

TREATMENT OF CANCER WITH A CDK INHIBITOR**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit of US Patent Application No. 63/515,752, filed on July 26, 2023; and US Patent Application No. 63/554,735, filed on February 16, 2024, each of which is hereby incorporated by reference in its entirety.

BACKGROUND

[0002] Cyclin-dependent kinases (CDKs) are a conserved family of proline-directed serine/threonine kinases that perform critical roles in the regulation of cell division and proliferation. Dysregulation of CDK2, CDK4 and CDK6 (CDK2/4/6) has been demonstrated to be a key driver of many cancers, and inhibition of CDK2/4/6 has become a validated treatment modality in some disease, such as breast cancer. Accordingly, therapies that target CDK2/4/6 kinase activity are desired for use in the treatment of cancer and other disorders characterized by aberrant CDK2/4/6 pathway signaling.

BRIEF SUMMARY

[0003] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.

[0004] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.

[0005] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.

[0006] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.

[0007] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-

hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile, or pharmaceutically acceptable salt or solvate thereof.

[0008] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile, or pharmaceutically acceptable salt or solvate thereof.

[0009] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.

[0010] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.

[0011] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.

[0012] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.

[0013] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.

[0014] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.

[0015] Another embodiment provides the method wherein the cancer is selected from the group consisting of breast cancer, ovarian cancer, fallopian tube cancer, primary peritoneal cancer (PPC), bladder cancer, uterine cancer, prostate cancer, lung cancer, non-small-cell lung cancer, (NSCLC), small-cell lung cancer (SCLC), squamous cell carcinoma, adenocarcinoma,

mesothelioma, esophageal cancer, head and neck cancer, head and neck squamous cell carcinoma (HNSCC), colorectal cancer (CRC), kidney cancer, renal cell carcinoma (RCC), liver cancer, hepatocellular carcinoma (HCC), pancreatic cancer, stomach cancer, gastric cancer, endometrial cancer, sarcoma, liposarcoma, osteosarcoma, primary brain tumors, high grade and low grade glioma, glioblastoma, thyroid cancer, hematologic cancer, acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), lymphoma, myeloma, neuroblastoma, Ewings sarcoma, osteosarcoma, and Wilms tumor.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] Fig. 1A and Fig. 1B illustrates the results of WM3629 (Class III BRAF mutant/CDK4 sensitive melanoma) cell line derived xenograft following treatment with Compound 1.

[0017] Fig. 2 illustrates the pharmacodynamic biomarker pRB modulation in WM3629 (Class III BRAF mutant/CDK4 sensitive melanoma) cell line derived xenograft tumors following 3 days of Compound 1 TID treatment.

INCORPORATION BY REFERENCE

[0018] All publications, patents, and patent applications mentioned in this specification are hereby incorporated by reference for the specific purposes identified herein.

DETAILED DESCRIPTION

Certain Terminology

[0019] As used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a plurality of such agents, and reference to "the cell" includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and sub-combinations of ranges and specific embodiments therein are intended to be included. The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range, in some instances, will vary between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, "consist of" or "consist essentially of" the described features.

[0020] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[0021] "Pharmaceutically acceptable salt" includes both acid and base addition salts. A pharmaceutically acceptable salt of the heterocyclic CDK2/4/6 inhibitor described herein is intended to encompass any and all pharmaceutically suitable salt forms. Preferred pharmaceutically acceptable salts of the compounds described herein are pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts.

[0022] "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid, hydrofluoric acid, phosphorous acid, and the like. Also included are salts that are formed with organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy alkanolic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. and include, for example, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Exemplary salts thus include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, nitrates, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, trifluoroacetates, propionates, caprylates, isobutyrate, oxalates, malonates, succinate suberates, sebacates, fumarates, maleates, mandelates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, phthalates, benzenesulfonates, toluenesulfonates, phenylacetates, citrates, lactates, malates, tartrates, methanesulfonates, and the like. Also contemplated are salts of amino acids, such as arginates, gluconates, and galacturonates (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science*, 66:1-19 (1997)). Acid addition salts of basic compounds are, in some embodiments, prepared by contacting the free base forms with a sufficient amount of the desired acid to produce the salt according to methods and techniques with which a skilled artisan is familiar.

[0023] "Pharmaceutically acceptable base addition salt" refers to those salts that retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Pharmaceutically acceptable base addition salts are, in some embodiments, formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Salts derived

from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, for example, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, *N,N*-dibenzylethylenediamine, chloroprocaine, hydrabamine, choline, betaine, ethylenediamine, ethylenedianiline, *N*-methylglucamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. See Berge et al., *supra*.

[0024] "Pharmaceutically acceptable solvate" refers to a composition of matter that is the solvent addition form. In some embodiments, solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are formed during the process of making with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of compounds described herein are conveniently prepared or formed during the processes described herein. The compounds provided herein optionally exist in either unsolvated as well as solvated forms.

[0025] The term "subject" or "patient" encompasses mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one aspect, the mammal is a human.

[0026] As used herein, "treatment" or "treating," or "palliating" or "ameliorating" are used interchangeably. These terms refer to an approach for obtaining beneficial or desired results including but not limited to therapeutic benefit and/or a prophylactic benefit. By "therapeutic benefit" is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient is still afflicted with the underlying disorder. For prophylactic benefit, the compositions are, in some embodiments, administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease has not been made. The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. In some embodiments, the term "treating"

includes slowing or delaying the progression of the disease or disorder to which the term is applied. Additionally, in some embodiments, the term “treating” is applied to one or more of the complications resulting from the disease or disorder to which the term is applied. The term “treatment”, as used herein, unless otherwise indicated, refers to the act of treating as “treating” is defined immediately above.

[0027] The term “tumor,” or “cancer” as used herein, and unless otherwise specified, refers to a neoplastic cell growth, and includes pre-cancerous and cancerous cells and tissues. Tumors usually present as a lesion or lump. As used herein, “treating” a tumor means that one or more symptoms of the disease, such as the tumor itself, vascularization of the tumor, or other parameters by which the disease is characterized, are reduced, ameliorated, inhibited, placed in a state of remission, or maintained in a state of remission. “Treating” a tumor also means that one or more hallmarks of the tumor may be eliminated, reduced or prevented by the treatment. Non-limiting examples of such hallmarks include uncontrolled degradation of the basement membrane and proximal extracellular matrix, migration, division, and organization of the endothelial cells into new functioning capillaries, and the persistence of such functioning capillaries.

[0028] The term “refractory” or “refractory to therapy” indicates that the patients have never responded to therapy.

[0029] The term “relapsed” or “relapsed after therapy” indicates that patients, after initially responding to prior therapy, have progressive disease due to acquired resistance and/or intolerance.

[0030] The term “resistance to therapy” or “acquired resistance to therapy” indicates the patients, after initially responding to prior therapy, have progressive disease due to clinical or molecular resistance to the therapy. The acquired resistance can result from emergence of resistant mutations in the molecular target of the therapy, or in the development of physiological functions such as efflux pumps.

[0031] The phrase “therapeutically effective amount”, as used herein, refers to that amount of drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor or other.

[0032] Other aspects, advantages, and features of the invention will become apparent from the detailed description below.

CDK2/4/6 Kinase

[0033] Cyclin-dependent kinases (CDKs) are a conserved family of proline-directed serine/threonine kinases that perform critical roles in the regulation of cell division and

proliferation. CDKs are members of the CMGC kinase family, which encompasses 63 family members including mitogen-activated protein kinase (MAPK), glycogen synthase kinase (GSK) and CDC-like kinase (CLK). The activity of CDKs is regulated through phosphorylation by interaction with cyclin proteins and other upstream kinases such as CDK-activating kinases (CAKs). At least 21 CDKs have been identified to date, including CDK1, 2, 4, and 6 (which regulate the transition of the cell cycle steps), CDK7, 8, 9, 12 and 13 (which regulate gene transcription through phosphorylation of the heptad repeats that comprise the C-terminal tail of RNA polymerase II), and CDK3 (which regulates the transition from G0 (quiescence) into G1 phase of cell division). CDKs regulate the transition between the four distinct phases of the eukaryotic cell cycle, i.e., the G1, S (DNA synthesis), G2 and M phases. Furthermore, CDKs are implicated in the progression of many different types of cancer. In particular, dysregulation of CDK4 and CDK6 (CDK4/6) has been demonstrated to be a key driver of many cancers, and inhibition of CDK4/6 has become a validated treatment modality in some diseases, such as breast cancer.

[0034] Structurally, CDK4 and 6 have a bilobal structure typically seen in other kinases, comprising a 5-stranded β -sheet on the N-terminal side of the protein and a predominantly helical C-terminal domain. The ATP binding site is located in the cleft between the domains. Although a structure for a CDK6 with its primary cyclin partner (cyclin D) has not yet been determined, the crystal structure of CDK6 bound to a viral cyclin has been solved and provides some structural insight to the function of CDK6. Furthermore, the structures of non-phosphorylated and phosphorylated CDK4 bound to cyclin D3 or cyclin D1 have been solved. The kinase binding sites of CDK4 and 6 are highly conserved and the structural similarity between these kinases is likely the reason that highly selective ATP-competitive inhibitors of both CDK4 and CDK6 (CDK4/6 inhibitors) have been developed.

[0035] CDK4 and CDK6 associate with the D-type cyclins, activating the CDK4/6 and causing them to phosphorylate and inactivate the retinoblastoma (Rb) protein family members. Cyclin D possesses a tertiary structure that is common to other cyclins, known as the cyclin fold. The cyclin fold contains a core of two compact domains, with each domain having five alpha helices. The first five-helix bundle is a conserved cyclin box, a region of about 100 amino acid residues shared by all cyclins. The cyclin box functions by binding to and activating CDKs. The second five-helix bundle is composed of the same arrangement of helices but comprises several differences in the primary sequence. All three D-type cyclins (D1, D2, D3) share a common alpha 1 helix hydrophobic patch, and each of these D-type cyclins bind to and activate CDK4 and 6, leading to cell cycle progression.

Cell Cycle

[0036] The eukaryotic cell division cycle is divided into two basic parts: mitosis and interphase. Mitosis (nuclear division) corresponds to the separation of daughter chromosomes and usually ends with cell division (cytokinesis). The period between mitoses is interphase, which generally accounts for approximately 95% of the cell cycle time (e.g., 23 hours of a 24-hour cycle).

During interphase, the chromosomes are decondensed and distributed throughout the nucleus, and the cell prepares itself for mitosis by regulating both cell growth and DNA replication. The cell grows at a steady rate throughout interphase, with most dividing cells doubling in size between mitosis cycles. In contrast, DNA is synthesized during only a relatively short portion of interphase.

[0037] The timing of the cycle of eukaryotic cells into four discrete phases is based on DNA synthesis and cell division. The M phase of the cycle corresponds to mitosis, which is usually followed by cytokinesis (cell division). This phase is followed by the G1 phase (gap 1), which corresponds to the interval between mitosis and initiation of DNA synthesis. During G1, the cell is metabolically active and continuously grows but does not replicate its DNA. Following G1, the cell enters the S phase (synthesis phase), during which DNA replication takes place. After completion of DNA synthesis, the cell contains two identical chromosome sets and enters the G2 phase (gap 2) of cell division. During the G2 phase, the cell continues to grow, and proteins are synthesized in preparation for the next round of mitosis (i.e., the next M cycle).

[0038] In some cell types, including many embryonic cells, cell division is perpetual, and the cells continuously cycle between the M, G1, S, and G2 phases. In contrast, many cells in adult animals either cease division altogether (e.g., nerve cells) or divide only as needed to replace cells that have been lost due to injury. Such intermittently dividing cells include skin fibroblasts and cells of many internal organs, including the liver, kidney, and lung. Such cells exit G1 to enter a quiescent stage of the cycle called G0, where they remain metabolically active but no longer proliferate unless called on to do so by appropriate extracellular signals, such as those resulting from an injury to the local tissue. However, in cancer, a relatively large subpopulation of the cells remain cycling through the four phases of cell division, driving tumor proliferation and disease progression.

[0039] To enter the cell cycle, a cell must progress from G1 to S phase via a restriction point, and most cells will only do so in the presence of the appropriate growth factors. Once the cell has passed through the restriction point, the cell is committed to proceed through S phase and the rest of the cell cycle, even in the absence of further growth factor stimulation. However, if appropriate growth factors are not available in G1, progression through the cell cycle generally stops at the restriction point, and the cell will enter G0 (the quiescent stage) until a signal is

received to resume cell division. The transition from G1 to S phase is mediated in part by the retinoblastoma protein (RB), which is usually regulated through a delicate balance of pro- and anti-mitotic signals. In healthy cells, the balance of pro- and anti-mitotic signals is tightly regulated, and specific mitogenic signals (e.g., growth factors) are necessary for normal cells to enter the cell division cycle.

Cell Signaling Networks

[0040] CDK4 and 6 are directly involved with mediating the transition from the G1 to S phase, with activated CDK4/6 initiating a downstream pathway that advances the cell into the S phase of cell division. According to the “classical” cell cycle model, the G1/S transition begins in early G1 when the balance between mitogenic stimulation (via growth factor receptor activation) and inhibition tips in favor of the former, triggering an increase in the levels of D-type cyclins (D1, D2, and D3). The expression level of the D type cyclins is controlled by growth factor signaling, with the transcription, turnover and nuclear transport of D type cyclins all dependent on this signaling. D-type cyclins bind to CDK4 or CDK6, and the cyclin-CDK complexes subsequently enter the nucleus where the cyclin-CDK complexes are phosphorylated by the CDK-activating kinase (CAK) complex.

[0041] Once activated, CDK4/6 complexes phosphorylate the retinoblastoma (RB) tumor suppressor protein, as well as the related p107 and p130 proteins. RB phosphorylation by CDK4/6 partially inhibits activity of the E2F family of transcription factors, which, in turn, increases the expression of E2F target genes including those for the E-type cyclins (cyclins E1 and E2). Cyclin E then binds to and activates CDK2, which hyper-phosphorylates RB. Hyper-phosphorylation of RB further increases the expression of E2F target genes, which are critical for initiation of DNA synthesis and entry into S-phase. This creates a positive feedback loop, as the E2Fs promote transcription of the E type cyclins, activating CDK2 and other proteins important for initiation of S phase and DNA synthesis.

[0042] Regulation of CDK4/6 is primarily achieved by two families of endogenous inhibitory proteins. The first is the INK4 family, comprising the p16INK4A, p15INK4B, p18INK4C, and p19INK4D proteins, which bind to CDKs 4 and 6, forming binary complexes that lack kinase activity. The second is the CIP/KIP family, which includes p27KIP1, p21CIP1, and p57KIP2. These proteins bind to a variety of CDKs having more diverse functions, potently inhibiting a number of CDKs (including CDK4/6, CDK2, and CDK1). However, in some circumstances, these proteins bind to and stabilize the cyclin D-CDK4/6 holoenzyme. These divergent functions may be regulated by the extent of phosphorylation of the CIP/KIP proteins.

Prior Art CDK4/6 Kinase Inhibitors

[0043] Several CDK inhibitors have been developed and tested in many different types of cancer. The first generation of CDK inhibitors, including flavopiridol (inhibitor of at least CDKs 1, 2, 4, and 9 inhibitor) and roscovitine (inhibitor of at least CDKs 1, 2, 5, 7, and 9), were pan inhibitors that acted on several kinases. These first-generation CDK inhibitors had limited clinical success due to an inadequate balance between efficacy and toxicity. The second generation of inhibitors, such as dinaciclib (inhibitor of CDKs 1, 2, 5, and 9) were developed with the aim to increase potency and selectivity for CDKs over other kinases. However, these compounds demonstrated limited efficacy and considerable toxicity in clinical studies. The toxicity of these compounds results from their broad-spectrum activity against numerous CDK isoforms, including CDK1 and CDK9, which are required for the proliferation (CDK1) and survival (CDK9) of normal cells. More recently, selective CDK4/6 inhibitors have been developed, which exhibit more targeted action on tumor cells and reduced toxicity. This third generation of CDK inhibitors selectively inhibit CDK4 and CDK6 with potent efficacy and reduced toxicity, selectively binding to the CDK4/6 ATP-binding pockets.

[0044] To date, three CDK4/6 inhibitors have received FDA approval for use in oncology: palbociclib, ribociclib, and abemaciclib. Additionally, trilaciclib is approved for the treatment of chemotherapy induced myelosuppression. Palbociclib received accelerated FDA approval in 2015 in combination with letrozole for the treatment of estrogen receptor positive (ER+) advanced breast cancer. In 2017, palbociclib in combination with an aromatase inhibitor received full FDA approval for use in hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer. Ribociclib was approved in 2017 for use in combination with an aromatase inhibitor (such as letrozole) to treat HR-positive, HER2-negative advanced or metastatic breast cancers. Abemaciclib was FDA approved in 2017 for use as a monotherapy or in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. In 2018 abemaciclib received a second approval for use in combination with an aromatase inhibitor as an initial endocrine based therapy for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. More recently, in 2021, abemaciclib was approved in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer.

[0045] The development of selective CDK4/6 inhibitor agents has radically changed the approach to managing this disease hormone receptor-positive, HER2-negative advanced breast cancer, approximately doubling the progression-free survival (PFS) for most patients. However, resistance to CDK4/6 inhibitors is considered to be nearly inevitable in most patients. Although mechanisms of resistance to these agents are multifactorial and research in this field is ongoing, several mechanisms of resistance to CDK 4/6 inhibitors have been identified to date.

[0046] First, overexpression of CDK6 (and potentially CDK4) is a major mechanism of resistance to CDK4/6 inhibitors. Studies in human cell lines have shown that increased expression of CDK6 reduced the response of CDK4/6 inhibitors, and subsequent knockdown of CDK6 rescued the therapy sensitivity, indicating that CDK6-mediated drug resistance may be independent of CDK4 expression. However, both increased and decreased expression of CDK4 has been detected in CDK4/6 inhibitor-resistant breast cancer cells, indicating that the role of CDK4 expression in CDK4/6 inhibitor resistance requires further investigation. Second, loss of Rb has been implicated as a driver of resistance to CDK4/6 inhibitors in several preclinical studies. Without the inhibitory influence of Rb, transcription factors of the E2F family continue unchecked, thus facilitating unregulated cellular progression to S-phase entry independently of CDK4/6 activity. Acquired CDK4/6 inhibitor resistance due to RB1 mutations has been identified in several patients treated with CDK 4/6 inhibitors. Third, decrease in cyclin D1 expression can lead to CDK4/6 inhibitor resistance. Cyclin D1 expression is regulated by the estrogen receptor (ER), and decreased ER expression results in reduced expression of cyclin D1. In preclinical trials, resistance to abemaciclib was associated with the loss of cyclin D1 and concomitant loss of ER/PR expression. Resistance in these patients may be related to the decrease in cyclin D1 due to the loss of ER. Another mechanism of resistance to CDK4/6 inhibitors occurs through upregulated activity of CDK2, through amplification of cyclin E. Therefore, CDK2/4/6 inhibitors could provide an opportunity to revert the acquired therapeutic resistance observed in clinical CDK4/6 inhibitors. Additional possible mechanisms of action include overexpression of Brk (breast tumor-related kinase), overexpression of the E2F2 transcription factor, and overexpression of cyclins E1 or E2. Thus, there exists a need for a new generation of CDK inhibitors that are not susceptible to one or more of these resistance mechanisms and provide longer progression-free survival.

Heterocyclic CDK2/4/6 Inhibitors and Prodrugs Thereof

[0047] Described herein are heterocyclic CDK2/4/6 inhibitors and prodrugs thereof disclosed in Table 1.

[0048] Compound 1 was disclosed in International Patent Application No. PCT/US2023/061287, and is a reversible small molecule CDK2/4/6 inhibitor. Also disclosed herein is compound 2 which is the valine ester prodrug of compound 1.

[0049] Compound 3 was disclosed in International Patent Application No. PCT/US2023/061287, and is a reversible small molecule CDK2/4/6 inhibitor. Also disclosed herein is compound 4 which is the valine ester prodrug of compound 3.

[0050] Compound 5 was disclosed in International Patent Application No. PCT/US2023/061287, and is a reversible small molecule CDK2/4/6 inhibitor. Also disclosed herein are compounds 6-10, 15 and 20 which are prodrugs of compound 5.

[0051] Compound 11 is provided herein along with the prodrug compound 12.

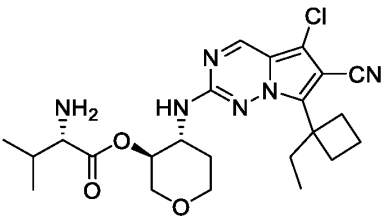
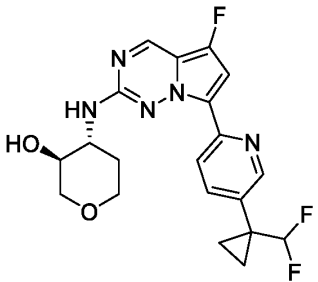
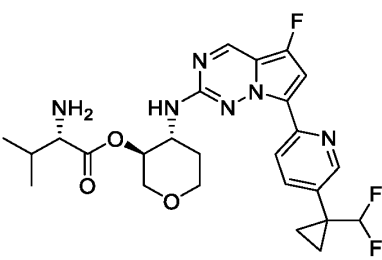
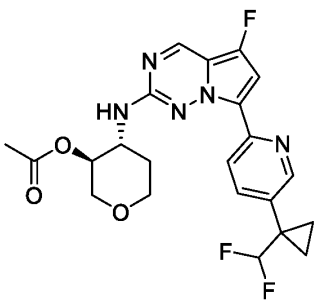
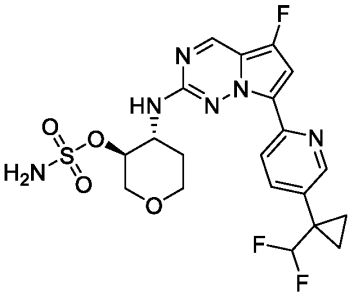
[0052] Compound 13 is provided herein along with the prodrug compound 14.

Compounds 16 and 17 are provided herein and are stereoisomers of compound 13.

[0053] Compound 18 is provided herein along with the prodrug compound 19.

Table 1

Example	Compound Structure	Compound Name	Observed [M + H] ⁺
1		(3 <i>S</i> ,4 <i>R</i>)-4-[(5-fluoro-7-{5-[(2 <i>S</i>)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1- <i>f</i>][1,2,4]triazin-2-yl)amino]oxan-3-ol	426.25
2		(3 <i>S</i> ,4 <i>R</i>)-4-[(5-fluoro-7-{5-[(2 <i>S</i>)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1- <i>f</i>][1,2,4]triazin-2-yl)amino]oxan-3-yl (2 <i>S</i>)-2-amino-3-methylbutanoate	525.25
3		5-chloro-7-(1-ethylcyclobutyl)-2-(((3 <i>S</i> ,4 <i>R</i>)-3-hydroxytetrahydro-2 <i>H</i> -pyran-4-yl)amino)pyrrolo[2,1- <i>f</i>][1,2,4]triazine-6-carbonitrile	376.15

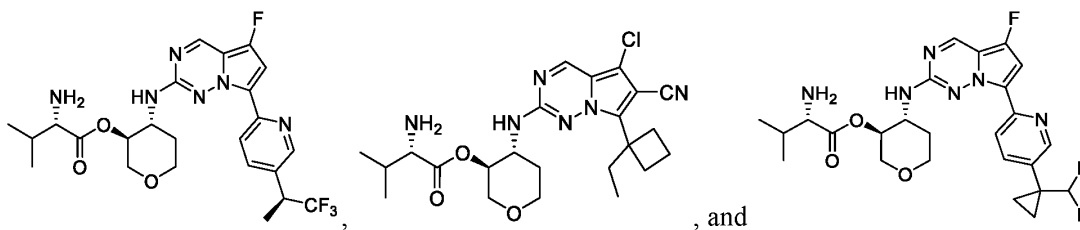
Example	Compound Structure	Compound Name	Observed [M + H] ⁺
4		(3 <i>S</i> ,4 <i>R</i>)-4-{{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-2-yl]amino}oxan-3-yl} (2 <i>S</i>)-2-amino-3-methylbutanoate	475.35
5		(3 <i>S</i> ,4 <i>R</i>)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1- <i>f</i>][1,2,4]triazin-2-yl)amino]oxan-3-ol	420.10
6		(3 <i>S</i> ,4 <i>R</i>)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1- <i>f</i>][1,2,4]triazin-2-yl)amino]oxan-3-yl} (2 <i>S</i>)-2-amino-3-methylbutanoate	519.35
7		(3 <i>S</i> ,4 <i>R</i>)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1- <i>f</i>][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate	462.20
8		(3 <i>S</i> ,4 <i>R</i>)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1- <i>f</i>][1,2,4]triazin-2-yl)amino]oxan-3-yl sulfamate	499.15

Example	Compound Structure	Compound Name	Observed [M + H] ⁺
9		[(3S,4R)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-f][1,2,4]triazin-2-yl)amino]oxan-3-yl]oxyphosphonic acid	500.10
10		(((3S,4R)-4-((7-(5-(1-(difluoromethyl)cyclopropyl)pyridin-2-yl)-5-fluoropyrrolo[2,1-f][1,2,4]triazin-2-yl)amino)tetrahydro-2H-pyran-3-yl)oxy)methyl)phosphonic acid	514.10
11		5-chloro-7-(1-ethylcyclobutyl)-2-{{{(3R,4S)-3-hydroxy-1-methanesulfonylpiperidin-4-yl}amino}}pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile	453.15
12		(3R,4S)-4-{{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-f][1,2,4]triazin-2-yl]amino}}-1-methanesulfonylpiperidin-3-yl(2S)-2-amino-3-methylbutanoate	552.15

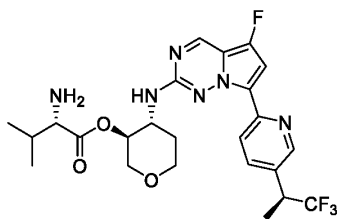
Example	Compound Structure	Compound Name	Observed [M + H] ⁺
13		5-chloro-7-(1-ethylcyclobutyl)- 2-{[(3S,4R)-3-hydroxy-1- methanesulfonylpiperidin-4- yl]amino}pyrrolo[2,1- f][1,2,4]triazine-6-carbonitrile	453.14
14		(3S,4R)-4-{[5-chloro-6-cyano- 7-(1- ethylcyclobutyl)pyrrolo[2,1- f][1,2,4]triazin-2-yl]amino}-1- methanesulfonylpiperidin-3-yl (2S)-2-amino-3- methylbutanoate	552.30
15		(3S,4R)-4-[(7-{5-[1- (difluoromethyl)cyclopropyl]py ridin-2-yl}-5-fluoropyrrolo[2,1- f][1,2,4]triazin-2- yl]amino]oxan-3-yl 2- methylpropanoate	490.20
16		5-chloro-7-(1-ethylcyclobutyl)- 2-{[(3R,4R)-3-hydroxy-1- methanesulfonylpiperidin-4- yl]amino}pyrrolo[2,1- f][1,2,4]triazine-6-carbonitrile	453.25
17		5-chloro-7-(1-ethylcyclobutyl)- 2-{[(3S,4S)-3-hydroxy-1- methanesulfonylpiperidin-4- yl]amino}pyrrolo[2,1- f][1,2,4]triazine-6-carbonitrile	453.30

Example	Compound Structure	Compound Name	Observed [M + H] ⁺
18		5-chloro-7-(1-ethylcyclobutyl)-2-([(3 <i>R</i> ,4 <i>S</i>)-3-hydroxy-1-(trifluoromethanesulfonyl)piperidin-4-yl]amino}pyrrolo[2,1- <i>f</i>][1,2,4]triazine-6-carbonitrile	507.05
19		(3 <i>R</i> ,4 <i>S</i>)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-2-yl]amino}-1-(trifluoromethanesulfonyl)piperidin-3-yl (2 <i>S</i>)-2-amino-3-methylbutanoate	606.45
20		diammonium {[(3 <i>S</i> ,4 <i>R</i>)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1- <i>f</i>][1,2,4]triazin-2-yl]amino]oxan-3-yl]oxy}methyl phosphate	530.20

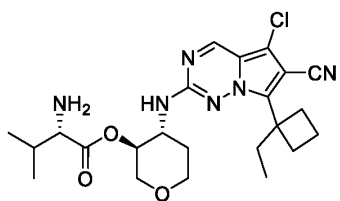
[0054] One embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, selected from the group consisting of:



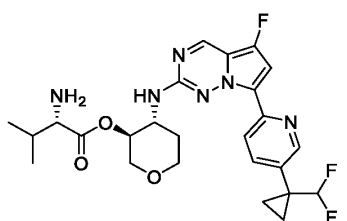
[0055] Another embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



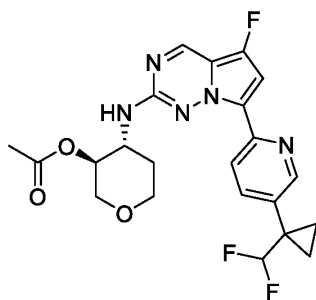
[0056] Another embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



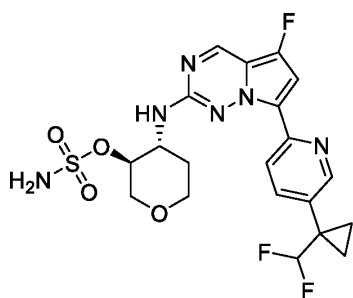
[0057] Another embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



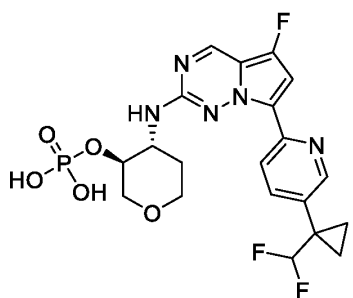
[0058] Another embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



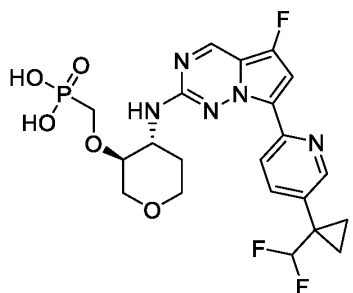
[0059] Another embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



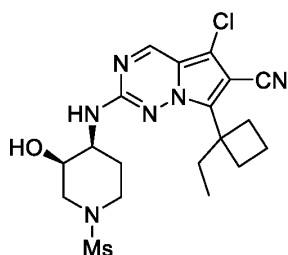
[0060] Another embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



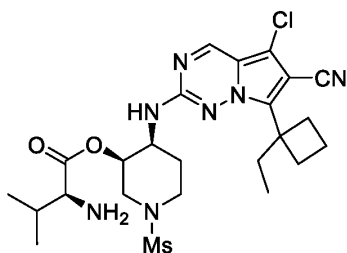
[0061] Another embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



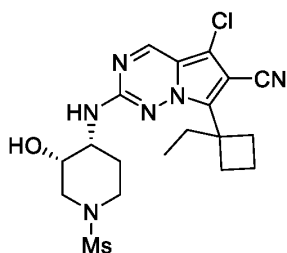
[0062] Another embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



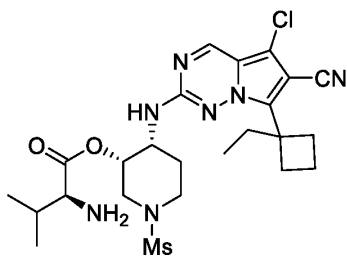
[0063] Another embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



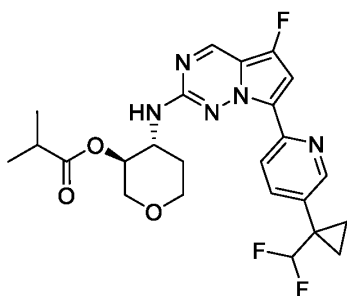
[0064] Another embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



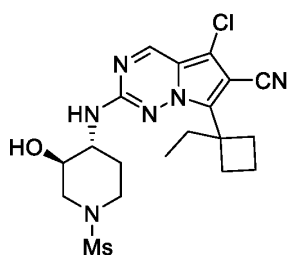
[0065] Another embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



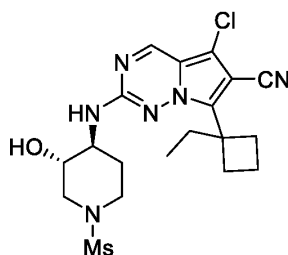
[0066] Another embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



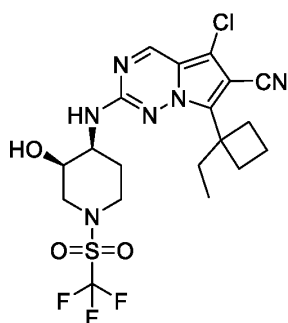
[0067] Another embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



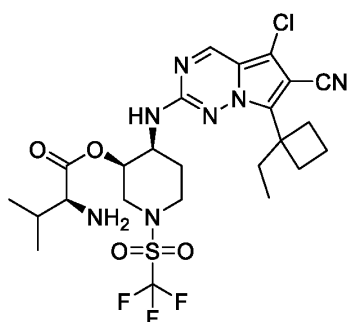
[0068] Another embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



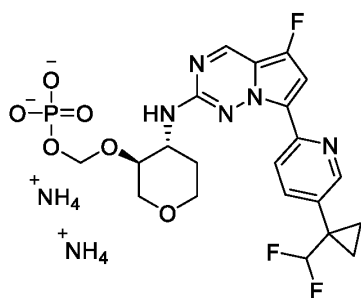
[0069] Another embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



[0070] Another embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



[0071] Another embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



Cancer and Methods of Treatment

[0072] In one embodiment is a method for inhibiting CDK2/4/6 enzyme comprising contacting the CDK2/4/6 enzyme with Compound 1, 3, or 5, as disclosed herein. In one embodiment is a method for inhibiting CDK2/4/6 enzyme comprising contacting the CDK2/4/6 enzyme with Compound 11, 13, 16, 17, or 18, as disclosed herein. In another embodiment the contacting occurs *in vitro*. In another embodiment the contacting occurs *in vivo*.

[0073] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol (compound 1), or pharmaceutically acceptable salt or solvate thereof.

[0074] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol (compound 1), or pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0075] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate (compound 2), or pharmaceutically acceptable salt or solvate thereof.

[0076] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate (compound 2), or pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient..

[0077] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (compound 3), or pharmaceutically acceptable salt or solvate thereof.

[0078] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (compound 3), or pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0079] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-{{5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate (compound 4), or pharmaceutically acceptable salt or solvate thereof.

[0080] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising (3*S*,4*R*)-4-{{5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate (compound 4), or pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0081] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(7-{{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl (compound 5), or pharmaceutically acceptable salt or solvate thereof.

[0082] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising (3*S*,4*R*)-4-[(7-{{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl (compound 5), or pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0083] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(7-{{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl (2*S*)-2-amino-3-methylbutanoate (compound 6), or pharmaceutically acceptable salt or solvate thereof.

[0084] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising (3*S*,4*R*)-4-[(7-{{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-yl (2*S*)-2-amino-3-methylbutanoate (compound 6), or pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0085] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a compound, or pharmaceutically acceptable salt or solvate thereof, selected from the group consisting of:

(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate (compound 7);
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl sulfamate (compound 8);
 [(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl]oxyphosphonic acid (compound 9);
 (((3*S*,4*R*)-4-((7-(5-(1-(difluoromethyl)cyclopropyl)pyridin-2-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-yl)oxy)methyl)phosphonic acid (compound 10);
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl 2-methylpropanoate (compound 15);
 and

diammonium {[(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl]oxy }methyl phosphate (compound 20).

[0086] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient, and a compound, or pharmaceutically acceptable salt or solvate thereof, selected from the group consisting of:

(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate (compound 7);
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl sulfamate (compound 8);
 [(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl]oxyphosphonic acid (compound 9);
 (((3*S*,4*R*)-4-((7-(5-(1-(difluoromethyl)cyclopropyl)pyridin-2-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-yl)oxy)methyl)phosphonic acid (compound 10);
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl 2-methylpropanoate (compound 15);
 and

diammonium {[(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl]oxy }methyl phosphate (compound 20).

[0087] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a compound, or pharmaceutically acceptable salt or solvate thereof, selected from the group consisting of:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3R,4S)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile (compound 11);

(3R,4S)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-f][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl (2S)-2-amino-3-methylbutanoate (compound 12);

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3S,4R)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile (compound 13);

(3S,4R)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-f][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl (2S)-2-amino-3-methylbutanoate (compound 14);

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3R,4R)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile (compound 16);

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3S,4S)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile (compound 17);

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3R,4S)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile (compound 18); and

(3R,4S)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-f][1,2,4]triazin-2-yl]amino}-1-trifluoromethanesulfonylpiperidin-3-yl (2S)-2-amino-3-methylbutanoate (compound 19).

[0088] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient, and a compound, or pharmaceutically acceptable salt or solvate thereof, selected from the group consisting of:

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3R,4S)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile (compound 11);

(3R,4S)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-f][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl (2S)-2-amino-3-methylbutanoate (compound 12);

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3S,4R)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile (compound 13);

(3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl (2*S*)-2-amino-3-methylbutanoate (compound 14);

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (compound 16);

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (compound 17);

5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*S*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (compound 18); and

(3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-trifluoromethanesulfonylpiperidin-3-yl (2*S*)-2-amino-3-methylbutanoate (compound 19).

[0089] Another embodiment provides the method wherein the cancer is selected from the group consisting of breast cancer, ovarian cancer, fallopian tube cancer, primary peritoneal cancer (PPC), bladder cancer, uterine cancer, prostate cancer, lung cancer, non-small-cell lung carcinoma, (NSCLC), small-cell lung carcinoma (SCLC), squamous cell carcinoma, adenocarcinoma, mesothelioma, esophageal cancer, head and neck cancer, head and neck squamous cell carcinoma (HNSCC), colorectal cancer (CRC), kidney cancer, renal cell carcinoma (RCC), liver cancer, hepatocellular carcinoma (HCC), pancreatic cancer, stomach cancer, gastric cancer, endometrial cancer, sarcoma, liposarcoma, osteosarcoma, primary brain tumors, high grade and low grade glioma, glioblastoma, thyroid cancer, hematologic cancer, acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), lymphoma, myeloma, neuroblastoma, Ewings sarcoma, osteosarcoma, and Wilms tumor.

[0090] In some embodiments, the cancer is locally or regionally advanced. In some embodiments, the cancer is a metastatic solid tumors. In some embodiments, the cancer is a metastatic brain tumor.

[0091] In some embodiments, the cancer is NSCLC. In some embodiments, the cancer is adenocarcinoma of NSCLC. In some embodiments, the cancer is prostate cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is liposarcoma.

[0092] In some embodiments, the cancer is breast cancer. In some embodiments, the breast cancer is advanced or metastatic breast cancer. In some embodiments, the breast cancer is locally advanced. In some embodiments, the breast cancer is metastatic breast cancer. In some embodiments, the breast cancer is hormone receptor positive (HR+), i.e., the breast cancer is estrogen receptor positive (ER+) and/or progesterone receptor positive (PR+). In some

embodiments, the breast cancer is hormone receptor negative (HR-), i.e., the breast cancer is estrogen receptor negative (ER-) and/or progesterone receptor negative (PR-). In some embodiments, the breast cancer is human epidermal growth factor receptor 2 negative (HER2-). In some embodiments, the breast cancer is human epidermal growth factor receptor 2 positive (HER2+). In some embodiments, the breast cancer is HR+/HER2- breast cancer. In some embodiments, the breast cancer is HR-/HER2+ breast cancer. In some embodiments, the breast cancer is ER+/HR+. In some embodiments, the breast cancer is ER+/HER2-. In some embodiments, the breast cancer is triple negative breast cancer (TNBC), i.e., the breast cancer is ER-, PR- and HER2-.

[0093] In some embodiments, the breast cancer is endocrine resistant breast cancer, trastuzumab or pertuzumab resistant breast cancer, or breast cancer demonstrating primary or acquired resistance to CDK4/CDK6 inhibition. In some embodiments, the breast cancer is resistant to treatment with a standard of care agent; for example, the breast cancer may demonstrate primary or acquired resistance to endocrine therapy, HER2-targeted agents (e.g., tamoxifen, trastuzumab emtansine, fam-trastuzumab deruxtecan, pertuzumab, lapatinib, neratinib or tucatinib), or CDK4/6 inhibitors. In some embodiments, the subject is refractory to endocrine therapy.

[0094] In some embodiments, the breast cancer is refractory or resistant to treatment with, or has progressed on, treatment with antineoplastic chemotherapeutic agents, such as platinum agents, taxanes, anthracyclines or anti-metabolites.

[0095] In some embodiments, the breast cancer has progressed during treatment or within 12 months of completion of adjuvant therapy with an aromatase inhibitor. In some embodiments, the breast cancer has progressed during treatment or within 12 months of completion of adjuvant therapy with tamoxifen.

[0096] In some embodiments, Compound 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, is administered as first line therapy. In other embodiments, Compound 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, is administered as second (or later) line therapy. In some embodiments, Compound 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, is administered as second (or later) line therapy following treatment with an endocrine therapeutic agent and/or a CDK4/CDK6 inhibitor. In some embodiments, Compound 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, is administered as second (or later) line therapy following treatment with an endocrine therapeutic agent, such as, an aromatase inhibitor; a selective estrogen receptor modulator (SERM), e.g., tamoxifen; or a selective estrogen degrader/downregulator (SERD). In some embodiments, Compound 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, is administered as second (or later) line therapy following treatment with one or more chemotherapy regimens. In some embodiments,

Compound 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, is administered as second (or later) line therapy following treatment with HER2 targeted agents.

[0097] In some embodiments, Compound 3 or 4, or a pharmaceutically acceptable salt or solvate thereof, is administered as first line therapy. In other embodiments, Compound 3 or 4, or a pharmaceutically acceptable salt or solvate thereof, is administered as second (or later) line therapy. In some embodiments, Compound 3 or 4, or a pharmaceutically acceptable salt or solvate thereof, is administered as second (or later) line therapy following treatment with an endocrine therapeutic agent and/or a CDK4/CDK6 inhibitor. In some embodiments, Compound 3 or 4, or a pharmaceutically acceptable salt or solvate thereof, is administered as second (or later) line therapy following treatment with an endocrine therapeutic agent, such as, an aromatase inhibitor; a selective estrogen receptor modulator (SERM), e.g., tamoxifen; or a selective estrogen degrader/downregulator (SERD). In some embodiments, Compound 3 or 4, or a pharmaceutically acceptable salt or solvate thereof, is administered as second (or later) line therapy following treatment with one or more chemotherapy regimens. In some embodiments, Compound 3 or 4, or a pharmaceutically acceptable salt or solvate thereof, is administered as second (or later) line therapy following treatment with HER2 targeted agents.

[0098] In some embodiments, Compound 5 or 6, or a pharmaceutically acceptable salt or solvate thereof, is administered as first line therapy. In other embodiments, Compound 5 or 6, or a pharmaceutically acceptable salt or solvate thereof, is administered as second (or later) line therapy. In some embodiments, Compound 5 or 6, or a pharmaceutically acceptable salt or solvate thereof, is administered as second (or later) line therapy following treatment with an endocrine therapeutic agent and/or a CDK4/CDK6 inhibitor. In some embodiments, Compound 5 or 6, or a pharmaceutically acceptable salt or solvate thereof, is administered as second (or later) line therapy following treatment with an endocrine therapeutic agent, such as, an aromatase inhibitor; a selective estrogen receptor modulator (SERM), e.g., tamoxifen; or a selective estrogen degrader/downregulator (SERD). In some embodiments, Compound 5 or 6, or a pharmaceutically acceptable salt or solvate thereof, is administered as second (or later) line therapy following treatment with one or more chemotherapy regimens. In some embodiments, Compound 5 or 6, or a pharmaceutically acceptable salt or solvate thereof, is administered as second (or later) line therapy following treatment with HER2 targeted agents.

[0099] In some embodiments, a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof, is administered as first line therapy. In other embodiments, a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof, is administered as second (or later) line therapy. In some embodiments, a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof, is administered as second (or later) line therapy following treatment with

an endocrine therapeutic agent and/or a CDK4/CDK6 inhibitor. In some embodiments, a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof, is administered as second (or later) line therapy following treatment with an endocrine therapeutic agent, such as, an aromatase inhibitor; a selective estrogen receptor modulator (SERM), e.g., tamoxifen; or a selective estrogen degrader/downregulator (SERD). In some embodiments, a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof, is administered as second (or later) line therapy following treatment with one or more chemotherapy regimens. In some embodiments, a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof, is administered as second (or later) line therapy following treatment with HER2 targeted agents.

[00100] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof, and an endocrine therapy agent.

[00101] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof, and an endocrine therapy agent.

[00102] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile, or pharmaceutically acceptable salt or solvate thereof, and an endocrine therapy agent.

[00103] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof, and an endocrine therapy agent.

[00104] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof, and an endocrine therapy agent.

[00105] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-

3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof, and an endocrine therapy agent.

[00106] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a compound of Table 1, or pharmaceutically acceptable salt or solvate thereof, and an endocrine therapy agent.

[00107] An "endocrine therapy agent" is a biological (large molecule) or chemical (small molecule) compound useful in the treatment of cancer, regardless of mechanism of action.

[00108] In some embodiments, the endocrine therapy agent is an aromatase inhibitor, an androgen receptor inhibitor, a selective estrogen receptor degrader (SERD), or a selective estrogen receptor modulator (SERM). In some embodiments, the endocrine therapy agent is an androgen receptor inhibitor. In some embodiments, the endocrine therapy agent is an aromatase inhibitor. In some such embodiments, the aromatase inhibitor is selected from the group consisting of letrozole, anastrozole and exemestane. In one embodiment, the aromatase inhibitor is letrozole. In some embodiments, the endocrine therapy agent is a SERD. In some such embodiments, the SERD is selected from the group consisting of fulvestrant, elacestrant (RAO-1901, Radius Health/Menarini), amcenestrant (SAR439859, Sanofi), giredestrant (GOC9545, Roche), RG6171 (Roche), camizestrant (AZO9833, AstraZeneca), AZO9496 (AstraZeneca), rintodestrant (G1 Therapeutics), ZN-c5 (Zentalis), LSZ102 (Novartis), 0-0502 (Inventisbio), LY3484356 (Eli Lilly), and SHR9549 (Jiansu Hengrui Medicine). In some embodiments, the SERD is fulvestrant. In some embodiments, the endocrine therapy agent is a SERM. In some such embodiments, the SERM is selected from the group consisting of tamoxifen, raloxifene, toremifene, lasofoxifene, bazedoxifene and afimoxifene. In some such embodiments, the SERM is tamoxifen or raloxifene. In preferred embodiments, the endocrine therapy agent is letrozole or fulvestrant.

[00109] In some embodiments, the endocrine therapy agent is administered according to the standard of care per package insert or provided by the health care professionals. The term "package insert" refers to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products.

[00110] In certain embodiments, the endocrine therapy agent is administered to the subject during the course of the treatment with any one of Compounds 1-6, or pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the first dose of the endocrine therapy agent is administered prior to administering the first dose of any one of Compounds 1-6, or pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the first dose of the

endocrine therapy agent is administered on the same day as administering the first dose of any one of Compounds 1-6, or pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the first dose of the endocrine therapy agent is administered after the start of the treatment with any one of Compounds 1-6, or pharmaceutically acceptable salt or solvate thereof.

[00111] In certain embodiments, prior to the administration of any one of Compounds 1-6, or pharmaceutically acceptable salt or solvate thereof, to the subject, the subject has been previously treated with one or more lines of endocrine therapy.

[00112] In certain embodiments, prior to the administration of any one of Compounds 1-6, or pharmaceutically acceptable salt or solvate thereof, to the subject, the subject has been previously treated with chemotherapy, radiotherapy, and/or surgical resection.

[00113] In certain embodiments, prior to the administration of any one of Compounds 1-6, or pharmaceutically acceptable salt or solvate thereof, to the subject, the subject has been previously treated with a CDK4/6 inhibitor.

[00114] In certain embodiments, the endocrine therapy agent is administered to the subject during the course of the treatment with a compound of Table 1, or pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the first dose of the endocrine therapy agent is administered prior to administering the first dose of a compound of Table 1, or pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the first dose of the endocrine therapy agent is administered on the same day as administering the first dose of a compound of Table 1, or pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the first dose of the endocrine therapy agent is administered after the start of the treatment with a compound of Table 1, or pharmaceutically acceptable salt or solvate thereof.

[00115] In certain embodiments, prior to the administration of a compound of Table 1, or pharmaceutically acceptable salt or solvate thereof, to the subject, the subject has been previously treated with one or more lines of endocrine therapy.

[00116] In certain embodiments, prior to the administration of a compound of Table 1, or pharmaceutically acceptable salt or solvate thereof, to the subject, the subject has been previously treated with chemotherapy, radiotherapy, and/or surgical resection.

[00117] In certain embodiments, prior to the administration of a compound of Table 1, or pharmaceutically acceptable salt or solvate thereof, to the subject, the subject has been previously treated with a CDK4/6 inhibitor.

[00118] In some embodiments, the treatment described herein results in complete response (CR), partial response (PR), or stable disease (SD) in the subject.

[00119] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof, wherein the cancer is a solid tumor characterized by:

- (a) a CDK4 amplification or mutation;
- (b) a Cyclin D1 amplification;
- (c) a Cyclin E amplification; or
- (d) a loss of negative regulator genes CDKN2A or CDKN2B.

[00120] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof, wherein the cancer is a solid tumor characterized by:

- (a) a CDK4 amplification or mutation;
- (b) a Cyclin D1 amplification;
- (c) a Cyclin E amplification; or
- (d) a loss of negative regulator genes CDKN2A or CDKN2B.

[00121] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile, or pharmaceutically acceptable salt or solvate thereof, wherein the cancer is a solid tumor characterized by:

- (a) a CDK4 amplification or mutation;
- (b) a Cyclin D1 amplification;
- (c) a Cyclin E amplification; or
- (d) a loss of negative regulator genes CDKN2A or CDKN2B.

[00122] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof, wherein the cancer is a solid tumor characterized by:

- (a) a CDK4 amplification or mutation;
- (b) a Cyclin D1 amplification;
- (c) a Cyclin E amplification; or

(d) a loss of negative regulator genes CDKN2A or CDKN2B.

[00123] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof, wherein the cancer is a solid tumor characterized by:

- (a) a CDK4 amplification or mutation;
- (b) a Cyclin D1 amplification;
- (c) a Cyclin E amplification; or
- (d) a loss of negative regulator genes CDKN2A or CDKN2B.

[00124] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof, wherein the cancer is a solid tumor characterized by:

- (a) a CDK4 amplification or mutation;
- (b) a Cyclin D1 amplification;
- (c) a Cyclin E amplification; or
- (d) a loss of negative regulator genes CDKN2A or CDKN2B.

[00125] One embodiment provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a compound of Table 1, or pharmaceutically acceptable salt or solvate thereof, wherein the cancer is a solid tumor characterized by:

- (a) a CDK4 amplification or mutation;
- (b) a Cyclin D1 amplification;
- (c) a Cyclin E amplification; or
- (d) a loss of negative regulator genes CDKN2A or CDKN2B.

[00126] Another embodiment provides the method wherein the solid tumor is characterized by a CDK4 amplification or mutation. Another embodiment provides the method wherein the solid tumor is characterized by a Cyclin D1 amplification. Another embodiment provides the method wherein the solid tumor is characterized by a Cyclin E amplification. Another embodiment provides the method wherein the solid tumor is characterized by a loss of negative regulator genes CDKN2A or CDKN2B.

[00127] Another embodiment provides the method wherein the patient has not received prior CDK4 inhibitor therapy. Another embodiment provides the method wherein the patient has resistance to CDK4 inhibitor or CDK6 inhibitor therapy.

Pharmaceutical Compositions

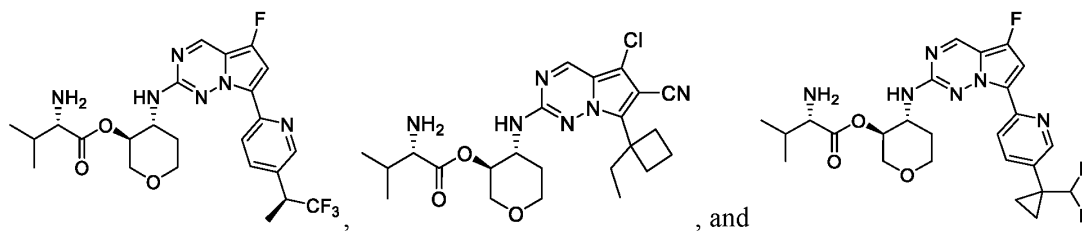
[00128] In certain embodiments, the heterocyclic CDK2/4/6 inhibitor described herein by Compounds 1-6, or pharmaceutically acceptable salt or solvate thereof, is administered as a pure chemical. In other embodiments, the heterocyclic CDK2/4/6 inhibitor described herein by Compounds 1-6, or pharmaceutically acceptable salt or solvate thereof, is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable or acceptable excipient, a physiologically suitable or acceptable excipient, or a physiologically suitable or acceptable carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice.

[00129] Provided herein is a pharmaceutical composition comprising the heterocyclic CDK2/4/6 inhibitor described herein by Compounds 1-6, or a stereoisomer, pharmaceutically acceptable salt, hydrate, or solvate thereof, together with one or more pharmaceutically acceptable carriers. The carrier(s) (or excipient(s)) is acceptable or suitable if the carrier is compatible with the other ingredients of the composition and not deleterious to the recipient (*i.e.*, the subject or the patient) of the composition.

[00130] In certain embodiments, the heterocyclic CDK2/4/6 inhibitor described herein by a compound of Table 1, or pharmaceutically acceptable salt or solvate thereof, is administered as a pure chemical. In other embodiments, the heterocyclic CDK2/4/6 inhibitor described herein by a compound of Table 1, or pharmaceutically acceptable salt or solvate thereof, is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable or acceptable excipient, a physiologically suitable or acceptable excipient, or a physiologically suitable or acceptable carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice.

[00131] Provided herein is a pharmaceutical composition comprising the heterocyclic CDK2/4/6 inhibitor described herein by a compound of Table 1, or a stereoisomer, pharmaceutically acceptable salt, hydrate, or solvate thereof, together with one or more pharmaceutically acceptable carriers. The carrier(s) (or excipient(s)) is acceptable or suitable if the carrier is compatible with the other ingredients of the composition and not deleterious to the recipient (*i.e.*, the subject or the patient) of the composition.

[00132] One embodiment provides a pharmaceutical composition comprising a compound, or pharmaceutically acceptable salt or solvate thereof, selected from the group consisting of:



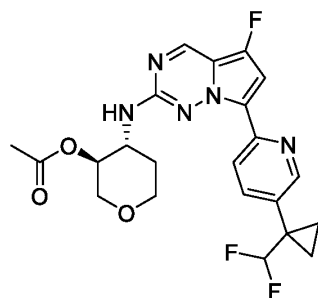
; and at least one pharmaceutically acceptable excipient.

[00133] Another embodiment provides a pharmaceutical composition comprising (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

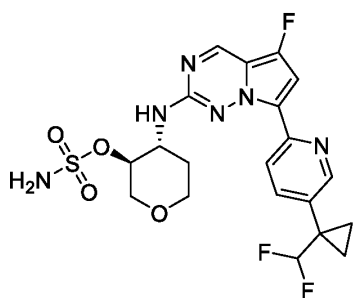
[00134] Another embodiment provides a pharmaceutical composition comprising (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

[00135] Another embodiment provides a pharmaceutical composition comprising (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

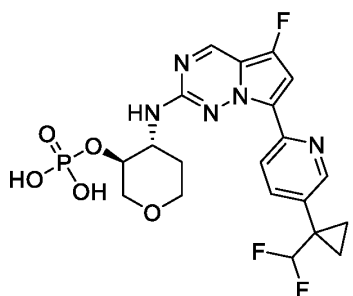
[00136] Another embodiment provides a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient, and a compound, or a pharmaceutically acceptable salt or solvate thereof, having the structure of:



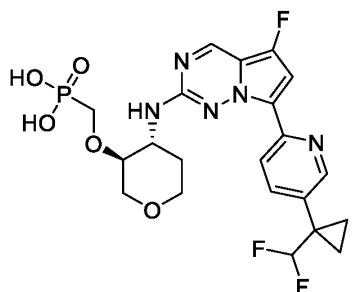
[00137] Another embodiment provides a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient, and a compound, or a pharmaceutically acceptable salt or solvate thereof, having the structure of:



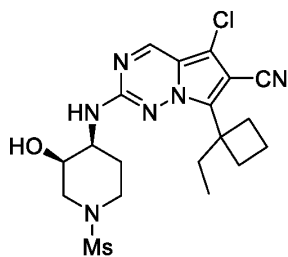
[00138] Another embodiment provides a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient, and a compound, or a pharmaceutically acceptable salt or solvate thereof, having the structure of:



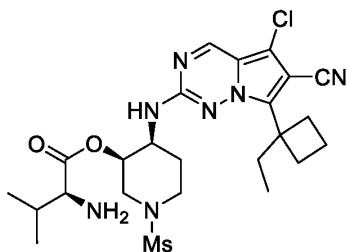
[00139] Another embodiment provides a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient, and a compound, or a pharmaceutically acceptable salt or solvate thereof, having the structure of:



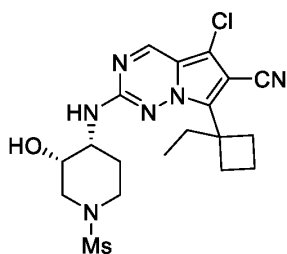
[00140] Another embodiment provides a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient, and a compound, or a pharmaceutically acceptable salt or solvate thereof, having the structure of:



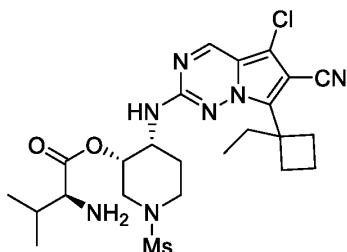
[00141] Another embodiment provides a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient, and a compound, or a pharmaceutically acceptable salt or solvate thereof, having the structure of:



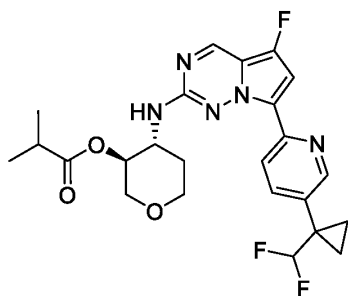
[00142] Another embodiment provides a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient, and a compound, or a pharmaceutically acceptable salt or solvate thereof, having the structure of:



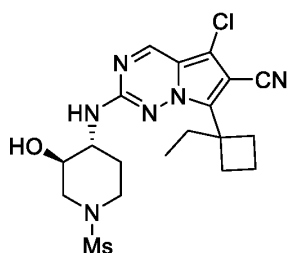
[00143] Another embodiment provides a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient, and a compound, or a pharmaceutically acceptable salt or solvate thereof, having the structure of:



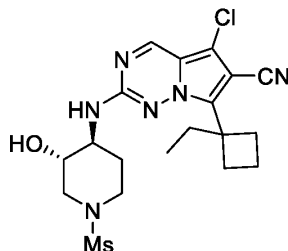
[00144] Another embodiment provides a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient, and a compound, or a pharmaceutically acceptable salt or solvate thereof, having the structure of:



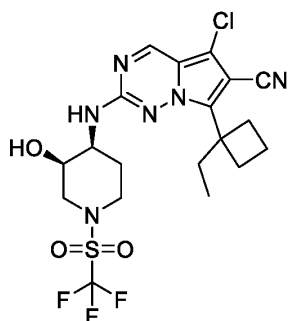
[00145] Another embodiment provides a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient, and a compound, or a pharmaceutically acceptable salt or solvate thereof, having the structure of:



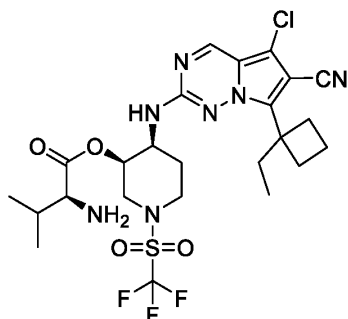
[00146] Another embodiment provides a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient, and a compound, or a pharmaceutically acceptable salt or solvate thereof, having the structure of:



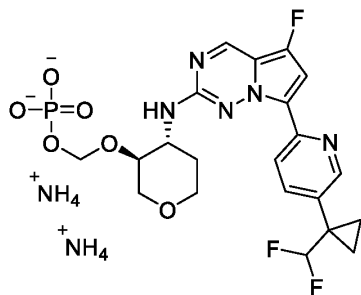
[00147] Another embodiment provides a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient, and a compound, or a pharmaceutically acceptable salt or solvate thereof, having the structure of:



[00148] Another embodiment provides a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient, and a compound, or a pharmaceutically acceptable salt or solvate thereof, having the structure of:



[00149] Another embodiment provides a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient, and a compound, or a pharmaceutically acceptable salt or solvate thereof, having the structure of:



[00150] One embodiment provides a method of preparing a pharmaceutical composition comprising mixing the heterocyclic CDK2/4/6 inhibitor as described herein, or a stereoisomer, pharmaceutically acceptable salt, hydrate, or solvate thereof, and a pharmaceutically acceptable carrier.

[00151] Provided herein is the method wherein the pharmaceutical composition is administered orally. Suitable oral dosage forms include, for example, tablets, pills, sachets, or capsules of hard or soft gelatin, methylcellulose or of another suitable material easily dissolved in the digestive tract. In some embodiments, suitable nontoxic solid carriers are used which include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like. (*See, e.g., Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

[00152] Provided herein is the method wherein the pharmaceutical composition is administered by injection. In some embodiments, the heterocyclic CDK2/4/6 inhibitor as described herein, or pharmaceutically acceptable salt or solvate thereof, is formulated for

administration by injection. In some instances, the injection formulation is an aqueous formulation. In some instances, the injection formulation is a non-aqueous formulation. In some instances, the injection formulation is an oil-based formulation, such as sesame oil, or the like.

[00153] The dose of the composition comprising the heterocyclic CDK2/4/6 inhibitor as described herein, or a stereoisomer, pharmaceutically acceptable salt, hydrate, or solvate thereof, differs depending upon the subject or patient's (e.g., human) condition. In some embodiments, such factors include general health status, age, and other factors. Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (e.g., an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity). Optimal doses are generally determined using experimental models and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the patient.

Numbered Embodiments

Embodiment 1. A method of treating a cancer in a patient in need thereof, comprising administering to the patient a compound, or pharmaceutically acceptable salt or solvate thereof, selected from the group consisting of:

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;
 (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;
 (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate.

Embodiment 2. A method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising a compound, or pharmaceutically acceptable salt or solvate thereof, selected from the group consisting of:

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;
 (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;
 (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate.

Embodiment 3. A method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 4. A method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 5. A method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 6. A method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 7. A method of treating a cancer in a patient in need thereof, comprising administering to the patient 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 8. A method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 9. A method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 10. A method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 11. A method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 12. A method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 13. A method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 14. A method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 15. The method of any one of embodiments 1 to 14, wherein the cancer is selected from the group consisting of breast cancer, ovarian cancer, fallopian tube cancer, primary peritoneal cancer (PPC), bladder cancer, uterine cancer, prostate cancer, lung cancer, non-small-cell lung cancer, (NSCLC), small-cell lung cancer (SCLC), squamous cell carcinoma, adenocarcinoma, mesothelioma, esophageal cancer, head and neck cancer, head and neck squamous cell carcinoma (HNSCC), colorectal cancer (CRC), kidney cancer, renal cell carcinoma (RCC), liver cancer, hepatocellular carcinoma (HCC), pancreatic cancer, stomach cancer, gastric cancer, endometrial cancer, sarcoma, liposarcoma, osteosarcoma, primary brain tumors, high grade and low grade glioma, glioblastoma, thyroid cancer, hematologic cancer, acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), lymphoma, myeloma, neuroblastoma, Ewings sarcoma, osteosarcoma, and Wilms tumor.

Embodiment 16. The method of embodiment 15, wherein the cancer is selected from the group consisting of breast cancer, ovarian cancer, bladder cancer, uterine cancer, prostate cancer, lung cancer, esophageal cancer, liver cancer, pancreatic cancer, stomach cancer, or combinations thereof.

Embodiment 17. The method of any one of embodiments 1 to 16, wherein the cancer is locally or regionally advanced or metastatic solid tumors.

Embodiment 18. The method of any one of embodiments 1 to 14, wherein the cancer is CNS metastatic disease.

Embodiment 19. The method of embodiment 15, wherein the cancer is NSCLC.

Embodiment 20. The method of embodiment 19, wherein the cancer is adenocarcinoma of NSCLC.

Embodiment 21. The method of embodiment 15, wherein the cancer is prostate cancer.

Embodiment 22. The method of embodiment 15, wherein the cancer is colorectal cancer.

Embodiment 23. The method of embodiment 15, wherein the cancer is liposarcoma.

Embodiment 24. The method of embodiment 15, wherein the cancer is breast cancer.

Embodiment 25. The method of embodiment 24, wherein the breast cancer is advanced or metastatic breast cancer.

Embodiment 26. The method of embodiment 24, wherein the breast cancer is locally advanced.

Embodiment 27. The method of embodiment 24, wherein the breast cancer is metastatic breast cancer.

Embodiment 28. The method of embodiment 24, wherein the breast cancer is hormone receptor positive (HR+).

Embodiment 29. The method of embodiment 24, wherein the breast cancer is estrogen receptor positive (ER+), progesterone receptor positive (PR+), or a combination thereof.

Embodiment 30. The method of embodiment 24, wherein the breast cancer is hormone receptor negative (HR-).

Embodiment 31. The method of embodiment 24, wherein the breast cancer is estrogen receptor negative (ER-), progesterone receptor negative (PR-), or a combination thereof.

Embodiment 32. The method of embodiment 24, wherein the breast cancer is human epidermal growth factor receptor 2 negative (HER2-).

Embodiment 33. The method of embodiment 24, wherein the breast cancer is human epidermal growth factor receptor 2 positive (HER2+).

Embodiment 34. The method of embodiment 24, wherein the breast cancer is HR+/HER2- breast cancer.

Embodiment 35. The method of embodiment 24, wherein the breast cancer is HR-/HER2+ breast cancer.

Embodiment 36. The method of embodiment 24, wherein the breast cancer is ER+/HR+.

Embodiment 37. The method of embodiment 24, wherein the breast cancer is ER+/HER2-.

Embodiment 38. The method of embodiment 24, wherein the breast cancer is triple negative breast cancer (TNBC).

Embodiment 39. The method of embodiment 24, wherein the breast cancer is ER-, PR- and HER2-.

Embodiment 40. The method of embodiment 24, wherein the breast cancer is endocrine resistant breast cancer, trastuzumab or pertuzumab resistant breast cancer, or breast cancer demonstrating primary or acquired resistance to CDK4/CDK6 inhibition.

Embodiment 41. The method of any one of embodiments 24-40, wherein the breast cancer is resistant to treatment with a standard of care agent.

Embodiment 42. The method of any one of embodiments 24-40, wherein the subject is refractory to endocrine therapy.

Embodiment 43. The method of any one of embodiments 24-40, wherein the breast cancer is refractory or resistant to treatment with, or has progressed on, treatment with antineoplastic chemotherapeutic agents.

Embodiment 44. The method of any one of embodiments 24-40, wherein the breast cancer has progressed during treatment or within 12 months of completion of adjuvant therapy with an aromatase inhibitor.

Embodiment 45. The method of any one of embodiments 24-40, wherein the breast cancer has progressed during treatment or within 12 months of completion of adjuvant therapy with tamoxifen.

Embodiment 46. The method of any one of embodiments 1-45, wherein the method is first line therapy.

Embodiment 47. The method of any one of embodiments 1-45, wherein the method is second, or later, line therapy.

Embodiment 48. The method of embodiment 47, wherein the method follows treatment with an endocrine therapeutic agent, a CDK4/CDK6 inhibitor, or a combination thereof.

Embodiment 49. The method of embodiment 47, wherein the method follows treatment with an endocrine therapeutic agent.

Embodiment 50. The method of embodiment 47, wherein the method follows treatment with one or more chemotherapy regimens.

Embodiment 51. The method of embodiment 47, wherein the method follows treatment with HER2 targeted agents.

Embodiment 52. A method of treating a breast cancer in a patient in need thereof, comprising administering to the patient a compound, or pharmaceutically acceptable salt or solvate thereof, selected from the group consisting of:

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;
(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;
(3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and

(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, and an endocrine therapy agent.

Embodiment 53. The method of embodiment 52, wherein the compound is (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 54. The method of embodiment 52, wherein the compound is (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 55. The method of embodiment 52, wherein the compound is 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 56. The method of embodiment 52, wherein the compound is (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 57. The method of embodiment 52, wherein the compound is (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 58. The method of embodiment 52, wherein the compound is (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 59. The method of any one of embodiments 52-58, wherein the endocrine therapy agent is selected from the group consisting of a biological large molecule agent or chemical small molecule compound useful in the treatment of cancer.

Embodiment 60. The method of any one of embodiments 52-58, wherein the endocrine therapy agent is selected from the group consisting of an aromatase inhibitor, an androgen receptor

inhibitor, a selective estrogen receptor degrader (SERD), or a selective estrogen receptor modulator (SERM).

Embodiment 61. The method of embodiment 60, wherein the endocrine therapy agent is an androgen receptor inhibitor.

Embodiment 62. The method of embodiment 60, wherein the endocrine therapy agent is an aromatase inhibitor.

Embodiment 63. The method of embodiment 62, wherein the aromatase inhibitor is selected from the group consisting of letrozole, anastrozole and exemestane.

Embodiment 64. The method of embodiment 62, wherein the aromatase inhibitor is letrozole.

Embodiment 65. The method of embodiment 60, wherein the endocrine therapy agent is a SERD.

Embodiment 66. The method of embodiment 60, wherein the SERD is selected from the group consisting of fulvestrant, elacestrant (RAO-1901), amcenestrant (SAR439859), giredestrant (GOC9545), RG6171, camizestrant (AZO9833), AZO9496, rintodestrant, ZN-c5, LSZ102, 0-0502, LY3484356, and SHR9549.

Embodiment 67. The method of embodiment 60, wherein the SERD is fulvestrant.

Embodiment 68. The method of embodiment 60, wherein the endocrine therapy agent is a SERM.

Embodiment 69. The method of embodiment 68, wherein the SERM is selected from the group consisting of tamoxifen, raloxifene, toremifene, lasofoxifene, bazedoxifene and afimoxifene.

Embodiment 70. The method of embodiment 68, wherein the SERM is tamoxifen or raloxifene.

Embodiment 71. The method of embodiment 60, wherein the endocrine therapy agent is letrozole or fulvestrant.

Embodiment 72. The method of any one of embodiments 52-71, wherein the endocrine therapy agent is administered to the subject during the course of the treatment with (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 73. The method of any one of embodiments 52-71, wherein the endocrine therapy agent is administered prior to administering the first dose of (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 74. The method of any one of embodiments 52-71, wherein the first dose of the endocrine therapy agent is administered on the same day as administering the first dose of (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 75. The method of any one of embodiments 52-71, wherein the first dose of the endocrine therapy agent is administered after the start of the treatment with (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 76. The method of any one of embodiments 52-71, wherein prior to the administration of (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof, to the subject, the subject has been previously treated with one or more lines of endocrine therapy.

Embodiment 77. The method of any one of embodiments 51-62, wherein prior to the administration of (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof, to the subject, the subject has been previously treated with chemotherapy, radiotherapy, and/or surgical resection.

Embodiment 78. The method of any one of embodiments 51-62, wherein prior to the administration of (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-

yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof, to the subject, the subject has been previously treated with a CDK4/6 inhibitor.

Embodiment 79. The method of embodiment 52, wherein the endocrine therapy agent is administered to the patient during the course of the treatment with a compound selected from the group consisting of:

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;
 (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;
 (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 80. The method of embodiment 52, wherein the endocrine therapy agent is administered to the patient prior to administering the first dose of a compound selected from the group consisting of:

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;
 (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;
 (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and

(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 81. The method of embodiment 52, wherein the first dose of the endocrine therapy agent is administered to the patient on the same day as administering the first dose of a compound selected from the group consisting of:

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;
 (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;
 (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 82. The method of embodiment 52, wherein the first dose of the endocrine therapy agent is administered to the patient after the start of the treatment with a compound selected from the group consisting of:

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;
 (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;
 (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and

(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.

Embodiment 83. The method of embodiment 52, wherein prior to the administration to the patient of a compound selected from the group consisting of:

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;
 (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;
 (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof, the patient has been previously treated with one or more lines of endocrine therapy.

Embodiment 84. The method of embodiment 1, wherein prior to the administration to the patient of a compound selected from the group consisting of:

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;
 (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;
 (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or

pharmaceutically acceptable salt or solvate thereof, the patient has been previously treated with chemotherapy, radiotherapy, and/or surgical resection.

Embodiment 85. The method of embodiment 1, wherein prior to the administration to the patient of a compound selected from the group consisting of:

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;

5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;

(3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;

(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and

(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or

pharmaceutically acceptable salt or solvate thereof, the patient has been previously treated with a CDK4/6 inhibitor.

Embodiment 86. The method of any one of the preceding embodiments, wherein the method results in complete response (CR), partial response (PR), or stable disease (SD) in the subject with regionally advanced or metastatic disease.

Embodiment 87. The method of any one of the preceding embodiments, wherein the treatment results in complete response, partial response or stable disease of intra-cranial metastatic disease or primary brain tumors.

Embodiment 88. The method of any one of the preceding embodiments, wherein the treatment results in a reduction of disease recurrence at the local site, or a distant site, or within the CNS, or a combination thereof.

Embodiment 89. The method of embodiment 18, wherein the disease site is the brain.

Embodiment 90. The method of embodiment 15, wherein the patient has a locally or a regionally advanced cancer.

Embodiment 91. A method of treating a cancer in a patient in need thereof, comprising administering to the patient a compound, or pharmaceutically acceptable salt or solvate thereof, selected from the group consisting of:

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;
 (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;
 (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate,
 and wherein the cancer is a solid tumor characterized by:

- (a) a CDK4 amplification or mutation;
- (b) a Cyclin D1 amplification;
- (c) a Cyclin E amplification; or
- (d) a loss of negative regulator genes CDKN2A or CDKN2B.

Embodiment 92. A method of treating a cancer in a patient in need thereof, comprising administering to the patient 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile, or pharmaceutically acceptable salt or solvate thereof, or (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof, wherein the cancer is a solid tumor characterized by:

- (a) a CDK4 amplification or mutation;
- (b) a Cyclin D1 amplification;
- (c) a Cyclin E amplification; or
- (d) a loss of negative regulator genes CDKN2A or CDKN2B.

Embodiment 93. A method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof, or (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof, wherein the cancer is a solid tumor characterized by:

- (a) a CDK4 amplification or mutation;
- (b) a Cyclin D1 amplification;
- (c) a Cyclin E amplification; or
- (d) a loss of negative regulator genes CDKN2A or CDKN2B.

Embodiment 94. A method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof, or (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof, wherein the cancer is a solid tumor characterized by:

- (a) a CDK4 amplification or mutation;
- (b) a Cyclin D1 amplification;
- (c) a Cyclin E amplification; or
- (d) a loss of negative regulator genes CDKN2A or CDKN2B.

Embodiment 95. The method of embodiment 91, wherein the solid tumor is characterized by a CDK4 amplification or mutation.

Embodiment 96. The method of embodiment 91, wherein the solid tumor is characterized by a Cyclin D1 amplification.

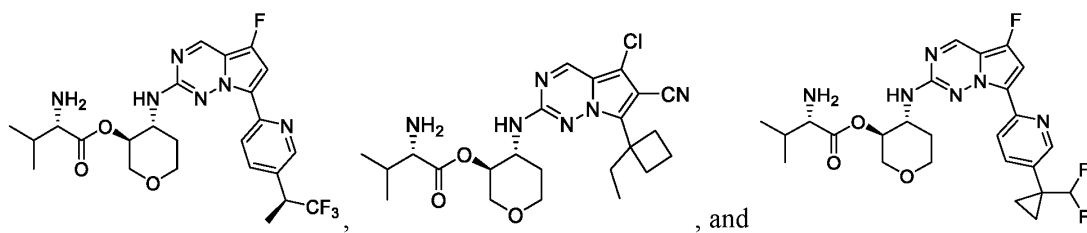
Embodiment 97. The method of embodiment 91, wherein the solid tumor is characterized by a Cyclin E amplification.

Embodiment 98. The method of embodiment 91, wherein the solid tumor is characterized by a loss of negative regulator genes CDKN2A or CDKN2B.

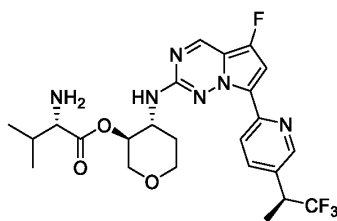
Embodiment 99. The method of any one of the preceding embodiments, wherein the patient has not received prior CDK4 inhibitor therapy.

Embodiment 100. The method of any one of the preceding embodiments, wherein the patient has resistance to CDK4 inhibitor or CDK6 inhibitor therapy.

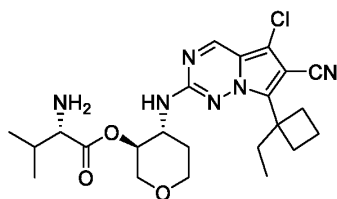
Embodiment 101. A compound, or pharmaceutically acceptable salt or solvate thereof, selected from the group consisting of:



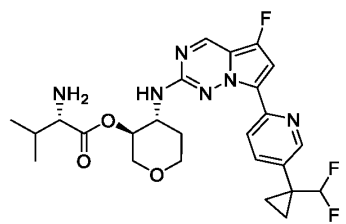
Embodiment 102. The compound of embodiment 101, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



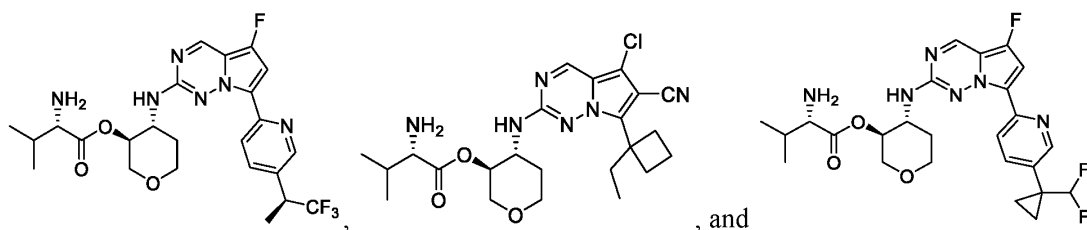
Embodiment 103. The compound of embodiment 101, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



Embodiment 104. The compound of embodiment 101, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



Embodiment 105. A pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and a compound, or pharmaceutically acceptable salt or solvate thereof, selected from the group consisting of:



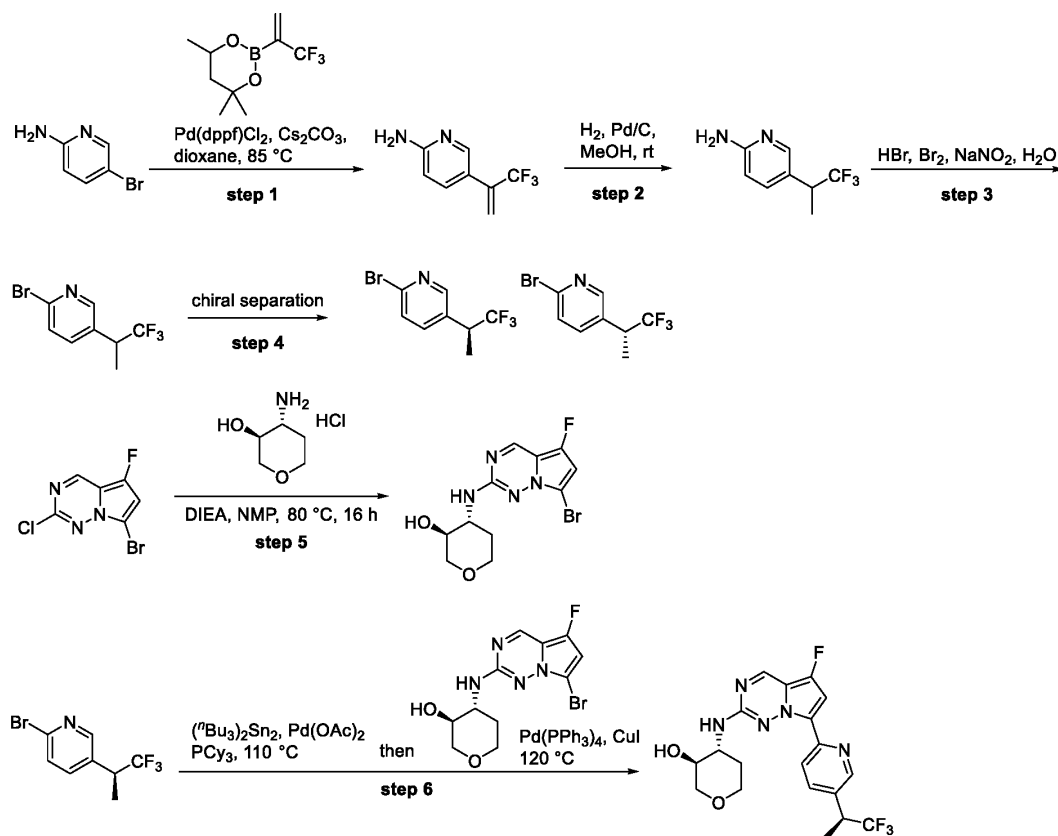
EXAMPLES

[00154] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

I. Chemical Synthesis

[00155] Example 1:

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-f][1,2,4]triazin-2-yl)amino]oxan-3-ol



Step 1: 5-(3,3,3-trifluoroprop-1-en-2-yl)pyridin-2-amine

To a solution of 5-bromopyridin-2-amine (50 g, 288.996 mmol) and 4,4,6-trimethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)-1,3,2-dioxaborinane (64.2 g, 288.996 mmol) in dioxane (500 mL) and water (100 mL) were added Cs_2CO_3 (188.3 g, 577.992 mmol) and $\text{Pd(dppf)Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (23.54 g, 28.900 mmol). The reaction mixture was stirred for 5 h at 85 °C under a nitrogen atmosphere. The resulting mixture was allowed to cool down to room temperature, then filtered. The filter cake was washed with EtOAc (3 x 500 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 5-(3,3,3-trifluoroprop-1-en-2-yl)pyridin-2-amine (48 g, 88%) as yellow oil. MS ESI calculated for $\text{C}_8\text{H}_7\text{F}_3\text{N}_2$ $[\text{M} + \text{H}]^+$, 189.06 found 189.10. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.17 (d, $J = 2.4$ Hz, 1H), 7.56 (dd, $J = 8.8, 2.4$ Hz, 1H), 6.53 (d, $J = 8.8$ Hz, 1H), 5.88 (q, $J = 1.6$ Hz, 1H), 5.70 (q, $J = 1.6$ Hz, 1H), 4.68 (br, 2H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -65.20 (3F).

Step 2: 5-(1,1,1-trifluoropropan-2-yl)pyridin-2-amine

To a solution of 5-(3,3,3-trifluoroprop-1-en-2-yl)pyridin-2-amine (48 g, 255.112 mmol) in MeOH (500 mL) was added Pd/C (10%, 9.23g). The mixture was hydrogenated for 4 h at room temperature under 2 atm hydrogen atmosphere. The resulting mixture was filtered, the filtrate

was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 5-(1,1,1-trifluoropropan-2-yl)pyridin-2-amine (40 g, 82%) as brown oil. MS ESI calculated for $C_8H_9F_3N_2$ $[M + H]^+$, 191.07 found 190.95. 1H NMR (400 MHz, Chloroform-*d*) δ 8.00 (d, $J = 2.4$ Hz, 1H), 7.44 (dd, $J = 8.4, 2.4$ Hz, 1H), 6.54 (dd, $J = 8.4$ Hz, 1H), 4.48 (br, 2H), 3.36-3.28 (m, 1H), 1.49 (d, $J = 7.2$ Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -72.12 (3F).

Step 3: 2-bromo-5-(1,1,1-trifluoropropan-2-yl)pyridine

To a stirred solution of 5-(1,1,1-trifluoropropan-2-yl)pyridin-2-amine (45 g, 236.632 mmol) in HBr (300 mL, 40% in water) was added Br_2 (58.6 mL, 1142.933 mmol) dropwise at $-20^\circ C$. The resulting mixture was stirred for 1.5 h at $-20^\circ C$. To this was added $NaNO_2$ (76.6 g, 1109.804 mmol) in water (450 mL) dropwise at $-20^\circ C$. The resulting mixture was stirred for additional 1 h at $10\sim 20^\circ C$. The mixture was allowed to cool down to $-20^\circ C$. The reaction was quenched with NaOH (300 g, 7503.601 mmol) in water (450 mL) at $-20^\circ C$. The resulting mixture was extracted with EtOAc (3 x 500 L). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (8/1) to afford 2-bromo-5-(1,1,1-trifluoropropan-2-yl)pyridine (42 g, 70%) as brown oil. MS ESI calculated for $C_8H_7BrF_3N$ $[M + H]^+$, 253.97, 255.97 found 253.90, 255.90. 1H NMR (400 MHz, Chloroform-*d*) δ 8.34 (d, $J = 2.4$ Hz, 1H), 7.57-7.51 (m, 2H), 3.54-3.41 (m, 1H), 1.55 (d, $J = 7.2$ Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -71.65 (3F).

Step 4: 2-bromo-5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridine

2-bromo-5-(1,1,1-trifluoropropan-2-yl)pyridine (60 g) was resolved by Prep-Chiral-HPLC with the following conditions: Column: CHIRAL ART Cellulose-SB, 7*25 cm, 10 μm ; Mobile Phase A: hexane, Mobile Phase B: EtOH; Flow rate: 200 mL/min; Gradient: A:B = 90:10; Wave Length: 220 nm.

RT₁: 6.0 min to afford 2-bromo-5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridine (29.4 g, 49%) as a yellow oil.

RT₂: 8.4 min to afford 2-bromo-5-[(2*R*)-1,1,1-trifluoropropan-2-yl]pyridine (27.4 g, 46%) as a yellow oil.

Step 5: (3*S*,4*R*)-4-({7-bromo-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol

A solution of 7-bromo-2-chloro-5-fluoropyrrolo[2,1-*f*][1,2,4]triazine (1.6 g, 6.388 mmol), (3*S*,4*R*)-4-aminooxan-3-ol hydrochloride (1.18 g, 7.666 mmol) and DIEA (3.34 mL, 19.164 mmol) in NMP (15 mL) was stirred for 16 h at $80^\circ C$. The resulting mixture was cooled down to room temperature and purified by reversed phase chromatography with the following conditions: column, C18 column; CH_3CN in water (10 mmol/L NH_4HCO_3), 20% to 45%; detector, UV

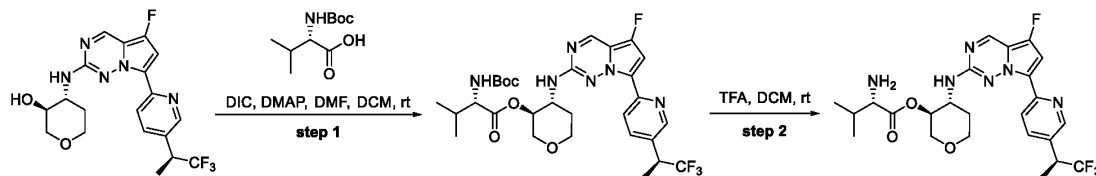
254/220 nm to afford (3*S*,4*R*)-4-({7-bromo-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (1.7 g, 80%) as a brown solid. MS ESI calculated for C₁₁H₁₂BrFN₄O₂ [M + H]⁺, 331.01, 333.01, found 331.05, 333.05. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.58 (s, 1H), 6.38 (s, 1H), 5.03 (brs, 1H), 4.13-4.08 (m, 1H), 4.05-3.96 (m, 1H), 3.87-3.79 (m, 1H), 3.71-3.62 (m, 1H), 3.54-3.47 (m, 1H), 3.29-3.23 (m, 1H), 2.16-2.08 (m, 1H), 1.78-1.67 (m, 1H). ¹⁹F NMR (376 MHz, Chloroform-*d*) δ -156.40 (1F).

Step 6: (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol

To a stirred mixture of 2-bromo-5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridine (17.84 g, 70.210 mmol) and hexabutylstannane (44.80 g, 77.232 mmol) were added Pd(OAc)₂ (0.74 g, 3.276 mmol) and PCy₃ (1.97 g, 7.021 mmol) at room temperature under a nitrogen atmosphere. The resulting mixture was stirred for 24 h at 110 °C under a nitrogen atmosphere. The resulting mixture was allowed to cool down to room temperature. To this were added (3*S*,4*R*)-4-({7-bromo-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl}amino)oxan-3-ol (15.5 g, 46.807 mmol), Pd(PPh₃)₄ (2.70 g, 2.340 mmol) and CuI (3.57 g, 18.723 mmol) at room temperature. The reaction mixture was stirred for additional 16 h at 120 °C under a nitrogen atmosphere. The resulting mixture was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (10/1). The crude product was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH₃CN in water (10 mmol/L NH₄HCO₃), 45% to 65%; detector, UV 254 nm to afford (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol (9.52 g, 47%) as a light yellow solid. MS ESI calculated for C₁₉H₁₉F₄N₅O₂ [M + H]⁺, 426.15 found 426.25. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.99 (s, 1H), 8.84 (d, *J* = 8.4 Hz, 1H), 8.67 (d, *J* = 1.2 Hz, 1H), 8.01 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.09 (s, 1H), 4.98 (d, *J* = 5.2 Hz, 1H), 4.03-3.91 (m, 1H), 3.89-3.85 (m, 2H), 3.78-3.70 (m, 1H), 3.62-3.55 (m, 1H), 3.52-3.41 (m, 1H), 3.18-3.13 (m, 1H), 2.17-2.14 (m, 1H), 1.58-1.45 (m, 4H). ¹⁹F NMR (377 MHz, DMSO-*d*₆) δ -70.17 (3F), -161.59 (1F).

[00156] Example 2:

**(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-
f][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate**



**Step 1: (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-
f][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoate**

To a stirred solution of (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoic acid (1.53 g, 7.053 mmol) in DMF (25 mL) was added *N,N*-diisopropylcarbodiimide (0.65 g, 5.172 mmol) at room temperature, followed by the addition of a solution of (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol (1 g, 2.351 mmol) and DMAP (28 mg, 0.235 mmol) in DCM (25 mL). The resulting mixture was stirred for 4 h at room temperature. The resulting mixture was diluted with water (200 mL) and extracted with CH₂Cl₂ (3 x 150 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-
f][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoate (1.4 g, 95%) as a light yellow solid. MS ESI calculated for C₂₉H₃₆F₄N₆O₅ [M + H]⁺, 625.27, found 625.30. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.79-8.69 (m, 2H), 8.62 (d, *J* = 2.4 Hz, 1H), 7.77 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.12 (s, 1H), 5.44 (brs, 1H), 5.09-5.04 (m, 2H), 4.25-3.97 (m, 4H), 3.73-3.44 (m, 3H), 2.52-2.37 (m, 1H), 2.15-2.12 (m, 1H), 1.79-1.75 (m, 1H), 1.60 (d, *J* = 7.2 Hz, 3H), 1.45 (s, 9H), 0.92-0.85 (m, 6H). ¹⁹F NMR (377 MHz, Chloroform-*d*) δ -71.41 (3F), -160.41 (1F).

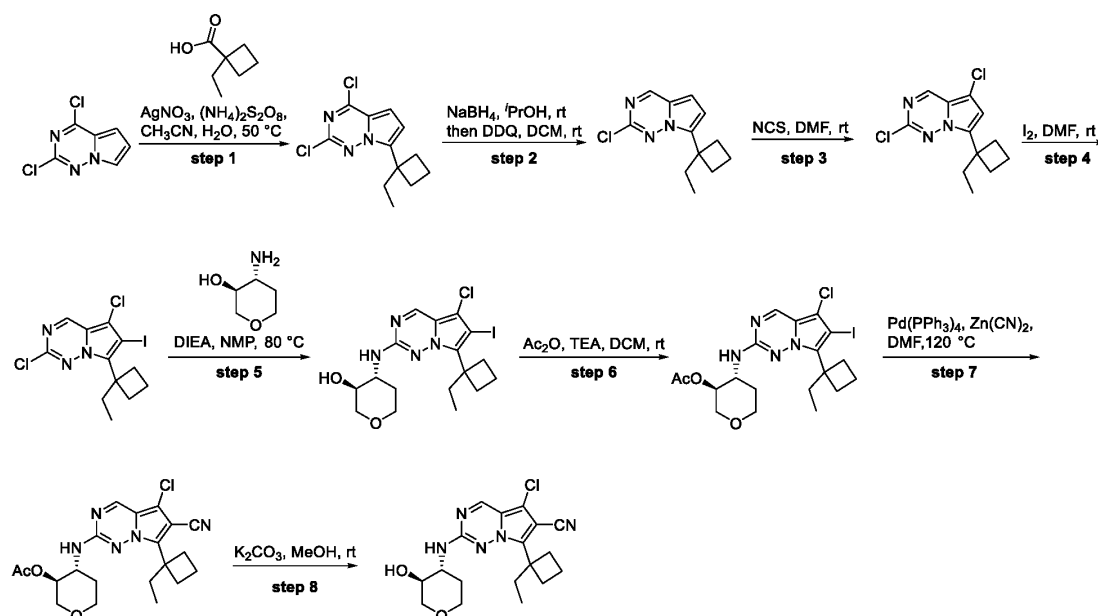
**Step 2: (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-
f][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate**

To a stirred solution of (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-
f][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoate (1.5 g, 2.401 mmol) in DCM (10 mL) was added TFA (2 mL) at room temperature. The resulting mixture was stirred for 1 h at room temperature. The mixture was basified to pH 8 with sat. NaHCO₃ and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH₃CN in Water (10

mmol/L NH_4HCO_3 , 20% to 50%; detector, UV 254 nm to afford (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate (1.00 g, 79%) as a yellow solid. MS ESI calculated for $\text{C}_{24}\text{H}_{28}\text{F}_4\text{N}_6\text{O}_3$ $[\text{M} + \text{H}]^+$, 525.22, found 525.25. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.00 (s, 1H), 8.86 (d, $J = 8.4$ Hz, 1H), 8.68 (s, 1H), 8.03 (d, $J = 8.4$, 1H), 7.40 (d, $J = 7.6$ Hz, 1H), 7.12 (s, 1H), 4.88-4.82 (m, 1H), 4.14-4.12 (m, 1H), 4.01-3.90 (m, 3H), 3.60-3.55 (m, 1H), 3.39-3.32 (m, 1H), 2.97 (d, $J = 5.2$ Hz, 1H), 2.13-2.10 (m, 1H), 1.81-1.69 (m, 2H), 1.58-1.51 (m, 5H), 0.65 (d, $J = 6.8$ Hz, 6H). ^{19}F NMR (377 MHz, $\text{DMSO}-d_6$) δ -70.19, -161.39.

[00157] Example 3:

5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile



Step 1: 2,4-dichloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine

To a stirred solution of 2,4-dichloropyrrolo[2,1-*f*][1,2,4]triazine (2.00 g, 10.638 mmol), 1-ethylcyclobutane-1-carboxylic acid (4.09 g, 31.914 mmol) and AgNO_3 (3.61 g, 21.276 mmol) in CH_3CN (50 mL) and H_2O (25 mL) was added $(\text{NH}_4)_2\text{S}_2\text{O}_8$ (12.14 g, 53.190 mmol) in H_2O (25 mL) dropwise at 50 °C. The resulting mixture was stirred for 2 h at 50 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (100 mL). The resulting mixture was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (10/1) to afford 2,4-dichloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (2.20 g, 76%) as yellow oil. MS ESI calculated for

$C_{12}H_{13}Cl_2N_3$ $[M + H]^+$ 270.05, found 269.95. 1H NMR (400 MHz, Chloroform-*d*) δ 7.03 (d, J = 4.8 Hz, 1H), 6.79 (d, J = 4.8 Hz, 1H), 2.52-2.44 (m, 2H), 2.33-2.26 (m, 2H), 2.10-2.06 (m, 3H), 1.95-1.87 (m, 1H), 0.61 (t, J = 7.2 Hz, 3H).

Step 2: 2-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine

To a stirred solution of 2,4-dichloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (2.20 g, 8.143 mmol) in *i*-PrOH (50 mL) was added $NaBH_4$ (0.46 g, 12.215 mmol). The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched with water (50 mL). The resulting mixture was extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. To the residue were added DDQ (2.77 g, 12.215 mmol) and DCM (50 mL). The resulting mixture was stirred for additional 2 h at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (50 mL). The resulting mixture was extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (10/1) to afford 2-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (1.30 g, 67%) as yellow oil. MS ESI calculated for $C_{12}H_{14}ClN_3$ $[M + H]^+$ 236.09 found 236.05. 1H NMR (400 MHz, Chloroform-*d*) δ 6.89 (s, 1H), 6.90 (d, J = 4.8 Hz, 1H), 6.77 (d, J = 4.8 Hz, 1H), 2.52-2.45 (m, 2H), 2.32-2.25 (m, 2H), 2.15-2.04 (m, 3H), 1.95-1.85 (m, 1H), 0.59 (t, J = 7.2 Hz, 3H).

Step 3: 2,5-dichloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine

A mixture of 2-chloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (3.3 g, 14.000 mmol) and NCS (1.96 g, 14.700 mmol) in DMF (50 mL) was stirred for 16 h at room temperature. The reaction was quenched by the addition of water (100 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 2,5-dichloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (3.0 g, 79%) as a yellow solid. MS ESI calculated for $C_{12}H_{13}Cl_2N_3$ $[M + H]^+$ 270.05, found 270.05. 1H NMR (400 MHz, Chloroform-*d*) δ 8.75 (s, 1H), 6.72 (s, 1H), 2.51-2.40 (m, 2H), 2.34-2.24 (m, 2H), 2.14-2.06 (m, 3H), 1.97-1.87 (m, 1H), 0.63 (t, J = 7.2 Hz, 3H).

Step 4: 2,5-dichloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazine

A mixture of 2,5-dichloro-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazine (3.0 g, 11.105 mmol) and I_2 (11.27 g, 44.420 mmol) in DMF (60 mL) was stirred for 16 h at room temperature. The reaction was quenched by the addition of sat. $Na_2S_2O_3$ (100 mL). The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (100

mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford 2,5-dichloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazine (3.0 g, 68%) as a yellow solid. MS ESI calculated for C₁₂H₁₂Cl₂IN₃ [M + H]⁺, 395.95; found 395.95. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 2.79-2.62 (m, 2H), 2.56-2.40 (m, 2H), 2.20-2.04 (m, 3H), 1.93-1.79 (m, 1H), 0.88-0.74 (m, 3H).

Step 5: (3*S*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol

To a stirred mixture of 2,5-dichloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazine (1 g, 2.525 mmol) and (3*S*,4*R*)-4-aminooxan-3-ol hydrochloride (0.78 g, 5.050 mmol) in DMSO (10 mL) were added DIEA (1.31 g, 10.100 mmol). The reaction mixture was stirred for 16 h at 80 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH₃CN in water (10mmol/L NH₄HCO₃), 30% to 80%; detector, UV 254 nm to afford (3*S*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (1 g, 82%) as a brown solid. MS ESI calculated for C₁₇H₂₂ClIN₄O₂ [M + H]⁺, 477.05, found 477.05. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.70 (s, 1H), 6.86 (d, *J* = 6.8 Hz, 1H), 4.92 (d, *J* = 5.2 Hz, 1H), 3.84-3.80 (m, 2H), 3.58-3.45 (m, 2H), 3.33-3.27 (m, 1H), 3.07-3.02 (m, 1H), 2.71-2.53 (m, 2H), 2.33-2.25 (m, 2H), 2.14-1.95 (m, 4H), 1.82-1.74 (m, 1H), 1.45-1.38 (m, 1H), 0.72 (t, *J* = 7.2 Hz, 3H).

Step 6: (3*S*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

To a stirred mixture of (3*S*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-ol (530 mg, 1.112 mmol) and TEA (675 mg, 6.672 mmol) in DCM (5 mL) was added Ac₂O (454 mg, 4.448 mmol). The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was diluted with water (30 mL). The resulting mixture was extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (4/1) to afford (3*S*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (570 mg, 98%) as a yellow solid. MS ESI calculated for C₁₉H₂₄ClIN₄O₃ [M + H]⁺, 519.06, found 519.10. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.53 (s, 1H), 5.05-4.82 (m, 2H), 4.15-3.93 (m, 2H), 3.87-3.83 (m, 1H), 3.57-3.51 (m, 1H), 3.45-3.40 (m, 1H), 2.83-2.63 (m, 2H), 2.47-2.30 (m, 3H), 2.16-2.06 (m, 6H), 1.93-1.79 (m, 1H), 1.68-1.62 (m, 1H), 0.81 (t, *J* = 7.2 Hz, 3H).

Step 7: (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate

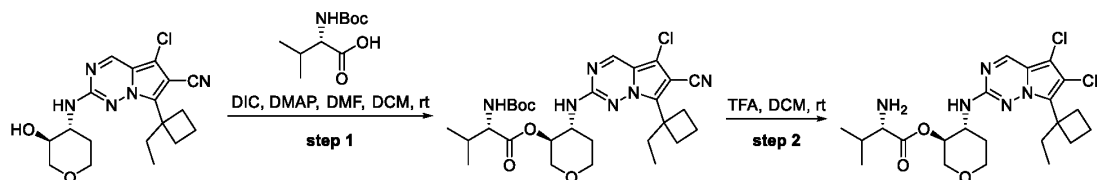
To a stirred solution of (3*S*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (130 mg, 0.251 mmol) and Zn(CN)₂ (44 mg, 0.377 mmol, 1.5 equiv) in DMF (3 mL) was added Pd(PPh₃)₄ (29 mg, 0.025 mmol) under nitrogen atmosphere. The reaction mixture was irradiated with microwave radiation for 2 h at 120 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3/1) to afford (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (90 mg, 86%) as a yellow solid. MS ESI calculated for C₂₀H₂₄ClN₅O₃ [M + H]⁺, 418.16, found 418.00. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.64 (s, 1H), 5.22 (d, *J* = 7.2 Hz, 1H), 4.96-4.91 (m, 1H), 4.05-3.89 (m, 2H), 3.86-3.73 (m, 1H), 3.53-3.47 (m, 1H), 3.42-3.37 (m, 1H), 2.73-2.62 (m, 2H), 2.44-2.24 (m, 3H), 2.24-2.02 (m, 6H), 1.99-1.87 (m, 1H), 1.68-1.63 (m, 1H), 0.79 (t, *J* = 7.2 Hz, 3H).

Step 8: 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

A solution of (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl acetate (80 mg, 0.191 mmol) and K₂CO₃ (53 mg, 0.382 mmol) in MeOH (2 mL) was stirred for 30 min at 0 °C. The reaction mixture was purified by reversed-phase chromatography with the following conditions: C18 column; Mobile Phase: CH₃CN in water (10 mM NH₄HCO₃), 20% to 60%; Detector: 254 nm to afford 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (45.3 mg, 63%) as an off-white solid. MS ESI calculated for C₁₈H₂₂ClN₅O₂ [M + H]⁺, 376.15, found 376.15. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.92 (s, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 4.95 (d, *J* = 4.8 Hz, 1H), 3.85-3.81 (m, 2H), 3.61-3.55 (m, 1H), 3.52-3.47 (m, 1H), 3.34-3.27 (m, 1H), 3.08-3.02 (m, 1H), 2.64-2.50 (m, 2H), 2.27-1.99 (m, 6H), 1.90-1.85 (m, 1H), 1.46-1.42 (m, 1H), 0.69 (t, *J* = 7.2 Hz, 3H).

[00158] Example 4:

(3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate



Step 1: (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoate

To a stirred mixture of (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoic acid (208 mg, 0.957 mmol) and *N,N*-diisopropylcarbodiimide (89 mg, 0.702 mmol) in DMF (1 mL) were added 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (120 mg, 0.319 mmol) and DMAP (4 mg, 0.032 mmol) in DCM (1 mL) room temperature. The resulting mixture was stirred for 30 min at room temperature. The resulting mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoate (117 mg, 64%) as a yellow solid. MS ESI calculated for C₂₈H₃₉ClN₆O₅ [M + H]⁺, 575.27, found 575.40.

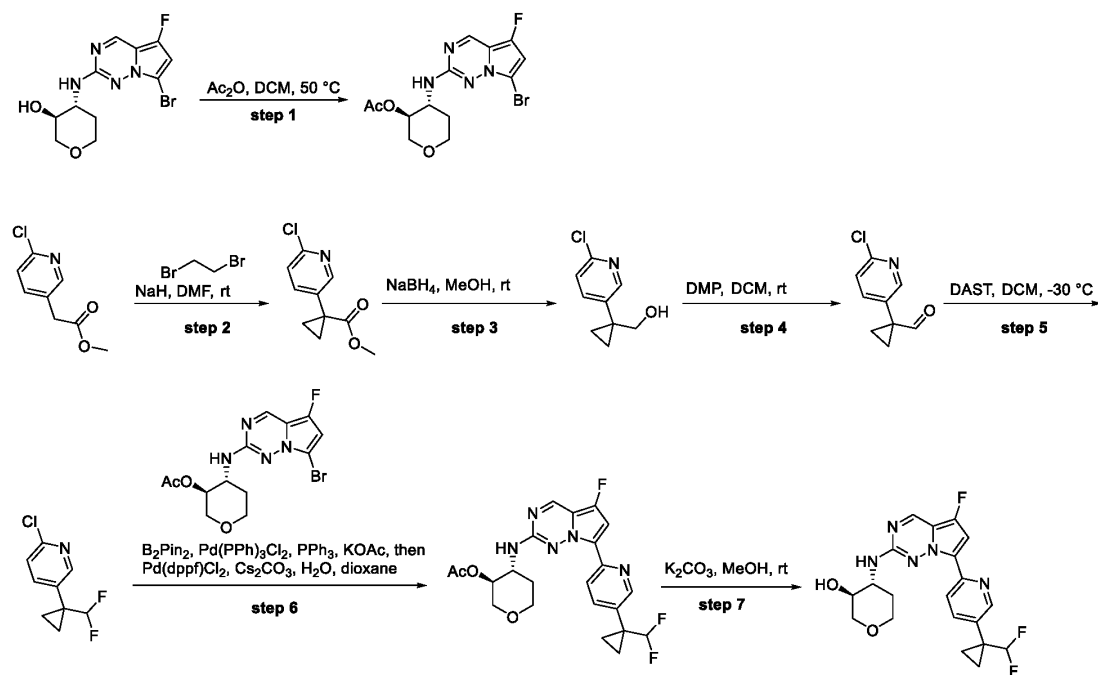
Step 2: (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate

To a solution (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoate (100 mg, 0.174 mmol) in DCM (1 mL) was added TFA (0.2 mL) dropwise at room temperature. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase: CH₃CN in water (10 mmol/L NH₄HCO₃), 44% to 74%; Wave Length: 254/220 nm to afford (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate (51.9 mg, 63%) as an off-white solid. MS ESI calculated for C₂₃H₃₁ClN₆O₃ [M + H]⁺, 475.21, found 475.35. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.95 (s, 1H), 7.58 (d, *J* = 6.8 Hz, 1H), 4.85-4.83 (m, 1H), 3.92-3.85 (m, 3H), 3.48-3.45 (m, 1H), 3.30-3.22 (m,

1H), 3.03 (d, $J = 5.2$ Hz, 1H), 2.64-2.54 (m, 2H), 2.27-2.01 (m, 6H), 1.89-1.86 (m, 1H), 1.76-1.71 (m, 2H), 1.69-1.58 (m, 2H), 1.79-1.68 (m, 9H).

[00159] Example 5:

(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol



Step 1: (3*S*,4*R*)-4-[(7-bromo-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate

A mixture of (3*S*,4*R*)-4-[(7-bromo-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol (6.1 g, 18.421 mmol), Ac₂O (2.82 g, 27.631 mmol) and TEA (12.8 mL, 92.105 mmol) in DCM (100 mL) was stirred for 16 h at 50 °C. The mixture was allowed to cool down to room temperature. The reaction was quenched with water (100 mL). The resulting mixture was extracted with DCM (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-[(7-bromo-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate (6.2 g, 90%) as a yellow solid. MS ESI calculated for C₁₃H₁₄BrFN₄O₃ [M + H]⁺, 373.02, 375.02, found 373.00, 375.00. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 6.35 (s, 1H), 5.13 (d, $J = 7.2$ Hz, 1H), 4.99-4.93 (m, 1H), 4.13-4.01 (m, 2H), 4.00-3.95 (m, 1H), 3.62-3.56 (m, 1H), 3.46-3.40 (m, 1H), 2.52-2.46 (m, 1H), 2.06 (s, 3H), 1.74-1.60 (m, 1H). ¹⁹F NMR (377 MHz, Chloroform-*d*) δ -157.88 (1F).

Step 2: methyl 1-(6-chloropyridin-3-yl)cyclopropane-1-carboxylate

To a stirred solution of methyl 2-(6-chloropyridin-3-yl)acetate (4 g, 21.551 mmol) in DMF (100 mL) was added NaH (2.1 g, 53.877 mmol, 60%) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at 0 °C under nitrogen atmosphere. To this was added dibromoethane (6.1 g, 32.326 mmol) dropwise at 0 °C. The resulting mixture was stirred for additional 2 h at room temperature. The reaction was quenched with sat. NH₄Cl (200 mL). The resulting mixture was diluted with water (200 mL) and extracted with EtOAc (2 x 400 mL). The combined organic layers were washed with brine (3 x 200 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (4/1) to afford methyl 1-(6-chloropyridin-3-yl)cyclopropane-1-carboxylate (3.3 g, 72%) as colorless oil. MS ESI calculated for C₁₀H₁₀ClNO₂ [M + H]⁺, 212.04, found 211.85. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.37 (d, *J* = 2.4 Hz, 1H), 7.65 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 3.66 (s, 3H), 1.73-1.68 (m, 2H), 1.22-1.19 (m, 2H).

Step 3: [1-(6-chloropyridin-3-yl)cyclopropyl]methanol

To a stirred solution of methyl 1-(6-chloropyridin-3-yl)cyclopropane-1-carboxylate (3.3 g, 15.592 mmol) in MeOH (100 mL) was added NaBH₄ (3.0 g, 77.960 mmol) in portions at 0 °C. The resulting mixture was stirred for 16 h at room temperature. The reaction was quenched with sat. NH₄Cl (100 mL). The resulting mixture was concentrated under reduced pressure to remove MeOH. The resulting mixture was diluted with water (200 mL) and extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with brine (2 x 300 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford [1-(6-chloropyridin-3-yl)cyclopropyl]methanol (1.1 g, 38%) as colorless oil. MS ESI calculated for C₉H₁₀ClNO [M + H]⁺, 184.05, found 184.05. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.39 (d, *J* = 2.4 Hz, 1H), 7.69 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 3.70 (s, 2H), 2.22 (s, 1H), 0.98-0.95 (m, 2H), 0.92-0.89 (m, 2H).

Step 4: 1-(6-chloropyridin-3-yl)cyclopropane-1-carbaldehyde

To a stirred solution of [1-(6-chloropyridin-3-yl)cyclopropyl]methanol (1.1 g, 5.990 mmol) in DCM (30 mL) was added DMP (5.1 g, 11.980 mmol). The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was filtered, and the filter cake was washed with DCM (3 x 50 mL). The combined filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (4/1) to afford 1-(6-chloropyridin-3-yl)cyclopropane-1-carbaldehyde (850 mg, 78%) as colorless oil. MS ESI calculated for C₉H₈ClNO [M + H]⁺, 182.03, found 181.90. ¹H NMR (400 MHz, Chloroform-*d*) δ

9.01 (s, 1H), 8.33 (d, $J = 2.4$ Hz, 1H), 7.62 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.35 (d, $J = 8.4$ Hz, 1H), 1.83-1.51 (m, 2H), 1.59-1.36 (m, 2H).

Step 5: 2-chloro-5-[1-(difluoromethyl)cyclopropyl]pyridine

To a stirred solution of 1-(6-chloropyridin-3-yl)cyclopropane-1-carbaldehyde (850 mg, 4.680 mmol) in DCM (20 mL) was added DAST (2.3 g, 14.040 mmol) dropwise at -30 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford 2-chloro-5-[1-(difluoromethyl)cyclopropyl]pyridine (700 mg, 73%) as light yellow oil. MS ESI calculated for $C_9H_8ClF_2N$ $[M + H]^+$, 204.03, found 204.00. 1H NMR (400 MHz, Chloroform- d) δ 8.43 (d, $J = 2.4$ Hz, 1H), 7.71 (dd, $J = 2.4, 8.4$ Hz, 1H), 7.32 (d, $J = 8.4$ Hz, 1H), 5.54 (t, $J = 56.4$ Hz, 1H), 1.33-1.17 (m, 2H), 1.03-0.96 (m, 2H). ^{19}F NMR (377 MHz, Chloroform- d) δ -116.04 (2F).

Step 6: (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1- f][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate

To a stirred mixture of (3*S*,4*R*)-4-({7-bromo-5-fluoropyrrolo[2,1- f][1,2,4]triazin-2-yl}amino)oxan-3-yl acetate (6 g, 16.078 mmol) and bis(pinacolato)diboron (8.17 g, 32.156 mmol) in dioxane (100 mL) were added KOAc (4.73 g, 48.234 mmol), PPh_3 (0.84 g, 3.216 mmol) and $Pd(PPh_3)_2Cl_2$ (1.13 g, 1.608 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. To this were added 2-chloro-5-[1-(difluoromethyl)cyclopropyl]pyridine (3.27 g, 16.078 mmol), Cs_2CO_3 (10.48 g, 32.156 mmol), H_2O (20 mL) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (1.31 g, 1.608 mmol) under nitrogen atmosphere. The resulting mixture was stirred for additional 2 h at 100 °C under nitrogen atmosphere. The resulting mixture was diluted with water (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1). The crude product was purified by reverse phase flash with the following conditions: C18 column; Mobile Phase: CH_3CN in water (10 mmol/L NH_4HCO_3), 20% to 70%; Wave Length: 254 nm to afford (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1- f][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate (4.8 g, 64%) as a yellow solid. MS ESI calculated for $C_{22}H_{22}F_3N_5O_3$ $[M + H]^+$, 462.17, found 462.20. 1H NMR (400 MHz, Chloroform- d) δ 8.78-8.61 (m, 3H), 7.90-7.76 (m, 1H), 7.12 (s, 1H), 5.62 (t, $J = 56.8$ Hz, 1H), 5.16-4.97 (m, 2H), 4.20-3.95 (m, 3H), 3.68-3.59 (m, 1H), 3.53-3.48 (m, 1H), 2.50-2.45 (m, 1H), 2.07 (s, 3H), 1.79-1.67 (m, 1H), 1.30-

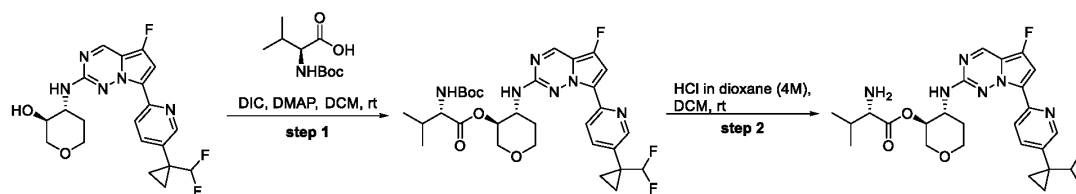
1.23 (m, 2H), 1.10-1.03 (m, 2H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -116.08 (2F), -160.58 (1F).

Step 7: (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol

To a stirred mixture of (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate (4.8 g, 10.402 mmol) in MeOH (100 mL) was added K_2CO_3 (4.31 g, 31.206 mmol). The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure. The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (10 mmol/L NH_4HCO_3), 10% to 50%; detector, UV 254 nm to afford (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol (1.19 g, 27%) as a yellow solid. MS ESI calculated for $\text{C}_{20}\text{H}_{20}\text{F}_3\text{N}_5\text{O}_2$ $[\text{M} + \text{H}]^+$, 420.16, found 420.10. ^1H NMR (400 MHz, DMSO-*d*₆) δ 9.01 (s, 1H), 8.80 (d, J = 8.4 Hz, 1H), 8.64 (d, J = 2.0 Hz, 1H), 7.95-7.91 (m, 1H), 7.16-7.12 (m, 1H), 7.08 (s, 1H), 5.92 (t, J = 56.0 Hz, 1H), 4.95 (d, J = 1.6 Hz, 1H), 3.90-3.84 (m, 2H), 3.75-3.71 (m, 1H), 3.61-3.56 (m, 1H), 3.50-3.44 (m, 1H), 3.19-3.13 (m, 1H), 2.17-2.13 (m, 1H), 1.54-1.44 (m, 1H), 1.22-1.18 (m, 2H), 1.11-1.07 (m, 2H). ^{19}F NMR (377 MHz, DMSO-*d*₆) δ -114.41 (2F), -161.58 (1F).

[00160] Example 6:

(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoate



Step 1: (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoate

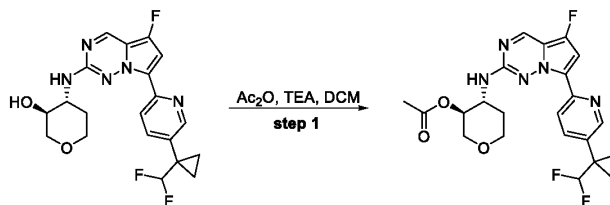
To a stirred solution of (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoic acid (2.07 g, 9.538 mmol) in DMF (40 mL) was added *N,N'*-diisopropylcarbodiimide (1.32 g, 10.492 mmol) at room temperature, followed by the addition of (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-

3-ol (2 g, 4.769 mmol) and DMAP (58 mg, 0.477 mmol) in DCM (40 mL). The resulting mixture was stirred for additional 2 h at room temperature. The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with DCM (3 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoate (2.8 g, 94%) as a yellow solid. MS ESI calculated for C₃₀H₃₇F₃N₆O₅ [M + H]⁺, 619.28, found 619.30.

Step 2: (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate

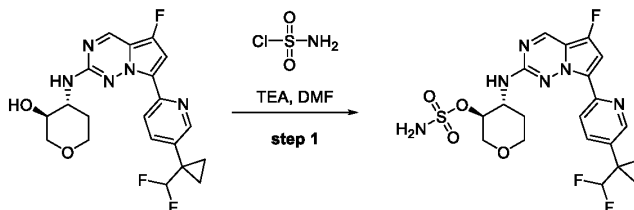
To a stirred solution of (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoate (2.8 g, 4.526 mmol) in DCM (30 mL) was added TFA (6 mL) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was basified to pH 8 with sat. NaHCO₃ (aq.). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: Column: WelFlash C18, Regular C18 20-40 μm, 330 g; Mobile Phase: CH₃CN in water (0.05% TFA), 22% to 52%; Wavelength: 254/220 nm; The resulting mixture was concentrated under reduced pressure to remove CH₃CN. Then the resulting mixture was basified to pH 8 with sat. NaHCO₃ (aq.) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was lyophilized to afford (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate (1.10 g, 46%) as a yellow solid. MS ESI calculated for C₂₅H₂₉F₃N₆O₃ [M + H]⁺, 519.23, found 519.35. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.00 (s, 1H), 8.80 (d, *J* = 8.4 Hz, 1H), 8.64 (d, *J* = 2.0 Hz, 1H), 7.95 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.10 (s, 1H), 5.91 (t, *J* = 56.0 Hz, 1H), 4.87-4.83 (m, 1H), 4.15-4.10 (m, 1H), 3.95-3.89 (m, 2H), 3.60-3.56 (m, 1H), 3.39-3.33 (m, 1H), 2.98 (d, *J* = 5.2 Hz, 1H), 2.13-2.07 (m, 1H), 1.77-1.67 (m, 2H), 1.49-1.47 (m, 2H), 1.23-1.20 (m, 2H), 1.10-1.08 (m, 2H), 0.68-0.65 (m, 6H). ¹⁹F NMR (377 MHz, DMSO-*d*₆) δ -114.36 (2F), -161.41 (1F).

[00161] Example 7:

(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate**Step 1: (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate**

To a stirred solution of (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol (100 mg, 0.238 mmol) and TEA (120 mg, 1.190 mmol) in DCM (2 mL) was added Ac₂O (36 mg, 0.357 mmol) at room temperature. The resulting mixture was stirred for 16 h at 50 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH₃CN in water (10 mmol/L NH₄HCO₃), 20% to 70%; detector, UV 254 nm to afford (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl acetate (50.4 mg, 45%) as a yellow solid. MS ESI calculated for C₂₂H₂₂F₃N₅O₃ [M + H]⁺, 462.17, found 462.20. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.99 (s, 1H), 8.77 (d, *J* = 8.4 Hz, 1H), 8.63 (d, *J* = 2.0 Hz, 1H), 7.92 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.09 (s, 1H), 5.91 (t, *J* = 56.0 Hz, 1H), 4.87-4.81 (m, 1H), 4.07-4.03 (m, 1H), 3.97-3.87 (m, 2H), 3.59-3.53 (m, 1H), 3.38-3.31 (m, 1H), 2.18-2.14 (m, 1H), 1.93 (s, 3H), 1.75-1.66 (m, 1H), 1.22-1.19 (m, 2H), 1.12-1.05 (m, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -114.33 (2F), -161.32 (1F).

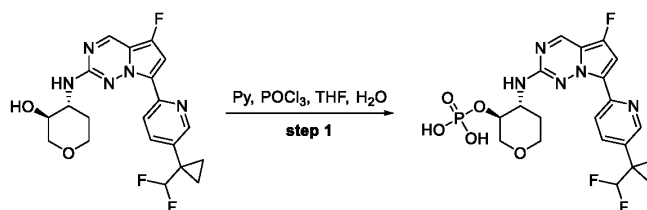
[00162] Example 8:

(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl sulfamate**Step 1: (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl sulfamate**

To a stirred solution of (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol (50 mg, 0.119 mmol) and TEA (36 mg, 0.357 mmol) in DMF (2 mL) was added sulfamoyl chloride (41 mg, 0.357 mmol) dropwise at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH₃CN in Water (10 mmol/L NH₄HCO₃), 20% to 60%; detector, UV 254 nm to afford (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl sulfamate (57 mg, 93%) as a yellow solid. MS ESI calculated for C₂₀H₂₁F₃N₆O₄S [M + H]⁺, 499.13, found 499.15. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.01 (s, 1H), 8.77 (d, *J* = 8.0 Hz, 1H), 8.64 (d, *J* = 2.0 Hz, 1H), 7.95 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.57 (s, 2H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.10 (s, 1H), 5.91 (t, *J* = 56.0 Hz, 1H), 4.50-4.44 (m, 1H), 4.17-4.09 (m, 2H), 3.90-3.86 (m, 1H), 3.59-3.50 (m, 2H), 2.19-2.15 (m, 1H), 1.75-1.71 (m, 1H), 1.24-1.20 (m, 2H), 1.11-1.08 (m, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -114.29 (2F), -161.40 (1F).

[00163] Example 9:

[(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl]oxyphosphonic acid



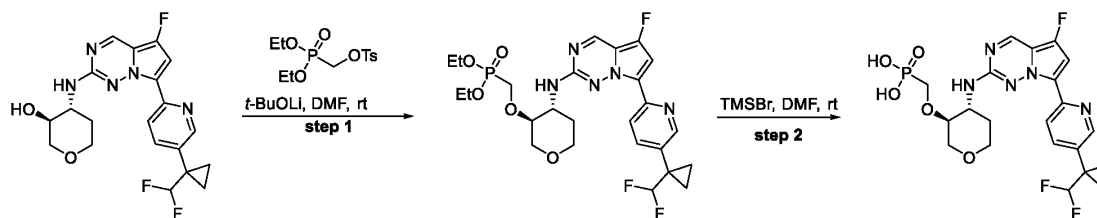
Step 1: [(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl]oxyphosphonic acid

To a stirred solution of (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol (50 mg, 0.119 mmol) and pyridine (18.8 mg, 0.238 mmol) in THF (1 mL) was added POCl₃ (36.5 mg, 0.238 mmol) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 4 h at room temperature under nitrogen atmosphere. To this was added H₂O (2 mL) dropwise at 0 °C. The resulting mixture was stirred for additional 1 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH₃CN in water (0.1% formic acid), 10% to 40%; detector, UV 254 nm to afford [(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl]oxyphosphonic acid (41.9 mg, 70%) as a yellow solid. MS ESI calculated for C₂₀H₂₁F₃N₅O₅P [M + H]⁺, 500.12, found 500.10. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.93 (s, 1H), 8.73 (d, *J* = 8.4 Hz, 1H), 8.60 (d, *J* = 2.0 Hz,

1H), 7.90 (dd, $J = 2.0, 8.4$ Hz, 1H), 7.65 (br, 1H), 7.05 (s, 1H), 5.89 (t, $J = 56.0$ Hz, 1H), 4.17-4.11 (m, 1H), 4.09-3.99 (m, 1H), 3.85-3.75 (m, 2H), 3.59-3.51 (m, 1H), 3.34-3.28 (m, 1H), 2.40-2.36 (m, 1H), 1.50-1.46 (m, 1H), 1.19-1.16 (m, 2H), 1.09-1.05 (m, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -114.44 (2F), -161.60 (1F). ^{31}P NMR (162 MHz, DMSO- d_6) δ -0.20.

[00164] Example 10:

(((3*S*,4*R*)-4-((7-(5-(1-(difluoromethyl)cyclopropyl)pyridin-2-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-yl)oxy)methyl)phosphonic acid



Step 1: diethyl (((3*S*,4*R*)-4-((7-(5-(1-(difluoromethyl)cyclopropyl)pyridin-2-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-yl)oxy)methyl)phosphonate

To a stirred solution of (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol (100 mg, 0.238 mmol) and *t*-BuOLi (0.16 mL, 0.357 mmol, 2.2 M in THF) in DMF (1 mL) was added diethyl [(4-methylbenzenesulfonyl)oxy]methanephosphonate (115 mg, 0.357 mmol) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH₃CN in Water (10 mmol/L NH₄HCO₃), 30% to 60%; detector, UV 254 nm to afford diethyl (((3*S*,4*R*)-4-((7-(5-(1-(difluoromethyl)cyclopropyl)pyridin-2-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-yl)oxy)methyl)phosphonate (70 mg, 51%) as a light yellow solid. MS ESI calculated for C₂₅H₃₁F₃N₅O₅P [M + H]⁺, 570.20, found 570.30.

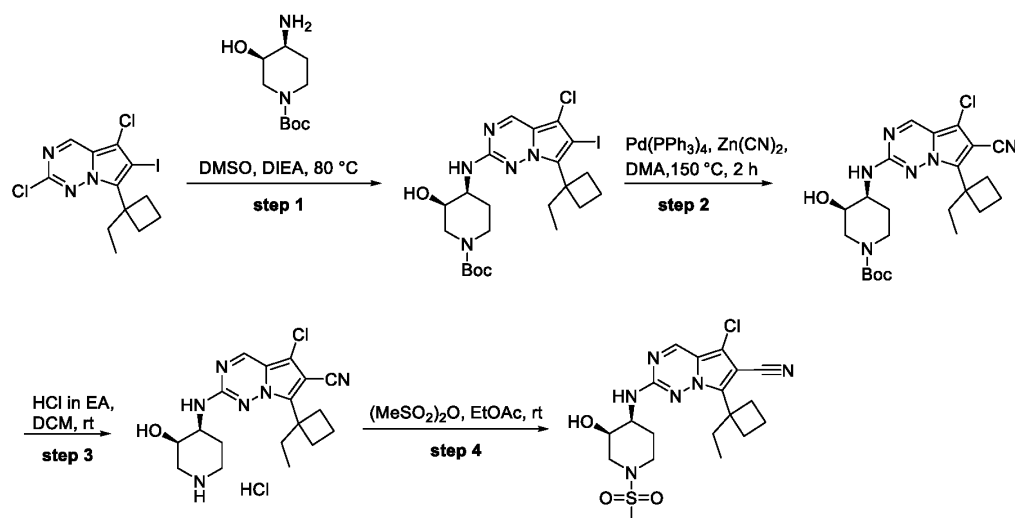
Step 2: (((3*S*,4*R*)-4-((7-(5-(1-(difluoromethyl)cyclopropyl)pyridin-2-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-yl)oxy)methyl)phosphonic acid

To a stirred solution of diethyl (((3*S*,4*R*)-4-((7-(5-(1-(difluoromethyl)cyclopropyl)pyridin-2-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino)tetrahydro-2*H*-pyran-3-yl)oxy)methyl)phosphonate (30 mg, 0.053 mmol) in DMF (1 mL) was added TMSBr (0.1 mL) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 3 h at room temperature under nitrogen atmosphere. The mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH₃CN in Water (0.1% formic acid), 20% to 45%; detector, UV 254 nm to afford (((3*S*,4*R*)-4-((7-(5-(1-(difluoromethyl)cyclopropyl)pyridin-2-yl)-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-

yl)amino)tetrahydro-2H-pyran-3-yl)oxy)methyl)phosphonic acid (1.2 mg, 4%) as a light yellow solid. MS ESI calculated for $C_{21}H_{23}F_3N_5O_5P$ $[M + H]^+$, 514.14; found 514.10. 1H NMR (400 MHz, DMSO- d_6) δ 8.95 (s, 1H), 8.76 (d, $J = 8.4$ Hz, 1H), 8.63 (s, 1H), 7.95 (d, $J = 8.4$ Hz, 1H), 7.88 (br, 1H), 7.05 (s, 1H), 5.93 (t, $J = 56.0$ Hz, 1H), 4.08-4.06 (m, 1H), 3.85-3.72 (m, 2H), 3.68-3.63 (m, 3H), 3.31-3.18 (m, 2H), 2.34-2.30 (m, 1H), 1.43-1.40 (m, 1H), 1.19-1.07 (m, 4H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -114.61 (2F), -161.69 (1F).

[00165] Example 11:

5-chloro-7-(1-ethylcyclobutyl)-2-yl-[(3R,4S)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile



Step 1: *tert*-butyl (3R,4S)-4-yl-[(5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-f][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

To a stirred solution of 2,5-dichloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-f][1,2,4]triazine (70 mg, 0.17 mmol) and *tert*-butyl (3R,4S)-4-amino-3-hydroxypiperidine-1-carboxylate (191 mg, 0.88 mmol) in DMF (2 mL) was added DIEA (137 mg, 1.06 mmol). The resulting mixture was stirred for 16 h at 80 °C. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH₃CN in water (10 mM NH₄HCO₃), 50% to 90%; detector, UV 254 nm to afford *tert*-butyl (3R,4S)-4-yl-[(5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-f][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (90 mg, 88%) as light yellow oil. MS ESI calculated for $C_{22}H_{31}ClIN_5O_3$ $[M + H]^+$, 576.12, found 576.15. 1H NMR (400 MHz, Chloroform- d) δ 8.54 (s, 1H), 5.11-5.08 (m, 1H), 4.10-4.06 (m, 2H), 3.83-3.74 (m, 1H), 3.11-3.07 (m, 1H), 2.99-2.87 (m, 1H), 2.75-2.70 (m, 2H), 2.37-2.33 (m, 3H), 2.19-2.04 (m, 2H), 1.95-1.73 (m, 3H), 1.50 (s, 9H), 0.81 (t, $J = 7.2$ Hz, 3H).

Step 2: *tert*-butyl (3R,4S)-4-yl-[(5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-f][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

To a stirred solution of *tert*-butyl (3*R*,4*S*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (75 mg, 0.13 mmol) and Pd(PPh₃)₄ (15 mg, 0.013 mmol) in DMF (1.5 mL) was added Zn(CN)₂ (9 mg, 0.07 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 150 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH₃CN in water (10 mM NH₄HCO₃), 10% to 50%; detector, UV 254 nm to afford *tert*-butyl (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (40 mg, 65%) as light yellow oil. MS ESI calculated for C₂₃H₃₁ClN₆O₃ [M + H]⁺, 475.21, found 475.35.

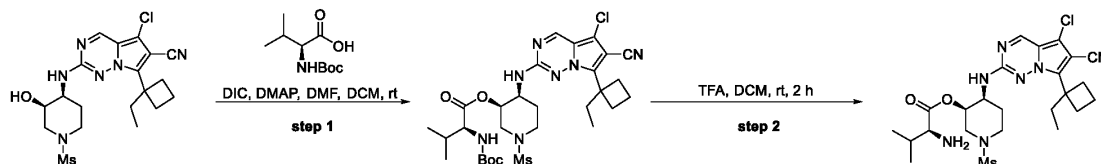
Step 3: 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*S*)-3-hydroxypiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride

To a stirred solution of *tert*-butyl (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (40 mg, 0.08 mmol) in DCM (2 mL) was added HCl (gas) in 1,4-dioxane (2 mL) dropwise at room temperature. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*S*)-3-hydroxypiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (40 mg, crude) as a light yellow solid. MS ESI calculated for C₁₈H₂₄Cl₂N₆O [M – Cl]⁺, 375.16, found 375.20.

Step 4: 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

To a stirred solution of 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*S*)-3-hydroxypiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (45 mg, 0.12 mmol) in EtOAc (2 mL) and sat. NaHCO₃ (2 mL) was added methanesulfonyl methanesulfonate (42 mg, 0.24 mmol) in portions at room temperature. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH₃CN in water (10 mM NH₄HCO₃), 40% to 70%; detector, UV 254 nm to afford 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (33.3 mg, 61%) as a light yellow solid. MS ESI calculated for C₁₉H₂₅ClN₆O₃S [M + H]⁺, 453.14, found 453.15. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.96 (s, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 5.16 (d, *J* = 4.4 Hz, 1H), 4.02-4.00 (m, 1H), 3.66-3.62 (m, 1H), 3.59-3.47 (m, 2H), 3.06-3.02 (m, 1H), 2.99-2.92 (m, 4H), 2.62-2.58 (m, 2H), 2.28-2.12 (m, 3H), 2.09-2.00 (m, 2H), 1.97-1.88 (m, 2H), 1.74-1.70 (m, 1H), 0.73-0.67 (m, 3H).

[00166] Example 12:

(3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl (2*S*)-2-amino-3-methylbutanoate**Step 1: (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoate**

To a stirred solution of 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*R*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (2.5 g, 5.519 mmol), (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoic acid (3.60 g, 16.557 mmol) and DMAP (0.07 g, 0.552 mmol) in DMF (50 mL) and DCM (50 mL) was added DIC (1.53 g, 12.142 mmol). The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of water/ice (100 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoate (3 g, 83%) as a yellow solid. MS ESI calculated for C₂₉H₄₂ClN₇O₆S [M + H]⁺, 652.26, found 652.30. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.63 (s, 1H), 5.65 (d, *J* = 8.0 Hz, 1H), 5.39 (s, 1H), 5.00 (d, *J* = 8.0 Hz, 1H), 4.13-4.02 (m, 2H), 3.94-3.92 (m, 2H), 3.05-3.01 (m, 1H), 2.97-2.93 (m, 1H), 2.91-2.88 (m, 3H), 2.79-2.65 (m, 2H), 2.34-2.28 (m, 2H), 2.25-1.94 (m, 4H), 1.47 (s, 9H), 1.14-0.94 (m, 7H), 0.83-0.79 (m, 3H).

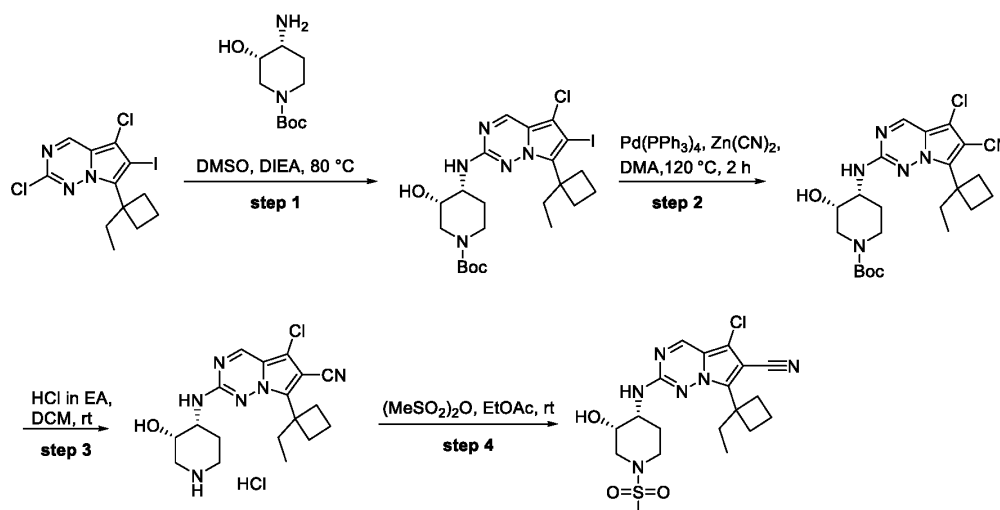
Step 2: (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl (2*S*)-2-amino-3-methylbutanoate

To a stirred mixture of (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl (2*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoate (3.5 g, 5.366 mmol) in DCM (35 mL) was added TFA (7 mL) dropwise at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The reaction was quenched by the addition of sat. NaHCO₃ (aq.) (200 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was

concentrated under reduced pressure. The residue was purified by trituration with acetonitrile/H₂O (1/2, 60 mL) to afford (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl (2*S*)-2-amino-3-methylbutanoate (2.18 g, 74%) as a yellow solid. MS ESI calculated for C₂₄H₃₄ClN₇O₄S [M + H]⁺, 552.21, found 552.15. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.96 (s, 1H), 7.62 (d, *J* = 6.0 Hz, 1H), 5.25 (s, 1H), 3.87-3.59 (m, 3H), 3.20 (d, *J* = 4.8 Hz, 1H), 3.12-3.09 (m, 1H), 2.98-2.92 (m, 4H), 2.63-2.59 (m, 2H), 2.31-2.22 (m, 2H), 2.21-1.81 (m, 7H), 1.59 (s, 2H), 0.86-0.80 (m, 6H), 0.72 (t, *J* = 7.2 Hz, 3H).

[00167] Example 13:

5-chloro-7-(1-ethylcyclobutyl)-2--{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile



Step 1: *tert*-butyl (3*S*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

To a stirred solution of 2,5-dichloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazine (90 mg, 0.227 mmol) and *tert*-butyl (3*S*,4*R*)-4-amino-3-hydroxypiperidine-1-carboxylate (246 mg, 1.136 mmol) in NMP (2 mL) was added DIEA (177 mg, 1.363 mmol). The resulting mixture was stirred for 16 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with PE/EtOAc (2/1) to afford *tert*-butyl (3*S*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (38 mg, 29%) as a yellow solid. MS ESI calculated for C₂₂H₃₁ClIN₅O₃ [M + H]⁺, 576.12, found 576.15.

Step 2: *tert*-butyl (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

To a stirred solution of *tert*-butyl (3*S*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (3 g, 5.209 mmol) and Zn(CN)₂ (0.2 g, 3.125 mmol) in DMF (30 mL) was added Pd(PPh₃)₄ (0.6 g, 0.521 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. The resulting mixture was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH₃CN in water (0.1% formic acid), 10% to 50% gradient in 10 min; detector, UV 254 nm to afford *tert*-butyl (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (2 g, 81%) as a yellow solid. MS ESI calculated for C₂₃H₃₁ClN₆O₃ [M + H]⁺, 475.21, found 475.25. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.66 (s, 1H), 5.50-5.43 (m, 1H), 4.25-4.20 (m, 1H), 4.17-4.02 (m, 2H), 3.76-3.72 (m, 1H), 3.06-3.02 (m, 1H), 2.95-2.84 (m, 1H), 2.69-2.63 (m, 2H), 2.31-2.27 (m, 2H), 2.11-2.02 (m, 3H), 1.99-1.88 (m, 2H), 1.86-1.74 (m, 1H), 1.49 (s, 9H), 0.80 (t, *J* = 7.2 Hz, 3H).

Step 3: 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxypiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride

A solution of *tert*-butyl (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (2 g, 4.211 mmol) and HCl (gas) in 1,4-dioxane (40 mL) in DCM (20 mL) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxypiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (2 g, crude) as a yellow solid. The crude product was used in the next step directly without further purification. MS ESI calculated for C₁₈H₂₄Cl₂N₆O [M – Cl]⁺, 375.16, found 375.15.

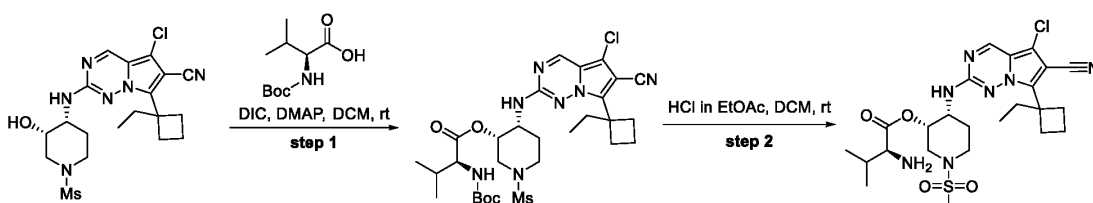
Step 4: 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

A solution of 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxypiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (2 g, 5.335 mmol) and Ms₂O (1.86 g, 10.670 mmol) in EtOAc (20 mL) was basified to pH 8 with sat. NaHCO₃. The resulting mixture was stirred for 1 h at room temperature. The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH₃CN in water (0.1% formic acid), 40 % to 60 %; detector, UV 254 nm to afford 5-

chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (1.5 g, 62%) as a light yellow solid. MS ESI calculated for $C_{19}H_{25}ClN_6O_3S$ $[M + H]^+$, 453.14, found 453.25. 1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 5.75 (d, $J = 7.6$ Hz, 1H), 4.15-4.10 (m, 1H), 4.01-3.93 (m, 1H), 3.89-2.84 (m, 1H), 3.79-3.69 (m, 1H), 3.08-3.04 (m, 1H), 2.93-2.86 (m, 4H), 2.76-2.62 (m, 2H), 2.35-2.25 (m, 2H), 2.19-2.15 (m, 1H), 2.06-2.02 (m, 3H), 2.01-1.83 (m, 2H), 0.80 (t, $J = 7.2$ Hz, 3H).

[00168] Example 14:

(3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl (2*S*)-2-amino-3-methylbutanoate



Step 1: (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoate

To a (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoic acid (532 mg, 2.45 mmol) and DIC (227 mg, 1.79 mmol) in DMF (4 mL) was added a solution of 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (370 mg, 0.81 mmol) and DMAP (10 mg, 0.08 mmol) in DCM (4 mL) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was diluted with water (100 mL) and extracted with DCM (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoate (400 mg, 75%) as a light yellow solid. MS ESI calculated for $C_{29}H_{42}ClN_7O_6S$ $[M + H]^+$, 652.26, found 652.35.

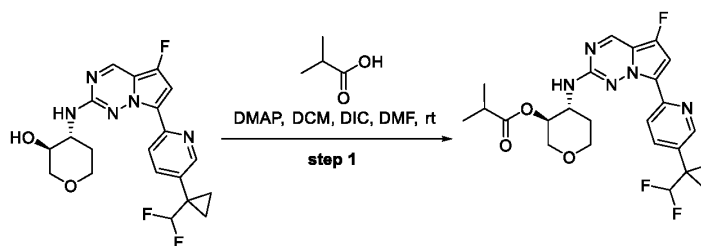
Step 2: (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl (2*S*)-2-amino-3-methylbutanoate

A solution of (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoate (400 mg, 0.61 mmol) and HCl (gas) in 1,4-dioxane (5 mL) in DCM (5 mL) was

stirred for 1 h at room temperature. The reaction was quenched with sat. NaHCO₃ (50 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography with the following conditions: C18 column; mobile phase, CH₃CN in water (10 mM NH₄HCO₃), 20% to 60%; detector, UV 254 nm to afford (3*S*,4*R*)-4-[[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl (2*S*)-2-amino-3-methylbutanoate (333.5 mg, 97%) as a light yellow solid. MS ESI calculated for C₂₄H₃₄ClN₇O₄S [M + H]⁺, 552.21, found 552.30. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.96 (s, 1H), 7.60 (brs, 1H), 5.33 (s, 1H), 3.78-3.68 (m, 2H), 3.65-3.61 (m, 1H), 3.16-3.07 (m, 2H), 3.02-2.92 (m, 4H), 2.68-2.58 (m, 2H), 2.34-1.82 (m, 9H), 1.70 (s, 2H), 0.87-0.83 (m, 3H), 0.75-0.66 (m, 6H).

[00169] Example 15:

(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl 2-methylpropanoate



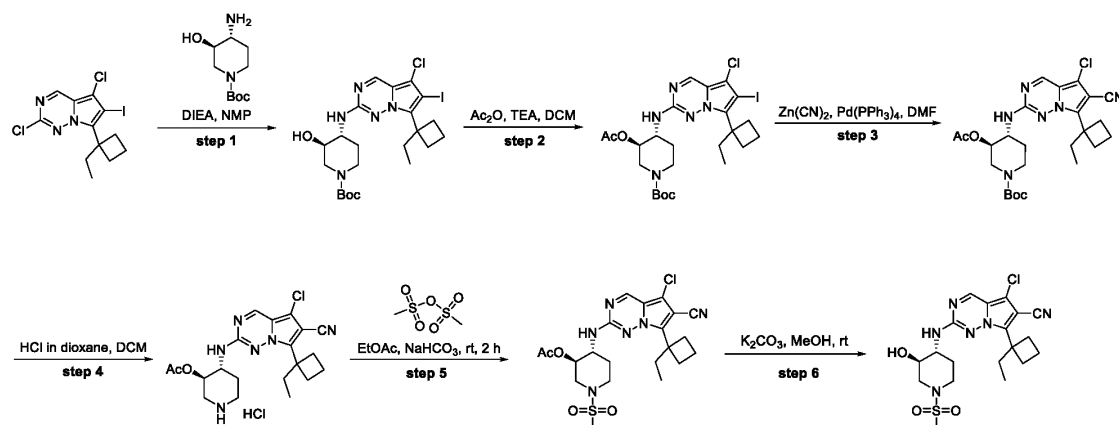
Step 1: (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl 2-methylpropanoate

To a stirred solution of isobutyric acid (63 mg, 0.715 mmol) in DMF (1 mL) was added DIC (66 mg, 0.525 mmol) at room temperature. Then to this was added a solution of (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol (100 mg, 0.238 mmol) and DMAP (3 mg, 0.024 mmol) in DCM (1 mL) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was quenched with water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: C18 column; mobile phase, acetonitrile in water (10 mM NH₄HCO₃), 20% to 60%; detector, UV 254 nm to afford (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl 2-methylpropanoate (55.5 mg, 47%) as a yellow solid. MS

ESI calculated for $C_{24}H_{26}F_3N_5O_3$ $[M + H]^+$, 490.20, found 490.20. 1H NMR (400 MHz, DMSO- d_6) δ 8.99 (s, 1H), 8.80 (d, J = 8.4 Hz, 1H), 8.64 (d, J = 2.0 Hz, 1H), 7.93 (dd, J = 8.0, 2.0 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.09 (s, 1H), 5.91 (t, J = 56.0 Hz, 1H), 4.85-4.79 (m, 1H), 4.16-4.12 (m, 1H), 3.95-3.90 (m, 2H), 3.59-3.53 (m, 1H), 3.34-3.32 (m, 1H), 2.43-2.36 (m, 1H), 2.11-2.08 (m, 1H), 1.79-1.73 (m, 1H), 1.23-1.20 (m, 2H), 1.10-1.09 (m, 2H), 0.95 (d, J = 7.2 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -114.30 (2F), -161.35 (1F).

[00170] Example 16:

5-chloro-7-(1-ethylcyclobutyl)-2-yl[(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile



Step 1: *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

A mixture of 2,5-dichloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazine (2.5 g, 6.312 mmol), *tert*-butyl (3*R*,4*R*)-4-amino-3-hydroxypiperidine-1-carboxylate (1.64 g, 7.574 mmol) and DIEA (3.26 g, 25.248 mmol) in NMP (50 mL) was stirred for 16 h at 80 °C. The reaction was quenched by the addition of water (100 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (3.3 g, 91%) as a yellow solid. MS ESI calculated for $C_{22}H_{31}ClIN_5O_3$ $[M + H]^+$, 576.12, found 576.15. 1H NMR (400 MHz, Chloroform-*d*) δ 8.51 (s, 1H), 4.96-4.92 (m, 1H), 4.32-4.25 (m, 1H), 4.16-4.10 (m, 2H), 3.66-3.57 (m, 2H), 2.90-2.85 (m, 1H), 2.80-2.66 (m, 3H), 2.40 (m, 2H), 2.25-2.05 (m, 3H), 1.85 (m, 1H), 1.50-1.48 (m, 10H), 0.81 (t, J = 7.2 Hz, 3H).

Step 2: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

A mixture of *tert*-butyl (3*R*,4*R*)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (3.3 g, 5.730 mmol), Ac₂O (0.88 g, 8.595 mmol) and TEA (2.32 g, 22.920 mmol) in DCM (50 mL) was stirred for 16 h at 50 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (3.3 g, 93%) as a yellow solid. MS ESI calculated for C₂₄H₃₃ClN₅O₄ [M + H]⁺, 618.13, found 618.15.

Step 3: *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate

A mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (3.3 g, 5.341 mmol), Zn(CN)₂ (345 mg, 2.938 mmol) and Pd(PPh₃)₄ (617 mg, 0.534 mmol) in DMF (40 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere. The reaction was quenched by the addition of water (100 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2/1) to afford *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (2.3 g, 83%) as a yellow solid. MS ESI calculated for C₂₅H₃₃ClN₆O₄ [M + H]⁺, 517.23, found 517.30. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.65 (s, 1H), 5.25 (brs, 1H), 4.92-4.88 (m, 1H), 4.09-4.03 (m, 1H), 3.94-3.87 (m, 1H), 3.78-3.75 (m, 1H), 3.13-3.08 (m, 2H), 2.74-2.68 (m, 2H), 2.37-2.28 (m, 3H), 2.23-1.92 (m, 7H), 1.52-1.48 (m, 10H), 0.81 (t, *J* = 7.2 Hz, 3H).

Step 4: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride

A mixture of *tert*-butyl (3*R*,4*R*)-3-(acetyloxy)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidine-1-carboxylate (1 g, 1.934 mmol) and HCl (gas) in 1,4-dioxane (10 mL, 1 M) in DCM (10 mL) was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (800 mg, 91%) as a yellow solid. MS ESI calculated for C₂₀H₂₆Cl₂N₆O₂ [M – Cl]⁺, 417.17, found 417.25.

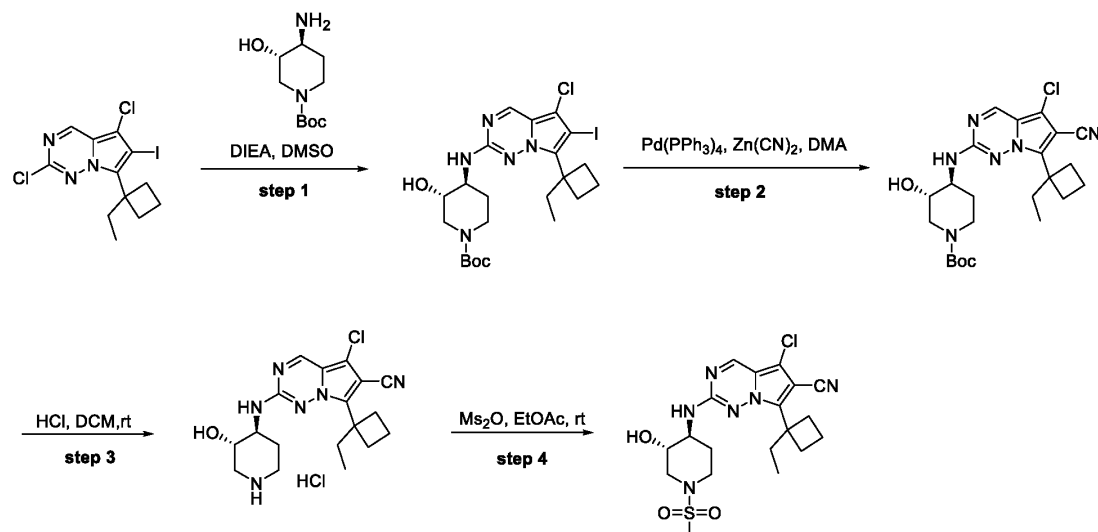
Step 5: (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate

A solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (50 mg, 0.120 mmol), NaHCO₃ (71 mg, 0.840 mmol) and methanesulfonic anhydride (42 mg, 0.240 mmol) in EtOAc (2 mL) and H₂O (2 mL) was stirred for 40 min at room temperature. The reaction was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: C18 column; mobile phase, CH₃CN in water (10 mM NH₄HCO₃), 40% to 60%; detector, UV 254 nm to afford (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (52 mg, 87%) as a light yellow solid. MS ESI calculated for C₂₁H₂₇ClN₆O₄S [M + H]⁺, 495.15, found 495.20.

Step 6: 5-chloro-7-(1-ethylcyclobutyl)-2-([(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

A solution of (3*R*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-methanesulfonylpiperidin-3-yl acetate (50 mg, 0.101 mmol) and K₂CO₃ (42 mg, 0.303 mmol) in MeOH (1 mL) was stirred for 30 min at room temperature. The mixture was purified by reversed-phase flash chromatography with the following conditions: C18 column; mobile phase, CH₃CN in water (10 mM NH₄HCO₃), 45% to 70%; detector, UV 254 nm to afford 5-chloro-7-(1-ethylcyclobutyl)-2-([(3*R*,4*R*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (28 mg, 61%) as a light yellow solid. MS ESI calculated for C₁₉H₂₅ClN₆O₃S [M + H]⁺, 453.14; found 453.25. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 5.07 (d, *J* = 6.8 Hz, 1H), 4.01-3.92 (m, 1H), 3.85-3.75 (m, 2H), 3.68-3.63 (m, 1H), 3.01-2.88 (m, 4H), 2.81-2.65 (m, 3H), 2.41-2.28 (m, 3H), 2.25-2.15 (m, 1H), 2.10-1.92 (m, 4H), 1.77-1.66 (m, 1H), 0.84-0.80 (m, 3H).

[00171] Example 17:

5-chloro-7-(1-ethylcyclobutyl)-2-[(3*S*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile**Step 1: *tert*-butyl (3*S*,4*S*)-4-[(5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate**

To a stirred solution of 2,5-dichloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazine (250 mg, 0.631 mmol) and *tert*-butyl (3*S*,4*S*)-4-amino-3-hydroxypiperidine-1-carboxylate (164 mg, 0.757 mmol) in DMSO (2.5 mL) was added DIEA (245 mg, 1.893 mmol). The resulting mixture was stirred for 4.5 h at 120 °C. The resulting mixture was allowed to cool down to room temperature and purified by reversed-phase flash chromatography with the following conditions: C18 column; mobile phase, CH_3CN in water (0.1% formic acid), 30% to 40%; detector, UV 254 nm to afford *tert*-butyl (3*S*,4*S*)-4-[(5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (330 mg, 91%) as a light yellow solid. MS ESI calculated for $\text{C}_{22}\text{H}_{31}\text{ClIN}_5\text{O}_3$. $[\text{M} + \text{H}]^+$, 576.12, found 576.15.

Step 2: *tert*-butyl (3*S*,4*S*)-4-[(5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate

To a stirred solution of *tert*-butyl (3*S*,4*S*)-4-[(5-chloro-7-(1-ethylcyclobutyl)-6-iodopyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (300 mg, 0.521 mmol) and Zn(CN)_2 (37 mg, 0.313 mmol) in DMA (3 mL) was added $\text{Pd(PPh}_3)_4$ (60 mg, 0.052 mmol). The resulting mixture was stirred for 2 h at 140 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water/ice (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous

Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: C18 column; mobile phase, CH₃CN in water (10 mM NH₄HCO₃), 40% to 60%; detector, UV 254 nm to afford *tert*-butyl (3*S*,4*S*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (200 mg, 81%) as a light yellow solid. MS ESI calculated for C₂₃H₃₁ClN₆O₃ [M + H]⁺, 475.21, found 475.25.

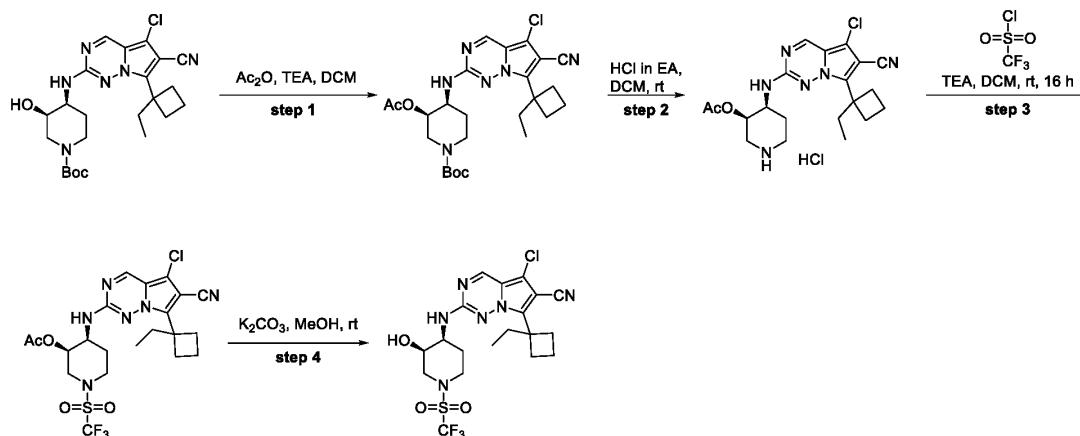
Step 3: 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*S*)-3-hydroxypiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride

To a stirred solution of *tert*-butyl (3*S*,4*S*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (200 mg, 0.421 mmol) in DCM (2 mL) was added HCl (gas) in 1,4-dioxane (2 mL) dropwise at room temperature. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*S*)-3-hydroxypiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (160 mg, crude) as a light yellow solid. MS ESI calculated for C₁₈H₂₄Cl₂N₆O [M – Cl]⁺, 375.16, found 375.15.

Step 4: 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

To a stirred solution of 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*S*)-3-hydroxypiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile hydrochloride (160 mg, 0.389 mmol) and NaHCO₃ (98 mg, 1.167 mmol) in H₂O (3 mL) and EtOAc (3 mL) was added methanesulfonic anhydride (135 mg, 0.778 mmol) in portions at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: C18 column; mobile phase, CH₃CN in water (10 mM NH₄HCO₃), 45% to 65%; detector, UV 254 nm to afford 5-chloro-7-(1-ethylcyclobutyl)-2-{[(3*S*,4*S*)-3-hydroxy-1-methanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (22.8 mg, 13%) as a light yellow solid. MS ESI calculated for C₁₉H₂₅ClN₆O₃S [M + H]⁺, 453.14, found 453.30. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 4.99-4.98 (m, 1H), 3.97-3.92 (m, 1H), 3.81-3.75 (m, 2H), 3.61-3.59 (m, 1H), 2.92-2.85 (m, 4H), 2.78-2.65 (m, 3H), 2.36-2.30 (m, 3H), 2.27-2.19 (m, 1H), 2.07-1.93 (m, 3H), 1.73-1.69 (m, 1H), 0.81-0.77 (m, 3H).

[00172] Example 18:

5-chloro-7-(1-ethylcyclobutyl)-2-[[[(3R,4S)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino]pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile

Step 1: *tert*-butyl (3*R*,4*S*)-3-(acetyloxy)-4-[[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino]piperidine-1-carboxylate

To a stirred solution of *tert*-butyl (3*R*,4*S*)-4-[[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino]-3-hydroxypiperidine-1-carboxylate (1 g, 2.105 mmol) and TEA (1.3 mL, 9.473 mmol) in DCM (10 mL) was added Ac₂O (0.4 mL, 4.210 mmol). The resulting mixture was stirred for 16 h at 50 °C. The resulting mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography, eluted with PE/EtOAc (5/1) to afford *tert*-butyl (3*R*,4*S*)-3-(acetyloxy)-4-[[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino]piperidine-1-carboxylate (1.0 g, 92%) as a yellow solid. MS ESI calculated for C₂₅H₃₃ClN₆O₄ [M + H]⁺, 517.23, found 517.25.

Step 2: (3*R*,4*S*)-4-[[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino]piperidin-3-yl acetate hydrochloride

A solution of *tert*-butyl (3*R*,4*S*)-3-(acetyloxy)-4-[[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino]piperidine-1-carboxylate (300 mg, 0.580 mmol) and DCM (10 mL) in HCl (gas) in 1,4-dioxane (20 mL) was stirred for 40 min at room temperature. The resulting mixture was concentrated under reduced pressure to afford (3*R*,4*S*)-4-[[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino]piperidin-3-yl acetate hydrochloride (200 mg, crude) as a yellow solid. MS ESI calculated for C₂₀H₂₆Cl₂N₆O₂ [M – Cl]⁺, 417.17, found 417.20.

Step 3: (3*R*,4*S*)-4-[[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino]-1-trifluoromethanesulfonylpiperidin-3-yl acetate

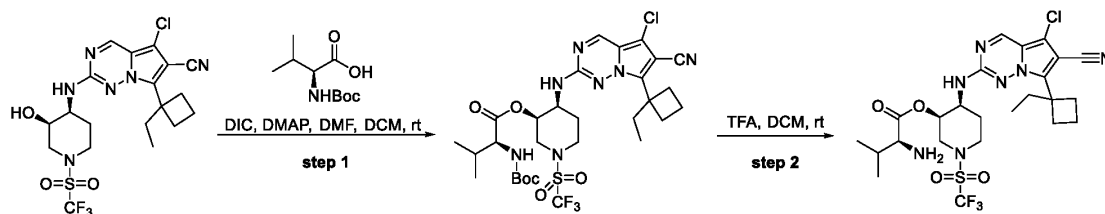
To a stirred solution of (3*R*,4*S*)-4-{{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}piperidin-3-yl acetate hydrochloride (200 mg, 0.480 mmol) and TEA (146 mg, 1.440 mmol) in DCM (2 mL) was added trifluoromethanesulfonyl chloride (162 mg, 0.960 mmol) dropwise at 0 °C. The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: C18 column; mobile phase, CH₃CN in Water (0.1% formic acid), 10% to 50%; detector, UV 254 nm to afford (3*R*,4*S*)-4-{{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-trifluoromethanesulfonylpiperidin-3-yl acetate (116 mg, 44%) as a yellow solid. MS ESI calculated for C₂₁H₂₄ClF₃N₆O₄S [M + H]⁺, 549.12, found 549.25.

Step 4: 5-chloro-7-(1-ethylcyclobutyl)-2-{{[(3*R*,4*S*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile

A solution of (3*R*,4*S*)-4-{{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-trifluoromethanesulfonylpiperidin-3-yl acetate (110 mg, 0.200 mmol) and K₂CO₃ (55 mg, 0.400 mmol) in MeOH (3 mL) was stirred for 25 min at room temperature. The resulting mixture was purified by reversed-phase flash chromatography with the following conditions: C18 column; mobile phase, CH₃CN in Water (0.1% formic acid), 45% to 75%; detector, UV 254 nm to afford 5-chloro-7-(1-ethylcyclobutyl)-2-{{[(3*R*,4*S*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (68.4 mg, 67%) as a light yellow solid. MS ESI calculated for C₁₉H₂₂ClF₃N₆O₃S [M + H]⁺, 507.11, found 507.05. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.97 (s, 1H), 7.15 (d, *J* = 6.4 Hz, 1H), 5.27 (d, *J* = 4.4 Hz, 1H), 4.08-4.04 (m, 1H), 3.80-3.68 (m, 3H), 3.48-3.42 (m, 1H), 3.38-3.34 (m, 1H), 2.67-2.52 (m, 2H), 2.27-2.23 (m, 2H), 2.18-2.11 (m, 1H), 2.09-1.82 (m, 4H), 1.78-1.72 (m, 1H), 0.75-0.72 (m, 3H). ¹⁹F NMR (377 MHz, DMSO-*d*₆) δ -75.43 (3F).

[00173] Example 19:

(3*R*,4*S*)-4-{{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-trifluoromethanesulfonylpiperidin-3-yl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoate



Step 1: (3*R*,4*S*)-4-{{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-trifluoromethanesulfonylpiperidin-3-yl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoate

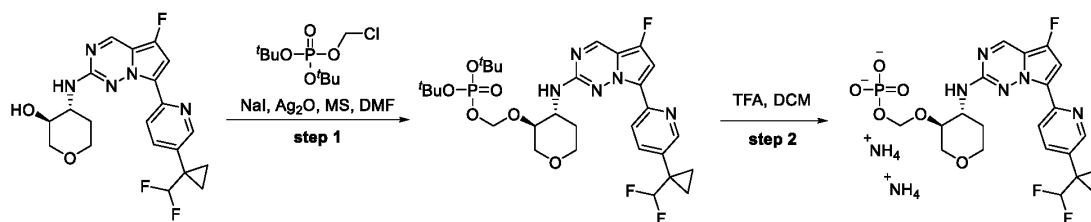
To a solution of (2*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoic acid (49 mg, 2.250 mmol) and DIC (208 mg, 1.650 mmol) in DMF (0.2 mL) was added a solution of 5-chloro-7-(1-ethylcyclobutyl)-2-[(3*R*,4*S*)-3-hydroxy-1-trifluoromethanesulfonylpiperidin-4-yl]amino}pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile (380 mg, 0.750 mmol) and DMAP (9 mg, 0.075 mmol) in DCM (2 mL) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was diluted with EtOAc (15 mL), washed with brine (3 x 5 mL), and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1/1) to afford (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-trifluoromethanesulfonylpiperidin-3-yl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoate (500 mg, 94%) as a yellow solid. MS ESI calculated for C₂₉H₃₉ClF₃N₇O₆S. [M + H]⁺, 706.23, found 706.30.

Step 2: (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-trifluoromethanesulfonylpiperidin-3-yl (2*S*)-2-amino-3-methylbutanoate

To a stirred mixture of (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-trifluoromethanesulfonylpiperidin-3-yl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoate (200 mg, 0.283 mmol) in DCM (2 mL) was added TFA (0.4 mL, 5.385 mmol) dropwise at 0 °C. The resulting mixture was stirred for 2h at room temperature. The reaction was quenched with sat. NaHCO₃ (20 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 5 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: C18 column; mobile phase, CH₃CN in Water (0.1% formic acid), 30% to 50%; detector, UV 254 nm to afford (3*R*,4*S*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}-1-trifluoromethanesulfonylpiperidin-3-yl (2*S*)-2-amino-3-methylbutanoate (68.4 mg, 39%) as a yellow solid. MS ESI calculated for C₂₄H₃₁ClF₃N₇O₄S [M + H]⁺, 606.18, found 606.45. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.97 (s, 1H), 7.64 (d, *J* = 6.0 Hz, 1H), 5.31 (s, 1H), 3.93-3.85 (m, 3H), 3.71-3.67 (m, 1H), 3.51-3.49 (m, 1H), 3.21-3.19 (m, 1H), 2.67-2.60 (m, 2H), 2.31-2.26 (m, 2H), 2.19-2.17 (m, 1H), 2.15-1.87 (m, 6H), 1.75 (brs, 2H), 2.04-2.03 (m, 3H), 2.01-2.00 (m, 3H), 1.98-1.97 (m, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -75.52 (3F).

[00174] Example 20:

diammonium }[(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl]oxy}methyl phosphate



Step 1: di-*tert*-butyl {[*(3S,4R)*-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl]oxy}methyl phosphate

To a mixture of (*3S,4R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol (500 mg, 1.192 mmol), NaI (536 mg, 3.576 mmol), Ag₂O (829 mg, 3.576 mmol) and 4 Å MS (750 mg) in DMF (6 mL) was added di-*tert*-butyl chloromethyl phosphate (3.08 g, 11.907 mmol) dropwise at room temperature. The resulting mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of ice/salt (100 mL). The resulting mixture was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: C18 column; mobile phase, CH₃CN in Water (0.1% formic acid), 10% to 80%; detector, UV 254 nm to afford di-*tert*-butyl {[*(3S,4R)*-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl]oxy}methyl phosphate (210 mg, 24%) as a yellow solid. MS ESI calculated for C₂₉H₃₉F₃N₅O₆P [M + H]⁺, 642.26, found 642.40.

Step 2: diammonium {[*(3S,4R)*-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl]oxy}methyl phosphate

To a stirred mixture of di-*tert*-butyl {[*(3S,4R)*-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl]oxy}methyl phosphate (100 mg, 0.156 mmol) in DCM (25 mL) was added TFA (1 mL) dropwise at -10 °C. The resulting mixture was stirred for 1 h at -10 °C. The reaction was quenched by the addition of sat. NH₄HCO₃ (aq.) (50 mL) at -10 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: C18 column; mobile phase, CH₃CN in water (10 mM NH₄HCO₃), 10% to 80%; detector, UV 254 nm to afford diammonium {[*(3S,4R)*-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl]oxy}methyl phosphate (12.9 mg, 14%) as a yellow solid. MS ESI calculated for C₂₁H₂₉F₃N₇O₆P [M + H - 2NH₄⁺]⁺, 530.13, found 530.20. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.96 (s, 1H), 8.78 (d, *J* = 8.4 Hz, 1H), 8.63 (d, *J* = 1.6 Hz, 1H), 7.95 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.86 (brs, 1H), 7.18 (brs, 2H), 7.10-7.06 (m, 1H), 5.93 (t, *J* = 56.0 Hz, 1H), 5.04-5.00 (m, 2H),

4.13-4.09 (m, 1H), 3.86-3.83 (m, 3H), 3.51-3.40 (m, 1H), 3.38-3.20 (m, 1H), 2.34-2.24 (m, 1H), 1.49-1.46 (m, 1H), 1.21-1.09 (m, 4H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -114.51 (2F), -161.67 (1F).

II. Biological Evaluation

[00175] Example 1: In-vitro Biochemical and Cellular Assay

AssayQuant CDK assay

CDK/Cyclin Fluorescent Assay

Small molecule inhibition of CDK4/Cyclin D1, CDK6/CyclinD3, CDK2/CyclinE1 kinase activities were evaluated using a fluorescence-based phosphosensor (AssayQuant Technologies). The sensing mechanism exploits a synthetic α-amino acid that relays information on the phosphorylation state of the kinase substrates. Upon phosphorylation of the substrate, fluorescence is turned on. The CDK/Cyclin complex catalyzes the phosphoryl transfer to the substrate peptide (AQT0258 for CDK4 and CDK6 complexes; AQT0297 for CDK2 complexes), leading to an increase in fluorescence that is directly proportional to the amount of phosphorylated substrate. CDK4/Cyclin D1 (Thermo Fisher, PR8064A) at 2.5 nM, CDK6/CyclinD3 (Carna Biosciences, 04-107) at 10nM, CDK2/CyclinE1 (Eurofins, 14-475M) at 1.25nM were prepared with 10uM substrate in a buffer containing 10mM MgCl₂, 54 mM HEPES, 0.55 mM EGTA, 0.01% Brij-35, 0.02% BSA, 1 mM DTT and 1% glycerol and pre-incubated at room temperature for 30 min prior to the start of the reaction. ATP is added to start the reaction (400uM for CDK4, 250uM for CDK6, 120uM for CDK2). The reaction is allowed to run for as long as 180 minutes at room temperature, then fluorescence read on the EnSight Reader. IC₅₀ values were calculated using the inhibition of conversion ratio using Dotmatics Knowledge Solutions Studies curve fitting (Dotmatics, Bishops Stortford, UK, CM23) and are presented in **Table 2**.

Phospho-Serine 807/811 Rb HTRF Assay

Cells were seeded at 25,000 cells or 20,000 cells per well in 90 μL growth media and allowed to adhere to the plate at 37° C. with 5% CO₂ overnight. The following day, compounds were serially diluted from a 10 mM top dose for a 10-point 3-fold dilution curve in DMSO. Following a 100-fold dilution in growth media, a further 10-fold dilution was made into the cell plate for a final volume of 100ul and 0.1% DMSO. Compounds and cells were incubated together for 18 hours at 37° C. with 5% CO₂. Phosphorylation at serine 807/811 was assessed using an HTRF sandwich assay (Cisbio, 64RBS807PEH). The specific signal modulates positively in proportion to phospho-Rb (Ser807/811). Following the 18 hour compound incubation period, cells were lysed for 45 minutes while shaking and then further homogenized. Specific Eu³⁺-Cryptate (donor) and d2 (acceptor) labeled antibodies were added to the cell

lysate and incubated overnight at room temperature. Specific signal was used to calculate IC₅₀ values within the Dotmatics Knowledge Solutions Studies curve fitting environment (Dotmatics, Bishops Stortford, UK, CM23) and are presented in **Table 2 and 3**.

Cyquant Assay

Cells are plated at densities ranging from 1000 cells/well to 2500 cells/well into 96-well poly-D-lysine coated plates and allowed to adhere overnight in an incubator at 37° C and 5% CO₂. The following day, compounds were serially diluted from a 10 mM top dose for a 9-point 3-fold dilution curve in DMSO. Following a 100-fold dilution in growth media, a further 10-fold dilution was made into the cell plate for a final volume of 150ul and 0.1% DMSO. Compounds and cells were incubated together for 6 days at 37° C with 5% CO₂. CyQuant (Invitrogen, C35011) detection buffer was prepared according to manufacturer's directions and the 2x solution added to the cells in culture. Following a 60-minute incubation of the detection reagent with cells at 37°C, fluorescence is read using the standard "green" filter set on the Envision reader. Specific signal was used to calculate IC₅₀ values within the Dotmatics Knowledge Solutions Studies curve fitting environment (Dotmatics, Bishops Stortford, UK, CM23) and are presented in **Table 2 and 3**.

Table 2

Example	CDK4 (CycD1) IC50 (nM)	CDK6 (CycD3) IC50 (nM)	CDK2 (CycE1) IC50 (nM)	CDK1 (CycB1) IC50 (nM)	GSK3B IC50 (nM)	WM3629 (pRb) IC50 (nM)	Kuramochi (CyQuant) IC50 (nM)	MCF7 (CyQuant) IC50 (nM)	MOLM13 (pRb) IC50 (nM)
1	0.7	6.0	149.4	289	>10uM	27.8	1280	107	250
2	30.3	340.8	>1uM	--	--	--	--	103	--
3	0.3	1.9	0.6	34.2	68.1	8.4	41.3	26.2	32.5
4	17.3	65.9	25.9	243.9	72.4	10.1	38.9	35.2	50.5
5	0.3	3.0	>1uM	>10uM	>10uM	11.6	1470	29.7	78.3
6	26.5	218.2	>1uM	>10uM	4154.5	20.9	3320	59.4	136
7	10.6	37.6	308.5	1073.4	722.1	17.6	2150	41.4	223
8	25.4	89.8	>1uM	1359.2	2344.3	841	3420	>1uM	>10uM
9	439	>1uM	>1uM	>10uM	>10uM	541	>10uM	>1uM	>10uM
10	239.3	>1uM	7648.4	7648.4	4862.3	>3uM	>10uM	>1uM	>10uM
11	5.9	8.2	0.2	8.2	157	143	10.3	38.4	203
12	276.9	404.7	18.8	608.1	>10uM	1740	11.8	71.8	1160
13	1.2	4.6	0.9	26	445	34.4	32.9	51.7	74.9
14	67.7	227.6	68.9	1434.2	--	284	53.9	88.6	472
15	113.9	>1uM	>1uM	2669	--	--	--	--	--
16	0.1	1.5	0.3	2.6	--	0.7	4.0	1.4	1.2

Example	CDK4 (CycD1) IC50 (nM)	CDK6 (CycD3) IC50 (nM)	CDK2 (CycE1) IC50 (nM)	CDK1 (CycB1) IC50 (nM)	GSK3B IC50 (nM)	WM3629 (pRb) IC50 (nM)	Kuramochi (CyQuant) IC50 (nM)	MCF7 (CyQuant) IC50 (nM)	MOLM13 (pRb) IC50 (nM)
17	21.9	29.2	3.5	50.1	132.7	--	--	--	--
18	33.5	68.8	1.8	68.2	960.5	2280	109	2240	6710
19	>1uM	>1uM	177.2	2744.4	>10uM	--	--	--	--
20	--	--	--	--	--	--	--	--	--

Table 3

Compound	Cell Line	Rationale	Cyquant Geomean (nM)	N	pRB 807 HTRF Geomean (nM)	N
1	DBTRG-05MG	Brain disease (GBM)	63.3	25	45.4	8
	T-47D	HR+ BC	54.1	4	13.0	2
	HCC-1143	TNBC	320	3	--	--
	ZR-75-1	CDK4 dependent HR+ BC	78.1	4	31.8	14
	NCI-H526	SCLC	--	--	--	--
3	DBTRG-05MG	Brain disease (GBM)	18.3	3	--	--
	T-47D	HR+ BC	32.7	5	--	--
	HCC-1143	TNBC	48.6	7	--	--
	ZR-75-1	CDK4 dependent HR+ BC	51	1	34.7	3
	NCI-H526	SCLC	327	3	--	--
5	DBTRG-05MG	Brain disease (GBM)	33.2	3	--	--
	T-47D	HR+ BC	18.6	5	--	--
	HCC-1143	TNBC	73.5	7	--	--
	ZR-75-1	CDK4 dependent HR+ BC	--	--	16.1	8
	NCI-H526	SCLC	>10uM	2	--	--
11	DBTRG-05MG	Brain disease (GBM)	39.6	3	--	--
	T-47D	HR+ BC	84.0	4	--	--
	HCC-1143	TNBC	42.6	7	--	--
	ZR-75-1	CDK4 dependent HR+ BC	--	--	419.0	2
	NCI-H526	SCLC	93.6	3	--	--

III. Xenograph Evaluation

[00176] **Example 2: Compound 1 Anti-tumor Activity and Pathway Inhibition in the WM3629 Melanoma Tumor Model**

[00177] Compound 1 was well-tolerated and efficacious in the athymic nude mouse xenograft model of a Class III BRAF mutant/CDK4 sensitive melanoma at doses up to 90 mg/kg TID daily (total dose of 270 mg/kg daily). Specifically, dose-dependent tumor growth and pathway inhibition was observed in the WM3629 cell line-derived xenograft model. The high dose of 90 mg/kg Compound 1 dosed orally three times daily led to significant TGI of 47% when compared to vehicle treatment ($p<0.001$). Consistent with the anti-tumor activity observed, 90 mg/kg Compound 1 significantly suppressed the tumor pharmacodynamic biomarker pRB by 56% when measured 1-hour post treatment when compared to vehicle treatment ($p<0.005$). These data identify that Compound 1 has potent antitumor activity in Class III BRAF mutant/CDK4 sensitive melanoma.

[00178] **Methods:** Athymic nude mice were inoculated subcutaneously with 1×10^7 WM3629 tumor cells. Groups and treatments were started when the mean tumor volume for each group reached approximately 300 mm³. Mice were assigned to respective groups based on their starting tumor volume and body weight such that the average values were the same for each treatment group. Animals were dosed three times daily and monitored for tumor growth, body weight changes, and general health/behavior. In a separate experiment, the tumor pharmacodynamic (PD) biomarker pRB was examined after the three days of treatment doses.

[00179] **Results:** Dose-dependent inhibition of tumor growth relative to vehicle treated tumors was observed with Compound 1 (**Table 4 and Fig. 1A**). The lower doses of 10 and 30 mg/kg Compound 1 yielded modest TGI of 34 and 32% that was not statistically different than vehicle treatment. The higher dose of 90 mg/kg Compound 1 induced TGI of 47% compared to vehicle ($p<0.001$). All of the tested doses were well tolerated, and no weight loss was observed in any Compound 1 treatment groups when compared to vehicle (**Fig. 1B**).

Table 4

Group	Treatment	WM3629 %TGI
1	Vehicle	-
2	Compound 1 10 mpk TID	34
3	Compound 1 30mpk TID	32
4	Compound 1 90mpk TID	47

TGI was assessed on day 18 post first dose compared to vehicle (n=8 animals/group).
Vehicle was 0.5% MC with 0.1% Tween 80.

[00180] The ability of Compound 1 to inhibit the tumor pharmacodynamic biomarker pRB was examined after 3-days of TID treatment with 10, 30 and 90 mg/kg Compound 1. Dose dependent inhibition of pRB by Compound 1 was observed (**Fig. 2**). The highest dose of 90mg/kg Compound 1 resulted in reductions of pRB by 56 and 63% when measured 1- and 7-hours post-dose, respectively, compared to vehicle treatment ($p<0.005$ for both timepoints).

[00181] Example 3: Compound 2 Anti-tumor Activity in the MCF7 Breast Cancer Model

Compound 2, which is the valine ester prodrug of compound 1, was well-tolerated and efficacious in the athymic nude mouse xenograft model of a CDKN2A mutant HR+ breast cancer model (MCF7) at doses up to 62 mg/kg BID daily (total dose of 124 mg/kg daily). Specifically, the high dose of 62 mg/kg Compound 2 (equivalent to 50 mg/kg Compound 1) administered orally twice daily led to TGI of 81% when compared to vehicle treatment ($p<0.001$).

[00182] Methods: Athymic nude mice were inoculated subcutaneously with 1.5×10^7 MCF7 tumor cells. Groups and treatments were started when the mean tumor volume for each group reached approximately 200 mm³. Mice were assigned to respective groups based on their starting tumor volume and body weight such that the average values were the same for each treatment group. Animals were dosed twice daily and monitored for tumor growth, body weight changes, and general health/behavior.

[00183] Results: Dose-dependent inhibition of tumor growth relative to vehicle treated tumors was observed with Compound 2. As summarized in **Table 5**, the 19 mg/kg BID dose of Compound 2 yielded a mean TGI of 59%. The higher dose of 62 mg/kg BID Compound 2 induced TGI of 81% compared to vehicle ($p<0.001$). Both tested doses were well tolerated, and no weight loss was observed in any Compound 2 treatment groups when compared to vehicle. These data identify that Compound 2 has potent antitumor activity in a CDKN2A mutant HR+ breast cancer model.

Table 5

Group	Treatment	MCF-7 %TGI
1	Vehicle 1	-
2	Vehicle 2	0
3	PF-0722060 2mpk BID	32
4	PF-0722060 6mpk BID	42
5	PF-0722060 20mpk BID	53

6	PF-0722060 60mpk BID	80
7	Compound 2 19mpk BID	59
8	Compound 2 62mpk BID	81

[00184] Example 4: Compound 4 and Compound 6 Anti-tumor Activity in the MCF7 Breast Cancer Model

[00185] Compound 4, which is the valine ester prodrug of compound 3, and Compound 6, which is the valine ester prodrug of compound 5, were efficacious in the athymic nude mouse xenograft model of a CDKN2A mutant HR+ breast cancer model (MCF7) at doses up to 113.4 mg/kg BID daily (total dose of 226.8 mg/kg daily for Compound 4) and 37.2 mg/kg BID daily (total dose of 74.4 mg/kg daily for Compound 6), respectively. Specifically, the high dose of 113.4 mg/kg Compound 4 (equivalent to 90mg/kg Compound 3) administered orally twice daily led to TGI of 59% when compared to vehicle treatment ($p<0.001$). The high dose of 37.2 mg/kg Compound 6 (equivalent to 30mg/kg Compound 5) administered orally twice daily led to TGI of 70% when compared to vehicle treatment ($p<0.001$). Modest body weight loss of 6% was observed after the 21-day treatment of 113.4 mg/kg BID Compound 4. Compound 6 was well-tolerated with no observed effects on body weight at doses up to 37.2mg/kg BID daily.

[00186] Methods: Athymic nude mice were inoculated subcutaneously with 1.5×10^7 MCF7 tumor cells. Groups and treatments were started when the mean tumor volume for each group reached approximately 200 mm³. Mice were assigned to respective groups based on their starting tumor volume and body weight such that the average values were the same for each treatment group. Animals were dosed twice daily and monitored for tumor growth, body weight changes, and general health/behavior.

[00187] Results: Dose-dependent inhibition of tumor growth relative to vehicle treated tumors was observed with Compound 4 and Compound 6. As summarized in **Table 6**, the low doses of 12.6 and 37.8 mg/kg BID of Compound 4 yielded mean TGI of 17 and 28%, respectively. The higher dose of 113.4 mg/kg BID Compound 4 induced TGI of 59% compared to vehicle ($p<0.001$). The two lower doses were well tolerated, and no weight loss was observed when compared to vehicle. The higher dose of 113.4mg/kg Compound 4 induced an overall mean body weight loss of 6% for the group. Compound 6 was well tolerated with no body weight loss observed in any groups when compared to vehicle treatment. The low doses of 3.72 and 12.4 mg/kg BID of Compound 6 yielded mean TGI of 17 and 36%, respectively. The higher dose of 37.2 mg/kg BID Compound 6 induced TGI of 70% compared to vehicle ($p<0.001$).

These data identify that Compound 4 and Compound 6 has potent antitumor activity in a CDKN2A mutant HR+ breast cancer model.

Table 6

Group	Treatment	MCF-7 %TGI
1	Vehicle 1	-
2	PF-0722060 15mpk BID	38
3	Compound 4 12.6mpk BID	17
4	Compound 4 37.8mpk BID	28
5	Compound 4 113.4mpk BID	59
6	Compound 6 3.72mpk BID	17
7	Compound 6 12.4mpk BID	36
8	Compound 6 37.2mpk BID	70

Note: TGI was assessed on day 21 post first dose compared to vehicle (n=8 animals/group).
Vehicle was 0.5% MC with 0.1% Tween 80.

IV. ADME and Pharmacokinetic Evaluation

[00188] Example 1: ADME evaluation of compounds 3, 4, 5, 6, 7, 8, 9, 10, 15 and 20

[00189] Kinetic *Solubility Assay*

[00190] The stock solutions of test compounds and control compound diclofenac sodium were prepared in DMSO at the concentration of 10 mM.

Procedure for solubility determination:

30 µL of stock solutions (10 mM) of test compounds and control compound were placed in order into their proper 96-well rack. 970 µL of PBS pH 2.0 or pH 7.4 was added into each vial of the cap-less Solubility Sample plate. The assay was performed in duplicate. Add one stir stick to each vial and seal using a molded PTFE/Silicone plug. Then the Solubility Sample plate was transferred to the Eppendorf Thermomixer Comfort plate shaker and shaken at 25 °C at 1100

RPM for 2 hours. After completion of the 2 hours, plugs were removed and the stir sticks were removed using a big magnet, the samples from the Solubility Sample plate were transferred into the filter plate. Using the Vacuum Manifold, all the samples were filtered. Aliquot of 5 μL was taken from the filtrate followed by addition of 5 μL DMSO and 490 μL of a mixture of H_2O and acetonitrile (1:1 in v/v). 200 μL of diluent was transferred to a new 96-well plate for LC-MS/MS analysis. The dilution factor was changed according to the solubility value and the LC-MS signal response.

Preparation of standards (STD):

From the 10 mM DMSO STD plate, 15 μL was transferred into the remaining empty plate, and then 485 μL of DMSO was added to that plate to have a STD concentration of 300 μM . From the 300 μM DMSO STD plate, 5 μL DMSO STD was transferred into the remaining empty plate, and then 5 μL PBS pH 2.0, pH 4.5 or pH 7.4 and 490 μL of a mixture of H_2O and acetonitrile (1:1 in v/v) was added to that plate to have a final STD concentration of 3 μM . 200 μL of diluent was transferred to a new 96-well plate for LC-MS/MS analysis. The concentrations of the standard samples were changed according to the LC-MS signal response.

Procedure for sample analysis:

The plate was placed into the well plate autosampler. The samples were evaluated by LC-MS/MS analysis.

Data analysis:

All calculations were carried out using Microsoft Excel. The filtrate was analyzed and quantified against a standard of known concentration using LC coupled with mass spectral peak identification and quantitation.

Human Hepatocyte Stability Protocol

Preparation of Working Solutions

Prepare 10 mM stock solutions of test compound(s) and positive control in appropriate solvent (DMSO). In separate conical tubes, dilute the 10 mM test compound and the positive control to 100 μM by combining 495 μL of 50% acetonitrile/50% water and 5 μL of 10 mM stock.

Preparation of Hepatocytes

Place incubation medium (William's E Medium supplemented with GlutaMAX) and hepatocyte thawing medium in a 37 $^{\circ}\text{C}$ water bath and allow warming for at least 15 minutes prior to use. Remove a vial of cryopreserved hepatocytes from storage, ensuring that vials remain at cryogenic temperatures until thawing process ensues. Thaw the cells by placing the vial in a 37 $^{\circ}\text{C}$ water bath and gently shaking the vials for 2 minutes. After thawing is completed, spray vial with 70% ethanol, transfer the vial to a biosafety cabinet. Use wide-bore pipette tip to transfer hepatocytes into 50 mL conical tube containing thawing medium. Place the 50 mL conical tube

into a centrifuge and spin at 100 g for 10 minutes. Upon completion of spin, aspirate thawing medium and resuspend hepatocytes in enough incubation medium to yield $\sim 1.5 \times 10^6$ cells/mL. Using AOPI staining solution, count cells and determine the viable cell density. Cells with poor viability (<75% viability) are not acceptable for use. Dilute cells with incubation medium to a working cell density of 0.5×10^6 viable cells/mL. A portion of the hepatocytes at 0.5×10^6 viable cells/mL should be boiled for 5 min prior to adding to the plate as representative of a negative control. This will eliminate the enzymatic activity so that little or no substrate turnover should be observed.

Procedure for Stability Determination

Pipette 198 μ L of hepatocytes into each well of a 96-well non-coated plate. Place the plate in the incubator on an orbital shaker to allow the hepatocytes to warm for 10 minutes. Pipette 2 μ L of the 100 μ M test compound or positive control into respective wells of the 96-well non-coated plate to start the reaction. The final concentration of test compound or control compounds was 1 μ M. Return the plate to the incubator and place on an orbital shaker. Remove well contents in 25 μ L aliquots at time points of 0, 15, 30, 60, 90 and 120 minutes. The aliquots are then mixed with 6 volumes (150 μ L) of acetonitrile containing internal standards (IS: 100 nM alprazolam, 200 nM labetalol, 200 nM caffeine and 2 μ M ketoprofen) to terminate the reaction. Centrifuge the plate for 20 minutes at 3,220 g. Aliquot of 100 μ L of the supernatant was mixed with 100 μ L of ultra-pure H₂O and then used for LC-MS/MS analysis. All incubations will be performed in duplicate.

Data analysis

All calculations were carried out using Microsoft Excel. Peak areas were determined from extracted ion chromatograms. Determine the in vitro half-life ($t_{1/2}$) of parent compound by regression analysis of the percent parent disappearance vs. time curve.

The in vitro half-life (in vitro $t_{1/2}$) was determined from the slope value: $\text{in vitro } t_{1/2} = 0.693 / k$

k = rate constant (-slope value);

Conversion of the in vitro $t_{1/2}$ (in min) into the scale-up intrinsic clearance (Scaled-up CL_{int}, in mL/min/kg) was done using the following equation (mean of duplicate determinations): Scaled-up CL_{int} = $kV/N \times \text{scaling factor}$

V = incubation volume (0.2 mL);

N = number of hepatocytes per well (0.1×10^6 cells).

Scaling factors for in vivo intrinsic clearance prediction using different species of hepatocytes are listed below in **Table 7**:

Table 7: Scaling Factors for Intrinsic Clearance Prediction in Hepatocytes

Species	Liver Weight (g liver/kg body weight)	Hepatocyte Concentration (106 cells/g liver)	Scaling Factor
Human	25.7	99	2544.3

[00191] The positive control compound (verapamil) was included in the assay. Any value of the compound that was not within the specified limits will be rejected and the experiment will be repeated. The negative control will be used to exclude the misleading factor that resulted from instability of chemical itself.

Human Liver Microsome Stability Protocol

The master solution was prepared according to the below in **Table 8**:

Table 8

Reagent	Stock Concentration	Volume	Final Concentration
Phosphate buffer	200 mM	200 μ L	100 mM
Ultra-pure H ₂ O	-	106 μ L	-
MgCl ₂ solution	50 mM	40 μ L	5 mM

[00192] Two separate experiments were performed as follows. a) With NADPH: 10 μ L of 20 mg/mL liver microsomes and 40 μ L of 10 mM NADPH were added to the incubations. The final concentrations of microsomes and NADPH were 0.5 mg/mL and 1 mM, respectively. b) Without NADPH: 10 μ L of 20 mg/mL liver microsomes and 40 μ L of ultra-pure H₂O were added to the incubations. The final concentration of microsomes was 0.5 mg/mL. The reaction was started with the addition of 4 μ L of 100 μ M test compound solution or control compound solution at the final concentration of 1 μ M and carried out at 37 °C. Aliquots of 50 μ L were taken from the reaction solution at 0, 15, 30, 45 and 60 min. The reaction was stopped by the addition of 4 volumes of cold acetonitrile with IS (100 nM alprazolam, 200 nM labetalol, 200 nM caffeine and 2 μ M ketoprofen). Samples were centrifuged at 3, 220 g for 40 minutes. Aliquot of 100 μ L of the supernatant was mixed with 100 μ L of ultra-pure H₂O and then used for LC-MS/MS analysis.

Data Analysis

All calculations were carried out using Microsoft Excel.

Peak areas were determined from extracted ion chromatograms. The slope value was determined by linear regression of the natural logarithm of the remaining percentage of the parent drug vs. incubation time curve.

The in vitro half-life (in vitro $t_{1/2}$) was determined from the slope value:

$$\text{in vitro } t_{1/2} = 0.693/k$$

Where: k is the rate constant (k= -slope value)

Conversion of the in vitro $t_{1/2}$ (min) into the in vitro intrinsic clearance (in vitro CL_{int}, in $\mu\text{L}/\text{min}/\text{mg}$ protein) was done using the following equation (mean of duplicate determinations):

$$\text{in vitro CL}_{\text{int}} = \frac{0.693}{t_{1/2}} \times \frac{\text{volume of incubation } (\mu\text{L})}{\text{amount of proteins (mg)}}$$

Conversion of the in vitro $t_{1/2}$ (min) into the scale-up unbound intrinsic clearance (Scale-up CL_{int}, in $\text{mL}/\text{min}/\text{kg}$) was done using the following equation (mean of duplicate determinations):

$$\text{Scale up CL}_{\text{int}} = \frac{0.693}{t_{1/2}} \times \frac{\text{volume of incubation } (\mu\text{L})}{\text{amount of proteins (mg)}} \times \text{Scaling Factor}$$

Table 9: Scaling Factors for Intrinsic Clearance Prediction in Liver Microsomes

Species	Liver Weight (g liver/kg body weight) ^a	Microsomal Concentration (mg/g liver) ^b	Liver blood flow (Q, mL/min/kg) ^a	Scaling Factor
Human	25.7	48.8	20.7	1254.2

a. Iwatsubo et al, Davies and Morris, 1993, 10 (7) pp 1093-1095.

b. Barter et al, 2007, Curr Drug Metab, 8(1), pp 33-45; Iwatsubo et al, 1997, JPET, 283 pp 462-469.

[00193] A summary of ADME parameters is presented in **Table 10**

Table 10

Example	5	6	7	8	9	10	15	20	3	4
Human liver microsomes ($t_{1/2}$, min)	76.6	16.3	2.5	32.6	>120	>120	1.3	>120	83.4	9.8
Human Hepatocytes ($t_{1/2}$, min)	59.6	15	2.4	195	>240	>240	2.5	38.8	57	29.3
Kinetic Solubility, pH=2.0 (uM)	51.2	279.6	64.4	288.4	271	279	258	275	0.5	255.2
Kinetic Solubility, pH=4.5 (uM)	0.86	278.3	0.8	1.2	266	285	0.04	273	0.4	250.1

Kinetic Solubility, pH=7.4 (uM)	0.58	3.2	0.7	0.9	301	293	0.03	271	0.3	0.1
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[00194] Example 2: Pharmacokinetic evaluation of compound 1, 3, 4, 5 and 6.

[00195] A summary of the PK parameters of compound 1 after *i.v.* administration across several species is presented in **Table 11**.

[00196] A summary of the PK parameters of compound 1 after oral administration across several species is presented in **Table 12**.

[00197] A summary of the PK parameters of compounds 3, 4, 5, and 6 after oral administration across two species is presented in **Table 13**.

Table 11

IV PK parameters	Unit	CD1 Mouse 2 mg/kg	SD Rat 5mg/kg		Beagle Dog 2mg/kg
		Male	Female	Male	Male
CL obs	mL/min/kg	52.4	16.3	21.9	20.2
V _{ss} obs	L/kg	2.12	1.70	2.02	4.43
T _{1/2}	h	0.53	2.41	2.15	6.49
AUC _{Inf}	h*ng/mL	533	5120	3950	1890

Table 12

Oral PK parameters	Unit	Male CD1 Mouse	Female SD Rat		Male SD Rat		Male Beagle Dog
		10 mg/kg	10 mg/kg	30 mg/kg	10 mg/kg	30 mg/kg	5 mg/kg
T _{1/2}	h	0.8	7.58	3.24		2.58	7.14
T _{max}	h	1.0	2.0	4.67	2.0	2.0	2.0
C _{max}	ng/mL	320	456	1070	308	762	35.7

AUC _{last}	h*ng/mL	704	1870	11700	1410	4980	235
AUC _{Inf}	h*ng/mL	709	4460	11900		3970	242
F	%	24	18.7	38.6	17.8	21.1	5.13

Table 13

Example	5	6	3	4
Female BalbC nude mouse, 30mpk PO AUC (ng*h/mL)	3782	28862	168	1708
Female BalbC nude mouse, 30mpk PO CMax (ng/mL)	680	5860	56.7	891
Fasted Male Beagle Dog, 5mpk PO AUC (ng*h/mL)	387	1568	--	--
Fasted Male Beagle Dog, 5mpk PO CMax (ng/mL)	49.8	286	--	--

Female BalbC nude mouse PO formulation: 20% HP-β-CD, in water

Fasted Male Beagle Dog PO formulation: 0.5% MC (400cp) /0.1% Tween 80 in DI water.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating a cancer in a patient in need thereof, comprising administering to the patient a compound, or pharmaceutically acceptable salt or solvate thereof, selected from the group consisting of:

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;

5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;

(3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;

(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and

(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate.
2. A method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising a compound, or pharmaceutically acceptable salt or solvate thereof, selected from the group consisting of:

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;

5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;

(3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;

(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and

(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate.
3. A method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-

yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.

4. A method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.
5. A method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.
6. A method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.
7. A method of treating a cancer in a patient in need thereof, comprising administering to the patient 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile, or pharmaceutically acceptable salt or solvate thereof.
8. A method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile, or pharmaceutically acceptable salt or solvate thereof.
9. A method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.
10. A method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.
11. A method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.

12. A method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.
13. A method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.
14. A method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.
15. The method of any one of claims 1 to 14, wherein the cancer is selected from the group consisting of breast cancer, ovarian cancer, fallopian tube cancer, primary peritoneal cancer (PPC), bladder cancer, uterine cancer, prostate cancer, lung cancer, non-small-cell lung cancer, (NSCLC), small-cell lung cancer (SCLC), squamous cell carcinoma, adenocarcinoma, mesothelioma, esophageal cancer, head and neck cancer, head and neck squamous cell carcinoma (HNSCC), colorectal cancer (CRC), kidney cancer, renal cell carcinoma (RCC), liver cancer, hepatocellular carcinoma (HCC), pancreatic cancer, stomach cancer, gastric cancer, endometrial cancer, sarcoma, liposarcoma, osteosarcoma, primary brain tumors, high grade and low grade glioma, glioblastoma, thyroid cancer, hematologic cancer, acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), lymphoma, myeloma, neuroblastoma, Ewings sarcoma, osteosarcoma, and Wilms tumor.
16. The method of claim 15, wherein the cancer is selected from the group consisting of breast cancer, ovarian cancer, bladder cancer, uterine cancer, prostate cancer, lung cancer, esophageal cancer, liver cancer, pancreatic cancer, stomach cancer, or combinations thereof.
17. The method of any one of claims 1 to 16, wherein the cancer is locally or regionally advanced or metastatic solid tumors.
18. The method of any one of claims 1 to 14, wherein the cancer is CNS metastatic disease.
19. The method of claim 15, wherein the cancer is NSCLC.
20. The method of claim 19, wherein the cancer is adenocarcinoma of NSCLC.
21. The method of claim 15, wherein the cancer is prostate cancer.

22. The method of claim 15, wherein the cancer is colorectal cancer.
23. The method of claim 15, wherein the cancer is liposarcoma.
24. The method of claim 15, wherein the cancer is breast cancer.
25. The method of claim 24, wherein the breast cancer is advanced or metastatic breast cancer.
26. The method of claim 24, wherein the breast cancer is locally advanced.
27. The method of claim 24, wherein the breast cancer is metastatic breast cancer.
28. The method of claim 24, wherein the breast cancer is hormone receptor positive (HR+).
29. The method of claim 24, wherein the breast cancer is estrogen receptor positive (ER+), progesterone receptor positive (PR+), or a combination thereof.
30. The method of claim 24, wherein the breast cancer is hormone receptor negative (HR-).
31. The method of claim 24, wherein the breast cancer is estrogen receptor negative (ER-), progesterone receptor negative (PR-), or a combination thereof.
32. The method of claim 24, wherein the breast cancer is human epidermal growth factor receptor 2 negative (HER2-).
33. The method of claim 24, wherein the breast cancer is human epidermal growth factor receptor 2 positive (HER2+).
34. The method of claim 24, wherein the breast cancer is HR+/HER2- breast cancer.
35. The method of claim 24, wherein the breast cancer is HR-/HER2+ breast cancer.
36. The method of claim 24, wherein the breast cancer is ER+/HR+.
37. The method of claim 24, wherein the breast cancer is ER+/HER2-.
38. The method of claim 24, wherein the breast cancer is triple negative breast cancer (TNBC).
39. The method of claim 24, wherein the breast cancer is ER-, PR- and HER2-.
40. The method of claim 24, wherein the breast cancer is endocrine resistant breast cancer, trastuzumab or pertuzumab resistant breast cancer, or breast cancer demonstrating primary or acquired resistance to CDK4/CDK6 inhibition.
41. The method of any one of claims 24-40, wherein the breast cancer is resistant to treatment with a standard of care agent.
42. The method of any one of claims 24-40, wherein the subject is refractory to endocrine therapy.
43. The method of any one of claims 24-40, wherein the breast cancer is refractory or resistant to treatment with, or has progressed on, treatment with antineoplastic chemotherapeutic agents.

44. The method of any one of claims 24-40, wherein the breast cancer has progressed during treatment or within 12 months of completion of adjuvant therapy with an aromatase inhibitor.
45. The method of any one of claims 24-40, wherein the breast cancer has progressed during treatment or within 12 months of completion of adjuvant therapy with tamoxifen.
46. The method of any one of claims 1-45, wherein the method is first line therapy.
47. The method of any one of claims 1-45, wherein the method is second, or later, line therapy.
48. The method of claim 47, wherein the method follows treatment with an endocrine therapeutic agent, a CDK4/CDK6 inhibitor, or a combination thereof.
49. The method of claim 47, wherein the method follows treatment with an endocrine therapeutic agent.
50. The method of claim 47, wherein the method follows treatment with one or more chemotherapy regimens.
51. The method of claim 47, wherein the method follows treatment with HER2 targeted agents.
52. A method of treating a breast cancer in a patient in need thereof, comprising administering to the patient a compound, or pharmaceutically acceptable salt or solvate thereof, selected from the group consisting of:

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;

5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;

(3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;

(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and

(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate,

and an endocrine therapy agent.
53. The method of claim 52, wherein the compound is (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.

54. The method of claim 52, wherein the compound is (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.
55. The method of claim 52, wherein the compound is 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile, or pharmaceutically acceptable salt or solvate thereof.
56. The method of claim 52, wherein the compound is (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.
57. The method of claim 52, wherein the compound is (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.
58. The method of claim 52, wherein the compound is (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.
59. The method of any one of claims 52-58, wherein the endocrine therapy agent is selected from the group consisting of a biological large molecule agent or chemical small molecule compound useful in the treatment of cancer.
60. The method of any one of claims 52-58, wherein the endocrine therapy agent is selected from the group consisting of an aromatase inhibitor, an androgen receptor inhibitor, a selective estrogen receptor degrader (SERD), or a selective estrogen receptor modulator (SERM).
61. The method of claim 60, wherein the endocrine therapy agent is an androgen receptor inhibitor.
62. The method of claim 60, wherein the endocrine therapy agent is an aromatase inhibitor.
63. The method of claim 62, wherein the aromatase inhibitor is selected from the group consisting of letrozole, anastrozole and exemestane.
64. The method of claim 62, wherein the aromatase inhibitor is letrozole.
65. The method of claim 60, wherein the endocrine therapy agent is a SERD.
66. The method of claim 60, wherein the SERD is selected from the group consisting of fulvestrant, elacestrant (RAO-1901), amcenestrant (SAR439859), giredestrant (GOC9545), RG6171, camizestrant (AZO9833), AZO9496, rintodestrant, ZN-c5, LSZ102, 0-0502, LY3484356, and SHR9549.
67. The method of claim 60, wherein the SERD is fulvestrant.

68. The method of claim 60, wherein the endocrine therapy agent is a SERM.
69. The method of claim 68, wherein the SERM is selected from the group consisting of tamoxifen, raloxifene, toremifene, lasofoxifene, bazedoxifene and afimoxifene.
70. The method of claim 68, wherein the SERM is tamoxifen or raloxifene.
71. The method of claim 60, wherein the endocrine therapy agent is letrozole or fulvestrant.
72. The method of any one of claims 52-71, wherein the endocrine therapy agent is administered to the subject during the course of the treatment with (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.
73. The method of any one of claims 52-71, wherein the endocrine therapy agent is administered prior to administering the first dose of (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.
74. The method of any one of claims 52-71, wherein the first dose of the endocrine therapy agent is administered on the same day as administering the first dose of (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.
75. The method of any one of claims 52-71, wherein the first dose of the endocrine therapy agent is administered after the start of the treatment with (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof.
76. The method of any one of claims 52-71, wherein prior to the administration of (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof, to the subject, the subject has been previously treated with one or more lines of endocrine therapy.
77. The method of any one of claims 51-62, wherein prior to the administration of (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof, to the subject, the subject has been previously treated with chemotherapy, radiotherapy, and/or surgical resection.
78. The method of any one of claims 51-62, wherein prior to the administration of (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof, to the subject, the subject has been previously treated with a CDK4/6 inhibitor.

79. The method of claim 52, wherein the endocrine therapy agent is administered to the patient during the course of the treatment with a compound selected from the group consisting of:
- (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;
- (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
- 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;
- (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
- (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and
- (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.
80. The method of claim 52, wherein the endocrine therapy agent is administered to the patient prior to administering the first dose of a compound selected from the group consisting of:
- (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;
- (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
- 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;
- (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
- (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and
- (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.
81. The method of claim 52, wherein the first dose of the endocrine therapy agent is administered to the patient on the same day as administering the first dose of a compound selected from the group consisting of:

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;
 (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;
 (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.

82. The method of claim 52, wherein the first dose of the endocrine therapy agent is administered to the patient after the start of the treatment with a compound selected from the group consisting of:

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;
 (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;
 (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof.

83. The method of claim 52, wherein prior to the administration to the patient of a compound selected from the group consisting of:

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;
 (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;

5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;
 (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or
 pharmaceutically acceptable salt or solvate thereof, the patient has been previously treated with one or more lines of endocrine therapy.

84. The method of claim 1, wherein prior to the administration to the patient of a compound selected from the group consisting of:

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;
 (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;
 (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or
 pharmaceutically acceptable salt or solvate thereof, the patient has been previously treated with chemotherapy, radiotherapy, and/or surgical resection.

85. The method of claim 1, wherein prior to the administration to the patient of a compound selected from the group consisting of:

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;
 (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;

(3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or
 pharmaceutically acceptable salt or solvate thereof, the patient has been previously
 treated with a CDK4/6 inhibitor.

86. The method of any one of the preceding claims, wherein the method results in complete response (CR), partial response (PR), or stable disease (SD) in the subject with regionally advanced or metastatic disease.
87. The method of any one of the preceding claims, wherein the treatment results in complete response, partial response or stable disease of intra-cranial metastatic disease or primary brain tumors.
88. The method of any one of the preceding claims, wherein the treatment results in a reduction of disease recurrence at the local site, or a distant site, or within the CNS, or a combination thereof.
89. The method of claim 18, wherein the disease site is the brain.
90. The method of claim 15, wherein the patient has a locally or a regionally advanced cancer.
91. A method of treating a cancer in a patient in need thereof, comprising administering to the patient a compound, or pharmaceutically acceptable salt or solvate thereof, selected from the group consisting of:

(3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol;
 (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile;
 (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate;
 (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol; and

(3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, and wherein the cancer is a solid tumor characterized by:

- (a) a CDK4 amplification or mutation;
- (b) a Cyclin D1 amplification;
- (c) a Cyclin E amplification; or
- (d) a loss of negative regulator genes CDKN2A or CDKN2B.

92. A method of treating a cancer in a patient in need thereof, comprising administering to the patient 5-chloro-7-(1-ethylcyclobutyl)-2-(((3*S*,4*R*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carbonitrile, or pharmaceutically acceptable salt or solvate thereof, or (3*S*,4*R*)-4-{[5-chloro-6-cyano-7-(1-ethylcyclobutyl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]amino}oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof, wherein the cancer is a solid tumor characterized by:

- (a) a CDK4 amplification or mutation;
- (b) a Cyclin D1 amplification;
- (c) a Cyclin E amplification; or
- (d) a loss of negative regulator genes CDKN2A or CDKN2B.

93. A method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof, or (3*S*,4*R*)-4-[(7-{5-[1-(difluoromethyl)cyclopropyl]pyridin-2-yl}-5-fluoropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate, or pharmaceutically acceptable salt or solvate thereof, wherein the cancer is a solid tumor characterized by:

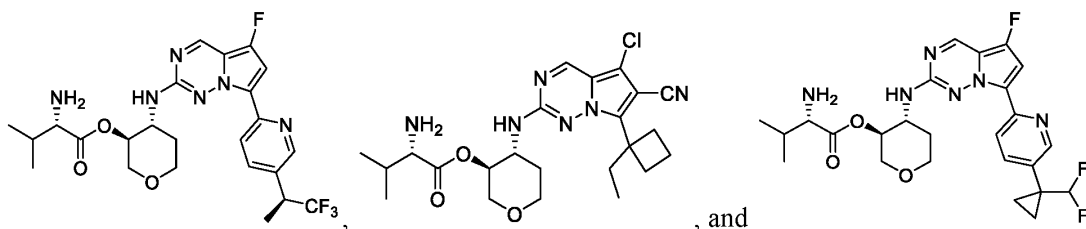
- (a) a CDK4 amplification or mutation;
- (b) a Cyclin D1 amplification;
- (c) a Cyclin E amplification; or
- (d) a loss of negative regulator genes CDKN2A or CDKN2B.

94. A method of treating a cancer in a patient in need thereof, comprising administering to the patient (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-ol, or pharmaceutically acceptable salt or solvate thereof, or (3*S*,4*R*)-4-[(5-fluoro-7-{5-[(2*S*)-1,1,1-trifluoropropan-2-yl]pyridin-2-yl}pyrrolo[2,1-*f*][1,2,4]triazin-2-yl)amino]oxan-3-yl (2*S*)-2-amino-3-methylbutanoate,

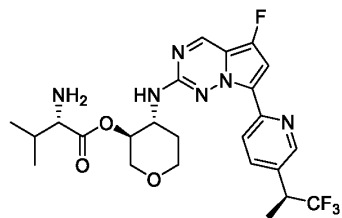
or pharmaceutically acceptable salt or solvate thereof, wherein the cancer is a solid tumor characterized by:

- (a) a CDK4 amplification or mutation;
- (b) a Cyclin D1 amplification;
- (c) a Cyclin E amplification; or
- (d) a loss of negative regulator genes CDKN2A or CDKN2B.

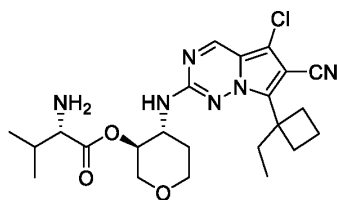
95. The method of claim 91, wherein the solid tumor is characterized by a CDK4 amplification or mutation.
96. The method of claim 91, wherein the solid tumor is characterized by a Cyclin D1 amplification.
97. The method of claim 91, wherein the solid tumor is characterized by a Cyclin E amplification.
98. The method of claim 91, wherein the solid tumor is characterized by a loss of negative regulator genes CDKN2A or CDKN2B.
99. The method of any one of the preceding claims, wherein the patient has not received prior CDK4 inhibitor therapy.
100. The method of any one of the preceding claims, wherein the patient has resistance to CDK4 inhibitor or CDK6 inhibitor therapy.
101. A compound, or pharmaceutically acceptable salt or solvate thereof, selected from the group consisting of:



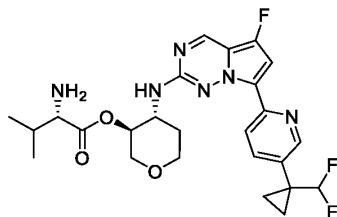
102. The compound of claim 101, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



103. The compound of claim 101, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



104. The compound of claim 101, or pharmaceutically acceptable salt or solvate thereof, having the structure of:



105. A pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and a compound, or pharmaceutically acceptable salt or solvate thereof, selected from the group consisting of:

