol) was dissolved in MeOH (4 ml) and added aq. 35% hydrochloric acid (163 mg, 4.4 mmol) by dissolving in MeOH

(1 ml) to above solution. The resulting clear solution was stirred for 30 min. After 30 mins, diluted with methyl *tert*-butyl ether (20 mL) and stirred for 1 h to obtain a solid. Filtered the solid and dried the solid under vacuum at 55°C on rotavapor to obtain the titled compound as a pale-yellow solid (195 mg). ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 9.42 (bs, 1H), 8.52 (d, J 3.6, 1H), 8.07 (d, J 11.6, 1H), 7.65 (s, 1H), 7.44 (bs, 1H), 6.00 (bs, 1H), 3.97-3.88 (m, 1H), 3.68-3.59 (m, 2H), 3.08-2.96 (m, 2H), 2.64-2.56 (m, 1H), 2.10-2.00 (m, 2H), 1.72 (s, 6H), 1.65-1.55 (m, 2H), 1.05-0.92 (m, 2H). MS (m/z): 518.56 [(*M*+H)-HCl]$^+$.

Example 93

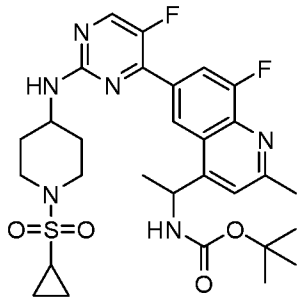
***N*-(1-((difluoromethyl)sulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoro-4-isopropyl-2-methylquinolin-6-yl)pyrimidin-2-amine**



[354] Intermediate 10 (400 mg, 1.2 mmol), Intermediate 94 (451 mg, 1.2 mmol), Sodium *tert*-butoxide (288 mg, 3 mmol) and Xantphos (146 mg, 0.25 mmol) were suspended in toluene (12 ml) and degassed with Nitrogen for 15 mins. Tris(benzylideneacetone)palladium (0) (187 mg, 0.2 mmol) was added to above reaction mixture and again degassed with Nitrogen for 15 mins. Reaction mixture was stirred at 100°C for 3 h. After 3 h, reaction mixture was filtered on cealite bed. Cealite bed was washed with a mixture of DCM and MeOH (9:1) (200 ml). Combined filtrates were washed with water (200 ml) and brine (200 ml). Organic layer was distilled under vacuum to obtain a crude. Crude was purified by Combi-flash using MeOH and DCM (2:98) as eluent to obtain titled compound as a brown solid (80 mg). Yield: 13%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.61 (bs, 1H), 8.53 (d, J 3.6, 1H), 8.06 (d, J 12, 1H), 7.53-7.48 (m, 2H), 7.13 (t, J 52.8, 1H), 4.05-3.95 (m, 1H), 3.82-3.75 (m, 2H), 3.72 (septet, J 6.8, 1H), 3.34-3.22 (m, 2H), 2.71 (s, 3H), 2.10-2.00 (m, 2H), 1.63-1.50 (m, 2H), 1.39 (d, J 6.8, 6H). MS (m/z): 512.60 (*M*+H)$^+$.

Example 94

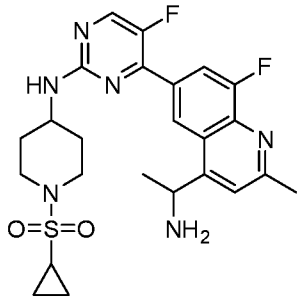
(±)-*Tert*-butyl (1-(6-(2-((1-(cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)ethyl)carbamate



[355] Intermediate 80 (340 mg, 1.7 mmol) and sodium bicarbonate (270 mg, 3.2 mmol) were suspended in DMF (6 ml). This mixture was stirred for 10 mins at 25°C. Intermediate 54 (600 mg, 1.4 mmol) was added to the above mixture and stirred at 100°C for 16 h. Reaction mixture diluted with water and extracted with MeOH and DCM (1:9) mixture (3*50 ml). Combined organic layers were distilled to obtain crude. Crude product was purified by combi-flash using MeOH and DCM (1.5:98.5) as eluent to obtain the titled compound as an Off-White solid (300 mg). Yield: 36 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.59 (bs, 1H), 8.53 (d, J 3.6, 1H), 8.07 (d, J 11.6, 1H), 7.77 (d, J 7.2, 1H), 7.53 (s, 1H), 7.48 (d, J 7.2, 1H), 5.42-5.35 (m, 1H), 3.98-3.89 (m, 1H), 3.67-3.59 (m, 2H), 3.06-2.96 (m, 2H), 2.71 (s, 3H), 2.62-2.55 (m, 1H), 2.10-1.98 (m, 2H), 1.65-1.52 (m, 2H), 1.46 (d, J 6.8, 3H), 1.36 (s, 9H), 1.04-0.90 (m, 4H). MS (m/z): 603.55 (M+H)$^+$.

Example 95

(±)-4-(4-(1-aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-N-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-fluoropyrimidin-2-amine

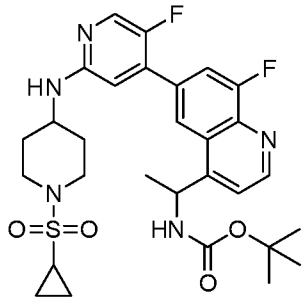


[356] (±)-4-(4-(1-aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-N-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-fluoropyrimidin-2-amine (Example: 94, 300 mg, 0.49

mmol) was dissolved in DCM (20 ml). To this mixture Con HCl (270 mg, 7.46 mmol) was added and stirred at rt for 30 mins. After 30 mins, DCM was evaporated to obtain a residue. Residue was dissolved in water (25 ml) and washed with DCM (5*50 ml). Aqueous layer was basified with aq. $NaHCO_3$ (50 ml) upto pH 8 (±0.5). Aqueous layer was extracted with MeOH and DCM mixture (1:9) (3*100 ml). Combined organic layers were distilled to obtain a crude solid. Diethyl ether (20 ml) was added to crude solid and stirred for 30 mins. After 30 mins, filtered the solid and washed with Diethyl ether (10 ml). Solid was dried under vacuum to obtain the titled compound as an off-white solid (150 mg). Yield: 60%. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.66 (bs, 1H), 8.52 (d, J 4, 1H), 8.05 (d, J 12, 1H), 7.78 (s, 1H), 7.46 (d, J 7.6, 1H), 4.82-4.74 (m, 1H), 3.96-3.88 (m, 1H), 3.68-3.59 (m, 2H), 3.07-2.98 (m, 2H), 2.71 (s, 3H), 2.62-2.55 (m, 1H), 2.20 (s, 2H, NH_2), 2.10-2.00 (m, 2H), 1.68-1.55 (m, 2H), 1.41 (d, J 6.4, 3H), 1.02-0.90 (m, 4H). MS (m/z): 502.19 $(M+H)^+$.

Example 96

(±)-Tert-butyl (1-(6-(2-((1-(cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyridin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate

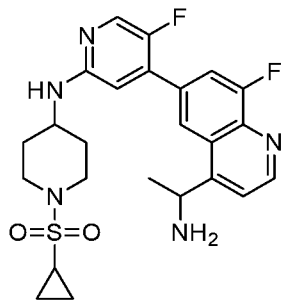


[357] Intermediate 80 (350 mg, 1.6 mmol), Intermediate 115 (640 mg, 1.52 mmol), Sodium *tert*-butoxide (220 mg, 2.28 mmol) and Xantphos (190 mg, 0.032 mmol) were suspended in toluene (10 ml) and degassed with Nitrogen for 15 mins. Tris(benzylideneacetone)palladium (0) (240 mg, 0.25 mmol) was added to above reaction mixture and again degassed with Nitrogen for 15 mins. Reaction mixture was stirred at 110°C for 2 h. After 2 h, reaction mixture was filtered on cealite bed. Cealite bed was washed with a mixture of DCM and MeOH (9:1) (100 ml). Combined filtrates were washed with water (100 ml) and brine (100 ml). Organic layer was distilled under vacuum to obtain a crude. Crude was purified by Combi-flash using MeOH and DCM (2:98) as eluent to obtain titled compound as a pale-yellow solid (350 mg). Yield: 39 %. ^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.99 (d, J 4.4, 1H), 8.18 (s, 1H), 8.10 (d,

J 2, 1H), 7.85-7.76 (m, 2H), 7.63 (d, J 4.4, 1H), 6.74 (d, J 5.2, 1H), 6.70 (d, J 7.2, 1H), 5.48-5.40 (m, 1H), 3.92-3.82 (m, 1H), 3.62-3.54 (m, 2H), 3.08-2.98 (m, 2H), 2.63-2.55 (m, 1H), 2.08-2.00 (m, 2H), 1.55-1.45 (m, 2H), 1.44 (d, J 6.8, 3H), 1.35 (s, 9H). MS (m/z): 588.47 $(M+H)^+$.

Example 97

(±)-4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-N-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-fluoropyridin-2-amine



[358] (±)-Tert-butyl (1-(6-(2-((1-(cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyridin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate (Example: 96, 350 mg, 0.59 mmol) was dissolved in DCM (20 ml). To this mixture Con HCl (320 mg, 8.93 mmol) was added and stirred at rt for 30 mins. After 30 mins, DCM was evaporated to obtain a residue. Residue was dissolved in water (40 ml) and washed with DCM (5*50 ml). Aqueous layer was basified with aq. $NaHCO_3$ (50 ml) upto pH 8 (±0.5). Aqueous layer was extracted with MeOH and DCM mixture (1:9) (3*100 ml). Combined organic layers were distilled to obtain a crude solid. Diethyl ether (20 ml) was added to crude solid and stirred for 30 mins. After 30 mins, filtered the solid and washed with Diethyl ether (10 ml). Solid was dried under vacuum to obtain the titled compound as a pale-brown solid (200 mg). Yield: 68 %.^{1}H-NMR (δ ppm, DMSO-d_6, 400 MHz): 8.98 (d, J 4.4, 1H), 8.22 (s, 1H), 8.10 (s, 1H), 7.88 (d, J 4.4, 1H), 7.76 (d, J 11.6, 1H), 6.76 (d, J 5.2, 1H), 6.69 (d, J 8.8, 1H), 4.90-4.80 (m, 1H), 3.92-3.82 (m, 1H), 3.62-3.55 (m, 2H), 3.08-2.98 (m, 2H), 2.62-2.55 (m, 1H), 2.30 (bs, 2H, NH_2), 2.08-2.00 (m, 2H), 1.55-1.45 (m, 2H), 1.41 (d, J 6.8, 3H). MS (m/z): 488.64 $(M+H)^+$.

BIOLOGICAL ASSAY

[359] The pharmacological properties of the compounds of this invention may be confirmed by several pharmacological assays. The pharmacological assays which can be carried out with

the compounds according to the invention and/or their pharmaceutically acceptable salts is exemplified below.

Example-A

CDK1 Enzyme Assay protocol for screening or IC_{50} determination of compounds of formula (I)

To screen for percent inhibition or determine IC_{50} for compounds for activity against the CDK1 enzyme, an ADP-Glo kinase assay may be used.

ADP-Glo Kinase Assay Protocol

The kinase assay has 3 steps: a) Enzymatic reaction, b) ATP-Depletion c) Kinase detection. The following protocol is designed for a 384-well plate using a 1:1:2 ratio for the 3 steps, respectively.

a) Enzymatic Reaction:

- Total volume of kinase reaction was 5µL. 1 µL of DMSO/drug (diluted in Kinase buffer as 5X) and final concentration in the well was 1X. 2 µL enzyme (prepared in kinase buffer as 1 ng/ µL). 2 µL of ATP/Susbtrate (Histone) mixture (2.5 x prepared in Kinase buffer) was added so that the final concentration of ATP/well was 50 µM and Histone per well was 125 ng.
- 1µL of 5X concentration of test compound was added to each well. For control wells (Blank and Enzyme Blank), 1µL of DMSO prepared in 1X buffer was added. Final concentration of DMSO in all the wells was maintained at 0.5 %.
- 2µL (1 ng/µl) of CDK1/cyclin A2 enzyme was added to Enzyme blank and drug treatment wells. 2µL of 1X kinase reaction buffer was added to the control (Blank) wells.
- Centrifuged the plate for 10 seconds and incubated at room temperature for 15 minutes.
- 2µL of ATP (2.5X) + Substrate (Histone protein) solution was added to each well (Final concentration of ATP/well was 50 µM and Histone protein was 125 ng/well).
- Centrifuged the plate for 10 seconds and incubated at room temperature for 60 minutes.

b) ATP-Depletion:

- ADP-glo reagent was thawed to room temperature before use.
- 5µL of ADP-Glo Reagent was added to stop the kinase reaction to deplete the unconsumed ATP.
- Centrifuged the plate for 10 seconds and incubated at room temperature for 40 minutes.

c) **Kinase Detection**:

- Kinase detection buffer was thawed to room temperature before use.
- 10 µL of Kinase Detection Reagent was added to convert ADP to ATP and introduce luciferase and luciferin to detect ATP.
- The plate was incubated at room temperature for 30 minutes.
- Luminescence was recorded using BMG Labtech, FLUOstar Omega.

Calculation for Screening:

1) Average for each well was calculated.

2) Average of blank wells was subtracted from the average of each enzyme blank and treatment well.

3) Average of blank subtracted wells was calculated.

4) Percent inhibitions were calculated based on the below formula

100 - (Average of blank subtracted treatment well * 100) / (Average of blank subtracted Enzyme Blank wells)

5) For IC_{50} calculations, the average blank subtracted values were used for plotting IC_{50} curve using GraphPad Prism.

Example-B

CDK2 Enzyme Assay Protocol for Screening or IC_{50} Determination of compounds of formula (I)

Objective

To screen for percent inhibition or determine IC_{50} for compounds for activity against the CDK2 enzyme, an ADP-Glo kinase assay may be used.

ADP-Glo Kinase Assay Protocol

The kinase assay has 3 steps: a) Enzymatic reaction, b) ATP-Depletion c) Kinase detection. The following protocol is designed for a 384-well plate using a 1:1:2 ratio for the 3 steps, respectively.

a) Enzymatic reaction:

- Total volume of kinase reaction was 5µL. 1 µL of DMSO/drug (diluted in Kinase buffer as 5X) and final concentration in the well was 1X. 2 µL enzyme (prepared in kinase buffer as 1 ng/ µL). 2 µLof ATP/Susbtrate (Histone) mixture (2.5 x prepared in Kinase buffer) was added so that the final concentration of ATP/well was 50 µM and Histone per well was 125 ng.
- 1µL of 5X concentration of test compound was added to each well. For control wells (Blank and Enzyme Blank), 1µL of DMSO prepared in 1X buffer was added. Final concentration of DMSO in all the wells was maintained at 0.5 %.
- 2µL (1 ng/µl) of CDK2/cyclin A2 enzyme was added to Enzyme blank and drug treatment wells. 2µL of 1X kinase reaction buffer was added to the control (Blank) wells.
- Centrifuged the plate for 10 seconds and incubated at room temperature for 15 minutes.
- 2µL of ATP (2.5X) + Substrate (Histone protein) solution was added to each well (Final concentration of ATP/well was 50 µM and Histone protein was 125 ng/well).
- Centrifuged the plate for 10 seconds and incubated at room temperature for 20 minutes.

b) ATP-Depletion:

- ADP-glo reagent was thawed to room temperature before use.
- 5µL of ADP-Glo Reagent was added to stop the kinase reaction to deplete the unconsumed ATP.
- Centrifuged the plate for 10 seconds and incubated at room temperature for 40 minutes.

c) Kinase Detection:

- Kinase detection buffer was thawed to room temperature before use.

- 10 µL of Kinase Detection Reagent was added to convert ADP to ATP and introduce luciferase and luciferin to detect ATP.
- The plate was incubated at room temperature for 30 minutes.
- Luminescence was recorded using BMG Labtech, FLUOstar Omega.

Calculation for screening:

1) Average for each well calculated

2) Average of blank wells was subtracted from the average of each enzyme blank and treatment well.

3) Average of blank subtracted wells was calculated

4) Percent inhibitions were calculated based on the below formula

100 - (Average of blank subtracted treatment well * 100)/ (Average of blank subtracted Enzyme Blank wells).

5) For IC_{50} calculations, the average blank subtracted values were used for plotting IC_{50} curve using GraphPad Prism.

Example-C

CDK4 Enzyme Assay protocol for screening or IC_{50} determination of compounds of formula (I)

Objective

To screen for percent inhibition or determine IC_{50} for compounds for activity against the CDK4 enzyme, an ADP-Glo kinase assay may be used.

ADP-Glo Kinase assay protocol

Kinase Assay has 3 steps: a) Enzymatic reaction, b) ATP-Depletion c) Kinase detection. The following protocol is designed for a 384-well plate using a 1:1:2 ratio for the 3 steps, respectively.

a) Enzymatic reaction:

- Total volume of kinase reaction was 5µL. 1 µL of DMSO/drug (diluted in Kinase buffer as 5X) and final concentration in the well was 1X. 2 µL enzyme (prepared in kinase buffer as 20 ng/ µL). 2 µL ATP (2.5 x prepared in Kinase buffer)/substrate (Rb protein)

so that the final concentration of ATP/well was 100 µM and Rb protein per well was 0.005 µg.

- 1µL of 5X concentration of test compound was added to each well. For control wells (Blank and Enzyme Blank), 1µL of DMSO prepared in 1X buffer was added. Final concentration of DMSO in all the wells was maintained at 0.5 %.
- 2µL (20 ng/µl) of CDK4/cyclin D3 enzyme was added to Enzyme blank and drug treatment wells. 2µL of 1X kinase reaction buffer was added to the control (Blank) wells. Centrifuged the plate for 10 seconds and incubated at room temperature for 15 minutes.
- 2µL of ATP (2.5X) + Substrate (Rb protein) solution was added to each well (Final concentration of ATP/well was 100 µM and Rb protein was 0.005 µg).
- Centrifuged the plate for 10 seconds and incubated at room temperature for 60 minutes.

b) ATP-Depletion:

- ADP-glo reagent was thawed to room temperature before use.
- 5µL of ADP-Glo Reagent was added to stop the kinase reaction to deplete the unconsumed ATP. Centrifuged the plate for 10 seconds and incubated at room temperature for 40 minutes.

c) Kinase detection:

- Kinase detection buffer was thawed to room temperature before use.
- 10 µL of Kinase Detection Reagent was added to convert ADP to ATP and introduce luciferase and luciferin to detect ATP.
- The plate was incubated at room temperature for 30 minutes.
- Luminescence was recorded using BMG Labtech, FLUOstar Omega.

Calculation for screening:

1) Average for each well calculated

2) Average of blank wells was subtracted from the average of each enzyme blank and treatment well.

3) Average of blank subtracted wells was calculated

4) Percent inhibitions were calculated based on the below formula

: 100-(Average of blank subtracted treatment well*100)/ (Average of blank subtracted Enzyme Blank wells)

5) For IC_{50} calculations, the average blank subtracted values were used for plotting IC_{50} curve using GraphPad Prism.

Example-D

CDK6 Enzyme Assay protocol for screening or IC_{50} determination of compounds of formula (I):

Objective

To screen for % inhibition and/or perform IC_{50} for compounds of the present invention against CDK6 enzyme using ADP-Glo kinase assay.

Kit

ADP-glow kinase kit was used for the CDK6 enzyme assay. Kit components included kinase detection reagent, ADP-glo reagent, ATP, substrate (Histone) and CDK6 enzyme. All the reagents were prepared and stored according to manufacturer's instructions.

ADP-Glo Kinase assay protocol

Kinase Assay has 3 steps: a) Enzymatic reaction, b) ATP-Depletion c) Kinase detection. The following protocol is designed for a 384-well plate using a 1:1:2 ratio for the 3 steps, respectively.

a) Enzymatic reaction:

- Total volume of kinase reaction was 5µL. 1 µL of DMSO/drug (diluted in Kinase buffer as 5X) and final concentration in the well was 1X. 2 µL enzyme (prepared in kinase buffer as 10 ng/ µL). 2 µL ATP (2.5 x prepared in Kinase buffer)/substrate (Histone) so that the final concentration of ATP/well was 250 µM and Histone per well was 0.025 µg
- 1 µL of 5X concentration of test compound was added to each well. For control wells (Blank and Enzyme Blank), 1 µL of DMSO prepared in 1X buffer was added. Final concentration of DMSO in all the wells was maintained at 0.5 %.

- 2 µL (10 ng/µl) of CDK6/cyclin D3 enzyme was added to Enzyme blank and drug treatment wells. 2 µL of 1X kinase reaction buffer was added to the control (Blank) wells.
- Centrifuged the plate for 10 seconds and incubated at room temperature for 15 minutes.
- 2 µL of ATP (2.5X) + Substrate solution was added to each well (Final concentration of ATP/well was 250 µM and histone was 0.025 µg.
- Centrifuged the plate for 10 seconds and incubated at room temperature for 60 minutes.

b) ATP-Depletion:

- ADP-glo reagent was thawed to room temperature before use.
- 5 µL of ADP-Glo Reagent was added to stop the kinase reaction to deplete the unconsumed ATP.
- Centrifuged the plate for 10 seconds and incubated at room temperature for 40 minutes.

c) Kinase detection:

- Kinase detection buffer was thawed to room temperature before use.
- 10 µL of Kinase Detection Reagent was added to convert ADP to ATP and introduce luciferase and luciferin to detect ATP.
- The plate was incubated at room temperature for 30 minutes.
- Luminescence was recorded using BMG Labtech, FLUOstar Omega.

Calculation for screening:

1) Average for each well calculated

2) Average of blank wells was subtracted from the average of each enzyme blank and treatment well.

3) Average of blank subtracted wells was calculated

4) Percent inhibitions were calculated based on the below formula

: 100-(Average of blank subtracted treatment well*100)/ (Average of blank subtracted Enzyme Blank wells)

5) For IC_{50} calculations, Average blank subtracted values were used for plotting IC_{50} curve using GraphPad Prism.

Results: Percent inhibition values are given below in table-2 and 3 and IC_{50} values are given below in table-4.

Example-E

Cell Proliferation assay protocol in breast cancer cell line for screening for GI_{50} for selected compounds of formula (I)

Objective:

To perform cell proliferation assay in Breast Cancer cell line (ZR.75.1, MCF-7, and MDA-MB-231) to determine the GI_{50} for the selected compounds of the present invention using MTT assay.

Method: MTT assay (3-(4,5-Dimethylthiazol-2-yl) -2,5-diphenyltetrazolium bromide)

Procedure: The cells were processed, pelleted, and counted. Cells were plated in 100 µl/well in complete media in a 96-well plate in triplicates at desired density and plates were incubated at 37 °C and 5% CO_2. Cells in each well were treated with the inhibitor dilutions prepared in complete media, in triplicates and plates were incubated at 37 °C and 5% CO_2 for 144 h. After 144 h, 15 µL of 5 mg/mL (final concentration of 1X) of MTT were added to the test wells and mixed well. Plates were incubated at 37 °C and 5% CO_2 for 3.5 hours. After incubation, cells are pelleted down at 4000 rpm for 10 min. Media was aspirated and 150 µL of DMSO per well were added. Crystals were dissolved by repeated pipetting. Absorbance was read at A560 nM and A640 nM. GI_{50} values were calculated using GraphPad Prism.

Results: GI_{50} values were determined for the selected compounds and are reported in table 4.

Table-2

Ex.	% Inhibition							
	CDK1		CDK2		CDK4		CDK6	
	100nM	1000nM	100nM	1000nM	30nM	100nM	30nM	100nM
2	A	A	A	A	B	A	D	B
3	B	A	A	A	-	-	-	-
4	A	A	A	A	C	A	D	B
5	A	A	A	A	B	A	D	B
6	A	A	A	A	D	B	C	B
7	A	A	A	A	C	A	C	C
8	A	A	A	A	C	B	-	D
9	A	A	A	A	C	A	C	B
10	A	A	A	A	B	B	D	C
11	B	A	A	A	D	B	D	C
12	B	A	A	A	D	B	D	D

Table-3

Ex.	% Inhibition							
	CDK1		CDK2		CDK4		CDK6	
	30nM	100nM	30nM	100nM	30nM	100nM	30nM	100nM
13	B	B	B	A	D	B	D	D
14	C	B	B	A	D	C	D	D
15	A	A	A	A	C	A	B	B
16	A	A	A	A	B	B	C	C
17	A	A	B	A	C	B	C	B
19	B	A	A	A	C	B	D	C
21	B	A	B	B	D	D	-	-
22	C	B	D	C	C	B	D	B
23	D	D	D	D	D	D	D	D
24	B	A	C	B	B	B	D	C
25	D	D	D	D	C	B	D	D

Ex.	% Inhibition							
	CDK1		CDK2		CDK4		CDK6	
	30nM	100nM	30nM	100nM	30nM	100nM	30nM	100nM
26	C	B	C	B	D	B	C	C
27	C	C	D	D	D	D	D	D
28	C	B	C	B	-	-	-	-
29	C	B	B	A	C	A	C	B
30	C	A	B	A	C	B	C	C
31	D	D	D	C	C	B	C	B
32	D	C	D	C	C	A	C	C
33	C	B	B	A	D	C	D	D
34	B	A	A	A	C	C	D	C
35	B	A	B	A	C	B	D	C
36	D	C	C	B	D	C	-	D
37	B	A	A	A	C	B	C	B
38	A	A	A	A	B	B	B	B
39	A	A	A	A	C	A	D	B
40	C	B	A	A	D	B	0	0
41	D	C	D	C	-	-	-	-
42	D	C	C	B	-	-	-	-
43	D	C	C	C	D	D	D	D
44	C	B	C	B	D	B	D	D
45	C	C	C	B	D	C	D	C
46	B	A	A	A	C	B	D	D
47	B	A	A	A	B	B	D	C
49	C	B	A	A	C	B	D	C
50	B	A	A	A	D	C	D	D
51	B	A	A	A	D	B	D	C
52	B	A	A	A	D	C	D	D
53	C	B	A	A	B	A	D	B
54	C	B	B	A	D	C	D	C
55	B	A	A	A	D	B	D	C

Ex.	% Inhibition							
	CDK1		CDK2		CDK4		CDK6	
	30nM	100nM	30nM	100nM	30nM	100nM	30nM	100nM
56	B	A	B	A	C	B	D	D
57	B	A	A	A	C	B	D	C
58	A	A	A	A	C	B	D	C
59	A	A	A	A	B	A	D	B
60	B	B	A	A	C	B	D	D
62	D	D	D	C	D	D	D	D
63	A	A	A	A	B	A	D	B
64	A	A	A	A	C	A	C	B
65	A	A	A	S	C	B	C	A
66	A	A	A	A	B	A	B	A
67	-	-	D	C	D	D	D	D
68	A	A	A	A	C	B	C	C
69	-	-	D	C	-	-	-	-
70	C	B	A	A	B	A	D	C
71	C	C	B	A	C	B	-	-
74	B	A	C	A	-	-	-	-
76	A	A	B	A	-	-	-	-
78	A	A	A	A	-	-	-	-
79	D	D	D	D	D	D	D	C
80	D	D	D	D	D	D	D	C
82	D	D	D	C	C	C	D	D
86	D	D	C	B	D	D	D	D
87	B	A	A	A	B	A	C	B
88	D	C	D	B	C	C	D	D
89	B	A	A	A	C	B	C	B
90	B	A	A	A	C	B	D	C
91	A	A	B	A	C	A	C	B
92	A	A	A	A	-	-	-	-
95	A	A	B	A	-	-	-	-

Ex.	% Inhibition							
	CDK1		CDK2		CDK4		CDK6	
	30nM	100nM	30nM	100nM	30nM	100nM	30nM	100nM
97	B	A	A	A	C	B	-	-

% Inhibition for both Tables 2 and 3: A represents >75% to 100%; B represents >50% to ≤75%; C represents >25% to ≤50% and D represents ≤25%;

Table-4

Ex.	IC50				GI50 (nM)		
	CDK1	CDK2	CDK4	CDK6	MCF-7	ZR-75.1	MDA-MB-231
2	+++++	+++++	+++++	+++	b	d	b
3	+++	++++			b	c	b
4	+++++	+++++	++++	++++	a	b	a
5	++++	+++++		+++	a	c	a
6	+++++	+++++		++			
7	+++++	+++++		+++			
8					a	b	c
9					a	a	a
10	+++++	+++++	+++++	++	b	d	b
15	+++++	+++++	++++	++++	a	b	a
16	+++++	+++++	++++	++	d	d	b
17	+++++	+++++	++++	+++	b	d	b
19						b	c
29	+++++	+++++			b	b	c
34	+++++	+++++		++	a	b	b
35	+++++	+++++	+++	++	b	b	a
36	+++	++++	+++	+	c	d	d
37							
38	+++++	+++++		++++	a	b	a
39	+++++	+++++	++++	++++	a	a	a
40	++++	+++++	++	+	c	b	b

Ex.	IC50				GI50 (nM)		
	CDK1	CDK2	CDK4	CDK6	MCF-7	ZR-75.1	MDA-MB-231
51					a	b	b
53	++++	+++++	++++	+++	a	b	a
70	++++	+++++	++++	++			

IC50: "+++++" represents 1 to ≤25nM; "++++" represents >25 to ≤50nM; "+++" represents >50 to ≤100nM; "++" is represents >100 to ≤200nM, "+" represents >200nM.

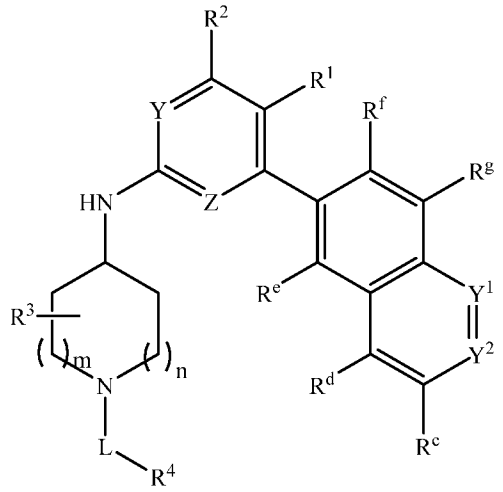
GI50: "a" represents 0 to ≤200nM; "b" represents >200 to ≤500nM; "c" represents >500 to ≤1000nM; "d" represents >1000 to ≤10000nM.

[360] Although the invention herein has been described with reference to embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present invention. It is therefore to be understood that numerous modifications may be made to the illustrative embodiments and that other arrangements may be devised without departing from the spirit and scope of the present invention as described above. It is intended that the appended claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

[361] All publications and patent and/or patent applications cited in this application are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated herein by reference.

We claim:

1. A compound of formula **(I)**:



(I)

or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof or pharmaceutically acceptable salt thereof,

wherein

Y^1 is selected from CR^a and N;

Y^2 is selected from CR^b and N; with the proviso that at least one of Y^1 and Y^2 is N;

R^a, R^b, R^c, R^d, R^e, R^f and R^g are independently selected from hydrogen, halogen, hydroxy, amino, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminoalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-C(O)OR^j$, and $-C(O)NR^ZR^Z$;

Y is selected from CR^h and N;

Z is selected from CR^i and N; with the proviso that at least one of Y and Z is N;

R^h, R^i, and R^j are independently selected from hydrogen, halogen, substituted or unsubstituted alkyl, and substituted or unsubstituted haloalkyl;

R^1 and R^2 are independently selected from hydrogen, halogen, hydroxy, amino, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heterocyclylalkyl;

L is selected from -S-, -S(O)-, -SO_2-, and –S(=NH)O-;

R^3 is selected from hydrogen, hydroxy, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkoxy, substituted or unsubstituted haloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heterocyclylalkyl;

R^4 is selected from hydrogen, hydroxy, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkoxy, substituted or unsubstituted haloalkyl, substituted or unsubstituted aminoalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, -NR^zR^z, -$NR^zC(=O)NR^zR^z$, -$NR^zS(=O)R^z$, -$NR^zS(=O)_2R^z$, -$NR^zC(=O)OR^z$, -$NR^zC(=O)R^z$, -$NR^xC(=S)R^y$. -$NR^zC(=S)NR^zR^z$, -$CR^xR^yC(=O)R^z$, and -$CR^xR^yC(=S)R^z$;

each occurrence of R^z is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocyclyl, substituted heterocyclylalkyl, and substituted or unsubstituted amino; or any two of R^z when bound to a common atom may be joined to form a (i) substituted or unsubstituted, saturated or unsaturated 3-14 membered ring, which may optionally include one or more heteroatoms which may be the

same or different and are selected from O, NR^{za} and S; or (ii) an oxo (=O), thio (=S), or imino ($=NR^{za}$) group;

R^{za}, R^x, and R^y at each occurrence are independently selected from hydrogen, halo, hydroxy, amino, alkoxy, C_{1-5} alkyl, C_{3-7} cycloalkyl, C_{5-7} aryl, C_{5-7} heteroaryl, and C_{3-7} heterocycloalkyl;

m is an integer selected from 0, 1, and 2; and

n is an integer selected from 0, 1, and 2.

2. The compound of claim 1, wherein Y^1 is N.

3. The compound of claim 1 or 2, wherein Y^2 is CR^b.

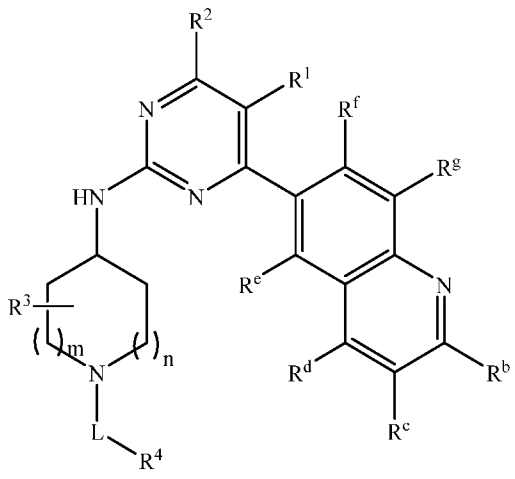
4. The compound of claim 3, wherein R^b is hydrogen, hydroxy, haloalkyl, and C_{1-6}alkyl.

5. The compound of any one of claims 1-4, wherein Y is N.

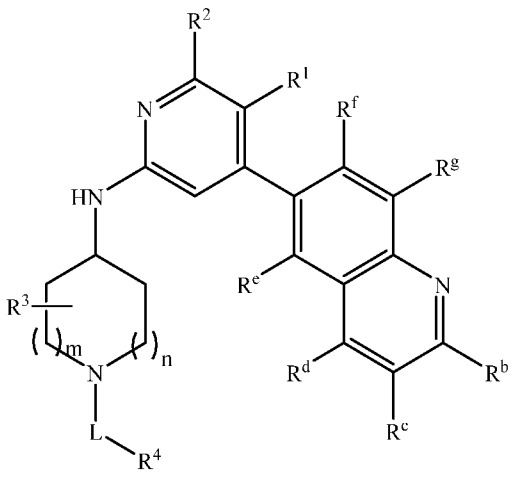
6. The compound of any one of claims 1-5, wherein Z is N.

7. The compound of any one of claims 1-5, wherein Z is CR^i and R^i is hydrogen.

8. The compound of claim 1, wherein the compound is of formula **(IA)** or **(IB)**:



(IA)



(IB)

or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof, wherein all the variables (including L, R^1, R^2, R^3, R^4, R^b, R^c, R^d, R^e, R^f, R^g, m and n) are as defined in formula **(I)**.

9. The compound of any one of claims 1-8, wherein R^1 is hydrogen, substituted or unsubstitued alkyl, halogen, hydroxy, or amine.

10. The compound of claim 9, wherein R^1 is substituted or unsubstitued -$C_{(1-6)}$alkyl, or halogen.

11. The compound of claim 10, wherein R^1 is methyl, fluorine, or chlorine.

12. The compound of any one of claims 1-11, wherein R^2 is hydrogen.

13. The compound of any one of claims 1-12, wherein R^3 is hydrogen or hydroxy.

14. The compound of any one of claims 1-13, wherein n and m are 1.

15. The compound of any one of claims 1-14, wherein L is -SO_2-.

16. The compound of any of the claims 1-15, wherein R^4 is selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aminoalkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and -NR^zR^z.

17. The compound of claim 16, wherein R^4 is -C_{1-3}alkyl, -C_{2-3}alkenyl, -CF_3, -CHF_2, -$N(CH_3)_2$, -$NH(C_2H_5)$, -$CH_2CH_2N(CH_3)_2$, -CH_2CH_2OH, cyclopropyl, 4-fluorophenyl, or pyridyl.

18. The compound of any of the claims 1-17, wherein R^c is hydrogen.

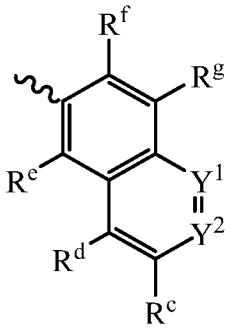
19. The compound of any of the claims 1-17, wherein R^d is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted aminoalkyl, cyano, -$C(O)OR^j$. or -$C(O)NR^zR^z$.

20. The compound of claim 19, wherein R^d is isopropyl, propan-2-ol, 1-hydroxyethyl, -CH_2OH, CN, -C(O)OH, -$C(O)OCH_3$, -$C(O)NH_2$, -$C(O)NHCH_3$, -C(O)NH-Boc, -$CH(NH_2)CH_3$, -$CH(NH_2)CH_2CH_3$, -CH(NH-Boc)CH_3, or -CH(NH-Boc)CH_2CH_3.

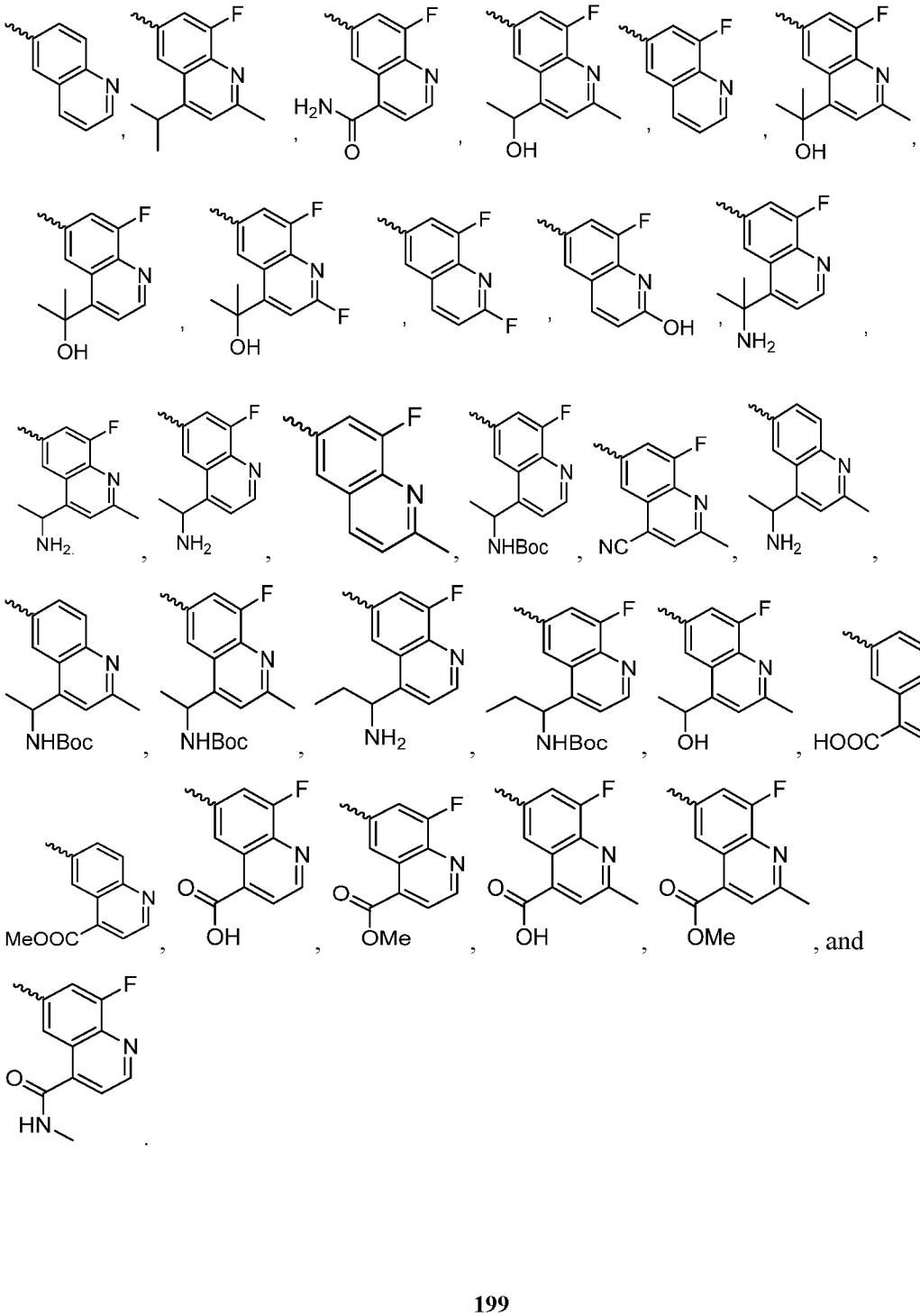
21. The compound of claim 1-20, wherein R^e and R^f are hydrogen.

22. The compound of claim 1-21, wherein R^g is hydrogen or halogen.

23. The compound of claim 1-22, wherein the moiety



is selected from



24. A compound selected from:

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine hydrochloride,

5-Fluoro-4-(8-fluoro-4-isopropyl-2-methylquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

2-(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)propan-2-ol,

N-(1-(Cyclopropylsulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(vinylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

N-(1-((2-(Dimethylamino)ethyl)sulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine,

N-(1-(ethylsulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine,

2-(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-4-yl)propan-2-ol,

2-((4-((5-Fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)ethan-1-ol,

4-((5-Fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-yl)amino)-N,N-dimethylpiperidine-1-sulfonamide,

N-Ethyl-4-((5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-yl)amino)piperidine-1-sulfonamide,

5-Fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)-4-(quinolin-6-yl)pyrimidin-2-amine,

5-Fluoro-N-(1-((4-fluorophenyl)sulfonyl)piperidin-4-yl)-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine,

2-(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)propan-2-ol dihydrochloride,

8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinoline-4-carboxamide,

1-(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)ethan-1-ol,

(±)-1-(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)ethan-1-ol,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(pyridin-3-ylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(pyridin-3-ylsulfonyl)piperidin-4-yl)pyrimidin-2-amine hydrochloride,

8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-N-methylquinoline-4-carboxamide,

8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-N-methylquinoline-4-carboxamide hydrochloride,

Methyl 8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinoline-4-carboxylate,

8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinoline-4-carboxylic acid,

Methyl 8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinoline-4-carboxylate,

8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinoline-4-carboxylic acid,

Methyl 6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinoline-4-carboxylate,

6-(5-Fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinoline-4-carboxylic acid,

5-Chloro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

5-Chloro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine hydrochloride,

(±)-1-(6-(5-Chloro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)ethan-1-ol,

(±)-4-((5-Fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-ol,

(±)-(3R,4R)-4-((5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-yl)amino)-1-(methylsulfonyl)piperidin-3-ol hydrochloride,

(±)-*Tert*-butyl (1-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)ethyl)carbamate,

(±)-4-(4-(1-Aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

(-)-4-(4-(1-Aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

(+)-4-(4-(1-Aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

(±)-*Tert*-butyl (1-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-4-yl)ethyl)carbamate,

(±)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

(-)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

(+)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

(±)-*Tert*-butyl (1-(6-(5-chloro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)ethyl)carbamate,

(±)-4-(4-(1-Aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-chloro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

(±)-*Tert*-butyl (1-(6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)ethyl)carbamate,

(±)-4-(4-(1-Aminoethyl)-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinoline-4-carbonitrile,

(±)-*Tert*-butyl (1-(6-(5-chloro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate,

(±)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-5-chloro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

5-Fluoro-4-(8-fluoro-2-methylquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

5-Fluoro-4-(8-fluoro-2-methylquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine hydrochloride,

(±)-*Tert*-butyl (1-(6-(2-((1-(ethylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate,

(±)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-N-(1-(ethylsulfonyl)piperidin-4-yl)-5-fluoropyrimidin-2-amine,

(±)-*Tert*-butyl (1-(6-(2-((1-(cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate,

4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-N-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-fluoropyrimidin-2-amine,

(±)-4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-N-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-fluoropyrimidin-2-amine,

(±)-4-(4-(1-aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine hydrochloride,

(±)-4-(4-(1-Aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine hemicitrate,

(±)-4-(4-(1-Aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine methanesulfonate,

(-)-4-(4-(1-Aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine hemicitrate,

(±)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine citrate,

(-)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine citrate,

(+)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine citrate,

(±)-Tert-butyl (1-(8-fluoro-6-(5-methyl-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-4-yl)ethyl)carbamate,

(±)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-5-methyl-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

(±)-1-(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-4-yl)ethan-1-ol,

(±)-1-(6-(2-((1-(Cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethanol,

2-(6-(2-((1-(Cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)propan-2-ol,

2-(6-(2-((1-(Cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)propan-2-ol,

(±)-*Tert*-butyl (1-(8-fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)propyl)carbamate,

(±)-4-(4-(1-Aminopropyl)-8-fluoro-2-methylquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)pyrimidin-2-amine,

N-(1-((Difluoromethyl)sulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine,

2-(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyridin-4-yl)-2-methylquinolin-4-yl)propan-2-ol,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyridin-2-amine,

(±)-Tert-butyl (1-(8-fluoro-6-(5-fluoro-2-((1-((trifluoromethyl)sulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-4-yl)ethyl)carbamate,

(±)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-5-fluoro-N-(1-((trifluoromethyl)sulfonyl)piperidin-4-yl)pyridin-2-amine,

(±)-*Tert*-butyl (1-(6-(2-((1-((difluoromethyl)sulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate,

(±)-4-(4-(1-Aminoethyl)-8-fluoroquinolin-6-yl)-N-(1-((difluoromethyl)sulfonyl)piperidin-4-yl)-5-fluoropyrimidin-2-amine,

(±)-*Tert*-butyl (1-(6-(2-((1-(cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)propyl)carbamate,

(±)-4-(4-(1-Aminopropyl)-8-fluoro-2-methylquinolin-6-yl)-N-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-fluoropyrimidin-2-amine,

N-(1-(Ethylsulfonyl)azetidin-3-yl)-5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)azetidin-3-yl)pyrimidin-2-amine,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)pyrrolidin-3-yl)pyrimidin-2-amine,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-3-yl)pyrimidin-2-amine,

5-Fluoro-4-(8-fluoroquinolin-6-yl)-N-(1-(methylsulfonyl)piperidin-3-yl)pyrimidin-2-amine hydrochloride,

6-(5-Fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)quinolin-2-ol,

4-(2-chloroquinolin-6-yl)-5-fluoro-N-(1-(methylsulfonyl)piperidin-4-yl)pyrimidin-2-amine,

N-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoroquinolin-6-yl)pyrimidin-2-amine hydrochloride,

(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)methanol,

2-(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)propan-2-ol methane sulfonate,

2-(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)propan-2-ol 4-methylbenzenesulfonate, or

1-(8-Fluoro-6-(5-fluoro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)-2-methylquinolin-4-yl)ethan-1-ol methanesulfonate;

2-(6-(2-((1-(Cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)propan-2-ol hydrochloride,

N-(1-((Difluoromethyl)sulfonyl)piperidin-4-yl)-5-fluoro-4-(8-fluoro-4-isopropyl-2-methylquinolin-6-yl)pyrimidin-2-amine,

Tert-butyl (1-(6-(2-((1-(cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyrimidin-4-yl)-8-fluoro-2-methylquinolin-4-yl)ethyl)carbamate,

4-(4-(1-Aminoethyl)-8-fluoro-2-methylquinolin-6-yl)-N-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-fluoropyrimidin-2-amine,

tert-butyl (1-(6-(2-((1-(cyclopropylsulfonyl)piperidin-4-yl)amino)-5-fluoropyridin-4-yl)-8-fluoroquinolin-4-yl)ethyl)carbamate, or

4-(4-(1-aminoethyl)-8-fluoroquinolin-6-yl)-N-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-fluoropyridin-2-amine; and

pharmaceutically acceptable salts thereof.

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

26. The pharmaceutical composition of claim 25, further comprising one or more additional therapeutic agents.

27. The pharmaceutical composition of claim 26, wherein the one or more additional therapeutic agents is an anti-cancer agent, anti-inflammatory agent, immunosuppressive agent, steroid, non-steroidal anti-inflammatory agent, antihistamine, analgesic, or any combination of any of the foregoing.

28. A method of inhibiting a catalytic activity of a CDK enzyme selected from CDK1, CDK2, CDK4, CDK6, and any combination of any of the foregoing present in a cell comprising contacting the cell with an effective amount of a compound of any one of claims 1-24.

29. The method of claim 28, wherein the inhibition takes place in a subject suffering from a disease or disorder which is cancer, a bone disorder, an inflammatory disease, an immune disease, a nervous system disease, a metabolic disease, a respiratory disease, thrombosis, or cardiac disease.

30. Use of a compound of any one of claims 1-24 in the manufacture of a medicament for the treatment of a disease, disorder, or condition that would benefit from inhibiting catalytic activity of a CDK enzyme selected from CDK1, CDK2, CDK4, CDK6, and any combination of any of the foregoing.

31. A method for the treatment of a disease, disorder, or condition associated with CDK1, CDK2, CDK4, CDK6, or any combination of any of the foregoing comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1-24.

32. The method of claim 31, further comprising the step of administering simultaneously or sequentially to the subject at least one other anti-cancer agent, anti-inflammatory agent, immunosuppressive agent, steroid, non-steroidal anti-inflammatory agent, antihistamine, analgesic, or any combination of any of the foregoing.

33. The method of claim 31 or claim 32, wherein the disease, disorder or condition is an immune system-related disease, a disease or disorder involving inflammation, cancer or other proliferative disease, a hepatic disease or disorder, or a renal disease or disorder.

34. The method of claim 31 or claim 32, wherein the disease, disorder or condition is selected from inflammation, glomerulonephritis, uveitis, hepatic diseases or disorders, renal diseases or disorders, chronic obstructive pulmonary disease, rheumatoid arthritis, inflammatory bowel disease, vasculitis, dermatitis, osteoarthritis, inflammatory muscle disease, allergic rhinitis, vaginitis, interstitial cystitis, scleroderma, osteoporosis, eczema, allogeneic or xenogeneic transplantation, graft rejection, graft-versus-host disease, lupus erythematosus, pulmonary fibrosis, dermatomyositis, thyroiditis, myasthenia gravis, autoimmune hemolytic anemia, cystic fibrosis, chronic relapsing hepatitis, primary biliary cirrhosis, allergic conjunctivitis, hepatitis, atopic dermatitis, asthma, Sjogren's syndrome, organ transplant rejection, multiple sclerosis, Guillain-Barre, autoimmune uveitis, autoimmune hemolytic anemia, pernicious anemia, autoimmune thrombocytopenia, temporal arteritis, anti-phospholipid syndrome, vasculitides, Wegener's granulomatosis, Behcet's disease, psoriasis, dermatitis herpetiformis, pemphigus vulgaris, vitiligo, Crohn's disease, colitis, ulcerative colitis, primary biliary cirrhosis, autoimmune hepatitis, Type 1 or immune-mediated diabetes mellitus, Grave's disease, Hashimoto's thyroiditis, autoimmune oophoritis and orchitis, autoimmune disorder of the adrenal gland, systemic lupus erythematosus, polymyositis, dermatomyositis, ankylosing spondylitis, transplant rejection, skin graft rejection, arthritis, bone diseases associated with increased bone resorption, ileitis, Barrett's syndrome, adult respiratory distress syndrome, chronic obstructive airway disease, corneal dystrophy, trachoma, onchocerciasis, sympathetic ophthalmitis, endophthalmitis, gingivitis, periodontitis, tuberculosis, leprosy, uremic complications, nephrosis, sclerodermatitis, psoriasis, chronic demyelinating diseases of the nervous system, AIDS-related neurodegeneration, Alzheimer's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis viral or autoimmune encephalitis, autoimmune disorders, immune-complex vasculitis, systemic lupus and erythematodes, systemic lupus erythematosus

(SLE), cardiomyopathy, ischemic heart disease, hypercholesterolemia, atherosclerosis, preeclampsia, chronic liver failure, brain and spinal cord trauma, and cancer.

35. The method of claim 31 or claim 32, wherein the disease, disorder or condition is selected from hematopoietic tumors of lymphoid lineage, leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burkett's lymphoma, hematopoietic tumors of myeloid lineage, acute myelogenous leukemias, chronic myelogenous leukemias, myelodysplastic syndrome, promyelocytic leukemia, carcinoma of the bladder, carcinoma of the breast, carcinoma of the colon, carcinoma of the kidney, carcinoma of the liver, carcinoma of the lung, small cell lung cancer, esophageal cancer, gall bladder cancer, ovarian cancer, pancreatic cancer, stomach cancer, cervical cancer, thyroid cancer, prostate cancer, skin cancer, squamous cell carcinoma, tumors of mesenchymal origin, fibrosarcoma, rhabdomyosarcoma, tumors of the central and peripheral nervous system, astrocytoma, neuroblastoma, glioma, schwannoma, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer, brain cancer and Kaposi's sarcoma.

36. The method of claim 31 or claim 32, wherein the disease, disorder or condition is selected from carcinoma of the breast, ovarian cancer, carcinoma of the liver, carcinoma of the lung, small cell lung cancer, esophageal cancer, gall bladder cancer, pancreatic cancer, brain cancer or stomach cancer.

37. The method of claim 31 or claim 32, wherein the disease, disorder or condition is carcinoma of the breast or ovarian cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2022/050026

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D405/14 A61P35/00 A61K31/506
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/026326 A1 (WYETH CORP [US]; PELLETIER JEFFREY CLAUDE [US] ET AL.) 26 February 2009 (2009-02-26) claims 1,40	1-37
A	WO 2019/207463 A1 (PFIZER [US]) 31 October 2019 (2019-10-31) claims 1,22	1-37
A	WO 2020/180959 A1 (INCYTE CORP [US]; LI ZHENWU [US] ET AL.) 10 September 2020 (2020-09-10) cited in the application claims 1,38	1-37

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 February 2022	16/02/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Johnson, Claire

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2022/050026

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-23, 25-37(all partially)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-23, 25-37(all partially)

The compounds claimed in claims 1 and 8 are defined in two parts, namely, by well-defined structural features of formula (I) or by the functional feature of being a prodrug thereof. Examples of potential prodrug groups are given on pp. 38-39.

In order for a claim containing a functionally defined feature to be clear, the person skilled in the art must be able to distinguish unambiguously the chemical compounds belonging to the claimed group from those not encompassed by it. It is apparent from the passage of the present description cited above that the skilled person using common general knowledge is able to identify specific derivatives of compounds of formula (I) as possible prodrug candidates. However, it is also evident that it would be perfectly possible to define these compounds in a precise manner in terms of clear structural features.

By defining the claimed compounds in functional rather than structural terms, the claims extend beyond the structures structurally defined in the description to as yet unexplored possibilities not made available to the skilled person based on common general knowledge. In the absence of common general knowledge, in order to clearly establish the structural combinations effectively encompassed by the term "prodrug", beyond those disclosed in the description, the skilled person would need to synthesise potential candidates and perform in vivo tests to establish their activity, toxicity and metabolic behaviour. This amounts to an invitation to perform a research programme, which constitutes an undue burden. Thus the claimed compounds defined as prodrugs do not fulfil the requirements of clarity.

The present opinion is given only for those parts of the claims not directed to prodrugs.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2022/050026

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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