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(54) Title: SMALL MOLECULE INHIBITORS OF DYRK/CLK AND USES THEREOF

(57) Abstract: This invention is in the field of medicinal chemistry. In particular, the invention relates to a new class of small-molecule compounds having a 6,6-heterocyclic structure (e.g., compounds having a naphthyridine, pyrido-pyridazine, pyrido-pyrazine, quinoline, pyrazino-pyridazine, pyrimido-pyrimidine, quinazoline, quinoxaline or cinnoline ring system) which function as inhibitors of DYRK1A, DYRK1B, DYRK2, DYRK3, CLK1, CLK2, CLK3, CLK4, CDK7, CDK8/19, PI3K, PDGFrA/B, mTOR, WNT, homeodomain-interacting kinases (HIPKs), and/or CMGC kinases leading to inhibition of WNT signaling, and their use as therapeutics for the treatment of Alzheimer's disease, down syndrome, Parkinson's disease, Huntington's disease, diabetes, autoimmune diseases, inflammatory disorders (e.g., airway inflammation, osteoarthritis (e.g., knee related osteoarthritis)), cancer (e.g., glioblastoma, prostate cancer, metastatic breast cancer, metastatic lung cancer, multiple myeloma, secondary metastatic tumors of the brain, colorectal cancer and metastatic colorectal cancer (e.g., metastatic colorectal cancer in the liver)), and other diseases.

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SMALL MOLECULE INHIBITORS OF DYRK/CLK AND USES THEREOF

STATEMENT OF GOVERNMENT SUPPORT

This invention was made with government support under Grant No. AG067926 awarded by National Institutes of Health. The government has certain rights in the invention.

FIELD OF THE INVENTION

This invention is in the field of medicinal chemistry. In particular, the invention relates to a new class of small-molecule compounds having a 6,6-heterocyclic structure (e.g., compounds having a naphthyridine, pyrido-pyridazine, pyrido-pyrazine, quinoline, pyrazino-pyridazine, pyrimido-pyrimidine, quinazoline, quinoxaline or cinnoline ring system) which function as inhibitors of DYRK1A, DYRK1B, DYRK2, DYRK3, CLK1, CLK2, CLK3, CLK4, CDK7, CDK8/19, PI3K, PDGFrA/B, mTOR, WNT, homeodomain-interacting kinases (HIPKs), and/or CMGC kinases leading to inhibition of WNT signaling, and their use as therapeutics for the treatment of Alzheimer's disease, down syndrome, Parkinson's disease, Huntington's disease, diabetes, autoimmune diseases, inflammatory disorders (e.g., airway inflammation, osteoarthritis (e.g., knee related osteoarthritis)), cancer (e.g., glioblastoma, prostate cancer, metastatic breast cancer, metastatic lung cancer, multiple myeloma, secondary metastatic tumors of the brain, colorectal cancer and metastatic colorectal cancer (e.g., metastatic colorectal cancer in the liver)), and other diseases.

INTRODUCTION

It's estimated that 2 million new cases of cancer will be shortly diagnosed per year with over 600,000 deaths in the US per annum. DYRK, CLK and CDK kinase inhibition affords opportunities across a spectrum of malignancies. Moreover, small molecule inhibition of DYRK and CLK kinases may play a role in mitigating disease progression of autoimmune disease and inflammatory disorders, exemplified by osteo-arthritis. DYRK1A has been revealed to play a key role in dementia and down syndrome pathogenesis. With > 40 million patients suffering, dementia is currently a leading unmet medical need and costly burden on public health. Seventy percent of these cases have been attributed to Alzheimer's disease (AD), a neurodegenerative pathology whose most evident symptom is a progressive decline in cognitive functions. The

underlying treatment of learning and/or memory disorders is a huge and significantly unmet medical need and also includes learning and memory repair after incidents of stroke or significant brain damage.

The present invention addresses these needs.

SUMMARY OF THE INVENTION

The proteasome (immuno- and constitutive), heat shock factor 1, and mammalian target of rapamycin (mTOR) are essential protein complexes responsible for maintaining growth, division, and survival of cells in eukaryotes and are required for almost all cellular activities. Any impairment of any one or more of the complexes often underlies neurodegenerative diseases, cancer, immune disorders, and the aging process. Targeting these complexes have been clinically proven to be effective against all forms of cancers. RNA interference, kinome-wide screen, and biochemical studies demonstrate that blocking 26S proteasome and heat shock factor 1 phosphorylations triggered by DYRK2 markedly impairs proteostasis and impedes cell proliferation (see, Guo et.al. 2016 Nature Cell Biology; Moreno et.al. 2021 Cell death and differentiation; Banerjee et.al. PNAS 2018; Banerjee et.al. PNAS 2019). Furthermore, inhibition of DYRK3 activity leads to loss of PRAS40 phosphorylation leading to loss of mTOR signaling which reduces cancer cell proliferation. Importantly, loss of DYRK2 and DYRK3 activities significantly inhibited tumor formation in mice (see, eg, Banerjee et.al. 2019 PNAS). Accordingly, small-molecule inhibitors of DYRK kinases, either used alone or in combination with existing chemotherapy and/or proteasome inhibitors, have unique therapeutic potentials in treating human cancers with deregulated growth and proliferation.

Moreover, canonical WNT signaling is a key developmental pathway that has garnered significant interest for therapeutic intervention. The ability to modulate the WNT pathway and thus restore the health of diseased tissues affords possibilities in regenerative therapeutics and oncology. Noteworthy, WNT signaling controls chondrocyte osteoblast and synovial cell functions in osteoarthritis (Tao et. al., Theranostics, 2017, 7, 180-195). Indeed, numerous biological processes and targets related to WNT activation have been reported (Zhan et. al., Oncogene 2017, 36, 1461-1473. Ahmed et. al., Cancers, 2016, 8, 66). Part of this set of targets comprises the serine/threonine kinase CLKs shown to modulate the Wnt pathway by regulating pre-mRNA splicing (Deshmukh et. al., Osteoarthritis Cartilage 2019, 27, 1347-1360, Wang et.

al., Nature 2008, 456-470-476). They consist as four isoforms in mammals (CLK1 through CLK4) and belong to the CMGC group of kinases which includes DYRKS, cyclin-dependent kinases (CDKs), GSK3, serine-arginine-rich protein kinases (SRPK) and others. CLK protein over-expression affects splicing site selection of pre-mRNA and as such, several CLK family inhibitors have been reported to play roles in the control mechanisms of mRNA splicing (Bossard et al., Cancer Res., 2020, 80, 5691. Deshmukh et. al., Osteoarthritis Cartilage 2019, 27, 1347-1360). Specifically, two high profile CLK inhibitors in clinical trials are SM08502 (Indication: Colorectal cancer, NCT03355066) and SM04690 (Indication: Osteoarthritis of the knee, Phase 3, NCT03928184).

CDKs have also shown to be heavily implicated in WNT inhibition. In particular CDK7 enhances the interaction between beta-catenin and TCF4 (see Duan et al., Cell Death & Differentiation, 2019, 26, 1442–1452), CDK8 has been identified as a gene that regulates b-catenin driven reporter activity in a loss of function RNAi screen (Rosenbluh et al., Trends Pharmacol Sci. 2014, 35, 103–109). Inhibitors of CDK7, 8 and 19 have shown utility in colorectal cancer and metastatic colon cancer in the liver and have been implicated in WNT signaling inhibiton. Moreover, CDK8 selectivity promotes growth of colon cancer metastases in the liver by regulating gene expression of TIMP3 and matrix metalloproteases (see Liang et. al., Cancer Res. 2018, 78(23), 6594–6606). CDK8 and its paralog CDK19 are two isoforms of the Mediator kinase, the enzymatic component of the CDK module that binds to the transcriptional Mediator complex and inhibition of the CDK8/19 Mediator kinase sensitizes HER2+ breast cancers to HER2-targeting drugs preventing resistance in vitro and in vivo (see, e.g., Ding et al., PNAS, 2022, 119 (32), 1-11, e2201073119). High profile CDK8/CDK19 inhibitors in clinical trials include RVU120 in patients with Acute Myeloid Leukemia (AML) or high-risk Myelodysplastic Syndrome (HR-MDS) (NCT04021368), TSN084 (NCT05300438) and Senexin B, the first selective CDK8/19 inhibitor to enter clinical trials (NCT03065010).

In addition to the overwhelmingly prominent β-amyloid hypothesis being evaluated in a multitude of clinical trials through small molecule modulation of γ- and β-secretases and numerous immune-based approaches, aberrant phosphorylation of the tau protein is believed to significantly contribute to the development of AD and thus affords an alternate approach for therapeutic development. Tau is a cytoplasmic protein involved in the stabilization of microtubules under normal conditions. In AD, neuronal tau has been found to be excessively

phosphorylated, with subsequent generation of aggregates of phosphorylated tau protein, known as "neurofibrillary tangles" (NFTs). NFTs and amyloid plaques are considered the most common hallmarks of AD and are correlated with neurofibrillary degeneration, neuronal death, and dementia.

Interestingly, several protein kinases have been implicated in neuronal development and, in particular, their overexpression and aberrant activation have been shown to play a significant role in the development of AD via tau phosphorylation. Dual specificity tyrosine phosphorylation regulated kinase-1A (DYRK1A) is important in neuronal development and plays a variety of functional roles within the adult central nervous system. The DYRK1A gene is located within the Down syndrome critical region (DSCR) on human chromosome 21 and current research suggests that overexpression of DYRK1A may be a significant factor leading to cognitive deficits in people with Alzheimer's disease (AD) and Down syndrome (DS).

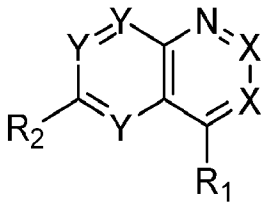
Experiments conducted during the course of developing embodiments for the present invention designed, synthesized and biologically evaluated compounds having a 6,6-heterocyclic structure (e.g., compounds having a naphthyridine, pyrido-pyridazine, pyrido-pyrazine, quinoline, pyrazino-pyridazine, pyrimido-pyrimidine, quinazoline, quinoxaline or cinnoline ring system) as inhibitors of the dual specificity tyrosine phosphorylation regulated kinases (DYRKS) and CLKs, and their potential for use as therapeutics against WNT driven cancers and other disorders related to DYRK1A, DYRK1B, DYRK2, DYRK3, and CLK1, CLK2, CLK3 and CLK4 activities (e.g., DS, other neuropathology, cancer including glioblastoma, prostate cancer, metastatic breast cancer, metastatic lung cancer, multiple myeloma, secondary metastatic tumors of the brain, triple negative breast cancer, diabetes (T1D/T2D), cognitive enhancement). Many of such compounds are likely to exhibit activity against dual specificity tyrosine phosphorylation regulated kinase-1B (DYRK1B), dual specificity tyrosine phosphorylation regulated kinase-2 (DYRK2) (see, Tandon, et al., J. Biol. Chem 296 (2021)), dual specificity tyrosine phosphorylation regulated kinase-3 (DYRK3) (see, Kim, et al., Intl. J. Molecular Sciences 22, 2982 (2021)), and exhibit activity against other kinases implicated in a variety of disease states (e.g., dual specificity protein kinase CLK1 (Clk-1) and the cyclin-dependent kinases CDK7, CDK8 and CDK19.

The DYRK/CLK inhibitors described herein can also be considered as potential therapeutics for the treatment of developmental diseases such as Down syndrome, and

neurodegenerative diseases such as Parkinson's disease, and Huntington's disease. Moreover, the DYRK inhibitors of the present invention have been also implicated as potential therapeutics for the treatment of glioblastomas and further potential utility is highlighted in the oncology arena (see, e.g., Ionescu et al., Mini-reviews in Medicinal Chemistry, 2012, 12, 1315-1329).

These novel DYRK/CLK inhibitors may also have utility as general cognitive enhancers, given the published findings that DYRK1A can phosphorylate sirtuin 1, a key regulator of learning and memory (see, e.g., Michan et al., J. Neurosci. 2010, 30(29), 9695-9707; Guo et al., J Biol. Chem. 2010, 285 (17), 13223-13232). Moreover, the effectiveness of small molecule inhibition of DYRK1A in mitigating both insoluble tau aggregates and amyloid plaques has been demonstrated (see, e.g., Branca et al., Aging Cell, 2017, 16(5), 1146-1154). The mechanistic rational for this was detailed previously (Smith et al., ACS Chem. Neuroscience, 2012, 3(11), 857-872). These novel DYRK/CLK inhibitors may also have further utility as results identify DYRK1A as a physiologically relevant regulator of T_{reg} cell differentiation and suggest a broader role for other DYRK family members in immune homeostasis. As such, new roles may be found in autoimmune diseases such as inflammatory bowel disease and type 1 diabetes (see, e.g., Khor B, et al., eLife 2015;4:e05920).

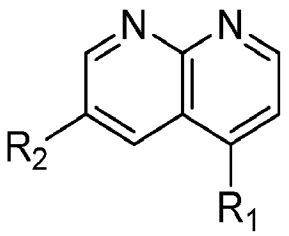
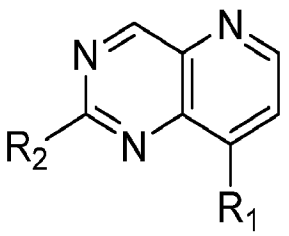
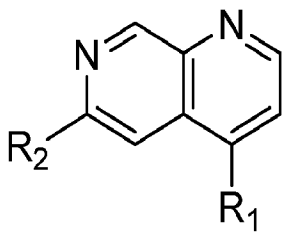
Accordingly, this invention relates to a new class of small-molecule compounds having a 6,6-heterocyclic structure (e.g., compounds having a naphthyridine, pyrido-pyridazine, pyrido-pyrazine, quinoline, pyrazino-pyridazine, pyrimido-pyrimidine, quinazoline, quinoxaline or cinnoline ring system) which function as inhibitors of DYRK1A, DYRK1B, DYRK2, DYRK3, CLK1, CLK2, CLK3, CLK4, CDK7, CDK8/19, PI3K, PDGFrA/B, mTOR, WNT, homeodomain-interacting kinases (HIPKs), and/or CMGC kinases leading to inhibition of WNT signaling, and their use as therapeutics for the treatment of Alzheimer's disease, down syndrome, Parkinson's disease, Huntington's disease, diabetes, autoimmune diseases, inflammatory disorders (e.g., airway inflammation, osteoarthritis (e.g., knee related osteoarthritis)), cancer (e.g., glioblastoma, prostate cancer, metastatic breast cancer, metastatic lung cancer, multiple myeloma, secondary metastatic tumors of the brain, colorectal cancer and metastatic colorectal cancer (e.g., metastatic colorectal cancer in the liver)), and other diseases.

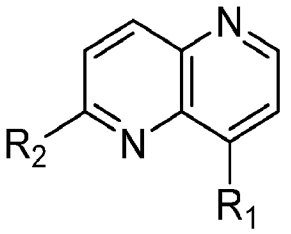
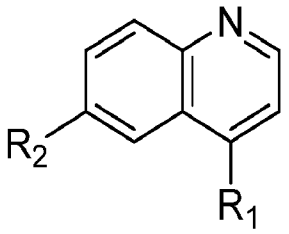
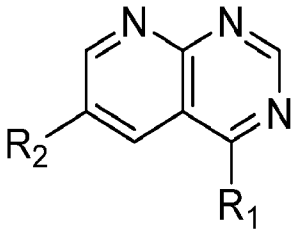
In a particular embodiment, compounds encompassed within the following formulas are provided:  (Formula I); including pharmaceutically acceptable salts, solvates, and/or prodrugs thereof.

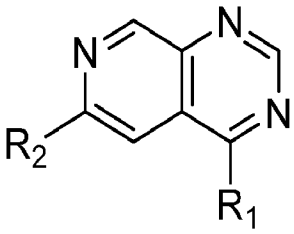
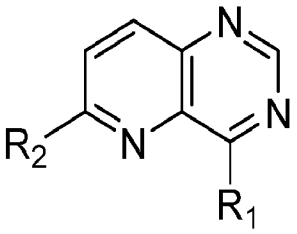
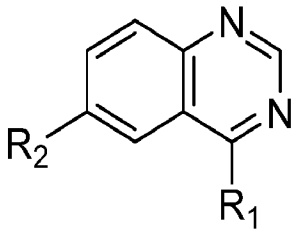
Formula I is not limited to a particular chemical moiety for X, Y, R1 and R2. In some embodiments, the particular chemical moiety for X, Y, R1 and R2 independently include any chemical moiety that permits the resulting compound to inhibit DYRK1A activity. In some embodiments, the particular chemical moiety for X, Y, R1 and R2 independently include any chemical moiety that permits the resulting compound to inhibit one or more of: DYRK1A related PI3K/Akt signaling; DYRK1A related tau phosphorylation; DYRK1A related NFAT phosphorylation; DYRK1A related ASK1/JNK1 pathway activation; DYRK1A related p53 phosphorylation; DYRK1A related Amph 1 phosphorylation; DYRK1A related Dynamin 1 phosphorylation; DYRK1A related Synaptojanin phosphorylation; DYRK1A related presenilin 1 (the catalytic sub-unit of γ-secretase) activity; DYRK1A related amyloid precursor protein phosphorylation; DYRK1A related SIRT1 activation; DYRK2 related heat shock factor 1 and 26S proteasome activities; DYRK3 related mTOR activity; DYRK3 phosphorylation (e.g., PRAS40); DYRK1B activity; CMGC/CLK kinase activity; CLK1 activity; CLK2 activity; CLK3 activity; CLK4 activity; CDK7 activity; CDK8 activity; CDK19 activity; PI3K activity; PI3K mutant activity; PDGFrA/B activity; mTOR activity; c-KIT activity; RYK activity; and WNT signaling.

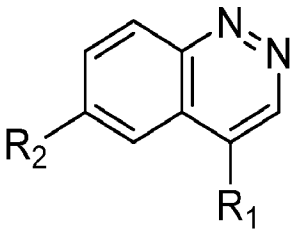
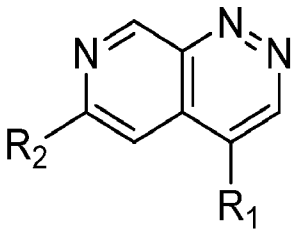
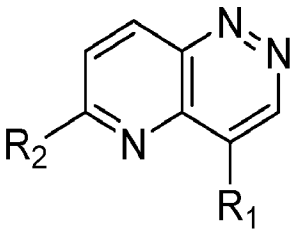
Such embodiments are not limited to a particular definition for each of the "X" and "Y" substituents.

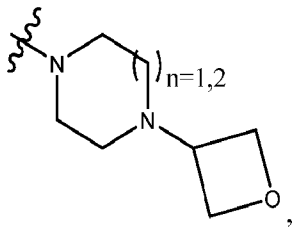
In some embodiments, one of the "X" substituents is carbon and the other is nitrogen, or both of the "X" substituents are carbon; and one of the "Y" substituents is nitrogen and the other "Y" substituents are carbon, or two of the "Y" substituents are nitrogen and one "Y" substituent is carbon, or all of the "Y" substituents are carbon; such that the resulting structure is one of the

following formulas: , , ,

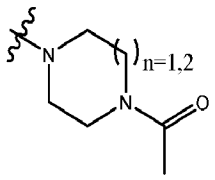
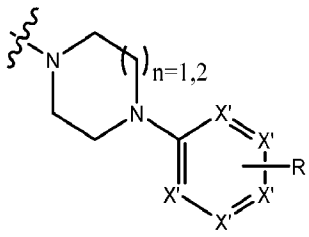
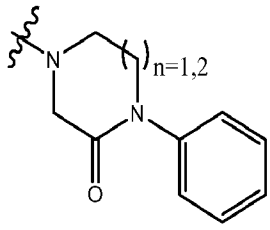
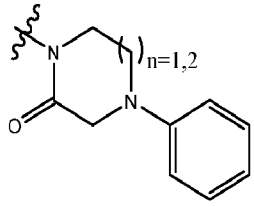
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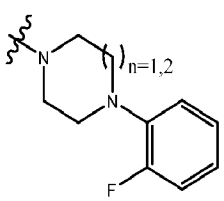
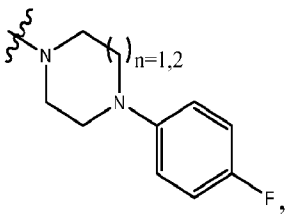
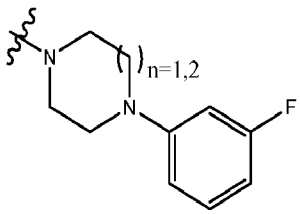
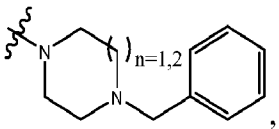
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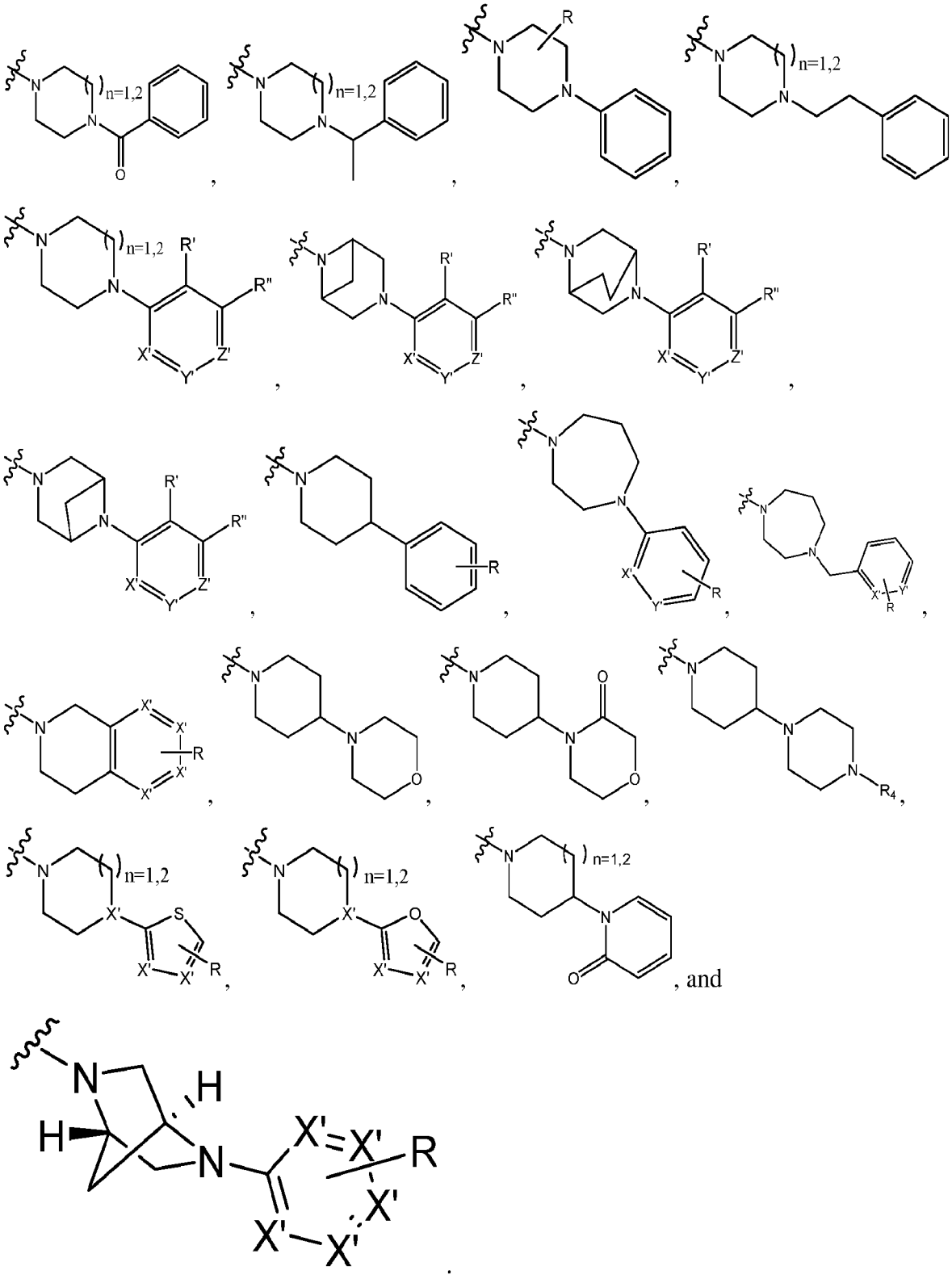
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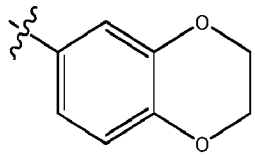
In some embodiments, R1 is selected from hydrogen,

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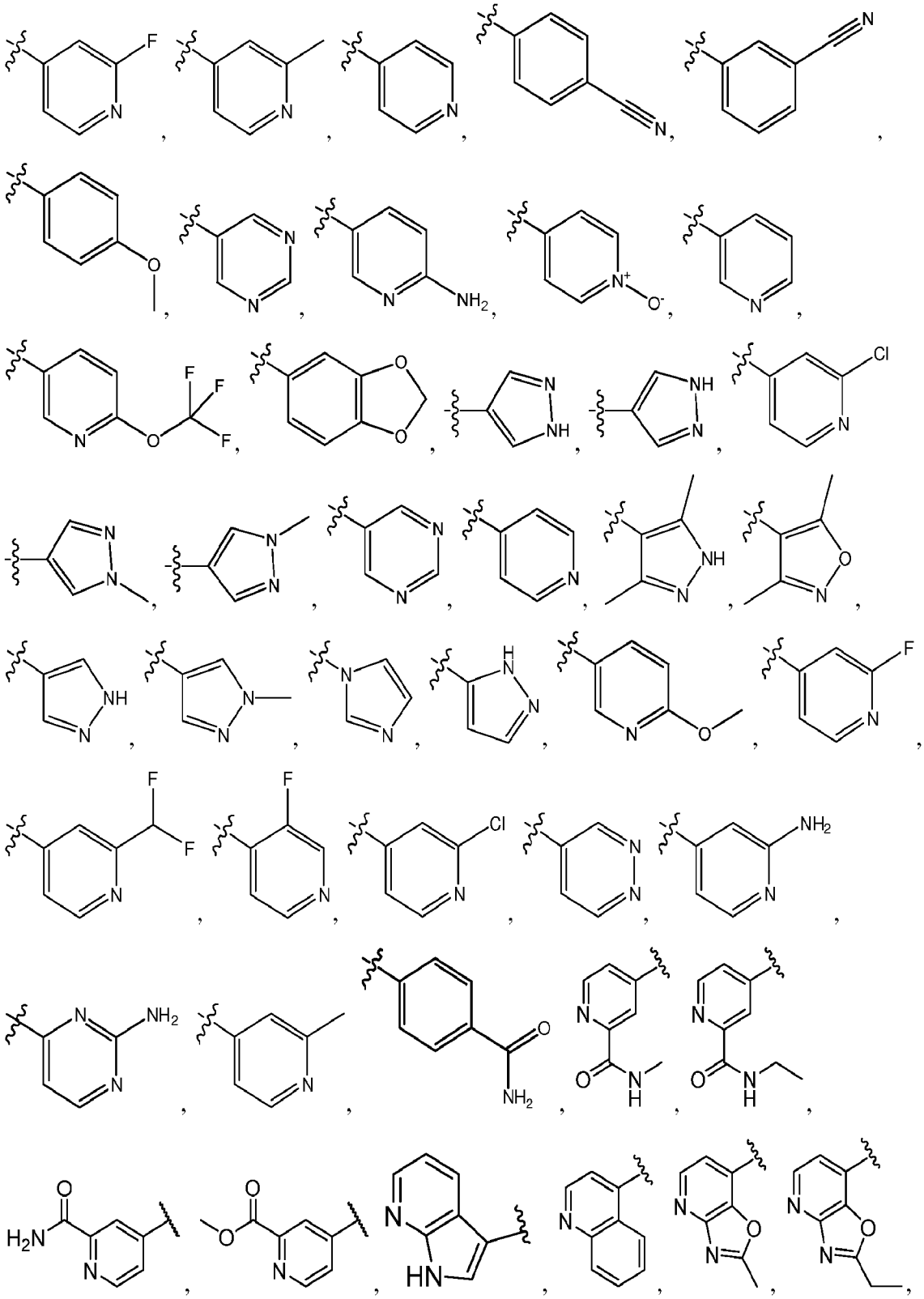
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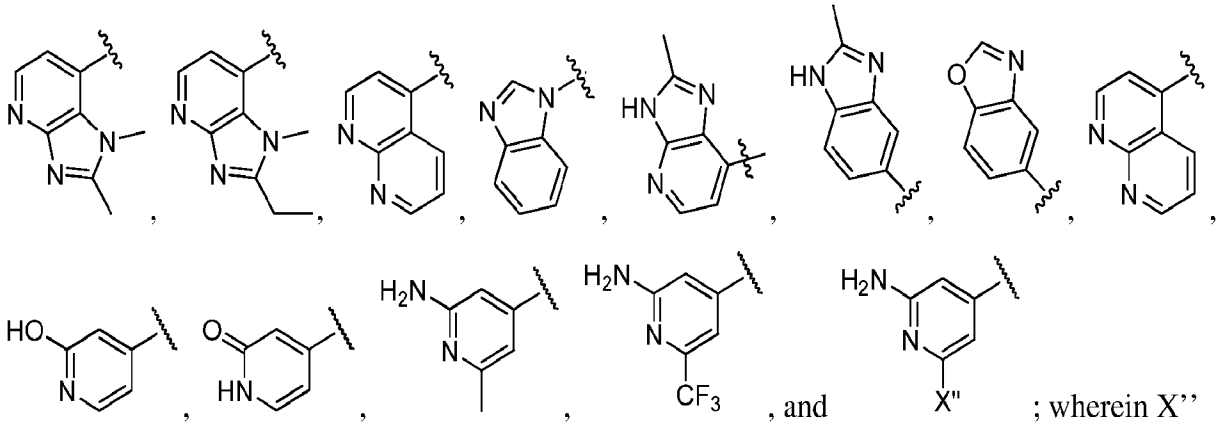


In some embodiments, R2 is selected from hydrogen, halogen (e.g., fluorine, bromine, iodine, chlorine), aryl, substituted aryl, heteroaryl, substituted heteroaryl, ,



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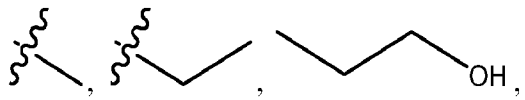


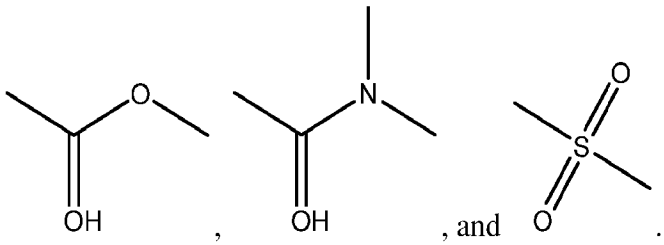
; wherein X'' is selected from alkyl, haloalkyl, amino, alkylamino, hydroxy, fluoro, chloro, bromo, and cyano groups.

In some embodiments, X', Y', and Z' are independently N, C or CR'.

In some embodiments, R, R' and R" are independently selected from hydrogen, halogen (e.g., fluorine, bromine, chlorine, iodine), di-halogen (di-fluorine, di-bromine, di-chlorine, di-iodine), CF3, OCH3, CHF2H, OCF3, methyl, di-methyl, alkoxy, alkylsulfonyl, cyano, carboxy, ester, amido, substituted amido, sulfonamide, substituted sulfonamide, methylenedioxy, heterocyclyl alkyl, heterocyclyl, heterocyclyl alkyl amido, a lipophilic moiety comprising ether, a secondary or tertiary amine moiety consisting of a heterocycloalkyl group that is bioisosteric to secondary amines (e.g., morpholine, piperidine, piperazine).

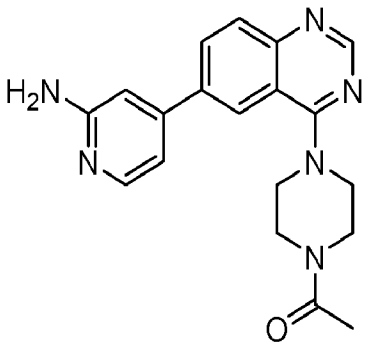
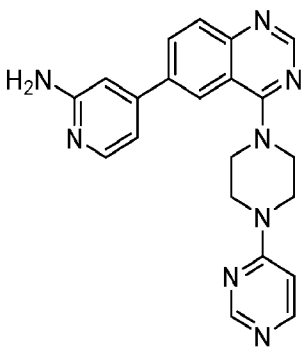
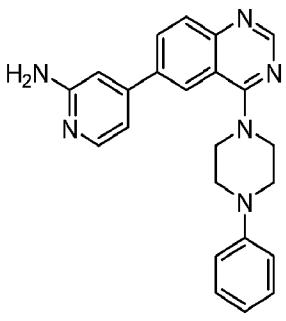
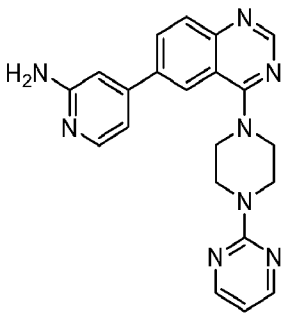
In some embodiments, R3 is selected from hydrogen, halogen (e.g., fluorine, bromine, chlorine, iodine), methyl, ethyl, and methoxy.

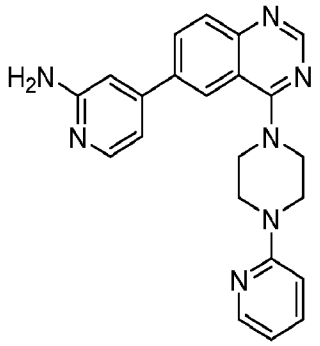
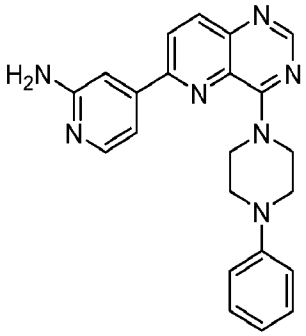
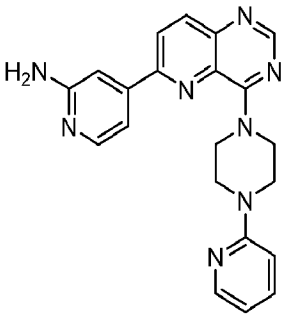
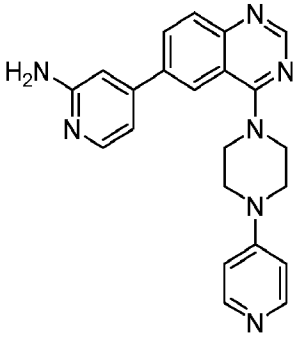
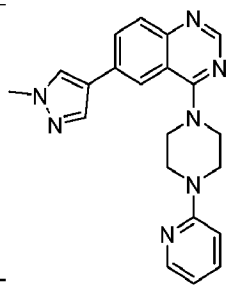
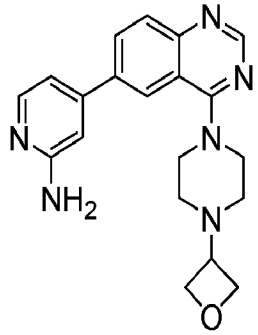
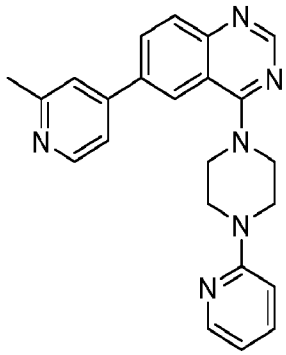
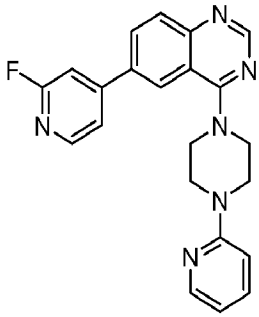
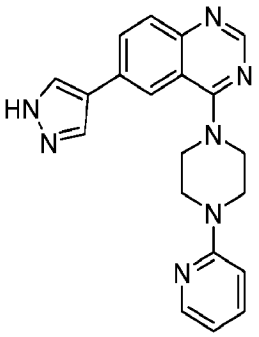
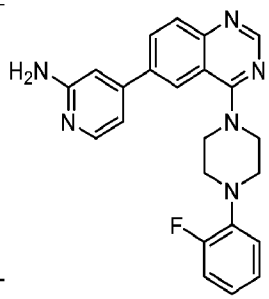
In some embodiments, R4 is selected from 

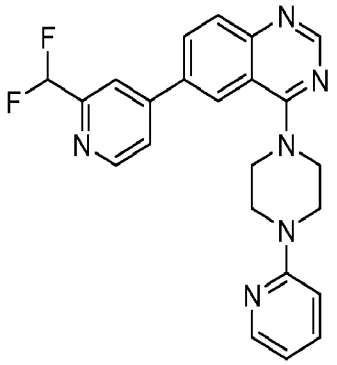
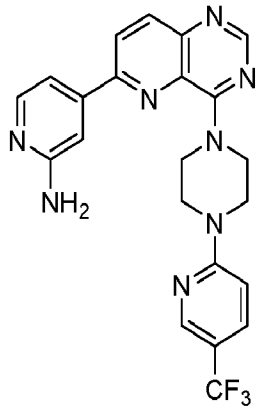
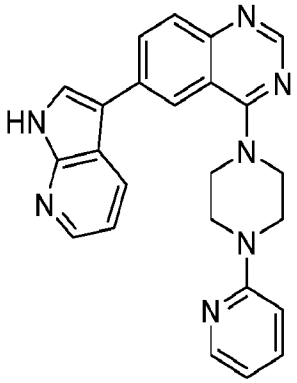
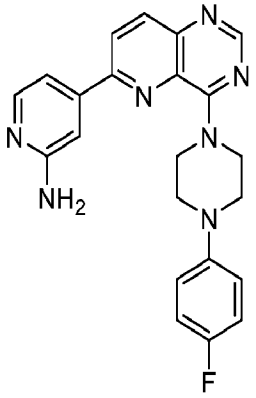
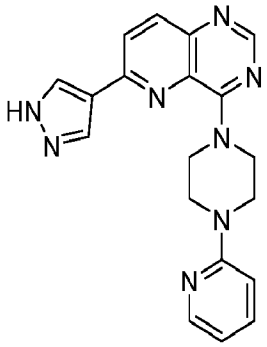
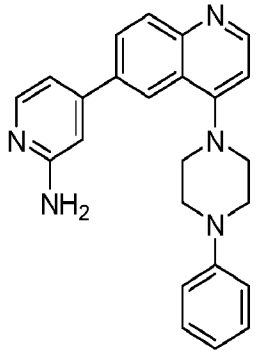
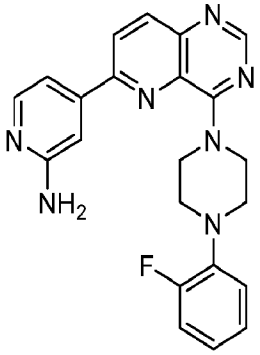
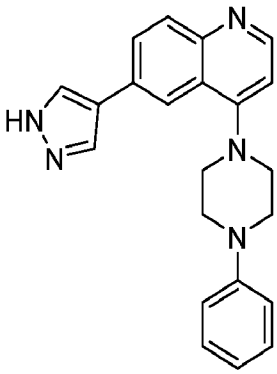


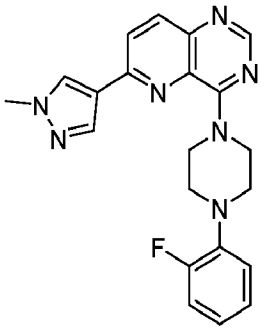
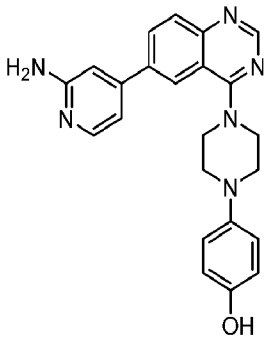
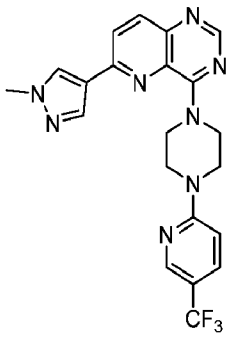
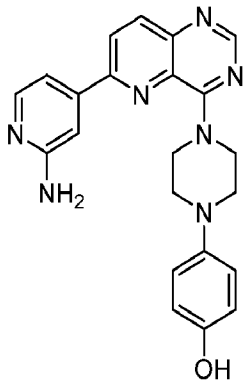
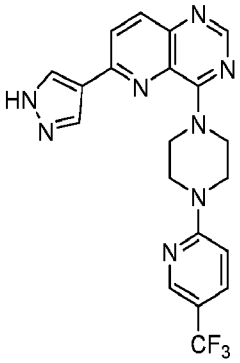
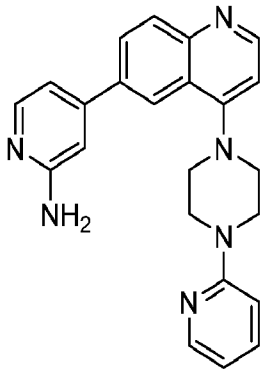
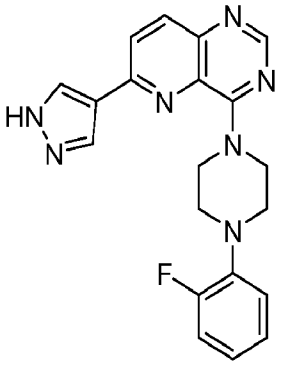
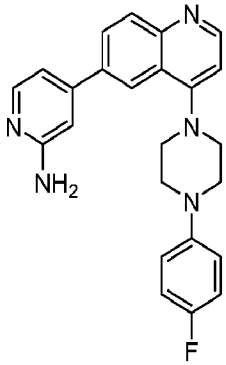
(HCEC) were cultured using 1x DMEM supplemented with 1% penicillin/streptomycin, 1% Glutamax, and 10% fetal bovine serum in 5% CO2 at 37°C. These cells were previously engineered to express the TopGFP reporter (Addgene #24304) using second generation lentiviral techniques. For the Wnt reporter assay, cells were seeded at 2000 cells per well in a 384-well black screenstar imaging microplates (Greiner #781866) and allowed to adhere overnight. The following day cells were stimulated to induce the Wnt pathway using 10μM CHIR99021 (Selleck #S1263). Simultaneously, DYR compounds were given in a dose-response using a Tecan d300e digital dispenser ranging from 0μM to 30μM concentrations. Cells were incubated for 24 hours before fixing for 30 minutes with 4% paraformaldehyde/sucrose solution. Cells were permeabilized with 0.1% triton-x in PBS for 10 minutes and stained for DAPI for 30 minutes. Plates were imaged on a Nikon Ti2 Eclipse fluorescent microscope for DAPI, GFP, and mCherry. Using Nikon Elements software for analysis, nuclei were segmented based on DAPI and mean object intensity per cell for both TopGFP and the internal control (mCherry) was measured. To calculate the amount of Wnt activity, we took the mean intensity of TopGFP and divided it by the mean intensity of mCherry per cell to normalize individual cells. Curves and EC50s were plotted and calculated using Graphpad Prism software.

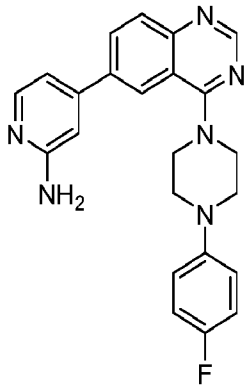
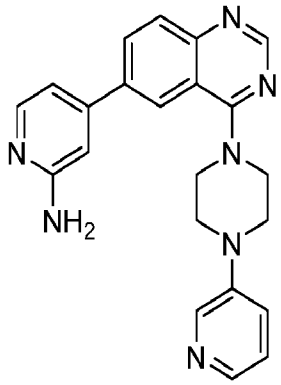
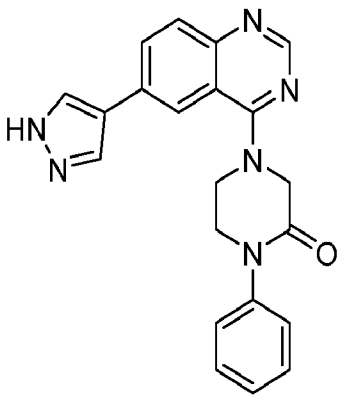
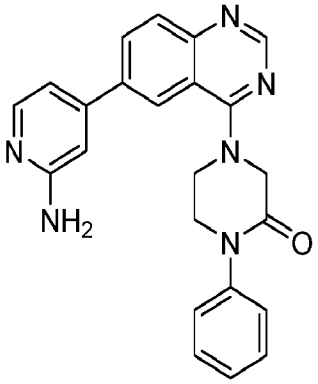
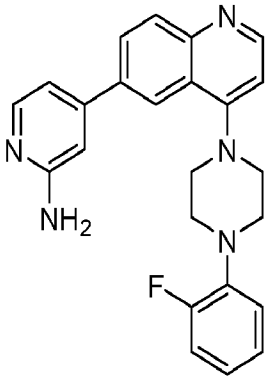
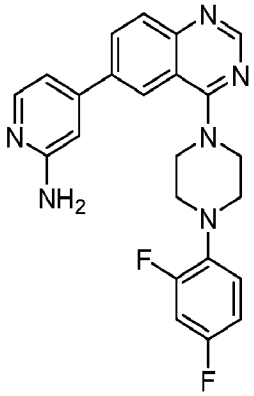
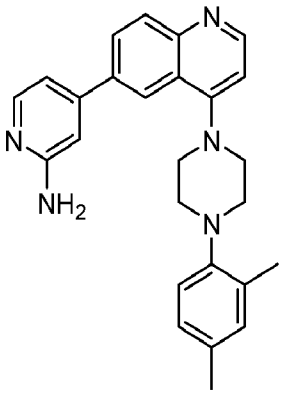
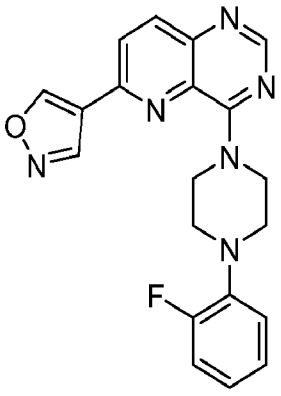
Table 1. Activity Key in WNT reporter (EC50) +++ < 100nM, ++ 100nM – 1uM, > 1uM

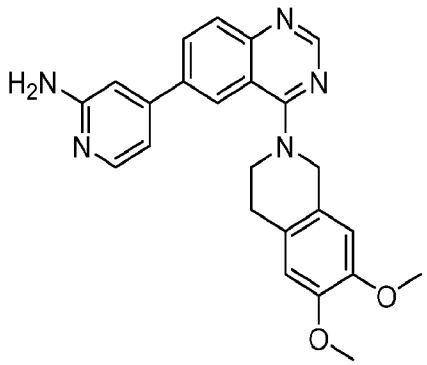
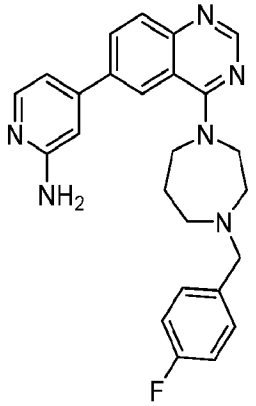
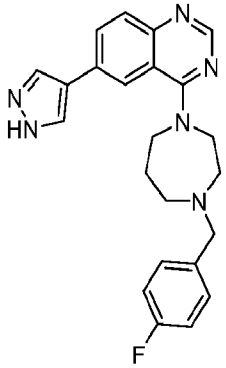
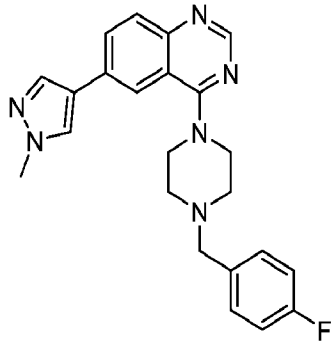
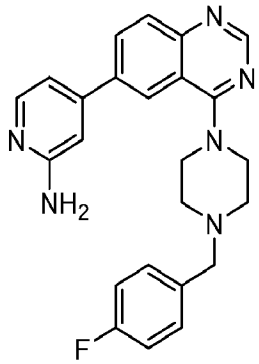
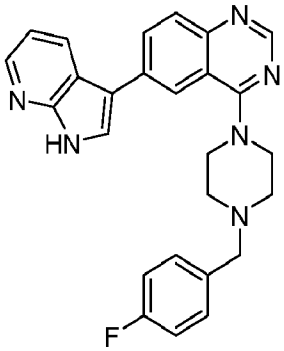
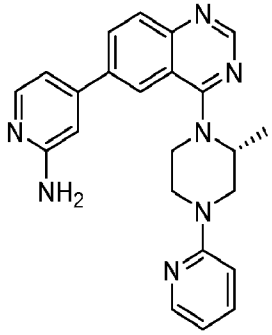
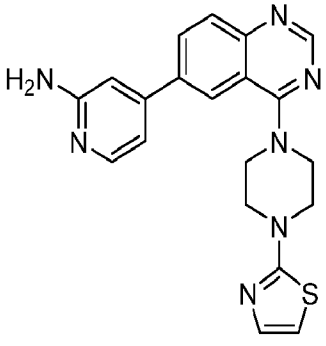
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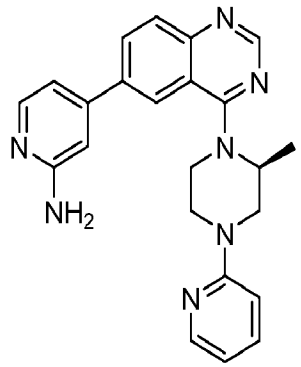
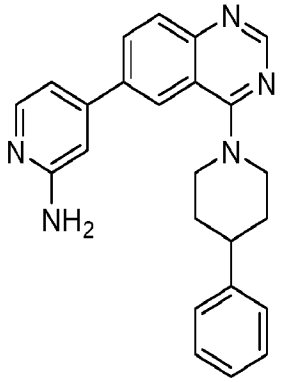
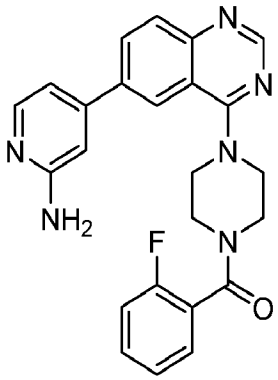
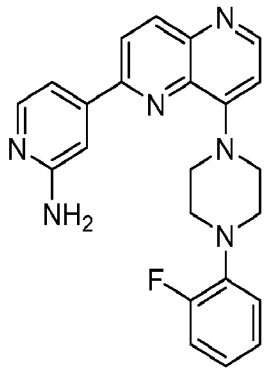
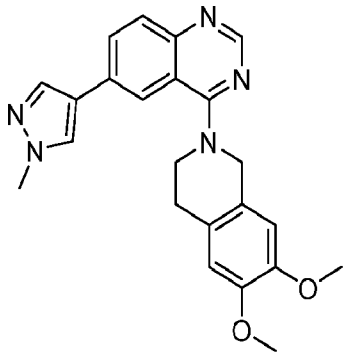
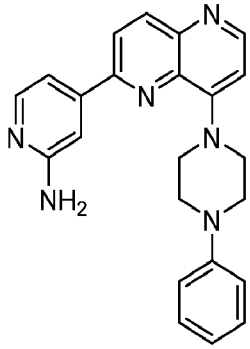
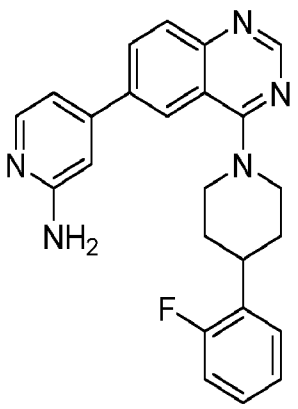
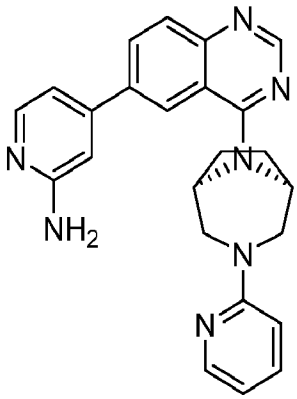
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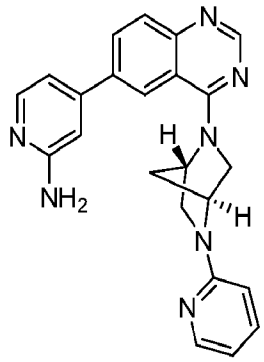
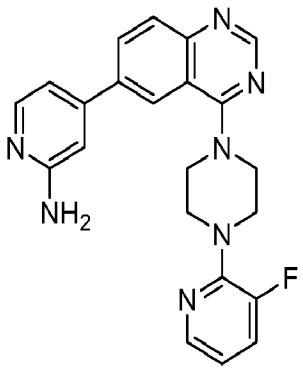
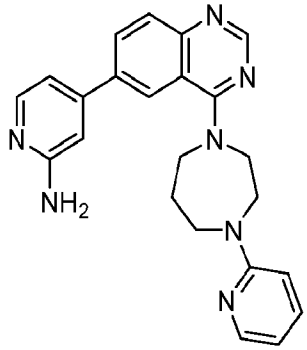
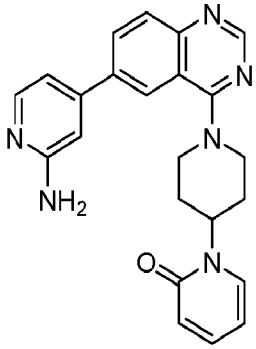
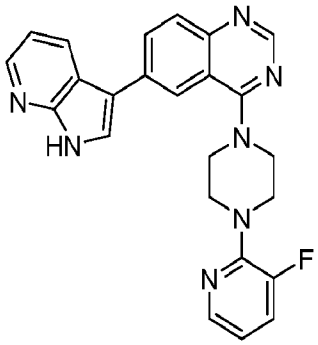
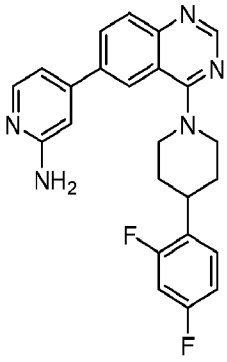
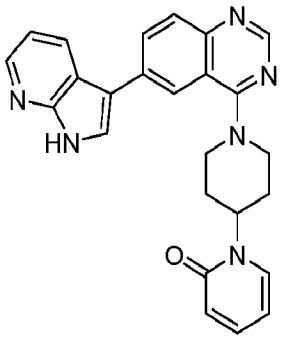
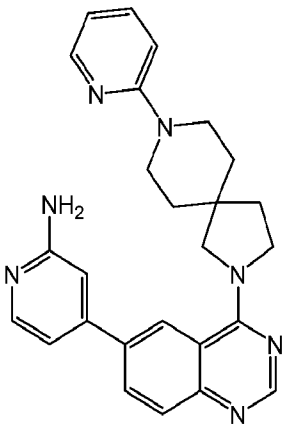
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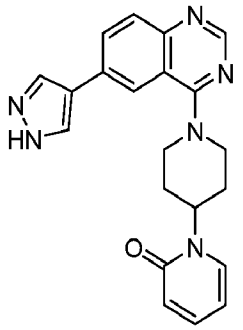
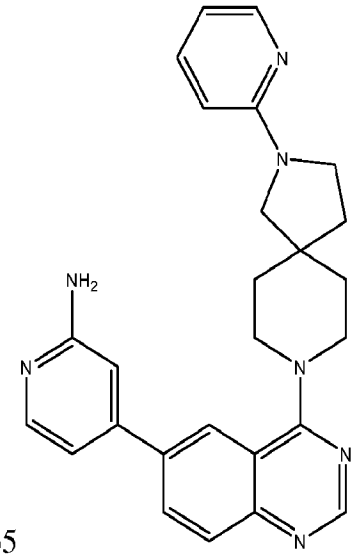
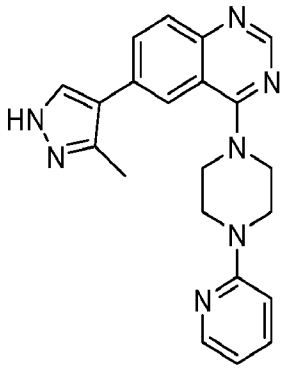
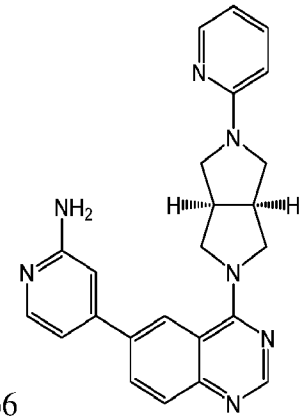
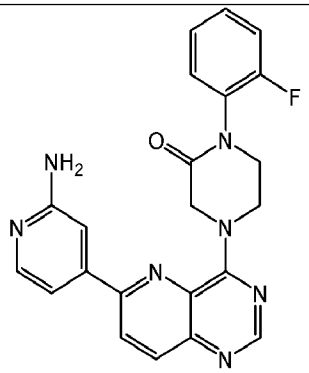
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The invention further provides processes for preparing any of the compounds of the present invention.

The invention also provides the use of compounds to not only inhibit DYRK1A activity but also signaling pathways dependent upon DYRK1A phosphorylation (e.g., Tau, PI3K/AKT, APP, PSI, ASF, RCAN-1, NFAT, p53, ASK1/JNK1, SIRT1, GluN2A and other NMDA

receptors), DYRK2 phosphorylation (e.g., 26S proteasome, heat shock factor 1, p53, MYC, and JUN), and DYRK3 phosphorylation (e.g., PRAS40). The invention also relates to the use of compounds for sensitizing cells to additional agent(s), such as agents known to be effective in the treatment of neurodegenerative disorders.

In certain embodiments, the compounds are used as DYRK protein degraders (see, Valazquez, et al, 2019 Molecular Neurobiology 1-12).

The compounds of the invention are useful for the treatment, amelioration, or prevention of disorders associated with DYRK1A, DYRK1B, DYRK2, DYRK3, CLK1, CLK2, CLK3, CLK4, homeodomain-interacting kinases (HIPKs), and/or CMGC kinases leading to inhibition of WNT signaling (e.g., Alzheimer's disease, down syndrome, Parkinson's disease, Huntington's disease, diabetes, autoimmune diseases, inflammatory disorders (e.g., airway inflammation, osteoarthritis (e.g., knee related osteoarthritis)), cancer (e.g., glioblastoma, prostate cancer, metastatic breast cancer, metastatic lung cancer, multiple myeloma, secondary metastatic tumors of the brain, colorectal cancer and metastatic colorectal cancer (e.g., metastatic colorectal cancer in the liver)), and other diseases), such as those responsive to DYRK isoform activity inhibition. In certain embodiments, the compounds can be used to treat, ameliorate, or prevent cancer that is associated with DYRK2 and DYRK3 activities (e.g., glioblastoma, prostate cancer, metastatic breast cancer, metastatic lung cancer, multiple myeloma, secondary metastatic tumors of the brain, colorectal cancer). In certain embodiments, the compounds can be used to treat, ameliorate, or prevent autoimmune diseases. In certain embodiments, the compounds can be used to treat, ameliorate, or prevent inflammatory disorders (e.g., airway inflammation, osteoarthritis (e.g., knee related osteoarthritis)).

The invention also provides pharmaceutical compositions comprising the compounds of the invention in a pharmaceutically acceptable carrier.

The invention also provides kits comprising a compound of the invention and instructions for administering the compound to an animal. The kits may optionally contain other therapeutic agents, e.g., agents useful in treating neurodegenerative disorders and/or anticancer agents.

DETAILED DESCRIPTION OF THE INVENTION

The DYRK family contains 5 kinases (DYRK1A, DYRK1B, DYRK2, DYRK3 and DYRK4). DYRKs belong to the CMGC group of proline-directed kinases, which also includes

cyclin-dependent kinases (CDKs), mitogen-activated protein kinases (MAPKs), glycogen synthase kinases (GSKs) and CDC2-like kinases (CLKs). While the signaling pathways of CDK and MAPK families have been extensively studied, much less is known on how DYRKs and CLKs are linked to other proteins and various physiological or pathological processes. The CLK family comprises CLK1 through CLK4. The cyclin-dependent kinases (CDKs) are a family of multifunctional enzymes that can modify various protein substrates involved in cell cycle progression, comprising CDK1 through CDK19.

The DYRK1A gene is located on chromosome 21 (21q22.2), a region known as the Down-Syndrome Critical Region (DSCR) (see, e.g., Hämmerle et al., 2011 Development 138, 2543-2554). The under- or over-expression of the Dyrk1a gene in mammals or of its orthologous gene minibrain (mnb) in Drosophila causes severe retardation of central nervous system development and maturation. At the molecular level, DYRK1A phosphorylates the nuclear factor of activated T cells (NFAT), counteracting the effect of calcium signaling and maintaining inactive NFAT (see, e.g., Arron et al., 2006 Nature 411, 595-600). DYRK1A has been identified as a negative regulator of the cell cycle that promotes the switch to a quiescent state or differentiation (see, e.g., Chen et al., 2013 Mol. Cell 52, 87-100). In malignant cells, DYRK1A promotes survival via inhibition of pro-apoptotic proteins (see, e.g., Guo et al., 2010 J. Bio. Chem. 285, 13223-13232; Seifert et al., 2008 FEBS J. 275, 6268-6280).

Experiments conducted during the course of developing embodiments for the present invention designed, synthesized and biologically evaluated compounds having a 6,6-heterocyclic structure (e.g., compounds having a naphthyridine, pyrido-pyridazine, pyrido-pyrazine, quinoline, pyrazino-pyridazine, pyrimido-pyrimidine, quinazoline, quinoxaline or cinnoline ring system) as inhibitors of the dual specificity tyrosine phosphorylation regulated kinases (DYRKs: 1A, 1B, 2, 3, 4) and CLK family members (1, 2, 3, 4) for use as therapeutics against AD, down syndrome, multiple malignancies, in particular those associated with inhibition of WNT signaling and other disorders related to DYRK/CLK activity (e.g., DS, other neuropathology, glioblastoma, prostate cancer, metastatic breast cancer, metastatic lung cancer, multiple myeloma, secondary metastatic tumors of the brain). Note DYRK1B plays roles in survival of certain cancer cells and myoblast differentiation and has been validated as a promising target for CRPC.

Moreover, the DYRK/CLK inhibitors of the present invention can be used for treating other cellular pathways involved in mental impairment and neurodegenerative dementia. Specifically, the DYRK/CLK inhibitors of the present invention can be used for inhibiting DYRK1A activated PI3K/Akt signaling, a pathway largely involved in neuronal development, growth, and survival. The DYRK1A inhibitors of the present invention DYRK1A can be used for inhibiting DYRK1A stimulated ASK1/JNK1 activity, thereby inducing neuronal death and apoptosis. In addition, the DYRK1A inhibitors of the present invention DYRK1A can be used to inhibit DYRK1A phosphorylation of p53 during embryonic brain development, thereby preventing neuronal proliferation alteration. The DYRK1A inhibitors of the present invention can be used to inhibit DYRK1A phosphorylation of synaptic proteins Amph 1, Dynamin 1, and Synaptojanin, involved in the regulation of endocytosis, thereby retaining synaptic plasticity through preventing alteration of the number, size, and morphology of dendritic spines. The DYRK1A inhibitors of the present invention can be used to inhibit presenilin 1 (the catalytic sub-unit of γ-secretase). The DYRK1A inhibitors of the present invention can be used to inhibit DYRK2/3 & 4 activity. The DYRK1A inhibitors of the present invention can be used to inhibit DYRK1B activity. The DYRK1A inhibitors of the present invention can be used to inhibit CMGC CLK1-4 kinase activity.

As such, the present invention addresses the need for effective therapies for GBM, AD and DS by providing potent and pan-selective DYRK/CLK inhibitors able to permeate the blood–brain barrier (BBB) and elicit on-mechanism therapeutic responses in animal models. Disease states in the periphery include colorectal cancer, castration-resistant prostate cancer and malignancies associated with inhibition of WNT signaling.

Accordingly, the present invention relates to a new class of small-molecule compounds having a 6,6-heterocyclic structure (e.g., compounds having a naphthyridine, pyrido-pyridazine, pyrido-pyrazine, quinoline, pyrazino-pyridazine, pyrimido-pyrimidine, quinazoline, quinoxaline or cinnoline ring system) which function as inhibitors of DYRK1A, DYRK1B, DYRK2, DYRK3, CLK1, CLK2, CLK3, CLK4, CDK7, CDK8/19, PI3K, PDGFrA/B, mTOR, WNT, homeodomain-interacting kinases (HIPKs), and/or CMGC kinases leading to inhibition of WNT signaling, and their use as therapeutics for the treatment of Alzheimer's disease, down syndrome, Parkinson's disease, Huntington's disease, diabetes, autoimmune diseases, inflammatory disorders (e.g., airway inflammation, osteoarthritis (e.g., knee related osteoarthritis)), cancer

(e.g., glioblastoma, prostate cancer, metastatic breast cancer, metastatic lung cancer, multiple myeloma, secondary metastatic tumors of the brain, colorectal cancer and metastatic colorectal cancer (e.g., metastatic colorectal cancer in the liver)), and other diseases.

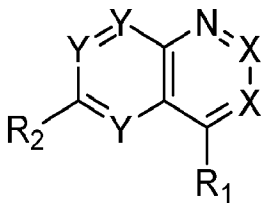
The CDC2-like kinase (CLK) family contains four isoforms which are important in regulating the function of the spliceosome complex (see, e.g., Fedorov et al, Chem Biol. 201 l;18(l):67-76). This complex, comprised of small nuclear RNAs (snRNA) and a large number of associated proteins, regulates the splicing of pre-mRNAs to give mature protein-encoding mRNAs. CLKl is known to regulate the activity of the spliceosome via phosphorylation of the constituent serine-arginine-rich (SR) proteins (see, e.g., Bullock et al, Structure. 2009;17(3):352-62). By controlling the activity of the spliceosome in this way, many genes are able express more than one mRNA leading to diversity in the translated proteins. The alternative protein iso forms transcribed from the same gene will often have different activities and physiological functions. Deregulation of alternative splicing has been linked to cancer, where a number of cancer-related proteins are known to be alternatively spliced (see, e.g., Druillennec et al, J Nucleic Acids. 2012;2012:639062). An example of an alternatively spliced protein in cancer is Cyclin Dl, important for the progression of cancer cells through the cell cycle (see, e.g., Wang et al, Cancer Res. 2008;68(14):5628-38).

Alternative splicing regulated by CLKl has also been described to play a role in neurodegenerative diseases, including Alzheimer's and Parkinson's, via phosphorylation of the SR proteins of the spliceosome (see, e.g., Jain et al, Curr Drug Targets. 2014;15(5):539-50). In the case of Alzheimer's, CLKl is known to regulate the alternative splicing of the microtubule-associated protein TAU leading to an imbalance between TAU iso forms which is sufficient to cause neurodegeneration and dementia (see, e.g., Liu et al, Mol Neurodegener. 2008;3:8).

Cyclin-dependent kinases (CDKs) have been shown to be heavily implicated in WNT inhibition. In particular, CDK7 enhances the interaction between beta-catenin and TCF4 (see Duan et al., Cell Death & Differentiation, 2019, 26, 1442–1452). CDK8 has been identified as a gene that regulates b-catenin driven reporter activity in a loss of function RNAi screen (see Rosenbluh et al., Trends Pharmacol Sci. 2014, 35, 103–109). Moreover, CDK8 selectivity promotes growth of colon cancer metatheses in the liver by regulating gene expression of TIMP3 and matrix metalloproteases (see Liang et. al., Cancer Res. 2018, 78(23), 6594–6606). Indeed, CDK8 and its paralog CDK19 are two isoforms of the Mediator kinase, the enzymatic

component of the CDK module that binds to the transcriptional Mediator complex and inhibition of the CDK8/19 Mediator kinase sensitizes HER2+ breast cancers to HER2-targeting drugs preventing resistance in vitro and in vivo (see, e.g., Ding et al., PNAS, 2022, 119 (32), 1-11, e2201073119). High profile CDK8/CDK19 inhibitors in clinical trials include RVU120 in patients with Acute Myeloid Leukemia (AML) or high-risk Myelodysplastic Syndrome (HR-MDS) (NCT04021368), TSN084 (NCT05300438) and Senexin B, the first selective CDK8/19 inhibitor to enter clinical trials (NCT03065010).

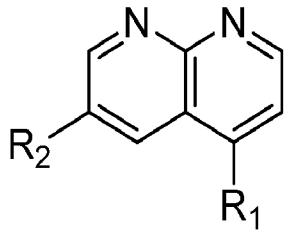
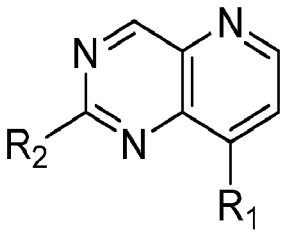
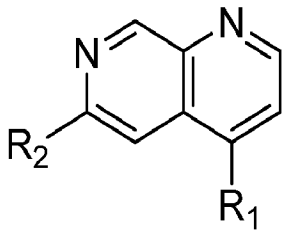
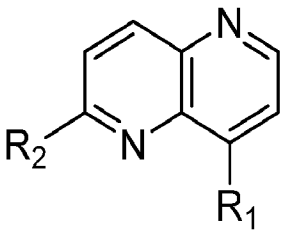
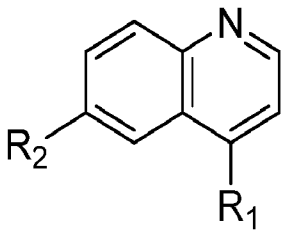
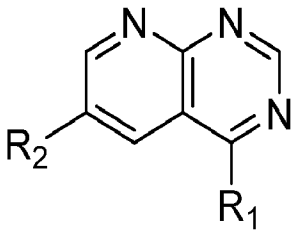
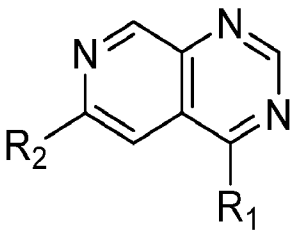
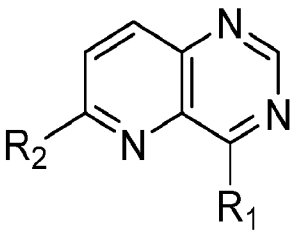
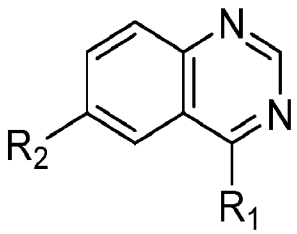
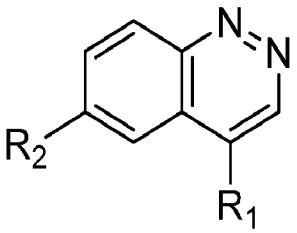
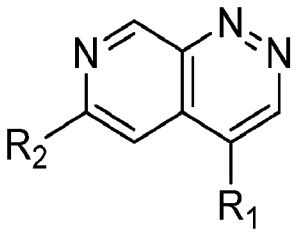
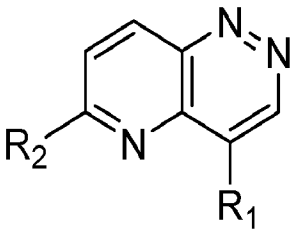
In the treatment of both cancer and neurological disease, there is thus undoubtedly an urgent need for compounds which potently inhibit DYRK and CLK kinases and CDK7, 8 and 19 whilst not affecting other closely-related kinases. The compounds described herein address this need.

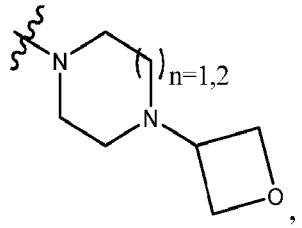
In a particular embodiment, compounds encompassed within the following formulas are provided:  (Formula I); including pharmaceutically acceptable salts, solvates, and/or prodrugs thereof.

Formula I is not limited to a particular chemical moiety for X, Y, R1 and R2. In some embodiments, the particular chemical moiety for X, Y, R1 and R2 independently include any chemical moiety that permits the resulting compound to inhibit DYRK1A activity. In some embodiments, the particular chemical moiety for X, Y, R1 and R2 independently include any chemical moiety that permits the resulting compound to inhibit one or more of: DYRK1A related PI3K/Akt signaling; DYRK1A related tau phosphorylation; DYRK1A related NFAT phosphorylation; DYRK1A related ASK1/JNK1 pathway activation; DYRK1A related p53 phosphorylation; DYRK1A related Amph 1 phosphorylation; DYRK1A related Dynamin 1 phosphorylation; DYRK1A related Synaptojanin phosphorylation; DYRK1A related presenilin 1 (the catalytic sub-unit of γ-secretase) activity; DYRK1A related amyloid precursor protein phosphorylation; DYRK1A related SIRT1 activation; DYRK2 related heat shock factor 1 and 26S proteasome activities; DYRK3 related mTOR activity; DYRK3 phosphorylation (e.g., PRAS40); DYRK1B activity; CMGC/CLK kinase activity; CLK1 activity; CLK2 activity; CLK3 activity; CLK4 activity; CDK7 activity; CDK8 activity; CDK19 activity; PI3K activity; PI3K

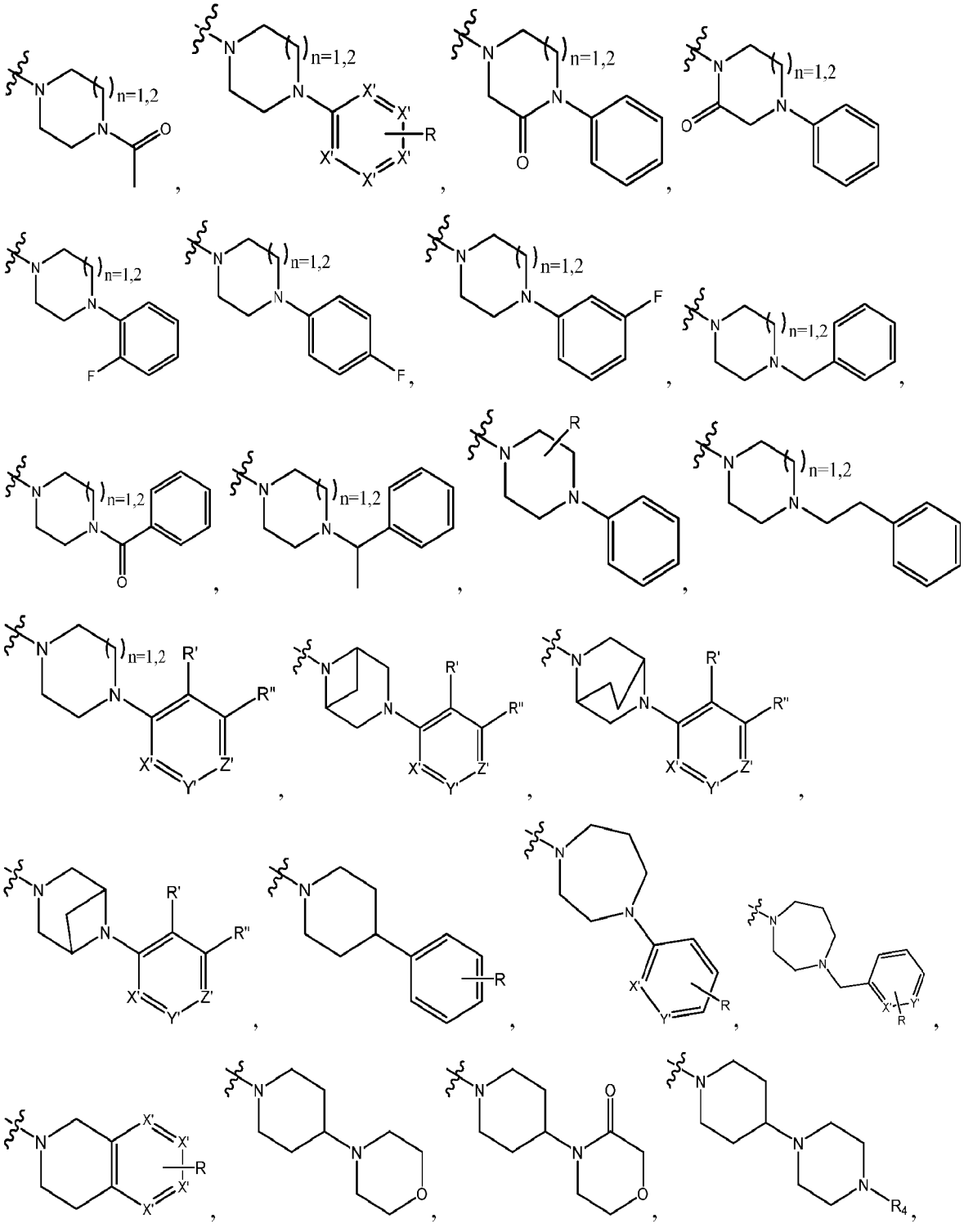
mutant activity; PDGFrA/B activity; mTOR activity; c-KIT activity; RYK activity; and WNT signaling.

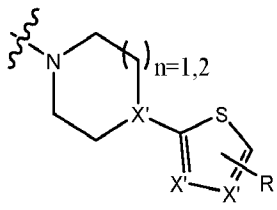
Such embodiments are not limited to a particular definition for each of the "X" and "Y" substituents.

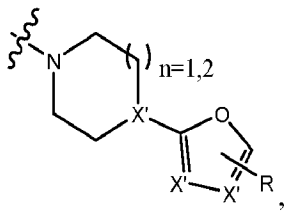
In some embodiments, one of the "X" substituents is carbon and the other is nitrogen, or both of the "X" substituents are carbon; and one of the "Y" substituents is nitrogen and the other "Y" substituents are carbon, or two of the "Y" substituents are nitrogen and one "Y" substituent is carbon, or all of the "Y" substituents are carbon; such that the resulting structure is one of the following formulas: , , , , , , , , , , , and .

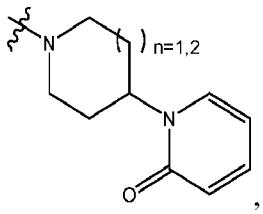


In some embodiments, R1 is selected from hydrogen,

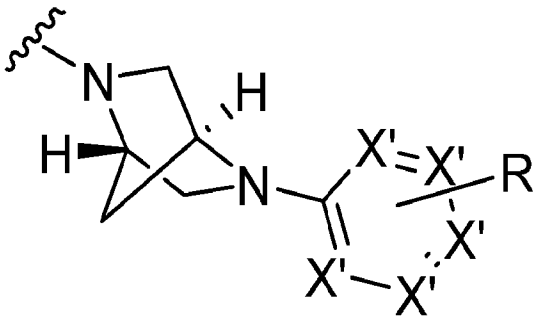




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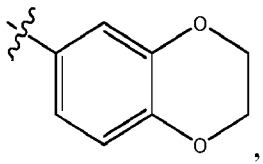
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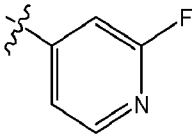


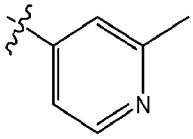
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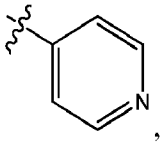
In some embodiments, R2 is selected from hydrogen, halogen (e.g., fluorine, bromine, iodine, chlorine), aryl, substituted aryl, heteroaryl, substituted heteroaryl, ,

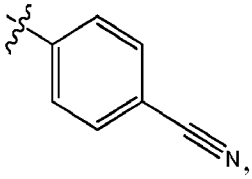


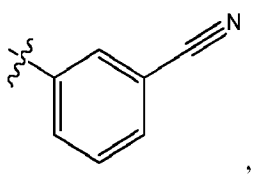
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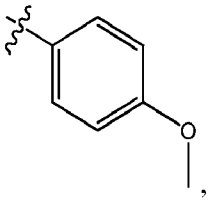


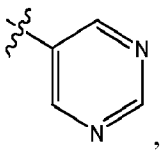
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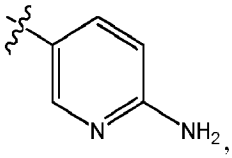
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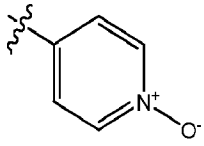
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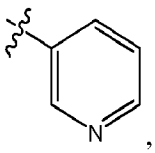
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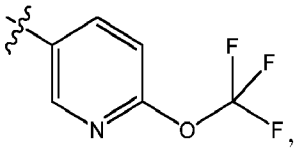
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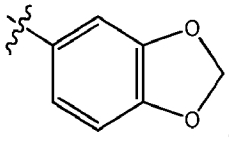
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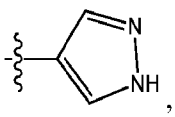
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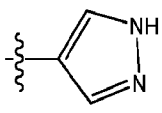
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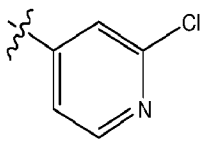
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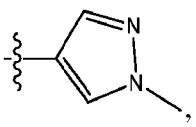
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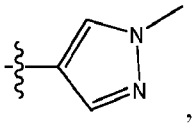
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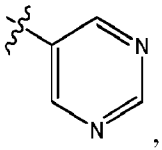
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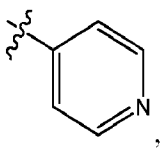
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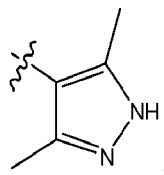
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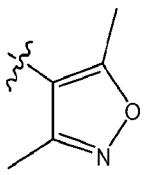
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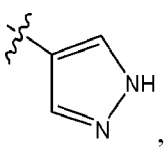
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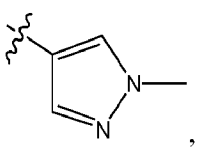
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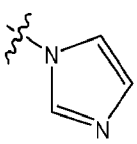
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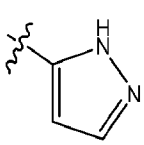
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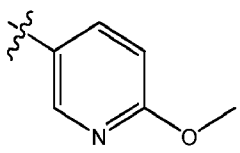
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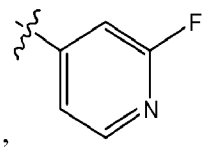
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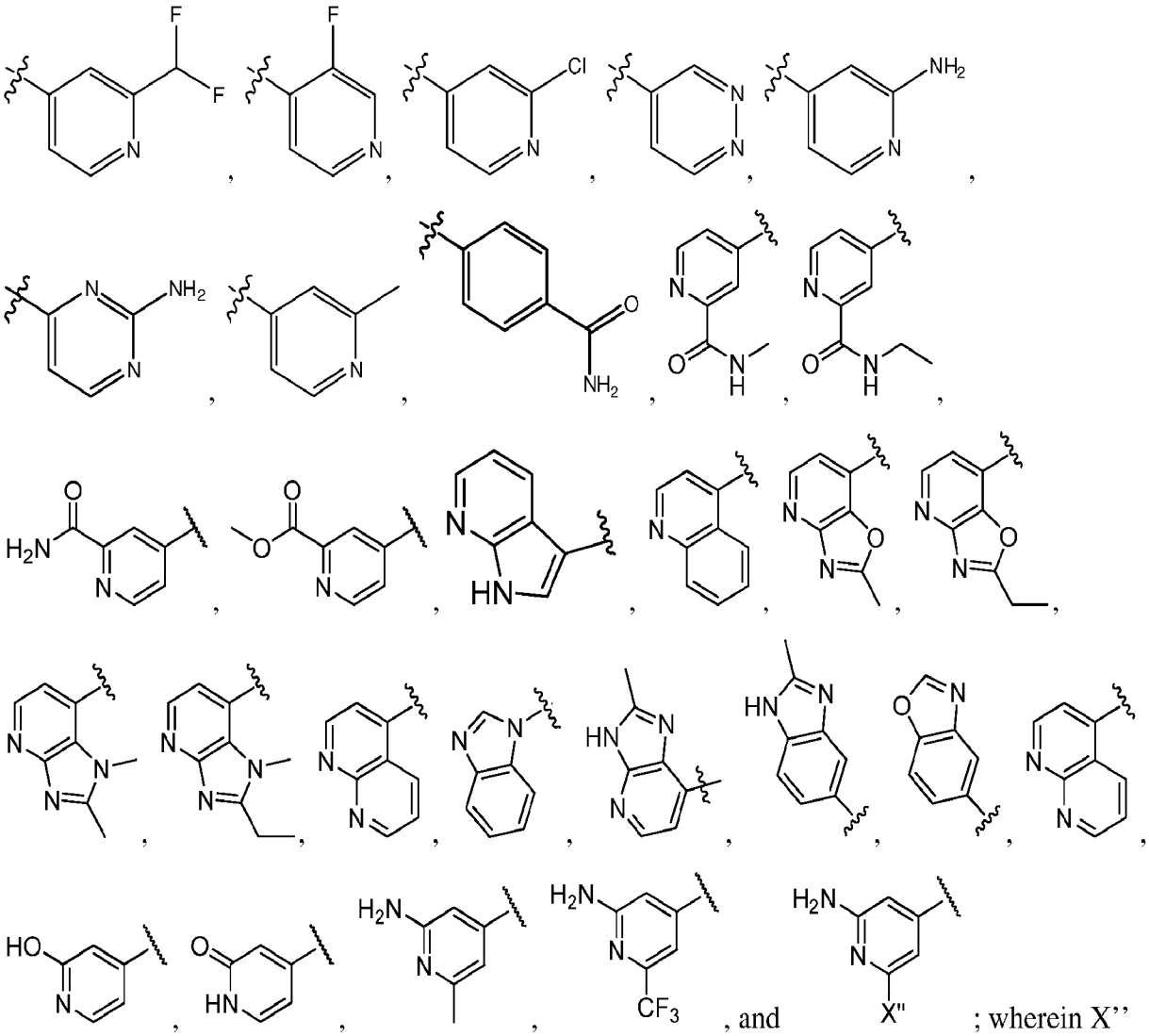
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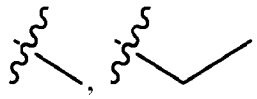
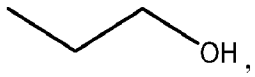
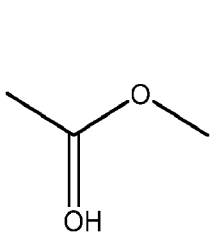
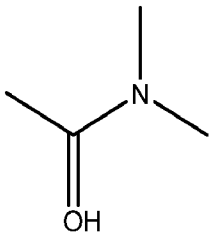
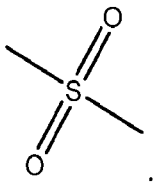


is selected from alkyl, haloalkyl, amino, alkylamino, hydroxy, fluoro, chloro, bromo, and cyano groups.

In some embodiments, X', Y', and Z' are independently N, C or CR'.

In some embodiments, R, R' and R" are independently selected from hydrogen, halogen (e.g., fluorine, bromine, chlorine, iodine), di-halogen (di-fluorine, di-bromine, di-chlorine, di-iodine), CF3, OCH3, CHF2H, OCF3, methyl, di-methyl, alkoxy, alkylsulfonyl, cyano, carboxy, ester, amido, substituted amido, sulfonamide, substituted sulfonamide, methylenedioxy, heterocyclyl alkyl, heterocyclyl, heterocyclyl alkyl amido, a lipophilic moiety comprising ether, a secondary or tertiary amine moiety consisting of a heterocycloalkyl group that is bioisosteric to secondary amines (e.g., morpholine, piperidine, piperazine).

In some embodiments, R3 is selected from hydrogen, halogen (e.g., fluorine, bromine, chlorine, iodine), methyl, ethyl, and methoxy.

In some embodiments, R4 is selected from , , , , , and .

In some embodiments, the compounds are recited in Table 1. In some embodiments, the compound is one of Compounds 1-67 recited in Example I.

The invention further provides processes for preparing any of the compounds of the present invention.

In some embodiments, the compositions and methods of the present invention are used to treat diseased cells, tissues, organs, or pathological conditions and/or disease states in an animal (*e.g.*, a mammalian patient including, but not limited to, humans and veterinary animals). In this regard, various diseases and pathologies are amenable to treatment or prophylaxis using the present methods and compositions. A non-limiting exemplary list of these diseases and conditions includes, but is not limited to, Alzheimer's disease, Down syndrome, Huntington's disease, Parkinson's disease, autoimmune diseases, cancer (e.g., glioblastoma, prostate cancer, metastatic breast cancer, metastatic lung cancer, multiple myeloma, secondary metastatic tumors of the brain), inflammatory disorders (e.g., airway inflammation), any neurodegenerative disorder related to DYRK1A, DYRK1B, DYRK2, DYRK3, CLK1, CLK2, CLK3, CLK4 activity, and/or CDK7, CDK8, CDK19 and any type of cancer related to DYRK1A, DYRK1B, DYRK2, DYRK3, CLK1, CLK2, CLK3, CLK4, and/or CDK7, CDK8, CDK19 activity, in particular those associated with disruption of WNT signaling.

Some embodiments of the present invention provide methods for administering an effective amount of a compound of the invention and at least one additional therapeutic agent (including, but not limited to, any agent useful in treating Alzheimer's disease, Down syndrome, Huntington's disease, Parkinson's disease, autoimmune diseases, inflammatory disorders (e.g., airway inflammation), any neurodegenerative disorder related to DYRK1A, DYRK1B, DYRK2, DYRK3, and/or CLK1, CLK2, CLK3 or CLK4 activity, in particular those associated with disruption of WNT signaling.

Compositions within the scope of this invention include all compositions wherein the compounds of the present invention are contained in an amount which is effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typically, the compounds may be administered to mammals, *e.g.* humans, orally at a dose of 0.0025 to 50 mg/kg, or an equivalent amount of the pharmaceutically acceptable salt thereof, per day of the body weight of the mammal being treated for disorders responsive to induction of apoptosis. In one embodiment, about 0.01 to about 25 mg/kg is orally administered to treat, ameliorate, or prevent such disorders. For intramuscular injection, the dose is generally about one-half of the oral dose. For example, a suitable intramuscular dose would be about 0.0025 to about 25 mg/kg, or from about 0.01 to about 5 mg/kg.

The unit oral dose may comprise from about 0.01 to about 1000 mg, for example, about 0.1 to about 100 mg of the compound. The unit dose may be administered one or more times daily as one or more tablets or capsules each containing from about 0.1 to about 10 mg, conveniently about 0.25 to 50 mg of the compound or its solvates.

In a topical formulation, the compound may be present at a concentration of about 0.01 to 100 mg per gram of carrier. In a one embodiment, the compound is present at a concentration of about 0.07-1.0 mg/ml, for example, about 0.1-0.5 mg/ml, and in one embodiment, about 0.4 mg/ml.

In addition to administering the compound as a raw chemical, the compounds of the invention may be administered as part of a pharmaceutical preparation containing suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the compounds into preparations which can be used pharmaceutically. The preparations, particularly those preparations which can be administered orally or topically and which can be used for one type of administration, such as tablets, slow release lozenges and capsules, mouth rinses and mouth washes, gels, liquid suspensions, hair rinses, hair gels, shampoos and also preparations which can be administered rectally, such as suppositories, as well as suitable solutions for administration by intravenous infusion, injection, topically or orally, contain from about 0.01 to 99 percent, in one embodiment from about 0.25 to 75 percent of active compound(s), together with the excipient.

The pharmaceutical compositions of the invention may be administered to any patient which may experience the beneficial effects of the compounds of the invention. Foremost among such patients are mammals, *e.g.*, humans, although the invention is not intended to be so limited. Other patients include veterinary animals (cows, sheep, pigs, horses, dogs, cats and the like).

The compounds and pharmaceutical compositions thereof may be administered by any means that achieve their intended purpose. For example, administration may be by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, buccal, intrathecal, intracranial, intranasal or topical routes. Alternatively, or concurrently, administration may be by the oral route. The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

The pharmaceutical preparations of the present invention are manufactured in a manner which is itself known, for example, by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets.

Suitable excipients are, in particular, fillers such as saccharides, for example lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, as well as binders such as starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of

suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules which may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are in one embodiment dissolved or suspended in suitable liquids, such as fatty oils, or liquid paraffin. In addition, stabilizers may be added.

Possible pharmaceutical preparations which can be used rectally include, for example, suppositories, which consist of a combination of one or more of the active compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, or paraffin hydrocarbons. In addition, it is also possible to use gelatin rectal capsules which consist of a combination of the active compounds with a base. Possible base materials include, for example, liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts and alkaline solutions. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension include, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

The topical compositions of this invention are formulated in one embodiment as oils, creams, lotions, ointments and the like by choice of appropriate carriers. Suitable carriers include vegetable or mineral oils, white petrolatum (white soft paraffin), branched chain fats or oils, animal fats and high molecular weight alcohol (greater than C_{12}). The carriers may be those in which the active ingredient is soluble. Emulsifiers, stabilizers, humectants and antioxidants may also be included as well as agents imparting color or fragrance, if desired. Additionally,

transdermal penetration enhancers can be employed in these topical formulations. Examples of such enhancers can be found in U.S. Pat. Nos. 3,989,816 and 4,444,762; each herein incorporated by reference in its entirety.

Ointments may be formulated by mixing a solution of the active ingredient in a vegetable oil such as almond oil with warm soft paraffin and allowing the mixture to cool. A typical example of such an ointment is one which includes about 30% almond oil and about 70% white soft paraffin by weight. Lotions may be conveniently prepared by dissolving the active ingredient, in a suitable high molecular weight alcohol such as propylene glycol or polyethylene glycol.

One of ordinary skill in the art will readily recognize that the foregoing represents merely a detailed description of certain preferred embodiments of the present invention. Various modifications and alterations of the compositions and methods described above can readily be achieved using expertise available in the art and are within the scope of the invention.

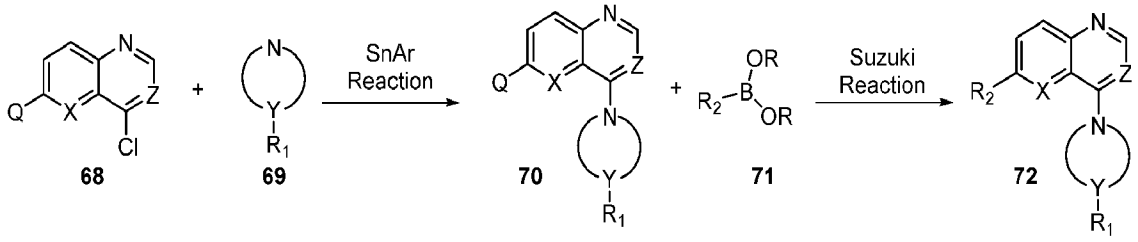
EXAMPLES

The following examples are illustrative, but not limiting, of the compounds, compositions, and methods of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered in clinical therapy and which are obvious to those skilled in the art are within the spirit and scope of the invention.

Example I.

This example provides synthesis and characterization information for compounds of the present invention.

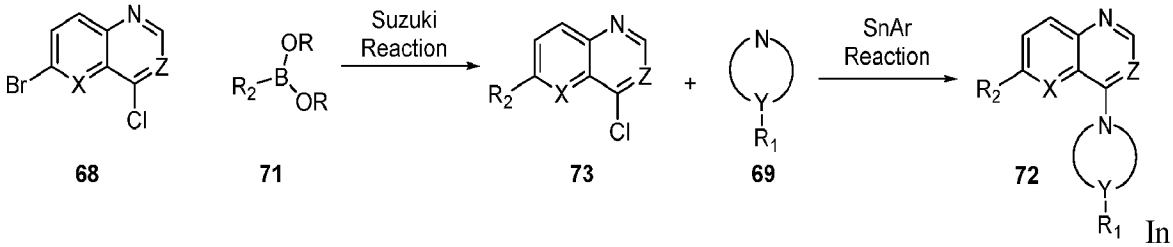
General Scheme 1:



In General Scheme 1 **68** is converted to **70** through standard SNAr chemistry by coupling with commercially available or synthetically prepared amines. **70** was then converted to **72** by Suzuki cross coupling chemistry by coupling with commercially available or synthetically prepared boronic acids and boronic esters. (X=CH or N, Q = Cl or Br, Z = CH or N, Y = N or CH).

General Scheme 2:

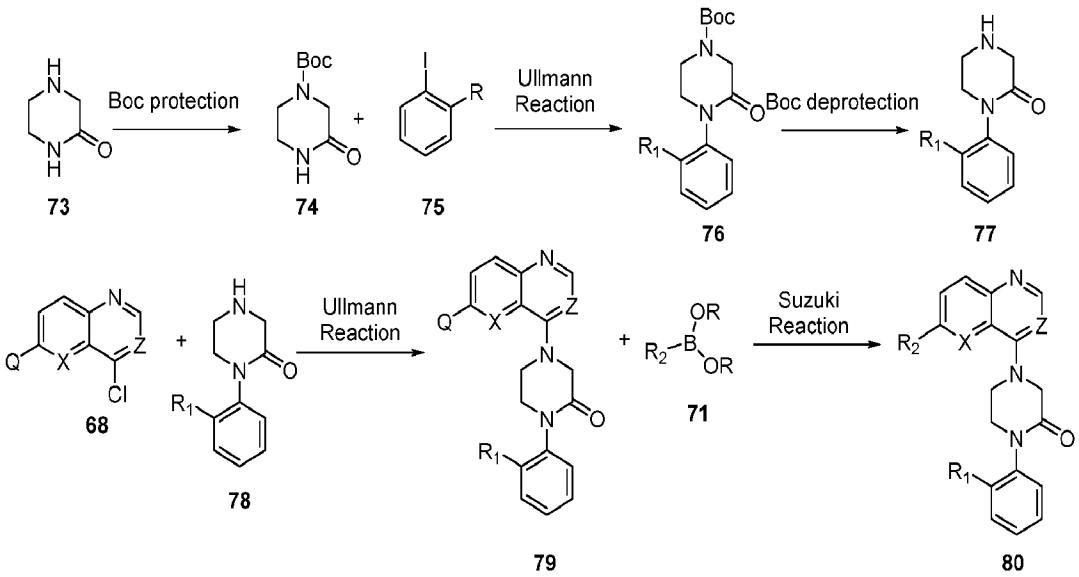
Four compounds (29, 30, 33, 34) were prepared by the following general route.



In General Scheme 1 **68** is converted to **73** by Suzuki cross coupling with commercially available boronic acids and boronic esters. **73** was then converted to **72** through standard SNAr chemistry by coupling with commercially available or synthetically prepared secondary amines (X=CH or N, Z = CH or N, Y = N or CH).

General Scheme 3:

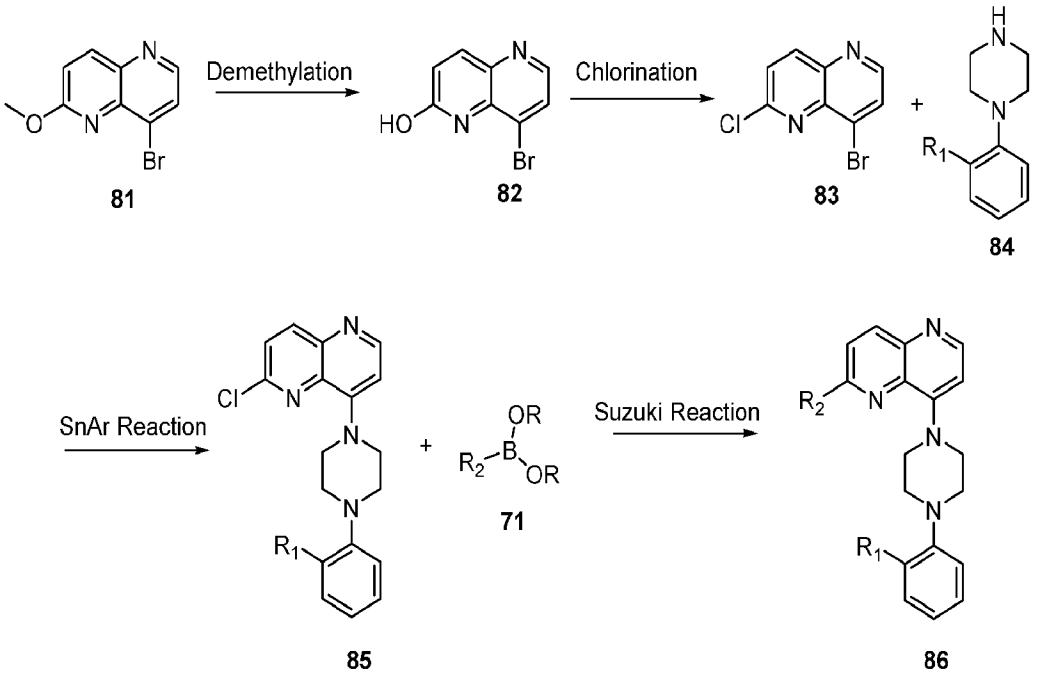
Two compounds (32, 67) were prepared by the following general route.



In General Scheme 3 **73** is converted to **74** through a boc protection followed by an Ullmann coupling reaction with commercially available aryl halides. **76** was then converted to **77** by a Boc deprotection. A second Ullmann coupling reaction was employed to afford **79**. **79** was then converted to **80** by Suzuki cross coupling chemistry by coupling with commercially available or synthetically prepared boronic acids and boronic esters. (X=CH or N, Q = Cl or Br, Z = CH or N, Y = N or CH).

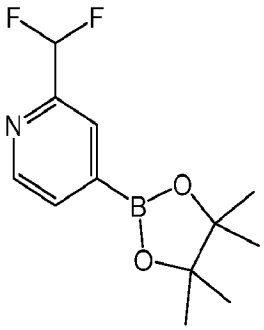
General Scheme 4:

Two compounds (52, 53) were prepared by the following general route.



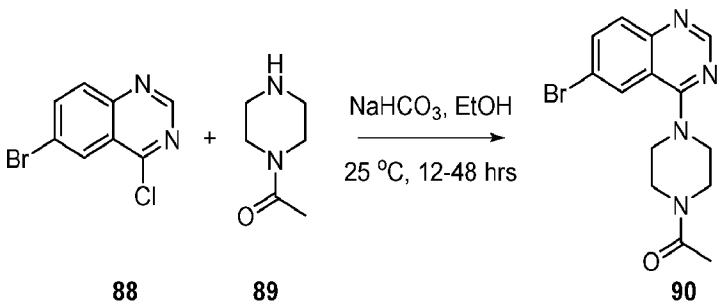
In General Scheme 4 **81** is converted to **82** by demethylation followed by chlorination reaction to afford **83**. Standard SnAr chemistry was employed to convert to **85** using commercially available or synthetically prepared secondary amines. **85** was then converted to **86** by Suzuki cross coupling chemistry by coupling with commercially available or synthetically prepared boronic acids and boronic esters.

2-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, 87.



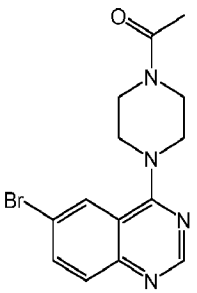
A 5 mL Biotage© microwave vial loaded with Bis(pinacolato)diborane (210 mg, 1.1 eq, 825 µmol), potassium acetate (147 mg, 2.0 eq, 1.50 mmol), [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II) Complex with Dichloromethane (61 mg, 0.10 eq, 75.0 µmol), and 4-Bromo-alpha,alpha-difluoro-2-picoline (156 mg, 95 µL, 1 eq, 750 µmol). The vial was capped, purged with argon, then injected with degassed 1,4-Dioxane (5.0 mL, 0.14 M), and heated to 80 ºC for 12 h. The reaction was cooled, concentrated, and the residue was taken up with sat NH4Cl, extracted with EtOAc and recrystallized with 75:25 Hexanes:DCM to afford 2-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, **87**, as a white solid and used without further characterization.

Step 1, General Scheme 1



88 **89** **90**

1-(4-(6-bromoquinazolin-4-yl)piperazin-1-yl)ethan-1-one, 90.

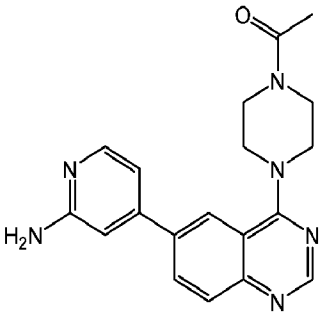


In a 5 mL microwave vial, 6-bromo-4-chloroquinazoline (300 mg, 1 eq, 1.23 mmol), sodium bicarbonate (259 mg, 2.5 eq, 3.08 mmol), and 1-(piperazin-1-yl)ethan-1-one (205 mg, 1.3 eq,

1.60 mmol) were added. The mixture was capped, EtOH (1.2 mL) was injected, and stirred overnight at 25 °C for 48 hours. After this time, the mixture was poured into 20 mL H_2O and the vial washed with 5 mL H_2O x4 and filtered and washed with H_2O (5 mL x 3), hexanes (5 mL x 5), and dried over vacuum for 15 minutes affording 1-(4-(6-bromoquinazolin-4-yl)piperazin-1-yl)ethan-1-one, **90**, (214 mg, 639 µmol, 52 %). ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.02 (dd, J = 1.9, 0.7 Hz, 1H), 7.88 – 7.77 (m, 2H), 3.85 – 3.80 (m, 4H), 3.79 – 3.70 (m, 4H), 2.18 (s, 3H). ^{13}CNMR (101 MHz, $CDCl_3$) δ 168.36, 163.90, 154.58, 150.20, 139.55, 132.16, 127.72, 121.01, 118.01, 55.60, 49.18, 45.75, 40.58, 23.92.

Step 2, General Scheme 1

1-(4-(6-(2-aminopyridin-4-yl)quinazolin-4-yl)piperazin-1-yl)ethan-1-one, 1.



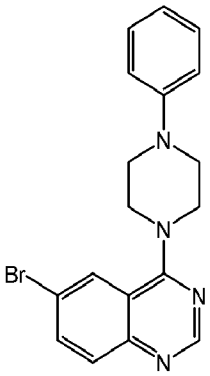
A 5 mL microwave vial was loaded with 1-(4-(6-bromoquinazolin-4-yl)piperazin-1-yl)ethan-1-one (150 mg, 1 eq, 447 µmol), tert-butyl (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate (158 mg, 1.1 eq, 492 µmol), $PdCl_2$(dppf) (35 mg, 0.1 eq, 44 µmol), and tripotassium phosphate (256 mg, 2.7 eq, 1.21 mmol), the vial capped then degassed for 10 minutes then injected with solvents degassed 1,4-dioxane (1.2 mL):water (0.30 mL), (4:1 v/v), degassed further for 10 min and heated to 130 °C for 60 min in an oil bath. The reaction was cooled and a vent needle was placed and conc HCl (2.20 g, 1.48 mL, 37% wt, 50 eq, 22.4 mmol) was added. The mixture was then stirred for 1 h and then 10% NaOH was added until basic. The mixture was diluted with H_2O and EtOAc and the aq. layer was extracted 3x with EtOAc. The pooled EtOAc extracts were washed 2x with brine and then the EtOAc layer was evaporated under vacuum and re-concentrated with DCM, dry-loaded onto silica gel and purified on a 12 g silica gel column (DCM/MeOH, 0-30%), affording 1-(4-(6-(2-aminopyridin-4-yl)quinazolin-4-yl)piperazin-1-yl)ethan-1-one, **1**, (58 mg, 0.17 mmol, 37 %) as a brown powder, which eluted at (0-10% DCM/MeOH). Mp 82-86 °C. LCMS $[M+H]^+$ 349. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.79

(s, 2H), 8.18 (d, J = 5.4 Hz, 2H), 8.06 (d, J = 1.7 Hz, 2H), 8.03 – 7.94 (m, 4H), 6.94 – 6.90 (m, 2H), 6.77 (s, 2H), 4.76 (s, 3H), 3.88 (dd, J = 6.8, 4.0 Hz, 4H), 3.85 (s, 3H), 3.74 (dd, J = 6.6, 3.7 Hz, 4H). ^{13}CNMR (100 MHz, $CDCl_3$) δ 21.42, 41.19, 45.81, 49.10, 50.14, 106.34, 112.46, 116.62, 122.83, 129.64, 131.48, 136.19, 148.66, 149.23, 152.02, 154.41, 159.04, 164.68, 169.38.

4-(4-(4-phenylpiperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 2.

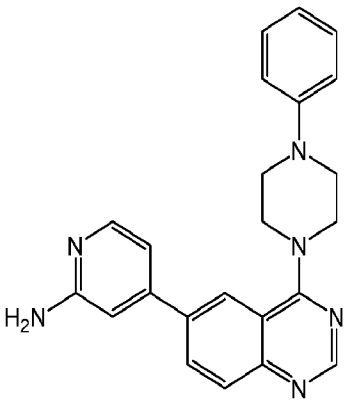
Compound **2** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

6-bromo-4-(4-phenylpiperazin-1-yl)quinazoline, 91.



In a 5 mL microwave vial, 6-bromo-4-chloroquinazoline (200 mg, 1 eq, 821 µmol), sodium bicarbonate (173 mg, 2.5 eq, 2.05 mmol), and 1-phenylpiperazine (150 mg, 141 µL, 1.13 eq, 925 µmol) were added. The mixture was capped, iPrOH (1.2 mL) was injected, and stirred overnight at 25 °C for 3 hours. After this time, the mixture was poured into 20 mL H_2O and the vial washed with H_2O (5 mL x 4) and filtered and washed with H_2O (5 mL x 3), hexanes (5 mL x 5), and dried over vacuum for 15 minutes affording 6-bromo-4-(4-phenylpiperazin-1-yl)quinazoline, **91**, (247 mg, 669 µmol, 81 %) as a white solid. δ 8.78 (s, 1H), 8.10 (d, J = 1.4 Hz, 1H), 7.86 (d, J = 1.3 Hz, 2H), 7.39 – 7.30 (m, 2H), 7.01 (d, J = 8.1 Hz, 2H), 6.95 (t, J = 7.3 Hz, 1H), 4.00 (t, J = 5.1 Hz, 4H), 3.45 (dd, J = 6.3, 3.9 Hz, 4H). ^{13}CNMR (100 MHz, $CDCl_3$) δ 163.47, 156.12, 154.00, 150.84, 143.99, 136.12, 130.27, 129.31, 127.26, 120.46, 118.87, 117.63, 116.34, 49.70, 49.18.

4-(4-(4-phenylpiperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 2.

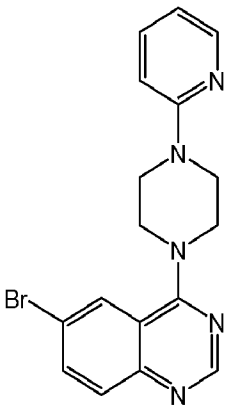


In a 5 mL microwave vial, 6-bromo-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline (100 mg, 1 eq, 0.27 mmol), tert-butyl (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate (95 mg, 1.10 eq, 0.297 mmol), tripotassium phosphate (83 mg, 1.5 eq, 0.41 mmol), and $PdCl_2$(dppf) (19 mg, 0.1 eq, 27 µmol) were added. The mixture was capped, dioxane (0.9 mL) was injected, and stirred at 130 °C for 30 min. After this time, the mixture was poured into 20 mL H_2O and the vial washed with H_2O (5 mL x 4) and filtered and washed with H_2O (5 mL x 3), hexanes (5 mL x 5), and dried over vacuum for 15 minutes affording 4-(4-(4-phenylpiperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, **2**, as a brown solid. M.p. 94-100 °C. LCMS $[M+H]^+$ 383. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.10 (d, *J* = 1.4 Hz, 1H), 7.86 (d, *J* = 1.3 Hz, 2H), 7.39 – 7.30 (m, 2H), 7.01 (d, *J* = 8.1 Hz, 2H), 6.95 (t, *J* = 7.3 Hz, 1H), 4.00 (t, *J* = 5.1 Hz, 4H), 3.45 (dd, *J* = 6.3, 3.9 Hz, 4H). ^{13}CNMR (101 MHz, $CDCl_3$) δ 163.47, 156.12, 154.00, 150.84, 143.99, 136.12, 130.27, 129.31, 127.26, 120.46, 118.87, 117.63, 116.34, 49.70, 49.18.

4-(4-(4-(pyridin-2-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 3.

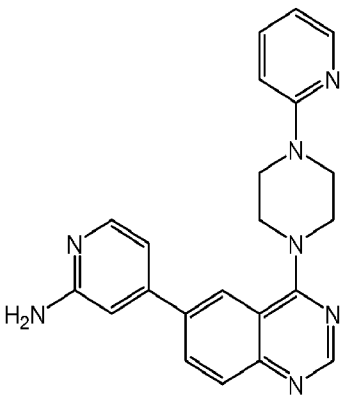
Compound **3** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

6-bromo-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline, 92.



In a 5 mL microwave vial, 6-bromo-4-chloroquinazoline (200 mg, 1 eq, 0.821 mmol), and 1-(pyridin-2-yl)piperazine (146 mg, 0.136 mL, 1.09 eq, 893 µmol) were added. The mixture was capped, EtOH (1.2 mL) was injected, and stirred at 25 °C for 48 hours. After this time, the mixture was poured into 20 mL H_2O and the vial washed with H_2O (5 mL x 4) and filtered and washed with H_2O (5 mL x 3), hexanes (5 mL x 5), and dried over vacuum for 15 minutes affording 6-bromo-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline, **92**, (258 mg, 697 µmol, 85%) as a brown powder. Mp 100-105 °C. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.25 (dd, *J* = 5.0, 1.8 Hz, 1H), 8.17 (dd, *J* = 16.8, 3.6 Hz, 2H), 8.03 – 7.95 (m, 2H), 7.56 (ddd, *J* = 8.8, 7.1, 2.0 Hz, 1H), 6.95 (d, *J* = 5.1 Hz, 1H), 6.79 (s, 1H), 6.75 – 6.68 (m, 2H), 4.79 (s, 1H), 4.00 (dd, *J* = 6.7, 3.7 Hz, 4H), 3.84 (dd, *J* = 6.5, 3.7 Hz, 4H). ^{13}CNMR (101 MHz, $CDCl_3$) δ 164.74, 159.15, 154.53, 152.04, 149.45, 149.20, 148.50, 148.01, 137.70, 135.80, 131.29, 129.51, 123.15, 116.68, 113.94, 112.54, 107.20, 106.37, 49.49, 45.02.

4-(4-(4-(pyridin-2-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 3.



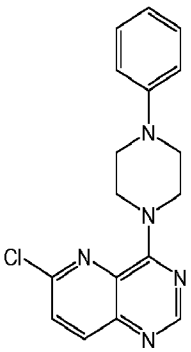
In a 5 mL microwave vial, 6-bromo-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline (100 mg, 1 eq, 0.270 mmol), tert-butyl (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate (95 mg, 1.10 eq, 0.297 mmol), tripotassium phosphate (83 mg, 1.5 eq, 0.41mmol), and $PdCl_2$(dppf) (19 mg, 0.1 eq, 27.0 µmol) were added. The mixture was capped, dioxane (0.9 mL) was injected, and stirred at 130 °C for 30 min. After this time, the mixture was poured into 20 mL H_2O and the vial washed with H_2O (5 mL x4) and filtered and washed with H_2O (5 mL x 3), hexanes (5 mL x 5), and dried over vacuum for 15 minutes affording 4-(4-(4-(pyridin-2-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, **3**, as a brown solid. Mp 100-105 °C. LCMS $[M+H]^+$ 384. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.25 (dd, *J* = 5.0, 1.8 Hz, 1H), 8.17 (dd, *J* = 16.8, 3.6 Hz, 2H), 8.03 – 7.95 (m, 2H), 7.56 (ddd, *J* = 8.8, 7.1, 2.0 Hz, 1H), 6.95 (d, *J* = 5.1 Hz, 1H), 6.79 (s, 1H), 6.75 – 6.68 (m, 2H), 4.79 (s, 1H), 4.00 (dd, *J* = 6.7, 3.7 Hz, 4H), 3.84 (dd,

J = 6.5, 3.7 Hz, 4H). ^{13}CNMR (101 MHz, $CDCl_3$) δ 164.74, 159.15, 154.53, 152.04, 149.45, 149.20, 148.50, 148.01, 137.70, 135.80, 131.29, 129.51, 123.15, 116.68, 113.94, 112.54, 107.20, 106.37, 49.49, 45.02.

4-(4-(4-phenylpiperazin-1-yl)pyrido[3,2-d]pyrimidin-6-yl)pyridin-2-amine, 4.

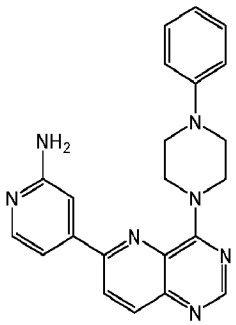
Compound **4** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

6-chloro-4-(4-phenylpiperazin-1-yl)pyrido[3,2-d]pyrimidine, 93.



In a 5 mL Biotage microwave vial, a stir bar, Sodium bicarbonate (33 mg, 15 µL, 1 eq, 400 µmol) and 1-phenylpiperazine (71 mg, 67 µL, 1.1 eq, 440 µmol), were added with EtOH (1.0 mL, 0.4 M) and stirred for 10 min. 4,6-dichloropyrido[3,2-d]pyrimidine (80 mg, 1 eq, 0.40 mmol) was added , the vial was sealed and heated at 25 °C for 12 hours. Upon completion, the reaction was diluted with water and filtered afford 6-chloro-4-(4-phenylpiperazin-1-yl)pyrido[3,2-d]pyrimidine, **93**, (0.11 g, 0.34 mmol, 84%), as a white solid. LCMS $[M+H]^+$ 326. 1H NMR (500 MHz, DMSO) δ 8.59 (d, J = 2.8 Hz, 1H), 8.20 (dd, J = 8.7, 2.8 Hz, 1H), 7.89 (dd, J = 8.7, 2.8 Hz, 1H), 7.24 (t, J = 7.8 Hz, 2H), 7.00 (d, J = 8.0 Hz, 2H), 6.81 (t, J = 7.3 Hz, 1H), 4.50 (s, 4H), 3.35 (t, J = 4.3 Hz, 4H). 13C NMR (126 MHz, DMSO) δ 158.10, 155.45, 151.12, 146.92, 145.43, 140.47, 132.75, 129.46, 119.53, 115.89, 48.65, 40.50, 40.33, 40.16, 40.00, 39.83, 39.66, 39.50.

4-(4-(4-phenylpiperazin-1-yl)pyrido[3,2-d]pyrimidin-6-yl)pyridin-2-amine, 4.

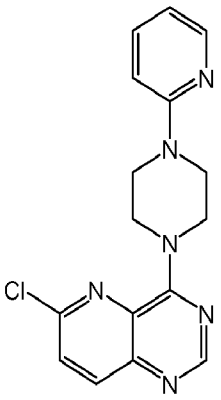


A 5 mL Biotage© microwave vial loaded with sodium bicarbonate (83 mg, 4.0 eq, 994 µmol), 1,1'-Bis(diphenylphosphino)ferrocenepalladium(II) dichloride (1 mg, 0.08 eq, 19 µmol), 6-chloro4-(4-phenylpiperazin-1-yl)pyrido[3,2-d]pyrimidine (81 mg, 1 eq, 249 µmol), and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2- yl)pyridin-2-amine (65 mg, 1.2 eq, 298 µmol). The vial was capped, purged with argon, then injected with degassed 4:1 Dioxane: H_2O (2.5 mL, 0.1 M), and heated to 80 °C for 12 h. The reaction was cooled, diluted with DCM/MeOH, filtered through celite, concentrated, dry-loaded onto silica gel and purified on a 12 g silica gel column (DCM/MeOH, 0-20%), affording 4-(4-(4-phenylpiperazin-1-yl)pyrido[3,2-d]pyrimidin-6-yl)pyridin-2-amine, **4**, (90 mg, 0.23 mmol, 94 %) as a brown solid, LCMS $[M+H]^+$ 384. 1H NMR (500 MHz, DMSO) δ 8.58 (d, J = 2.1 Hz, 1H), 8.33 (dd, J = 8.9, 2.2 Hz, 1H), 8.24 (dd, J = 8.9, 2.2 Hz, 1H), 8.13 – 8.08 (m, 1H), 7.29 – 7.21 (m, 3H), 7.19 (s, 1H), 7.03 (d, J = 8.0 Hz, 2H), 6.81 (t, J = 7.3 Hz, 1H), 6.31 (s, 2H), 4.64 (s, 4H), 3.43 (t, J = 4.9 Hz, 4H). 13C NMR (126 MHz, DMSO) δ 160.89, 159.11, 155.31, 151.16, 147.23, 146.40, 137.69, 133.33, 129.49, 125.15, 119.44, 115.81, 109.85, 105.65, 48.69, 40.48, 40.31, 40.14, 39.98, 39.81, 39.64, 39.48.

4-(4-(4-(pyridin-2-yl)piperazin-1-yl)pyrido[3,2-d]pyrimidin-6-yl)pyridin-2-amine, 5.

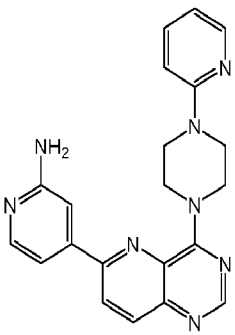
Compound **5** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

6-chloro-4-(4-(pyridin-2-yl)piperazin-1-yl)pyrido[3,2-d]pyrimidine, 94.



In a 5 mL Biotage microwave vial, a stir bar, sodium bicarbonate (33 mg, 15 µL, 1 eq, 400 µmol) and 1-(pyridin-2-yl)piperazine (65 mg, 61 µL, 1.0 eq, 400 µmol), were added with EtOH (1.0 mL, 0.4 M) and stirred for 10 min. 4,6-dichloropyrido[3,2-d]pyrimidine (8 mg, 1 eq, 0.4 mmol) was added , the vial was sealed and stirred at 25 °C for 12 h. Upon completion, the reaction was diluted with water and filtered afford 6-chloro-4-(4-(pyridin-2-yl)piperazin-1-yl)pyrido[3,2-d]pyrimidine, **94**, (0.11 g, 0.34 mmol, 84 %) as a white solid. LCMS $[M+H]^+$ 327. 1H NMR (500 MHz, DMSO) δ 8.60 (s, 1H), 8.20 (d, J = 8.8 Hz, 1H), 8.15 (dd, J = 5.0, 1.9 Hz, 1H), 7.90 (d, J = 8.7 Hz, 1H), 7.57 (ddd, J = 9.0, 7.0, 2.0 Hz, 1H), 6.89 (d, J = 8.6 Hz, 1H), 6.68 (dd, J = 7.1, 4.9 Hz, 1H), 4.46 (s, 4H), 3.75 – 3.69 (m, 4H). 13C NMR (126 MHz, DMSO) δ 159.16, 158.21, 155.46, 148.05, 146.91, 145.44, 140.42, 138.08, 132.78, 129.43, 113.64, 107.55, 44.84, 40.50, 40.33, 40.16, 40.00, 39.83, 39.66, 39.50.

4-(4-(4-(pyridin-2-yl)piperazin-1-yl)pyrido[3,2-d]pyrimidin-6-yl)pyridin-2-amine, 5.



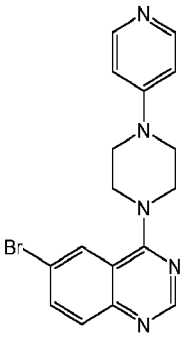
A 5 mL Biotage© microwave vial loaded with sodium bicarbonate (83 mg, 4 eq, 991 µmol), 1,1'-Bis(diphenylphosphino)ferrocenepalladium(II) dichloride (14 mg, 0.08 eq, 19 µmol), 6-chloro4-(4-(pyridin-2-yl)piperazin-1-yl)pyrido[3,2-d]pyrimidine (0.0810 g, 1 eq, 248 µmol), and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (65 mg, 1.2 eq, 297 µmol). The vial was capped, purged with argon, then injected with degassed 4:1 Dioxane: H_2O (2.5 mL, 0.1

M), and heated to 80 ºC for 12 h. The reaction was cooled, diluted with DCM/MeOH, filtered through celite, concentrated, dry-loaded onto silica gel and purified on a 12g silica gel column (DCM/MeOH, 0-20%), affording 4-(4-(4-(pyridin-2-yl)piperazin-1-yl)pyrido[3,2-d]pyrimidin-6-yl)pyridin-2-amine, **5**, (90 mg, 0.23 mmol, 94 %) as a brown solid. LCMS $[M+H]^+$ 385. 1H NMR (500 MHz, DMSO) δ 8.58 (s, 1H), 8.33 (d, J = 8.7 Hz, 1H), 8.23 (d, J = 8.8 Hz, 1H), 8.16 (d, J = 4.8 Hz, 1H), 8.11 (d, J = 5.3 Hz, 1H), 7.59 (t, J = 7.9 Hz, 1H), 7.25 – 7.18 (m, 2H), 6.90 (d, J = 8.6 Hz, 1H), 6.68 (t, J = 6.1 Hz, 1H), 6.33 (s, 2H), 4.60 (s, 4H), 3.79 (t, J = 5.1 Hz, 4H). 13C NMR (126 MHz, DMSO) δ 160.85, 159.15, 155.30, 151.76, 148.78, 148.05, 147.22, 146.45, 138.09, 137.63, 133.37, 125.13, 113.54, 109.86, 107.43, 105.74, 44.88, 40.48, 40.31, 40.24, 40.15, 39.98, 39.81, 39.65, 39.48.

4-(4-(4-(pyridin-4-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 6.

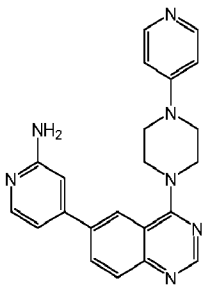
Compound **6** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

6-bromo-4-(4-(pyridin-4-yl)piperazin-1-yl)quinazoline, 95.



In a 5 mL Biotage© microwave vial, a stir bar, sodium bicarbonate (42 mg, 1 eq, 500 µmol) and 1-(pyridin-4-yl)piperazine (97 mg, 1.2 eq, 600 µmol), and EtOH (2.0 mL, 0.4 M) were added stirred for 5 minutes. 6-bromo-4-chloroquinazoline (122 mg, 1 eq, 0.5 mmol) was added and the vial was sealed and heated at 50 °C for 12 hours. Upon completion, the reaction was diluted with water and extracted with DCM (10 mL x 3) to afford 6-bromo-4-(4-(pyridin-4-yl)piperazin-1-yl)quinazoline, **82**, (0.15 g, 0.41 mmol, 81 %) as a white solid. LCMS $[M+H]^+$ 370. This compound was used without further purification or characterization.

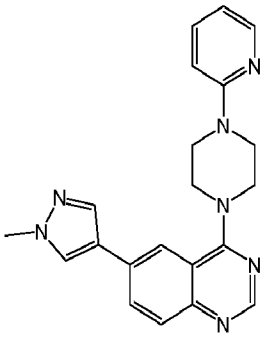
4-(4-(4-(pyridin-4-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 6.



A 5 mL Biotage© microwave vial loaded with sodium bicarbonate (90 mg, 4.0 eq, 1.08 mmol), 1,1'-Bis(diphenylphosphino)ferrocenepalladium(II) dichloride (15 mg, 0.08 eq, 21 µmol), 6-bromo4-(4-(pyridin-4-yl)piperazin-1-yl)quinazoline (0.1 g, 1 eq, 270 µmol), and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (71 mg, 1.2 eq, 324 µmol). The vial was capped, purged with argon, then injected with degassed 4:1 MeOH: H_2O (2.7 mL, 0.1 M), and heated to 80 °C for 12 h. The reaction was cooled, diluted with DCM/MeOH, filtered through celite, concentrated, dry-loaded onto silica gel and purified on a 12 g silica gel column (DCM/MeOH, 0-30%), affording 4-(4-(4-(pyridin-4-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, **6**, (96 mg, 0.25 mmol, 93 %) as a brown solid. LCMS [M+H] 384. 1H NMR (500 MHz, DMSO) δ 8.67 (s, 1H), 8.24 (s, 2H), 8.10 (d, J = 8.9 Hz, 1H), 8.03 (d, J = 5.3 Hz, 1H), 7.91 (d, J = 8.7 Hz, 1H), 6.93 (t, J = 7.2 Hz, 3H), 6.86 (s, 1H), 6.09 (s, 2H), 4.07 – 4.01 (m, 4H), 3.71 (t, J = 5.0 Hz, 5H). 13C NMR (126 MHz, DMSO) δ 163.73, 161.03, 155.07, 154.46, 151.94, 149.15, 147.94, 147.52, 135.56, 131.49, 129.22, 123.42, 116.22, 110.52, 105.72, 48.49, 45.25, 40.48, 40.31, 40.14, 39.98, 39.81, 39.64, 39.48.

6-(1-methyl-1H-pyrazol-4-yl)-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline, 7.

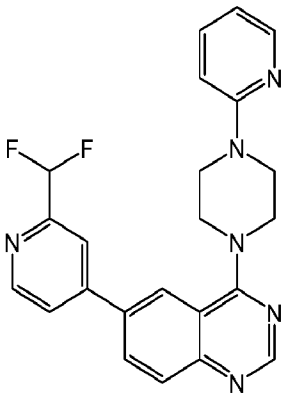
Compound **7** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.



A 5 mL Biotage© microwave vial loaded with sodium bicarbonate (68 mg, 4.0 eq, 0.81 mmol), 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II) dichloride (12 mg, 0.08 eq, 16 µmol), 6-bromo-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline (0.075 g, 1 eq, 0.20 mmol), and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (51 mg, 1.2 eq, 0.24 mmol). The vial was capped, purged with argon, then injected with degassed 4:1 Dioxane: H_2O (2.0 mL, 0.1 M), and heated to 160 °C for 25 min. The reaction was cooled, diluted with DCM/MeOH, filtered through celite, concentrated, dry-loaded onto silica gel and purified on a 12 g silica gel column (DCM/MeOH, 0-20%), affording 6-(1-methyl-1H-pyrazol-4-yl)-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline, **7**, (61 mg, 0.16 mmol, 81 %) as a tan solid. LCMS $[M+H]^+$ 372. 1H NMR (500 MHz, DMSO) δ 8.53 (s, 1H), 8.27 (s, 1H), 8.09 (dd, J = 5.0, 2.0 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.99 (dd, J = 8.6, 1.9 Hz, 1H), 7.97 (s, 1H), 7.74 (d, J = 8.6 Hz, 1H), 7.52 (ddd, J = 8.9, 7.0, 2.0 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 6.61 (dd, J = 7.1, 4.9 Hz, 1H), 3.83 (d, J = 5.6 Hz, 7H), 3.71 (dd, J = 6.8, 3.7 Hz, 4H). 13C NMR (126 MHz, DMSO) δ 163.97, 159.27, 153.46, 148.09, 138.09, 136.96, 131.14, 130.53, 129.10, 128.98, 121.65, 120.03, 116.87, 113.61, 107.48, 49.24, 44.70, 40.37, 40.29, 40.21, 40.04, 39.87, 39.70, 39.54, 39.22.

6-(2-(difluoromethyl)pyridin-4-yl)-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline, 8.

Compound **8** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.



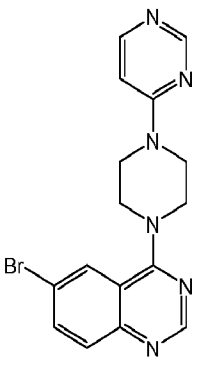
The boronate **87** was employed in this procedure. A 5 mL Biotage© microwave vial loaded with sodium bicarbonate (90 mg, 4.0 eq, 1.08 mmol), 1,1'-Bis(diphenylphosphino)ferrocene-

palladium(II) dichloride (15 mg, 0.08 eq, 21 µmol), 6-bromo-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline (100 mg, 1.0 eq, 270 µmol), and 2-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (75 mg, 1.1 eq, 297 µmol). The vial was capped, purged with argon, then injected with degassed 4:1 Dioxane: H_2O (2.7 mL, 0.1 M), and heated to 160 ℃ for 25 min. The reaction was cooled, diluted with DCM/MeOH, filtered through celite, concentrated, dry-loaded onto silica gel and purified on a 12 g silica gel column (DCM/MeOH, 0-20%), affording 6-(2-(difluoromethyl)pyridin-4-yl)-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline, **8**, (58 mg, 0.14 mmol, 51%) as a brown solid. LCMS $[M+H]^+$ 419. 1H NMR (500 MHz, DMSO) δ 8.80 (d, J = 5.2 Hz, 1H), 8.67 (s, 1H), 8.42 (d, J = 2.1 Hz, 1H), 8.29 (dd, J = 8.7, 2.0 Hz, 1H), 8.18 – 8.11 (m, 2H), 8.11 – 8.04 (m, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.58 (ddd, J = 8.9, 7.1, 2.0 Hz, 1H), 7.05 (s, 1H), 6.84 (d, J = 8.6 Hz, 1H), 6.68 (dd, J = 7.1, 4.9 Hz, 1H), 4.11 – 4.00 (m, 4H), 3.80 – 3.76 (m, 4H). 13C NMR (126 MHz, DMSO) δ 163.95, 159.13, 154.90, 152.50, 150.97, 148.33, 148.10, 138.10, 133.57, 131.78, 129.44, 124.80, 124.10, 118.76, 116.28, 114.26, 113.56, 107.39, 49.03, 44.58, 40.54, 40.38, 40.21, 40.04, 39.88, 39.71, 39.54, 0.57.

4-(4-(4-(pyrimidin-4-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 9.

Compound **9** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

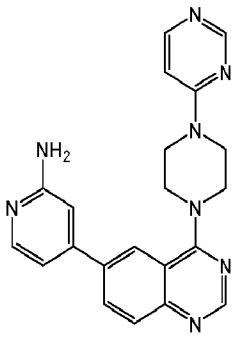
6-bromo-4-(4-(pyrimidin-4-yl)piperazin-1-yl)quinazoline, 96.



In a 5 mL Biotage© microwave vial, a stir bar, sodium bicarbonate (42 mg, 1 eq, 500 µmol), 4-(piperazin-1-yl)pyrimidine (98 mg, 1.2 eq, 600 µmol), and EtOH (2.0 mL, 0.4 M) were added and stirred for 5 minutes. 6-bromo-4chloroquinazoline (122 mg, 1 eq, 0.5 mmol) was added and the vial was sealed and heated at 50 °C for 12 hours. Upon completion, the reaction was diluted

with water and extracted with DCM (10 mL x 3) to afford 6-bromo-4-(4-(pyrimidin-4-yl)piperazin-1-yl)quinazoline, **96**, (0.15 g, 0.40 mmol, 81%) as a yellow solid. LCMS $[M+H]^+$ 371. This compound was used without further purification or characterization.

4-(4-(4-(pyrimidin-4-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 9.

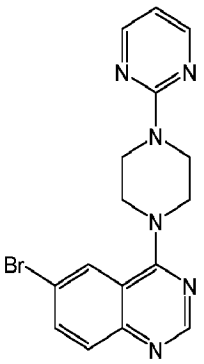


A 5 mL Biotage© microwave vial loaded with sodium bicarbonate (90 mg, 4.0 eq, 1.08 mmol), 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II) dichloride (15 mg, 0.08 eq, 2 µmol), 6-bromo-4-(4-(pyrimidin-4-yl)piperazin-1-yl)quinazoline (0.1 g, 1 eq, 269 µmol), and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (71 mg, 1.2 eq, 324 µmol). The vial was capped, purged with argon, then injected with degassed 4:1 MeOH: H_2O (2.7 mL, 0.1 M), and heated to 80 °C for 12 h. The reaction was cooled, diluted with DCM/MeOH, filtered through celite, concentrated, dry-loaded onto silica gel and purified on a 12 g silica gel column (DCM/MeOH, 0-30%), affording 4-(4-(4-(pyrimidin-4-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, **9**, (99 mg, 0.26 mmol, 96 %) as a brown solid. LCMS $[M+H]^+$ 385. 1H NMR (500 MHz, DMSO) δ 8.67 (s, 1H), 8.55 (s, 1H), 8.24 (d, J = 8.5 Hz, 2H), 8.10 (d, J = 8.7 Hz, 1H), 8.03 (d, J = 5.4 Hz, 1H), 7.92 (d, J = 8.6 Hz, 1H), 6.94 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 15.2 Hz, 2H), 6.08 (s, 2H), 4.03 – 3.97 (m, 4H), 3.89 (t, J = 5.2 Hz, 4H). 13C NMR (126 MHz, DMSO) δ 163.88, 161.32, 161.01, 158.36, 156.02, 154.46, 151.96, 149.21, 147.55, 135.64, 131.52, 129.24, 123.41, 110.56, 105.68, 79.65, 48.74, 43.18, 40.48, 40.31, 40.14, 39.98, 39.81, 39.64, 39.48.

4-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 10.

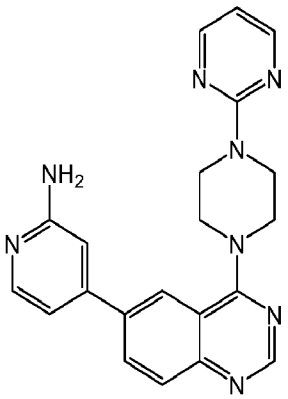
Compound **10** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

6-bromo-4-(4-(pyrimidin-2-yl)piperazin-1-yl)quinazoline, 97.



In a 5 mL Biotage microwave vial, a stir bar, sodium bicarbonate (34 mg, 16 µL, 1 eq, 413 µmol), 2-(piperazin-1-yl)pyrimidine (8 mg, 1.2 eq, 496 µmol), and EtOH (2.0 mL, 0.4 M) were added and stirred for 5 minutes. 6-bromo4-chloroquinazoline (100 mg, 1 eq, 413 µmol) was added and the vial was sealed and heated at 50 °C for 12 hours. Upon completion, the reaction was diluted with water and filtered to afford 6-bromo-4-(4-(pyrimidin-2-yl)piperazin-1-yl)quinazoline, **97**, (0.12 g, 0.32 mmol, 78%) as a white solid. LCMS $[M+H]^+$ 371. This compound was used without further purification or characterization.

4-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 10.



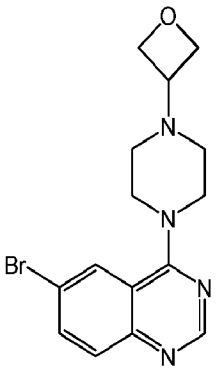
A 5 mL Biotage© microwave vial loaded with sodium bicarbonate (85 mg, 4.0 eq, 1.01 mmol), 1,1'-Bis(diphenylphosphino)ferrocenepalladium(II) dichloride (14 mg, 0.08 eq, 20 µmol), 6-bromo-4-(4-(pyrimidin-2-yl)piperazin-1-yl)quinazoline (0.0940 g, 1 eq, 253 µmol), and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (66 mg, 1.2 eq, 304 µmol). The vial was capped, purged with argon, then injected with degassed 4:1 MeOH: H_2O (2.5 mL, 0.1 M), and heated to 80 ºC for 12 h. The reaction was cooled, diluted with DCM/MeOH, filtered through celite, concentrated, dry-loaded onto silica gel and purified on a 12 g silica gel column

(DCM/MeOH, 0-30%), affording 4-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, **10**, (0.091 g, 0.24 mmol, 93 %) as a brown solid. LCMS $[M+H]^+$ 385. 1H NMR (500 MHz, DMSO) δ 8.67 (s, 1H), 8.42 (d, J = 4.7 Hz, 2H), 8.22 (s, 1H), 8.10 (dd, J = 8.7, 1.9 Hz, 1H), 8.03 (d, J = 5.3 Hz, 1H), 7.92 (d, J = 8.7 Hz, 1H), 6.96 (d, J = 5.4 Hz, 1H), 6.85 (s, 1H), 6.69 (t, J = 4.8 Hz, 1H), 6.14 (s, 2H), 4.02 – 3.92 (m, 8H). 13C NMR (126 MHz, DMSO) δ 164.09, 161.59, 160.84, 158.48, 154.48, 151.97, 148.86, 147.74, 135.61, 131.53, 129.24, 123.44, 116.31, 110.89, 110.62, 105.86, 49.22, 43.49, 40.48, 40.31, 40.15, 39.98, 39.81, 39.65, 39.48.

4-(4-(4-(oxetan-3-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 11.

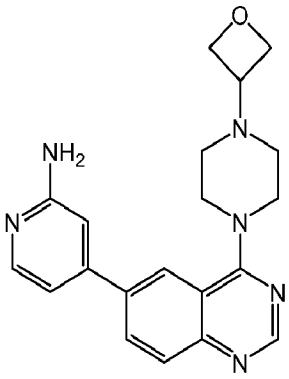
Compound **11** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

6-bromo-4-(4-(oxetan-3-yl)piperazin-1-yl)quinazoline, 98.



In a 5 mL Biotage microwave vial, a stir bar, 1-(oxetan-3-yl)piperazine (70 mg, 64 µL, 1.2 eq, 493 µmol), sodium bicarbonate (34 mg, 1 eq, 411 µmol), and EtOH (2.0 mL, 0.2 M) were added stirred for 5 minutes. 6-bromo-4-chloroquinazoline (0.1 g, 1 eq, 411 µmol) was added and the vial was sealed and heated at 50 °C for 12 hours. Upon completion, the reaction was diluted with water and extracted with DCM (10 mL x 3) to afford 6-bromo-4-(4-(oxetan-3-yl)piperazin-1-yl)quinazoline, **98**, (0.13 g, 0.37 mmol, 91%) as a tan solid. LCMS $[M+H]^+$ 349. This compound was used without further purification or characterization.

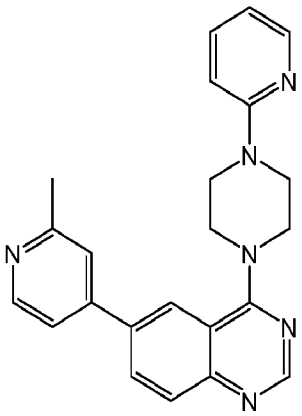
4-(4-(4-(oxetan-3-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 11.



A 5 mL Biotage© microwave vial loaded with sodium bicarbonate (144 mg, 4.0 eq, 1.7 mmol), 1,1'-Bis(diphenylphosphino)ferrocenepalladium(II) dichloride (25 mg, 0.08 eq, 34 µmol), 6-bromo-4-(4-(oxetan-3-yl)piperazin-1-yl)quinazoline (0.15 g, 1 eq, 429 µmol), and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (104 mg, 1.1 eq, 472 µmol). The vial was capped, purged with argon, then injected with degassed 4:1 MeOH: H_2O (4.3 mL, 0.1 M), and heated to 80 °C for 12 h. The reaction was cooled, diluted with DCM/MeOH, filtered through celite, concentrated, dry-loaded onto silica gel and purified on a 12 g silica gel column (DCM/MeOH, 0-30%), affording 4-(4-(4-(oxetan-3-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, **11**, (0.15 g, 0.41 mmol, 96 %) as a brown solid. LCMS $[M+H]^+$ 363. 1H NMR (500 MHz, DMSO) δ 8.65 (s, 1H), 8.11 (s, 1H), 8.07 (d, J = 8.8 Hz, 1H), 8.03 (d, J = 5.3 Hz, 1H), 7.90 (d, J = 8.6 Hz, 1H), 6.90 (d, J = 5.3 Hz, 1H), 6.80 (s, 1H), 6.12 (s, 2H), 4.58 (t, J = 6.6 Hz, 2H), 4.49 (t, J = 6.1 Hz, 2H), 3.84 (t, J = 4.8 Hz, 4H), 3.50 (p, J = 6.4 Hz, 1H), 2.48 (d, J = 5.3 Hz, 4H). 13C NMR (126 MHz, DMSO) δ 164.21, 160.89, 154.48, 151.95, 149.03, 147.69,135.73, 131.56, 129.31, 123.22, 116.28, 110.54, 105.76, 74.78, 58.81, 49.45, 49.42, 40.49, 40.32,40.15, 39.99, 39.82, 39.65, 39.49.

6-(2-methylpyridin-4-yl)-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline, 12.

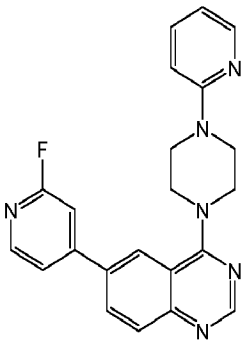
Compound **12** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.



A 5 mL Biotage© microwave vial loaded with sodium bicarbonate (68 mg, 4.0 eq, 0.81 mmol), 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II) dichloride (12 mg, 0.08 eq, 16 µmol), 6-bromo-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline (0.075 g, 1 eq, 0.20 mmol), and 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (53 mg, 1.2 eq, 0.24 mmol). The vial was capped, purged with argon, then injected with degassed 4:1 Dioxane: H_2O (2.0 mL, 0.1 M), and heated to 160 ºC for 25 min. The reaction was cooled, diluted with DCM/MeOH, filtered through celite, concentrated, dry-loaded onto silica gel and purified on a 12 g silica gel column (DCM/MeOH, 0-20%), affording 6-(2-methylpyridin-4-yl)-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline, **12**, (0.064 g, 0.17 mmol, 83 %) as a brown solid. LCMS $[M+H]^+$ 383. 1H NMR (500 MHz, DMSO) δ 8.67 (s, 1H), 8.56 (d, J = 5.2 Hz, 1H), 8.35 (d, J = 2.1 Hz, 1H), 8.23 (dd, J = 8.7, 2.0 Hz, 1H), 8.16 (dd, J = 4.8, 2.0 Hz, 1H), 7.93 (d, J = 8.7 Hz, 1H), 7.73 (d, J = 1.9 Hz, 1H), 7.66 (dd, J = 5.3, 1.9 Hz, 1H), 7.59 (ddd, J = 8.9, 7.1, 2.1 Hz, 1H), 6.86 (d, J = 8.6 Hz, 1H), 6.68 (dd, J = 7.1, 4.9 Hz, 1H), 4.04 – 3.99 (m, 4H), 3.81 – 3.75 (m, 4H), 2.58 (s, 3H). 13C NMR (126 MHz, DMSO) δ 163.98, 159.25, 159.14, 154.66, 152.19, 150.15, 148.09, 138.10, 131.76, 129.31, 124.08, 121.22, 119.19, 116.33, 113.56, 107.41, 49.08, 44.59, 40.54, 40.37, 40.21, 40.04, 39.87, 39.71, 39.54, 24.66.

6-(2-fluoropyridin-4-yl)-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline, 13.

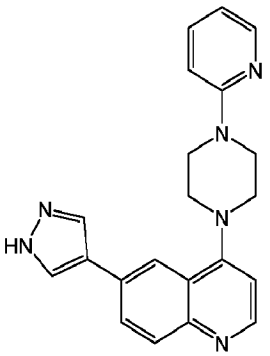
Compound **13** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.



A 5 mL Biotage© microwave vial loaded with sodium bicarbonate (68 mg, 4.0 eq, 0.81 mmol), 1,1' Bis(diphenylphosphino)ferrocene-palladium(II) dichloride (12 mg, 0.08 eq, 16 µmol), 6-bromo-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline (0.075 g, 1 eq, 0.20 mmol), and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (54 mg, 1.2 eq, 0.24 mmol). The vial was capped, purged with argon, then injected with degassed 4:1 Dioxane: H_2O (2.0 mL, 0.1 M), and heated to 160 °C for 25 min. The reaction was cooled, diluted with DCM/MeOH, filtered through celite, concentrated, dry-loaded onto silica gel and purified on a 12 g silica gel column (DCM/MeOH, 0-20%), affording 6-(2-fluoropyridin-4-yl)-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline, **13**, (0.054 g, 0.14 mmol, 69 %) as a creme solid. LCMS $[M+H]^+$ 387. 1H NMR (500 MHz, DMSO) δ 8.72 (s, 1H), 8.47 (d, J = 2.1 Hz, 1H), 8.42 (d, J = 5.3 Hz, 1H), 8.33 (dd, J = 8.7, 2.0 Hz, 1H), 8.21 (dd, J = 4.9, 2.0 Hz, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.91 (dd, J= 5.2, 2.0 Hz, 1H), 7.76 (s, 1H), 7.64 (ddd, J = 8.9, 7.1, 2.0 Hz, 1H), 6.90 (d, J = 8.6 Hz, 1H), 6.73 (dd, J = 7.1, 4.9 Hz, 1H), 4.11 – 4.06 (m, 4H), 3.86 – 3.80 (m, 4H). 13C NMR (126 MHz, DMSO) δ 163.89, 163.68, 159.13, 154.95, 152.60, 148.77, 148.65, 148.10, 138.09, 133.10, 131.76, 129.34, 124.90, 120.50, 116.19, 113.55, 107.68, 107.38, 48.99, 44.57, 40.54, 40.37, 40.20, 40.04, 39.87, 39.70, 39.54.

6-(1H-pyrazol-4-yl)-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline, 14.

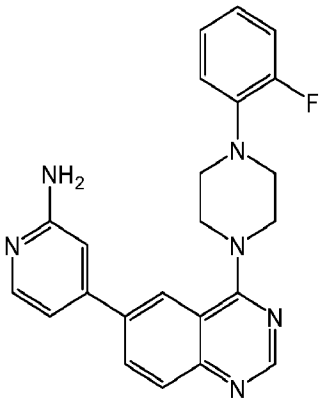
Compound **14** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.



A 5 mL Biotage© microwave vial loaded with sodium bicarbonate (68 mg, 4.0 eq, 0.81 mmol), 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II) dichloride (12 mg, 0.08 eq, 16 µmol), 6-bromo-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline (0.075 g, 1 eq, 0.20 mmol), and 4-(4,4,5,5-tetramethyl-1,3,2- dioxaborolan-2-yl)-1H-pyrazole (47 mg, 1.2 eq, 0.24 mmol). The vial was capped, purged with argon, then injected with degassed 4:1 Dioxane: H_2O (2.0 mL, 0.1 M), and heated to 160 °C for 25 min. The reaction was cooled, diluted with DCM/MeOH, filtered through celite, concentrated, dry-loaded onto silica gel and purified on a 12 g silica gel column (DCM/MeOH, 0-20%), affording 6-(1H-pyrazol-4-yl)-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline, **14**, (52 mg, 0.15 mmol, 72 %) as a tan solid. LCMS $[M+H]^+$ 358. 1H NMR (500 MHz, DMSO) δ 13.12 (s, 1H), 8.66 (s, 1H), 8.45 (s, 1H), 8.24 – 8.14 (m, 4H), 7.87 (d, J = 8.7 Hz, 1H), 7.64 (ddd, J = 8.9, 7.1, 2.0 Hz, 1H), 6.92 (d, J= 8.6 Hz, 1H), 6.74 (dd, J = 7.1, 4.9 Hz, 1H), 3.96 (dd, J = 6.8, 3.7 Hz, 4H), 3.83 (dd, J = 6.7, 3.6 Hz, 4H). 13C NMR (126 MHz, DMSO) δ 163.95, 159.27, 153.41, 150.39, 148.09, 138.09, 131.41, 130.86, 129.01, 120.97, 120.17, 116.85, 113.59, 107.46, 49.23, 44.68, 40.54, 40.37, 40.20, 40.04, 39.87, 39.70, 39.54.

4-(4-(4-(2-fluorophenyl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 15.

Compound **15** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.

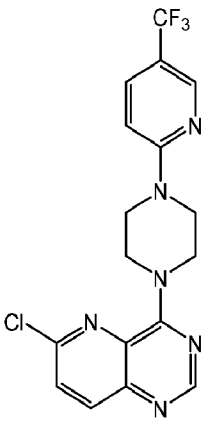


A 5 mL Biotage© microwave vial loaded with sodium bicarbonate (9 mg, 4.0 eq, 1.08 mmol), 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II) dichloride (15 mg, 0.08 eq, 2 µmol), 6-bromo-4-(4-(2-fluorophenyl)piperazin-1-yl)quinazoline (0.105 g, 1 eq, 271 µmol), and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (6 mg, 1.1 eq, 298 µmol). The vial was capped, purged with argon, then injected with degassed 4:1 MeOH: H_2O (2.8 mL, 0.1 M), and heated to 80 ºC for 12 h. The reaction was cooled, diluted with DCM/MeOH, filtered through celite, concentrated, dry-loaded onto silica gel and purified on a 12 g silica gel column (DCM/MeOH, 0-30%), affording 4-(4-(4-(2-fluorophenyl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, **15**, (77 mg, 0.19 mmol, 71 %) as a creme solid. LCMS $[M+H]^+$ 401. 1H NMR (500 MHz, DMSO) δ 8.61 (s, 1H), 8.12 (d, J = 2.0 Hz, 1H), 8.02 (dd, J = 8.7, 2.0 Hz, 1H), 7.96 (d, J = 5.3 Hz, 1H), 7.85 (d, J = 8.7 Hz, 1H), 7.14 – 7.09 (m, 1H), 7.05 (td, J = 7.4, 4.8 Hz, 2H), 6.98 – 6.90 (m, 1H), 6.86 (dd, J = 5.3, 1.7 Hz, 1H), 6.76 (s, 1H), 5.98 (s, 2H), 3.92 (t, J = 4.8 Hz, 4H), 3.18 (t, J = 4.7 Hz, 4H). 13C NMR (126 MHz, DMSO) δ 164.26, 161.01, 154.49, 151.99, 149.23, 147.56, 135.87, 131.60, 129.35, 125.39, 125.36, 123.19, 119.96, 116.59, 116.43, 116.36, 110.60, 105.71, 50.51, 49.75, 40.55, 40.38, 40.21, 40.05, 39.88, 39.71, 39.54.

4-(4-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)pyrido[3,2-d]pyrimidin-6-yl)pyridin-2-amine, 16.

Compound **16** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

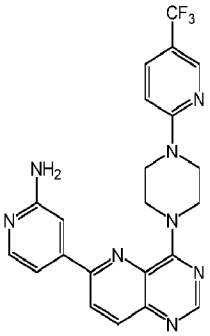
6-chloro-4-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)pyrido[3,2-d]pyrimidine, 99.



In a 5 mL Biotage microwave vial, sodium bicarbonate (63 mg, 1 eq, 750 µmol) and 1-(5-(trifluoromethyl)pyridin-2-yl)piperazine (173 mg, 1.0 eq, 750 µmol), were added with EtOH (1.8 mL, 0.4 M) and stirred for 10 min. 4,6-dichloropyrido[3,2-d]pyrimidine (150 mg, 1 eq, 750 µmol

mol) was added, the vial was sealed, and stirred at 25 °C for 12 hours. Upon completion, the reaction was diluted with water and filtered to afford 6-chloro-4-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)pyrido[3,2-d]pyrimidine, **99**, (0.187 g, 0.474 µmol, 63%) as a white solid. LCMS $[M+H]^+$ 395. 1H NMR (500 MHz, DMSO) δ 8.60 (s, 1H), 8.48 – 8.42 (m, 1H), 8.20 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.85 (dd, J = 9.1, 2.6 Hz, 1H), 7.00 (d, J = 9.1 Hz, 1H), 4.46 (s, 4H), 3.97 – 3.76 (m, 4H).

4-(4-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)pyrido[3,2-d]pyrimidin-6-yl)pyridin-2-amine, 16.

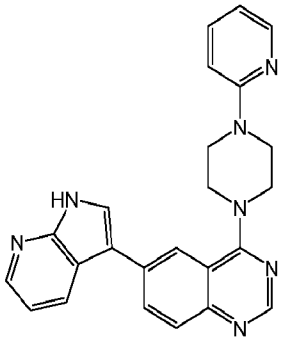


In a 5 mL microwave vial, 6-chloro-4-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)pyrido[3,2-d]pyrimidine (54 mg, 1 eq, 0.14 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (36 mg, 1.2 eq, 0.16 mmol), tripotassium phosphate (87 mg, 3 eq, 0.41mmol), and [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (9.0 mg, 0.08 eq, 11.0 µmol) were added. The mixture was capped, purged with argon, then injected with degassed 1,4- dioxane (0.8 mL) and water (0.2 mL), and was heated at 80 °C for 12 h. After this time, the mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (10 mL x 3). The aqueous layer was washed with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine (20 mL xx 2), dried over sodium sulfate, and evaporated *in vacuo* to obtain the crude product. The crude product was dry-loaded onto silica gel and purified on a 12 g silica gel column (0-20% MeOH/DCM) to afford 4-(4-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)pyrido[3,2-d]pyrimidin-6-yl)pyridin-2-amine, **16**, (49 mg, 110 µmol, 81%) as a tan solid. LCMS $[M+H]^+$ 452.95. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.44 (d, *J* = 2.4 Hz, 1H), 8.23 (d, *J* = 8.7 Hz, 1H), 8.20 (d, *J* = 5.3 Hz, 1H), 8.09 (d, *J* = 8.7 Hz, 1H), 7.69 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.28 (d, *J* = 5.4 Hz, 1H), 7.17 (s, 1H), 6.70 (d, *J* = 8.9 Hz, 1H), 5.06 (s, 2H), 4.69 (s, 4H), 3.94 (t, *J* = 5.3 Hz, 4H). ^{13}C

NMR (126 MHz, $CDCl_3$) δ 160.21, 159.61, 158.87, 155.58, 151.47, 148.21, 147.48, 145.92, 137.66, 134.86, 133.80, 124.53, 123.58, 115.74, 111.81, 106.62, 105.64, 44.64.

4-(4-(pyridin-2-yl)piperazin-1-yl)-6-(1H-pyrrolo[2,3-b]pyridin-3-yl)quinazoline, 17.

Compound **17** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.

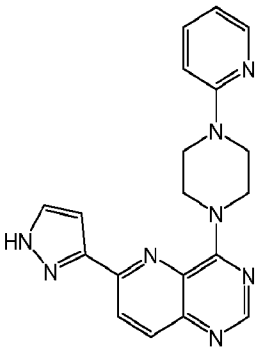


A 5 mL Biotage© microwave vial loaded with sodium bicarbonate (55 mg, 4.0 eq, 0.65 mmol), tert-butyl 3-(4,4,5,5-tetramethyl1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (62 mg, 1.1 eq, 0.18 mmol), [1,1'-Bis(diphenylphosphino) ferrocene] dichloropalladium (II) Complex With Dichloromethane (11 mg, 0.08 eq, 13 µmol), and 6-bromo-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline (61 mg, 1.0 eq, 0.16 mmol). The vial was capped, purged with argon, then injected with degassed 1,4-Dioxane (1.5 mL, 0.14 M), and heated to 80 ºC for 12 h. The reaction was cooled, concentrated, The reaction was cooled, diluted with DCM/MeOH, filtered through celite, concentrated, dry-loaded onto silica gel and purified on a 12 g silica gel column (DCM/MeOH, 0-20%), affording tert-butyl 3-(4-(4-(pyridin-2-yl)piperazin-1-yl)quinazolin-6-yl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate, LCMS $[M+H]^+$ 508, which was then subjected to 1M HCl in EtOAc in which 4-(4-(pyridin-2-yl)piperazin-1-yl)-6-(1H-pyrrolo[2,3-b]pyridin-3-yl)quinazoline, **17**, (23 mg, 56 µmol, 34 %) precipitated out as tan solid LCMS $[M+H]^+$ 408. 1H NMR (500 MHz, DMSO) δ 12.09 (s, 1H), 8.64 (s, 1H), 8.36 (d, J = 8.0 Hz, 1H), 8.32 (d, J = 4.5 Hz, 1H), 8.24 (d, J = 6.8 Hz, 2H), 8.16 (d, J = 4.8 Hz, 1H), 8.11 (s, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.24 (dd, J = 8.0, 4.6 Hz, 1H), 6.88 (d, J = 8.6 Hz, 1H), 6.68 (dd, J = 7.1, 4.9 Hz, 1H), 3.97 – 3.92 (m, 4H), 3.79 (t, J = 4.9 Hz, 4H). 13C NMR (126 MHz, DMSO) δ 163.99, 159.27, 153.48, 150.28, 149.71, 148.10, 138.10, 133.00, 132.37, 129.13, 125.56, 121.13, 117.63, 116.94, 113.63, 107.49, 49.32, 44.77, 40.54, 40.38,

40.30, 40.21, 40.14, 40.04, 39.87, 39.71, 39.54, 0.57.

6-(1H-pyrazol-3-yl)-4-(4-(pyridin-2-yl)piperazin-1-yl)pyrido[3,2-d]pyrimidine, 18.

Compound **18** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.

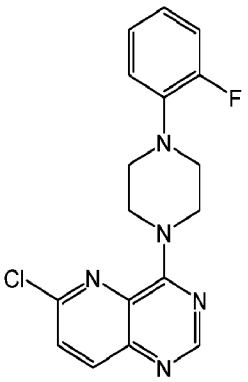


A 5 mL Biotage© microwave vial loaded with tripotassium phosphate (0.14 g, 3 eq, 0.68 mmol), [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (15 mg, 0.08 eq, 18 µmol), 6-chloro-4-(4-(pyridin-2-yl)piperazin-1-yl)pyrido[3,2-d]pyrimidine (74 mg, 1 eq, 0.23 mmol), and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (53 mg, 1.2 eq, 0.27 mmol). The vial was capped, purged with argon, then injected with degassed 4:1 Dioxane:H2O (2 mL, 0.1 M) and heated to 80 °C for 12 h. The reaction was cooled, diluted with DCM:MeOH, filtered through celite, concentrated, dry-loaded onto silica gel and purified on 12 g column (DCM/MeOH 0-20%), affording 6-(1H-pyrazol-4-yl)-4-(4-(pyridin-2-yl)piperazin-1-yl)pyrido[3,2-d]pyrimidine, **18**, (17 mg, 48.0 µmol, 21 %) as a pale yellow solid. LCMS $[M+H]^+$ 356. 1H NMR (500 MHz, DMSO) δ 13.23 (s, 1H), 8.50 (d, J = 5.7 Hz, 2H), 8.21 – 8.12 (m, 3H), 8.09 (d, J = 8.8 Hz, 1H), 7.58 (ddd, J = 8.8, 7.1, 2.0 Hz, 1H), 6.90 (d, J = 8.6 Hz, 1H), 6.68 (dd, J = 7.0, 4.9 Hz, 1H), 4.55 (s, 4H), 3.87 – 3.62 (m, 4H). 13C NMR (126 MHz, DMSO) δ 158.82, 158.38, 153.59, 149.17, 147.58, 145.46, 137.76, 137.58, 136.60, 132.73, 128.16, 124.77, 121.88, 113.08, 107.04, 44.55.

4-(4-(4-(2-fluorophenyl)piperazin-1-yl)pyrido[3,2-d]pyrimidin-6-yl)pyridin-2-amine, 19.

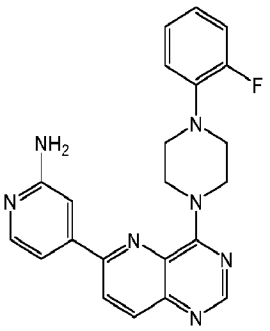
Compound **19** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

6-chloro-4-(4-(2-fluorophenyl)piperazin-1-yl)pyrido[3,2-d]pyrimidine, 100.



In a 5 mL Biotage microwave vial, sodium bicarbonate (71 mg, 1 eq, 850 µmol) and 1-(2-fluorophenyl)piperazine (153 mg, 134 µL, 1.0 eq, 850 µmol), were added with EtOH (2.0 mL, 0.4 M) and stirred for 10 min. 4,6-dichloropyrido[3,2-d]pyrimidine (170 mg, 1 eq, 850 µmol mol) was added, the vial was sealed and stirred at 25 °C for 12 h. Upon completion, the reaction was diluted with water and filtered to afford 6-chloro-4-(4-(2-fluorophenyl)piperazin-1-yl)pyrido[3,2-d]pyrimidine, **100**, (0.193 g, 0.561 µmol, 66%) as a white solid. LCMS $[M+H]^+$ 344. 1H NMR (500 MHz, DMSO) δ 8.59 (s, 1H), 8.20 (d, J = 8.8 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.21 – 7.13 (m, 1H), 7.09 (qd, J = 7.4, 1.7 Hz, 2H), 7.00 (tdd, J = 7.6, 4.7, 2.2 Hz, 1H), 4.51 (s, 4H), 3.20 (t, J = 5.0 Hz, 4H).

4-(4-(4-(2-fluorophenyl)piperazin-1-yl)pyrido[3,2-d]pyrimidin-6-yl)pyridin-2-amine, 19.

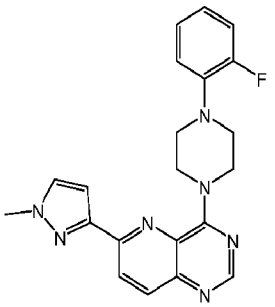


In a 5 mL microwave vial, 6-chloro-4-(4-(2-fluorophenyl)piperazin-1-yl)pyrido[3,2-d]pyrimidine (40 mg, 1 eq, 0.12 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (31 mg, 1.2 eq, 0.14 mmol), tripotassium phosphate (99 mg, 4 eq, 0.47 mmol), and [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (7 mg, 0.08 eq, 9 µmol) were added. The mixture was capped, purged with argon, then injected with degassed 4:1 Dioxane:H_2O (0.7 mL, 0.2 M) and was heated at 80 °C for 12 h. After this time, the

mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (10 mL x 3). The aqueous layer was washed with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate, and evaporated *in vacuo* to obtain the crude product. The crude product was dry-loaded onto silica gel and purified on a 12 g silica gel column (0-20% MeOH/DCM) to afford 4-(4-(4-(2-fluorophenyl)piperazin-1-yl)pyrido[3,2-d]pyrimidin-6-yl)pyridin-2-amine, **19**, (36 mg, 90 µmol, 78%) as a pale yellow solid. LCMS $[M+H]^+$ 402. 1H NMR (500 MHz, CDCl3) δ 8.65 (s, 1H), 8.22 (d, J = 8.7 Hz, 1H), 8.18 (d, J = 5.6 Hz, 1H), 8.08 (d, J = 8.9 Hz, 1H), 7.31 – 7.27 (d, 1H), 7.19 (s, 1H), 7.11 – 7.04 (m, 2H), 7.02 – 6.95 (m, 2H), 5.13 (s, 2H), 4.74 (s, 4H), 3.35 – 3.28 (t, 4H).

4-(4-(2-fluorophenyl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-3-yl)pyrido[3,2-d]pyrimidine, 20.

Compound **20** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.

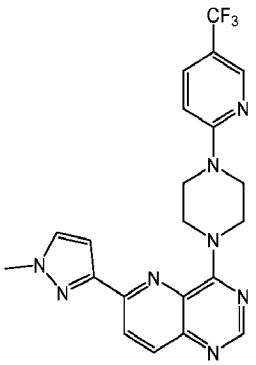


A 5 mL Biotage© microwave vial loaded with tripotassium phosphate (0.12 g, 4 eq, 0.58 mmol), [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (9 mg, 0.08 eq, 12 µmol), 6-chloro-4-(4-(2-fluorophenyl)piperazin-1-yl)pyrido[3,2-d]pyrimidine (50 mg, 1 eq, 0.15 mmol), and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (36 mg, 1.2 eq, 0.17 mmol). The vial was capped, purged with argon, then injected with degassed 4:1 Dioxane:H_2O (0.7 mL, 0.2 M) and heated to 80 ºC for 12 h. The reaction was cooled, diluted with DCM:MeOH, filtered through celite, concentrated, dry-loaded onto silica gel and purified on 12 g column (DCM/MeOH 0-20%), affording 4-(4-(2-fluorophenyl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-3-yl)pyrido[3,2-d]pyrimidine, **20**, (26 mg, 67 µmol, 46 %) as a tan solid. LCMS $[M+H]^+$ 390. 1H NMR (500 MHz, DMSO) δ 8.50 (s, 1H),

8.41 (s, 1H), 8.13 (s, 1H), 8.09 (s, 2H), 7.21 – 7.08 (m, 3H), 7.01 (dtd, J = 8.1, 4.8, 3.1 Hz, 1H), 3.93 (d, J = 4.0 Hz, 4H), 3.26 (t, J = 5.0 Hz, 4H), 1.07 (s, 3H). 13C NMR (126 MHz, DMSO) δ 158.32, 156.00, 154.05, 153.55, 148.83, 145.49, 139.66, 139.60, 137.69, 136.75, 132.71, 130.29, 124.87, 124.85, 124.56, 122.66, 122.59, 122.36, 119.54, 116.06, 115.90, 73.49, 50.40, 24.94.

6-(1-methyl-1H-pyrazol-3-yl)-4-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)pyrido[3,2-d]pyrimidine, 21.

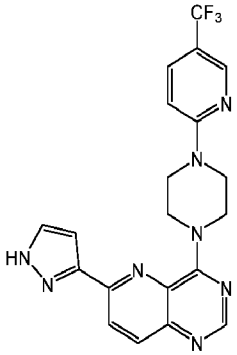
Compound **21** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.



A 5 mL Biotage© microwave vial loaded with tripotassium phosphate (0.11 g, 4 eq, 0.51 mmol), [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (8 mg, 0.08 eq, 10 µmol), 6-chloro-4-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)pyrido[3,2-d]pyrimidine (50 mg, 1 eq, 0.13 mmol), and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (32 mg, 1.2 eq, 0.15 mmol). The vial was capped, purged with argon, then injected with degassed 4:1 Dioxane:H_2O (0.7 mL, 0.2 M) and heated to 80 °C for 12 h. The reaction was cooled, diluted with DCM:MeOH, filtered through celite, concentrated, dry-loaded onto silica gel and purified on 12 g column (DCM/MeOH 0-20%), affording 6-(1-methyl-1H-pyrazol-3-yl)-4-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)pyrido[3,2-d]pyrimidine, **21**, (21 mg, 48 µmol, 39 %) as a white solid. LCMS $[M+H]^+$ 441. 1H NMR (500 MHz, DMSO) δ 8.50 (s, 1H), 8.47 – 8.45 (m, 1H), 8.44 (s, 1H), 8.18 – 8.13 (m, 1H), 8.10 (s, 2H), 7.86 (dd, J = 9.1, 2.6 Hz, 1H), 7.01 (d, J = 9.1 Hz, 1H), 4.56 (s, 4H), 3.94 (s, 3H), 3.92 (t, J = 5.3 Hz, 4H).

6-(1H-pyrazol-3-yl)-4-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)pyrido[3,2-d]pyrimidine, 22.

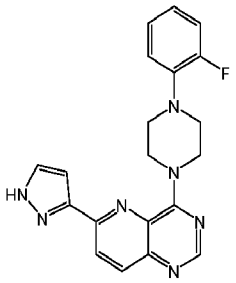
Compound **22** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.



A 5 mL Biotage© microwave vial loaded with tripotassium phosphate (0.15 g, 4 eq, 0.71 mmol), [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (12 mg, 0.08 eq, 14 µmol), 6-chloro-4-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)pyrido[3,2-d] (70 mg, 1 eq, 0.18 mmol), and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (63 mg, 1.2 eq, 0.21 mmol). The vial was capped, purged with argon, then injected with degassed 4:1 Dioxane:H_2O (1.0 mL, 0.2 M) and heated to 80 °C for 12 h. The reaction was cooled, diluted with DCM:MeOH, filtered through celite, and concentrated. A mixture of DCM:TFA (1:2, 1 mL) was added to the crude mixture and stirred at room temperature overnight and basified with 1N NaOH. The mixture was extracted with DCM, washed with 10% NaOH, water, brine, and the organic layer was dried over sodium sulfate, concentrated, and dry-loaded onto silica gel and purified on a 12 g column (DCM/MeOH 0-20%), affording 6-(1H-pyrazol-3-yl)-4-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)pyrido[3,2-d]pyrimidine, **22**, (14 mg, 34 µmol, 19 %) as a tan solid. LCMS $[M+H]^+$ 427. 1H NMR (500 MHz, DMSO) δ 13.23 (s, 1H), 8.52 (s, 1H), 8.51 (s, 1H), 8.48 – 8.44 (m, 1H), 8.20 (d, J = 1.9 Hz, 1H), 8.15 (d, J = 8.8 Hz, 1H), 8.10 (d, J = 8.8 Hz, 1H), 7.85 (dd, J = 9.1, 2.6 Hz, 1H), 7.02 (d, J = 9.1 Hz, 1H), 4.56 (s, 4H), 4.00 – 3.82 (m, 4H).

4-(4-(2-fluorophenyl)piperazin-1-yl)-6-(1H-pyrazol-3-yl)pyrido[3,2-d]pyrimidine, 23.

Compound **23** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.

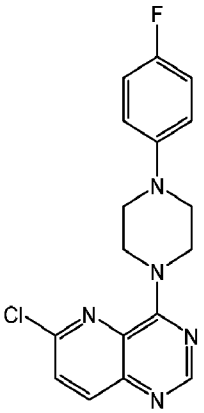


A 5 mL Biotage© microwave vial loaded with tripotassium phosphate (0.17 g, 4 eq, 0.81 mmol), [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (13 mg, 0.08 eq, 16 µmol), 6-chloro-4-(4-(2-fluorophenyl)piperazin-1-yl)pyrido[3,2-d]pyrimidine (70 mg, 1 eq, 0.20 mmol), and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (72 mg, 1.2 eq, 0.24 mmol). The vial was capped, purged with argon, then injected with degassed 4:1 Dioxane:H2O (1.0 mL, 0.2 M) and heated to 80 ºC for 12 h. The reaction was cooled, diluted with DCM:MeOH, filtered through celite, and concentrated. A mixture of DCM:TFA (1:2, 1.2 mL) was added to the crude mixture and stirred at room temperature overnight and basified with 1N NaOH. The mixture was extracted with DCM, washed with 10% NaOH, water, brine, and the organic layer was dried over sodium sulfate, concentrated, and dry loaded onto silica gel and purified on a 12 g column (DCM/MeOH 0-20%), affording 4-(4-(2-fluorophenyl)piperazin-1-yl)-6-(1H-pyrazol-3-yl)pyrido[3,2-d], **23**, (64 mg, 173 µmol, 85 %) as a yellow/orange solid. LCMS $[M+H]^+$ 376. 1H NMR (500 MHz, DMSO) δ 8.76 (s, 1H), 8.40 (s, 2H), 8.29 (d, J = 8.7 Hz, 1H), 8.17 (d, J = 8.8 Hz, 1H), 7.23 – 7.14 (m, 2H), 7.13 (d, J = 2.6 Hz, 1H), 7.02 (dtd, J = 8.0, 5.0, 3.1 Hz, 1H), 4.80 (s, 4H), 3.35 (s, 4H). 13C NMR (126 MHz, DMSO) δ 158.73, 158.46, 156.41, 154.47, 151.18, 150.35, 139.64, 139.58, 138.67, 131.75, 131.52, 126.75, 125.40, 125.37, 123.32, 123.26, 121.65, 120.07, 120.05, 116.63, 116.47, 50.76.

4-(4-(4-(4-fluorophenyl)piperazin-1-yl)pyrido[3,2-d]pyrimidin-6-yl)pyridin-2-amine, 24.

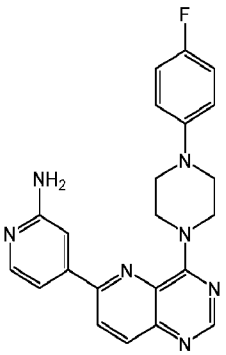
Compound **24** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

6-chloro-4-(4-(4-fluorophenyl)piperazin-1-yl)pyrido[3,2-d]pyrimidine, 101.



In a 5 mL Biotage microwave vial, sodium bicarbonate (55 mg, 1 eq, 760 µmol) and 1-(4-fluorophenyl)piperazine (117 mg, 1.0 eq, 650 µmol), were added with EtOH (1.6 mL, 0.4 M) and stirred for 10 min. 4,6-dichloropyrido[3,2-d]pyrimidine (130 mg, 1 eq, 650 µmol) was added, the vial was sealed, and stirred at 25 °C for 12 h. Upon completion, the reaction was diluted with water and filtered to afford 6-chloro-4-(4-(4-fluorophenyl)piperazin-1-yl)pyrido[3,2-d]pyrimidine, **101**, (0.140 g, 0.407 µmol, 63%). LCMS $[M+H]^+$ 344. 1H NMR (500 MHz, DMSO) δ 8.59 (s, 1H), 8.19 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.08 (t, J = 8.8 Hz, 2H), 7.02 (dd, J = 9.2, 4.7 Hz, 2H), 4.64 – 4.38 (s, 4H), 3.29 (t, J = 5.2 Hz, 4H).

4-(4-(4-(4-fluorophenyl)piperazin-1-yl)pyrido[3,2-d]pyrimidin-6-yl)pyridin-2-amine, 24.



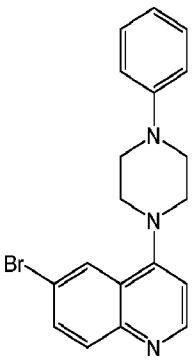
In a 5 mL microwave vial, 6-chloro-4-(4-(4-fluorophenyl)piperazin-1-yl)pyrido[3,2-d]pyrimidine (50 mg, 1 eq, 0.15 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (38 mg, 1.2 eq, 0.17 mmol), tripotassium phosphate (120 mg, 4 eq, 0.58 mmol), and [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (9 mg, 0.08 eq, 12.0 µmol) were added. The mixture was capped, purged with argon, then injected with degassed 4:1 Dioxane:H_2O (1.0 mL, 0.1 M), and was heated at 80 °C for 12 h. After this time, the mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (10 mL). The aqueous layer was washed with ethyl acetate (20 mL x 3). The

combined organic layer was washed with brine (20 mL x 2), dried over sodium sulfate, and evaporated *in vacuo* to obtain the crude product. The crude product was dry-loaded onto silica gel and purified on a 12 g silica gel column (0-20% MeOH/DCM) to afford 4-(4-(4-(4-fluorophenyl)piperazin-1-yl)pyrido[3,2-d]pyrimidin-6-yl)pyridin-2-amine, 24, (43 mg, 109 µmol, 75%) as an orange solid. LCMS $[M+H]^+$ 402. 1H NMR (500 MHz, DMSO) δ 8.56 (s, 1H), 8.31 (d, J = 8.8 Hz, 1H), 8.22 (d, J = 8.8 Hz, 1H), 8.10 (d, J = 5.3 Hz, 1H), 7.20 (d, J = 5.4 Hz, 1H), 7.15 (s, 1H), 7.09 (t, J = 8.8 Hz, 2H), 7.03 (dd, J = 9.3, 4.6 Hz, 2H), 6.18 (s, 2H), 4.63 (s, 4H), 3.36 (t, J = 5.1 Hz, 4H). 13C NMR (126 MHz, DMSO) δ 161.20, 159.11, 157.55, 155.68, 155.25, 151.96, 149.47, 148.11, 148.09, 147.22, 146.15, 137.69, 133.32, 125.11, 117.72, 117.66, 115.92, 115.74, 109.85, 105.43, 49.58.

4-(4-(4-phenylpiperazin-1-yl)quinolin-6-yl)pyridin-2-amine, 25.

Compound **25** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

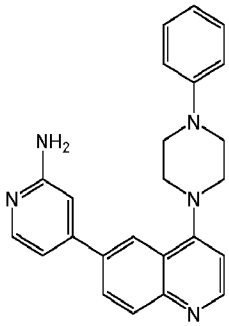
6-bromo-4-(4-phenylpiperazin-1-yl)quinoline, 102.



In a 5 mL microwave vial of 1-phenylpiperazine (1.2 g, 1.17 mL, 6 eq, 7.42 mmol) dissolved in isopropyl alcohol (3.0 mL, 0.4 M) was added N,N-Diisopropylethylamine (799 mg, 1.1 mL, 5 eq, 6.19 mmol) and 6-bromo-4-chloroquinoline (300 mg, 1 eq, 1.24 mmol). The reaction mixture was stirred at 100 °C for 12 h. Upon cooling to room temperature, the reaction was poured into water and extracted with EtOAc (20 mL x 2), washed with brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to obtain the crude product. The crude product was dry-loaded onto silica gel and purified on a 24 g silica gel column (5-50% EtOAc/Hexanes) to afford 6-bromo-4-(4-phenylpiperazin-1-yl)quinoline, **102**, (350 mg, 0.95 mmol, 77%). LCMS $[M+H]^+$

369. 1H NMR (500 MHz, CDCl3) δ 8.75 (d, J = 5.0 Hz, 1H), 8.21 (d, J = 2.2 Hz, 1H), 7.97 (d, J = 8.9 Hz, 1H), 7.75 (dd, J = 9.0, 2.3 Hz, 1H), 7.39 – 7.28 (m, 2H), 7.09 – 6.99 (m, 2H), 6.97 – 6.88 (m, 2H), 3.53 – 3.44 (m, 4H), 3.40 (dd, J = 6.3, 3.4 Hz, 4H). 13C NMR (126 MHz, CDCl3) δ 155.96, 151.17, 151.06, 148.17, 132.64, 131.86, 129.29, 126.03, 124.86, 120.41, 119.63, 116.45, 109.70, 52.25, 49.40.

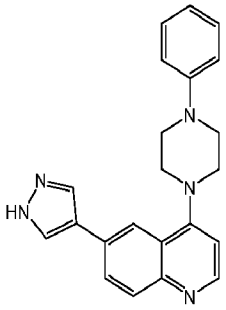
4-(4-(4-phenylpiperazin-1-yl)quinolin-6-yl)pyridin-2-amine, 25.



In a 5 mL microwave vial, 6-bromo-4-(4-phenylpiperazin-1-yl)quinoline (80 mg, 1 eq, 0.22 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (57 mg, 1.2 eq, 0.26 mmol), tripotassium phosphate (180 mg, 4 eq, 0.87 mmol), and [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (14 mg, 0.08 eq, 17.0 µmol) were added. The mixture was capped, purged with argon, then injected with degassed 4:1 Dioxane:H2O (2.0 mL, 0.1 M), and was heated at 80 °C for 6 h. After this time, the mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (10 mL x 3). The aqueous layer was washed with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate, and evaporated *in vacuo* to obtain the crude product. The crude product was dry-loaded onto silica gel and purified on a 12 g silica gel column (0-20% MeOH/DCM) to afford 4-(4-(4-phenylpiperazin-1-yl)quinolin-6-yl)pyridin-2-amine, **25**, (38 mg, 101 µmol, 47%) as yellow solid. LCMS $[M+H]^+$ 382. 1H NMR (500 MHz, CDCl3) δ 8.79 (d, J = 5.1 Hz, 1H), 8.29 (d, J = 2.0 Hz, 1H), 8.20 (d, J = 8.7 Hz, 1H), 8.12 (d, J = 5.6 Hz, 1H), 7.90 (dd, J = 8.6, 2.0 Hz, 1H), 7.36 – 7.28 (m, 2H), 7.04 (d, J = 8.1 Hz, 2H), 7.01 (d, J = 5.6 Hz, 1H), 6.97 (d, J = 5.1 Hz, 1H), 6.94 (t, J = 7.3 Hz, 1H), 6.87 (s, 1H), 5.10 (s, 2H), 3.51 (d, J = 5.1 Hz, 4H), 3.48 (d, J = 5.4 Hz, 4H). 13C NMR (126 MHz, DMSO) δ 160.56, 156.29, 151.42, 150.89, 149.09, 148.76, 147.51, 135.02, 130.45, 129.00, 127.47, 122.75, 121.07, 119.25, 115.66, 110.04, 109.67, 105.07, 51.79, 48.33.

4-(4-phenylpiperazin-1-yl)-6-(1H-pyrazol-4-yl)quinoline, 26.

Compound **26** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.

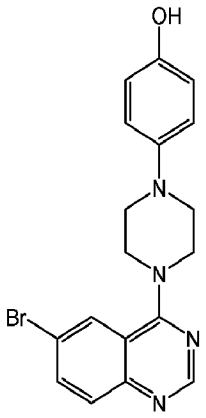


A 5 mL Biotage© microwave vial loaded with tripotassium phosphate (0.22 g, 4 eq, 1.0 mmol), [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (17 mg, 0.08 eq, 20 µmol), 6-bromo-4-(4-phenylpiperazin-1-yl)quinoline (94 mg, 1 eq, 0.26 mmol), and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (90 mg, 1.2 eq, 0.31 mmol). The vial was capped, purged with argon, then injected with degassed 4:1 Dioxane:H2O (1.5 mL, 0.1 M) and heated to 80 ºC for 5 h. The reaction was cooled, diluted with DCM:MeOH, filtered through celite, and concentrated. A mixture of DCM:TFA (1:2, 1.5 mL) was added to the crude mixture and stirred at room temperature overnight and basified with 1N NaOH. The mixture was extracted with DCM, washed with 10% NaOH, water, brine, and the organic layer was dried over sodium sulfate, concentrated, and dry-loaded onto silica gel and purified on a 12 g column (DCM/MeOH 0-20%), affording 4-(4-phenylpiperazin-1-yl)-6-(1H-pyrazol-4-yl)quinoline, **26**, (12 mg, 35 µmol, 14 %) as a red-brown solid. LCMS $[M+H]^+$ 356. 1H NMR (500 MHz, DMSO) δ 13.11 (s, 1H), 8.65 (d, J = 5.8 Hz, 1H), 8.40 (s, 1H), 8.21 (d, J = 1.9 Hz, 1H), 8.11 (dd, J = 8.9, 1.8 Hz, 2H), 7.96 (d, J = 8.7 Hz, 1H), 7.30 – 7.24 (m, 2H), 7.13 (d, J = 5.8 Hz, 1H), 7.04 (d, J = 8.0 Hz, 2H), 6.83 (t, J = 7.3 Hz, 1H), 3.66 (s, 4H), 3.50 (t, J = 5.0 Hz, 4H).

4-(4-(6-(2-aminopyridin-4-yl)quinazolin-4-yl)piperazin-1-yl)phenol, 27.

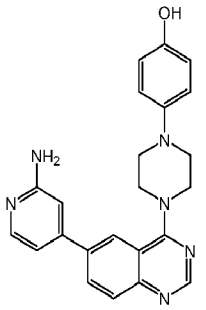
Compound **27** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

4-(4-(6-bromoquinazolin-4-yl)piperazin-1-yl)phenol, 103.



In a 5 mL Biotage microwave vial, sodium bicarbonate (45 mg, 1 eq, 0.534 mmol) and 4-(piperazin-1-yl)phenol (95 mg, 1.0 eq, 0.534 mmol), were added with EtOH (1.3 mL, 0.4 M) and stirred for 10 min. 6-bromo-4-chloroquinazoline (130 mg, 1 eq, 0.534 mmol) was added, the vial was sealed, and stirred at 25 °C for 12 h. Upon completion, the reaction was diluted with water and filtered to afford 4-(4-(6-bromoquinazolin-4-yl)piperazin-1-yl)phenol, **103**, (0.158 g, 0.410 mmol, 77%) as a tan solid. LCMS $[M+H]^+$ 386. 1H NMR (500 MHz, CDCl3) δ 8.54 (t, J = 4.3 Hz, 1H), 8.29 (s, 1H), 7.91 (t, J = 4.1 Hz, 1H), 7.67 (d, J = 4.9 Hz, 2H), 7.25 (d, J = 4.8 Hz, 1H), 6.73 (s, 1H), 6.64 (dt, J = 8.6, 4.2 Hz, 2H), 3.84 (s, 4H), 3.09 (p, J = 4.5 Hz, 4H).

4-(4-(6-(2-aminopyridin-4-yl)quinazolin-4-yl)piperazin-1-yl)phenol, 27.



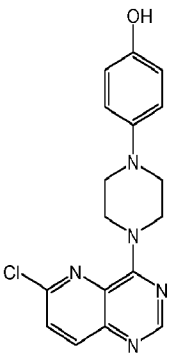
In a 5 mL microwave vial, 4-(4-(6-chloroquinazolin-4-yl)piperazin-1-yl)phenol (50 mg, 1 eq, 0.15 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (39 mg, 1.2 eq, 0.18 mmol), tripotassium phosphate (120 mg, 4 eq, 0.59 mmol), and [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (9 mg,

0.08 eq, 12 µmol) were added. The mixture was capped, purged with argon, then injected with degassed 4:1 Dioxane:H_2O (1.0 mL, 0.1 M), and was heated at 80 °C for 12 h. After this time, the mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (10 mL x 3). The aqueous layer was washed with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate, and evaporated *in vacuo* to obtain the crude product. The crude product was dry-loaded onto silica gel and purified on a 12 g silica gel column (0-10% MeOH/DCM) to afford 4-(4-(6-(2-aminopyridin-4-yl)quinazolin-4-yl)piperazin-1-yl)phenol, **27**, (24 mg, 60 µmol, 41%) as a light brown solid. LCMS $[M+H]^+$ 399. 1H NMR (500 MHz, DMSO) δ 8.89 (s, 1H), 8.67 (s, 1H), 8.18 (d, J = 2.1 Hz, 1H), 8.09 (dd, J = 8.7, 2.0 Hz, 1H), 8.03 (d, J = 5.3 Hz, 1H), 7.92 (d, J = 8.7 Hz, 1H), 6.92 (dd, J = 5.3, 1.7 Hz, 1H), 6.90 – 6.83 (m, 2H), 6.82 (dd, J = 1.7, 0.7 Hz, 1H), 6.72 – 6.65 (m, 2H), 6.06 (s, 2H), 3.94 (t, J = 5.0 Hz, 4H), 3.20 (t, J = 5.1 Hz, 4H). 13C NMR (126 MHz, DMSO) δ 163.80, 160.55, 154.03, 151.46, 151.27, 148.78, 147.09, 143.89, 135.31, 131.10, 128.85, 122.69, 118.15, 115.89, 115.53, 110.05, 105.16, 50.07, 49.33.

4-(4-(6-(2-aminopyridin-4-yl)pyrido[3,2-d]pyrimidin-4-yl)piperazin-1-yl)phenol, 28.

Compound **28** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

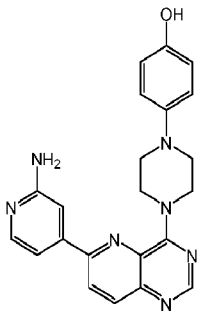
4-(4-(6-chloropyrido[3,2-d]pyrimidin-4-yl)piperazin-1-yl)phenol, 104.



In a 20 mL Biotage microwave vial, sodium bicarbonate (189 mg, 1 eq, 2.25 mmol) and 4-(piperazin-1-yl)phenol (401 mg, 1.0 eq, 2.25 mmol), were added with EtOH (5.0 mL, 0.4 M) and stirred for 10 min. 4,6-dichloropyrido[3,2-d]pyrimidine (450 mg, 1 eq, 2.25 mmol) was added, the vial was sealed, and stirred at 25 °C for 2 days. Upon completion, the reaction was diluted

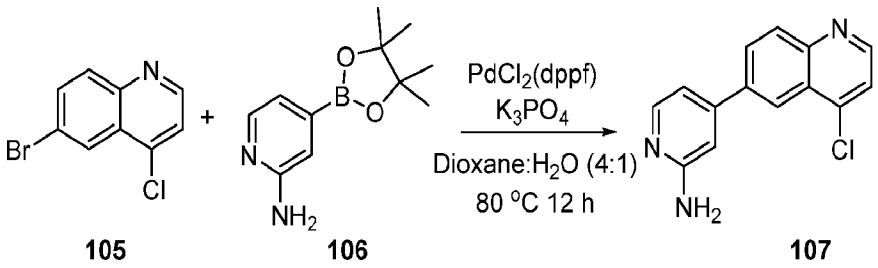
with water and filtered to afford 4-(4-(6-chloropyrido[3,2-d]pyrimidin-4-yl)piperazin-1-yl)phenol, **104**, (0.429 g, 1.26 mmol, 56%) as a tan solid. LCMS $[M+H]^+$ 342. 1H NMR (500 MHz, DMSO) δ 8.86 (s, 1H), 8.57 (s, 1H), 8.18 (d, J = 8.8 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 6.89 – 6.81 (m, 2H), 6.73 – 6.61 (m, 2H), 4.47 (s, 4H), 3.24 – 3.02 (m, 4H). 13C NMR (126 MHz, DMSO) δ 157.60, 154.96, 151.22, 146.46, 144.90, 143.78, 140.00, 132.25, 128.95, 118.07, 115.48, 50.24.

4-(4-(6-(2-aminopyridin-4-yl)pyrido[3,2-d]pyrimidin-4-yl)piperazin-1-yl)phenol, 28.



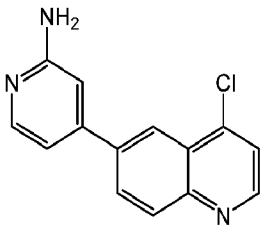
In a 20 mL microwave vial, 4-(4-(6-chloropyrido[3,2-d]pyrimidin-4-yl)piperazin-1-yl)phenol (429 mg, 1 eq, 1.26 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (331 mg, 1.2 eq, 1.51 mmol), tripotassium phosphate (1.07 g, 4 eq, 5.02 mmol), and [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (82 mg, 0.08 eq, 100 µmol) were added. The mixture was capped, purged with argon, then injected with degassed 4:1 Dioxane:H_2O (10 mL, 0.1 M), and was heated at 80 °C for 5 h. After this time, the mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (10 mL x 3). The aqueous layer was washed with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate, and evaporated *in vacuo* to obtain the crude product. The crude product was dry-loaded onto silica gel and purified on a 24 g silica gel column (0-20% MeOH/DCM) to afford 4-(4-(6-(2-aminopyridin-4-yl)pyrido[3,2-d]pyrimidin-4-yl)piperazin-1-yl)phenol, **28**, (200 mg, 501 µmol, 40%) as a tan solid. LCMS $[M+H]^+$ 400. 1H NMR (500 MHz, DMSO) δ 8.90 (s, 1H), 8.56 (s, 1H), 8.31 (d, J = 8.8 Hz, 1H), 8.22 (d, J = 8.8 Hz, 1H), 8.09 (d, J = 5.3 Hz, 1H), 7.19 (dd, J = 5.4, 1.6 Hz, 1H), 7.15 (dd, J = 1.7, 0.8 Hz, 1H), 6.91 – 6.85 (m, 2H), 6.72 – 6.65 (m, 2H), 6.17 (s, 2H), 4.61 (s, 5H), 3.22 (t, J = 4.8 Hz, 4H).

Step 1, General Scheme 2



105 106 107

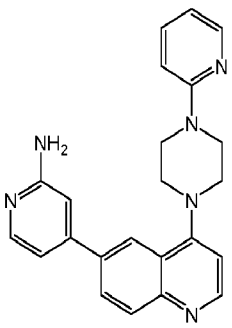
4-(4-chloroquinolin-6-yl)pyridin-2-amine, 107.



A 100 mL RBF was loaded with tripotassium phosphate (1.05 g, 1.5 eq, 4.95 mmol), [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (270 mg, 0.1 eq, 330 µmol), 6-bromo-4-chloroquinoline (800 mg, 1 eq, 3.30 mmol), and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (799 mg, 1.1 eq, 3.63 mmol). The mixture was injected with degassed 4:1 Dioxane:H_2O (16 mL, 0.2 M), purged with argon for 10 minutes, and refluxed at 80 ºC for 12 h. The reaction was cooled, diluted with DCM:MeOH, filtered through celite, concentrated, dry-loaded onto silica gel and purified on 24 g column (DCM/MeOH 0-8%), affording 4-(4-chloroquinolin-6-yl)pyridin-2-amine, **107**, (428 mg, 1.67 mmol, 51%). LCMS $[M+H]^+$ 256. 1H NMR (500 MHz, CDCl3) δ 8.82 (d, J = 4.7 Hz, 1H), 8.44 (d, J = 1.9 Hz, 1H), 8.26 – 8.10 (m, 2H), 7.99 (dd, J = 8.8, 2.0 Hz, 1H), 7.55 (d, J = 4.7 Hz, 1H), 7.04 (d, J = 5.0 Hz, 1H), 6.90 (s, 1H), 4.95 (s, 2H).

Step 2, General Scheme 2

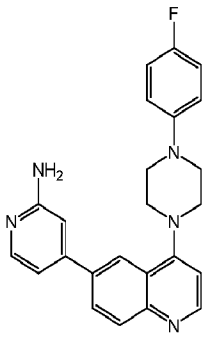
4-(4-(4-phenylpiperazin-1-yl)quinolin-6-yl)pyridin-2-amine, 29.



In a 5 mL microwave vial of 1-(pyridin-2-yl)piperazine (0.11 g, 0.10 mL, 6 eq, 0.68 mmol) dissolved in isopropyl alcohol (0.8 mL, 0.1 M) was added N,N-Diisopropylethylamine (73 mg, 99 µL, 5 eq, 0.57 mmol) and 4-(4-chloroquinolin-6-yl)pyridin-2-amine (29 mg, 1 eq, 0.11 mmol). The reaction mixture was stirred at 100 °C for 12 h. Upon cooling to room temperature, the reaction was poured into water (10 mL) and extracted with EtOAc (40 mL) , washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, and evaporated *in vacuo* to obtain the crude product. The crude product was dry-loaded onto silica gel and purified on a 12 g silica gel column (0-20% MeOH/DCM) to afford 4-(4-(4-phenylpiperazin-1-yl)quinolin-6-yl)pyridin-2-amine, **29**, (33 mg, 0.11 mmol, 77%) as a tan solid. LCMS $[M+H]^+$ 383. 1H NMR (500 MHz, DMSO) δ 8.74 (d, J = 4.9 Hz, 1H), 8.30 (d, J = 2.1 Hz, 1H), 8.17 (dd, J = 5.1, 1.9 Hz, 1H), 8.07 (d, J = 8.7 Hz, 1H), 8.03 (d, J = 5.3 Hz, 1H), 7.99 (dd, J = 8.8, 2.0 Hz, 1H), 7.60 (ddd, J = 8.9, 7.1, 2.0 Hz, 1H), 7.10 (d, J = 5.0 Hz, 1H), 6.97 – 6.89 (m, 2H), 6.86 (d, J = 1.7 Hz, 1H), 6.71 (dd, J = 7.1, 4.9 Hz, 1H), 6.06 (s, 2H), 3.81 (d, J = 5.5 Hz, 4H), 3.35 (d, J = 5.0 Hz, 4H).

4-(4-(4-(4-fluorophenyl)piperazin-1-yl)quinolin-6-yl)pyridin-2-amine, 30.

Compound **30** was prepared via General Scheme 2 via the two step procedure reported for the preparation of compound **29**. The second step is reported below.



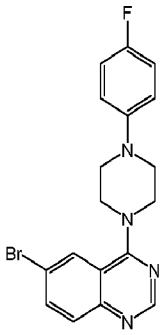
Prepared in an analogous manner to Step 2, General Scheme 2 as seen for 4-(4-(4-phenylpiperazin-1-yl)quinolin-6-yl)pyridin-2-amine, **29**. 4-(4-(4-(4-fluorophenyl)piperazin-1-yl)quinolin-6-yl)pyridin-2-amine, **30**, (13 mg, 0.16 mmol, 21%) as a tan solid. LCMS $[M+H]^+$ 400. 1H NMR (500 MHz, CDCl3) δ 8.78 (d, J = 5.0 Hz, 1H), 8.26 (d, J = 2.1 Hz, 1H), 8.15 (d, J = 8.4 Hz, 2H), 7.88 (dd, J = 8.7, 2.0 Hz, 1H), 6.99 (dddd, J = 17.3, 12.6, 7.5, 3.7 Hz, 6H), 6.82 (s, 1H), 4.82 (s, 2H), 3.48 – 3.37 (m, 8H). 13C NMR (101 MHz, CDCl3) δ 158.85, 158.75,

157.11, 156.37, 151.39, 150.25, 149.60, 148.07, 147.69, 147.67, 135.59, 130.79, 127.99, 123.48, 121.92, 118.28, 118.21, 115.83, 115.61, 112.71, 109.49, 106.64, 52.35, 50.40.

4-(4-(4-(4-fluorophenyl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 31.

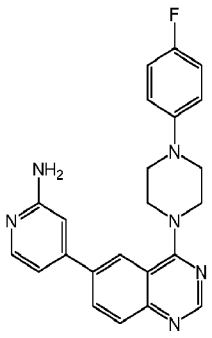
Compound **31** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

6-bromo-4-(4-(4-fluorophenyl)piperazin-1-yl)quinazoline, 108.



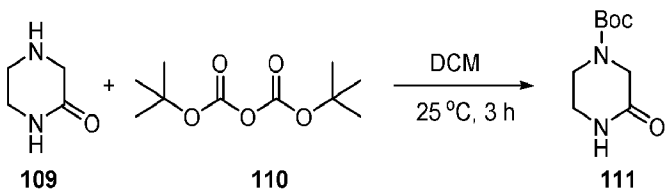
In a 5 mL Biotage microwave vial, 1-(4-fluorophenyl)piperazine (96 mg, 96 µL, 1.0 eq, 534 µmol) and sodium bicarbonate (45 mg, 1 eq, 534 µmol) were dissolved in EtOH (1.3 mL, 0.4 M), and stirred for 10 mins. 6-bromo-4-chloroquinazoline (130 mg, 1 eq, 534 µmol) was added, vial capped, and stirred at 25°C for 12 hrs. After this time, the mixture was cooled to room temperature, diluted with water and filtered to afford 6-bromo-4-(4-(4-fluorophenyl)piperazin-1-yl)quinazoline, **108** (169 mg, 437 µmol, 82%) as a tan solid. LCMS $[M+H]^+$ 388. 1H NMR (500 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.07 (d, J = 2.1 Hz, 1H), 7.94 – 7.78 (m, 2H), 7.07 – 6.97 (m, 2H), 6.97 – 6.90 (m, 2H), 3.99 (t, J = 5.1 Hz, 4H), 3.51 – 3.24 (m, 4H).

4-(4-(4-(4-fluorophenyl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 31.



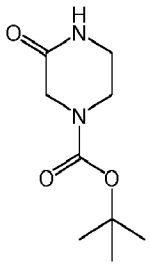
In a 5 mL microwave vial, 6-chloro-4-(4-(4-fluorophenyl)piperazin-1-yl)quinazoline (60 mg, 1 eq, 0.18 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (46 mg, 1.2 eq, 0.21 mmol), tripotassium phosphate (0.15 mg, 4 eq, 0.7 mmol), and [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (11 mg, 0.08 eq, 14 µmol) were added. The mixture was capped, purged with argon, then injected with degassed 4:1 Dioxane:H_2O (1.5 mL, 0.1 M), and was heated at 80 °C for 6 h. After this time, the mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (10 mL x 3). The aqueous layer was washed with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate, and evaporated *in vacuo* to obtain the crude product. The crude product was dry-loaded onto silica gel and purified on a 12 g silica gel column (0-10% MeOH/DCM) to afford 4-(4-(4-(4-fluorophenyl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, **31**, (28 mg, 0.18 mmol, 40%) as a yellow solid. LCMS $[M+H]^+$ 401. 1H NMR (500 MHz, CDCl3) δ 8.79 (s, 1H), 8.13 (d, J = 5.5 Hz, 1H), 8.11 (d, J = 2.0 Hz, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.96 (dd, J = 8.7, 1.9 Hz, 1H), 7.04 – 6.97 (m, 2H), 6.97 – 6.91 (m, 3H), 6.81 (d, J = 1.6 Hz, 1H), 4.98 (s, 2H), 4.00 (t, J = 5.0 Hz, 4H), 3.34 (t, J = 5.0 Hz, 4H). 13C NMR (101 MHz, CDCl3) δ 164.94, 159.01, 158.91, 156.53, 154.72, 152.23, 149.75, 148.41, 147.77, 147.74, 135.99, 131.46, 129.74, 123.26, 118.43, 118.35, 116.86, 116.00, 115.78, 112.67, 106.60, 50.40, 50.01.

Step 1, General Scheme 3



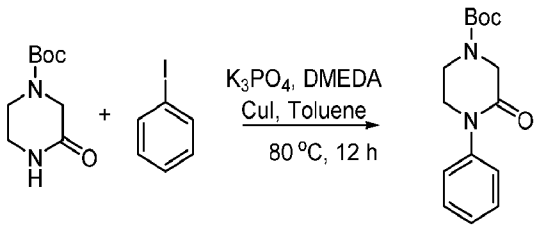
109 **110** **111**

tert-butyl 3-oxopiperazine-1-carboxylate, 111.



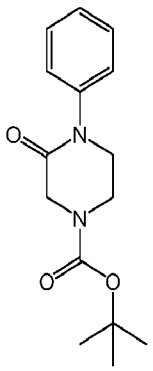
In a 100 mL RBF was added piperazin-2-one (600 mg, 1.0 eq, 5.99 mmol) in DCM (40 mL, 0.15 M). Di-tert-butyl dicarbonate (1.44 g, 1.41 mL, 1.1 eq, 6.59 mmol) was added via syringe and stirred at room temperature for 3 h. Upon completion, reaction mixture was diluted with DCM (30 mL) and washed with water (50 mL). The aqueous layer was washed with DCM (50 x 2 mL). The combined organic layer was washed with brine (30 x 2 mL), dried over sodium sulfate, and evaporated *in vacuo* to obtain tert-butyl 3-oxopiperazine-1-carboxylate, **111**, (1.2 g, 5.5 mmol, 92%) as a white solid. LCMS $[M+H]^+$ 101. 1H NMR (500 MHz, CDCl3) δ 6.68 (s, 1H), 4.08 (s, 2H), 3.62 (t, J = 5.4 Hz, 2H), 3.38 (td, J = 5.3, 2.6 Hz, 2H), 1.47 (s, 9H).

Step 2, General Scheme 3



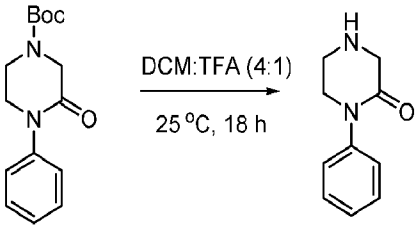
111 **112** **113**

tert-butyl 3-oxo-4-phenylpiperazine-1-carboxylate, 113.



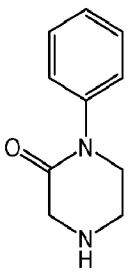
To a solution of tert-butyl 3-oxopiperazine-1-carboxylate (300 mg, 1.2 eq, 1.50 mmol), iodobenzene (255 mg, 140 µL, 1 eq, 1.25 mmol), N,N'-dimethylethylenediamine (11 mg, 14 µL, 0.1 eq, 125 µmol), and tripotassium phosphate (530 mg, 2 eq, 2.50 mmol) in toluene (2.3 mL, 0.6 M) was added Copper Iodide (11 mg, 0.05 eq, 62 µmol). The reaction mixture was heated to 80 °C for 12 hours. The reaction mixture was cooled to room temperature, diluted with DCM, and filtered through a plug of silica using 40% EtOAc/Hexane as eluent to afford tert-butyl 3-oxo-4-phenylpiperazine-1-carboxylate, **113**, (191 mg, 0.693 mmol, 56%) as a white solid. LCMS $[M+H]^+$ 277. 1H NMR (500 MHz, CDCl3) δ 7.42 (dd, J = 8.7, 7.1 Hz, 2H), 7.32 – 7.26 (m, 3H), 4.26 (s, 2H), 3.79 (dd, J = 6.6, 3.7 Hz, 2H), 3.74 (dd, J = 6.9, 4.4 Hz, 2H), 1.50 (s, 9H).

Step 3, General Scheme 3



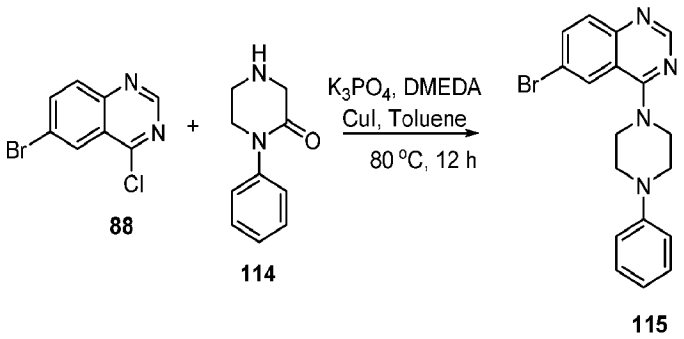
113 **114**

1-phenylpiperazin-2-one, 114.

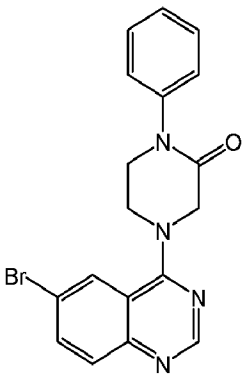


A mixture of DCM:TFA (1:4, 14.6 mL) was added to the crude mixture and stirred at room temperature overnight. Upon completion, the remaining TFA was evaporated off in vacuo to afford 1-phenylpiperazin-2-one (128 mg, 662 µmol, 34 %) as a TFA salt. LCMS $[M+H]^+$ 195. 1H NMR (500 MHz, CDCl3) δ 7.25 (d, J = 2.9 Hz, 1H), 6.95 (tq, J = 6.9, 2.3 Hz, 2H), 6.84 (dddd, J = 10.0, 8.4, 3.6, 2.1 Hz, 2H), 3.48 (d, J = 5.3 Hz, 2H), 3.46 (d, J = 4.5 Hz, 2H), 3.12 (dd, J = 6.6, 4.3 Hz, 2H).

Step 4, General Scheme 3



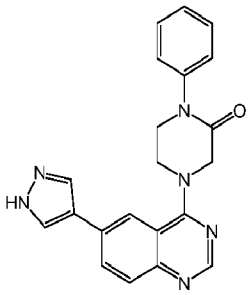
4-(6-bromoquinazolin-4-yl)-1-phenylpiperazin-2-one, 115.



To a solution of 1-phenylpiperazin-2-one, trifluoroacetic acid (100 mg, 1.2 eq, 345 µmol), 6-bromo-4-chloroquinazoline (69 mg, 1.0 eq, 287 µmol), N,N'-dimethylethylenediamine (2.5 mg, 3 µL, 0.1 eq, 28 µmol), and K3PO4 (122 mg, 2 eq, 574 µmol) in Toluene (0.8 mL, 0.4 M) was added Copper Iodide (2. mg, 0.05 eq, 14 µmol). The reaction mixture was heated to 80 °C for 12 hours. The reaction mixture was cooled to room temp, diluted with DCM, and filtered through a plug of silica using 5% MeOH:DCM as eluent. The filtrate was dry loaded onto silica gel and purified on a 12 g column (DCM/MeOH 0-8%), affording 4-(6-bromoquinazolin-4-yl)-1-phenylpiperazin-2-one, **115**, (76 mg, 198 µmol, 69 %). LCMS $[M+H]^+$ 384. 1H NMR (500 MHz, CDCl3) δ 8.82 (s, 1H), 8.17 (s, 2H), 7.93 (s, 1H), 7.49 – 7.39 (m, 2H), 7.38 – 7.28 (m, 3H), 4.73 (s, 2H), 4.31 (s, 2H), 4.00 (t, J = 5.1 Hz, 2H).

4-(6-(1H-pyrazol-4-yl)quinazolin-4-yl)-1-phenylpiperazin-2-one, 32.

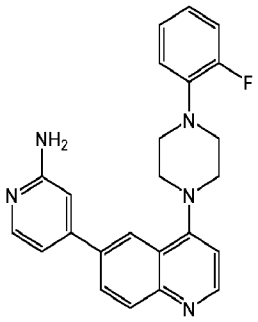
Compound **32** was prepared via General Scheme 3 via the five step procedure. The fifth step is reported below.



A 5 mL Biotage© microwave vial loaded with tripotassium phosphate (96 mg, 4 eq, 455 µmol), [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (7.4 mg, 0.08 eq, 9.09 µmol), 4-(6-chloroquinazolin-4-yl)-1-phenylpiperazin-2-one (38 mg, 1 eq, 114 µmol), and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (40 mg, 1.2 eq, 136 µmol). The vial was capped, purged with argon, then injected with degassed 4:1 Dioxane:H2O (1.5 mL, 76 mM) and heated to 80 °C for 12 h. The reaction was cooled, diluted with DCM:MeOH, filtered through celite, and concentrated. A mixture of DCM:TFA (1:2, 1.5 mL) was added to the crude mixture and stirred at room temperature overnight and basified with 1N NaOH. The mixture was extracted with DCM, washed with 10% NaOH, water, brine, and the organic layer was dried over sodium sulfate, concentrated, and dry-loaded onto silica gel and purified on a 12 g column (DCM/MeOH 0-10%), affording 4-(6-(1H-pyrazol-4-yl)quinazolin-4-yl)-1-phenylpiperazin-2-one, **32** (22 mg, 59 µmol, 52%) as a tan solid. LCMS $[M+H]^+$ 371. 1H NMR (500 MHz, DMSO) δ 13.08 (s, 1H), 8.63 (s, 1H), 8.43 (s, 1H), 8.20 (d, J = 1.9 Hz, 1H), 8.17 – 8.12 (m, 2H), 7.84 (d, J = 8.6 Hz, 1H), 7.42 (d, J = 5.3 Hz, 4H), 7.28 (ddd, J = 10.2, 5.8, 3.1 Hz, 1H), 4.55 (s, 2H), 4.24 (t, J = 5.2 Hz, 2H), 3.97 (t, J = 5.2 Hz, 2H).13C NMR (126 MHz, CD3OD_SPE) δ 176.88, 167.02, 163.03, 152.74, 149.59, 141.63, 131.48, 131.15, 128.99, 127.63, 127.17, 125.83, 121.19, 120.01, 116.46, 52.65, 49.01, 46.46.

4-(4-(4-(2-fluorophenyl)piperazin-1-yl)quinolin-6-yl)pyridin-2-amine, 33.

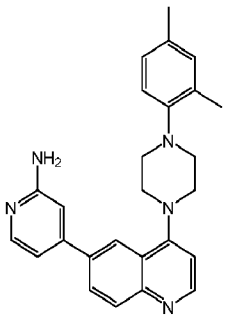
Compound **33** was prepared via General Scheme 2 via the two step procedure reported for the preparation of compound **29**. The second step is reported below.



Prepared in analogous manner to Step 2, General Scheme 2 as used for compound **29**. 4-(4-(4-(2-fluorophenyl)piperazin-1-yl)quinolin-6-yl)pyridin-2-amine, **33**, (31 mg, 0.16 mmol, 49%) as a tan solid. LCMS $[M+H]^+$ 400. 1H NMR (500 MHz, CDCl3) δ 8.79 (d, J = 5.1 Hz, 1H), 8.28 (d, J = 2.0 Hz, 1H), 8.19 (d, J = 8.7 Hz, 1H), 8.14 (d, J = 5.4 Hz, 1H), 7.89 (dd, J = 8.7, 2.0 Hz, 1H), 7.21 – 7.05 (m, 3H), 7.04 – 6.99 (m, 2H), 6.98 (d, J = 5.1 Hz, 1H), 6.86 (s, 1H), 4.99 (s, 2H), 3.49 (dd, J = 5.8, 3.3 Hz, 4H), 3.45 – 3.39 (m, 4H). 13C NMR (126 MHz, CDCl3) δ 158.88, 157.23, 156.81, 154.85, 151.45, 150.21, 149.62, 148.34, 139.75, 139.68, 135.59, 130.81, 127.98, 124.62, 124.59, 123.50, 123.12, 123.06, 121.98, 119.22, 119.20, 116.41, 116.25, 112.84, 109.55, 106.59, 52.46, 50.64.

4-(4-(4-(2,4-dimethylphenyl)piperazin-1-yl)quinolin-6-yl)pyridin-2-amine, 34.

Compound **34** was prepared via General Scheme 2 via the two step procedure reported for the preparation of compound **29**. The second step is reported below.

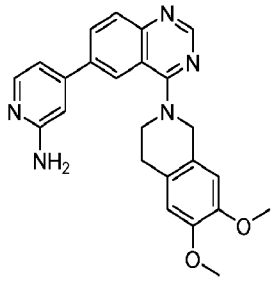


Prepared in analogous manner to Step 2, General Scheme 2 as used for compound **29.** 4-(4-(4-(2,4-dimethylphenyl)piperazin-1-yl)quinolin-6-yl)pyridin-2-amine, **34**, (33 mg, 80 μmol, 41%) as a tan solid. LCMS $[M+H]^+$ 410. 1H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, J = 5.1 Hz, 1H), 8.30

(d, J = 2.1 Hz, 1H), 8.21 (d, J = 8.7 Hz, 1H), 8.11 (d, J = 5.7 Hz, 1H), 7.89 (dd, J = 8.8, 2.1 Hz, 1H), 7.10 – 7.03 (m, 3H), 7.03 – 6.99 (m, 1H), 6.97 (d, J = 5.2 Hz, 1H), 6.90 (d, J = 1.6 Hz, 1H), 5.21 (s, 2H), 3.48 (dt, J = 5.4, 2.3 Hz, 4H), 3.24 – 3.15 (m, 4H), 2.33 (s, 3H), 2.30 (s, 3H).

4-(4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)quinazolin-6-yl)pyridin-2-amine, 35.

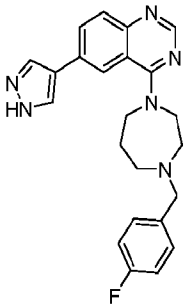
Compound **35** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.



To a microwave vial potassium phosphate, tribasic (318 mg, 3 eq, 1.50 mmol), $PdCl_2$(dppf) (36 mg, 0.1 eq, 50 µmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (121 mg, 1.1 eq, 550 µmol), and 6-bromo-4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)quinazoline (200 mg, 1 eq, 500 µmol) was added and the vial was sealed. The solids were dissolved in 1,4-Dioxane (2.0 mL) and water (0.40 mL), and the reaction mixture was heated to 90 °C where it stirred for 16 h. After time elapsed, the reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through a thick celite pad. The filtrate was collected and concentrated via rotary evaporation. The resulting residue was dissolved in 50 mL of ethyl acetate and washed with water (3 x 50mL). The organic layer was dried over sodium sulfate, filtered, and concentrated via rotary evaporation. The crude concentrate was purified via column chromatography (0-10% MeOH/DCM) producing 4-(4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)quinazolin-6-yl)pyridin-2-amine, **35**, (157 mg, 380 µmol, 76%). LCMS: $[M+H]^+$ 414. ^1H NMR (400 MHz, MeOD) δ 8.60 (s, 1H), 8.21 (s, 1H), 8.03 (dd, *J* = 16.2, 7.0 Hz, 2H), 7.86 (d, *J* = 8.8 Hz, 1H), 6.92 (d, *J* = 5.4 Hz, 1H), 6.90 – 6.67 (m, 3H), 4.01 (d, *J* = 5.9 Hz, 2H), 3.70 (d, *J* = 9.4 Hz, 6H), 3.02 (t, *J* = 5.8 Hz, 2H), 2.48 (s, 2H).

4-(4-(4-fluorobenzyl)-1,4-diazepan-1-yl)-6-(1H-pyrazol-4-yl)quinazoline, 36.

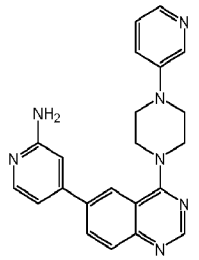
Compound **36** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.



Potassium acetate (156 mg, 3 eq, 1.59 mmol), $PdCl_2$(dppf) (38 mg, 0.1 eq, 53 µmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (171 mg, 1.1 eq, 583 µmol), 6-bromo-4-(4-(4-fluorobenzyl)-1,4-diazepan-1-yl)quinazoline (220 mg, 1 eq, 530 µmol) were added to a MWV, the solids were degassed then dissolved in degassed solvent 1,4-Dioxane (1.75 mL) and water (350 µL), the solution was heated to 90 °C and stirred using magnetic stirring for 16 h. After time elapsed the solution was diluted with EtOAc and filtered through a pad of celite. the filtrate was then concentrated via rotary evaporation and the residue was dissolved in EtOAc and washed twice with water and once with brine. The organic layer was collected and dried using Sodium Sulfate, which was then concentrated *in vacuo*, the residue was further purified using flash chromatography (MeOH/DCM 0-20%) resulting in a black sludge. The crude tert-butyl 4-(4-(4-(4-fluorobenzyl)-1,4-diazepan-1-yl)quinazolin-6-yl)-1H-pyrazole-1-carboxylate (66 mg, 1 eq, 0.13 mmol) was suspended in DCM (5 mL) and TFA (75 mg, 51 µL, 5 eq, 0.66 mmol) added. The solution stirred for 2 h at room temperature, after time elapsed the reaction mixture was concentrated via rotary evaporation. the residue was dissolved in ethyl acetate and washed with 2M NaOH solution (2 x 75mL). The organic layer was collected, dried with sodium sulfate, filtered and concentrated resulting in 4-(4-(4-fluorobenzyl)-1,4-diazepan-1-yl)-6-(1H-pyrazol-4-yl)quinazoline, **36**, (48 mg, 0.12 mmol, 91%). LCMS $[M+H]^+$ 403. ^1H NMR (400 MHz, DMSO-D_6) δ 13.06 (s, 1H), 8.39 (s, 1H), 8.18 – 8.09 (m, 3H), 7.98 (dd, J = 8.6, 1.8 Hz, 1H), 7.68 (d, J = 8.6 Hz, 1H), 7.27 (ddd, J = 8.8, 5.6, 2.6 Hz, 2H), 7.07 (td, J = 9.1, 2.5 Hz, 2H), 3.95 (q, J = 5.8 Hz, 4H), 3.54 (d, J = 3.6 Hz, 2H), 2.86 – 2.79 (m, 2H), 2.58 – 2.51 (m, 2H), 2.04 – 1.93 (m, 2H).

4-(4-(4-(pyridin-3-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 37.

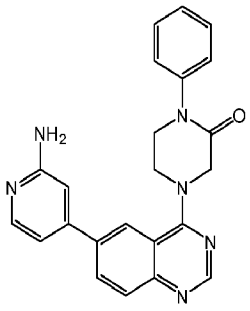
Compound **37** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.



In a 5 mL microwave vial, 6-chloro-4-(4-(pyridin-3-yl)piperazin-1-yl)quinazoline (30 mg, 1 eq, 93 µmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (24 mg, 1.2 eq, 112 µmol), tripotassium phosphate (79 mg, 4 eq, 374 µmol), and [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (6 mg, 0.08 eq, 7.5 µmol) were added. The mixture was capped, purged with argon, then injected with degassed 4:1 Dioxane:H2O (1.4 mL, 67 mM), and was heated at 80 °C for 12 h. After this time, the mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (10 mL x 2). The aqueous layer was washed with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate, and evaporated *in vacuo* to obtain the crude product. The crude product was dry-loaded onto silica gel and purified on a 12 g silica gel column (0-10% MeOH/DCM) to afford 4-(4-(4-(pyridin-3-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, **37**, (17 mg, 93 µmol, 49%) as a yellow solid. LCMS $[M+H]^+$ 384. 1H NMR (500 MHz, CDCl3) δ 8.80 (s, 1H), 8.39 (d, J = 2.9 Hz, 1H), 8.18 – 8.13 (m, 2H), 8.12 (d, J = 2.0 Hz, 1H), 8.01 (d, J = 8.7 Hz, 1H), 7.97 (dd, J = 8.7, 1.9 Hz, 1H), 7.26 – 7.24 (m, 1H), 7.22 (dd, J = 8.4, 4.5 Hz, 1H), 6.94 (dd, J = 5.5, 1.6 Hz, 1H), 6.81 (d, J = 1.6 Hz, 1H), 4.96 (s, 2H), 4.02 (t, J = 5.1 Hz, 4H), 3.51 – 3.43 (m, 4H). 13C NMR (126 MHz, CDCl3) δ 164.78, 158.72, 154.58, 152.08, 149.73, 147.89, 146.63, 141.31, 138.67, 135.90, 131.41, 129.68, 123.65, 123.08, 122.73, 116.70, 112.51, 106.61, 77.28, 77.02, 76.77, 49.57, 48.46.

4-(6-(2-aminopyridin-4-yl)quinazolin-4-yl)-1-phenylpiperazin-2-one, 38.

Compound **38** was prepared via General Scheme 3 as shown for the preparation of compound **32**. The fifth step is reported below.

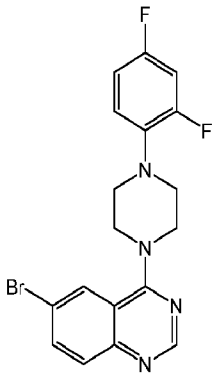


Prepared in analogous manner to Step 5, General Scheme 3 as used for compound **32.** 4-(6-(2-aminopyridin-4-yl)quinazolin-4-yl)-1-phenylpiperazin-2-one, **38**, (18 mg, 46 µmol, 41%) as a tan solid. LCMS $[M+H]^+$ 397. 1H NMR (500 MHz, MeOD) δ 7.97 (s, 1H), 7.63 (d, J = 2.0 Hz, 1H), 7.44 (dd, J = 8.8, 2.0 Hz, 1H), 7.30 (d, J = 5.5 Hz, 1H), 7.24 (d, J = 8.7 Hz, 1H), 6.74 (t, J = 7.8 Hz, 2H), 6.70 – 6.65 (m, 2H), 6.65 – 6.59 (m, 1H), 6.31 (dd, J = 5.5, 1.7 Hz, 1H), 6.26 (d, J = 1.7 Hz, 1H), 4.05 (s, 2H), 3.68 (t, J = 5.3 Hz, 2H), 3.30 (t, J = 5.3 Hz, 2H). 13C NMR (126 MHz, CD3OD_SPE) δ 166.74, 163.13, 160.16, 153.79, 151.12, 149.03, 147.40, 141.58, 136.25, 131.66, 128.99, 127.82, 127.18, 125.78, 123.17, 115.96, 110.99, 106.49, 52.72, 48.91, 46.35.

4-(4-(4-(2,4-difluorophenyl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 39.

Compound **39** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

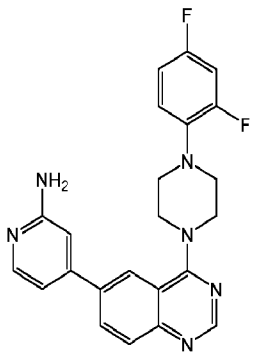
6-bromo-4-(4-(2,4-difluorophenyl)piperazin-1-yl)quinazoline, 116.



In a 5 mL Biotage microwave vial, sodium bicarbonate (17 mg, 1 eq, 0.20 mmol) and 1-(2,4-difluorophenyl)piperazine (40 mg, 1 eq, 0.20 mmol) were added with EtOH (0.5 mL, 0.4 M) and stirred for 10 mins. 6-bromo-4-chloroquinazoline (49 mg, 1 eq, 0.20 mmol) was added, vial sealed, and stirred at 25 °C for 12 h. Upon completion, the reaction was extracted in EtOAc,

washed with brine, dried over sodium sulfate, and concentrated. The crude product was dry-loaded onto silica gel and purified on a 12 g silica gel column (0-10% EtOAc/Hexanes) to give 6-bromo-4-(4-(2,4-difluorophenyl)piperazin-1-yl)quinazoline, **116** (48 mg, 120 µmol, 59%). LCMS $[M+H]^+$ 406. 1H NMR (500 MHz, CDCl3) δ 8.73 (s, 1H), 8.07 (d, J = 2.1 Hz, 2H), 7.89 (dd, J = 8.7, 2.1 Hz, 1H), 6.95 (td, J = 9.0, 5.6 Hz, 1H), 6.85 (tdd, J = 11.9, 8.5, 2.9 Hz, 2H), 4.12 (s, 4H), 3.25 (t, J = 4.9 Hz, 4H).

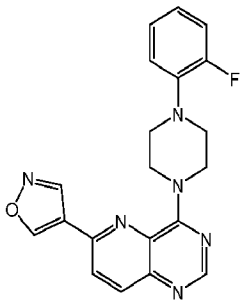
4-(4-(4-(2,4-difluorophenyl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 39.



In a 5 mL microwave vial, 6-chloro-4-(4-(2,4-difluorophenyl)piperazin-1-yl)quinazoline (49 mg, 1 eq, 0.14 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (36 mg, 1.2 eq, 0.16 mmol), tripotassium phosphate (120 mg, 4 eq, 0.54 mmol), and [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (8.9 mg, 0.08 eq, 11 µmol) were added. The mixture was capped, purged with argon, then injected with degassed 4:1 dioxane:H_2O (0.8 mL, 0.2 M), and was heated at 80 °C for 6 h. After this time, the mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (10 mL). The aqueous layer was washed with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate, and evaporated *in vacuo* to obtain the crude product. The crude product was dry-loaded onto silica gel and purified on a 12 g silica gel column (0-10% MeOH/DCM) to afford 4-(4-(4-(2,4-difluorophenyl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, **39**, (27 mg, 65 µmol, 48%) as a light brown solid. LCMS $[M+H]^+$ 419. 1H NMR (400 MHz, CDCl3) δ 8.78 (s, 1H), 8.14 (d, J = 5.4 Hz, 1H), 8.09 (d, J = 1.9 Hz, 1H), 8.03 – 7.76 (m, 2H), 7.01 – 6.89 (m, 2H), 6.89 – 6.77 (m, 3H), 4.91 (s, 2H), 4.01 (t, J = 4.9 Hz, 4H), 3.24 (t, J = 4.9 Hz, 4H).

4-(4-(4-(2-fluorophenyl)piperazin-1-yl)pyrido[3,2-d]pyrimidin-6-yl)isoxazole, 40.

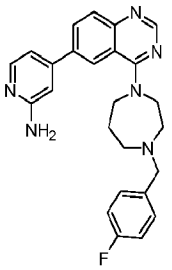
Compound **40** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.



In a 5 mL microwave vial, 6-bromo-4-(4-(2-fluorophenyl)piperazin-1-yl)pyrido[3,2-d]pyrimidine (60 mg, 1 eq, 0.15 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (36 mg, 1.2 eq, 0.19 mmol), tripotassium phosphate (130 mg, 4 eq, 0.62 mmol), and [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (9.0 mg, 0.08 eq, 12 µmol) were added. The mixture was capped, purged with argon, then injected with degassed 4:1 Dioxane:H_2O (1.0 mL, 0.2 M), and was heated at 65 °C for 4 h. After this time, the mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (10 mL). The aqueous layer was washed with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate, and evaporated *in vacuo* to obtain the crude product. The crude product was dry-loaded onto silica gel and purified on a 12 g silica gel column (60-70% EtOAc/Hexanes) to afford 4-(4-(4-(2-fluorophenyl)piperazin-1-yl)pyrido[3,2-d]pyrimidin-6-yl)isoxazole, **40**, (9.7 mg, 26 µmol, 17%) as a yellow solid. LCMS $[M+H]^+$ 377. 1H NMR (400 MHz, DMSO) δ 9.78 (s, 1H), 9.30 (s, 1H), 8.55 (s, 1H), 8.23 (d, J = 2.0 Hz, 2H), 7.23 – 7.09 (m, 3H), 7.01 (ddd, J = 8.9, 5.7, 2.9 Hz, 1H), 4.59 (s, 4H), 3.27 (t, J = 4.9 Hz, 4H). 13C NMR (101 MHz, DMSO-D6) δ 158.33, 158.28, 156.23, 154.45, 153.80, 148.53, 146.22, 145.25, 139.67, 139.59, 137.33, 132.78, 125.69, 124.90, 124.87, 122.67, 122.59, 121.55, 119.52, 119.50, 116.11, 115.91, 50.42.

4-(4-(4-(4-fluorobenzyl)-1,4-diazepan-1-yl)quinazolin-6-yl)pyridin-2-amine, 41.

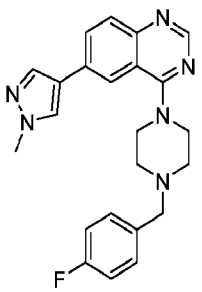
Compound **41** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.



Potassium acetate (156 mg, 3 Eq, 1.59 mmol), $PdCl_2$(dppf) (38 mg, 0.1 eq, 53 µmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (128 mg, 1.1 eq, 583 µmol),6-bromo-4-(4-(4-fluorobenzyl)-1,4-diazepan-1-yl)quinazoline (220 mg, 1 eq, 530 µmol), were added to a MWV, the solids were degassed then dissolved in degassed solvent water (350 µL), 1,4-Dioxane (1.75 mL), the solution was heated to 60 °C and stirred using magnetic stirring for 16 h. After time elapsed the solution was diluted with EtOAc and filtered through a pad of celite. the filtrate was then concentrated via rotary evaporation and the residue was dissolved in EtOAc and washed twice with water and once with brine. The organic layer was collected and dried using Sodium Sulfate, which was then concentrated *in vacuo*, the residue was further purified using flash chromatography (MeOH/DCM 0-20%) resulting in a black sludge. Which was then further purified by dissolving in 1:1:1 DCM:MeOH:IPA and adding a metal scavenger Silica, and stirred for 72 h, the silica was then filtered off, and concentrated, resulting in 4-(4-(4-(4-fluorobenzyl)-1,4-diazepan-1-yl)quinazolin-6-yl)pyridin-2-amine, **41**, (45 mg, 0.11 mmol, 20 %) a white fluffy powder. LCMS $[M+H]^+$ 429. ^1H NMR (400 MHz, DMSO) δ 8.46 (s, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.97 (t, J = 6.4 Hz, 2H), 7.78 (d, J = 8.6 Hz, 1H), 7.29 (dd, J = 8.3, 5.6 Hz, 2H), 7.08 (t, J = 8.7 Hz, 2H), 6.83 (d, J = 5.4 Hz, 1H), 6.74 (s, 1H), 3.98 (m, 4H), 3.56 (m, 2H), 2.86 (m, J = 5.6 Hz, 2H), 2.61 – 2.53 (m, 2H), 2.01 (m, 2H).

4-(4-(4-fluorobenzyl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)quinazoline, 42.

Compound **42** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.

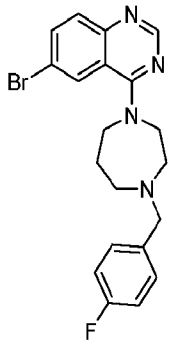


Potassium phosphate, tribasic (198 mg, 3 eq, 935 µmol), $PdCl_2$(dppf) (22.8 mg, 0.1 eq, 31 µmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (71 mg, 1.1 eq, 343 µmol),6-bromo-4-(4-(4-fluorobenzyl)piperazin-1-yl)quinazoline (125 mg, 1 eq, 312 µmol), were added to a MWV, the solids were degassed then dissolved in degassed solvent water (0.30 mL), 1,4-Dioxane (1.5 mL), the solution was heated to 90 °C and stirred using magnetic stirring for 16 hours. After time elapsed the solution was diluted with EtOAc and filtered through a pad of celite. the filtrate was then concentrated via rotary evaporation and the residue was dissolved in EtOAc and washed twice with water and once with brine. The organic layer was collected and dried using Sodium Sulfate, which was then concentrated *in vacuo*, the residue was further purified using flash chromatography (MeOH/DCM 0-20%) resulting in a black sludge. Which was then further purified by dissolving in 1:1:1 DCM:MeOH:IPA and adding a metal scavenger silica, and stirred for 72 h, the silica was then filtered off resulting in 4-(4-(4-fluorobenzyl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)quinazoline, **42**, (101 mg, 251 µmol, 80 %) a white fluffy powder. LCMS $[M+H]^+$ 403. ^{1}H NMR (400 MHz, DMSO) δ 8.53 (s, 1H), 8.26 (s, 1H), 8.02 – 7.91 (m, 3H), 7.75 (d, J = 8.7 Hz, 1H), 7.40 – 7.31 (m, 2H), 7.18 – 7.08 (m, 2H), 3.85 (s, 3H), 3.78 – 3.69 (m, 4H), 3.51 (s, 2H), 2.55 (t, J = 4.8 Hz, 4H).

4-(4-(4-(4-fluorobenzyl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 43.

Compound **43** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

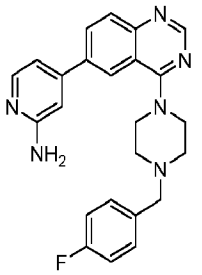
6-bromo-4-(4-(4-fluorobenzyl)-1,4-diazepan-1-yl)quinazoline, 117.



To a microwave vial, 6-bromo-4-chloroquinazoline (0.300 g, 1 eq, 1.23 mmol), 1-(4-fluorobenzyl)-1,4-diazepane (513 mg, 478 µL, 2 eq, 2.46 mmol), and a stir bar was added and the vial was capped. NMP (8.0 mL) followed by TEA (312 mg, 429 µL, 2.5 eq, 3.08 mmol) was added to the reaction vial, and the solution was heated to 80 °C and stirred for 2 hours. After the

reaction was complete, the reaction mixture was diluted with EtOAc (50 mL), then washed with water (25 mL x 4). The organic layer was separated, dried over sodium sulfate, filtered, and concentrated via rotary evaporation. the resulting residue was purified via column chromatography (MeOH:DCM 0-5%) resulting in 6-bromo-4-(4-(4-fluorobenzyl)-1,4-diazepan-1-yl)quinazoline (0.420 g, 1.01 mmol, 82%). LCMS $[M+H]^+$ 416. This compound was used without further characterization.

4-(4-(4-(4-fluorobenzyl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 43.

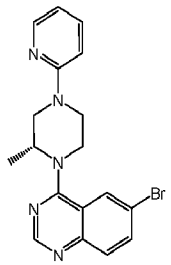


Potassium phosphate, tribasic (198 mg, 3 eq, 935 µmol), $PdCl_2$(dppf) (22.8 mg, 0.1 eq, 31.2 µmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (75 mg, 1.1 eq, 343 µmol),6-bromo-4-(4-(4-fluorobenzyl)piperazin-1-yl)quinazoline (125 mg, 1 eq, 312 µmol), were added to a MWV, the solids were degassed then dissolved in degassed solvent water (0.30 mL), 1,4-Dioxane (1.5 mL), the solution was heated to 90 °C and stirred using magnetic stirring for 16 hours. After time elapsed the solution was diluted with EtOAc and filtered thru a pad of celite. the filtrate was then concentrated via rotary evaporation and the residue was dissolved in EtOAc and washed twice with water and once with brine. The organic layer was collected and dried using Sodium Sulfate, which was then concentrated *in vacuo*, the residue was further purified using flash chromatography (MeOH/DCM 0-20%) resulting in a black sludge. Which was then further purified by dissolving in 1:1:1 DCM:MeOH:IPA (3mL) and adding a metal scavenger silica, and stirred for 72 h, the silica was then filtered off resulting in 4-(4-(4-(4-fluorobenzyl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, **43**, (84 mg, 0.20 mmol, 65%) a white fluffy powder. LCMS $[M+H]^+$ 415. ^1H NMR (400 MHz, DMSO) δ 8.59 (s, 1H), 8.10 – 7.94 (m, 3H), 7.84 (d, J = 8.7 Hz, 1H), 7.33 (t, J = 6.9 Hz, 2H), 7.12 (t, J = 8.7 Hz, 2H), 6.84 (d, J = 5.3 Hz, 1H), 6.75 (s, 1H), 3.76 (s, 4H), 3.49 (s, 2H), 2.56 – 2.48 (m, 4H).

(R)-4-(4-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 44.

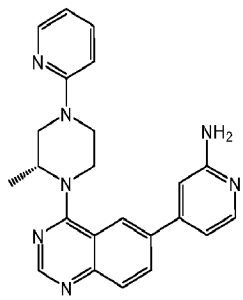
Compound **44** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

(R)-6-bromo-4-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)quinazoline, 118.



In a 5 mL microwave vial, 6-bromo-4-chloroquinazoline (96 mg, 1 eq, 0.39 mmol), sodium bicarbonate (100 mg, 3 eq, 1.2 mmol), and (R)-3-methyl-1-(pyridin-2-yl)piperazine (70 mg, 1.0 eq, 0.39 mmol) were added. The mixture was capped, DMSO (1.0 mL, 0.4 M) was injected, and stirred overnight at 60 °C for 18 hours. After this time, the mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (10 mL x 3). The aqueous layer was washed with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine (20 mL x 3), dried over sodium sulfate, and evaporated *in vacuo* to obtain the crude product. The crude product was dry-loaded onto silica gel and purified on a 12 g silica gel column (0-50% EtOAc/Hexanes) to afford (R)-6-bromo-4-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)quinazoline, **118** (105 mg, 0.273 mmol, 69%). LCMS $[M+H]^+$ 385. 1H NMR (500 MHz, CDCl3) δ 8.72 (s, 1H), 8.25 – 8.17 (m, 1H), 8.06 (d, J = 2.2 Hz, 1H), 7.87 (dd, J = 8.9, 2.1 Hz, 1H), 7.68 – 7.56 (m, 1H), 6.73 (s, 2H), 4.89 (s, 1H), 4.43 – 4.24 (m, 3H), 4.17 (d, J = 12.9 Hz, 1H), 3.87 (t, J = 12.2 Hz, 1H), 3.54 (d, J = 12.9 Hz, 1H), 3.41 – 3.30 (m, 1H), 1.52 (d, J = 6.7 Hz, 3H).

(R)-4-(4-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 44.

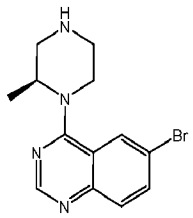


In a 5 mL microwave vial, (R)-6-bromo-4-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)quinazoline (105 mg, 1 eq, 0.273 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (72 mg, 1.2 eq, 0.328 mmol), tripotassium phosphate (232 mg, 4 eq, 1.09 mmol), and [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (16 mg, 0.08 eq, 21.9 µmol) were added. The mixture was capped, purged with argon, then injected with degassed 4:1 Dioxane:H_2O (1.4 mL, 0.2 M), and was heated at 80 °C for 6 h. After this time, the mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (10 mL x 2). The aqueous layer was washed with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate, and evaporated *in vacuo* to obtain the crude product. The crude product was dry-loaded onto silica gel and purified on a 12 g silica gel column (0-5% MeOH/DCM) to afford (R)-4-(4-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, **44**, (57 mg, 0.14 mmol, 52%) as a yellow solid. LCMS $[M+H]^+$ 398. 1H NMR (500 MHz, CDCl3) δ 8.76 (s, 1H), 8.20 (dd, J = 5.0, 1.8 Hz, 1H), 8.12 (s, 2H), 7.97 (q, J = 8.7 Hz, 2H), 7.60 – 7.43 (m, 1H), 6.99 – 6.81 (m, 2H), 6.74 – 6.56 (m, 2H), 5.24 (s, 2H), 4.88 – 4.75 (m, 1H), 4.34 – 4.19 (m, 2H), 4.08 (dd, J = 12.9, 3.0 Hz, 1H), 3.90 – 3.78 (m, 1H), 3.30 (td, J = 12.1, 3.6 Hz, 1H), 2.61 (s, 1H), 1.48 (d, J = 6.6 Hz, 3H).

(S)-4-(4-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 45.

Compound **45** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. However this compound requires an additional SnAR step to add on a pyridyl group. This step is shown below.

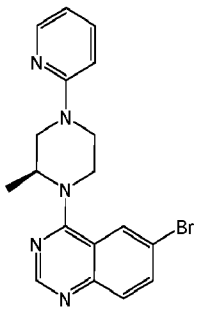
(S)-6-bromo-4-(2-methylpiperazin-1-yl)quinazoline, 119.



In a 5 mL Biotage microwave vial, sodium bicarbonate (311 mg, 3 eq, 3.70 mmol) and tert-butyl (S)-3-methylpiperazine-1-carboxylate (247 mg, 1 eq, 1.23 mmol) were added with DMSO (3.08 mL, 0.4 M) and stirred for 10 mins. 6-bromo-4-chloroquinazoline (300 mg, 1 eq, 1.23 mmol) was added, vial sealed, and stirred at 60 °C for 6 hours. Upon completion, the reaction was

extracted in EtOAc, washed with brine, dried over sodium sulfate, concentrated, and dry loaded onto silicia and purified on a 12 g silica gel column from (0-15% EtOAc:Hexanes) to afford tert-butyl (S)-4-(6-bromoquinazolin-4-yl)-3-methylpiperazine-1-carboxylate (369 mg, 907.7 µmol, 73.7 %) as a yellow solid. LCMS $[M+H]^+$ 407. 1H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.89 (d, J = 8.9 Hz, 1H), 7.83 (dd, J = 9.0, 2.0 Hz, 1H), 4.65 (s, 1H), 4.32 – 3.79 (m, 3H), 3.62 (t, J = 13.4 Hz, 1H), 3.39 – 3.01 (m, 2H), 1.49 (s, 9H), 1.41 (d, J = 6.9 Hz, 3H). In a scintillation vial, tert-butyl (S)-4-(6-bromoquinazolin-4-yl)-3-methylpiperazine-1-carboxylate (369 mg, 1.0 eq, 907 µmol) was dissolved in DCM:TFA (4:1, 9.5 mL) and stirred at room temperature overnight and basified with 1N NaOH. The mixture was extracted with DCM, washed with 10% NaOH, water, brine, and the organic layer was dried over sodium sulfate, and concentrated to afford (S)-6-bromo-4-(2-methylpiperazin-1-yl)quinazoline, **119**, (213 mg, 693 µmol, 56 %). LCMS $[M+H]^+$ 307. 1H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.98 (d, J = 2.0 Hz, 1H), 7.84 – 7.73 (m, 3H), 4.56 (td, J = 7.0, 3.7 Hz, 1H), 3.99 (dt, J = 13.7, 3.1 Hz, 1H), 3.63 (ddd, J = 13.6, 11.4, 3.2 Hz, 1H), 3.18 (td, J = 12.0, 3.5 Hz, 2H), 3.05 (td, J = 11.9, 3.4 Hz, 1H), 2.95 (dt, J = 12.4, 1.7 Hz, 1H), 1.49 (d, J = 6.8 Hz, 3H).

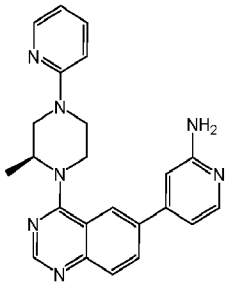
(S)-6-bromo-4-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)quinazoline, 120.



To a 5 mL Biotage microwave vial was added potassium carbonate (297 mg, 3 eq, 2.08 mmol), (S)-6-bromo-4-(2-methylpiperazin-1-yl)quinazoline (213 mg, 1 eq, 0.693 mmol) in DMSO (1.39 mL, 0.5 M) and stirred at room temperature for 15 mins. Then 2-fluoropyridine (202 mg, 0.18 mL, 3 eq, 2.08 mmol) was injected via syringe, purged with nitrogen, and heated at 140 °C for 24 hours. The reaction mixture was then cooled to room temperature, extracted in EtOAc. The combined organic layers were washed with brine (x3) and water (x3), dried over sodium sulfate, filtered, concentrated, and dry-loaded onto silica gel and purified on a 12 g column (Hexanes/EtOAc 0-10%), affording (S)-6-bromo-4-(2-methyl-4-(pyridin-2-yl)piperazin-1-

yl)quinazoline, **120**, (81 mg, 0.21 mmol, 30 %) as a yellow orange oil. LCMS $[M+H]^+$ 385. 1H NMR (500 MHz, CDCl3) δ 8.72 (s, 1H), 8.22 (dt, J = 7.5, 3.7 Hz, 1H), 8.06 (d, J = 2.1 Hz, 1H), 7.99 (s, 1H), 7.88 (dd, J = 8.8, 2.0 Hz, 1H), 7.62 (d, J = 8.7 Hz, 1H), 6.74 (t, J = 6.8 Hz, 2H), 4.90 (s, 1H), 4.45 – 4.24 (m, 2H), 4.18 (d, J = 12.9 Hz, 1H), 3.88 (t, J = 12.3 Hz, 1H), 3.54 (d, J = 13.0 Hz, 1H), 3.38 (s, 1H), 1.52 (d, J = 6.6 Hz, 3H).

(S)-4-(4-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 45.

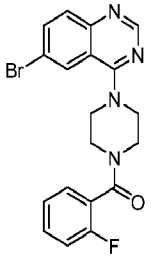


In a 5 mL microwave vial, (S)-6-bromo-4-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)quinazoline (81 mg, 1 eq, 0.21 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (56 mg, 1.2 eq, 0.25 mmol), tripotassium phosphate (180 mg, 4 eq, 0.84 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (12 mg, 0.08 eq, 17 μmol) were added. The mixture was capped, purged with argon, then injected with degassed 4:1 Dioxane:H_2O (1.1 mL, 0.2 M), and was heated at 80 °C for 18 h. After this time, the mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (10 mL x 2). The aqueous layer was washed with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate, and evaporated in vacuo to obtain the crude product. The crude product was dry-loaded onto silica gel and purified on a 12 g silica gel column (0-5% MeOH/DCM) to afford (S)-4-(4-(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, **45**, (29 mg, 0.75 mmol, 35%) as a brown solid. LCMS $[M+H]^+$ 398. 1H NMR (400 MHz, CDCl3) δ 8.76 (s, 1H), 8.24 – 8.17 (m, 1H), 8.16 (s, 1H), 8.09 – 7.85 (m, 3H), 7.53 (t, J = 7.6 Hz, 1H), 7.09 (s, 1H), 6.96 (d, J = 5.4 Hz, 1H), 6.77 – 6.62 (m, 2H), 4.87 (s, 1H), 4.29 (t, J = 14.9 Hz, 2H), 4.10 (d, J = 12.7 Hz, 1H), 3.88 (t, J = 12.3 Hz, 1H), 3.52 (d, J = 13.0 Hz, 1H), 3.33 (t, J = 11.8 Hz, 1H), 1.50 (d, J = 6.6 Hz, 3H). 13C NMR (126 MHz, DMSO) δ 163.42, 160.58, 159.10, 153.94, 151.63, 148.71, 147.53, 147.15, 137.58, 135.09, 130.96, 128.82, 122.67, 116.11, 112.86, 110.07, 106.73, 105.21, 52.29, 48.57, 44.27, 43.79, 15.73.

(4-(6-(2-aminopyridin-4-yl)quinazolin-4-yl)piperazin-1-yl)(2-fluorophenyl)methanone, 46.

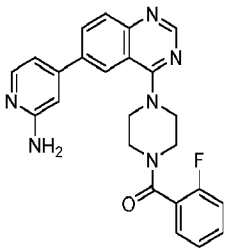
Compound **46** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

(4-(6-bromoquinazolin-4-yl)piperazin-1-yl)(2-fluorophenyl)methanone, 121.



Prepared in a similar manner as compound **117**. (4-(6-bromoquinazolin-4-yl)piperazin-1-yl)(2-fluorophenyl)methanone, **121**, (287 mg, 0.691 mol, 84%). LCMS $[M+H]^+$ 416. ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.92 (s, 1H), 7.73 (s, 2H), 7.40 – 7.31 (m, 2H), 7.16 (t, J = 7.5 Hz, 1H), 7.04 (t, J = 9.1 Hz, 1H), 3.97 – 3.90 (m, 2H), 3.80 (t, J = 5.1 Hz, 2H), 3.69 (t, J = 5.0 Hz, 2H), 3.50 (d, J = 6.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.51, 163.55, 159.37, 156.91, 154.04, 150.24, 136.27, 131.81, 130.51, 129.38, 126.99, 124.99, 123.69, 119.23, 117.70, 116.03, 115.82, 49.92, 49.63, 46.65, 41.81.

(4-(6-(2-aminopyridin-4-yl)quinazolin-4-yl)piperazin-1-yl)(2-fluorophenyl)methanone, 46.



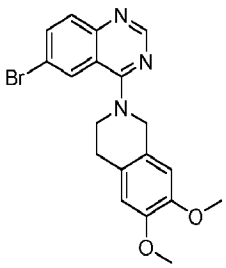
To a microwave vial potassium phosphate, tribasic (276 mg, 3 eq, 1.30 mmol), $PdCl_2$(dppf) (31 mg, 0.1 eq, 43 µmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (105 mg, 1.1 eq, 477 µmol), and (4-(6-bromoquinazolin-4-yl)piperazin-1-yl)(2-fluorophenyl)methanone (180 mg, 1 eq, 433 µmol) was added and the vial was sealed. The solids were dissolved in 1,4-dioxane (2 mL) and water (0.4 mL), and the reaction mixture was heated to 90 °C where it stirred for 16 h. After time elapsed, the reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through a thick celite pad. The filtrate was collected and concentrated

via rotary evaporation. The resulting residue was dissolved in 50 mL of ethyl acetate and washed with water (3 x 50mL). The organic layer was dried over sodium sulfate, filtered, and concentrated via rotary evaporation. The crude concentrate was purified via column chromatography (0-10% MeOH/DCM) producing (4-(6-(2-aminopyridin-4-yl)quinazolin-4-yl)piperazin-1-yl)(2-fluorophenyl)methanone, **46**, (118 mg, 275 µmol, 63%). LCMS $[M+H]^+$ 429. ^1H NMR (400 MHz, CDCl3) δ 8.74 (s, 1H), 8.08 (d, *J* = 5.4 Hz, 1H), 8.02 (s, 1H), 7.98 – 7.87 (m, 2H), 7.39 (q, *J* = 6.7 Hz, 2H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.08 (t, *J* = 9.1 Hz, 1H), 6.89 – 6.79 (m, 2H), 3.99 (s, 2H), 3.90 (t, *J* = 4.9 Hz, 2H), 3.78 (t, *J* = 5.0 Hz, 2H), 3.54 (t, *J* = 4.8 Hz, 2H).

4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-6-(1-methyl-1H-pyrazol-4-yl)quinazoline, 47.

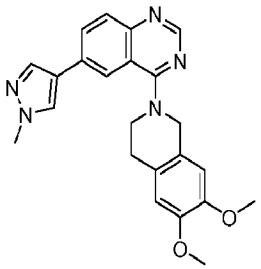
Compound **47** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

6-bromo-4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)quinazoline, 122.



Prepared in a similar manner as compound **117**. 6-bromo-4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)quinazoline, **122**, (486 mg, 1.21 mol, 85%). LCMS $[M+H]^+$ 401. This compound was used without further characterization.

4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-6-(1-methyl-1H-pyrazol-4-yl)quinazoline, 47.

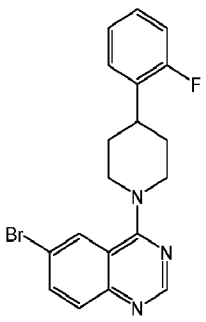


To a microwave vial potassium phosphate, tribasic (318 mg, 3 eq, 1.50 mmol), $PdCl_2$(dppf) (36.6 mg, 0.1 eq, 50.0 µmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (114 mg, 1.1 eq, 550 µmol), and 6-bromo-4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)quinazoline (200 mg, 1 eq, 500 µmol) was added and the vial was sealed. The solids were dissolved in 1,4-dioxane (2.0 mL) and water (0.40 mL), and the reaction mixture was heated to 90 °C where it stirred for 16 hours. After time elapsed, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a thick celite pad. The filtrate was collected and concentrated via rotary evaporation. The resulting residue was dissolved in 50 mL of ethyl acetate and washed with water (3 x 50 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated via rotary evaporation. The crude concentrate was purified via column chromatography (0-10% MeOH/DCM) producing 4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-6-(1-methyl-1H-pyrazol-4-yl)quinazoline, **47**, (169 mg, 421 µmol, 84%). LCMS $[M+H]^+$ 402. ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.34 (s, 1H), 8.13 (d, J = 1.8 Hz, 1H), 8.09 – 7.97 (m, 2H), 7.81 (d, J = 8.6 Hz, 1H), 6.90 (s, 1H), 6.82 (s, 1H), 4.90 (s, 2H), 4.01 (t, J = 5.7 Hz, 2H), 3.95 (s, 3H), 3.77 (d, J = 7.4 Hz, 6H), 3.08 (t, J = 5.7 Hz, 2H).

4-(4-(4-(2-fluorophenyl)piperidin-1-yl)quinazolin-6-yl)pyridin-2-amine, 48.

Compound **48** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.

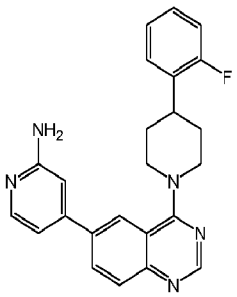
6-bromo-4-(4-(2-fluorophenyl)piperidin-1-yl)quinazoline, 123.



Prepared in similar manner as compound **126**. 6-bromo-4-(4-(2-fluorophenyl)piperidin-1-yl)quinazoline, **123**, (143 mg, 370 µmol, 66%). LCMS $[M+H]^+$ 387. 1H NMR (500 MHz, CDCl3) δ 8.73 (s, 1H), 8.04 (d, J = 1.9 Hz, 1H), 7.86 – 7.76 (m, 2H), 7.28 (dd, J = 7.6, 1.8 Hz, 1H), 7.22 (tdd, J = 7.4, 5.2, 1.8 Hz, 1H), 7.13 (td, J = 7.5, 1.3 Hz, 1H), 7.05 (ddd, J = 10.7, 8.2,

1.3 Hz, 1H), 4.53 (dt, J = 13.4, 2.3 Hz, 2H), 3.37 – 3.28 (m, 2H), 3.25 (ddt, J = 11.7, 8.2, 4.2 Hz, 1H), 2.08 – 1.94 (m, 4H).

4-(4-(4-(2-fluorophenyl)piperidin-1-yl)quinazolin-6-yl)pyridin-2-amine, 48.

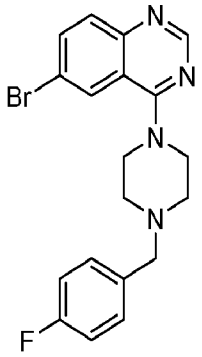


In a 5 mL microwave vial, 6-bromo-4-(4-(2-fluorophenyl)piperidin-1-yl)quinazoline (143 mg, 1 eq, 0.370 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (97 mg, 1.2 eq, 0.444 mmol), tripotassium phosphate (314 mg, 4 eq, 1.48 mmol), and [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (21 mg, 0.08 eq, 29 µmol) were added. The mixture was capped, purged with argon, then injected with degassed 4:1 Dioxane:H_2O (1.9 mL, 0.2 M), and was heated at 80 °C for 18 h. After this time, the mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (10 mL x 2). The aqueous layer was washed with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate, and evaporated *in vacuo* to obtain the crude product. The crude product was dry-loaded onto silica gel and purified on a 12 g silica gel column (0-5% MeOH/DCM) to 4-(4-(4-(2-fluorophenyl)piperidin-1-yl)quinazolin-6-yl)pyridin-2-amine, **48**, (39 mg, 98 µmol, 26%) as a pale yellow solid. LCMS $[M+H]^+$ 400. 1H NMR (500 MHz, CDCl3) δ 8.76 (s, 1H), 8.10 (d, J = 2.1 Hz, 2H), 7.98 (d, J = 8.7 Hz, 1H), 7.94 (dd, J = 8.7, 1.9 Hz, 1H), 7.29 (dd, J = 7.5, 1.8 Hz, 1H), 7.22 (tdd, J = 7.4, 5.2, 1.8 Hz, 1H), 7.13 (td, J = 7.5, 1.3 Hz, 1H), 7.05 (ddd, J = 10.6, 8.2, 1.3 Hz, 1H), 6.94 (dd, J = 5.6, 1.5 Hz, 1H), 6.84 (s, 1H), 5.18 (s, 2H), 4.58 (d, J = 13.2 Hz, 2H), 3.41 – 3.30 (m, 2H), 3.30 – 3.21 (m, 1H), 2.09 – 1.97 (m, 4H). 13C NMR (126 MHz, CDCl3) δ 164.98, 161.77, 159.82, 158.44, 154.81, 152.20, 150.49, 146.60, 135.16, 131.87, 131.75, 131.20, 129.50, 128.15, 128.08, 127.75, 127.71, 124.49, 124.46, 123.74, 116.76, 115.76, 115.58, 112.51, 107.12, 50.88, 35.97, 32.05.

4-(4-(4-fluorobenzyl)piperazin-1-yl)-6-(1H-pyrrolo[2,3-b]pyridin-3-yl)quinazoline, 49.

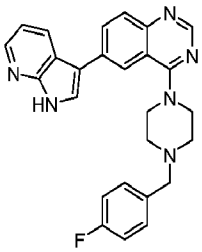
Compound **49** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

6-bromo-4-(4-(4-fluorobenzyl)piperazin-1-yl)quinazoline, 124.



Prepared in a similar manner as compound 117. 6-bromo-4-(4-(4-fluorobenzyl)piperazin-1-yl)quinazoline, **124**, (mg amount, mol, 99%). LCMS $[M+H]^+$ 402. This compound was used without further characterization.

4-(4-(4-fluorobenzyl)piperazin-1-yl)-6-(1H-pyrrolo[2,3-b]pyridin-3-yl)quinazoline, 49.



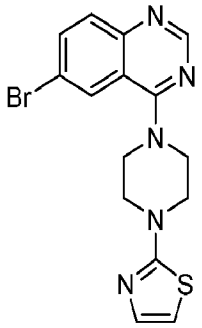
Potassium phosphate, tribasic (198 mg, 3 eq, 935 µmol), $PdCl_2$(dppf) (22.8 mg, 0.1 eq, 31.2 µmol), tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (118 mg, 1.1 eq, 343 µmol),6-bromo-4-(4-(4-fluorobenzyl)piperazin-1-yl)quinazoline (125 mg, 1 eq, 312 µmol), were added to a MWV, the solids were degassed then dissolved in degassed solvent water (350 µL), 1,4-Dioxane (1.75 mL), the solution was heated to 90 °C and stirred using magnetic stirring for 16 hour. After time elapsed the solution was diluted with EtOAc and filtered through a pad of celite. the filtrate was then concentrated via rotary evaporation and the residue was dissolved in EtOAc and washed twice with water and once with brine. The organic layer was collected and dried using sodium sulfate, which was then concentrated *in vacuo*, the residue was further purified using flash chromatography (MeOH/DCM 0-20%) resulting in a black sludge, which was then further purified by dissolving in 1:1:1 DCM:MeOH:IPA and adding a metal scavenger silica, and stirred for 72 h, the silica was

then filtered off resulting in 4-(4-(4-fluorobenzyl)piperazin-1-yl)-6-(1H-pyrrolo[2,3-b]pyridin-3-yl)quinazoline, **49**, (50 mg, 0.11 mmol, 37 %) a white fluffy powder. LCMS $[M+H]^+$ 439. ^1H NMR (400 MHz, DMSO) δ 12.06 (s, 1H), 8.56 (s, 1H), 8.26 (dd, J = 17.6, 6.3 Hz, 2H), 8.15 (d, J = 8.7 Hz, 1H), 8.08 (s, 1H), 8.02 (d, J = 2.6 Hz, 1H), 7.82 (d, J = 8.7 Hz, 1H), 7.56 – 7.41 (m, 1H), 7.37 – 7.29 (m, 2H), 7.13 (dt, J = 17.3, 8.2 Hz, 2H), 3.78 – 3.71 (m, 4H), 3.50 (s, 2H), 2.56 (t, J = 4.7 Hz, 4H).

4-(4-(4-(thiazol-2-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 50.

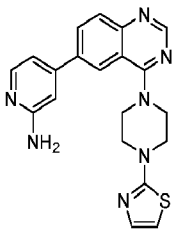
Compound **50** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

2-(4-(6-bromoquinazolin-4-yl)piperazin-1-yl)thiazole, 125.



Prepared in a similar manner as compound **117**. 2-(4-(6-bromoquinazolin-4-yl)piperazin-1-yl)thiazole, **125**, (112 mg, 0.298 mol, 32%) LCMS $[M+H]^+$ 377. This compound was used without further characterization.

4-(4-(4-(thiazol-2-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 50.



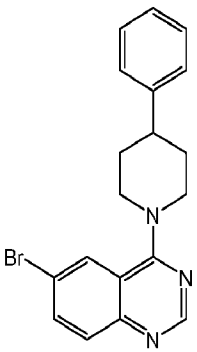
To a microwave vial potassium phosphate, tribasic (190 mg, 3 eq, 893 µmol), $PdCl_2$(dppf) (21.8 mg, 0.1 eq, 29.8 µmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (72 mg, 1.1 eq, 327 µmol), and 2-(4-(6-bromoquinazolin-4-yl)piperazin-1-yl)thiazole (112 mg, 1 eq, 298 µmol) was added and the vial was sealed. The solids were dissolved in 1,4-Dioxane (1 mL) and water (0.2 mL), and the reaction mixture was heated to 90 °C where it stirred for 16 hour. After

time elapsed, the reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through a thick celite pad. The filtrate was collected and concentrated via rotary evaporation. The resulting residue was dissolved in 50 mL of ethyl acetate and washed with water (3 x 50mL). The organic layer was dried over sodium sulfate, filtered, and concentrated via rotary evaporation. The crude concentrate was purified via column chromatography (0-10% MeOH/DCM) producing 4-(4-(4-(thiazol-2-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, **50**, (74 mg, 0.19 mmol, 64%). LCMS $[M+H]^+$ 390. ^1H NMR (400 MHz, DMSO) δ 8.69 (s, 1H), 8.19 (d, *J* = 2.0 Hz, 1H), 8.13 – 7.99 (m, 2H), 7.93 (d, *J* = 8.7 Hz, 1H), 7.22 (d, *J* = 3.6 Hz, 1H), 6.95 (dd, *J* = 5.4, 1.6 Hz, 1H), 6.87 (dd, *J* = 17.4, 2.6 Hz, 2H), 3.95 (dd, *J* = 6.7, 3.8 Hz, 4H), 3.72 – 3.64 (m, 4H).

4-(4-(4-phenylpiperidin-1-yl)quinazolin-6-yl)pyridin-2-amine, 51.

Compound **51** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

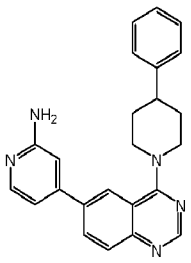
6-bromo-4-(4-phenylpiperidin-1-yl)quinazoline, 126.



A solution of 6-bromo-4-chloroquinazoline (300 mg, 1.2 eq, 1.23 mmol), 4-phenylpiperidine (166 mg, 1.0 eq, 1.03 mmol), and potassium carbonate (426 mg, 3.0 eq, 3.08 mmol) in DMSO (2.46 mL, 0.4 M) was stirred at 60 °C for 6 h. Upon cooling to room temperature, the reaction was extracted with EtOAc, washed with brine (x3) and water (x3), dried over anhydrous sodium sulfate, filtered, concentrated, and dry-loaded onto silica gel and purified on a 12 g silica gel column (0-10% EtOAc/Hexanes) to afford 6-bromo-4-(4-phenylpiperidin-1-yl)quinazoline, **126**, (347 mg, 0.942mmol, 92%). LCMS $[M+H]^+$ 367. 1H NMR (400 MHz, CDCl3) δ 8.63 (d, J = 2.6 Hz, 1H), 8.28 (t, J = 5.8 Hz, 1H), 8.06 (t, J = 2.4 Hz, 1H), 7.92 (dt, J = 9.0, 2.4 Hz, 1H), 7.33 (qd,

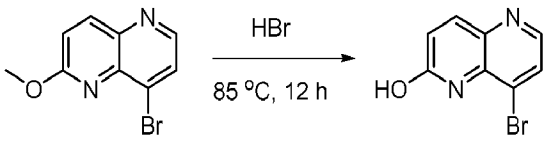
J = 8.5, 2.3 Hz, 3H), 7.24 (d, J = 4.2 Hz, 2H), 4.89 (s, 2H), 3.51 (t, J = 13.0 Hz, 2H), 3.13 – 2.92 (m, 1H), 2.19 (s, 2H), 1.94 (tdd, J = 15.7, 9.8, 3.5 Hz, 2H).

4-(4-(4-phenylpiperidin-1-yl)quinazolin-6-yl)pyridin-2-amine, 51.



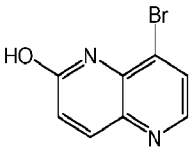
In a 5 mL microwave vial, 6-chloro-4-(4-phenylpiperidin-1-yl)quinazoline (57 mg, 1 eq, 0.18 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (46 mg, 1.2 eq, 0.21 mmol), tripotassium phosphate (150 mg, 4 eq, 0.70 mmol), and [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (10 mg, 0.08 eq, 14 µmol) were added. The mixture was capped, purged with argon, then injected with degassed 4:1 dioxane:H_2O (0.9 mL, 0.2 M), and was heated at 80 °C for 18 h. After this time, the mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (10 mL x 2). The aqueous layer was washed with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate, and evaporated *in vacuo* to obtain the crude product. The crude product was dry loaded onto silica gel and purified on a 12 g silica gel column (0-5% MeOH/DCM) to afford 4-(4-(4-phenylpiperidin-1-yl)quinazolin-6-yl)pyridin-2-amine, **51**, (23 mg, 0.18 mmol, 34%) as a pale yellow solid. LCMS $[M+H]^+$ 382. 1H NMR (400 MHz, CDCl3) δ 8.74 (s, 1H), 8.12 (d, J = 5.5 Hz, 1H), 8.08 (s, 1H), 7.93 (q, J = 8.6 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.27 (s, 1H), 7.21 (d, J = 7.3 Hz, 2H), 6.91 (d, J = 5.3 Hz, 1H), 6.77 (s, 1H), 4.87 (s, 2H), 4.54 (d, J = 13.1 Hz, 2H), 3.36 – 3.21 (m, 2H), 2.94 – 2.81 (m, 1H), 2.10 – 1.89 (m, 4H). 13C NMR (101 MHz, CDCl3) δ 165.06, 159.02, 154.76, 152.16, 149.70, 148.48, 145.28, 135.58, 131.24, 129.45, 128.76, 126.93, 126.73, 123.53, 116.85, 112.63, 106.51, 50.89, 42.98, 33.43.

Step 1, General Scheme 4



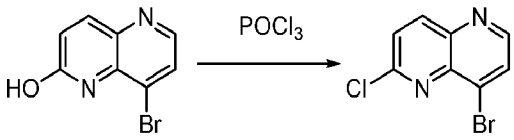
81 82

8-bromo-1,5-naphthyridin-2-ol, 82



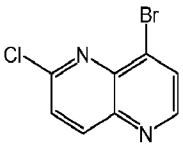
In a 5 mL microwave vial, 8-bromo-2-methoxy-1,5-naphthyridine (54 mg, 1 eq, 0.23 mmol) was added followed by dropwise addition of hydrogen bromide (0.37 g, 0.25 mL, 20 eq, 4.5 mmol) at room temperature. The resulting mixture was heated at 85 °C for 12 hours. Upon completion, excess hydrogen bromide was evaporated *in vacuo*. The resulting crude mixture was dissolved in DCM:MeOH (9:1) and filtered off to afford 8-bromo-1,5-naphthyridin-2-ol, **82**, (37 mg, 0.16 mmol, 73%) as a tan solid. LCMS $[M+H]^+$ 226. 1H NMR (500 MHz, DMSO) δ 8.34 (d, J = 5.0 Hz, 1H), 7.97 (d, J = 9.7 Hz, 1H), 7.90 (d, J = 5.0 Hz, 1H), 6.86 (d, J = 9.7 Hz, 1H), 4.41 (s, 1H).

Step 2, General Scheme 4



82 83

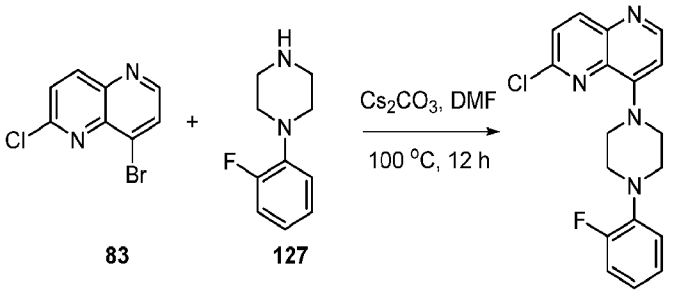
8-bromo-2-chloro-1,5-naphthyridine, 83.



In a 5 mL microwave vial, a mixture of 8-bromo-1,5-naphthyridin-2-ol (165 mg, 1 eq, 733 µmol) in phosphoryl trichloride (674 mg, 411 µL, 6 eq, 4.40 mmol) was refluxed for 2 h. Upon completion, the reaction mixture was added dropwise to ice water and extracted in ethyl acetate. The combined organic layer was washed with brine (20 x 2 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to obtain the crude product. The crude product was dry-

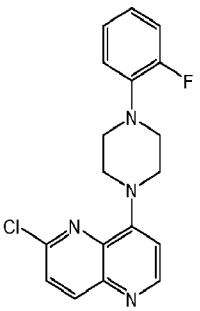
loaded onto silica gel and purified on a 12 g silica gel column (0-50% EtOAc/Hexanes) to afford 8-bromo-2-chloro-1,5-naphthyridine, **83**, (94 mg, 386 µmol, 40%). LCMS $[M+H]^+$ 244. 1H NMR (500 MHz, CDCl3) δ 8.85 (d, J = 4.8 Hz, 1H), 8.39 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 4.7 Hz, 1H), 7.70 (d, J = 8.7 Hz, 1H).

Step 3, General Scheme 4



83 **127** **128**

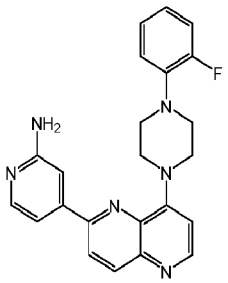
2-chloro-8-(4-(2-fluorophenyl)piperazin-1-yl)-1,5-naphthyridine, 128.



In a 5 mL Biotage microwave vial, 1-(2-fluorophenyl)piperazine (18 mg, 16 µL, 1.2 eq, 99 µmol) and cesium carbonate (54 mg, 2 eq, 0.16 mmol) were added, injected with DMF (0.8 mL, 0.1M), and stirred for 10 mins. 8-bromo-2-chloro-1,5-naphthyridine (20 mg, 1 eq, 82 µmol) was added, vial capped, and heated at 100 °C for 3 h. After this time, the mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (10 mL). The aqueous layer was washed with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine (20 mL x 2), dried over sodium sulfate, and evaporated in vacuo to obtain the crude product. The crude product was dry-loaded onto silica gel and purified on a 12 g silica gel column (0-5% MeOH/DCM) to afford 2-chloro-8-(4-(2-fluorophenyl)piperazin-1-yl)-1,5-naphthyridine, **128**, (24 mg, 69 µmol, 84%). LCMS $[M+H]^+$ 343. 1H NMR (500 MHz, CDCl3) δ 8.46 (d, J = 5.0 Hz, 1H), 7.67 (s, 1H), 7.33 (t, J = 9.5 Hz, 1H), 7.19 – 7.03 (m, 3H), 7.03 – 6.95 (m, 2H), 4.05 (s, 4H), 3.29 – 3.22 (m, 4H).

Step 4, General Scheme 4

4-(8-(4-(2-fluorophenyl)piperazin-1-yl)-1,5-naphthyridin-2-yl)pyridin-2-amine, 52.

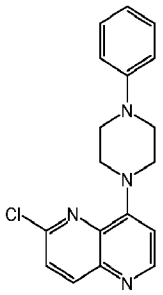


In a 5 mL Biotage microwave vial, 2-chloro-8-(4-(2-fluorophenyl)piperazin-1-yl)-1,5-naphthyridine (23 mg, 1 eq, 67 µmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (16 mg, 1.2 eq, 74 µmol), [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (5.5 mg, 0.08 eq, 6.7 µmol), and cesium carbonate (66 mg, 3 eq, 200 µmol), were added. The vial was capped, purged with nitrogen, then injected with degassed 4:1 Dioxane:H_2O (1.3 mL, 52 mM), and was heated at 95 °C for 12 hrs. After this time, the mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (20 mL). The aqueous layer was washed with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine (20 mL x 2), dried over sodium sulfate, and evaporated *in vacuo* to obtain the crude product. The crude product was dry-loaded onto silica gel and purified on a 12 g silica gel column (50-100% EtOAc/Hexanes) to afford 4-(8-(4-(2-fluorophenyl)piperazin-1-yl)-1,5-naphthyridin-2-yl)pyridin-2-amine, **52**, (11 mg, 94 µmol, 28%) as a yellow solid. LCMS $[M+H]^+$ 401. 1H NMR (500 MHz, CDCl3) δ 8.71 (d, J = 4.4 Hz, 1H), 8.18 (dd, J = 9.4, 4.6 Hz, 1H), 7.92 (d, J = 6.3 Hz, 1H), 7.46 (d, J = 4.4 Hz, 1H), 7.30 (d, J = 9.4 Hz, 1H), 7.23 (dd, J = 6.2, 1.4 Hz, 1H), 7.17 (s, 1H), 7.07 (dd, J = 12.2, 6.7 Hz, 2H), 6.98 (qd, J = 7.5, 4.9 Hz, 2H), 6.54 (s, 1H), 3.89 – 3.81 (m, 4H), 3.20 (t, J = 5.2 Hz, 4H).

4-(8-(4-phenylpiperazin-1-yl)-1,5-naphthyridin-2-yl)pyridin-2-amine, 53.

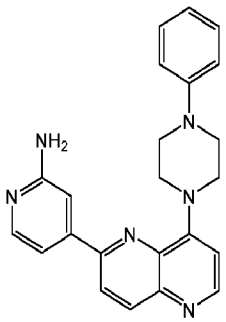
2-chloro-8-(4-phenylpiperazin-1-yl)-1,5-naphthyridine, 129.

Compound **53** was prepared via General Scheme 4 via the four step procedure reported for the preparation of compound **52**. The third and fourth steps are reported below.



Prepared in a similar manner to Step 3, General Scheme 4 as used for compound **52**. 2-chloro-8-(4-phenylpiperazin-1-yl)-1,5-naphthyridine, **129**, (32 mg, 99 µmol, 80%). LCMS $[M+H]^+$ 325. 1H NMR (500 MHz, CDCl3) δ 8.47 (d, J = 4.8 Hz, 1H), 8.17 (d, J = 9.4 Hz, 1H), 7.59 (d, J = 4.8 Hz, 1H), 7.41 – 7.28 (m, 3H), 7.01 (d, J = 8.2 Hz, 2H), 6.93 (t, J = 7.3 Hz, 1H), 4.03 (t, J = 5.2 Hz, 4H), 3.37 (dd, J = 6.1, 4.2 Hz, 4H).

4-(8-(4-phenylpiperazin-1-yl)-1,5-naphthyridin-2-yl)pyridin-2-amine, 53.

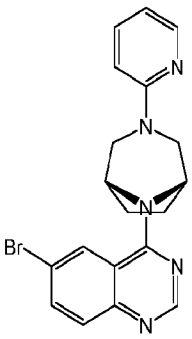


Compound **53** was prepared via General Scheme 4 in an analogous manner to compound **52,** step 4. 4-(8-(4-phenylpiperazin-1-yl)-1,5-naphthyridin-2-yl)pyridin-2-amine, **53**, (11 mg, 98 µmol, 31%) as a yellow solid. LCMS $[M+H]^+$ 383. 1H NMR (500 MHz, CDCl3) δ 8.68 (d, J = 4.4 Hz, 1H), 8.18 (d, J = 9.3 Hz, 1H), 8.14 (d, J = 5.5 Hz, 1H), 7.46 (d, J = 4.4 Hz, 1H), 7.33 – 7.27 (m, 3H), 7.13 (dd, J = 5.4, 1.4 Hz, 1H), 7.01 – 6.94 (m, 3H), 6.89 (q, J = 8.4 Hz, 1H), 4.86 (s, 2H), 3.86 (dd, J = 6.5, 3.8 Hz, 4H), 3.30 (t, J = 5.2 Hz, 4H).13C NMR (101 MHz, CDCl3) δ 157.88, 156.56, 151.05, 148.26, 146.07, 145.68, 142.00, 140.82, 140.48, 139.04, 129.26, 123.57, 120.29, 116.40, 115.98, 112.77, 110.31, 77.32, 77.00, 76.68, 49.21, 45.05.

4-(4-((1R,5S)-3-(pyridin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)quinazolin-6-yl)pyridin-2-amine, 54.

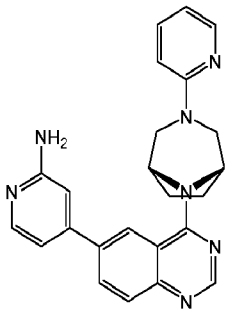
Compound **54** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

6-bromo-4-((1R,5S)-3-(pyridin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)quinazoline, 130.



In a 5 mL Biotage microwave vial, potassium carbonate (178 mg, 3 eq, 1.29 mmol) and (1R,5S)-3-(pyridin-2-yl)-3,8-diazabicyclo[3.2.1]octane, trifluoroacetic acid (130 mg, 1 eq, 429 µmol) were added with DMF (2.14 mL, 0.2 M) and stirred for 10 mins. 6-bromo-4-chloroquinazoline (104 mg, 1 eq, 429 µmol) was added, vial sealed, and stirred at 110 °C for 18 h. After this time, the mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (10 mL). The aqueous layer was washed with ethyl acetate (20 mL). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate, and evaporated *in vacuo* to obtain the crude product. The crude product was dry loaded onto silica gel and purified on a 12 g silica gel column (0-10% EtOAc/Hexanes) to afford 6-bromo-4-((1R,5S)-3-(pyridin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)quinazoline, **130**, (20 mg, 51 µmol, 12%). LCMS $[M+H]^+$ 397. 1H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.20 (dd, J = 5.2, 1.9 Hz, 1H), 8.13 (d, J = 2.1 Hz, 1H), 7.84 – 7.72 (m, 2H), 7.50 (ddd, J = 9.0, 7.1, 2.0 Hz, 1H), 6.71 – 6.60 (m, 2H), 4.96 (t, J = 3.4 Hz, 2H), 4.10 (dd, J = 12.0, 2.4 Hz, 2H), 3.39 (dd, J = 11.9, 2.3 Hz, 2H), 2.05 – 1.85 (m, 4H).

4-(4-((1R,5S)-3-(pyridin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)quinazolin-6-yl)pyridin-2-amine, 54.

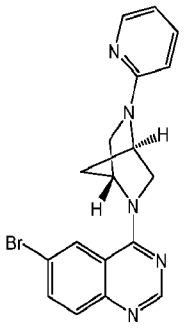


A solution of (1R,5S)-3-(pyridin-2-yl)-3,8-diazabicyclo[3.2.1]octane (100 mg, 1.0 eq, 0.528 mmol) in NMP (2.64 mL, 0.18 M) was added triethylamine (134 mg, 184 µL, 2.5 eq, 1.32 mmol) and tert-butyl (4-(4-chloroquinazolin-6-yl)pyridin-2-yl)carbamate (189 mg, 1 eq, 0.528 mmol). The mixture was stirred at 80 °C for 2 hrs. Upon cooling to room temperature, the reaction was extracted with EtOAc, washed with brine (x3) and water (x3), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. A mixture of DCM:TFA (4:1, 2.2 mL) was added to the crude mixture and stirred at room temperature overnight and basified with 1N NaOH. The mixture was extracted with DCM, washed with 10% NaOH, water, brine, and the organic layer was dried over sodium sulfate, concentrated, and dry-loaded onto silica gel and purified on a 12 g column (DCM/MeOH 0-10%), affording 4-(4-((1R,5S)-3-(pyridin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)quinazolin-6-yl)pyridin-2-amine, **54**, (22 mg, 55 µmol, 19%) as a yellow solid. LCMS $[M+H]^+$ 410. 1H NMR (500 MHz, CDCl3) δ 8.71 (s, 1H), 8.24 – 8.16 (m, 2H), 8.11 (d, J = 5.6 Hz, 1H), 7.95 (d, J = 1.7 Hz, 2H), 7.51 (ddd, J = 8.9, 7.1, 1.9 Hz, 1H), 6.92 (dd, J = 5.5, 1.5 Hz, 1H), 6.80 (s, 1H), 6.70 – 6.60 (m, 2H), 5.08 (s, 2H), 5.01 (d, J = 4.0 Hz, 2H), 4.12 (dd, J = 12.0, 2.4 Hz, 2H), 3.43 (dd, J = 11.9, 2.2 Hz, 2H), 2.04 – 1.86 (m, 4H).13C NMR (126 MHz, CDCl3) δ 163.08, 159.89, 158.65, 155.08, 151.95, 150.14, 147.90, 147.24, 137.77, 135.73, 131.51, 129.48, 123.28, 117.03, 113.80, 112.50, 106.89, 57.79, 51.53, 41.17, 27.13.

4-(4-((1R,4R)-5-(pyridin-2-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)quinazolin-6-yl)pyridin-2-amine, 55.

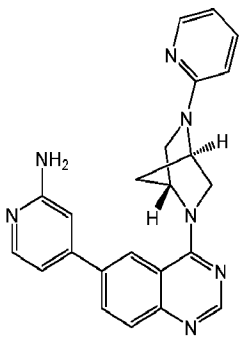
Compound **55** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

6-bromo-4-((1R,4R)-5-(pyridin-2-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)quinazoline, 131.



A solution of (1S,4S)-2-(pyridin-2-yl)-2,5-diazabicyclo[2.2.1]heptane (43.5 mg, 1.0 eq, 0.248 mmol) in NMP (1.24 mL, 0.18 M) was added triethylamine (62.8 mg, 86.5 µL, 2.5 eq, 0.621 mmol) and 6-bromo-4-chloroquinazoline (60 mg, 1 eq, 0.248 mmol). The mixture was stirred at 80 °C for 2 hrs. Upon cooling to room temperature, the reaction was extracted with EtOAc, washed with brine (x3) and water (x3), dried over anhydrous sodium sulfate, filtered, and concentrated, and dry-loaded onto silica gel and purified on a 12 g column (Hexanes/EtOAc 50%), affording 6-bromo-4-((1R,4R)-5-(pyridin-2-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)quinazoline, **131**, (91 mg, 0.24 mmol, 96%). LCMS $[M+H]^+$ 383. 1H NMR (500 MHz, CDCl3) δ 8.55 (s, 1H), 8.12 – 8.02 (m, 2H), 7.74 – 7.60 (m, 2H), 7.39 (ddd, J = 8.8, 7.1, 1.9 Hz, 1H), 6.52 (dd, J = 7.1, 5.0 Hz, 1H), 6.29 (d, J = 8.4 Hz, 1H), 5.39 (t, J = 1.8 Hz, 1H), 5.13 (s, 1H), 4.24 (dd, J = 9.1, 1.9 Hz, 1H), 3.91 (d, J = 9.1 Hz, 1H), 3.71 (dd, J = 9.4, 2.1 Hz, 1H), 3.58 (d, J = 9.4 Hz, 1H), 2.13 (s, 2H).

4-(4-((1R,4R)-5-(pyridin-2-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)quinazolin-6-yl)pyridin-2-amine, 55.



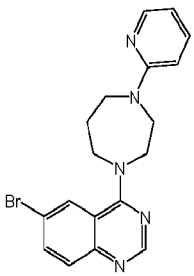
In a 5 mL microwave vial, 6-bromo-4-((1S,4S)-5-(pyridin-2-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)quinazoline (65 mg, 1 eq, 0.17 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-

2-amine (45 mg, 1.2 eq, 0.2 mmol), tripotassium phosphate (140 mg, 4 eq, 0.68 mmol), and [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (10 mg, 0.08 eq, 14 µmol) were added. The mixture was capped, purged with argon, then injected with degassed 4:1 Dioxane:H_2O (0.85 mL, 0.2 M), and was heated at 90 °C for 6 h. After this time, the mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (10 mL x 2). The aqueous layer was washed with ethyl acetate (20 mL). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate, and evaporated *in vacuo* to obtain the crude product. The crude product was dry-loaded onto silica gel and purified on a 12 g silica gel column (0-5% MeOH/DCM) to 4-(4-((1R,4R)-5-(pyridin-2-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)quinazolin-6-yl)pyridin-2-amine, **55**, (39 mg, 98 µmol, 26%) as a white solid. LCMS $[M+H]^+$ 396. 1H NMR (500 MHz, CDCl3) δ 8.61 (d, J = 1.3 Hz, 1H), 8.22 (d, J = 3.3 Hz, 1H), 8.07 (dd, J = 5.4, 1.9 Hz, 1H), 8.02 (d, J = 5.7 Hz, 1H), 7.88 (d, J = 1.7 Hz, 2H), 7.48 – 7.37 (m, 1H), 6.96 (d, J = 11.6 Hz, 1H), 6.87 (d, J = 5.6 Hz, 1H), 6.55 (dt, J = 7.6, 4.1 Hz, 1H), 6.35 (dd, J = 8.6, 4.0 Hz, 1H), 5.67 (s, 2H), 5.50 – 5.40 (m, 1H), 5.16 (s, 1H), 4.43 (d, J = 9.4 Hz, 1H), 4.07 – 3.98 (m, 1H), 3.77 (dt, J = 9.5, 2.5 Hz, 1H), 3.65 (d, J = 9.3 Hz, 1H), 2.27 – 2.12 (m, 2H). 13C NMR (126 MHz, CDCl3) δ 160.34, 157.77, 156.44, 154.98, 151.88, 151.08, 147.40, 143.53 138.09, 134.10, 130.87, 129.14, 123.70, 116.51, 112.71, 111.77, 108.01, 107.49, 60.64, 59.56, 57.16, 54.30, 36.73.

4-(4-(4-(pyridin-2-yl)-1,4-diazepan-1-yl)quinazolin-6-yl)pyridin-2-amine, 56.

Compound **56** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

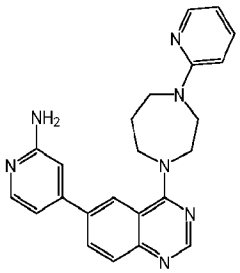
6-bromo-4-(4-(pyridin-2-yl)-1,4-diazepan-1-yl)quinazoline, 132.



Prepared using same procedure as seen for compound **131**. 6-bromo-4-(4-(pyridin-2-yl)-1,4-diazepan-1-yl)quinazoline, **132**, (167 mg, 434 µmol). LCMS $[M+H]^+$ 385. 1H NMR (500 MHz, CDCl3) δ 8.58 (s, 1H), 8.12 (t, J = 1.3 Hz, 1H), 8.08 (dt, J = 4.9, 1.7 Hz, 1H), 7.85 – 7.74 (m,

2H), 7.44 (ddd, J = 8.9, 7.1, 2.0 Hz, 1H), 6.59 – 6.49 (m, 2H), 4.18 (t, J = 5.3 Hz, 2H), 4.07 (t, J = 5.4 Hz, 2H), 4.00 – 3.91 (m, 2H), 3.77 (t, J = 6.0 Hz, 2H), 2.30 – 2.15 (m, 2H).

4-(4-(4-(pyridin-2-yl)-1,4-diazepan-1-yl)quinazolin-6-yl)pyridin-2-amine, 56.

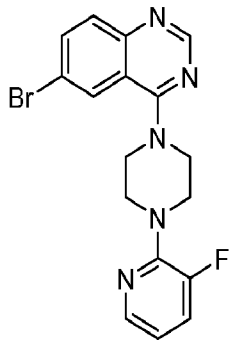


Specifically compound **56** was prepared in analogous fashion to conditions employed for compound **31** (28 mg, 70 µmol, 18% yield). LCMS $[M+H]^+$ 398. 1H NMR (500 MHz, CDCl3) δ 8.62 (s, 1H), 8.19 (s, 1H), 8.11 (s, 1H), 8.07 (d, J = 5.0 Hz, 1H), 7.91 (s, 2H), 7.44 (t, J = 8.0 Hz, 1H), 6.91 (d, J = 5.1 Hz, 1H), 6.84 (s, 1H), 6.63 – 6.47 (m, 2H), 5.12 (s, 2H), 4.22 (d, J = 5.5 Hz, 2H), 4.10 (d, J = 5.3 Hz, 2H), 3.99 (d, J = 5.7 Hz, 2H), 3.79 (t, J = 6.2 Hz, 2H), 2.26 (s, 2H).

4-(4-(3-fluoropyridin-2-yl)piperazin-1-yl)-6-(1H-pyrrolo[2,3-b]pyridin-3-yl)quinazoline , 57.

Compound **57** was prepared via General Scheme 1 via the two procedure reported for the preparation of compound **1**. The two steps are reported below.

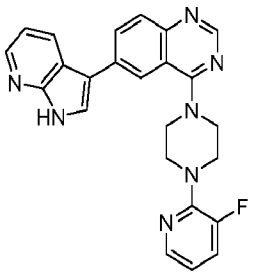
6-bromo-4-(4-(3-fluoropyridin-2-yl)piperazin-1-yl)quinazoline, 133.



Prepared in a similar manner as compound **117**. (mg amount, mol, 68%). LCMS $[M+H]^+$ 389. ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.99 – 7.90 (m, 2H), 7.76 – 7.65 (m, 2H), 7.24 – 7.12 (m, 1H), 6.72 (ddd, *J* = 7.9, 4.8, 3.1 Hz, 1H), 3.94 – 3.80 (m, 4H), 3.68 – 3.58 (m, 4H).^{13}C NMR

(101 MHz, $CDCl_3$) δ 163.45, 154.23, 151.25, 150.46, 149.49, 148.70, 142.80, 135.76, 130.46, 127.13, 123.37, 123.18, 118.60, 117.68, 116.33, 49.54, 47.36.

4-(4-(3-fluoropyridin-2-yl)piperazin-1-yl)-6-(1H-pyrrolo[2,3-b]pyridin-3-yl)quinazoline , 57.



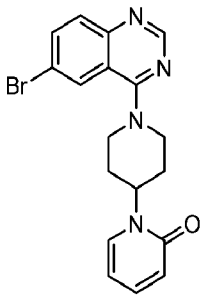
Tert-butyl 3-(4-(4-(3-fluoropyridin-2-yl)piperazin-1-yl)quinazolin-6-yl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (163 mg, 1 eq, 311 µmol) was suspended in DCM (3 mL)and TFA (710 mg, 479 µL, 20 Eq, 6.229 mmol) added. The solution stirred for 2 h at room temperature, after time elapsed the reaction mixture was concentrated via rotary evaporation. the residue was dissolved in ethyl acetate and washed with 2M NaOH solution twice (2 x 75mL). The organic layer was collected, dried with sodium sulfate, filtered and concentrated resulting in 4-(4-(3-fluoropyridin-2-yl)piperazin-1-yl)-6-(1H-pyrrolo[2,3-b]pyridin-3-yl)quinazoline, **57**, (120 mg, 282 µmol, 90 %). LCMS $[M+H]^+$ 426. ^1H NMR (500 MHz, MeOD) δ 8.53 (s, 1H), 8.27 (dd, *J* = 7.9, 1.5 Hz, 1H), 8.24 – 8.15 (m, 2H), 8.09 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.92 (dt, *J* = 4.9, 1.4 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.71 (s, 1H), 7.30 (ddd, *J* = 13.1, 7.9, 1.5 Hz, 1H), 7.18 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.79 (ddd, *J* = 8.0, 4.9, 3.2 Hz, 1H), 4.00 – 3.95 (m, 4H), 3.67 – 3.61 (m, 4H).

1-(1-(6-(1H-pyrrolo[2,3-b]pyridin-3-yl)quinazolin-4-yl)piperidin-4-yl)pyridin-2(1H)-one, 58.

Compound **58** was prepared via General Scheme 1 via the procedure reported for the preparation of compound **1**; however, an additional step was required to remove a BOC proteecting group. The second and final steps are reported below.

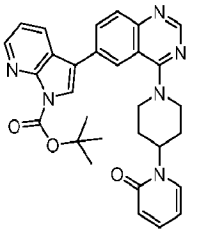
1-(1-(6-bromoquinazolin-4-yl)piperidin-4-yl)pyridin-2(1H)-one, 134.

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Prepared in a similar manner as compound **117**. 1-(1-(6-bromoquinazolin-4-yl)piperidin-4-yl)pyridin-2(1H)-one, **134**, (556 mg, 1.44 mol, 86%). LCMS $[M+H]^+$ 386. ^1H NMR (500 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.84 (dd, *J* = 5.1, 2.0 Hz, 1H), 7.69 (d, *J* = 2.1 Hz, 1H), 7.48 – 7.38 (m, 2H), 7.26 (ddd, *J* = 8.9, 7.1, 2.1 Hz, 1H), 6.54 (dd, *J* = 7.1, 5.0 Hz, 1H), 6.43 (d, *J* = 8.3 Hz, 1H), 5.10 (tt, *J* = 7.6, 3.8 Hz, 1H), 3.75 (ddd, *J* = 13.5, 7.3, 3.6 Hz, 2H), 3.42 – 3.34 (m, 2H), 1.92 (ddt, *J* = 14.3, 7.4, 3.7 Hz, 2H), 1.71 (dtd, *J* = 11.9, 7.8, 3.6 Hz, 2H).

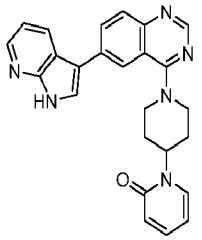
Tert-butyl 3-(4-(4-(2-oxopyridin-1(2H)-yl)piperidin-1-yl)quinazolin-6-yl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate, 135.



To a microwave vial potassium phosphate, tribasic (306 mg, 3 eq, 1.44 mmol), $PdCl_2$(dppf) (35 mg, 0.1 eq, 48.0 µmol), tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (174 mg, 1.05 eq, 504 µmol), and 1-(1-(6-bromoquinazolin-4-yl)piperidin-4-yl)pyridin-2(1H)-one (185 mg, 1 eq, 480 µmol) was added and the vial was sealed. The solids were dissolved in 1,4-Dioxane (2.0 mL) and water (0.40 mL), and the reaction mixture was heated to 90 °C where it stirred for 16 hours. After time elapsed, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a thick celite pad. The filtrate was collected and concentrated via rotary evaporation. The resulting residue was dissolved in 50 mL of ethyl acetate and washed with water (3 x 50mL). The organic layer was dried over sodium sulfate, filtered, and concentrated via rotary evaporation. The crude concentrate was purified via column chromatography (0-10% MeOH/DCM) producing tert-butyl 3-(4-(4-(2-oxopyridin-1(2H)-yl)piperidin-1-yl)quinazolin-6-yl)-1H-

pyrrolo[2,3-b]pyridine-1-carboxylate, **135**, (126 mg, 242 μmol, 50%). LCMS $[M+H]^+$ 523. This compound was carried forward to the next step without other characterization.

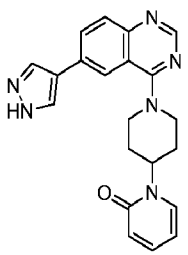
1-(1-(6-(1H-pyrrolo[2,3-b]pyridin-3-yl)quinazolin-4-yl)piperidin-4-yl)pyridin-2(1H)-one, 58.



Tert-butyl 3-(4-(4-(2-oxopyridin-1(2H)-yl)piperidin-1-yl)quinazolin-6-yl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (126 mg, 1 eq, 242 μmol) was suspended in DCM (2 mL)and TFA (553 mg, 373 μL, 20 Eq, 4.85 mmol) added. The solution stirred for 2 h at room temperature, after time elapsed the reaction mixture was concentrated via rotary evaporation. the residue was dissolved in ethyl acetate and washed with 2M NaOH solution twice (2 x 75mL). The organic layer was collected, dried with sodium sulfate, filtered and concentrated resulting in 1-(1-(6-(1H-pyrrolo[2,3-b]pyridin-3-yl)quinazolin-4-yl)piperidin-4-yl)pyridin-2(1H)-one, **58**, (100 mg, 237 μmol, 97%). LCMS $[M+H]^+$ 423. ^1H NMR (400 MHz, $CDCl_3$) δ 12.20 (s, 1H), 8.78 (s, 1H), 8.49 – 8.43 (m, 1H), 8.30 (dd, *J* = 8.0, 1.3 Hz, 1H), 8.21 – 8.08 (m, 2H), 8.08 – 7.95 (m, 2H), 7.70 (s, 1H), 7.59 (ddd, *J* = 8.4, 7.1, 2.0 Hz, 1H), 7.30 – 7.20 (m, 1H), 6.88 (ddd, *J* = 7.1, 5.0, 1.0 Hz, 1H), 6.77 (dt, *J* = 8.3, 0.9 Hz, 1H), 5.45 (tt, *J* = 7.6, 3.8 Hz, 1H), 4.23 – 4.11 (m, 2H), 3.76 (ddd, *J* = 13.2, 8.2, 3.4 Hz, 2H), 2.29 (ddt, *J* = 13.8, 7.3, 3.4 Hz, 2H), 2.14 – 2.02 (m, 2H).

1-(1-(6-(1H-pyrazol-4-yl)quinazolin-4-yl)piperidin-4-yl)pyridin-2(1H)-one, 59.

Compound **59** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.

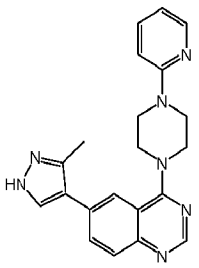


To a microwave vial potassium phosphate, tribasic (306 mg, 3 eq, 1.44 mmol), $PdCl_2$(dppf) (35.1 mg, 0.1 eq, 48.0 μmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-

1-carboxylate (148 mg, 1.05 eq, 504 µmol), and 1-(1-(6-bromoquinazolin-4-yl)piperidin-4-yl)pyridin-2(1H)-one (185 mg, 1 eq, 480 µmol) was added and the vial was sealed. The solids were dissolved in 1,4-dioxane (2.0 mL) and water (0.40 mL), and the reaction mixture was heated to 90 °C where it stirred for 16 hours. After time elapsed, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a thick celite pad. The filtrate was collected and concentrated via rotary evaporation. The resulting residue was dissolved in 50 mL of ethyl acetate and washed with water (3 x 50mL). The organic layer was dried over sodium sulfate, filtered, and concentrated via rotary evaporation. The crude concentrate was purified via column chromatography (0-10% MeOH/DCM) producing 1-(1-(6-(1H-pyrazol-4-yl)quinazolin-4-yl)piperidin-4-yl)pyridin-2(1H)-one, **59**, (123 mg, 330 µmol, 68%). LCMS $[M+H]^+$ 373. ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.19 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 8.00 – 7.83 (m, 3H), 7.67 – 7.37 (m, 2H), 6.91 (ddd, *J* = 7.1, 5.1, 1.0 Hz, 1H), 6.80 (s, 1H), 6.78 (s, 1H), 5.46 (tt, *J* = 7.7, 3.9 Hz, 1H), 4.14 (ddd, *J* = 11.2, 6.8, 3.6 Hz, 2H), 3.82 – 3.67 (m, 2H), 2.31 (ddd, *J* = 12.9, 7.2, 3.6 Hz, 2H), 2.08 (dtd, *J* = 12.2, 8.0, 3.5 Hz, 2H).

6-(3-methyl-1H-pyrazol-4-yl)-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline, 60.

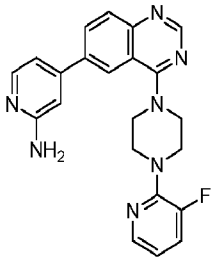
Compound **60** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.



Compound **60** was prepared according to the same procedure to synthesize compound **50**. 6-(3-methyl-1H-pyrazol-4-yl)-4-(4-(pyridin-2-yl)piperazin-1-yl)quinazoline, **60**, (61 mg, 165 µmol, 41% yield) as a tan solid. LCMS $[M+H]^+$ 372. 1H NMR (500 MHz, DMSO) δ 12.80 (s, 1H), 8.62 (s, 1H), 8.15 (dd, J = 5.0, 2.0 Hz, 1H), 7.99 (d, J = 7.4 Hz, 3H), 7.83 (d, J = 8.8 Hz, 1H), 7.57 (ddd, J = 8.8, 7.1, 2.0 Hz, 1H), 6.86 (d, J = 8.6 Hz, 1H), 6.67 (dd, J = 7.1, 4.9 Hz, 1H), 3.87 (dd, J = 7.0, 3.6 Hz, 4H), 3.75 (dd, J = 6.9, 3.7 Hz, 4H), 2.50 (d, J = 3.0 Hz, 3H).

4-(4-(4-(3-fluoropyridin-2-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, 61.

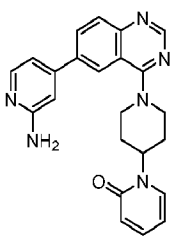
Compound **61** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.



To a microwave vial potassium phosphate, tribasic (328 mg, 3 eq, 1.548 mmol), $PdCl_2$(dppf) (37.7 mg, 0.1 Eq, 51.5 µmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (124 mg, 1.1 eq, 567 µmol), and 6-bromo-4-(4-(3-fluoropyridin-2-yl)piperazin-1-yl)quinazoline (200 mg, 1 eq, 515 µmol) was added and the vial was sealed. The solids were dissolved in 1,4-Dioxane (2.0 mL) and water (0.40 mL), and the reaction mixture was heated to 90 °C where it stirred for 16 hours. After time elapsed, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a thick celite pad. The filtrate was collected and concentrated via rotary evaporation. The resulting residue was dissolved in 50 mL of ethyl acetate and washed with water (3 x 50mL). The organic layer was dried over sodium sulfate, filtered, and concentrated via rotary evaporation. The crude concentrate was purified via column chromatography (0-10% MeOH/DCM) producing 4-(4-(4-(3-fluoropyridin-2-yl)piperazin-1-yl)quinazolin-6-yl)pyridin-2-amine, **61**, (141 mg, 352.0 µmol, 68%). LCMS $[M+H]^+$ 402. ^1H NMR (500 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.13 (d, J = 5.4 Hz, 1H), 8.06 (d, J = 2.0 Hz, 1H), 8.00 (dd, J = 4.8, 1.7 Hz, 1H), 7.95 – 7.85 (m, 2H), 7.27 – 7.19 (m, 1H), 6.89 – 6.84 (m, 1H), 6.77 (ddd, J = 7.9, 4.8, 3.1 Hz, 1H), 6.71 (s, 1H), 3.95 – 3.89 (m, 4H), 3.71 – 3.65 (m, 4H).

1-(1-(6-(2-aminopyridin-4-yl)quinazolin-4-yl)piperidin-4-yl)pyridin-2(1H)-one, 62.

Compound **62** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.

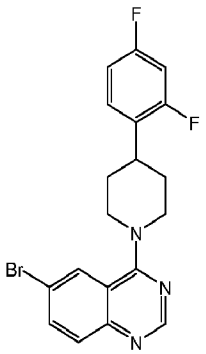


To a microwave vial potassium phosphate, tribasic (306 mg, 3 eq, 1.44 mmol), $PdCl_2$(dppf) (35 mg, 0.1 eq, 48.0 µmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (111 mg, 1.05 eq, 504 µmol), and 1-(1-(6-bromoquinazolin-4-yl)piperidin-4-yl)pyridin-2(1H)-one (185 mg, 1 eq, 480 µmol) was added and the vial was sealed. The solids were dissolved in 1,4-Dioxane (2.0 mL) and water (0.40 mL), and the reaction mixture was heated to 90 °C where it stirred for 16 hours. After time elapsed, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a thick celite pad. The filtrate was collected and concentrated via rotary evaporation. The resulting residue was dissolved in 50 mL of ethyl acetate and washed with water (3 x 50mL). The organic layer was dried over sodium sulfate, filtered, and concentrated via rotary evaporation. The crude concentrate was purified via column chromatography (0-10% MeOH/DCM) producing 1-(1-(6-(2-aminopyridin-4-yl)quinazolin-4-yl)piperidin-4-yl)pyridin-2(1H)-one, **62**, (142 mg, 358 µmol, 74%). LCMS $[M+H]^+$ 402. ^1H NMR (500 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.13 – 8.07 (m, 2H), 8.03 – 7.97 (m, 1H), 7.91 – 7.82 (m, 2H), 7.56 – 7.49 (m, 1H), 6.87 – 6.78 (m, 2H), 6.72 – 6.66 (m, 2H), 5.36 (tt, *J* = 7.8, 3.8 Hz, 1H), 4.08 (ddd, *J* = 11.9, 7.2, 3.6 Hz, 2H), 3.68 (ddd, *J* = 12.9, 8.4, 3.3 Hz, 2H), 2.19 (ddt, *J* = 14.4, 7.5, 3.6 Hz, 2H), 1.98 (dtd, *J* = 12.2, 8.0, 3.4 Hz, 2H).

4-(4-(4-(2,4-difluorophenyl)piperidin-1-yl)quinazolin-6-yl)pyridin-2-amine, 63.

Compound **63** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

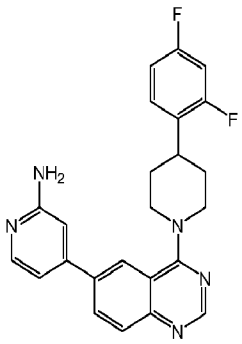
6-bromo-4-(4-(2,4-difluorophenyl)piperidin-1-yl)quinazoline, 136.



A solution of 6-bromo-4-chloroquinazoline (74 mg, 1.2 eq, 0.30 mmol) and 4-(2,4-difluorophenyl)piperidine (50 mg, 1.0 eq, 0.25 mmol) in NMP (0.51 mL, 0.4 M) was added

triethylamine (64 mg, 88 µL, 2.5 eq, 0.63 mmol). The mixture was stirred at 80 °C for 2 h. Upon cooling to room temperature, the reaction was extracted with EtOAc, washed with brine (x 3) and water (x 3), dried over anhydrous sodium sulfate, filtered, concentrated, and dry-loaded onto silica gel and purified on a 12 g silica gel column (0-10% EtOAc/Hexanes) to afford 6-bromo-4-(4-(2,4-difluorophenyl)piperidin-1-yl)quinazoline, **136**, (78 mg, 0.19 mmol, 76%). LCMS $[M+H]^+$ 405. 1H NMR (400 MHz, CDCl3) δ 8.73 (s, 1H), 8.05 (d, J = 2.0 Hz, 1H), 7.90 (d, J = 9.1 Hz, 1H), 7.83 (dd, J = 8.9, 2.1 Hz, 1H), 7.18 (tt, J = 8.3, 6.3 Hz, 1H), 6.88 (t, J = 8.5 Hz, 2H), 4.57 (d, J = 13.1 Hz, 2H), 3.39 (tt, J = 12.4, 3.8 Hz, 1H), 3.29 (t, J = 12.8 Hz, 2H), 2.36 (qd, J = 12.9, 3.8 Hz, 2H), 2.02 – 1.88 (m, 2H).

4-(4-(4-(2,4-difluorophenyl)piperidin-1-yl)quinazolin-6-yl)pyridin-2-amine, 63.



In a 5 mL microwave vial, 6-bromo-4-(4-(2,4-difluorophenyl)piperidin-1-yl)quinazoline (78 mg, 1 eq, 0.19 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (51 mg, 1.2 eq, 0.23 mmol), tripotassium phosphate (160 mg, 4 eq, 0.77 mmol), and [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (11 mg, 0.08 eq, 15 µmol) were added. The mixture was capped, purged with argon, then injected with degassed 4:1 dioxane:H_2O (1.0 mL, 0.2 M), and was heated at 80 °C for 18 h. After this time, the mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (10 mL x 2). The aqueous layer was washed with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate, and evaporated *in vacuo* to obtain the crude product. The crude product was dry-loaded onto silica gel and purified on a 12 g silica gel column (0-3% MeOH/DCM) to 4-(4-(4-(2,4-difluorophenyl)piperidin-1-yl)quinazolin-6-yl)pyridin-2-amine, **63**, (20 mg, 0.19 mmol, 25%) as a brown solid. LCMS $[M+H]^+$ 418. 1H NMR (500 MHz, CDCl3) δ 8.75 (s, 1H), 8.18 – 8.05 (m, 2H), 8.00 – 7.88 (m, 2H), 7.17 (tt, J = 8.3, 6.3 Hz, 1H), 6.92 (d, J = 5.1 Hz, 1H), 6.87 (t, J = 8.5 Hz, 2H), 6.81 (s, 1H), 4.98 (s, 2H),

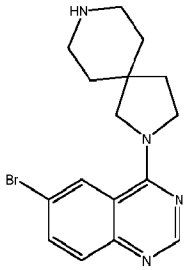
4.55 (d, J = 13.3 Hz, 2H), 3.37 (ddt, J = 12.4, 7.6, 3.8 Hz, 1H), 3.28 (t, J = 12.8 Hz, 2H), 2.45 – 2.29 (m, 2H), 1.96 – 1.85 (m, 2H). 13C NMR (126 MHz, DMSO) δ 163.78, 161.83, 161.75, 160.51, 159.88, 159.80, 154.08, 151.53, 148.60, 147.30, 135.20, 131.05, 128.84, 128.77, 128.68, 122.75, 119.80, 119.66, 119.51, 115.84, 112.19, 111.98, 109.98, 105.38, 50.01, 32.57, 29.88.

4-(4-(8-(pyridin-2-yl)-2,8-diazaspiro[4.5]decan-2-yl)quinazolin-6-yl)pyridin-2-amine, 64.

Compound **64** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. However this compound requires an additional step to add a pyridyl group. This step is shown below.

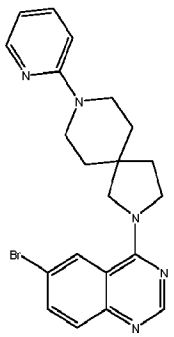
4-(4-(8-(pyridin-2-yl)-2,8-diazaspiro[4.5]decan-2-yl)quinazolin-6-yl)pyridin-2-amine, 64.

2-(6-bromoquinazolin-4-yl)-2,8-diazaspiro[4.5]decane, 137.



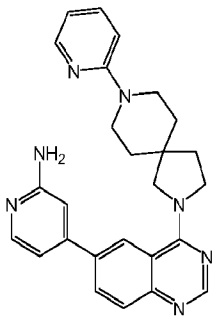
Prepared following similar procedure that was used to synthesize compound **117**. tert-butyl 2-(6-bromoquinazolin-4-yl)-2,8-diazaspiro[4.5]decane-8-carboxylate, **137**, (398 mg, 832 µmol, 100%) LCMS $[M+H]^+$ 448. 1H NMR (400 MHz, CDCl3) δ 8.59 (s, 1H), 8.27 – 8.21 (m, 1H), 7.80 – 7.72 (m, 2H), 4.05 (t, J = 7.0 Hz, 2H), 3.47 (td, J = 6.3, 4.5 Hz, 4H), 3.41 – 3.31 (m, 1H), 2.42 – 2.32 (m, 1H), 2.02 – 1.94 (m, 2H), 1.62 (q, J = 5.5 Hz, 4H), 1.44 (d, J = 0.9 Hz, 9H). tert-butyl 2-(6-bromoquinazolin-4-yl)-2,8-diazaspiro[4.5]decane-8-carboxylate was then subjected to TFA in DCM (1:4, 7,8 mL) and let stir at room temperature for 3 h. Excess TFA was evaporated *in vacuo* to afford 2-(6-bromoquinazolin-4-yl)-2,8-diazaspiro[4.5]decane as a TFA salt (376 mg, 815 µmol, 98%). LCMS $[M+H]^+$ 348. This compound was used without any further purification or characterization.

2-(6-bromoquinazolin-4-yl)-8-(pyridin-2-yl)-2,8-diazaspiro[4.5]decane, 138.



To a 5 mL Biotage microwave vial was added 2-(6-bromoquinazolin-4-yl)-2,8-diazaspiro[4.5]decane, Trifluoroacetic acid (376 mg, 1.0 eq, 815 µmol) and potassium carbonate (338 mg, 3.0 eq, 2.45 mmol). The vial was capped and 2-fluoropyridine (237 mg, 3.0 eq, 2.45 mmol) and DMSO (1.63 mL, 0.5 M) were injected. The reaction was heated at 140°C for 5 h. Upon completion, the reaction was extracted in EtOAc, washed with brine (x 3) and water (x 3), dried over sodium sulfate, filtered, concentrated *in vacuo,* and dry-loaded onto silica gel and purified on a 12 g silica gel column (0-20% EtOAc:Hexanes) to afford 2-(6-bromoquinazolin-4-yl)-8-(pyridin-2-yl)-2,8-diazaspiro[4.5]decane, **138**, (144 mg, 339 µmol, 70%). LCMS $[M+H]^+$ 425. 1H NMR (500 MHz, CDCl3) δ 8.39 (s, 1H), 8.04 (d, J = 2.1 Hz, 1H), 7.98 (ddd, J = 5.0, 2.0, 0.8 Hz, 1H), 7.54 (dd, J = 8.9, 2.0 Hz, 1H), 7.49 (d, J = 8.9 Hz, 1H), 7.26 (ddd, J = 8.9, 7.1, 2.0 Hz, 1H), 6.46 (dd, J = 8.6, 1.0 Hz, 1H), 6.40 (ddd, J = 7.2, 4.9, 0.9 Hz, 1H), 3.84 (t, J = 7.0 Hz, 2H), 3.59 (s, 2H), 3.41 (dtdd, J = 17.7, 13.3, 9.1, 4.4 Hz, 4H), 1.80 (t, J = 7.0 Hz, 2H), 1.64 – 1.47 (m, 4H).

4-(4-(8-(pyridin-2-yl)-2,8-diazaspiro[4.5]decan-2-yl)quinazolin-6-yl)pyridin-2-amine, 64.



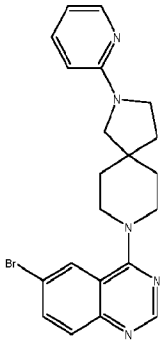
Compound **64** was prepared according to the same procedure to synthesize compound **50**. 4-(4-(8-(pyridin-2-yl)-2,8-diazaspiro[4.5]decan-2-yl)quinazolin-6-yl)pyridin-2-amine, **64**, (76 mg, 173 µmol, 51% yield) as a brown solid. LCMS $[M+H]^+$ 438. 1H NMR (500 MHz, CDCl3) δ 8.63 (s, 1H), 8.33 (d, J = 1.3 Hz, 1H), 8.22 – 8.15 (m, 2H), 7.90 (d, J = 1.3 Hz, 2H), 7.47 (ddd, J = 8.9, 7.1, 2.0 Hz, 1H), 6.90 (dd, J = 5.4, 1.6 Hz, 1H), 6.75 – 6.70 (m, 1H), 6.68 (dd, J = 8.6, 1.2

Hz, 1H), 6.61 (ddd, J = 7.2, 4.9, 0.9 Hz, 1H), 4.57 (s, 2H), 4.14 (t, J = 7.0 Hz, 2H), 3.87 (s, 2H), 3.72 – 3.53 (m, 4H), 2.04 (d, J = 14.0 Hz, 2H), 1.82 – 1.74 (m, 4H). 13C NMR (126 MHz, CDCl3) δ 160.25, 159.47, 159.18, 155.07, 151.97, 149.86, 149.15, 148.17, 137.67, 135.13, 130.92, 129.11, 123.81, 116.64, 113.29, 112.79, 107.39, 106.28, 60.74, 49.68, 43.03, 41.18, 36.01, 34.15.

4-(4-(2-(pyridin-2-yl)-2,8-diazaspiro[4.5]decan-8-yl)quinazolin-6-yl)pyridin-2-amine, 65.

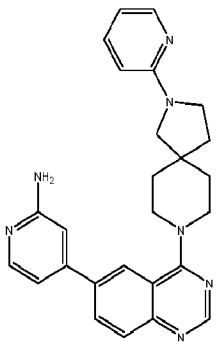
Compound **65** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The two steps are reported below.

8-(6-bromoquinazolin-4-yl)-2-(pyridin-2-yl)-2,8-diazaspiro[4.5]decane, 139.



Prepared using same procedure as seen for compound **131.** 8-(6-bromoquinazolin-4-yl)-2-(pyridin-2-yl)-2,8-diazaspiro[4.5]decane, **139**, (263 mg, 620 µmol, 44%). LCMS $[M+H]^+$ 425. 1H NMR (500 MHz, CDCl3) δ 8.53 (s, 1H), 7.98 (dd, J = 5.3, 1.9 Hz, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.62 – 7.52 (m, 2H), 7.26 (ddd, J = 8.8, 7.1, 2.0 Hz, 1H), 6.43 – 6.31 (m, 1H), 6.17 (d, J = 8.5 Hz, 1H), 3.76 – 3.63 (m, 2H), 3.50 (ddd, J = 13.1, 7.4, 4.7 Hz, 2H), 3.36 (t, J = 7.0 Hz, 2H), 3.31 (s, 2H), 1.82 (q, J = 6.9 Hz, 2H), 1.71 – 1.57 (m, 4H).

4-(4-(2-(pyridin-2-yl)-2,8-diazaspiro[4.5]decan-8-yl)quinazolin-6-yl)pyridin-2-amine, 65.

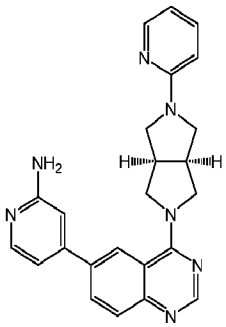


Compound **65** was prepared according to the same procedure to synthesize compound **50**. 4-(4-(2-(pyridin-2-yl)-2,8-diazaspiro[4.5]decan-8-yl)quinazolin-6-yl)pyridin-2-amine, **65**, (79 mg,

181 µmol, 29% yield) as a brown solid. LCMS $[M+H]^+$ 438. 1H NMR (500 MHz, CDCl3) δ 8.74 (s, 1H), 8.21 – 8.13 (m, 2H), 8.05 (d, J = 1.9 Hz, 1H), 7.99 – 7.89 (m, 2H), 7.45 (ddd, J = 8.8, 7.1, 1.9 Hz, 1H), 6.90 (dd, J = 5.4, 1.5 Hz, 1H), 6.73 (t, J = 1.0 Hz, 1H), 6.55 (ddd, J = 7.1, 5.1, 1.0 Hz, 1H), 6.36 (dt, J = 8.6, 1.0 Hz, 1H), 4.61 (s, 2H), 3.95 (dt, J = 13.5, 5.2 Hz, 2H), 3.75 (ddd, J = 13.0, 7.4, 4.8 Hz, 2H), 3.55 (t, J = 7.0 Hz, 2H), 3.51 (s, 2H), 2.01 (t, J = 7.0 Hz, 2H), 1.91 – 1.81 (m, 4H). 13C NMR (126 MHz, CDCl3) δ 165.00, 159.22, 157.40, 154.73, 152.18, 149.44, 149.18, 148.36, 137.22, 135.78, 131.27, 129.50, 123.38, 116.82, 112.71, 111.71, 106.47, 106.29, 56.55, 47.83, 45.17, 41.16, 36.65, 35.20.

4-(4-((3aR,6aS)-5-(pyridin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)quinazolin-6-yl)pyridin-2-amine, 66.

Compound **66** was prepared via General Scheme 1 via the two step procedure reported for the preparation of compound **1**. The second step is reported below.

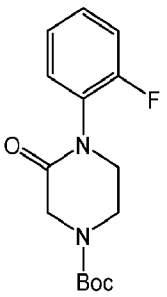


Compound **66** was prepared according to the same procedure to synthesize compound **50**. 4-(4-((3aR,6aS)-5-(pyridin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)quinazolin-6-yl)pyridin-2-amine, **66**, (14 mg, 34 µmol, 13% yield) as a brown solid. LCMS $[M+H]^+$ 410. 1H NMR (500 MHz, DMSO) δ 8.50 – 8.41 (m, 2H), 8.06 (dd, J = 5.3, 1.9 Hz, 1H), 8.03 – 7.94 (m, 2H), 7.79 (d, J = 8.6 Hz, 1H), 7.48 (ddd, J = 8.8, 7.1, 2.0 Hz, 1H), 6.91 (dd, J = 5.3, 1.7 Hz, 1H), 6.80 (d, J = 1.7 Hz, 1H), 6.55 (dd, J = 7.1, 5.0 Hz, 1H), 6.43 (d, J = 8.5 Hz, 1H), 6.01 (s, 2H), 4.30 (dd, J = 11.7, 6.5 Hz, 2H), 3.95 (dd, J = 11.7, 3.9 Hz, 2H), 3.69 (dd, J = 10.7, 6.8 Hz, 2H), 3.43 (dd, J = 10.9, 3.8 Hz, 2H), 3.18 (t, J = 5.3 Hz, 2H). 13C NMR (126 MHz, DMSO) δ 160.46, 159.18, 156.95, 154.38, 151.25, 148.63, 147.82, 147.52, 136.95, 134.37, 130.41, 128.16, 123.68, 115.92, 111.42, 110.14, 106.53, 105.13, 54.38, 50.23.

4-(6-(2-aminopyridin-4-yl)pyrido[3,2-d]pyrimidin-4-yl)-1-(2-fluorophenyl)piperazin-2-one, 67.

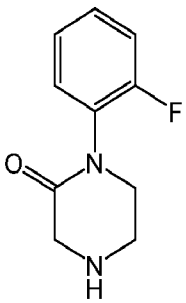
Compound **67** was prepared via General Scheme 3 via the five step procedure as reported for compound **32**.

tert-butyl 4-(2-fluorophenyl)-3-oxopiperazine-1-carboxylate, 140.



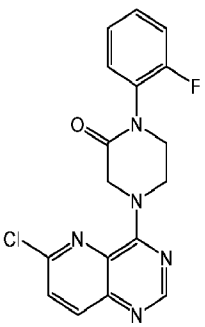
Prepared in an analogous manner as Step 2, General Scheme 3 as seen for compound **32**. tert-butyl 4-(2-fluorophenyl)-3-oxopiperazine-1-carboxylate, **140**, (539 mg, 1.83 mmol, 100%). LCMS $[M+H]^+$ 295. 1H NMR (500 MHz, CDCl3) δ 7.35 – 7.27 (m, 2H), 7.23 – 7.14 (m, 2H), 4.27 (s, 2H), 3.80 (t, J = 5.3 Hz, 2H), 3.68 (t, J = 5.3 Hz, 2H), 1.50 (s, 9H).

1-(2-fluorophenyl)piperazin-2-one, 141



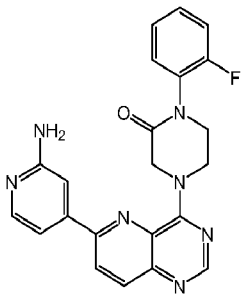
Prepared in an analogous manner as Step 3, General Scheme 3 as seen for compound **32**. 1-(2-fluorophenyl)piperazin-2-one, **141**, (129 mg, 662 µmol, 34%). LCMS $[M+H]^+$ 195. This compound was used without any further purification or characterization.

4-(6-chloropyrido[3,2-d]pyrimidin-4-yl)-1-(2-fluorophenyl)piperazin-2-one, 142.



Prepared in an analogous manner as Step 4, General Scheme 3 as seen for compound **32**. 4-(6-chloropyrido[3,2-d]pyrimidin-4-yl)-1-(2-fluorophenyl)piperazin-2-one, **142**, (120 mg, 336 µmol, 60%). LCMS $[M+H]^+$ 358. 1H NMR (500 MHz, DMSO) δ 8.27 (s, 1H), 7.86 (d, J = 8.9 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.10 (td, J = 7.8, 1.7 Hz, 1H), 7.06 – 6.98 (m, 1H), 6.95 (ddd, J = 10.0, 8.3, 1.5 Hz, 1H), 6.89 (td, J = 7.6, 1.5 Hz, 1H), 4.70 (s, 2H), 4.27 (s, 2H), 3.49 (t, J = 5.3 Hz, 2H).

4-(6-(2-aminopyridin-4-yl)pyrido[3,2-d]pyrimidin-4-yl)-1-(2-fluorophenyl)piperazin-2-one, 67.



Prepared in an analogous manner as Step 4, General Scheme 3 as seen for compound **32.** 4-(6-(2-aminopyridin-4-yl)pyrido[3,2-d]pyrimidin-4-yl)-1-(2-fluorophenyl)piperazin-2-one, **67**, (34 mg, 83 µmol, 42%) as a tan solid. LCMS $[M+H]^+$ 416. 1H NMR (500 MHz, DMSO) δ 8.64 (s, 1H), 8.35 (d, J = 8.8 Hz, 1H), 8.28 (d, J = 8.8 Hz, 1H), 8.07 (d, J = 5.3 Hz, 1H), 7.50 (td, J = 7.7, 1.7 Hz, 1H), 7.43 – 7.38 (m, 1H), 7.34 (ddd, J = 10.1, 8.3, 1.5 Hz, 1H), 7.28 (td, J = 7.6, 1.5 Hz, 1H), 7.21 (dd, J = 5.4, 1.6 Hz, 1H), 7.16 (s, 1H), 6.18 (s, 2H), 5.01 (s, 4H), 3.98 (s, 2H).

INCORPORATION BY REFERENCE

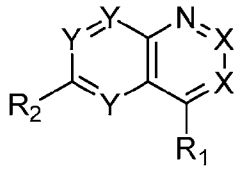
The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

What Is Claimed Is:

1. A compound encompassed within one of the following formulas:



(Formula I); including pharmaceutically acceptable salts, solvates, and/or prodrugs thereof,

wherein each of X, Y, R1 and R2 independently include any chemical moiety that permits the resulting compound to inhibit DYRK1A, DYRK1B, DYRK2, DYRK3, CLK1, CLK2, CLK3, CLK4, homeodomain-interacting kinases (HIPKs), and/or CMGC kinases leading to inhibition of WNT signaling.

2. The compound of Claim 1, wherein each of X, Y, R1 and R2 independently include any chemical moiety that permits the resulting compound to inhibit one or more of

DYRK1A activity;

DYRK1A related PI3K/Akt signaling;

DYRK1A related tau phosphorylation;

DYRK1A related NFAT phosphorylation;

DYRK1A related ASK1/JNK1 pathway activation;

DYRK1A related p53 phosphorylation;

DYRK1A related Amph 1 phosphorylation;

DYRK1A related Dynamin 1 phosphorylation;

DYRK1A related Synaptojanin phosphorylation;

DYRK1A related presenilin 1 (the catalytic sub-unit of γ-secretase) activity;

DYRK1A related amyloid precursor protein phosphorylation;

DYRK1A related SIRT1 activation;

DYRK2 related heat shock factor 1 and 26S proteasome activities;

DYRK3 related mTOR activity;

DYRK3 phosphorylation (e.g., PRAS40);

DYRK1B activity;

CMGC/CLK kinase activity;
CLK1 activity;
CLK2 activity;
CLK3 activity;
CLK4 activity;
CDK7 activity;
CDK8 activity;
CDK19 activity;
CDK8/19 activity;
PI3K activity;
PI3K mutant activity;
PDGFrA/B activity;
mTOR activity;
c-KIT activity;
RYK activity; and
WNT signaling.

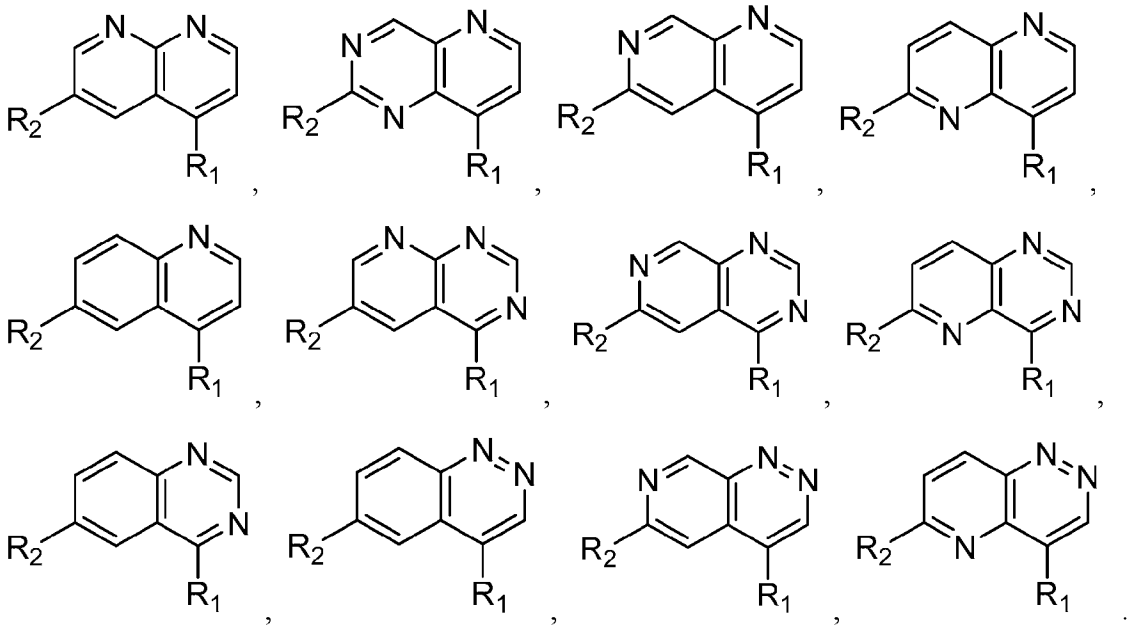
3. The compound of Claim 1, wherein each of X, Y, R1 and R2 independently include any chemical moiety that permits the resulting compound capable of binding to a DYRK or CLK protein.

4. The compound of Claim 1,

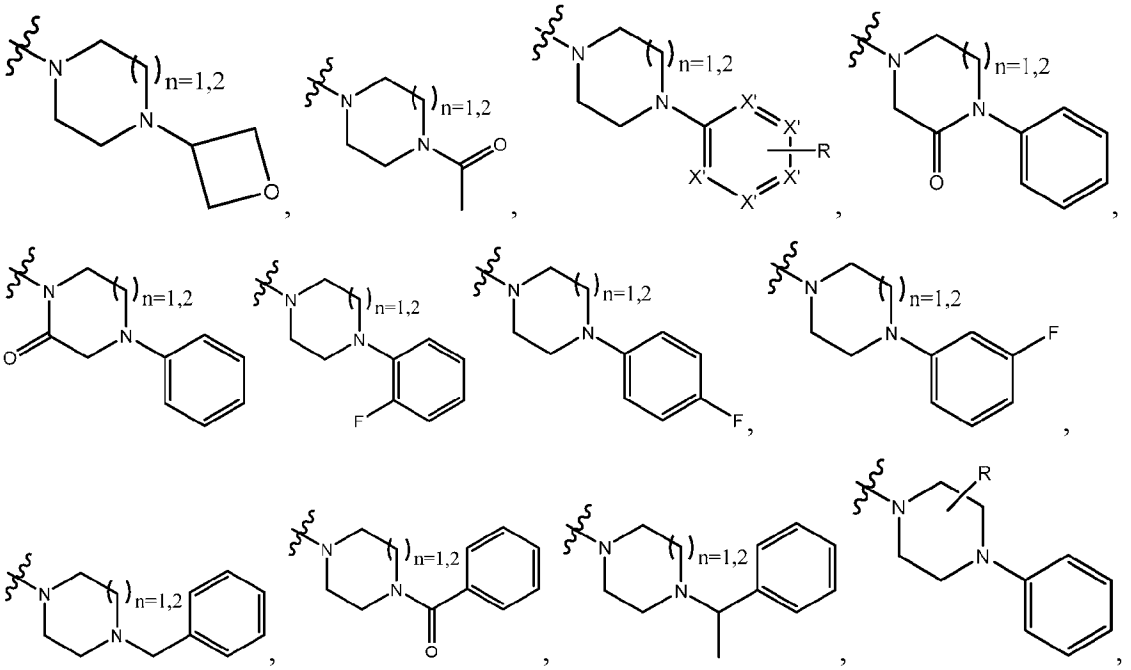
wherein one of the "X" substituents is carbon and the other is nitrogen, or wherein both of the "X" substituents are carbon; and

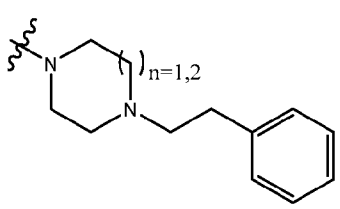
wherein one of the "Y" substituents is nitrogen and the other "Y" substituents are carbon, or wherein two of the "Y" substituents are nitrogen and one "Y" substituent is carbon, or wherein all of the "Y" substituents are carbon.

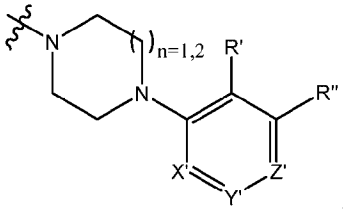
5. The compound of Claim 4, wherein the resulting formula is selected from:

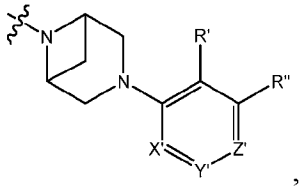


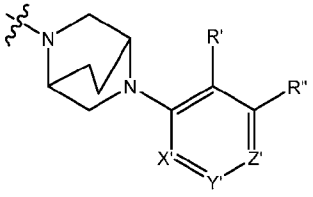
6. The compound of Claim 1, wherein R1 is selected from from hydrogen,

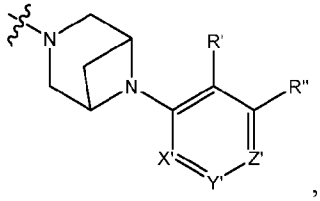


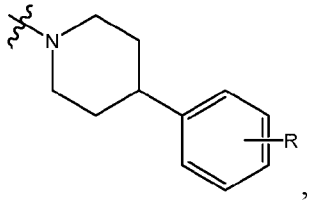


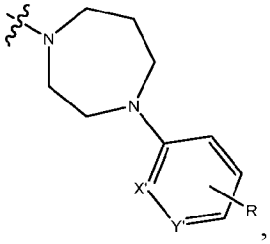
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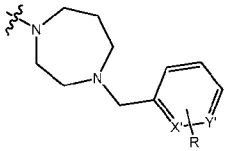
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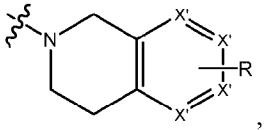
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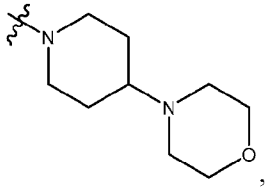
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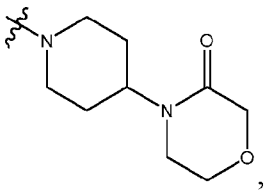
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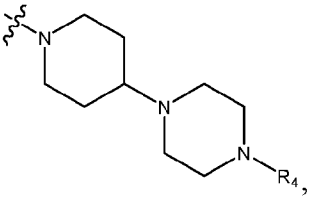
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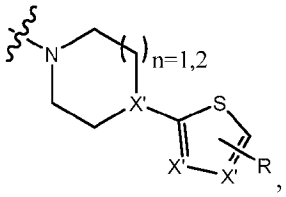
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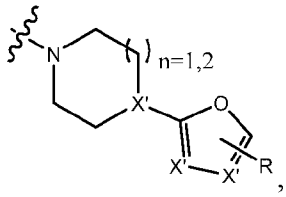
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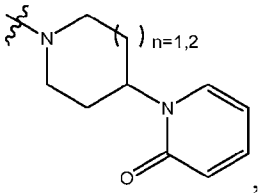
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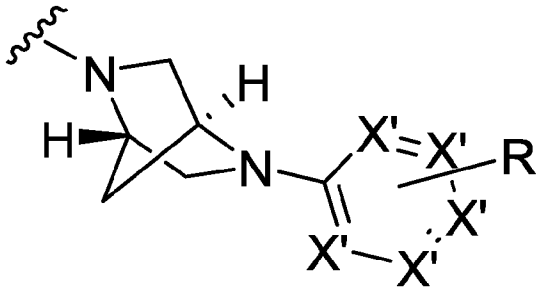
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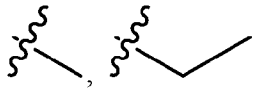
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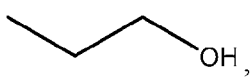
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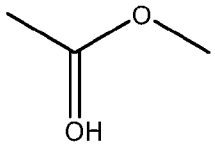
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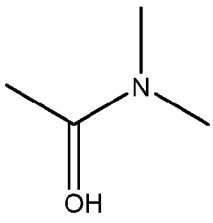
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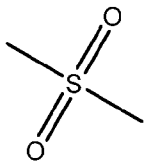
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; wherein R4 is selected from

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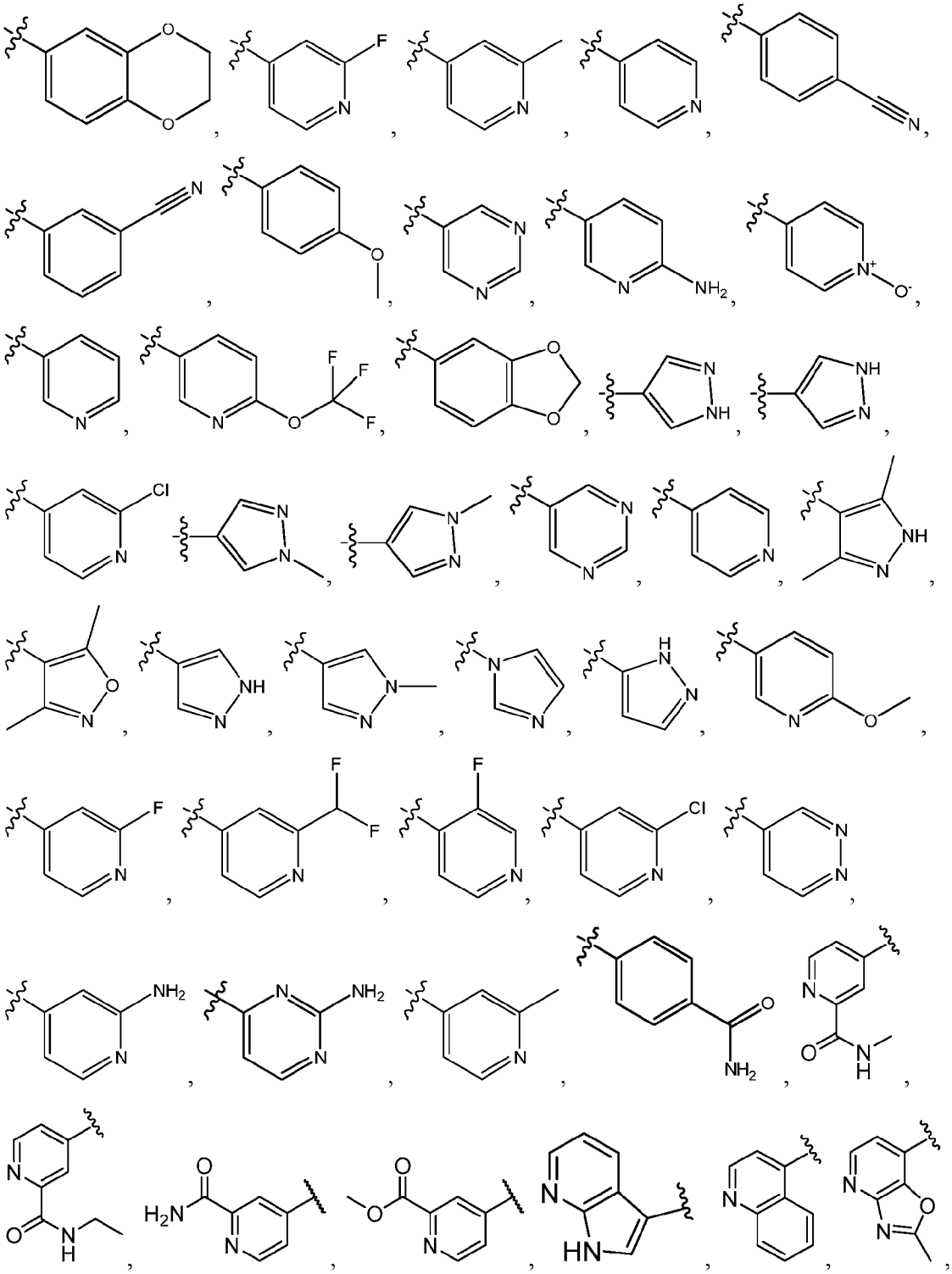
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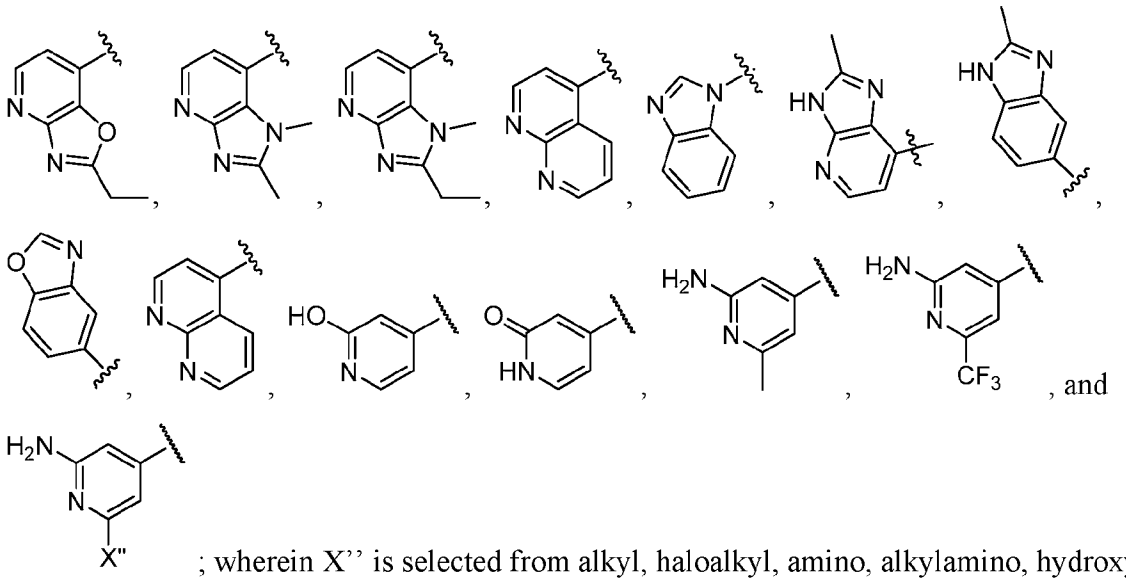
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7. The compound of Claim 1, wherein R2 is selected from hydrogen, halogen (e.g., fluorine, bromine, iodine, chlorine), aryl, substituted aryl, heteroaryl, substituted heteroaryl, ,





; wherein X'' is selected from alkyl, haloalkyl, amino, alkylamino, hydroxy, fluoro, chloro, bromo, and cyano groups.

8. The compound of Claim 6, wherein X', Y', and Z' are independently N, C or CR'.

9. The compound of Claim 6 or Claim 7, wherein R, R', and R" are independently selected from hydrogen, halogen (e.g., fluorine, bromine, chlorine, iodine), di-halogen (di-fluorine, di-bromine, di-chlorine, di-iodine), CF3, OCH3, CHF2H, OCF3, methyl, di-methyl, alkoxy, alkylsulfonyl, cyano, carboxy, ester, amido, substituted amido, sulfonamide, substituted sulfonamide, methylenedioxy, heterocyclyl alkyl, heterocyclyl, heterocyclyl alkyl amido, a lipophilic moiety comprising ether.

10. The compound of Claim 6 or Claim 7, wherein R3 is selected from hydrogen, halogen (e.g., fluorine, bromine, chlorine, iodine), methyl, ethyl, and methoxy.

11. The compound of Claim 1, wherein said compound is selected from the group of compounds recited in Table 1 and/or Compounds 1-67 recited in Example I.

12. A pharmaceutical composition comprising a compound of Claim 1.

13. A method of treating, ameliorating, or preventing a disorder related to one or more of DYRK1A activity, DYRK1B activity, DYRK2 activity, DYRK3 activity, CLK1 activity, CLK2 activity, CLK3 activity, CLK4 activity, CDK7 activity, CDK8/19 activity, PI3K activity, PDGFrA/B activity, mTOR activity, WNT signaling activity, HIPK activity, and CMGC kinase activity leading to inhibition of WNT signaling, in a patient comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition of Claim 12.

14. The method of Claim 13, wherein said disorder is selected from Alzheimer's disease, down syndrome, diabetes, autoimmune diseases, inflammatory disorders (e.g., airway inflammation, osteoarthritis (e.g., knee related osteoarthritis)), cancer (e.g., glioblastoma, prostate cancer, metastatic breast cancer, metastatic lung cancer, multiple myeloma, secondary metastatic tumors of the brain, colorectal cancer and metastatic colorectal cancer (e.g., metastatic colorectal cancer in the liver)), and other diseases.

15. The method of Claim 13, wherein said patient is a human patient.

16. The method of Claim 13, further comprising administering to said patient one or more agents for treating Alzheimer's disease, down syndrome, diabetes, autoimmune diseases, inflammatory disorders (e.g., airway inflammation, osteoarthritis (e.g., knee related osteoarthritis)), cancer (e.g., glioblastoma, prostate cancer, metastatic breast cancer, metastatic lung cancer, multiple myeloma, secondary metastatic tumors of the brain, colorectal cancer and metastatic colorectal cancer (e.g., metastatic colorectal cancer in the liver)), and other diseases.

17. A kit comprising a compound of Claim 1 and instructions for administering said compound to a patient having a disorder related to one or more of DYRK1A activity, DYRK1B activity, DYRK2 activity, DYRK3 activity, CLK1 activity, CLK2 activity, CLK3 activity, CLK4 activity, CDK7 activity, CDK8/19 activity, PI3K activity, PDGFrA/B activity, mTOR activity, WNT signaling activity, HIPK activity, and CMGC kinase activity leading to inhibition of WNT signaling.

18. The kit of Claim 17, wherein the disorder is Alzheimer's disease, down syndrome, diabetes, autoimmune diseases, inflammatory disorders (e.g., airway inflammation, osteoarthritis (e.g., knee related osteoarthritis)), cancer (e.g., glioblastoma, prostate cancer, metastatic breast cancer, metastatic lung cancer, multiple myeloma, secondary metastatic tumors of the brain, colorectal cancer and metastatic colorectal cancer (e.g., metastatic colorectal cancer in the liver)), and other diseases.

19. The kit of Claim 17, further comprising one or more agents for treating Alzheimer's disease, down syndrome, diabetes, autoimmune diseases, inflammatory disorders (e.g., airway inflammation, osteoarthritis (e.g., knee related osteoarthritis)), cancer (e.g., glioblastoma, prostate cancer, metastatic breast cancer, metastatic lung cancer, multiple myeloma, secondary metastatic tumors of the brain, colorectal cancer and metastatic colorectal cancer (e.g., metastatic colorectal cancer in the liver)), and other diseases.

20. A method for inhibiting one or more of DYRK1A activity, DYRK1B activity, DYRK2 activity, DYRK3 activity, CLK1 activity, CLK2 activity, CLK3 activity, CLK4 activity, CDK7 activity, CDK8/19 activity, PI3K activity, PDGFrA/B activity, mTOR activity, WNT signaling activity, HIPK activity, and CMGC kinase activity leading to inhibition of WNT signaling in a subject, comprising administering to the subject a compound of Claim 1.

21. The method of Claim 20, wherein administration of the compound results in inhibition of one or more of

DYRK1A activity;
DYRK1A related PI3K/Akt signaling;
DYRK1A related tau phosphorylation;
DYRK1A related NFAT phosphorylation;
DYRK1A related ASK1/JNK1 pathway activation;
DYRK1A related p53 phosphorylation;
DYRK1A related Amph 1 phosphorylation;
DYRK1A related Dynamin 1 phosphorylation;
DYRK1A related Synaptojanin phosphorylation;

DYRK1A related presenilin 1 (the catalytic sub-unit of γ-secretase) activity;
DYRK1A related amyloid precursor protein phosphorylation;
DYRK1A related SIRT1 activation;
DYRK2 related heat shock factor 1 and 26S proteasome activities;
DYRK3 related mTOR activity;
DYRK3 phosphorylation (e.g., PRAS40);
DYRK1B activity;
CMGC/CLK kinase activity;
CLK1 activity;
CLK2 activity;
CLK3 activity;
CLK4 activity;
CDK7 activity;
CDK8 activity;
CDK19 activity;
CDK8/19 activity;
PI3K activity;
PI3K mutant activity;
PDGFrA/B activity;
mTOR activity;
c-KIT activity;
RYK activity; and
WNT signaling.

22. The method of Claim 20, wherein the subject is human subject suffering from or at risk for developing a disorder related to DYRK1A activity, DYRK1B activity, DYRK2 activity, DYRK3 activity, CLK1 activity, CLK2 activity, CLK3 activity, CLK4 activity, CDK7 activity, CDK8/19 activity, PI3K activity, PDGFrA/B activity, mTOR activity, WNT signaling activity, HIPK activity, and CMGC kinase activity leading to inhibition of WNT signaling.

23. The method of Claim 20, wherein the disorder is Alzheimer's disease, down syndrome, diabetes, autoimmune diseases, inflammatory disorders (e.g., airway inflammation, osteoarthritis (e.g., knee related osteoarthritis)), cancer (e.g., glioblastoma, prostate cancer, metastatic breast cancer, metastatic lung cancer, multiple myeloma, secondary metastatic tumors of the brain, colorectal cancer and metastatic colorectal cancer (e.g., metastatic colorectal cancer in the liver)), and other diseases.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/025973

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - INV. - C07D 487/04; A61P 25/28, 29/00, 3/10, 35/04, 37/00; C07D 403/14, 413/14, 417/14 (2023.01)
ADD.

CPC - INV. - C07D 487/04; A61P 25/28, 29/00, 3/10, 35/04, 37/00; C07D 403/14, 413/14, 417/14 (2023.08)
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)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic database consulted during the international search (name of database and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CAMPOS et al., Review on the Synthesis and Therapeutic Potential of Pyrido[2,3-d], [3,2-d], [3,4-d] and [4,3-d]pyrimidine Derivatives, Pharmaceuticals, Vol. 15, No. 352, 14 March 2022 [retrieved on 26 October 2023]. Retrieved from the Internet: <URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8949896/>. Pgs. 1-27	1-7, 12
A	US 2020/0039989 A1 (ARIZONA BOARD OF REGENTS ON BEHALF OF THE UNIVERSITY OF ARIZONA) 06 February 2020 (06.02.2020) entire document	1-7, 12-23
A	SMITH et al., Recent Advances in the Design, Synthesis, and Biological Evaluation of Selective DYRK1A Inhibitors: A New Avenue for a Disease Modifying Treatment of Alzheimer's?, ACS Chemical Neuroscience, Vol. 3, 28 August 2012 [retrieved on 30 October 2023]. Retrieved from the Internet: <URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3503344/>. Pgs. 857-872	1-7, 12-23

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 October 2023	DEC 11 2023
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Taina Matos Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/025973

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.:
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:

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:

See extra sheet(s).

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 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.:

1-7, 12-23

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/025973

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-23 are drawn to compounds of Formula I, pharmaceutical compositions thereof, methods of treating, ameliorating, or preventing a disorder thereof, kits thereof, and methods for inhibiting thereof.

The first invention of Group I+ is restricted to a compound encompassed within the following formula: including a pharmaceutically acceptable salt, solvate, and/or prodrugs thereof, wherein each of X, Y, R1 and R2 independently include any moiety that permits the resulting compound to inhibit DYRK1A, where the X substituent adjacent to the ring nitrogen atom is carbon, and the other X substituent is nitrogen; each Y substituent directly adjacent to the ring carbon atom containing the R2 substituent is independently carbon, and the remaining Y substituent is nitrogen; R1 is hydrogen; and R2 is hydrogen; pharmaceutical compositions thereof; methods of treating, ameliorating, or preventing a disorder thereof; kits thereof; and methods for inhibiting thereof. The first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Specifically, the first named invention was selected based on the first listed element for each of the variables presented in the claims (X, Y – claim 4; R1 – claim 6; R2 – claim 7). It is believed that claims 1-7 and 12-23 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound encompassed within the following formula: including a pharmaceutically acceptable salt, solvate, and/or prodrugs thereof, wherein each of X, Y, R1 and R2 independently include any moiety that permits the resulting compound to inhibit DYRK1A, where the X substituent adjacent to the ring nitrogen atom is nitrogen, and the other X substituent is carbon; each Y substituent directly adjacent to the ring carbon atom containing the R2 substituent is independently carbon, and the remaining Y substituent is nitrogen; R1 is hydrogen; and R2 is hydrogen; pharmaceutical compositions thereof; methods of treating, ameliorating, or preventing a disorder thereof; kits thereof; and methods for inhibiting thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables X, Y, R1, and R2 and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of a compound having a core formula: including a pharmaceutically acceptable salt, solvate, and/or prodrugs thereof; a pharmaceutical composition comprising a compound; a method of treating, ameliorating, or preventing a disorder related to one or more of DYRK1A activity, DYRK1B activity, DYRK2 activity, DYRK3 activity, CLK1 activity, CLK2 activity, CLK3 activity, CLK4 activity, CDK7 activity, CDK8/19 activity, PI3K activity, PDGFrA/B activity, mTOR activity, WNT signaling activity, HIPK activity, and CMGC kinase activity leading to inhibition of WNT signaling in a patient comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition; a kit comprising a compound and instructions for administering said compound to a patient having a disorder related to one or more of DYRK1A activity, DYRK1B activity, DYRK2 activity, DYRK3 activity, CLK1 activity, CLK2 activity, CLK3 activity, CLK4 activity, CDK7 activity, CDK8/19 activity, PI3K activity, PDGFrA/B activity, mTOR activity, WNT signaling activity, HIPK activity, and CMGC kinase activity leading to inhibition of WNT signaling; and a method for inhibiting one or more of DYRK1A activity, DYRK1B activity, DYRK2 activity, DYRK3 activity, CLK1 activity, CLK2 activity, CLK3 activity, CLK4 activity, CDK7 activity, CDK8/19 activity, PI3K activity, PDGFrA/B activity, mTOR activity, WNT signaling activity, HIPK activity, and CMGC kinase activity leading to inhibition of WNT signaling in a subject, comprising administering to the subject a compound, these shared technical features do not represent a contribution over the prior art as disclosed by US 2020/0039989 A1 to Arizona Board of Regents on Behalf of the University of Arizona.

US 2020/0039989 A1 to Arizona Board of Regents on Behalf of the University of Arizona teaches a compound having a core formula: including a pharmaceutically acceptable salt, solvate, and/or prodrugs thereof (Pg. 22, Table 1-continued, Compound 46, see shown structure); a pharmaceutical composition comprising a compound (Para. [0037], pharmaceutical compositions comprising the compounds of the invention); a method of treating, ameliorating, or preventing a disorder related to one or more of DYRK1A activity, DYRK1B activity, DYRK2 activity, DYRK3 activity, CLK1 activity, CLK2 activity, CLK3 activity, CLK4 activity, CDK7 activity, CDK8/19 activity, PI3K activity, PDGFrA/B activity, mTOR activity, WNT signaling activity, HIPK activity, and CMGC kinase activity leading to inhibition of WNT signaling in a patient comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition (Claim 23, method of treating, ameliorating, or preventing a disorder related to DYRK1A activity in a patient comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition; Claim 33, subject is human subject suffering from or at risk for developing a disorder related to DYRK1A activity); a kit comprising a compound and instructions for administering said compound to a patient having a disorder related to one or more of DYRK1A activity, DYRK1B activity, DYRK2 activity, DYRK3 activity, CLK1 activity, CLK2 activity, CLK3 activity, CLK4 activity, CDK7 activity, CDK8/19 activity, PI3K activity, PDGFrA/B activity, mTOR activity, WNT signaling activity, HIPK activity, and CMGC kinase activity leading to inhibition of WNT signaling (Para. [0038], kits comprising a compound of the invention and instructions for administering the compound to an animal; Claim 33, subject is human subject suffering from or at risk for developing a disorder related to DYRK1A activity); and a method for inhibiting one or more of DYRK1A activity, DYRK1B activity, DYRK2 activity, DYRK3 activity, CLK1 activity, CLK2 activity, CLK3 activity, CLK4 activity, CDK7 activity, CDK8/19 activity, PI3K activity, PDGFrA/B activity, mTOR activity, WNT signaling activity, HIPK activity, and CMGC kinase activity leading to inhibition of WNT signaling in a subject, comprising administering to the subject a compound (Claim 30, method for inhibiting DYRK1A related activity in a subject, comprising administering to the subject a compound).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.