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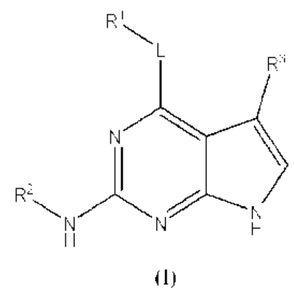
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(54) **Titre : METHODES DE TRAITEMENT D'UN CANCER A L'AIDE DE COMPOSES DE PYRROLOPYRIMIDINE SUBSTITUES, COMPOSITIONS DE CEUX-CI**
(54) **Title: METHODS OF TREATING A CANCER USING SUBSTITUTED PYRROLOPYRIMIDINE COMPOUNDS, COMPOSITIONS THEREOF**



(I)

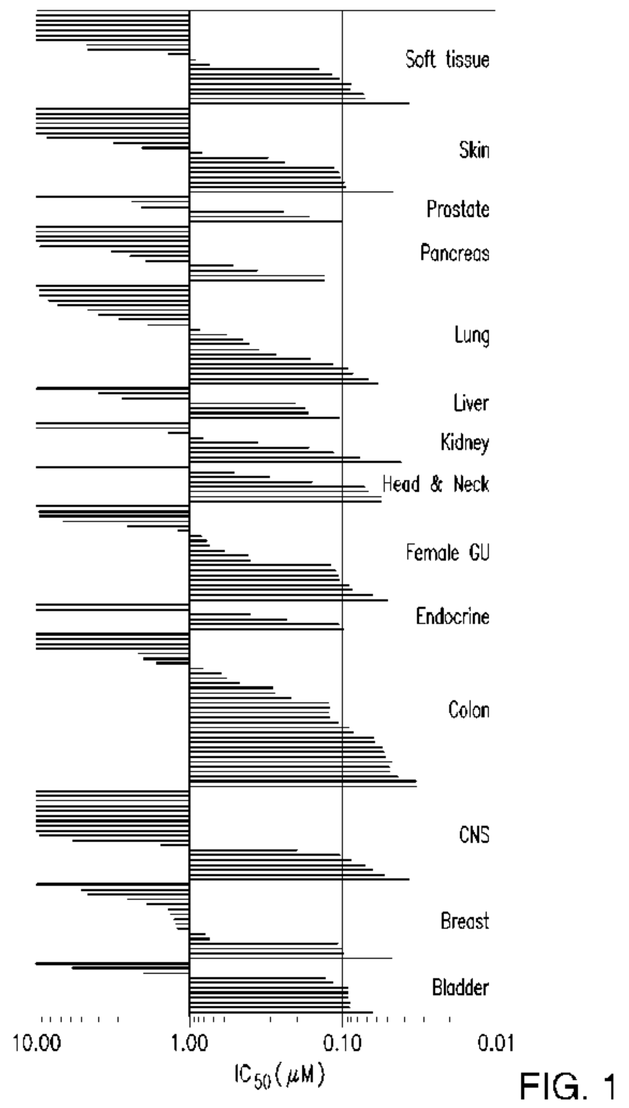


FIG. 1

(57) **Abrégé/Abstract:**
Provided herein are methods for treating or preventing a cancer, in particular solid tumors and hematological cancers, comprising administering to a subject in need thereof an effective amount of a compound of formula (I): (I).

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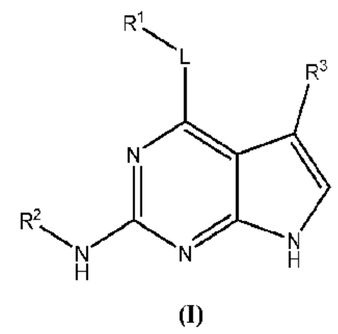
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[Continued on next page]

(54) Title: METHODS OF TREATING A CANCER USING SUBSTITUTED PYRROLOPYRIMIDINE COMPOUNDS, COMPOSITIONS THEREOF

(57) Abstract: Provided herein are methods for treating or preventing a cancer, in particular solid tumors and hematological cancers, comprising administering to a subject in need thereof an effective amount of a compound of formula (I): (I).



(I)

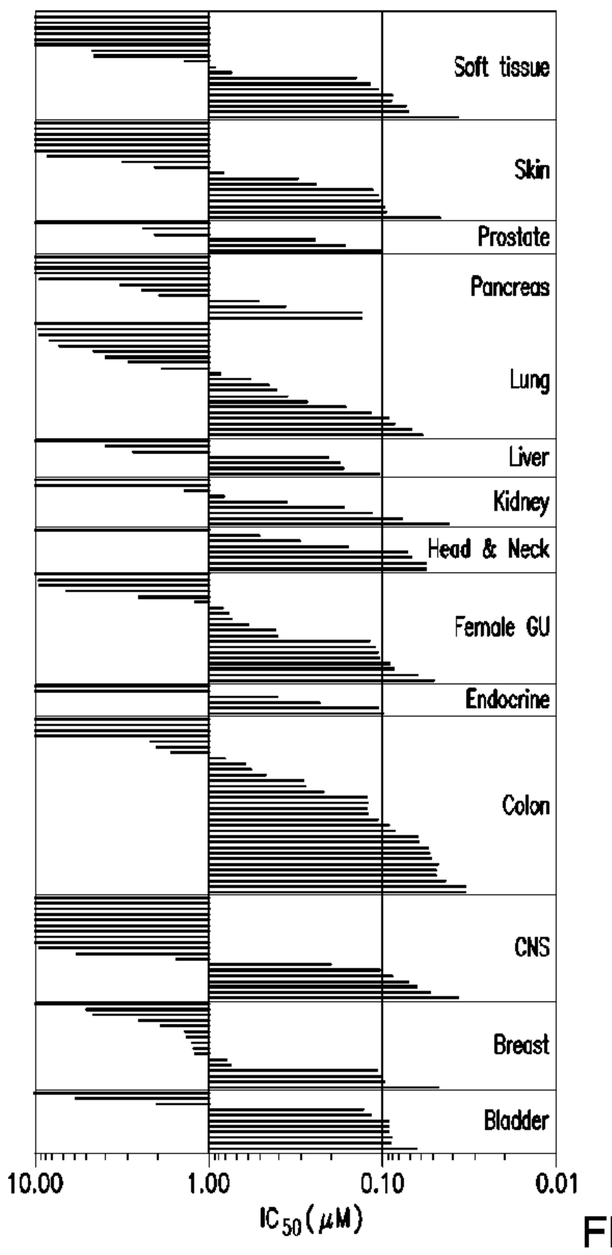


FIG. 1

WO 2016/010886 A1

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METHODS OF TREATING A CANCER USING SUBSTITUTED PYRROLOPYRIMIDINE COMPOUNDS, COMPOSITIONS THEREOF

[0001] This application claims the benefit of U.S. Provisional Application No. 62/024,158, filed July 14, 2014, the entire contents of which are incorporated herein by reference.

FIELD

[0002] Provided herein are methods for treating or preventing a cancer, in particular solid tumors and hematological cancers as described herein, comprising administering an effective amount of a pyrrolopyrimidine compounds to a subject in need thereof. Also provided herein are Pyrrolopyrimidine Compounds that can be used in said methods.

BACKGROUND

[0003] Cancer is characterized primarily by an increase in the number of abnormal cells derived from a given normal tissue, invasion of adjacent tissues by these abnormal cells, or lymphatic or blood-borne spread of malignant cells to regional lymph nodes and to distant sites (metastasis). Clinical data and molecular biologic studies indicate that cancer is a multistep process that begins with minor preneoplastic changes, which may under certain conditions progress to neoplasia. The neoplastic lesion may evolve clonally and develop an increasing capacity for invasion, growth, metastasis, and heterogeneity, especially under conditions in which the neoplastic cells escape the host's immune surveillance (Roitt, I., Brostoff, J and Kale, D., Immunology, 17.1-17.12 (3rd ed., Mosby, St. Louis, Mo., 1993)).

[0004] Cancers figure among the leading causes of death worldwide, accounting for 8.2 million deaths in 2012. It is expected that annual cancer cases will rise from 14 million in 2012 to 22 million within the next two decades (See Cancer Fact sheet N°297, World Health Organization, February 2014, retrieved 10 June 2014 and Globocan 2012, IARC).

[0005] The current drugs used in cancer treatment are highly toxic and often non-specific. Current anticancer therapy strategies are typically focused on rapid proliferating cells, which can shrink primary and metastatic tumors, but such effects are usually transient and tumor relapse of most metastatic cancers frequently occur. One possible reason for failure is the existence of cancer stem cells. Unlike most cells within the tumor, cancer stem cells are resistant to well-defined chemotherapy, and after treatment, they can regenerate all the cell types in the tumor through their stem cell-like behavior of largely quiescent nature and their abundant expression of drug transporters.

[0006] There is an enormous variety of cancers which are described in detail in the medical literature. The incidence of cancer continues to climb as the general population ages, as new cancers develop, and as susceptible populations (e.g., people infected with AIDS or excessively exposed to sunlight) grow. However, options for the treatment of cancer are limited. A tremendous demand therefore exists for new methods and compositions that can be used to treat patients with cancer.

SUMMARY

[0007] Provided herein are Pyrrolopyrimidine Compounds that can be used in the methods provided herein.

[0008] Provided herein are methods of treating a cancer, in particular a solid tumor or a hematological cancer. The Pyrrolopyrimidine Compound provided herein can be used in the methods for treating or preventing the cancer, in particular the solid tumor or the hematological cancer. The methods comprise administering to a subject in need thereof an effective amount of Pyrrolopyrimidine Compound.Also provided herein are methods for preventing cancer metastasis, comprising administering to a subject in need thereof an effective amount of a Pyrrolopyrimidine Compound as provided herein. The Pyrrolopyrimidine Compound provided herein can be used in the methods for preventing cancer metastasis. Additionally, provided herein are methods of eradicating cancer stem cells in a subject, comprising administering to a subject in need thereof an effective amount of a Pyrrolopyrimidine Compound as provided herein. The Pyrrolopyrimidine Compound provided herein can be used in the methods of eradicating cancer stem cells in a subject. Also provided are methods of inducing differentiation in cancer stem cells in a

subject, comprising administering to a subject in need thereof an effective amount of a Pyrrolopyrimidine Compound as provided herein. The Pyrrolopyrimidine Compound provided herein can be used in the methods of inducing differentiation in cancer stem cells in a subject. In another aspect, provided are methods of inducing cancer stem cell death in a subject, comprising administering to a subject in need thereof an effective amount of a Pyrrolopyrimidine Compound as provided herein. The Pyrrolopyrimidine Compound provided herein can be used in the methods of inducing cancer stem cell death in a subject. In yet another aspect, provided herein are methods for treating or preventing a cancer, in particular a solid tumor or hematological cancer, comprising administering to a subject in need thereof an effective amount of a compound that inhibits TTK, CLK1, and CLK2 kinase activity, and optionally CAMKK2 kinase activity. The compound that inhibits TTK, CLK1, and CLK2 kinase activity, and optionally CAMKK2 kinase activity can be used in the methods for treating or preventing a cancer, in particular a solid tumor or hematological cancer. Also provided are methods for treating or preventing a cancer associated with the pathways involving TTK, CLK1, and CLK2 and mutants or isoforms thereof, comprising administering to a subject in need thereof an effective amount of a compound that inhibits TTK, CLK1, and CLK2 kinase activity, and optionally CAMKK2 kinase activity. The compound that inhibits TTK, CLK1, and CLK2 kinase activity, and optionally CAMKK2 kinase activity can be used in the methods for treating or preventing a cancer associated with the pathways involving TTK, CLK1, and CLK2 and mutants or isoforms thereof.

[0009] The compound that inhibits TTK, CLK1, and CLK2 kinase activity, and optionally CAMKK2 kinase activity is a Pyrrolopyrimidine Compound as provided herein.

[0010] Compounds useful in the methods disclosed herein are Pyrrolopyrimidine Compounds as described herein, such as, for example, in Table A, or a pharmaceutically acceptable salt, tautomer, stereoisomer, enantiomer, or isotopologue thereof.

[0011] The present embodiments can be understood more fully by reference to the detailed description and examples, which are intended to exemplify non-limiting embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] **Figure 1:** Pyrrolopyrimidine Compounds showed anti-proliferative activity in a variety of solid tumors, namely, cancers of the bladder, breast, CNS, colon, endocrine, female GU, head and neck, kidney, liver, lung, pancreas, prostate, skin and soft-tissue (exemplified by Cmpd. 38 in Figure 1).

[0013] **Figure 2:** Pyrrolopyrimidine Compounds showed anti-proliferative activity in a variety of hematological cancers, namely, a variety of lymphomas (ST486, CRO-AP2, Faji, MHH-PREB-1, BC-1, DOHH-2, DB, SR, RamosRA1, Daudi, HT, EB-3, SKO-007) and leukemias MOLT-16, BV-173, J-RT3-T3-5, Jurkat, NALM-6, MX1, ARH-77, CML-T1, CCRF-CEM, MV-4-11, EM-2, MOLT-3, CEM-C1, HEL-92-1-7, MEG-01, K-562, THP-1)/myeloma (RPMI-8226, U266B1) (exemplified by Cmpd. 38 in Figure 2).

[0014] **Figure 3:** Pyrrolopyrimidine Compounds demonstrated potency against several mesenchymal GBM CSCs (8311, 32612, 81611) with IC_{50}s in the range of 1-2 μM. The data indicated that Pyrrolopyrimidine Compounds, exemplified by Cmpd. 38, are particularly potent against two GBM CSC sphere models derived from proneural subtype GBM patients (52810 and 1912) with IC_{50} in the range of 50-190 nM.

[0015] **Figure 4:** Induction of GBM-CSC differentiation by Pyrrolopyrimidine Compounds (for example, Cmpd. 38) is shown in Figure 4 (left panel: DMSO, right panel: Cmpd. 38). Abbreviations: DMSO = dimethyl sulfoxide; Oct4=octamer-binding transcription factor 4; Tuj1=tubulin β3; DAPI= 4',6-diamidino-2-phenylindole. The 8311 GBM CSCs and HUAEC cells were allowed to co-culture for 1 day prior to compound administration. After 3 days of compound or mock/DMSO-treatment, cells were fixed and monitored for expression of Oct4 and Tuj1 by indirect immunofluorescence. Pyrrolopyrimidine Compounds (exemplified by Cmpd. 38) induced differentiation of GBM CSCs in the context of a HUAEC co-culture model.

DETAILED DESCRIPTION

DEFINITIONS

[0016] An "alkyl" group is a saturated, partially saturated, or unsaturated straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms, typically from 1 to 8 carbons or, in some embodiments, from 1 to 6, 1 to 4, or 2 to 6 or 2 to 4 carbon atoms.

Representative alkyl groups include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl and -n-hexyl; while saturated branched alkyls include -isopropyl, -*sec*-butyl, -isobutyl, -*tert*-butyl, -isopentyl, -neopentyl, *tert*-pentyl, -2-methylpentyl, -3-methylpentyl, -4-methylpentyl, -2,3-dimethylbutyl and the like. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, allyl, -CH=CH(CH_3), -CH=C(CH_3)$_2$, -C(CH_3)=CH_2, -C(CH_3)=CH(CH_3), -C(CH_2CH_3)=CH_2, -C≡CH, -C≡C(CH_3), -C≡C(CH_2CH_3), -CH_2C≡CH, -CH_2C≡C(CH_3) and -CH_2C≡C(CH_2CH_3), among others. An alkyl group can be substituted or unsubstituted. When the alkyl groups described herein are said to be "substituted," they may be substituted with any substituent or substituents as those found in the exemplary compounds and embodiments disclosed herein, as well as halogen (chloro, iodo, bromo, or fluoro); alkyl; hydroxyl; alkoxy; alkoxyalkyl; amino; alkylamino; carboxy; nitro; cyano; thiol; thioether; imine; imide; amidine; guanidine; enamine; aminocarbonyl; acylamino; phosphonate; phosphine; thiocarbonyl; sulfinyl; sulfone; sulfonamide; ketone; aldehyde; ester; urea; urethane; oxime; hydroxyl amine; alkoxyamine; aralkoxyamine; N-oxide; hydrazine; hydrazide; hydrazone; azide; isocyanate; isothiocyanate; cyanate; thiocyanate; B(OH)$_2$, or O(alkyl)aminocarbonyl.

[0017] A "cycloalkyl" group is a saturated, or partially saturated cyclic alkyl group of from 3 to 10 carbon atoms having a single cyclic ring or multiple condensed or bridged rings which can be optionally substituted with from 1 to 3 alkyl groups. In some embodiments, the cycloalkyl group has 3 to 8 ring members, whereas in other embodiments the number of ring carbon atoms ranges from 3 to 5, 3 to 6, or 3 to 7. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 1-methylcyclopropyl, 2-methylcyclopentyl, 2-methylcyclooctyl, and the like, or multiple or bridged ring structures such as 1-bicyclo[1.1.1]pentyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, adamantyl and the like. Examples of unsaturared cycloalkyl groups include cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, hexadienyl, among others. A cycloalkyl group can be substituted or unsubstituted. Such substituted cycloalkyl groups include, by way of example, cyclohexanol and the like.

[0018] An "aryl" group is an aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (*e.g.*, phenyl) or multiple condensed rings (*e.g.*, naphthyl or anthryl).

In some embodiments, aryl groups contain 6-14 carbons, and in others from 6 to 12 or even 6 to 10 carbon atoms in the ring portions of the groups. Particular aryls include phenyl, biphenyl, naphthyl and the like. An aryl group can be substituted or unsubstituted. The phrase "aryl groups" also includes groups containing fused rings, such as fused aromatic-aliphatic ring systems (e.g., indanyl, tetrahydronaphthyl, and the like).

[0019] A "heteroaryl" group is an aryl ring system having one to four heteroatoms as ring atoms in a heteroaromatic ring system, wherein the remainder of the atoms are carbon atoms. In some embodiments, heteroaryl groups contain 3 to 6 ring atoms, and in others from 6 to 9 or even 6 to 10 atoms in the ring portions of the groups. Suitable heteroatoms include oxygen, sulfur and nitrogen. In certain embodiments, the heteroaryl ring system is monocyclic or bicyclic. Non-limiting examples include but are not limited to, groups such as pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, benzisoxazolyl (e.g., benzo[d]isoxazolyl), thiazolyl, pyrolyl, pyridazinyl, pyrimidyl, pyrazinyl, thiophenyl, benzothiophenyl, furanyl, benzofuranyl, indolyl (e.g., indolyl-2-onyl or isoindolin-1-onyl), azaindolyl (pyrrolopyridyl or 1H-pyrrolo[2,3-b]pyridyl), indazolyl, benzimidazolyl (e.g., 1H-benzo[d]imidazolyl), imidazopyridyl (e.g., azabenzimidazolyl or 1H-imidazo[4,5-b]pyridyl), pyrazolopyridyl, triazolopyridyl, benzotriazolyl (e.g., 1H-benzo[d][1,2,3]triazolyl), benzoxazolyl (e.g., benzo[d]oxazolyl), benzothiazolyl, benzothiadiazolyl, isoxazolopyridyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl (e.g., 3,4-dihydroisoquinolin-1(2H)-onyl), tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups.

[0020] A "heterocyclyl" is an aromatic (also referred to as heteroaryl) or non-aromatic cycloalkyl in which one to four of the ring carbon atoms are independently replaced with a heteroatom from the group consisting of O, S and N. In some embodiments, heterocyclyl groups include 3 to10 ring members, whereas other such groups have 3 to 5, 3 to 6, or 3 to 8 ring members. Heterocyclyls can also be bonded to other groups at any ring atom (i.e., at any carbon atom or heteroatom of the heterocyclic ring). A heterocycloalkyl group can be substituted or unsubstituted. Heterocyclyl groups encompass unsaturated, partially saturated and saturated ring systems, such as, for example, imidazolyl, imidazolinyl and imidazolidinyl (e.g., imidazolidin-4-one or imidazolidin-2,4-dionyl) groups. The phrase heterocyclyl includes fused ring species, including those comprising fused aromatic and

non-aromatic groups, such as, for example, 1-and 2-aminotetraline, benzotriazolyl (e.g., 1H-benzo[d][1,2,3]triazolyl), benzimidazolyl (e.g., 1H-benzo[d]imidazolyl), 2,3-dihydrobenzo[l,4]dioxinyl, and benzo[l,3]dioxolyl. The phrase also includes bridged polycyclic ring systems containing a heteroatom such as, but not limited to, quinuclidyl. Representative examples of a heterocyclyl group include, but are not limited to, aziridinyl, azetidinyl, azepanyl, oxetanyl, pyrrolidyl, imidazolidinyl (e.g., imidazolidin-4-onyl or imidazolidin-2,4-dionyl), pyrazolidinyl, thiazolidinyl, tetrahydrothiophenyl, tetrahydrofuranyl, dioxolyl, furanyl, thiophenyl, pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, benzisoxazolyl (e.g., benzo[d]isoxazolyl), thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, piperidyl, piperazinyl (e.g., piperazin-2-onyl), morpholinyl, thiomorpholinyl, tetrahydropyranyl (e.g., tetrahydro-2H-pyranyl), tetrahydrothiopyranyl, oxathianyl, dioxyl, dithianyl, pyranyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl, dihydropyridyl, dihydrodithiinyl, dihydrodithionyl, 1,4-dioxaspiro[4.5]decanyl, homopiperazinyl, quinuclidyl, indolyl (e.g., indolyl-2-onyl or isoindolin-1-onyl), indolinyl, isoindolyl, isoindolinyl, azaindolyl (pyrrolopyridyl or 1H-pyrrolo[2,3-b]pyridyl), indazolyl, indolizinyl, benzotriazolyl (e.g. 1H-benzo[d][1,2,3]triazolyl), benzimidazolyl (e.g., 1H-benzo[d]imidazolyl or 1H-benzo[d]imidazol-2(3H)-onyl), benzofuranyl, benzothiophenyl, benzothiazolyl, benzoxadiazolyl, benzoxazinyl, benzodithiinyl, benzoxathiinyl, benzothiazinyl, benzoxazolyl (i.e., benzo[d]oxazolyl), benzothiazolyl, benzothiadiazolyl, benzo[l,3]dioxolyl, pyrazolopyridyl (for example, 1H-pyrazolo[3,4-b]pyridyl, 1H-pyrazolo[4,3-b]pyridyl), imidazopyridyl (e.g., azabenzimidazolyl or 1H-imidazo[4,5-b]pyridyl), triazolopyridyl, isoxazolopyridyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl (e.g., 3,4-dihydroisoquinolin-1(2H)-onyl), quinolizinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl, pteridinyl, thianaphthalenyl, dihydrobenzothiazinyl, dihydrobenzofuranyl, dihydroindolyl, dihydrobenzodioxinyl, tetrahydroindolyl, tetrahydroindazolyl, tetrahydrobenzimidazolyl, tetrahydrobenzotriazolyl, tetrahydropyrrolopyridyl, tetrahydropyrazolopyridyl, tetrahydroimidazopyridyl, tetrahydrotriazolopyridyl, tetrahydropyrimidin-2(1H)-one and tetrahydroquinolinyl groups. Representative non-aromatic heterocyclyl groups do not include fused ring species that comprise a fused aromatic group. Examples of non-

aromatic heterocyclyl groups include aziridinyl, azetidinyl, azepanyl, pyrrolidyl, imidazolidinyl (e.g., imidazolidin-4-onyl or imidazolidin-2,4-dionyl), pyrazolidinyl, thiazolidinyl, tetrahydrothiophenyl, tetrahydrofuranyl, piperidyl, piperazinyl (e.g., piperazin-2-onyl), morpholinyl, thiomorpholinyl, tetrahydropyranyl (e.g., tetrahydro-2H-pyranyl), tetrahydrothiopyranyl, oxathianyl, dithianyl, 1,4-dioxaspiro[4.5]decanyl, homopiperazinyl, quinuclidyl, or tetrahydropyrimidin-2(1H)-one. Representative substituted heterocyclyl groups may be mono-substituted or substituted more than once, such as, but not limited to, pyridyl or morpholinyl groups, which are 2-, 3-, 4-, 5-, or 6-substituted, or disubstituted with various substituents such as those listed below.

[0021] A "cycloalkylalkyl" group is a radical of the formula: -alkyl-cycloalkyl, wherein alkyl and cycloalkyl are as defined above. Substituted cycloalkylalkyl groups may be substituted at the alkyl, the cycloalkyl, or both the alkyl and the cycloalkyl portions of the group. Representative cycloalkylalkyl groups include but are not limited to methylcyclopropyl, methylcyclobutyl, methylcyclopentyl, methylcyclohexyl, ethylcyclopropyl, ethylcyclobutyl, ethylcyclopentyl, ethylcyclohexyl, propylcyclopentyl, propylcyclohexyl and the like.

[0022] An "aralkyl" group is a radical of the formula: -alkyl-aryl, wherein alkyl and aryl are defined above. Substituted aralkyl groups may be substituted at the alkyl, the aryl, or both the alkyl and the aryl portions of the group. Representative aralkyl groups include but are not limited to benzyl and phenethyl groups and fused (cycloalkylaryl)alkyl groups such as 4-ethyl-indanyl.

[0023] An "heterocyclylalkyl" group is a radical of the formula: -alkyl-heterocyclyl, wherein alkyl and heterocyclyl are defined above. Substituted heterocyclylalkyl groups may be substituted at the alkyl, the heterocyclyl, or both the alkyl and the heterocyclyl portions of the group. Representative heterocylylalkyl groups include but are not limited to 4-ethyl-morpholinyl, 4-propylmorpholinyl, furan-2-yl methyl, furan-3-yl methyl, pyridin-3-yl methyl, tetrahydrofuran-2-yl ethyl, and indol-2-yl propyl.

[0024] A "halogen" is chloro, iodo, bromo, or fluoro.

[0025] A "hydroxyalkyl" group is an alkyl group as described above substituted with one or more hydroxy groups.

[0026] An "alkoxy" group is -O-(alkyl), wherein alkyl is defined above.

[0027] An "alkoxyalkyl" group is -(alkyl)-O-(alkyl), wherein alkyl is defined above.

[0028] An "amine" group is a radical of the formula: $-NH_2$.

[0029] A "hydroxyl amine" group is a radical of the formula: $-N(R^{\#})OH$ or -NHOH, wherein $R^{\#}$ is a substituted or unsubstituted alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl or heterocyclyl group as defined herein.

[0030] An "alkoxyamine" group is a radical of the formula: $-N(R^{\#})O$-alkyl or -NHO-alkyl, wherein $R^{\#}$ is as defined above.

[0031] An "aralkoxyamine" group is a radical of the formula: $-N(R^{\#})O$-aryl or -NHO-aryl, wherein $R^{\#}$ is as defined above.

[0032] An "alkylamine" group is a radical of the formula: -NH-alkyl or $-N(alkyl)_2$, wherein each alkyl is independently as defined above.

[0033] An "aminocarbonyl" group is a radical of the formula: $-C(=O)N(R^{\#})_2$, $-C(=O)NH(R^{\#})$ or $-C(=O)NH_2$, wherein each $R^{\#}$ is as defined above.

[0034] An "acylamino" group is a radical of the formula: $-NHC(=O)(R^{\#})$ or $-N(alkyl)C(=O)(R^{\#})$, wherein each alkyl and $R^{\#}$ are independently as defined above.

[0035] An "O(alkyl)aminocarbonyl" group is a radical of the formula: $-O(alkyl)C(=O)N(R^{\#})_2$, $-O(alkyl)C(=O)NH(R^{\#})$ or $-O(alkyl)C(=O)NH_2$, wherein each $R^{\#}$ is independently as defined above.

[0036] An "N-oxide" group is a radical of the formula: $-N^{+}-O^{-}$.

[0037] A "carboxy" group is a radical of the formula: -C(=O)OH.

[0038] A "ketone" group is a radical of the formula: $-C(=O)(R^{\#})$, wherein $R^{\#}$ is as defined above.

[0039] An "aldehyde" group is a radical of the formula: -CH(=O).

[0040] An "ester" group is a radical of the formula: $-C(=O)O(R^{\#})$ or $-OC(=O)(R^{\#})$, wherein $R^{\#}$ is as defined above.

[0041] A "urea" group is a radical of the formula: $-N(alkyl)C(=O)N(R^{\#})_2$, $-N(alkyl)C(=O)NH(R^{\#})$, $-N(alkyl)C(=O)NH_2$, $-NHC(=O)N(R^{\#})_2$, $-NHC(=O)NH(R^{\#})$, or $-NHC(=O)NH_2{}^{\#}$, wherein each alkyl and $R^{\#}$ are independently as defined above.

[0042] An "imine" group is a radical of the formula: $-N=C(R^{\#})_2$ or $-C(R^{\#})=N(R^{\#})$, wherein each $R^{\#}$ is independently as defined above.

[0043] An "imide" group is a radical of the formula: -C(=O)N(R#)C(=O)($R^{\#}$) or -N((C=O)($R^{\#}$))$_2$, wherein each $R^{\#}$ is independently as defined above.

[0044] A "urethane" group is a radical of the formula: -OC(=O)N($R^{\#}$)$_2$, -OC(=O)NH($R^{\#}$), -N($R^{\#}$)C(=O)O($R^{\#}$), or -NHC(=O)O($R^{\#}$), wherein each $R^{\#}$ is independently as defined above.

[0045] An "amidine" group is a radical of the formula: -C(=N($R^{\#}$))N($R^{\#}$)$_2$, -C(=N($R^{\#}$))NH($R^{\#}$), -C(=N($R^{\#}$))NH_2, -C(=NH)N($R^{\#}$)$_2$, -C(=NH)NH($R^{\#}$), -C(=NH)NH_2, -N=C($R^{\#}$)N($R^{\#}$)$_2$, -N=C($R^{\#}$)NH($R^{\#}$), -N=C($R^{\#}$)NH_2, -N($R^{\#}$)C($R^{\#}$)=N($R^{\#}$), -NHC($R^{\#}$)=N($R^{\#}$), -N($R^{\#}$)C($R^{\#}$)=NH, or -NHC($R^{\#}$)=NH, wherein each $R^{\#}$ is independently as defined above.

[0046] A "guanidine" group is a radical of the formula: -N($R^{\#}$)C(=N($R^{\#}$))N($R^{\#}$)$_2$, -NHC(=N($R^{\#}$))N($R^{\#}$)$_2$, -N($R^{\#}$)C(=NH)N($R^{\#}$)$_2$, -N($R^{\#}$)C(=N($R^{\#}$))NH($R^{\#}$), -N($R^{\#}$)C(=N($R^{\#}$))NH_2, -NHC(=NH)N($R^{\#}$)$_2$, -NHC(=N($R^{\#}$))NH($R^{\#}$), -NHC(=N($R^{\#}$))NH_2, -NHC(=NH)NH($R^{\#}$), -NHC(=NH)NH_2, -N=C(N($R^{\#}$)$_2$)$_2$, -N=C(NH($R^{\#}$))$_2$, or -N=C(NH_2)$_2$, wherein each $R^{\#}$ is independently as defined above.

[0047] A "enamine" group is a radical of the formula: -N($R^{\#}$)C($R^{\#}$)=C($R^{\#}$)$_2$, -NHC($R^{\#}$)=C($R^{\#}$)$_2$, -C(N($R^{\#}$)$_2$)=C($R^{\#}$)$_2$, -C(NH($R^{\#}$))=C($R^{\#}$)$_2$, -C(NH_2)=C($R^{\#}$)$_2$, -C($R^{\#}$)=C($R^{\#}$)(N($R^{\#}$)$_2$), -C($R^{\#}$)=C($R^{\#}$)(NH($R^{\#}$)) or -C($R^{\#}$)=C($R^{\#}$)(NH_2), wherein each $R^{\#}$ is independently as defined above.

[0048] An "oxime" group is a radical of the formula: -C(=NO($R^{\#}$))($R^{\#}$), -C(=NOH)($R^{\#}$), -CH(=NO($R^{\#}$)), or -CH(=NOH), wherein each $R^{\#}$ is independently as defined above.

[0049] A "hydrazide" group is a radical of the formula: -C(=O)N($R^{\#}$)N($R^{\#}$)$_2$, -C(=O)NHN($R^{\#}$)$_2$, -C(=O)N($R^{\#}$)NH($R^{\#}$), -C(=O)N($R^{\#}$)NH_2, -C(=O)NHNH($R^{\#}$)$_2$, or -C(=O)$NHNH_2$, wherein each $R^{\#}$ is independently as defined above.

[0050] A "hydrazine" group is a radical of the formula: -N($R^{\#}$)N($R^{\#}$)$_2$, -NHN($R^{\#}$)$_2$, -N($R^{\#}$)NH($R^{\#}$), -N($R^{\#}$)NH_2, -NHNH($R^{\#}$)$_2$, or -$NHNH_2$, wherein each $R^{\#}$ is independently as defined above.

[0051] A "hydrazone" group is a radical of the formula: -C(=N-N($R^{\#}$)$_2$)($R^{\#}$)$_2$, -C(=N-NH($R^{\#}$))($R^{\#}$)$_2$, -C(=N-NH_2)($R^{\#}$)$_2$, -N($R^{\#}$)(N=C($R^{\#}$)$_2$), or -NH(N=C($R^{\#}$)$_2$), wherein each $R^{\#}$ is independently as defined above.

[0052] An "azide" group is a radical of the formula: -N_3.

[0053] An "isocyanate" group is a radical of the formula: -N=C=O.

[0054] An "isothiocyanate" group is a radical of the formula: -N=C=S.

[0055] A "cyanate" group is a radical of the formula: -OCN.

[0056] A "thiocyanate" group is a radical of the formula: -SCN.

[0057] A "thioether" group is a radical of the formula; -S($R^{\#}$), wherein $R^{\#}$ is as defined above.

[0058] A "thiocarbonyl" group is a radical of the formula: -C(=S)($R^{\#}$), wherein $R^{\#}$ is as defined above.

[0059] A "sulfinyl" group is a radical of the formula: -S(=O)($R^{\#}$), wherein $R^{\#}$ is as defined above.

[0060] A "sulfone" group is a radical of the formula: -S(=O)$_2$($R^{\#}$), wherein $R^{\#}$ is as defined above.

[0061] A "sulfonylamino" group is a radical of the formula: -NHSO$_2$($R^{\#}$) or -N(alkyl)SO$_2$($R^{\#}$), wherein each alkyl and $R^{\#}$ are defined above.

[0062] A "sulfonamide" group is a radical of the formula: -S(=O)$_2$N($R^{\#}$)$_2$, or -S(=O)$_2$NH($R^{\#}$), or -S(=O)$_2$NH$_2$, wherein each $R^{\#}$ is independently as defined above.

[0063] A "phosphonate" group is a radical of the formula: -P(=O)(O($R^{\#}$))$_2$, -P(=O)(OH)$_2$,-OP(=O)(O($R^{\#}$))($R^{\#}$), or -OP(=O)(OH)($R^{\#}$), wherein each $R^{\#}$ is independently as defined above.

[0064] A "phosphine" group is a radical of the formula: -P($R^{\#}$)$_2$, wherein each $R^{\#}$ is independently as defined above.

[0065] When the groups described herein, with the exception of alkyl group, are said to be "substituted," they may be substituted with any appropriate substituent or substituents. Illustrative examples of substituents are those found in the exemplary compounds and embodiments disclosed herein, as well as halogen (chloro, iodo, bromo, or fluoro); alkyl; hydroxyl; alkoxy; alkoxyalkyl; amine; alkylamine; carboxy; nitro; cyano; thiol; thioether; imine; imide; amidine; guanidine; enamine; aminocarbonyl; acylamino; phosphonate; phosphine; thiocarbonyl; sulfinyl; sulfone; sulfonamide; ketone; aldehyde; ester; urea; urethane; oxime; hydroxyl amine; alkoxyamine; aralkoxyamine; N-oxide; hydrazine; hydrazide; hydrazone; azide; isocyanate; isothiocyanate; cyanate; thiocyanate; oxygen (=O); B(OH)$_2$, O(alkyl)aminocarbonyl; cycloalkyl, which may be monocyclic or fused or

non-fused polycyclic (e.g., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl), or a heterocyclyl, which may be monocyclic or fused or non-fused polycyclic (e.g., pyrrolidyl, piperidyl, piperazinyl, morpholinyl, or thiazinyl); monocyclic or fused or non-fused polycyclic aryl or heteroaryl (e.g., phenyl, naphthyl, pyrrolyl, indolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, tetrazolyl, pyrazolyl, pyridyl, quinolinyl, isoquinolinyl, acridinyl, pyrazinyl, pyridazinyl, pyrimidyl, benzimidazolyl, benzothiophenyl, or benzofuranyl) aryloxy; aralkyloxy; heterocyclyloxy; and heterocyclyl alkoxy.

[0066] As used herein, the term "Pyrrolopyrimidine Compound" refers to compounds of formula (I), as well as to further embodiments provided herein. In one embodiment, a "Pyrrolopyrimidine Compound" is a compound set forth in Table 1. The term "Pyrrolopyrimidine Compound" includes pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers and isotopologues of the compounds provided herein.

[0067] As used herein, the term "pharmaceutically acceptable salt(s)" refers to a salt prepared from a pharmaceutically acceptable non-toxic acid or base including an inorganic acid and base and an organic acid and base. Suitable pharmaceutically acceptable base addition salts of the compounds of formula (I) include, but are not limited to metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methyl-glucamine) and procaine. Suitable non-toxic acids include, but are not limited to, inorganic and organic acids such as acetic, alginic, anthranilic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, formic, fumaric, furoic, galacturonic, gluconic, glucuronic, glutamic, glycolic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phenylacetic, phosphoric, propionic, salicylic, stearic, succinic, sulfanilic, sulfuric, tartaric acid, and p-toluenesulfonic acid. Specific non-toxic acids include hydrochloric, hydrobromic, maleic, phosphoric, sulfuric, and methanesulfonic acids. Examples of specific salts thus include hydrochloride and mesylate salts. Others are well-known in the art, see for example, *Remington's Pharmaceutical Sciences*, 18th eds., Mack Publishing, Easton PA (1990) or *Remington: The Science and Practice of Pharmacy*, 19th eds., Mack Publishing, Easton PA (1995).

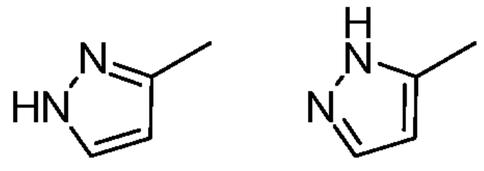
[0068] As used herein and unless otherwise indicated, the term "stereoisomer" or "stereomerically pure" means one stereoisomer of a Pyrrolopyrimidine Compound that is substantially free of other stereoisomers of that compound. For example, a stereomerically pure compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, or greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. The Pyrrolopyrimidine Compounds can have chiral centers and can occur as racemates, individual enantiomers or diastereomers, and mixtures thereof. All such isomeric forms are included within the embodiments disclosed herein, including mixtures thereof.

[0069] The use of stereomerically pure forms of such Pyrrolopyrimidine Compounds, as well as the use of mixtures of those forms, are encompassed by the embodiments disclosed herein. For example, mixtures comprising equal or unequal amounts of the enantiomers of a particular Pyrrolopyrimidine Compound may be used in methods and compositions disclosed herein. These isomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. *See, e.g.*, Jacques, J., *et al., Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen, S. H., *et al., Tetrahedron* 33:2725 (1977); Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

[0070] It should also be noted the Pyrrolopyrimidine Compounds can include E and Z isomers, or a mixture thereof, and cis and trans isomers or a mixture thereof. In certain embodiments, the Pyrrolopyrimidine Compounds are isolated as either the E or Z isomer.

In other embodiments, the Pyrrolopyrimidine Compounds are a mixture of the E and Z isomers.

[0071] "Tautomers" refers to isomeric forms of a compound that are in equilibrium with each other. The concentrations of the isomeric forms will depend on the environment the compound is found in and may be different depending upon, for example, whether the compound is a solid or is in an organic or aqueous solution. For example, in aqueous solution, pyrazoles may exhibit the following isomeric forms, which are referred to as tautomers of each other:



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[0072] As readily understood by one skilled in the art, a wide variety of functional groups and other stuctures may exhibit tautomerism and all tautomers of compounds of formula (I) are within the scope of the present invention.

[0073] It should also be noted the Pyrrolopyrimidine Compounds can contain unnatural proportions of atomic isotopes at one or more of the atoms. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I), sulfur-35 (^{35}S), or carbon-14 (^{14}C), or may be isotopically enriched, such as with deuterium (^{2}H), carbon-13 (^{13}C), or nitrogen-15 (^{15}N). As used herein, an "isotopologue" is an isotopically enriched compound. The term "isotopically enriched" refers to an atom having an isotopic composition other than the natural isotopic composition of that atom. "Isotopically enriched" may also refer to a compound containing at least one atom having an isotopic composition other than the natural isotopic composition of that atom. The term "isotopic composition" refers to the amount of each isotope present for a given atom. Radiolabeled and isotopically encriched compounds are useful as therapeutic agents, e.g., breast cancer therapeutic agents, research reagents, e.g., binding assay reagents, and diagnostic agents, e.g., in vivo imaging agents. All isotopic variations of the Pyrrolopyrimidine Compounds as described herein, whether radioactive or not, are intended to be encompassed within the scope of the embodiments provided herein. In some embodiments, there are provided isotopologues of the Pyrrolopyrimidine Compounds, for example, the isotopologues are deuterium, carbon-13, or nitrogen-15 enriched Pyrrolopyrimidine Compounds.

[0074] It should be noted that if there is a discrepancy between a depicted structure and a name for that structure, the depicted structure is to be accorded more weight.

[0075] "Treating" as used herein, means an alleviation, in whole or in part, of a disorder, disease or condition, or one or more of the symptoms associated with a disorder, disease, or condition, or slowing or halting of further progression or worsening of those symptoms, or alleviating or eradicating the cause(s) of the disorder, disease, or condition itself. In one embodiment, the disorder is a cancer, in particular, a solid tumor or hematological cancer. In some embodiments, "treating" means an alleviation, in whole or in part, of a cancer, or symptoms associated with a cancer, in particular, a solid tumor or hematological cancer, or a slowing, or halting of further progression or worsening of those symptoms.

[0076] "Preventing" as used herein, means a method of delaying and/or precluding the onset, recurrence or spread, in whole or in part, of a cancer, in particular, a solid tumor or hematological cancer; barring a subject from acquiring a cancer, in particular, a solid tumor or hematological cancer; or reducing a subject's risk of acquiring a cancer, in particular, a solid tumor or hematological cancer.

[0077] The term "effective amount" in connection with a Pyrrolopyrimidine Compound means an amount capable of treating or preventing cancer, in particular, a solid tumor or hematological cancer, or symptoms thereof, as disclosed herein. The effective amount of Pyrrolopyrimidine Compound, for example in a pharmaceutical composition, may be at a level that will exercise the desired effect; for example, about 0.005 mg/kg of a subject's body weight to about 100 mg/kg of a patient's body weight in unit dosage for parenteral administration. As will be apparent to those skilled in the art, it is to be expected that the effective amount of a Pyrrolopyrimidine Compound disclosed herein may vary depending on the severity of the indication being treated.

[0078] The terms "patient" and "subject" as used herein include an animal, including, but not limited to, an animal such a cow, monkey, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit or guinea pig, in one embodiment a mammal, in another embodiment a human. In one embodiment, a subject is a human having or at risk for having cancer, in particular, a solid tumor or hematological cancer, or symptoms thereof. In one embodiment, a patient is a human having histologically or cytologically-confirmed

solid tumor or hematological cancer, including subjects who have progressed on (or not been able to tolerate) standard anticancer therapy or for whom no standard anticancer therapy exists.

[0079] As used herein, and unless otherwise specified, the terms "cancer" refers to or describes the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include solid tumors and hematological cancer. In some embodiments, the cancer is a primary cancer, in others, the cancer is metastasized.

[0080] As used herein "solid tumors" includes, but is not limited to, bladder cancer (including, but not limited to, superficial bladder cancer), breast cancer (including, but not limited to, luminal B type, ER+, PR+ and Her2+ breast cancer), central nervous system cancer (including, but no tlimited to, glioblastoma multiforme (GBM), glioma, medulloblastoma, and astrocytoma), colorectal cancer, gastrointestinal cancer (including, but not limited to, stomach cancer, oesophagus cancer, and rectum cancer), endocrine cancer (including, but not imited to, thyroid cancer, and adrenal gland cancer), eye cancer (including, but not limited to, retinoblastoma), female genitourinary cancer (including, but not limited to, cancer of the placenta, uterus, vulva, ovary, cervix), head and neck cancer (including, but not limited to, cancer of the pharynx, oesophagus, and tongue), liver cancer, lung cancer (including, but not limited to, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), mucoepidermoid, bronchogenic, squamous cell carcinoma (SQCC), and analplastic/NSCLC), skin cancer (including, but not limited to, melanoma, and SQCC), soft tissue cancer (including but not limited to, sarcoma, Ewing's sarcoma, and rhabdomyosarcoma), bone cancer (including, but not limited to, sarcoma, Ewing's sarcoma, and osteosarcoma), squamous cell cancer (including, but not limited to, lung, esophageal, cervical, and head and neck cancer), pancreas cancer, kidney cancer (including, but not limited to, renal Wilm's tumor and renal cell carcinoma), and prostate cancer. In one embodiment, the solid tumor is not triple negative breast cancer (TNBC). In some embodiments, the solid tumor is breast cancer, colon cancer, lung cancer or bladder cancer. In one such embodiment, the solid tumor is superficial bladder cancer. In another, the solid tumor is lung squamous cell carcinoma. In yet another embodiment, the solid tumor is luminal B type breast cancer.

[0081] As used herein "hematological cancer" includes, but is not limited to, leukemia (including, but not limited to, acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), acute T-cell leukemia, B cell precursor leukemia, acute promyelocytic leukemia (APML), plasma cell leukemia, myelomonoblastic/T-ALL, B myelomonocytic leukemia, erythroleukemia, and acute myeloid leukemia (AML)), lymphoma (including but not limited to Hodgkin's lymphoma, non-Hodgkin's lymphoma (NHL), Burkitt's lymphoma (BL), B cell lymphoma, lymphoblastic lymphoma, follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), large cell immunoblastic lymphoma), and multiple myeloma.

[0082] In the context of a cancer, inhibition may be assessed by inhibition of disease progression, inhibition of tumor growth, reduction of primary tumor, relief of tumor-related symptoms, inhibition of tumor secreted factors (including tumor secreted hormones, such as those that contribute to carcinoid syndrome), delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors, increased Time To Progression (TTP), increased Progression Free Survival (PFS), increased Overall Survival (OS), among others. OS as used herein means the time from randomization until death from any cause, and is measured in the intent-to-treat population. TTP as used herein means the time from randomization until objective tumor progression; TTP does not include deaths. As used herein, PFS means the time from randomization until objective tumor progression or death. In one embodiment, PFS rates will be computed using the Kaplan-Meier estimates. In the extreme, complete inhibition, is referred to herein as prevention or chemoprevention. In this context, the term "prevention" includes either preventing the onset of clinically evident cancer altogether or preventing the onset of a preclinically evident stage of a cancer. Also intended to be encompassed by this definition is the prevention of transformation into malignant cells or to arrest or reverse the progression of premalignant cells to malignant cells. This includes prophylactic treatment of those at risk of developing a cancer.

[0083] In certain embodiments, the treatment of lymphoma may be assessed by the International Workshop Criteria (IWC) for non-Hodgkin lymphoma (NHL) (*see* Cheson

BD, Pfistner B, Juweid, ME, et. al. Revised Response Criteria for Malignant Lymphoma. J. Clin. Oncol: 2007: (25) 579-586), using the response and endpoint definitions shown below:

Response	Definition	Nodal Masses	Spleen, liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		

Response	Definition	Nodal Masses	Spleen, liver	Bone Marrow
PD or relapsed disease	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) ≥1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identifed node ≥1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	≥50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

[0084] Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

End point	Patients	Definition	Measured from
Primary			
Overall survival	All	Death as a result of any cause	Entry onto study
Progression-free survival	All	Disease progression or death as a result of any cause	Entry onto study
Secondary			
Event-free survival	All	Failure of treatment or death as result of any cause	Entry onto study
Time to progression	All	Time to progression or death as a result of lymphoma	Entry onto study
Disease-free survival	In CR	Time to relapse or death as a result of lymphoma or acute toxicity of treatment	Documentation of response
Response duration	In CR or PR	Time to relapse or progression	Documentation of response
Lymphoma-specific survival	All	Time to death as a result of lymphoma	Entry onto study

End point	Patients	Definition	Measured from
Time to next treatment	All	Time to new treatment	End of primary treatment

Abbreviations: CR: complete remission; PR: partial remission.

[0085] In one embodiment, the end point for lymphoma is evidence of clinical benefit. Clinical benefit may reflect improvement in quality of life, or reduction in patient symptoms, transfusion requirements, frequent infections, or other parameters. Time to reappearance or progression of lymphoma-related symptoms can also be used in this end point.

[0086] In certain embodiments, the treatment of CLL may be assessed by the International Workshop Guidelines for CLL (*see* Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood, 2008; (111) 12: 5446-5456) using the response and endpoint definitions shown therein and in particular:

Parameter	CR	PR	PD
Group A			
Lymphadenopathy†	None > 1.5 cm	Decrease ≥ 50%	Increase ≥ 50%
Hepatomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Blood lymphocytes	< 4000/μL	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline
Marrow‡	Normocellular, < 30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines CRi (5.1.6).	50% reduction in marrow infiltrate, or B-lymphoid nodules	
Group B			
Platelet count	> 100 000/μL	> 100 000/μL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL
Hemoglobin	> 11.0 g/dL	> 11 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL

Parameter	CR	PR	PD
Neutrophils‡	> 1500/μL	> 1500/μL or > 50% improvement over baseline	

[0087] Group A criteria define the tumor load; Group B criteria define the function of the hematopoietic system (or marrow). CR (complete remission): all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms; PR (partial remission): at least two of the criteria of group A plus one of the criteria of group B have to be met; SD is absence of progressive disease (PD) and failure to achieve at least a PR; PD: at least one of the above criteria of group A or group B has to be met. Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical examination in general practice). These parameters are irrelevant for some response categories.

[0088] In certain embodiments, the treatment of multiple myeloma may be assessed by the International Uniform Response Criteria for Multiple Myeloma (IURC) (*see* Durie BGM, Harousseau J-L, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia, 2006; (10) 10: 1-7), using the response and endpoint definitions shown below:

Response Subcategory	Response Criteria[a]
sCR	CR as defined below plus Normal FLC ratio and Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
CR	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow[b]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100mg per 24 h

Response Subcategory	Response Criteria[a]
PR	≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by≥90% or to <200mg per 24 h If the serum and urine M-protein are unmeasurable,[d] a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
SD (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)	Not meeting criteria for CR, VGPR, PR or progressive disease

[0089] Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response; [a]All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements; [b]Confirmation with repeat bone marrow biopsy not needed; [c]Presence/absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.[d]Measurable disease defined by at least one of the following measurements: Bone marrow plasma cells ≥30%; Serum M-protein ≥1 g/dl (≥10 gm/l)[10 g/l]; Urine M-protein ≥200 mg/24 h; Serum FLC assay: Involved FLC level ≥10 mg/dl (≥100 mg/l); provided serum FLC ratio is abnormal.

[0090] In certain embodiments, the treatment of a cancer may be assessed by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (*see* Thereasse P., et al. New Guidelines to Evaluate the Response to Treatment in Solid Tumors. J. of the National Cancer Institute; 2000; (92) 205-216 and Eisenhauer E.A., Therasse P., Bogaerts J., et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European J. Cancer; 2009; (45) 228–247). Overall responses for all possible combinations of tumor responses in target and non-target lesions with our without the appearance of new lesions are as follows:

Target lesions	**Non-target lesions**	**New lesions**	**Overall response**
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease.

[0091] With respect to the evaluation of target lesions, complete response (CR) is the disappearance of all target lesions, partial response (PR) is at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter, progressive disease (PD) is at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions and stable disease (SD) is neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

[0092] With respect to the evaluation of non-target lesions, complete response (CR) is the disappearance of all non-target lesions and normalization of tumor marker level; incomplete response/stable disease (SD) is the persistence of one or more non-target lesion(s) and/or the maintenance of tumor marker level above the normal limits, and progressive disease (PD) is the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

[0093] The procedures, conventions, and definitions described below provide guidance for implementing the recommendations from the Response Assessment for Neuro-Oncology (RANO) Working Group regarding response criteria for high-grade gliomas (Wen P., Macdonald, DR., Reardon, DA., et al. Updated response assessment criteria for highgrade gliomas: Response assessment in neuro-oncology working group. J Clin Oncol 2010; 28: 1963-1972). Primary modifications to the RANO criteria for Criteria for Time Point Responses (TPR) can include the addition of operational conventions for defining changes in glucocorticoid dose, and the removal of subjects' clinical deterioration component to focus on objective radiologic assessments. The baseline MRI scan is defined as the assessment performed at the end of the post-surgery rest period, prior to re-initiating compound treatment. The baseline MRI is used as the reference for assessing complete response (CR) and partial response (PR). Whereas, the smallest SPD (sum of the products of perpendicular diameters) obtained either at baseline or at subsequent assessments will be designated the nadir assessment and utilized as the reference for determining progression. For the 5 days preceding any protocol-defined MRI scan, subjects receive either no glucocorticoids or are on a stable dose of glucocorticoids. A stable dose is defined as the same daily dose for the 5 consecutive days preceding the MRI scan. If the prescribed glucocorticoid dose is changed in the 5 days before the baseline scan, a new baseline scan is required with glucocorticoid use meeting the criteria described above. The following definitions will be used.

[0094] Measurable Lesions: Measurable lesions are contrast-enhancing lesions that can be measured bidimensionally. A measurement is made of the maximal enhancing tumor diameter (also known as the longest diameter, LD). The greatest perpendicular diameter is measured on the same image. The cross hairs of bidimensional measurements should cross and the product of these diameters will be calculated.

[0095] Minimal Diameter: T1-weighted image in which the sections are 5 mm with 1 mm skip. The minimal LD of a measurable lesion is set as 5 mm by 5 mm. Larger diameters may be required for inclusion and/or designation as target lesions. After baseline, target lesions that become smaller than the minimum requirement for measurement or become no longer amenable to bidimensional measurement will be recorded at the default value of 5 mm for each diameter below 5 mm. Lesions that disappear will be recorded as 0 mm by 0 mm.

[0096] Multicentric Lesions: Lesions that are considered multicentric (as opposed to continuous) are lesions where there is normal intervening brain tissue between the two (or more) lesions. For multicentric lesions that are discrete foci of enhancement, the approach is to separately measure each enhancing lesion that meets the inclusion criteria. If there is no normal brain tissue between two (or more) lesions, they will be considered the same lesion.

[0097] Nonmeasurable Lesions: All lesions that do not meet the criteria for measurable disease as defined above will be considered non-measurable lesions, as well as all nonenhancing and other truly nonmeasurable lesions. Nonmeasurable lesions include foci of enhancement that are less than the specified smallest diameter (i.e., less than 5 mm by 5 mm), nonenhancing lesions (e.g., as seen on T1-weighted post-contrast, T2-weighted, or fluid-attenuated inversion recovery (FLAIR) images), hemorrhagic or predominantly cystic or necrotic lesions, and leptomeningeal tumor. Hemorrhagic lesions often have intrinsic T1-weighted hyperintensity that could be misinterpreted as enhancing tumor, and for this reason, the pre-contrast T1-weighted image may be examined to exclude baseline or interval sub-acute hemorrhage.

[0098] At baseline, lesions will be classified as follows: Target lesions: Up to 5 measurable lesions can be selected as target lesions with each measuring at least 10 mm by 5 mm, representative of the subject's disease; Non-target lesions: All other lesions, including all nonmeasurable lesions (including mass effects and T2/FLAIR findings) and any measurable lesion not selected as a target lesion. At baseline, target lesions are to be measured as described in the definition for measurable lesions and the SPD of all target lesions is to be determined. The presence of all other lesions is to be documented. At all post-treatment evaluations, the baseline classification of lesions as target and non-target

lesions will be maintained and lesions will be documented and described in a consistent fashion over time (*e.g.*, recorded in the same order on source documents and eCRFs). All measurable and nonmeasurable lesions must be assessed using the same technique as at baseline (e.g., subjects should be imaged on the same MRI scanner or at least with the same magnet strength) for the duration of the study to reduce difficulties in interpreting changes. At each evaluation, target lesions will be measured and the SPD calculated. Non-target lesions will be assessed qualitatively and new lesions, if any, will be documented separately. At each evaluation, a time point response will be determined for target lesions, non-target lesions, and new lesion. Tumor progression can be established even if only a subset of lesions is assessed. However, unless progression is observed, objective status (stable disease, PR or CR) can only be determined when all lesions are assessed.

[0099] Confirmation assessments for overall time point responses of CR and PR will be performed at the next scheduled assessment, but confirmation may not occur if scans have an interval of < 28 days. Best response, incorporating confirmation requirements, will be derived from the series of time points.

[00100] TTK (also known as Mps1, hMps1 or PYT) is a dual specificity protein kinase with the ability to phosphorylate tyrosine, serine and threonine. Associated with cell proliferation, this protein is essential for chromosome alignment at the centromere during mitosis and is required for centrosome duplication. It has been found to be a critical mitotic checkpoint protein for accurate segregation of chromosomes during mitosis. Tumorigenesis may occur when this protein fails to degrade and produces excess centrosomes resulting in aberrant mitotic spindles. Alternative splicing results in multiple transcript variants. [RefSeq, Nov 2009]. TTK is essential for spindle checkpoint function and its inhibition accelerates cell progression through mitosis. TTK also plays an important role for cancer stem cell survival.

[00101] CLK1 is a member of the CDC2-like (or LAMMER) family of dual specificity protein kinases. In the nucleus, the encoded protein phosphorylates serine/arginine-rich (SR) proteins involved in pre-mRNA processing, releasing them into the nucleoplasm. The choice of splice sites during pre-mRNA processing may be regulated by the concentration and localization of splicing factors, including serine/arginine rich (SR)

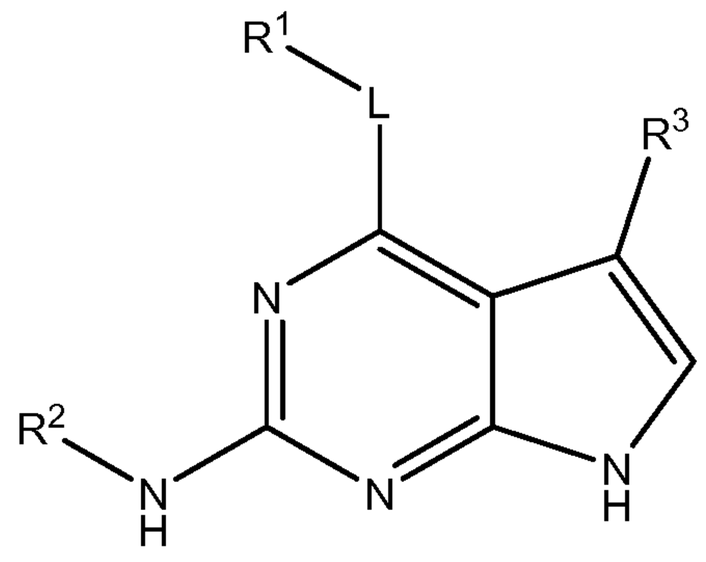
proteins. Therefore, the encoded protein may play an indirect role in governing splice site selection. Multiple transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, Jun 2009]

[00102] CLK2 is a member of the CLK family of dual specificity protein kinases. CLK family members have been shown to interact with, and phosphorylate, serine/arginine-rich (SR) proteins of the spliceosomal complex, which is a part of the regulatory mechanism that enables the SR proteins to control RNA splicing. This protein kinase is involved in the regulation of several cellular processes and may serve as a link between cell cycle progression, apoptosis, and telomere length regulation [RefSeq, Jul 2008]. Inhibition of CLK2 changes the expression of protein isoforms, many of which contribute to the oncogenic phenotype.

[00103] CAMKK2 belongs to the serine/threonine-specific protein kinase family, and to the Ca^{++}/calmodulin-dependent protein kinase subfamily. This protein plays a role in the calcium/calmodulin-dependent (CaM) kinase cascade by phosphorylating the downstream kinases CaMK1 and CaMK4 [RefSeq, Jul 2012]. CAMKK2 reportedly plays a role in tumor energy homeostasis.

PYRROLOPYRIMIDINE COMPOUNDS

[00104] Provided herein are compounds having the following formula (I):



(I)

and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, and isotopologues thereof,

wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, or substituted or unsubstituted non-aromatic heterocyclyl;

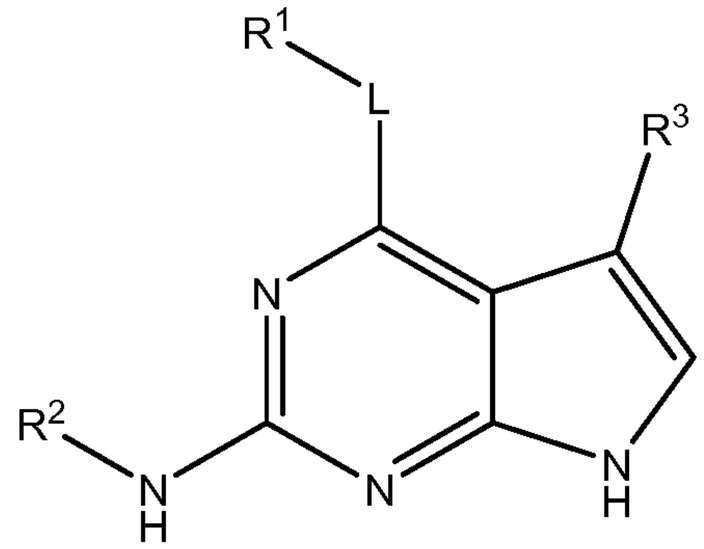
R^2 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is substituted or unsubstituted heterocyclyl or substituted or unsubstituted aryl, and

L is NH or O;

provided that when L is NH, R^3 is not pyridyl.

[00105] Provided herein are compounds having the following formula (I):



(I)

and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, and isotopologues thereof,

wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, or substituted or unsubstituted non-aromatic heterocyclyl;

R^2 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is substituted or unsubstituted heterocyclyl or substituted or unsubstituted aryl, and

L is NH or O;

provided

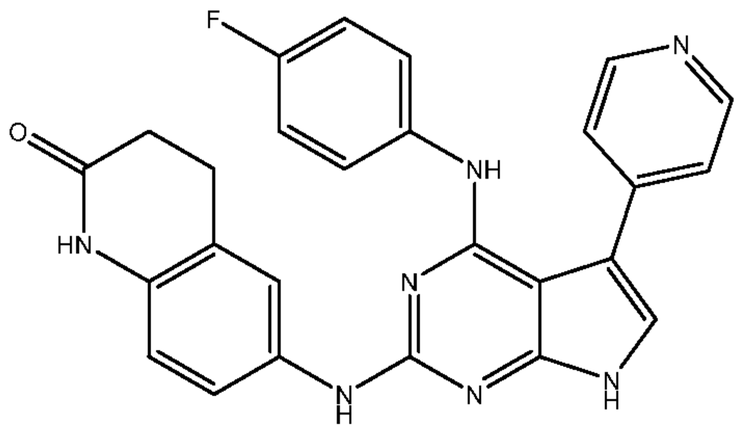
R^3 is not pyridyl when L is NH or when R^2 is pyrazolyl; and

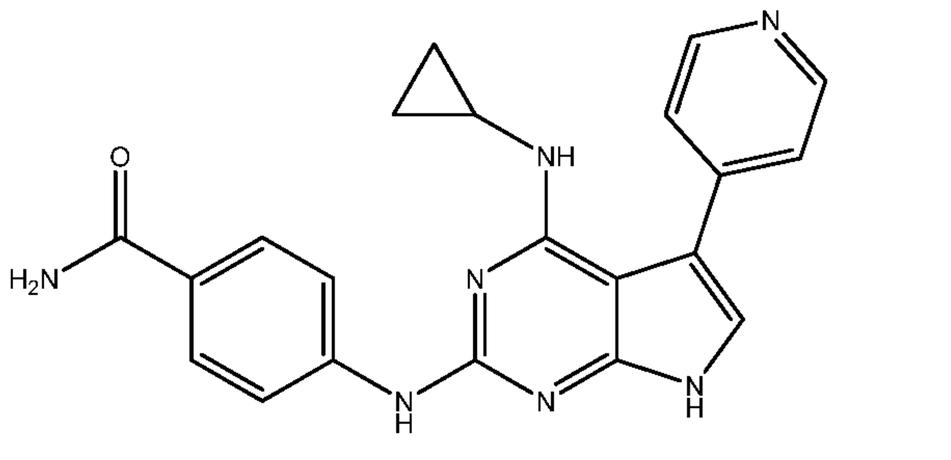
the compound is not

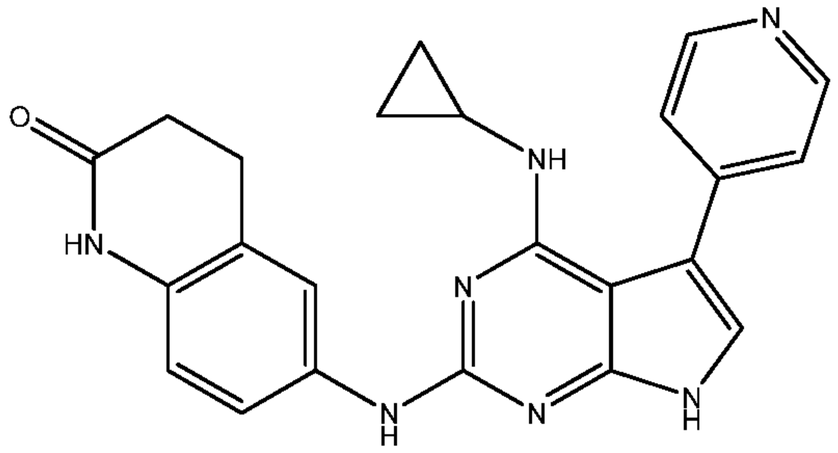
N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-4-yl)-2-[(1-methyl-1Hpyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]-2-propenamide; or

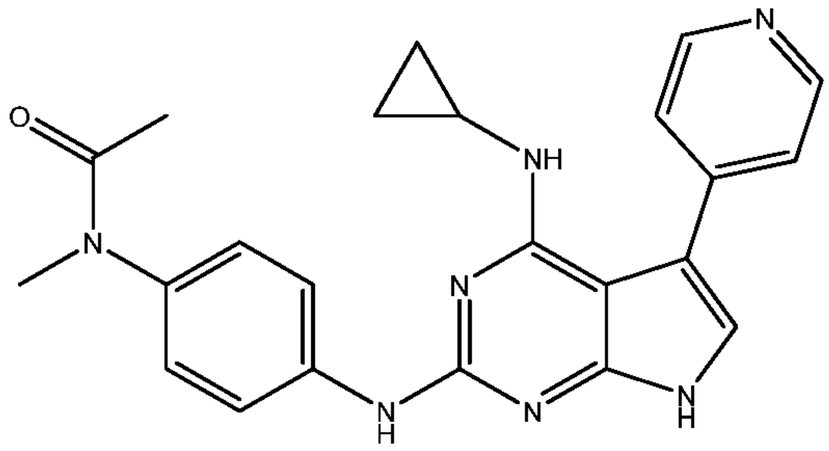
N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-3-yl)-2-[(1-methyl-1Hpyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]- 2-propenamide.

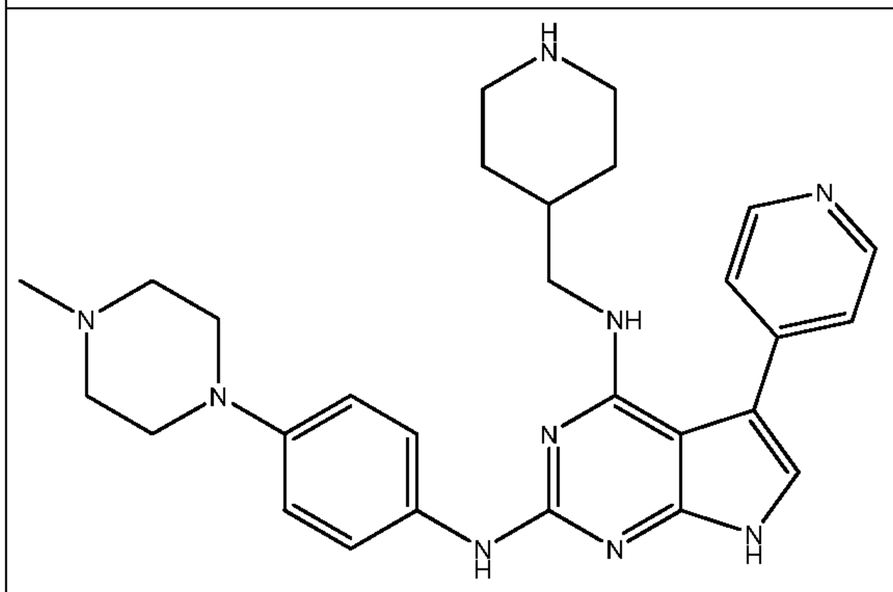
[00106] The compound as described herein is not a compound selected from:

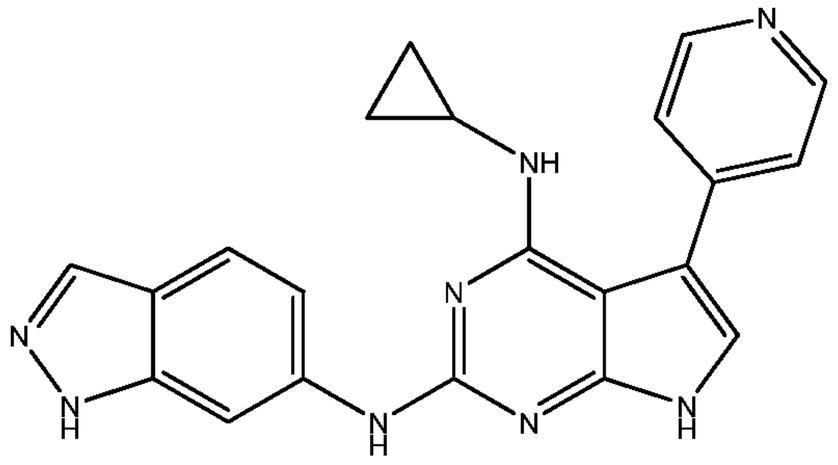


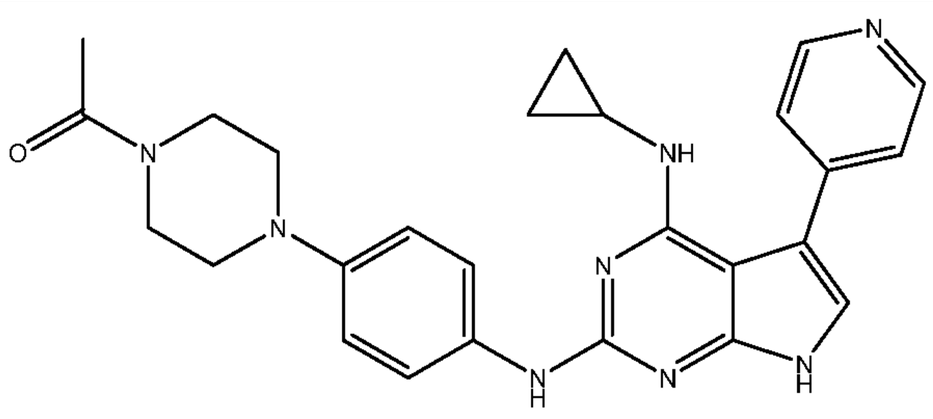


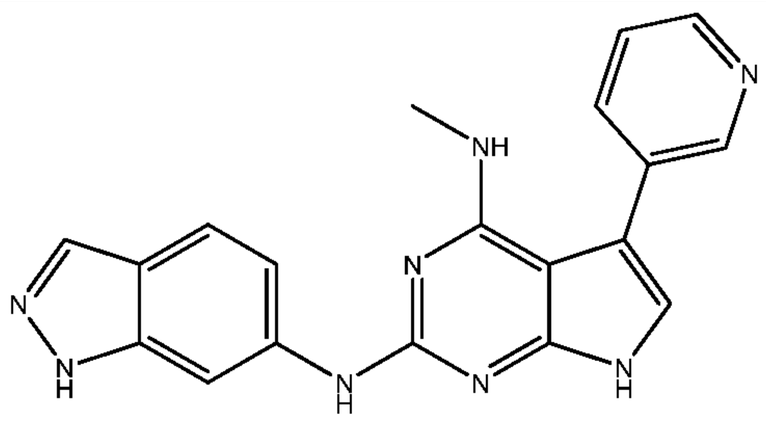


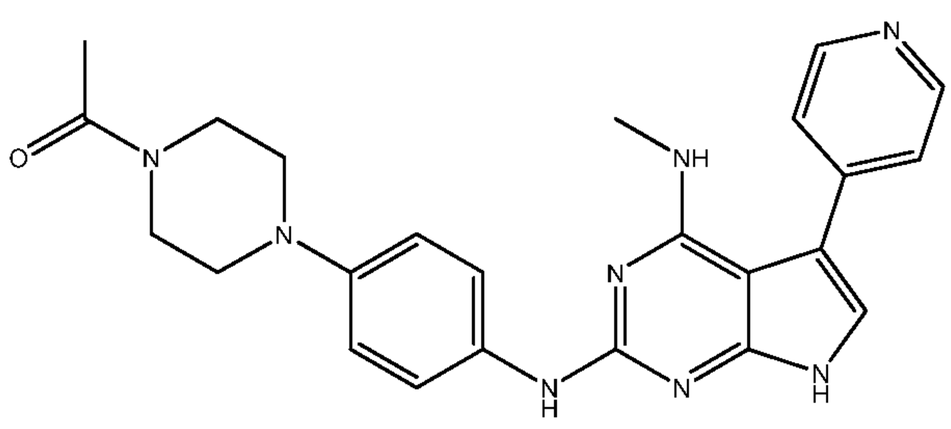


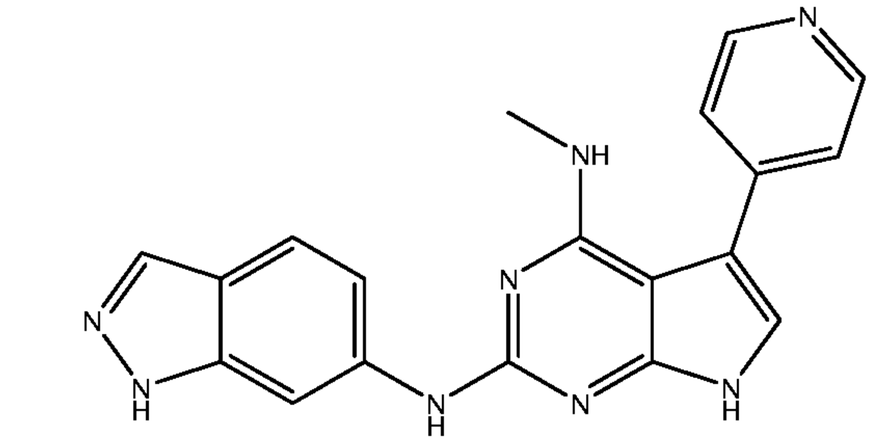




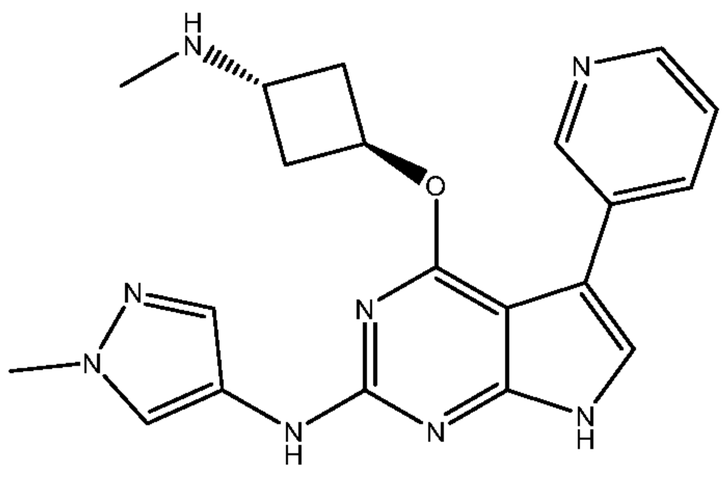
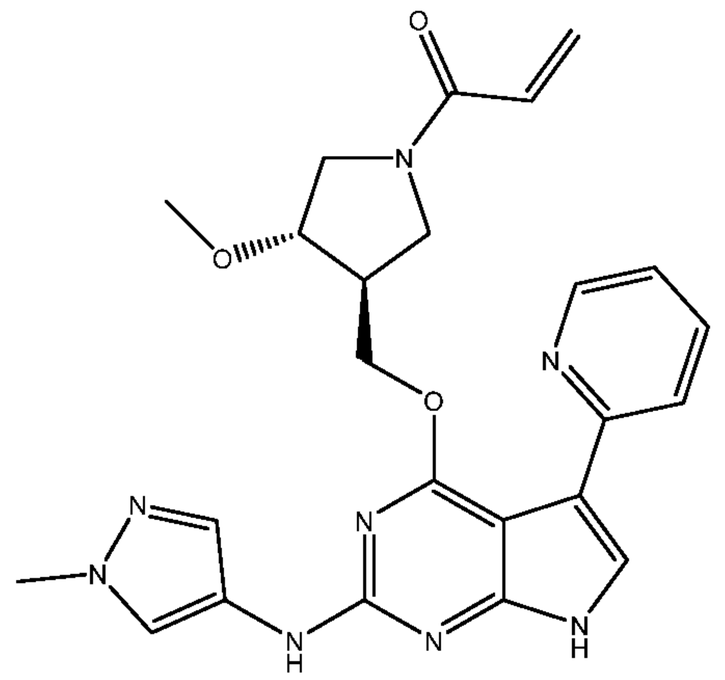
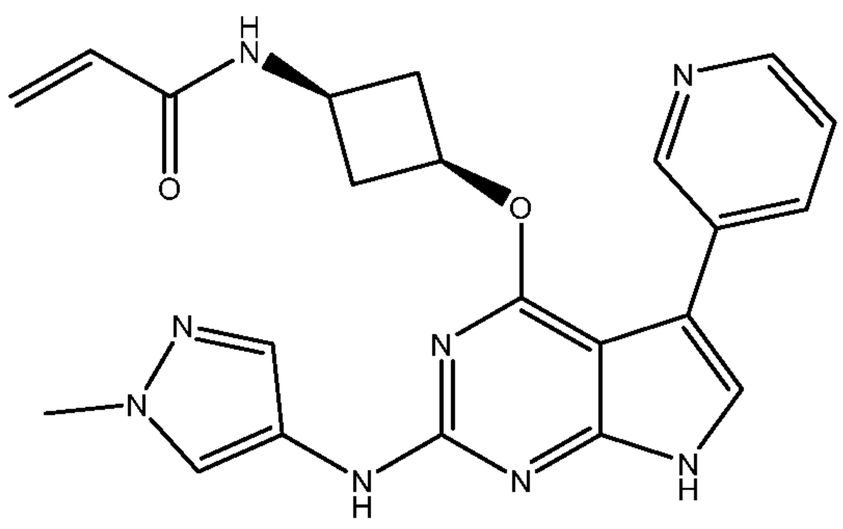
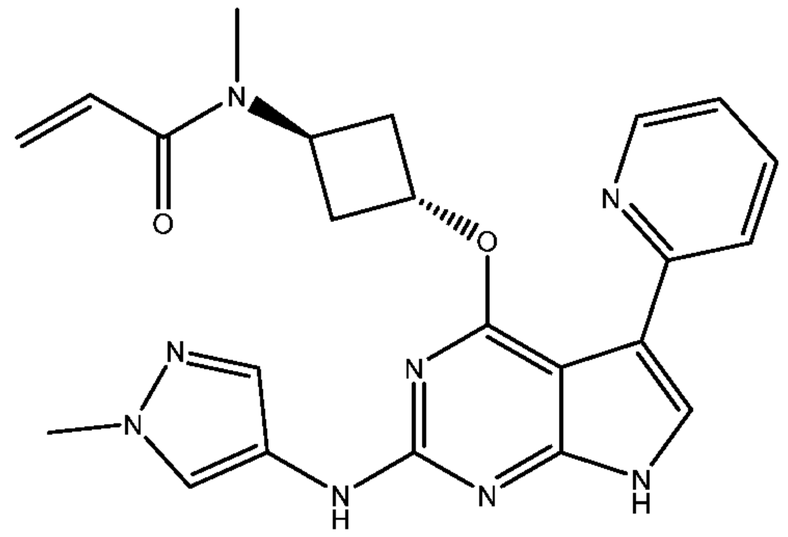
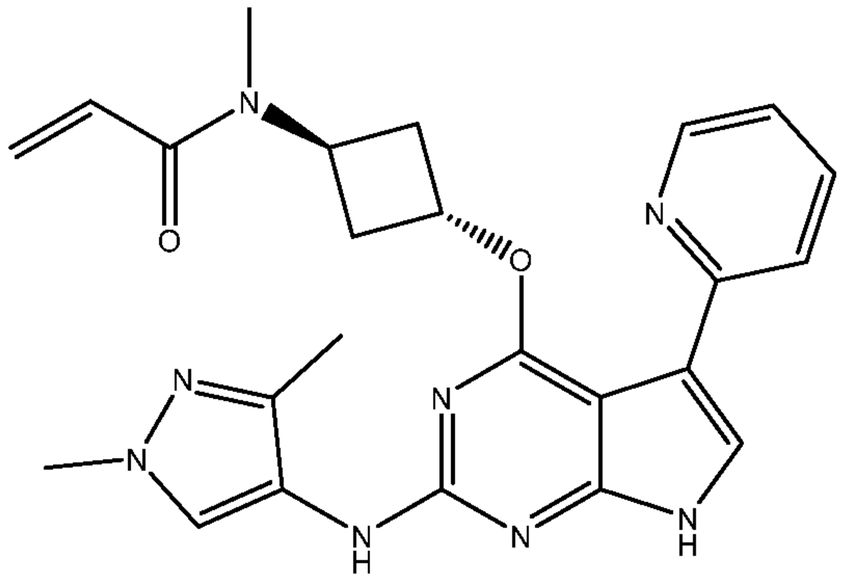
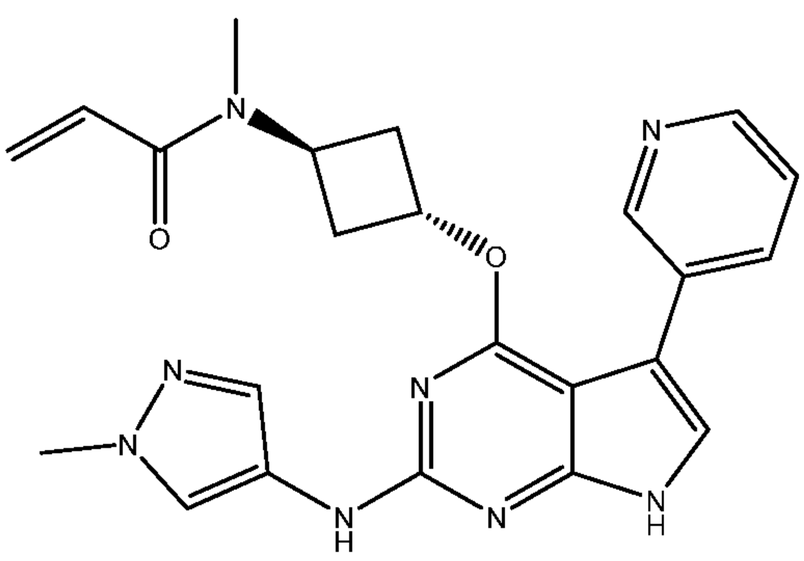
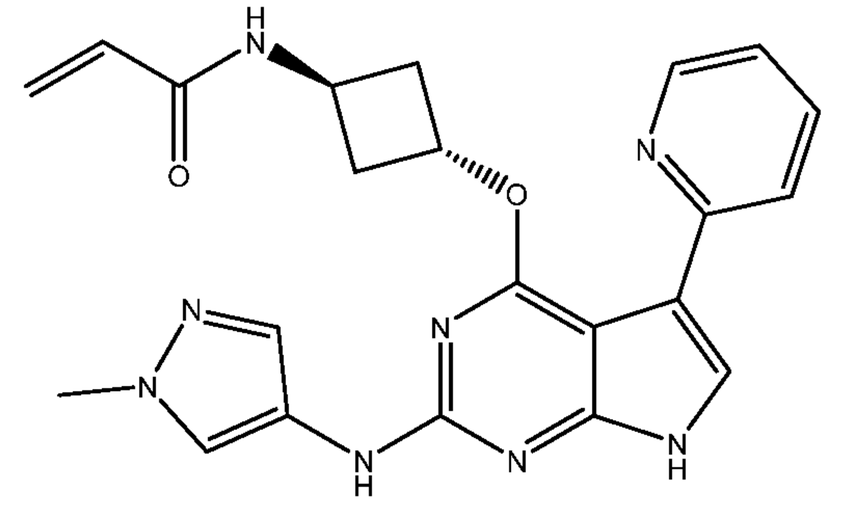
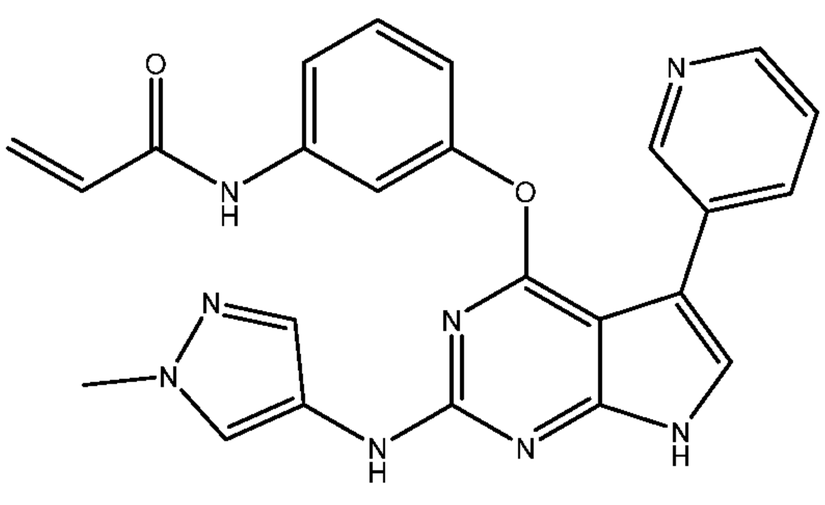




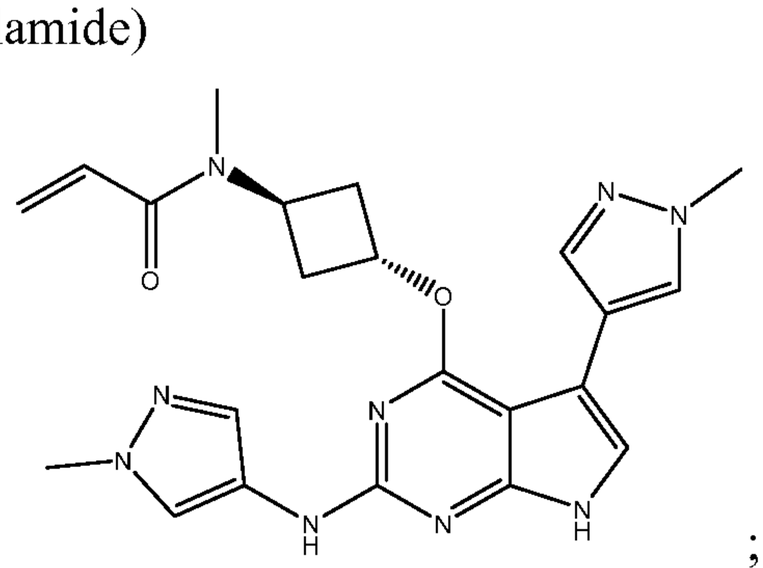




[00107] As described herein, the compound is not

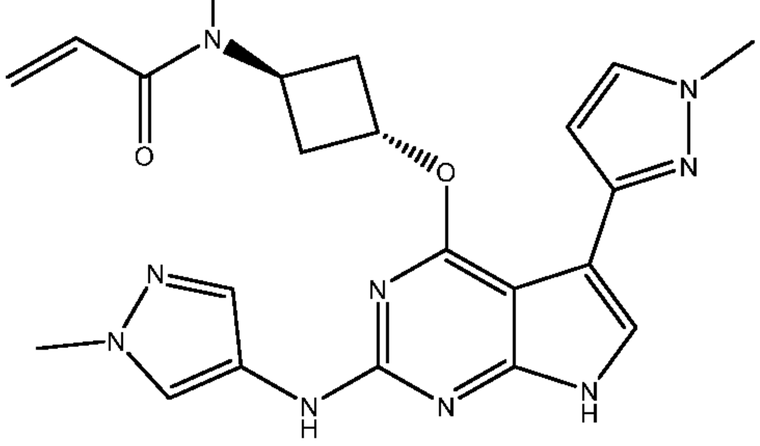
	
	
	
	

[00108] In one embodiment, the compound is not N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-4-yl)-2-[(1-methyl-1Hpyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]-2-propenamide (also named N-methyl-N-((1r,3r)-3-((5-(1-methyl-1H-pyrazol-4-yl)-2-((1-methyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)cyclobutyl)acrylamide)



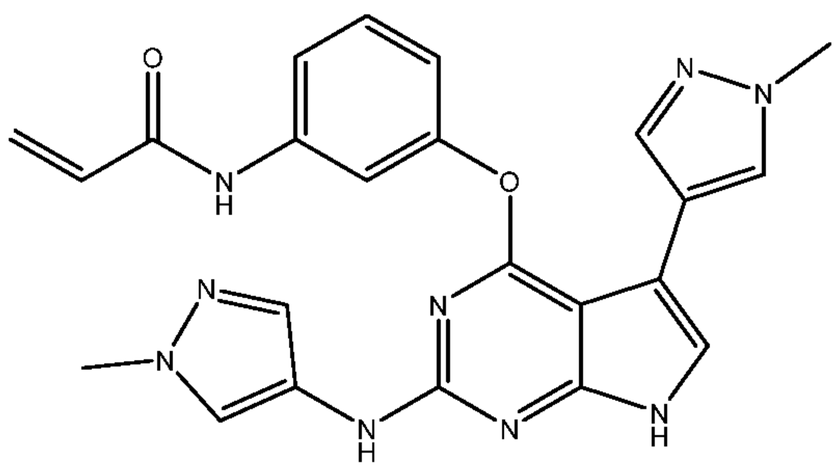
;

or N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-3-yl)-2-[(1-methyl-1Hpyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]-2-propenamide (also named N-methyl-N-((1r,3r)-3-((5-(1-methyl-1H-pyrazol-3-yl)-2-((1-methyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)cyclobutyl)acrylamide)



.

[00109] In yet another embodiment, the compound is not

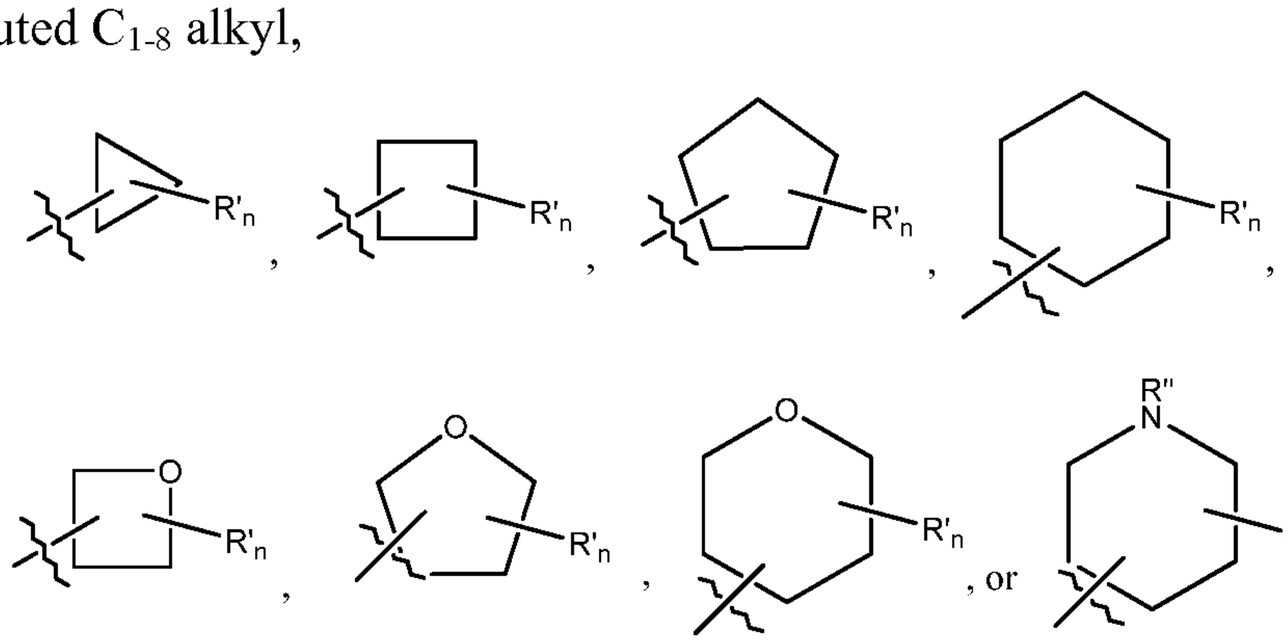


[00110] In one embodiment, provided herein are compounds of formula (I), wherein L is O.

[00111] In some embodiments of compounds of formula (I), R^1 is substituted or unsubstituted alkyl, for example, R^1 is substituted or unsubstituted methyl, ethyl, propyl,

isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, sec-pentyl, tert-pentyl, or 2,2-dimethylpropyl. In some embodiments, R^1 is substituted or unsubstituted methyl, ethyl, isopropyl, sec-butyl, t-butyl, or 2,2-dimethylpropyl. In some embodiments of formula (I), wherein R^1 is alkyl, the alkyl is substituted with one or more -OR or $-NR_2$, wherein each R is independently -H or substituted or unsubstituted (C_{1-4})alkyl. For example R^1 is $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$, or $-CH_2CH_2NHCH_3$. In other embodiments of compounds of formula (I), R^1 is substituted or unsubstituted C_{3-8} cycloalkyl, for example, R^1 is substituted or unsubstituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl. In some such embodiments, the cycloalkyl is substituted with one or more -CN, halogen, -OR or a substituted or unsubstituted C_{1-3} alkyl, wherein each R is independently –H or substituted or unsubstituted (C_{1-4})alkyl. For example, in some embodiments the cycloalkyl is substituted with one or more -CN, -F, -OH, or $-CH_3$. In some other embodiments of compounds of formula (I), R^1 is substituted or unsubstituted non-aromatic heterocyclyl, for example, R^1 is substituted or unsubstituted oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, or piperidinyl.

[00112] In some other embodiments of compounds of formula (I), R^1 is substituted or unsubstituted C_{1-8} alkyl,



wherein

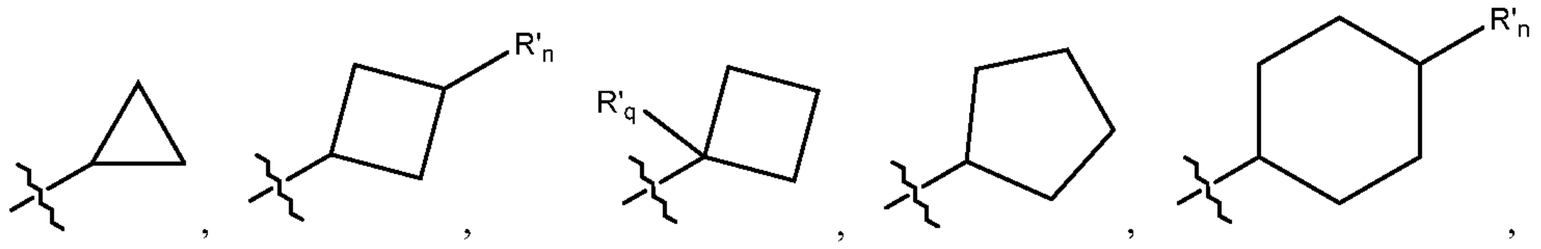
each R' is independently -CN, halogen, -OR or C_{1-3} alkyl;

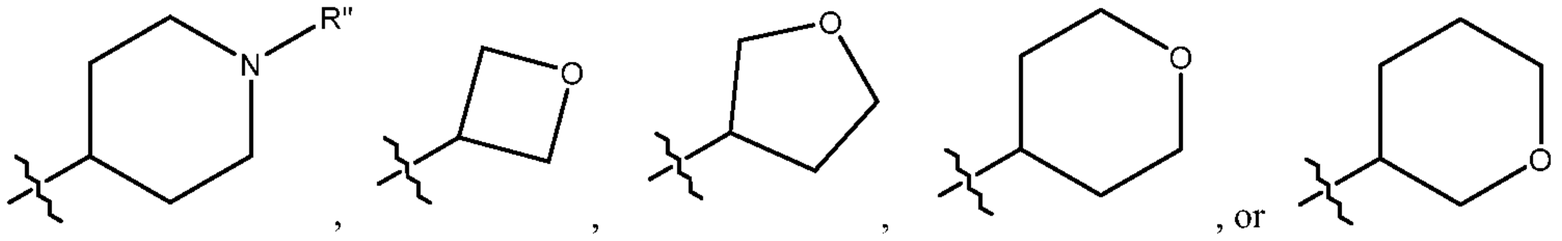
R" is -H or C_{1-3} alkyl;

each R is independently –H or substituted or unsubstituted (C_{1-4})alkyl; and

n is 0-2.

[00113] In some such embodiments, R^1 is substituted or unsubstituted methyl, ethyl, isopropyl, sec-butyl, t-butyl, or 2,2-dimethylpropyl,





and R' is -CN, -F, -OH, or $-CH_3$;

R" is $-CH_3$;

n is 0, 1 or 2; and

q is 0 or 1.

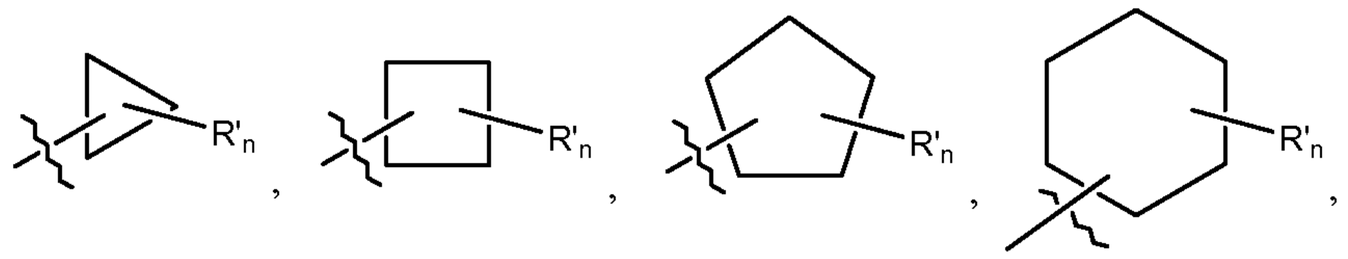
[00114] Also provided herein are compounds of formula (I), wherein R^2 is substituted phenyl. In some such embodiments, R^2 is phenyl, substituted with one or more substituted or unsubstituted C_{1-6} alkyl, halogen, -CN, $-OR^5$, $-C(=O)NR^5_2$, -C(=O)(substituted or unsubstituted heterocyclyl), -C(=O)(substituted or unsubstituted alkylheterocyclyl), $-NHC(=O)R^5$, $-SO_2NR^5_2$, or substituted or unsubstituted heteroaryl, wherein each R^5 is independently -H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted alkylheterocyclyl. For example, R^2 is phenyl, substituted with one or more -(C_{1-3} alkyl), -(C_{1-3} alkyl)NR_2, $-CF_3$, -Cl, -F, -CN, $-OCH_3$, $-OCF_3$, $-C(=O)NR_2$, -C(=O)NR(substituted or unsubstituted cycloalkyl), $-C(=O)NR(CH_2)_{0-2}CR_2(CH_2)_{0-2}OR$, $-C(=O)NR(CH_2)_{0-2}CR_2(CH_2)_{0-2}NR_2$, $-C(=O)NR(CH_2)_{0-2}CR_2(CH_2)_{0-2}C(=O)NR_2$, $-C(=O)N$(substituted or unsubstituted cycloalkyl)$(CH_2)_{0-2}OR$, $-C(=O)NR(CH_2)_{0-3}$(substituted or unsubstituted heterocyclyl), $-C(=O)(CH_2)_{0-3}$(substituted or unsubstituted heterocyclyl), $-C(=NR)NR_2$, $-NRC(=O)R$, $-SO_2NR_2$, $-SO_2R$, or substituted or unsubstituted heterocyclyl, wherein each R is independently -H or substituted or unsubstituted (C_{1-4})alkyl. In some such embodiments, each R is independently -H or $-CH_3$.

[00115] In some embodiments of compounds of formula (I), R^2 is phenyl, substituted with one or more –CH_3, -CH_2CH_3, -CH_2 CH_2CH_3, -$CH(CH_3)_2$, -CH_2NH_2, -CF_3, -Cl, - F, -CN, -OCH_3, -OCF_3, -C(=O)NH_2, -C(=O)$NHCH_3$, -C(=O)$N(CH_3)_2$, -C(=O)$NC(CH_3)_3$, -C(=O)$NHCH_2CH_2F$, -C(=O)$NHCH_2CHF_2$, -C(=O)$NHCH_2CF_3$, -C(=O)$NHCH_2CF_2CH_3$, -C(=O)$NHCH_2CN$, -C(=O)$N(CH_3)CH_2CN$, -C(=O)$NHCH_2CH_2CN$, -C(=O)$N(CH_3)CH_2CH_2CN$, -C(=O)NH-cyclobutyl, -C(=O)NH-(hydroxy-cyclobutyl), -C(=O)NH-cyclopentyl, -C(=O)NH-(hydroxyl-cyclopentyl), -C(=O)$NHCH_2CH_2OH$, -C(=O)$NHCH_2CH_2OCH_3$, -C(=O)$N(CH_3)CH_2CH_2OH$, -C(=O)$N(CH_3)CH_2CH_2OCH_3$, -C(=O)$NHCH_2CH_2CH_2OH$, -C(=O)$N(CH_3)CH_2CH_2CH_2OH$, -C(=O)$N(CH_3)CH_2CH_2CH_2OCH_3$, -C(=O)$NHCH_2CH(CH_3)OH$, -C(=O)$NHCH_2C(CH_3)_2OH$, -C(=O)$NHCH(CH_3)CH_2OH$, -C(=O)$NHC(CH_3)_2CH_2OH$, -C(=O)$NHCH_2CH_2NH_2$, -C(=O)$NHCH_2CH_2NH(CH_3)$, -C(=O)$NHCH_2CH_2N(CH_3)_2$, -C(=O)$NHCH_2C(=O)NH_2$, -C(=O)$N(CH_3)CH_2C(=O)NH_2$, -C(=O)$NHCH_2CH_2C(=O)NH_2$, -C(=O)$N(CH_3)CH_2CH_2C(=O)NH_2$, -C(=O)N(cyclopropyl)CH_2CH_2OH, -C(=O)NH-oxetanyl, -C(=O)$N(CH_3)$-oxetanyl, -C(=O)NH-(methyl-oxetanyl), -C(=O)NH-azetidinyl, -C(=O)NH-(methylazetidinyl), -C(=O)NH-(1-acetylazetidinyl), -C(=O)NH-pyrrolidyl, -C(=O)NH-piperidyl, -C(=O)NH-tetrahydrofuranyl, -C(=O)$N(CH_3)$-tetrahydrofuranyl, -C(=O)NH-tetrahydropyranyl, -C(=O)$N(CH_3)$-tetrahydropyranyl, -C(=O)$NHCH_2$-oxetanyl, -C(=O)$N(CH_3)CH_2$-oxetanyl, -C(=O)$NHCH_2$-(methyl-oxetanyl), -C(=O)$N(CH_3)CH_2$-(methyl-oxetanyl), -C(=O)$NHCH_2$-tetrahydrofuranyl, -C(=O)$NHCH_2$-tetrahydropyranyl, -C(=O)$NHCH_2$-dioxanyl, -C(=O)aziridinyl, -C(=O)(methyl-aziridinyl), -C(=O)(dimethyl-aziridinyl), -C(=O)(hydroxymethyl-aziridinyl), -C(=O)azetidinyl, -C(=O)pyrrolidinyl, -C(=O)(hydroxyl-pyrrolidinyl), -C(=O)(hydroxyl, methoxypyrrolidinyl), -C(=O)(dimethoxypyrrolidinyl), -C(=O)morpholinyl, -C(=O)piperazinyl, -C(=O)(methylpiperazinyl), -C(=O)(hydroxy-piperidyl), -C(=O)(fluoropiperidinyl), -(C=O)(methoxy-piperidyl), -C(=NH)NH_2, -$NHC(=O)CH_3$, -SO_2NHCH_3, -SO_2CH_3, or substituted or unsubstituted pyrazolyl. In some other embodiments, R^2 is phenyl, substituted with one or more -CH_3, -CH_2CH_3, -CH_2 CH_2CH_3, -$CH(CH_3)_2$, -CH_2NH_2, -CF_3, -Cl,- F, -CN, -OCH_3, -OCF_3, -C(=O)NH_2, -C(=O)$NHCH_3$, -C(=O)$N(CH_3)_2$, -C(=O)$NC(CH_3)_3$, -C(=O)$NHCH_2CH_2F$, -C(=O)$NHCH_2CF_2CH_3$, -C(=O)$N(CH_3)CH_2CN$,

-C(=O)N(CH_3)CH_2CH_2CN, -C(=O)NH-(3-hydroxy-cyclobutyl), -C(=O)NH-cyclopentyl, -C(=O)NH-(2-hydroxycyclopentyl),-C(=O)NHCH_2CH_2OH, -C(=O)N$HCH_2CH_2OCH_3$, -C(=O)N(CH_3)CH_2CH_2OH, -C(=O)N(CH_3)$CH_2CH_2OCH_3$, -C(=O)N$HCH_2CH_2CH_2OH$, -C(=O)N(CH_3)$CH_2CH_2CH_2OH$, -C(=O)N$HCH_2CH(CH_3)OH$, -C(=O)N$HCH_2C(CH_3)_2OH$, -C(=O)NHCH(CH_3)CH_2OH, -C(=O)N$HC(CH_3)_2CH_2OH$, -C(=O)N$HCH_2CH_2NH_2$, -C(=O)N$HCH_2CH_2NH(CH_3)$, -C(=O)N$HCH_2CH_2N(CH_3)_2$, -C(=O)N(CH_3)$CH_2C(=O)NH_2$, -C(=O)N(CH_3)$CH_2CH_2C(=O)NH_2$, -C(=O)N(cyclopropyl)CH_2CH_2OH, -C(=O)NH-oxetanyl, -C(=O)N(CH_3)-oxetanyl, -C(=O)NH-(3-methyl-oxetanyl), -C(=O)NH-(1-methylazetidinyl), -C(=O)NH-(1-acetylazetidinyl), -C(=O)NH-piperidyl, -C(=O)NH-tetrahydrofuranyl, -C(=O)NH-tetrahydropyranyl, -C(=O)N(CH_3)-tetrahydropyranyl, -C(=O)NHCH_2-oxetanyl, -C(=O)N(CH_3)CH_2-(3-methyl-oxetanyl), -C(=O)NHCH_2-tetrahydrofuranyl, -C(=O)NHCH_2-tetrahydropyranyl, -C(=O)NHCH_2-dioxanyl, -C(=O)aziridinyl, -C(=O)(2-methyl-aziridinyl), -C(=O)(2,2-dimethyl-aziridinyl), -C(=O)(2-(hydroxymethyl)aziridinyl), -C(=O)azetidinyl, -C(=O)pyrrolidinyl, -C(=O)(3-hydroxy-4-methoxypyrrolidinyl), -C(=O)(3,4-dimethoxypyrrolidinyl), -C(=O)morpholinyl, -C(=O)piperazinyl, -C(=O)(4-methylpiperazinyl), -C(=O)(4-hydroxy-piperidyl), -C(=O)(4,4-difluoropiperidinyl), -(C=O)(4-methoxy-piperidyl), -C(=NH)NH_2,-NHC(=O)CH_3, -SO_2NHCH_3, -SO_2CH_3, or substituted or unsubstituted pyrazolyl.

[00116] In some embodiments of compounds of formula (I), R^2 is substituted or unsubstituted pyrazolyl, substituted or unsubstituted pyridyl, substituted or unsubstituted indazolyl or substituted or unsubstituted isoindolinone. In some such embodiments, R^2 is substituted with one or more halogen, substituted or unsubstituted (C_{1-4})alkyl, -OR, -C(=O)NR_2, or substituted or unsubstituted heterocyclyl, wherein each R is independently –H or substituted or unsubstituted (C_{1-4})alkyl. For example, R^2 is pyrazolyl substituted with one or more -Cl, -CH_3, -CH_2CH_3, -$CH(CH_3)_2$, -$CH_2CH_2OCH_3$, -$CH_2C(CH_3)_2OH$, or tetrahydropyranyl. Alternatively, R^2 is pyridyl, substituted with one or more –OCH_3, C(=O)NHCH_3, or tetrahydropyranyl. In yet other embodiments, R^2 is indazolyl or isoindolinone, substituted with one or more -CH_3.

[00117] In some such embodiments of R^2, R^1 is substituted or unsubstituted C_{1-8} alkyl,



, or

,

wherein

each R' is independently -OR or C_{1-3} alkyl;

R" is -H or C_{1-3} alkyl;

each R is independently -H or substituted or unsubstituted (C_{1-4})alkyl; and

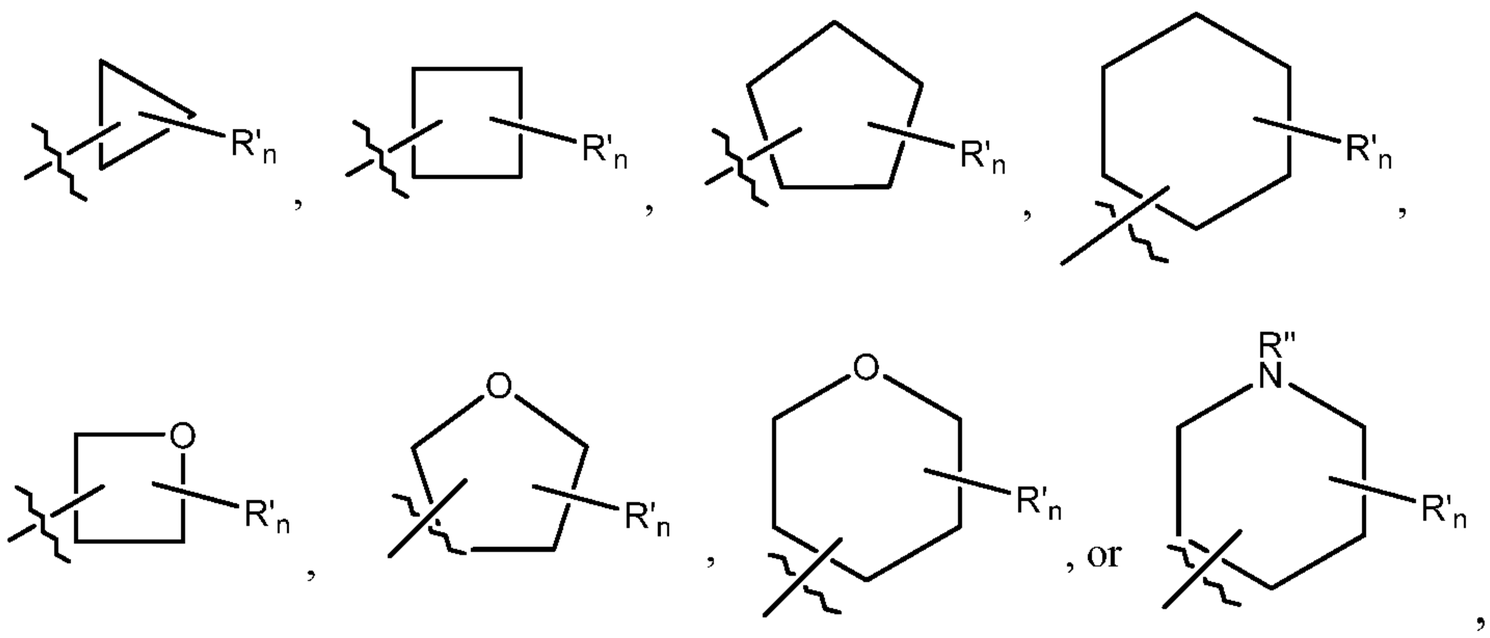
n is 0-2.

[00118] In yet other embodiments of compounds of formula (I), R^3 is substituted or unsubstituted heterocyclyl, for example, substituted or unsubstituted pyrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, benztriazolyl, indazolyl, indolyl, benzoxazolyl, benzisoxazolyl, benzthiazolyl, benzoxazolonyl, benzoxadiazolyl, benzimidazolyl, or quinolyl. In some such embodiments, the heterocyclyl is substituted with one or more substituents selected from substituted or unsubstituted (C_{1-4})alkyl, halogen, -OR, -CN, $-NR_2$, $-C(=O)NR_2$, -NRC(=O)R, or substituted or unsubstituted triazolyl, wherein each R is independently –H or substituted or unsubstituted (C_{1-4})alkyl. For example, the heterocyclyl is substituted with one or more substituents selected from $-CH_3$, $-CH(CH_3)_2$, -F, -Cl, -OH, $-OCH_3$, $-OCH_2CH_3$, -CN, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)NH(CH_3)$, $-NHC(=O)CH_3$, or substituted or unsubstituted triazolyl. In some such embodiments, the pyrazolyl is substituted with one or more $-CH_3$, or -Cl. In others, the pyridyl is substituted with one or more $-CH_3$, -F, -Cl, -OH, $-OCH_3$, $-OCH_2CH_3$, -CN, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)NH(CH_3)$, or $-NHC(=O)CH_3$. In still others, the benzoxazolyl is substituted with one or more $-CH_3$, $-CH(CH_3)_2$, -F or $-OCH_2CH_3$.

[00119] In other embodiments of compounds of formula (I), R^3 is substituted or unsubstituted aryl, for example, R^3 is substituted or unsubstituted phenyl. In some such

embodiments, the phenyl is substituted with one or more substituents selected from substituted or unsubstituted C_{1-4} alkyl, halogen, -CN, -OR, -NR_2, -$NRSO_2R'$, -$NR(C=O)NR_2$, -$NR(C=O)R'$, -COOR, -$(C=O)NR_2$, -$C(=NH)NR_2$, -SO_2R', or substituted or unsubstituted heteroaryl, wherein each R is independently –H or substituted or unsubstituted (C_{1-4})alkyl, and R' is C_{1-3} alkyl. In yet other embodiments, the phenyl is substituted with one or more substituents selected from -CH_3, -CH_2OH, -$CH(OH)CH_3$, -$C(CH_3)_2OH$, -CN, -F, -Cl, -OH, -OCH_3, -NH_2, -$N(CH_3)_2$, -$NHSO_2CH_3$, -$NH(C=O)NH_2$, -$NH(C=O)CH_3$, -$COOCH_3$, -$(C=O)NHCH_3$, -$C(=N)NH_2$, -SO_2CH_3, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazolyl, or substituted or unsubstituted imidazolyl.

[00120] In some such embodiments of R^3, R^1 is substituted or unsubstituted C_{1-8} alkyl,



wherein

each R' is independently -OR or C_{1-3} alkyl;

R" is -H or C_{1-3} alkyl;

each R is independently -H or substituted or unsubstituted (C_{1-4})alkyl; and

n is 0-2.

[00121] In some such embodiments, R^2 is phenyl, substituted with one or more -$(C_{1-3}$ alkyl), -$(C_{1-3}$ alkyl)NR_2, -CF_3, -Cl, -F, -CN, -OCH_3, -OCF_3, -$C(=O)NR_2$, -C(=O)NR(substituted or unsubstituted cycloalkyl), -$C(=O)NR(CH_2)_{0-2}CR_2(CH_2)_{0-2}OR$, -$C(=O)NR(CH_2)_{0-2}CR_2(CH_2)_{0-2}NR_2$, -$C(=O)NR(CH_2)_{0-2}CR_2(CH_2)_{0-2}C(=O)NR_2$, -C(=O)N(substituted or unsubstituted cycloalkyl)$(CH_2)_{0-2}OR$, -$C(=O)NR(CH_2)_{0-3}$(substituted or unsubstituted heterocyclyl), -$C(=O)(CH_2)_{0-3}$(substituted or unsubstituted heterocyclyl), -$C(=NR)NR_2$, -$NRC(=O)R$, -SO_2NR_2, -SO_2R, or

substituted or unsubstituted heterocyclyl, wherein each R is independently –H or substituted or unsubstituted (C_{1-4})alkyl.

[00122] Further embodiments provided herein include combinations of one or more of the particular embodiments set forth above.

[00123] In some embodiments of compounds of formula (I), the compound is selected from Table A, or a pharmaceutically acceptable salt, tautomer, stereoisomer, enantiomer, or isotopologue thereof.

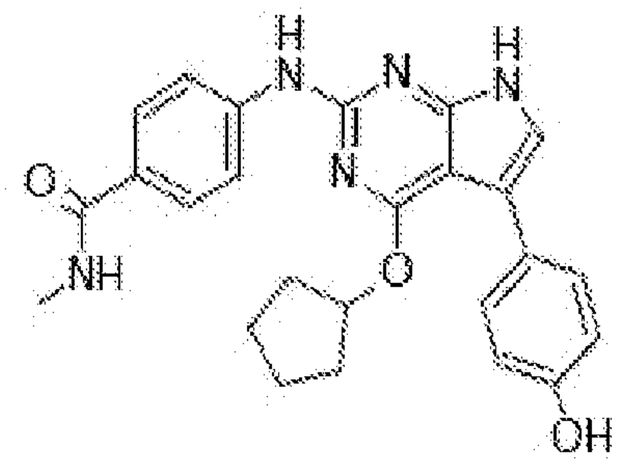
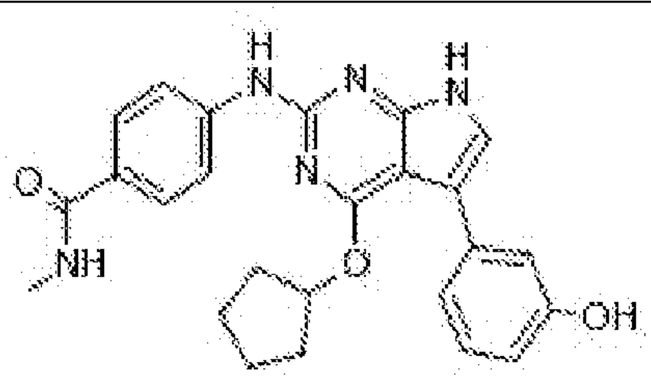
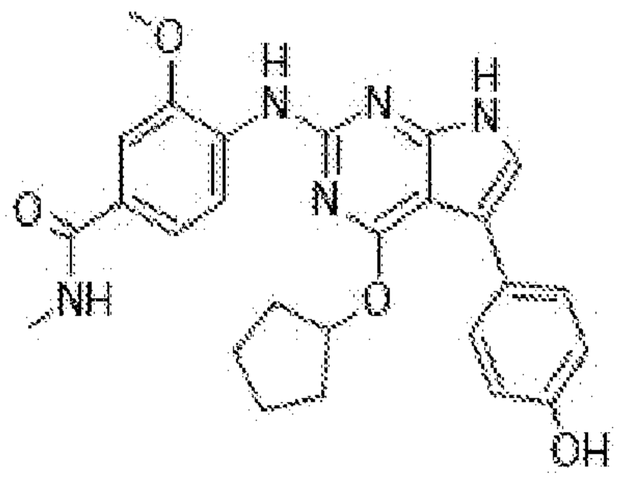
[00124] Pyrrolopyrimidine Compounds set forth in Table A were tested in the assays described herein and were found to have activity as cancer treatment agents, in particular for the treatment of solid tumors and hematological cancers as described herein. In some embodiments, the solid tumor is bladder cancer (including superficial bladder cancer), breast cancer (including luminal B type, ER+, PR+ and Her2+ breast cancer), central nervous system cancer (including glioblastoma multiforme (GBM), glioma, medulloblastoma, and astrocytoma), colorectal cancer, gastrointestinal cancer (including stomach cancer, oesophagus cancer, and rectum cancer), endocrine cancer (including thyroid cancer, and adrenal gland cancer), eye cancer (including retinoblastoma), female genitourinary cancer (including cancer of the placenta, uterus, vulva, ovary, cervix), head and neck cancer (including cancer of the pharynx, oesophagus, and tongue), liver cancer, lung cancer (including non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), mucoepidermoid, bronchogenic, squamous cell carcinoma (SQCC), and analplastic/NSCLC), skin cancer (including melanoma, and SQCC), soft tissue cancer (including sarcoma, Ewing's sarcoma, and rhabdomyosarcoma), bone cancer (including sarcoma, Ewing's sarcoma, and osteosarcoma), squamous cell cancer (including lung, esophageal, cervical, and head and neck cancer), pancreas cancer, kidney cancer (including renal Wilm's tumor and renal cell carcinoma), or prostate cancer. In some embodiments, the solid tumor is breast cancer, colon cancer, lung cancer or bladder cancer. In one such embodiment, the solid tumor is superficial bladder cancer. In another, the solid tumor is lung squamous cell carcinoma. In yet another embodiment, the solid tumor is luminal B type breast cancer.

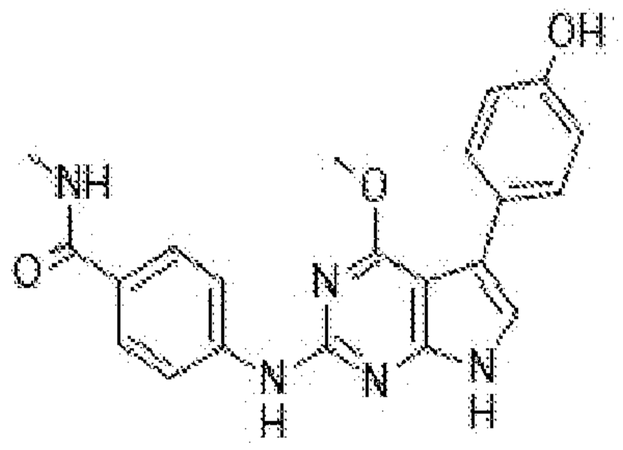
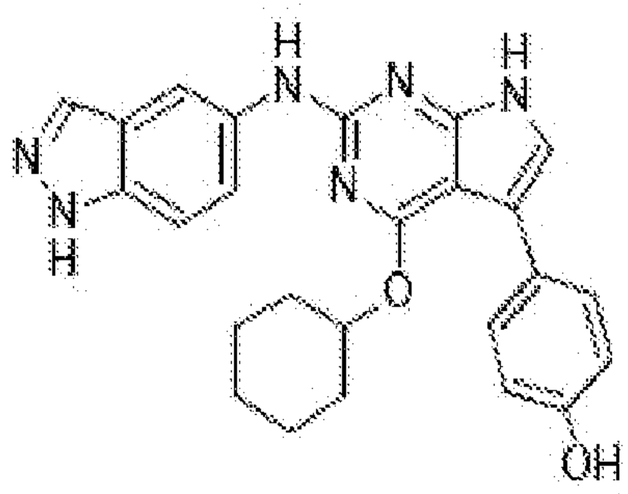
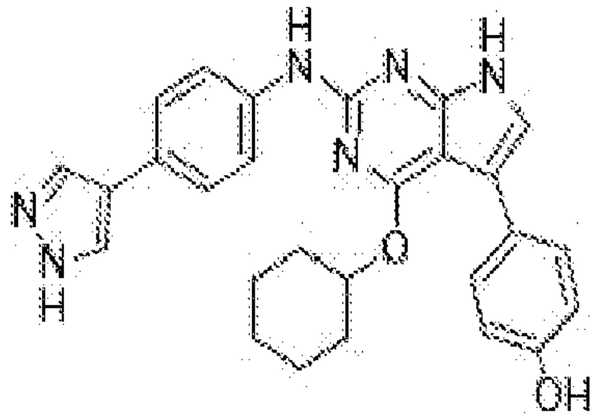
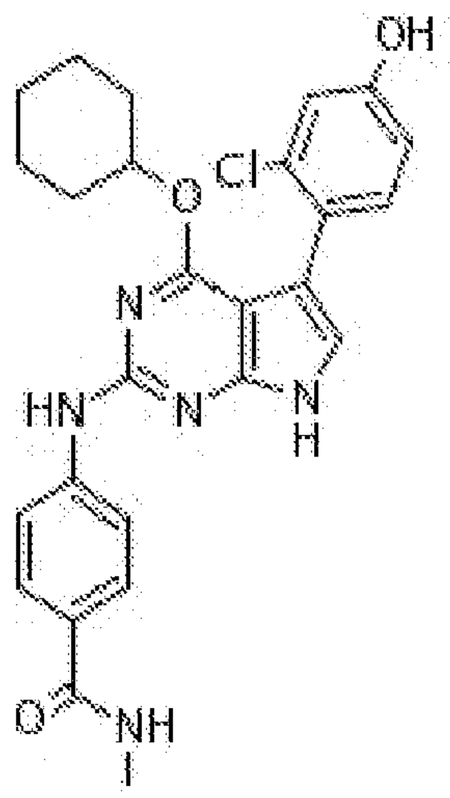
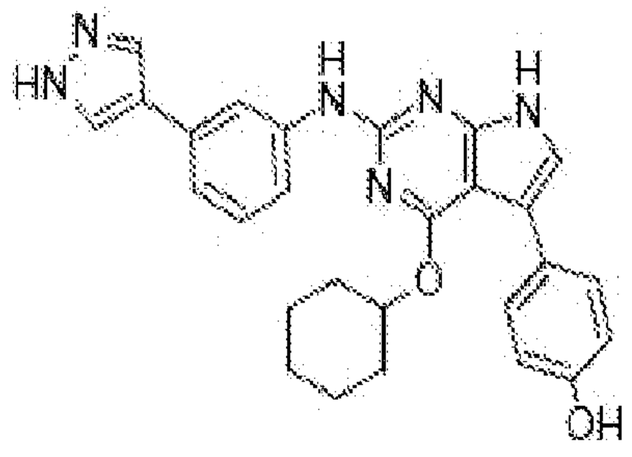
[00125] In some embodiments, the hematological cancer is leukemia (including acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), acute T-cell leukemia, B

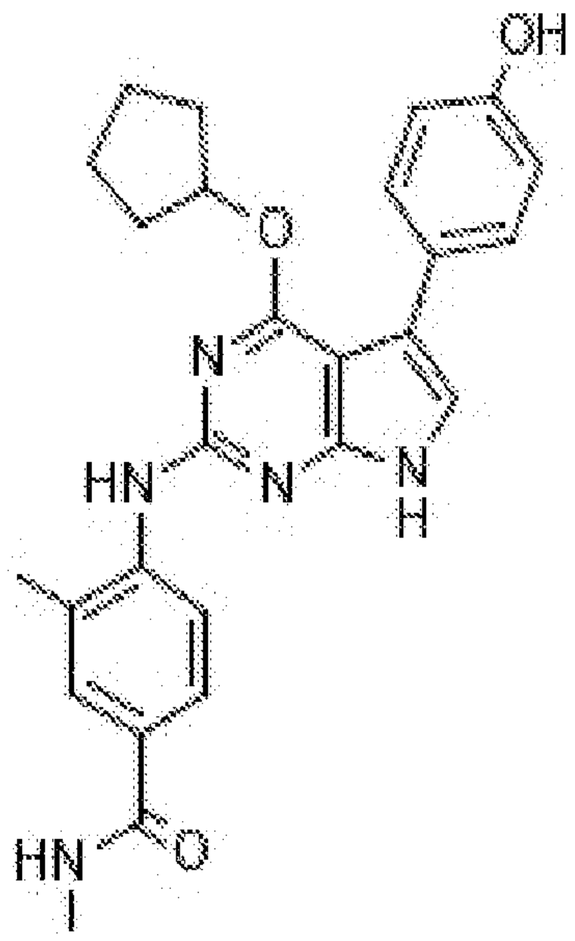
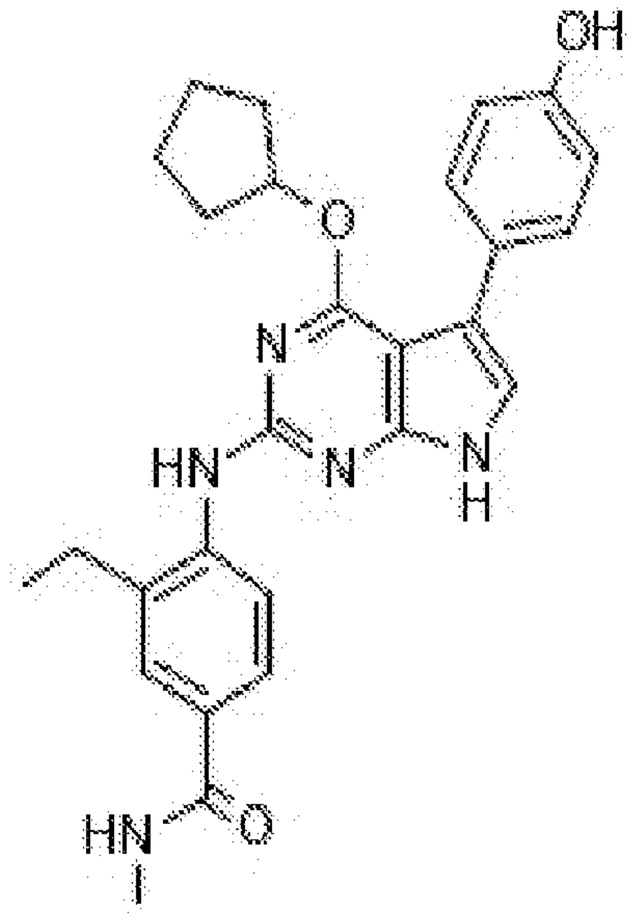
cell precursor leukemia, acute promyelocytic leukemia (APML), plasma cell leukemia, myelomonoblastic/T-ALL, B myelomonocytic leukemia, erythroleukemia, and acute myeloid leukemia (AML)), lymphoma (including Hodgkin's lymphoma, non-Hodgkin's lymphoma (NHL), Burkitt's lymphoma (BL), B cell lymphoma, lymphoblastic lymphoma, follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and large cell immunoblastic lymphoma), or multiple myeloma.

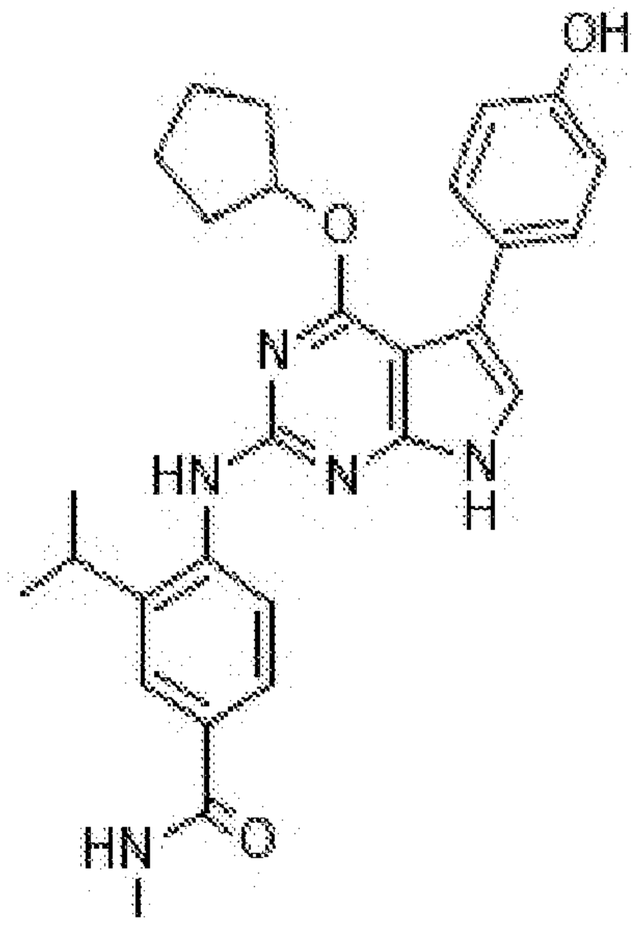
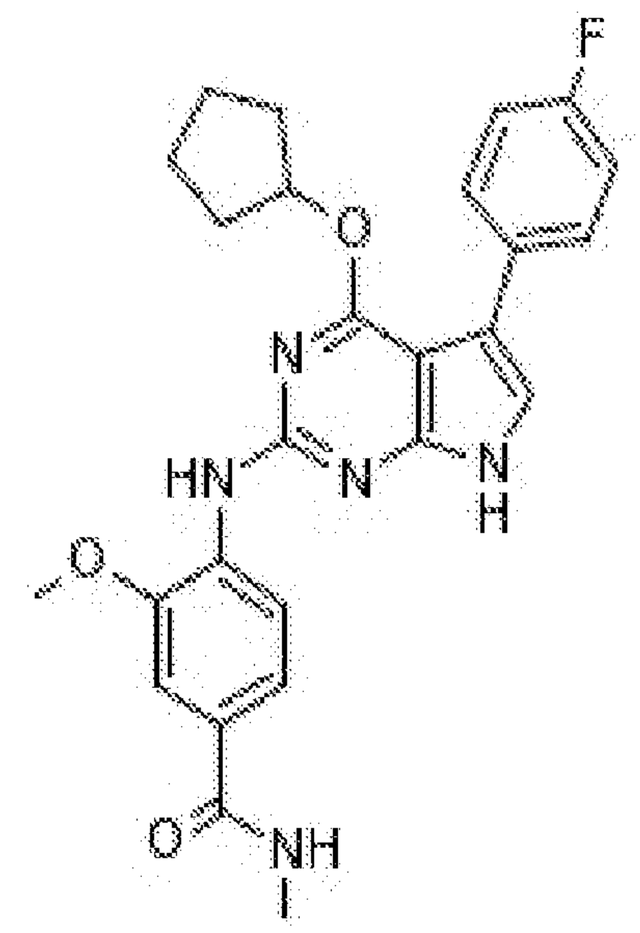
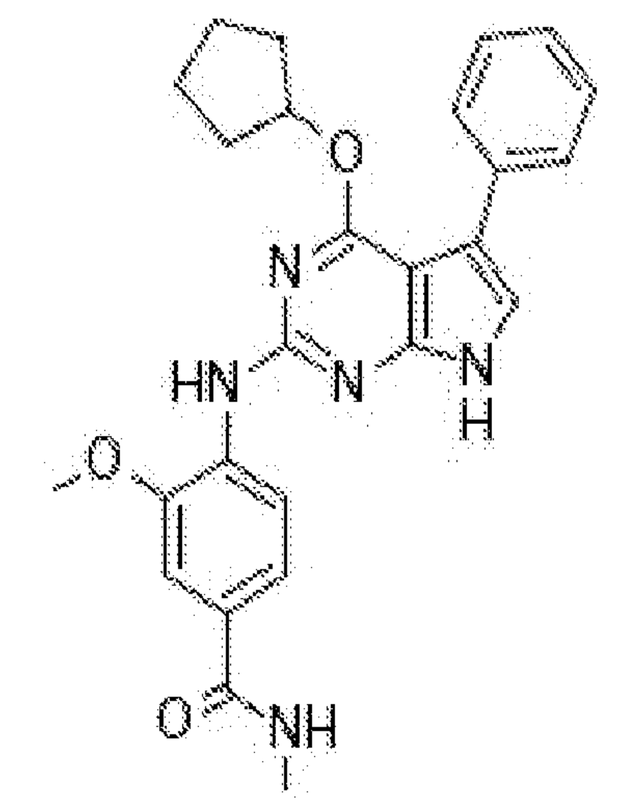
[00126] In one embodiment, the Pyrrolopyrimidine Compound is a compound as described herein, wherein the compound at a concentration of 10 μM inhibits cancer cell proliferation, for example solid tumor or hematological cancer cell proliferation, as described herein, by at least about 50% or more.

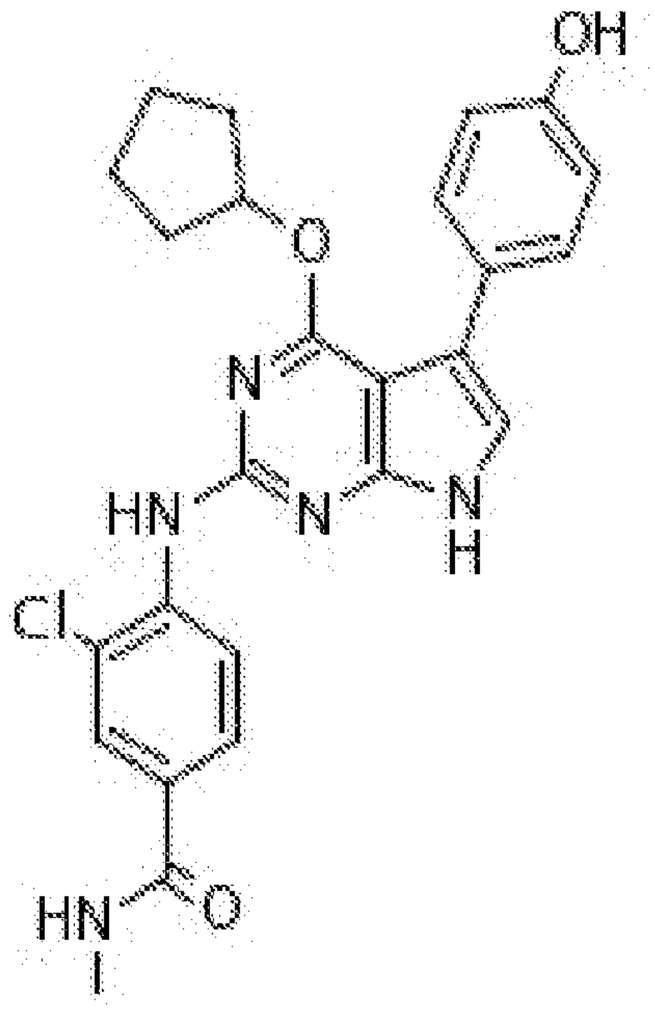
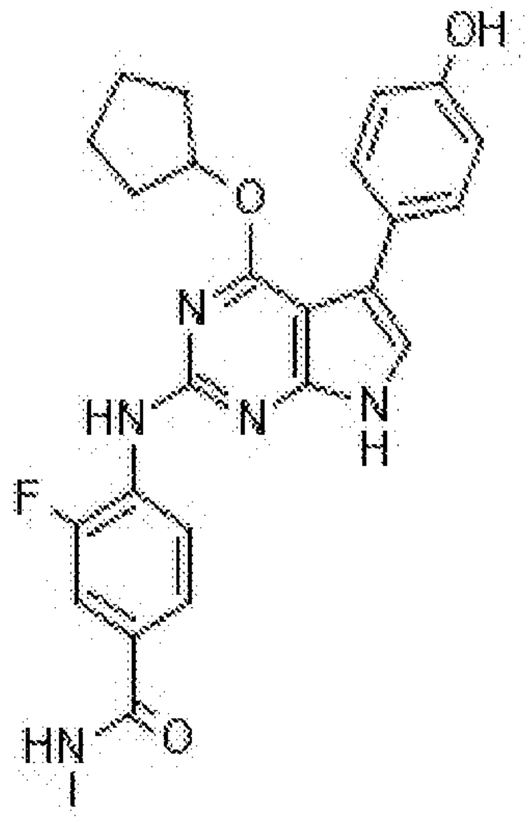
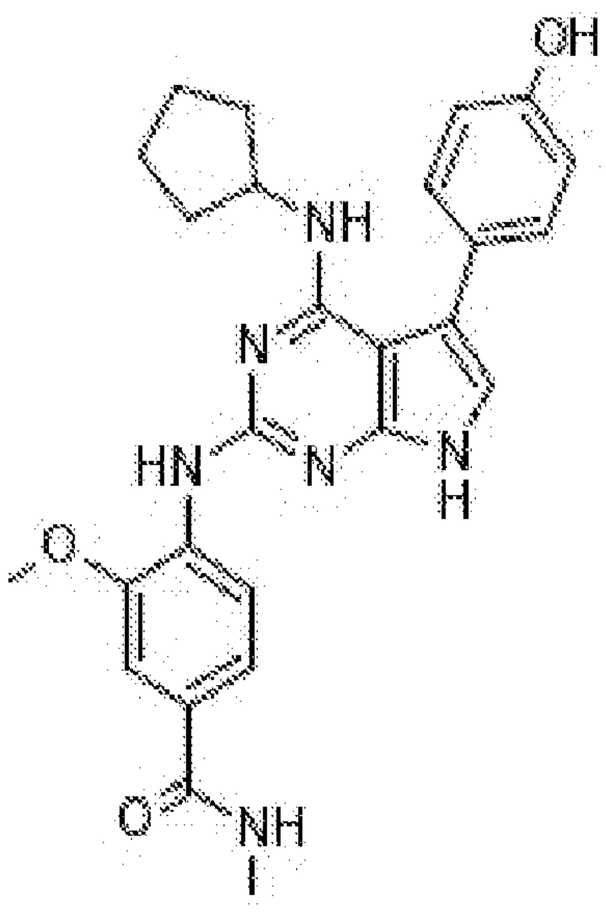
[00127] **Table A**.

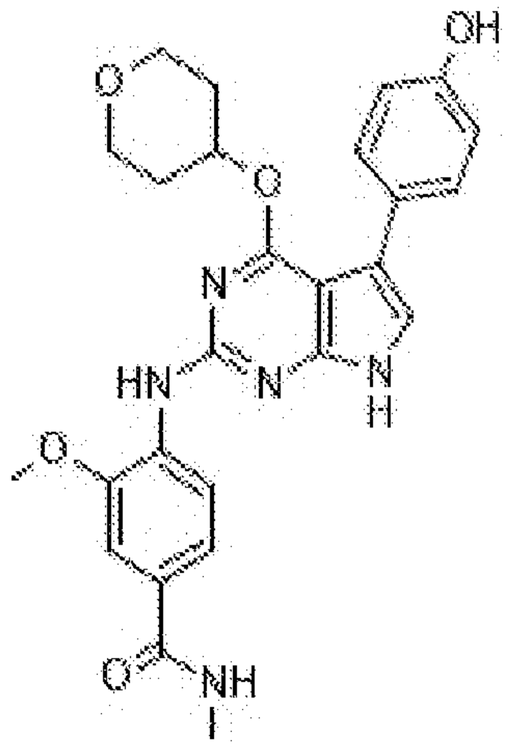
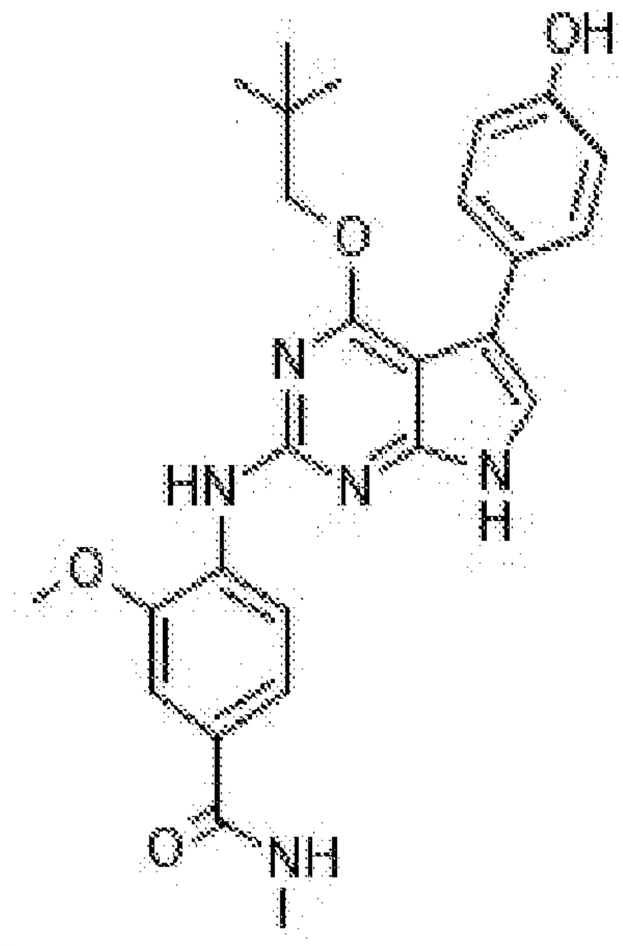
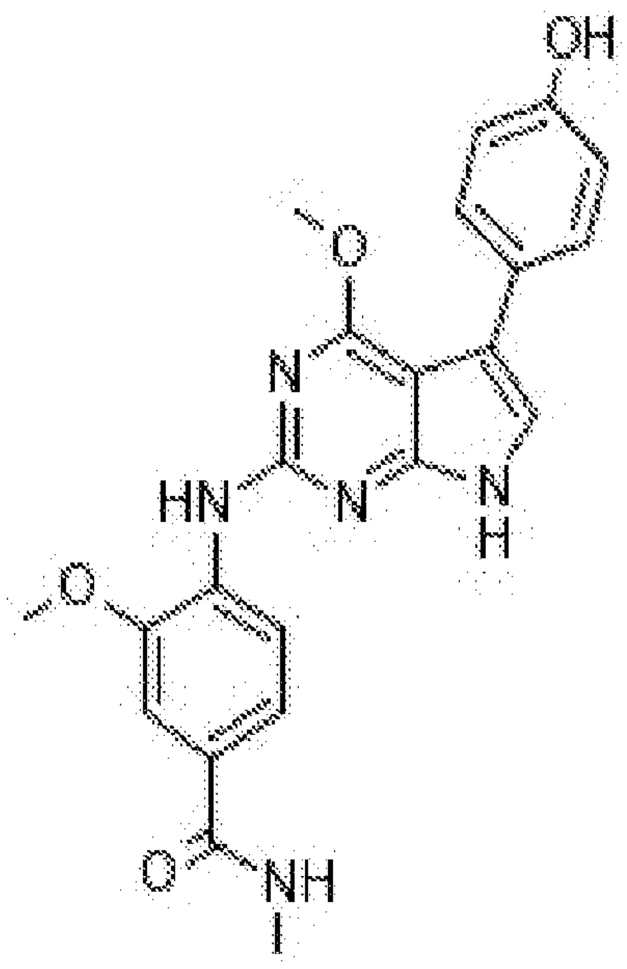
Cmpd No.	Structure	Name
1		4-(4-(cyclopentyloxy)-5-(4-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide
2		4-(4-(cyclopentyloxy)-5-(3-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide
3		4-(4-(cyclopentyloxy)-5-(4-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

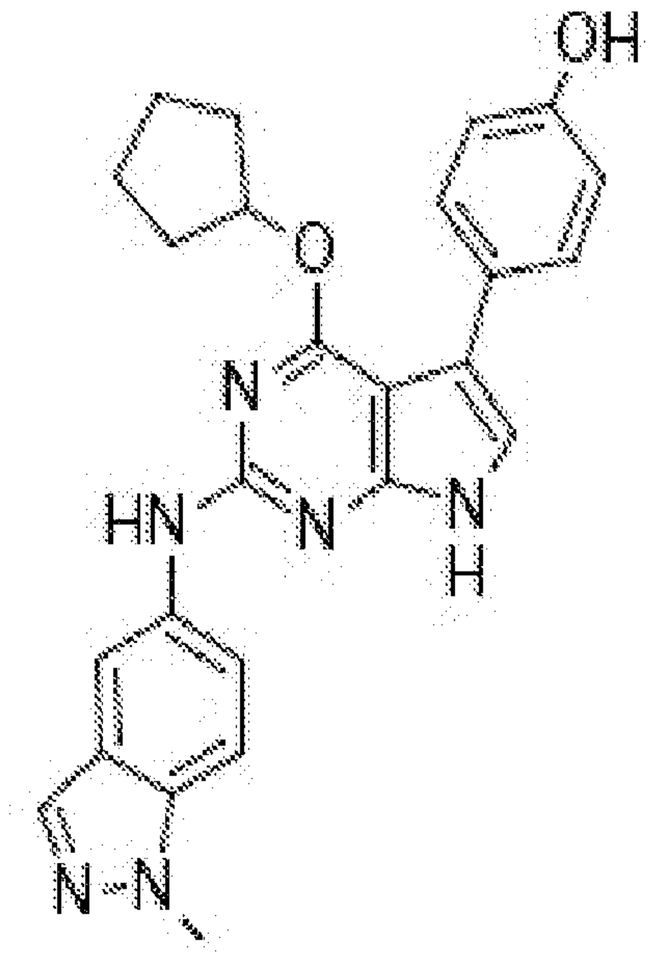
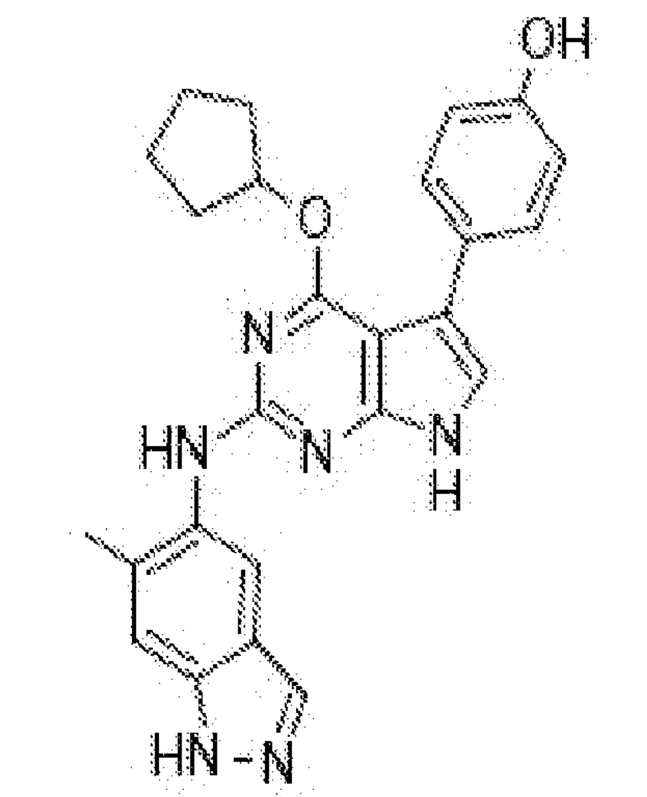
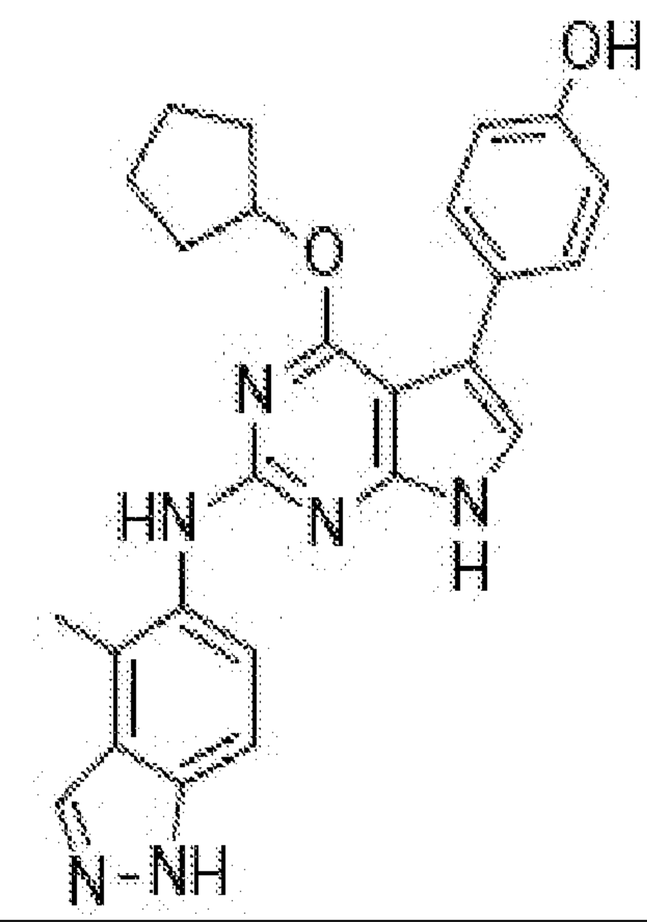
Cmpd No.	Structure	Name
4		4-(5-(4-hydroxyphenyl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide
5		4-(2-(1H-indazol-5-ylamino)-4-(cyclohexyloxy)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenol
6		4-(2-(4-(1H-pyrazol-4-yl)phenylamino)-4-(cyclohexyloxy)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenol
7		4-(5-(2-chloro-4-hydroxyphenyl)-4-(cyclohexyloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide
8		4-(2-(3-(1H-pyrazol-4-yl)phenylamino)-4-(cyclohexyloxy)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenol

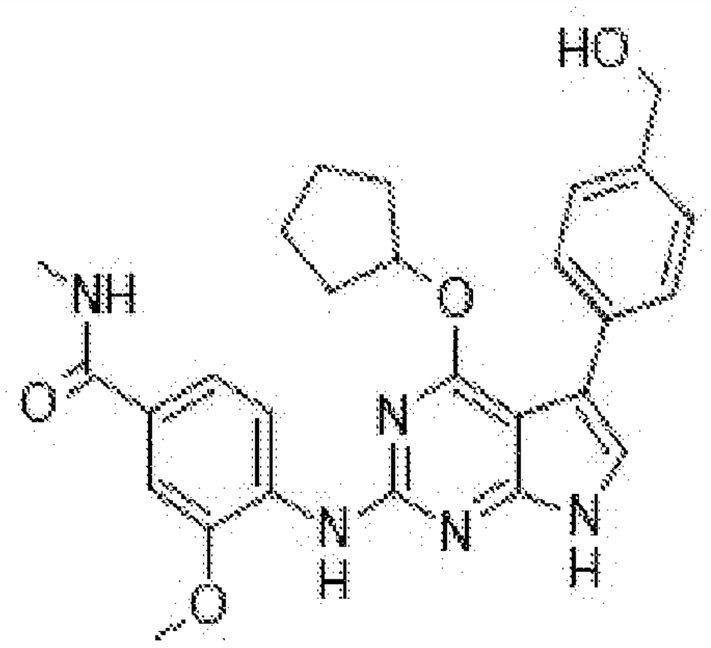
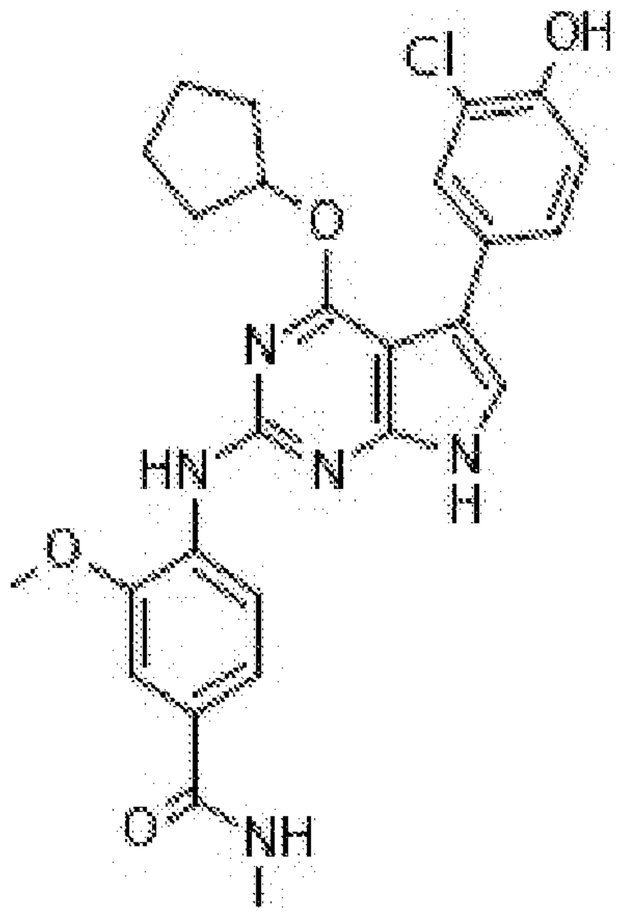
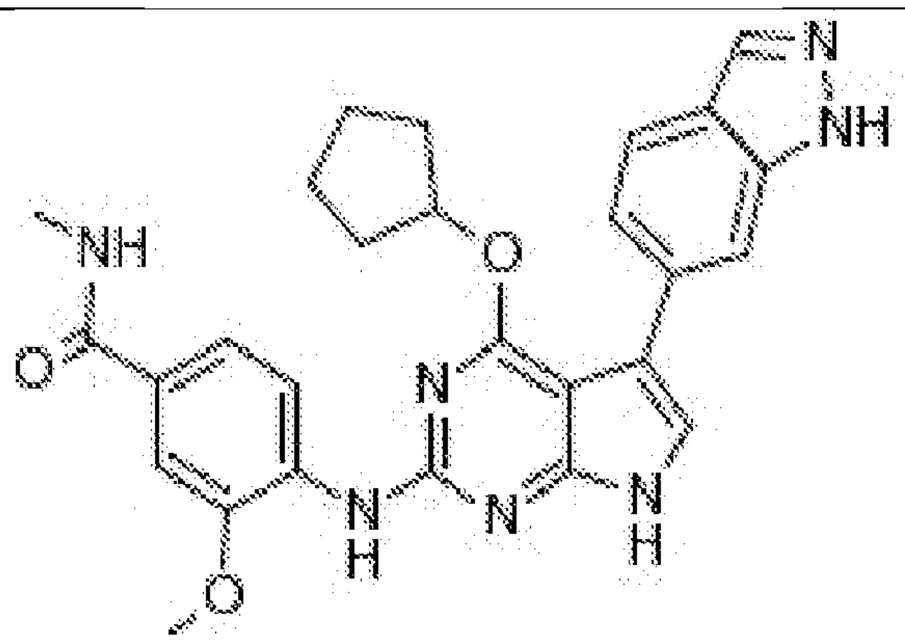
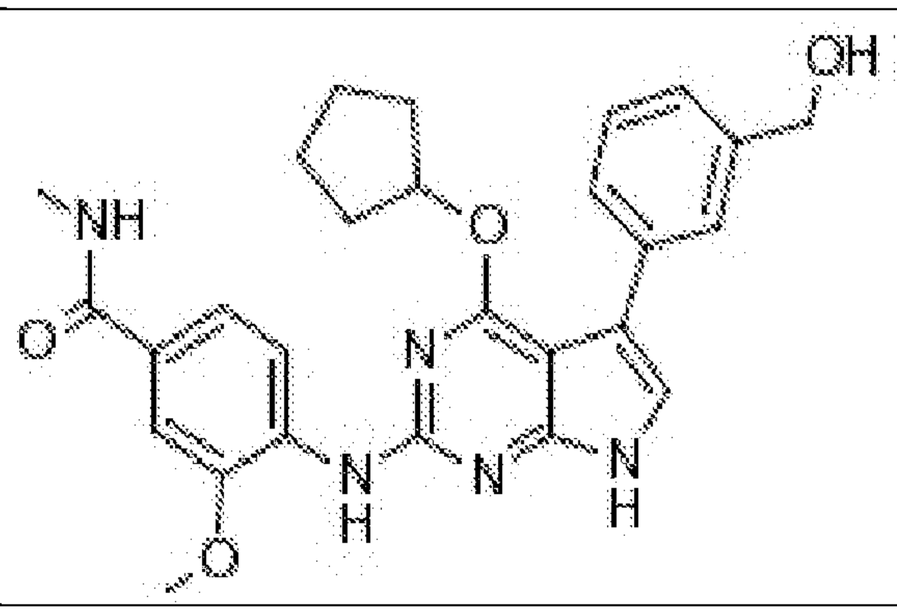
Cmpd No.	Structure	Name
9		4-(4-(cyclopentyloxy)-5-(4-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,3-dimethylbenzamide
10		4-(4-(cyclopentyloxy)-5-(4-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-ethyl-N-methylbenzamide

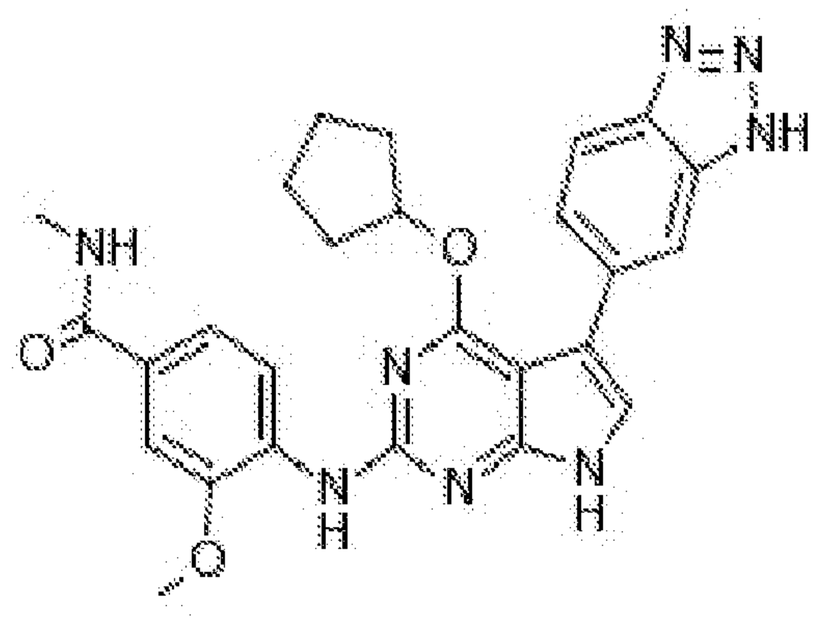
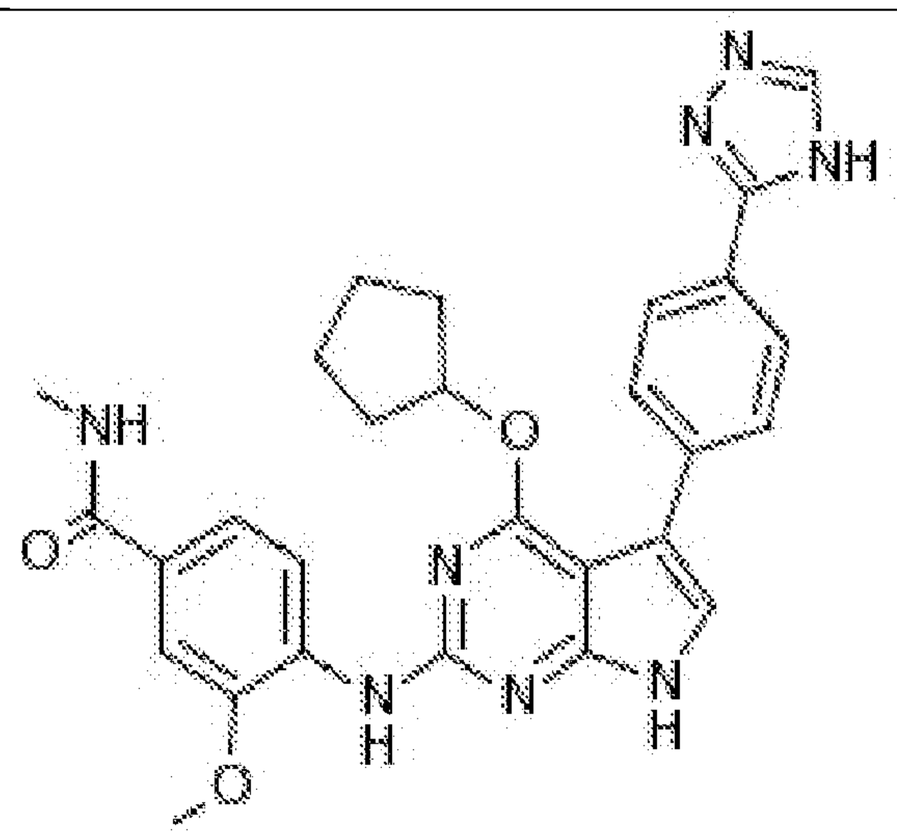
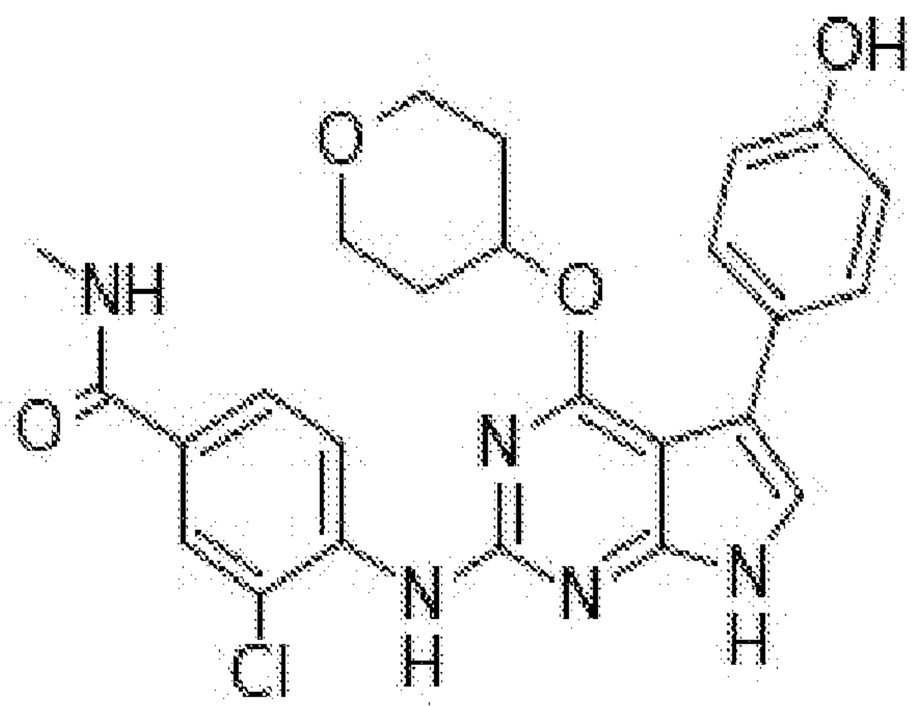
Cmpd No.	Structure	Name
11		4-(4-(cyclopentyloxy)-5-(4-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-isopropyl-N-methylbenzamide
12		4-(4-(cyclopentyloxy)-5-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
13		4-(4-(cyclopentyloxy)-5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

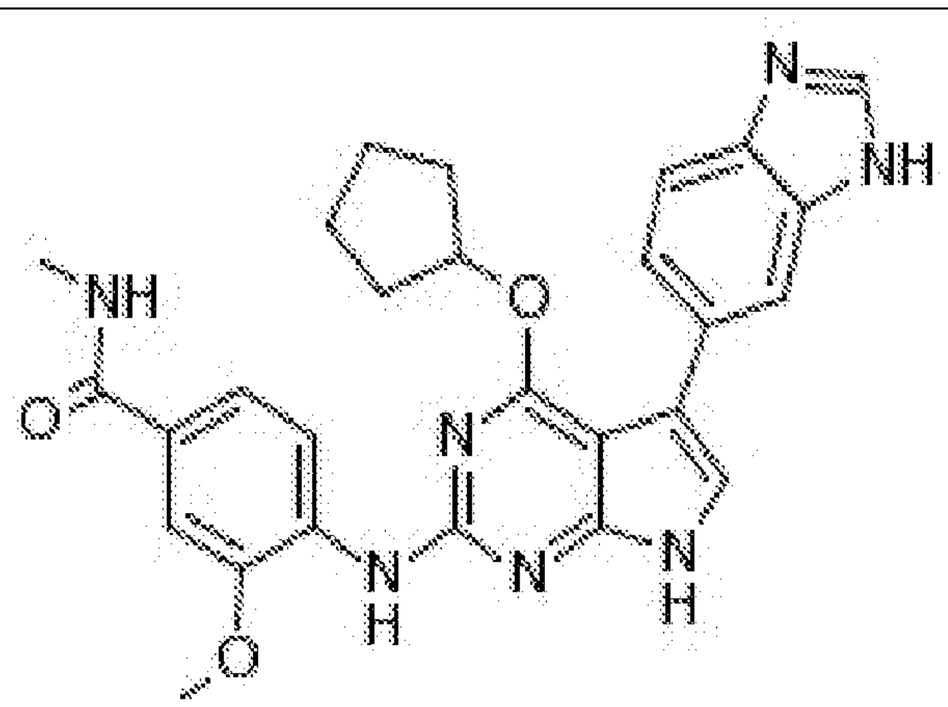
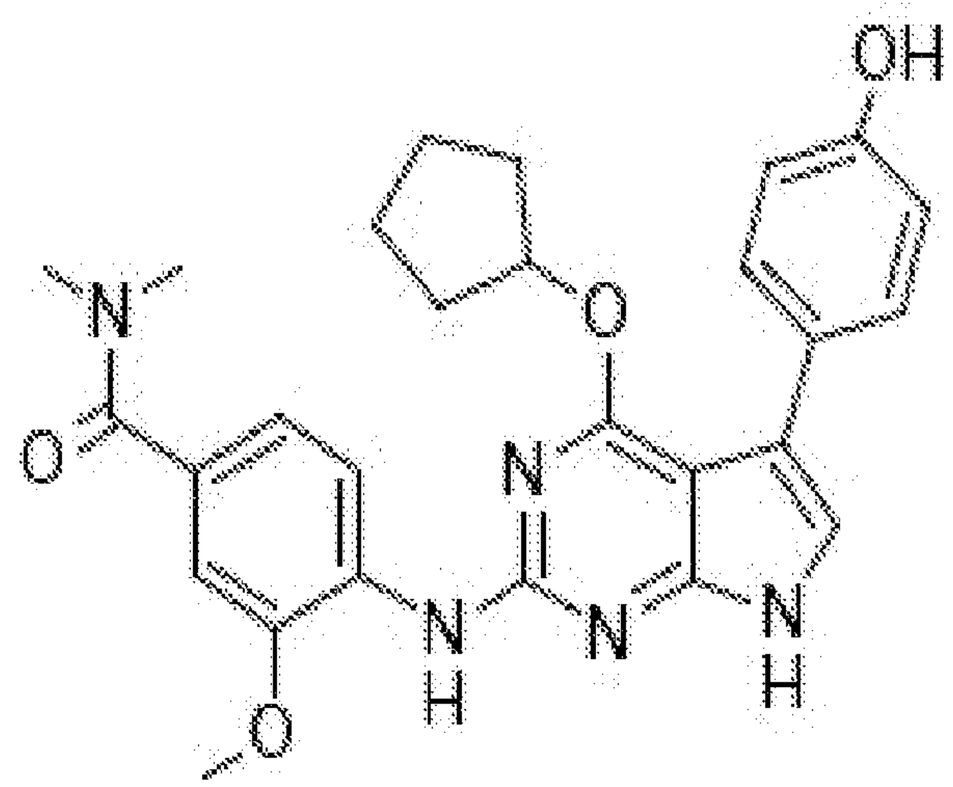
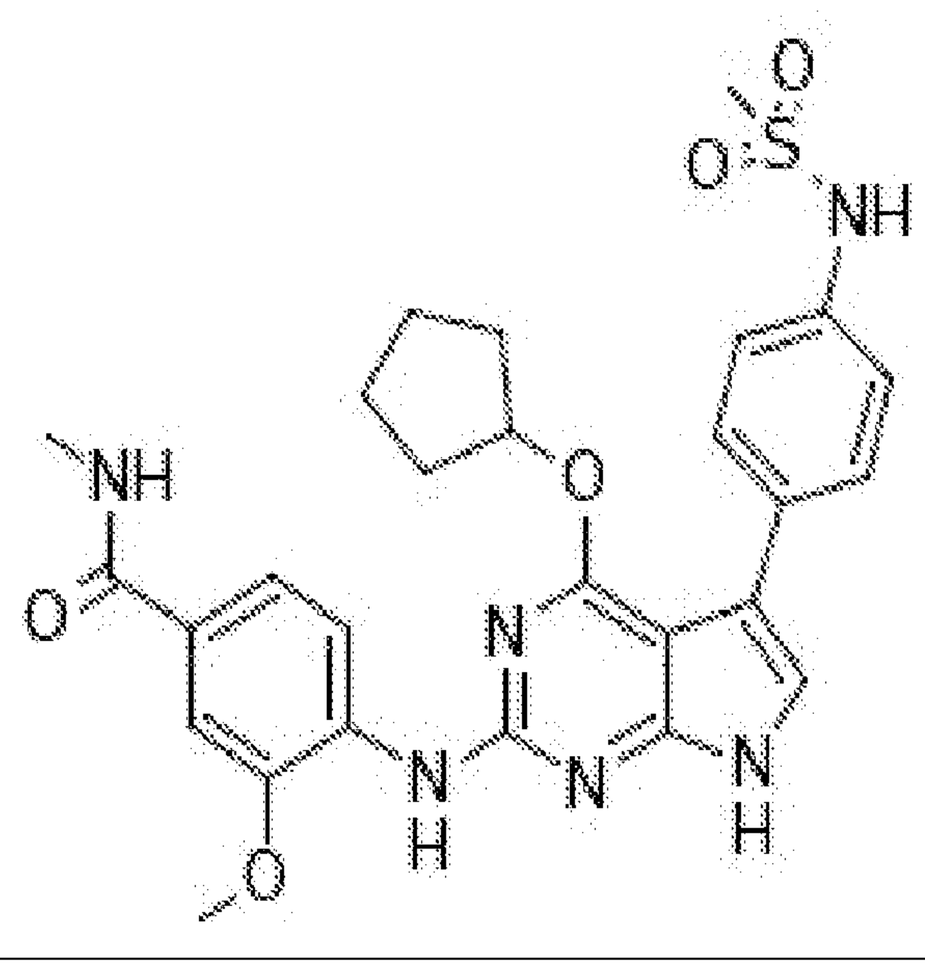
Cmpd No.	Structure	Name
14		3-chloro-4-(4-(cyclopentyloxy)-5-(4-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide
15		4-(4-(cyclopentyloxy)-5-(4-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-fluoro-N-methylbenzamide
16		4-(4-(cyclopentylamino)-5-(4-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

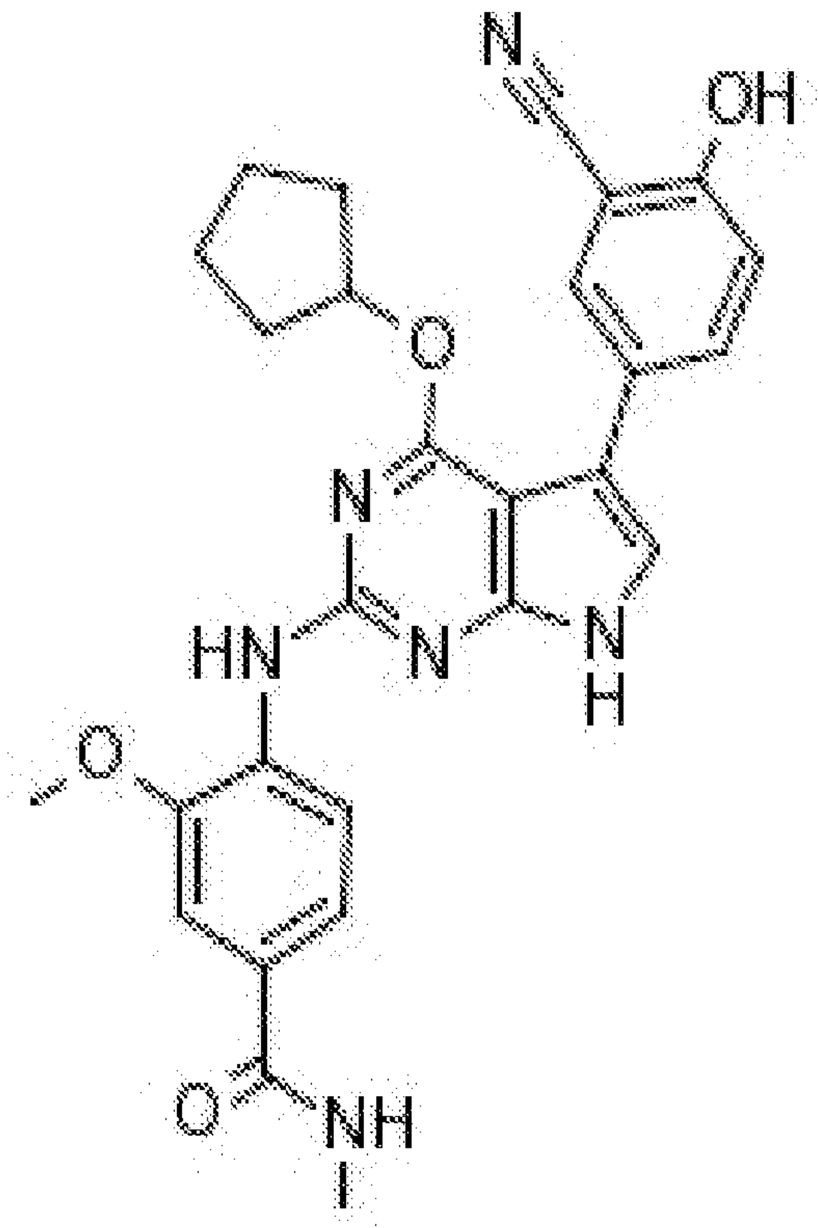
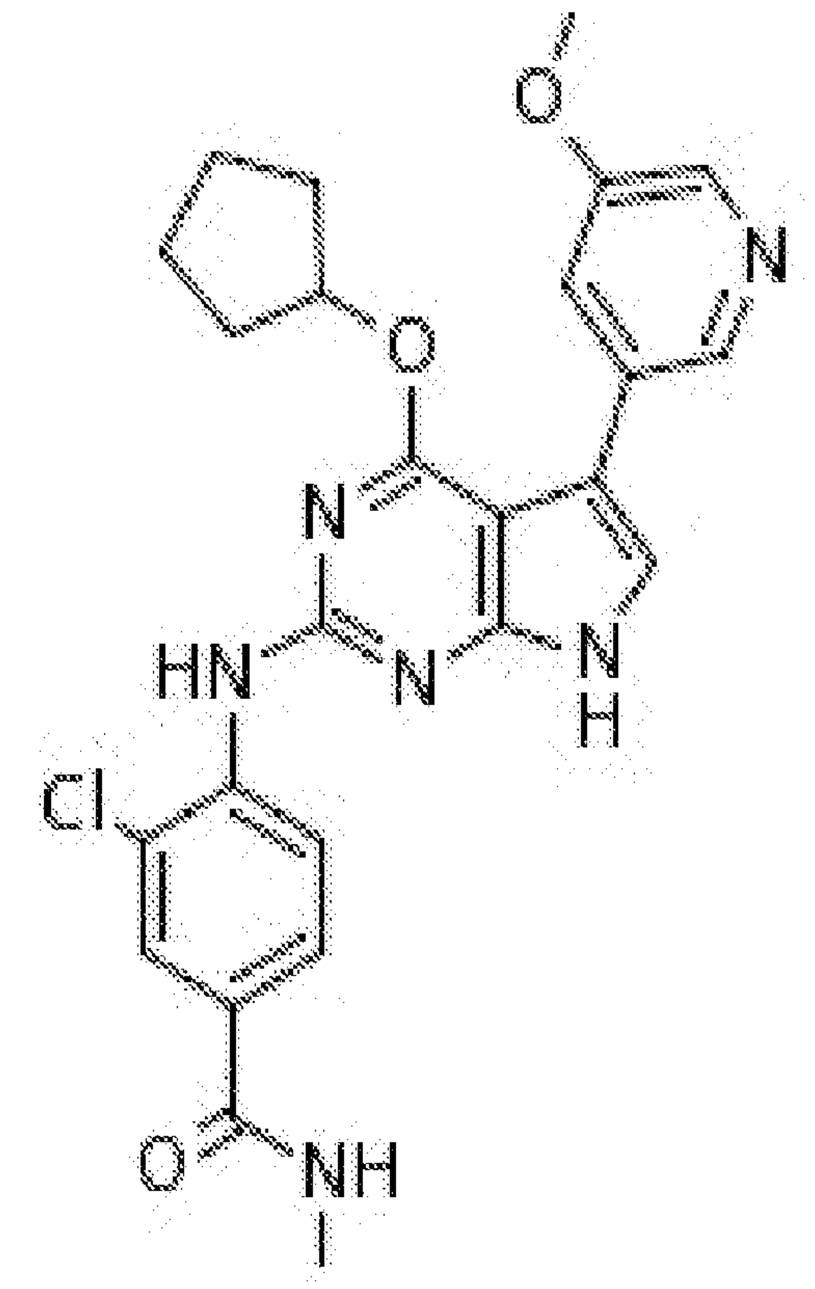
Cmpd No.	Structure	Name
17		4-(5-(4-hydroxyphenyl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
18		4-(5-(4-hydroxyphenyl)-4-(neopentyloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
19		4-(5-(4-hydroxyphenyl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

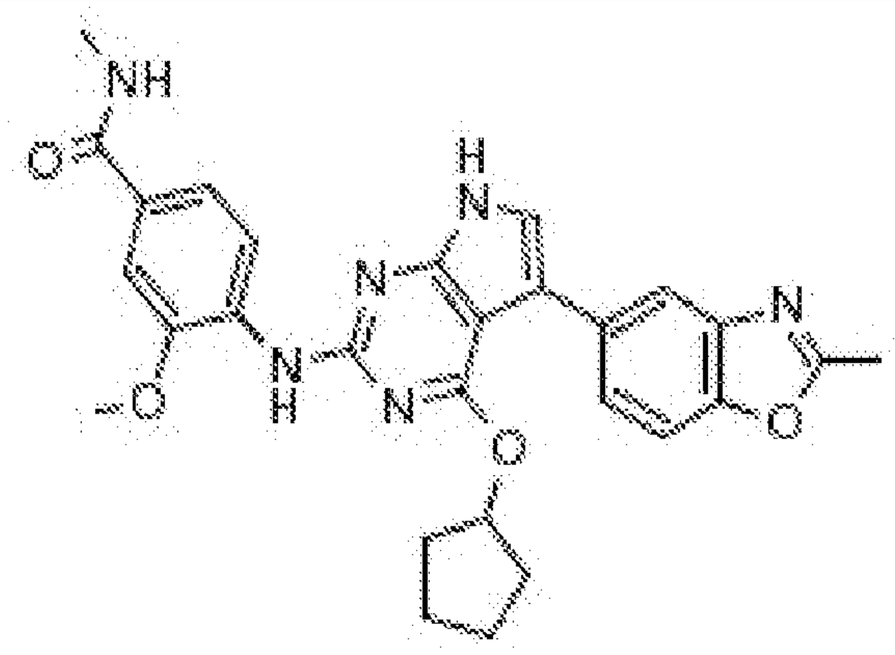
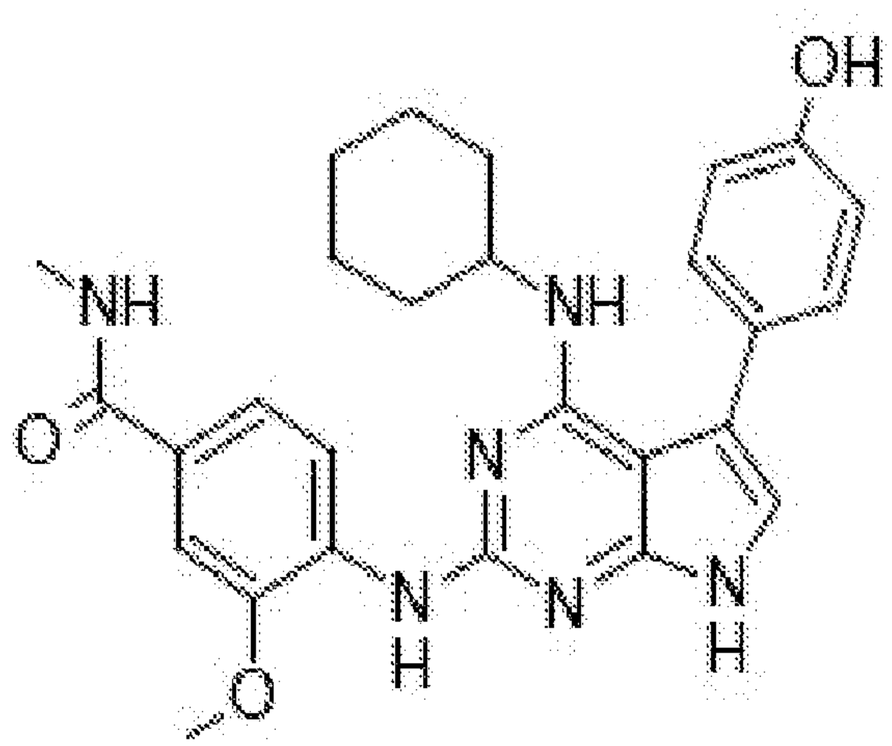
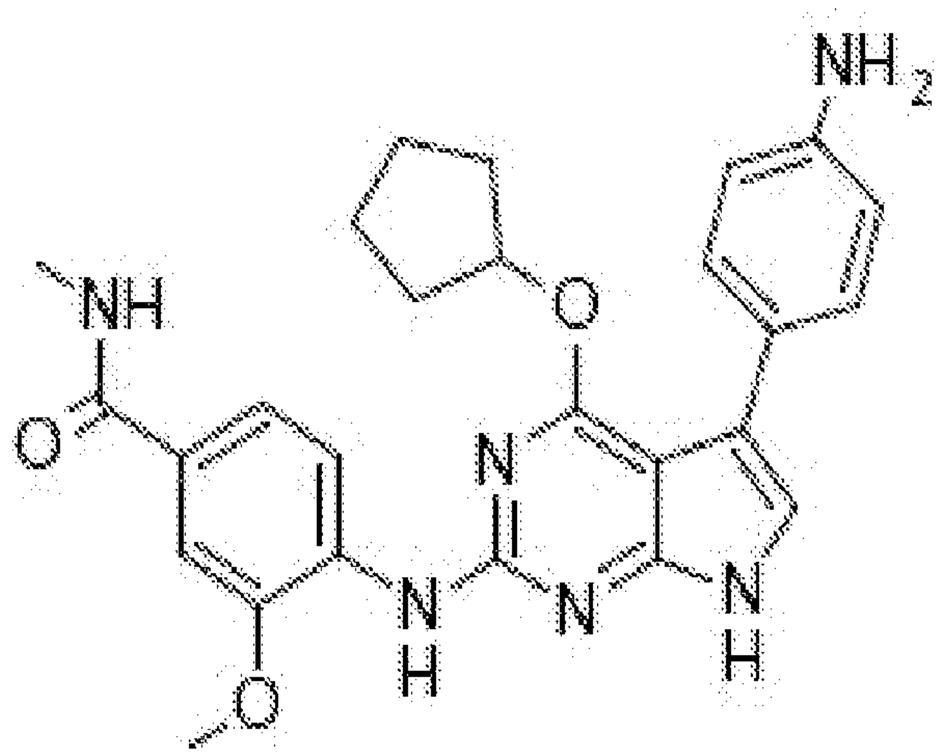
Cmpd No.	Structure	Name
20		4-(4-(cyclopentyloxy)-2-(1-methyl-1H-indazol-5-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenol
21		4-(4-(cyclopentyloxy)-2-(6-methyl-1H-indazol-5-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenol
22		4-(4-(cyclopentyloxy)-2-(4-methyl-1H-indazol-5-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenol

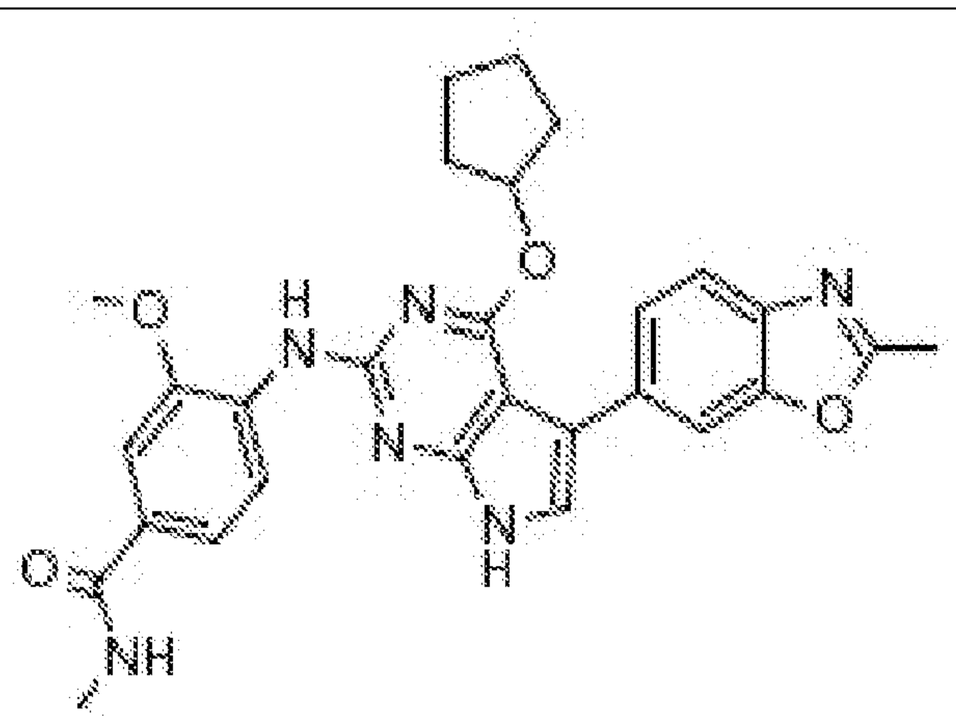
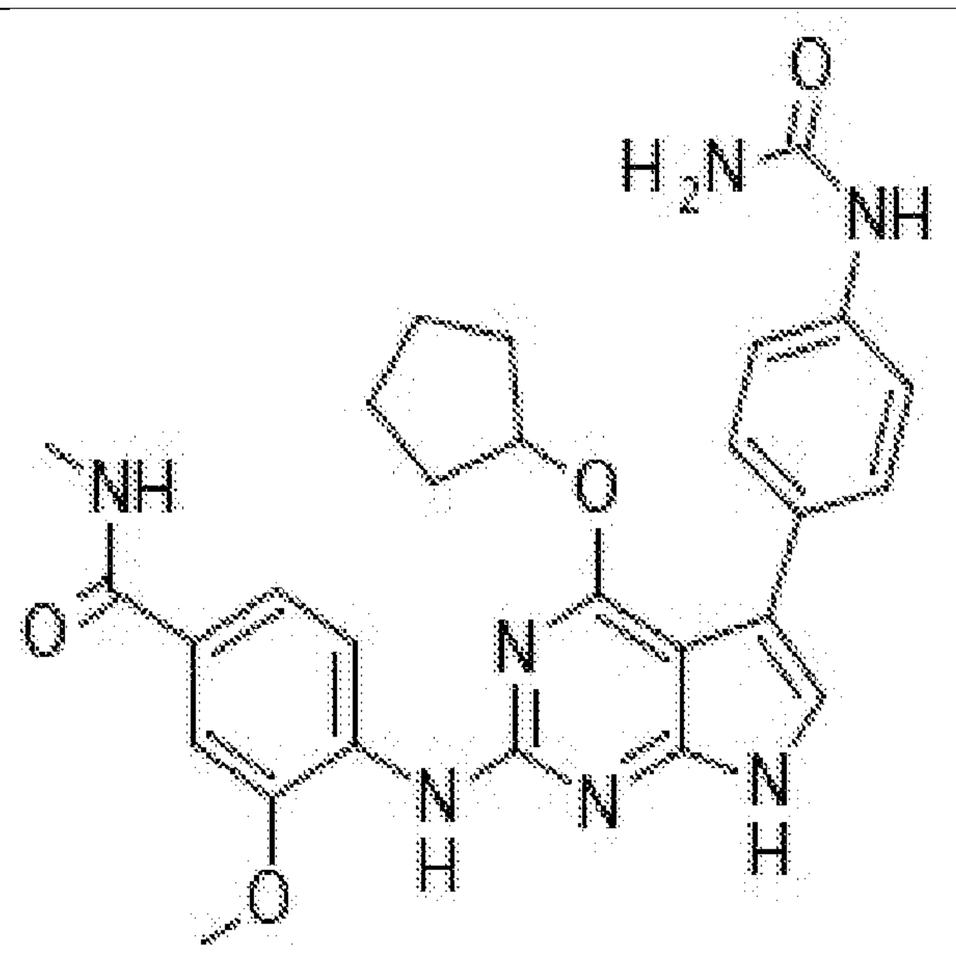
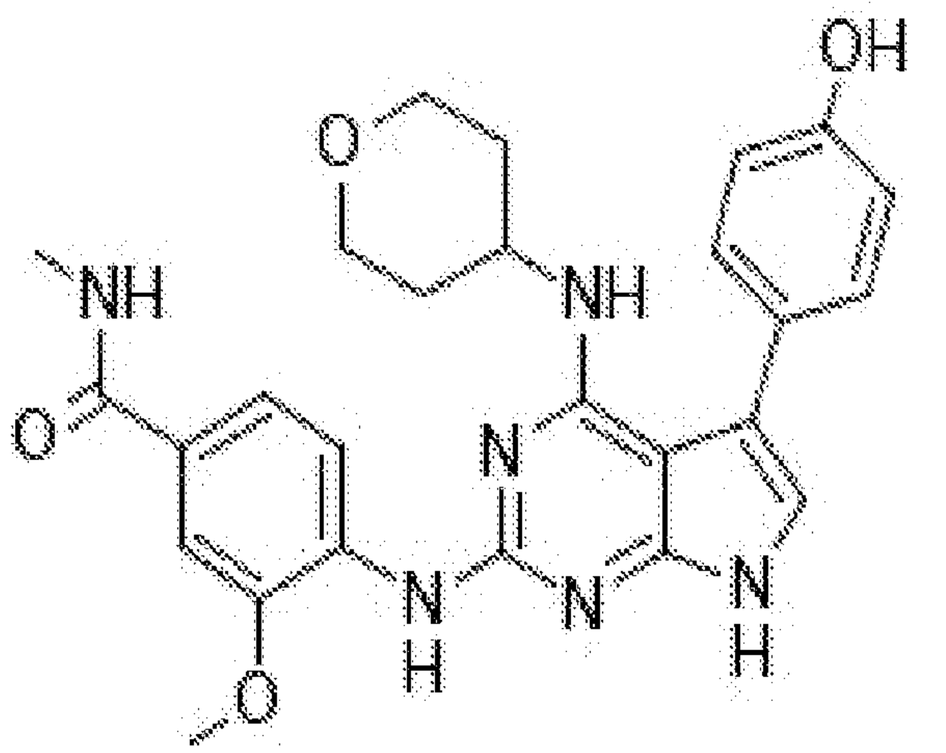
Cmpd No.	Structure	Name
23		4-(4-(cyclopentyloxy)-5-(4-(hydroxymethyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
24		4-(5-(3-chloro-4-hydroxyphenyl)-4-(cyclopentyloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
25		4-(4-(cyclopentyloxy)-5-(1H-indazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
26		4-(4-(cyclopentyloxy)-5-(3-(hydroxymethyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

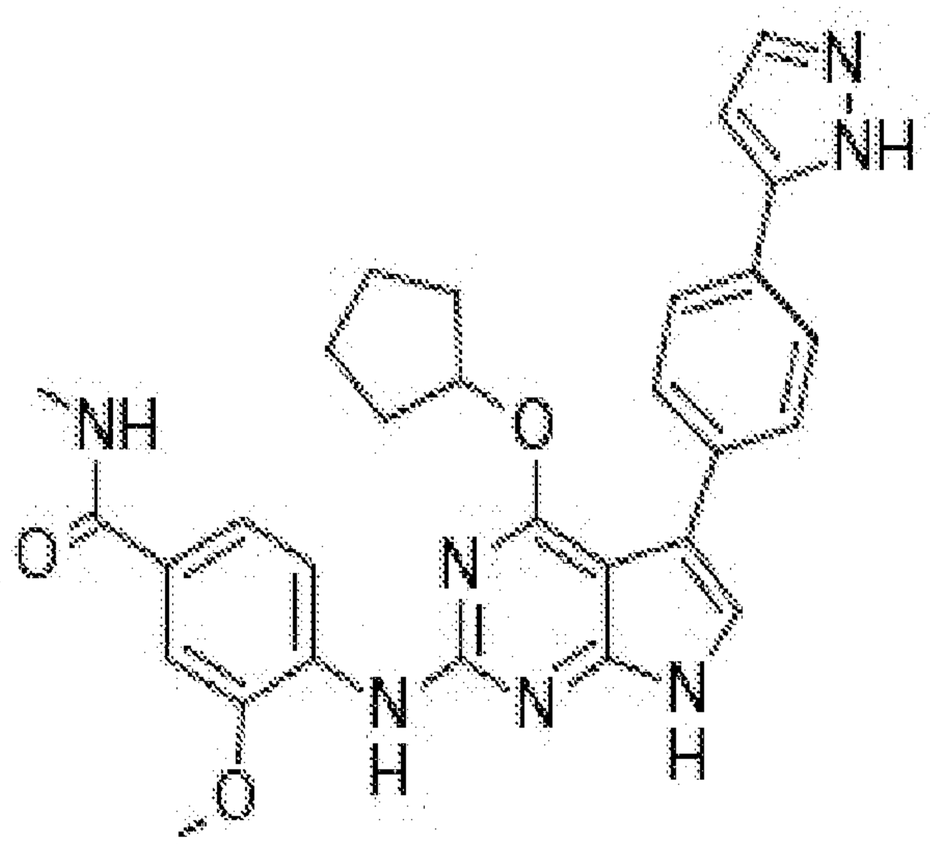
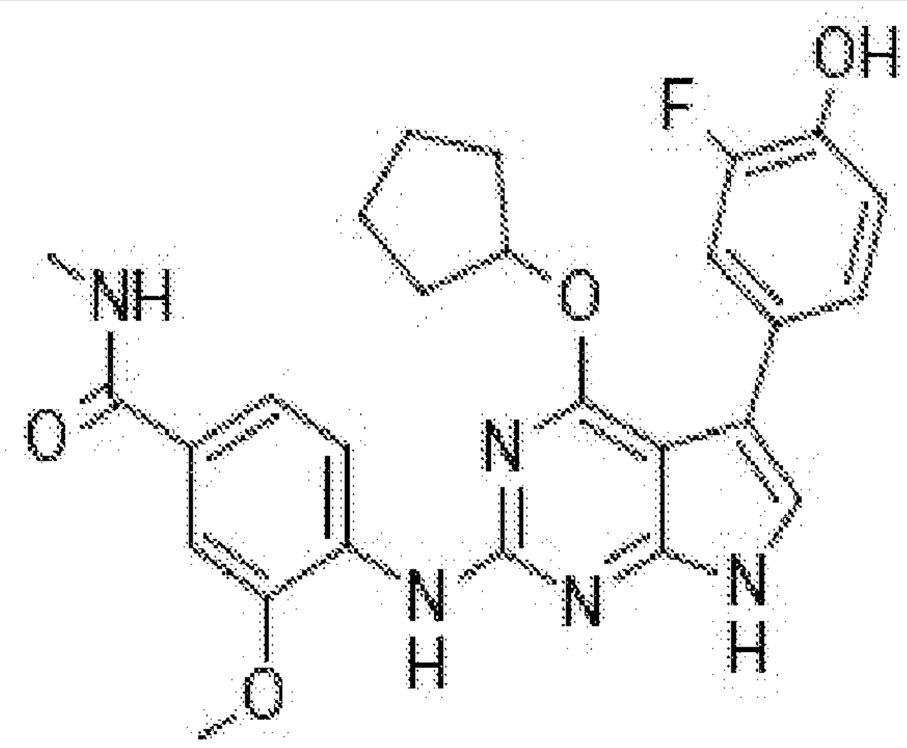
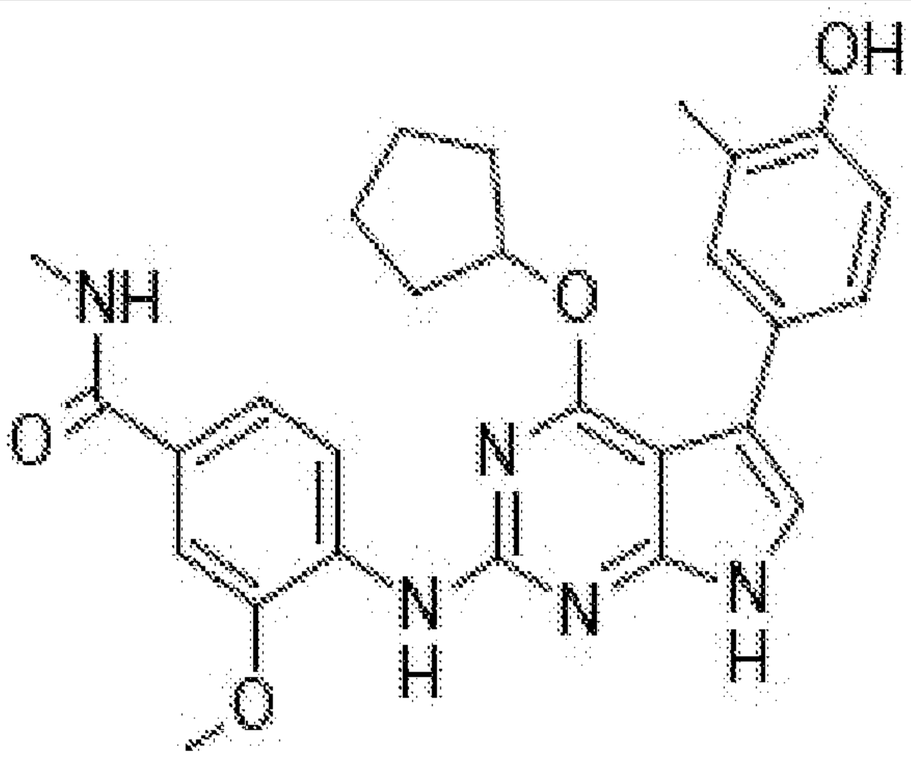
Cmpd No.	Structure	Name
27		4-(5-(1H-benzo[d][1,2,3]triazol-6-yl)-4-(cyclopentyloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
28		4-(5-(4-(4H-1,2,4-triazol-3-yl)phenyl)-4-(cyclopentyloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
29		3-chloro-4-(5-(4-hydroxyphenyl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide

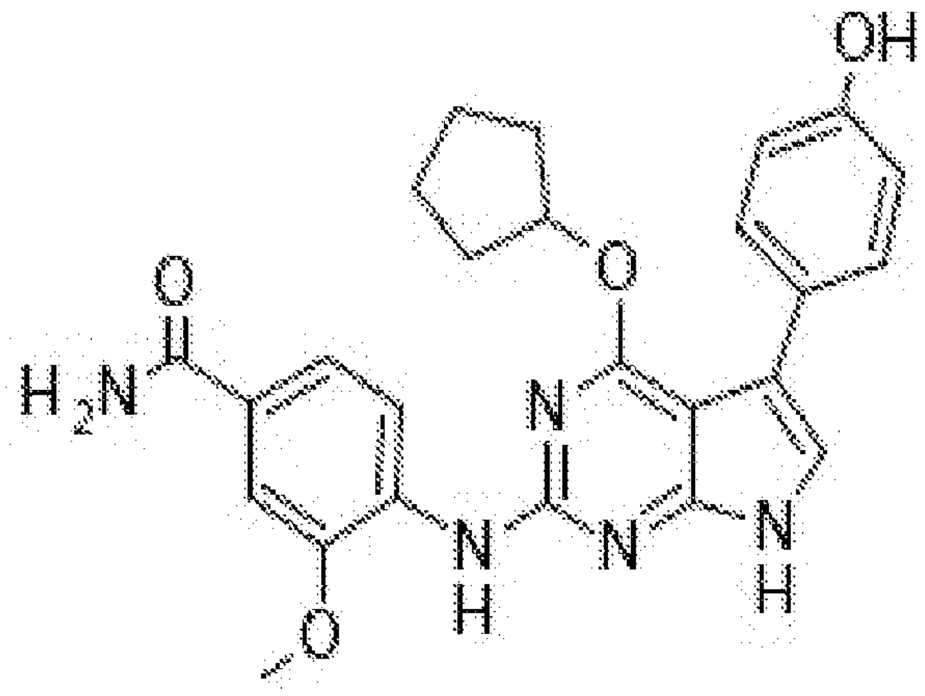
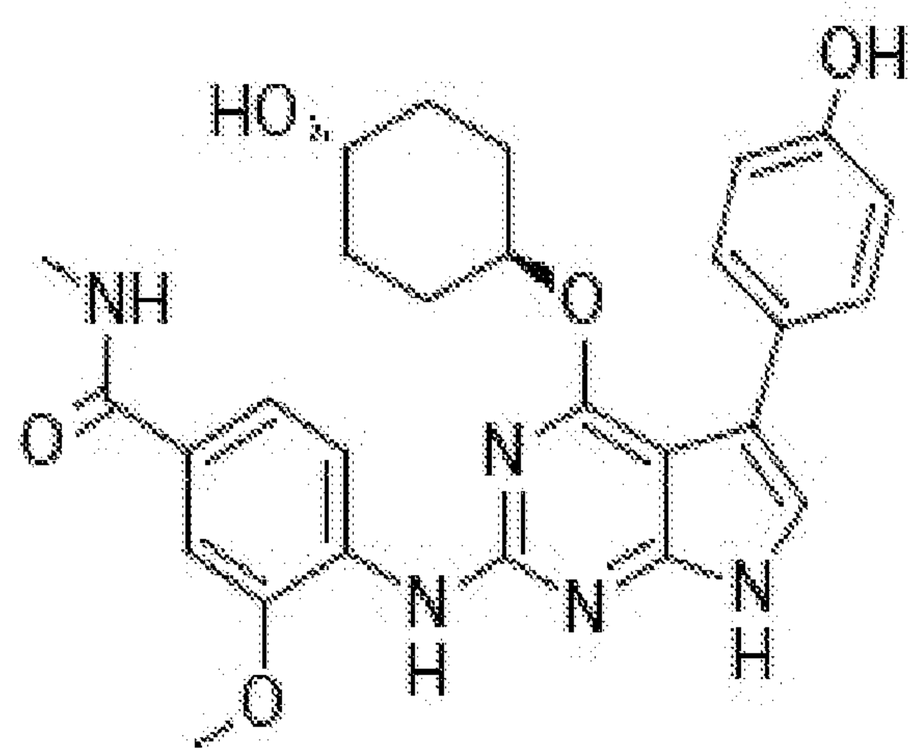
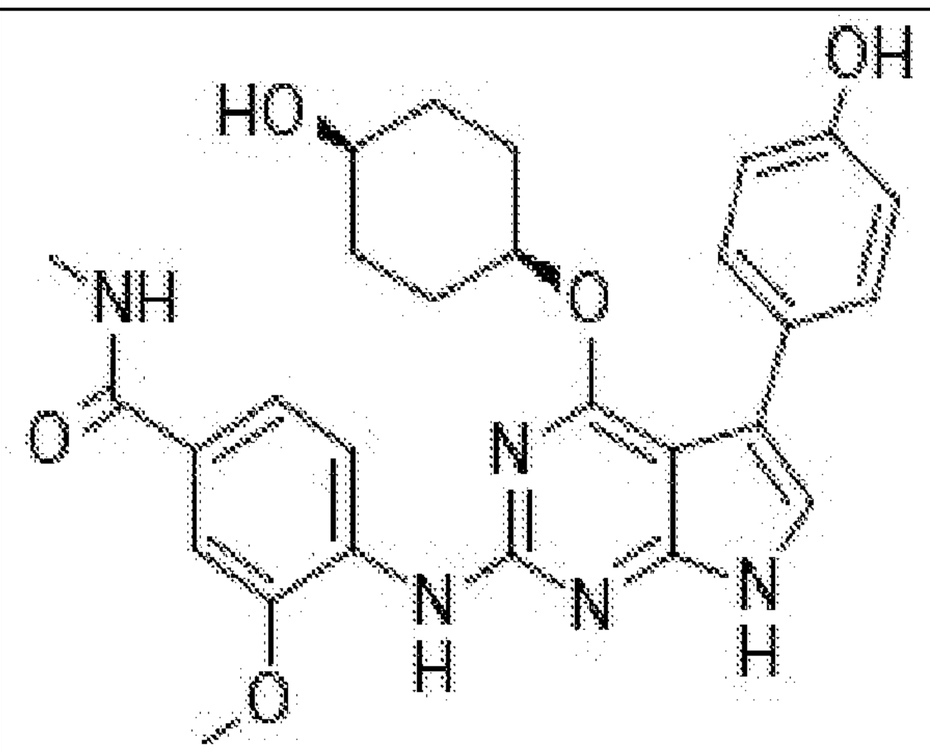
Cmpd No.	Structure	Name
30		4-(5-(1H-benzo[d]imidazol-6-yl)-4-(cyclopentyloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
31		4-(4-(cyclopentyloxy)-5-(4-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N,N-dimethylbenzamide
32		4-(4-(cyclopentyloxy)-5-(4-(methylsulfonamido)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

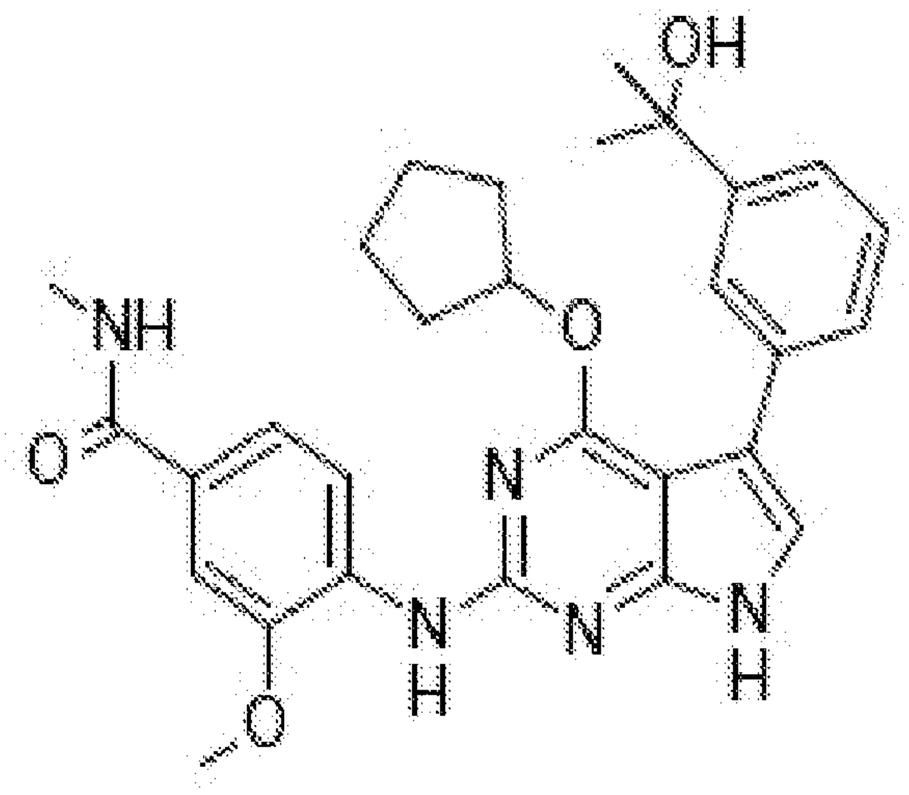
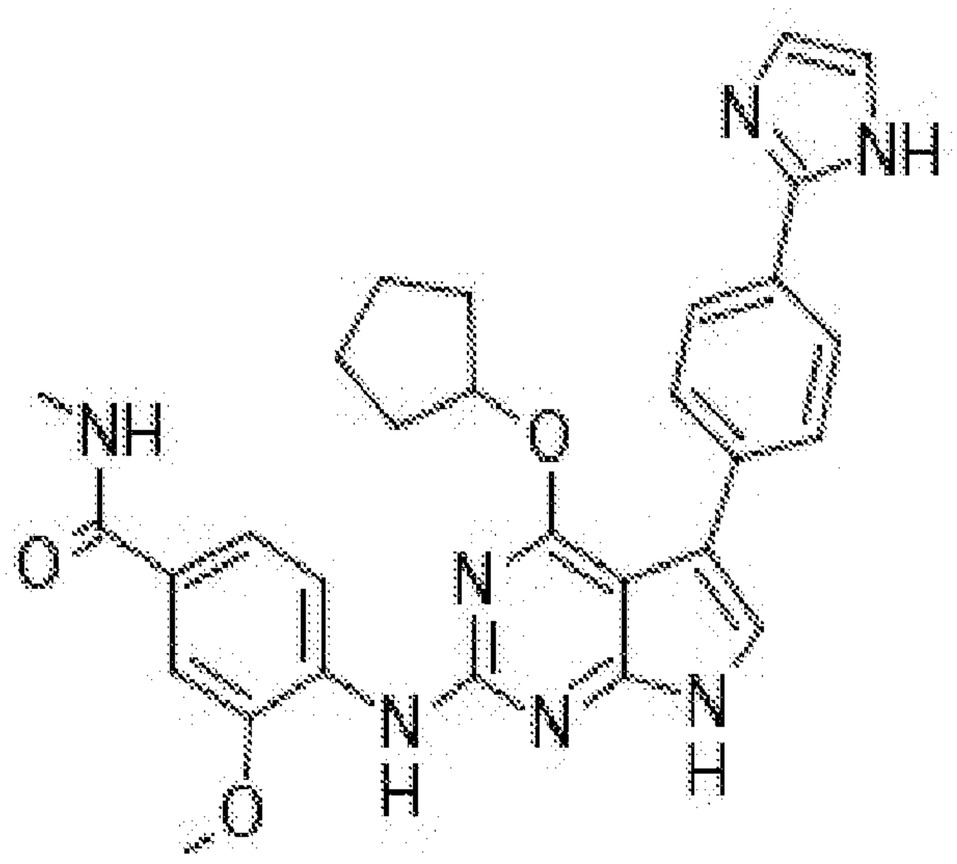
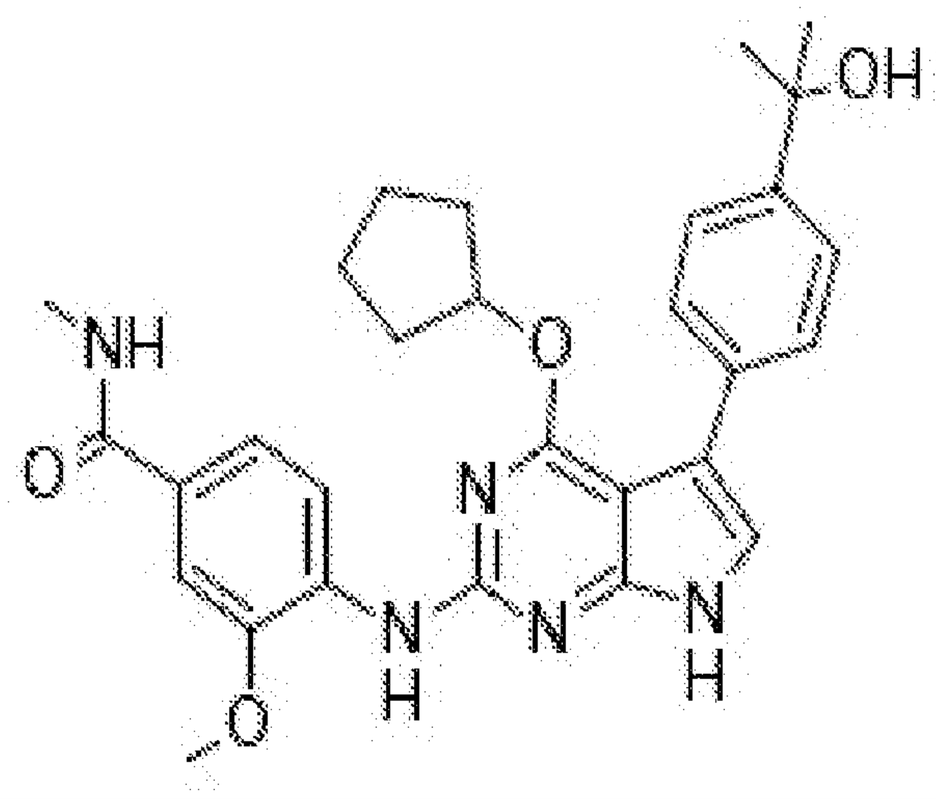
Cmpd No.	Structure	Name
33		4-(5-(3-cyano-4-hydroxyphenyl)-4-(cyclopentyloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
34		3-chloro-4-(4-(cyclopentyloxy)-5-(5-methoxypyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide

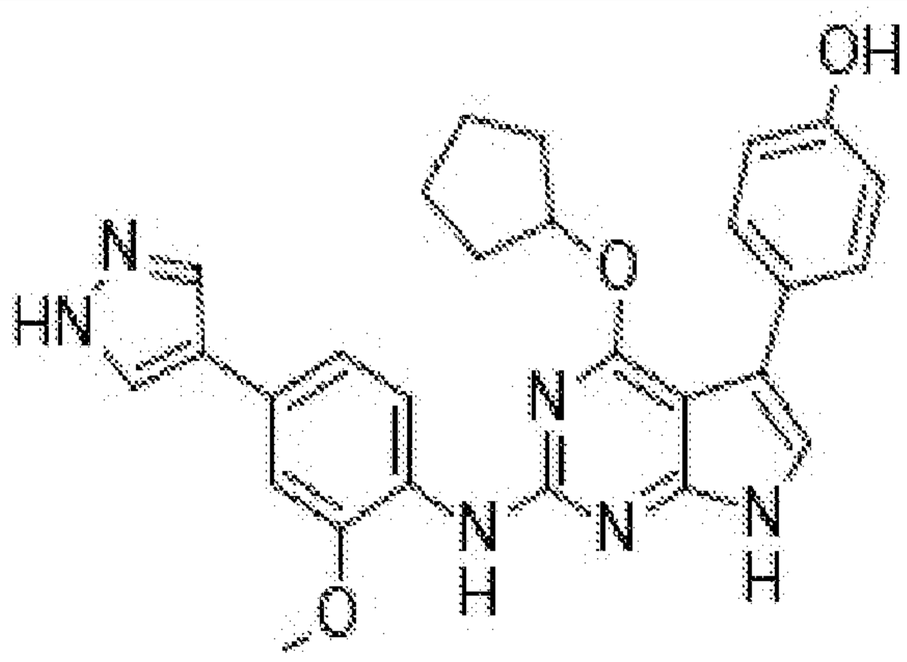
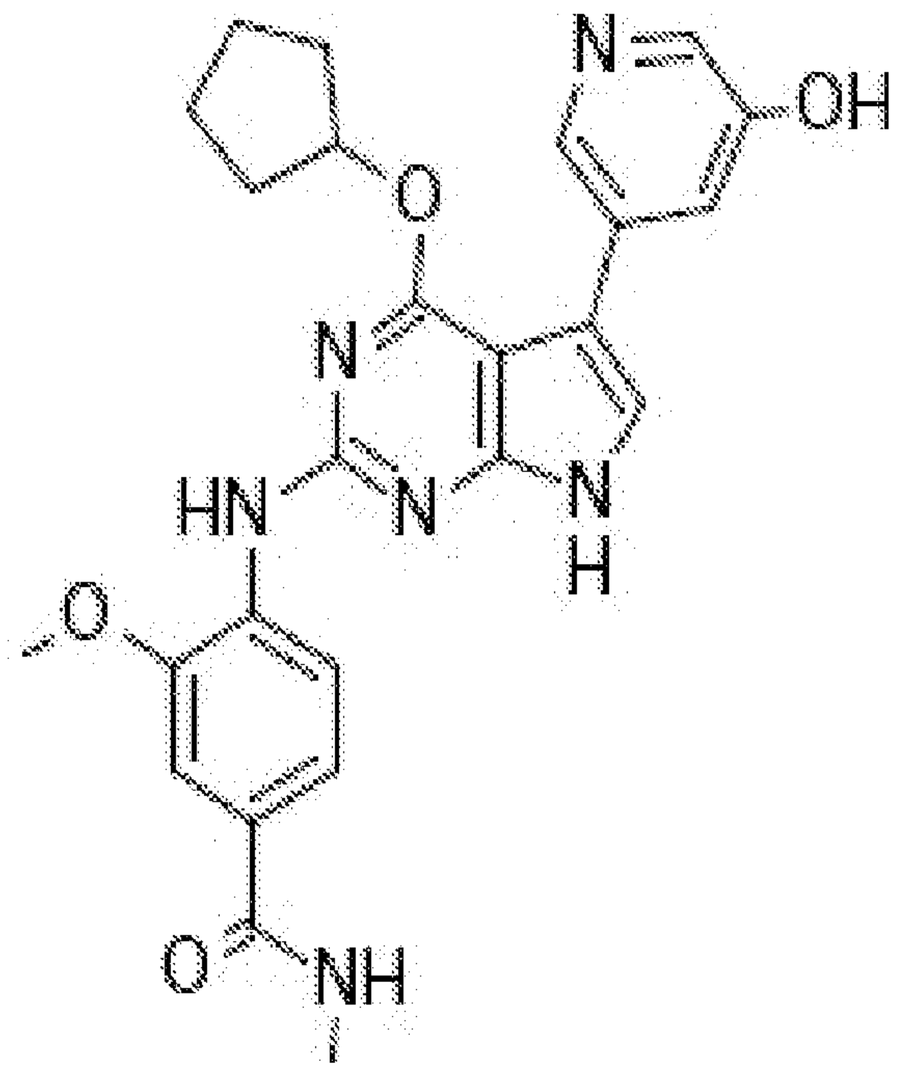
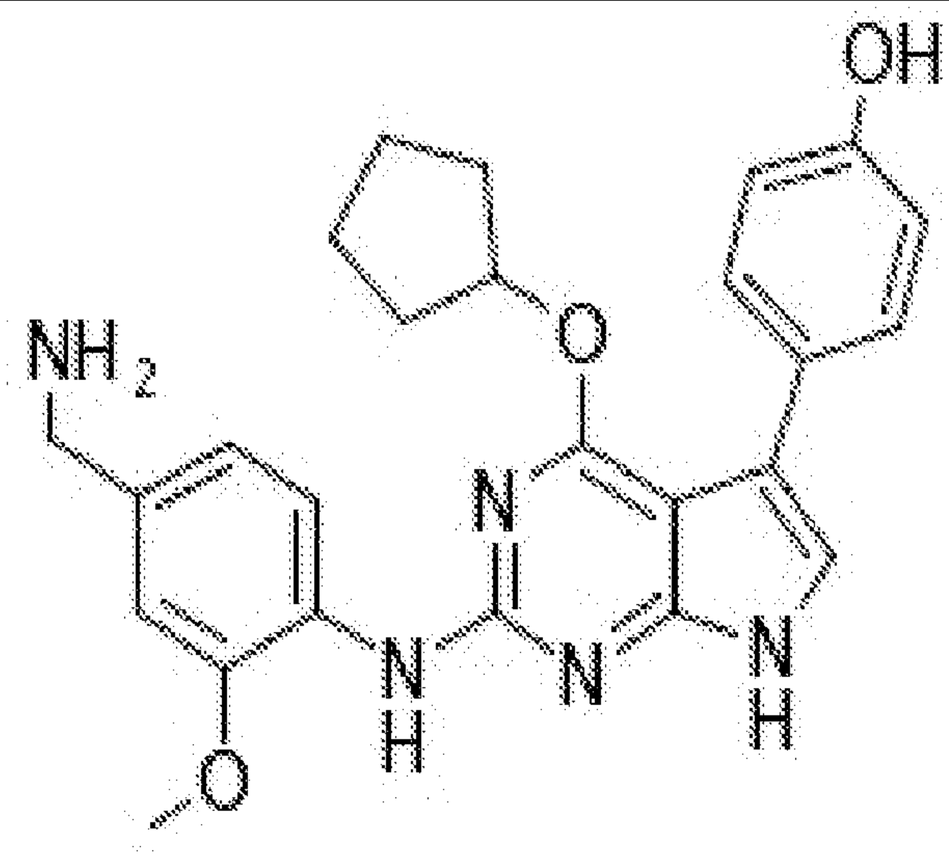
Cmpd No.	Structure	Name
35		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
36		4-(4-(cyclohexylamino)-5-(4-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
37		4-(5-(4-aminophenyl)-4-(cyclopentyloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

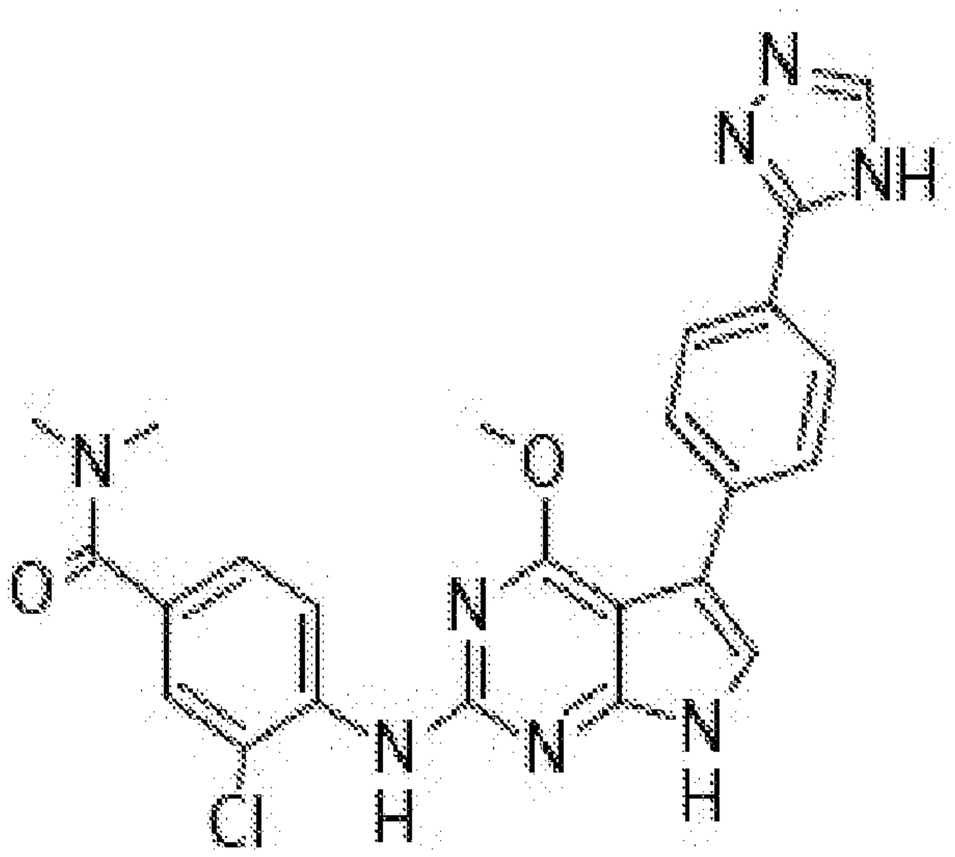
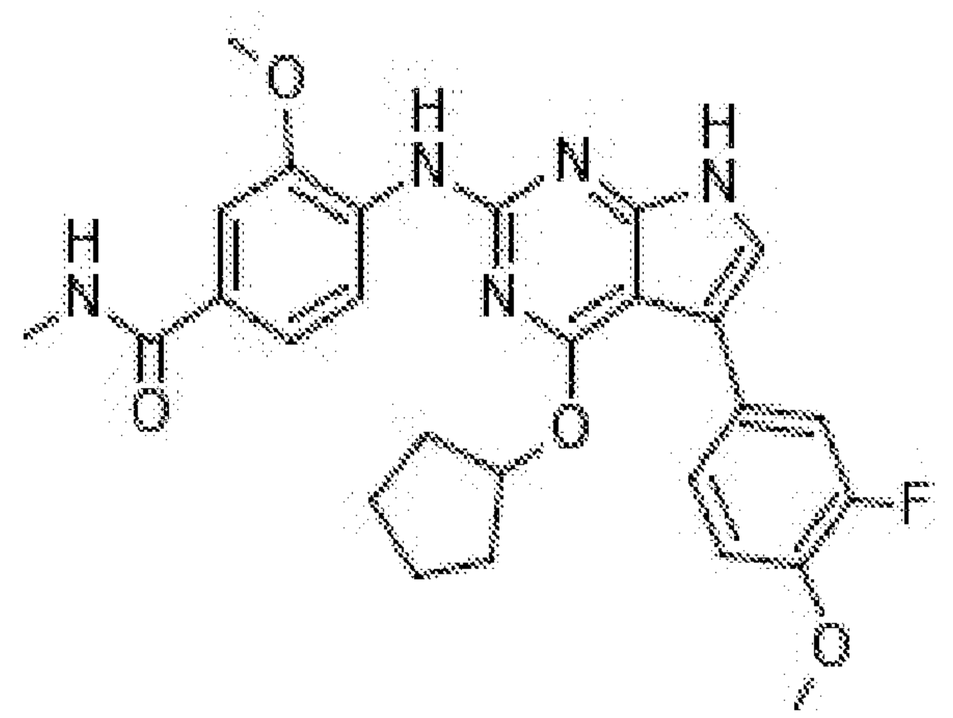
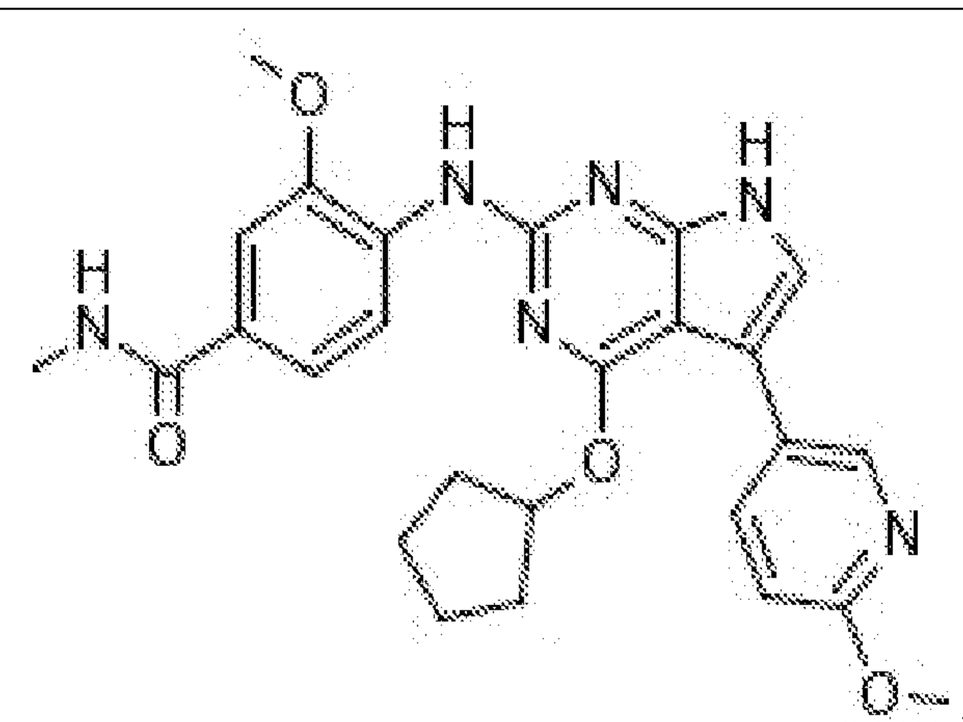
Cmpd No.	Structure	Name
38		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
39		4-(4-(cyclopentyloxy)-5-(4-ureidophenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
40		4-(5-(4-hydroxyphenyl)-4-(tetrahydro-2H-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

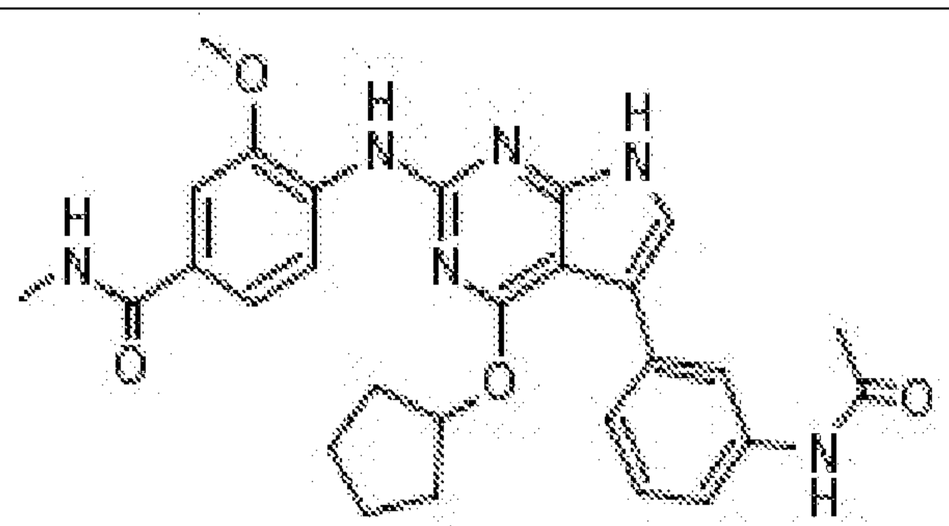
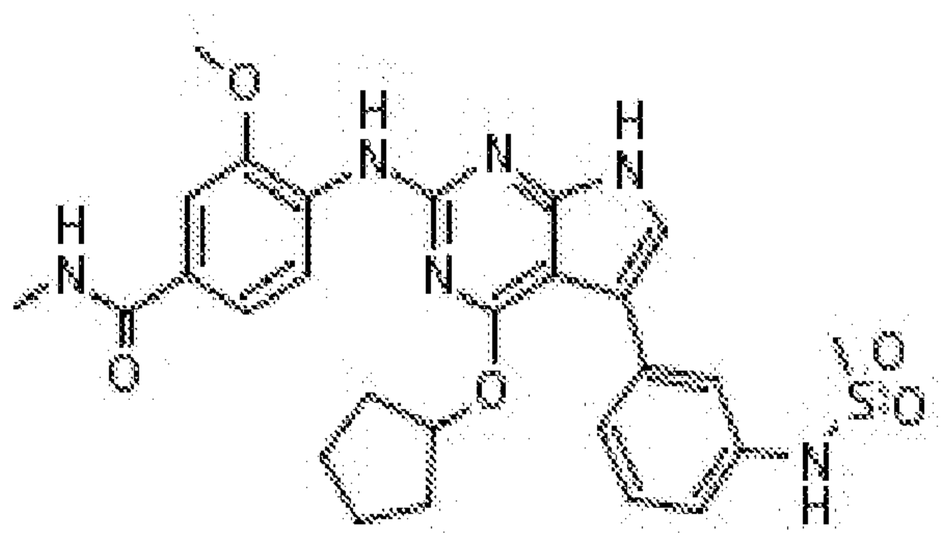
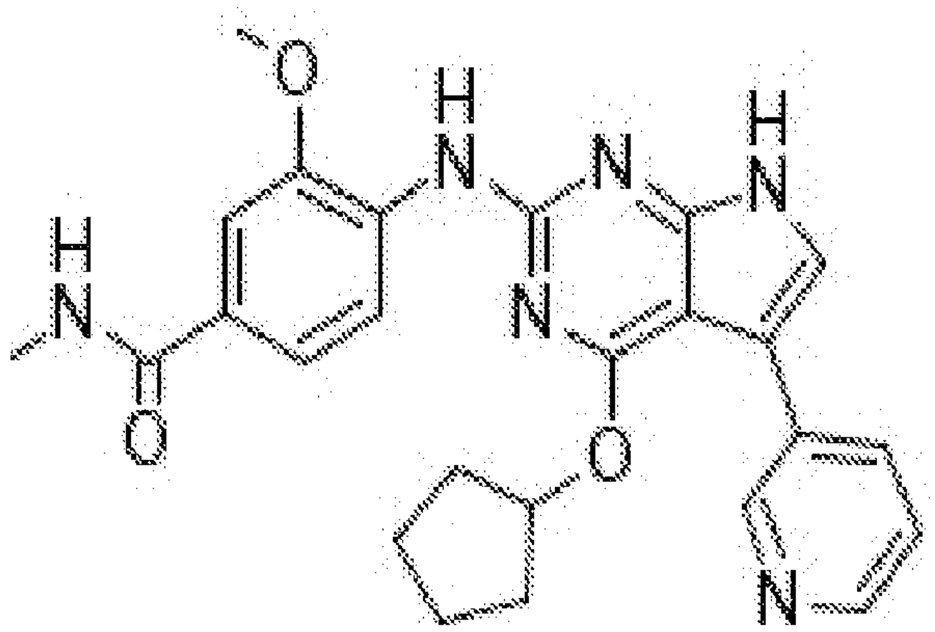
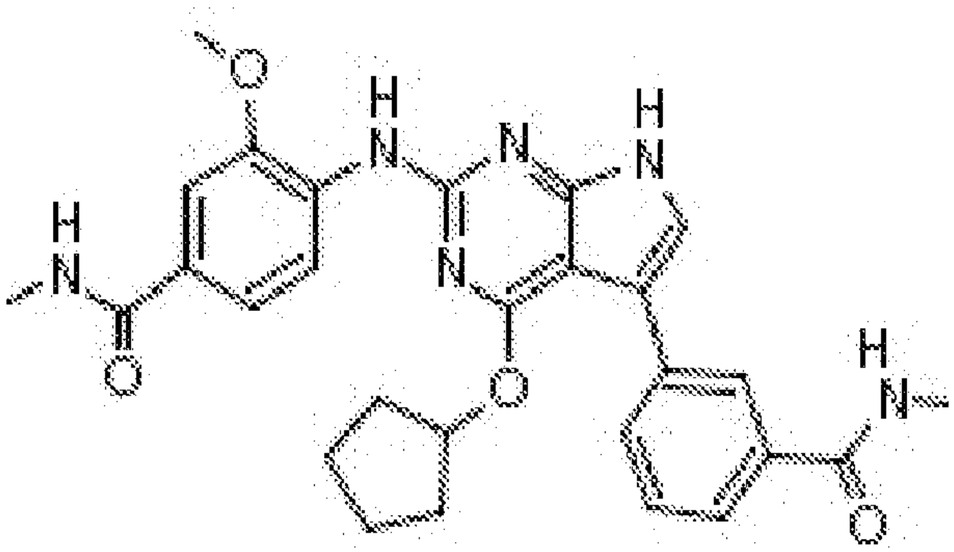
Cmpd No.	Structure	Name
41		4-(5-(4-(1H-pyrazol-5-yl)phenyl)-4-(cyclopentyloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
42		4-(4-(cyclopentyloxy)-5-(3-fluoro-4-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
43		4-(4-(cyclopentyloxy)-5-(4-hydroxy-3-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

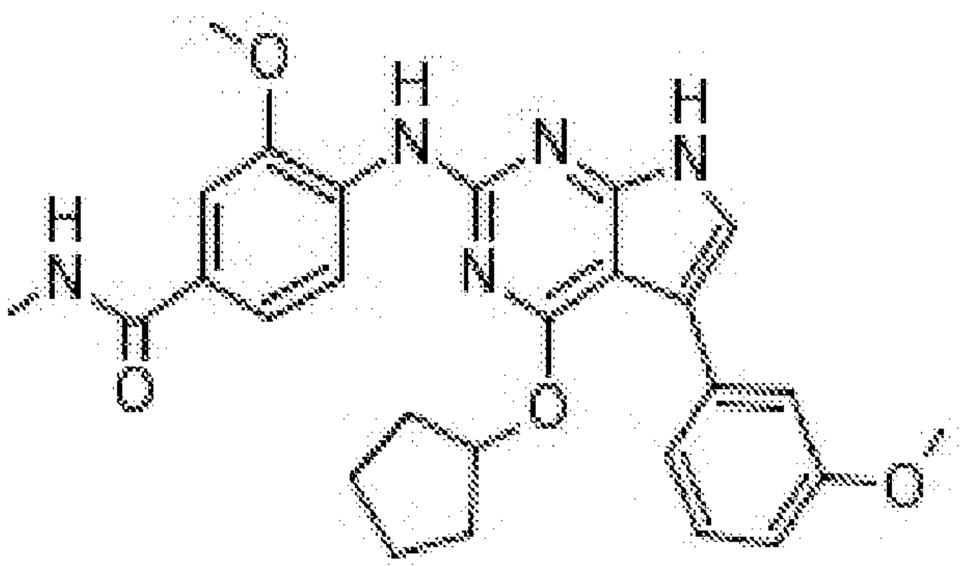
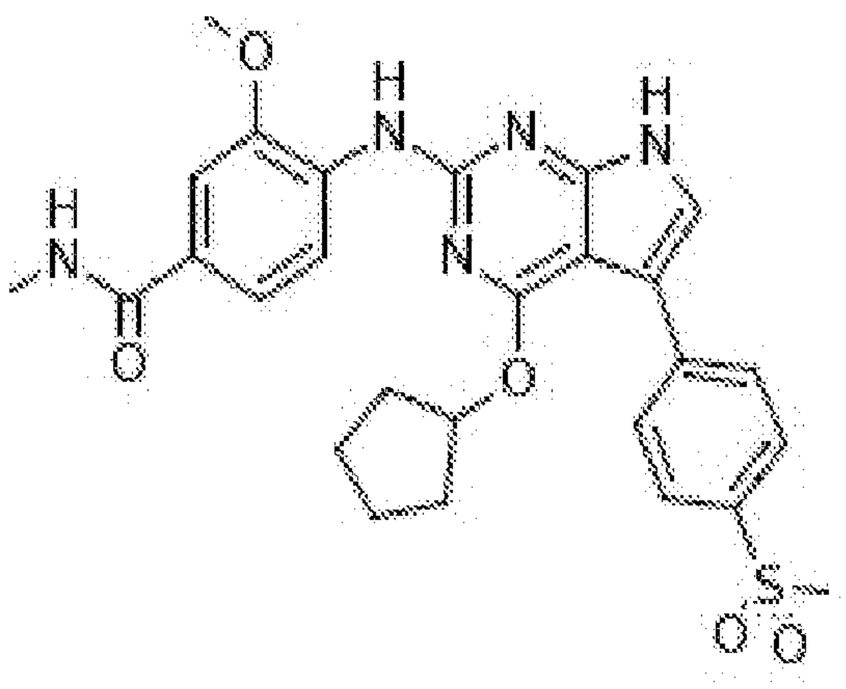
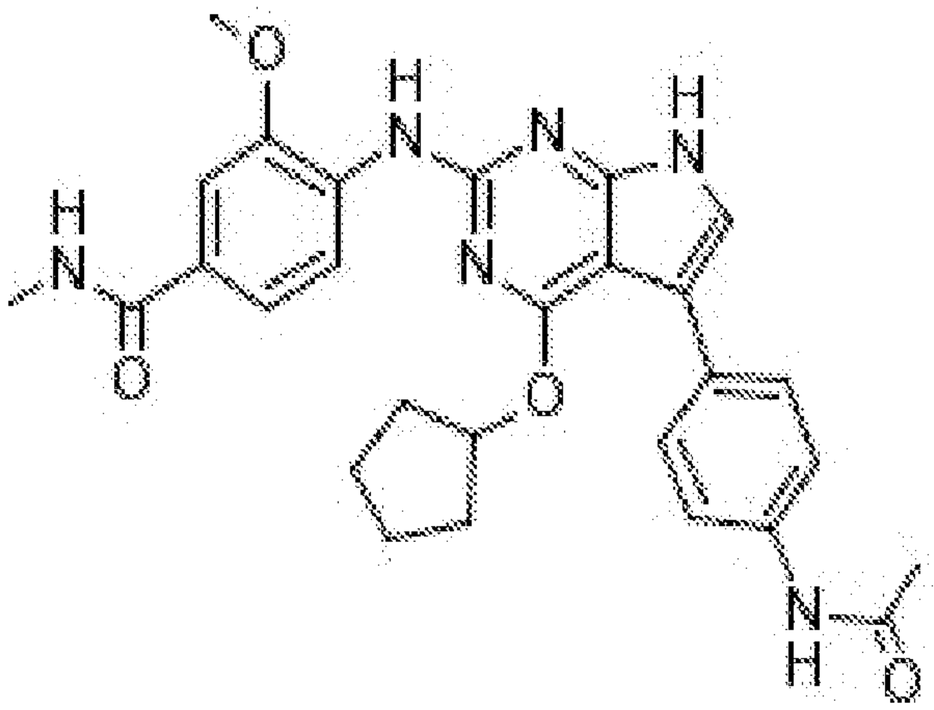
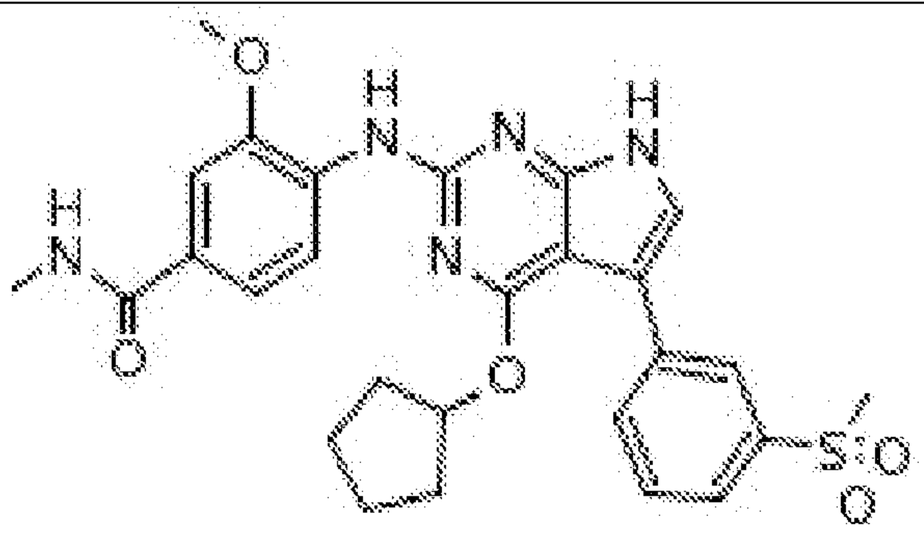
Cmpd No.	Structure	Name
44		4-(4-(cyclopentyloxy)-5-(4-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxybenzamide
45		4-(4-((1r,4r)-4-hydroxycyclohexyloxy)-5-(4-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
46		4-(4-((1s,4s)-4-hydroxycyclohexyloxy)-5-(4-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

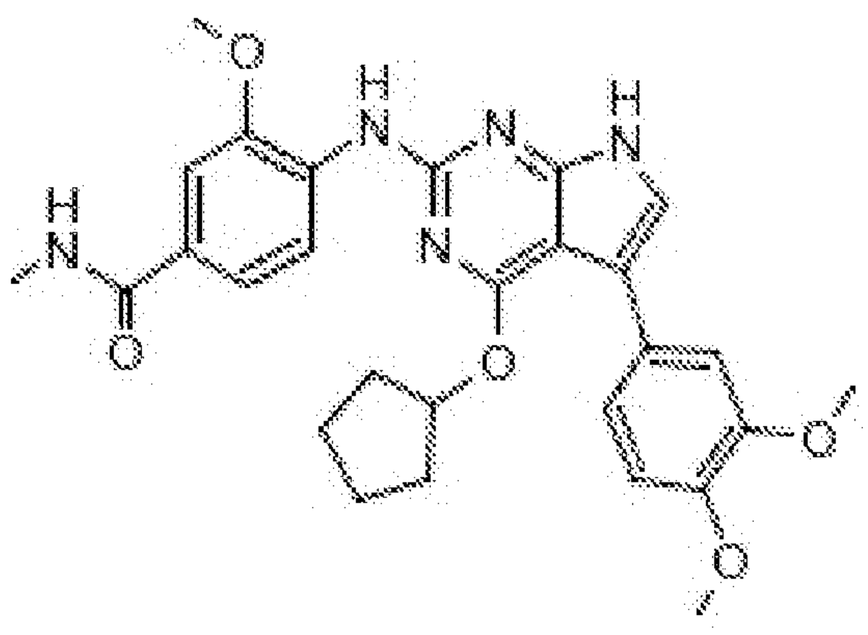
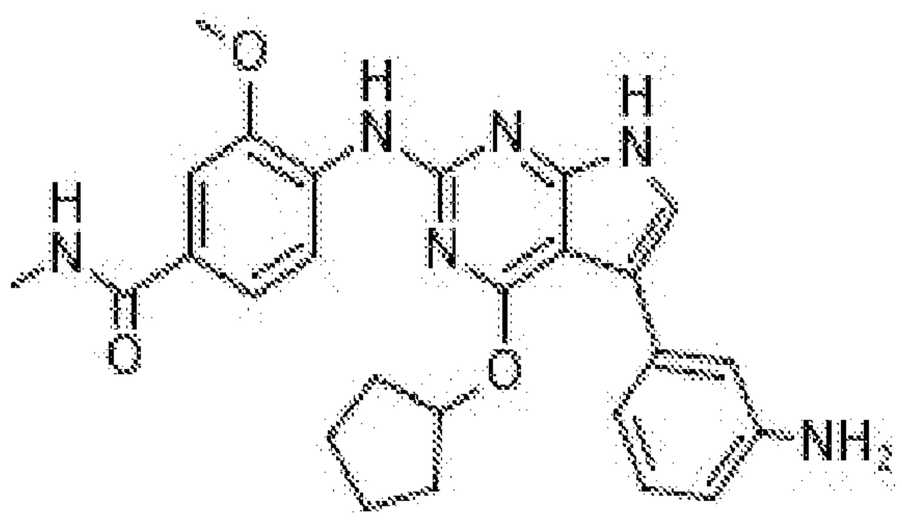
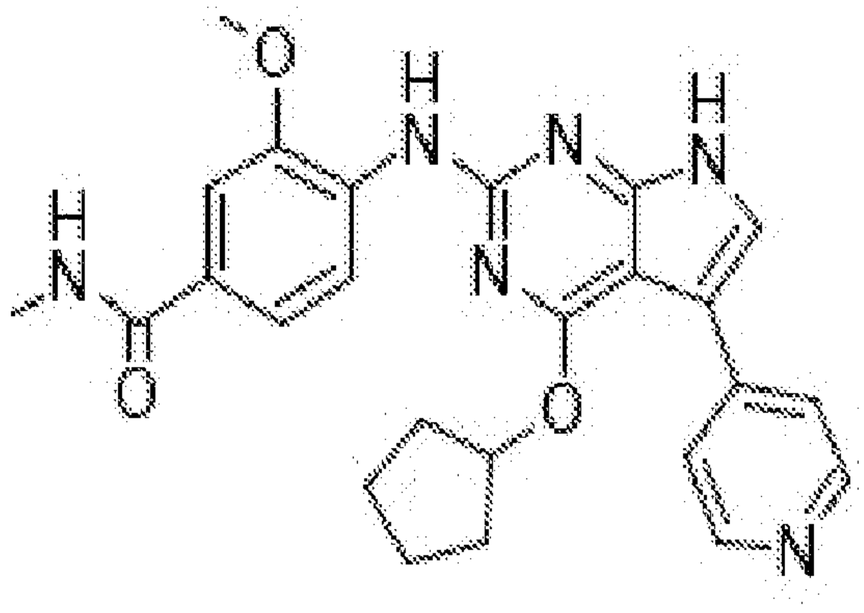
Cmpd No.	Structure	Name
47		4-(4-(cyclopentyloxy)-5-(3-(2-hydroxypropan-2-yl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
48		4-(5-(4-(1H-imidazol-2-yl)phenyl)-4-(cyclopentyloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
49		4-(4-(cyclopentyloxy)-5-(4-(2-hydroxypropan-2-yl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

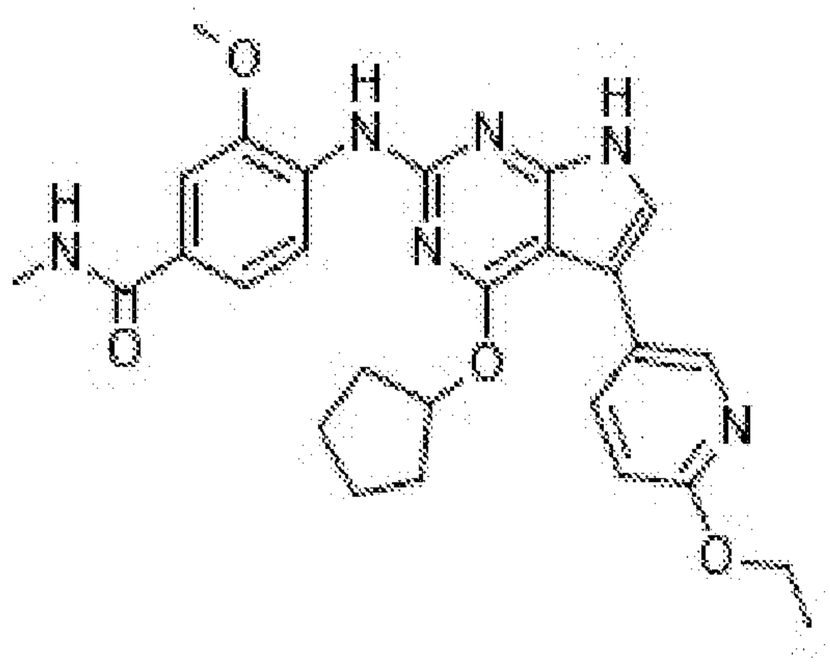
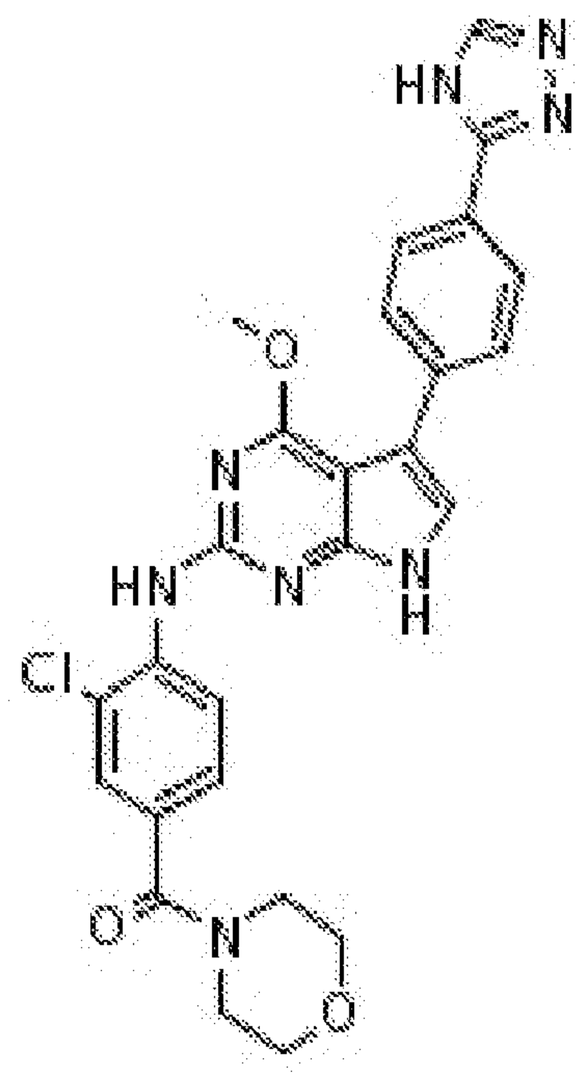
Cmpd No.	Structure	Name
50		4-(4-(cyclopentyloxy)-2-(2-methoxy-4-(1H-pyrazol-4-yl)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenol
51		4-(4-(cyclopentyloxy)-5-(5-hydroxypyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
52		4-(2-(4-(aminomethyl)-2-methoxyphenylamino)-4-(cyclopentyloxy)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenol

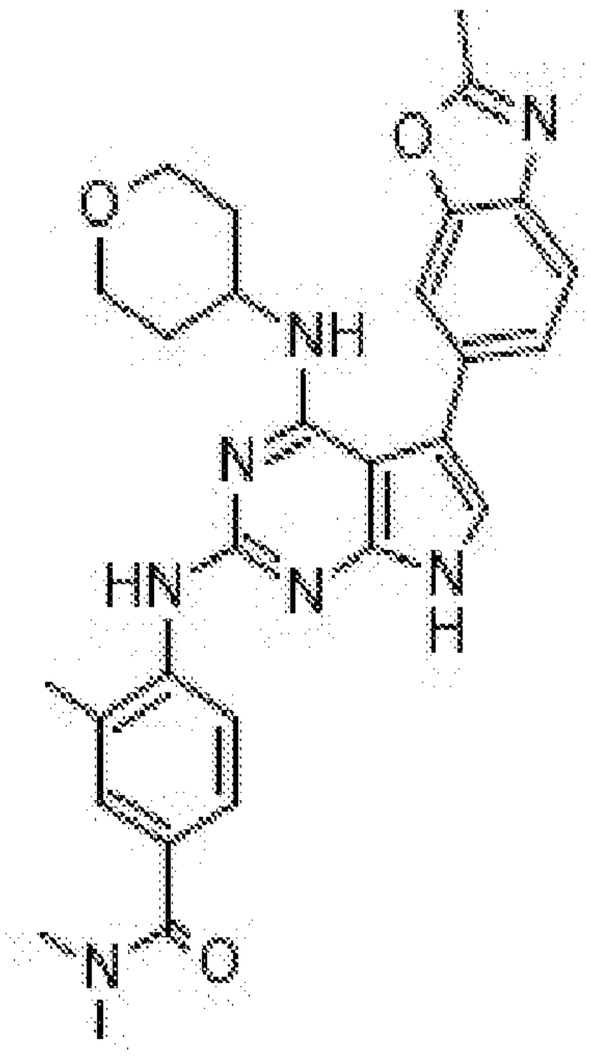
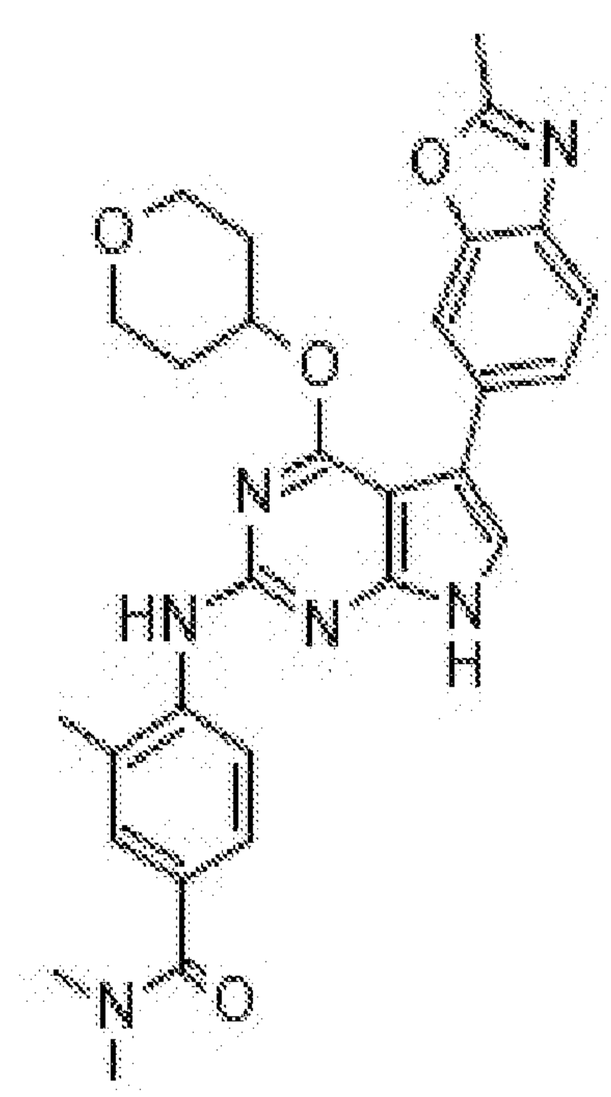
Cmpd No.	Structure	Name
53		4-(5-(4-(4H-1,2,4-triazol-3-yl)phenyl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-chloro-N,N-dimethylbenzamide
54		4-(4-(cyclopentyloxy)-5-(3-fluoro-4-methoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
55		4-(4-(cyclopentyloxy)-5-(6-methoxypyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

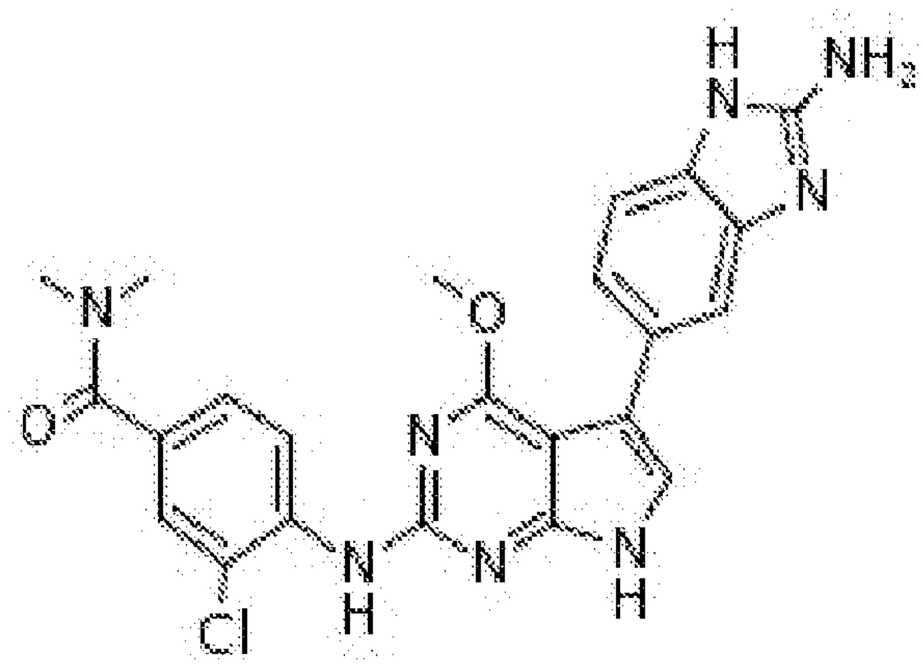
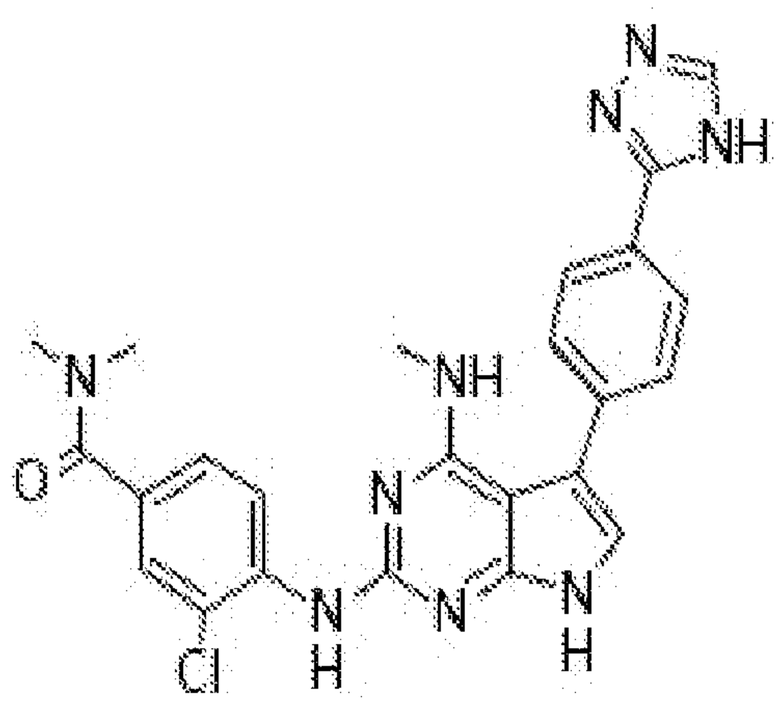
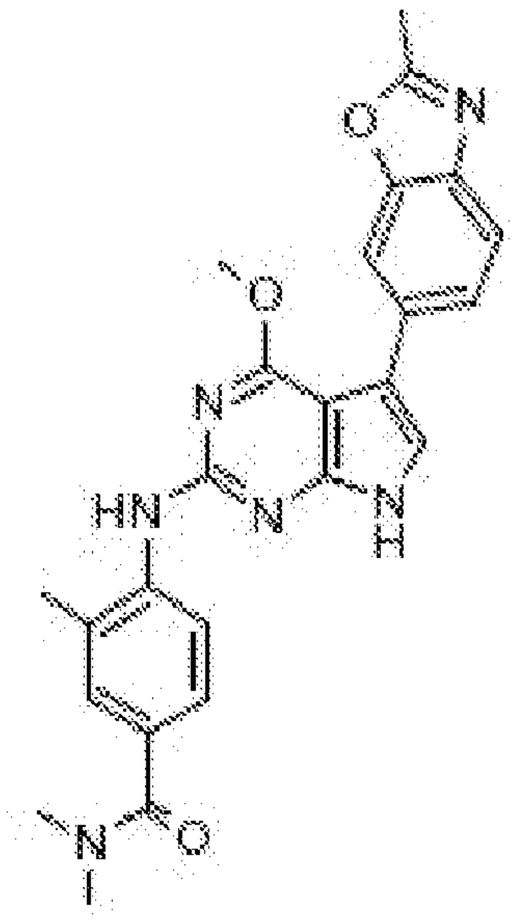
Cmpd No.	Structure	Name
56		4-(5-(3-acetamidophenyl)-4-(cyclopentyloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
57		4-(4-(cyclopentyloxy)-5-(3-(methylsulfonamido)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
58		4-(4-(cyclopentyloxy)-5-(pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
59		4-(4-(cyclopentyloxy)-5-(3-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

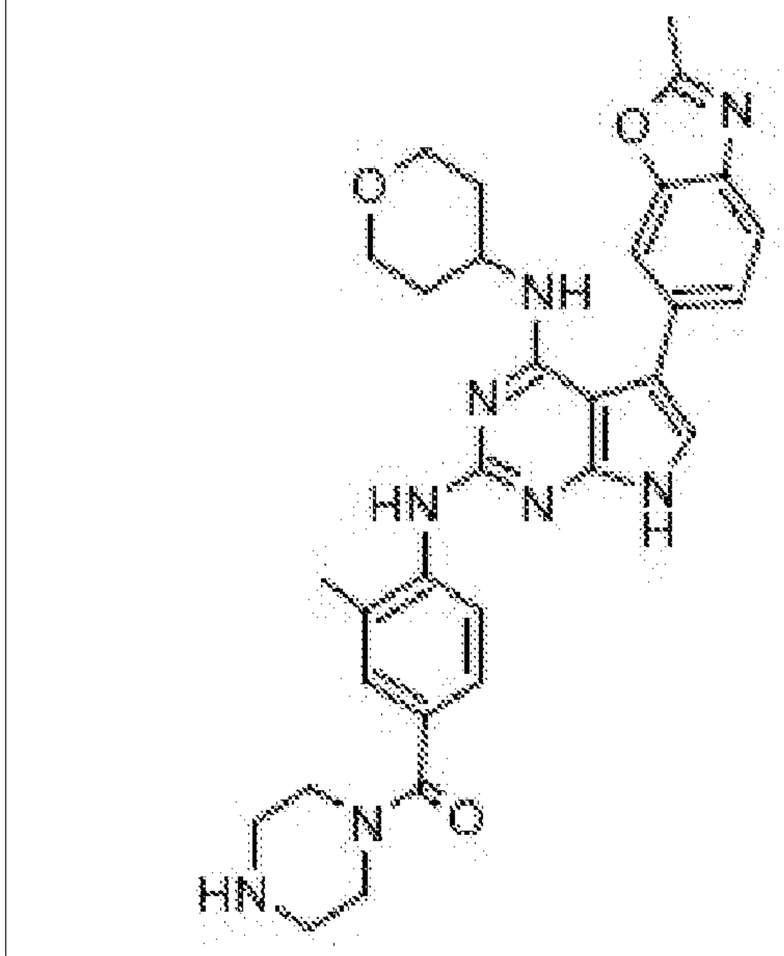
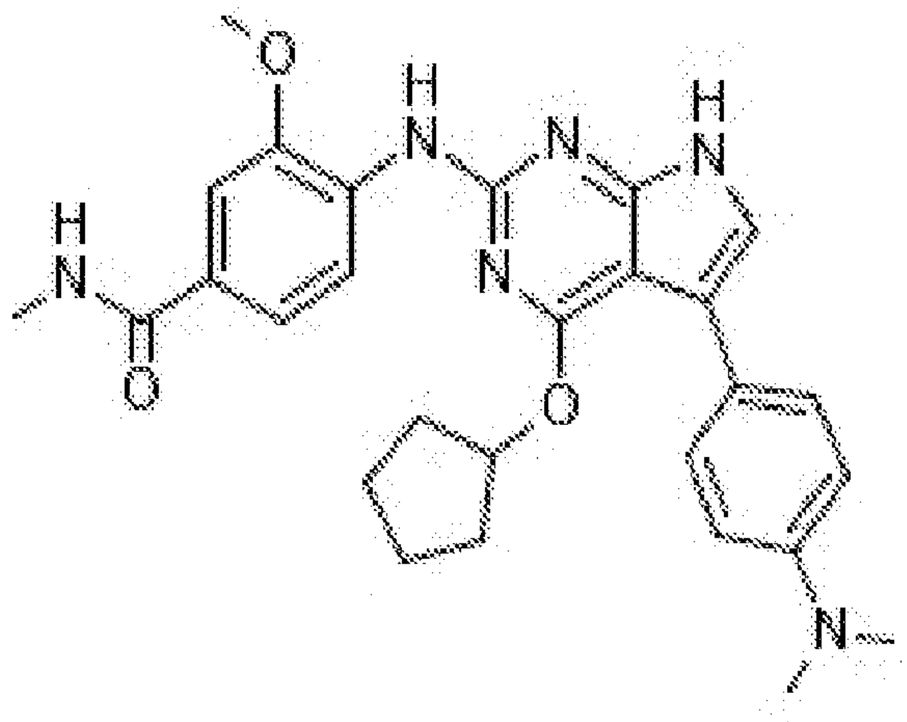
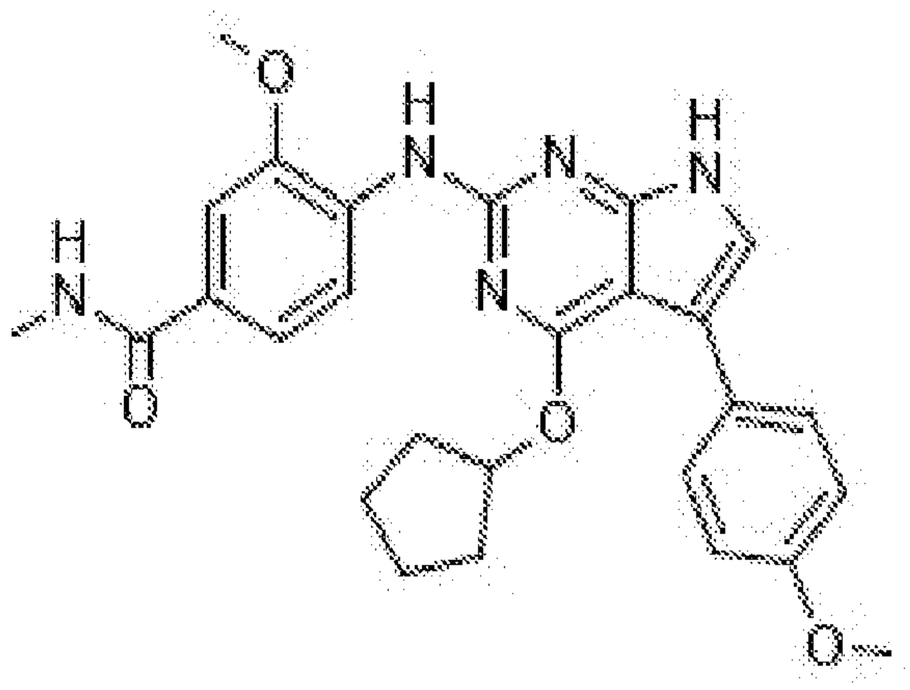
Cmpd No.	Structure	Name
60		4-(4-(cyclopentyloxy)-5-(3-methoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
61		4-(4-(cyclopentyloxy)-5-(4-(methylsulfonyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
62		4-(5-(4-acetamidophenyl)-4-(cyclopentyloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
63		4-(4-(cyclopentyloxy)-5-(3-(methylsulfonyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

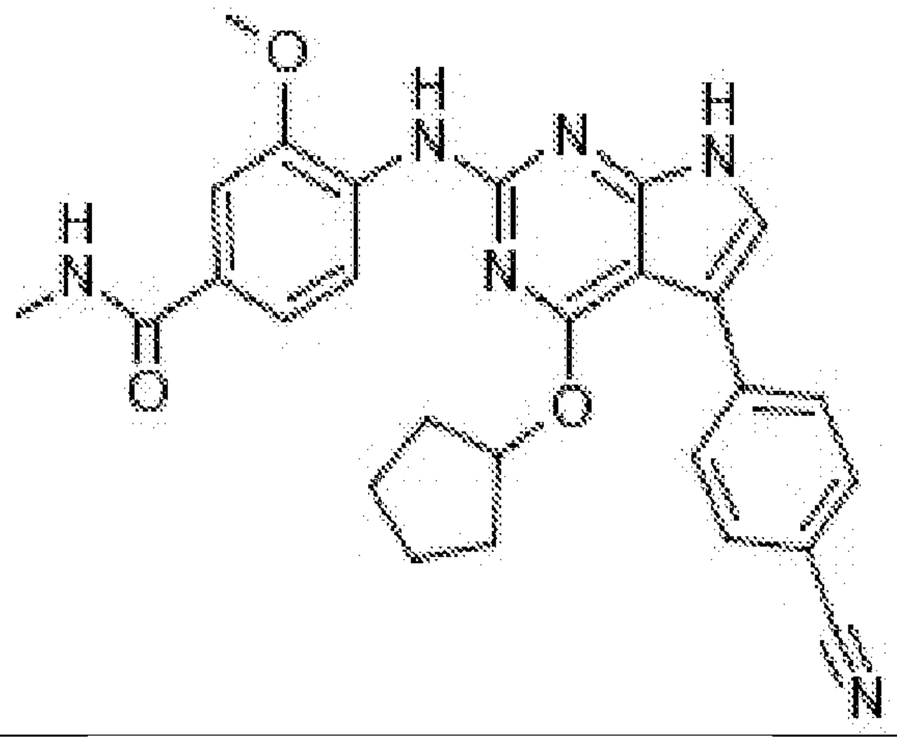
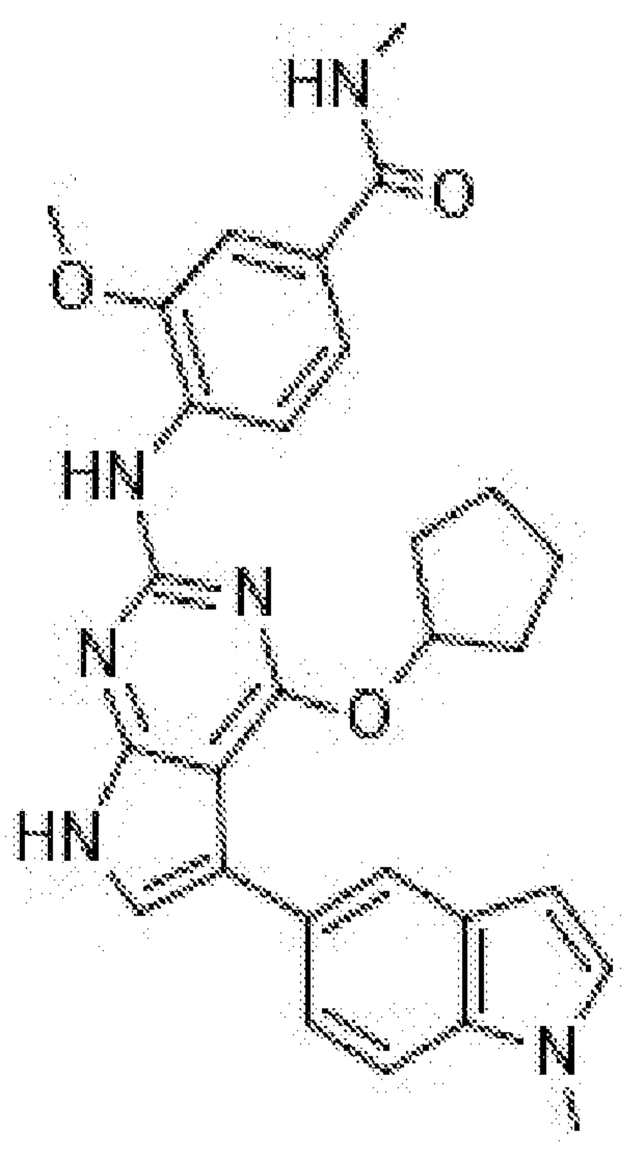
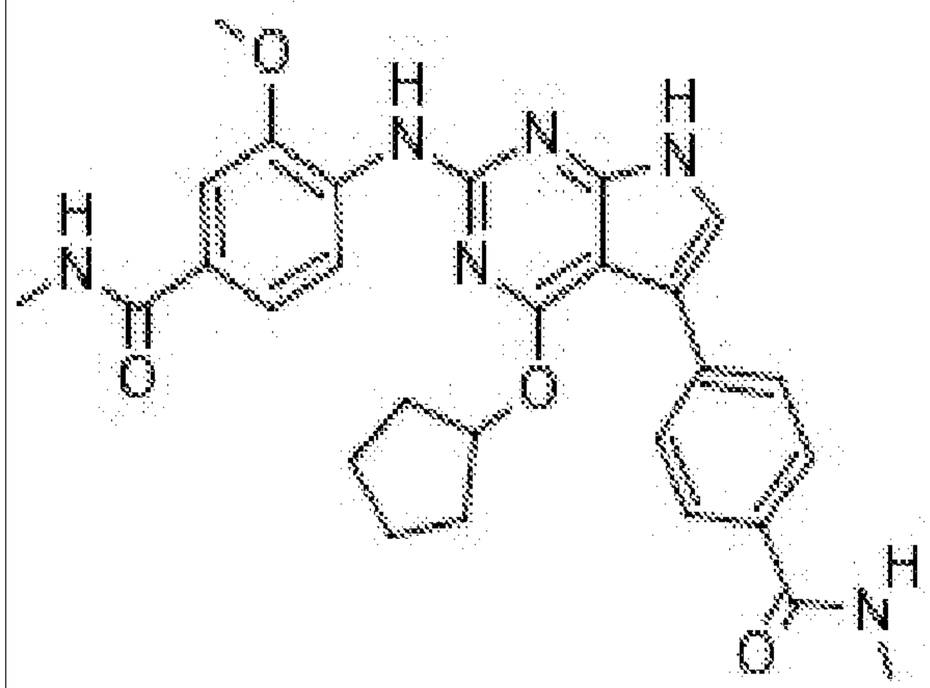
Cmpd No.	Structure	Name
64		4-(4-(cyclopentyloxy)-5-(3,4-dimethoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
65		4-(5-(3-aminophenyl)-4-(cyclopentyloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
66		4-(4-(cyclopentyloxy)-5-(pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

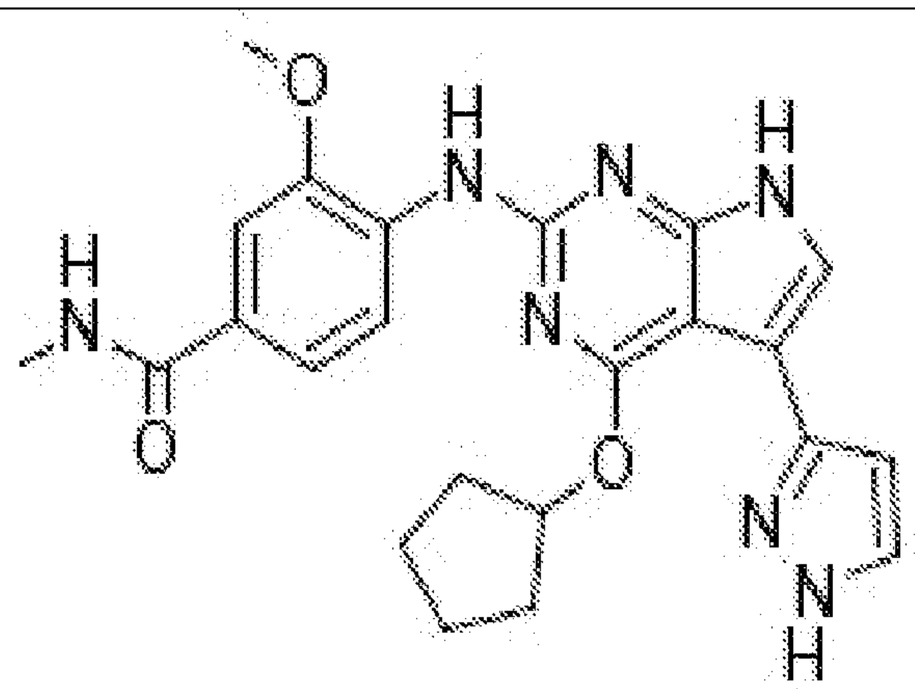
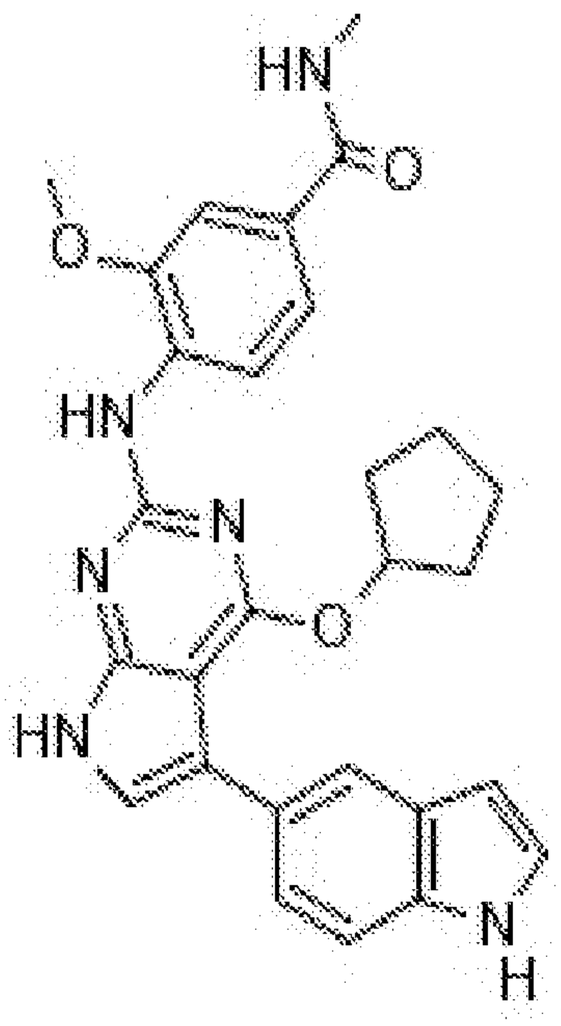
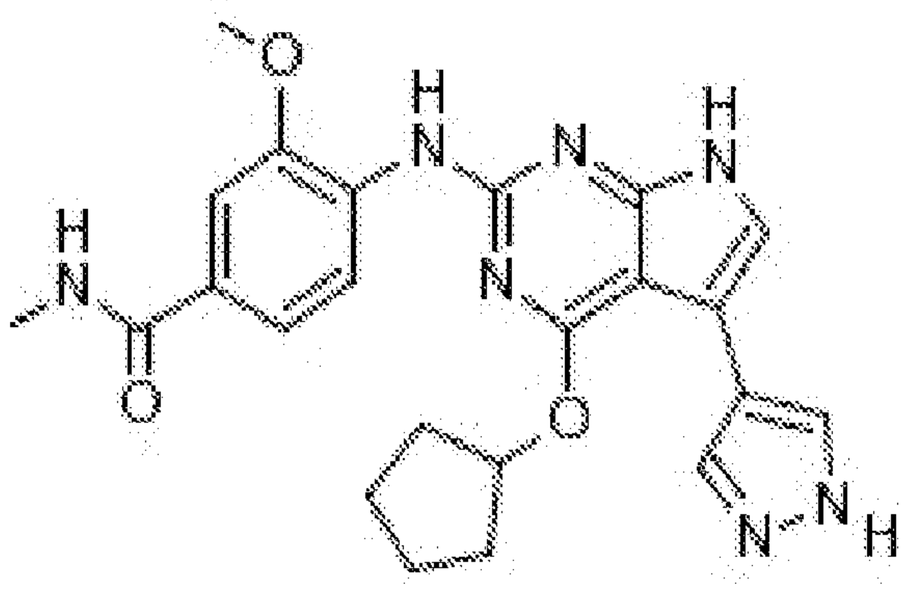
Cmpd No.	Structure	Name
67		4-(4-(cyclopentyloxy)-5-(6-ethoxypyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
68		(4-(5-(4-(4H-1,2,4-triazol-3-yl)phenyl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-chlorophenyl)(morpholino)-methanone

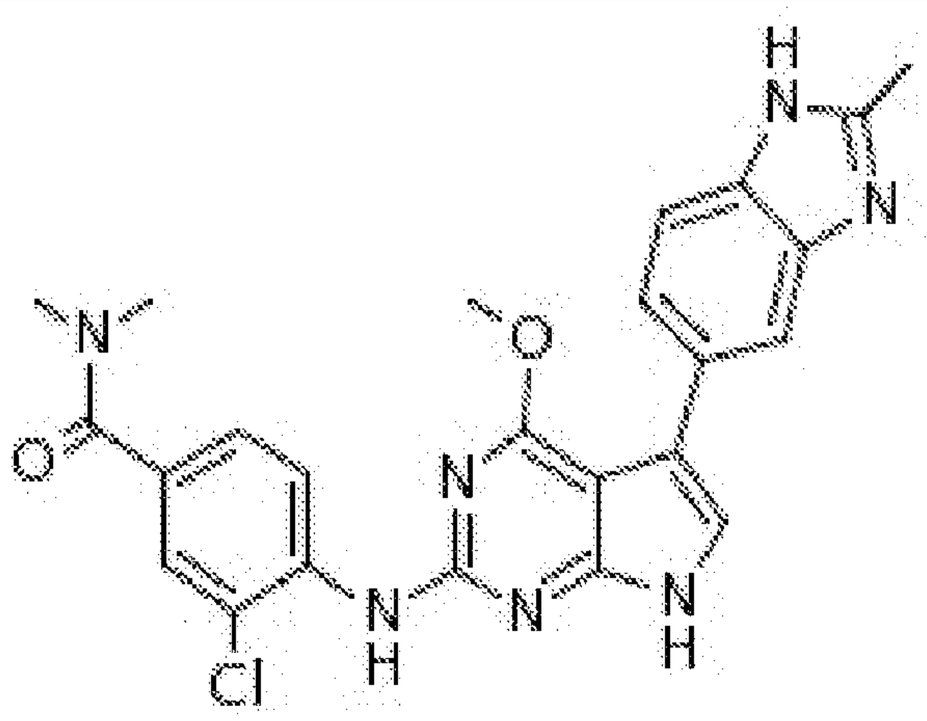
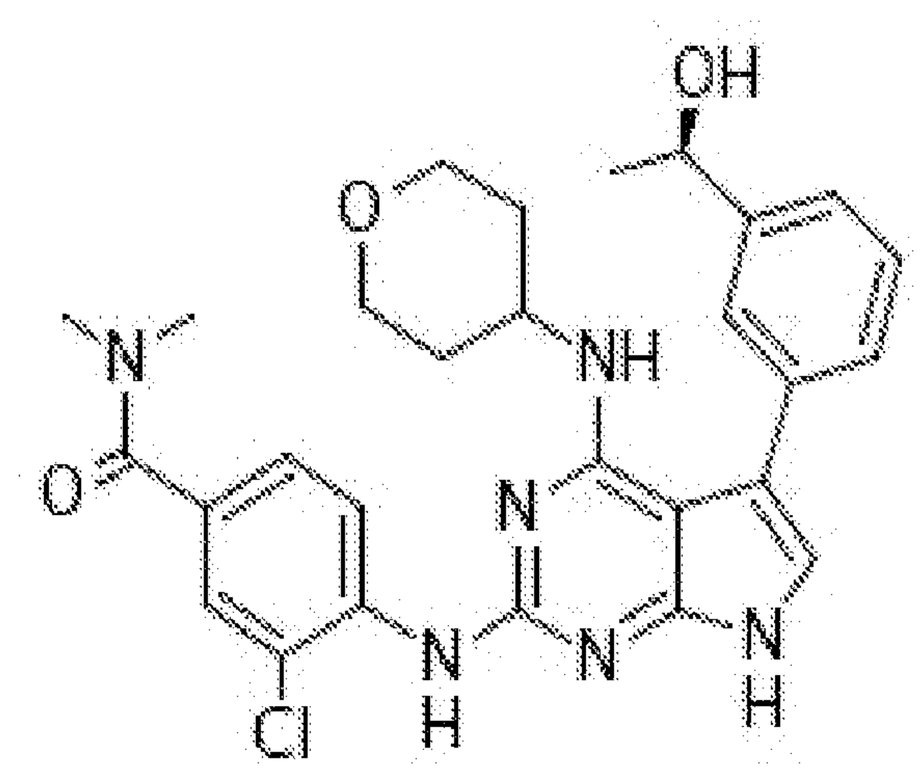
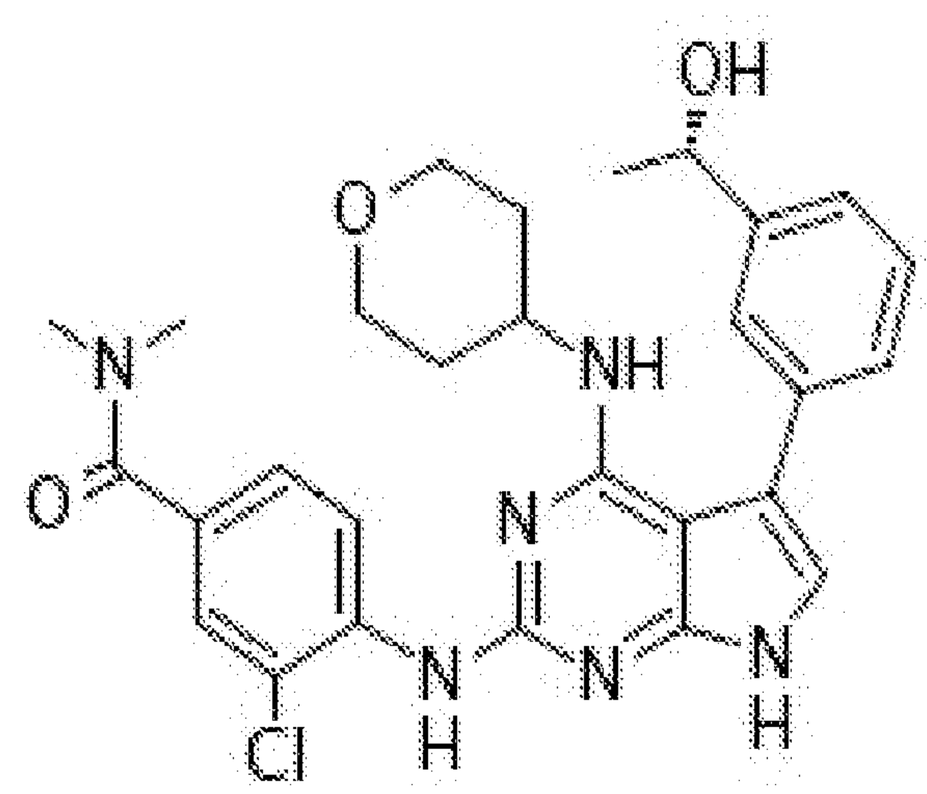
Cmpd No.	Structure	Name
69		N,N,3-trimethyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
70		N,N,3-trimethyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

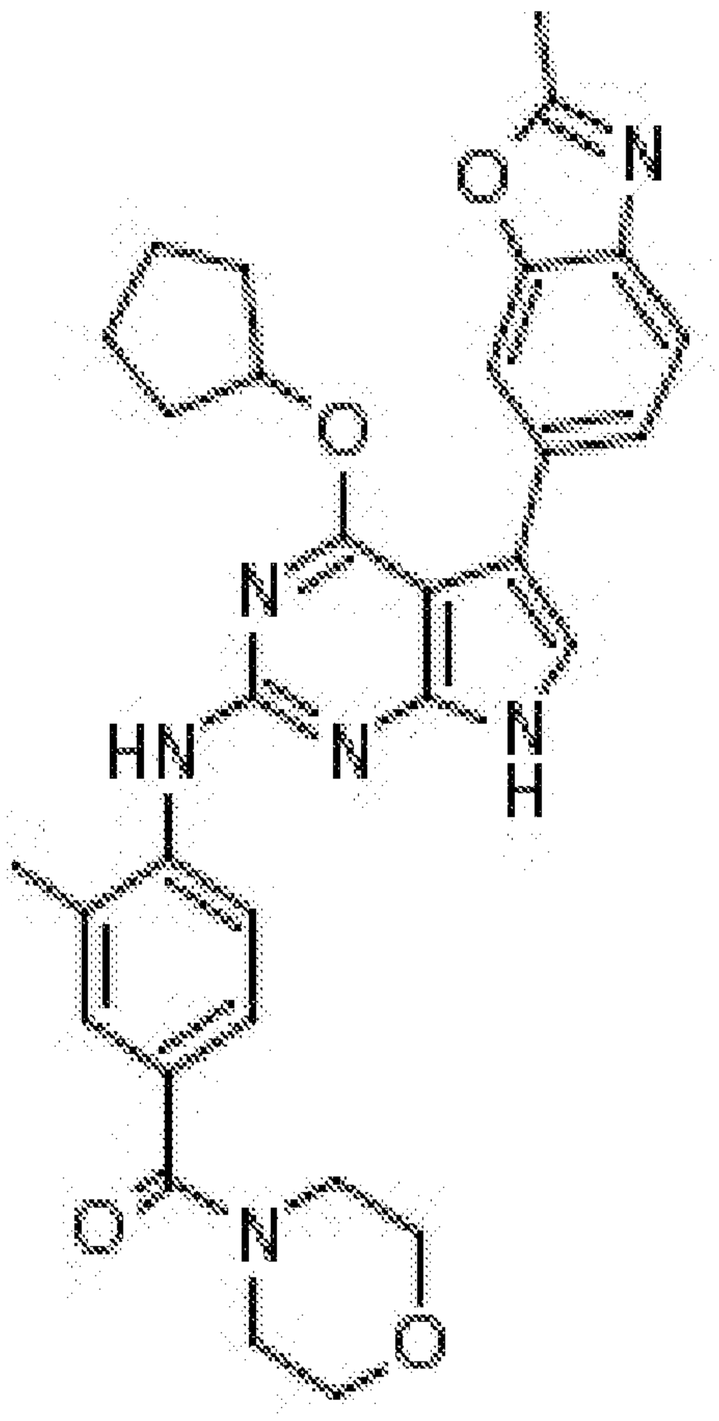
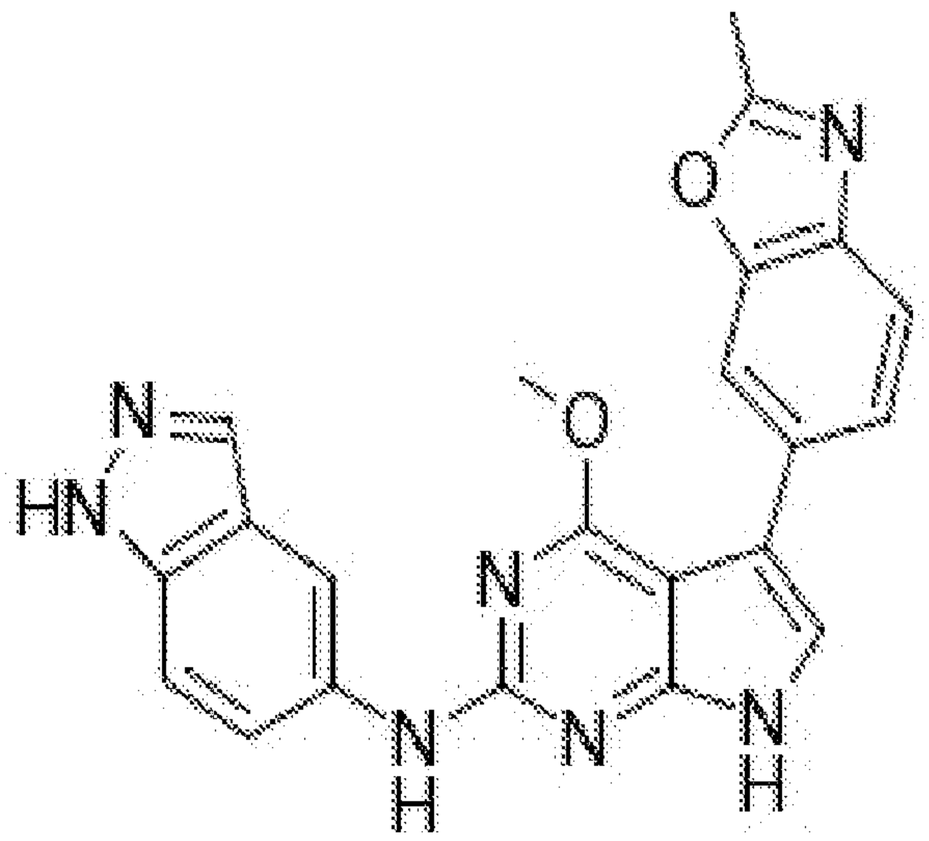
Cmpd No.	Structure	Name
71		4-(5-(2-amino-1H-benzo[d]imidazol-5-yl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-chloro-N,N-dimethylbenzamide
72		4-(5-(4-(4H-1,2,4-triazol-3-yl)phenyl)-4-(methylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-chloro-N,N-dimethylbenzamide
73		4-(4-methoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N,3-trimethylbenzamide

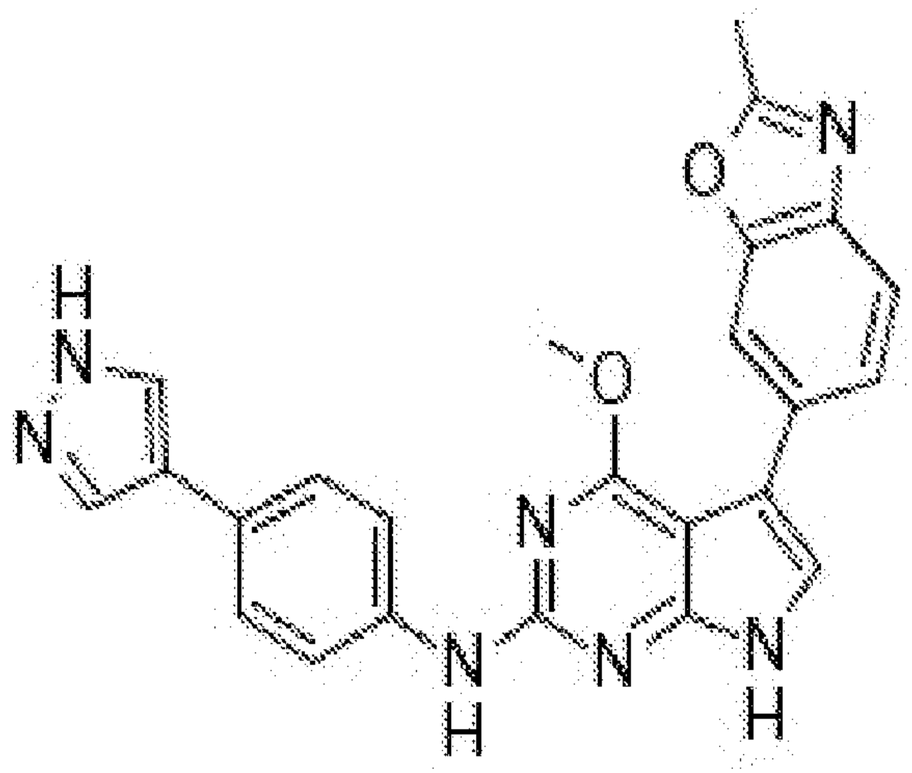
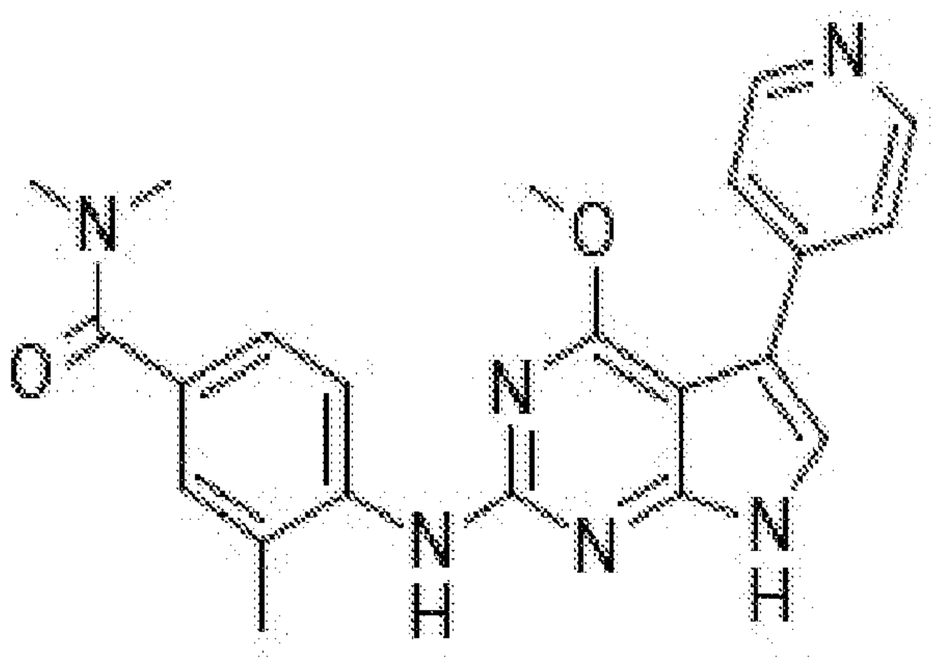
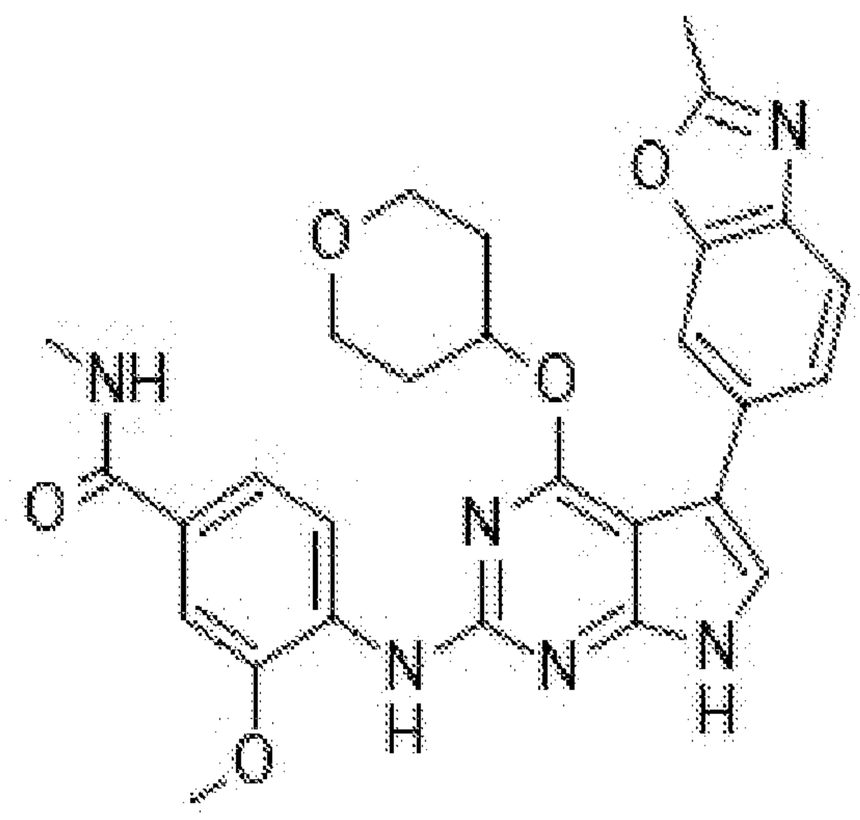
Cmpd No.	Structure	Name
74		(3-methyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)phenyl)(piperazin-1-yl)methanone
75		4-(4-(cyclopentyloxy)-5-(4-(dimethylamino)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
76		4-(4-(cyclopentyloxy)-5-(4-methoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

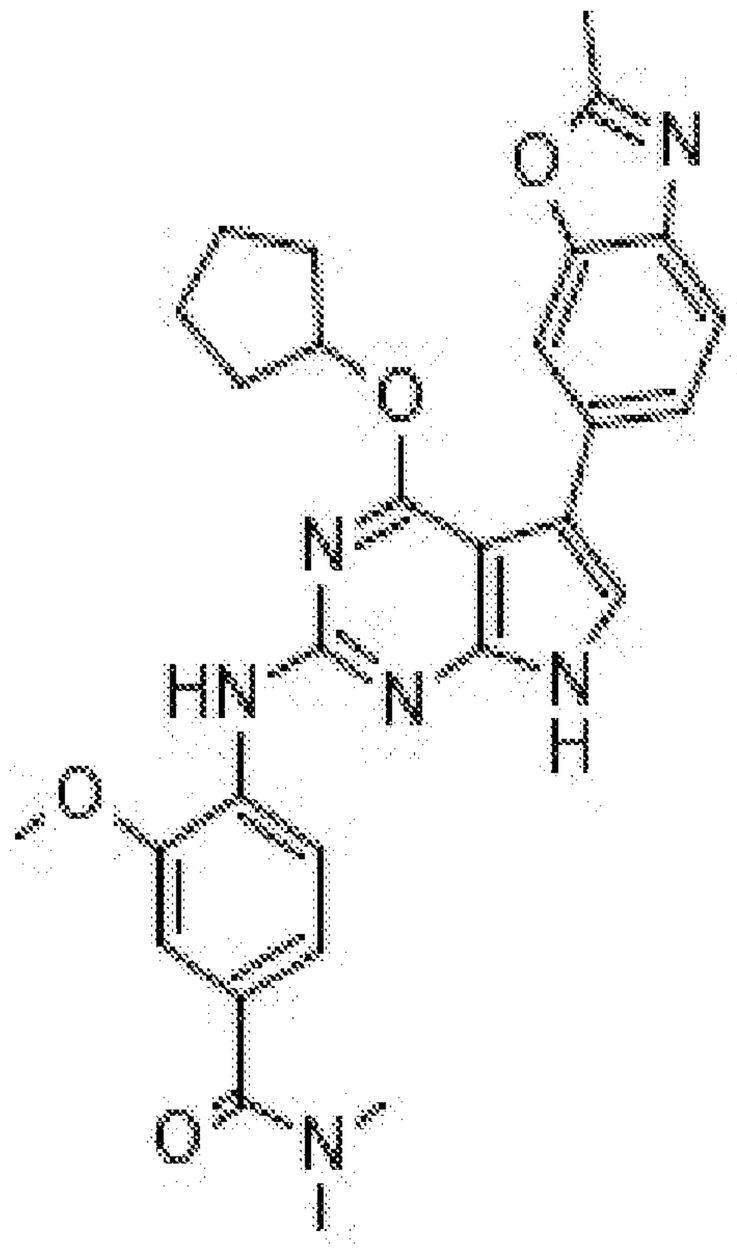
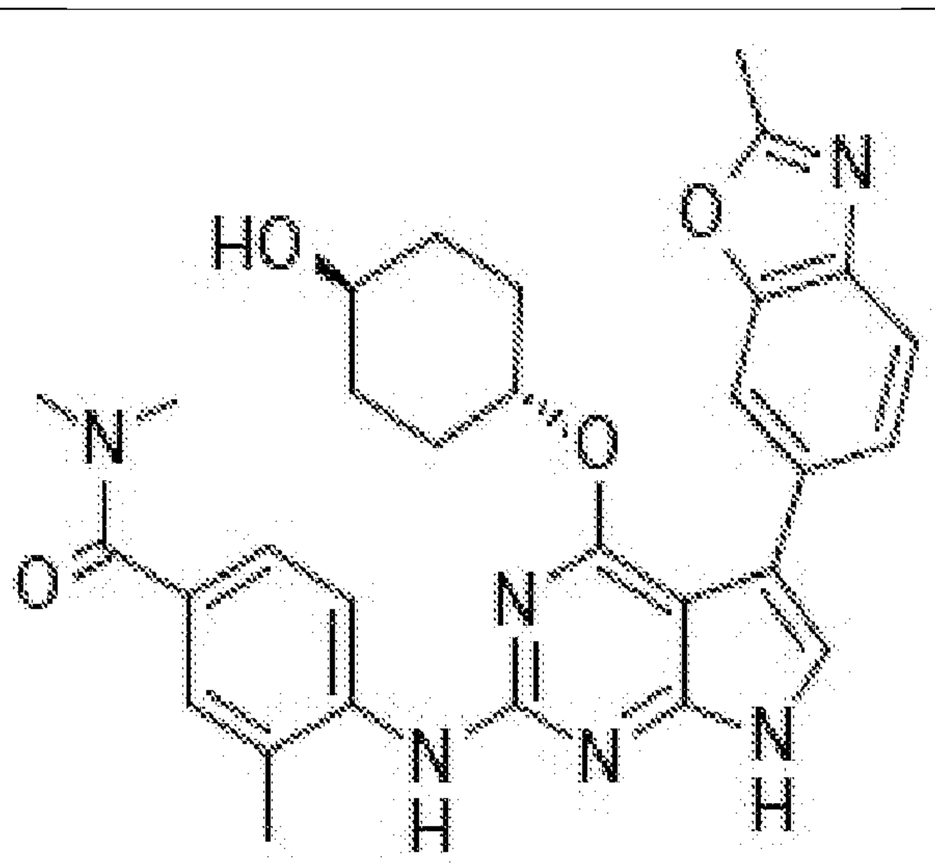
Cmpd No.	Structure	Name
77		4-(5-(4-cyanophenyl)-4-(cyclopentyloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
78		4-(4-(cyclopentyloxy)-5-(1-methyl-1H-indol-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
79		4-(4-(cyclopentyloxy)-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

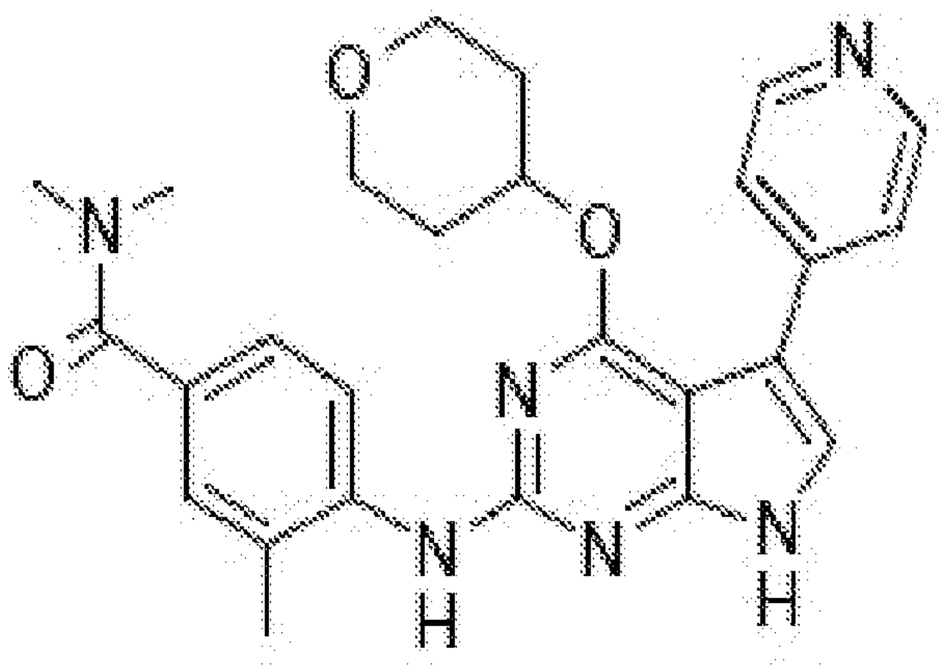
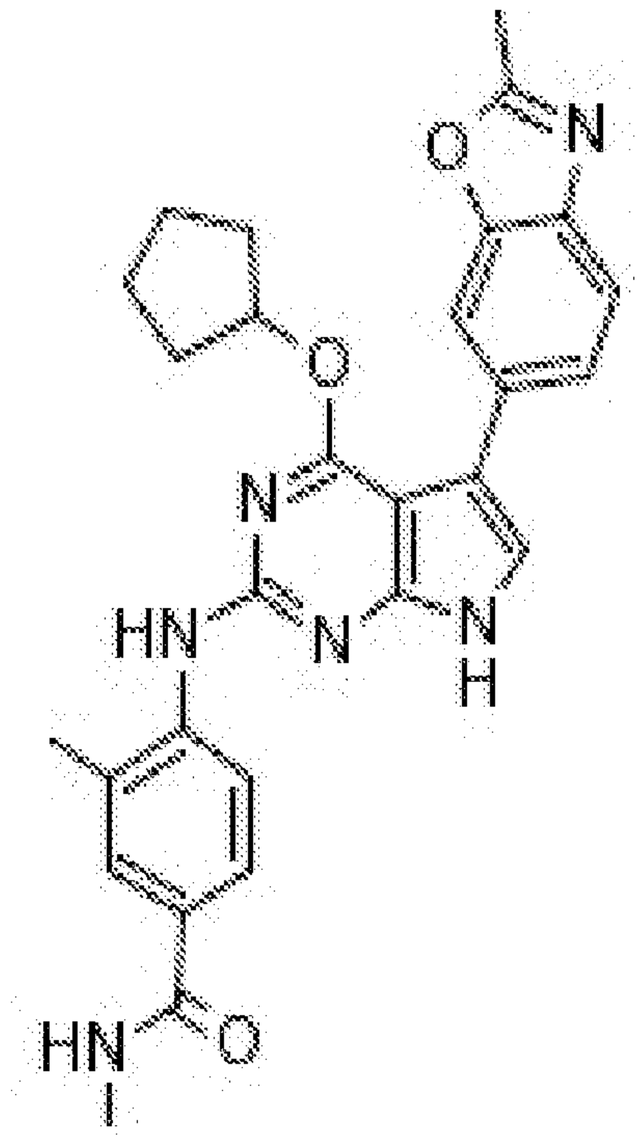
Cmpd No.	Structure	Name
80		4-(4-(cyclopentyloxy)-5-(1H-pyrazol-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
81		4-(4-(cyclopentyloxy)-5-(1H-indol-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
82		4-(4-(cyclopentyloxy)-5-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

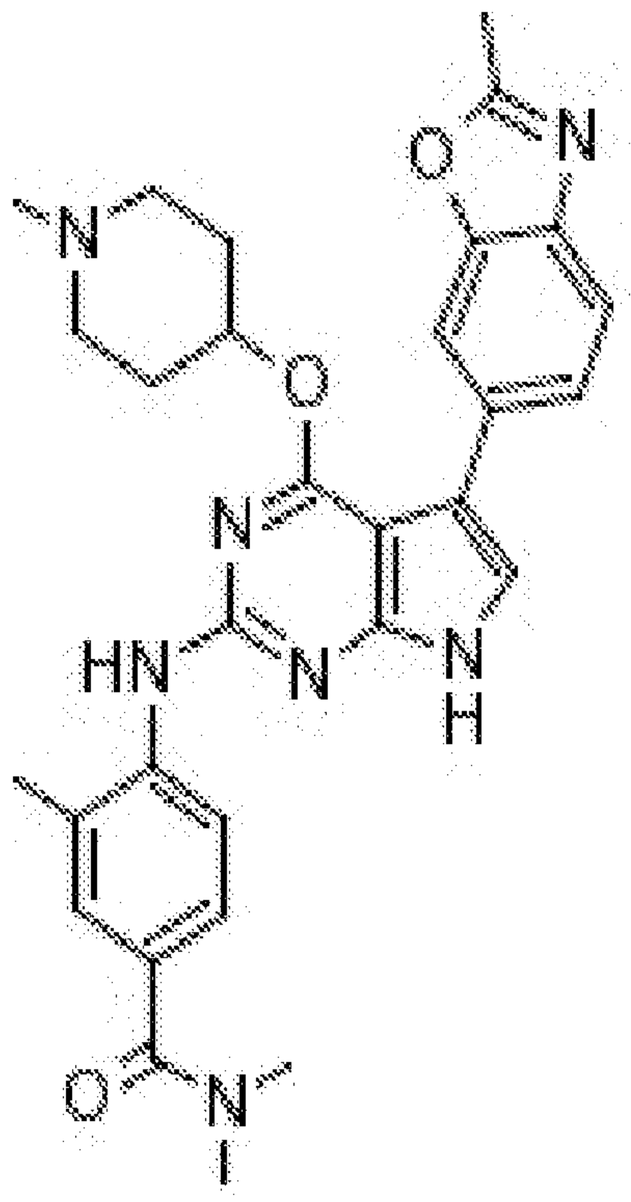
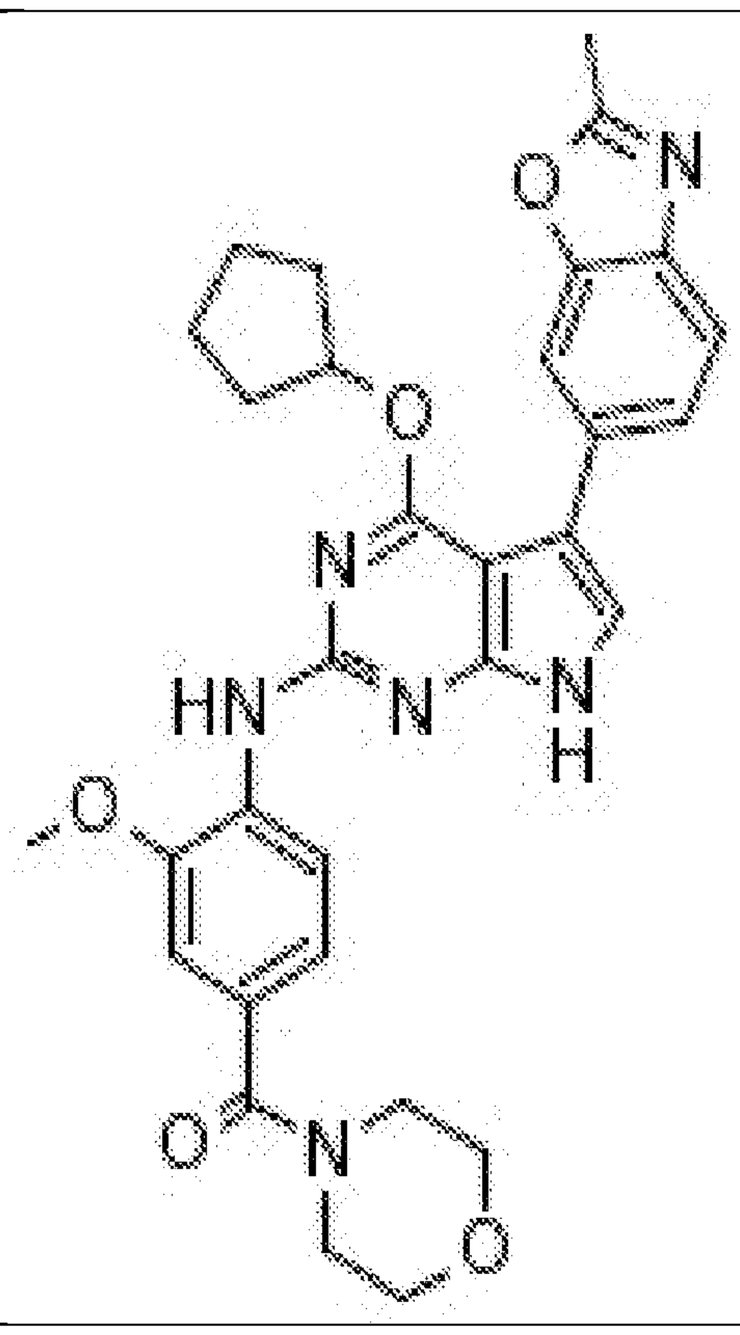
Cmpd No.	Structure	Name
83		3-chloro-4-(4-methoxy-5-(2-methyl-1H-benzo[d]imidazol-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N-dimethylbenzamide
84		(R)-3-chloro-4-(5-(3-(1-hydroxyethyl)phenyl)-4-(tetrahydro-2H-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N-dimethylbenzamide
85		(S)-3-chloro-4-(5-(3-(1-hydroxyethyl)phenyl)-4-(tetrahydro-2H-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N-dimethylbenzamide

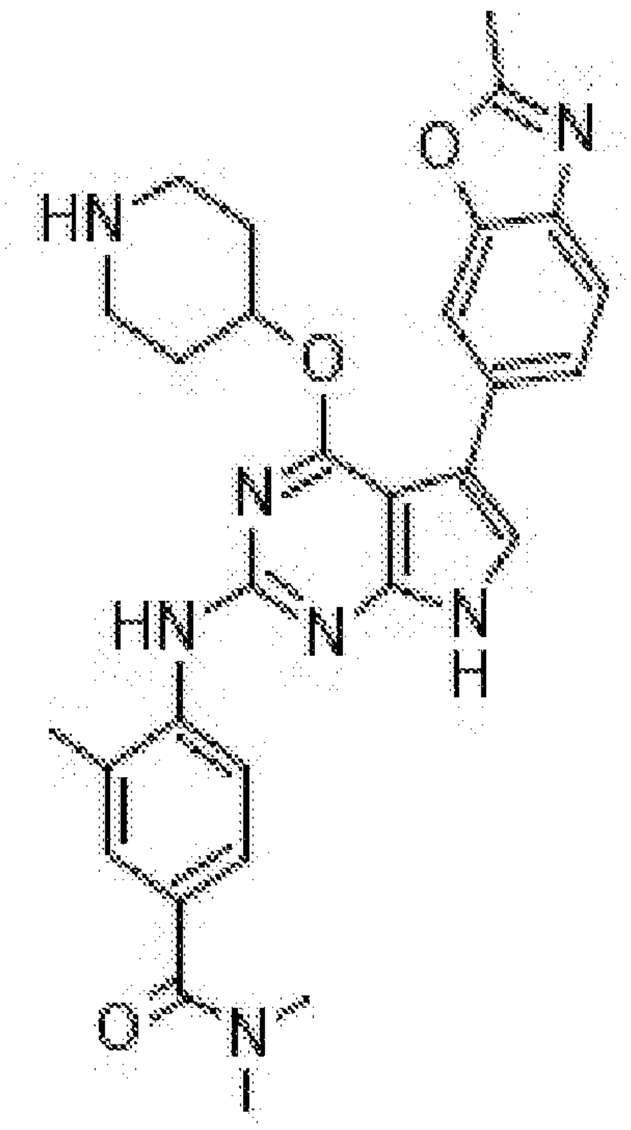
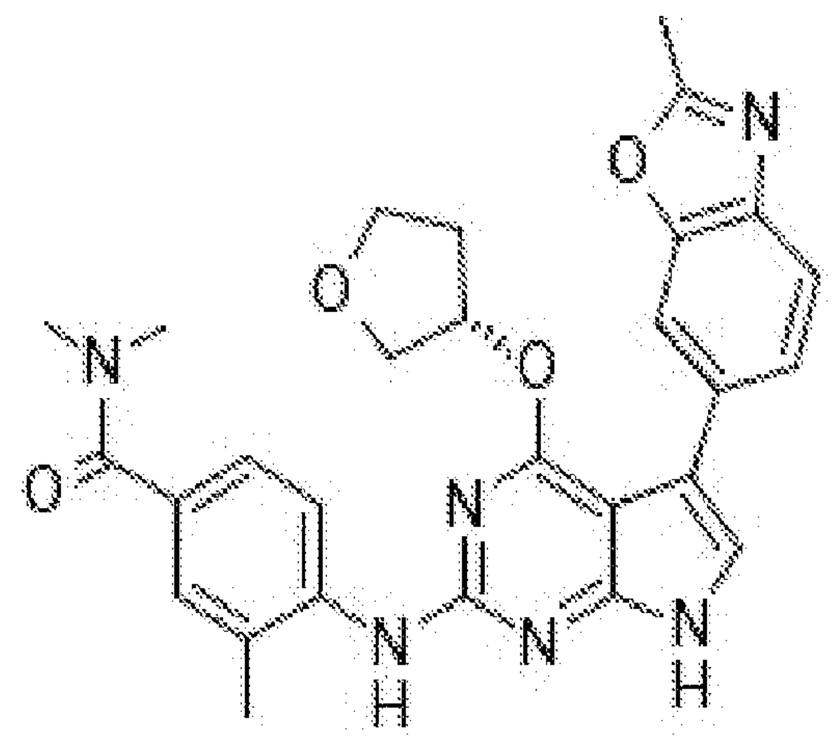
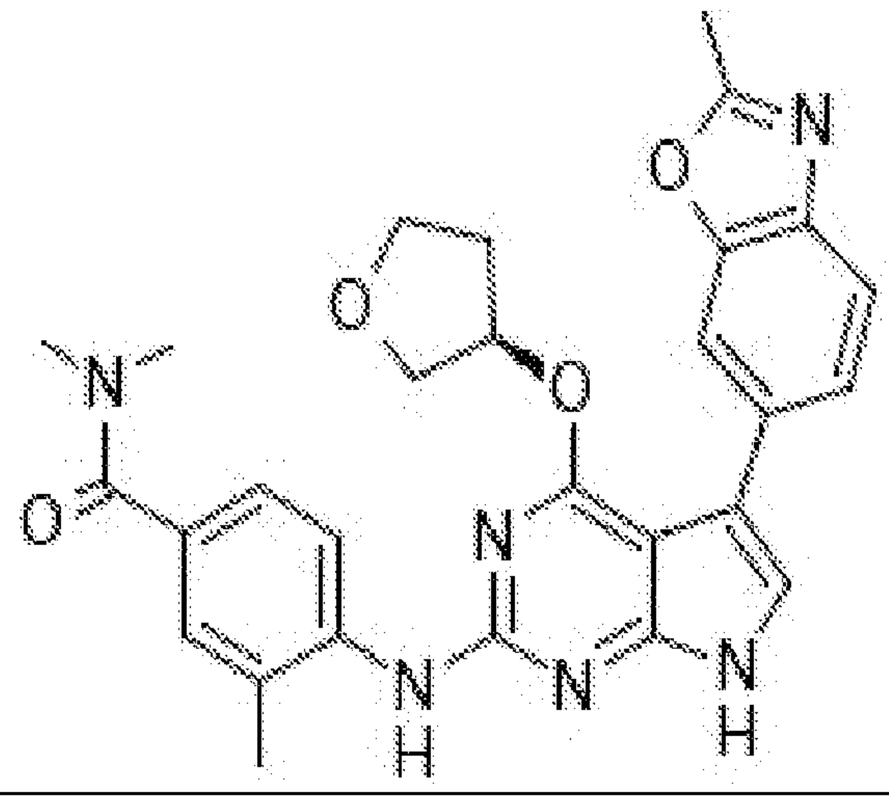
Cmpd No.	Structure	Name
86		(4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methylphenyl)(morpholino) methanone
87		N-(1H-indazol-5-yl)-4-methoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine

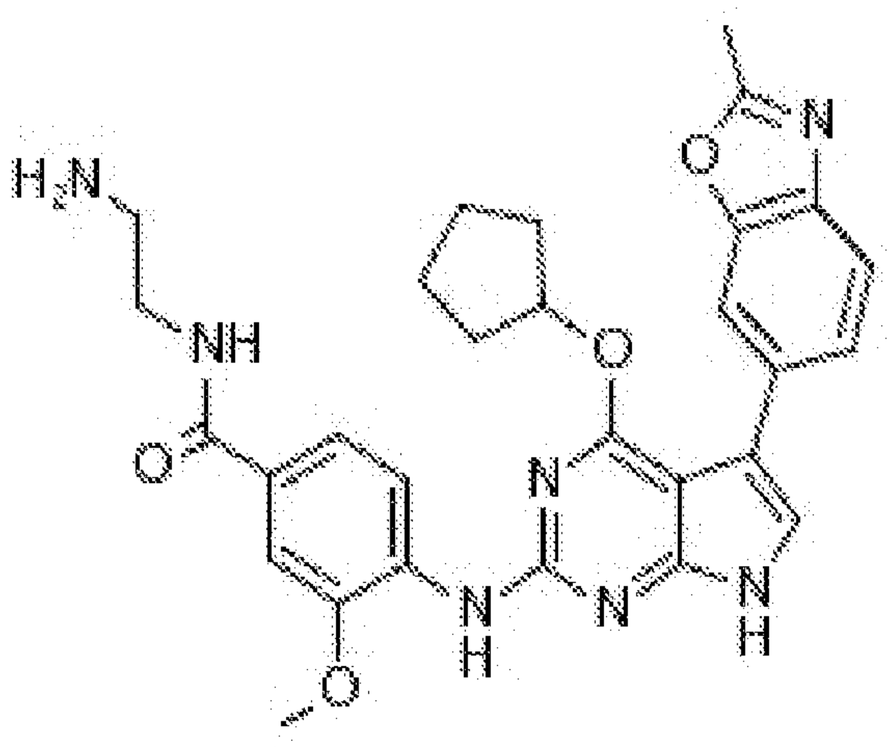
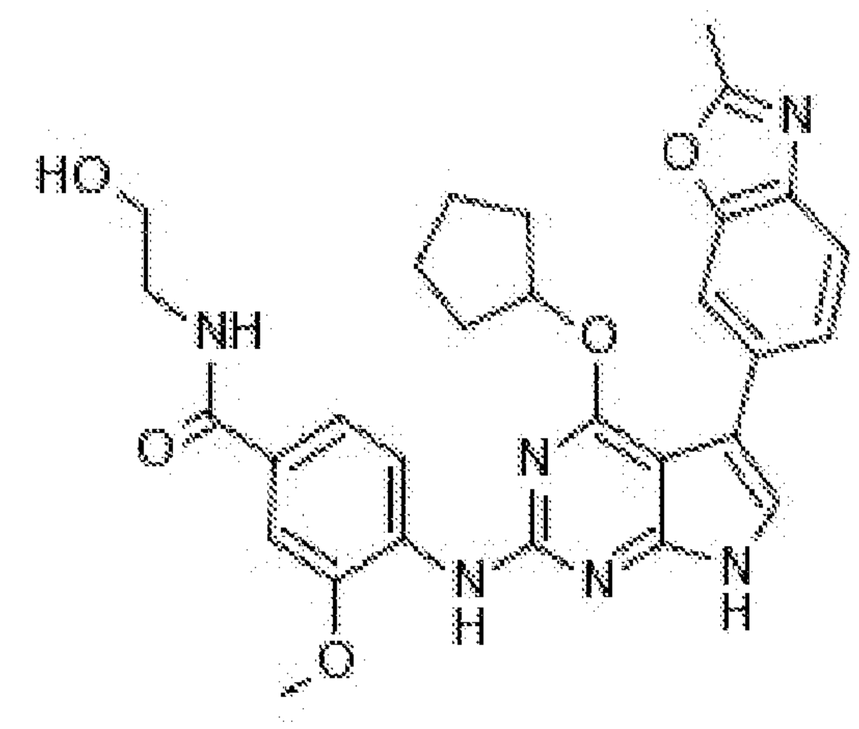
Cmpd No.	Structure	Name
88		N-(4-(1H-pyrazol-4-yl)phenyl)-4-methoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine
89		4-(4-methoxy-5-(pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N,3-trimethylbenzamide
90		3-methoxy-N-methyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

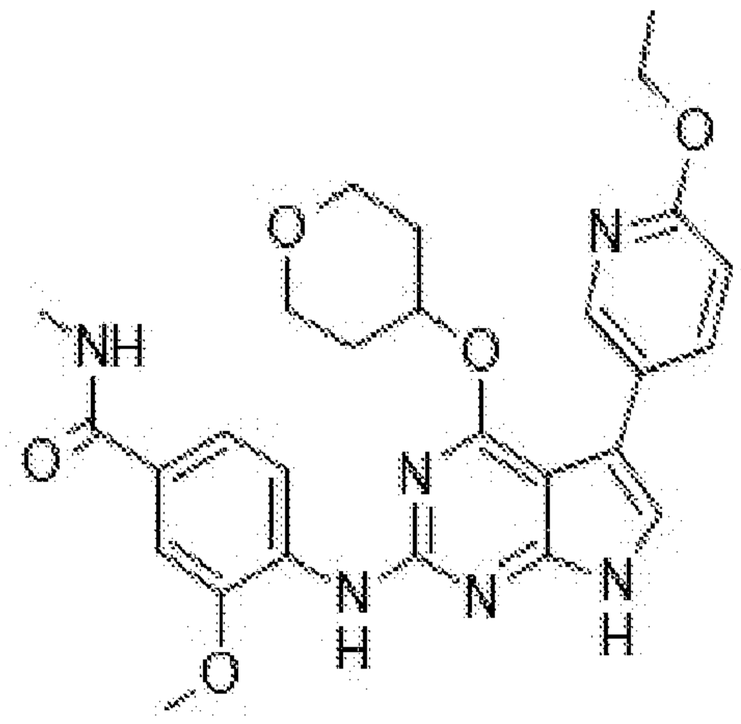
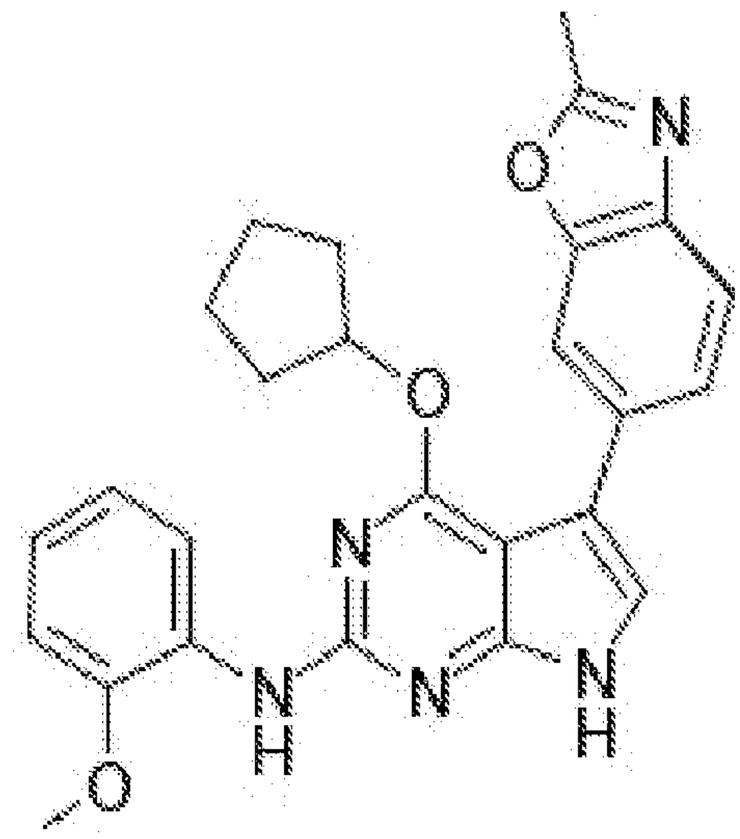
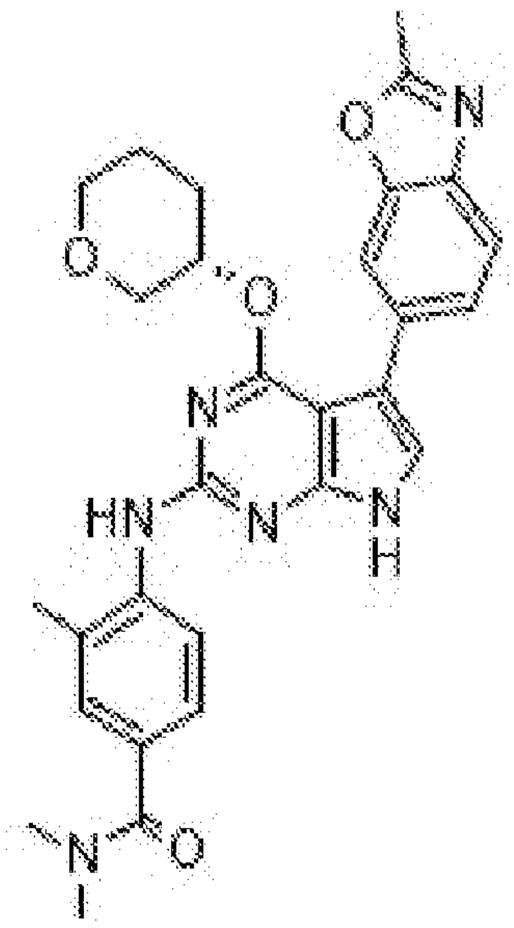
Cmpd No.	Structure	Name
91		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N,N-dimethylbenzamide
92		4-(4-((1r,4r)-4-hydroxycyclohexyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N,3-trimethylbenzamide

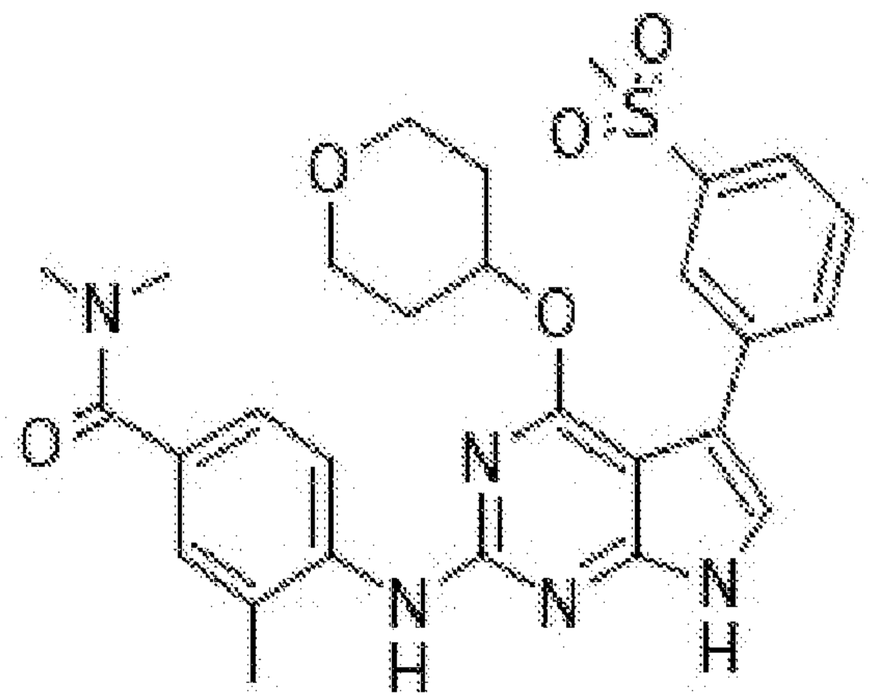
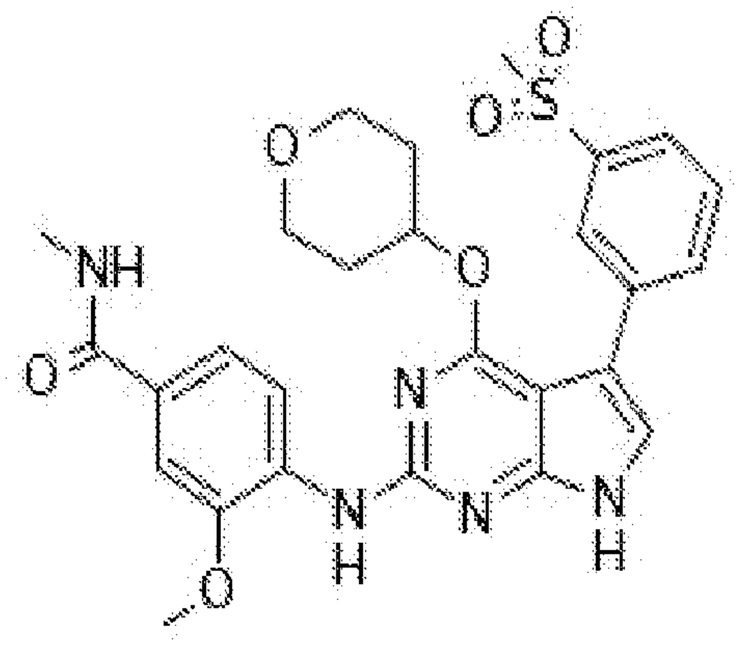
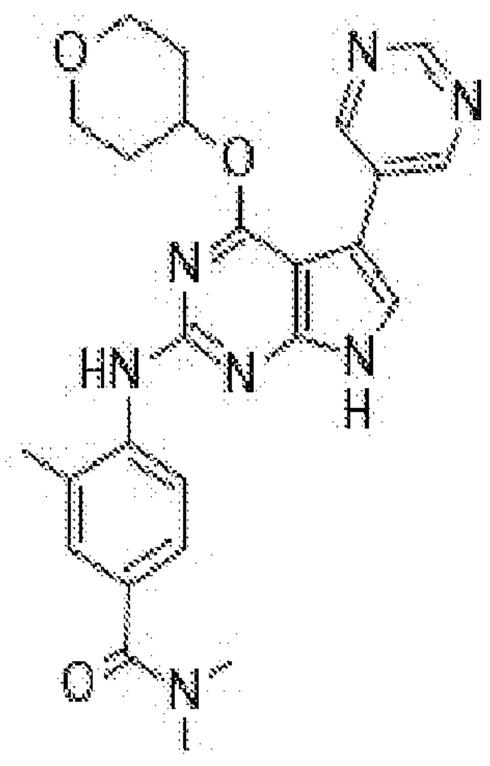
Cmpd No.	Structure	Name
93		N,N,3-trimethyl-4-(5-(pyridin-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
94		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,3-dimethylbenzamide

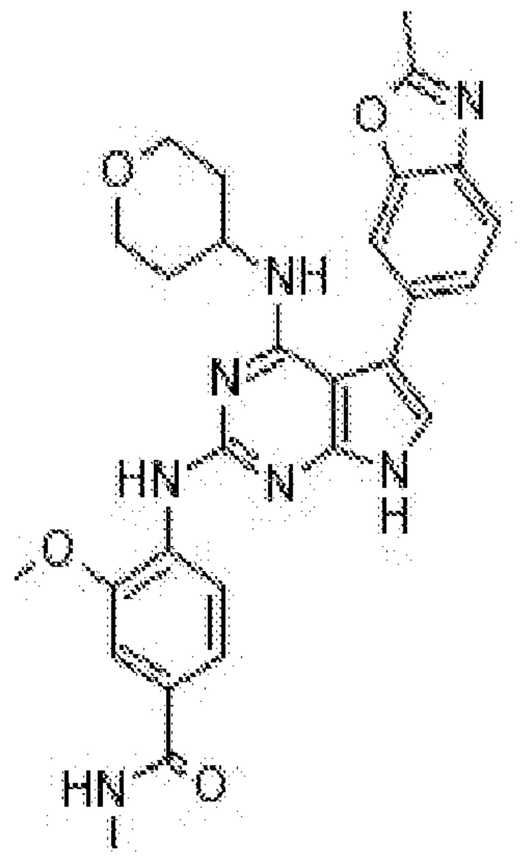
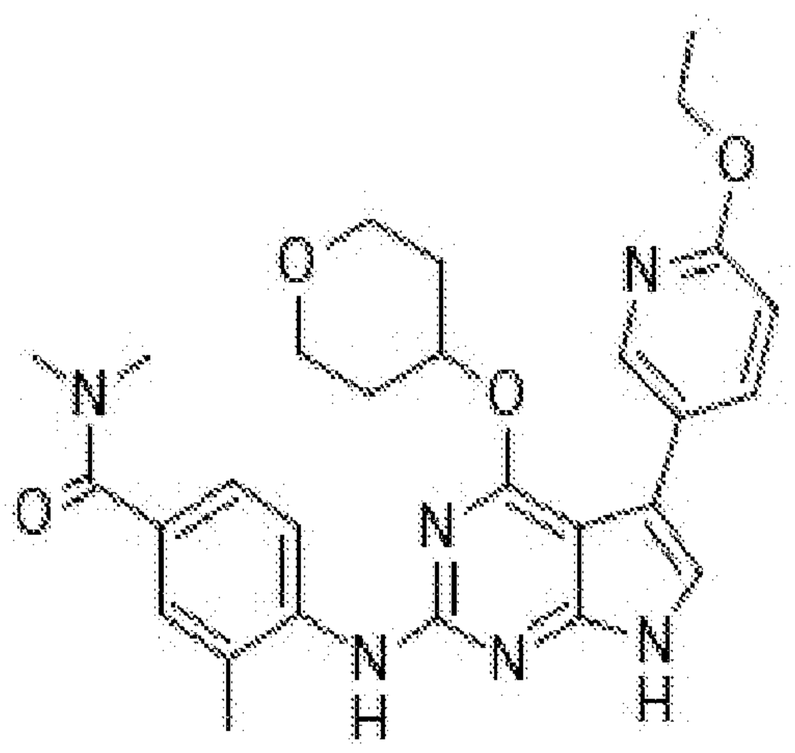
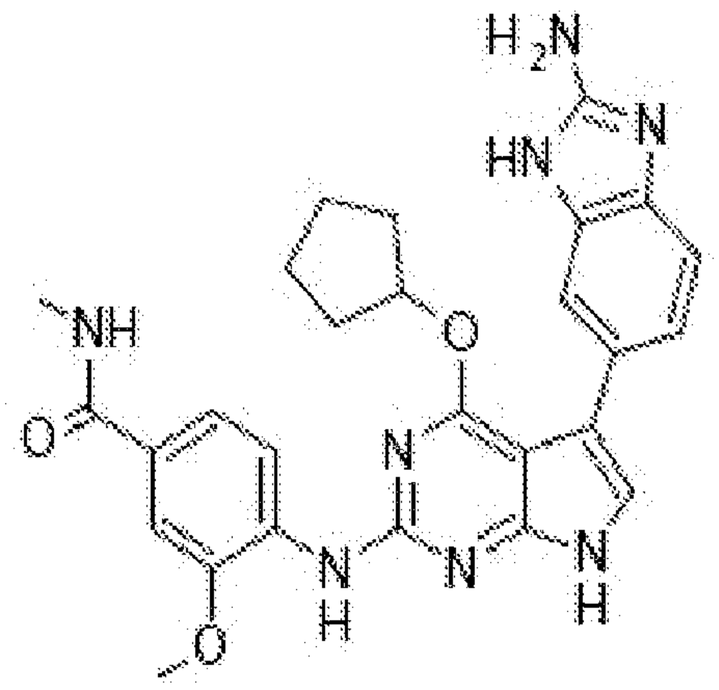
Cmpd No.	Structure	Name
95		N,N,3-trimethyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(1-methylpiperidin-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
96		(4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxyphenyl)(morpholino)methanone

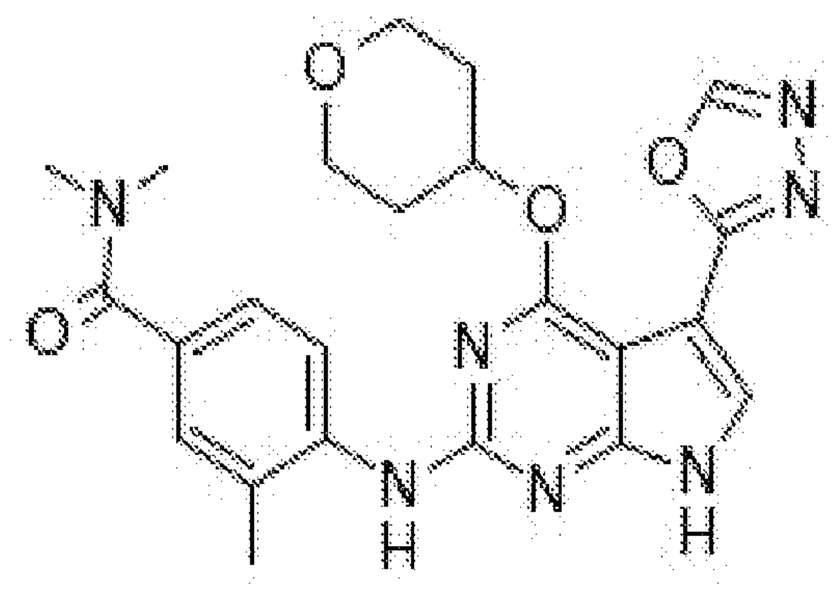
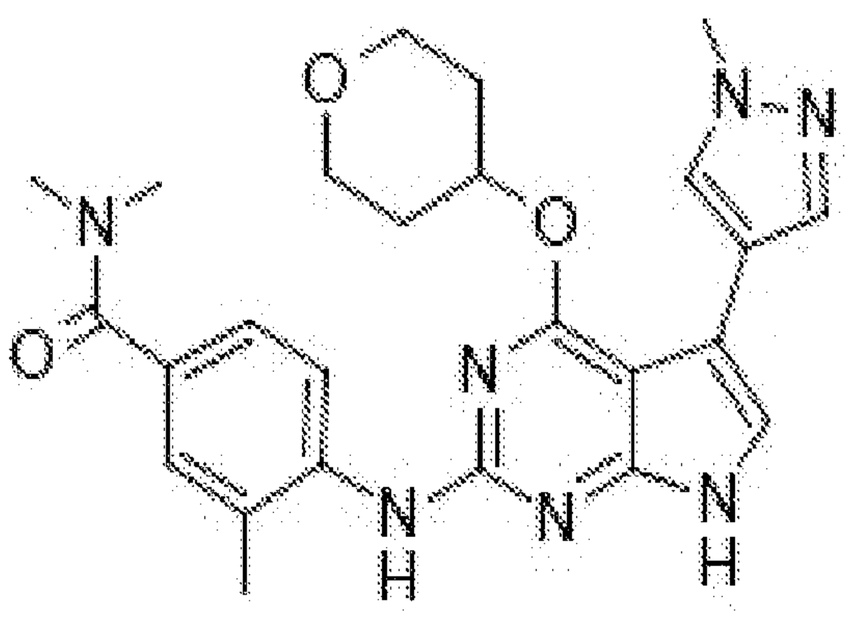
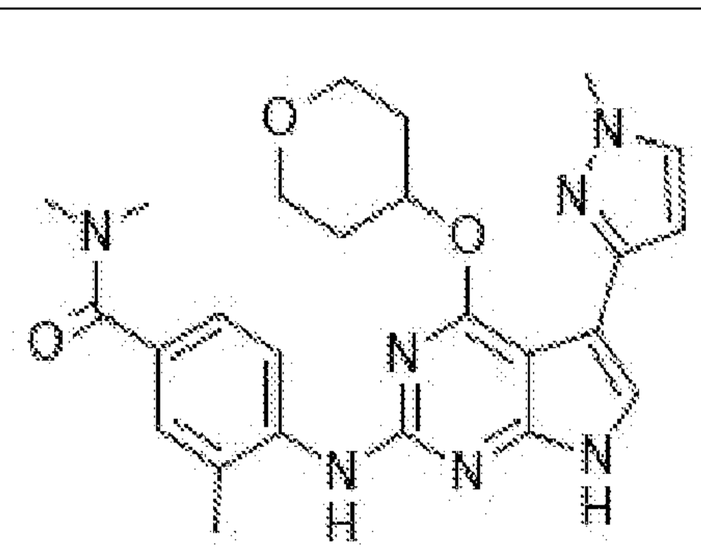
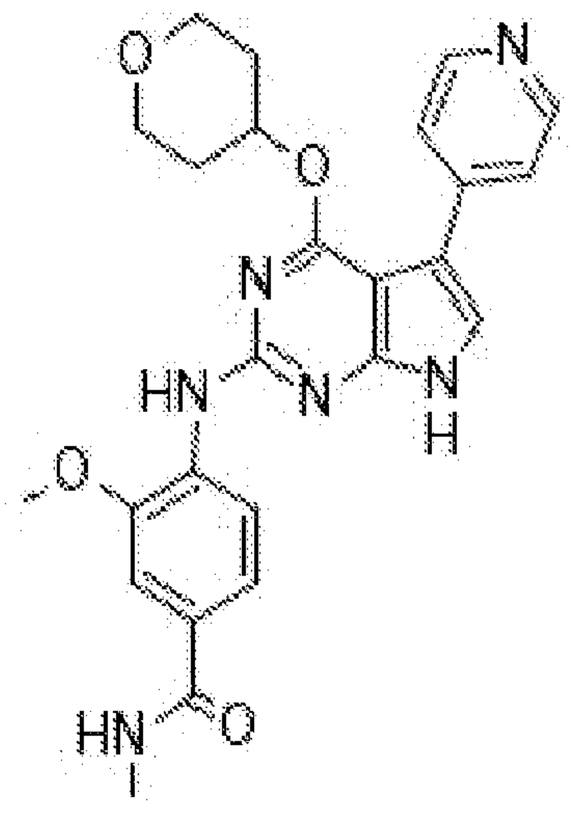
Cmpd No.	Structure	Name
97		N,N,3-trimethyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(piperidin-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
98		(S)-N,N,3-trimethyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
99		(R)-N,N,3-trimethyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

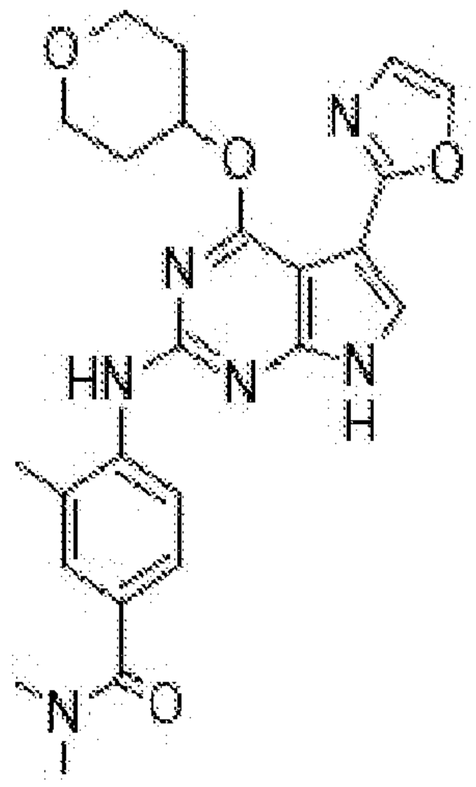
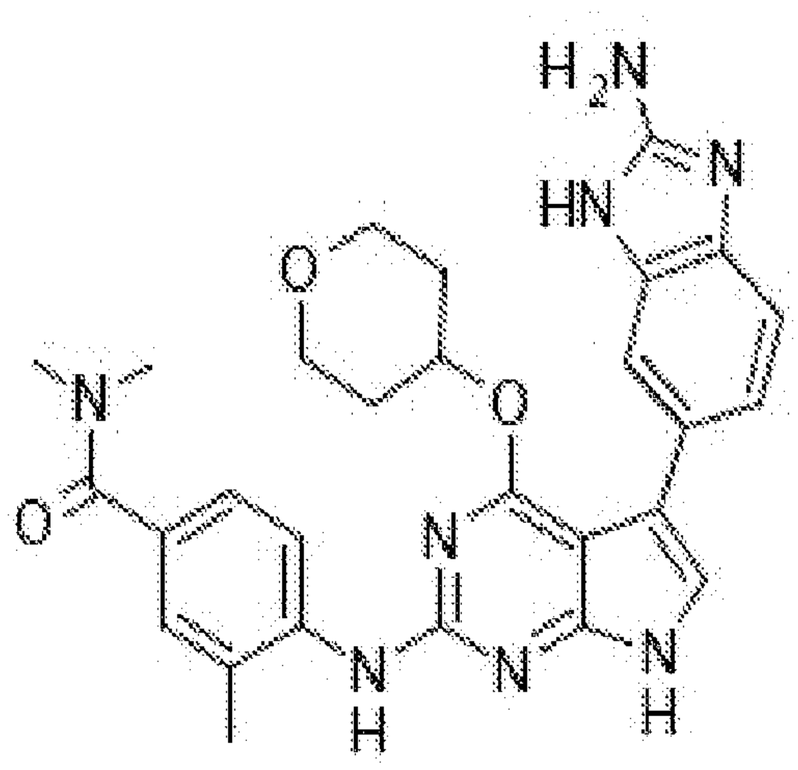
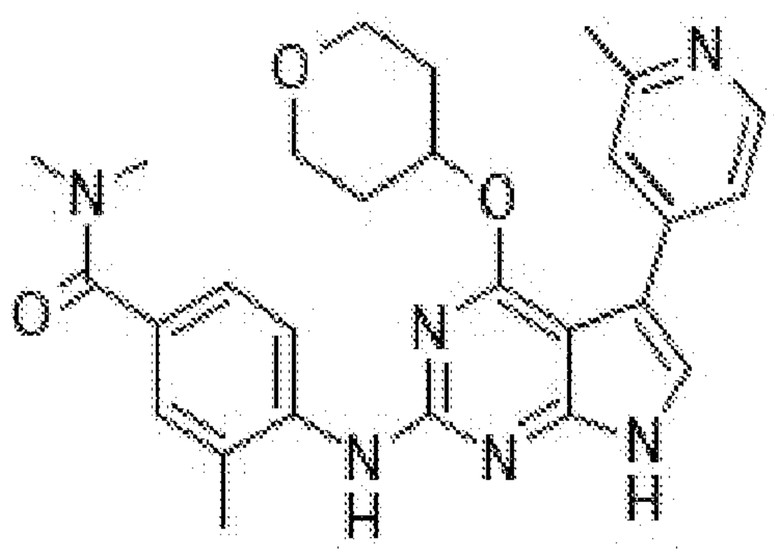
Cmpd No.	Structure	Name
100		N-(2-aminoethyl)-4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxybenzamide
101		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(2-hydroxyethyl)-3-methoxybenzamide

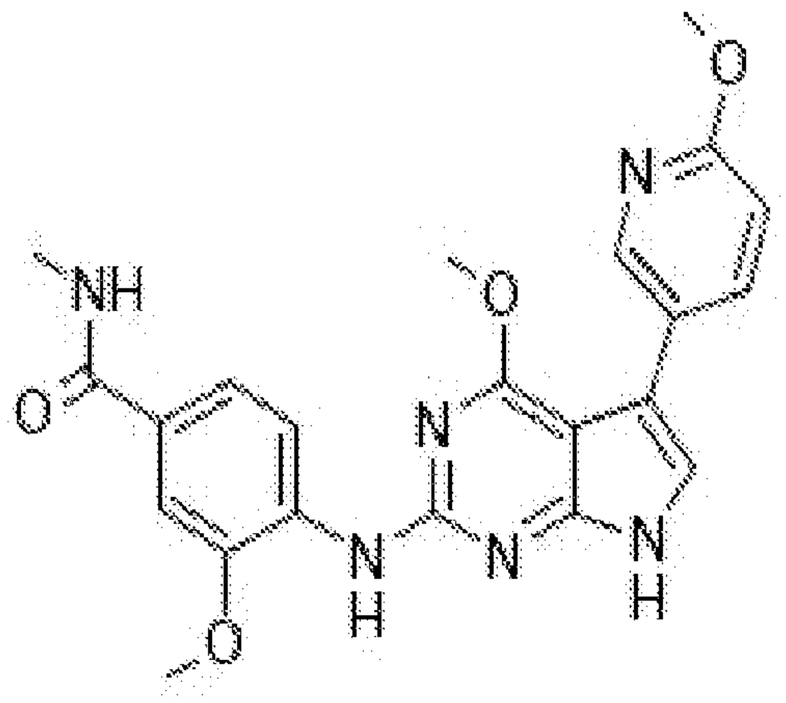
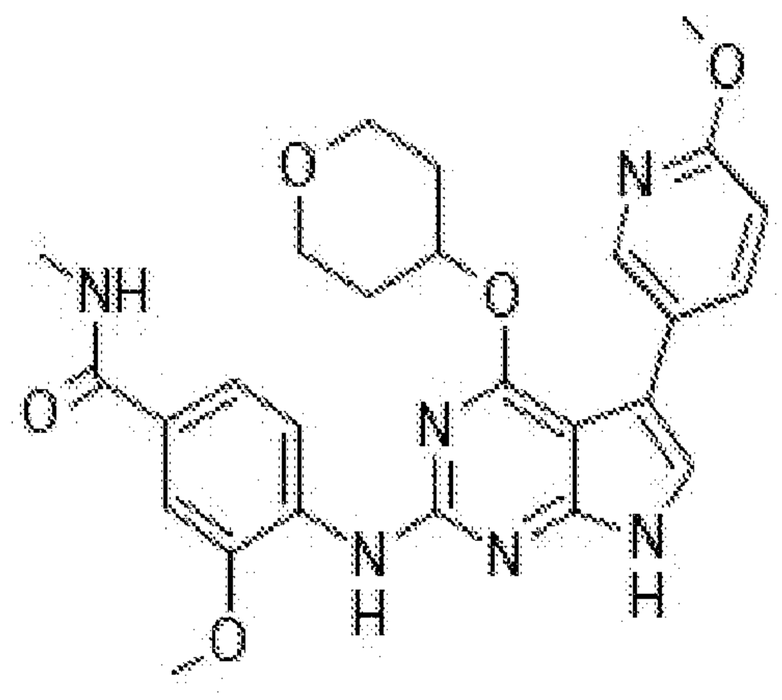
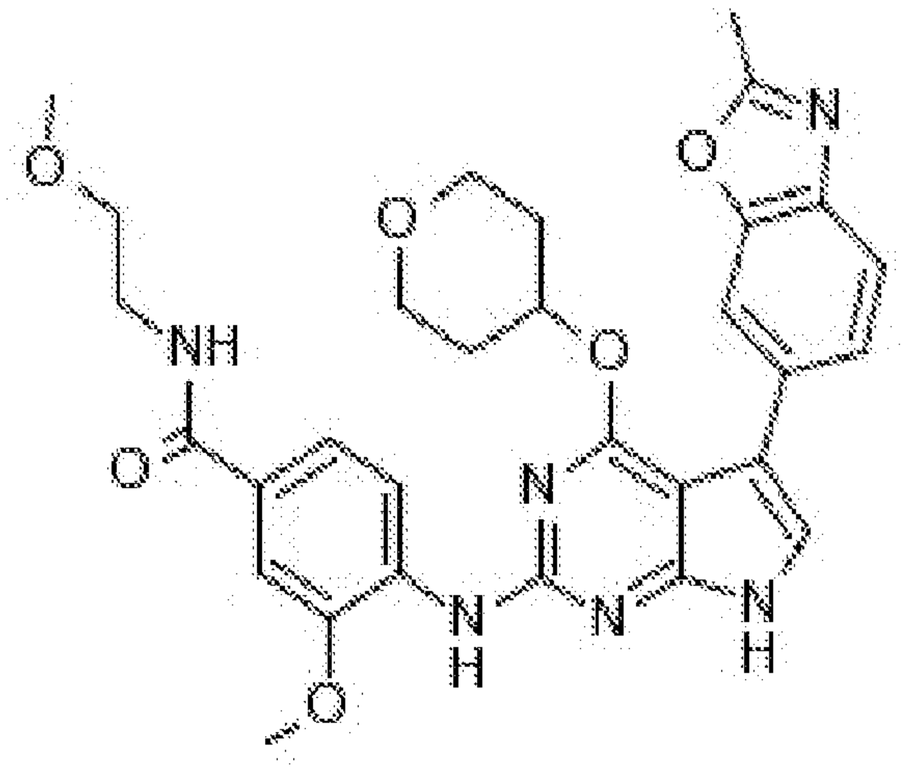
Cmpd No.	Structure	Name
102		4-(5-(6-ethoxypyridin-3-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
103		4-(cyclopentyloxy)-N-(2-methoxyphenyl)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine
104		(S)-N,N,3-trimethyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

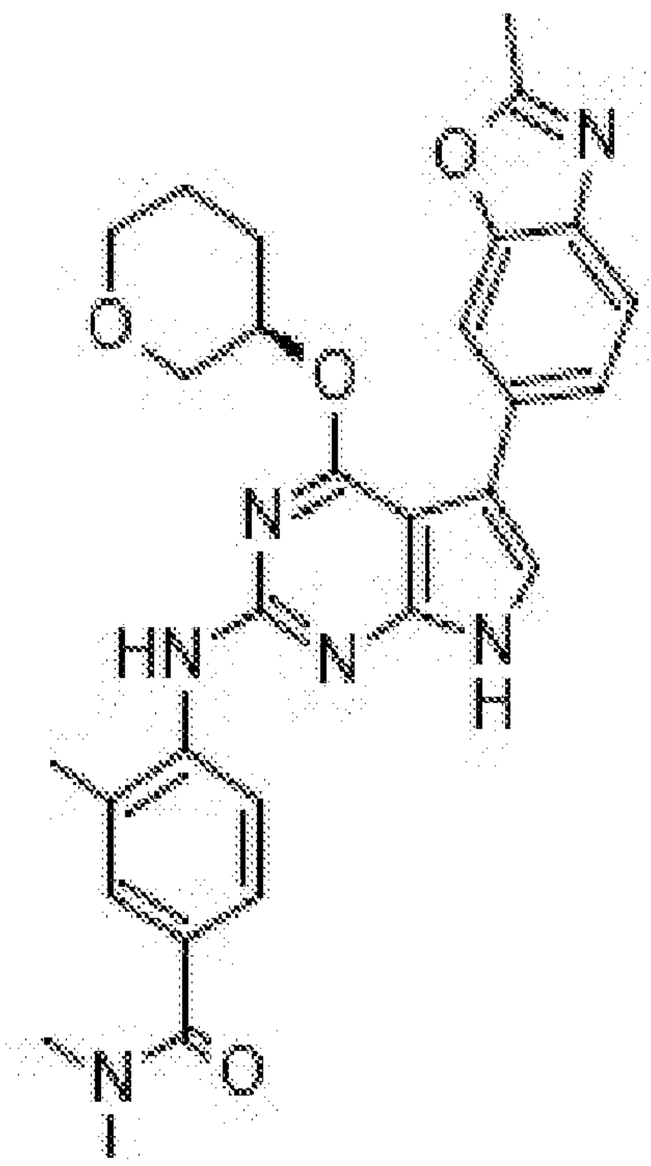
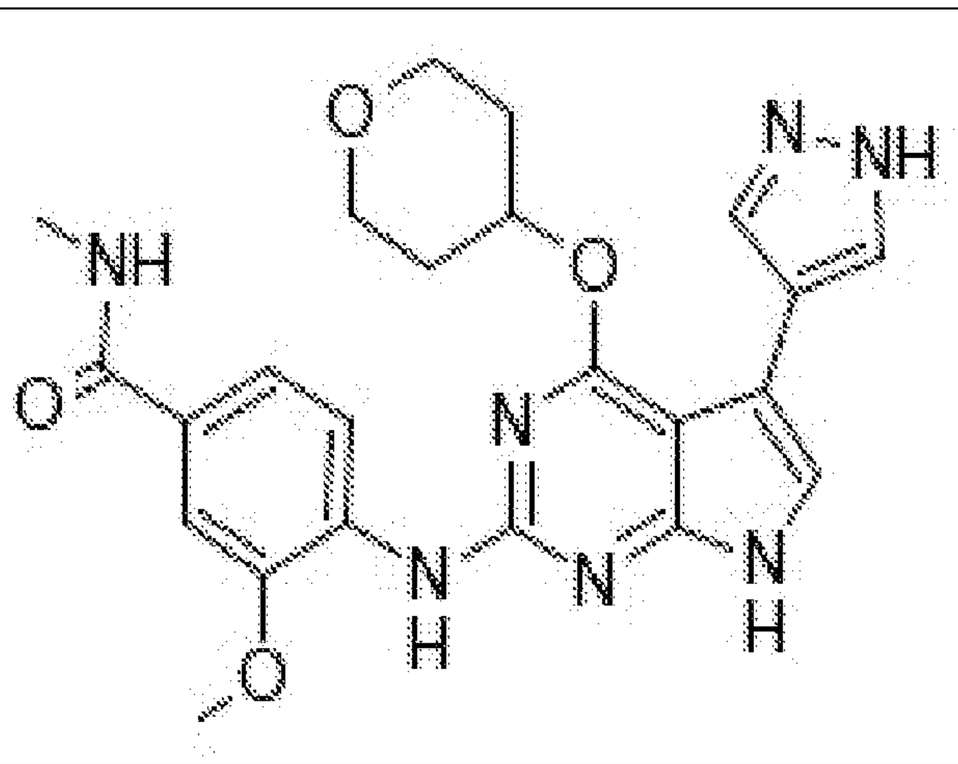
Cmpd No.	Structure	Name
105		N,N,3-trimethyl-4-(5-(3-(methylsulfonyl)phenyl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
106		3-methoxy-N-methyl-4-(5-(3-(methylsulfonyl)phenyl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
107		N,N,3-trimethyl-4-(5-(pyrimidin-5-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

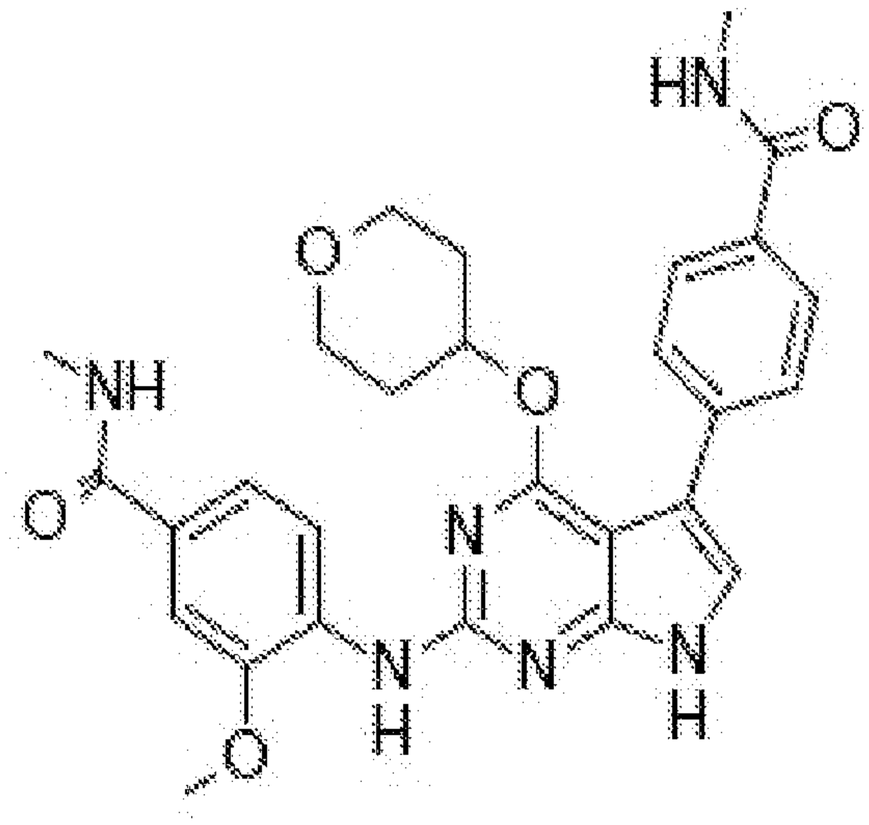
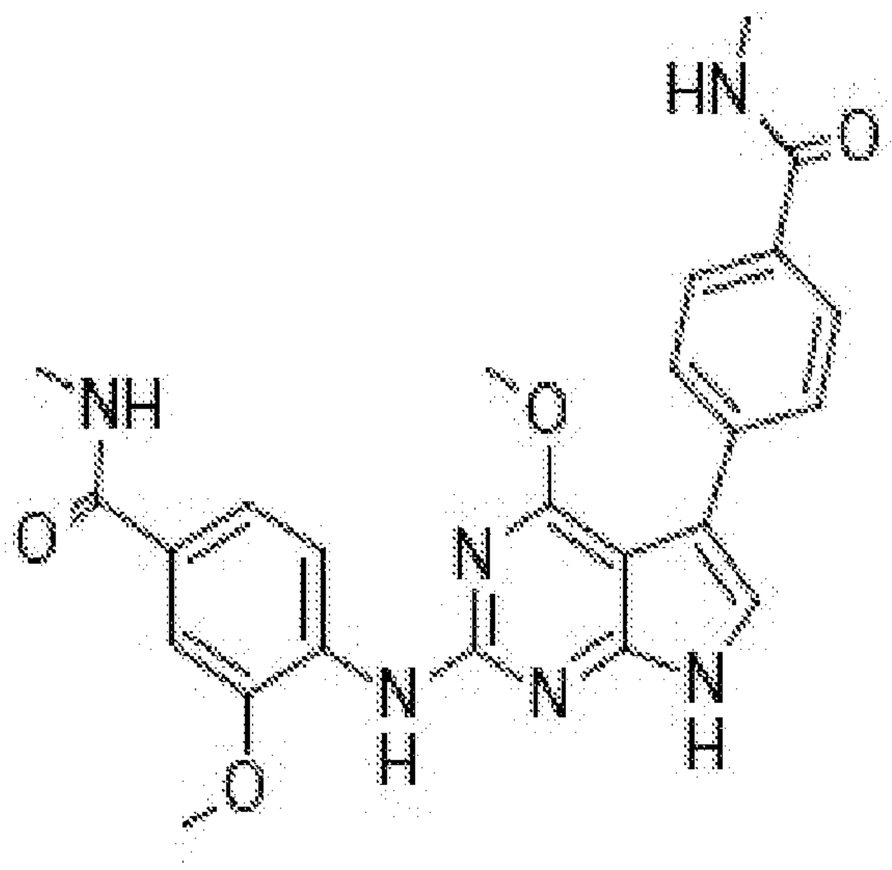
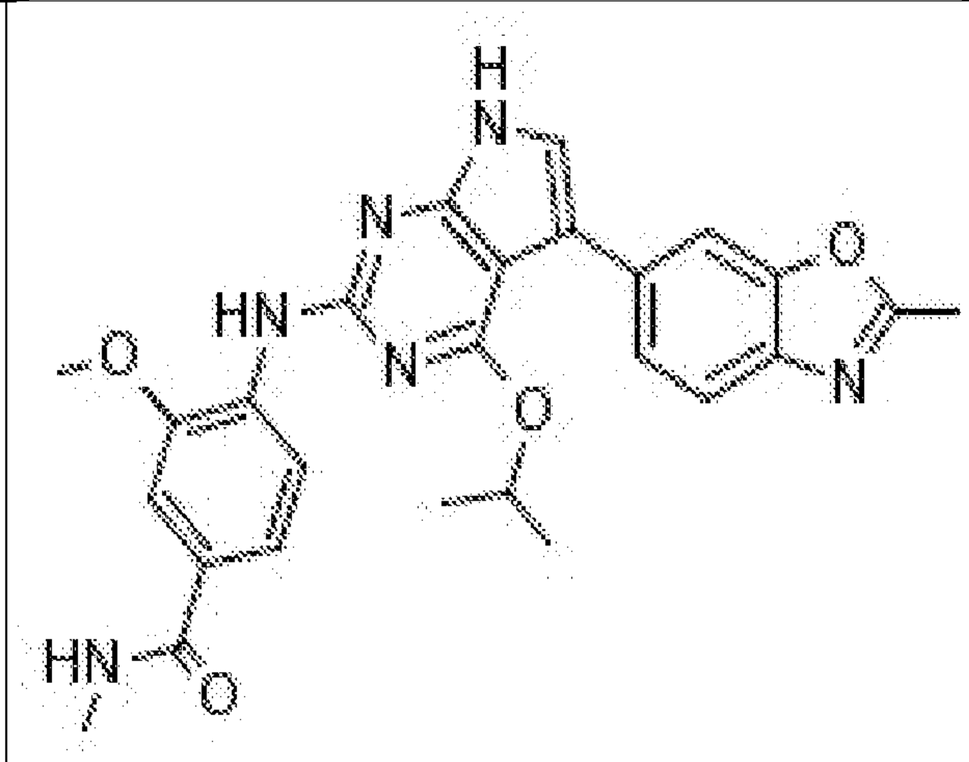
Cmpd No.	Structure	Name
108		3-methoxy-N-methyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
109		4-(5-(6-ethoxypyridin-3-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N,3-trimethylbenzamide
110		4-(5-(2-amino-1H-benzo[d]imidazol-6-yl)-4-(cyclopentyloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

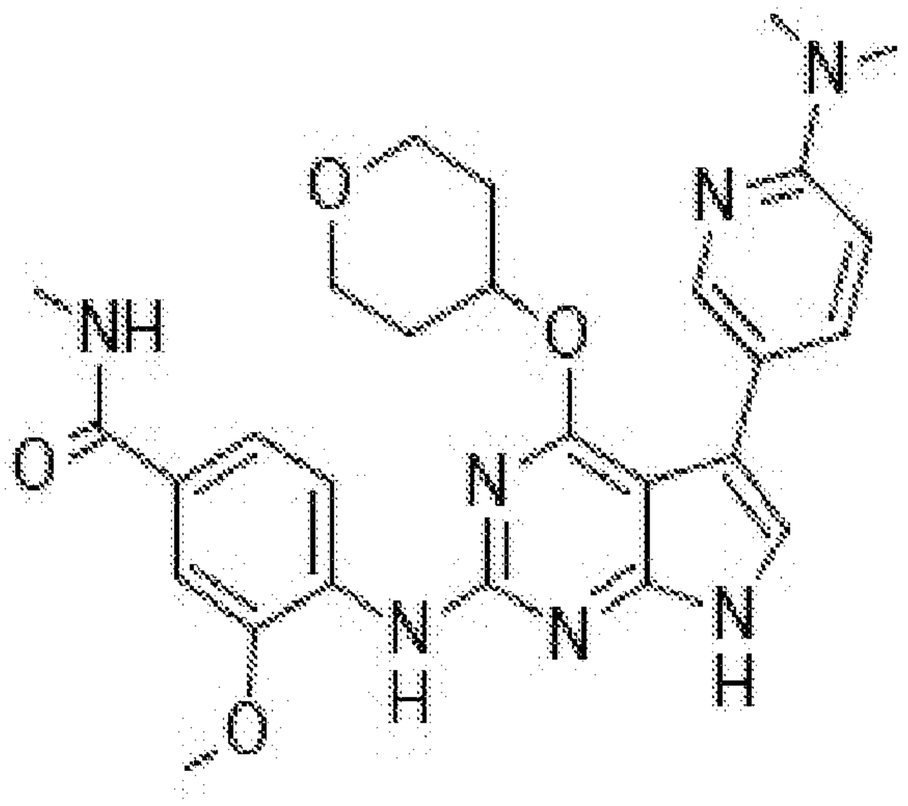
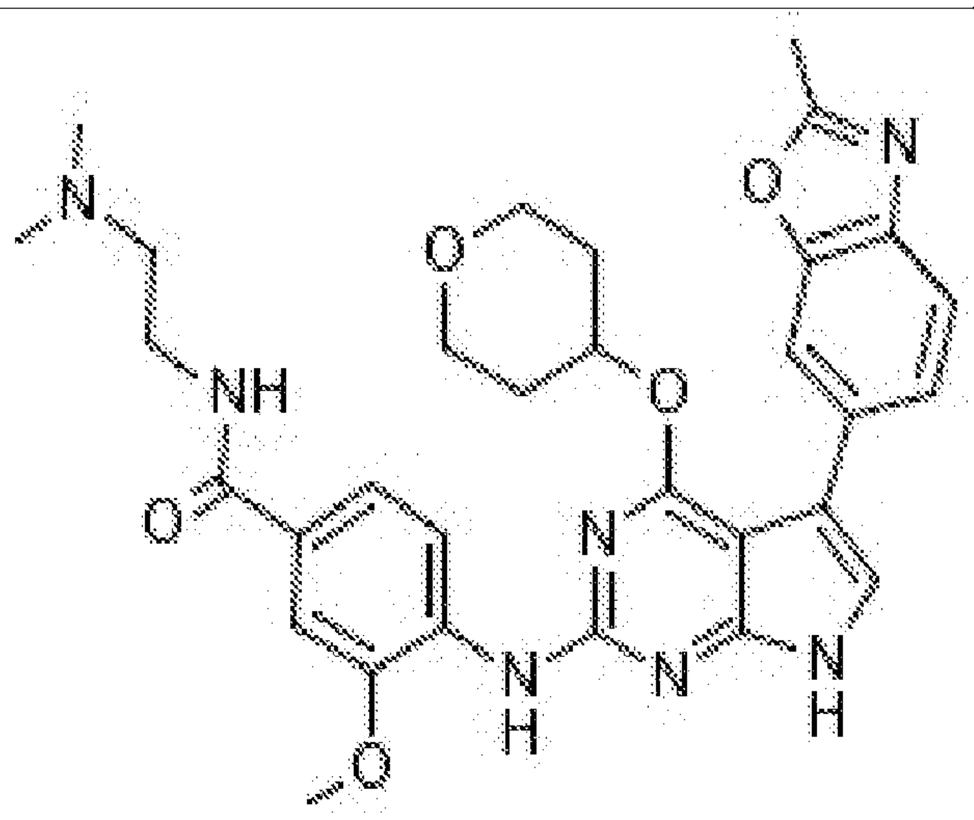
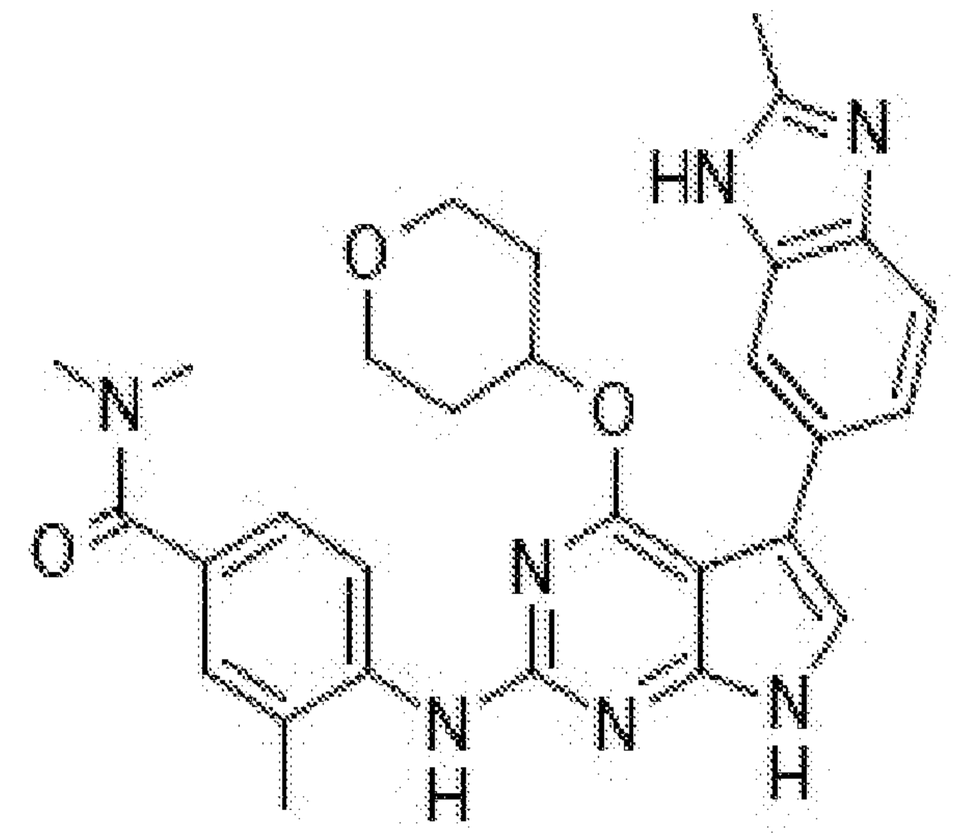
Cmpd No.	Structure	Name
111		4-(5-(1,3,4-oxadiazol-2-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N,3-trimethylbenzamide
112		N,N,3-trimethyl-4-(5-(1-methyl-1H-pyrazol-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
113		N,N,3-trimethyl-4-(5-(1-methyl-1H-pyrazol-3-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
114		3-methoxy-N-methyl-4-(5-(pyridin-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

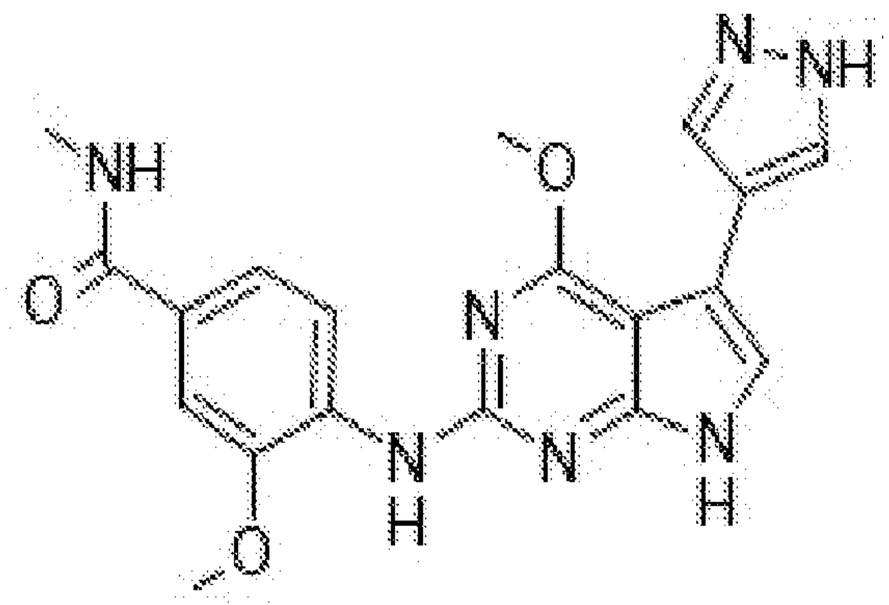
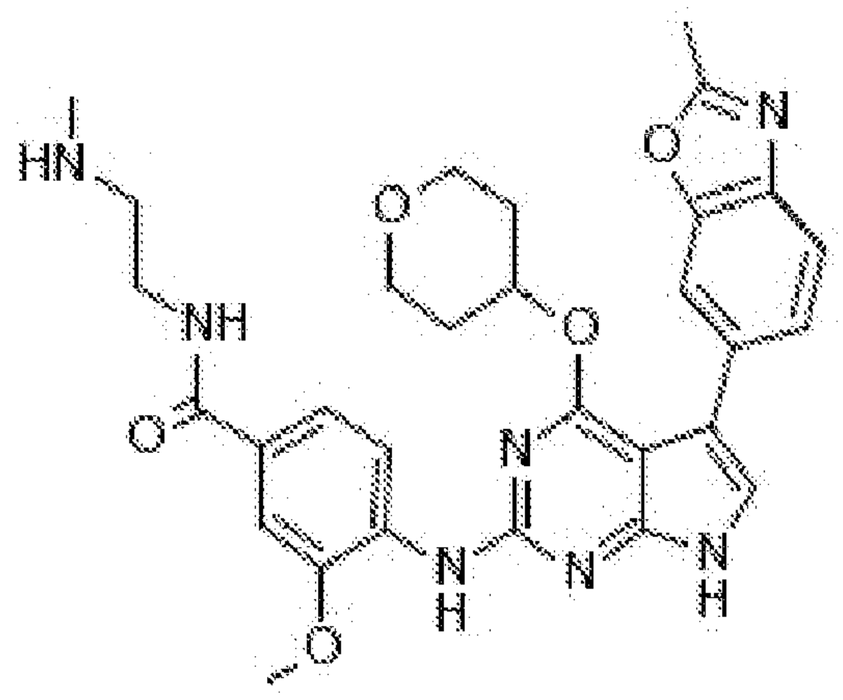
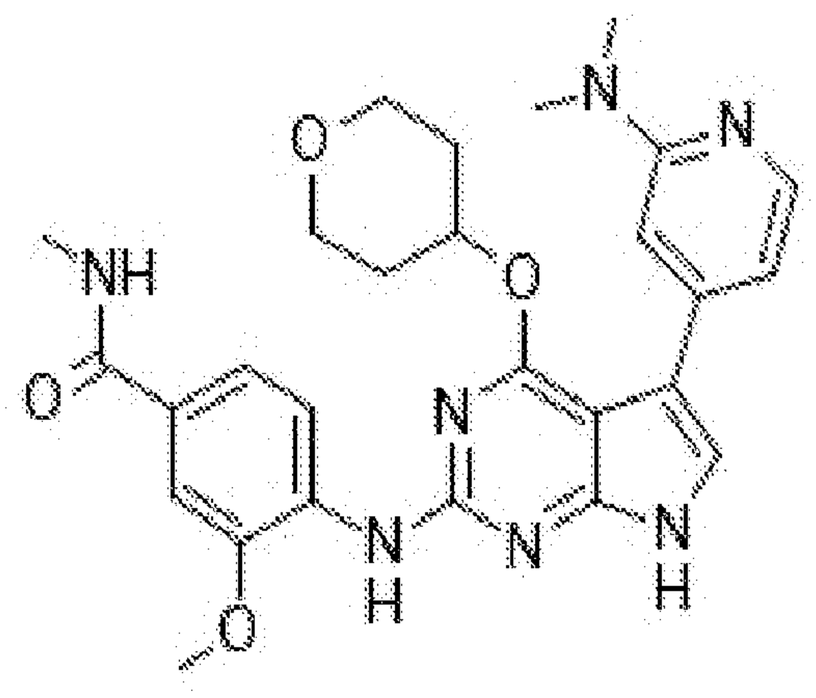
Cmpd No.	Structure	Name
115		N,N,3-trimethyl-4-(5-(oxazol-2-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
116		4-(5-(2-amino-1H-benzo[d]imidazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N,3-trimethylbenzamide
117		N,N,3-trimethyl-4-(5-(2-methylpyridin-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

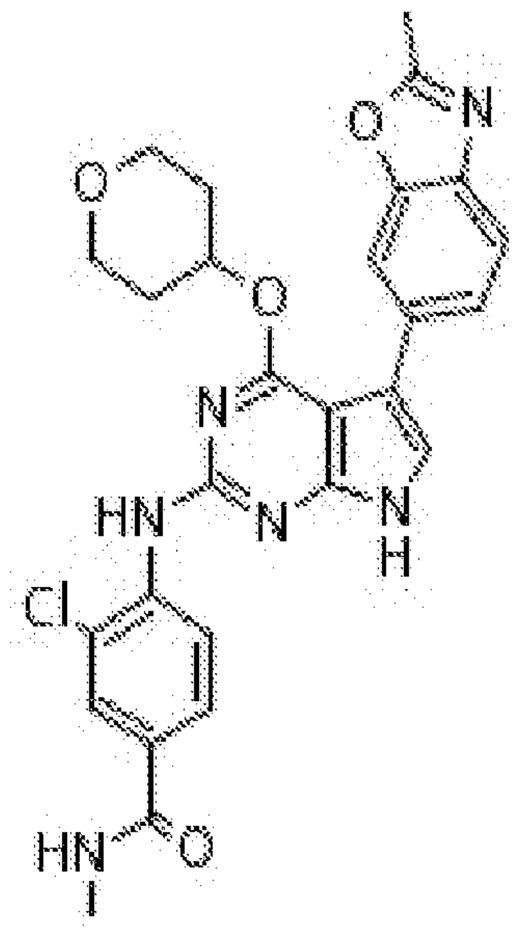
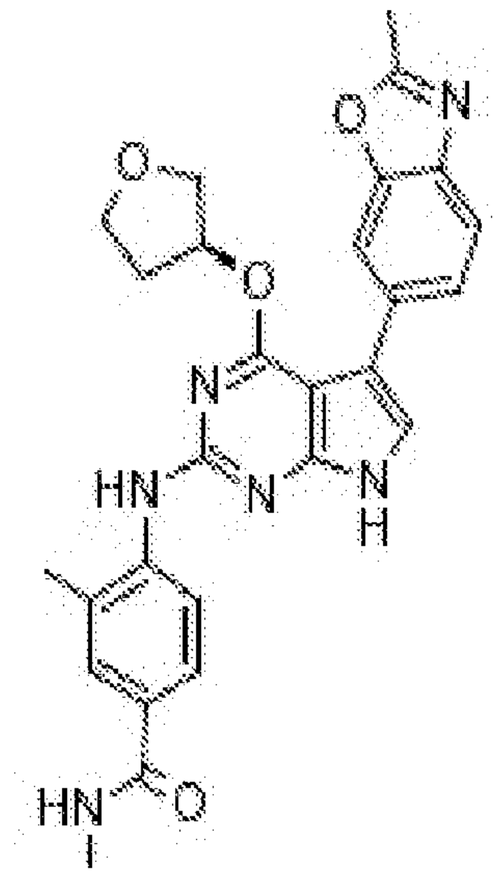
Cmpd No.	Structure	Name
118		3-methoxy-4-(4-methoxy-5-(6-methoxypyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide
119		3-methoxy-4-(5-(6-methoxypyridin-3-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide
120		3-methoxy-N-(2-methoxyethyl)-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

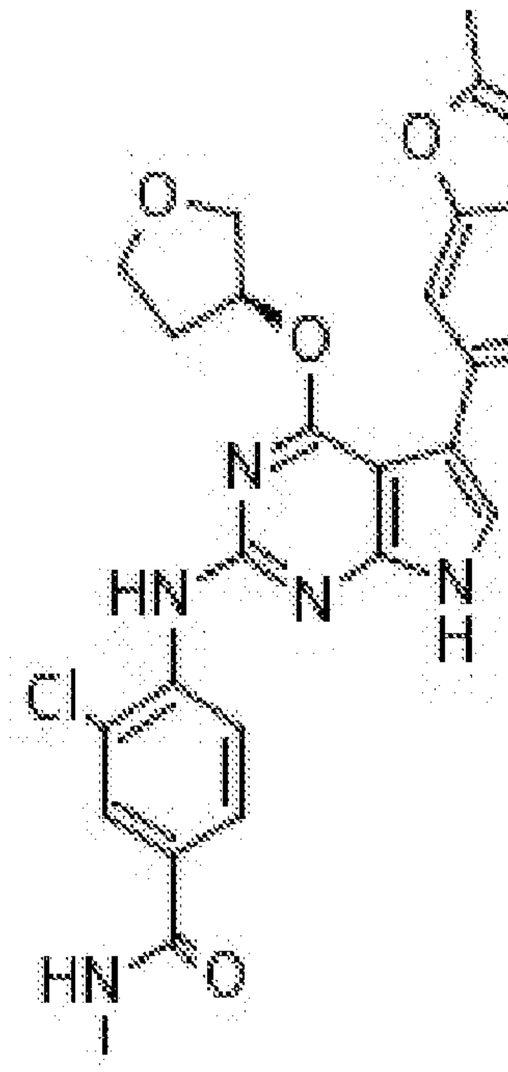
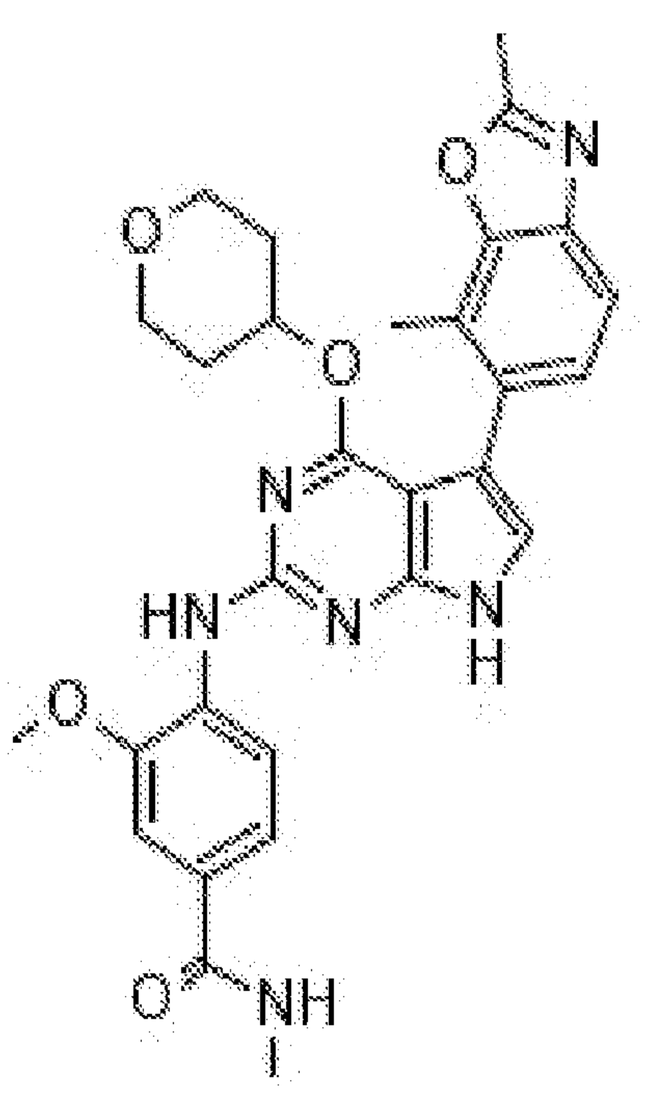
Cmpd No.	Structure	Name
121		(R)-N,N,3-trimethyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
122		4-(5-(1H-pyrazol-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

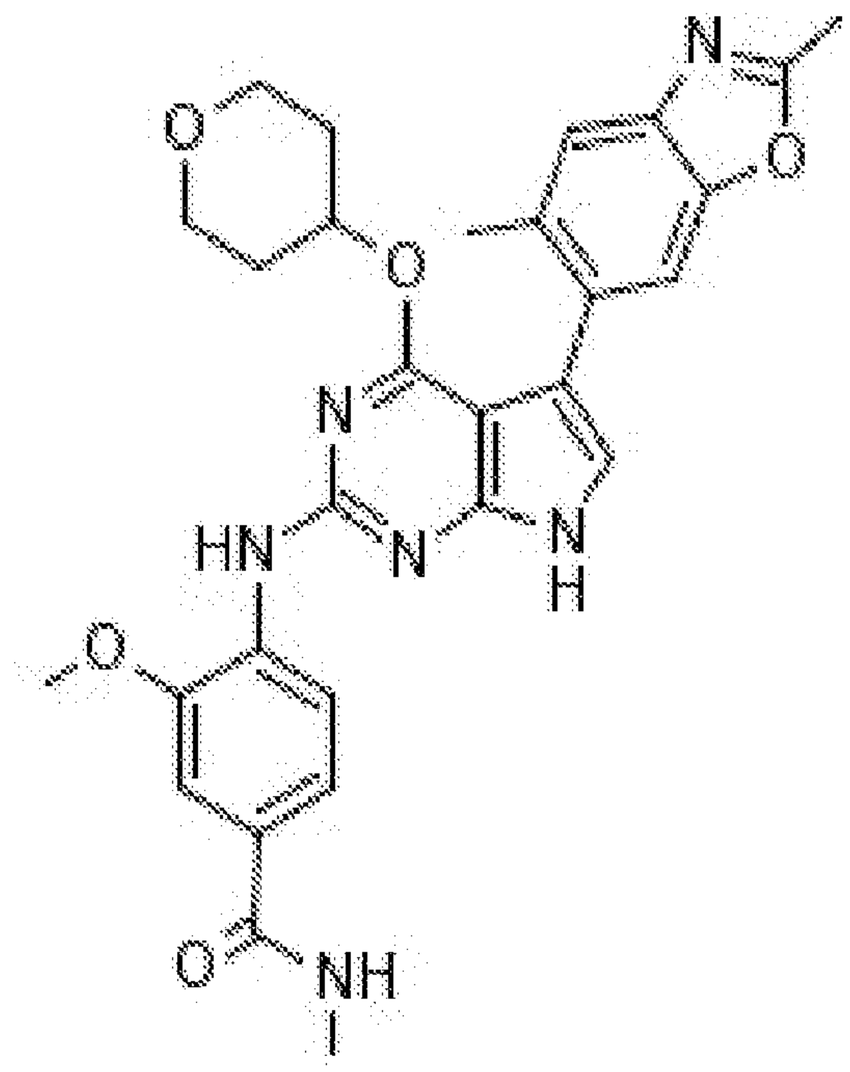
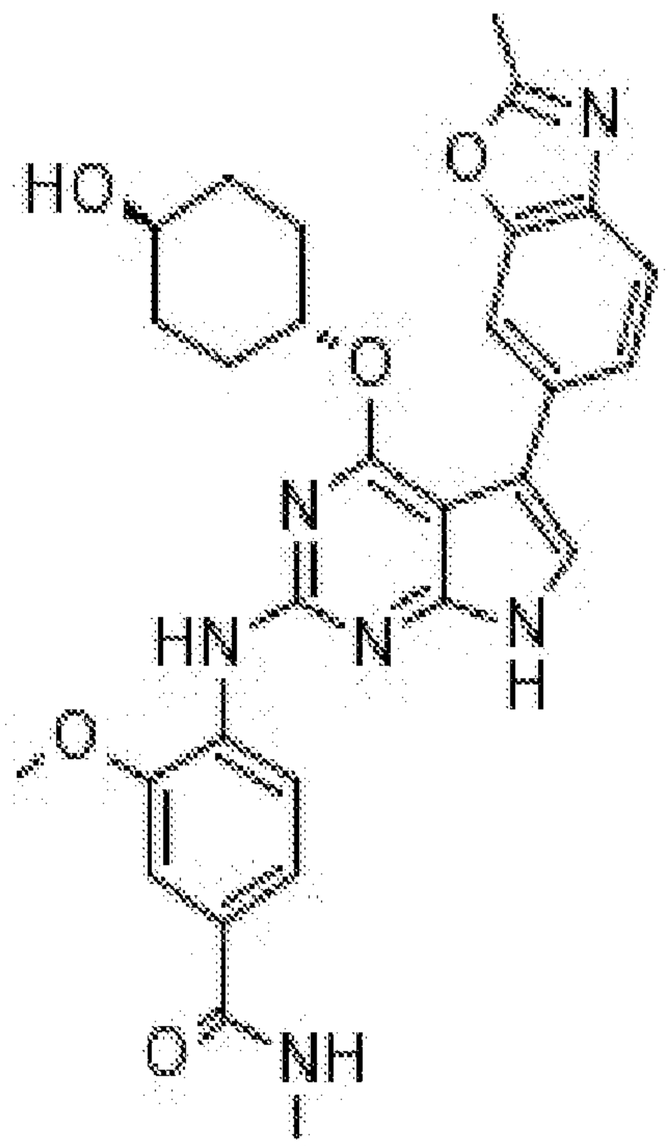
Cmpd No.	Structure	Name
123		3-methoxy-N-methyl-4-(5-(4-(methylcarbamoyl)phenyl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
124		3-methoxy-4-(4-methoxy-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide
125		4-(4-isopropoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

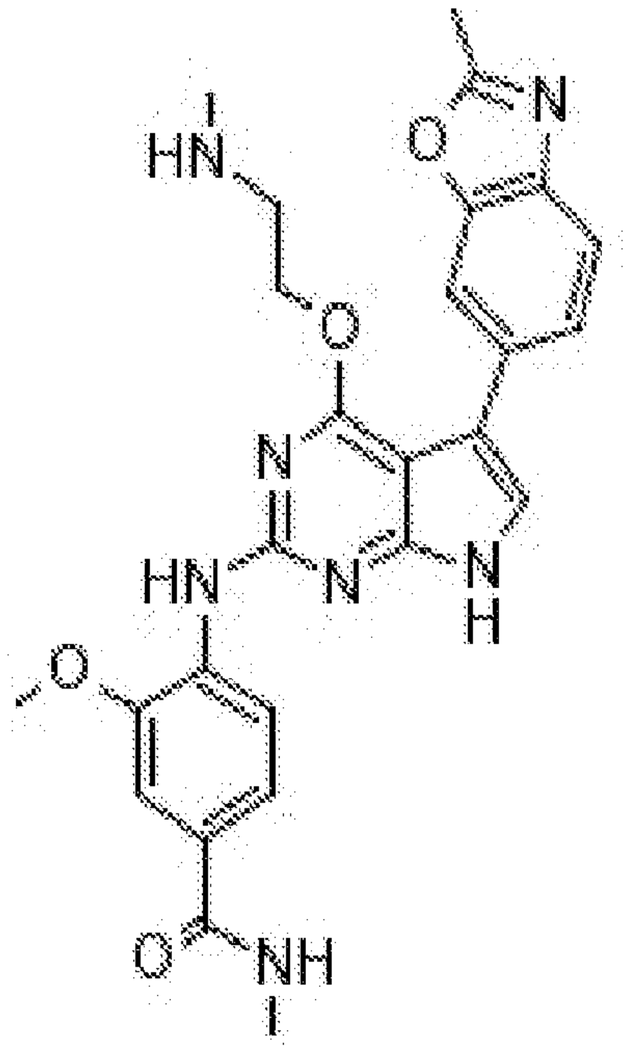
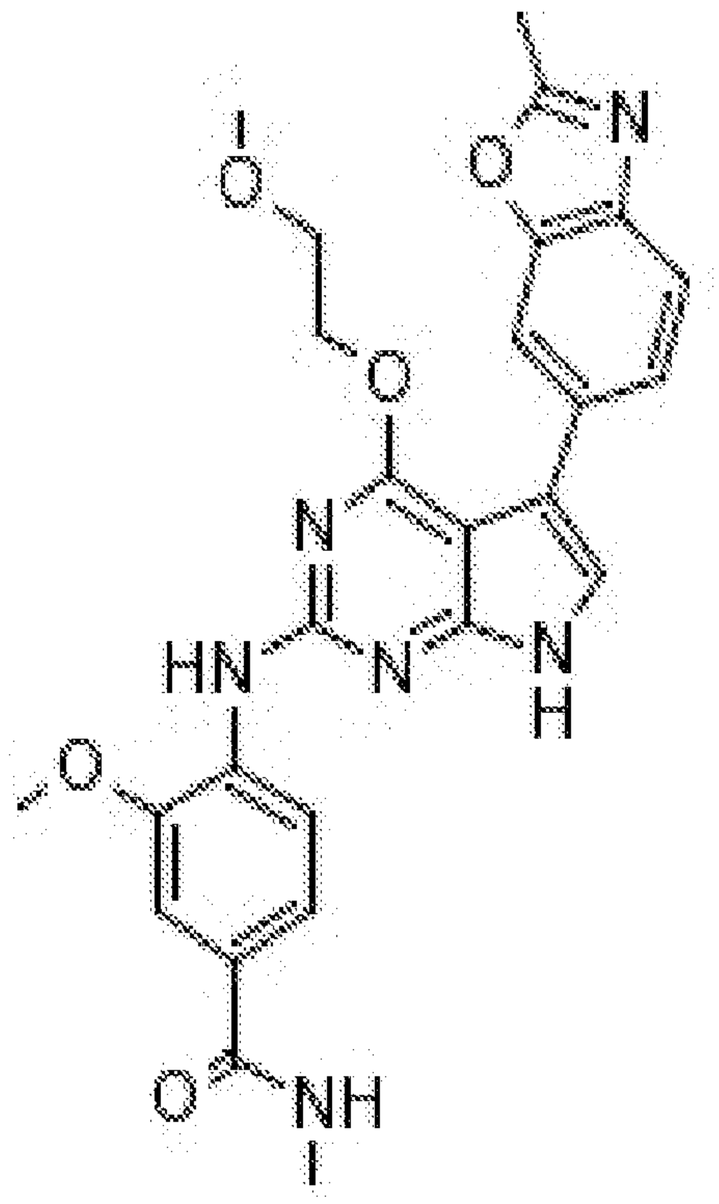
Cmpd No.	Structure	Name
126		4-(5-(6-(dimethylamino)pyridin-3-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
127		N-(2-(dimethylamino)ethyl)-3-methoxy-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
128		N,N,3-trimethyl-4-(5-(2-methyl-1H-benzo[d]imidazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

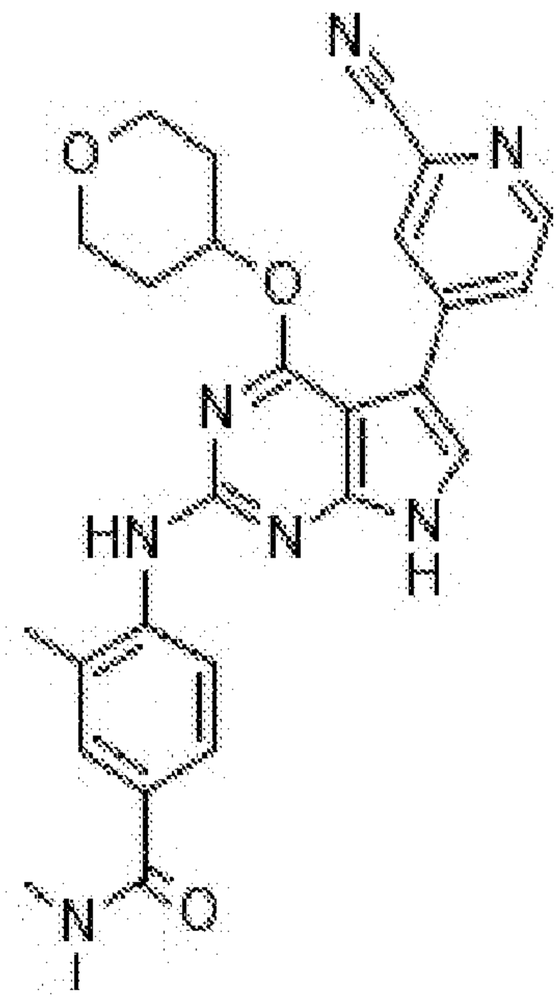
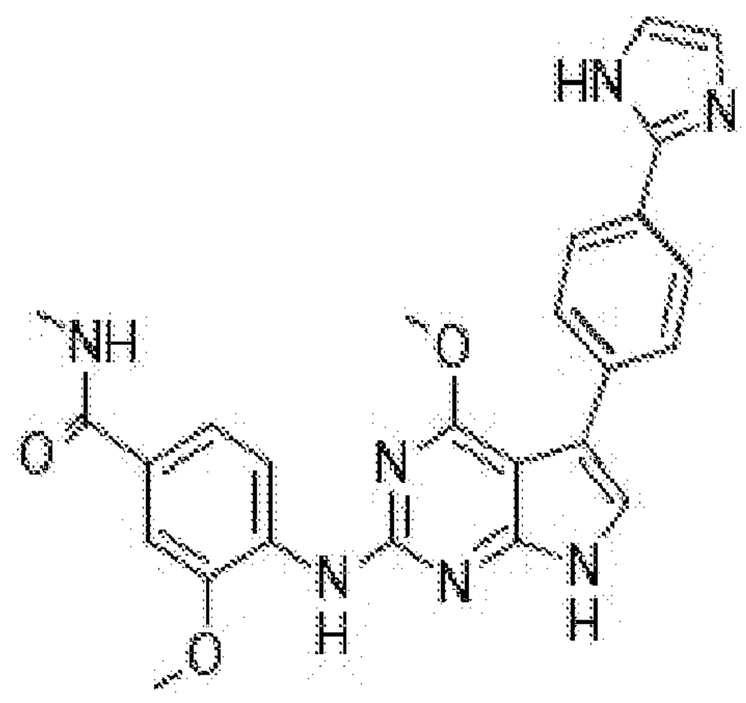
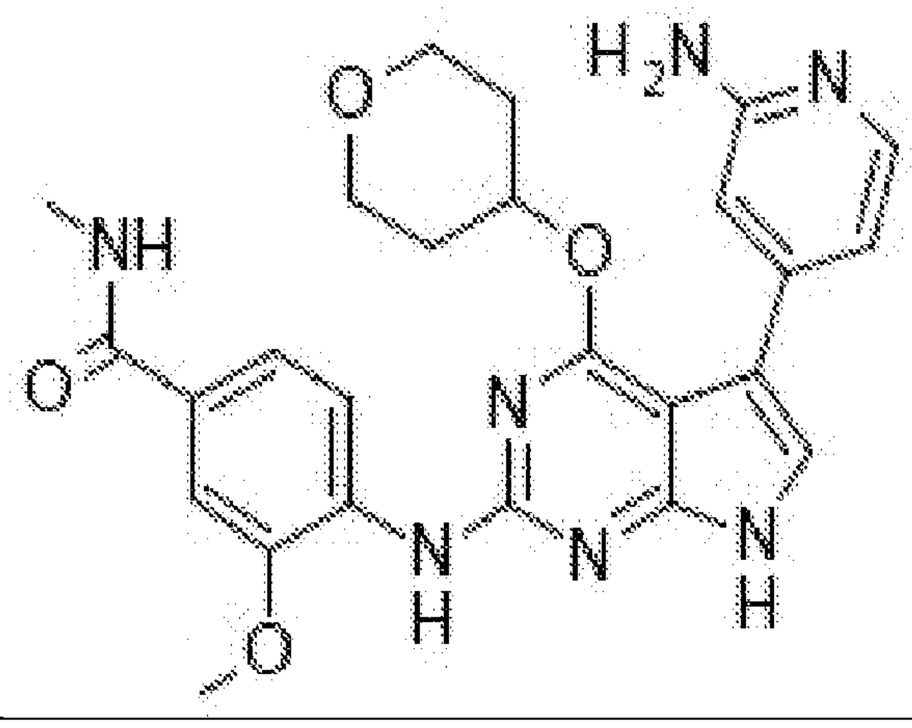
Cmpd No.	Structure	Name
129		3-methoxy-4-(4-methoxy-5-(1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide
130		3-methoxy-N-(2-(methylamino)ethyl)-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
131		4-(5-(2-(dimethylamino)pyridin-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

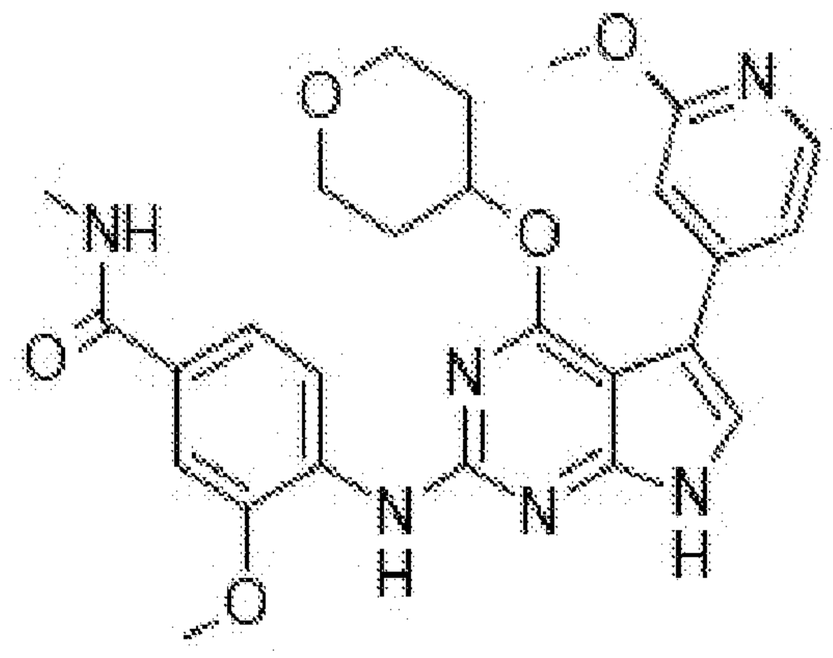
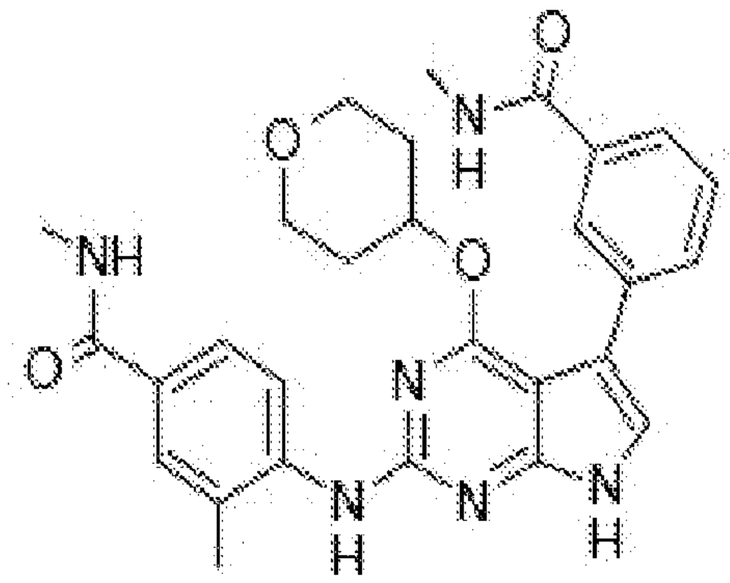
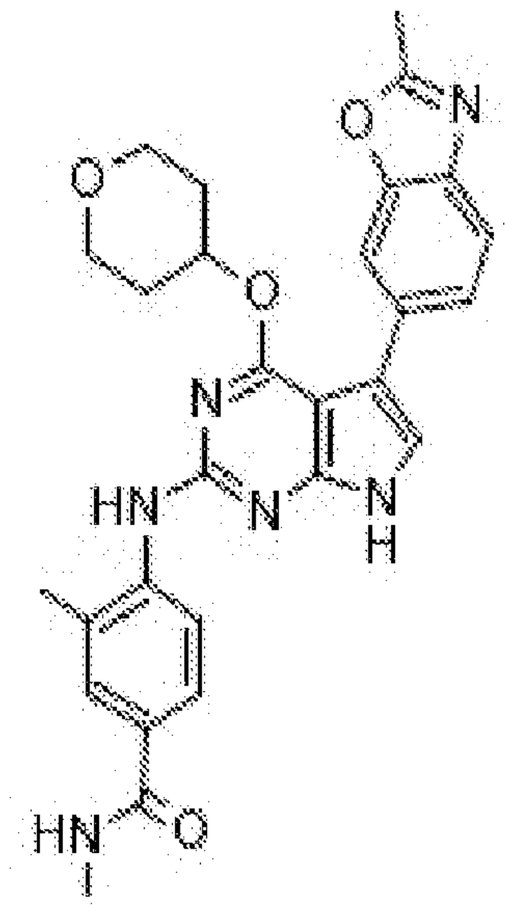
Cmpd No.	Structure	Name
132		3-chloro-N-methyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
133		(S)-N,3-dimethyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

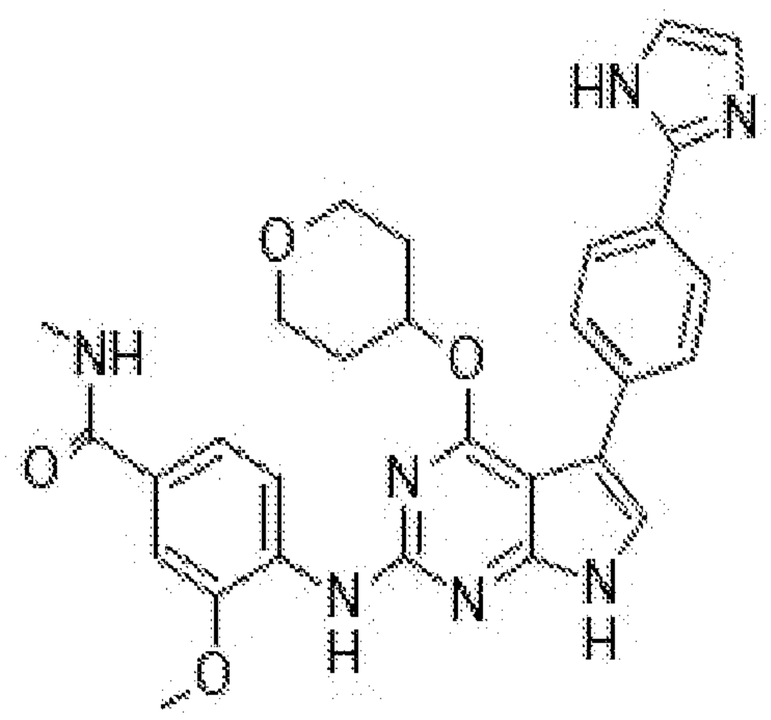
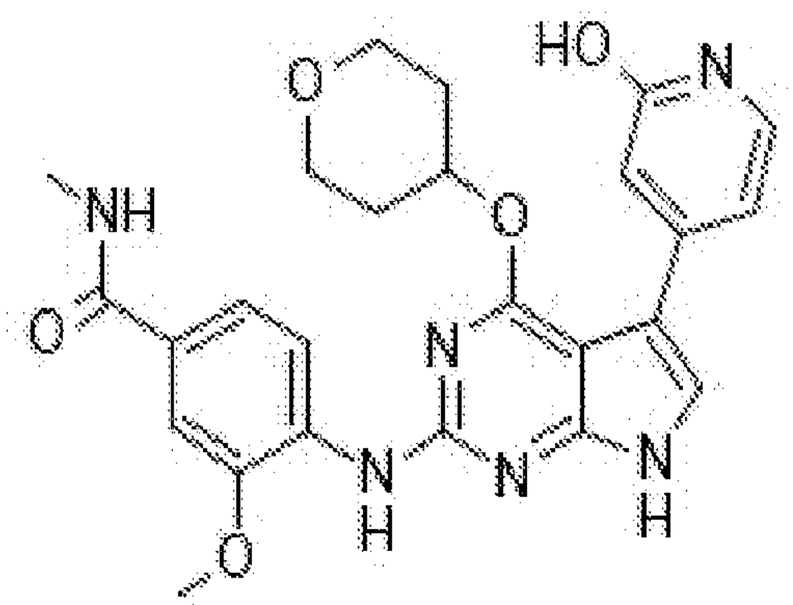
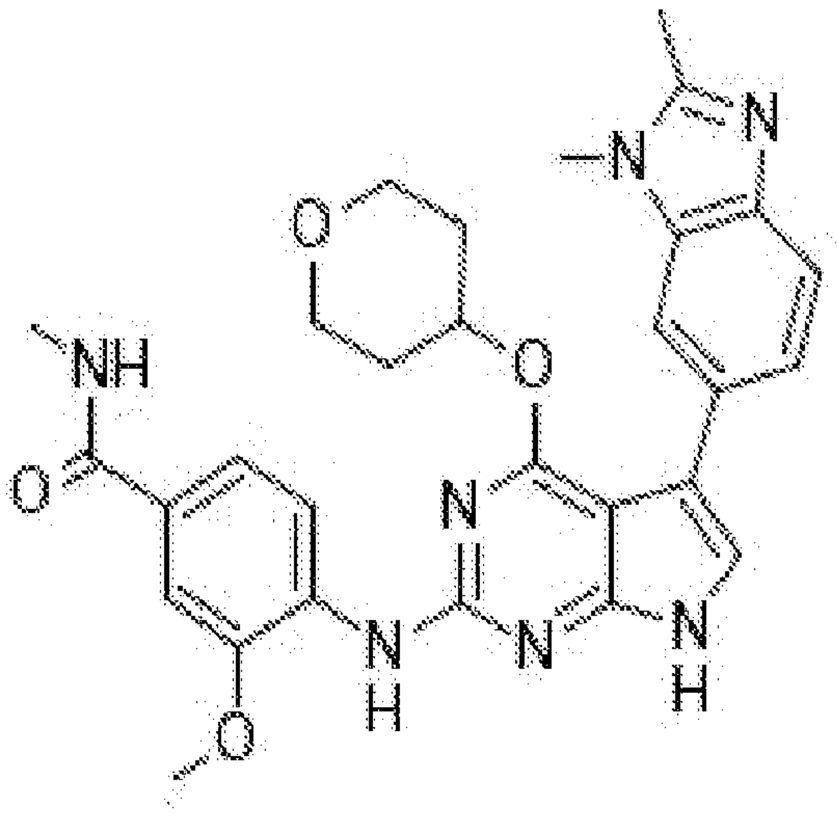
Cmpd No.	Structure	Name
134		(S)-3-chloro-N-methyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
135		4-(5-(2,7-dimethylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

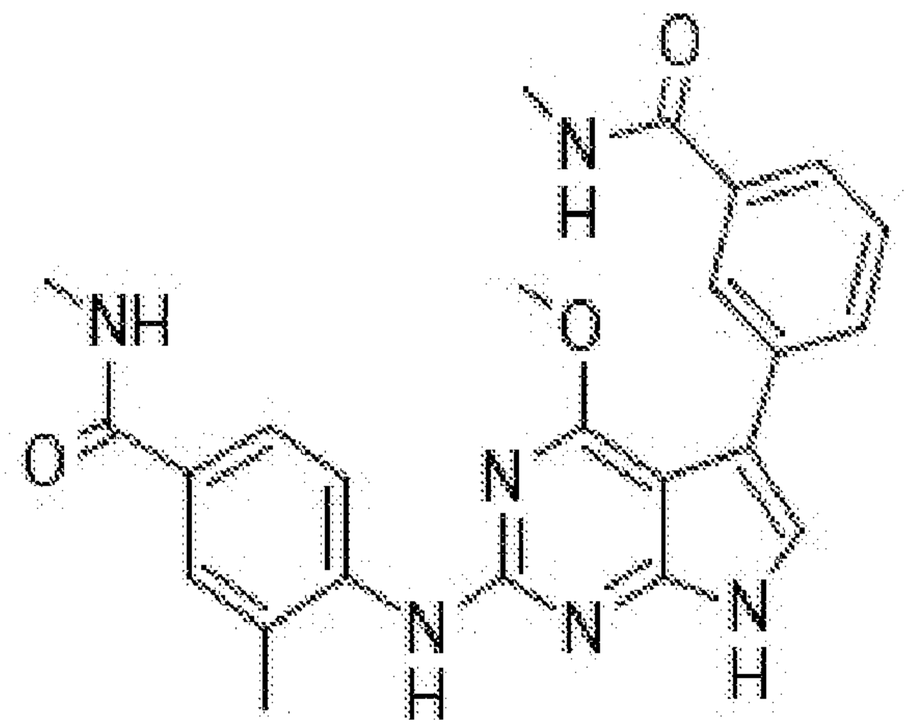
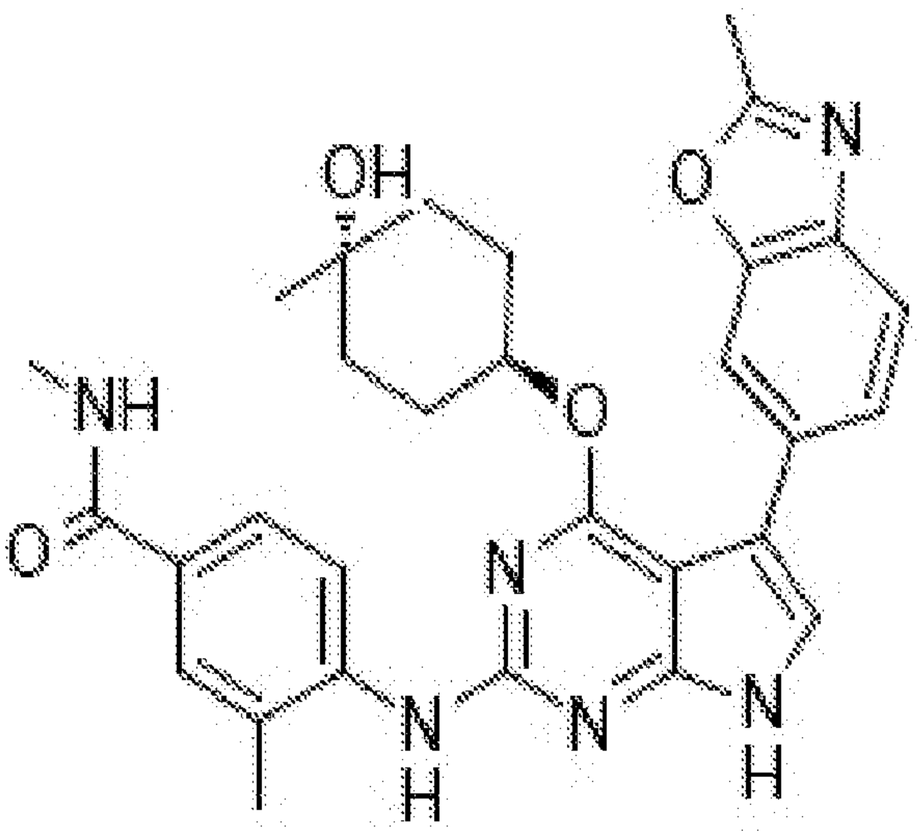
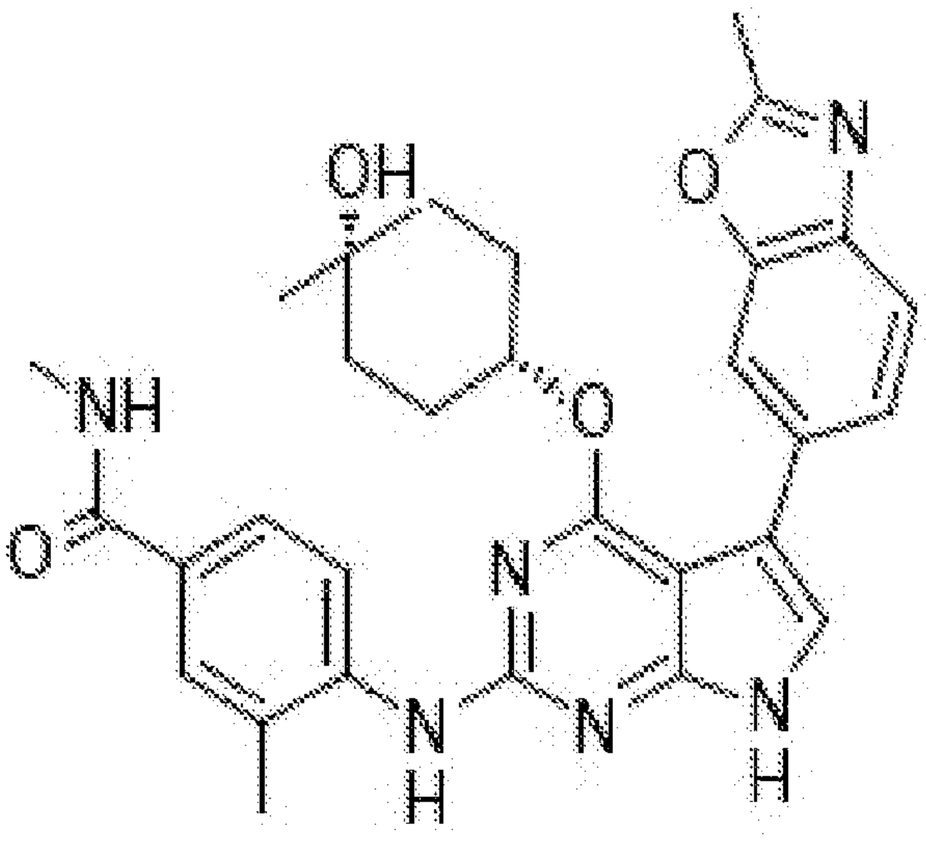
Cmpd No.	Structure	Name
136		4-(5-(2,5-dimethylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
137		4-(4-((1r,4r)-4-hydroxycyclohexyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

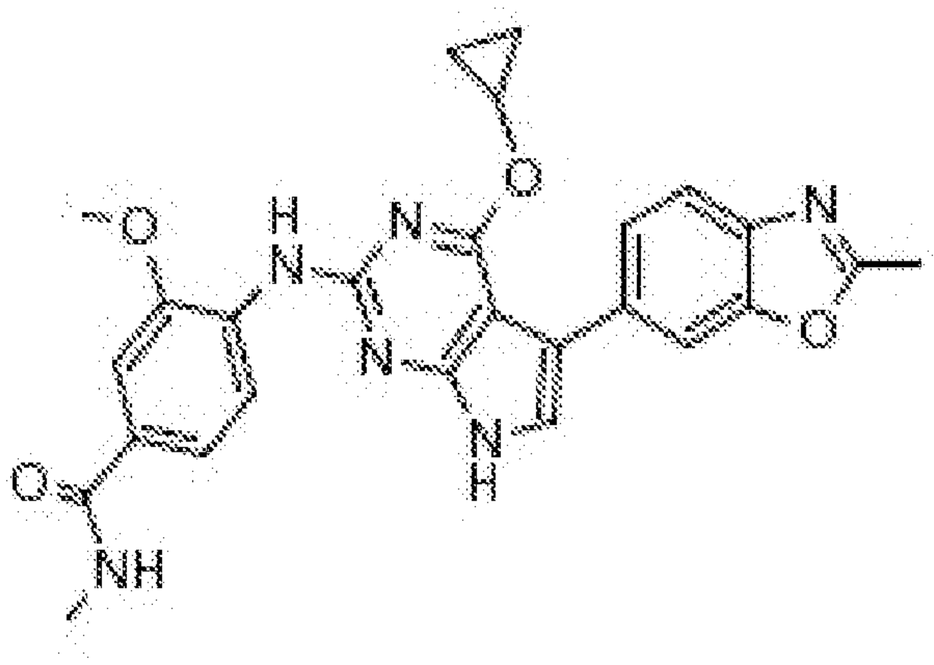
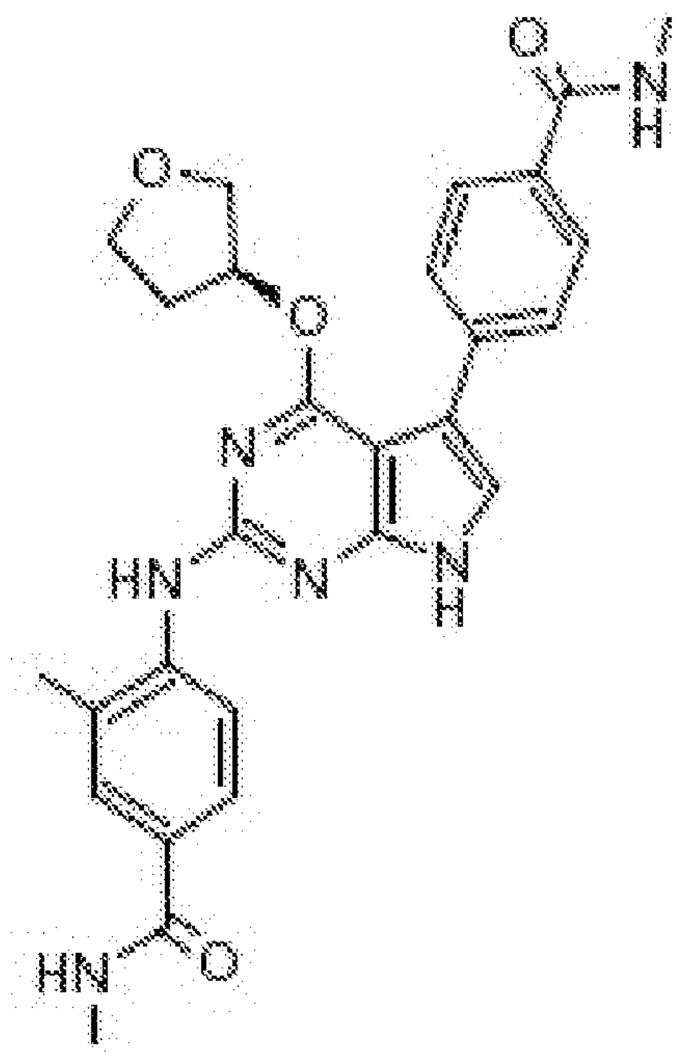
Cmpd No.	Structure	Name
138		3-methoxy-N-methyl-4-(4-(2-(methylamino)ethoxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
139		3-methoxy-4-(4-(2-methoxyethoxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide

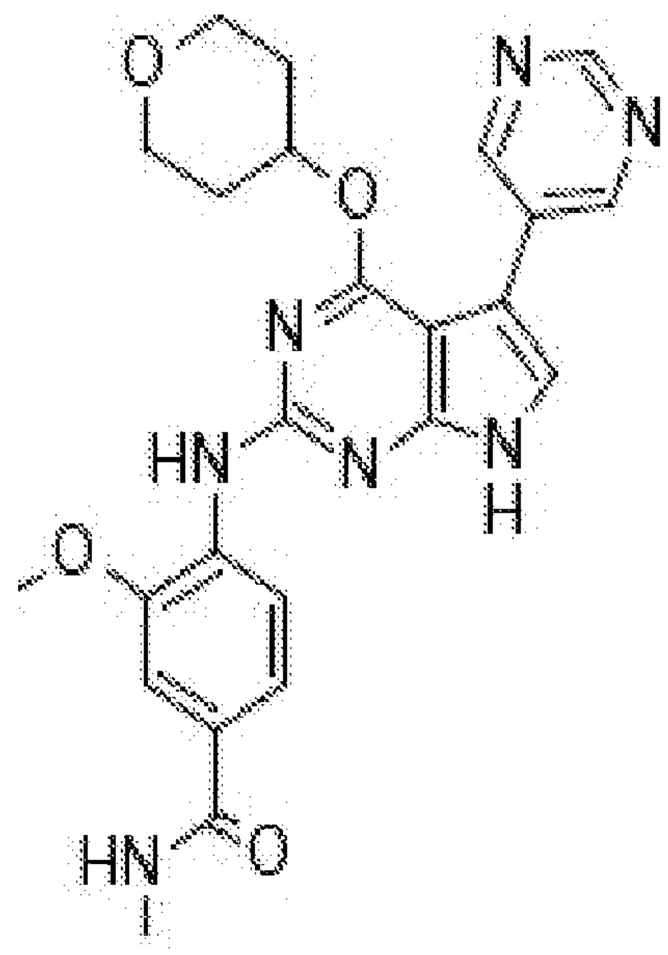
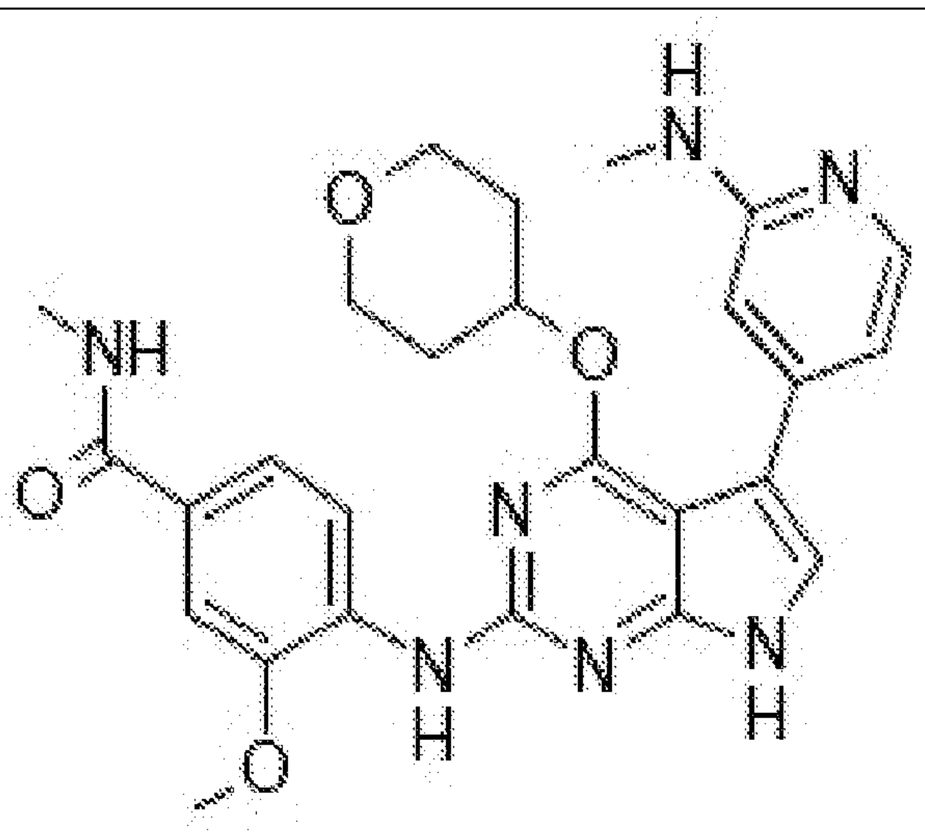
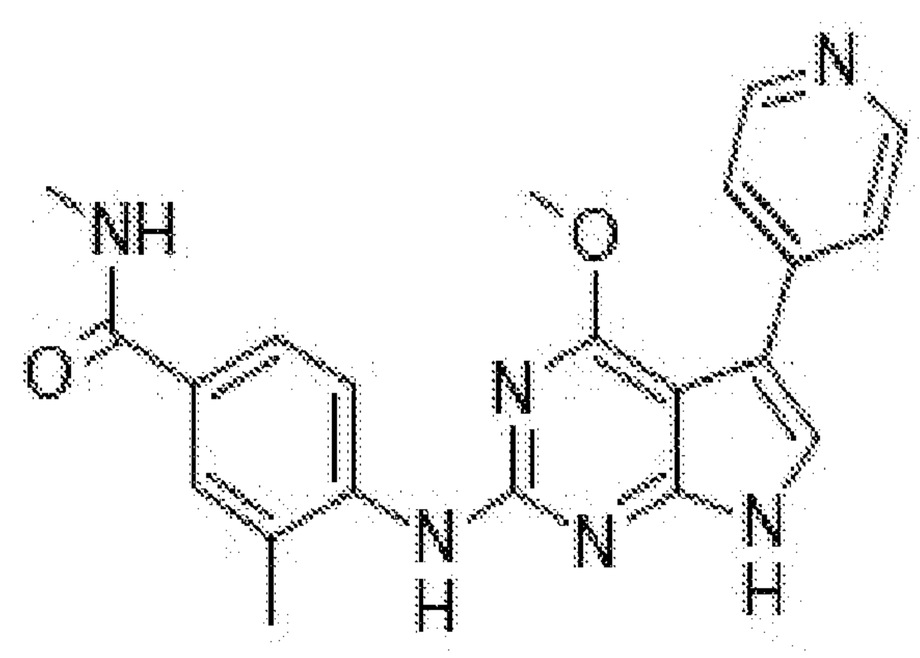
Cmpd No.	Structure	Name
140		4-(5-(2-cyanopyridin-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N,3-trimethylbenzamide
141		4-(5-(4-(1H-imidazol-2-yl)phenyl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
142		4-(5-(2-aminopyridin-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

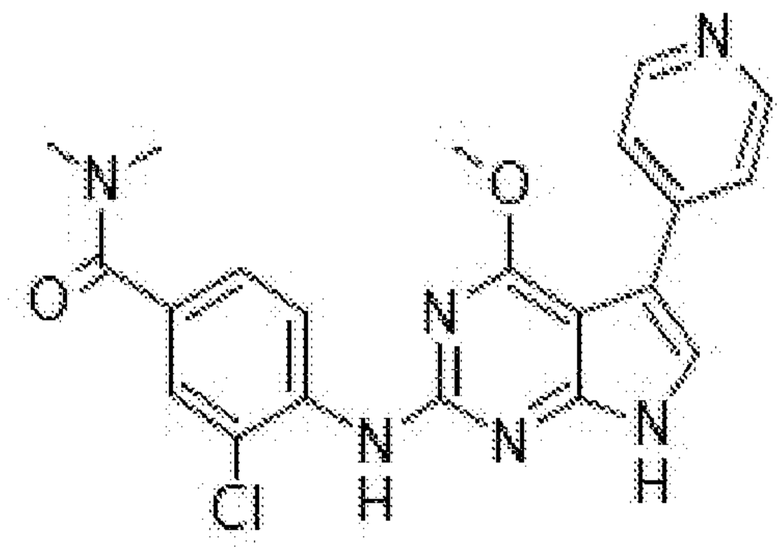
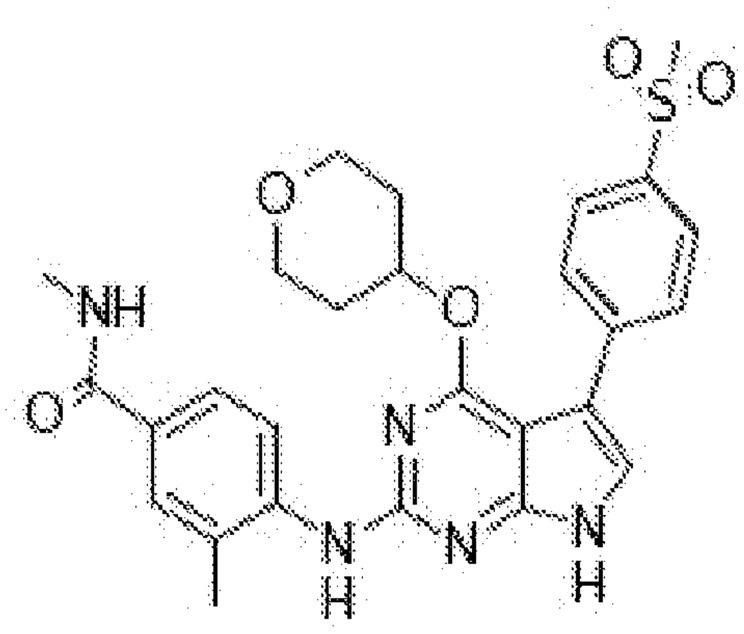
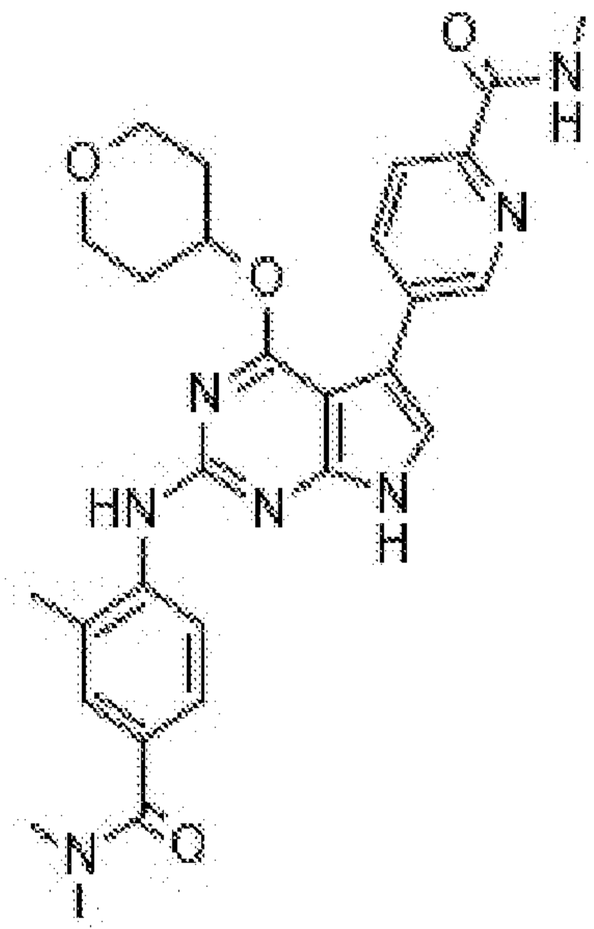
Cmpd No.	Structure	Name
143		3-methoxy-4-(5-(2-methoxypyridin-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide
144		N,3-dimethyl-4-(5-(3-(methylcarbamoyl)phenyl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
145		N,3-dimethyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

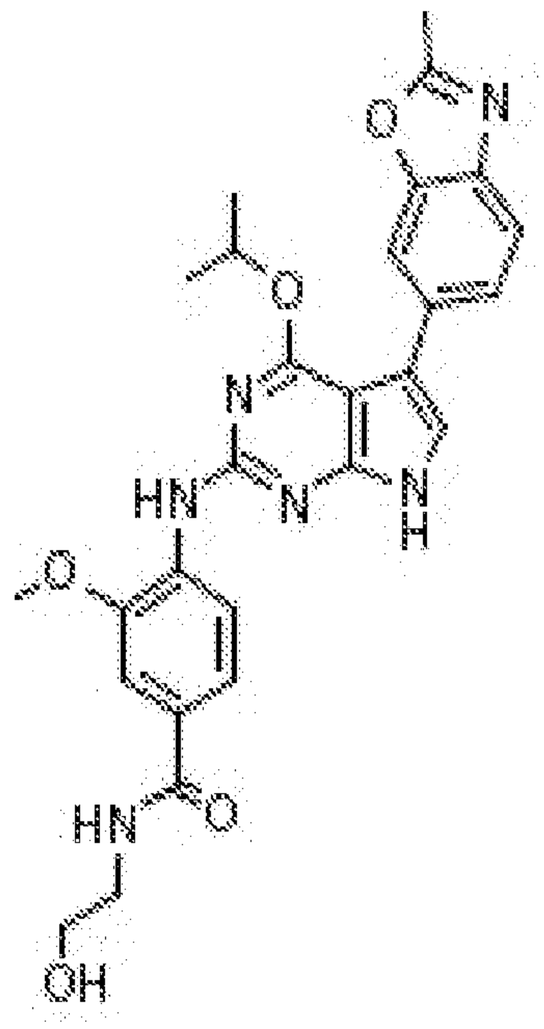
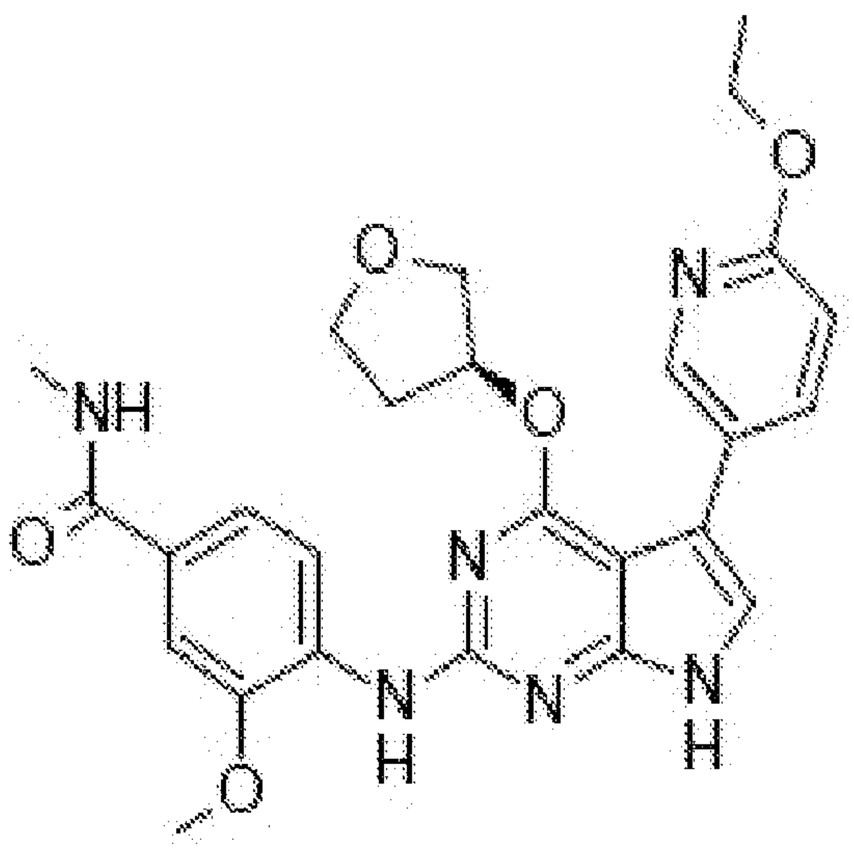
Cmpd No.	Structure	Name
146		4-(5-(4-(1H-imidazol-2-yl)phenyl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
147		4-(5-(2-hydroxypyridin-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
148		4-(5-(1,2-dimethyl-1H-benzo[d]imidazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

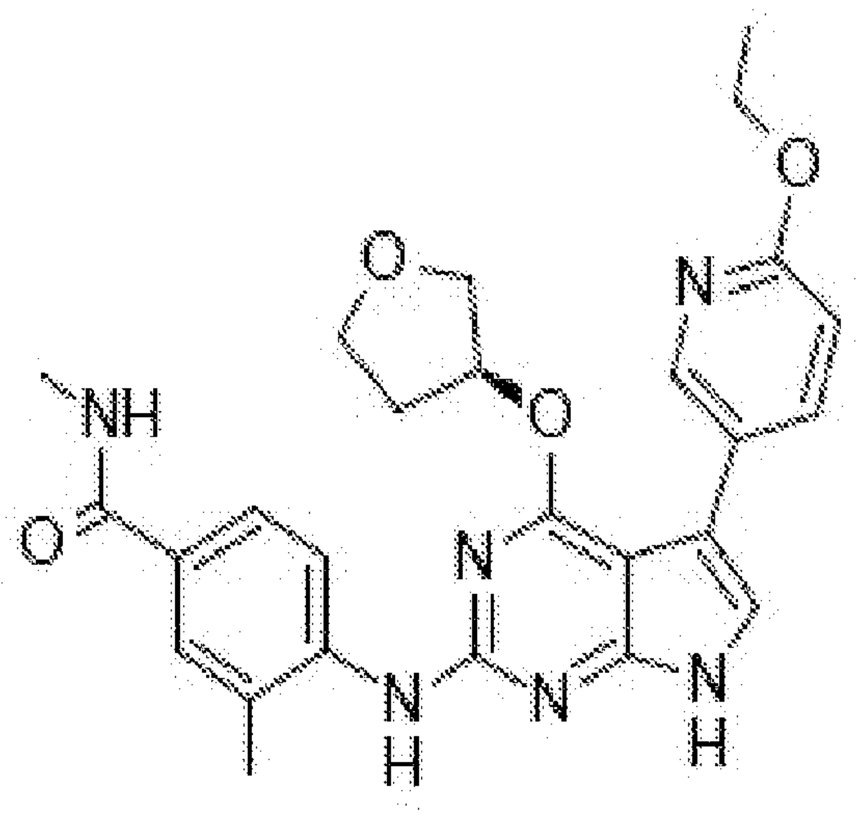
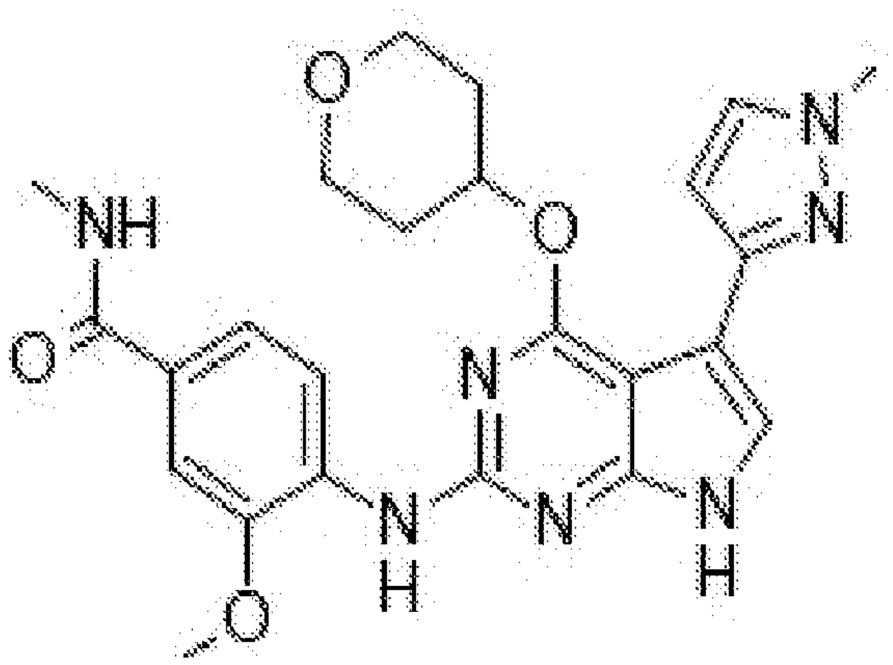
Cmpd No.	Structure	Name
149		4-(4-methoxy-5-(3-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,3-dimethylbenzamide
150		4-(4-((1r,4r)-4-hydroxy-4-methylcyclohexyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,3-dimethylbenzamide
151		4-(4-((1s,4s)-4-hydroxy-4-methylcyclohexyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,3-dimethylbenzamide

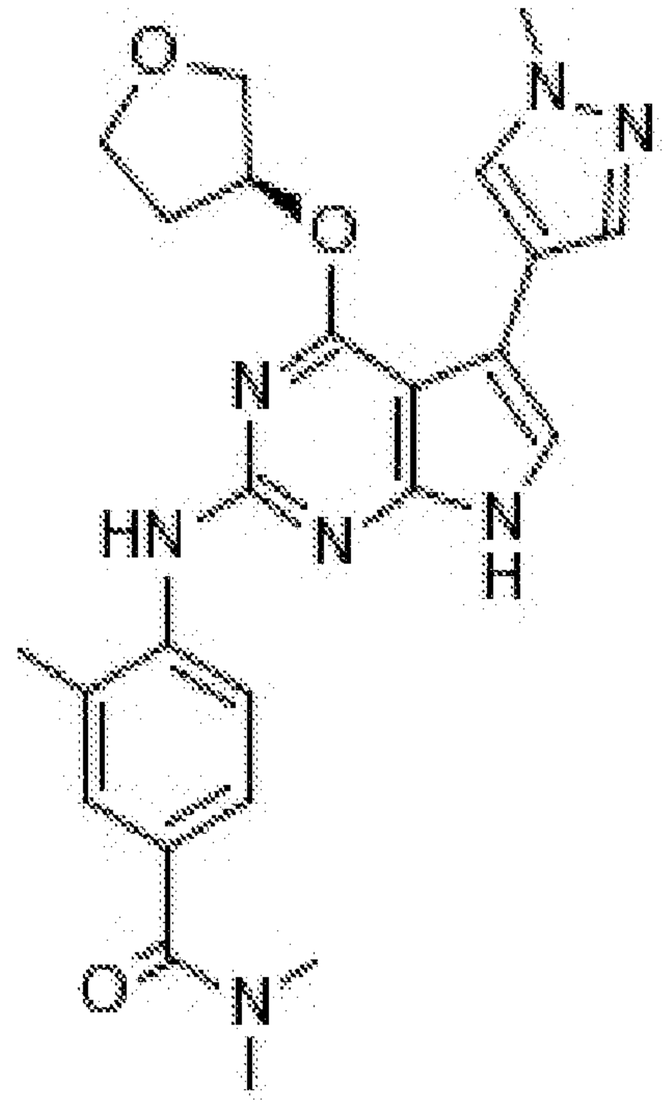
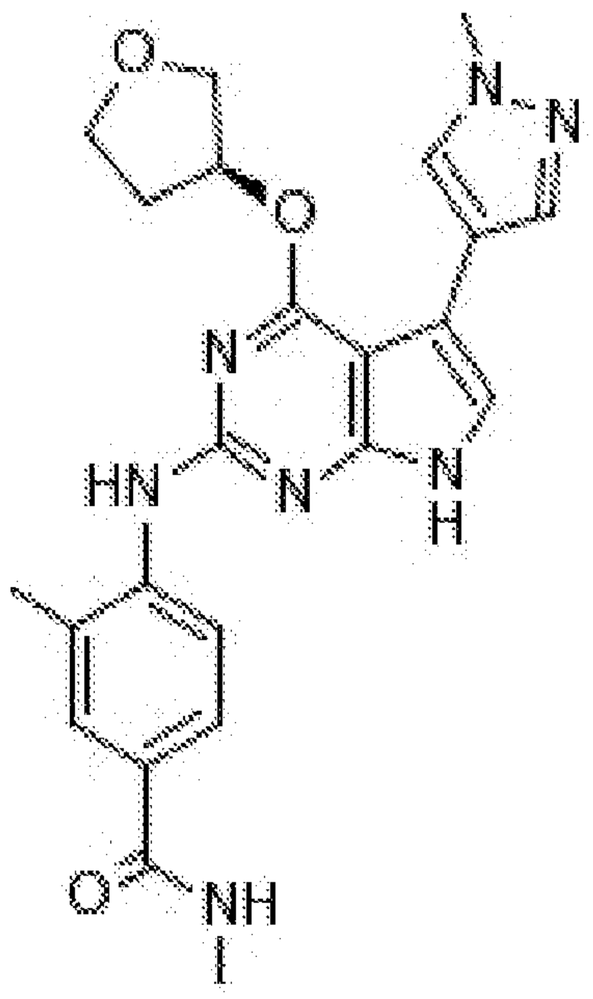
Cmpd No.	Structure	Name
152		4-(4-cyclopropoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
153		(S)-N,3-dimethyl-4-(5-(4-(methylcarbamoyl)phenyl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

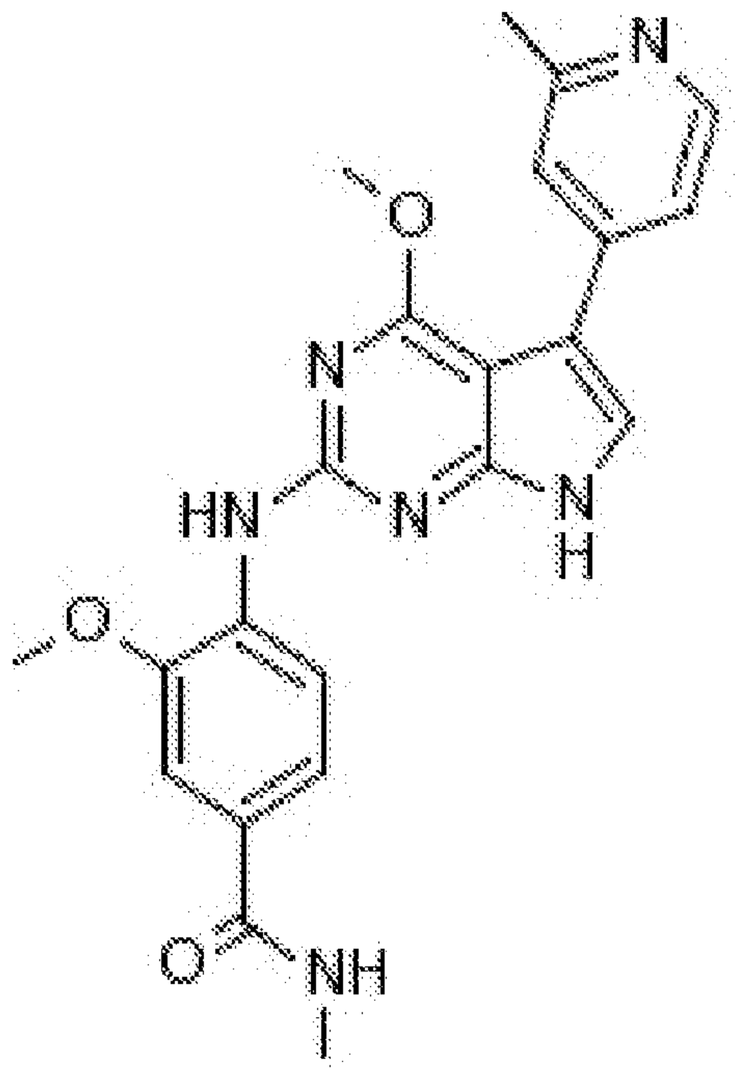
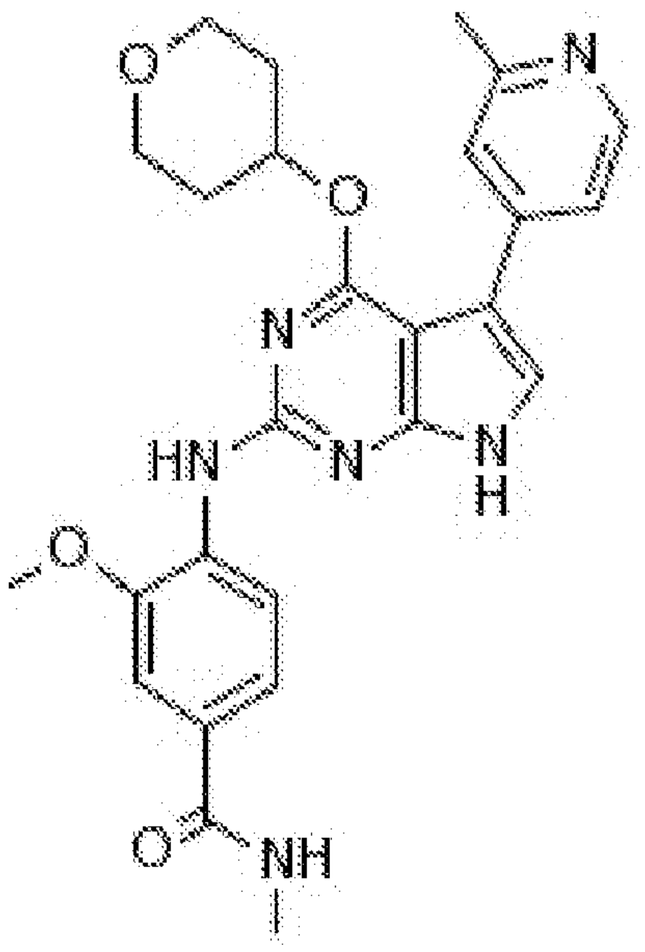
Cmpd No.	Structure	Name
154		3-methoxy-N-methyl-4-(5-(pyrimidin-5-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
155		3-methoxy-N-methyl-4-(5-(2-(methylamino)pyridin-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
156		4-(4-methoxy-5-(pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,3-dimethylbenzamide

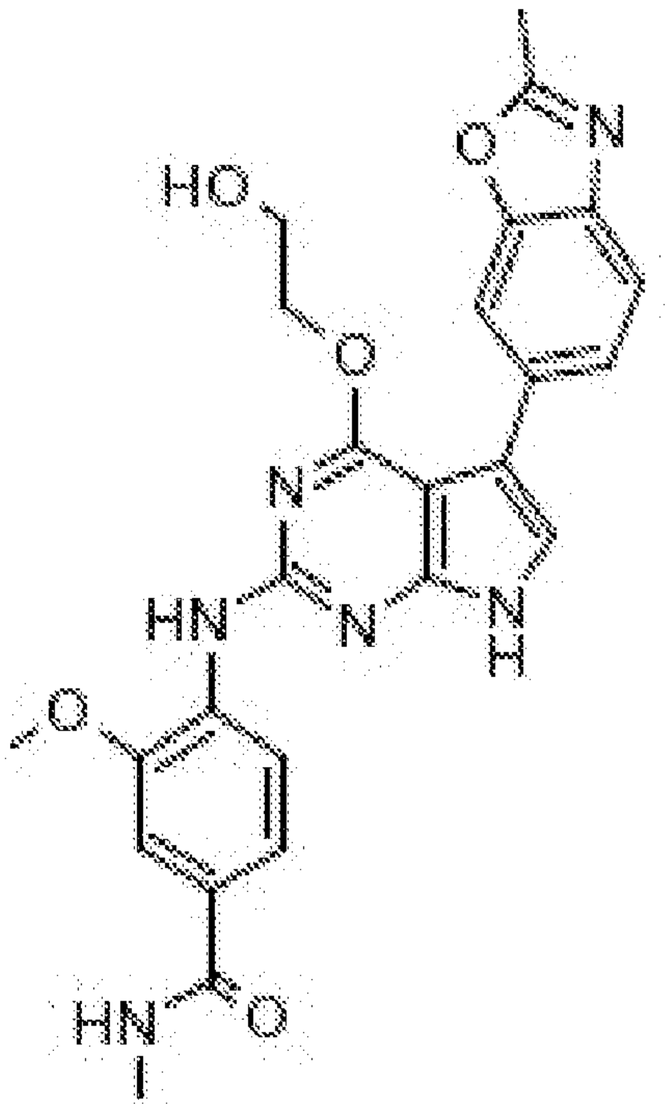
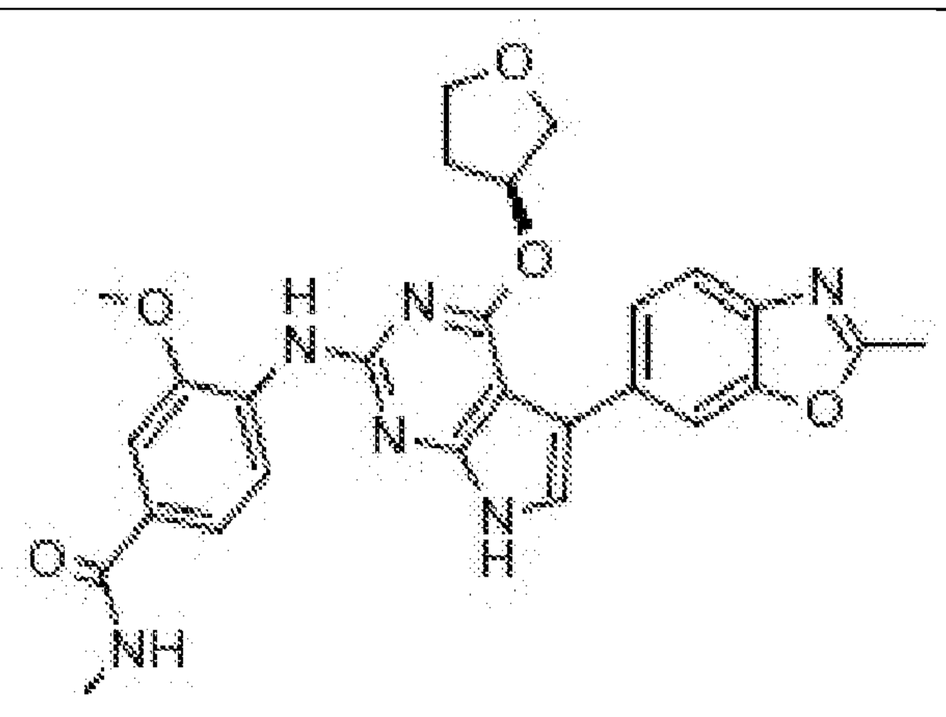
Cmpd No.	Structure	Name
157		3-chloro-4-(4-methoxy-5-(pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N-dimethylbenzamide
158		N,3-dimethyl-4-(5-(4-(methylsulfonyl)phenyl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
159		5-(2-(4-(dimethylcarbamoyl)-2-methylphenylamino)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-N-methylpicolinamide

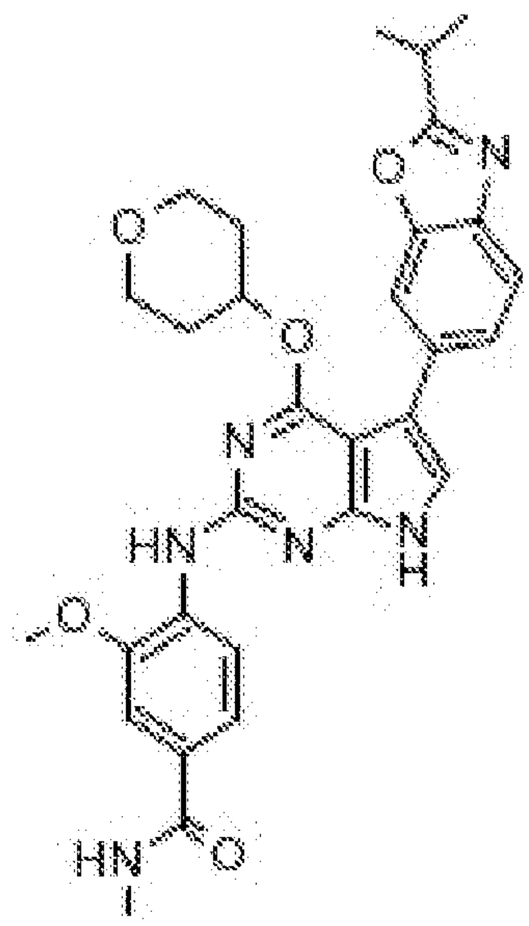
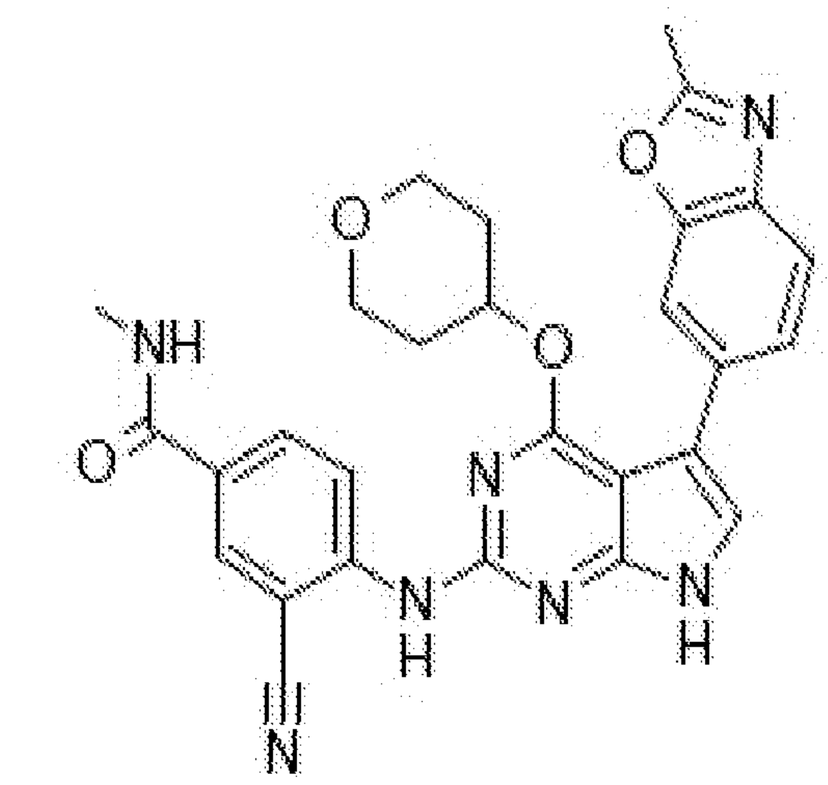
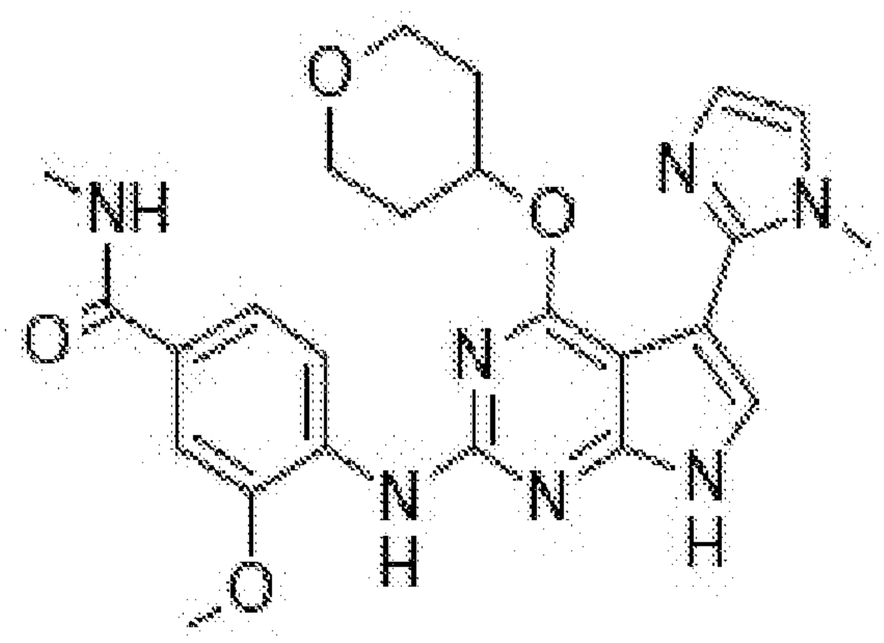
Cmpd No.	Structure	Name
160		N-(2-hydroxyethyl)-4-(4-isopropoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxybenzamide
161		(S)-4-(5-(6-ethoxypyridin-3-yl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

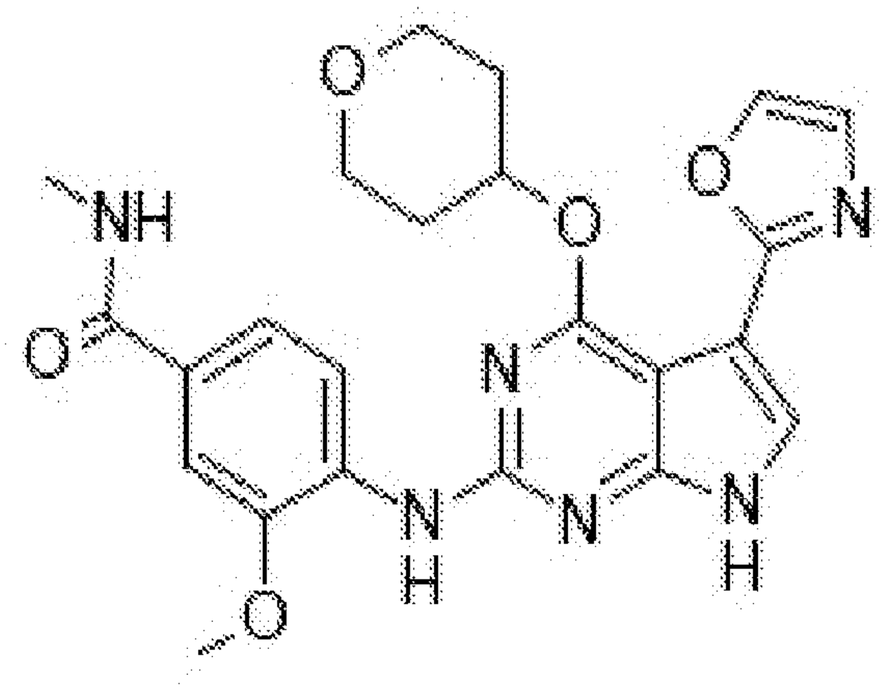
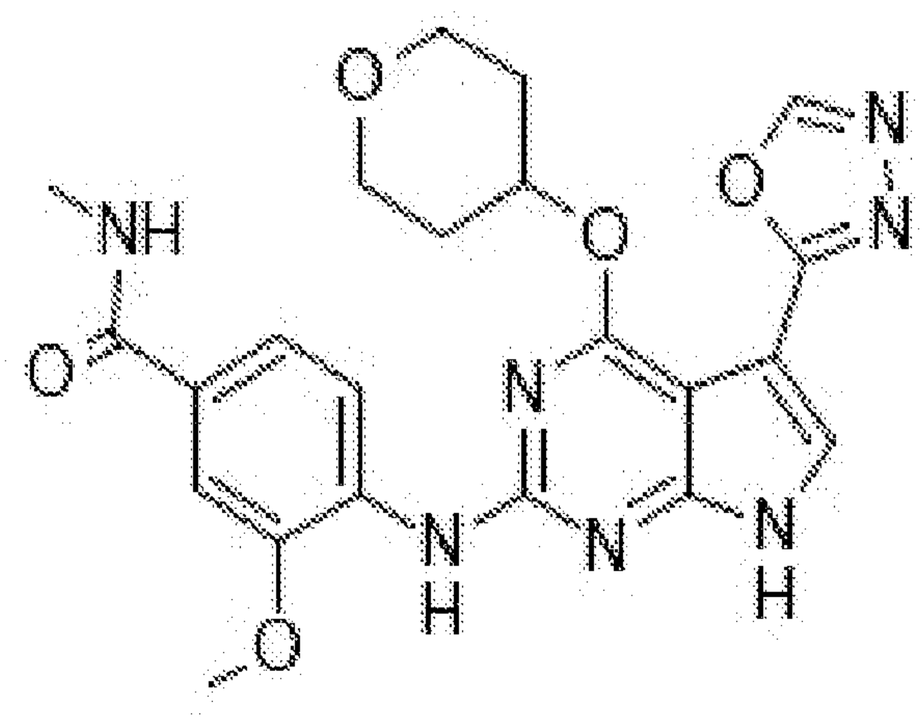
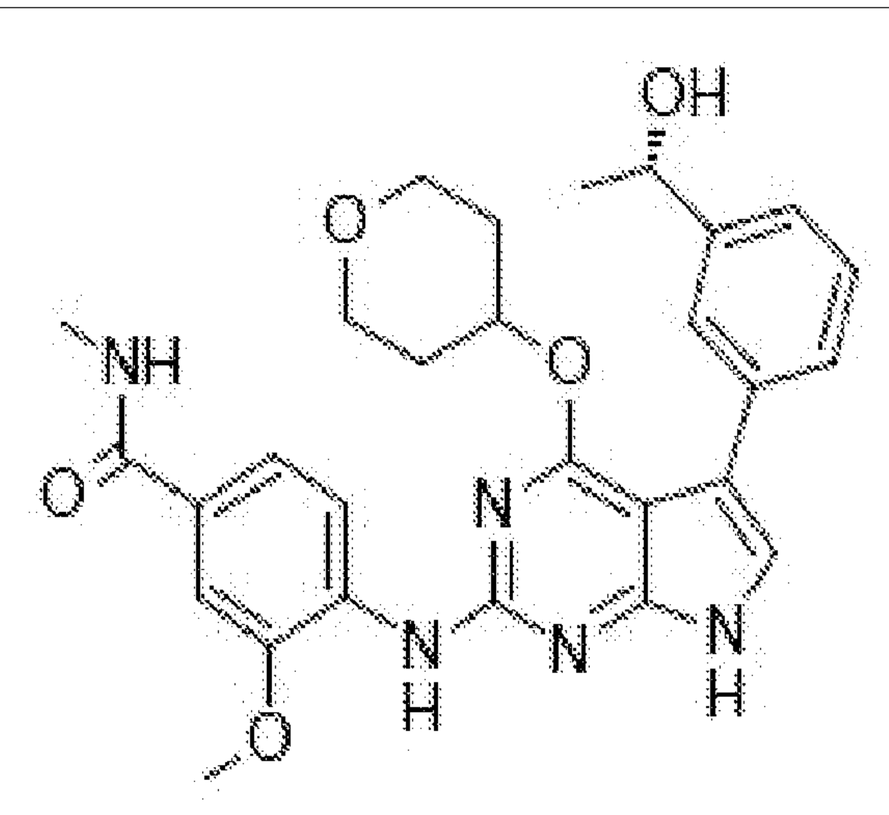
Cmpd No.	Structure	Name
162		(S)-4-(5-(6-ethoxypyridin-3-yl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,3-dimethylbenzamide
163		3-methoxy-N-methyl-4-(5-(1-methyl-1H-pyrazol-3-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

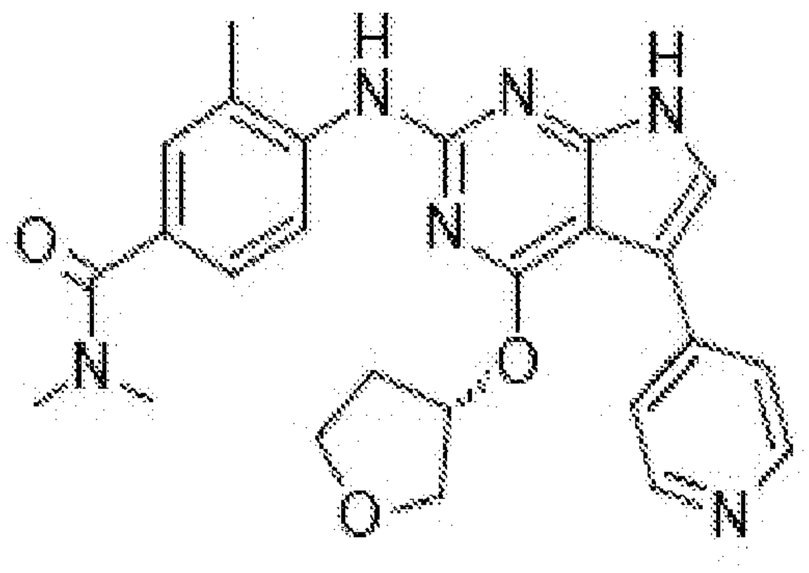
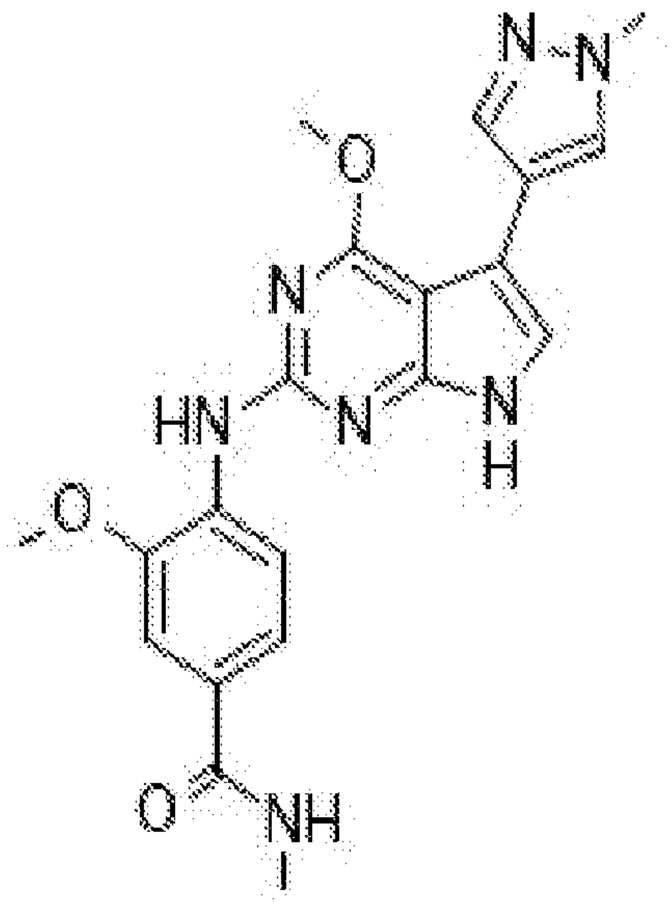
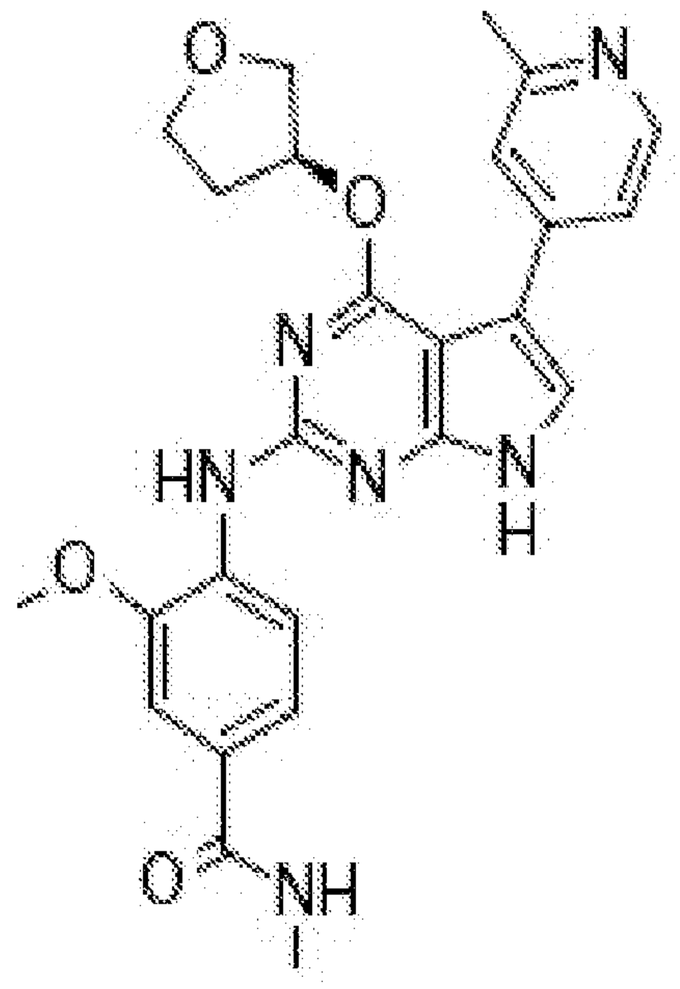
Cmpd No.	Structure	Name
164		(S)-N,N,3-trimethyl-4-(5-(1-methyl-1H-pyrazol-4-yl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
165		(S)-N,3-dimethyl-4-(5-(1-methyl-1H-pyrazol-4-yl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

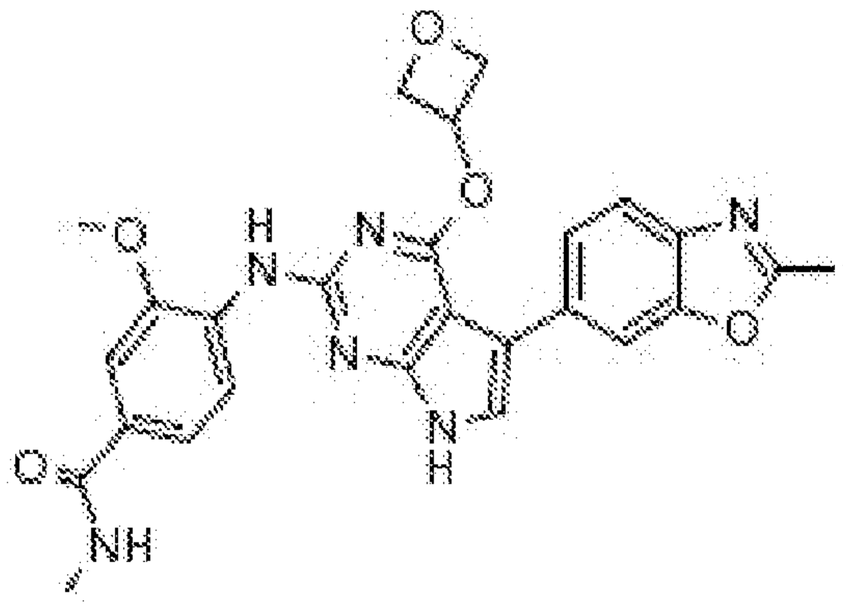
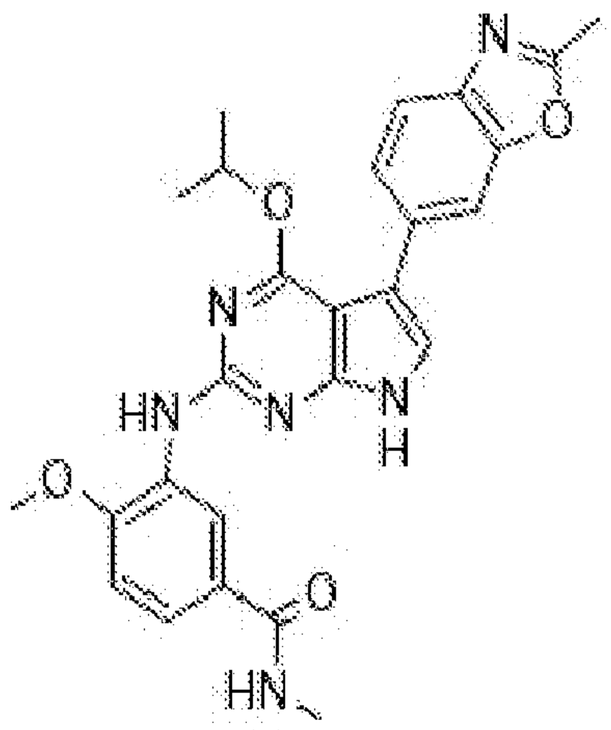
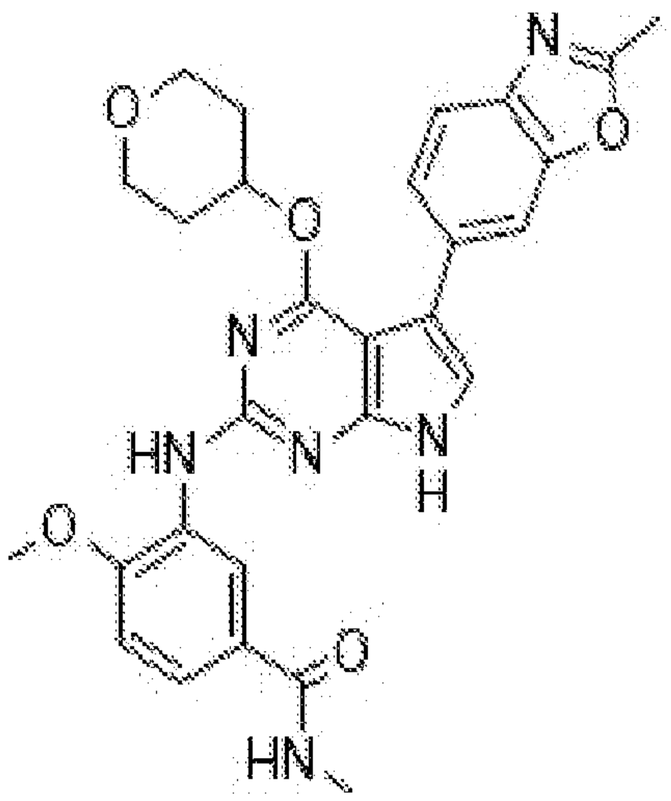
Cmpd No.	Structure	Name
166		3-methoxy-4-(4-methoxy-5-(2-methylpyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide
167		3-methoxy-N-methyl-4-(5-(2-methylpyridin-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

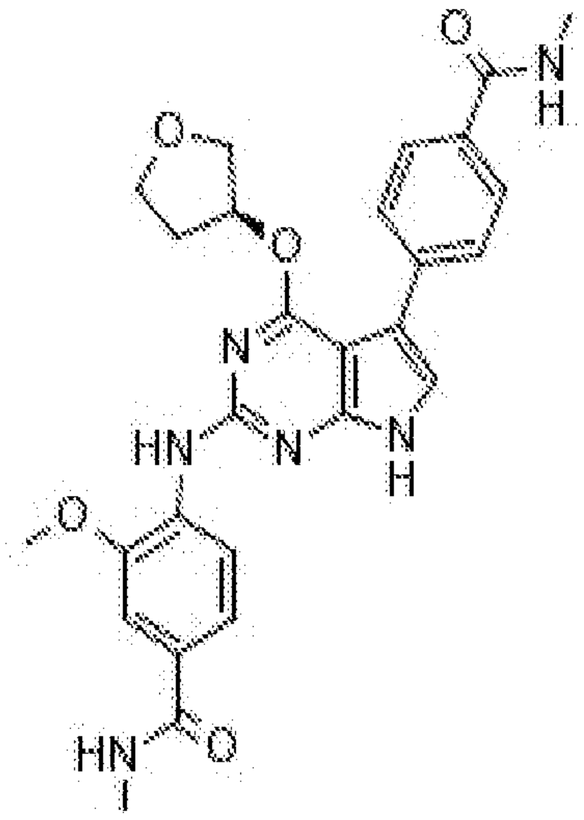
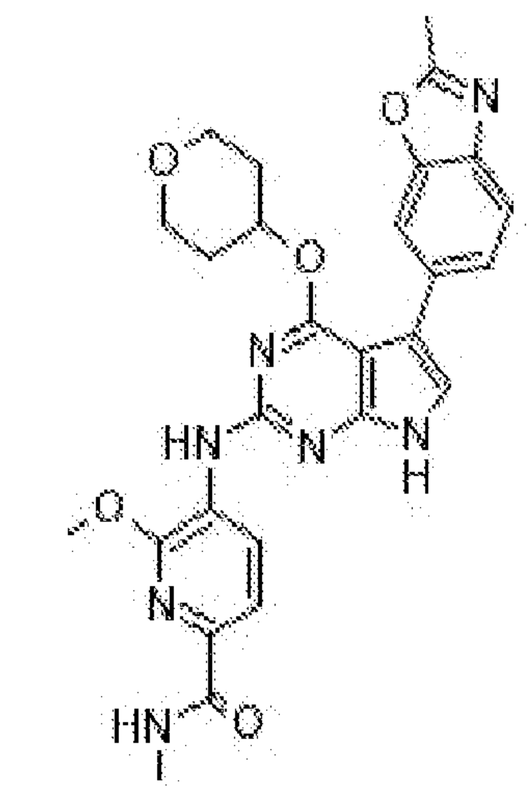
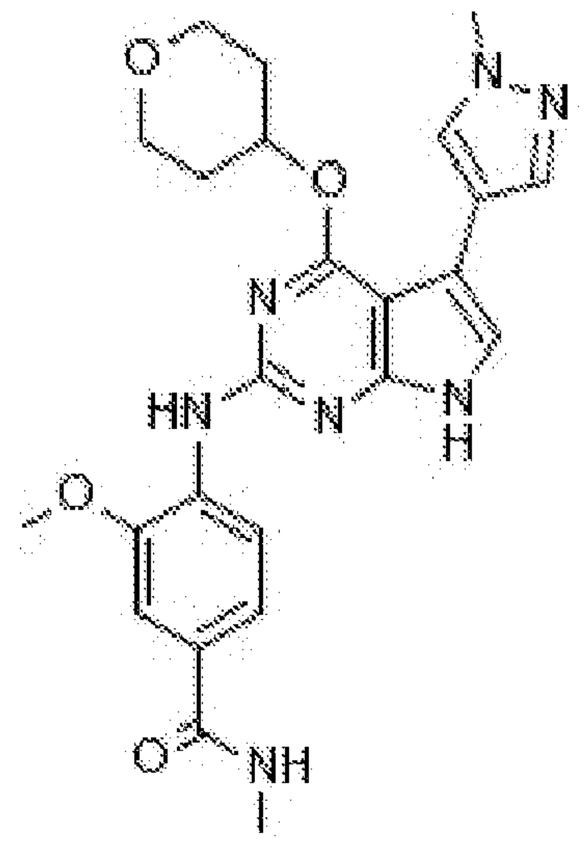
Cmpd No.	Structure	Name
168		4-(4-(2-hydroxyethoxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
169		(S)-3-methoxy-N-methyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

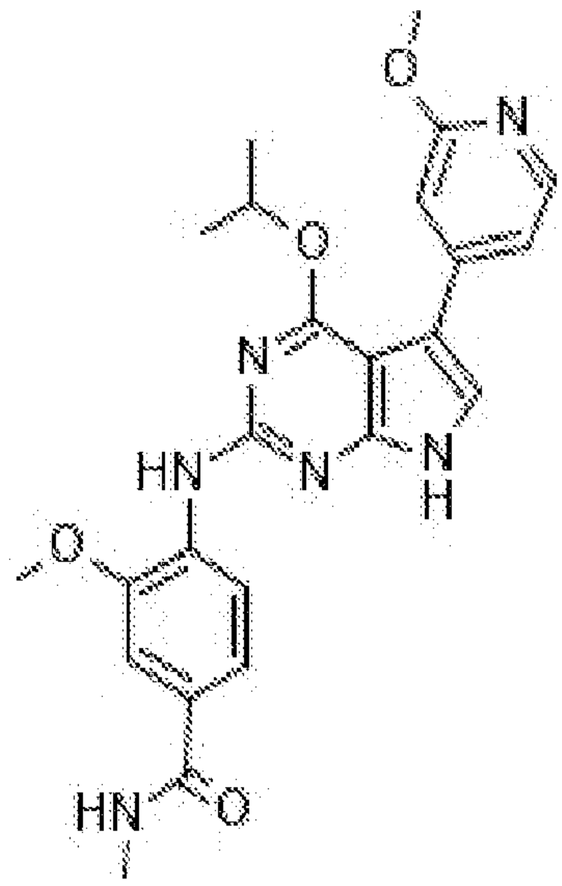
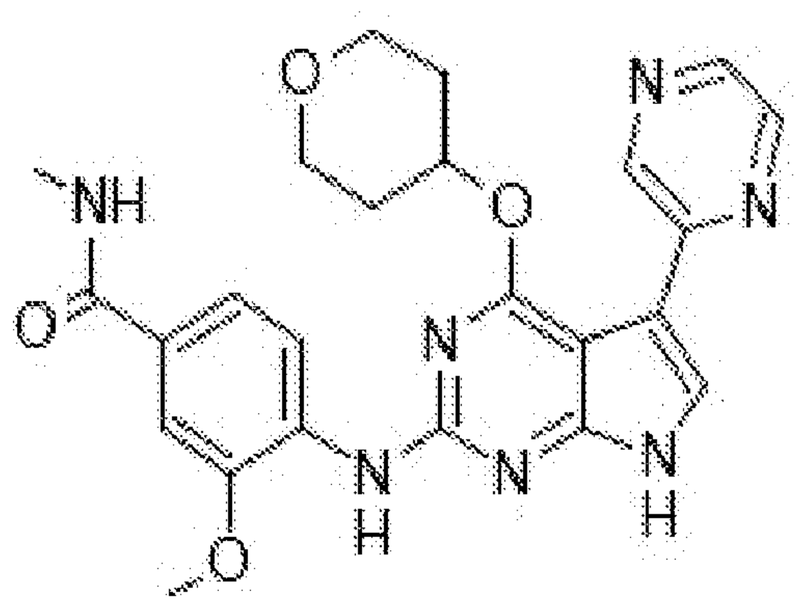
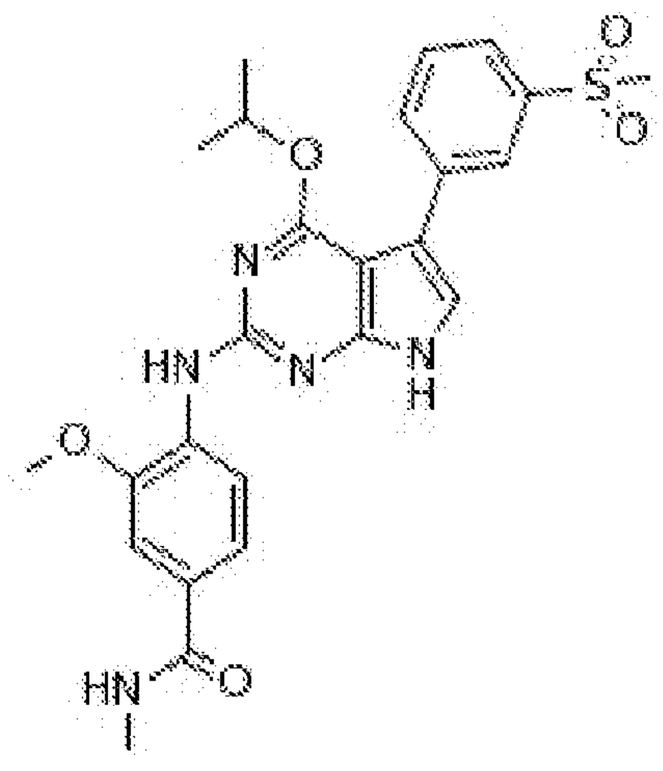
Cmpd No.	Structure	Name
170		4-(5-(2-isopropylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
171		3-cyano-N-methyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
172		3-methoxy-N-methyl-4-(5-(1-methyl-1H-imidazol-2-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

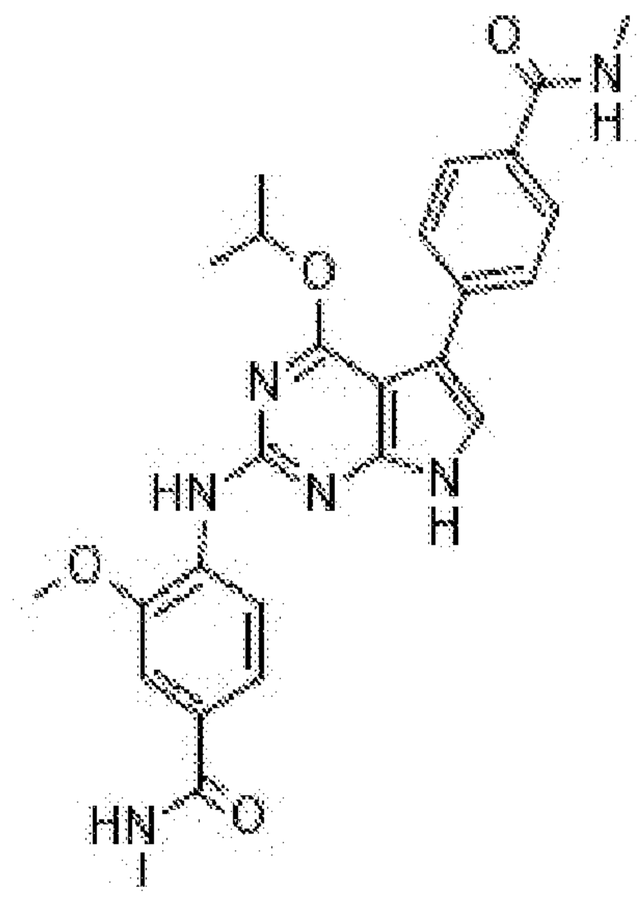
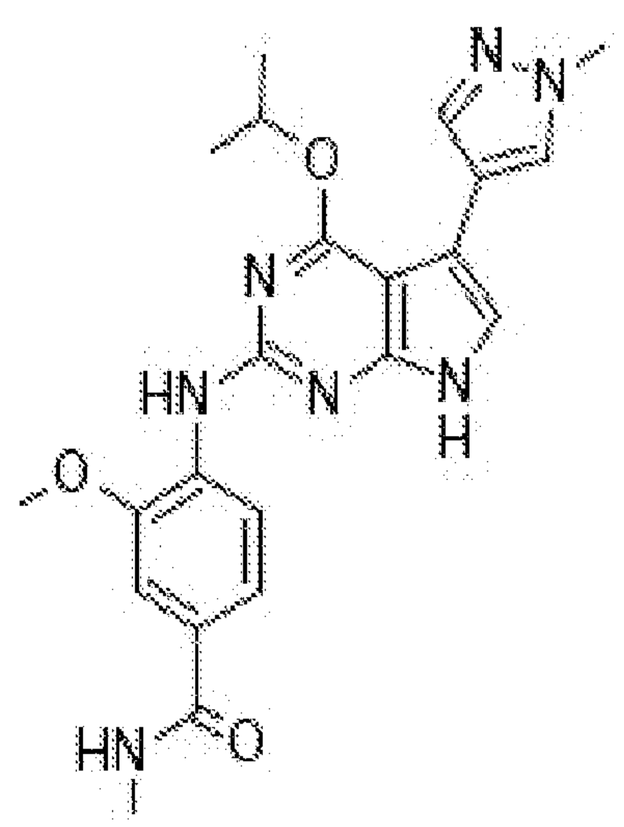
Cmpd No.	Structure	Name
173		3-methoxy-N-methyl-4-(5-(oxazol-2-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
174		4-(5-(1,3,4-oxadiazol-2-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
175		(S)-4-(5-(3-(1-hydroxyethyl)phenyl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

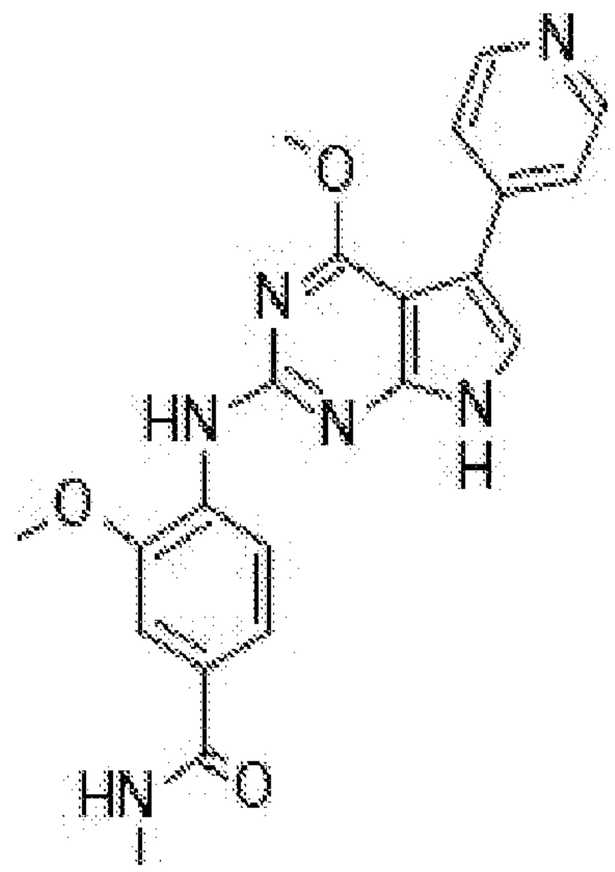
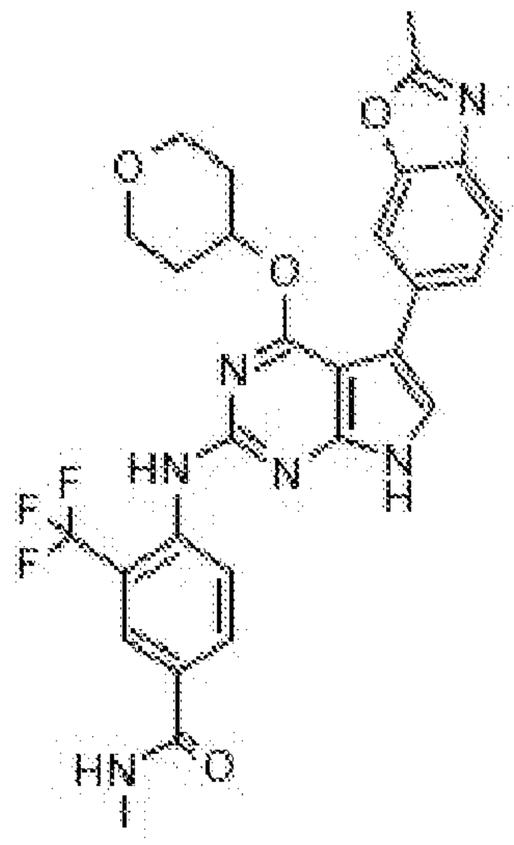
Cmpd No.	Structure	Name
176		(S)-N,N,3-trimethyl-4-(5-(pyridin-4-yl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
177		3-methoxy-4-(4-methoxy-5-(1-methyl-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide
178		(S)-3-methoxy-N-methyl-4-(5-(2-methylpyridin-4-yl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

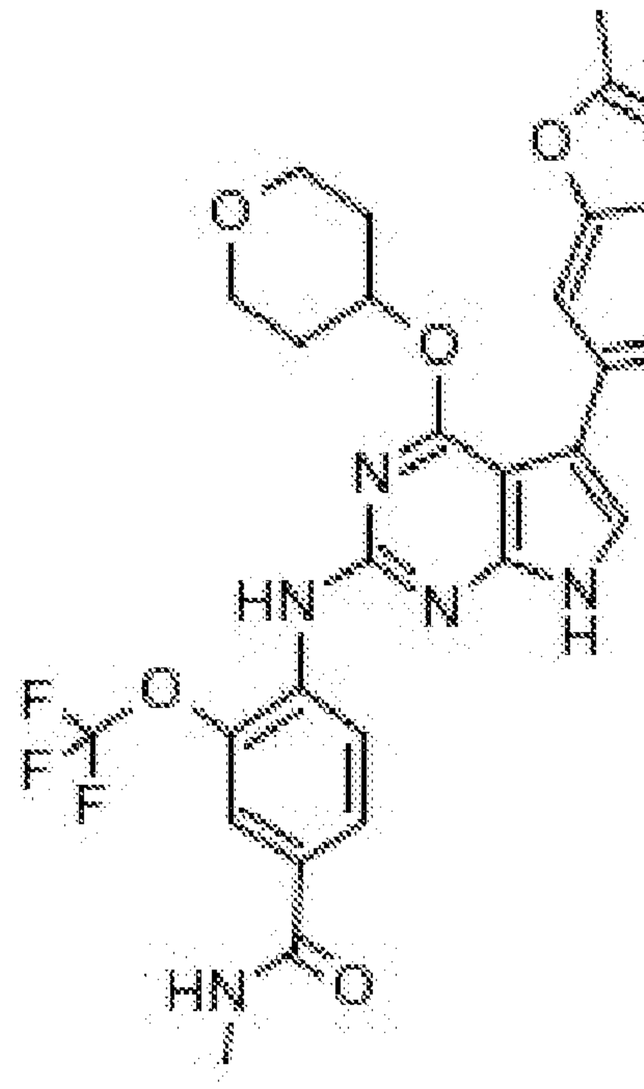
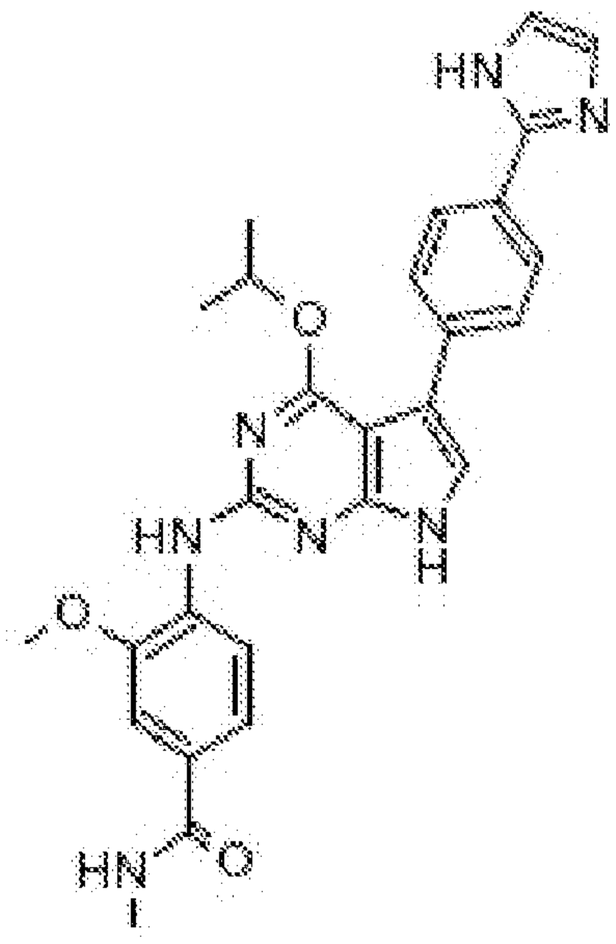
Cmpd No.	Structure	Name
179		3-methoxy-N-methyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(oxetan-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
180		3-(4-isopropoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-4-methoxy-N-methylbenzamide
181		4-methoxy-N-methyl-3-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

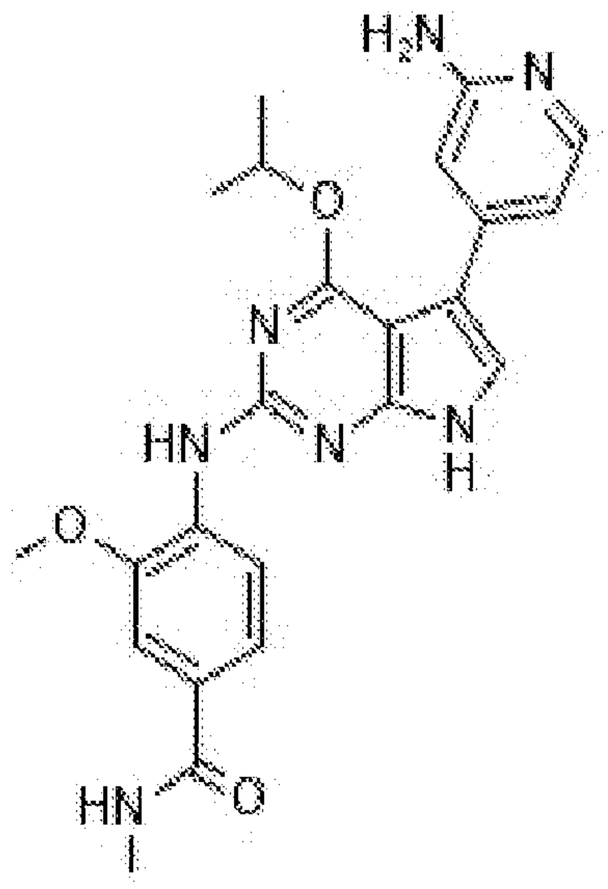
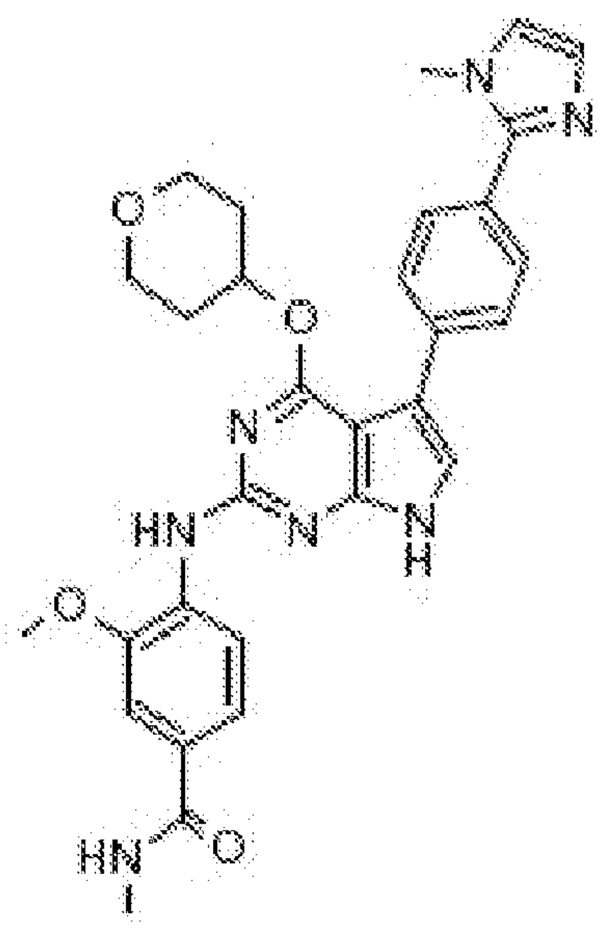
Cmpd No.	Structure	Name
182		(S)-3-methoxy-N-methyl-4-(5-(4-(methylcarbamoyl)phenyl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
183		6-methoxy-N-methyl-5-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)picolinamide
184		3-methoxy-N-methyl-4-(5-(1-methyl-1H-pyrazol-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

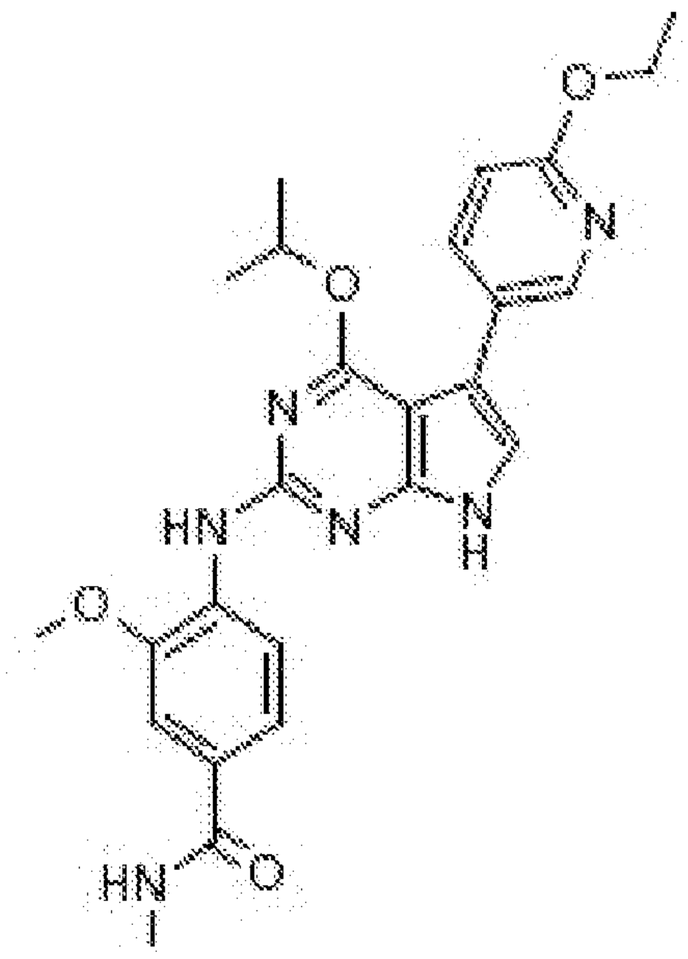
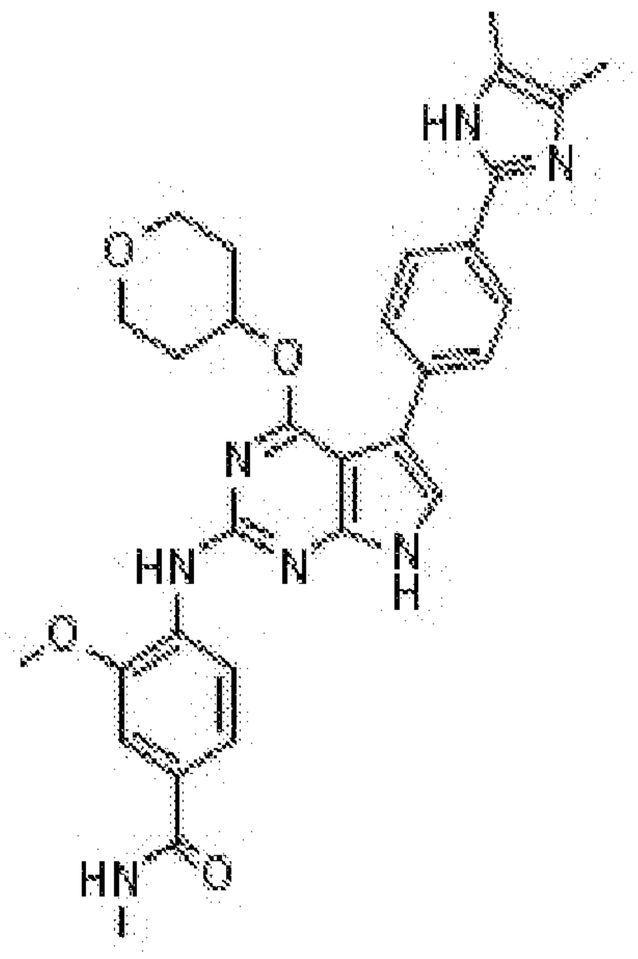
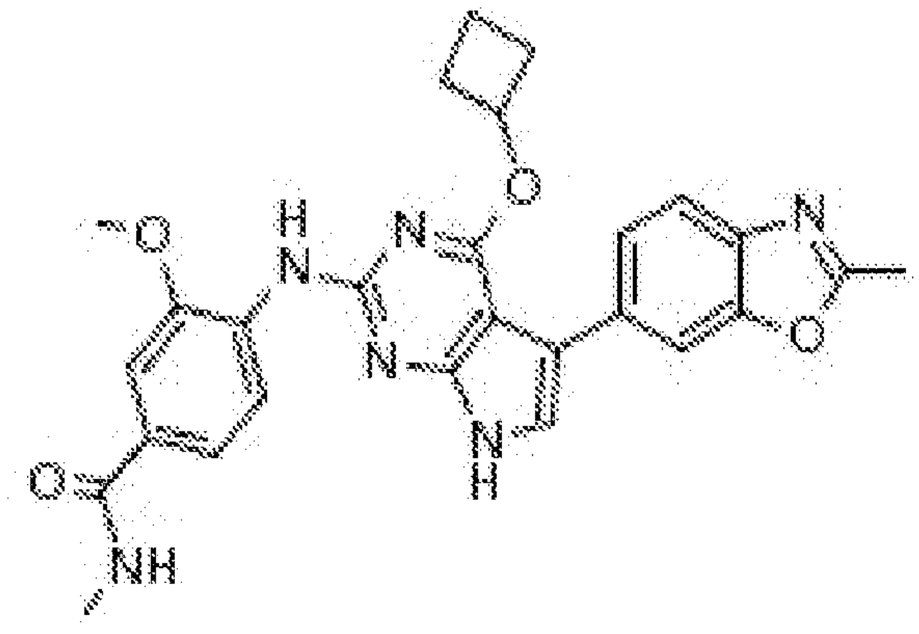
Cmpd No.	Structure	Name
185		4-(4-isopropoxy-5-(2-methoxypyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
186		3-methoxy-N-methyl-4-(5-(pyrazin-2-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
187		4-(4-isopropoxy-5-(3-(methylsulfonyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

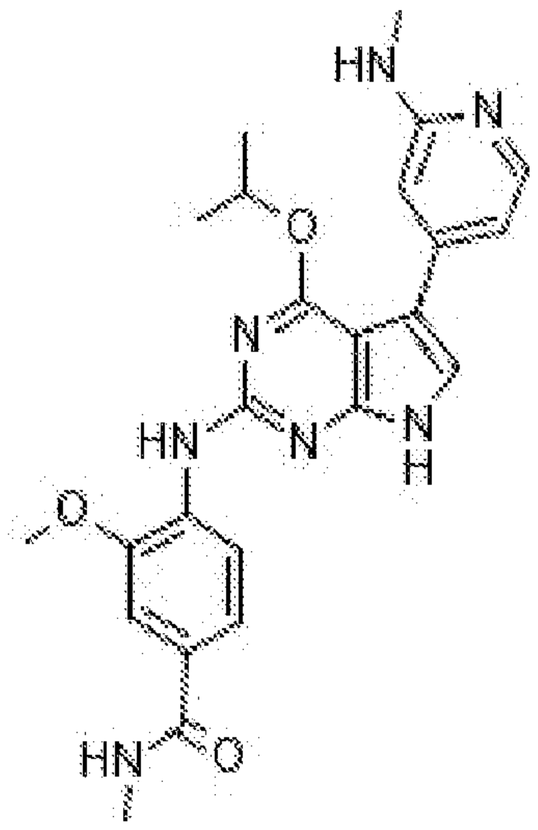
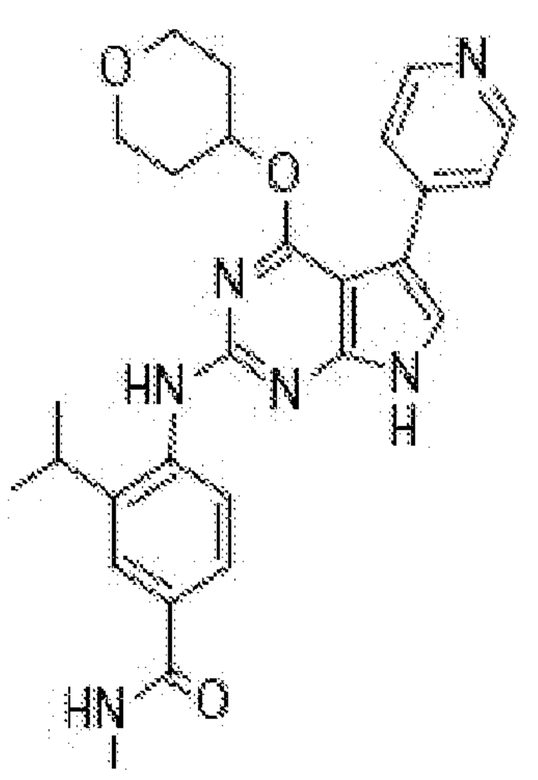
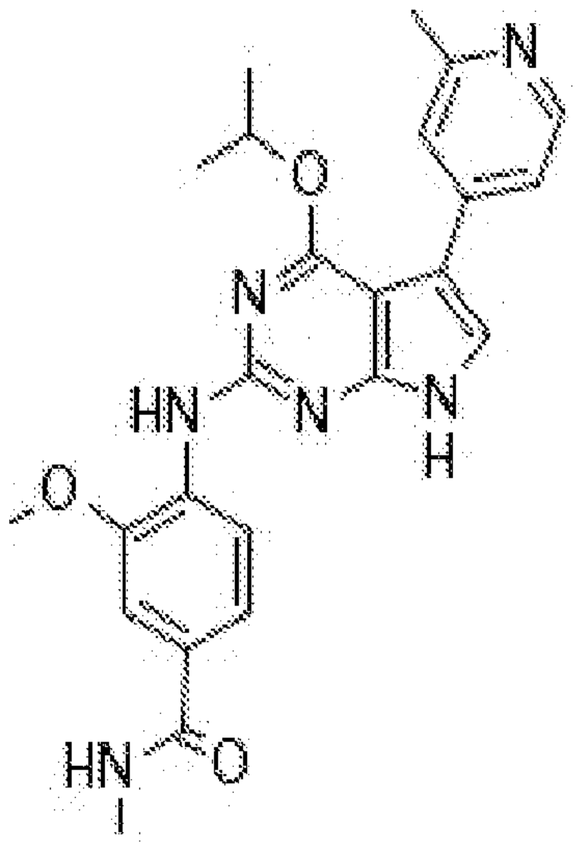
Cmpd No.	Structure	Name
188		4-(4-isopropoxy-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
189		4-(4-isopropoxy-5-(1-methyl-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

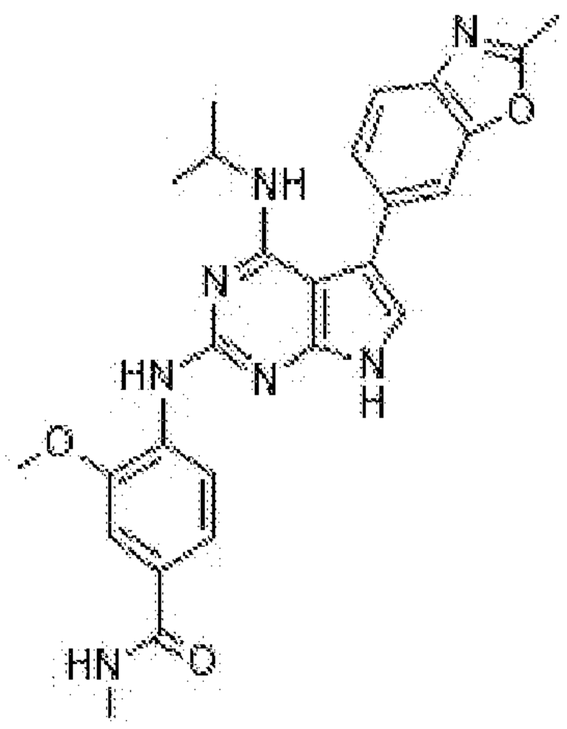
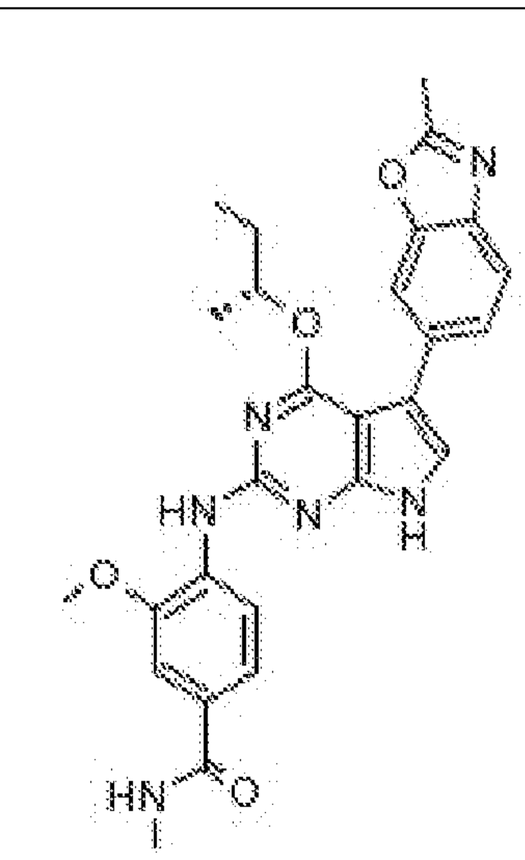
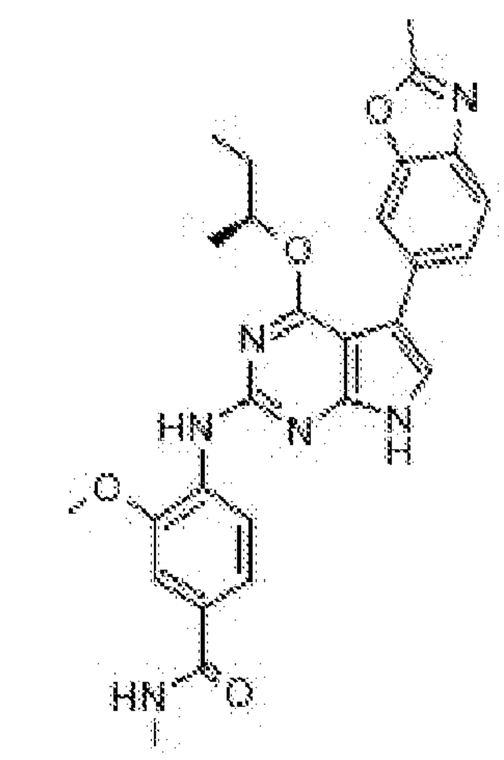
Cmpd No.	Structure	Name
190		3-methoxy-4-(4-methoxy-5-(pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide
191		N-methyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-(trifluoromethyl)benzamide

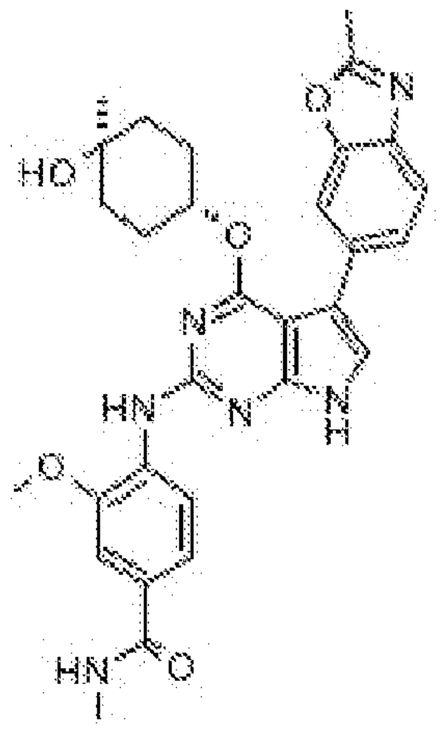
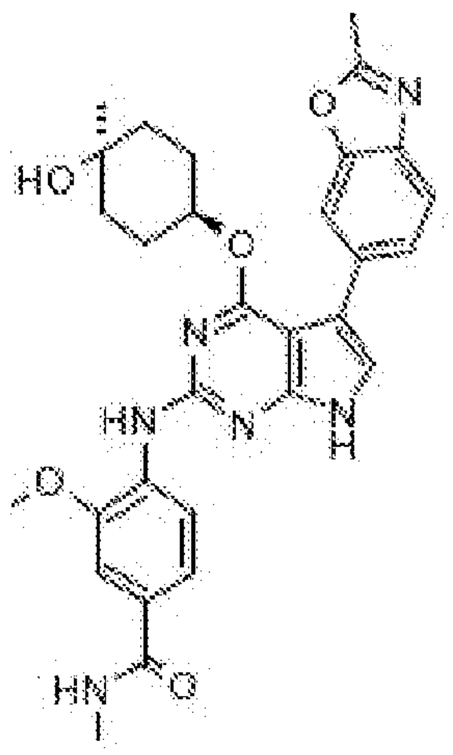
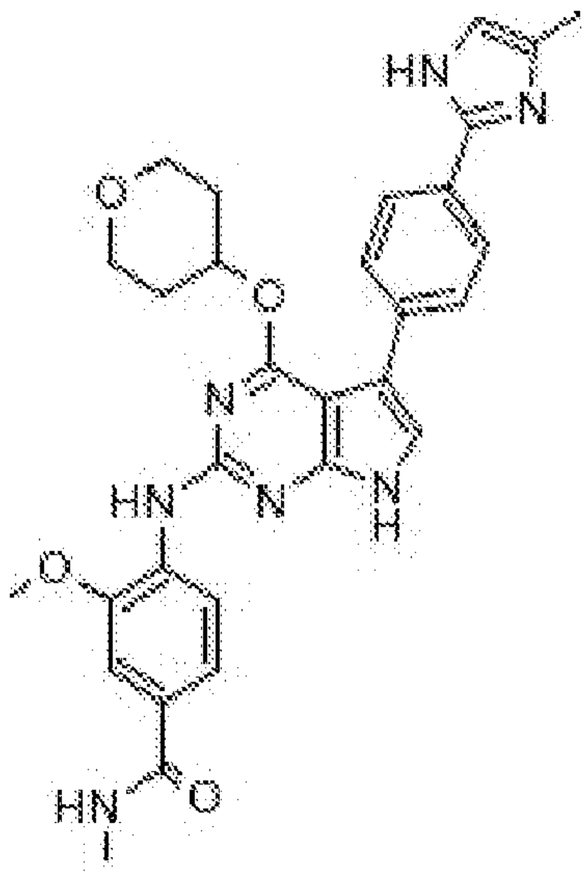
Cmpd No.	Structure	Name
192		N-methyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-(trifluoromethoxy)benzamide
193		4-(5-(4-(1H-imidazol-2-yl)phenyl)-4-isopropoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

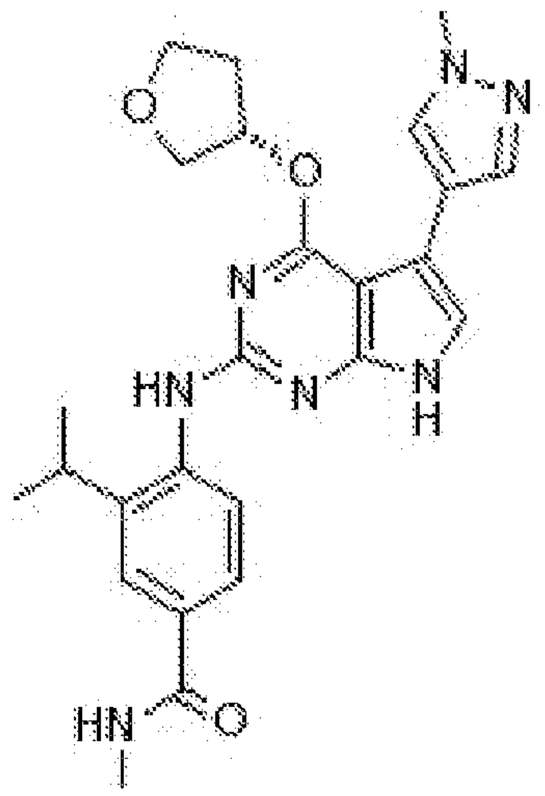
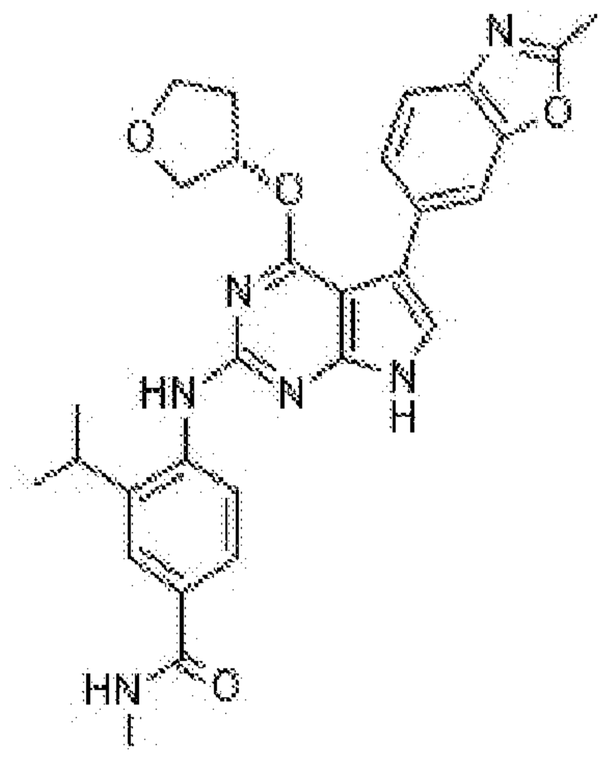
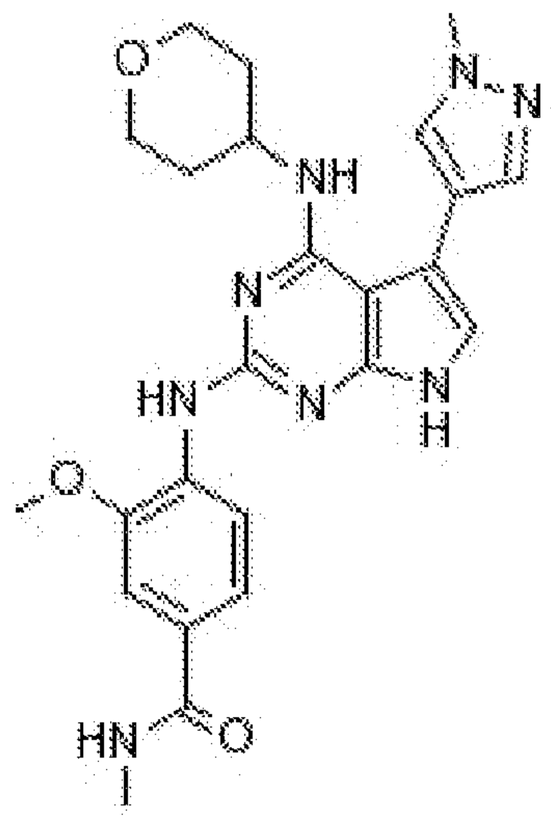
Cmpd No.	Structure	Name
194		4-(5-(2-aminopyridin-4-yl)-4-isopropoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
195		3-methoxy-N-methyl-4-(5-(4-(1-methyl-1H-imidazol-2-yl)phenyl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

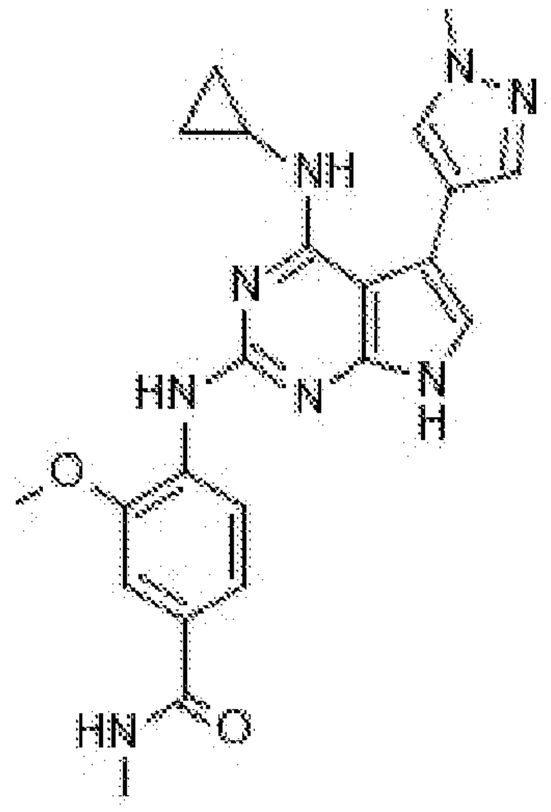
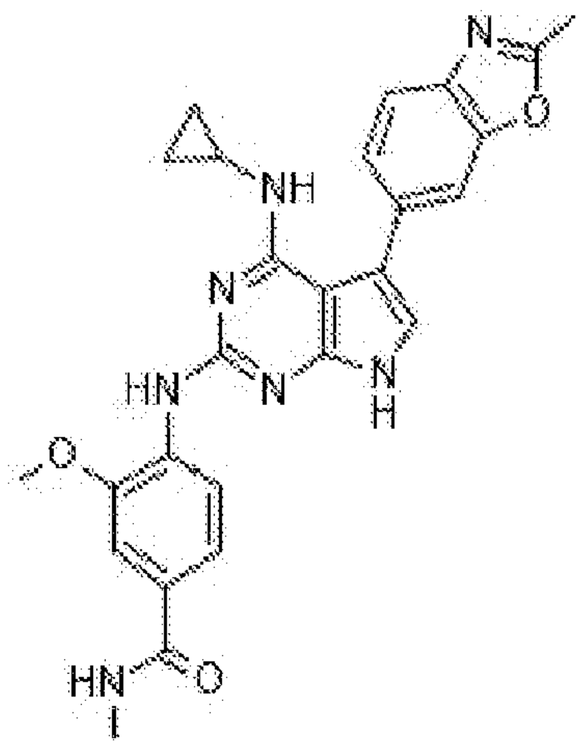
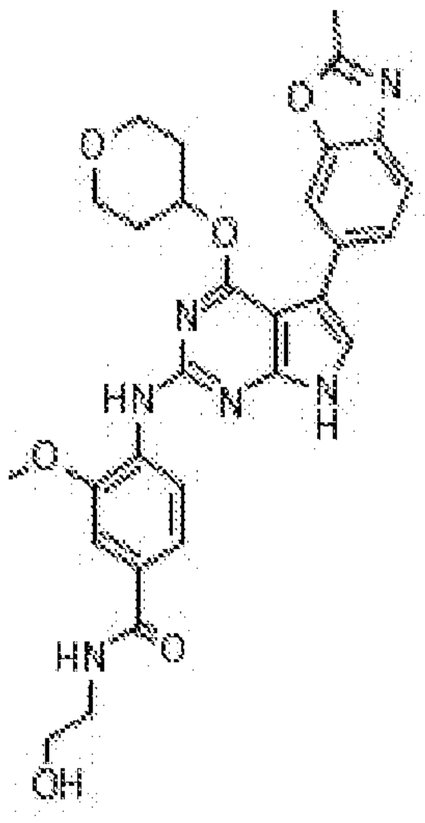
Cmpd No.	Structure	Name
196		4-(5-(6-ethoxypyridin-3-yl)-4-isopropoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
197		4-(5-(4-(4,5-dimethyl-1H-imidazol-2-yl)phenyl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
198		4-(4-cyclobutoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

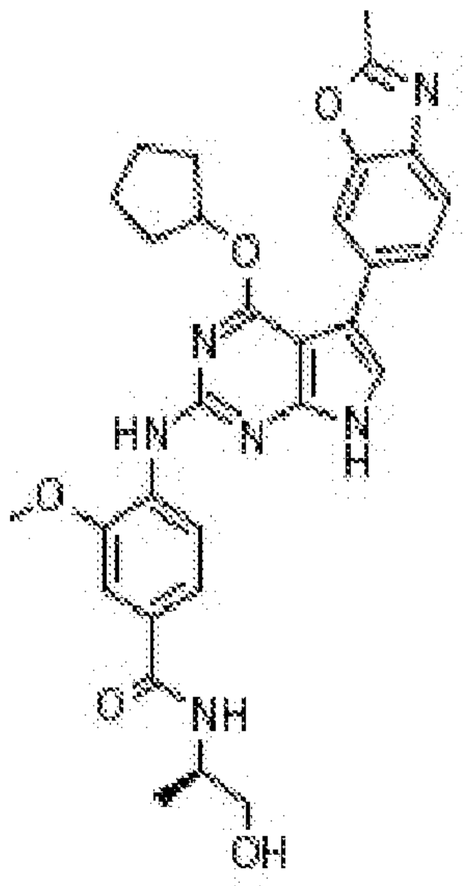
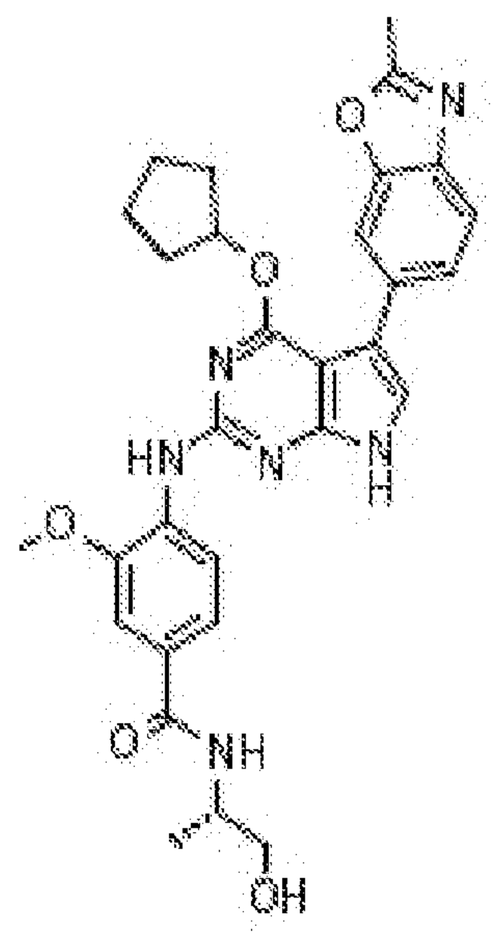
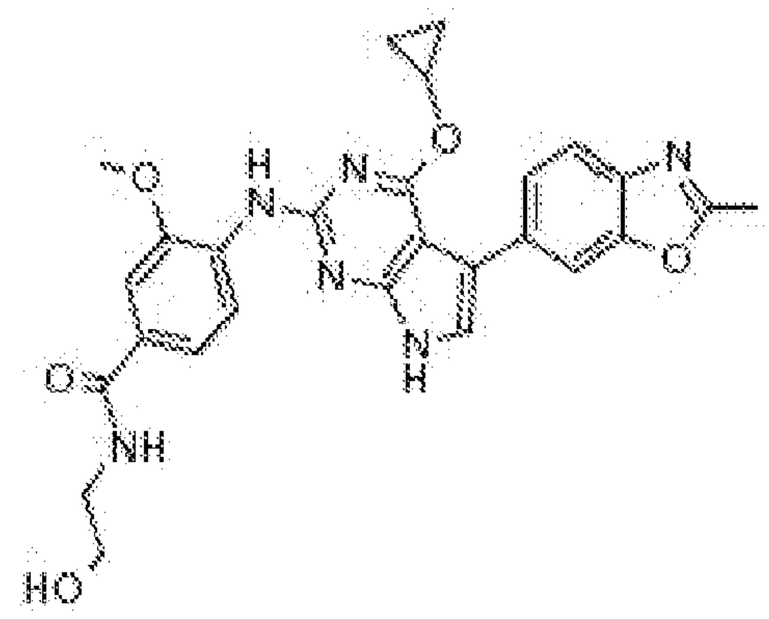
Cmpd No.	Structure	Name
199		4-(4-isopropoxy-5-(2-(methylamino)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
200		3-isopropyl-N-methyl-4-(5-(pyridin-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
201		4-(4-isopropoxy-5-(2-methylpyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

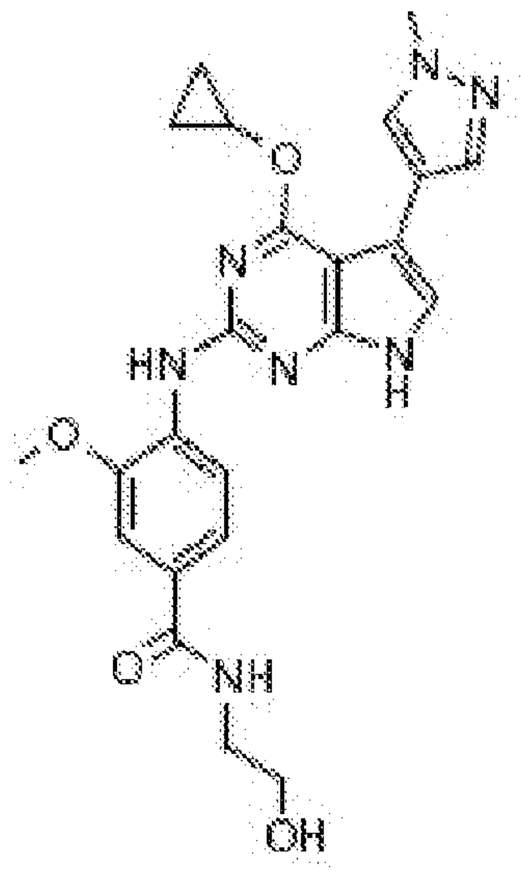
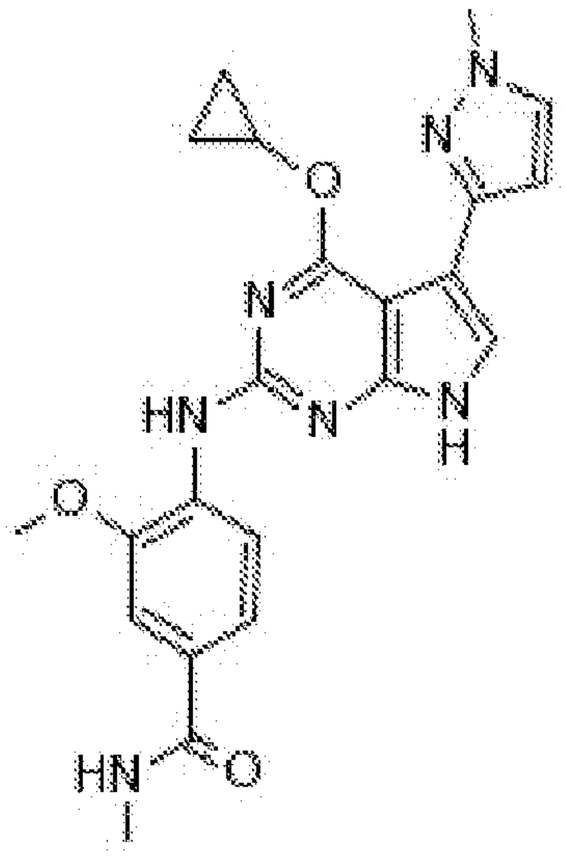
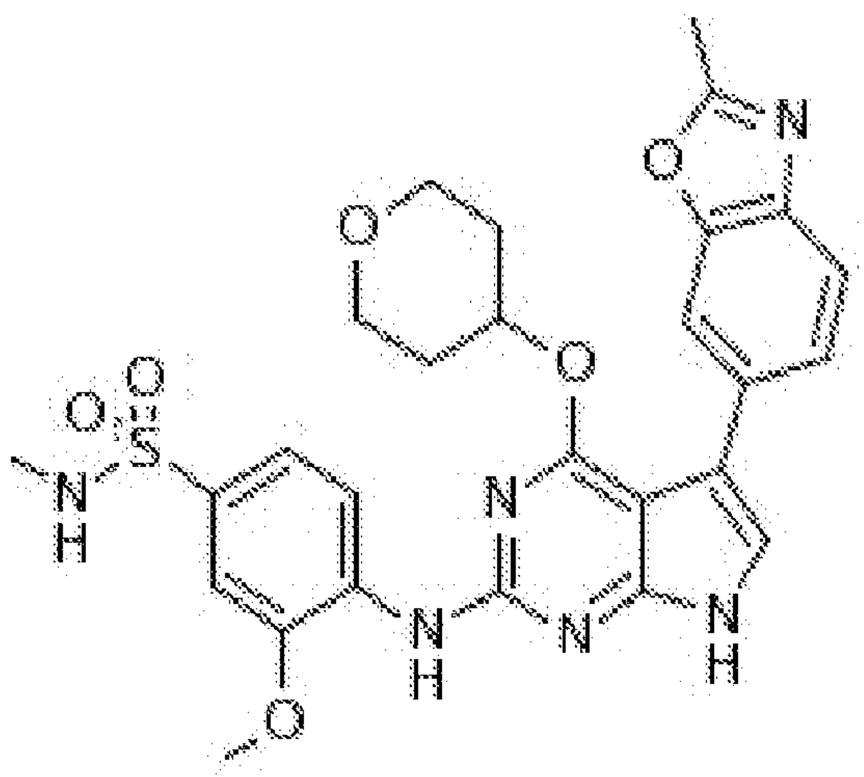
Cmpd No.	Structure	Name
202		4-(4-(isopropylamino)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
203		(R)-4-(4-sec-butoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
204		(S)-4-(4-sec-butoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

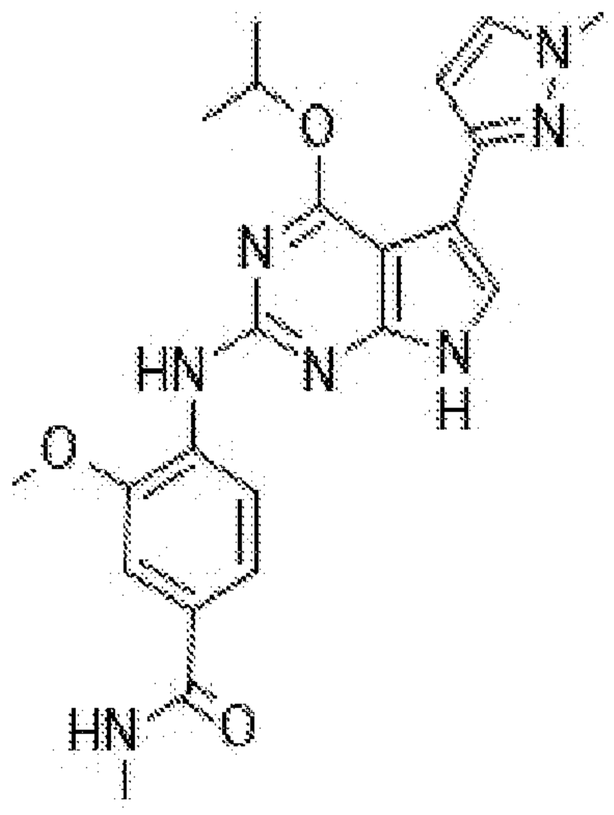
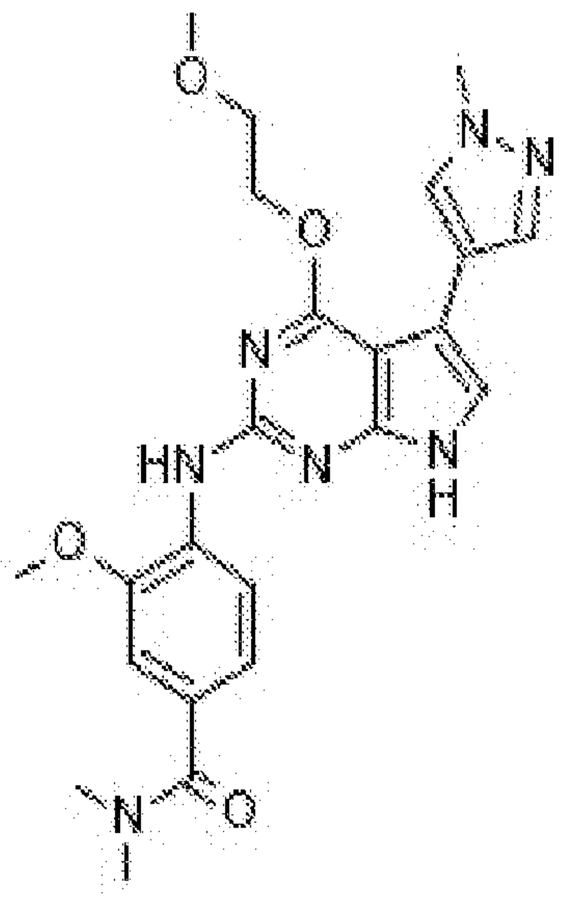
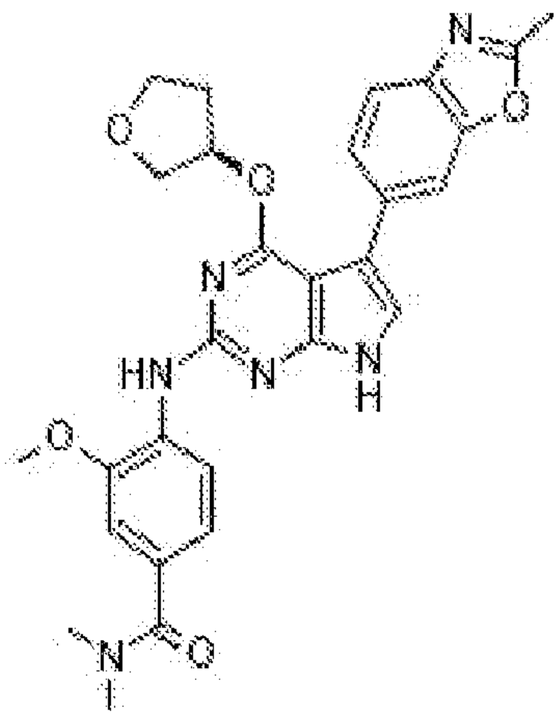
Cmpd No.	Structure	Name
205		4-(4-((1r,4r)-4-hydroxy-4-methylcyclohexyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
206		4-(4-((1s,4s)-4-hydroxy-4-methylcyclohexyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
207		3-methoxy-N-methyl-4-(5-(4-(4-methyl-1H-imidazol-2-yl)phenyl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

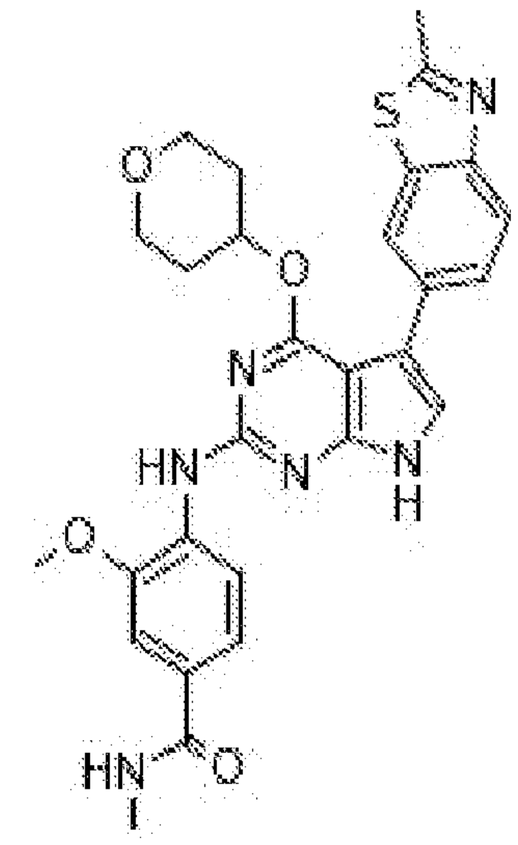
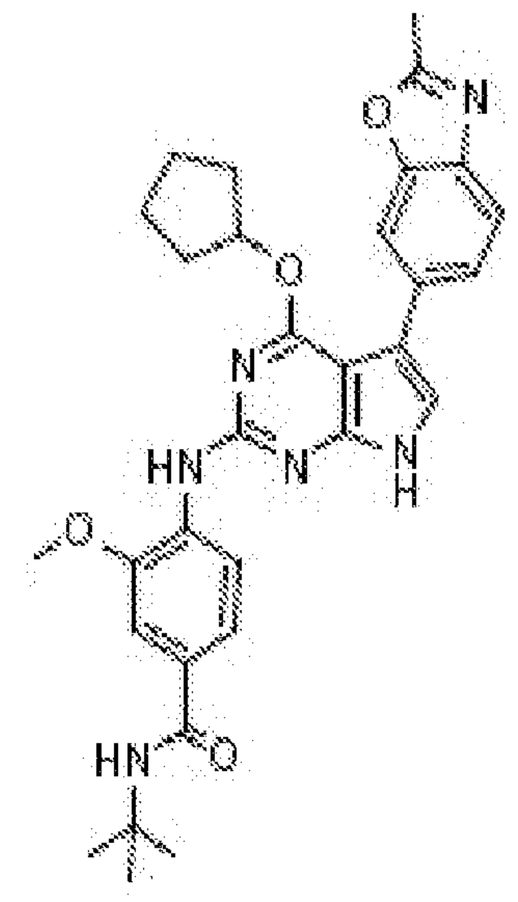
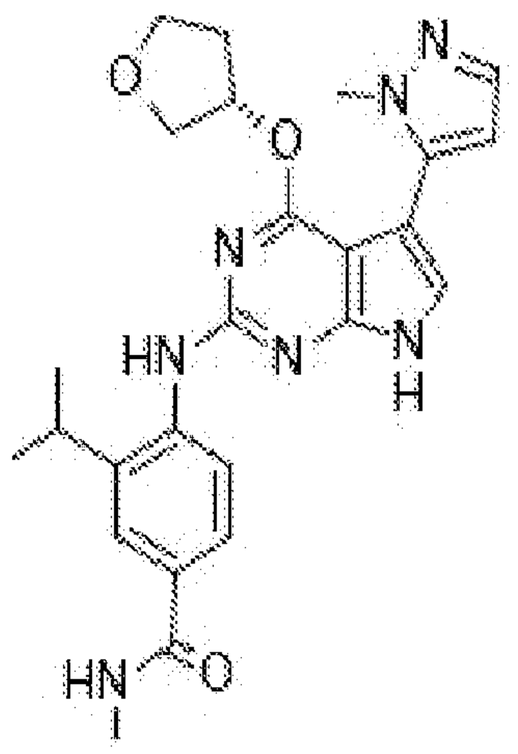
Cmpd No.	Structure	Name
208		(S)-3-isopropyl-N-methyl-4-(5-(1-methyl-1H-pyrazol-4-yl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
209		(S)-3-isopropyl-N-methyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
210		3-methoxy-N-methyl-4-(5-(1-methyl-1H-pyrazol-4-yl)-4-(tetrahydro-2H-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

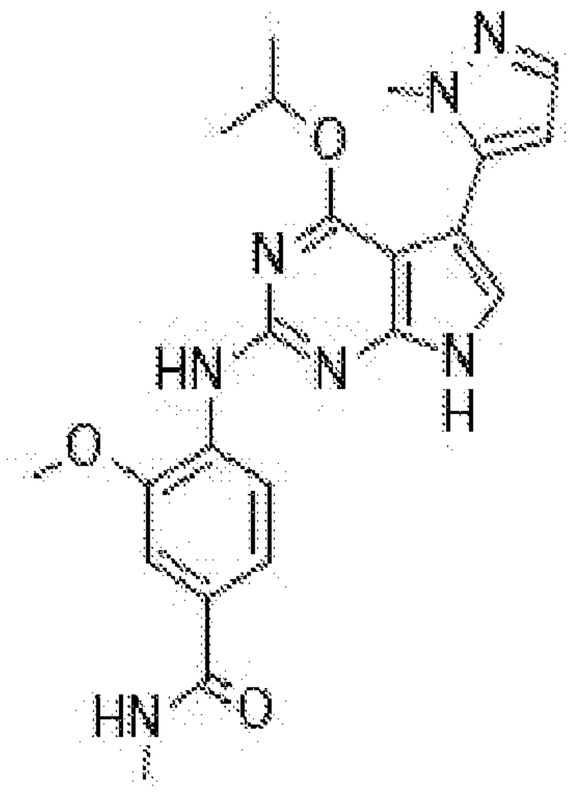
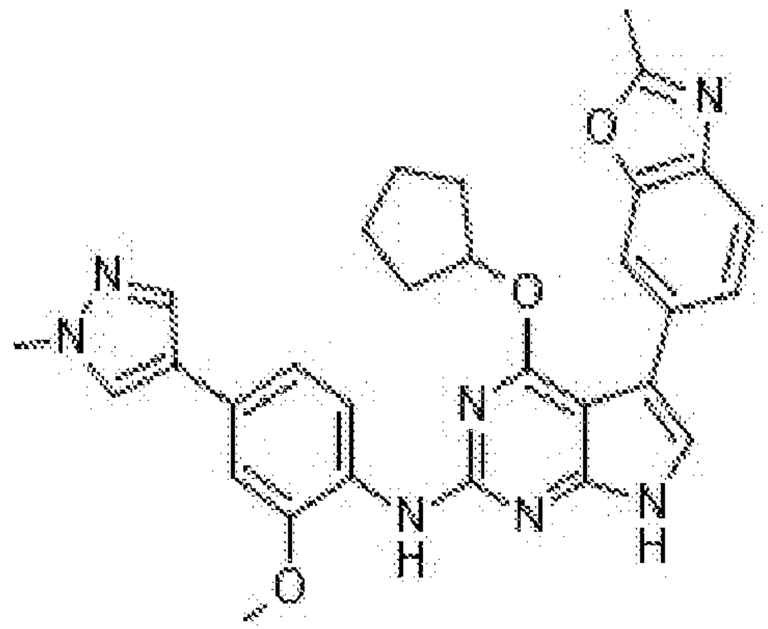
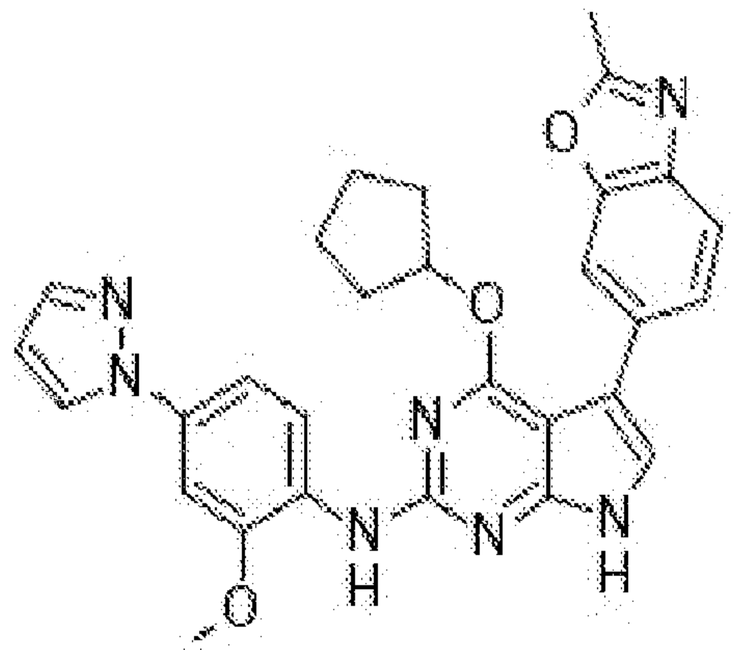
Cmpd No.	Structure	Name
211		4-(4-(cyclopropylamino)-5-(1-methyl-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
212		4-(4-(cyclopropylamino)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
213		N-(2-hydroxyethyl)-3-methoxy-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

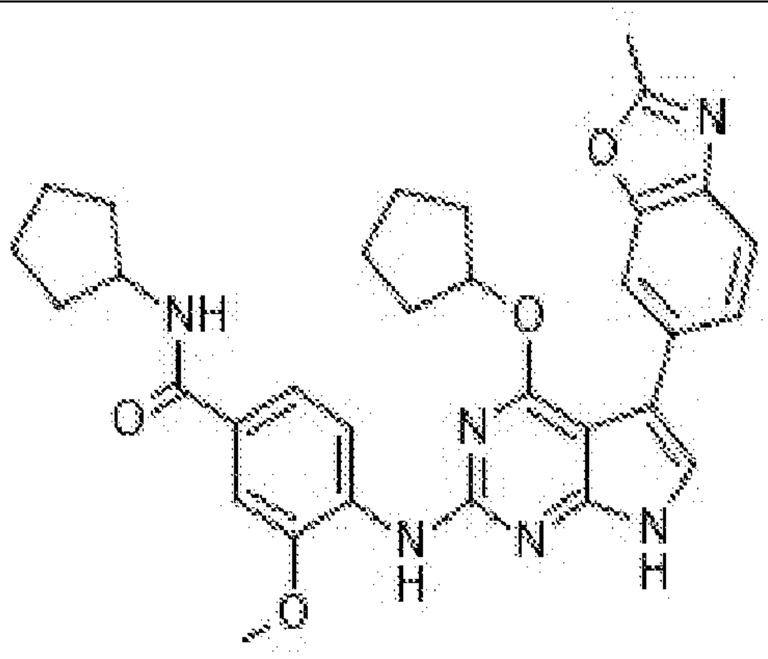
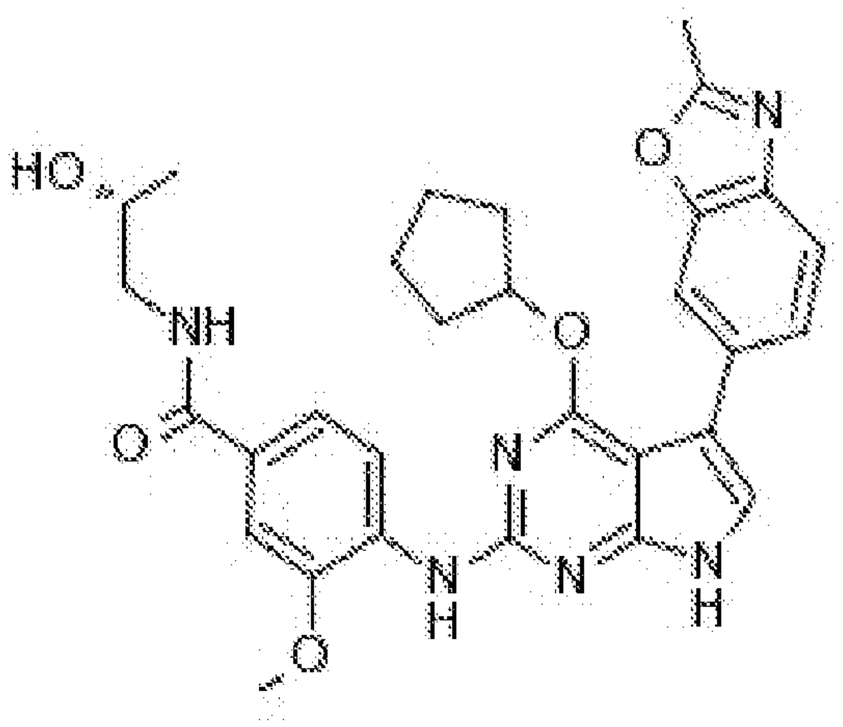
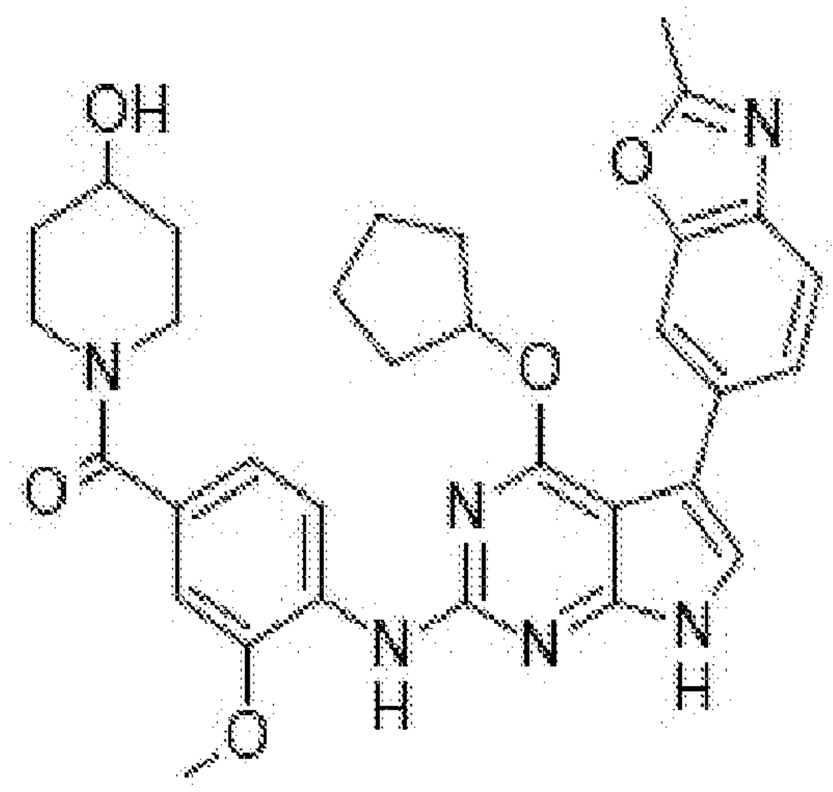
Cmpd No.	Structure	Name
214		(R)-4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(1-hydroxypropan-2-yl)-3-methoxybenzamide
215		(S)-4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(1-hydroxypropan-2-yl)-3-methoxybenzamide
216		4-(4-cyclopropoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(2-hydroxyethyl)-3-methoxybenzamide

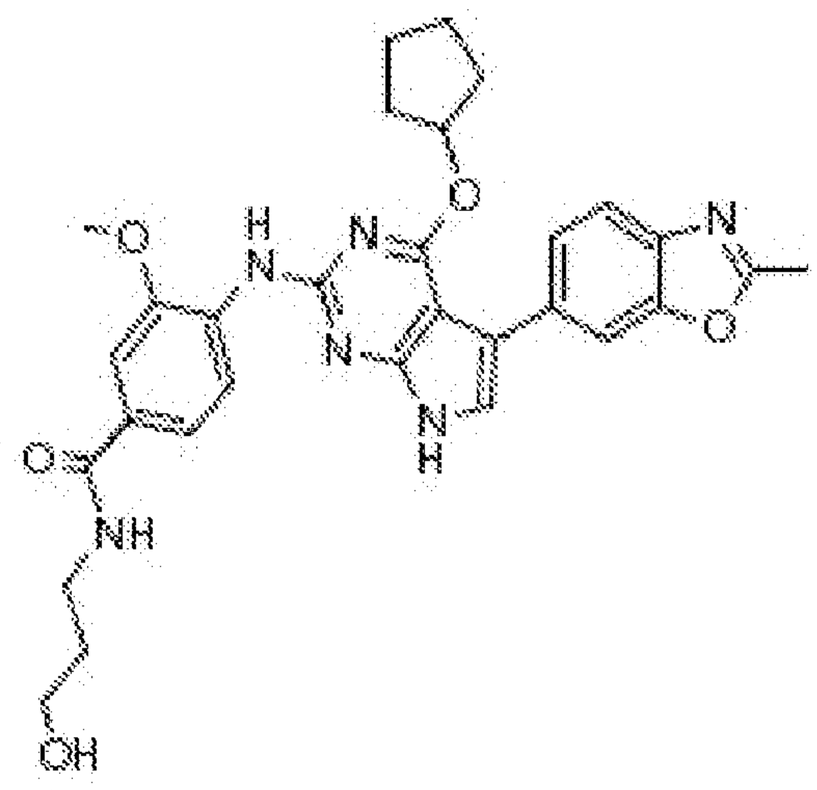
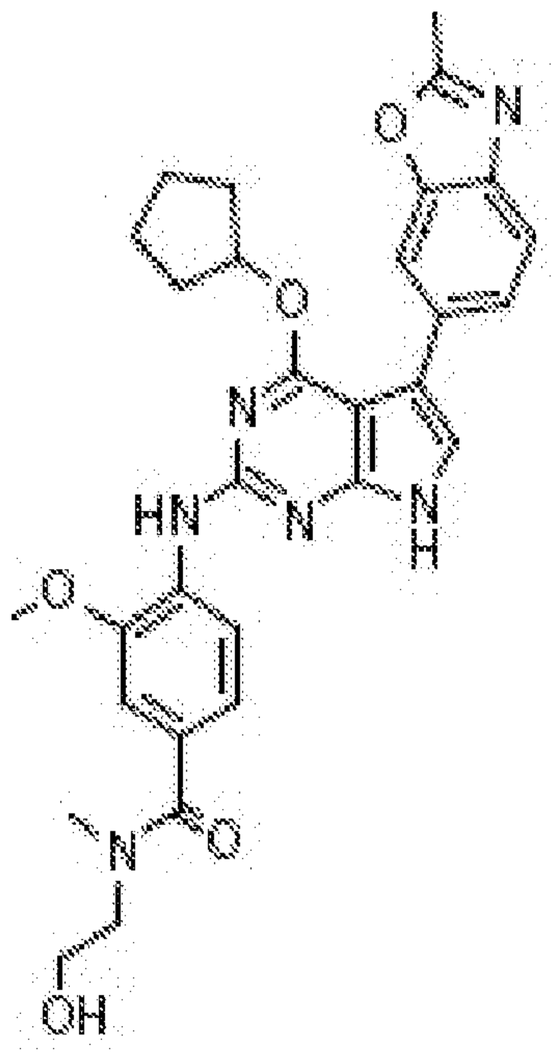
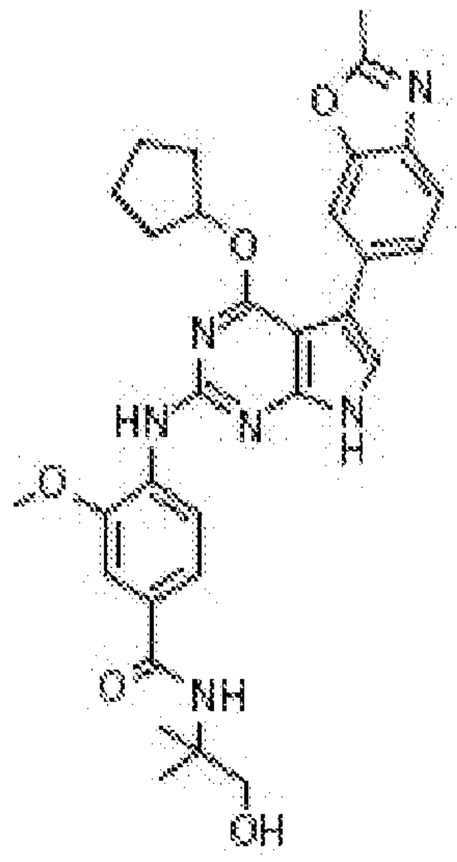
Cmpd No.	Structure	Name
217		4-(4-cyclopropoxy-5-(1-methyl-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(2-hydroxyethyl)-3-methoxybenzamide
218		4-(4-cyclopropoxy-5-(1-methyl-1H-pyrazol-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
219		3-methoxy-N-methyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzenesulfonamide

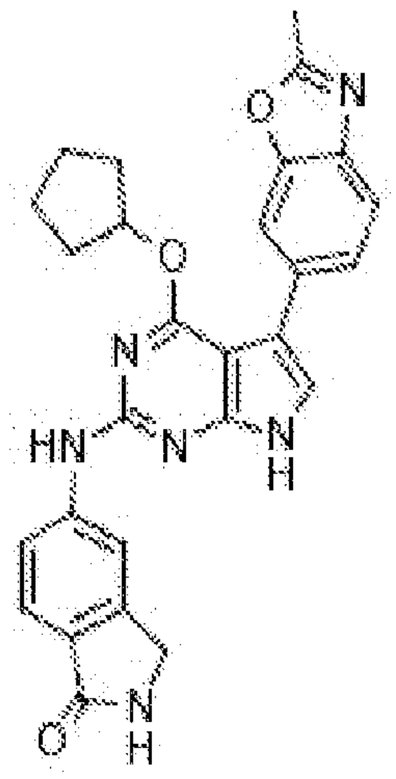
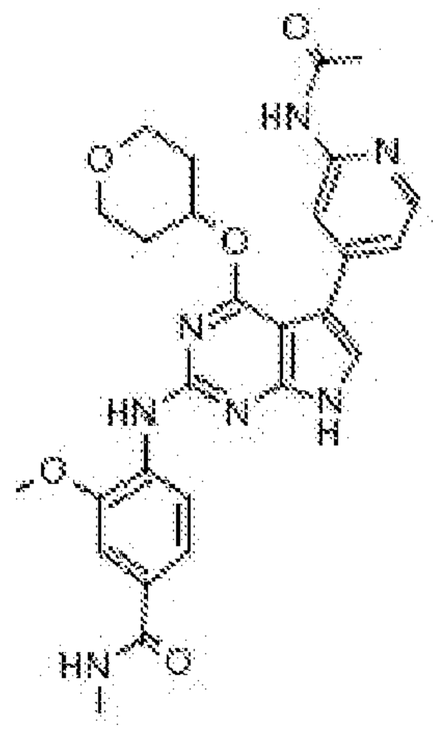
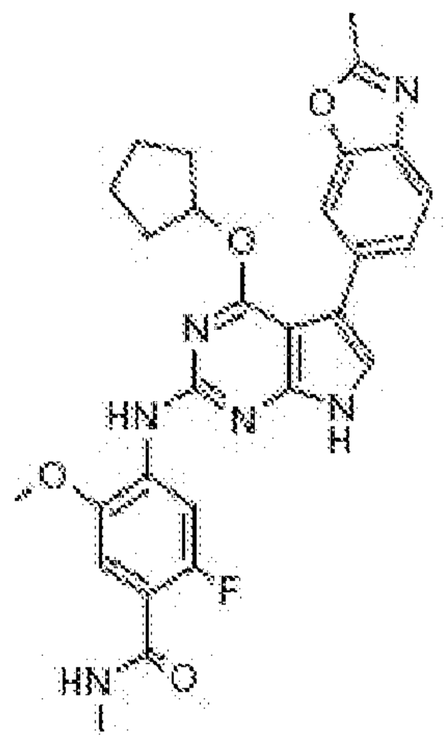
Cmpd No.	Structure	Name
220		4-(4-isopropoxy-5-(1-methyl-1H-pyrazol-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
221		3-methoxy-4-(4-(2-methoxyethoxy)-5-(1-methyl-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N-dimethylbenzamide
222		(R)-3-methoxy-N,N-dimethyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

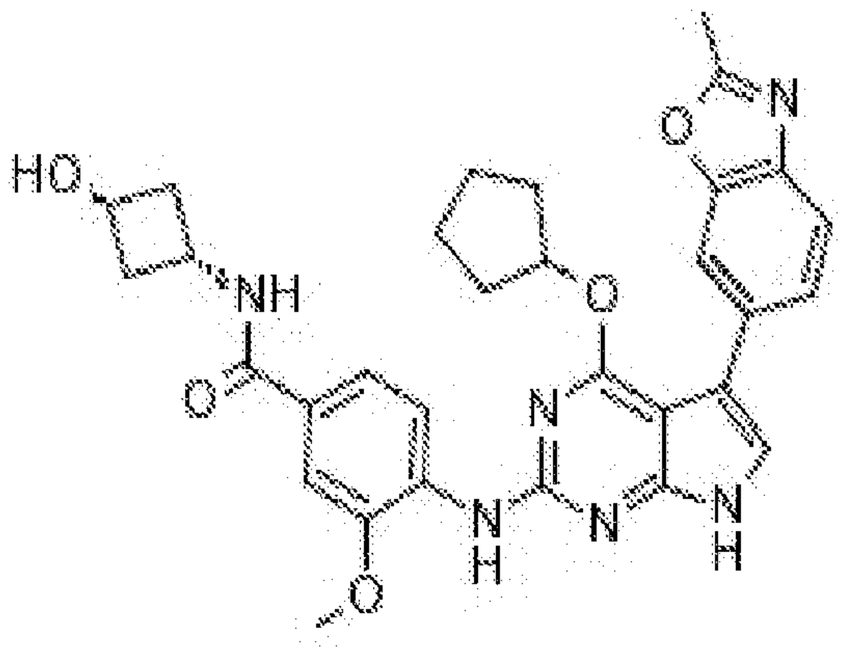
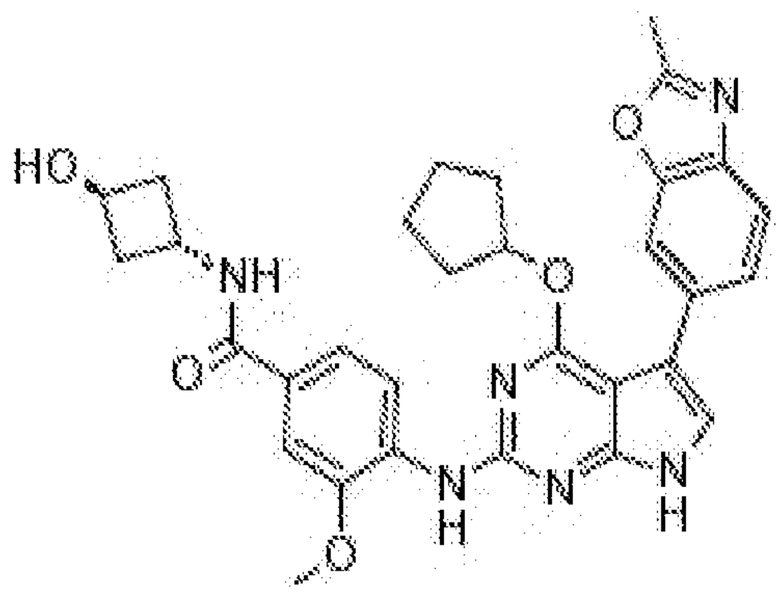
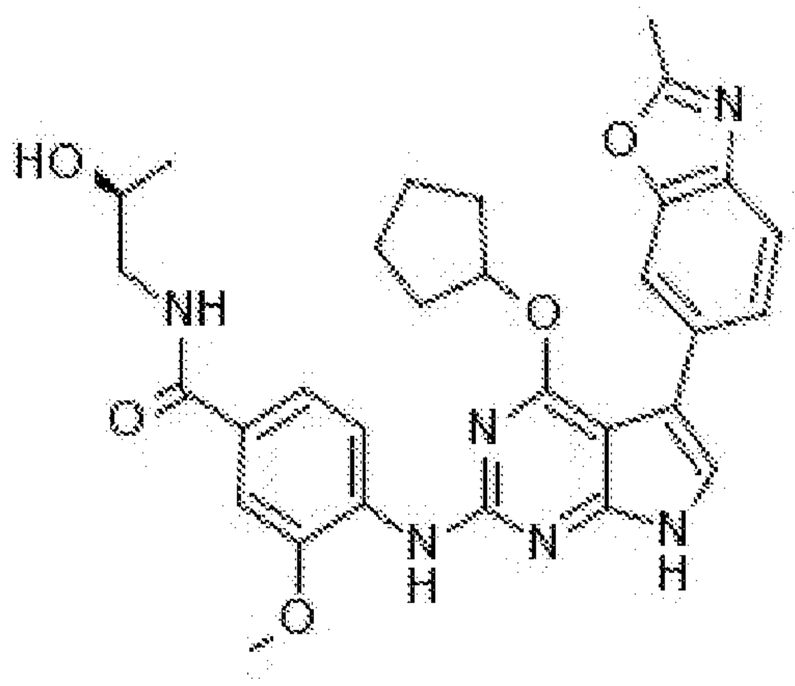
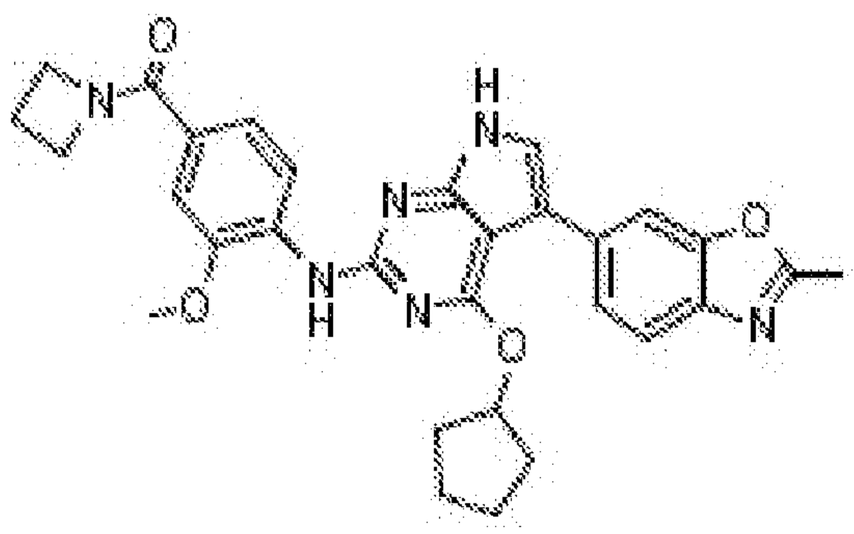
Cmpd No.	Structure	Name
223		3-methoxy-N-methyl-4-(5-(2-methylbenzo[d]thiazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
224		N-tert-butyl-4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxybenzamide
225		(S)-3-isopropyl-N-methyl-4-(5-(1-methyl-1H-pyrazol-5-yl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

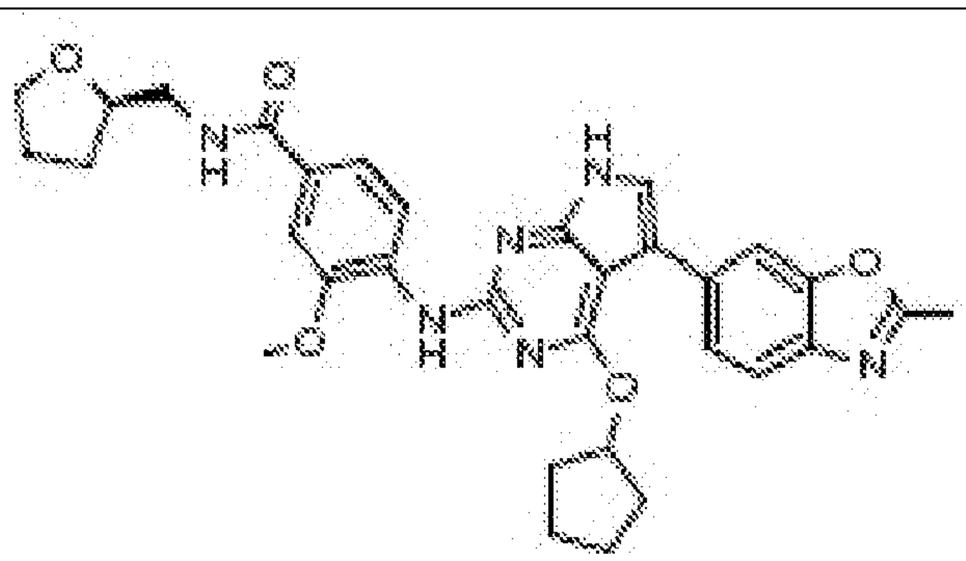
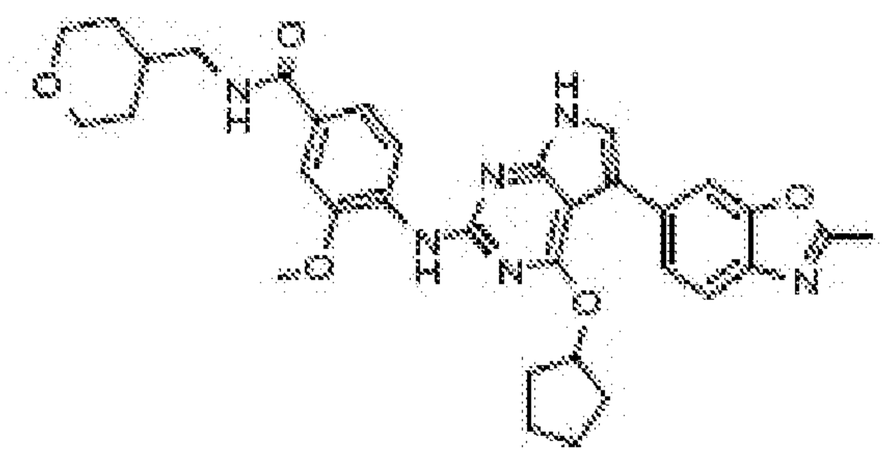
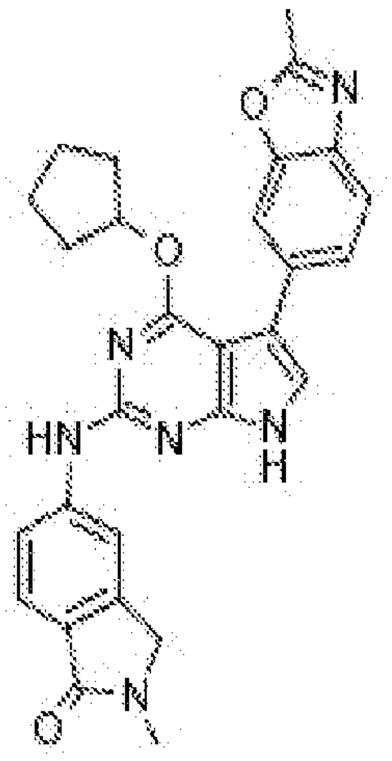
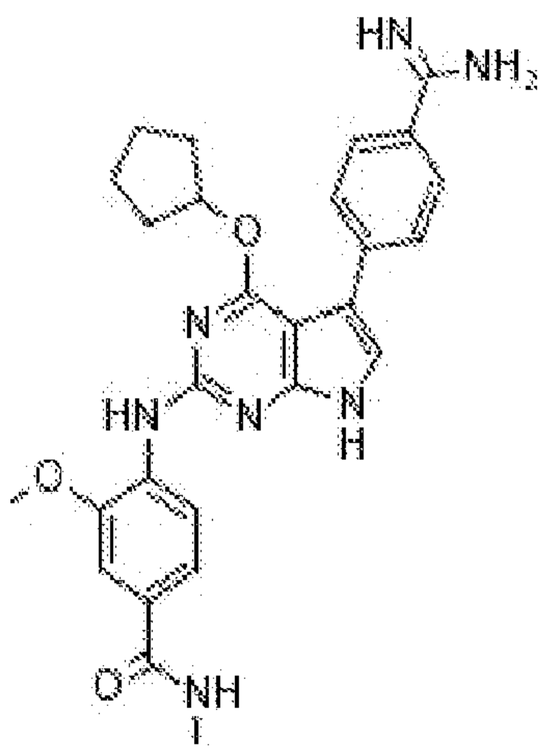
Cmpd No.	Structure	Name
226		4-(4-isopropoxy-5-(1-methyl-1H-pyrazol-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
227		4-(cyclopentyloxy)-N-(2-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine
228		4-(cyclopentyloxy)-N-(2-methoxy-4-(1H-pyrazol-1-yl)phenyl)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine

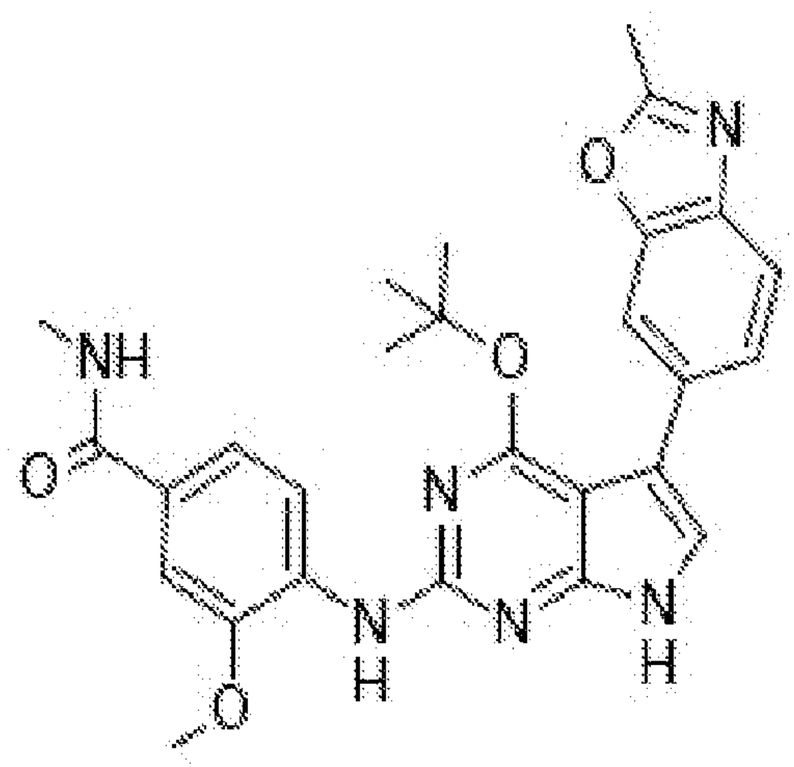
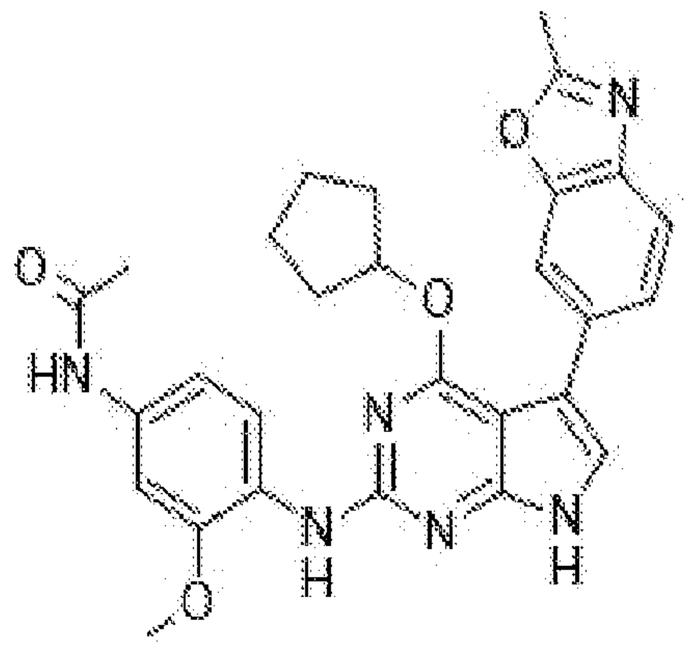
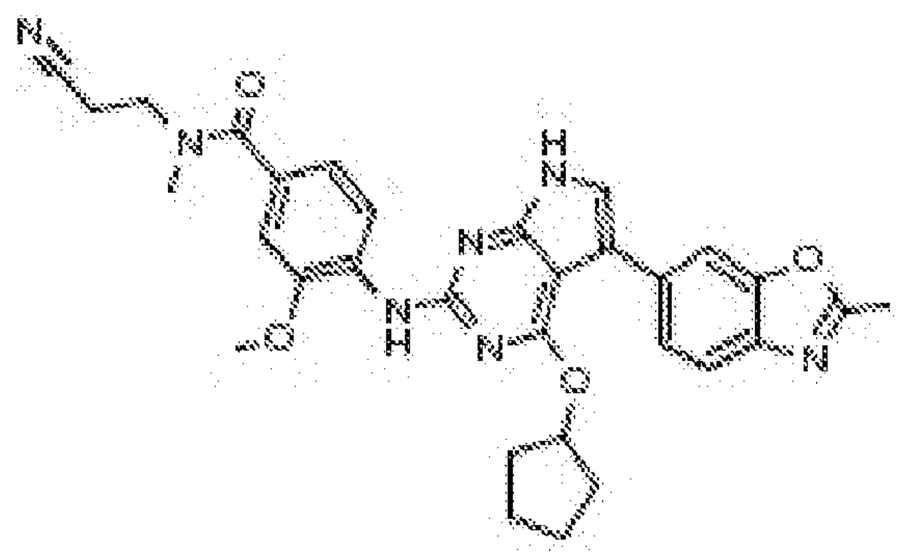
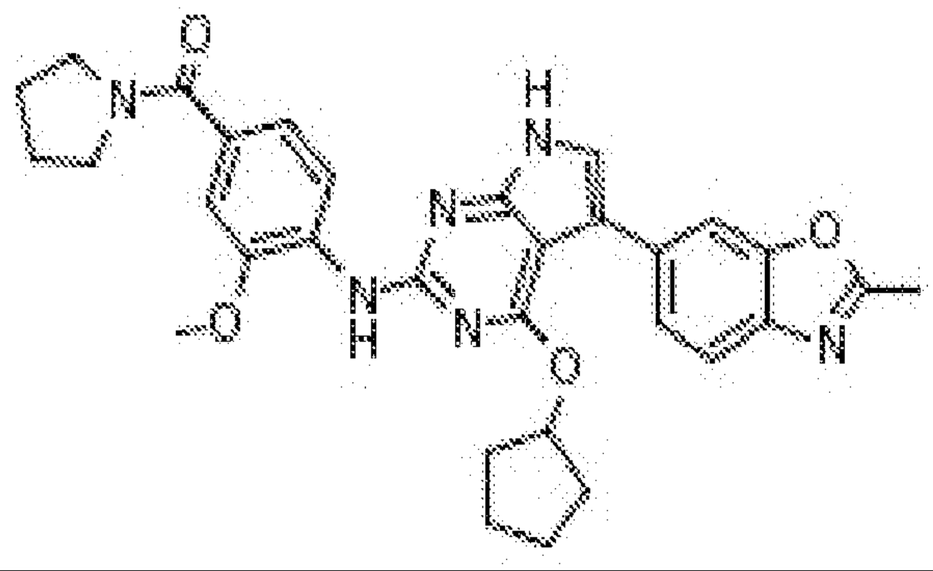
Cmpd No.	Structure	Name
229		N-cyclopentyl-4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxybenzamide
230		(R)-4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(2-hydroxypropyl)-3-methoxybenzamide
231		(4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxyphenyl)(4-hydroxypiperidin-1-yl)methanone

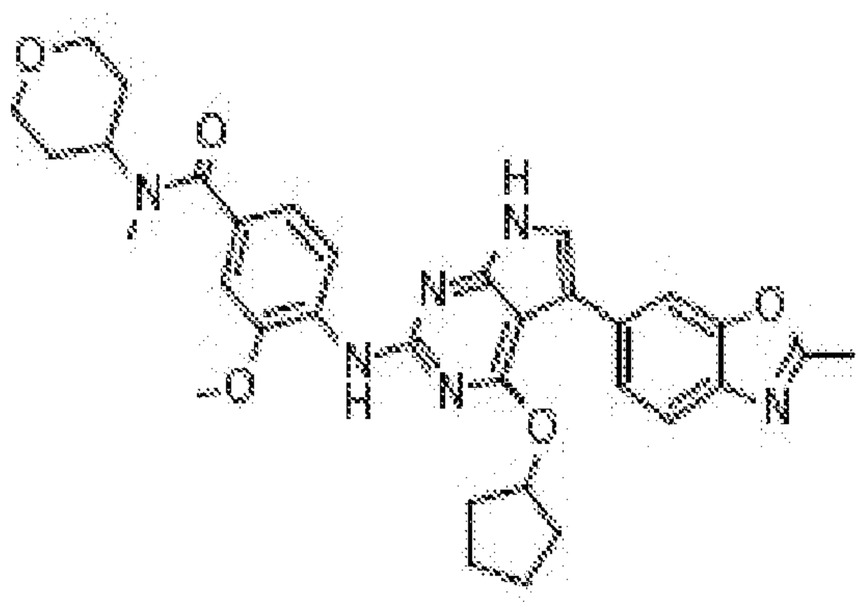
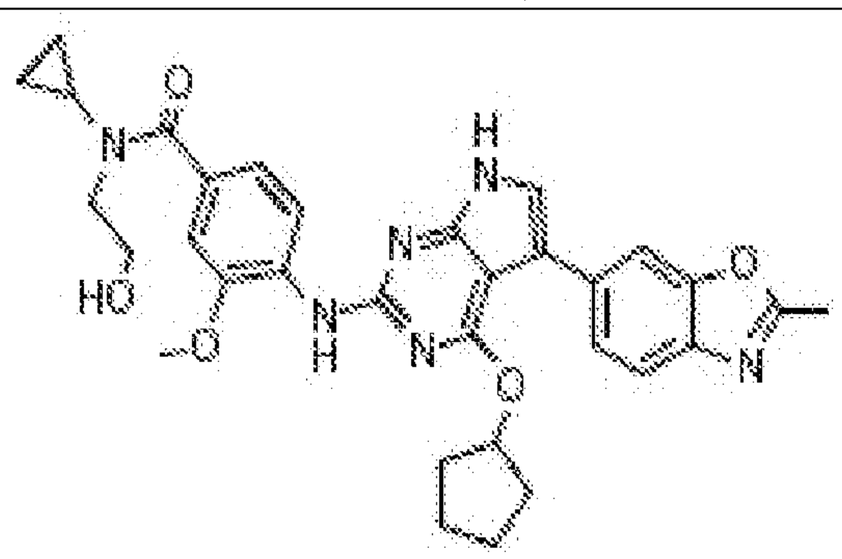
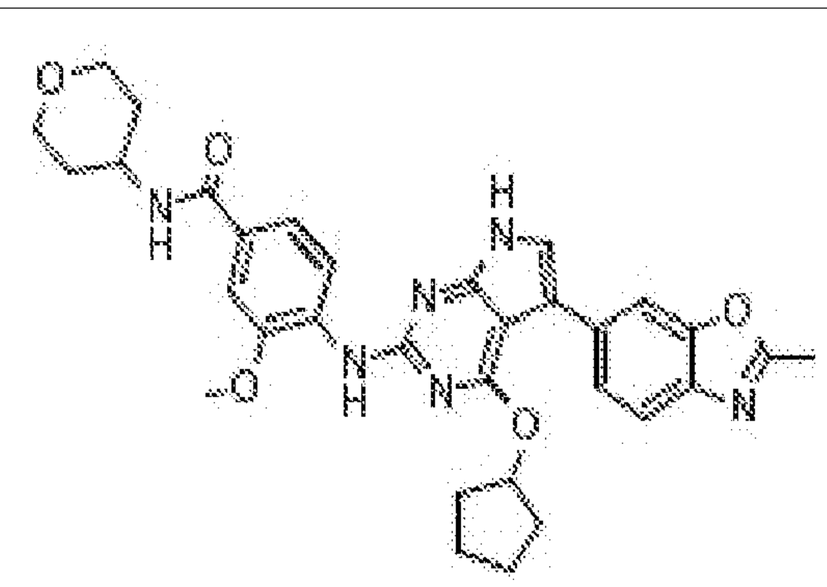
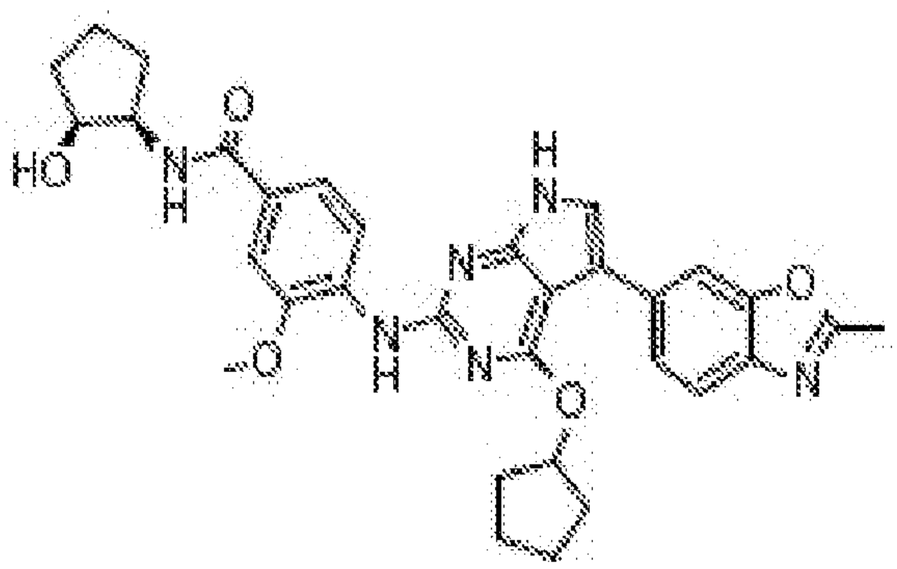
Cmpd No.	Structure	Name
232		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(3-hydroxypropyl)-3-methoxybenzamide
233		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(2-hydroxyethyl)-3-methoxy-N-methylbenzamide
234		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(1-hydroxy-2-methylpropan-2-yl)-3-methoxybenzamide

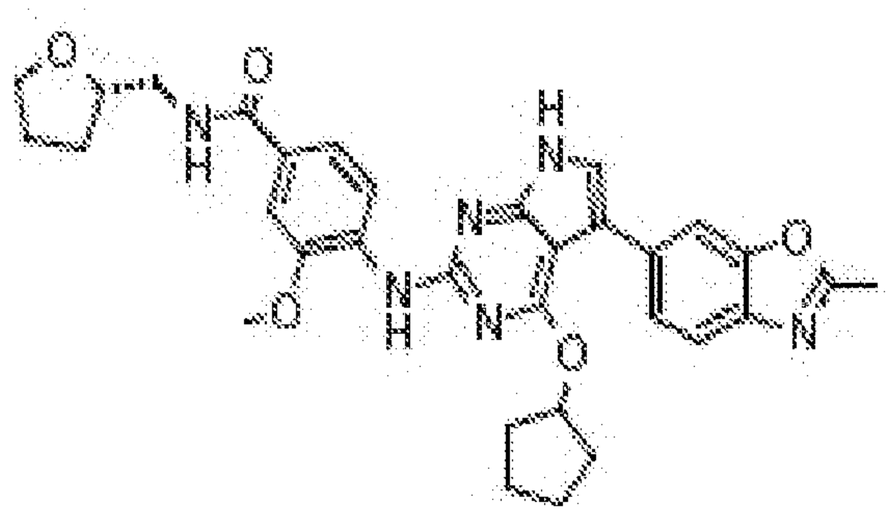
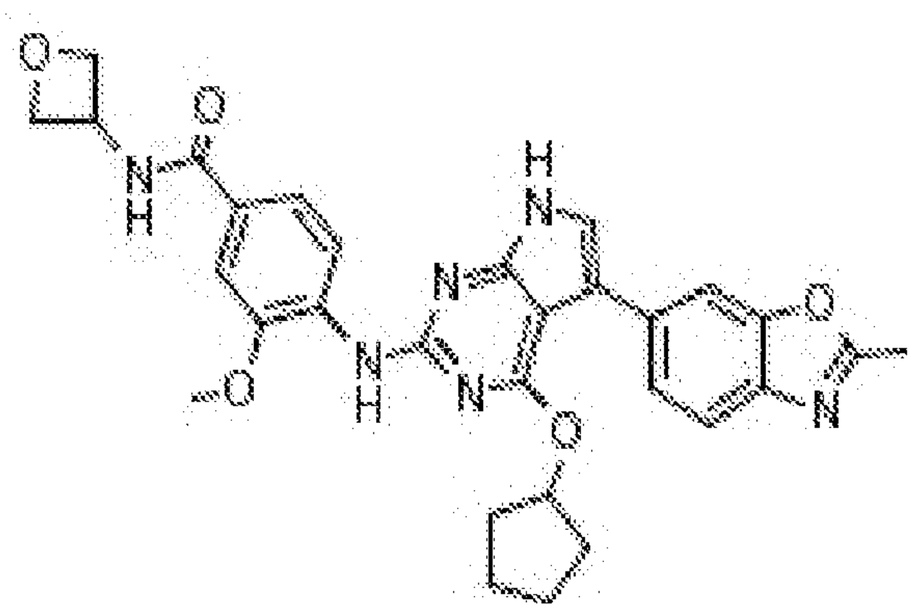
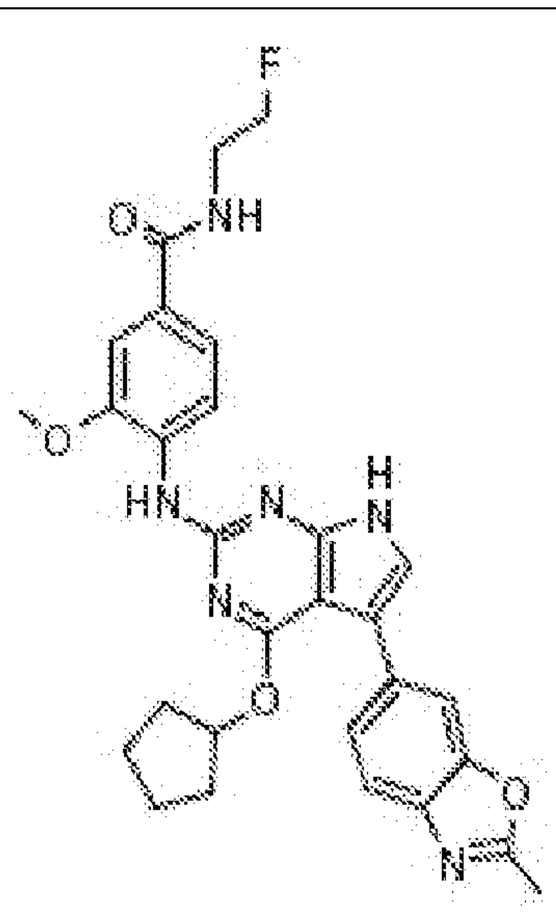
Cmpd No.	Structure	Name
235		5-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)isoindolin-1-one
236		4-(5-(2-acetamidopyridin-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
237		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-fluoro-5-methoxy-N-methylbenzamide

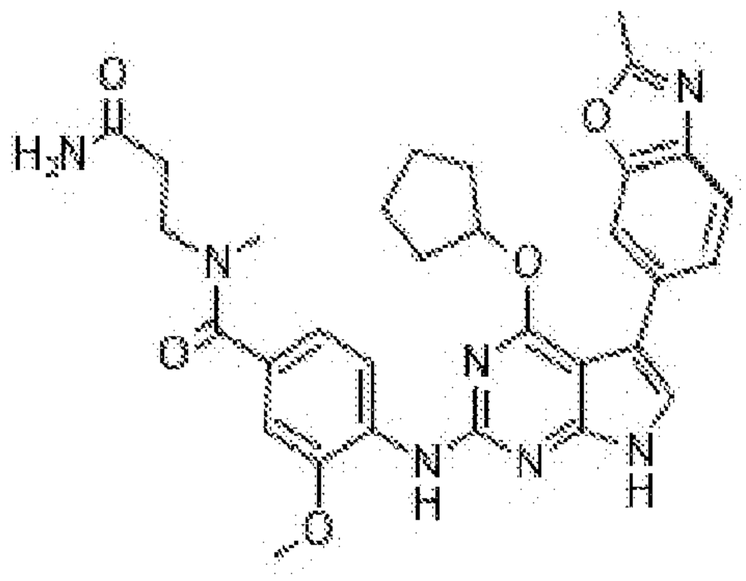
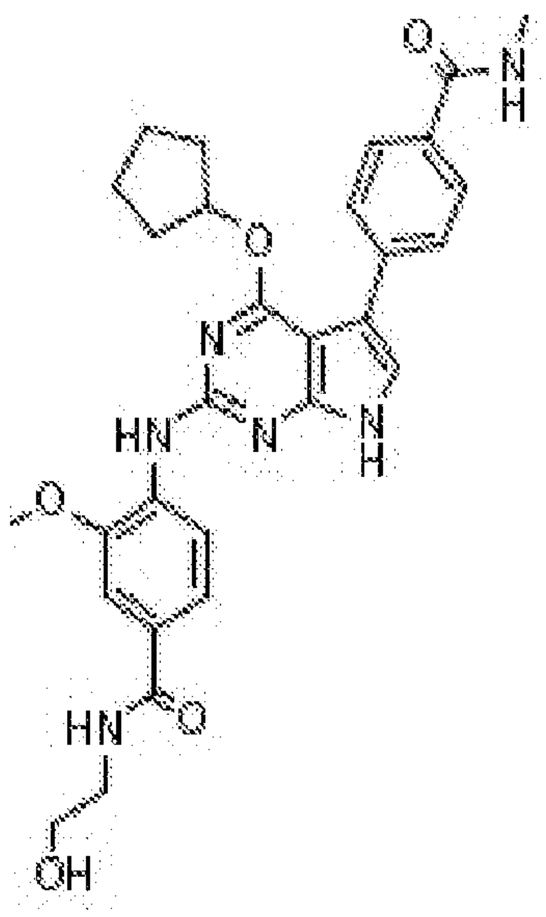
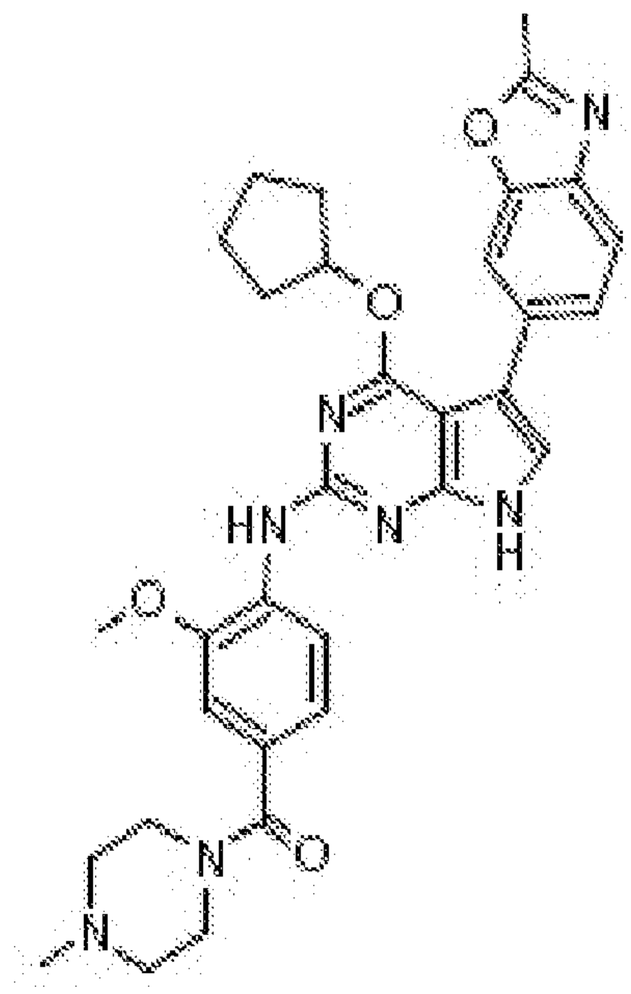
Cmpd No.	Structure	Name
238		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-((1s,3s)-3-hydroxycyclobutyl)-3-methoxybenzamide
239		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-((1r,3r)-3-hydroxycyclobutyl)-3-methoxybenzamide
240		(S)-4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(2-hydroxypropyl)-3-methoxybenzamide
241		azetidin-1-yl(4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxyphenyl)methanone

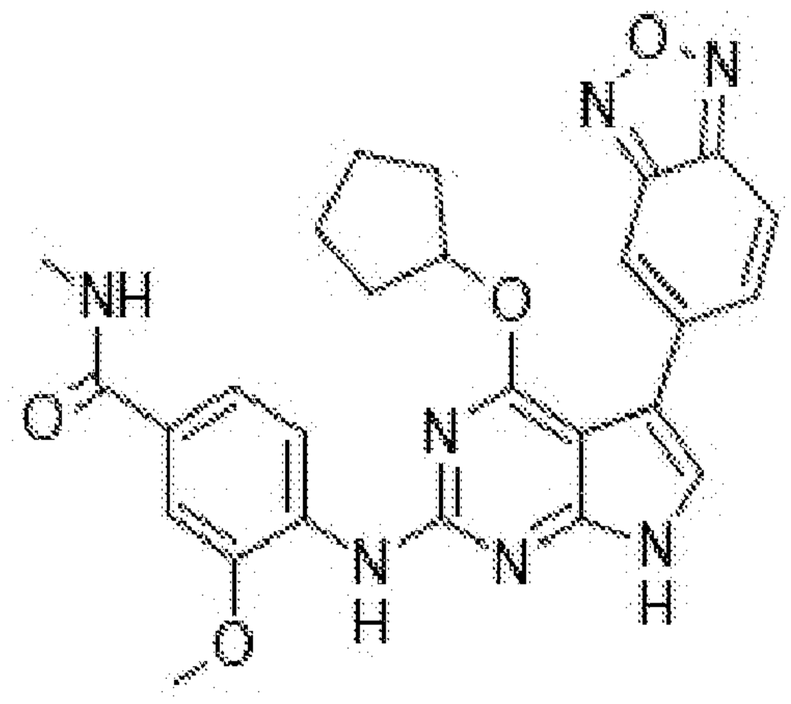
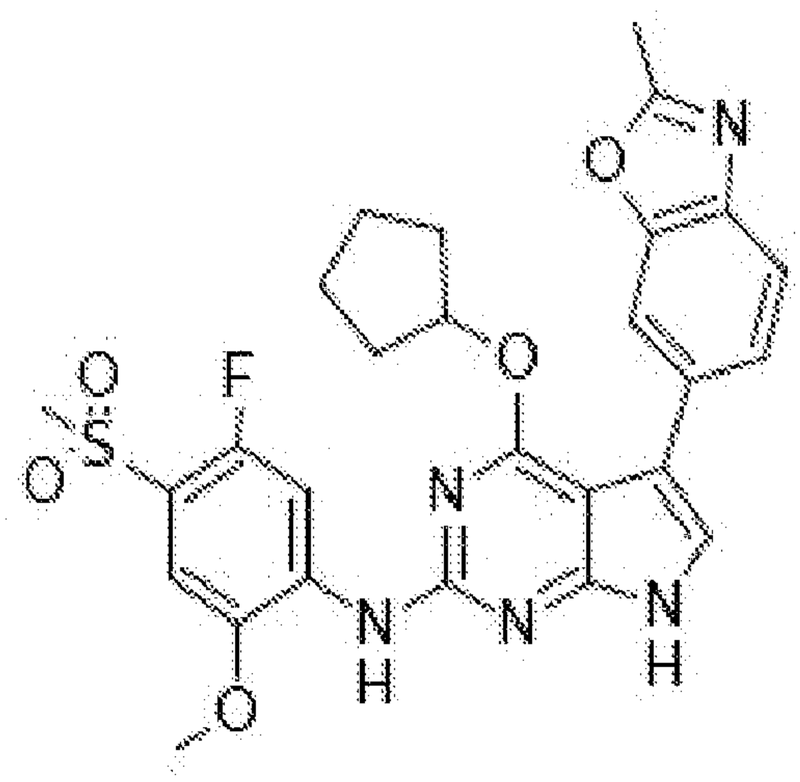
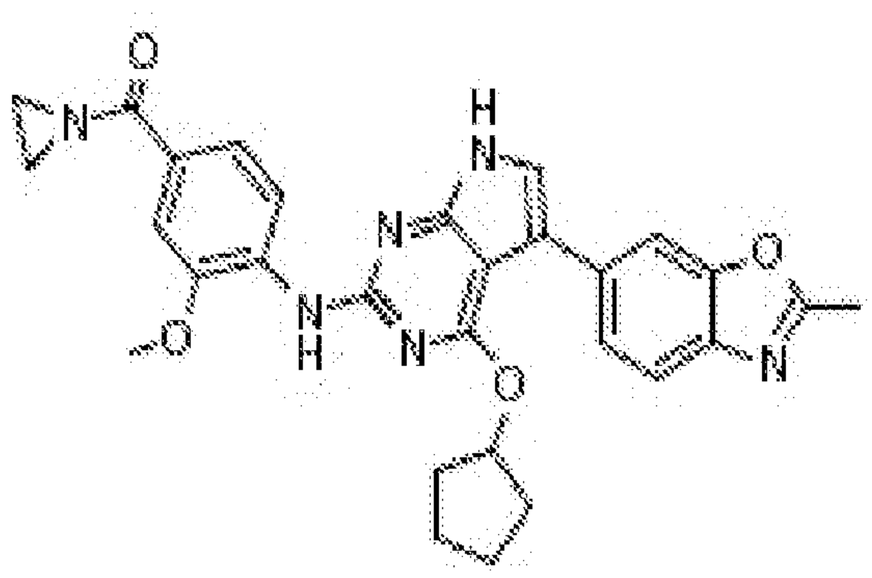
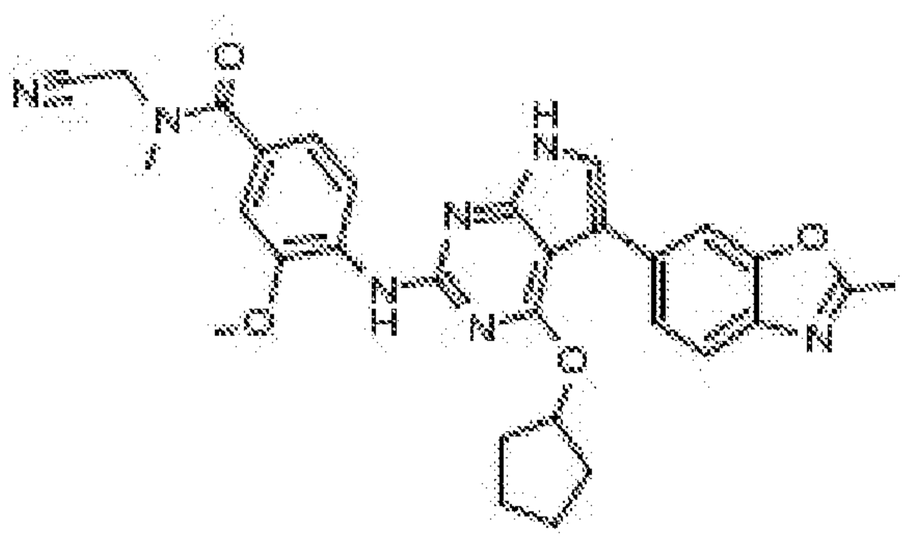
Cmpd No.	Structure	Name
242		(R)-4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-((tetrahydrofuran-2-yl)methyl)benzamide
243		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-((tetrahydro-2H-pyran-4-yl)methyl)benzamide
244		5-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-2-methylisoindolin-1-one
245		4-(5-(4-carbamimidoylphenyl)-4-(cyclopentyloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

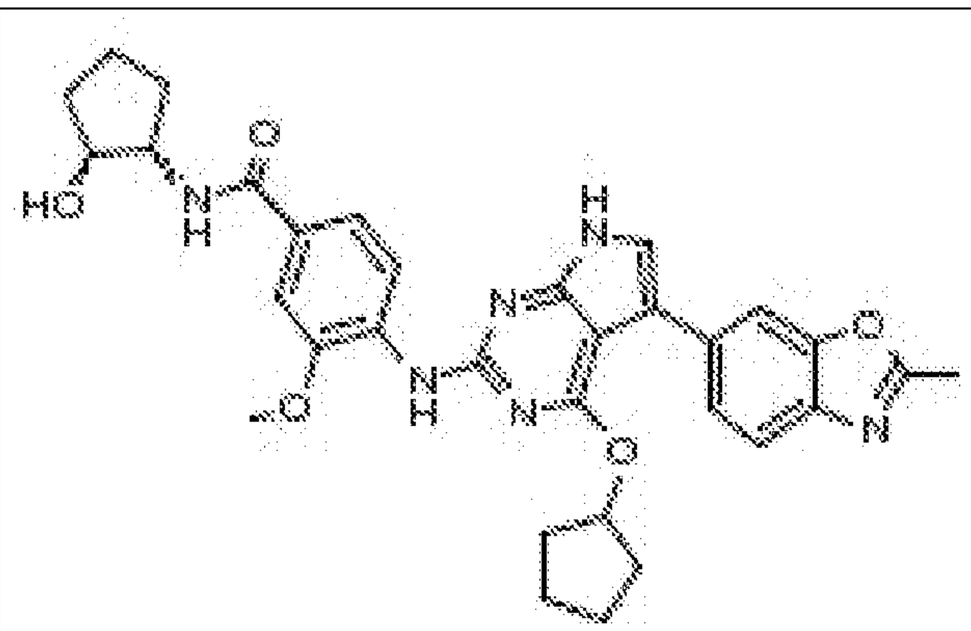
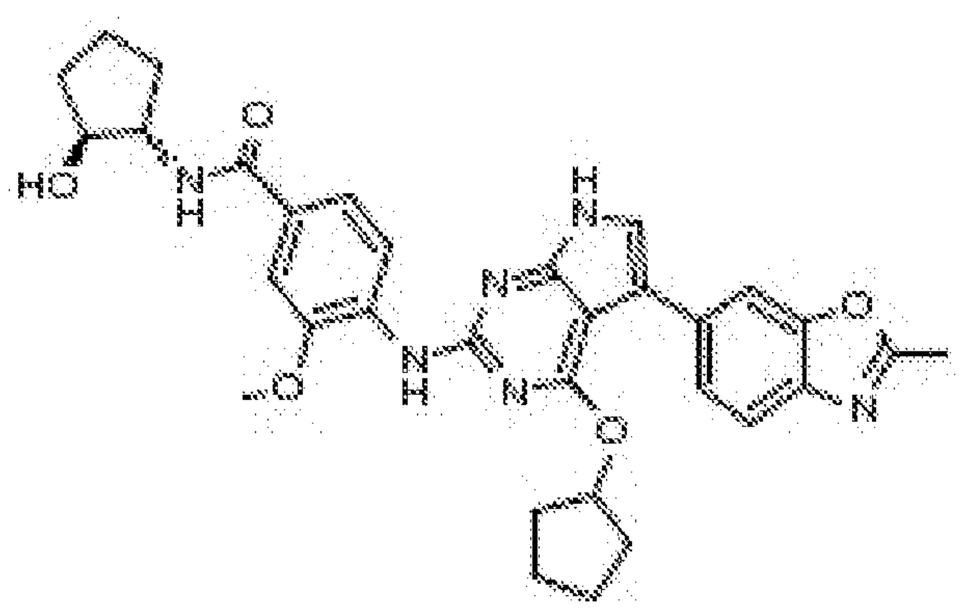
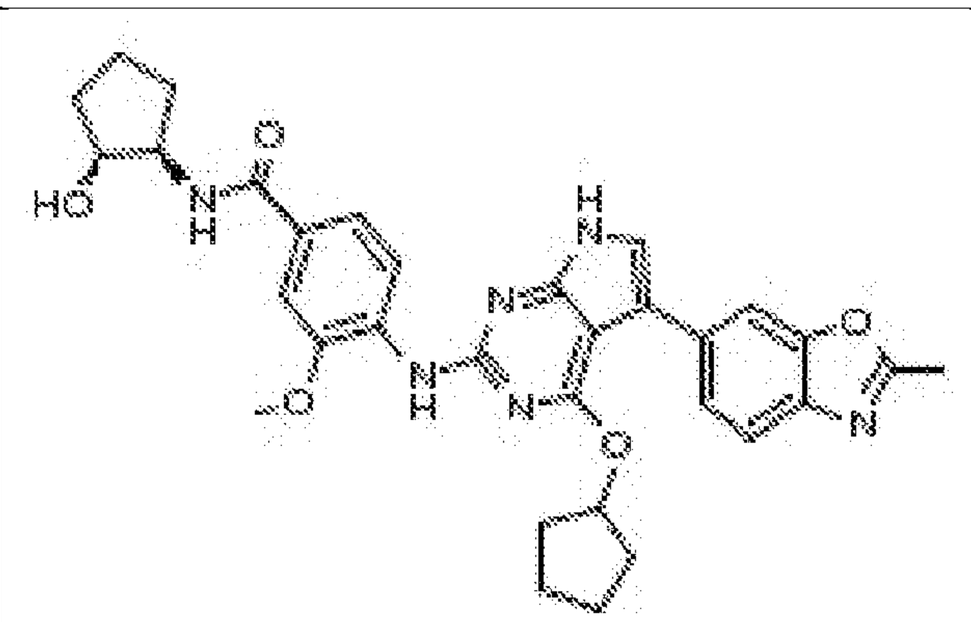
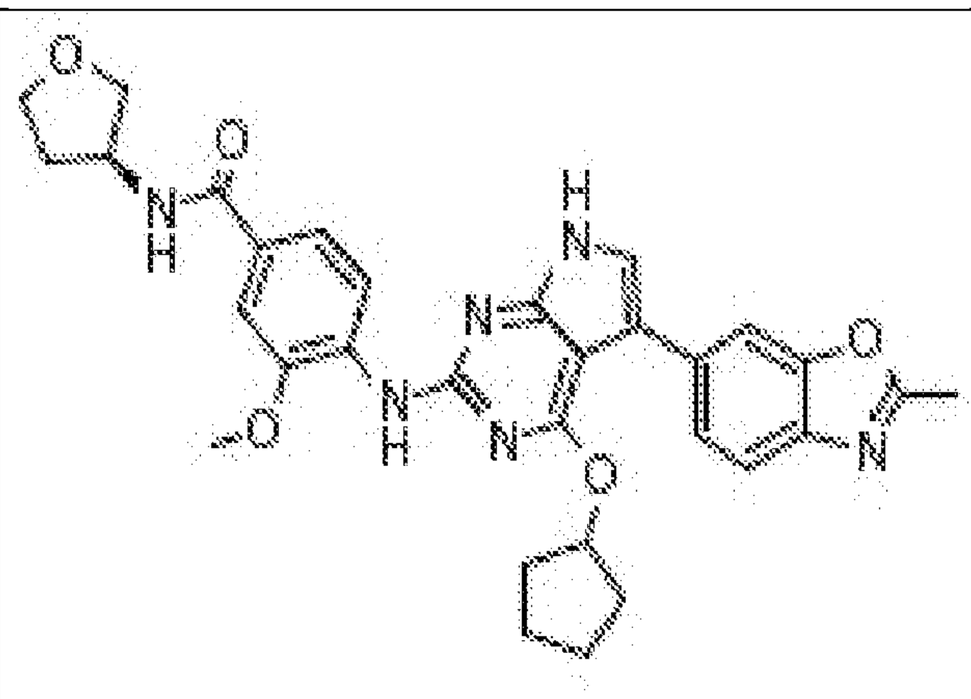
Cmpd No.	Structure	Name
246		4-(4-tert-butoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
247		N-(4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxyphenyl)acetamide
248		N-(2-cyanoethyl)-4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
249		(4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxyphenyl)(pyrrolidin-1-yl)methanone

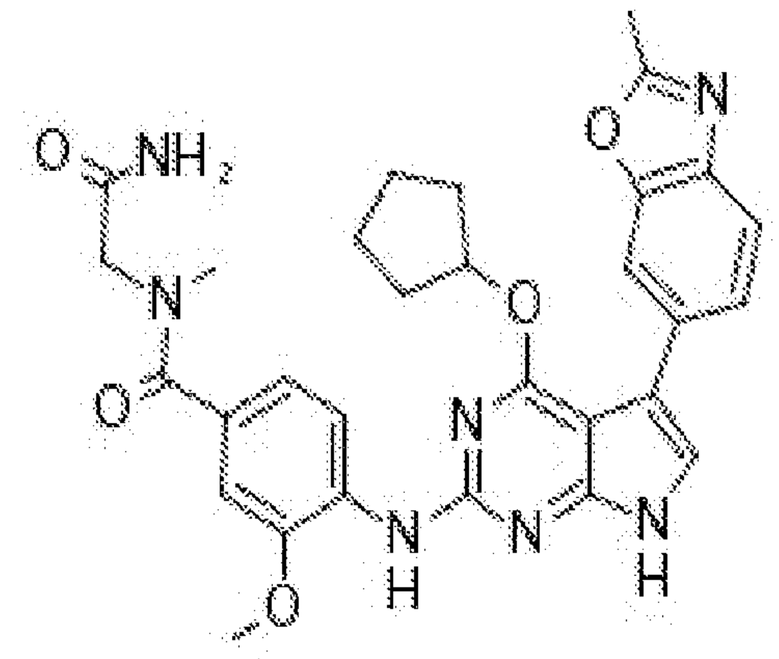
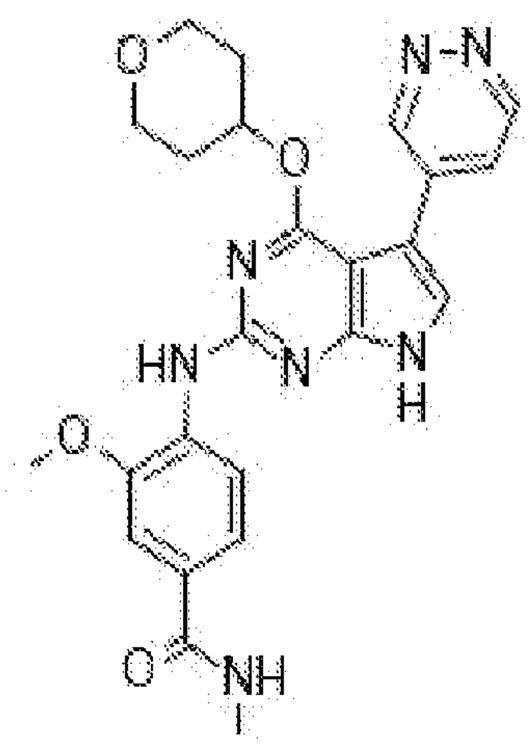
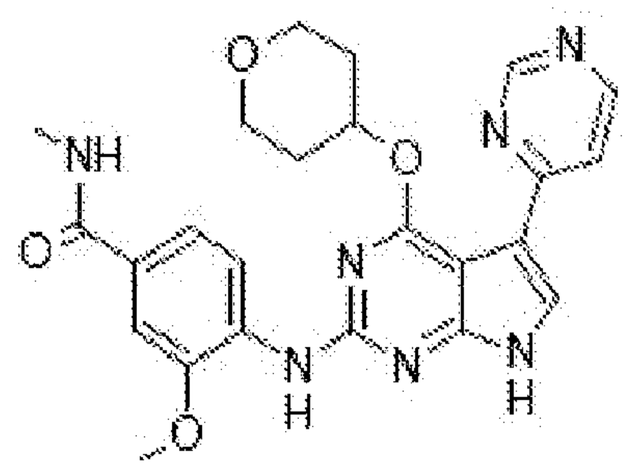
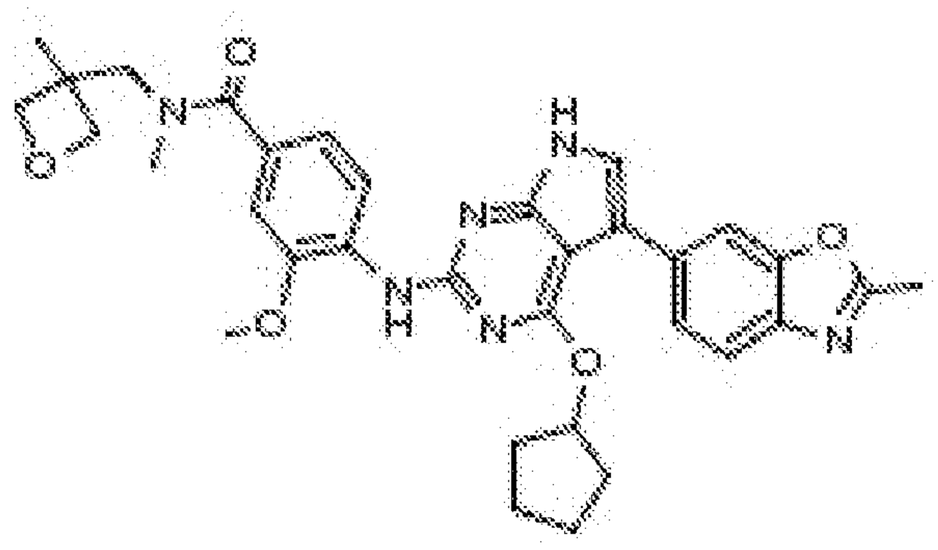
Cmpd No.	Structure	Name
250		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methyl-N-(tetrahydro-2H-pyran-4-yl)benzamide
251		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-cyclopropyl-N-(2-hydroxyethyl)-3-methoxybenzamide
252		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(tetrahydro-2H-pyran-4-yl)benzamide
253		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-((1R,2S)-2-hydroxycyclopentyl)-3-methoxybenzamide

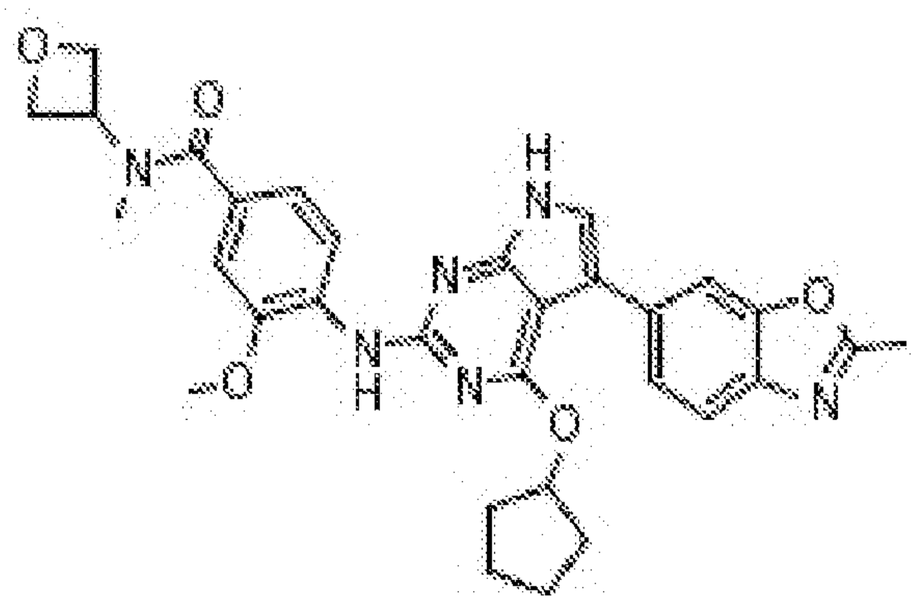
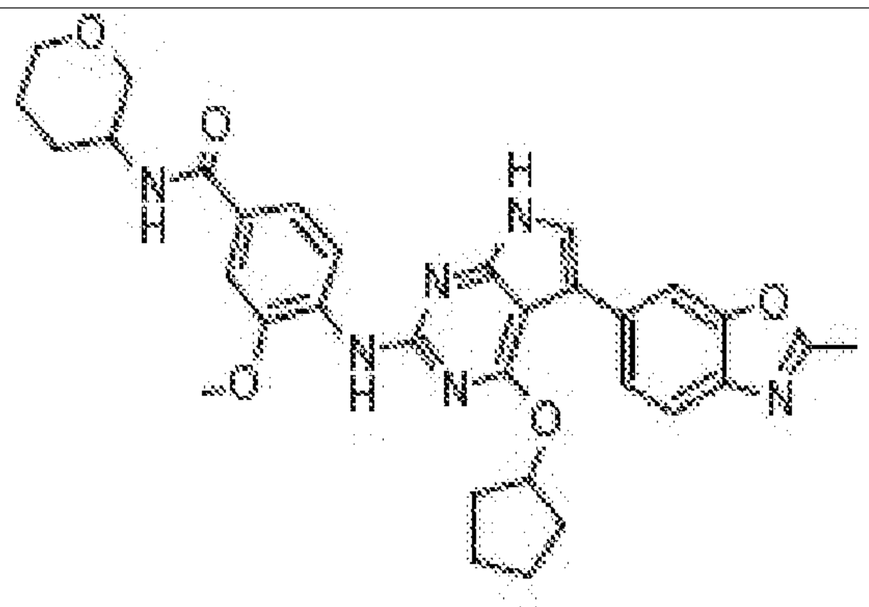
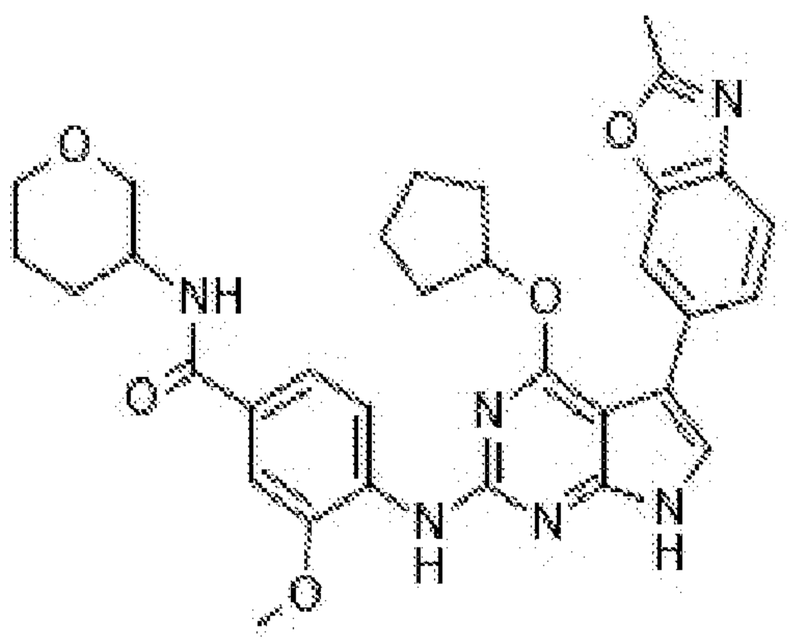
Cmpd No.	Structure	Name
254		(S)-4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-((tetrahydrofuran-2-yl)methyl)benzamide
255		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide
256		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(2-fluoroethyl)-3-methoxybenzamide

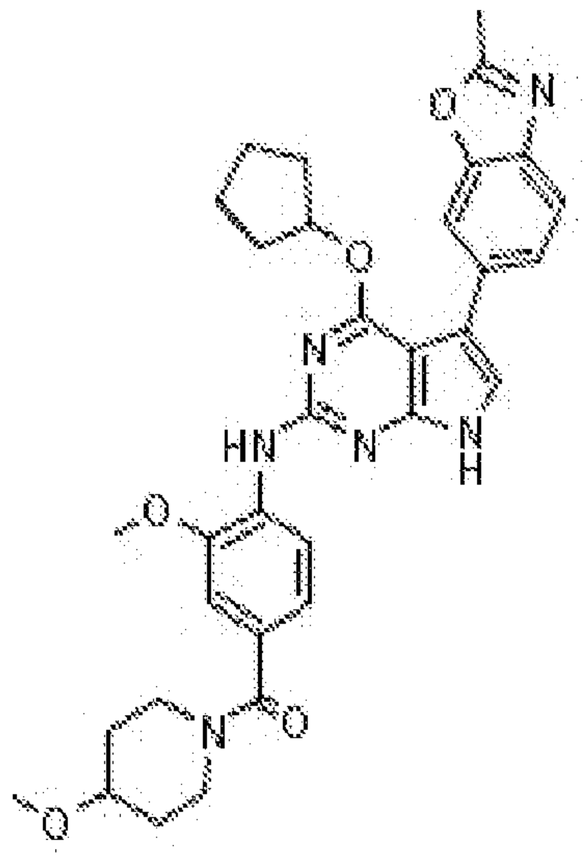
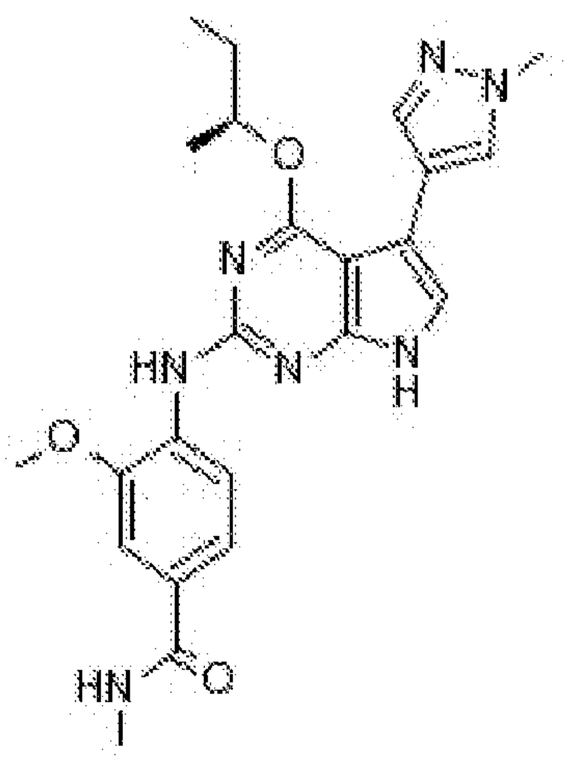
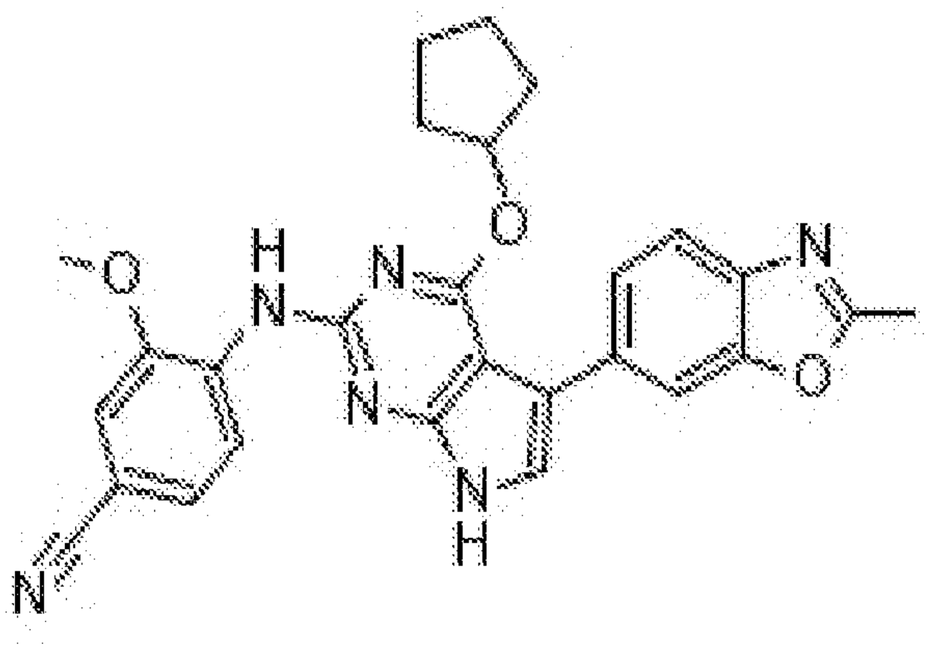
Cmpd No.	Structure	Name
257		N-(3-amino-3-oxopropyl)-4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
258		4-(4-(cyclopentyloxy)-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(2-hydroxyethyl)-3-methoxybenzamide
259		(4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxyphenyl)(4-methylpiperazin-1-yl)methanone

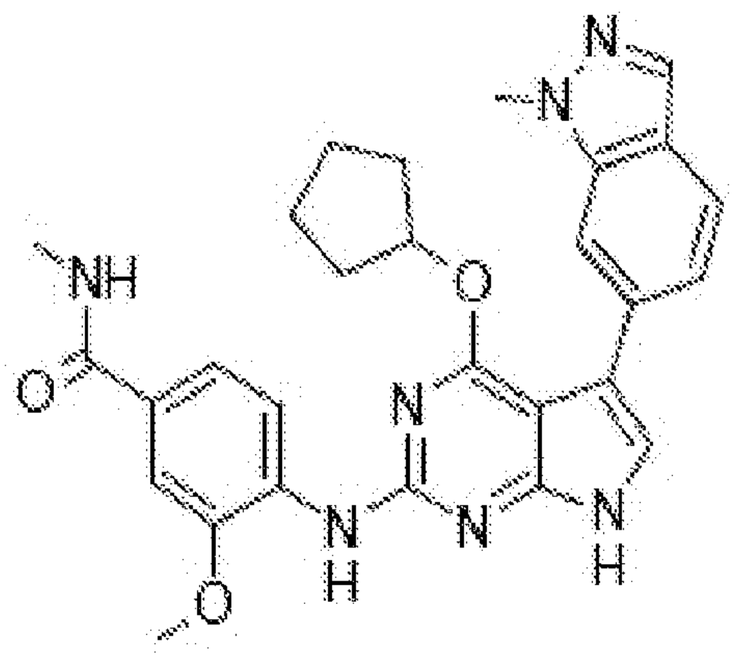
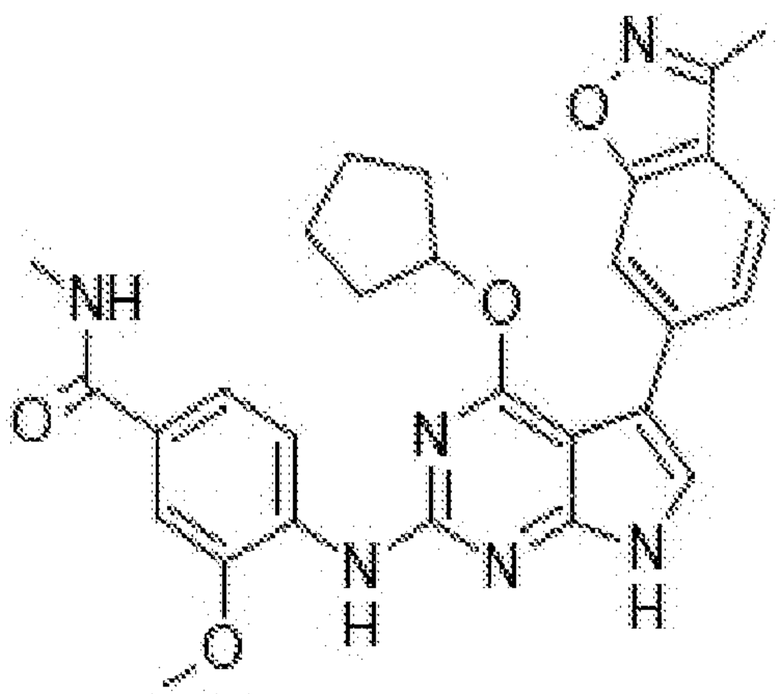
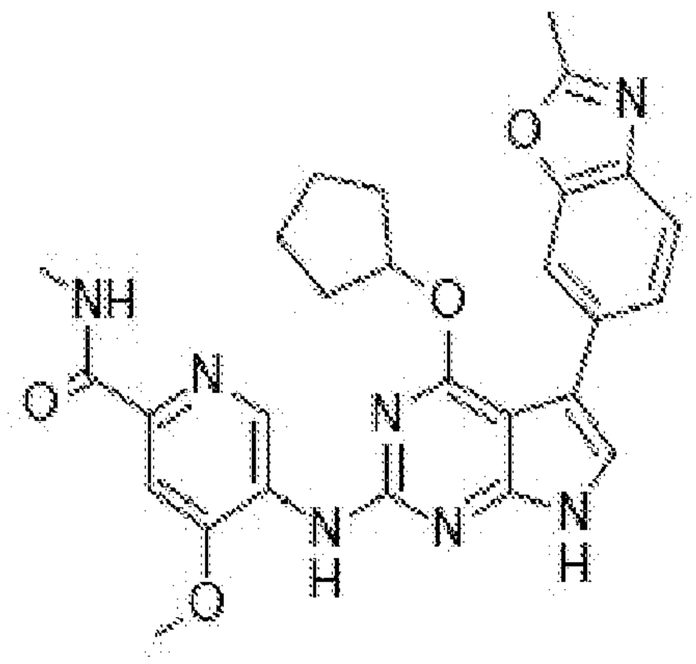
Cmpd No.	Structure	Name
260		4-(5-(benzo[c][1,2,5]oxadiazol-5-yl)-4-(cyclopentyloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
261		4-(cyclopentyloxy)-N-(5-fluoro-2-methoxy-4-(methylsulfonyl)phenyl)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine
262		aziridin-1-yl(4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxyphenyl)methanone
263		N-(cyanomethyl)-4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

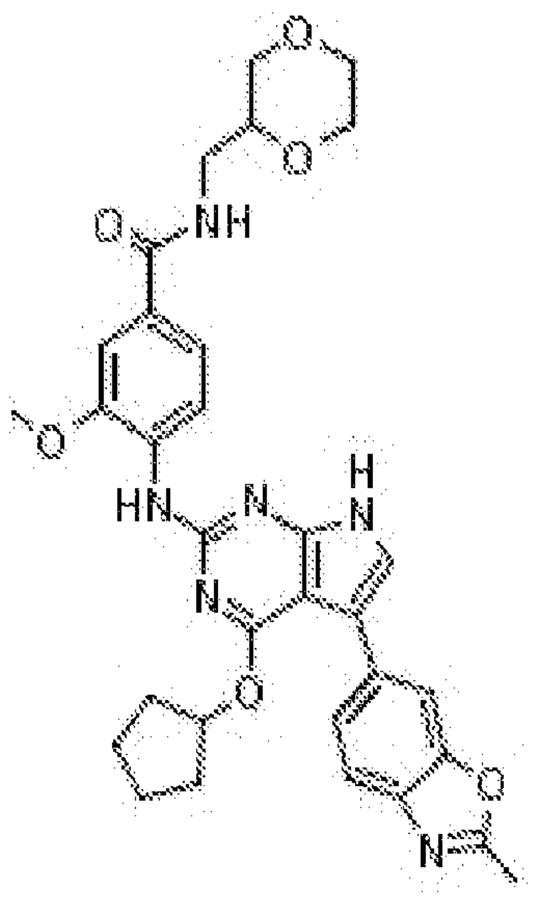
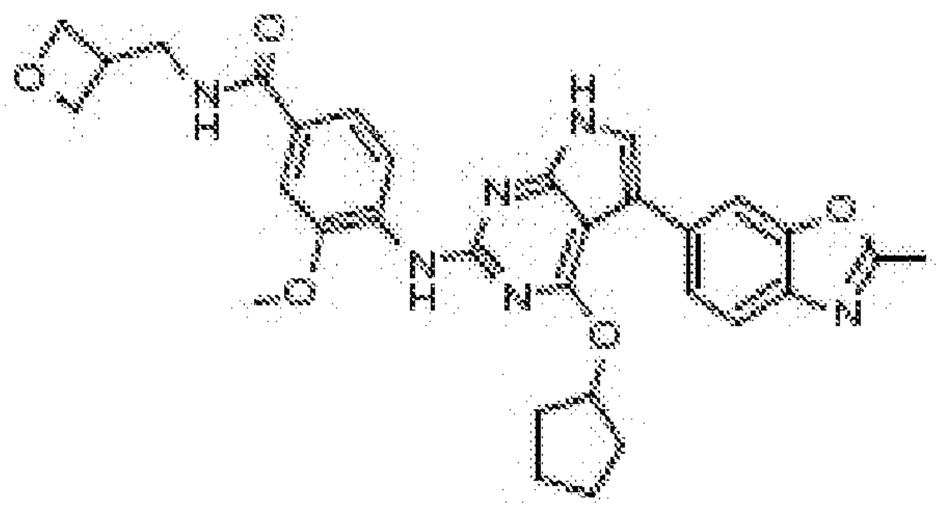
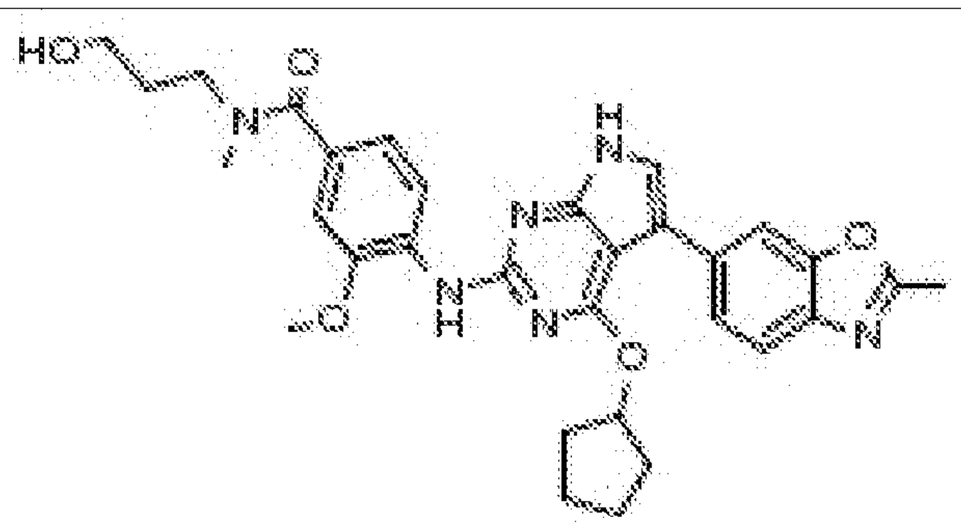
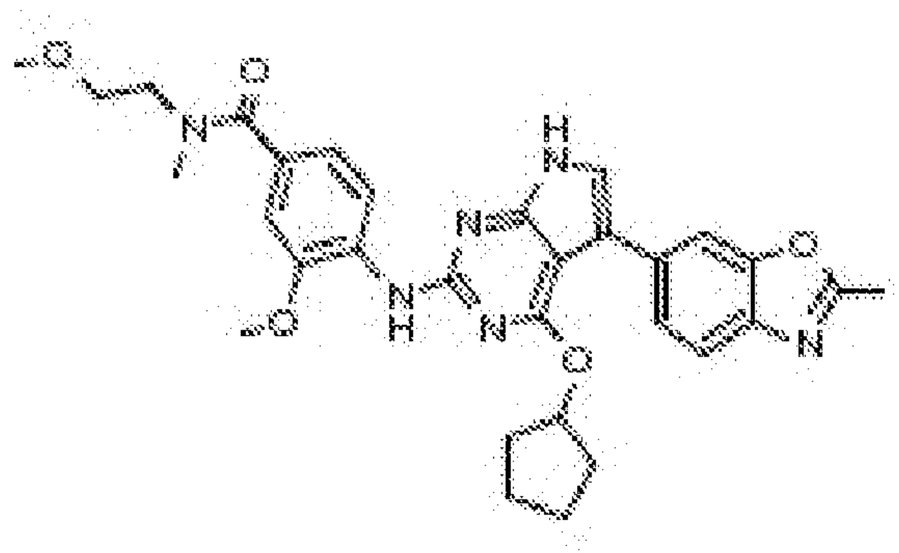
Cmpd No.	Structure	Name
264		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-((1S,2R)-2-hydroxycyclopentyl)-3-methoxybenzamide
265		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-((1S,2S)-2-hydroxycyclopentyl)-3-methoxybenzamide
266		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-((1R,2R)-2-hydroxycyclopentyl)-3-methoxybenzamide
267		(S)-4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(tetrahydrofuran-3-yl)benzamide

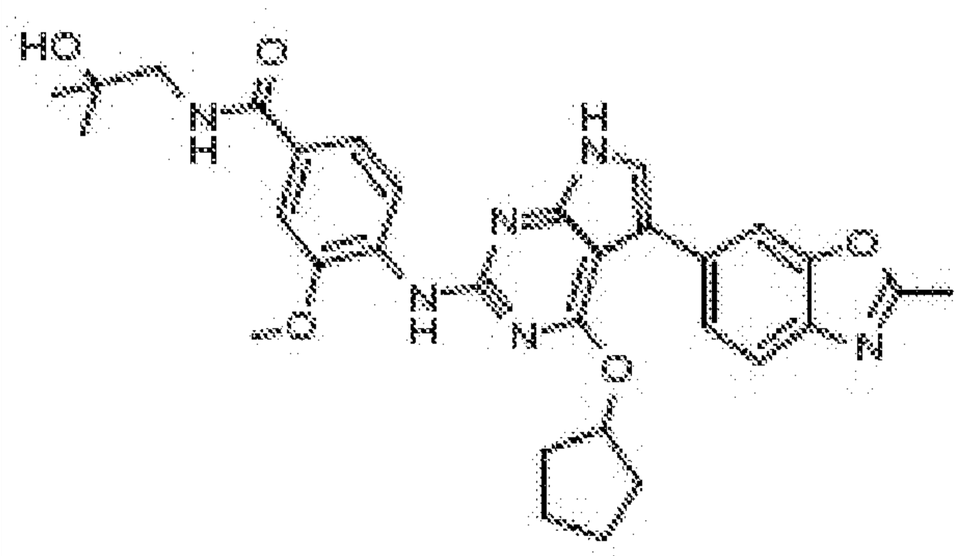
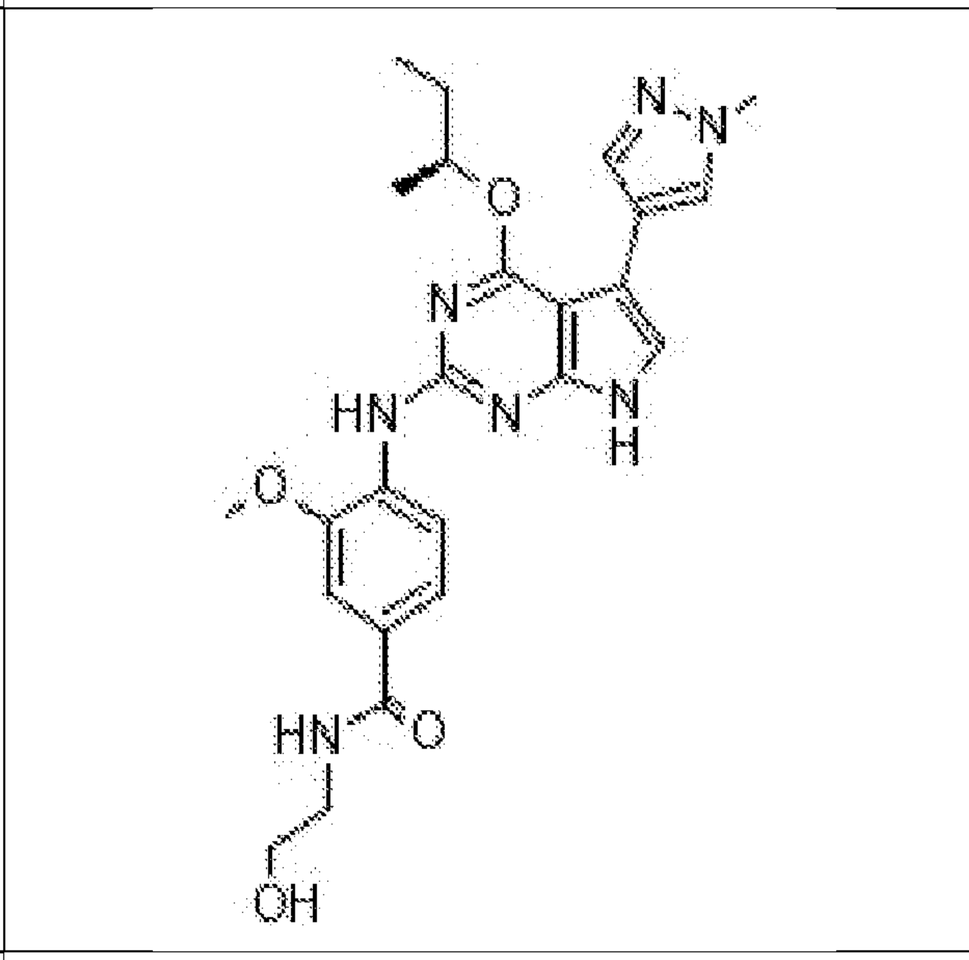
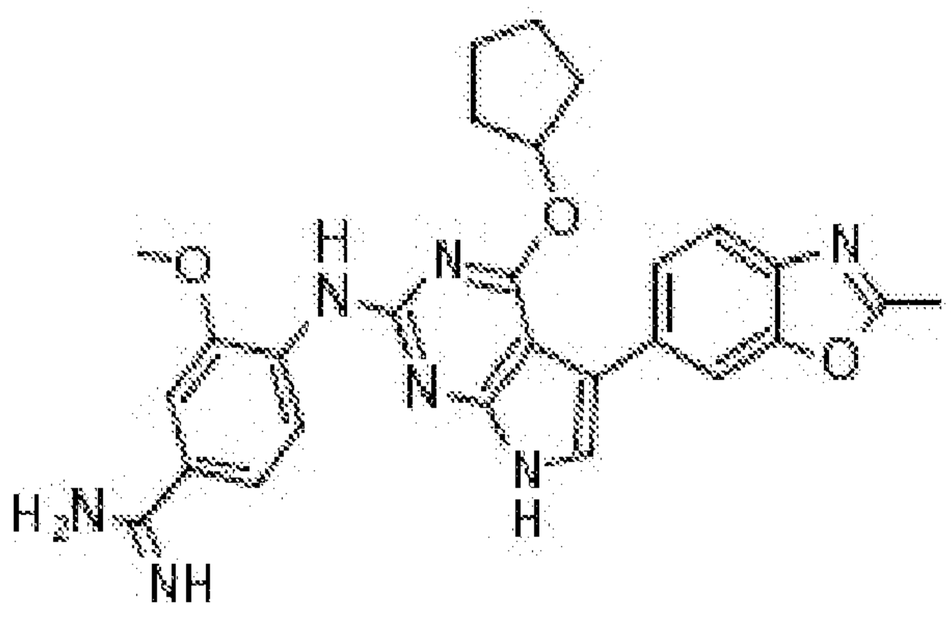
Cmpd No.	Structure	Name
268		N-(2-amino-2-oxoethyl)-4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
269		3-methoxy-N-methyl-4-(5-(pyridazin-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
270		3-methoxy-N-methyl-4-(5-(pyrimidin-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
271		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methyl-N-((3-methyloxetan-3-yl)methyl)benzamide

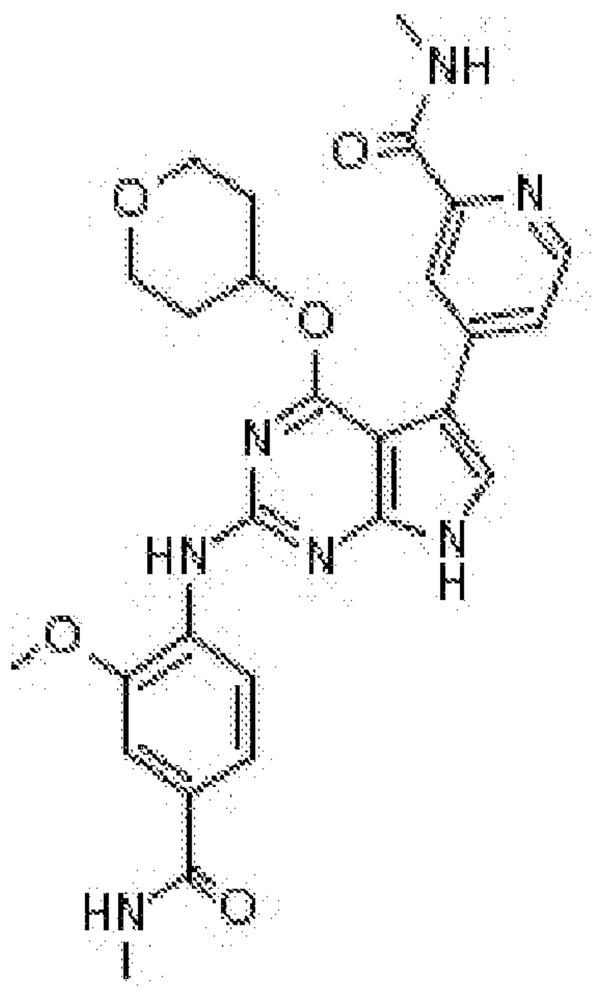
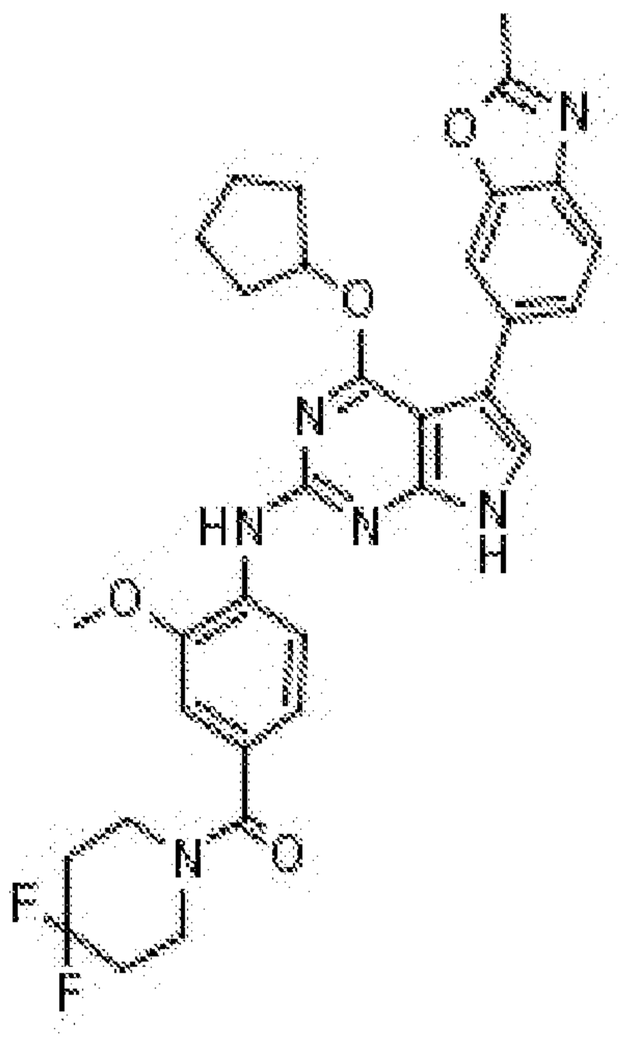
Cmpd No.	Structure	Name
272		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methyl-N-(oxetan-3-yl)benzamide
273		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(tetrahydro-2H-pyran-3-yl)benzamide
274		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(tetrahydro-2H-pyran-3-yl)benzamide

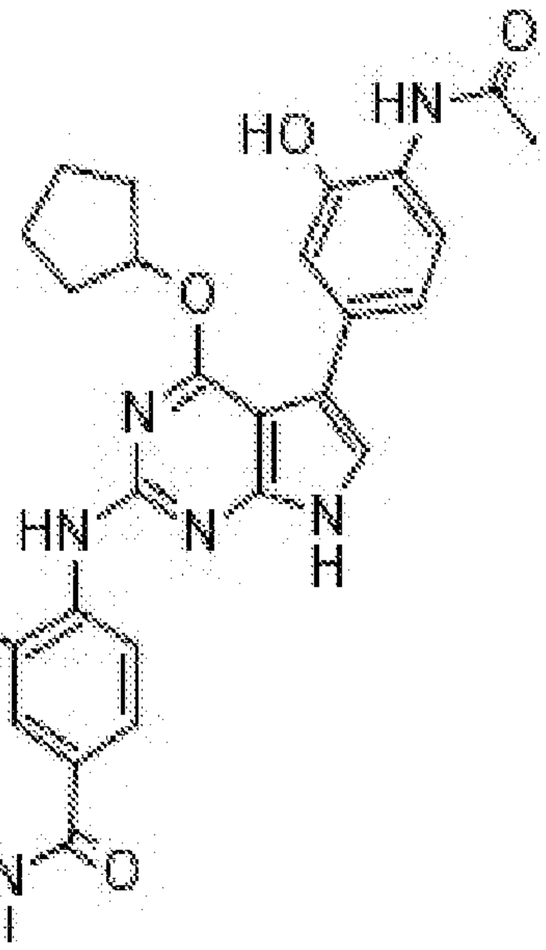
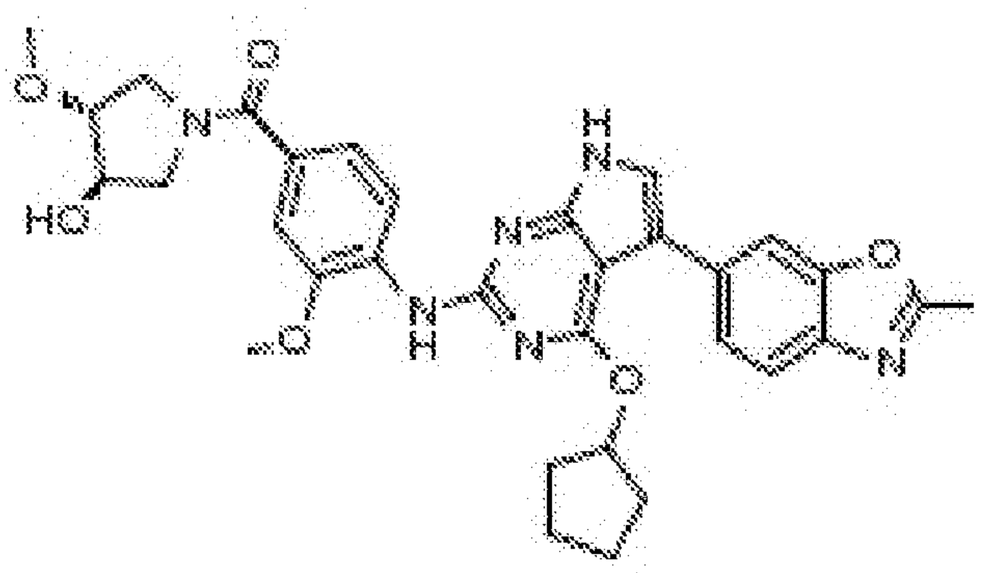
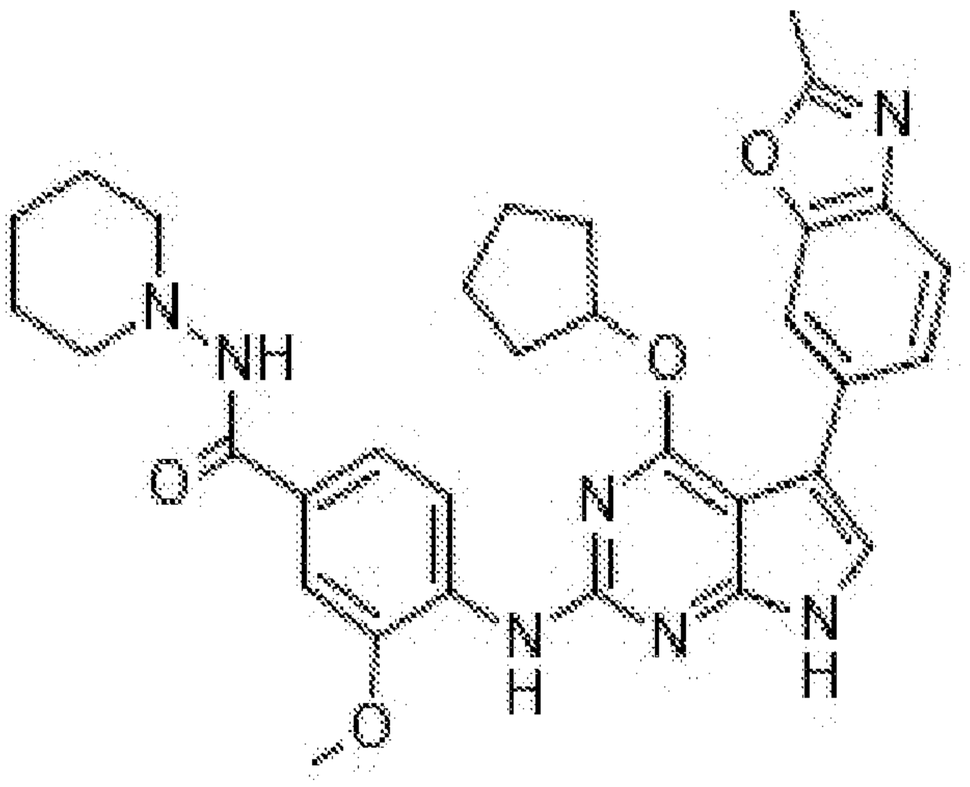
Cmpd No.	Structure	Name
275		(4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxyphenyl)(4-methoxypiperidin-1-yl)methanone
276		(S)-4-(4-sec-butoxy-5-(1-methyl-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
277		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxybenzonitrile

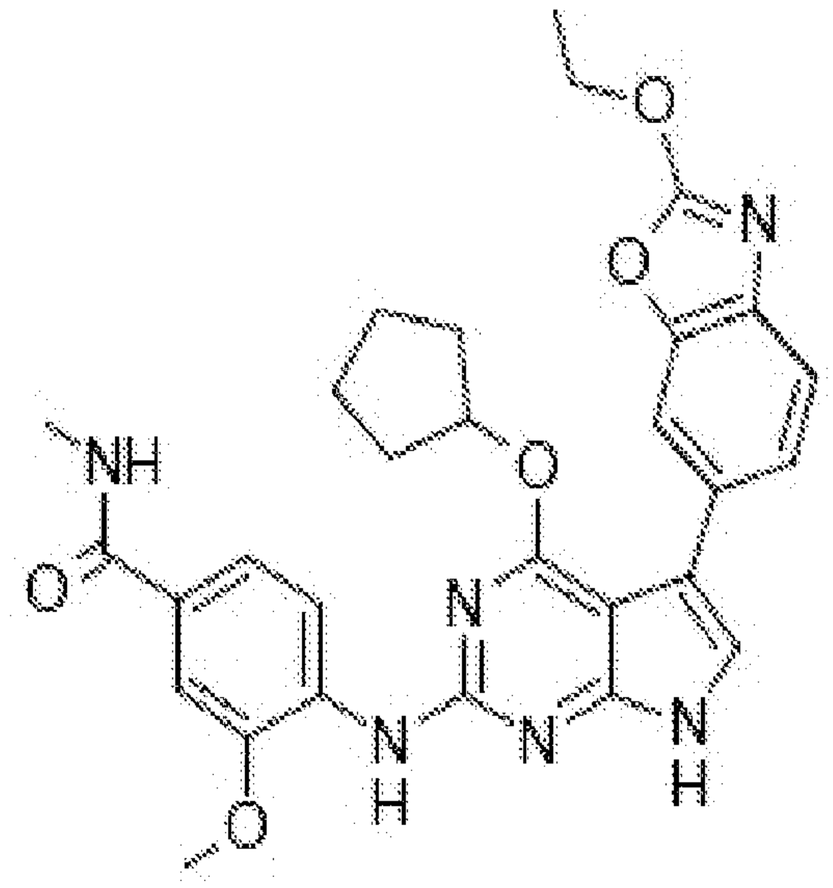
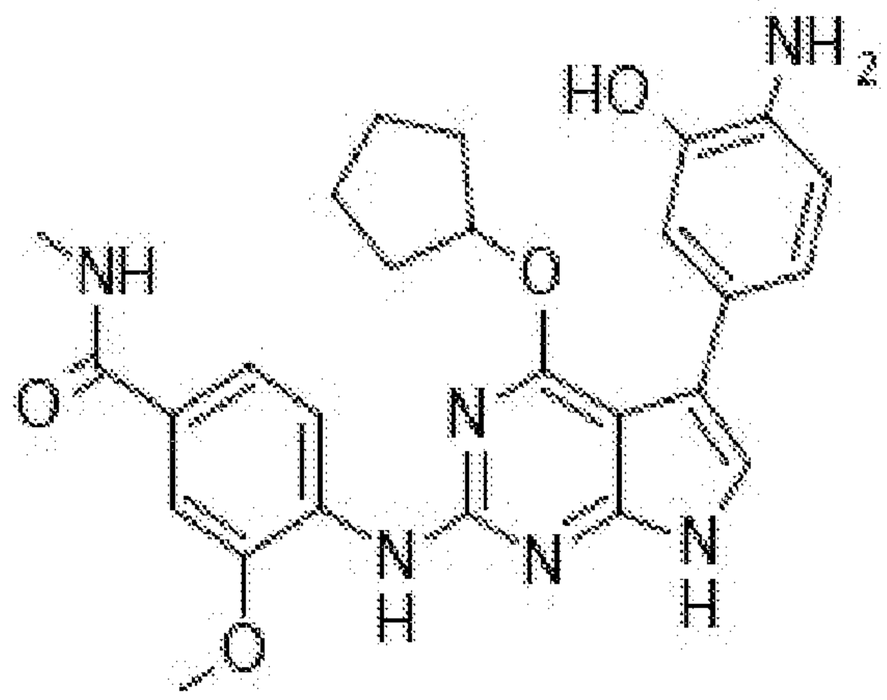
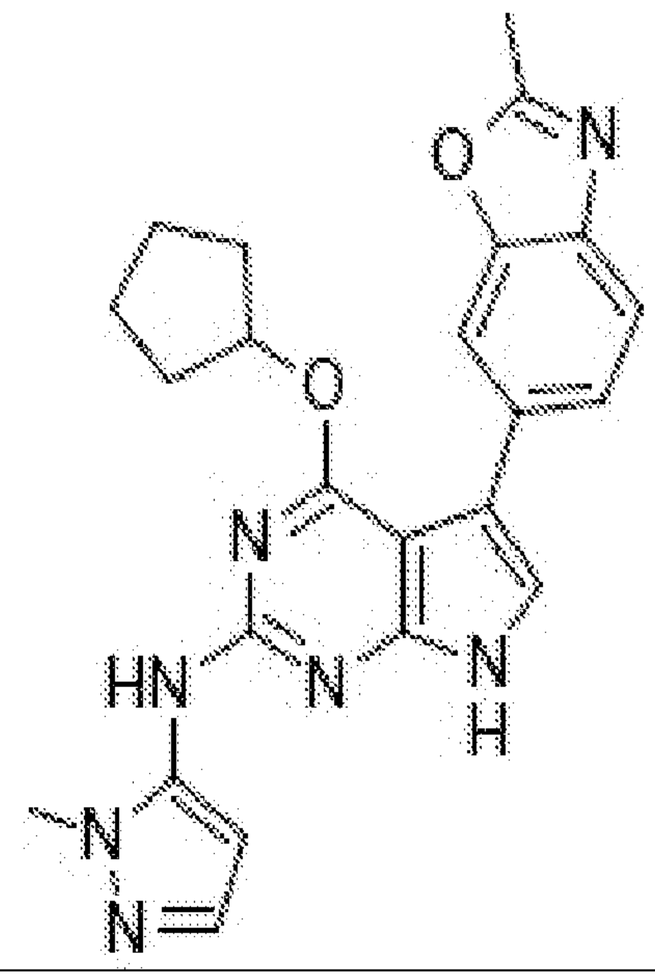
Cmpd No.	Structure	Name
278		4-(4-(cyclopentyloxy)-5-(1-methyl-1H-indazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
279		4-(4-(cyclopentyloxy)-5-(3-methylbenzo[d]isoxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
280		5-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-4-methoxy-N-methylpicolinamide

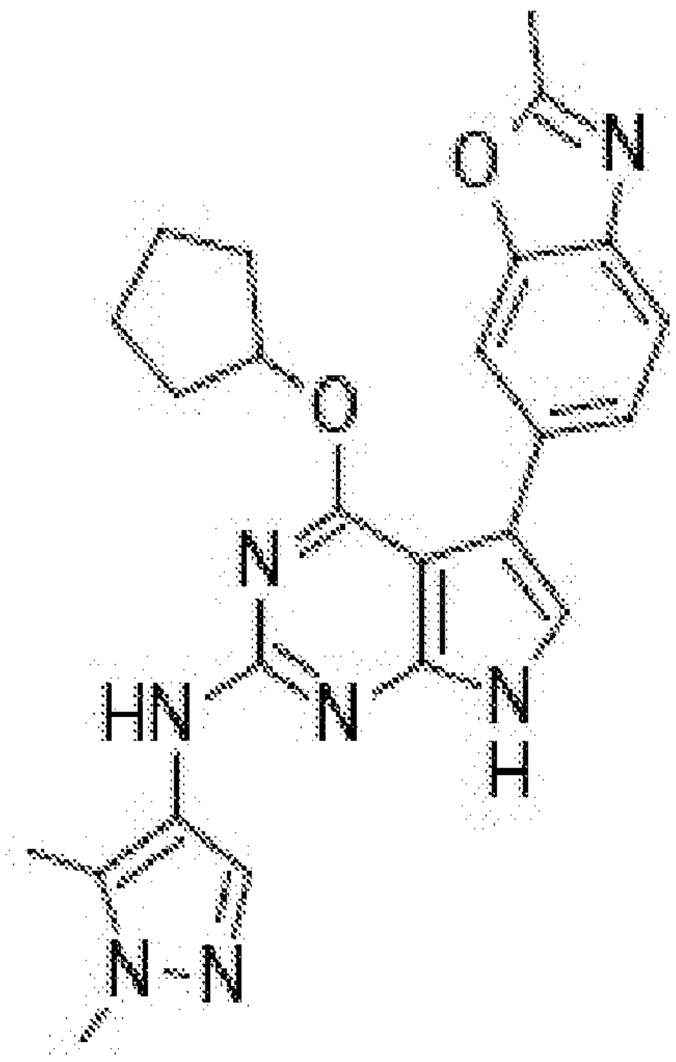
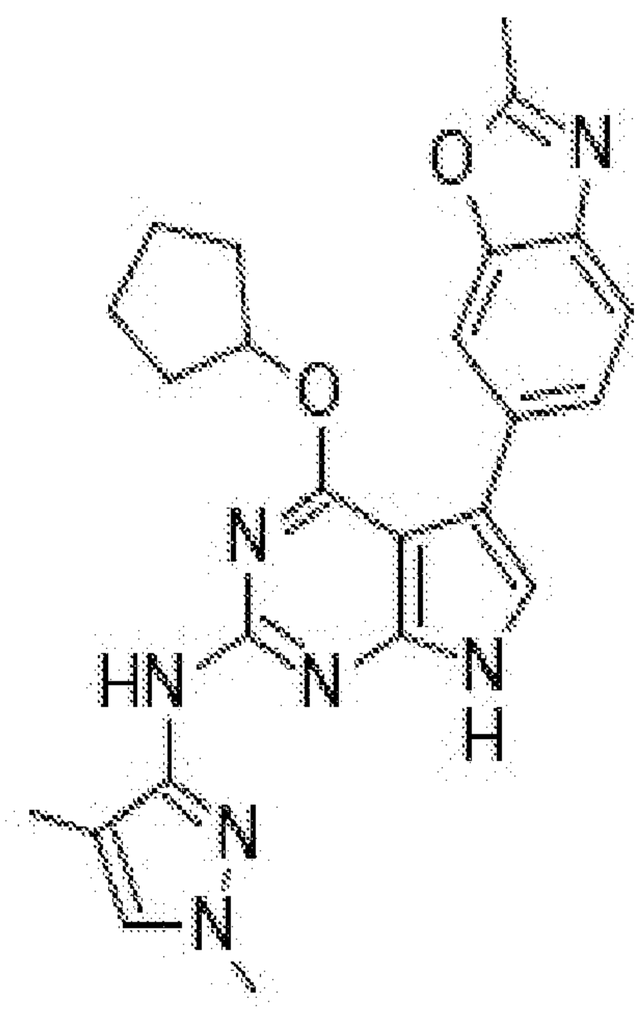
Cmpd No.	Structure	Name
281		N-((1,4-dioxan-2-yl)methyl)-4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxybenzamide
282		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-ylmethyl)benzamide
283		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(3-hydroxypropyl)-3-methoxy-N-methylbenzamide
284		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(2-methoxyethyl)-N-methylbenzamide

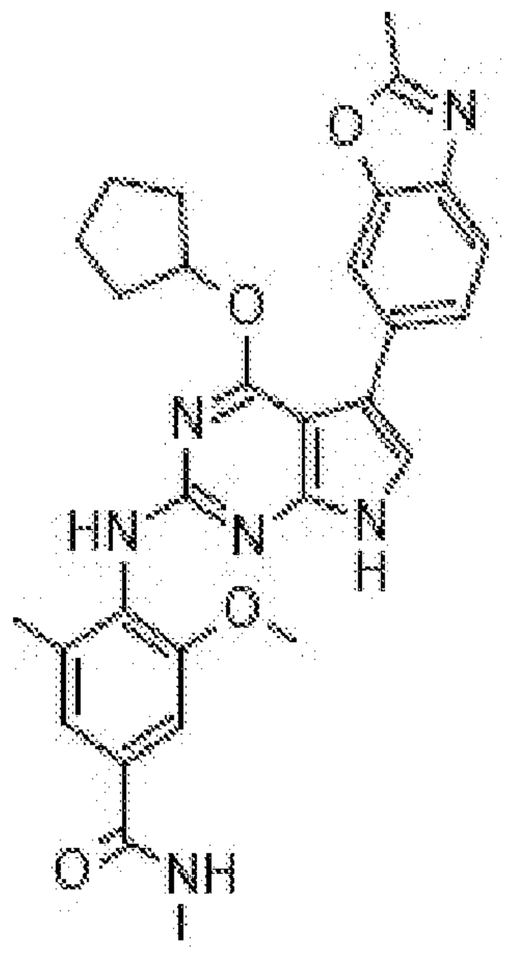
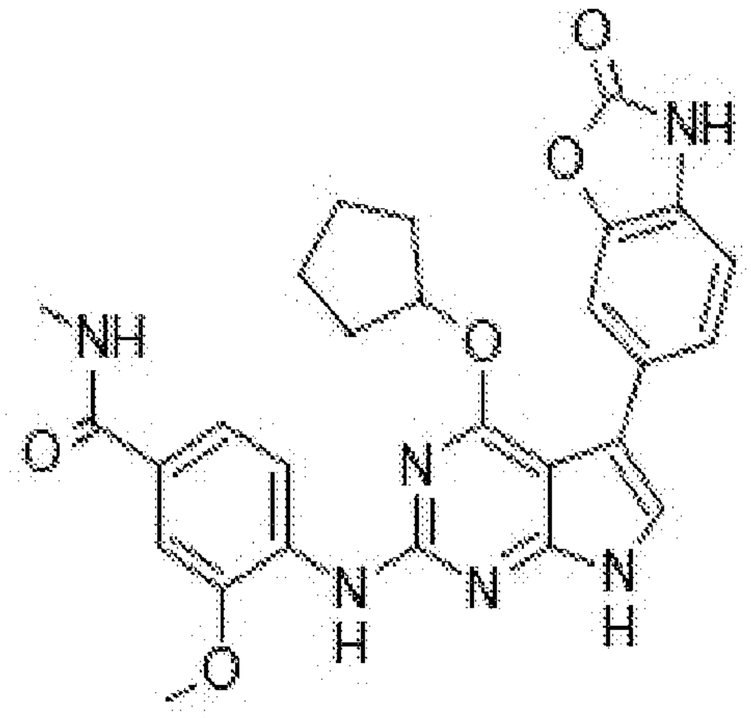
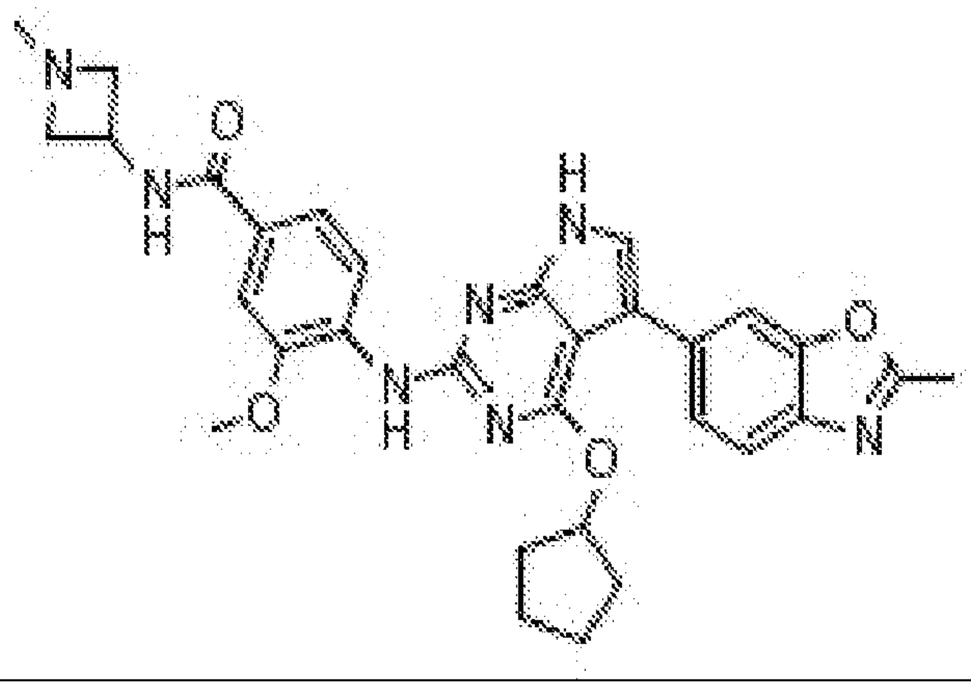
Cmpd No.	Structure	Name
285		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(2-hydroxy-2-methylpropyl)-3-methoxybenzamide
286		(S)-4-(4-sec-butoxy-5-(1-methyl-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(2-hydroxyethyl)-3-methoxybenzamide
287		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxybenzimidamide

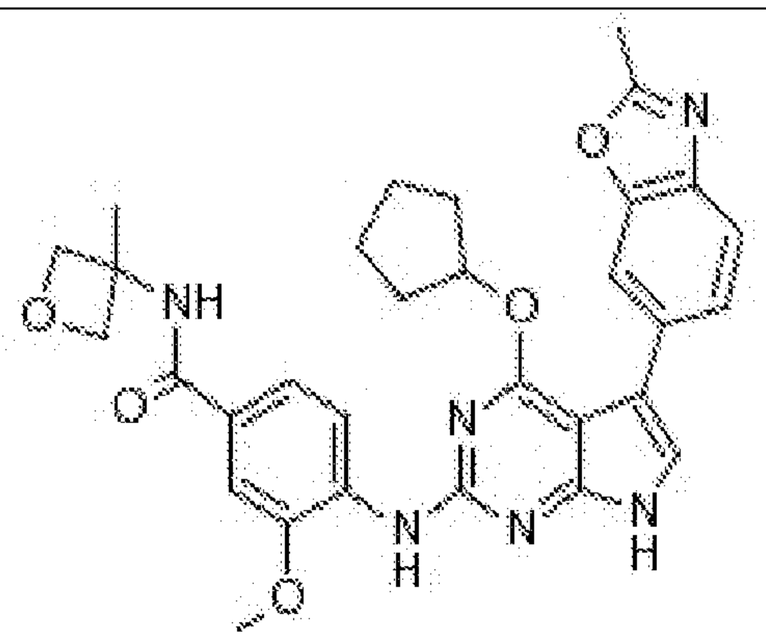
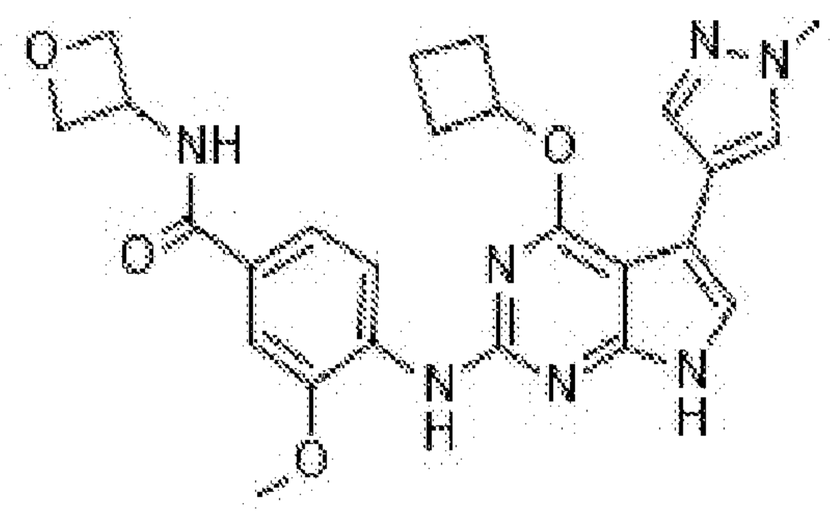
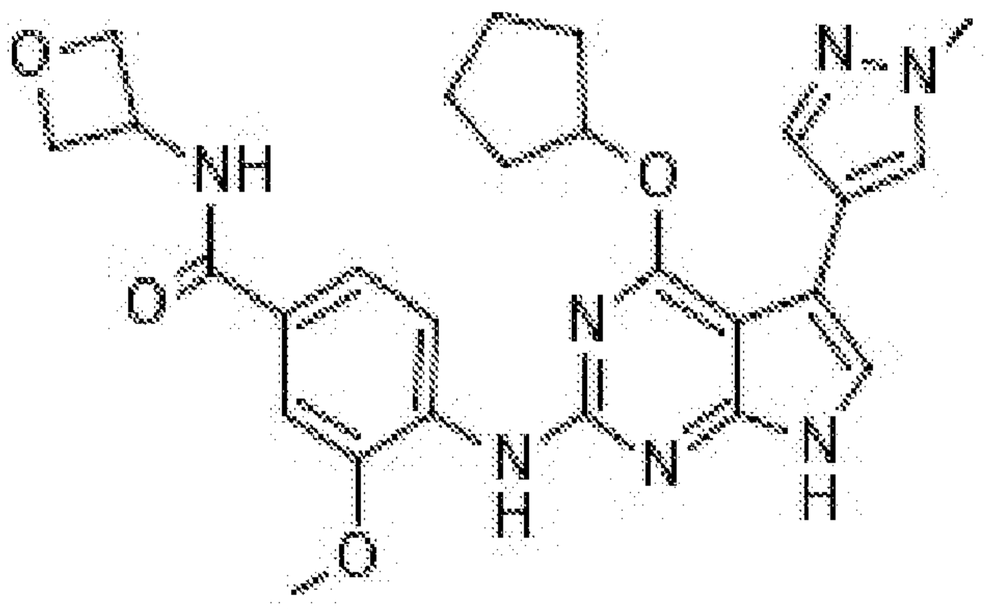
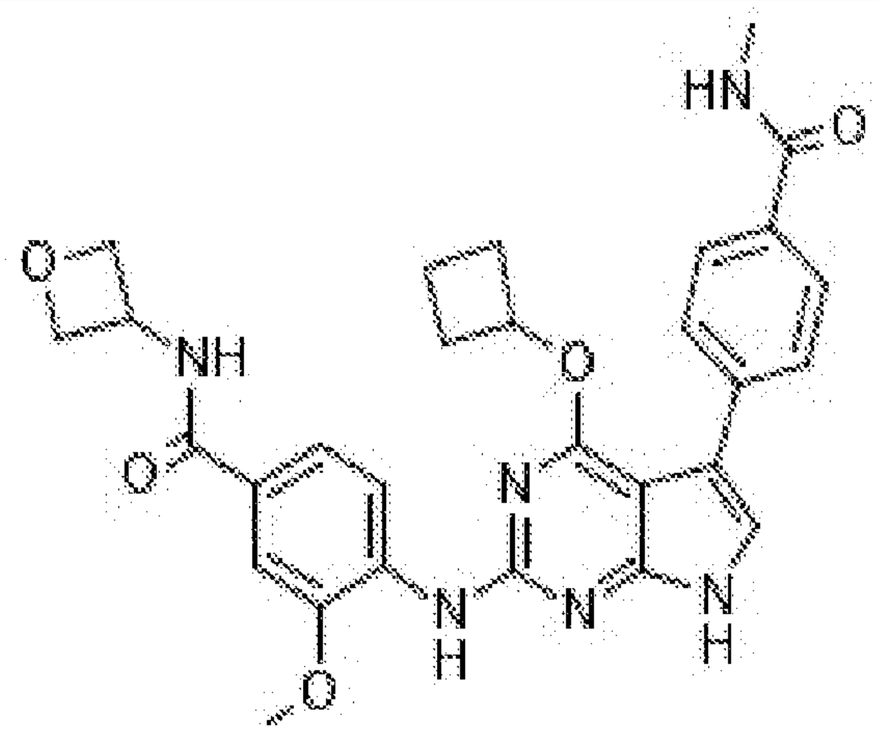
Cmpd No.	Structure	Name
288		4-(2-(2-methoxy-4-(methylcarbamoyl)phenylamino)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-N-methylpicolinamide
289		(4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxyphenyl)(4,4-difluoropiperidin-1-yl)methanone

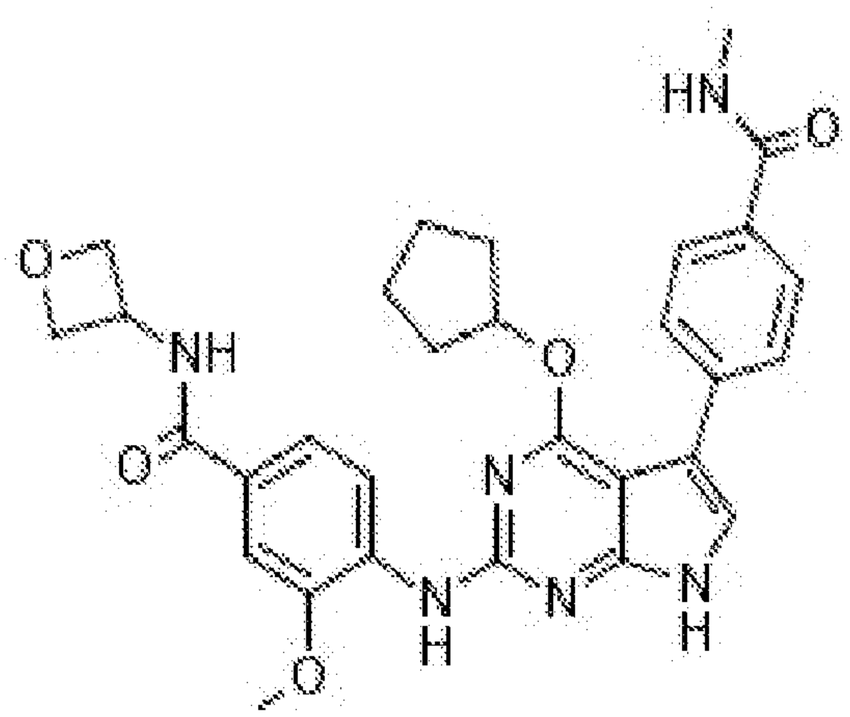
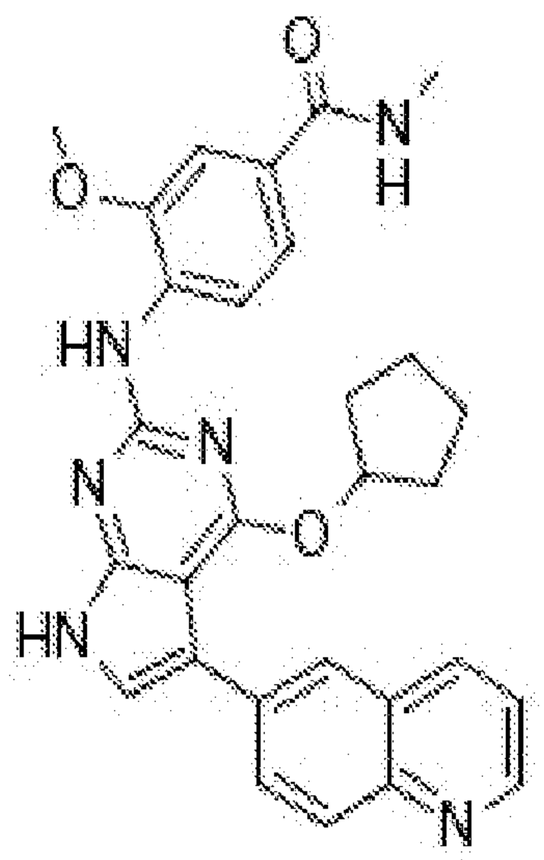
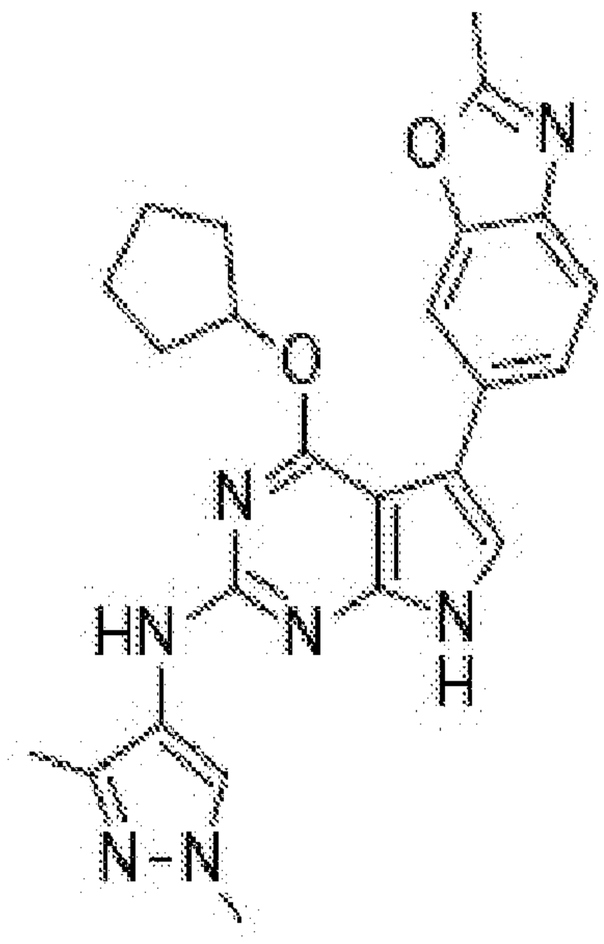
Cmpd No.	Structure	Name
290		4-(5-(4-acetamido-3-hydroxyphenyl)-4-(cyclopentyloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
291		(4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxyphenyl)((3R,4R)-3-hydroxy-4-methoxypyrrolidin-1-yl)methanone
292		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(piperidin-1-yl)benzamide

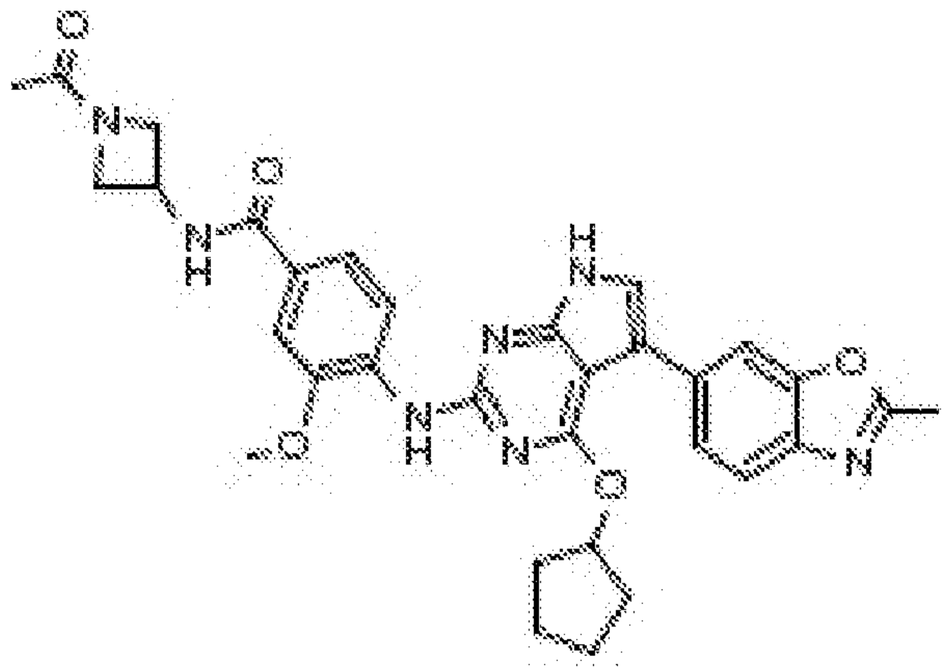
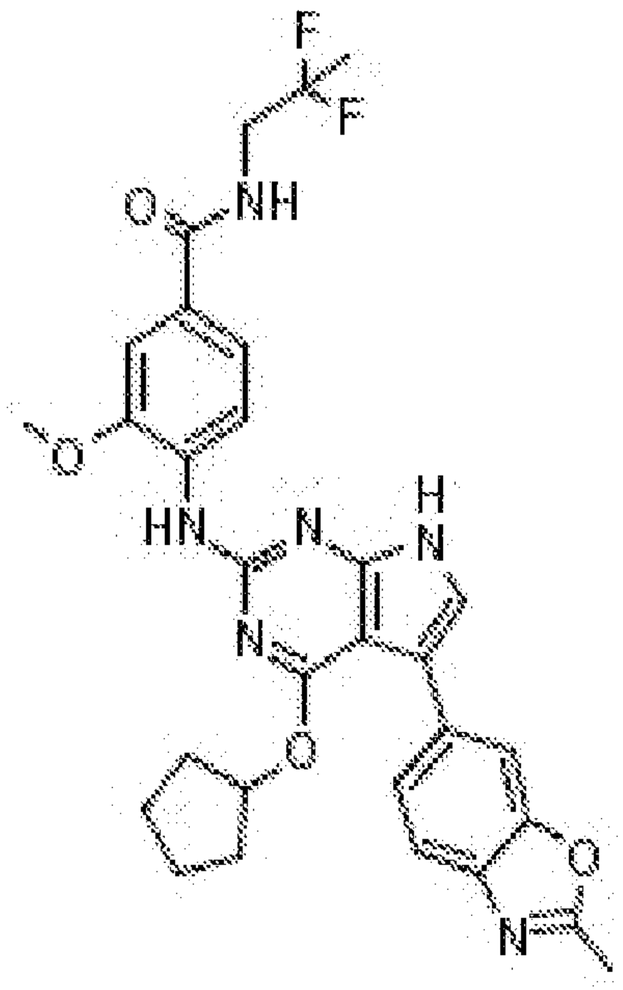
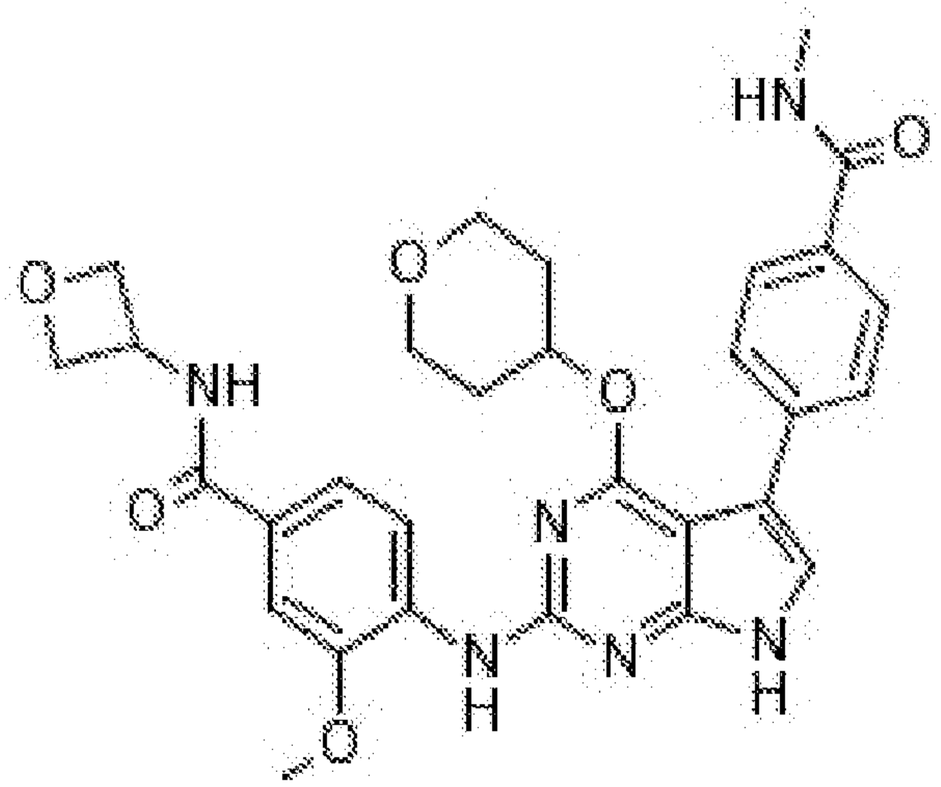
Cmpd No.	Structure	Name
293		4-(4-(cyclopentyloxy)-5-(2-ethoxybenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
294		4-(5-(4-amino-3-hydroxyphenyl)-4-(cyclopentyloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
295		4-(cyclopentyloxy)-N-(1-methyl-1H-pyrazol-5-yl)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine

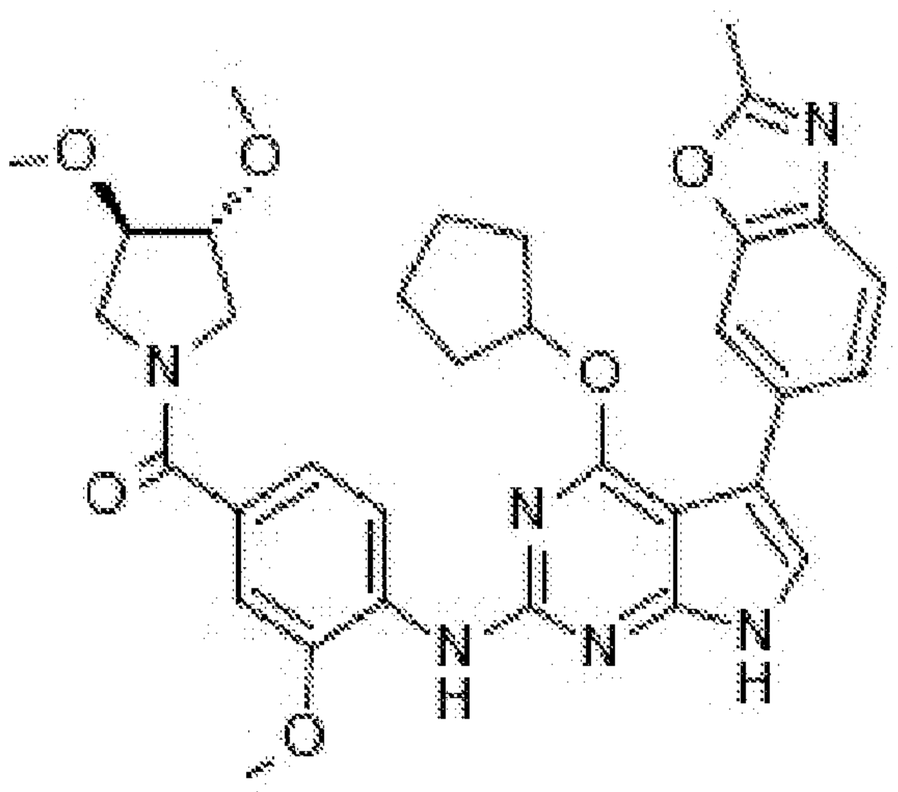
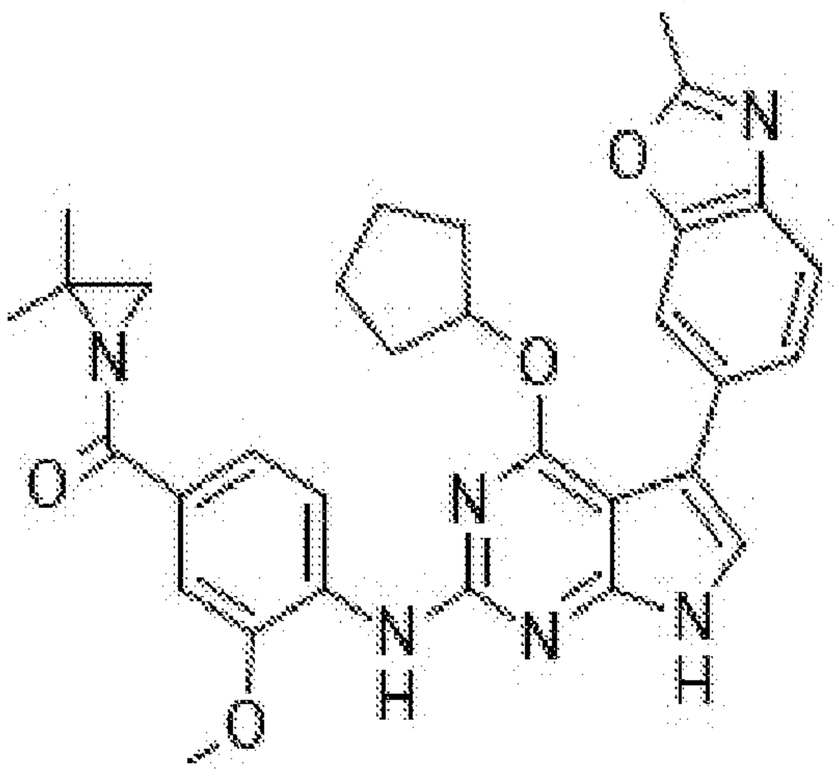
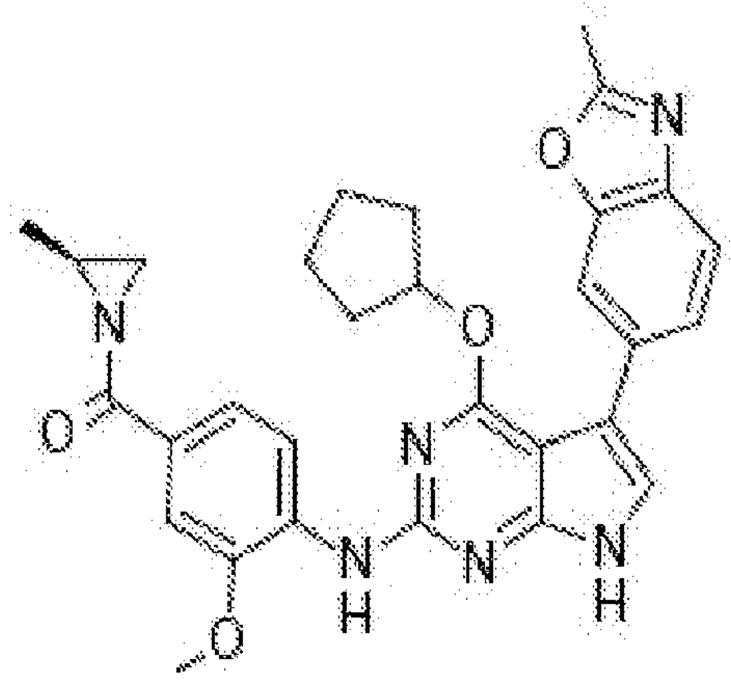
Cmpd No.	Structure	Name
296		4-(cyclopentyloxy)-N-(1,5-dimethyl-1H-pyrazol-4-yl)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine
297		4-(cyclopentyloxy)-N-(1,4-dimethyl-1H-pyrazol-3-yl)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine

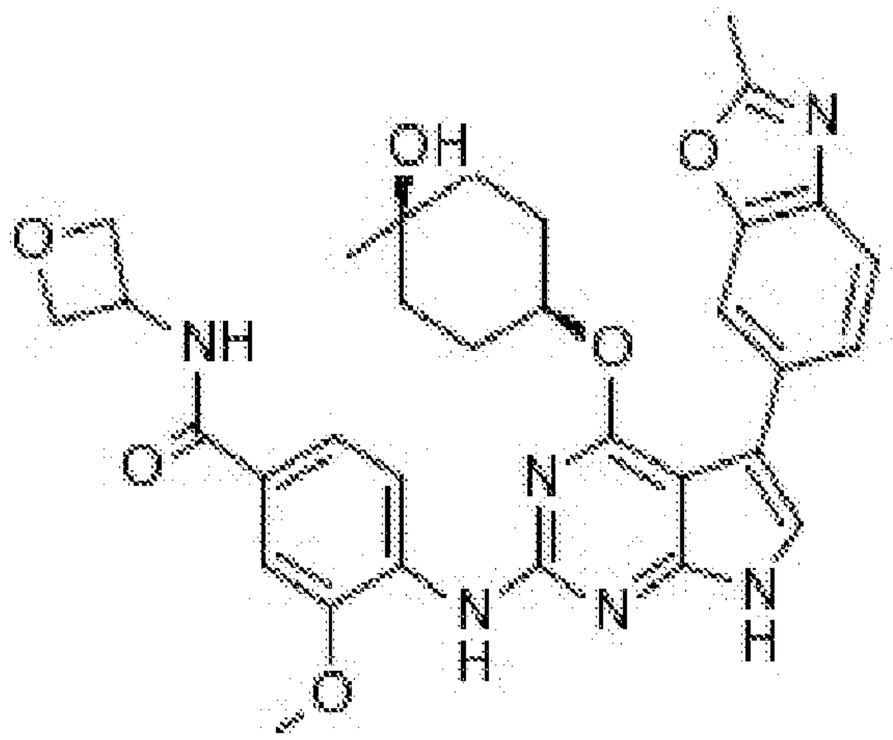
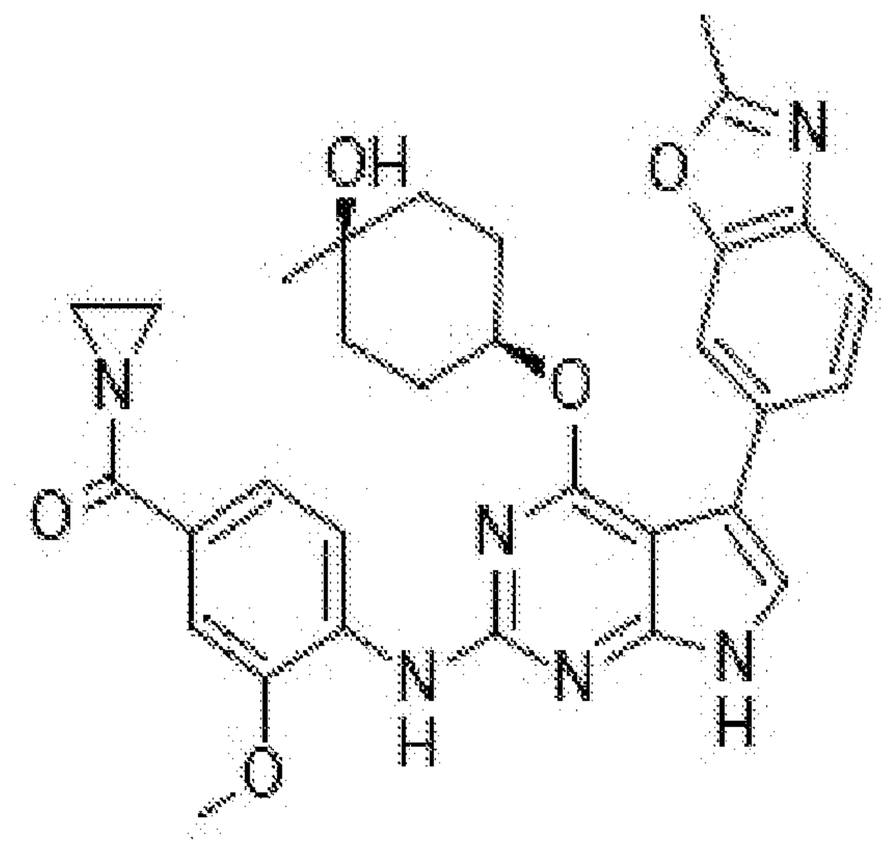
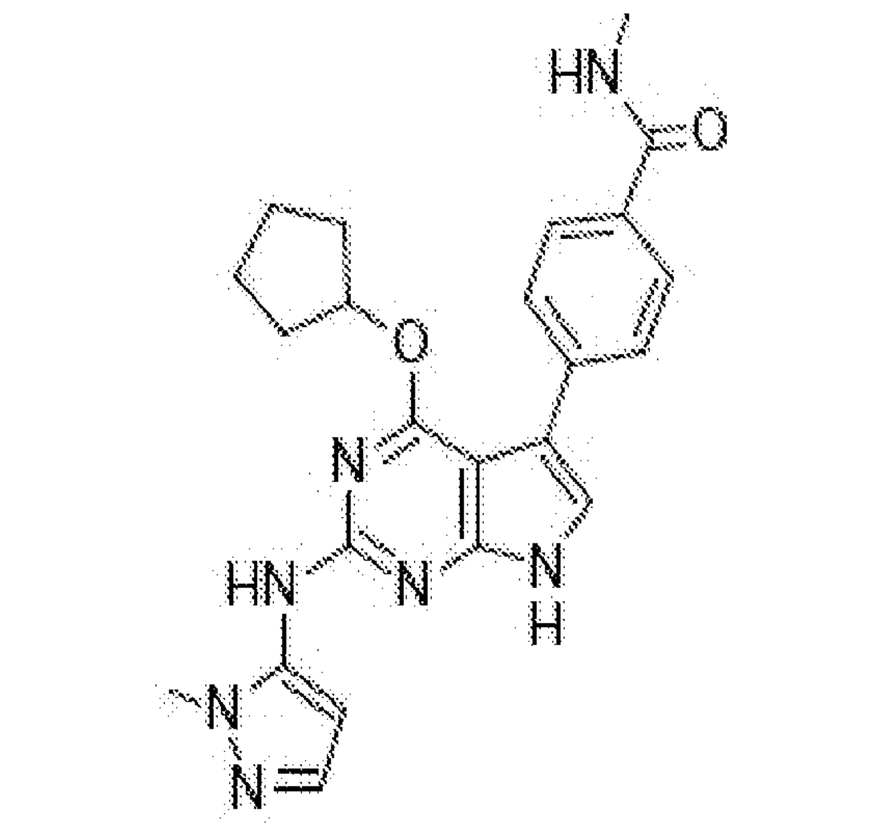
Cmpd No.	Structure	Name
298		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N,5-dimethylbenzamide
299		4-(4-(cyclopentyloxy)-5-(2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
300		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(1-methylazetidin-3-yl)benzamide

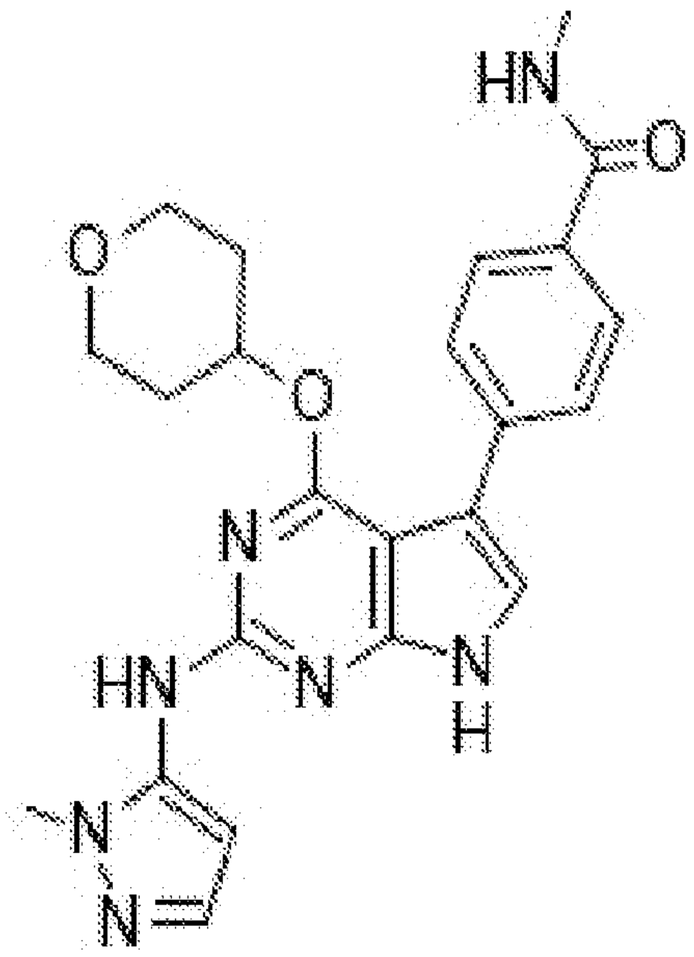
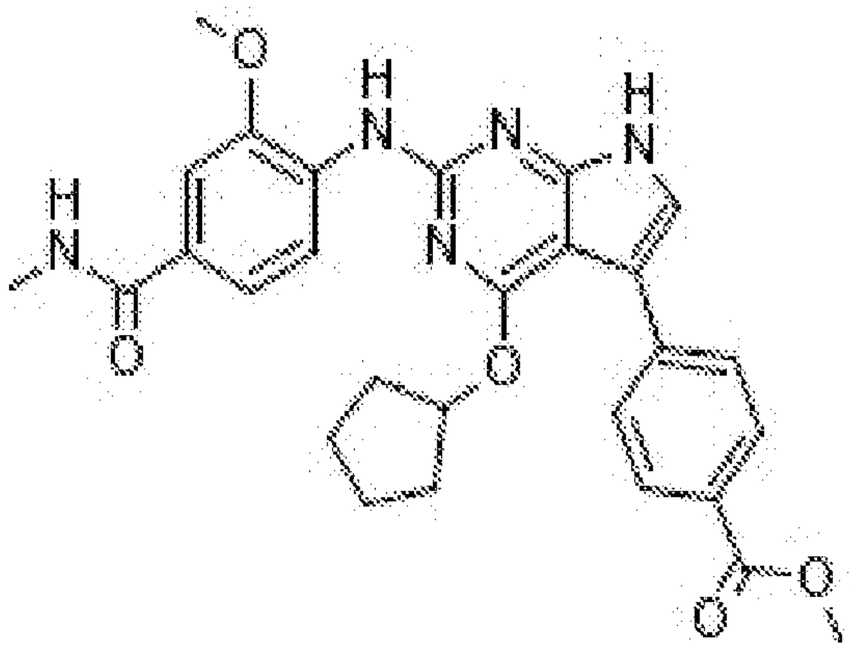
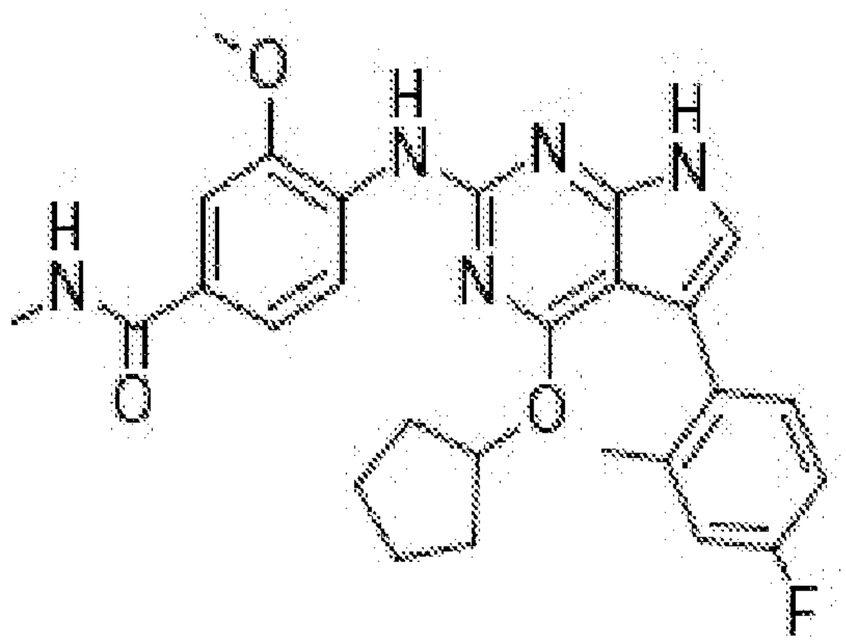
Cmpd No.	Structure	Name
301		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(3-methyloxetan-3-yl)benzamide
302		4-(4-cyclobutoxy-5-(1-methyl-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide
303		4-(4-(cyclopentyloxy)-5-(1-methyl-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide
304		4-(4-cyclobutoxy-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide

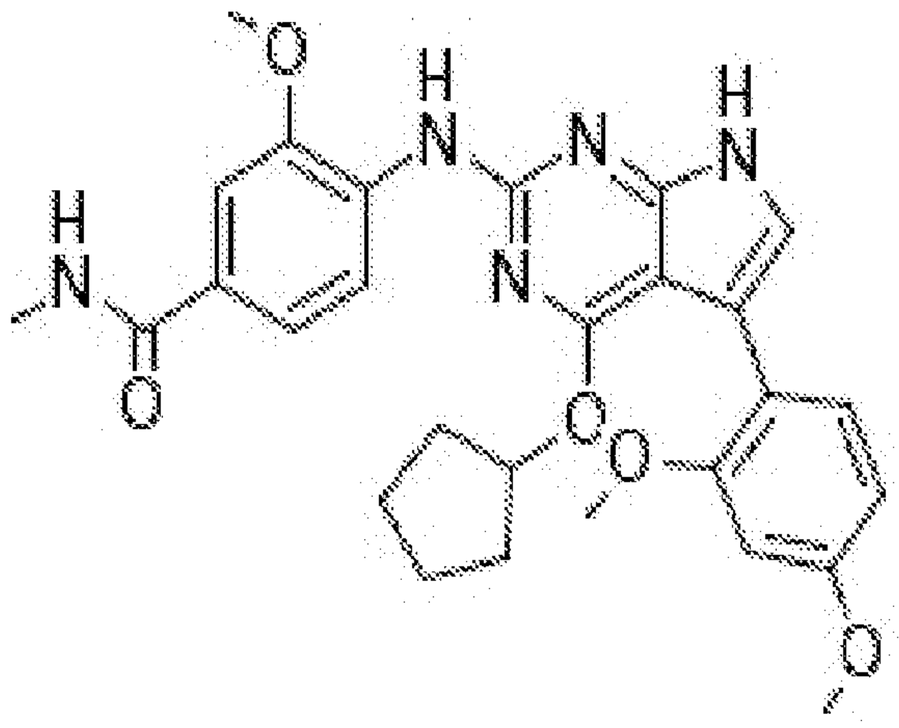
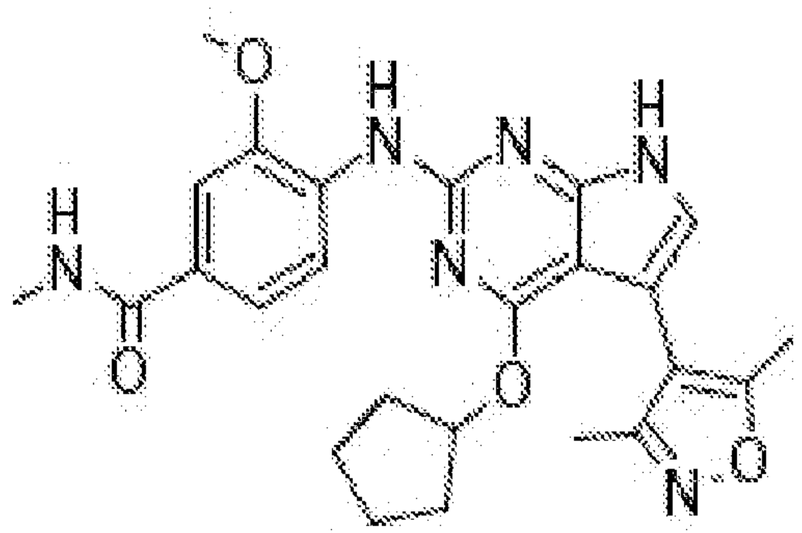
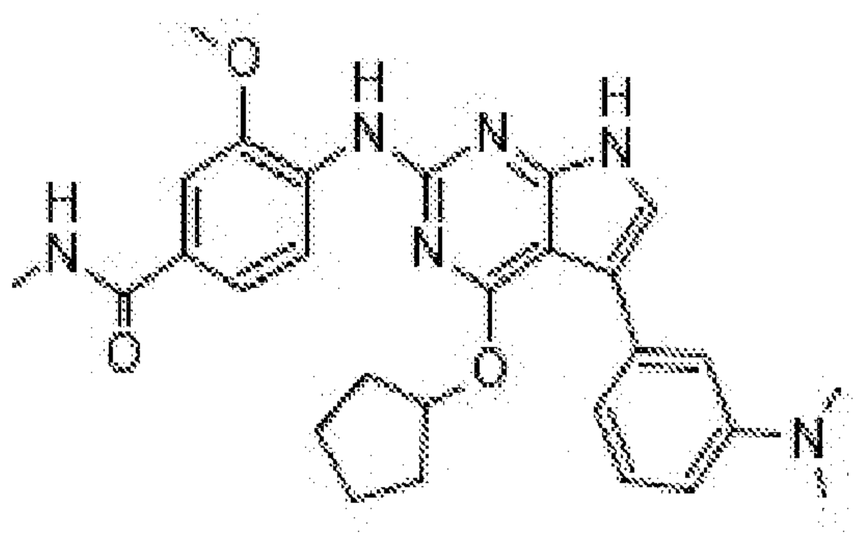
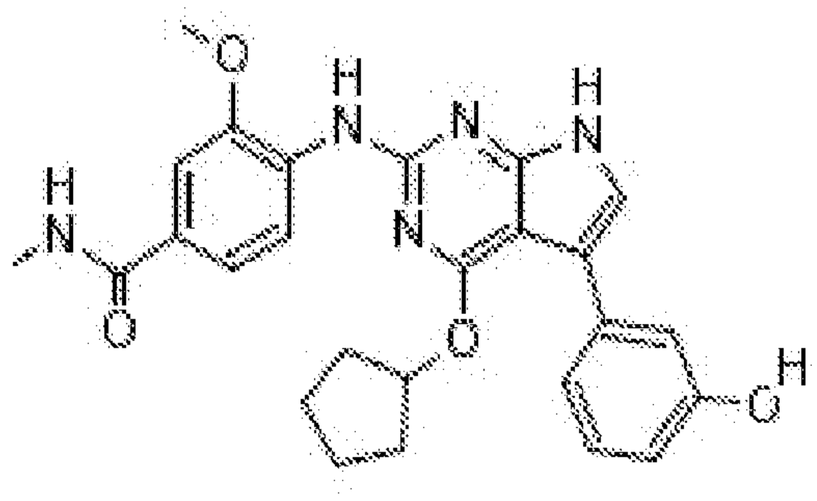
Cmpd No.	Structure	Name
305		4-(4-(cyclopentyloxy)-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide
306		4-(4-(cyclopentyloxy)-5-(quinolin-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
307		4-(cyclopentyloxy)-N-(1,3-dimethyl-1H-pyrazol-4-yl)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine

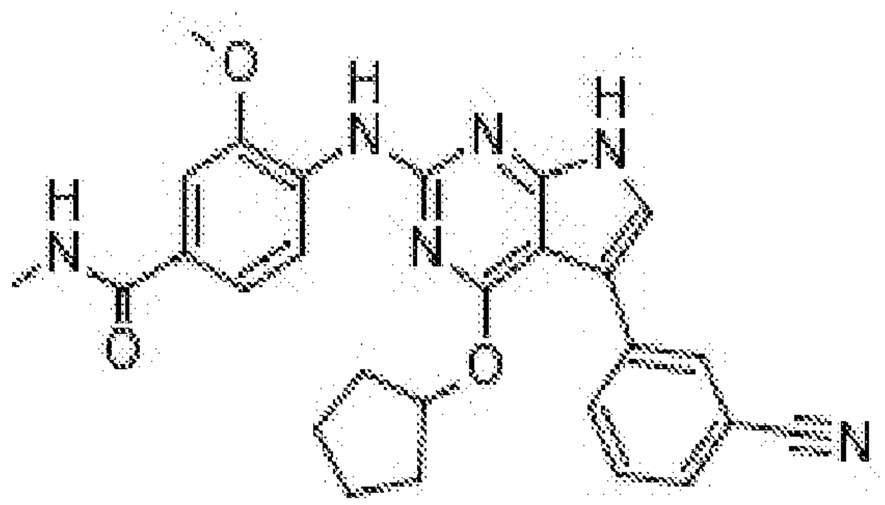
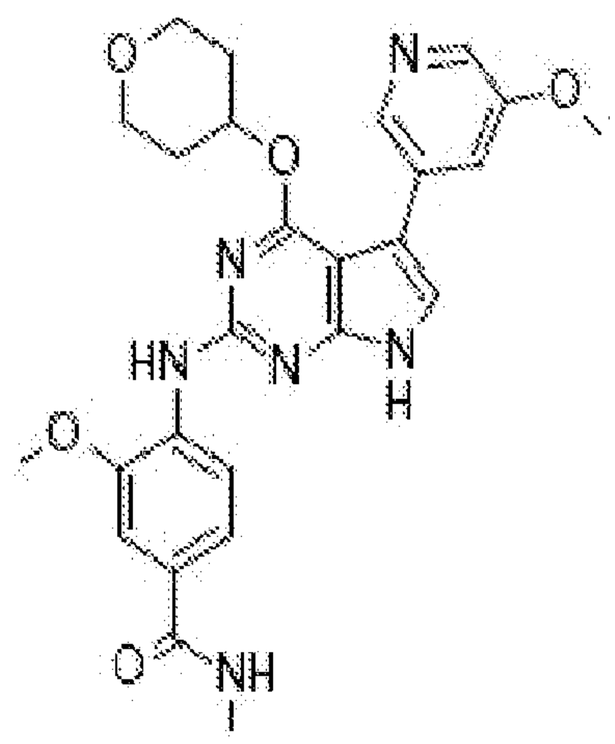
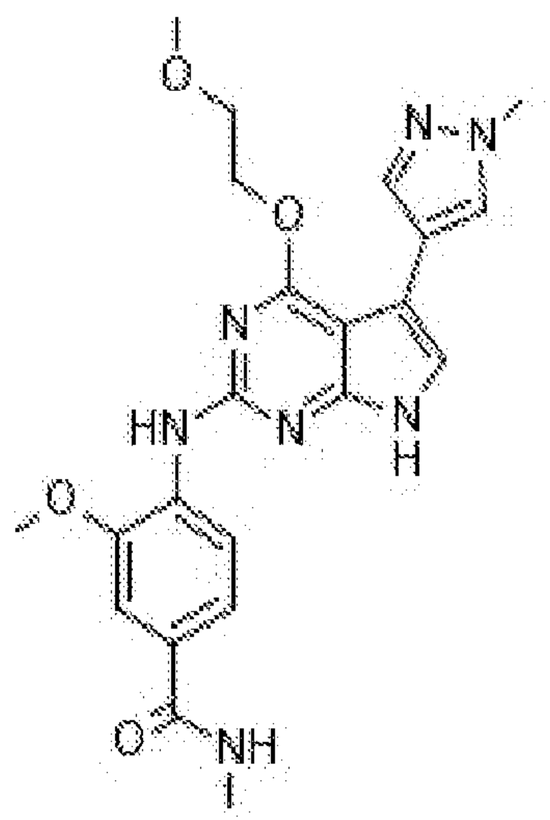
Cmpd No.	Structure	Name
308		N-(1-acetylazetidin-3-yl)-4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxybenzamide
309		4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(2,2-difluoropropyl)-3-methoxybenzamide
310		3-methoxy-4-(5-(4-(methylcarbamoyl)phenyl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(oxetan-3-yl)benzamide

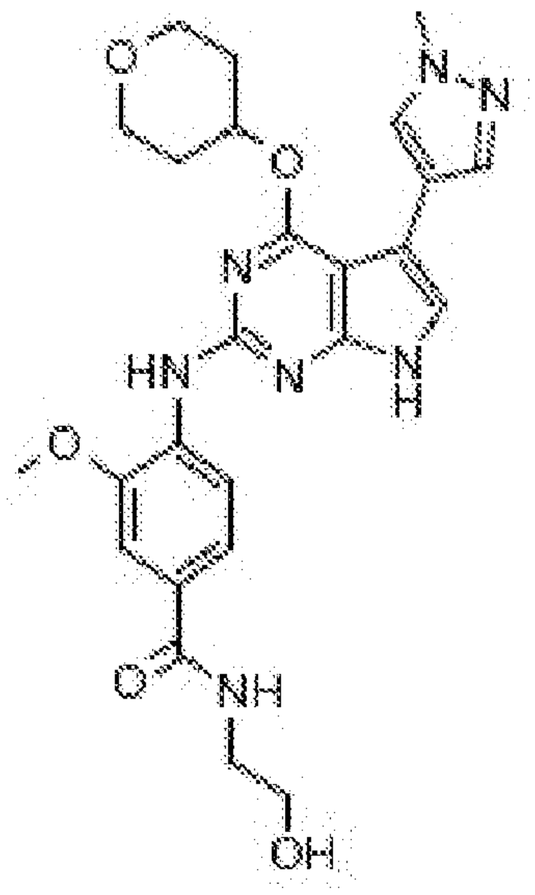
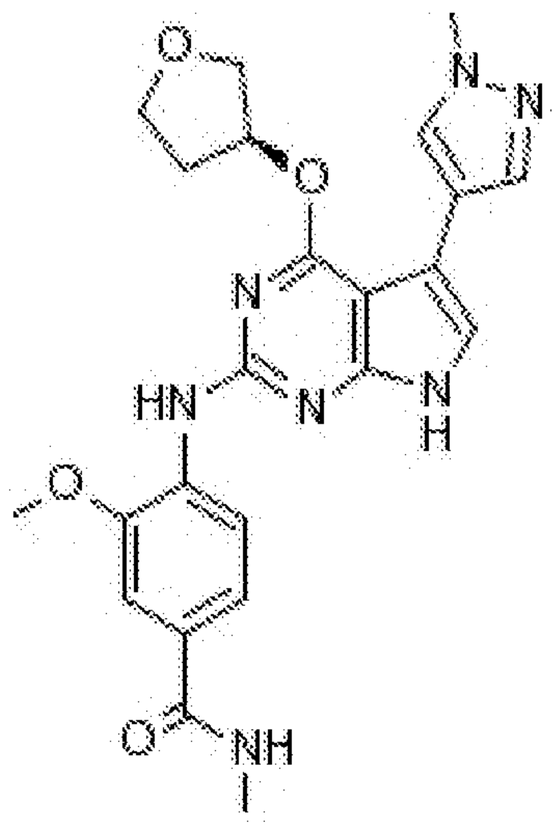
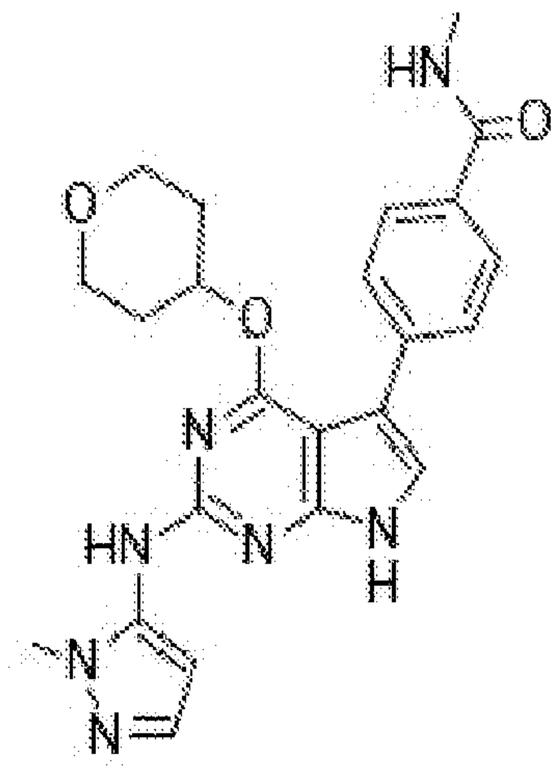
Cmpd No.	Structure	Name
311		(4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxyphenyl)((3R,4R)-3,4-dimethoxypyrrolidin-1-yl)methanone
312		(4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxyphenyl)(2,2-dimethylaziridin-1-yl)methanone
313		(S)-(4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxyphenyl)(2-methylaziridin-1-yl)methanone

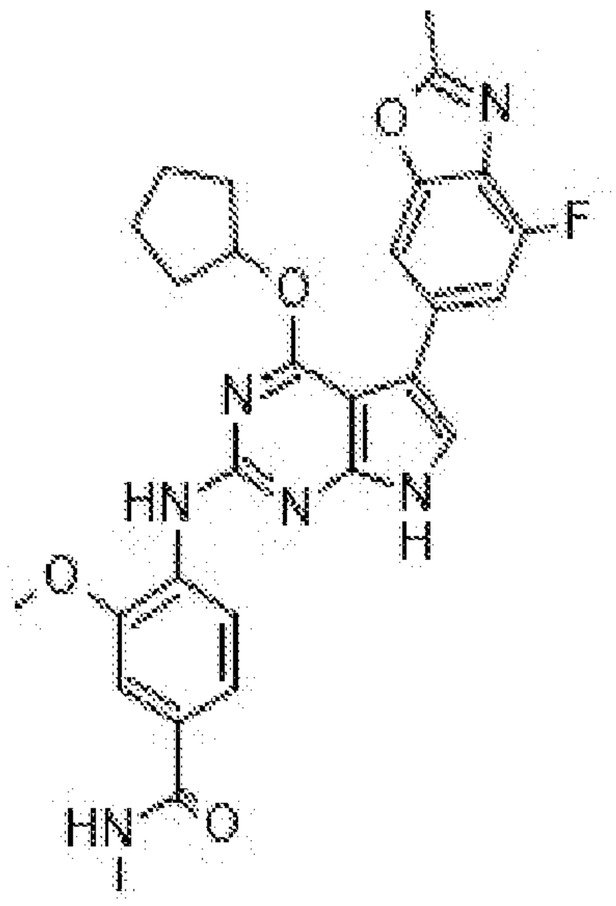
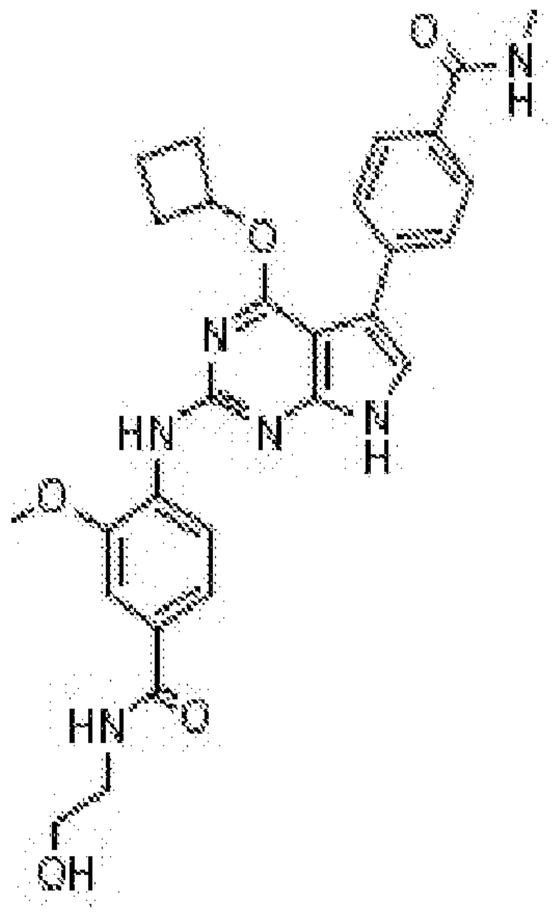
Cmpd No.	Structure	Name
314		4-(4-((1s,4s)-4-hydroxy-4-methylcyclohexyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide
315		aziridin-1-yl(4-(4-((1s,4s)-4-hydroxy-4-methylcyclohexyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxyphenyl)methanone
316		4-(4-(cyclopentyloxy)-2-(1-methyl-1H-pyrazol-5-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-N-methylbenzamide

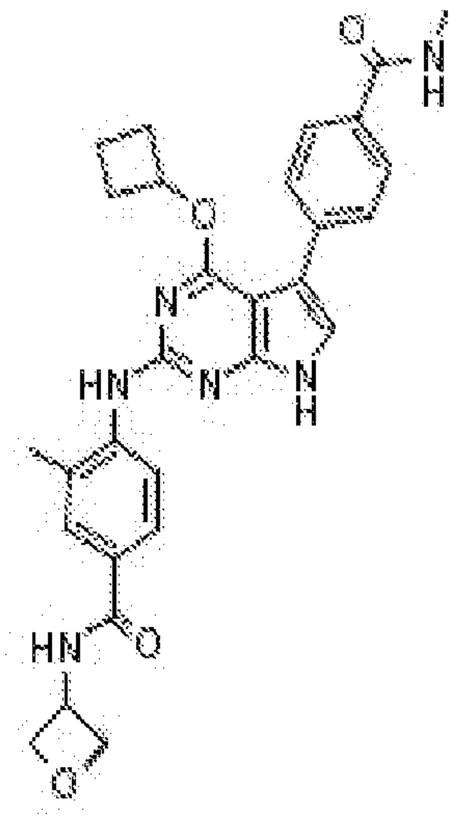
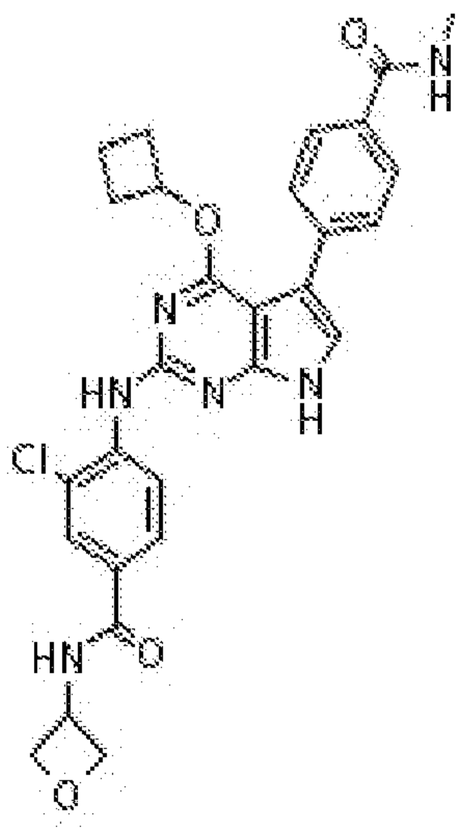
Cmpd No.	Structure	Name
317		N-methyl-4-(2-(1-methyl-1H-pyrazol-5-ylamino)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzamide
318		methyl 4-(4-(cyclopentyloxy)-2-(2-methoxy-4-(methylcarbamoyl)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzoate
319		4-(4-(cyclopentyloxy)-5-(4-fluoro-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

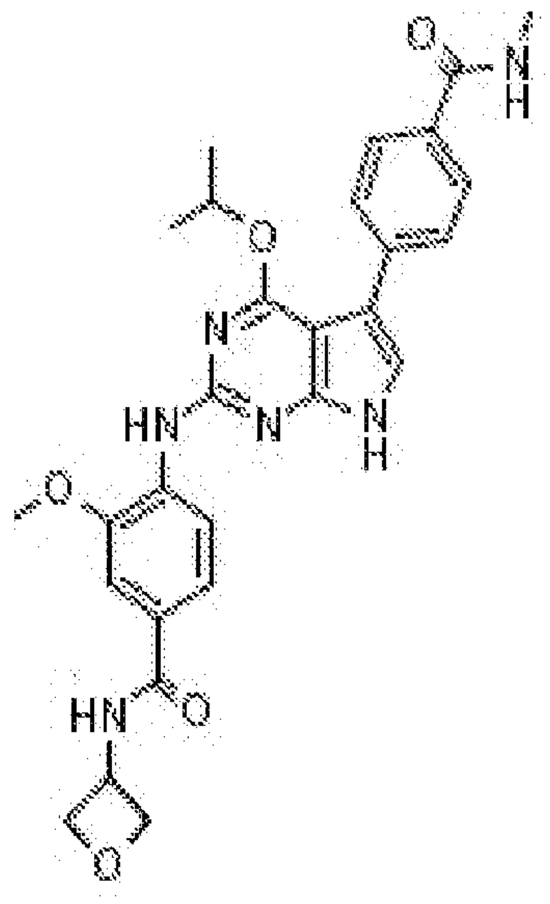
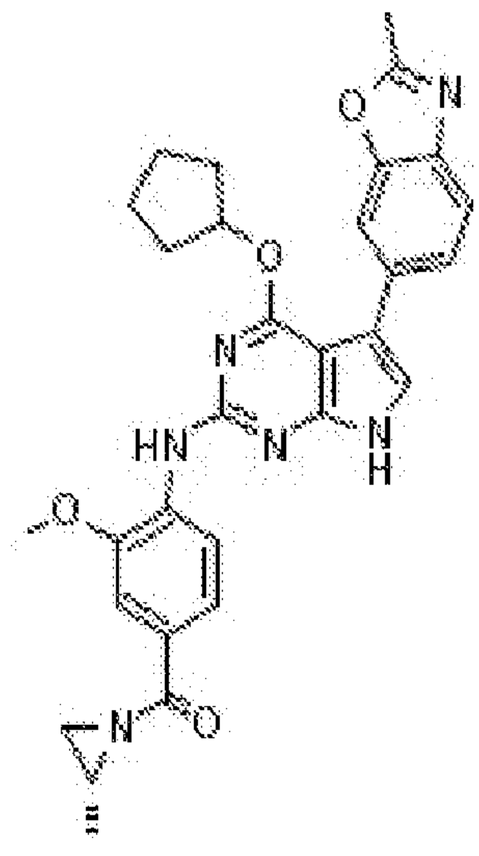
Cmpd No.	Structure	Name
320		4-(4-(cyclopentyloxy)-5-(2,4-dimethoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
321		4-(4-(cyclopentyloxy)-5-(3,5-dimethylisoxazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
322		4-(4-(cyclopentyloxy)-5-(3-(dimethylamino)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
323		4-(4-(cyclopentyloxy)-5-(3-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide

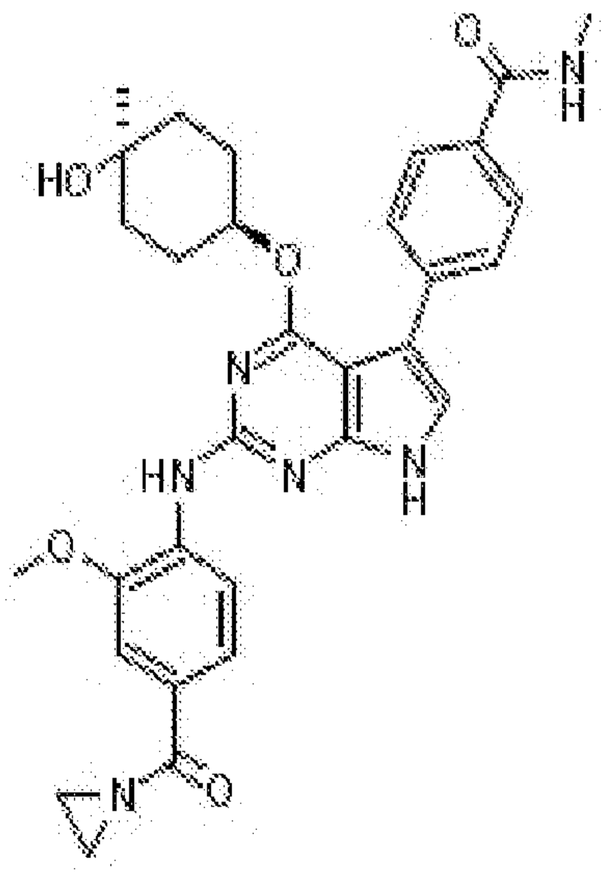
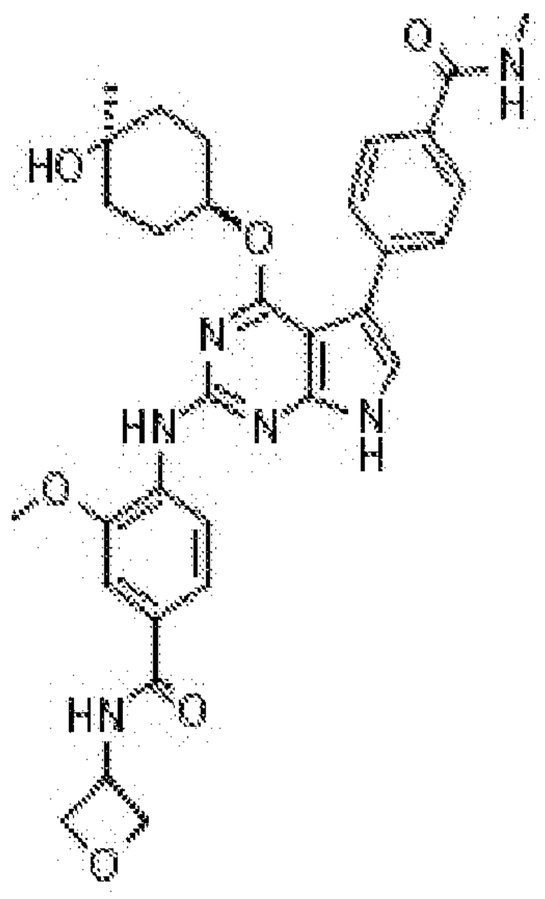
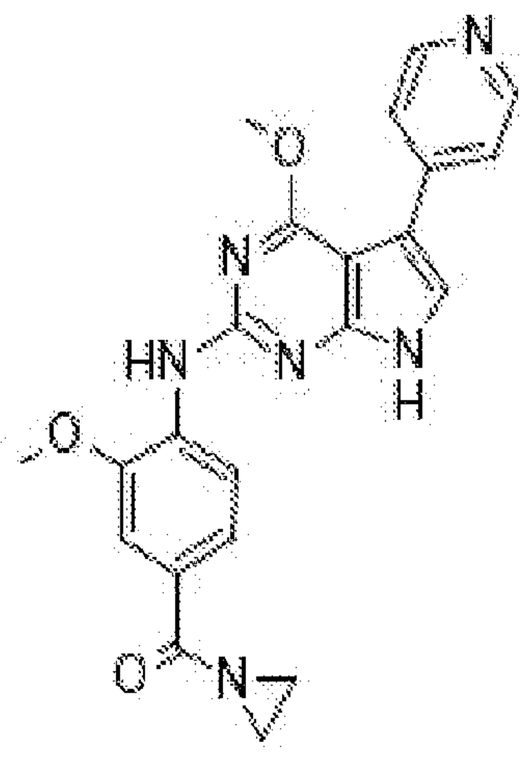
Cmpd No.	Structure	Name
324		4-(5-(3-cyanophenyl)-4-(cyclopentyloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
325		3-methoxy-4-(5-(5-methoxypyridin-3-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide
326		3-methoxy-4-(4-(2-methoxyethoxy)-5-(1-methyl-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide

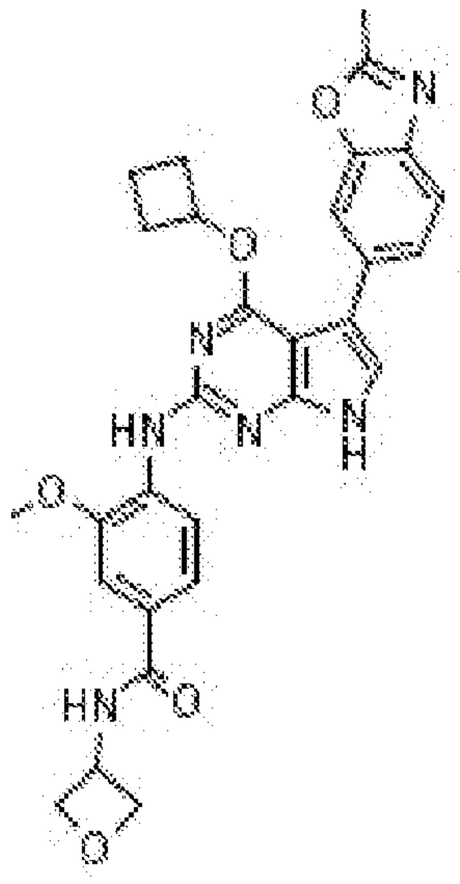
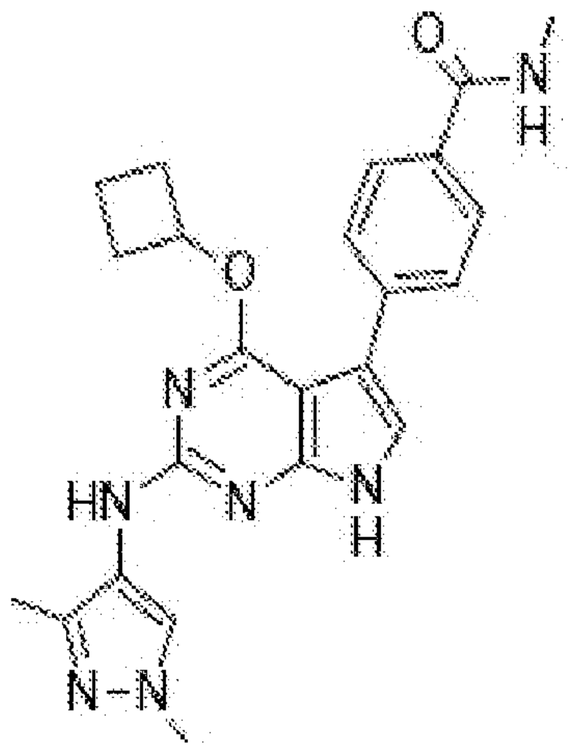
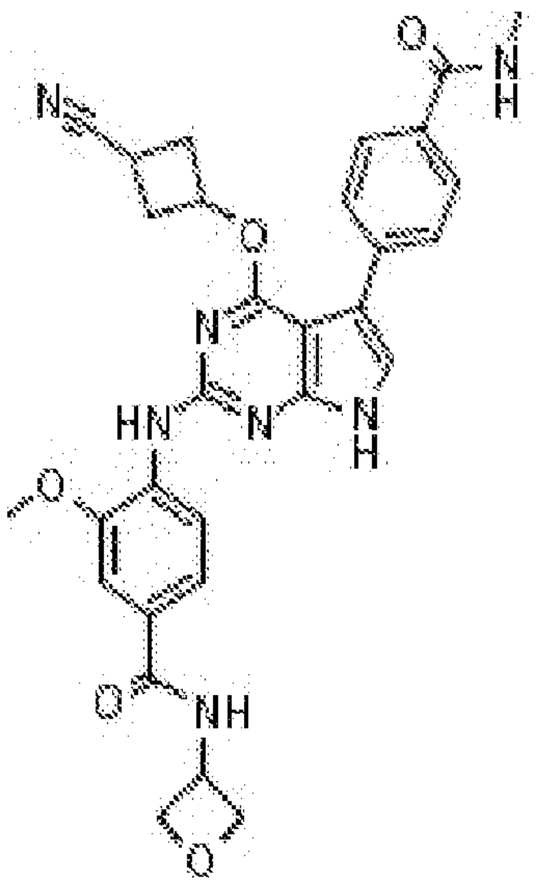
Cmpd No.	Structure	Name
327		N-(2-hydroxyethyl)-3-methoxy-4-(5-(1-methyl-1H-pyrazol-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
328		(S)-3-methoxy-N-methyl-4-(5-(1-methyl-1H-pyrazol-4-yl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
329		N-methyl-4-(2-(1-methyl-1H-pyrazol-5-ylamino)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzamide

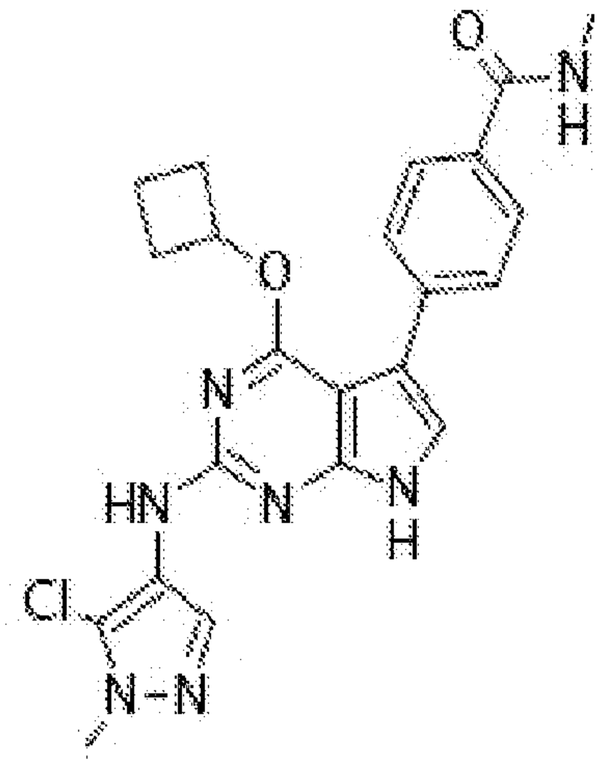
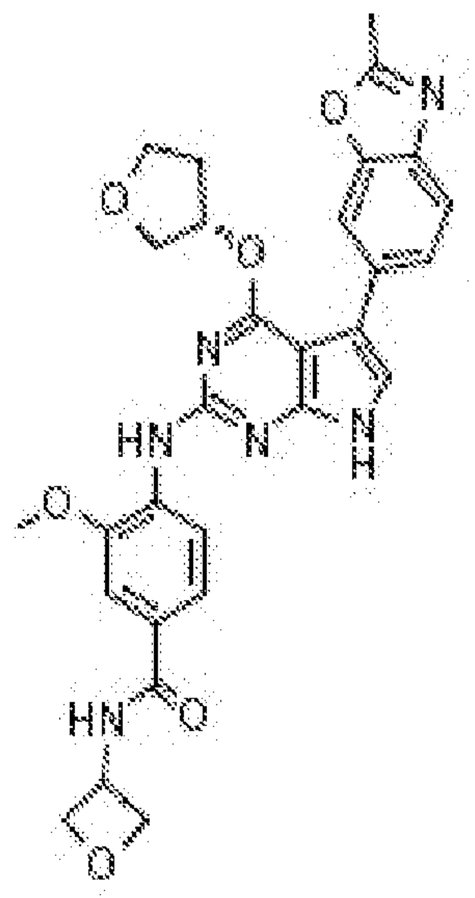
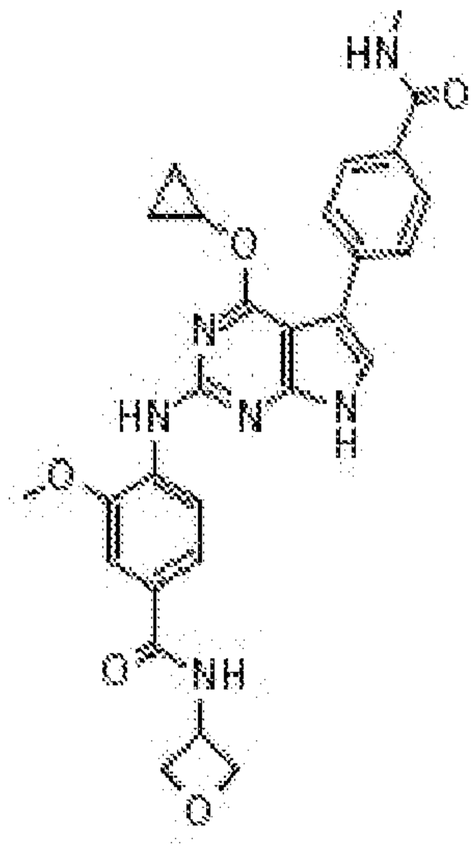
Cmpd No.	Structure	Name
330		4-(4-(cyclopentyloxy)-5-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methylbenzamide
331		4-(4-cyclobutoxy-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(2-hydroxyethyl)-3-methoxybenzamide

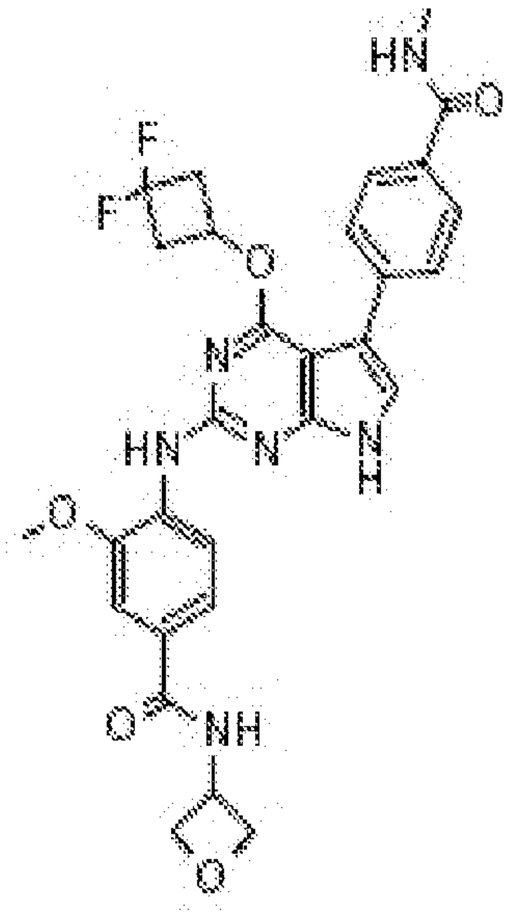
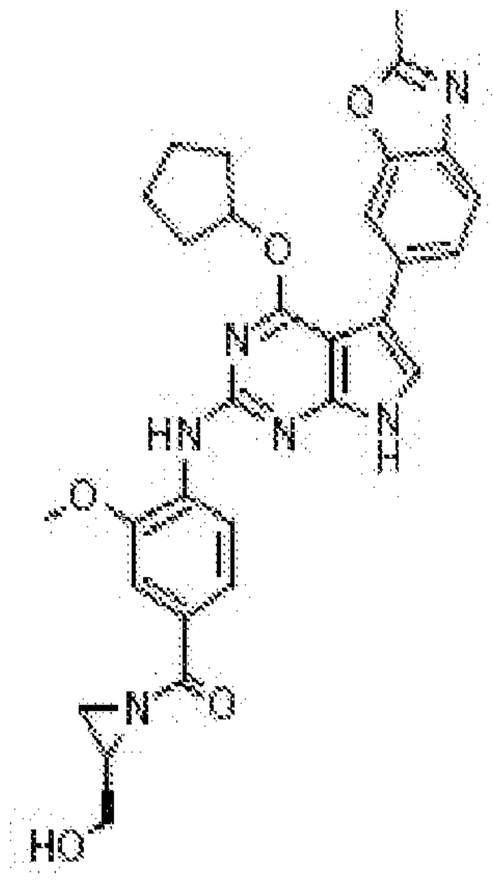
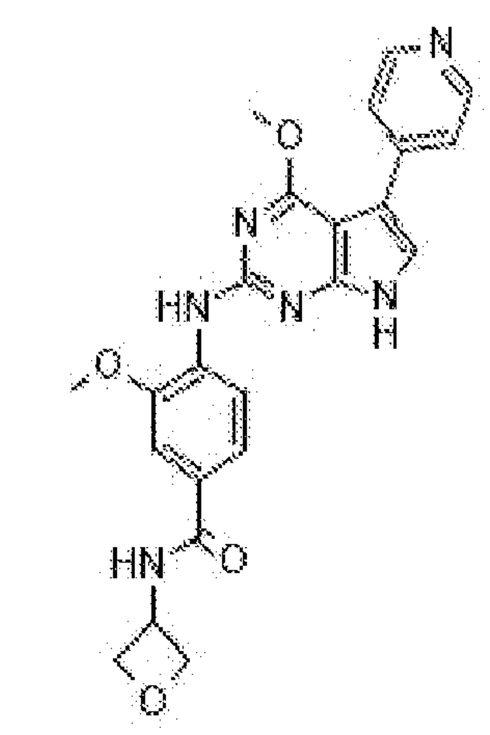
Cmpd No.	Structure	Name
332		4-(4-cyclobutoxy-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methyl-N-(oxetan-3-yl)benzamide
333		3-chloro-4-(4-cyclobutoxy-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(oxetan-3-yl)benzamide

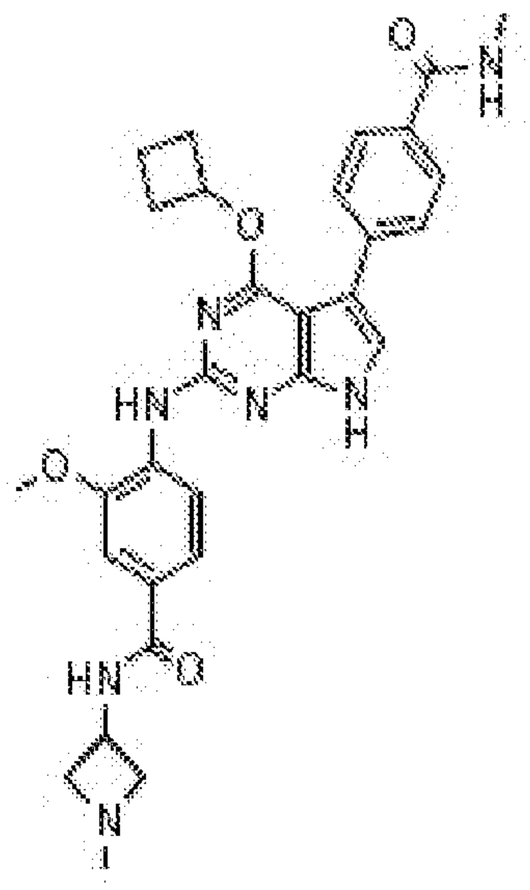
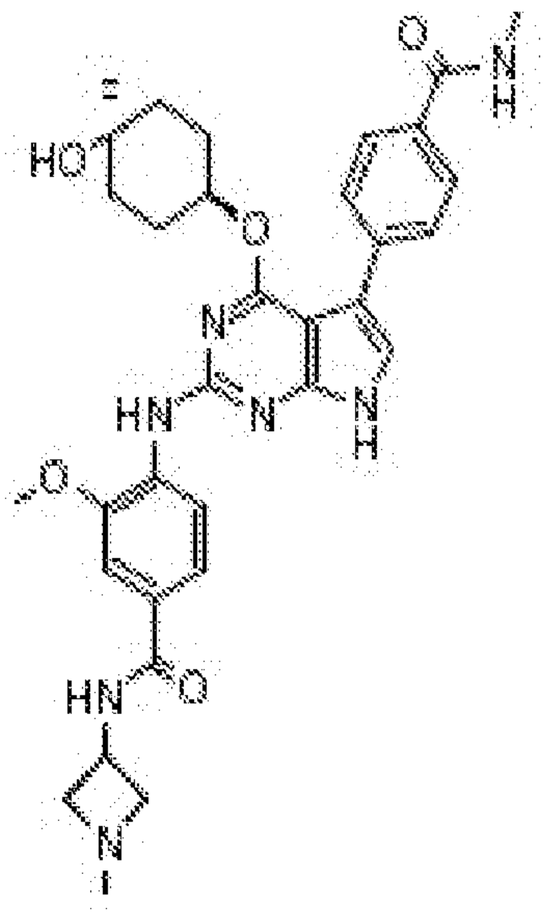
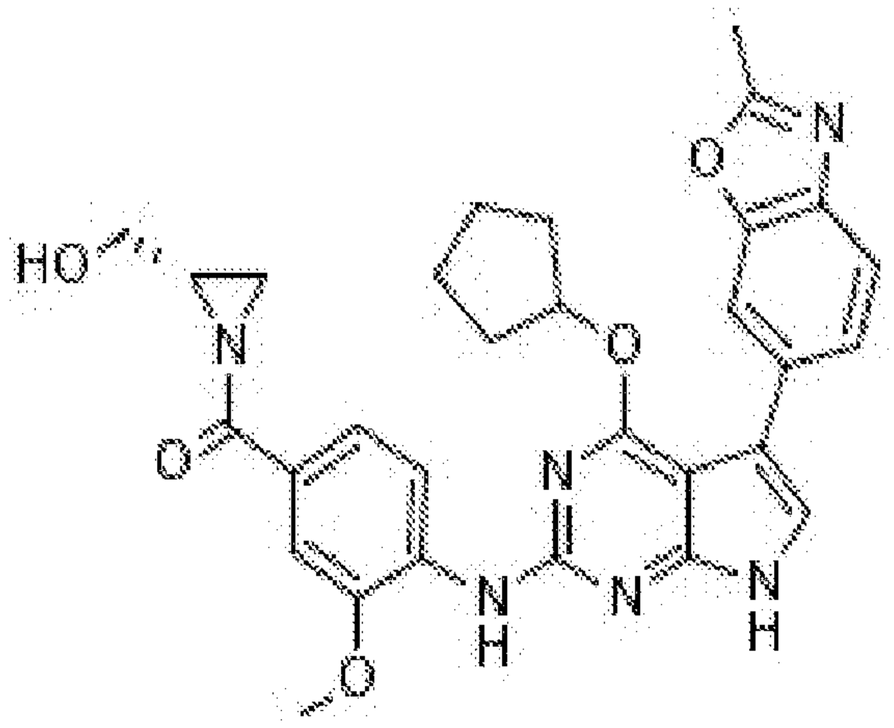
Cmpd No.	Structure	Name
334		4-(4-isopropoxy-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide
335		(R)-(4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxyphenyl)(2-methylaziridin-1-yl)methanone

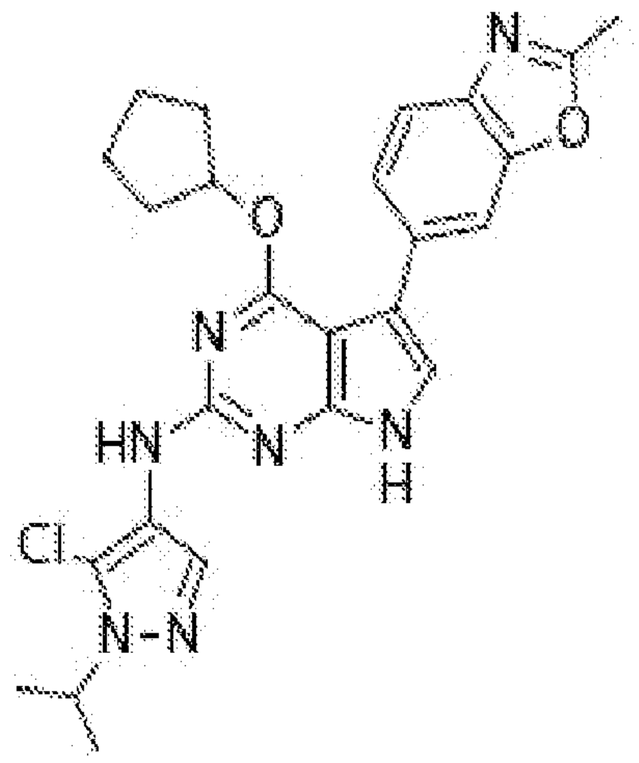
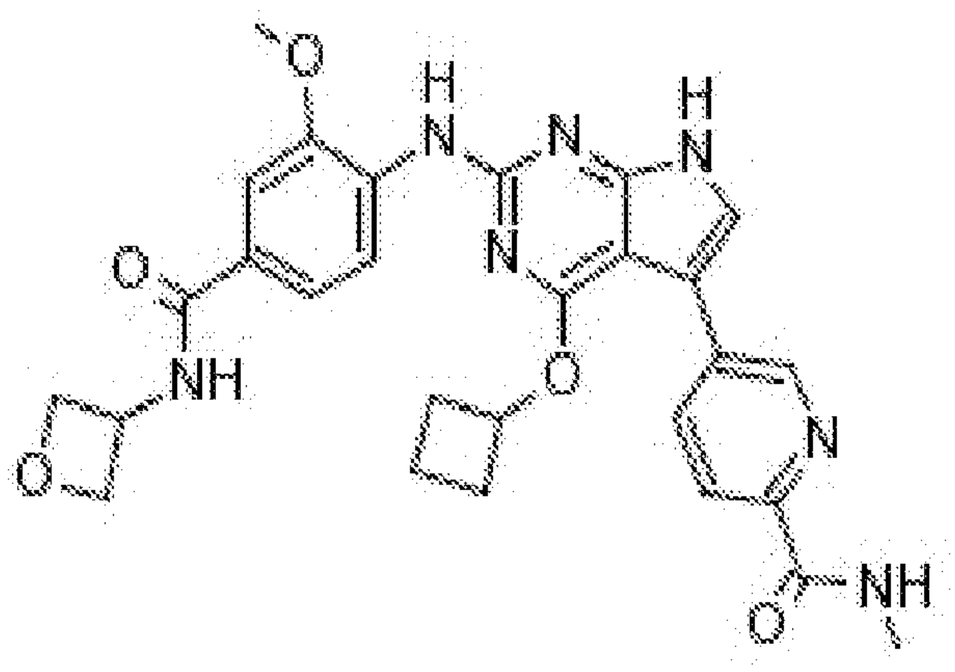
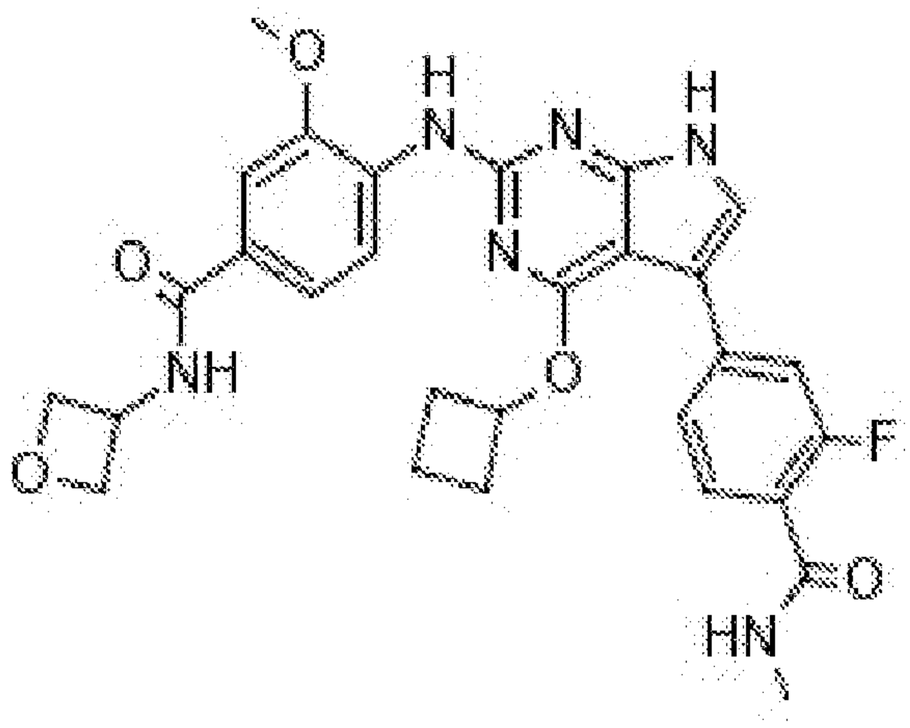
Cmpd No.	Structure	Name
336		4-(2-(4-(aziridine-1-carbonyl)-2-methoxyphenylamino)-4-((1s,4s)-4-hydroxy-4-methylcyclohexyloxy)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-N-methylbenzamide
337		4-(4-((1s,4s)-4-hydroxy-4-methylcyclohexyloxy)-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide
338		aziridin-1-yl(3-methoxy-4-(4-methoxy-5-(pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)phenyl)methanone

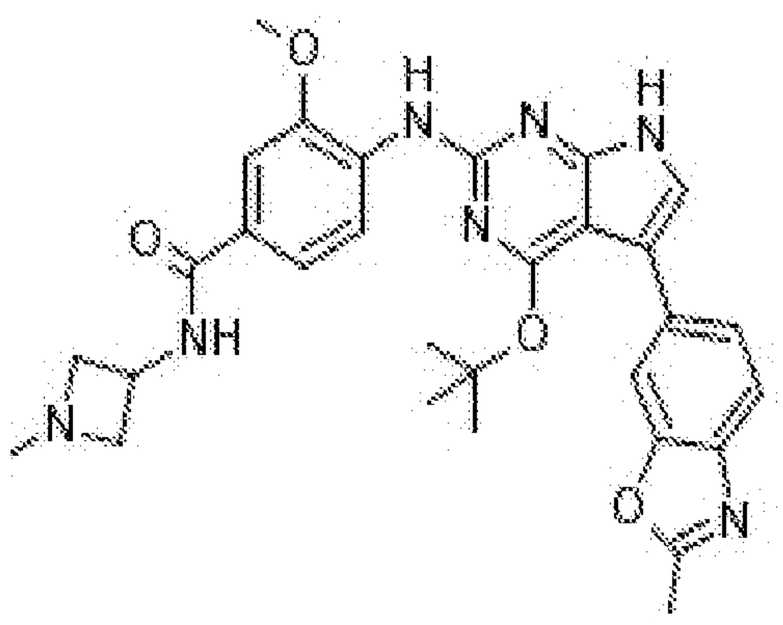
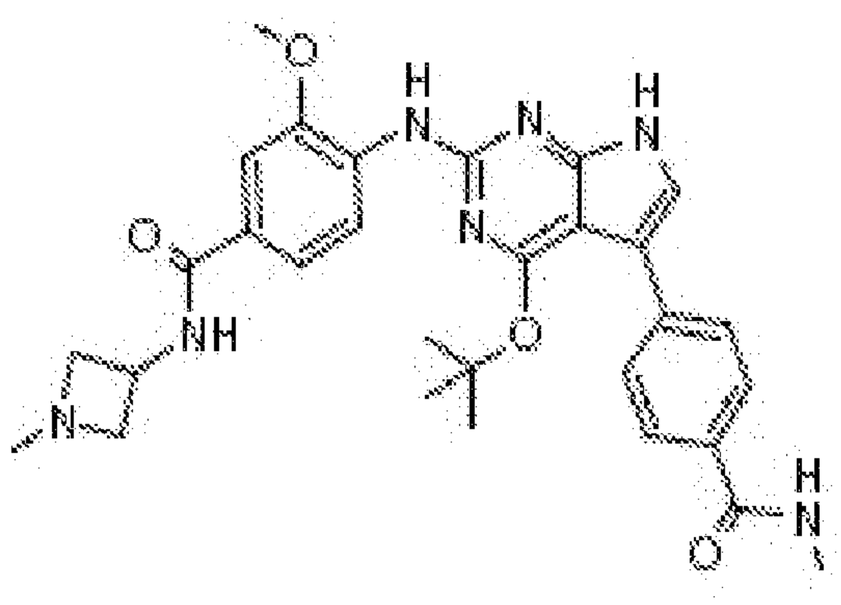
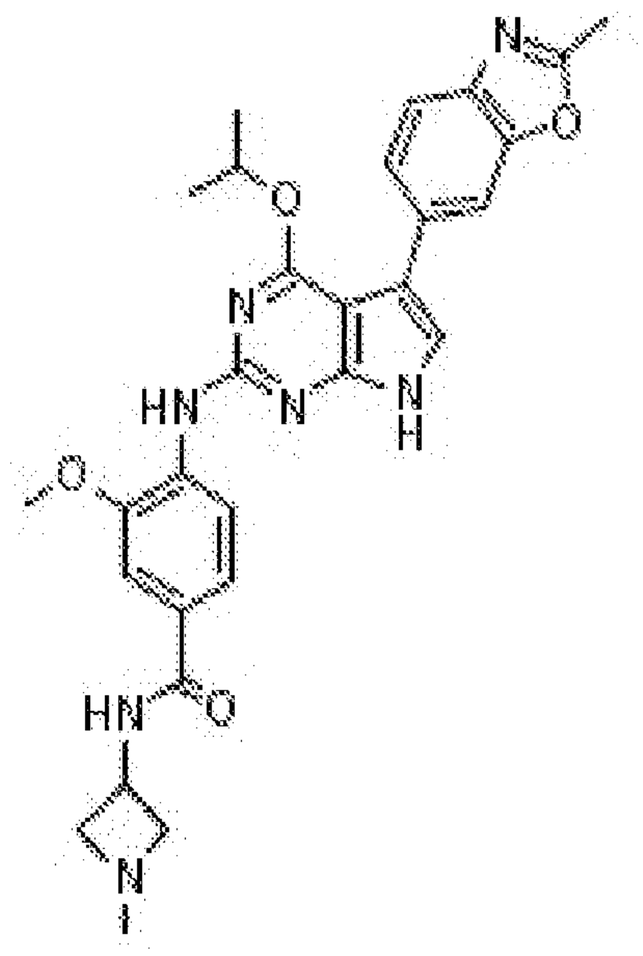
Cmpd No.	Structure	Name
339		4-(4-cyclobutoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide
340		4-(4-cyclobutoxy-2-(1,3-dimethyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-N-methylbenzamide
341		4-(4-(3-cyanocyclobutoxy)-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide

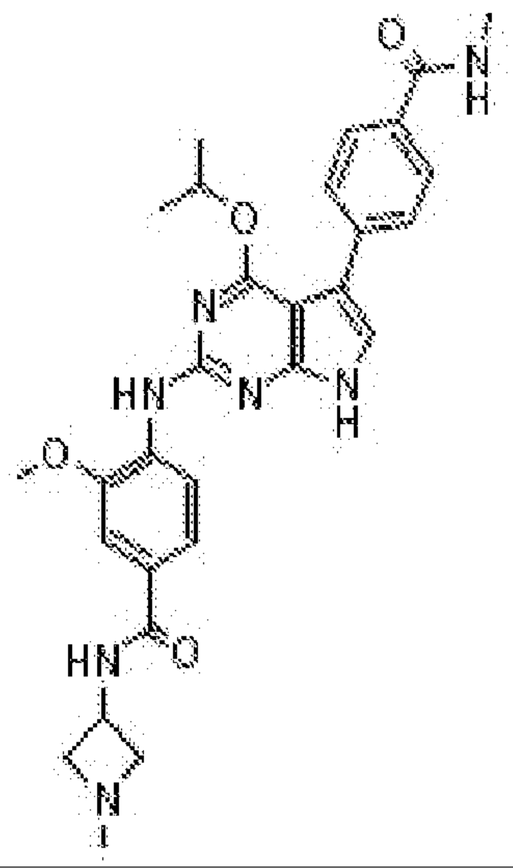
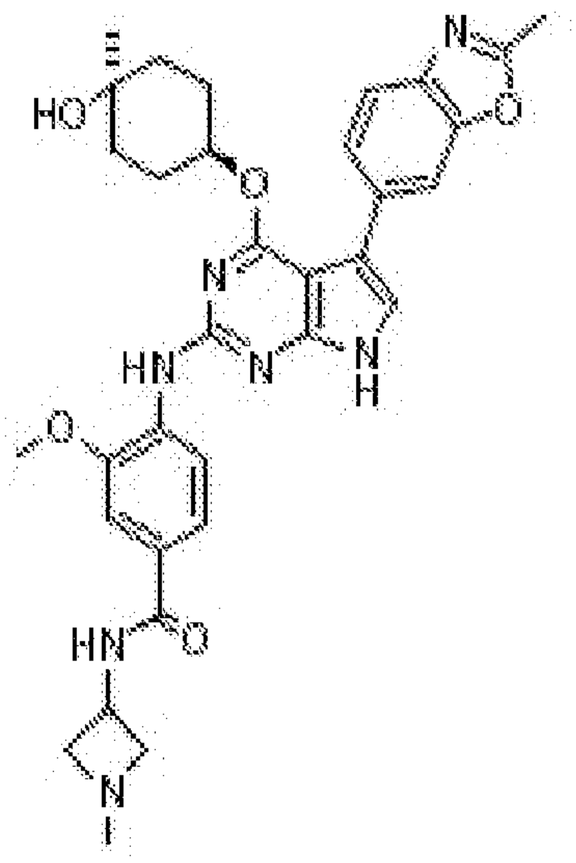
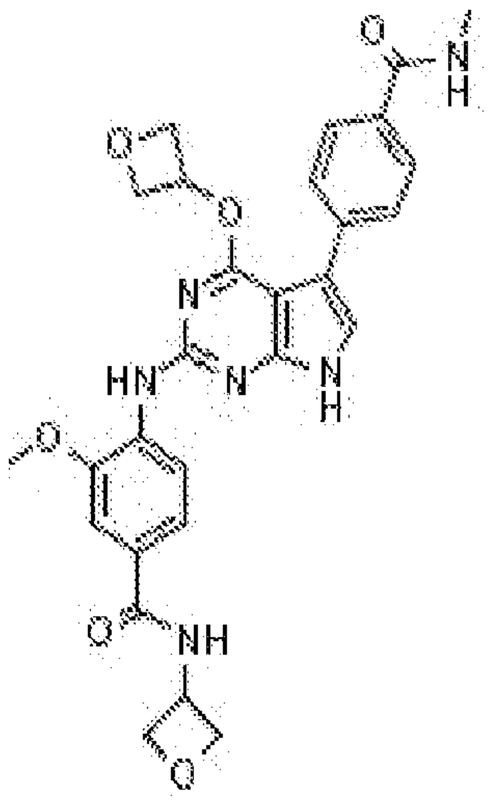
Cmpd No.	Structure	Name
342		4-(2-(5-chloro-1-methyl-1H-pyrazol-4-ylamino)-4-cyclobutoxy-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-N-methylbenzamide
343		(S)-3-methoxy-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(oxetan-3-yl)benzamide
344		4-(4-cyclopropoxy-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide

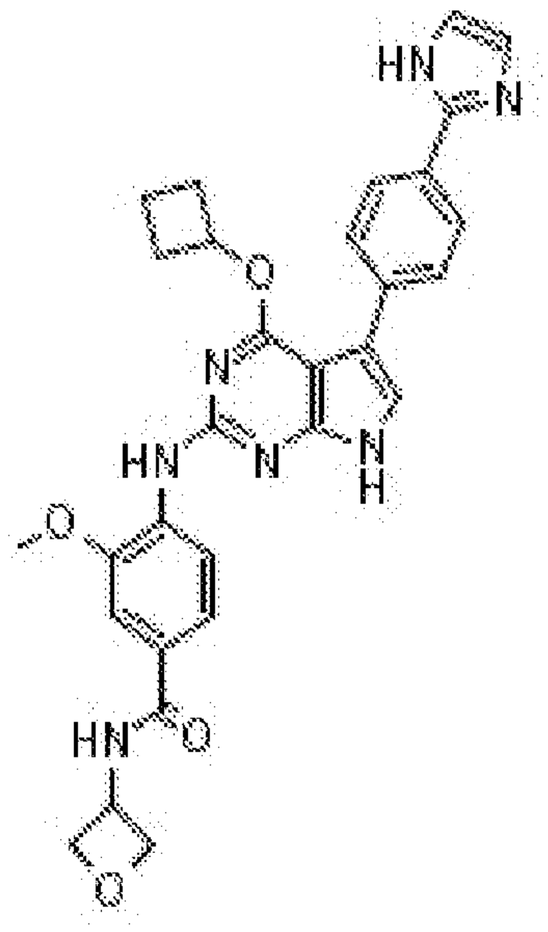
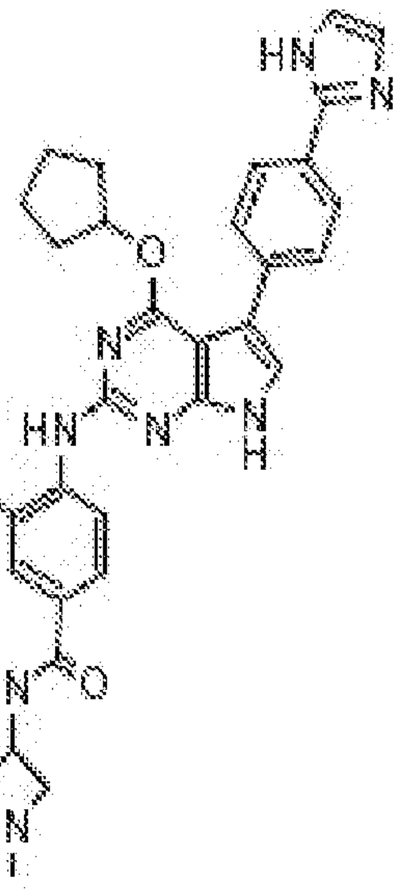
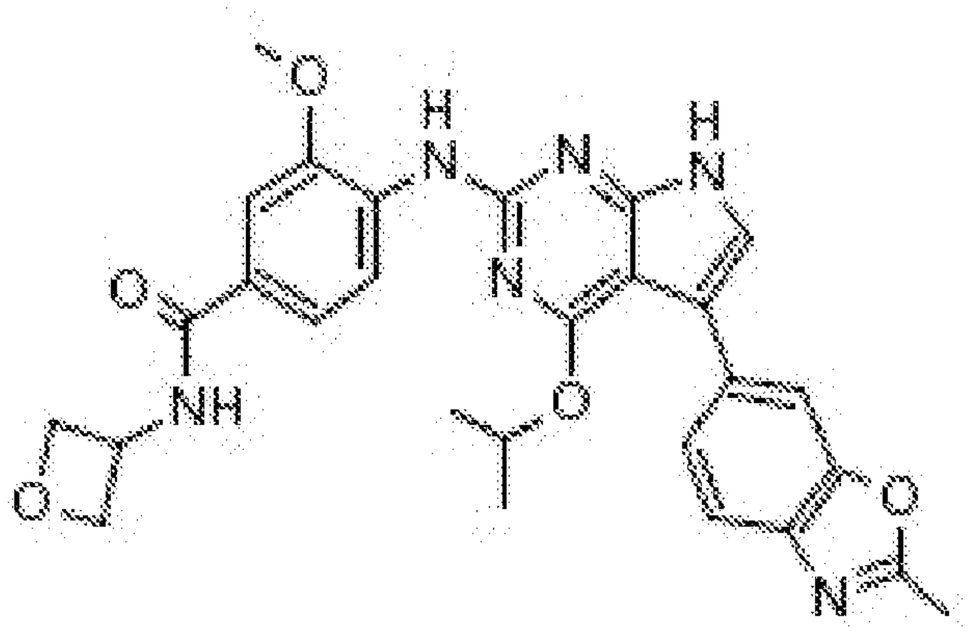
Cmpd No.	Structure	Name
345		4-(4-(3,3-difluorocyclobutoxy)-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide
346		(R)-(4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxyphenyl)(2-(hydroxymethyl)aziridin-1-yl)methanone
347		3-methoxy-4-(4-methoxy-5-(pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(oxetan-3-yl)benzamide

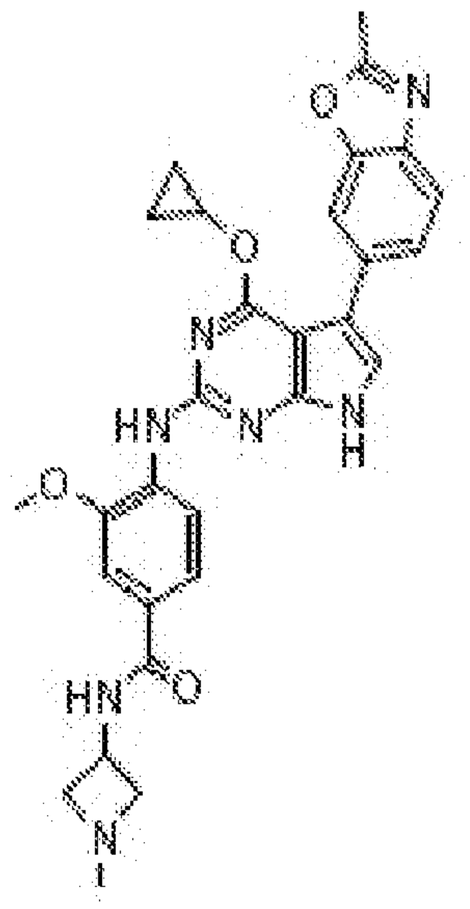
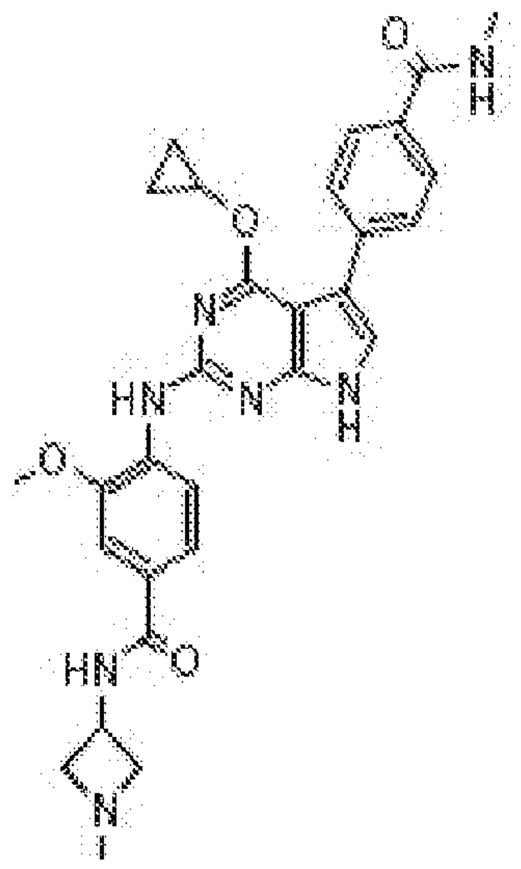
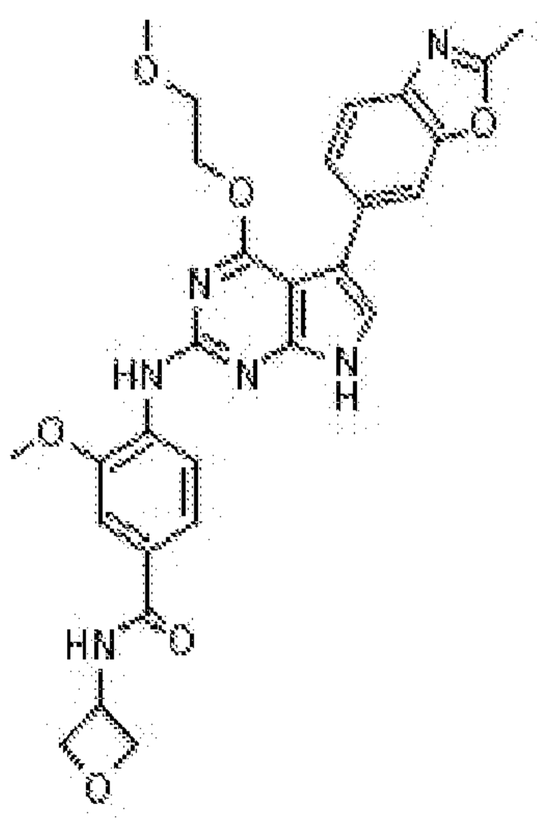
Cmpd No.	Structure	Name
348		4-(4-cyclobutoxy-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(1-methylazetidin-3-yl)benzamide
349		4-(4-((1s,4s)-4-hydroxy-4-methylcyclohexyloxy)-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(1-methylazetidin-3-yl)benzamide
350		(S)-(4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxyphenyl)(2-(hydroxymethyl)aziridin-1-yl)methanone

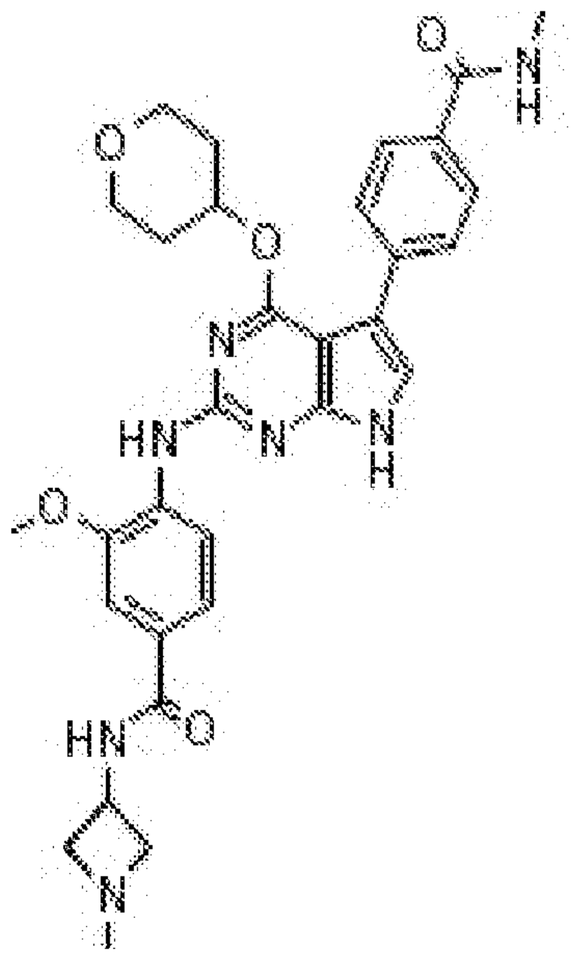
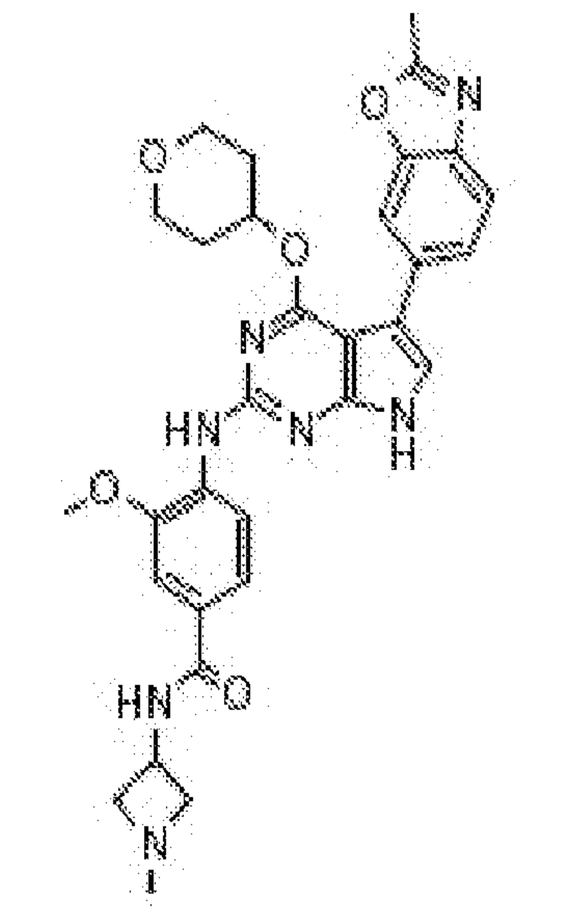
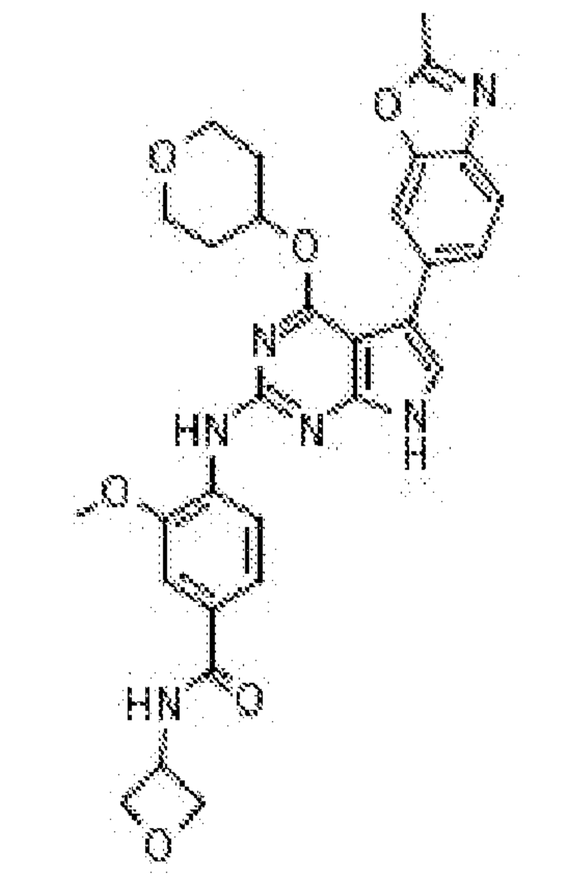
Cmpd No.	Structure	Name
351		N-(5-chloro-1-isopropyl-1H-pyrazol-4-yl)-4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine
352		5-(4-cyclobutoxy-2-(2-methoxy-4-(oxetan-3-ylcarbamoyl)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-N-methylpicolinamide
353		4-(4-cyclobutoxy-2-(2-methoxy-4-(oxetan-3-ylcarbamoyl)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluoro-N-methylbenzamide

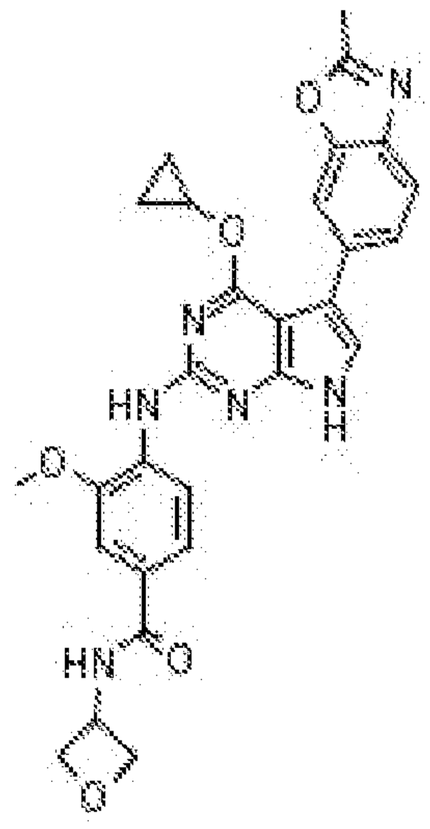
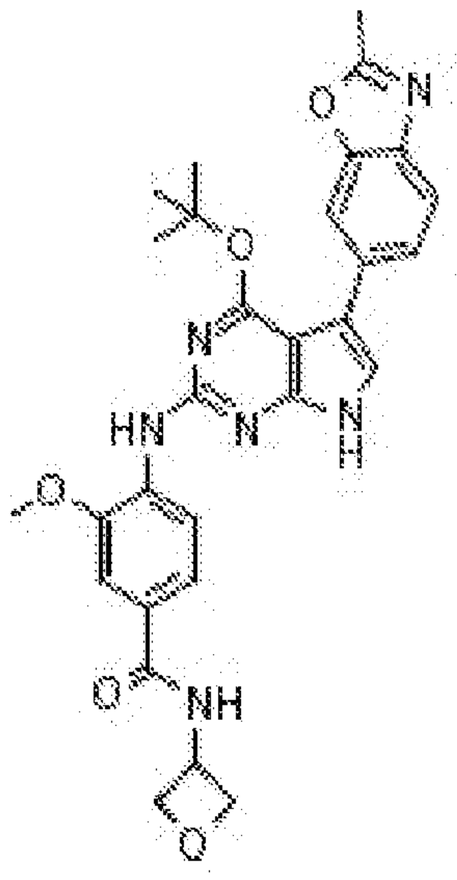
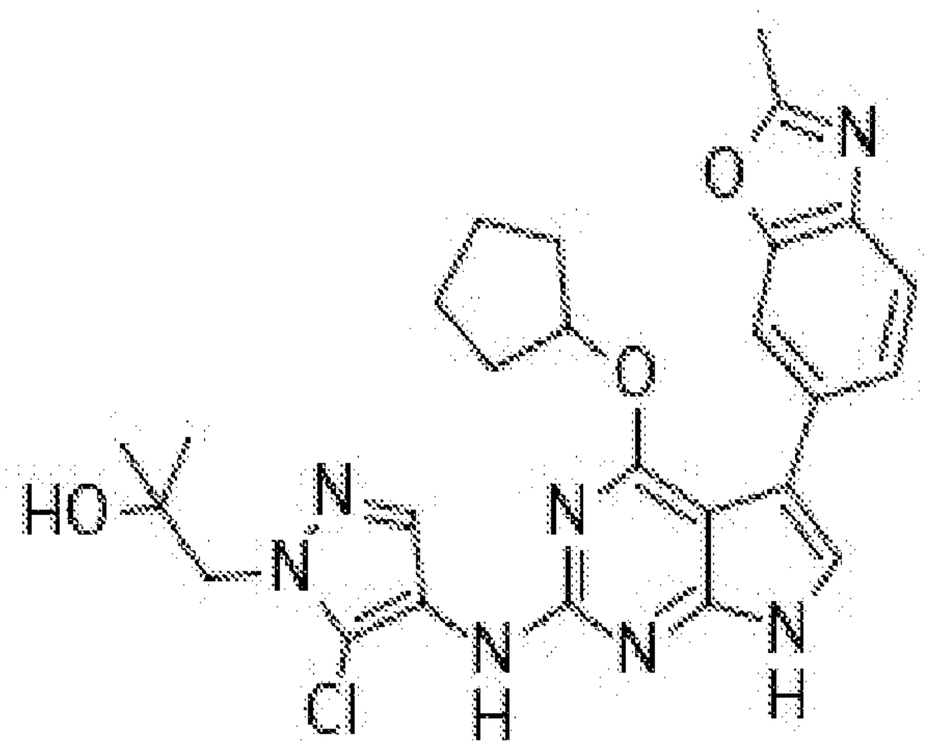
Cmpd No.	Structure	Name
354		4-(4-tert-butoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(1-methylazetidin-3-yl)benzamide
355		4-(4-tert-butoxy-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(1-methylazetidin-3-yl)benzamide
356		4-(4-isopropoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(1-methylazetidin-3-yl)benzamide

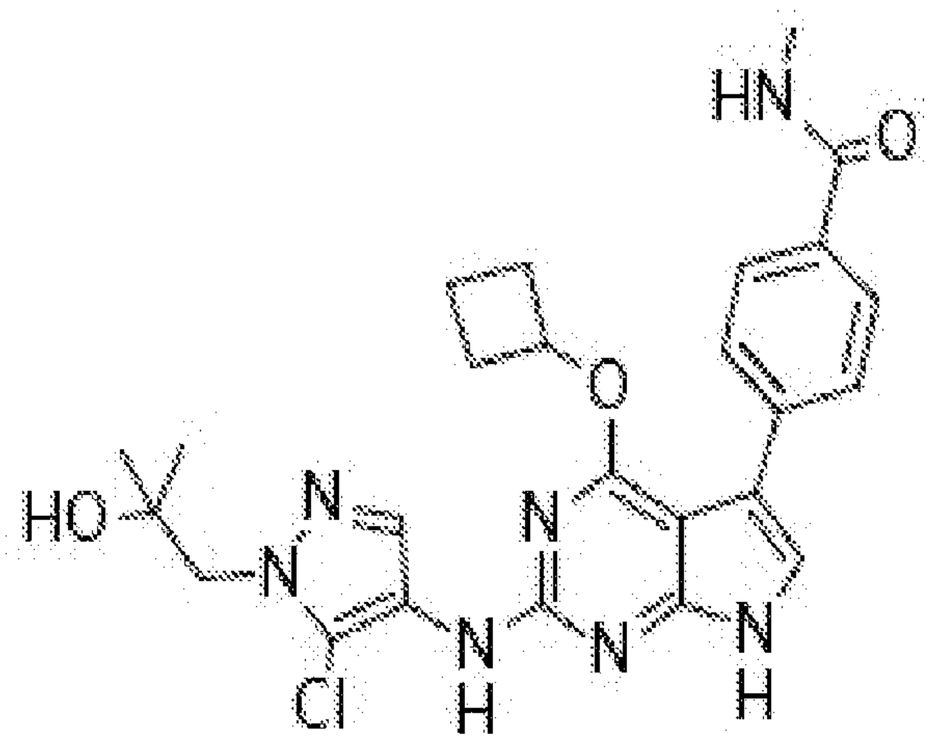
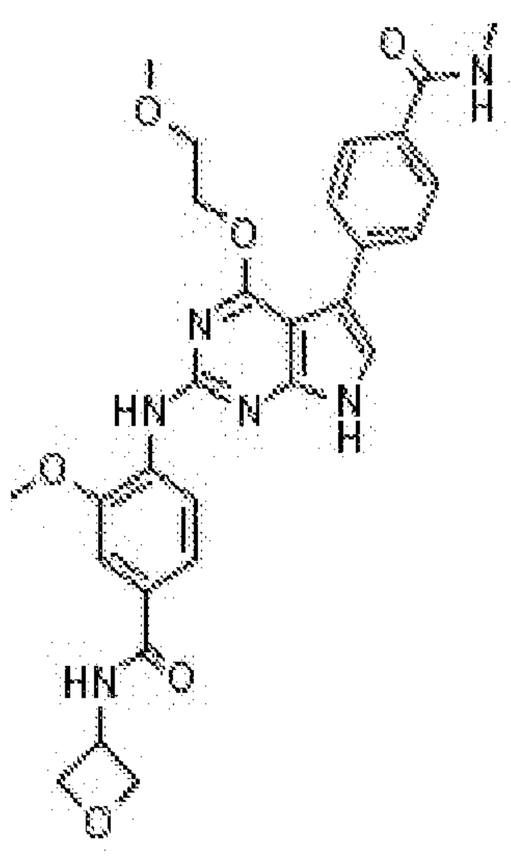
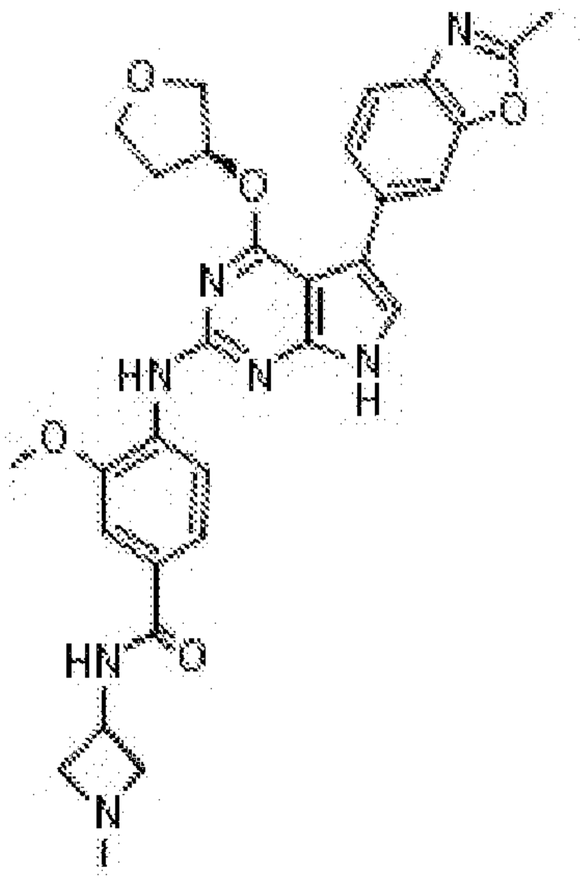
Cmpd No.	Structure	Name
357		4-(4-isopropoxy-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(1-methylazetidin-3-yl)benzamide
358		4-(4-((1s,4s)-4-hydroxy-4-methylcyclohexyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(1-methylazetidin-3-yl)benzamide
359		3-methoxy-4-(5-(4-(methylcarbamoyl)phenyl)-4-(oxetan-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(oxetan-3-yl)benzamide

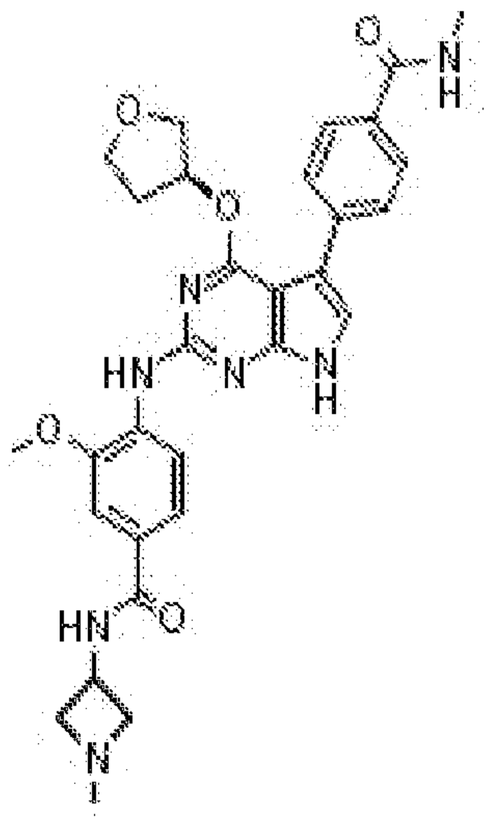
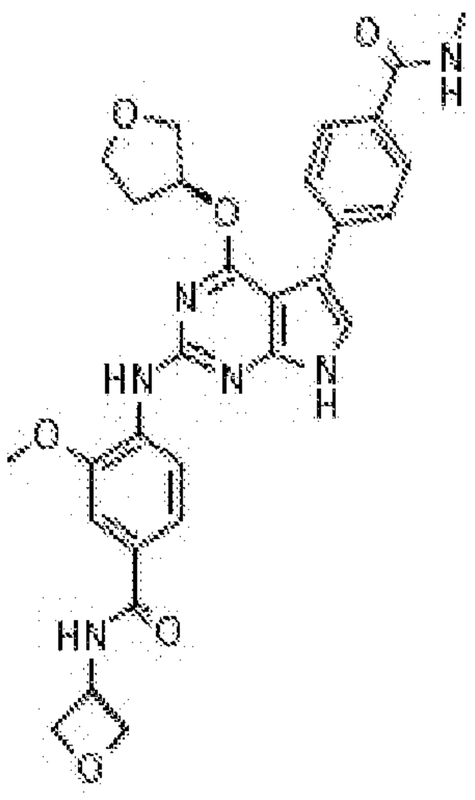
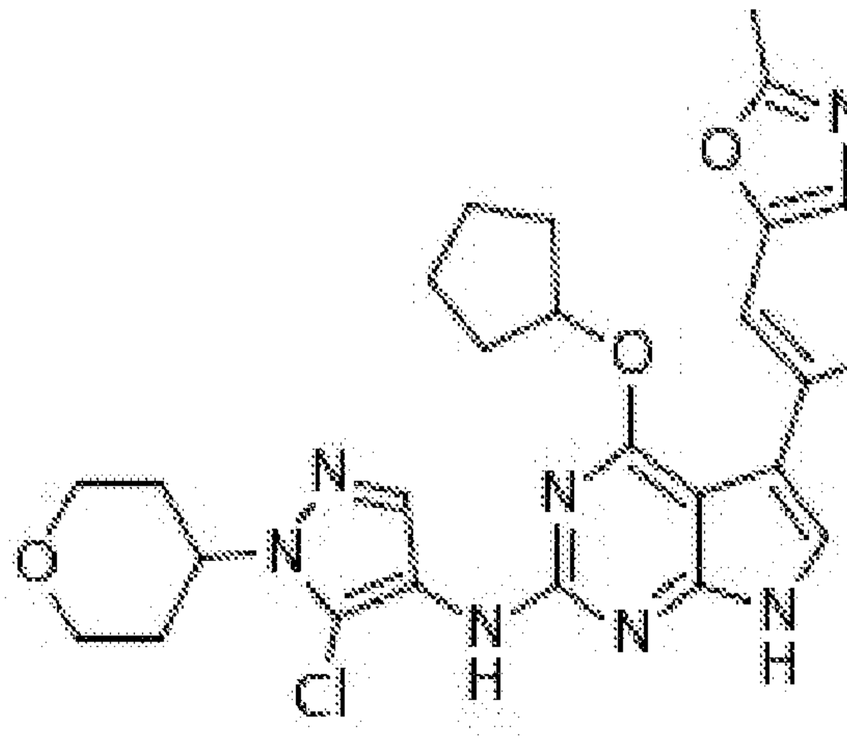
Cmpd No.	Structure	Name
360		4-(5-(4-(1H-imidazol-2-yl)phenyl)-4-cyclobutoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide
361		4-(5-(4-(1H-imidazol-2-yl)phenyl)-4-(cyclopentyloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(1-methylazetidin-3-yl)benzamide
362		4-(4-isopropoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide

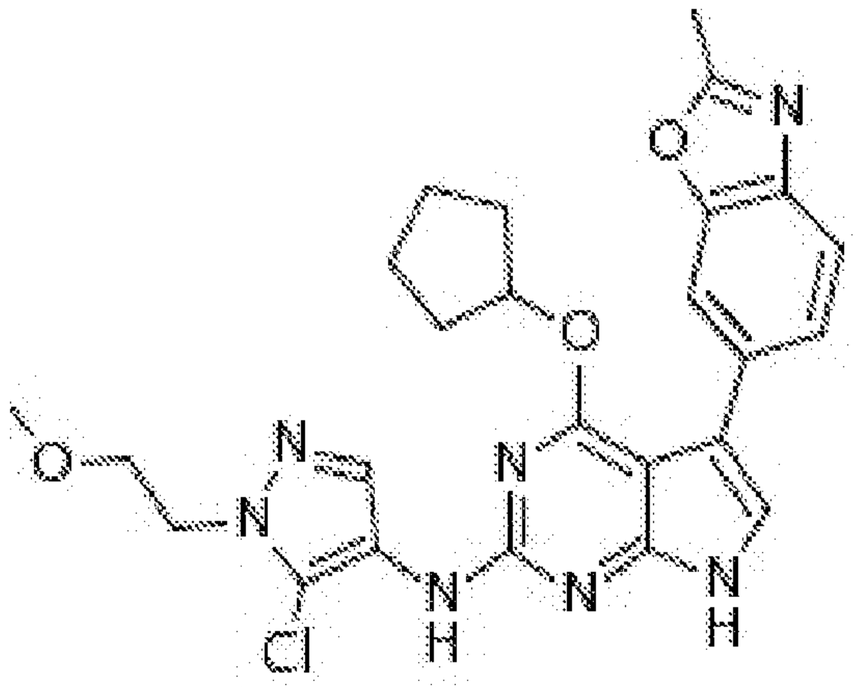
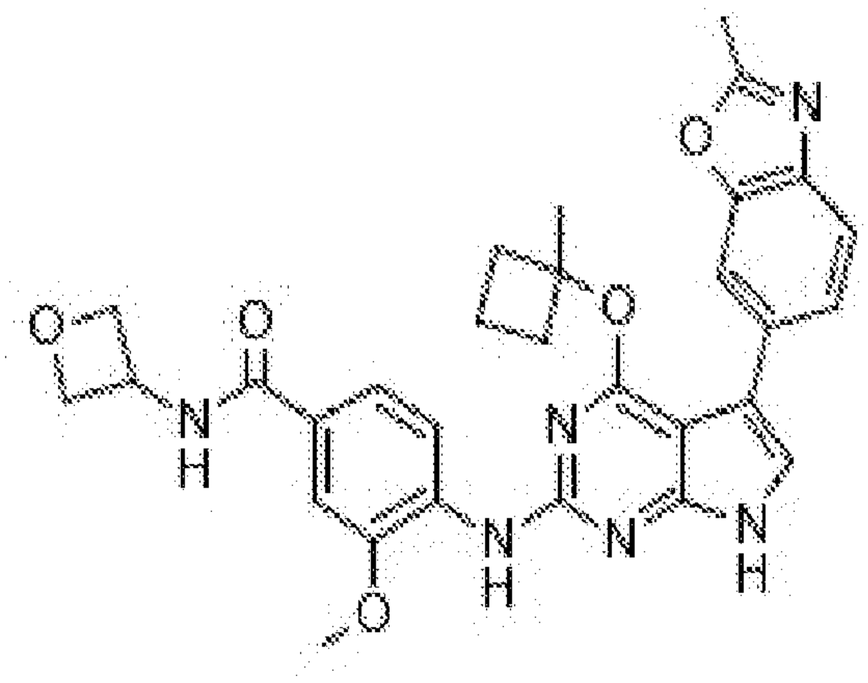
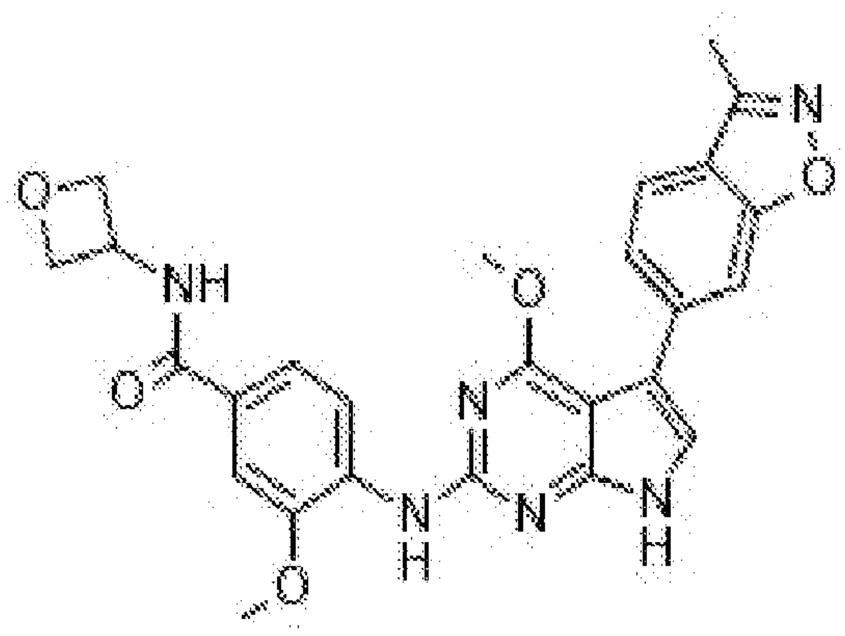
Cmpd No.	Structure	Name
363		4-(4-cyclopropoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(1-methylazetidin-3-yl)benzamide
364		4-(4-cyclopropoxy-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(1-methylazetidin-3-yl)benzamide
365		3-methoxy-4-(4-(2-methoxyethoxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(oxetan-3-yl)benzamide

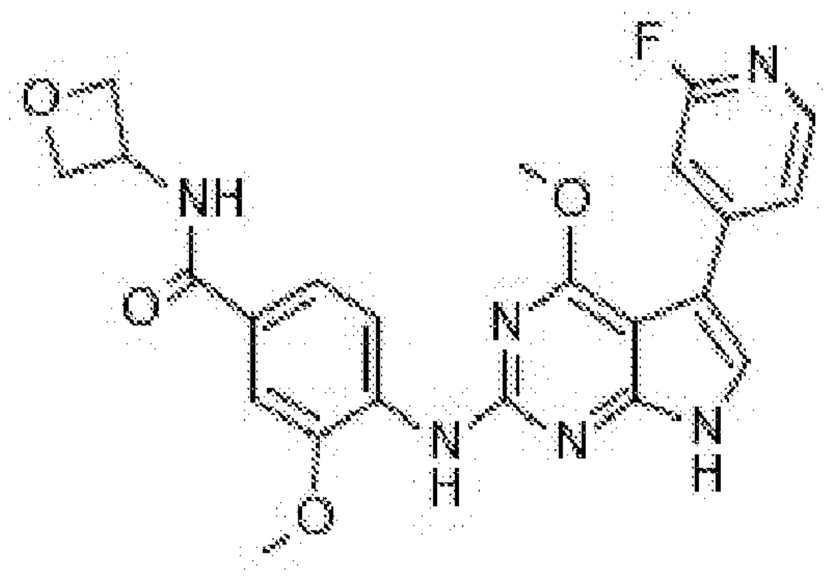
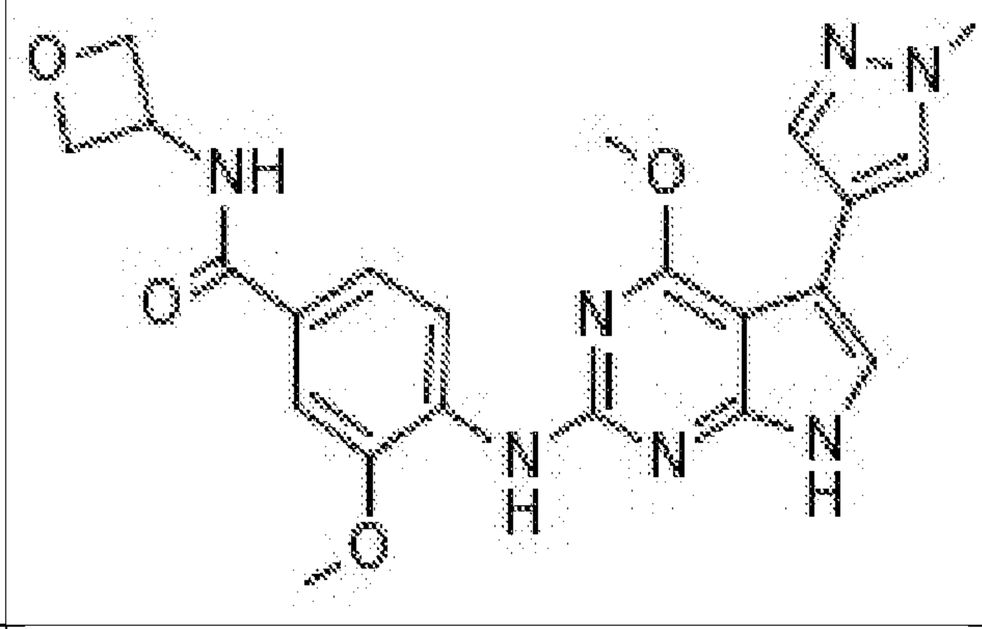
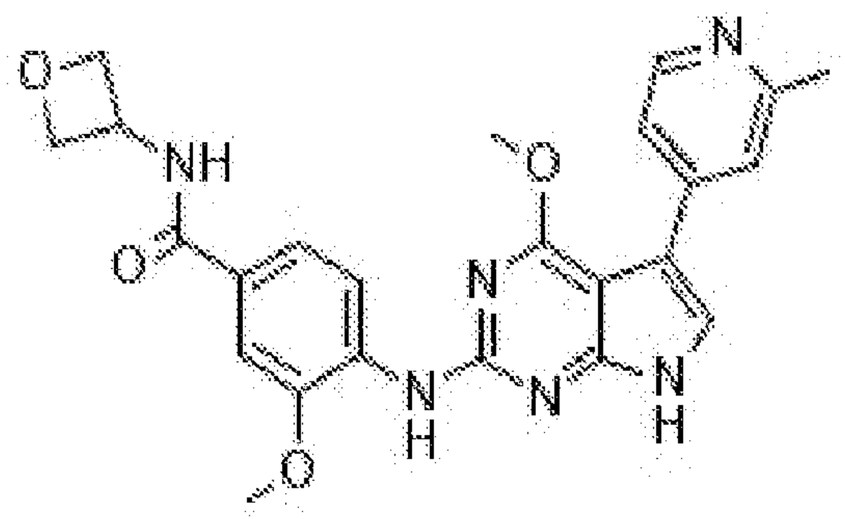
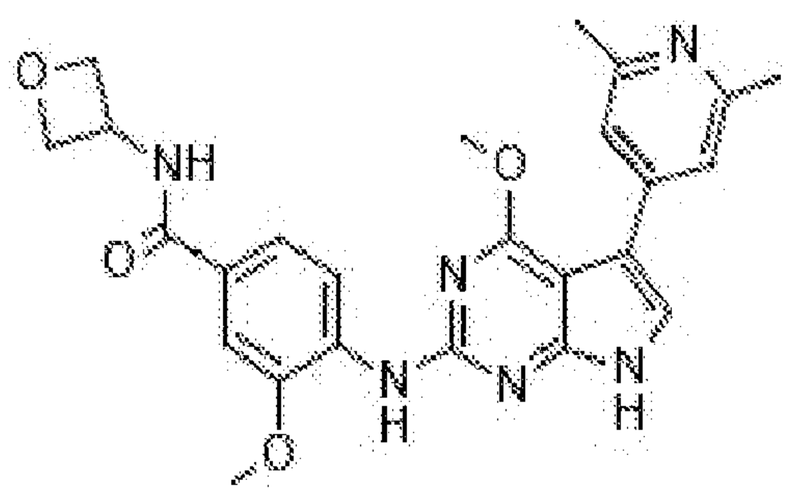
Cmpd No.	Structure	Name
366		3-methoxy-N-(1-methylazetidin-3-yl)-4-(5-(4-(methylcarbamoyl)phenyl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
367		3-methoxy-N-(1-methylazetidin-3-yl)-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
368		3-methoxy-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(oxetan-3-yl)benzamide

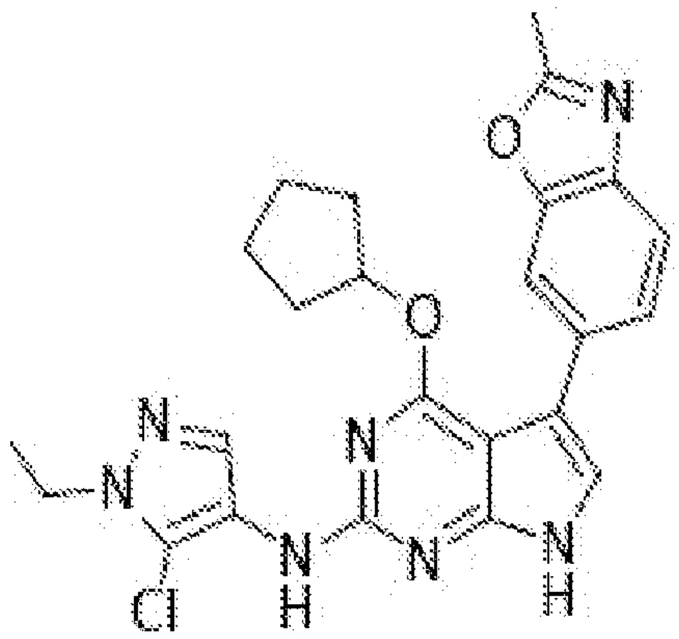
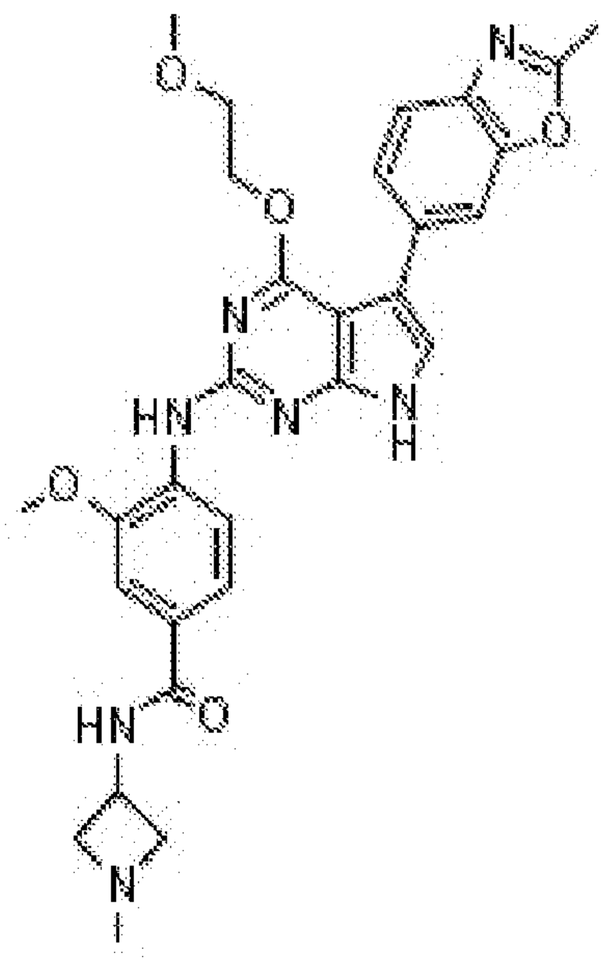
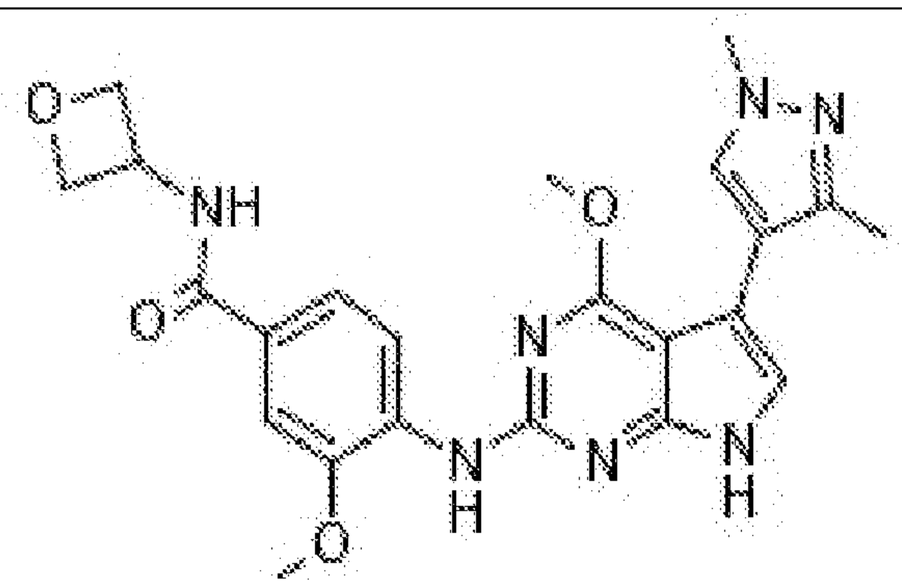
Cmpd No.	Structure	Name
369		4-(4-cyclopropoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide
370		4-(4-tert-butoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide
371		1-(5-chloro-4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-1H-pyrazol-1-yl)-2-methylpropan-2-ol

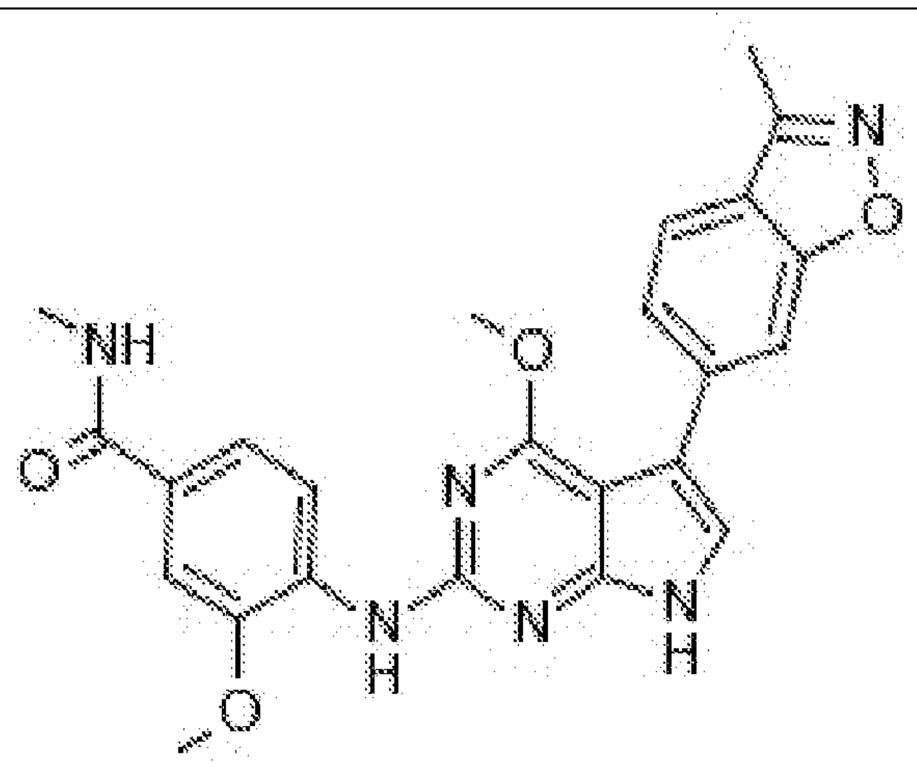
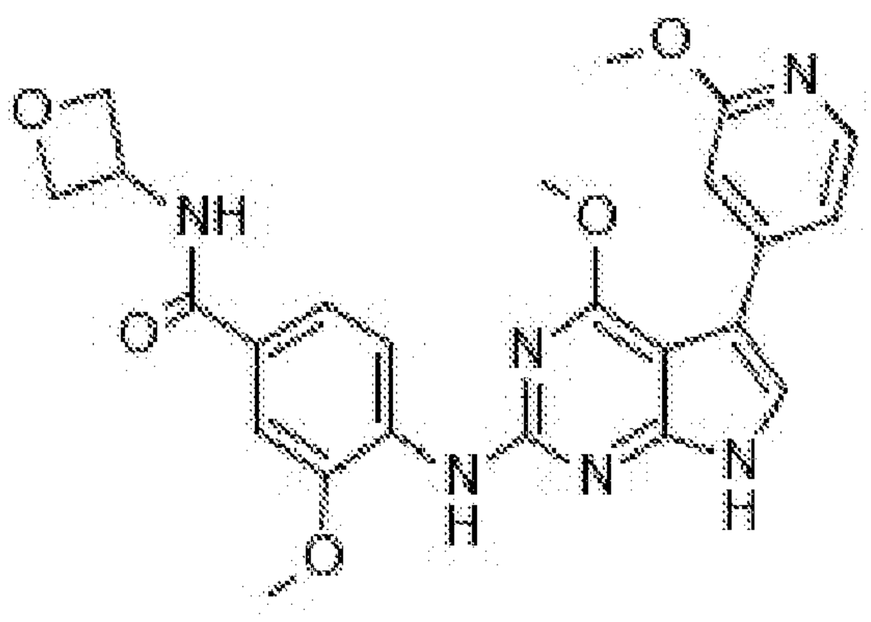
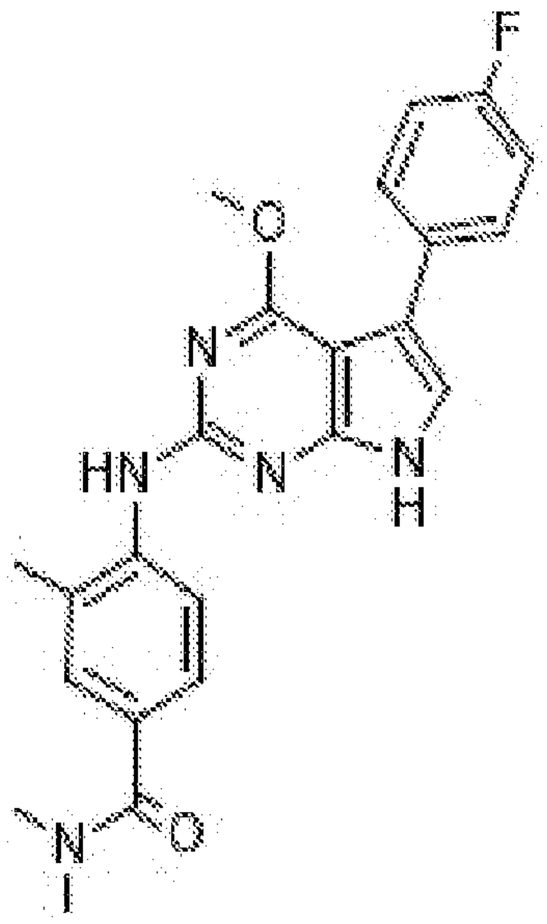
Cmpd No.	Structure	Name
372		4-(2-(5-chloro-1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-ylamino)-4-cyclobutoxy-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-N-methylbenzamide
373		3-methoxy-4-(4-(2-methoxyethoxy)-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(oxetan-3-yl)benzamide
374		(S)-3-methoxy-N-(1-methylazetidin-3-yl)-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

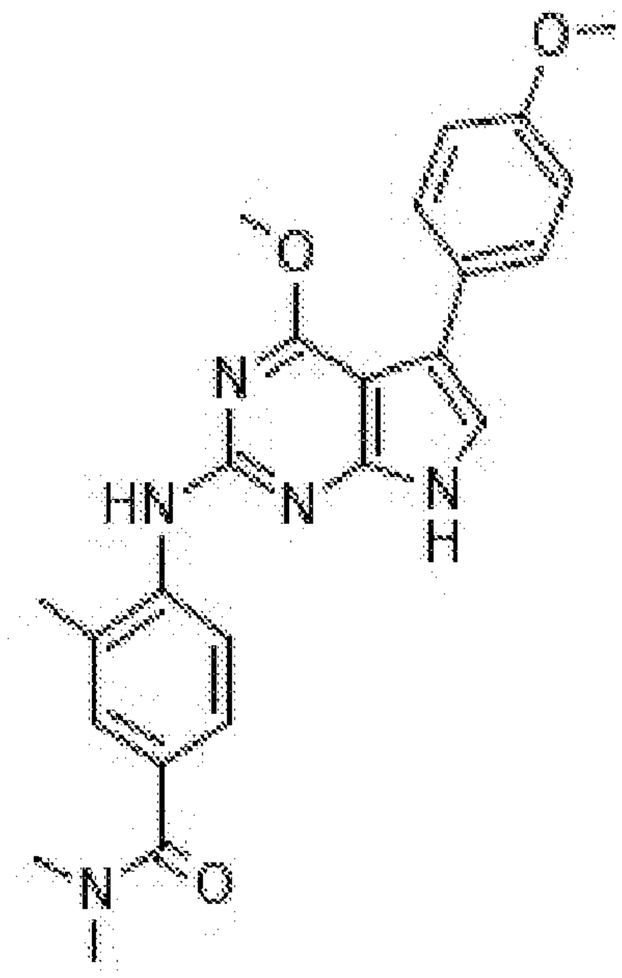
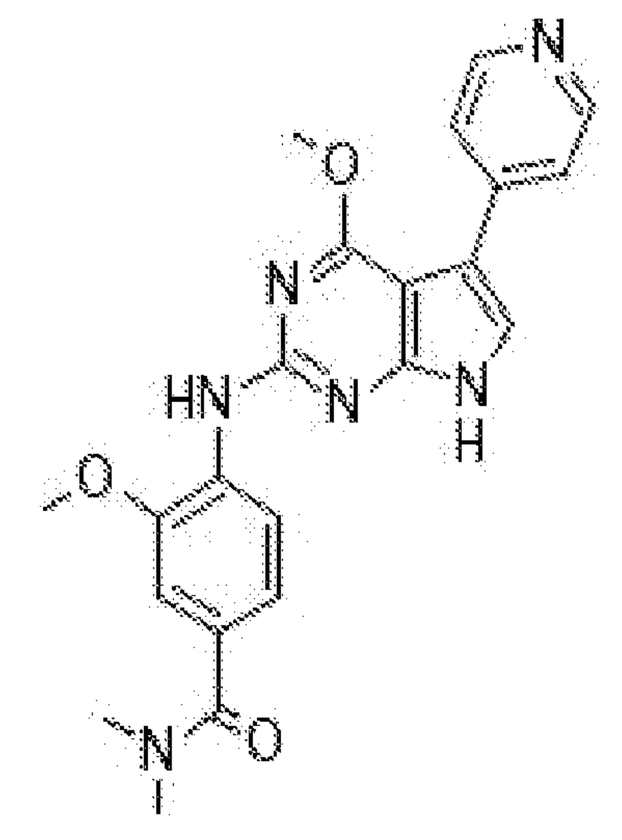
Cmpd No.	Structure	Name
375		(S)-3-methoxy-N-(1-methylazetidin-3-yl)-4-(5-(4-(methylcarbamoyl)phenyl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
376		(S)-3-methoxy-4-(5-(4-(methylcarbamoyl)phenyl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(oxetan-3-yl)benzamide
377		N-(5-chloro-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)-4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine

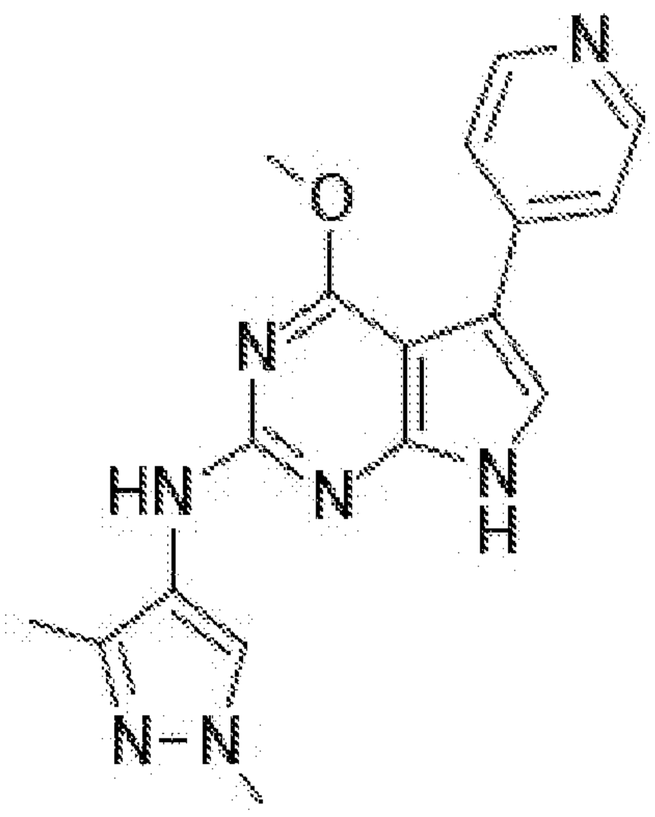
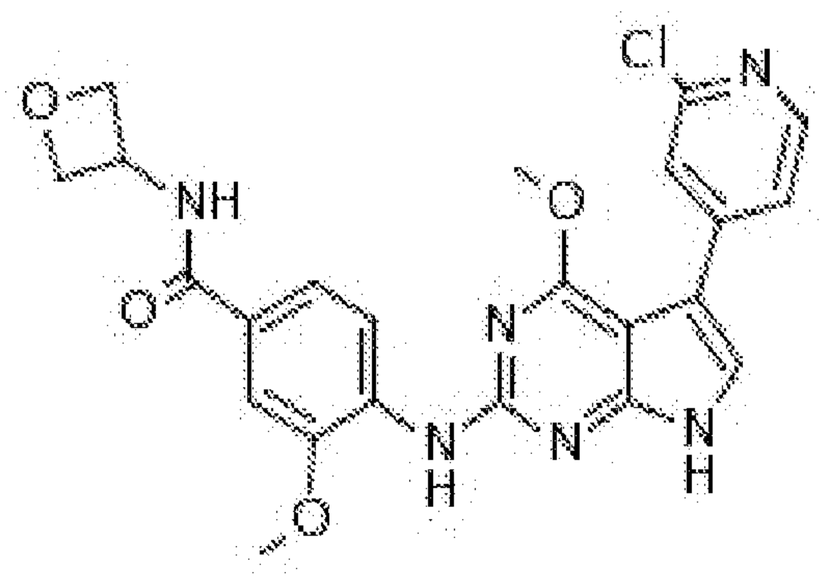
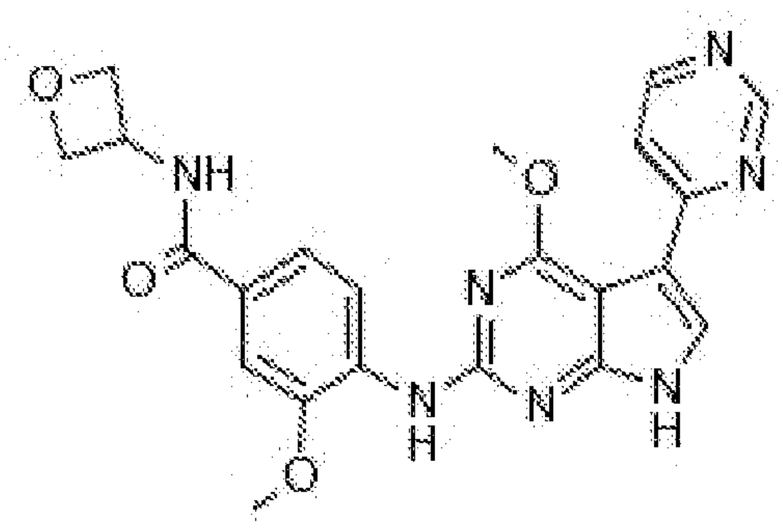
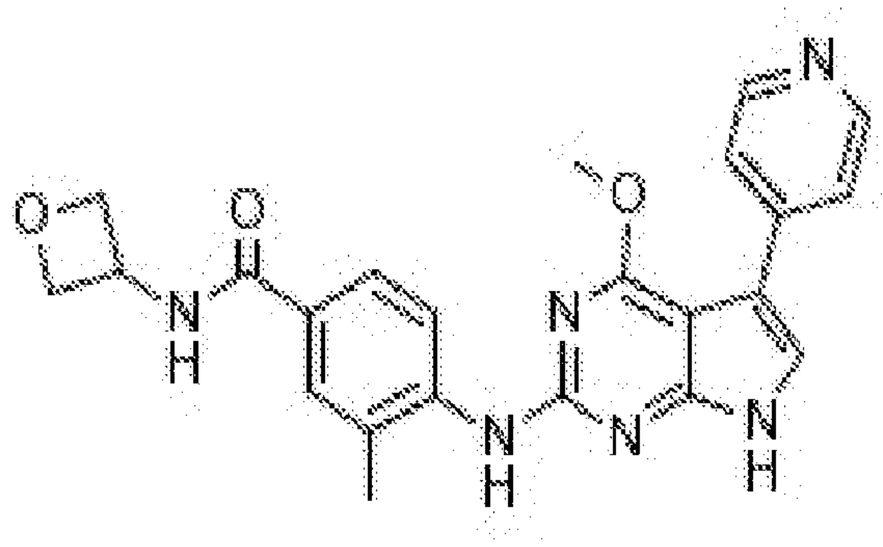
Cmpd No.	Structure	Name
378		N-(5-chloro-1-(2-methoxyethyl)-1H-pyrazol-4-yl)-4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine
379		3-methoxy-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(1-methylcyclobutoxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(oxetan-3-yl)benzamide
380		3-methoxy-4-(4-methoxy-5-(3-methylbenzo[d]isoxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(oxetan-3-yl)benzamide

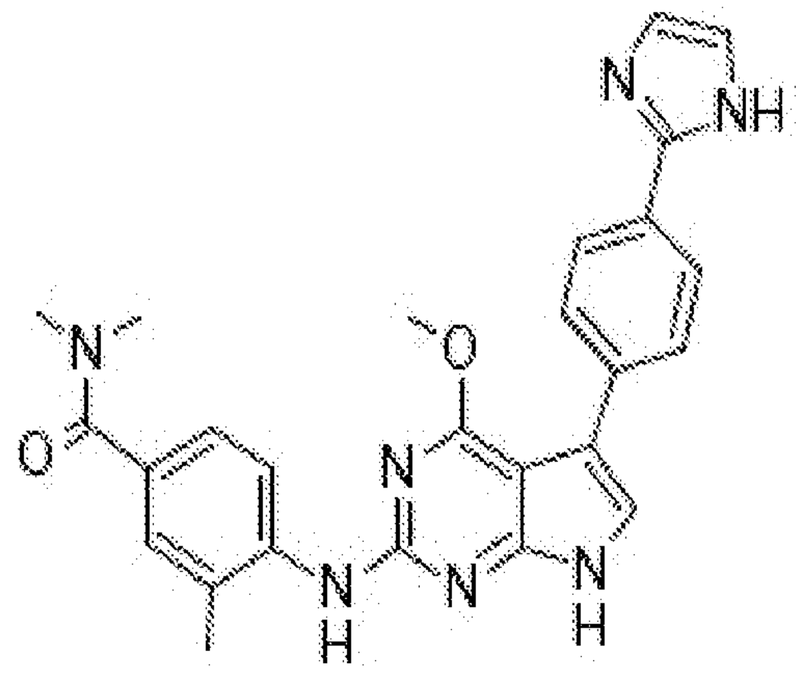
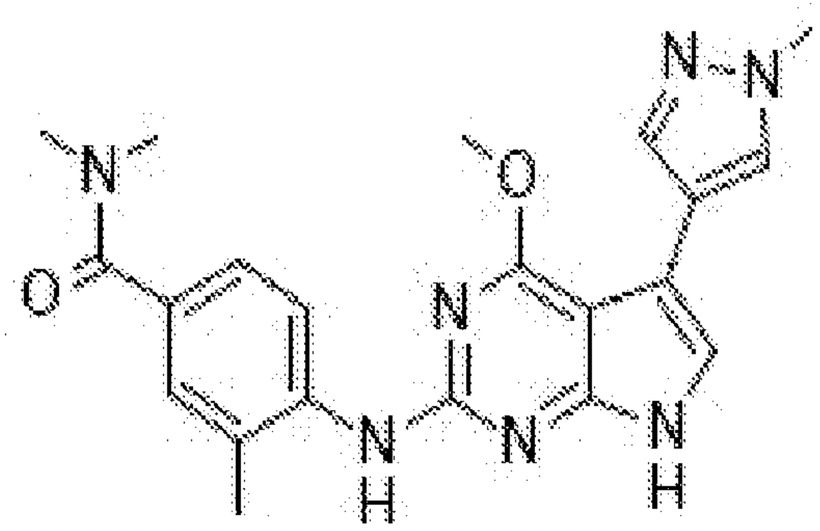
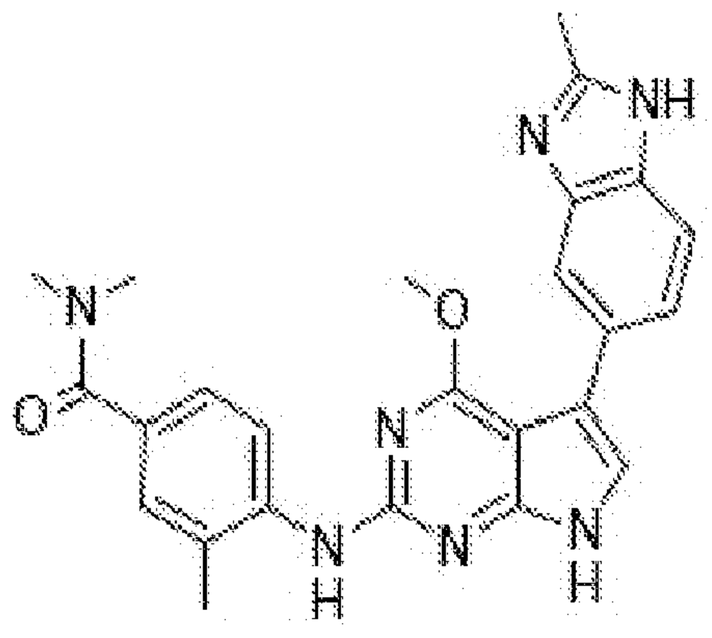
Cmpd No.	Structure	Name
381		4-(5-(2-fluoropyridin-4-yl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide
382		3-methoxy-4-(4-methoxy-5-(1-methyl-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(oxetan-3-yl)benzamide
383		3-methoxy-4-(4-methoxy-5-(2-methylpyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(oxetan-3-yl)benzamide
384		4-(5-(2,6-dimethylpyridin-4-yl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide

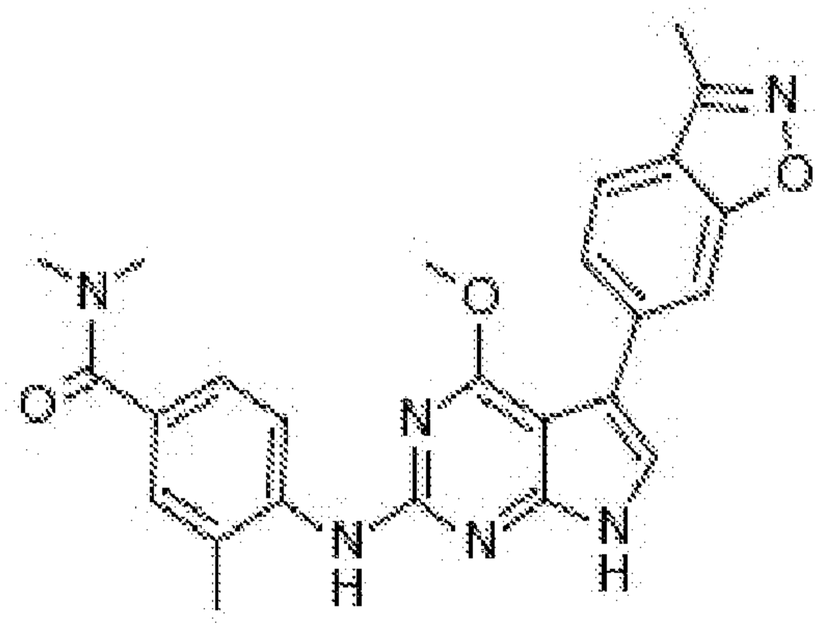
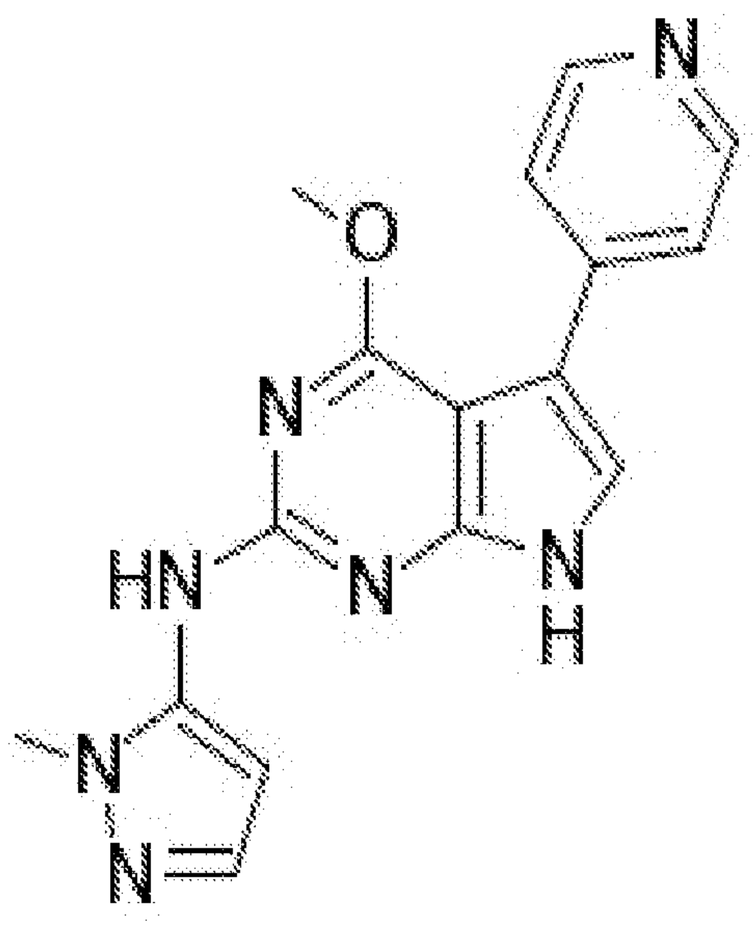
Cmpd No.	Structure	Name
385		N-(5-chloro-1-ethyl-1H-pyrazol-4-yl)-4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine
386		3-methoxy-4-(4-(2-methoxyethoxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(1-methylazetidin-3-yl)benzamide
387		4-(5-(1,3-dimethyl-1H-pyrazol-4-yl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide

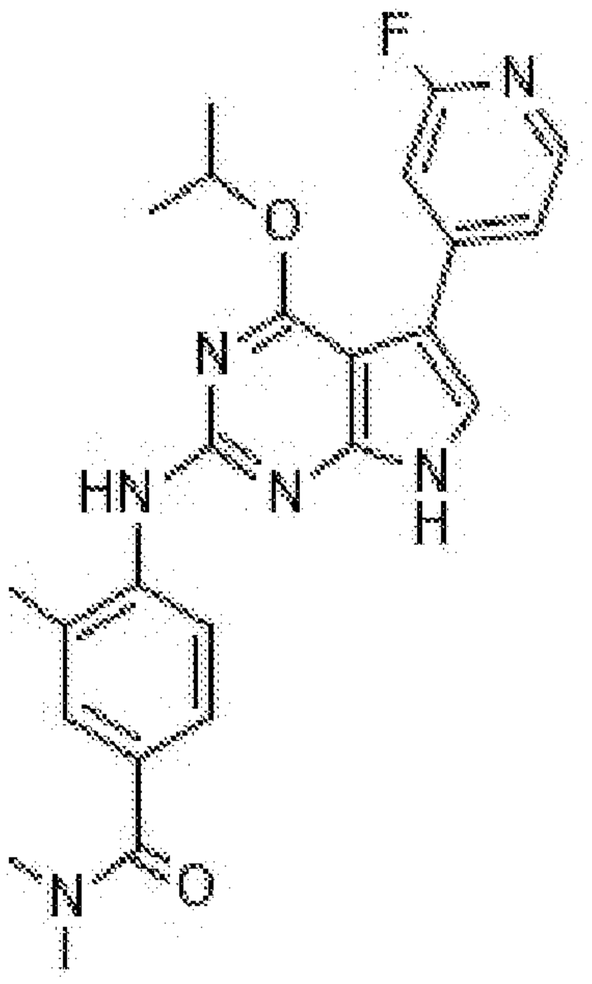
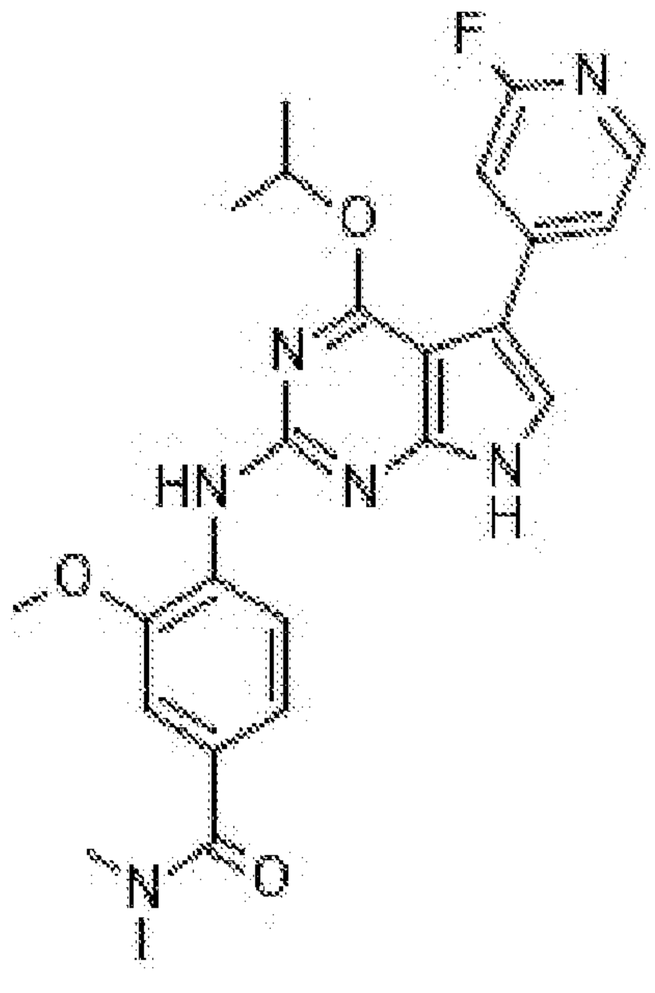
Cmpd No.	Structure	Name
388		3-methoxy-4-(4-methoxy-5-(3-methylbenzo[d]isoxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide
389		3-methoxy-4-(4-methoxy-5-(2-methoxypyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(oxetan-3-yl)benzamide
390		4-(5-(4-fluorophenyl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N,3-trimethylbenzamide

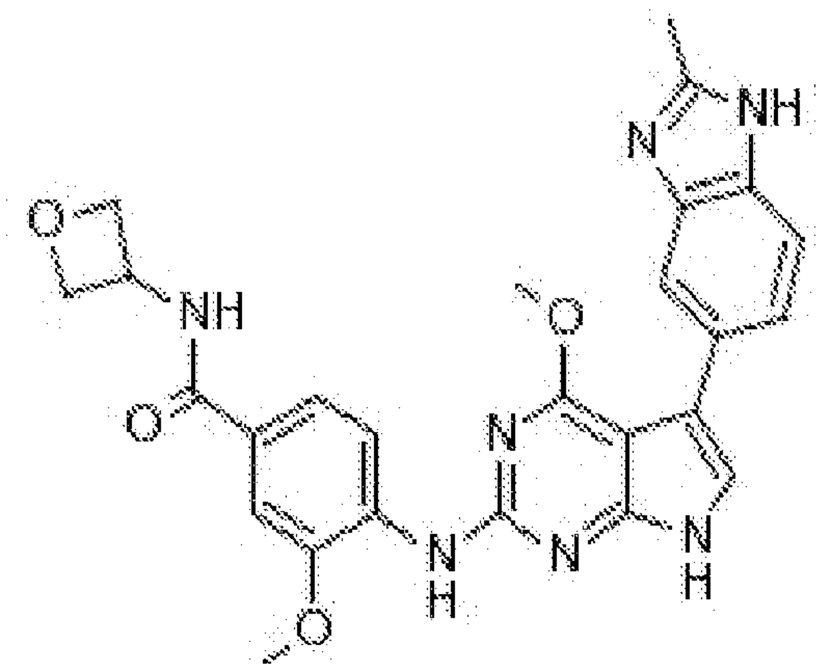
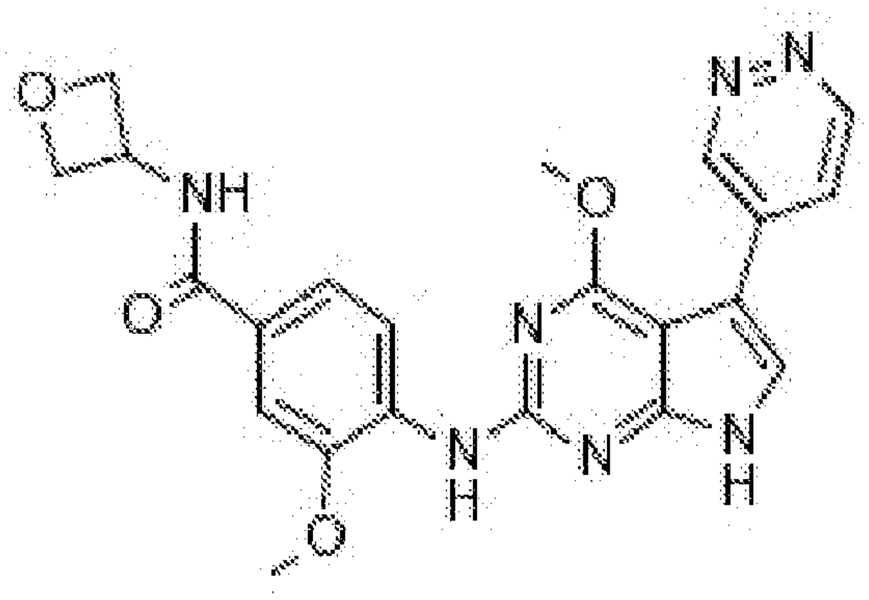
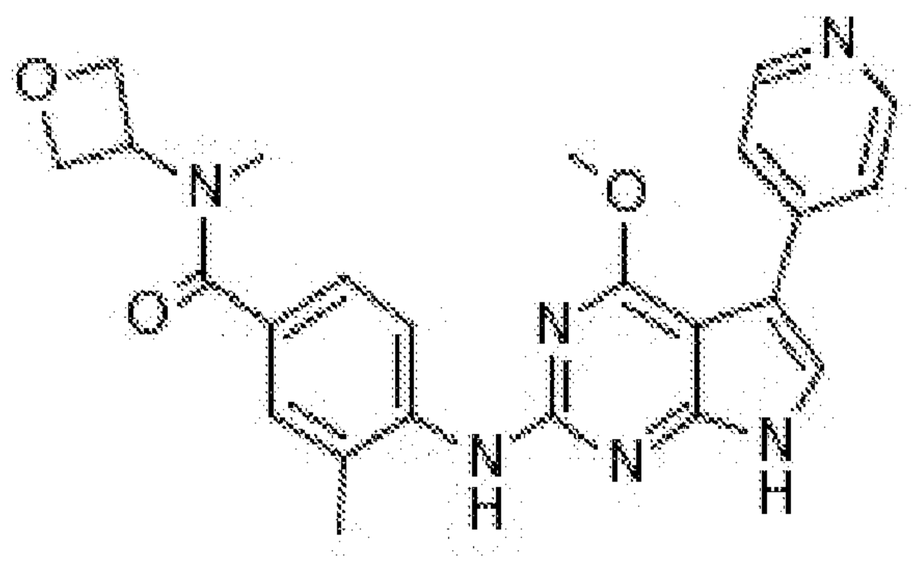
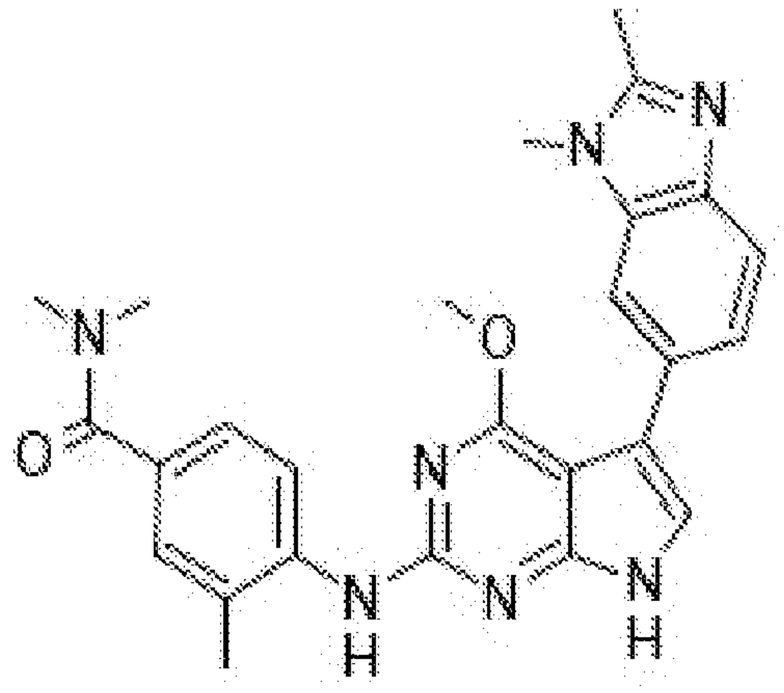
Cmpd No.	Structure	Name
391		4-(4-methoxy-5-(4-methoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N,3-trimethylbenzamide
392		3-methoxy-4-(4-methoxy-5-(pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N-dimethylbenzamide

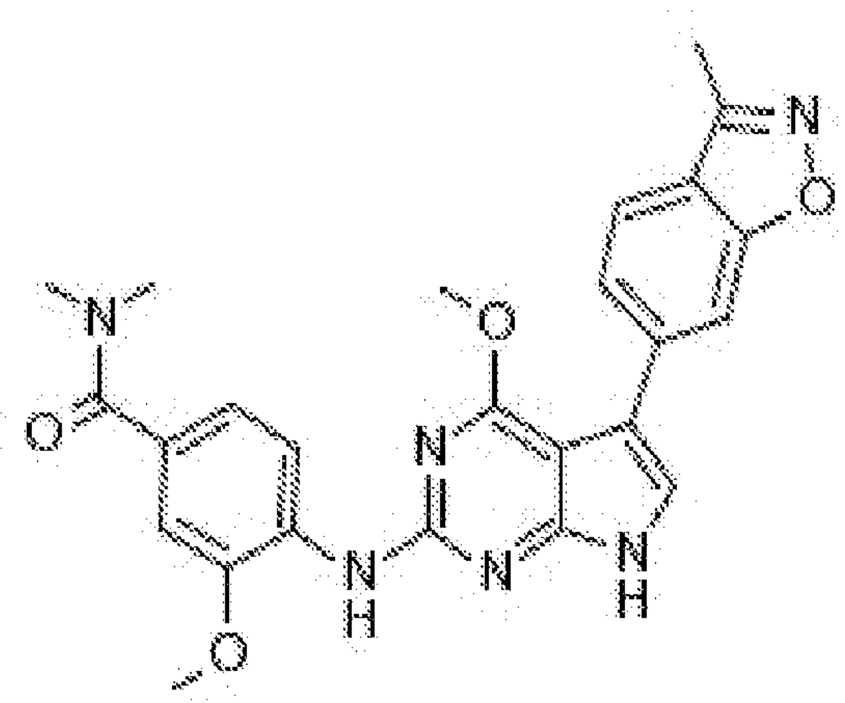
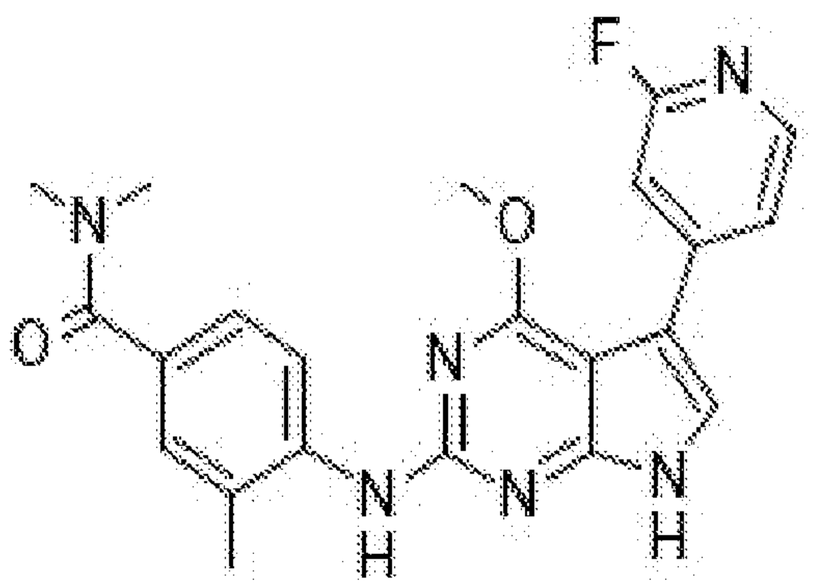
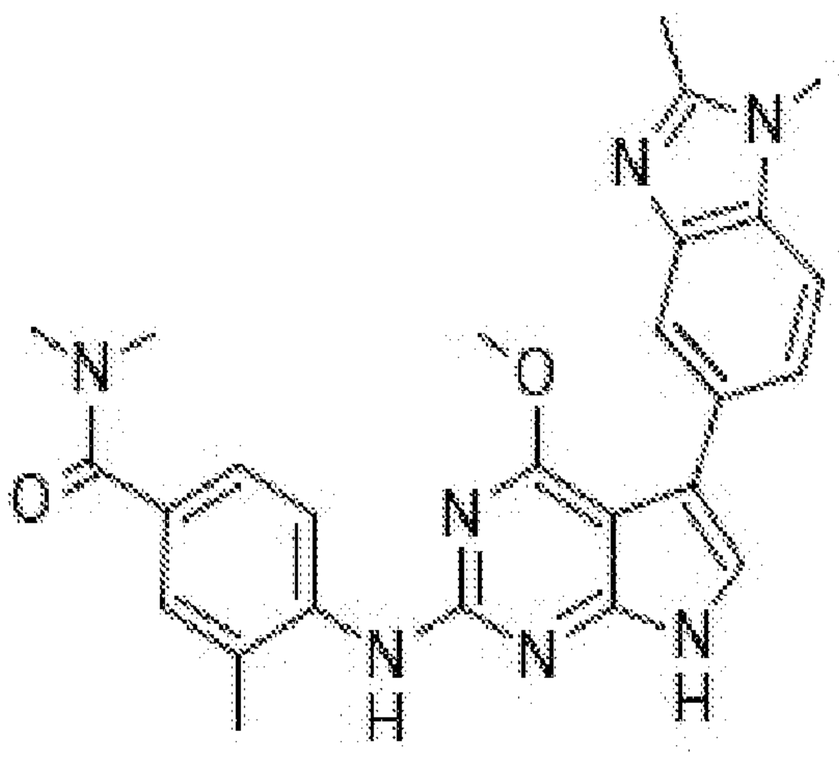
Cmpd No.	Structure	Name
393		N-(1,3-dimethyl-1H-pyrazol-4-yl)-4-methoxy-5-(pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine
394		4-(5-(2-chloropyridin-4-yl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide
395		3-methoxy-4-(4-methoxy-5-(pyrimidin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(oxetan-3-yl)benzamide
396		4-(4-methoxy-5-(pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methyl-N-(oxetan-3-yl)benzamide

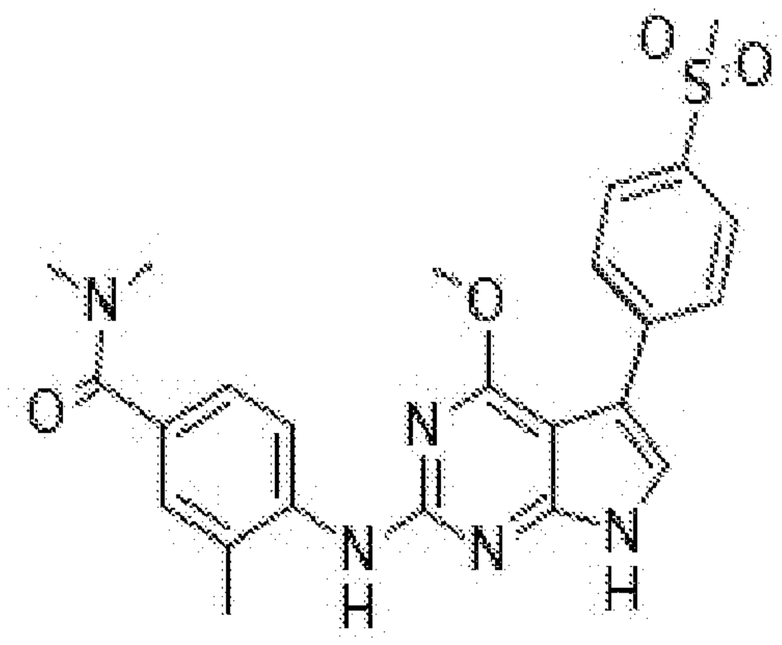
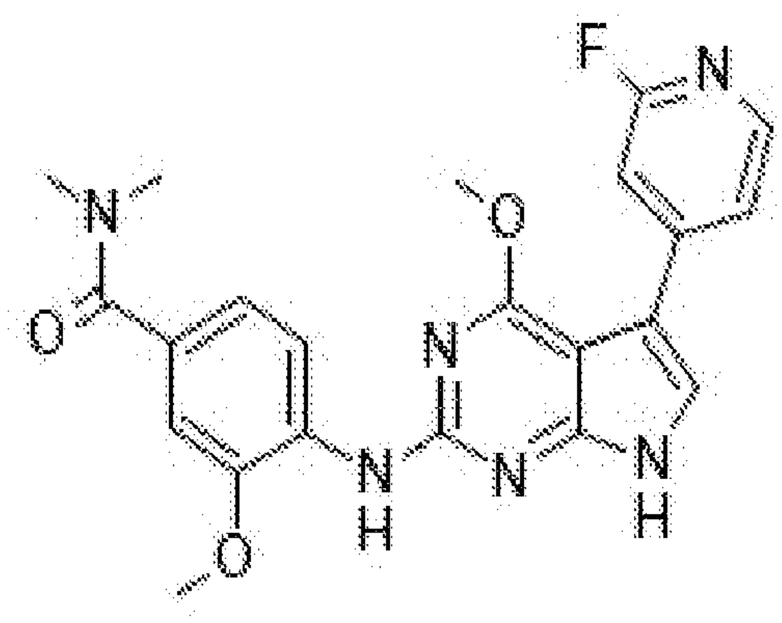
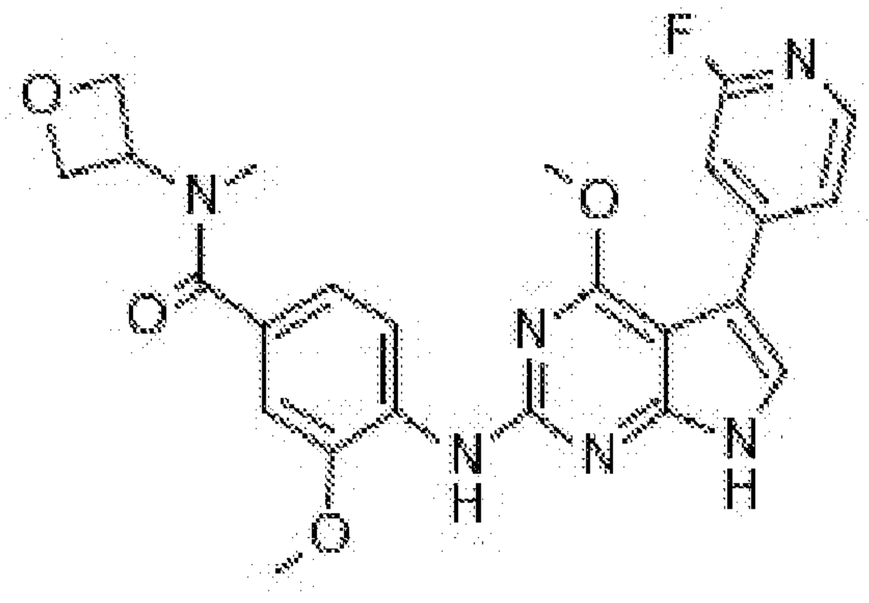
Cmpd No.	Structure	Name
397		4-(5-(4-(1H-imidazol-2-yl)phenyl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N,3-trimethylbenzamide
398		4-(4-methoxy-5-(1-methyl-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N,3-trimethylbenzamide
399		4-(4-methoxy-5-(2-methyl-1H-benzo[d]imidazol-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N,3-trimethylbenzamide

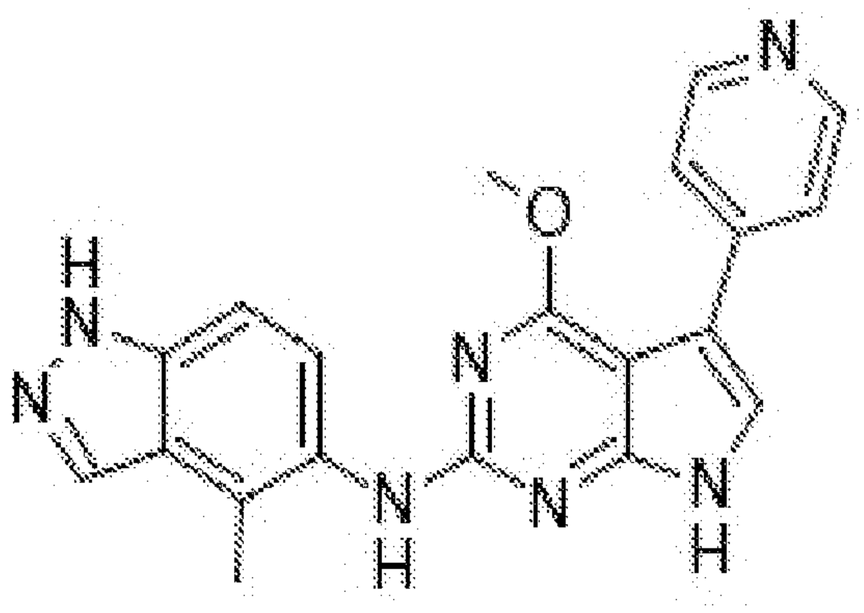
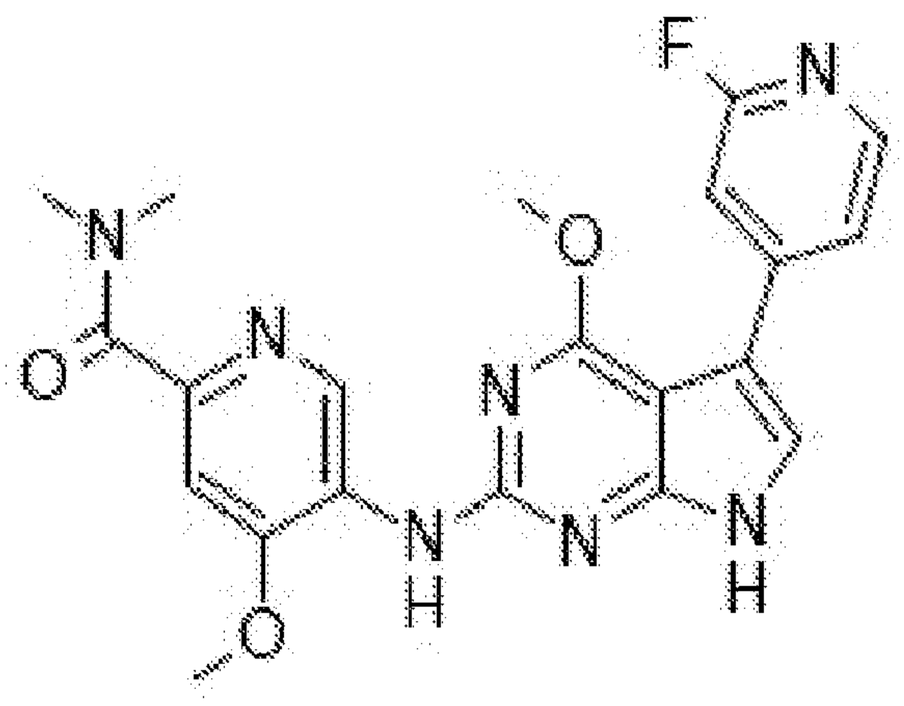
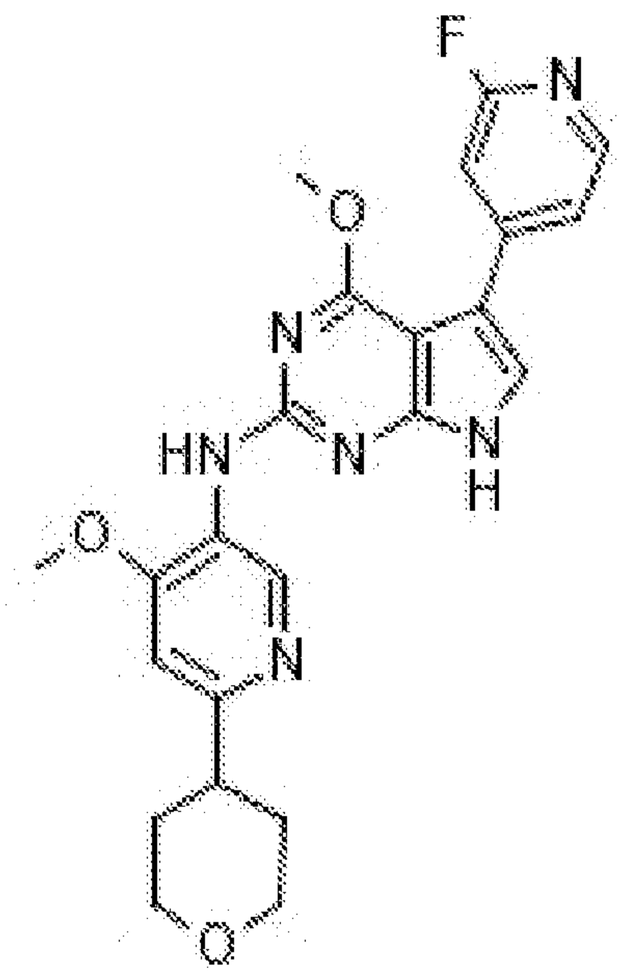
Cmpd No.	Structure	Name
400		4-(4-methoxy-5-(3-methylbenzo[d]isoxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N,3-trimethylbenzamide
401		4-methoxy-N-(1-methyl-1H-pyrazol-5-yl)-5-(pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine

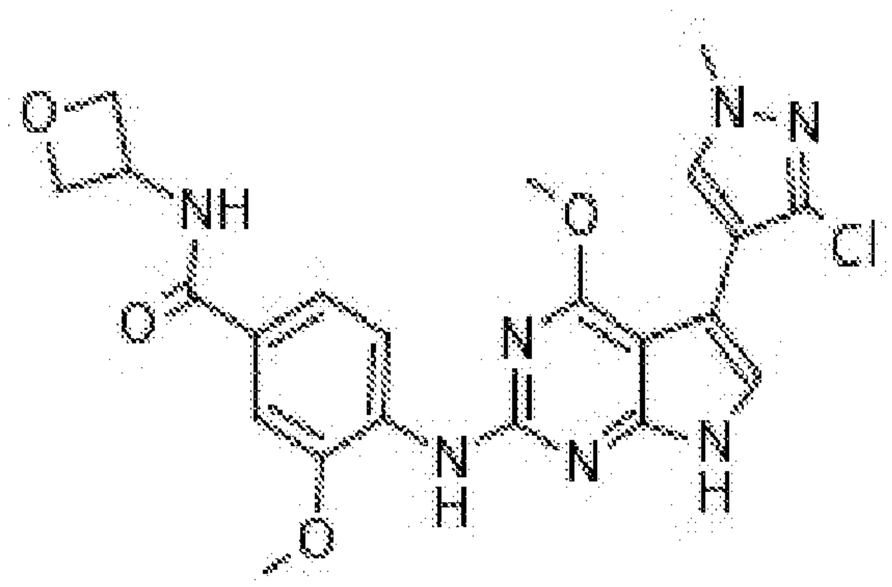
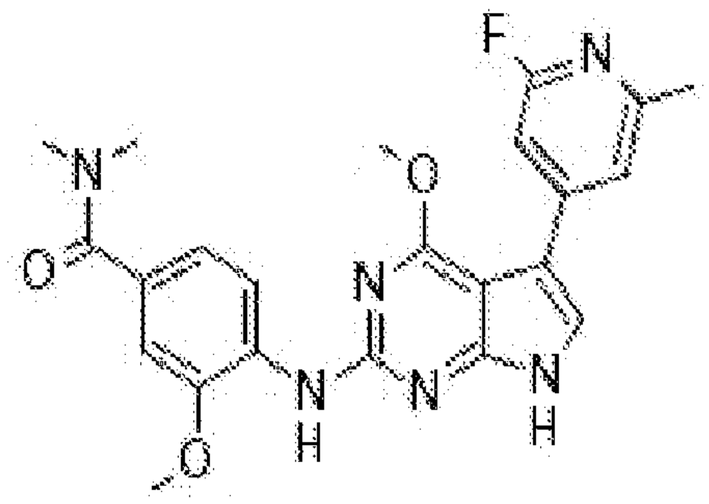
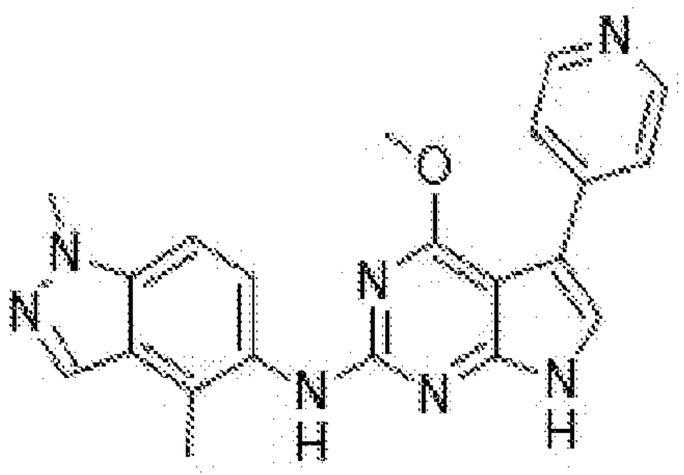
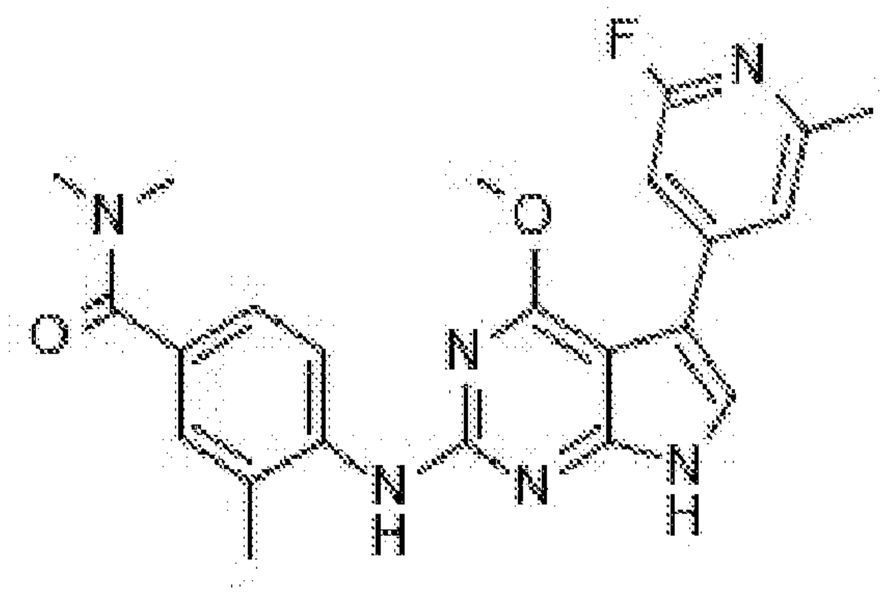
Cmpd No.	Structure	Name
402		4-(5-(2-fluoropyridin-4-yl)-4-isopropoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N,3-trimethylbenzamide
403		4-(5-(2-fluoropyridin-4-yl)-4-isopropoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N,N-dimethylbenzamide

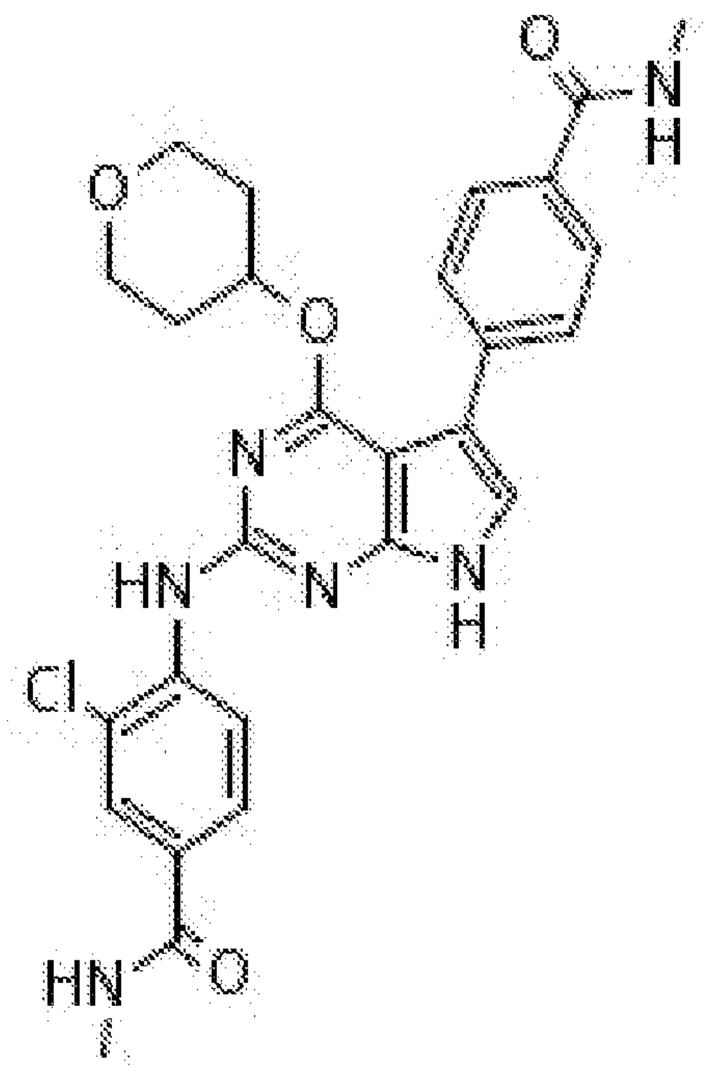
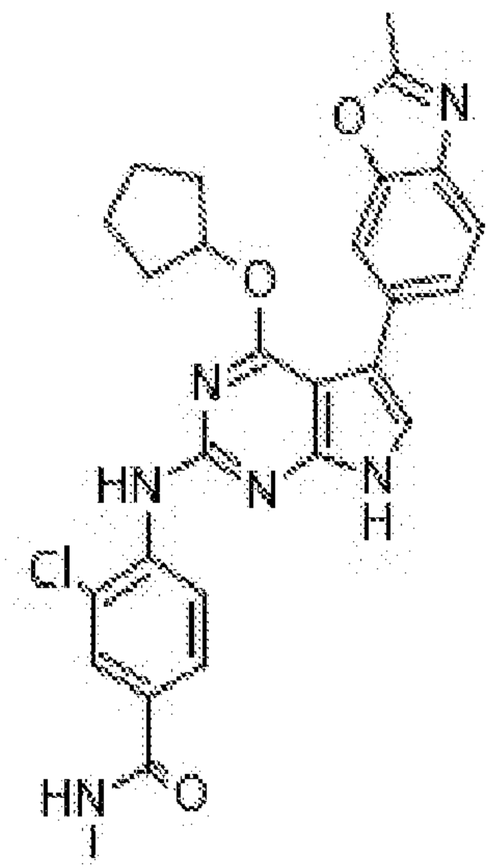
Cmpd No.	Structure	Name
404		3-methoxy-4-(4-methoxy-5-(2-methyl-1H-benzo[d]imidazol-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(oxetan-3-yl)benzamide
405		3-methoxy-4-(4-methoxy-5-(pyridazin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(oxetan-3-yl)benzamide
406		4-(4-methoxy-5-(pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,3-dimethyl-N-(oxetan-3-yl)benzamide
407		4-(5-(1,2-dimethyl-1H-benzo[d]imidazol-6-yl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N,3-trimethylbenzamide

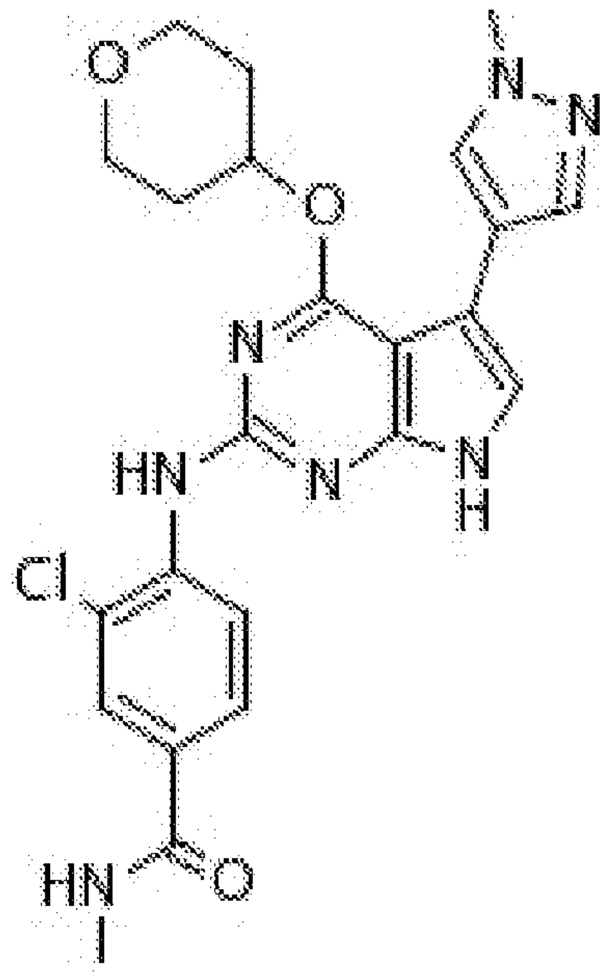
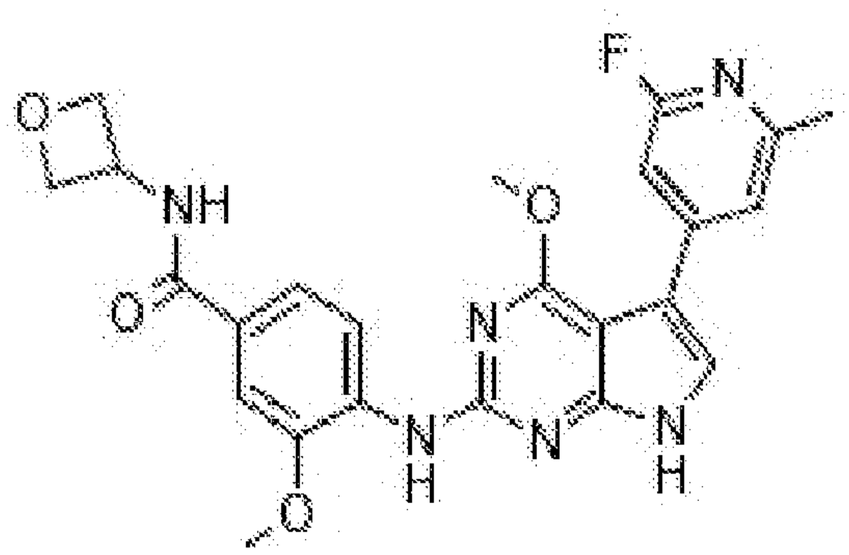
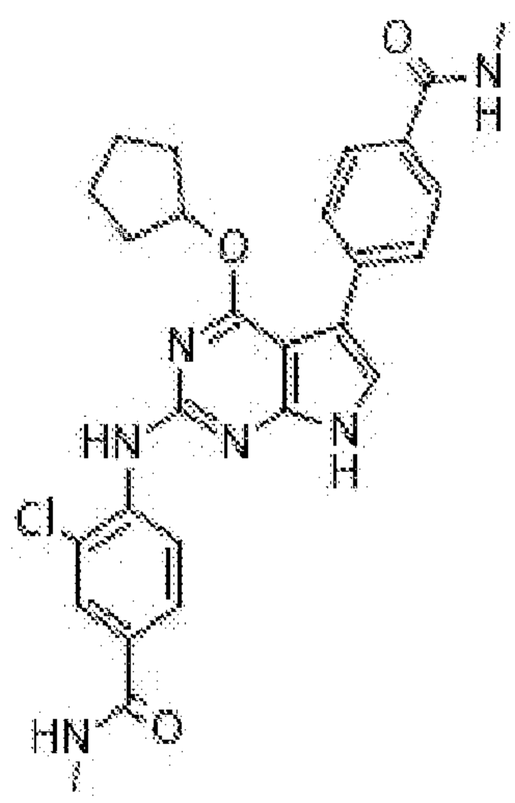
Cmpd No.	Structure	Name
408		3-methoxy-4-(4-methoxy-5-(3-methylbenzo[d]isoxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N-dimethylbenzamide
409		4-(5-(2-fluoropyridin-4-yl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N,3-trimethylbenzamide
410		4-(5-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N,3-trimethylbenzamide

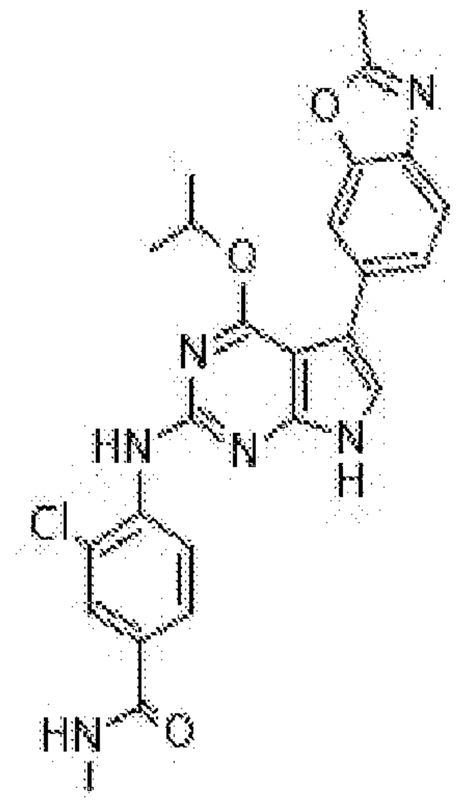
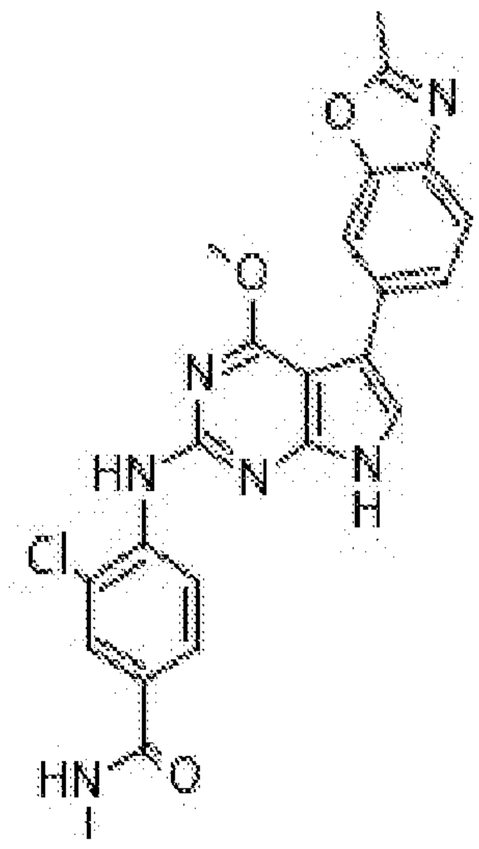
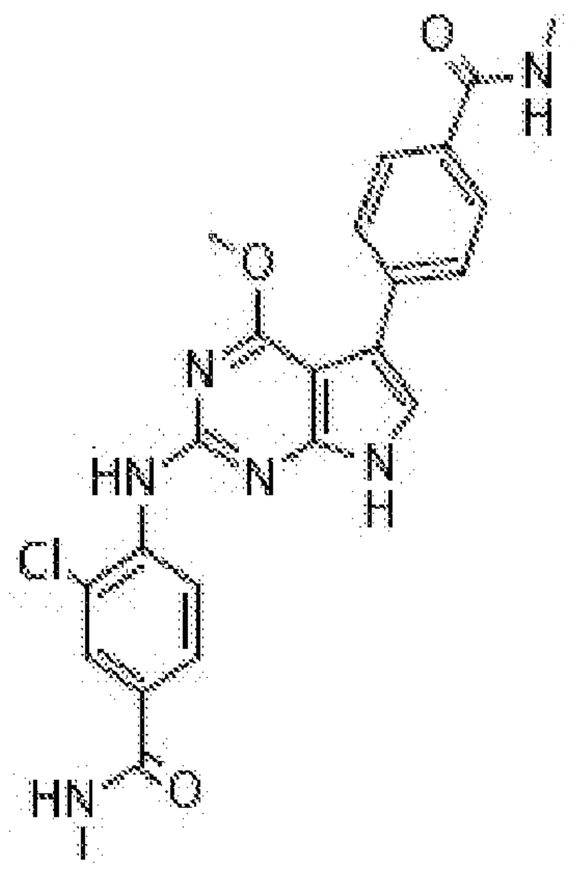
Cmpd No.	Structure	Name
411		4-(4-methoxy-5-(4-(methylsulfonyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N,3-trimethylbenzamide
412		4-(5-(2-fluoropyridin-4-yl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N,N-dimethylbenzamide
413		4-(5-(2-fluoropyridin-4-yl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-methyl-N-(oxetan-3-yl)benzamide

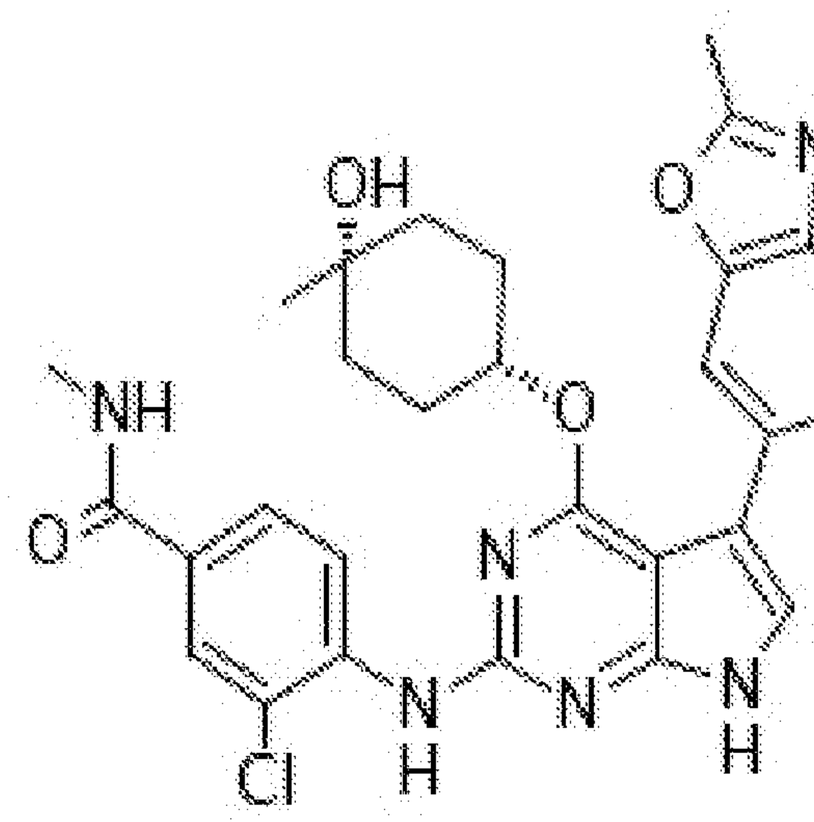
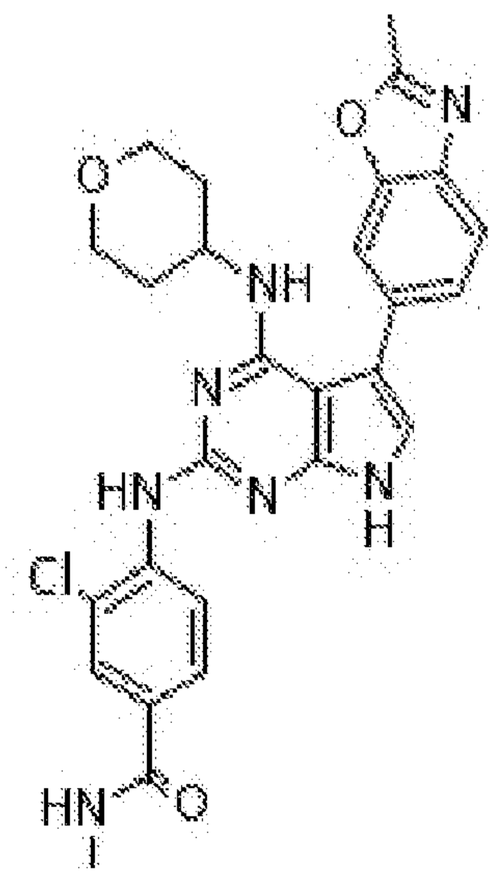
Cmpd No.	Structure	Name
414		4-methoxy-N-(4-methyl-1H-indazol-5-yl)-5-(pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine
415		5-(5-(2-fluoropyridin-4-yl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-4-methoxy-N,N-dimethylpicolinamide
416		5-(2-fluoropyridin-4-yl)-4-methoxy-N-(4-methoxy-6-(tetrahydro-2H-pyran-4-yl)pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine

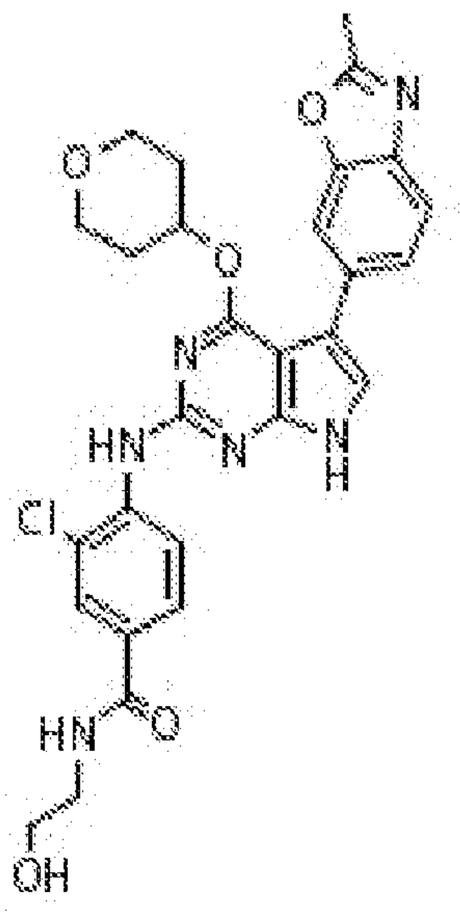
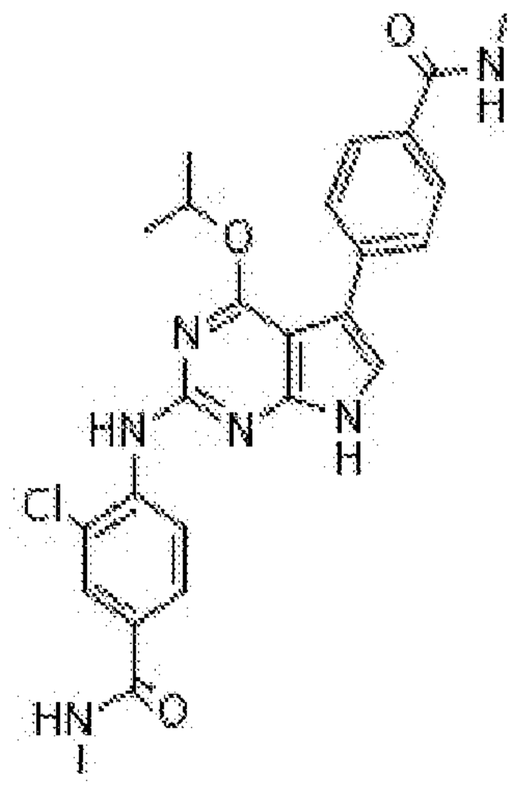
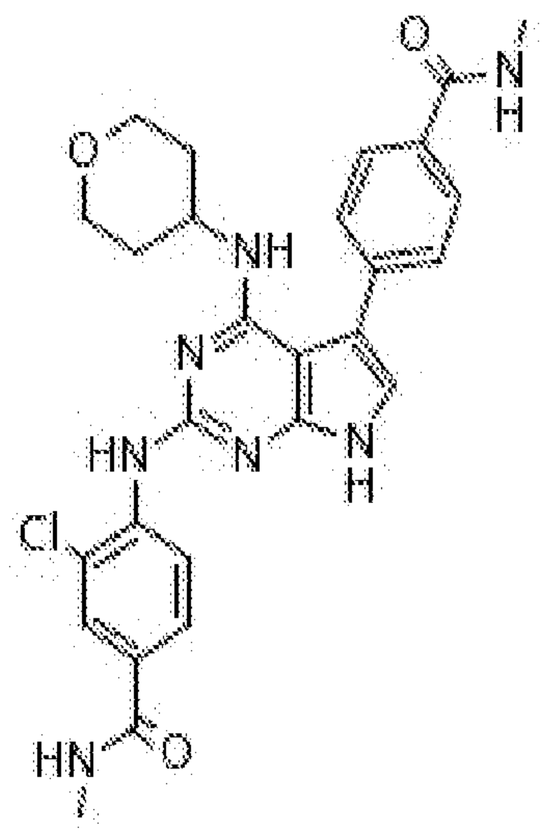
Cmpd No.	Structure	Name
417		4-(5-(3-chloro-1-methyl-1H-pyrazol-4-yl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide
418		4-(5-(2-fluoro-6-methylpyridin-4-yl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N,N-dimethylbenzamide
419		N-(1,4-dimethyl-1H-indazol-5-yl)-4-methoxy-5-(pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine
420		4-(5-(2-fluoro-6-methylpyridin-4-yl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N,N,3-trimethylbenzamide

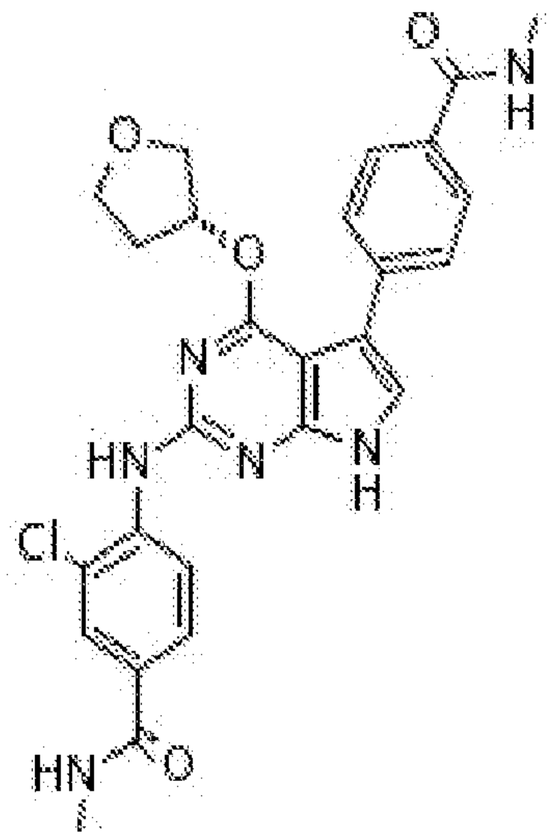
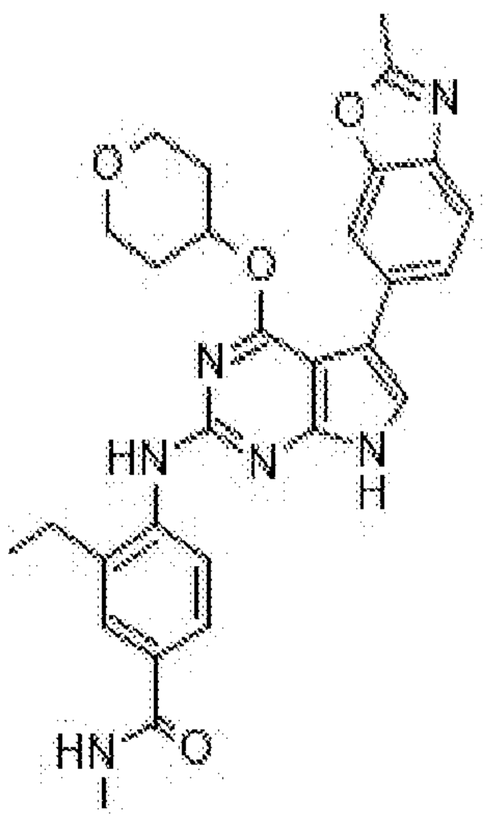
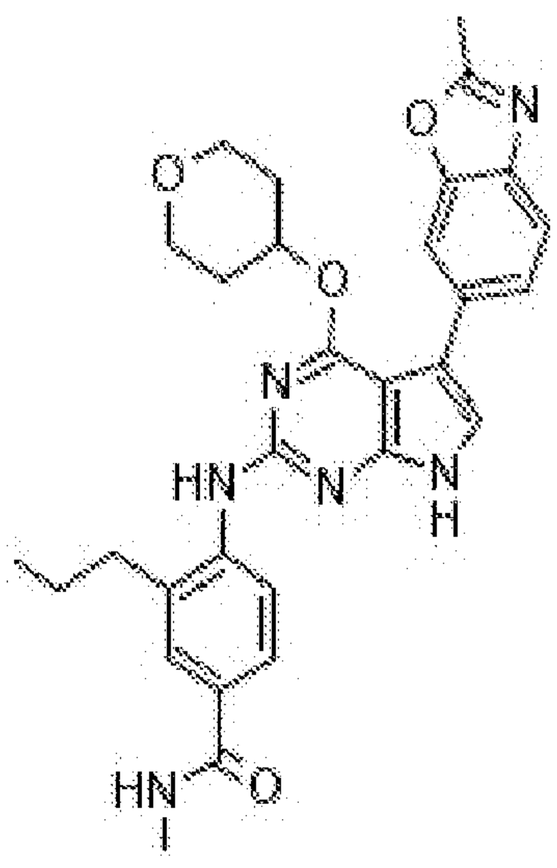
Cmpd No.	Structure	Name
421		3-chloro-N-methyl-4-(5-(4-(methylcarbamoyl)phenyl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
422		3-chloro-4-(4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide

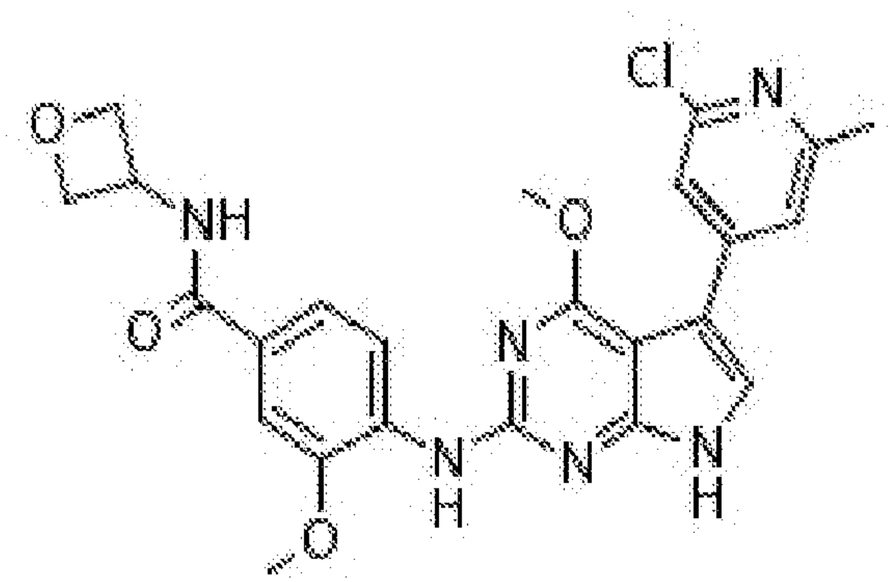
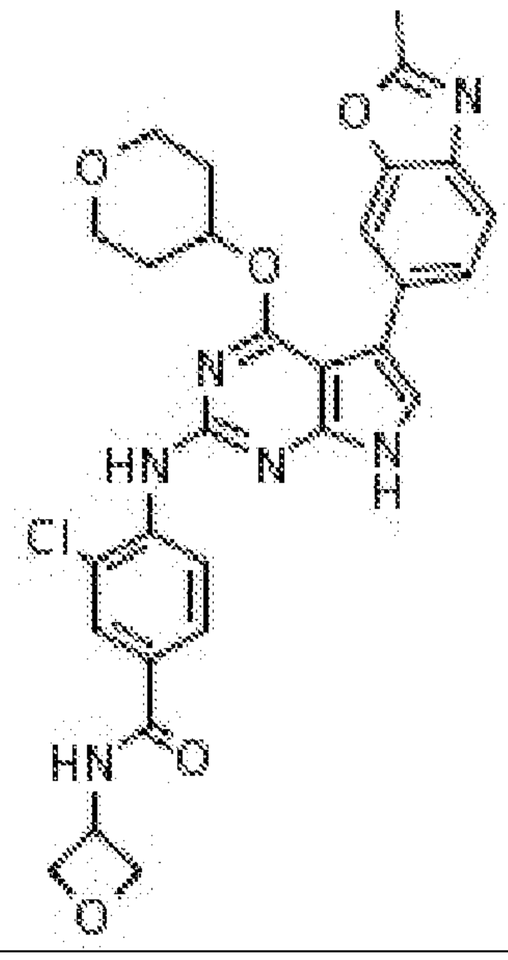
Cmpd No.	Structure	Name
423		3-chloro-N-methyl-4-(5-(1-methyl-1H-pyrazol-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
424		4-(5-(2-fluoro-6-methylpyridin-4-yl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide
425		3-chloro-4-(4-(cyclopentyloxy)-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide

Cmpd No.	Structure	Name
426		3-chloro-4-(4-isopropoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide
427		3-chloro-4-(4-methoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide
428		3-chloro-4-(4-methoxy-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide

Cmpd No.	Structure	Name
429		3-chloro-4-(4-((1s,4s)-4-hydroxy-4-methylcyclohexyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide
430		3-chloro-N-methyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

Cmpd No.	Structure	Name
431		3-chloro-N-(2-hydroxyethyl)-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
432		3-chloro-4-(4-isopropoxy-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-methylbenzamide
433		3-chloro-N-methyl-4-(5-(4-(methylcarbamoyl)phenyl)-4-(tetrahydro-2H-pyran-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide

Cmpd No.	Structure	Name
434		(R)-3-chloro-N-methyl-4-(5-(4-(methylcarbamoyl)phenyl)-4-(tetrahydrofuran-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
435		3-ethyl-N-methyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)benzamide
436		N-methyl-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-propylbenzamide

Cmpd No.	Structure	Name
437		4-(5-(2-chloro-6-methylpyridin-4-yl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-3-methoxy-N-(oxetan-3-yl)benzamide
438		3-chloro-4-(5-(2-methylbenzo[d]oxazol-6-yl)-4-(tetrahydro-2H-pyran-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino)-N-(oxetan-3-yl)benzamide

METHODS FOR MAKING PYRROLOPYRIMIDINE COMPOUNDS

[00128] The Pyrrolopyrimidine Compounds described herein can be obtained using conventional organic syntheses and commercially available starting materials.

[00129] Starting materials useful for preparing compounds of formula (I) and intermediates therefore, are commercially available or can be prepared from commercially available materials using known synthetic methods and reagents.

[00130] Particular methods for preparing compounds of formula (I) are disclosed in U.S. Patent Application No. 14/155,485, filed January 15, 2014, and U.S. Patent Application No. 14/155,498, filed January 15, 2014, each incorporated by reference herein in their entirety.

METHODS OF USE

[00131] The Pyrrolopyrimidine Compounds have utility as pharmaceuticals to treat, prevent or improve cancer in animals or humans. Accordingly, the Pyrrolopyrimidine Compounds provided herein can be used in all the methods as provided herein. Particularly, the Pyrrolopyrimidine Compounds provided herein can be used in the treatment, prevention or improvement of all diseases disorders, or conditions provided herein. Accordingly, provided herein are uses of the Pyrrolopyrimidine Compounds, including the treatment or prevention of those cancers set forth below. The methods provided herein comprise the administration of an effective amount of one or more Pyrrolopyrimidine Compound(s) to a subject in need thereof.

[00132] In another aspect, provided herein are methods for treating or preventing a cancer, comprising administering to a subject in need thereof an effective amount of a Pyrrolopyrimidine Compound, as described herein. In some embodiments, the cancer is a solid tumor or a hematological tumor. In some embodiments, the cancer is not triple negative breast cancer (TNBC).

[00133] In some embodiments, the solid tumor is bladder cancer (including superficial bladder cancer), breast cancer (including luminal B type, ER+, PR+ and Her2+ breast cancer), central nervous system cancer (including glioblastoma multiforme (GBM), glioma, medulloblastoma, and astrocytoma), colorectal cancer, gastrointestinal cancer (including stomach cancer, oesophagus cancer, and rectum cancer), endocrine cancer (including thyroid cancer, and adrenal gland cancer), eye cancer (including retinoblastoma), female genitourinary cancer (including cancer of the placenta, uterus, vulva, ovary, cervix), head and neck cancer (including cancer of the pharynx, oesophagus, and tongue), liver cancer, lung cancer (including non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), mucoepidermoid, bronchogenic, squamous cell carcinoma (SQCC), and analplastic/NSCLC), skin cancer (including melanoma, and SQCC), soft tissue cancer (including sarcoma, Ewing's sarcoma, and rhabdomyosarcoma), bone cancer (including sarcoma, Ewing's sarcoma, and osteosarcoma), squamous cell cancer (including lung, esophageal, cervical, and head and neck cancer), pancreas cancer, kidney cancer (including renal Wilm's tumor and renal cell carcinoma), or prostate cancer. In some embodiments, the solid tumor is breast cancer, colon cancer, lung cancer or bladder

cancer. In one such embodiment, the solid tumor is superficial bladder cancer. In another, the solid tumor is lung squamous cell carcinoma. In yet another embodiment, the solid tumor is luminal B type breast cancer.

[00134] In some embodiments, the hematological cancer is leukemia (including acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), acute T-cell leukemia, B cell precursor leukemia, acute promyelocytic leukemia (APML), plasma cell leukemia, myelomonoblastic/T-ALL, B myelomonocytic leukemia, erythroleukemia, and acute myeloid leukemia (AML)), lymphoma (including Hodgkin's lymphoma, non-Hodgkin's lymphoma (NHL), Burkitt's lymphoma (BL), B cell lymphoma, lymphoblastic lymphoma, follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and large cell immunoblastic lymphoma), or multiple myeloma.

[00135] In some embodiments, provided herein are methods for preventing cancer metastasis, comprising administering to a subject in need thereof an effective amount of a Pyrrolopyrimidine Compound, as described herein. In some embodiments, the cancer is a metastatic cancer, in particular, a metastatic solid tumor or metastatic hematologic cancer, wherein the solid tumor and hematologic cancer is as described herein. In other embodiments, provided herein are methods of preventing cancer metastasis, comprising administering to a subject in need thereof an effective amount of a Pyrrolopyrimidine Compound, as described herein. In yet another aspect, provided herein are methods of eradicating cancer stem cells in a subject, comprising administering to a subject in need thereof an effective amount of a Pyrrolopyrimidine Compound, as described herein. In other embodiments, provided herein are methods of inducing differentiation in cancer stem cells in a subject, comprising administering to a subject in need thereof an effective amount of a Pyrrolopyrimidine Compound, as described herein. In other embodiments, provided herein are methods of inducing cancer stem cell death in a subject, comprising administering to a subject in need thereof an effective amount of a Pyrrolopyrimidine Compound, as described herein. In some such embodiments, the cancer is a solid tumor, for example a CNS cancer (e.g. GBM) or breast cancer, or a hematological cancer, such as leukemia.

[00136] In another aspect, provided herein are methods for treating or preventing a cancer, in particular a solid tumor or a hematological tumor as described herein, comprising

administering to a subject in need thereof an effective amount of a compound that inhibits TTK, CLK1, and CLK2 kinase activity, and optionally CAMKK2 kinase activity. In some embodiments, provided are methods for treating or preventing a cancer, in particular a solid tumor or a hematological tumor as described herein, comprising administering to a subject in need thereof an effective amount of a compound that inhibits TTK, CLK1, and CLK2 kinase activity. In some embodiments, the TTK, CLK1, and CLK2 kinase activity is inhibited in a cell. In some embodiments, the TTK, CLK1, and CLK2 kinase activity is inhibited in vivo. In some embodiments, the compound that inhibits TTK, CLK1, and CLK2 kinase activity is a Pyrrolopyrimidine Compound as described herein. In another aspect, provided herein are methods for treating or preventing a cancer associated with the pathways involving TTK, CLK1, and CLK2, and optionally CAMKK2, and mutants or isoforms thereof, comprising administering to a subject in need thereof an effective amount of a compound that inhibits TTK, CLK1, and CLK2 kinase activity, and optionally CAMKK2 kinase activity. In some embodiments, the cancer associated with the TTK, CLK1, and CLK2, and optionally CAMKK2, pathways include a solid tumor or a hematological tumor as described herein. In some embodiments, the TTK, CLK1, and CLK2, and optionally CAMKK2, pathway is inhibited in a cell. In some embodiments, the TTK, CLK1, and CLK2, and optionally CAMKK2, pathway is inhibited in vivo. In some embodiments, the compound that inhibits TTK, CLK1, and CLK2, and optionally CAMKK2, pathway is a Pyrrolopyrimidine Compound as described herein.

[00137] In certain embodiments, provided herein are methods for measuring inhibition of TTK, CLK1, and CLK2 kinase activity, and optionally CAMKK2 kinase activity, in a patient having a cancer, for example a solid tumor or a hematological tumor as described herein, comprising administering an effective amount of a Pyrrolopyrimidine Compound to said patient, measuring the amount of TTK, CLK1, and CLK2 kinase activity in said patient, and comparing said amount of TTK, CLK1, and CLK2 kinase activity to that of said patient prior to administration of an effective amount of a Pyrrolopyrimidine Compound. In certain embodiments, less TTK, CLK1, and CLK2 kinase activity, and optionally CAMKK2 kinase activity, in said biological sample obtained after administration of said Pyrrolopyrimidine Compound relative to the amount of TTK, CLK1, and CLK2 kinase activity, and optionally CAMKK2 kinase activity, in said

biological sample obtained prior to administration of said Pyrrolopyrimidine Compound indicates inhibition.

[00138] In one embodiment, the kinase activity is measured using a radioactivity based kinase assay, which measures the incorporation of a radioactively labeled phosphate moiety (for example, ^{33}P labeled phosphate) into a substrate, for example, a peptide substrate. Reduced levels of radioactively labeled phosphate incorporation into the substrate indicates inhibition of kinase activity. In another embodiment, the kinase activity is measured using a time-resolved-fluorescence resonance energy transfer (TR-FRET) based kinase assay, which measures loss of fluorescence as a result of substrate phosphorylation, for example, a peptide substrate (see for example Invitrogen Z'-Lyte assay®). Increased levels of fluorescence indicates inhibition of kinase activity. In another embodiment, the kinase activity is measured using a competitive tracer binding assay (for example, Invitrogen Lanthascreen® Eu binding assay), which measures fluorescence as a result of tracer binding (for example ATP site binding). Reduced fluorescence indicates displacement of tracer binding, which indicates inhibition of kinase activity. In yet another embodiment, the kinase activity is measured using a cellular biomarker assay, which measures the phosphorylation of a substrate, for example a downstream substrate, using Western Blot, ELISA or Mesoscale. Reduced phosphorylation of the substrate indicates inhibition of kinase activity.

[00139] In some embodiments, the inhibition of TTK, CLK1, and CLK2 kinase activity, and optionally CAMKK2 kinase activity, is assessed in a biological sample of the patient, such as in circulating blood cells, or tumor or skin biopsies. In such embodiments, the amount of inhibition of kinase activity is assessed by comparison of the amount of phosphorylated substrate (for example for TTK: phospho-TTK, such as p-TTK T686, or phosphorylated borealin, BubR1, Chk2,c-Abl, p53, Mip1 or TACC2; and for CLK2 (phospho-SRp75, or phosphorylated PP2A regulatory subunit B56β (PPP2R5B, B'β) or PGC-1α) before and after administration of the Pyrrolopyrimidine Compound to the patient. In some such embodiments, less phosphorylated TTK substrate and less phosphorylated CLK2 substrate, in said biological sample, obtained after administration of said Pyrrolopyrimidine Compound relative to the amount of phosphorylated TTK substrate and phosphorylated CLK2 substrate, in said biological sample obtained prior to

administration of said Pyrrolopyrimidine Compound indicates inhibition. In some such embodiments, less phospho-TTK (for example p-TTK T686) and phospho-SRp75, in said biological sample obtained after administration of said Pyrrolopyrimidine Compound relative to the amount of phospho-TTK (for example p-TTK T686) and phospho-SRp75, in said biological sample obtained prior to administration of said Pyrrolopyrimidine Compound indicates inhibition.

[00140] In certain embodiments, provided herein are methods for inhibiting TTK, CLK1, and CLK2 kinase activity, and optionally CAMKK2 kinase activity, in a patient having a cancer, in particular a solid tumor or a hematological tumor as described herein, comprising administering an effective amount of a Pyrrolopyrimidine Compound to said patient. In some embodiments, the methods additionally comprise comparing the amount of TTK, CLK1, and CLK2 kinase activity, and optionally CAMKK2 activity, in a biological sample of a patient obtained prior to and after administration of said Pyrrolopyrimidine Compound, wherein less TTK, CLK1, and CLK2 kinase activity, and optionally CAMKK2 kinase activity, in said biological sample obtained after administration of said Pyrrolopyrimidine Compound relative to the amount of TTK, CLK1, and CLK2 kinase activity, and optionally CAMKK2 kinase activity, in said biological sample obtained prior to administration of said Pyrrolopyrimidine Compound indicates inhibition.

[00141] In some embodiments, the methods additionally comprise comparing the amount of phosphorylated substrate (for example for TTK: phospho-TTK, such as p-TTK T686, or phosphorylated borealin, BubR1, Chk2,c-Abl, p53, Mip1 or TACC2; and for CLK2 (phospho-SRp75, or phosphorylated PP2A regulatory subunit B56β (PPP2R5B, B'β) or PGC-1α) in a biological sample of a patient obtained prior to and after administration of said Pyrrolopyrimidine Compound, wherein less phosphorylated substrate in said biological sample obtained after administration of said Pyrrolopyrimidine Compound relative to the amount of phosphorylated substrate in said biological sample obtained prior to administration of said Pyrrolopyrimidine Compound indicates inhibition. In other embodiments, the methods additionally comprise comparing the amount of phospho-TTK (for example p-TTK T686) and phospho-SRp75, in a biological sample of a patient obtained prior to and after administration of said Pyrrolopyrimidine Compound, wherein

less phospho-TTK (for example p-TTK T686) and phospho-SRp75, in said biological sample obtained after administration of said Pyrrolopyrimidine Compound relative to the amount of phospho-TTK (for example p-TTK T686) and phospho-SRp75, in said biological sample obtained prior to administration of said Pyrrolopyrimidine Compound indicates inhibition.

[00142] In some embodiments, the TTK kinase activity is inhibited with an IC_{50} no greater than about 20 nM. In another, the TTK kinase activity is inhibited with an IC_{50} between about 0.01 nM and about 20 nM. In others, the TTK kinase activity is inhibited with an IC_{50} between about 0.01 nM and about 100 nM. In still others, the TTK kinase activity is inhibited with an IC_{50} between about 0.01 nM and about 200 nM. In yet others, the TTK kinase activity is inhibited with an IC_{50} between about 0.1 nM and about 500 nM. In some embodiments, the CLK1 kinase activity is inhibited with an IC_{50} no greater than about 300 nM. In some embodiments, the CLK1 kinase activity is inhibited with an IC_{50} between about 1 nM and about 100 nM. In others, the CLK1 kinase activity is inhibited with an IC_{50} between about 1 nM and about 500 nM. In yet others, the CLK1 kinase activity is inhibited with an IC_{50} between about 1 nM and about 1000 nM. In some embodiments, the CLK2 kinase activity is inhibited with an IC_{50} no greater than about 10 nM. In another, the CLK2 kinase activity is inhibited with an IC_{50} between about 0.01 nM and about 20 nM. In others, the CLK2 kinase activity is inhibited with an IC_{50} between about 0.01 nM and about 100 nM. In still others, the CLK2 kinase activity is inhibited with an IC_{50} between about 0.01 nM and about 200 nM. In yet others, the CLK2 kinase activity is inhibited with an IC_{50} between about 0.1 nM and about 500 nM. In some embodiments, the CAMKK2 kinase activity is inhibited with an IC_{50} no greater than about 1000 nM. In another, the CAMKK2 kinase activity is inhibited with an IC_{50} between about 1 nM and about 500 nM. In others, the CAMKK2 kinase activity is inhibited with an IC_{50} between about 1 nM and about 1000 nM. In still others, the CAMKK2 kinase activity is inhibited with an IC_{50} between about 1 nM and about 2000 nM. In yet others, the CAMKK2 kinase activity is inhibited with an IC_{50} between about 1 nM and about 5000 nM.

[00143] In one embodiment, provided herein are methods for achieving a Response Evaluation Criteria in Solid Tumors (RECIST 1.1) of complete response, partial response

or stable disease in a patient comprising administering an effective amount of a Pyrrolopyrimidine Compound to a patient having a cancer, in particular a solid tumor as described herein. In another embodiment, provided herein are methods to increase Progression Free Survival rates, as determined by Kaplan-Meier estimates.

[00144] In one embodiment, provided herein are methods for preventing or delaying a Response Evaluation Criteria in Solid Tumors (RECIST 1.1) of progressive disease in a patient, comprising administering an effective amount of a Pyrrolopyrimidine Compound to a patient having a solid tumor as described herein. In one embodiment the prevention or delaying of progressive disease is characterized or achieved by a change in overall size of the target lesions, of for example, between -30% and +20% compared to pre-treatment. In another embodiment, the change in size of the target lesions is a reduction in overall size of more than 30%, for example, more than 50% reduction in target lesion size compared to pre-treatment. In another, the prevention is characterized or achieved by a reduction in size or a delay in progression of non-target lesions compared to pre-treatment. In one embodiment, the prevention is achieved or characterized by a reduction in the number of target lesions compared to pre-treatment. In another, the prevention is achieved or characterized by a reduction in the number or quality of non-target lesions compared to pre-treatment. In one embodiment, the prevention is achieved or characterized by the absence or the disappearance of target lesions compared to pre-treatment. In another, the prevention is achieved or characterized by the absence or the disappearance of non-target lesions compared to pre-treatment. In another embodiment, the prevention is achieved or characterized by the prevention of new lesions compared to pre-treatment. In yet another embodiment, the prevention is achieved or characterized by the prevention of clinical signs or symptoms of disease progression compared to pre-treatment, such as cancer-related cachexia or increased pain.

[00145] In certain embodiments, provided herein are methods for decreasing the size of target lesions in a patient compared to pre-treatment, comprising administering an effective amount of a Pyrrolopyrimidine Compound to a patient having a cancer, in particular a solid tumor as described herein.

[00146] In certain embodiments, provided herein are methods for decreasing the size of a non-target lesion in a patient compared to pre-treatment, comprising administering an

effective amount of a Pyrrolopyrimidine Compound to a patient having a cancer, in particular a solid tumor as described herein.

[00147] In certain embodiments, provided herein are methods for achieving a reduction in the number of target lesions in a patient compared to pre-treatment, comprising administering an effective amount of a Pyrrolopyrimidine Compound to a patient having a cancer, in particular a solid tumor as described herein.

[00148] In certain embodiments, provided herein are methods for achieving a reduction in the number of non-target lesions in a patient compared to pre-treatment, comprising administering an effective amount a Pyrrolopyrimidine Compound to a patient having a cancer, in particular a solid tumor as described herein.

[00149] In certain embodiments, provided herein are methods for achieving an absence of all target lesions in a patient, comprising administering an effective amount of a Pyrrolopyrimidine Compound to a patient having a cancer, in particular a solid tumor as described herein.

[00150] In certain embodiments, provided herein are methods for achieving an absence of all non-target lesions in a patient, comprising administering an effective amount of a Pyrrolopyrimidine Compound to a patient having a cancer, in particular a solid tumor as described herein.

[00151] In certain embodiments, provided herein are methods for treating a cancer, in particular a solid tumor as described herein, the methods comprising administering an effective amount of a Pyrrolopyrimidine Compound to a patient having a cancer, in particular a solid tumor, wherein the treatment results in a complete response, partial response or stable disease, as determined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

[00152] In certain embodiments, provided herein are methods for treating a cancer, in particular a solid tumor as described herein, the methods comprising administering an effective amount of a Pyrrolopyrimidine Compound to a patient having a cancer, in particular a solid tumor as described herein, wherein the treatment results in a reduction in target lesion size, a reduction in non-target lesion size and/or the absence of new target and/or non-target lesions, compared to pre-treatment.

[00153] In certain embodiments, provided herein are methods for treating a cancer, in particular a solid tumor as described herein, the methods comprising administering an effective amount a Pyrrolopyrimidine Compound to a patient having a cancer, in particular a solid tumor as described herein, wherein the treatment results in prevention or retarding of clinical progression, such as cancer-related cachexia or increased pain.

[00154] In another embodiment, provided herein are methods for inducing a therapeutic response characterized with the International Workshop Criteria (IWC) for NHL (*see* Cheson BD, Pfistner B, Juweid, ME, et. al. Revised Response Criteria for Malignant Lymphoma. J. Clin. Oncol: 2007: (25) 579-586) of a patient, comprising administering an effective amount a Pyrrolopyrimidine Compound to a patient having a cancer, in particular hematological cancers such as lymphoma, as described herein. In another embodiment, provided herein are methods for achieving complete remission, partial remission or stable disease, as determined by the International Workshop Criteria (IWC) for NHL in a patient, comprising administering an effective amount of a Pyrrolopyrimidine Compound to a patient having a cancer, in particular hematological cancers such as lymphoma, as described herein. In another embodiment, provided herein are methods for achieving an increase in overall survival, progression-free survival, event-free survival, time to progression, disease-free survival or lymphoma-free survival as determined by the International Workshop Criteria (IWC) for NHL in a patient, comprising administering an effective amount of a Pyrrolopyrimidine Compound to a patient having a cancer, in particular hematological cancers such as lymphoma, as described herein.

[00155] In another embodiment, provided herein are methods for inducing a therapeutic response assessed with the International Uniform Response Criteria for Multiple Myeloma (IURC) (*see* Durie BGM, Harousseau J-L, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia, 2006; (10) 10: 1-7) of a patient, comprising administering an effective amount of a Pyrrolopyrimidine Compound to a patient having a cancer, in particular multiple myeloma. In another embodiment, provided herein are methods for achieving a stringent complete response, complete response, or very good partial response, as determined by the International Uniform Response Criteria for Multiple Myeloma (IURC) in a patient, comprising administering an effective amount of a Pyrrolopyrimidine Compound to a patient having a cancer, in particular multiple

myeloma. In another embodiment, provided herein are methods for achieving an increase in overall survival, progression-free survival, event-free survival, time to progression, or disease-free survival in a patient, comprising administering an effective amount of a Pyrrolopyrimidine Compound to a patient having a cancer, in particular multiple myeloma.

[00156] In another embodiment, provided herein are methods for inducing a therapeutic response assessed with the Response Assessment for Neuro-Oncology (RANO) Working Group for GBM (*see* Wen P., Macdonald, DR., Reardon, DA., et al. Updated response assessment criteria for highgrade gliomas: Response assessment in neuro-oncology working group. J. Clin. Oncol. 2010; 28: 1963-1972) of a patient, comprising administering an effective amount of a Pyrrolopyrimidine Compound to a patient having a cancer, in particular glioblastoma multiforme (GBM). In one embodiment, RANO will be used to establish the proportion of subjects progression-free at 6 months from Day 1 relative to efficacy evaluable subjects in the GBM type.

[00157] In another embodiment, provided herein are methods for improving the Eastern Cooperative Oncology Group Performance Status (ECOG) of a patient, comprising administering an effective amount a Pyrrolopyrimidine Compound to a patient having a cancer, in particular a solid tumor or hematological cancer as described herein.

[00158] In another embodiment, provided herein are methods for inducing a therapeutic response assessed by Positron Emission Tomography (PET) outcome of a patient, comprising administering an effective amount of a Pyrrolopyrimidine Compound to a patient having a cancer, in particular a solid tumor or hematological cancer as described herein. In certain embodiments, provided herein are methods for treating a cancer, in particular a solid tumor or hematological cancer as described herein, the methods comprising administering an effective amount of a Pyrrolopyrimidine Compound to a patient having a cancer, in particular a solid tumor or hematological cancer as described herein, wherein the treatment results in a reduction in tumor metabolic activity, for example, as measured by PET imaging.

[00159] In some embodiments of the methods described herein, the Pyrrolopyrimidine Compound is a compound as described herein. In one embodiment, the Pyrrolopyrimidine Compound is a compound of formula (I). In another embodiment, the Pyrrolopyrimidine

Compound is a compound from Table A. In one embodiment, the Pyrrolopyrimidine Compound is a Pyrrolopyrimidine Compound set forth herein having molecular formula $C_{26}H_{24}N_6O_4$. In another, the Pyrrolopyrimidine Compound is a Pyrrolopyrimidine Compound set forth herein having molecular formula $C_{26}H_{26}N_6O_4$. In yet another, the Pyrrolopyrimidine Compound is a Pyrrolopyrimidine Compound set forth herein having molecular formula $C_{26}H_{27}N_5O_4$. In yet another, the Pyrrolopyrimidine Compound is a Pyrrolopyrimidine Compound set forth herein having molecular formula $C_{28}H_{28}N_6O_4$. In still another, the Pyrrolopyrimidine Compound is a Pyrrolopyrimidine Compound set forth herein having molecular formula $C_{28}H_{30}N_6O_4$. In another embodiment, the Pyrrolopyrimidine Compound is a Pyrrolopyrimidine Compound set forth herein having molecular formula $C_{29}H_{30}N_6O_5$. In one embodiment, the Pyrrolopyrimidine Compound is 4-((4-(cyclopentyloxy)-5-(4-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-methoxy-N-methylbenzamide (Compound 3). In another, the Pyrrolopyrimidine Compound is 4-((4-cyclopropoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-methoxy-N-methylbenzamide (Compound 152). In yet another, the Pyrolopyrimidine is 4-((4-isopropoxy-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-methoxy-N-methylbenzamide (Compound 125). In still another, the Pyrolopyrimidine is 4-((4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-methoxy-N-methylbenzamide (Compound 38). In another embodiment, the Pyrolopyrimidine is 4-((4-(cyclopentyloxy)-5-(4-(methylcarbamoyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-methoxy-N-methylbenzamide (Compound 79). In yet another embodiment, the Pyrolopyrimidine is 4-((4-(cyclopentyloxy)-5-(2-methylbenzo[d]oxazol-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)amino)-N-(2-hydroxyethyl)-3-methoxybenzamide (Compound 101).

[00160] Further provided herein are methods for treating patients who have been previously treated for a cancer, in particular a solid tumor or a hematological cancer as described herein, as well as those who have not previously been treated. Because patients with a cancer have heterogenous clinical manifestations and varying clinical outcomes, the treatment given to a patient may vary, depending on his/her prognosis. The skilled clinician will be able to readily determine without undue experimentation specific

secondary agents, types of surgery, and types of non-drug based standard therapy that can be effectively used to treat an individual patient with a cancer.

PHARMACEUTICAL COMPOSITIONS AND ROUTES OF ADMINISTRATION

[00161] The Pyrrolopyrimidine Compounds can be administered to a subject parenterally in the conventional form of preparations, such as injections, suspensions, solutions and emulsions. Suitable vehicles that can be used to provide intravenous formulations of a Pyrrolopyrimidine Compound are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate. An intravenous formulation can be prepared by reconstituting a Pyrrolopyrimidine Compound with such a suitable liquid vehicle. A desired concentration of the intravenous formulation can be obtained by reconstituting an appropriate amount of a Pyrrolopyrimidine Compound with an appropriate volume of liquid vehicle. A desired concentration of the intravenous formulation provides a therapeutically effective amount of a Pyrrolopyrimidine Compound to the patient in need of the intravenous formulation and maintains a therapeutically effective level of a Pyrrolopyrimidine Compound in the patient. The dose which is therapeutically effective will depend on the rate at which the intravenous formulation is delivered to the patient and the concentration of the intravenous formulation.

[00162] The effective amount of the Pyrrolopyrimidine Compound in the pharmaceutical composition may be at a level that will exercise the desired effect; for example, about 0.005 mg/kg of a subject's body weight to about 100 mg/kg of a subject's body weight in unit dosage for parenteral administration.

[00163] The dose of a Pyrrolopyrimidine Compound to be administered to a subject is rather widely variable and can be subject to the judgment of a health-care practitioner. In

general, the Pyrrolopyrimidine Compounds can be administered one to seven times a week, once every two weeks, once every three weeks or once every four weeks in a dose of about 0.005 mg/kg of a subject's body weight to about 10 mg/kg of a subject's body weight in a subject, but the above dosage may be properly varied depending on the age, body weight and medical condition of the subject and the type of administration. In one embodiment, the dose is about 0.01 mg/kg of a subject's body weight to about 5 mg/kg of a subject's body weight, about 0.05 mg/kg of a subject's body weight to about 1 mg/kg of a subject's body weight, about 0.1 mg/kg of a subject's body weight to about 0.75 mg/kg of a subject's body weight or about 0.25 mg/kg of a subject's body weight to about 0.5 mg/kg of a subject's body weight. In one embodiment, one dose is given per week. In others, one dose is given two, three or four times per week. In still others, one dose is given per two weeks, per three weeks or per four weeks. In any given case, the amount of the Pyrrolopyrimidine Compound administered will depend on such factors as the solubility of the active component, the formulation used and the route of administration.

[00164] In another embodiment, provided herein are methods for the treatment or prevention of a disease or disorder comprising the administration of about 0.375 mg/dose to about 750 mg/dose, about 0.75 mg/dose to about 375 mg/dose, about 3.75 mg/dose to about 75 mg/dose, about 7.5 mg/dose to about 55 mg/dose or about 18 mg/dose to about 37 mg/dose of a Pyrrolopyrimidine Compound to a subject in need thereof.

[00165] In another embodiment, provided herein are methods for the treatment or prevention of a disease or disorder comprising the administration of about 1 mg/dose to about 1200 mg/dose, about 10 mg/dose to about 1200 mg/dose, about 100 mg/dose to about 1200 mg/dose, about 400 mg/dose to about 1200 mg/dose, about 600 mg/dose to about 1200 mg/dose, about 400 mg/dose to about 800 mg/dose or about 600 mg/dose to about 800 mg/dose of a Pyrrolopyrimidine Compound to a subject in need thereof. In a particular embodiment, the methods disclosed herein comprise the administration of 400 mg/dose, 600 mg/dose or 800 mg/dose of a Pyrrolopyrimidine Compound to a subject in need thereof.

[00166] In another embodiment, provided herein are unit dosage formulations that comprise between about 1 mg and 200 mg, about 35 mg and about 1400 mg, about 125

mg and about 1000 mg, about 250 mg and about 1000 mg, or about 500 mg and about 1000 mg of a Pyrrolopyrimidine Compound.

[00167] In a particular embodiment, provided herein are unit dosage formulations comprising about 100 mg or 400 mg of a Pyrrolopyrimidine Compound.

[00168] In another embodiment, provided herein are unit dosage formulations that comprise 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 35 mg, 50 mg, 70 mg, 100 mg, 125 mg, 140 mg, 175 mg, 200 mg, 250 mg, 280 mg, 350 mg, 500 mg, 560 mg, 700 mg, 750 mg, 1000 mg or 1400 mg of a Pyrrolopyrimidine Compound.

[00169] A Pyrrolopyrimidine Compound can be administered once, twice, three, four or more times daily. In a particular embodiment, doses of 600 mg or less are administered as a once daily dose and doses of more than 600 mg are administered twice daily in an amount equal to one half of the total daily dose.

[00170] In another embodiment, provided herein are compositions comprising an effective amount of a Pyrrolopyrimidine Compound and a pharmaceutically acceptable carrier or vehicle, wherein a pharmaceutically acceptable carrier or vehicle can comprise an excipient, diluent, or a mixture thereof. In one embodiment, the composition is a pharmaceutical composition.

[00171] The compositions can be in the form of solutions, parenteral solutions, and suspensions and the like. Compositions can be formulated to contain a single dose, or a convenient fraction of a single dose, in a dosage unit, which may be a single vial or convenient volume of a liquid. In one embodiment, the solutions are prepared from water-soluble salts, such as the hydrochloride salt. In general, all of the compositions are prepared according to known methods in pharmaceutical chemistry.

[00172] The effect of the Pyrrolopyrimidine Compound can be delayed or prolonged by proper formulation. The parenteral preparations can be made long-acting, by dissolving or suspending the Pyrrolopyrimidine Compound in oily or emulsified vehicles that allow it to disperse slowly in the serum.

EXAMPLES

[00173] The following Examples are presented by way of illustration, not limitation.

ENZYME ASSAYS

[00174] **CLK1 kinase assay**. A fluorescence resonance energy transfer-based Z′-LYTE® kinase assay kit– Ser/Thr 09 (Invitrogen, Carlsbad, CA, cat.# PV3324) was used to determine the IC_{50} values for inhibition of CLK1 kinase activity. The reactions were performed in a 384-well plate with a 10 µl reaction volume per well containing CLK1 enzyme (16.2 - 128 ng), 25 µM adenosine triphosphate (ATP), 2 µM Z'-Lyte® Ser/Thr 9 peptide substrate in 50 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), pH 7.5, 0.01% Brij-35, 10 mM magnesium chloride ($MgCl_2$), 1 mM ethylene glycol tetraacetic acid (EGTA) buffer with a serial 3-fold dilution of the test compounds. After a 1 hour incubation, 5 µL of Development Reagent A (1:256 dilution) was added, and the fluorescence ratio was calculated. The dose-response curves were fitted to a sigmoidal dose-response model using XL*fit* from IDBS. The IC_{50} values were determined as the concentration of compound resulting in 50% of remaining enzyme activity. Results for certain Pyrrolopyrimidine Compounds are shown in Tables B and C.

[00175] **CLK2 kinase assay**. A fluorescence resonance energy transfer-based Z′-LYTE® kinase assay kit–Ser/Thr 6 peptide (Invitrogen, Carlsbad, CA, cat.# PV3179) was used to determine the IC_{50} values for inhibition of CLK2 kinase activity. The reactions were performed in a 384-well plate with a 10 µl reaction volume per well containing CLK2 enzyme (ranging from 0.97-11.5 ng), 25 µM ATP, 2 µM Z'-Lyte® Ser/Thr 6 peptide substrate in 50 mM HEPES, pH 7.5, 0.01% Brij-35, 10 mM $MgCl_2$, 1 mM EGTA buffer with a serial 3-fold dilution of the test compounds. After a 1 hour incubation, 5 µL of Development Reagent A (1:2048 dilution) was added, and the fluorescence ratio was calculated. A dose-response curves were fitted to a sigmoidal dose-response model using XL*fit* from IDBS. The IC_{50} values were determined as the concentration of compound resulting in 50% of remaining enzyme activity. Results for certain Pyrrolopyrimidine Compounds are shown in Tables B and C.

[00176] **TTK kinase assay.** The LanthaScreen® Eu Kinase Binding Assay (Invitrogen, Carlsbad, CA cat.#) was used to determine the IC_{50} values for inhibition of TTK kinase activity. The reaction was performed in a 384-well plate

with a 16 μL reaction volume per well containing 5 nM TTK enzyme, 30 nM of Tracer 236 (Invitrogen PV5592), and 2 nM LanthaScreen® Eu-anti-GST antibody in 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM $MgCl_2$, 1 mM EGTA buffer with a serial 3-fold dilution of test compound. The reaction was incubated for 1 hour at room temperature and then read on a fluoresence plate reader (Excitation 340 nm, Kinase Tracer 236 Emission: 665 nm, LanthaScreen™ Eu-anti-Tag Antibody: Emission 615 nm). The TR-FRET ratio was calculated as the intensity of the acceptor signal (665 nm) divided by the intensity of the donor signal (615 nm). The dose-response curves were fitted to a sigmoidal dose-response model using XL*fit* from IDBS. The IC_{50} values were determined as the concentration of compound resulting in 50% of displaced Tracer 236 (ATP competive inhibitor). Results for certain Pyrrolopyrimidine Compounds are shown in Tables B and C.

[00177] **CAMKK2 kinase assay.** The LanthaScreen® Eu Kinase Binding Assay (Invitrogen, Carlsbad, CA) was used to determine the IC_{50} values for inhibition of CAMKK2 kinase activity. The reaction was performed in a 384-well plate with a 16 μL reaction volume per well containing 5 nM CAMKK2 enzyme, 10 nM of Kinase Tracer 236, and 2 nM LanthaScreen® Eu-anti-GST antibody in 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM MgCl2, 1 mM EGTA buffer with a serial 3-fold dilution of test compound. The reaction was incubated for 1 hour at room temperature and then read on a fluoresence plate reader (Excitation 340 nm, Kinase Tracer 236 Emission: 665 nm, and LanthaScreen™ Eu-anti-Tag Antibody: Emission 615 nm). The TR-FRET ratio was calculated as the intensity of the acceptor signal (665 nm) divided by the intensity of the donor signal (615 nm). The dose-response curves were fitted to a sigmoidal dose-response model using XL*fit* from IDBS. The IC_{50} values were determined as the concentration of compound resulting in 50% of displaced Tracer 236 (ATP competive inhibitor).

[00178] **Alternative CAMKK2 kinase assay.** CAMKK2 enzyme was mixed with 1 μM of Ca^{2+}-Calmodulin and 10 μM of the Mylein Basic Protein (MBP) substrate in reaction buffer; 20 mM 4-(2-hydroxyethyl)-1-piperazineethane sulfonic acid (HEPES), 10 mM magnesium chloride ($MgCl_2$), 1 mM ethyleneglycoltetraacetic acid (EGTA), 0.02% Brij35, 0.02 mg/ml bovine serum albumin (BSA), 0.1 mM sodium orthovanadate, 2 mM

dithiothreitol (DTT), 1% dimethyl sulfoxide (DMSO) at pH 7.5. Compounds were delivered into the reaction, followed 20 min later by addition of a mixture of ATP (Sigma) and ^{33}P ATP (PerkinElmer) to a final concentration of 10 μM. Reactions were carried out at 25 °C for 120 min, followed by spotting of the reactions onto P81 ion exchange filter paper (Whatman). Unbound phosphate was removed by extensive washing of filters in 0.75% phosphoric acid. After subtraction of background derived from control reactions containing inactive enzyme, kinase activity data were expressed as the percent remaining kinase activity in test samples compared to the DMSO vehicle reactions. IC_{50} values and curve fits were obtained using Prism (GraphPad Software). Results for certain Pyrrolopyrimidine Compounds are shown in Tables C.

[00179] **Table B**. Inhibition by Pyrrolopyrimidine Compounds of TTK, CLK1, and CLK2 kinase activity (% inhibition at 3 μM.

Cmpd No.	TTK (% Inh.)	CLK1 (% Inh.)	CLK2 (% Inh.)
3		91	104
11		95	94
16		92	90
17		97	98
38		99	98
58		96	103
64		68	99
79		97	97
89		101	100
90		101	101
98		103	104
101		95	98
118	102	98	98
132		92	98
133		104	101
134		101	100
139		104	99

Cmpd No.	TTK (% Inh.)	CLK1 (% Inh.)	CLK2 (% Inh.)
140		97	103
145		96	97
146		103	100
148		99	106
150		99	111
152		99	100
157		95	105
160		98	108
162		100	106
163		100	102
169		100	105
171		97	102
184		101	98
185		98	106
191		100	99
192	102	101	103
193		100	99
197		100	103
198		93	100
201		100	103
202		99	99
203		98	99
204		98	99
205		99	103
206		92	97
207		99	99
213		99	100
214		97	100
216		99	99

Cmpd No.	TTK (% Inh.)	CLK1 (% Inh.)	CLK2 (% Inh.)
237		93	100
296		101	104
300		100	100
304		53	101
307		99	103
334		95	104
339	100	63	98
340	105	100	99
349	95	101	102
371		100	100
377		99	100
384	102	57	88
392	99	106	99
421		99	101
422		94	99
423		99	100
426	98	101	101
429	101	96	101
435	100	100	101

[00180] **Table C**. Inhibition by Pyrrolopyrimidine Compounds of TTK, CLK1, CLK2 and CAMKK2 kinase activity.

Cmpd No.	TTK (IC_{50}, μM)	CLK1 (IC_{50}, μM)	CLK2 (IC_{50}, μM)	CAMKK2 (IC_{50}, μM)
3		1.435624	0.05389	
11		0.298738	0.034896	
16		0.225404	0.025999	
17		0.082369	0.00433	
38	0.014	0.267	0.008168	0.728
55	0.013312			
67	0.016027			
79	0.002379	0.058587	0.001911	0.034

Cmpd No.	TTK (IC_{50}, μM)	CLK1 (IC_{50}, μM)	CLK2 (IC_{50}, μM)	CAMKK2 (IC_{50}, μM)
89	<1.5e-003	0.041473	0.004557	
90	0.001675	0.12394	0.003497	
101	0.002128	0.099779	0.003377	0.501
118	0.005136		0.002294	
132	0.004116	0.225986	0.029057	
134	0.001678	0.130033	0.00227	
145	0.002451	0.219809	0.040123	
146	0.002121			
152	0.00296			
171	0.001471	0.082812	0.002317	
191	0.003653	0.172406	0.009409	
237	0.008062	0.237221	0.010372	
300	0.004536			
304	0.00235			
334	0.001418			
339	0.007004	0.526142	0.005915	
349	0.001145	0.059278	0.001429	
421		0.084639	0.002095	
422	0.011578	0.504877	0.012494	
423	0.001904	0.097765	0.003294	

[00181] **Conclusion**. Tables B and C show that Pyrrolopyrimidine Compounds, as described herein, inhibit the kinase activity of TTK, CLK1, and CLK2. In some embodiments, the Pyrrolopyrimidine Compounds also inhibit the kinase activity of CAMKK2.

CELL ASSAYS

[00182] **Breast cancer cell line growth inhibition**. The 49 breast cancer cell lines used in the study are shown in Table 1. The luminal and basal subtype classification was based upon public information that was verified internally. The estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status of each cell line was based upon public information that was verified internally.

[00183] **Table 1: Breast Cancer Cell Lines**

Cell Line	Subtype1	Subtype2	Vendor	Media
AU565	Luminal	Her2+	ATCC	RPMI+10% FBS
BT-20	Basal	TN	ATCC	DMEM+10% FBS
BT-474	Luminal	Her2+	ATCC	RPMI+10% FBS
BT-483	Luminal	ER+/PR+	ATCC	RPMI+10% FBS
BT-549	Basal	TN	ATCC	RPMI+10% FBS
CAL-120	Basal	TN	DSMZ	DMEM+10% FBS
CAL-148	Luminal	TN	DSMZ	DMEM+10% FBS
CAL-51	Basal	TN	DSMZ	DMEM+10% FBS
CAL-85-1	Basal	TN	DSMZ	DMEM+10% FBS
CAMA-1	Luminal	ER+/PR+	ATCC	DMEM+10% FBS
DU4475	Basal	TN	ATCC	RPMI+10% FBS
EFM-19	Luminal	ER+/PR+	DSMZ	RPMI+10% FBS
EFM-192A	Luminal	Her2+	DSMZ	RPMI+10% FBS
EVSA-T	Luminal	ER+/PR+	DSMZ	DMEM+10% FBS
HCC1143	Basal	TN	ATCC	RPMI+10% FBS
HCC1187	Basal	TN	ATCC	RPMI+10% FBS
HCC1419	Luminal	Her2+	ATCC	RPMI+10% FBS
HCC1428	Luminal	ER+/PR+	ATCC	RPMI+10% FBS
HCC1500	Luminal	ER+/PR+	ATCC	RPMI+10% FBS
HCC1569	Basal	Her2+	ATCC	RPMI+10% FBS
HCC1806	Basal	TN	ATCC	RPMI+10% FBS
HCC1937	Basal	TN	ATCC	RPMI+10% FBS
HCC1954	Basal	Her2+	ATCC	RPMI+10% FBS
HCC202	Luminal	Her2+	ATCC	RPMI+10% FBS
HCC38	Basal	TN	ATCC	RPMI+10% FBS
HCC70	Basal	TN	ATCC	RPMI+10% FBS
HCC2157	Basal	TN	ATCC	RPMI+10% FBS
HDQ-P1	Basal	TN	DSMZ	DMEM+10% FBS
HS578T	Basal	TN	ATCC	RPMI+10% FBS
JIMT-1	Basal	Her2+	DSMZ	DMEM+10% FBS
KPL-1	Luminal	ER+/PR+	DSMZ	DMEM+10% FBS

Cell Line	Subtype1	Subtype2	Vendor	Media
MB157	Basal	TN	ATCC	DMEM+10% FBS
MCF7	Luminal	ER+/PR+	NCI	RPMI+10% FBS
MCF10A	Basal	TN	ATCC	RPMI+10% FBS
MCF12A	Basal	TN	ATCC	DMEM+10% FBS
MDA-MB-134-VI	Luminal	ER+/PR+	ATCC	DMEM+10% FBS
MDA-MB-157	Basal	TN	ATCC	DMEM+10% FBS
MDA-MB-175-VII	Luminal	ER+/PR+	ATCC	RPMI+10% FBS
MDA-MB-231	Basal	TN	ATCC	RPMI+10% FBS
MDA-MB-361	Luminal	Her2+	ATCC	DMEM+10% FBS
MDA-MB-415	Luminal	ER+/PR+	ATCC	DMEM+10% FBS
MDA-MB-436	Basal	TN	ATCC	DMEM+10% FBS
MDA-MB-453	Luminal	Her2+	ATCC	DMEM+10% FBS
MDA-MB-468	Basal	TN	ATCC	DMEM+10% FBS
MFM-223	Luminal	ER+/PR+	DSMZ	DMEM+10% FBS
MT-3	Basal	TN	DSMZ	RPMI+10% FBS
SK-BR-3	Luminal	Her2+	ATCC	RPMI+10% FBS
T47D	Luminal	ER+/PR+	ATCC	RPMI+10% FBS
UACC-812	Luminal	Her2+	ATCC	DMEM+10% FBS
UACC-893	Luminal	Her2+	ATCC	DMEM+10% FBS
ZR-75-1	Luminal	ER+/PR+	ATCC	RPMI+10% FBS
ZR-75-30	Luminal	Her2+	ATCC	RPMI+10% FBS

ATCC = American Type Culture Collection; DMEM = Dulbecco's Modified Eagle's Medium; DSMZ = Deutsche Sammlung von. Mikroorganismen und Zellkulturen; ER = estrogen receptor; FBS = fetal bovine serum; HER2 = human epidermal growth factor receptor 2; NCI = National Cancer Institute; PR = progesterone receptor; TN = triple negative breast cancer: ER-, PR-, and HER2-.

[00184] **Experimental Procedures.** All breast cancer cell lines were maintained and tested in the culture media indicated in Table 1. The seeding density for each cell line was optimized to ensure assay linearity in 384-well plates. Increasing concentrations of compound were spotted via an acoustic dispenser (EDC ATS-100) into an empty 384-well plate. Compound was spotted in a 10-point serial dilution fashion (3-fold dilution) in duplicate within the plate. The dimethyl sulfoxide

(DMSO) concentration was kept constant for a final assay concentration of 0.1% DMSO. Plates were replicated for use against different cell lines and testing periods. After compound plate replication, all plates were sealed (Agilent ThermoLoc) and stored at -20 °C for up to 1 month. When ready for testing, plates were removed from the freezer, thawed, and unsealed just prior to the addition of the test cell. Prior to testing, cells were grown and expanded in culture flasks to provide sufficient amounts of starting material. Cells were then diluted to their desired densities and added directly to the compound-spotted 384-well plates. Cells were allowed to grow for 96 hours at 37 °C/5% CO_2. At the time of setup (t_0), initial cell number was assessed via a viability assay (Cell Titer-Glo) and read for luminescence. After 96 hours, viability of compound-treated cells was assessed via Cell Titer-Glo and read for luminescence.

[00185] Cell lines were assayed for growth inhibition by the Pyrrolopyrimidine Compounds for at least two independent tests. To ensure a comparable compound response throughout the assay period to complete all 49 cell lines, a control cell line (A549) was included in each of the assays. All data was normalized and represented as a percentage of the DMSO-treated control cells. Results were then expressed as an IC_{50} (Table 2). In addition, GI_{50} was calculated (Table 3).

[00186] All statistical analyses were implemented using R software (R Development Core Team, 2009).

[00187] **Determination of Inhibitory Concentration and Growth Inhibition (IC_{50} and GI_{50}).** IC_{50} is the concentration of the compound when Y = 50% of DMSO control. GI_{50} is the concentration of the compound when Y = $(YMax+Yt_0)/2$. All growth inhibition curves were processed and evaluated using Activity Base XE (IDBS).

[00188] **Table 2.** Growth Inhibition IC_{50} (μM)

Cell Line	Cmpd 79	Cmpd 101	Cmpd 125	Cmpd 38	Cmpd 152	Cmpd 3
AU565	0.019	0.213	0.021	0.038	0.047	1.099
BT-20	0.053	0.897	0.044	0.049	0.094	0.608
BT-474	0.358	10.000	0.595	10.000	5.423	16.345
BT-483	10.000	10.000	3.402	10.000	10.000	10.000

Cell Line	Cmpd 79	Cmpd 101	Cmpd 125	Cmpd 38	Cmpd 152	Cmpd 3
BT-549	0.013	0.292	0.066	0.051	0.079	0.180
CAL-120	0.592	10.000	0.272	10.000	4.638	10.000
CAL-148	0.003	0.074	0.168	0.065	0.069	
CAL-51	0.001	0.069	0.010	0.010	0.018	0.009
CAL-85-1	0.029	0.423	0.093	0.052	0.087	0.076
CAMA-1	10.000	10.000	0.763	10.000	10.000	10.706
DU4475	0.087	0.248	0.246	2.253	0.244	0.560
EFM-19	0.083	0.263	0.181	0.196	0.221	0.730
EFM-192A	2.085	10.000	1.279	10.000	5.042	10.000
EVSA-T	0.311	9.438	0.206	10.000	1.720	
HCC1143	0.308	0.685	0.481	0.579	0.711	17.483
HCC1187	0.002	0.119	0.031	0.042	0.066	0.881
HCC1419	10.000	10.000	2.511	10.000	10.000	
HCC1428	0.523	8.149	0.472	10.000	0.945	4.967
HCC1500	10.000	10.000	2.279	10.000	10.000	13.857
HCC1569	0.170	0.327	0.408	0.288	1.037	5.434
HCC1806	0.001	0.062	0.011	0.009	0.022	
HCC1937	0.695	10.000	0.311	10.000	5.646	10.000
HCC1954	0.016	0.258	0.068	0.039	0.102	0.482
HCC202	0.216	2.104	0.190	3.072	0.462	15.961
HCC2157						0.120
HCC38	0.001	0.052	0.012	0.011	0.021	0.047
HCC70	0.047	6.705	0.268	1.300	1.023	1.950
HDQ-P1	0.128	1.775	0.083	0.326	0.204	
HS578T	0.012	0.221	0.041	0.052	0.059	0.183
JIMT-1	5.336	9.074	0.165	0.111	0.215	
KPL-1	0.429	6.464	0.064	5.202	0.318	0.693
MB157	0.351	9.404	0.419	10.000	5.318	
MCF10A						17.449
MCF12A						3.151
MCF7	0.002	0.079	0.012	0.012	0.025	0.170
MDA-MB-134-VI	10.000	10.000	3.168	10.000	10.000	1.386

Cell Line	Cmpd 79	Cmpd 101	Cmpd 125	Cmpd 38	Cmpd 152	Cmpd 3
MDA-MB-157	1.636	10.000	0.631	6.290	10.000	0.695
MDA-MB-175-VII	10.000	10.000	2.843	10.000	10.000	8.497
MDA-MB-231	0.004	0.135	0.031	0.024	0.054	0.038
MDA-MB-361	2.830	10.000	1.472	10.000	10.000	18.751
MDA-MB-415	10.000	10.000	5.512	10.000	10.000	13.454
MDA-MB-436	1.108	4.194	0.510	7.821	0.718	2.100
MDA-MB-453	0.316	10.000	0.668	10.000	0.443	2.788
MDA-MB-468	0.001	0.096	0.024	0.027	0.057	0.032
MFM-223	0.355	0.984	0.172	1.879	0.429	
MT-3	10.000	10.000	8.500	10.000	10.000	
SK-BR-3	0.323	0.570	0.272	0.578	0.417	3.688
T47D	0.419	10.000	0.336	1.651	0.715	0.418
UACC-812	4.375	8.030	0.296	10.000	0.888	1.794
UACC-893	10.000	10.000	0.787	10.000	1.833	
ZR-75-1	10.000	10.000	3.314	10.000	10.000	6.386
ZR-75-30	1.268	3.413	0.715	10.000	1.576	30.000

[00189] **Table 3**. Growth inhibition GI_{50} (μM)

Cell Line	Cmpd 79	Cmpd 101	Cmpd 125	Cmpd 38	Cmpd 152	Cmpd 3
AU565	0.005	0.100	0.016	0.011	0.024	0.426
BT-20	0.019	0.553	0.028	0.028	0.057	0.289
BT-474	0.106	7.373	10.000	0.202	0.645	6.016
BT-483	n/a	n/a	n/a	n/a	n/a	0.704
BT-549	0.006	0.166	0.034	0.043	0.055	0.085
CAL-120	0.521	10.000	10.000	0.245	3.462	10.000
CAL-148	0.002	0.048	0.047	0.060	0.052	
CAL-51	0.001	0.059	0.009	0.009	0.016	0.008
CAL-85-1	0.014	0.218	0.029	0.061	0.055	0.025
CAMA-1	1.066	0.628	0.590	0.261	0.308	4.895

Cell Line	Cmpd 79	Cmpd 101	Cmpd 125	Cmpd 38	Cmpd 152	Cmpd 3
DU4475	0.004	0.046	0.038	0.058	0.059	0.082
EFM-19	0.006	0.051	0.035	0.047	0.065	0.067
EFM-192A	0.309	0.451	0.294	0.424	0.411	10.000
EVSA-T	0.121	6.665	6.000	0.130	0.557	
HCC1143	0.093	0.325	0.215	0.275	0.374	0.286
HCC1187	0.002	0.083	0.027	0.021	0.044	0.470
HCC1419	1.684	6.162	10.000	1.008	1.491	
HCC1428	0.215	0.516	0.326	0.206	0.288	1.086
HCC1500	0.058	0.090	0.103	0.112	0.103	0.053
HCC1569	0.036	0.116	0.088	0.140	0.102	0.073
HCC1806	0.001	0.057	0.008	0.010	0.020	
HCC1937	0.245	8.128	6.376	0.161	0.426	7.460
HCC1954	0.007	0.159	0.027	0.041	0.061	0.131
HCC202	0.009	0.052	0.028	0.018	0.044	15.026
HCC2157						0.024
HCC38	0.001	0.040	0.009	0.010	0.017	0.017
HCC70	0.005	0.128	0.047	0.080	0.086	0.442
HDQ-P1	0.037	0.890	0.106	0.046	0.108	
HS578T	0.010	0.203	0.047	0.038	0.055	0.104
JIMT-1	2.098	2.498	0.061	0.116	0.154	
KPL-1	0.136	2.884	0.126	0.034	0.108	0.245
MCF10A						0.426
MCF12A						0.486
MB157	0.026	0.425	0.116	0.067	0.123	
MCF7	0.001	0.070	0.011	0.010	0.021	0.124
MDA-MB-134-VI	n/a	n/a	n/a	n/a	n/a	0.874
MDA-MB-157	0.018	5.117	0.114	0.176	0.110	0.225
MDA-MB-175-VII	0.700	0.534	5.285	0.523	1.087	0.400
MDA-MB-231	0.003	0.104	0.019	0.022	0.041	0.022
MDA-MB-361	0.043	0.110	0.091	0.231	0.143	5.481

Cell Line	Cmpd 79	Cmpd 101	Cmpd 125	Cmpd 38	Cmpd 152	Cmpd 3
MDA-MB-415	10.000	9.995	10.000	0.441	10.000	11.707
MDA-MB-436	0.433	1.020	0.999	0.289	0.327	1.382
MDA-MB-453	0.212	5.387	10.000	0.475	0.390	0.799
MDA-MB-468	0.001	0.083	0.023	0.020	0.049	0.027
MFM-223	0.009	0.050	0.043	0.035	0.058	
MT-3	1.093	1.117	5.757	1.659	10.000	
SK-BR-3	0.051	0.102	0.081	0.082	0.124	1.181
T47D	0.040	0.386	0.081	0.106	0.140	0.162
UACC-812	0.369	0.748	0.319	0.110	0.201	0.842
UACC-893	n/a	n/a	n/a	n/a	n/a	
ZR-75-1	0.002	0.039	0.032	0.050	0.062	1.136
ZR-75-30	n/a	n/a	n/a	n/a	n/a	11.619

n/a: not applicable

[00190] **Conclusions**. As can be seen from Tables 2 and 3, Pyrrolopyrimidine Compounds inhibited breast cancer cell line growth, as measured by IC_{50} and GI_{50}. Cell proliferation inhibition was shown in TNBC, as well as ER+/PR+ and Her2+, to variying degrees.

[00191] **Non-small cell lung cancer cell line growth inhibition**. Sixteen non small cell lung cancer (NSCLC) cell lines were purchased from the American Tissue Culture Collection and maintained in growth media consisting of 90% RPMI1640 (Invitrogen) and 10% fetal bovine serum (Hyclone). All cells were cultured at 37 °C in 95% air and 5% CO_2. Cells were plated at optimal density for each cell line (see Table 5) per well in a 96-well plate in 100 μL of growth media. After overnight culture, compound stock solutions (30 mM) were diluted serially in DMSO, further diluted in growth media, and was added to each well as a 10x concentrated solution in a volume of 11 μL, mixed, and allowed to incubate with cells. The compound vehicle (DMSO) was maintained at a final concentration of 0.2% in all wells. After 72 hrs, 100 μL of Cell Titer Glo solution (Promega) were added to each well of the 96-well plate. The plate was placed on a shaker for 2 minutes. After 10 minutes incubation, luminescence signal was detected with

Envision microplate reader (Perkin Elmer). The IC_{50} values were calculated as the concentration of compound at which the level of luminescence signal was reduced to 50% of the signal window. Table 4 shows the results for Compound 3. Compounds show or will show an IC_{50} value ranging from 0.01 - 30 μM in this assay.

[00192] **Table 4**. Growth Inhibition IC_{50} Values and Growth Conditions

Cell Line	Plating Density	Average IC_{50} (μM)	SD
H1734	16000	0.91	0.59
H1838	12000	16.11	19.65
H2228	20000	1.58	0.41
H441	16000	2.10	0.32
H1437	12000	0.39	0.33
Hop62	2800	0.05	N/A
H1650	8000	0.62	0.02
HOP92	6000	1.27	0.62
H520	32000	1.45	0.18
H1299	2800	0.36	0.34
H2291	16000	16.29	19.39
H1563	6000	1.77	0.09
SK-LU-1	5000	0.83	0.10
SW1573	5000	0.96	0.23
A549	2500	0.05	0.04
H460	1500	0.04	0.01

[00193] **Conclusion.** Pyrrolopyrimidine Compounds demonstrated potent growth inhibition over a panel of non small cell lung cancer cell (NSCLC) lines profiled, as shown in Table 4. The majority of NSCLC lines (14 out of 16) are sensitive to growth inhibition by Pyrrolopyrimidine Compounds (for example, Compound 3) with a IC_{50} values ≤ 2 μM.

[00194] **Multiplexed Cytotoxicity Assay.** Cells were grown in RPMI1640, 10% FBS, 2 mM L-alanyl-L-Glutamine, 1 mM Na pyruvate or a special medium in a humidified atmosphere of 5% CO_2 at 37 °C. Cells were seeded into 384-well

plates and incubated in a humidified atmosphere of 5% CO_2 at 37 °C. Compounds were added 24 hours post cell seeding. At the same time, a time zero untreated cell plate was generated. After a 72 hour incubation period, cells were fixed and stained with fluorescently labeled antibodies and nuclear dye to allow visualization of nuclei, apoptotic cells and mitotic cells. Apoptotic cells were detected using an anti-active caspase-3 antibody. Mitotic cells were detected using an anti phospho-histone-3 antibody. Compounds were serially diluted 3.16-fold and assayed over 10 concentrations in a final assay concentration of 0.1% DMSO from the highest test concentration of 10 μM. Automated fluorescence microscopy was carried out using a GE Healthcare IN Cell Analyzer 1000, and images were collected with a 4X objective.

[00195] **Data Analysis.** Twelve bit tiff images were acquired using the InCell Analyzer 1000 3.2 and analyzed with Developer Toolbox 1.6 software. Cell proliferation was measured by the signal intensity of the incorporated nuclear dye. Results for Compound 38 are shown in Table 6. The cell proliferation assay output is referred to as the relative cell count. To determine the cell proliferation end point, the cell proliferation data output is transformed to percentage of control (POC) using the following formula:

POC = relative cell count (compound wells) / relative cell count (vehicle wells) x 100

[00196] Relative cell count IC_{50} is the test compound concentration at 50% of maximal possible response relative to the DMSO control. GI_{50} is the concentration needed to reduce the observed growth by half. This is the concentration that inhibits the growth to the level midway between growth in untreated cells and the number of cells seeded in the well (Time zero value). The IC_{50} values were calculated using nonlinear regression to fit data to a sigmoidal 4 point, 4 parameter One-Site dose response model, where :

$$y\ (fit) = A + [(B - A)/(1 + ((C/x)\ \hat{}\ D))].$$

[00197] The activated caspase-3 marker labels cells from early to late stage apoptosis. The output is shown as a fold increase of apoptotic cells over vehicle background normalized to the relative cell count in each well. Concentrations of

test compound that cause a 5-fold induction in the caspase-3 signal (Cal_X5) indicate significant apoptosis induction. The maximal induction of caspase 3 by compound in comparison with DMSO control is reported as Max_Fold_Change.

[00198] **Table 5**. Cell lines

Cell line	Tumor Type	Subtype	Classification
5637	Bladder		
639-V	Bladder		
647-V	Bladder		
BFTC-905	Bladder		
HT1197	Bladder		
HT1376	Bladder		
J82	Bladder		
SCaBER	Bladder		
T24	Bladder		
TCCSUP	Bladder		
UM-UC-3	Bladder		
AU565	Breast	Luminal	Luminal
BT-20	Breast	Basal	Basal
BT-474	Breast	Luminal	Luminal
BT-549	Breast	Basal	Basal
CAMA-1	Breast	Luminal	Luminal
EFM-19	Breast	Luminal	Luminal
HS578T	Breast	Basal	Basal
KPL-1	Breast	Luminal	Luminal
MCF7	Breast	Luminal	Luminal
MDA-MB-231	Breast	Basal	Basal
MDA-MB-436	Breast	Basal	Basal
MDA-MB-453	Breast	Luminal	Luminal
MDA-MB-468	Breast	Basal	Basal
MT-3	Breast	Basal	Basal
SK-BR-3	Breast	Luminal	Luminal
T47D	Breast	Luminal	Luminal
A172	CNS	Glioblastoma	Glioblastoma
BE(2)C	CNS		
CCF-STTG1	CNS	Astrocytoma	Astrocytoma
CHP-212	CNS		
D-283MED	CNS		
Daoy	CNS	Medulloblastoma	Medulloblastoma
DBTRG-05MG	CNS	Glioblastoma	Glioblastoma
DK-MG	CNS	Glioblastoma	Glioblastoma

Cell line	Tumor Type	Subtype	Classification
H4	CNS	Neuroglioma	Neuroglioma
MC-IXC	CNS		
SK-N-AS	CNS		
SK-N-DZ	CNS		
SK-N-FI	CNS		
SNB-19	CNS	Glioblastoma	Glioblastoma
SW1088	CNS	Astrocytoma	Astrocytoma
SW1783	CNS	Astrocytoma	Astrocytoma
T98G	CNS	Glioblastoma	Glioblastoma
U-138MG	CNS	Glioblastoma	Glioblastoma
U-87-MG	CNS	Astrocytoma	Astrocytoma
COLO-201	Colon	Large Intestine	
COLO-205	Colon	Large Intestine	
COLO-320DM	Colon	Large Intestine	
COLO-320-HSR	Colon	Large Intestine	
DLD-1	Colon	Large Intestine	
HCT-116	Colon	Large Intestine	
HCT-15	Colon	Large Intestine	
HCT-8	Colon	Large Intestine	
HT29	Colon	Large Intestine	
LS-1034	Colon	Large Intestine	
LS-174T	Colon	Large Intestine	
NCI-H508	Colon	Large Intestine	
NCI-H747	Colon	Large Intestine	
RKO	Colon	Large Intestine	
RKO-AS45-1	Colon	Large Intestine	
RKO-E6	Colon	Large Intestine	
SW1417	Colon	Large Intestine	
SW403	Colon	Large Intestine	
SW48	Colon	Large Intestine	
SW480	Colon	Large Intestine	
SW620	Colon	Large Intestine	
SW837	Colon	Large Intestine	
SW948	Colon	Large Intestine	
WiDr	Colon	Large Intestine	
AGS	Colon/ GI	Stomach	
HS746T	Colon/ GI	Stomach	
KATOIII	Colon/ GI	Stomach	
OE19	Colon/ GI	Oesophagus	
SNU-1	Colon/ GI	Stomach	

Cell line	Tumor Type	Subtype	Classification
SNU-16	Colon/ GI	Stomach	
SNU-5	Colon/ GI	Stomach	
SW1463	Colon	Rectum	
BHT-101	Endocrine	Thyroid	
CAL-62	Endocrine	Thyroid	
CGTH-W-1	Endocrine	Thyroid	
NCI-H295	Endocrine	Adrenal cortex	
SW13	Endocrine	Adrenal gland	
SW579	Endocrine	Thyroid	
Y79	Eye	Retinoblastoma	
AN3 CA	Female GU	Uterus	
BeWo	Female GU	Placenta	
C-33-A	Female GU	Cervix	
C4-1	Female GU	Cervix	
C4-2	Female GU	Cervix	
Caov-3	Female GU	Ovary	
DoTc2-4510	Female GU	Cervix	
ES-2	Female GU	Ovary	
HEC-1-A	Female GU	Uterus	
HeLa	Female GU	Cervix	
HT3	Female GU	Cervix	
JAR	Female GU	Placenta	
JEG-3	Female GU	Placenta	
KLE	Female GU	Uterus	
Ovcar-3	Female GU	Ovary	
RL95-2	Female GU	Uterus	
SiHa	Female GU	Cervix	
SK-OV-3	Female GU	Ovary	
SW954	Female GU	Vulva	
SW962	Female GU	Vulva	
CAL-27	Head and Neck	Tongue	
Detroit562	Head and Neck	Pharynx	
FADU	Head and Neck	Pharynx	
OE21	Head and Neck		
OE33	Head and Neck	Oesophagus	
SCC-25	Head and Neck	Tongue	
SCC-4	Head and Neck	Tongue	
SCC-9	Head and Neck	Tongue	
L428	Hodgkin's lymphoma		

Cell line	Tumor Type	Subtype	Classification
RPMI-6666	Hodgkin's lymphoma		
769-P	Kidney		
786-0	Kidney		
A498	Kidney		
ACHN	Kidney		
CAKI-1	Kidney		
CAKI-2	Kidney		
G-401	kidney		
G-402	Kidney		
SK-NEP-1	Kidney		
ARH-77	Myeloma	Plasma cell	
BV-173	Leukemia	CML	
CCRF-CEM	Leukemia	myelomonoblastic	T-ALL
CEM-C1	Leukemia	ALL	
CML-T1	Leukemia	CML	
EM-2	Leukemia	CML	
HEL-92-1-7	Leukemia	Erythroleukemia	
J-RT3-T3-5	Leukemia	Acute T cell	
Jurkat	Leukemia	Acute T cell	
K-562	Leukemia	CML	CML
MEG-01	Leukemia	CML	
MOLT-16	Leukemia	ALL	
MOLT-3	Leukemia	ALL	
MV-4-11	Leukemia	B myelomonocytic	
MX1	Leukemia	APML	
NALM-6	Leukemia	B cell precursor	
THP-1	Leukemia	AML	AML
HepG2	Liver		
HLE	Liver		
HLF	Liver		
HuCCT1	Liver		
HUH-6-clone5	Liver		
OCUG-1	Liver		
SNU-423	Liver		
A427	Lung		
A549	Lung		NSCLC
Calu-1	Lung	SQCC	NSCLC
Calu-6	Lung	Anaplastic	NSCLC
ChaGo-K-1	Lung	Bronchogenic	

Cell line	Tumor Type	Subtype	Classification
COR-L105	Lung		
COR-L23	Lung		NSCLC
DMS-114	Lung	SCLC	SCLC
DMS-273	Lung		SCLC
DMS-53	Lung	SCLC	SCLC
NCI-H292	Lung		Mucoepidermoid
NCI-H441	Lung	NSCLC	NSCLC
NCI-H446	Lung		SCLC
NCI-H460	Lung		NSCLC
NCI-H520	Lung	NSCLC	NSCLC
NCI-H596	Lung	NSCLC	NSCLC
NCI-H661	Lung		NSCLC
NCI-H69	Lung		SCLC
SHP-77	Lung		SCLC
SK-MES-1	Lung	SQCC	SQCC
SW900	Lung	SQCC	NSCLC
Wi38	Lung	Normal fibroblasts	Normal Fibroblasts
BC-1	Lymphoma		
CRO-AP2	Lymphoma	B cell	
Daudi	Lymphoma	BL	BL
DB	Lymphoma	Large cell	DLBCL
DOHH-2	Lymphoma	B cell	FL
EB-3	Lymphoma	BL	
HT	Lymphoma	Diffuse mixed	DLBCL
MHH-PREB-1	Lymphoma	B cell	Lymphoblastic
Raji	Lymphoma	BL	BL
Ramos RA1	Lymphoma	BL	BL
SKO-007	Lymphoma	B lymphocyte	
SR	Lymphoma	Large cell immunoblastic	Large
ST486	Lymphoma	BL	
RPMI-8226	Myeloma	Plasmacytoma; myeloma	B-cell
U266B1	Myeloma	Myeloma	B-cell
AsPC-1	Pancreas		
BxPC-3	Pancreas		
CAPAN-1	Pancreas		
CAPAN-2	Pancreas		
CFPAC-1	Pancreas		
HPAF-II	Pancreas		
HS766T	Pancreas		

Cell line	Tumor Type	Subtype	Classification
HuP-T4	Pancreas		
MIA-PaCa-2	Pancreas		
PANC-1	Pancreas		
SU.86.86	Pancreas		
YAPC	Pancreas		
22RV1	Prostate		
BM-1604	Prostate		
BPH-1	Prostate		
BPH-1	Prostate		
BPH-1	Prostate		
DU-145	Prostate		
LNCaP	Prostate		
PC-3	Prostate		
A101D	Skin	Melanoma	
A375	Skin	Melanoma	
A431	Skin	SQCC	
A7	Skin	Melanoma	
C32	Skin	Melanoma	
C32TG	Skin	Melanoma	
CHL-1	Skin	Melanoma	
COLO-829	Skin	Melanoma	
HMCB	Skin	Melanoma	
HS294T	Skin	Melanoma	
HS695T	Skin	Melanoma	
MALME-3M	Skin	Melanoma	
Mewo	Skin	Melanoma	
RPMI-7951	Skin	Melanoma	
SH-4	Skin	Melanoma	
SK-MEL-1	Skin	Melanoma	
SK-MEL-28	Skin	Melanoma	
SK-MEL-3	Skin	Melanoma	
A204	Soft Tissue	Rhabdomyosarcoma	
A673	Soft Tissue	Sarcoma	
HOS	Bone	Sarcoma	
HT1080	Soft Tissue	Sarcoma	
KHOS-240S	Bone	Osteosarcoma	
MES-SA	Soft Tissue	Sarcoma	
MG-63	Bone	Sarcoma	
RD	Soft Tissue	Sarcoma	
Saos-2	Bone	Sarcoma	

Cell line	Tumor Type	Subtype	Classification
SJRH30	Soft Tissue	Rhabdomyosarcoma	
SJSA-1	Bone	Osteosarcoma	
SK-LMS-1	Soft Tissue	Sarcoma	
SK-UT-1	Soft Tissue	Sarcoma	
SW1353	Bone	Sarcoma	
SW684	Soft Tissue	Sarcoma	
SW872	Soft Tissue	Sarcoma	
SW982	Soft Tissue	Sarcoma	
TE 381.T	Soft Tissue	Rhabdomyosarcoma	
U-2-OS	Bone	Sarcoma	

[00199] **Table 6**. Cell line screening results

Cell Line	GI_{50} (μM)	IC_{50} (μM)	Max. Fold. Change	Cal_X
5637	0.0905	0.0946	51.0	0.1026
639-V	0.0855	0.0904	13.5	0.0540
647-V	0.1022	0.1177	12.4	0.0757
BFTC-905	0.0626	0.0649	22.1	0.0428
HT1197	1.7581	5.7255	5.5	8.8398
HT1376	0.9204	1.9883	5.3	9.1659
J82	1.0029	10.0000	4.9	10.0000
SCaBER	0.0894	0.0927	16.3	0.0581
T24	0.0941	0.0960	68.3	0.0008
TCCSUP	0.0657	0.0958	5.2	0.0974
UM-UC-3	0.1021	0.1314	70.6	0.0372
AU565	0.4598	1.2290	33.8	0.2656
BT-20	0.4591	1.2935	4.4	10.0000
BT-474	0.0837	4.3719	20.0	1.1580
BT-549	1.7310	4.8054	5.6	0.2720
CAMA-1	0.4279	1.1890	7.5	5.2170
EFM-19	0.0618	0.1036	32.5	0.0686
HS578T	10.0000	10.0000	3.8	10.0000
KPL-1	0.8217	2.4194	67.2	0.0888
MCF7	0.1287	0.8192	26.2	0.0625
MDA-MB-231	0.3690	0.7750	5.6	0.2184
MDA-MB-436	0.8881	1.8798	1.8	10.0000
MDA-MB-453	0.0810	0.1111	9.7	0.1290
MDA-MB-468	0.0928	0.1017	14.1	0.1679
MT-3	0.0395	0.0478	7.3	0.0696

Cell Line	GI_{50} (μM)	IC_{50} (μM)	Max. Fold. Change	Cal_X
SK-BR-3	0.2868	1.3152	4.4	10.0000
T47D	0.2919	1.1604	10.4	4.9403
A172	0.0457	10.0000	11.9	0.0521
BE(2)C	0.0796	0.0893	29.6	0.0468
CCF-STTG1	4.4267	5.6280	5.0	10.0000
CHP-212	0.0278	0.0364	11.4	0.0458
D-283MED	0.0584	0.0654	26.0	0.0580
Daoy	0.0887	0.1043	13.1	0.0849
DBTRG-05MG	4.2986	10.0000	4.4	10.0000
DK-MG	10.0000	10.0000	9.2	5.4460
H4	0.0718	0.0736	44.9	0.0422
MC-IXC	0.0471	0.0539	51.6	0.0439
SK-N-AS	0.4244	1.5168	14.5	0.0515
SK-N-DZ	0.1618	0.2077	34.8	0.2178
SK-N-FI	2.2181	9.5496	3.2	10.0000
SNB-19	10.0000	10.0000	1.6	10.0000
SW1088	0.0469	10.0000	13.1	0.0560
SW1783	10.0000	10.0000	3.1	10.0000
T98G	2.6239	10.0000	61.2	0.0426
U-138MG	10.0000	10.0000	4.8	10.0000
U-87-MG	0.1044	10.0000	11.2	0.0659
COLO-201	0.1052	0.1272	8.2	0.3152
COLO-205	0.0824	0.0838	182.5	0.0440
COLO-320DM	0.0927	0.1254	75.6	0.0723
COLO-320-HSR	0.1034	0.1261	37.3	0.0717
DLD-1	0.0473	0.0496	45.1	0.0338
HCT-116	0.0479	0.0488	37.9	0.0385
HCT-15	0.0531	0.0559	58.9	0.0377
HCT-8	0.0298	0.0312	282.4	0.0138
HT29	0.1156	0.1265	35.8	0.0632
LS-1034	0.1033	0.1061	6.7	0.2283
LS-174T	0.0665	0.0914	16.1	0.0479
NCI-H508	0.2291	0.5928	30.5	0.0649
NCI-H747	0.3733	1.6297	3.3	10.0000
RKO	0.0504	0.0526	35.1	0.0394
RKO-AS45-1	0.0415	0.0445	24.5	0.0371
RKO-E6	0.0513	0.0527	14.4	0.0490
SW1417	4.5665	10.0000	6.5	6.7147
SW403	0.2573	0.2969	12.2	0.4506

Cell Line	GI_{50} (μM)	IC_{50} (μM)	Max. Fold. Change	Cal_X
SW48	0.0459	0.0497	12.0	0.0623
SW480	1.0169	2.1065	25.3	3.9577
SW620	0.0572	0.0636	20.3	0.0559
SW837	0.3301	0.8362	34.9	0.0815
SW948	0.2469	0.2875	26.6	0.2257
WiDr	0.3583	0.6266	22.3	0.1700
AGS	0.0308	0.0328	12.1	0.0312
HS746T	10.0000	10.0000	2.6	10.0000
KATOIII	1.0051	1.9453	31.3	0.0715
OE19	0.0575	0.0636	33.6	0.0524
SNU-1	0.2788	0.4798	12.6	0.0473
SNU-16	0.1487	0.2269	3.9	10.0000
SNU-5	5.9807	10.0000	2.3	10.0000
SW1463	5.0067	10.0000	4.3	10.0000
BHT-101	0.3120	0.4093	64.6	0.1877
CAL-62	0.0972	0.0987	35.2	0.0450
CGTH-W-1	0.1027	0.1096	32.2	0.0429
NCI-H295	10.0000	10.0000	3.1	10.0000
SW13	0.1621	0.2426	19.3	0.0657
SW579	2.6704	10.0000	6.6	0.0772
Y79	0.1843	0.2576	6.4	1.6819
AN3 CA	0.5117	1.1664	14.1	3.7957
BeWo	0.5064	0.7466	5.2	9.4738
C-33-A	0.0745	0.1220	33.7	0.3941
C4-1	0.0804	0.1144	20.8	0.0827
C4-2	0.2487	0.4270	16.3	1.1314
Caov-3	0.0666	0.1061	4.0	10.0000
DoTc2-4510	0.3552	0.7875	12.9	0.7698
ES-2	0.0915	0.0936	33.3	0.0487
HEC-1-A	0.1656	0.4534	4.3	10.0000
HeLa	0.3882	0.6010	6.5	0.8340
HT3	1.3798	2.5017	6.2	7.0920
JAR	0.0495	0.0519	24.8	0.0576
JEG-3	0.0859	0.0954	15.8	0.0726
KLE	2.3130	6.4698	15.4	4.5020
Ovcar-3	0.4434	0.8643	135.6	0.7343
RL95-2	0.0455	0.0649	4.0	10.0000
SiHa	10.0000	10.0000	6.0	8.3919
SK-OV-3	10.0000	10.0000	8.0	1.8718

Cell Line	GI_{50} (μM)	IC_{50} (μM)	Max. Fold. Change	Cal_X
SW954	0.0866	0.0887	11.0	0.1179
SW962	10.0000	10.0000	3.6	10.0000
CAL-27	0.0538	0.0567	15.5	0.0493
Detroit562	0.0471	0.0537	22.6	0.0553
FADU	0.1223	0.1661	8.0	0.0792
OE21	0.0651	0.0682	12.3	0.0738
OE33	0.1965	0.3052	8.8	0.2006
SCC-25	0.0673	0.0731	19.5	0.0894
SCC-4	8.3155	10.0000	3.0	10.0000
SCC-9	0.2650	0.5288	17.0	0.2767
L428	3.2804	4.5993	4.8	10.0000
RPMI-6666	0.1481	0.1535	7.8	0.2252
769-P	0.2663	0.3597	4.9	10.0000
786-0	0.1115	0.1199	22.1	0.0690
A498	0.4915	1.3982	7.3	0.0728
ACHN	0.3960	0.8495	60.4	0.0460
CAKI-1	0.1284	10.0000	3.9	10.0000
CAKI-2	10.0000	10.0000	3.0	10.0000
G-401	0.0794	0.0817	12.7	0.7392
G-402	0.0378	0.0431	16.3	0.0566
SK-NEP-1	0.1270	0.1681	17.4	0.3116
ARH-77	0.0594	0.0618	26.4	0.0525
BV-173	0.0444	0.0454	29.4	0.0427
CCRF-CEM	0.0813	0.0819	16.6	0.0617
CEM-C1	0.4524	0.4805	18.3	0.0529
CML-T1	0.0689	0.0716	29.8	0.0430
EM-2	0.0903	0.0988	13.5	0.0766
HEL-92-1-7	0.5351	0.6301	20.7	1.1545
J-RT3-T3-5	0.0463	0.0534	13.4	0.0286
Jurkat	0.0501	0.0551	19.0	0.0460
K-562	2.6980	4.7723	13.7	0.6802
MEG-01	2.1931	3.8366	3.1	10.0000
MOLT-16	0.0383	0.0388	12.0	0.0798
MOLT-3	0.1187	0.4689	4.5	10.0000
MV-4-11	0.0906	0.0940	14.8	0.3032
MX1	0.0576	0.0589	44.7	0.0394
NALM-6	0.0547	0.0560	72.7	0.0359
THP-1	10.0000	10.0000	4.8	10.0000
HepG2	0.1366	0.2124	18.1	0.0853

Cell Line	GI_{50} (μM)	IC_{50} (μM)	Max. Fold. Change	Cal_X
HLE	0.1020	0.1067	4.5	10.0000
HLF	0.1232	0.1817	29.3	0.0430
HuCCT1	1.4582	2.6967	13.2	0.0503
HUH-6-clone5	0.1433	0.1756	31.2	0.1025
OCUG-1	1.2036	3.9346	11.5	0.2126
SNU-423	10.0000	10.0000	3.2	10.0000
A427	0.0794	0.1168	15.7	0.0238
A549	0.0528	0.0602	61.6	0.0287
Calu-1	2.9029	9.0678	11.7	0.1295
Calu-6	4.6564	8.1661	5.2	8.9974
ChaGo-K-1	0.1465	0.3720	4.4	10.0000
COR-L105	0.1447	0.5875	4.7	10.0000
COR-L23	0.1414	0.1531	7.2	0.1411
DMS-114	1.3925	4.6519	4.0	10.0000
DMS-273	0.0674	0.0690	15.9	0.0568
DMS-53	1.7366	6.6828	48.7	0.2879
NCI-H292	0.0817	0.0921	30.5	0.0722
NCI-H441	0.8207	3.0855	4.2	10.0000
NCI-H446	0.3539	0.4244	6.5	1.9460
NCI-H460	0.0870	0.0877	98.0	0.0407
NCI-H520	0.3189	0.4497	7.9	1.2581
NCI-H596	0.2824	10.0000	2.2	10.0000
NCI-H661	1.7213	4.2789	10.7	0.0680
NCI-H69	NaN	NaN	3.0	10.0000
SHP-77	0.1818	0.2783	6.9	1.9384
SK-MES-1	0.4135	0.9021	18.5	0.1941
SW900	10.0000	10.0000	2.1	10.0000
Wi38	0.6851	1.8760	6.8	0.0772
BC-1	0.0621	0.0655	60.2	0.0548
CRO-AP2	0.0458	0.0494	87.5	0.0602
Daudi	0.0953	0.0974	14.8	0.0573
DB	0.0758	0.0833	40.8	0.0742
DOHH-2	0.0677	0.0714	17.5	0.0971
EB-3	0.2738	0.4248	8.4	0.2986
HT	0.1784	0.2437	3.1	10.0000
MHH-PREB-1	0.0637	0.0653	44.2	0.0422
Raji	0.0511	0.0544	21.3	0.0504
RamosRA1	0.0871	0.0881	50.0	0.0617
SKO-007	0.9528	1.2076	10.7	2.0090

Cell Line	GI_{50} (μM)	IC_{50} (μM)	Max. Fold. Change	Cal_X
SR	0.0855	0.0867	33.0	0.0603
ST486	0.0361	0.0401	27.5	0.0584
RPMI-8226	0.1150	0.1836	13.8	0.5722
U266B1	0.1590	0.3756	7.6	4.1758
AsPC-1	1.5312	10.0000	6.9	5.2046
BxPC-3	0.0814	0.1361	8.8	0.0630
CAPAN-1	0.9358	2.4121	3.1	10.0000
CAPAN-2	0.2937	10.0000	28.8	0.0583
CFPAC-1	10.0000	10.0000	15.2	0.0568
HPAF-II	0.2492	0.3684	11.5	0.2588
HS766T	10.0000	10.0000	5.7	0.7781
HuP-T4	0.1092	0.1366	12.6	0.2143
MIA-PaCa-2	0.3260	0.5436	15.6	0.0639
PANC-1	3.3504	9.5585	3.4	10.0000
SU.86.86	0.8641	1.9177	17.9	0.0704
YAPC	0.8691	3.1871	51.2	0.0322
22RV1	0.1405	0.2485	39.2	0.0361
BM-1604	1.1194	2.0149	20.8	0.2011
BPH-1	0.1498	0.1669	7.5	0.2422
DU-145	0.0958	0.0991	394.0	0.0382
LNCaP	9.6042	10.0000	2.9	10.0000
PC-3	1.2048	2.3542	14.1	1.2528
A101D	0.3510	0.8607	18.1	0.1754
A375	0.0460	0.0475	38.5	0.0356
A431	0.0924	0.0986	13.5	0.1298
A7	0.1262	0.2490	9.0	0.0468
C32	1.1087	10.0000	13.0	1.9676
C32TG	0.8305	2.0288	15.1	0.2294
CHL-1	0.0972	0.1044	41.1	0.0180
COLO-829	2.0590	8.5007	6.8	0.7345
HMCB	0.0964	0.0988	20.4	0.0619
HS294T	0.0970	0.1178	16.5	0.0567
HS695T	0.7708	3.0838	18.4	3.0148
MALME-3M	1.6636	10.0000	1.8	10.0000
Mewo	10.0000	10.0000	4.5	10.0000
RPMI-7951	0.0999	0.1052	5.1	0.2834
SH-4	0.0565	0.3220	9.9	0.0396
SK-MEL-1	10.0000	10.0000	1.9	10.0000
SK-MEL-28	10.0000	10.0000	6.6	0.2632

Cell Line	GI_{50} (μM)	IC_{50} (μM)	Max. Fold. Change	Cal_X
SK-MEL-3	2.5742	10.0000	4.1	10.0000
A204	0.0579	0.1457	9.2	0.0629
A673	0.0560	0.0735	4.3	10.0000
HOS	0.0737	0.0756	85.6	0.0362
HT1080	0.0855	0.0899	17.5	0.0672
KHOS-240S	0.0991	0.1100	16.3	0.0789
MES-SA	0.0354	0.0379	47.3	0.0241
MG-63	2.0387	4.6830	7.5	0.4768
RD	0.4567	0.7541	26.7	0.1603
Saos-2	1.8273	4.5508	3.6	10.0000
SJRH30	0.5334	1.3424	6.9	0.0992
SJSA-1	10.0000	10.0000	89.2	0.0538
SK-LMS-1	4.4020	10.0000	4.5	10.0000
SK-UT-1	0.2891	0.9592	10.1	0.3581
SW1353	10.0000	10.0000	8.3	0.2769
SW684	10.0000	10.0000	3.0	10.0000
SW872	0.1001	0.1204	53.3	0.0551
SW982	3.6570	10.0000	2.7	10.0000
TE 381.T	4.8712	10.0000	6.8	0.2981
U-2-OS	0.0821	0.0887	35.6	0.0438

Note: NaN: variable data

[00200] **Conclusion**. As shown in Table 6 and Figures 1 and 2, Pyrrolopyrimidine Compounds (exemplified by Compound 38) showed anti-proliferative activity in a variety of cancers, comprising solid tumors (Figure 1), for example, cancers of the bladder, breast, CNS, colon, endocrine, female GU, head and neck, kidney, liver, lung, pancreas, prostate, skin, bone and soft-tissue, and hematological cancers (Figure 2), for example, lymphomas, leukemias and multiple myeloma.

[00201] **GBM cancer stem cell viability assay.** Five high grade glioblastoma-derived tumor cultures in defined serum-free medium that enriches the GBM-CSC tumor subfraction were established, as described previously [Mao P, *et al. Proc Nat Acad Sci* 2013; 110(21): 8644-9]. Clinical diagnoses and stem cell marker analyses were performed. The cancer stem cells (CSCs) (8311, 81611, 32612, 1912,and 52810), were plated in a 20 μL/well volume of serum-free growth medium at a density of 800 cells/well in a 384-well format. GBM CSCs were mechanically-dissociated by trituration prior to

counting and plating. As a normal cell control, 1200 HUVECs were plated in 20 μL per well of a 384-well plate in Endothelial Growth Media Microvascular-2. After 1 day of cultivation, 20 μL/well of respective fresh medium for each cell type was added and the cells were treated with Pyrrolopyrimidine Compounds at multiple concentrations or 0.04 μL DMSO for 3 days under 5% CO_2/37 °C culture conditions. After 3 days of compound treatment, cells were lysed through the addition of 30 μL of CellTiter-Glo (CTG) reagent to evaluate relative cell density. The plate was placed at room temperature for 30 minutes after which luminescent signal was monitored.

[00202] **Results.** Table 7 summarizes the GBM subtype affiliation of each GBM-CSC model utilized. The impact of Pyrrolopyrimidine Compounds on the growth of GBM-CSCs was tested under defined serum-free culture conditions by CTG. The concentration of compound that inhibited the cell growth by 50% was determined in those five models (data for Compound 38 is summarized in Figure 3). Pyrrolopyrimidine Compounds (exemplified by Compound 38) demonstrated potency against mesenchymal GBM CSCs with IC_{50}s in the range of 1-2 μM. This data also indicated that Pyrrolopyrimdine Compounds (as shown for Compound 38) were particularly potent against two GBM CSC sphere models derived from proneural subtype GBM patients with IC_{50} in the range of 50-190 nM.

[00203] **Table 7**. Characteristics of GBM-Cancer Stem Cells

Patient CSCs	Clinical Diagnosis	Subtype
8311	**GBM**	**Mesenchymal (Mes)**
52810	**GBM**	**Proneural (PN)**
81611	**GBM**	**PN/Relapse**
32612	**GBM**	**Mesenchymal (Mes)**
1912	**GBM**	**Proneural (PN)**

[00204] **Stem cell marker Oct-4 assay**. 1200 HUAECs were plated per well of a 384-well plate. After 1 day 8311 GBM CSCs were mechanically-dissociated by trituration and added at a density of 600 cells per well. The cells were allowed to co-culture for 1 day and then treated with various concentrations of

Pyrrolopyrimidine Compound or DMSO for 3 days in 5% CO_2 at 37 °C. After incubation with compound, 40 µL of 4% paraformaldehyde was added. Cell fixation was allowed to proceed at room temperature for 1 hour and each well was washed 5 times with a 50 µL volume of PBS. Each well was treated overnight at 4 °C with a 50 µL volume of PBS supplemented with 3% goat serum and 0.25% triton X-100. Cells were the incubated overnight at 4 °C with anti Oct4 and anti Tuj1 antibodies diluted 1:100 and 1:1000 respectively in PBS/3% goat serum/0.25% triton. Cells were washed 5 times with PBS/0.25% triton and incubated with AlexaFluor-labeled secondary antibodies for 3 hours at room temperature after which the wells were washed 5 times with PBS/0.25% Triton. Images of 4 randomly chosen fields were acquired using an EVOS Cell Imaging System at 10X magnification. Adobe Photoshop (Adobe Systems Incorporated) was used to process raw images, assign and merge channels. Representative images are shown in Figure 4.

[00205] **Results**. A defining property of stem cells is their capacity to generate differentiated progeny. GBM CSCs demonstrated the ability to undergo neuronal and astrocytic differentiation upon growth factor withdrawal or following exposure to BMP-4 [Pollard *et al Cell Stem Cell* 2009; 4(6):568-80]. We evaluated the impact of Pyrrolopyrimidine Compounds on 8311 glioma stem cells in a pathologically relevant GBM-CSC/HUAEC co-culture model. Endothelial cells are known to interact closely with self-renewal GBM-CSC and secret factors maintaining these cells in stem-cell like state [Calabrese *et al. Cancer cell* 2007;11(1):69-82]. In this assay, Oct 4 was used as stem cell marker and Tuj-1 was used as neuronal marker for GBM-CSC and differentiated neuronal cell populations, respectively. As shown in Figure 4, upon Pyrrolopyrimidine Compound treatment (as shown for Compound 38), the Oct4 positive GBM CSC population was decreased while the proportion of Tuj-1 positive neuronal cells was increased. This data indicates that Pyrrolopyrimidine Compounds can eliminate the Oct-4 positive cancer stem cell population and induce neuronal differentiation in the 8311/HUAEC co-culture model.

[00206] **Conclusions**. Pyrrolopyrimidine Compounds were shown to impair the proliferation of GBM CSC models. Five models isolated from primary GBM patient specimens, representative of mesenchymal and proneural GBM subclasses, were utilized

to test Pyrrolopyrimidine Compound activity upon GBM CSCs. Pyrrolopyrimidine Compounds (as exemplified by Compound 38) potently inhibited proliferation of proneural 52810 and 1912 cells with IC_{50} values of 0.048 and 0.19 μM, respectively. Pyrrolopyrimidine Compounds (exemplified by Compound 38) had less potency in the inhibition of mesenchymal models 8311 and 32612 cells with IC_{50} values of 1.6 and 1.8 μM, respectively. Furthermore, Pyrrolopyrimidine Compounds (exemplified by Compound 38) induced differentiation of GBM CSCs in the context of a HUAEC co-culture model. Hence, our data indicates that Pyrrolopyrimidine Compounds can both inhibit proliferation and induce neuronal differentiation of GBM CSCs.

ANIMAL MODELS

[00207] **Cancer xenograft model.** For xenograft model studies human cancer cell lines were injected into SCID (severe combined immunodeficiency) mice. Cancer cell lines were propagated in culture *in vitro*. Tumor bearing animals were generated by injecting precisely determined numbers of cells into mice. Following inoculation of animals, the tumors were allowed to grow to a certain size prior to randomization. The mice bearing xenograft tumors, typically ranging between 100 and 400 mm^3, were pooled together and randomized into various treatment groups. Primary tumorgrafts were propagated *in vivo*. Tumor fragments from donor mice were implanted into small numbers of mice for maintenance, or larger numbers of mice for study initiation. A typical efficacy study design involved administering one or more compounds at various dose levels to tumor-bearing mice. Additionally, reference chemotherapeutic agents (positive control) and negative controls were similarly administered and maintained. Routes of administration can include subcutaneous (SC), intraperitoneal (IP), intravenous (IV), intramuscular (IM) and oral (PO). Tumor measurements and body weights were taken over the course of the study and morbidity and mortality were recorded. Necropsy, histopathology, and PCR can also be performed to enhance understanding of disease and drug action.

[00208] Some of the typical human bladder cancer cell lines, for example transitional cell carcinoma, that were or can be used in the above xenograft models are: HT-1376, HT-1197, UMUC-3, KU-7, and KU-19-19 cell lines.

[00209] Some of the typical human breast cancer cell lines that were or can be used in the above xenograft models are: luminal-B type cell lines, for example BT-474, or ZR-75, and basal type cell lines, for example, MDA-MB-231, T47D, and Cal-51 cell lines.

[00210] Some of the typical human lung squamous cell carcinoma cell lines, that were or can be used in the above xenograft models are: SK-MES-1, NCI-H1703, HCC-15, and Calu-1 cell line.

[00211] Some of the typical human esophageal squamous carcinoma cell lines that were or can be used in the above xenograft models are: Kyse-140 and KYSE-510 cell lines.

[00212] Some of the typical human squamous cervical cancer cell lines that were or can be used in the above xenograft models are: A-431 and SiHa cell lines.

[00213] Some of the typical human squamous head and neck cancer cell lines that were or can be used in the above xenograft models are: FaDu and SCC-15 cell lines.

[00214] Some of the typical human leukemia cell lines that were or can be used in the above xenograft models are: CCRF-CEM and MOLT-4.

[00215] Some of the typical human lymphoma cell lines that were or can be used in the above xenograft models are: WSU-DLCL2 and OCI-Ly10.

[00216] Some of the typical human colorectal cancer (CRC) cell lines that were or can be used in the above xenograft models are: HCT-116, HT-29, and LOVO.

[00217] Some of the typical human thyroid cáncer cell lines that were or can be used in the above xenograft models are: TT and 8305C.

[00218] Some of the typical human central nervous system (CNS) cáncer cell lines that were or can be used in the above xenograft models are: U87MG and U-118.

[00219] Some of the typical human pancreas cancer cell lines that were or can be used in the above xenograft models are: PANC-1 and BxPC3.

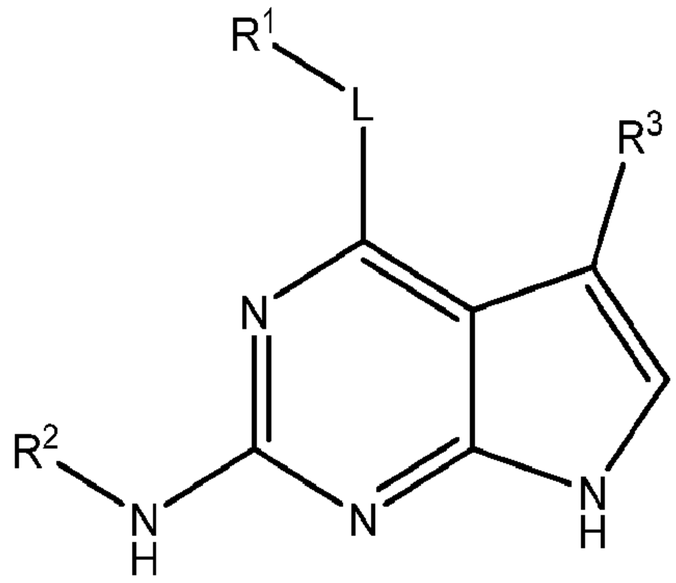
[00220] For a typical xenograft study, SCID mice bearing tumors were randomized and dosed with compounds ranging from, for example, 100 mg/kg to 0.1 mg/kg with different dose scheduling. The mice were dosed for 2-4 weeks. Tumors were measured twice a week using calipers and tumor volumes were calculated using the formula of $W^2 \times L / 2$.

[00221] In thesexenograft cancer models, Pyrrolopyrimidine Compounds have, or are expected to have, an ED_{50} value of <100 mg/kg, with some compounds having an ED_{50} of <10 mg/kg and others an ED_{50} of <1 mg/kg.

[00222] A number of references have been cited, the disclosures of which are incorporated herein by reference in their entirety.

What is claimed is:

1. A method for treating or preventing a cancer, comprising administering to a subject in need thereof an effective amount of Pyrrolopyrimidine Compound, wherein the cancer is a solid tumor or a hematological cancer, and wherein the Pyrrolopyrimidine Compound is a compound of formula (I):



(I)

and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, and isotopologues thereof,

wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, or substituted or unsubstituted non-aromatic heterocyclyl;

R^2 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is substituted or unsubstituted heterocyclyl or substituted or unsubstituted aryl, and

L is NH or O;

provided

R^3 is not pyridyl when L is NH or when R^2 is pyrazolyl; and

the compound is not

N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-4-yl)-2-[(1-methyl-1H-pyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]-2-propenamide; or

N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-3-yl)-2-[(1-methyl-1H-pyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]-2-propenamide.

2. The method of claim 1, wherein the solid tumor is bladder cancer, breast cancer,

central nervous system cancer, colorectal cancer, gastrointestinal cancer, endocrine cancer, eye cancer, female genitourinary cancer, head and neck cancer, liver cancer, lung cancer, skin cancer, soft tissue cancer, bone cancer, squamous cell cancer, pancreas cancer, kidney cancer, and prostate cancer.

3. The method of claim 1, wherein the solid tumor is colon cancer, lung cancer or bladder cancer.

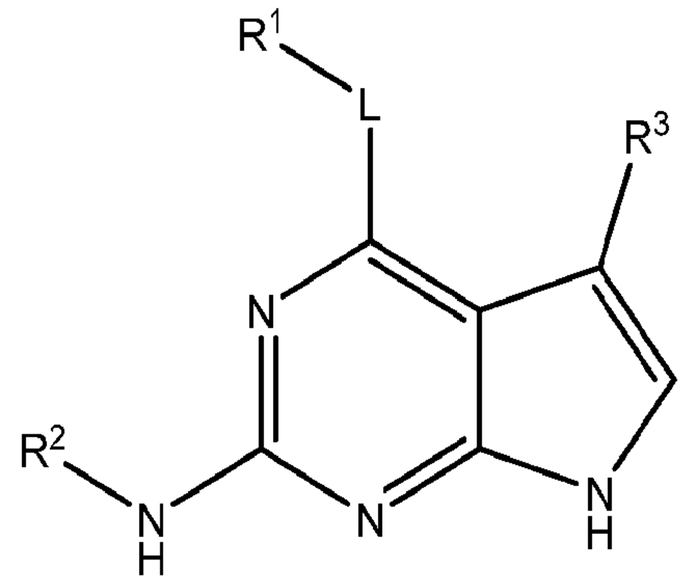
4. The method of claim 1, wherein the hematological cancer is leukemia, lymphoma or multiple myeloma.

5. The method of claim 4, wherein the leukemia is selected from acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), acute T-cell leukemia, B cell precursor leukemia, acute promyelocytic leukemia (APML), plasma cell leukemia, myelomonoblastic/T-ALL, B myelomonocytic leukemia, erythroleukemia, and acute myeloid leukemia (AML).

6. The method of claim 4, wherein the lymphoma is selected from Hodgkin's lymphoma, non Hodgkin's lymphoma (NHL), Burkitt's lymphoma (BL), B cell lymphoma, lymphoblastic lymphoma, follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and large cell immunoblastic lymphoma).

7. The method of claim 4, wherein the the hematological cancer is multiple myeloma.

8. A method for preventing cancer metastasis, comprising administering to a subject in need thereof an effective amount of a Pyrrolopyrimidine Compound, wherein the Pyrrolopyrimidine Compound is a compound of formula (I):



(I)

and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, and isotopologues thereof,

wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, or substituted or unsubstituted non-aromatic heterocyclyl;

R^2 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is substituted or unsubstituted heterocyclyl or substituted or unsubstituted aryl, and

L is NH or O;

provided

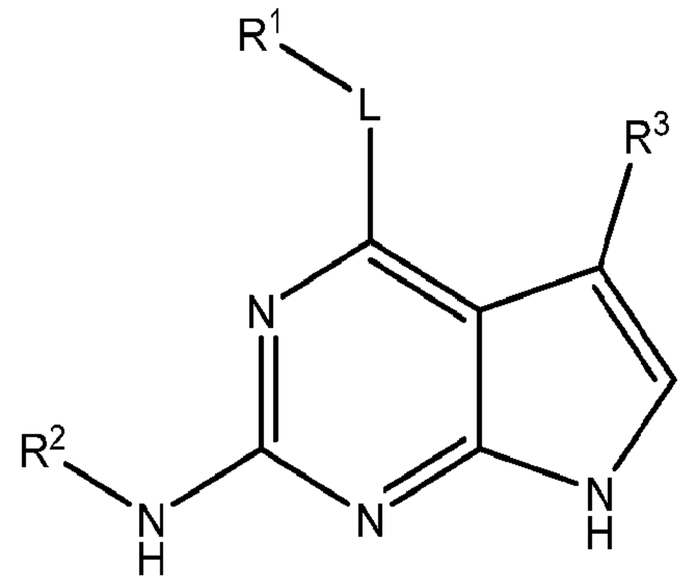
R^3 is not pyridyl when L is NH or when R^2 is pyrazolyl; and

the compound is not

N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-4-yl)-2-[(1-methyl-1H-pyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]-2-propenamide; or

N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-3-yl)-2-[(1-methyl-1H-pyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]-2-propenamide.

9. A method of eradicating cancer stem cells in a subject, comprising administering to a subject in need thereof an effective amount of a Pyrrolopyrimidine Compound, wherein the Pyrrolopyrimidine Compound is a compound of formula (I):



(I)

and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, and isotopologues thereof,

wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, or substituted or unsubstituted non-aromatic heterocyclyl;

R^2 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is substituted or unsubstituted heterocyclyl or substituted or unsubstituted aryl, and

L is NH or O;

provided

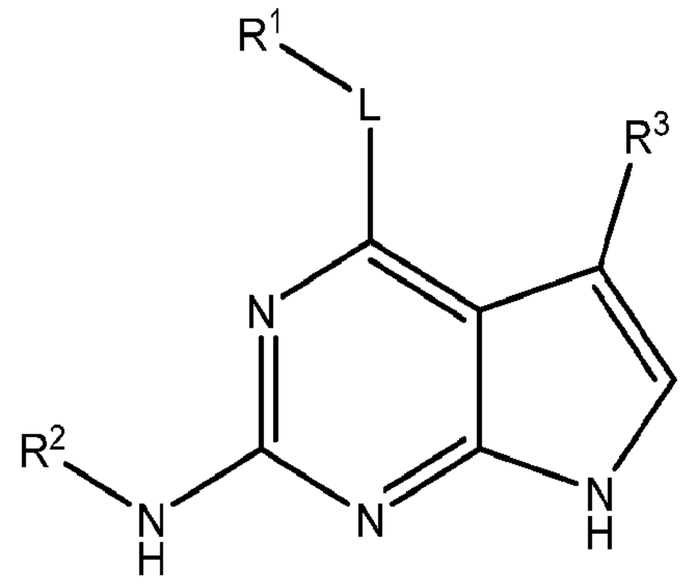
R^3 is not pyridyl when L is NH or when R^2 is pyrazolyl; and

the compound is not

N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-4-yl)-2-[(1-methyl-1H-pyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]-2-propenamide; or

N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-3-yl)-2-[(1-methyl-1H-pyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]-2-propenamide.

10. A method of inducing differentiation in cancer stem cells in a subject, comprising administering to a subject in need thereof an effective amount of a Pyrrolopyrimidine Compound, wherein the Pyrrolopyrimidine Compound is a compound of formula (I):



(I)

and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, and isotopologues thereof,

wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, or substituted or unsubstituted non-aromatic heterocyclyl;

R^2 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is substituted or unsubstituted heterocyclyl or substituted or unsubstituted aryl, and

L is NH or O;

provided

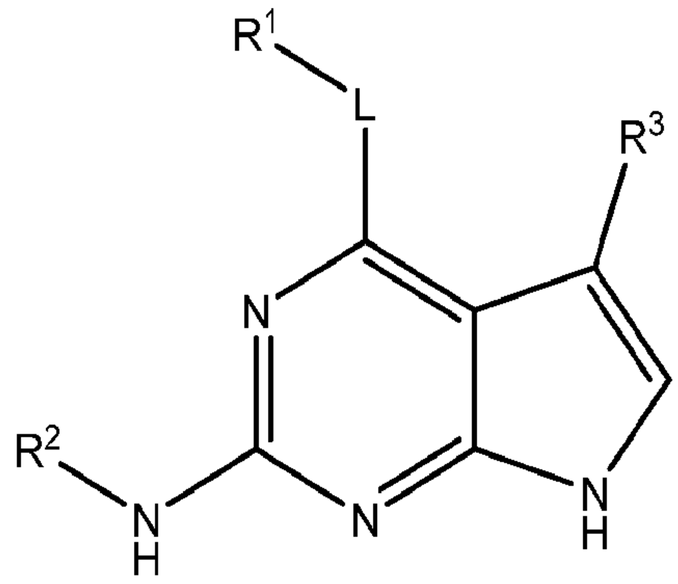
R^3 is not pyridyl when L is NH or when R^2 is pyrazolyl; and

the compound is not

N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-4-yl)-2-[(1-methyl-1H-pyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]-2-propenamide; or

N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-3-yl)-2-[(1-methyl-1H-pyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]-2-propenamide.

11. A method of inducing cancer stem cell death in a subject, comprising administering to a subject in need thereof an effective amount of a Pyrrolopyrimidine Compound, wherein the Pyrrolopyrimidine Compound is a compound of formula (I):



(I)

and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, and isotopologues thereof,

wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, or substituted or unsubstituted non-aromatic heterocyclyl;

R^2 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is substituted or unsubstituted heterocyclyl or substituted or unsubstituted aryl, and

L is NH or O;

provided

R^3 is not pyridyl when L is NH or when R^2 is pyrazolyl; and

the compound is not

N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-4-yl)-2-[(1-methyl-1H-pyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]-2-propenamide; or

N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-3-yl)-2-[(1-methyl-1H-pyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]-2-propenamide.

12. The method of claim 8, 9, 10, or 11, wherein the cancer is a solid tumor or a hematological cancer.

13. The method of claim 12, wherein the solid tumor is bladder cancer, breast cancer,

central nervous system cancer, colorectal cancer, gastrointestinal cancer, endocrine cancer, eye cancer, female genitourinary cancer, head and neck cancer, liver cancer, lung cancer, skin cancer, soft tissue cancer, bone cancer, squamous cell cancer, pancreas cancer, kidney cancer, and prostate cancer.

14. The method of claim 13, wherein the solid tumor is a central nervous system cancer or breast cancer.

15. The method of claim 12, wherein the hematological cancer is leukemia.

16. A method for treating or preventing a cancer, comprising administering to a subject in need thereof an effective amount of a compound that inhibits TTK, CLK1, and CLK2 kinase activity, and optionally CAMKK2 kinase activity.

17. A method for treating or preventing a cancer associated with the pathways involving TTK, CLK1, and CLK2 and mutants or isoforms thereof, comprising administering to a subject in need thereof an effective amount of a compound that inhibits TTK, CLK1, and CLK2 kinase activity, and optionally CAMKK2 kinase activity.

18. The method of claim 12 or claim 17, wherein the cancer is a solid tumor or a hematological cancer.

19. The method of claim 18, wherein the solid tumor is bladder cancer, breast cancer, central nervous system cancer, colorectal cancer, gastrointestinal cancer, endocrine cancer, eye cancer, female genitourinary cancer, head and neck cancer, liver cancer, lung cancer, skin cancer, soft tissue cancer, bone cancer, squamous cell cancer, pancreas cancer, kidney cancer, and prostate cancer.

20. The method of claim 18, wherein the solid tumor is colon cancer, lung cancer or bladder cancer.

21. The method of claim 18, wherein the hematological cancer is leukemia, lymphoma or multiple myeloma.

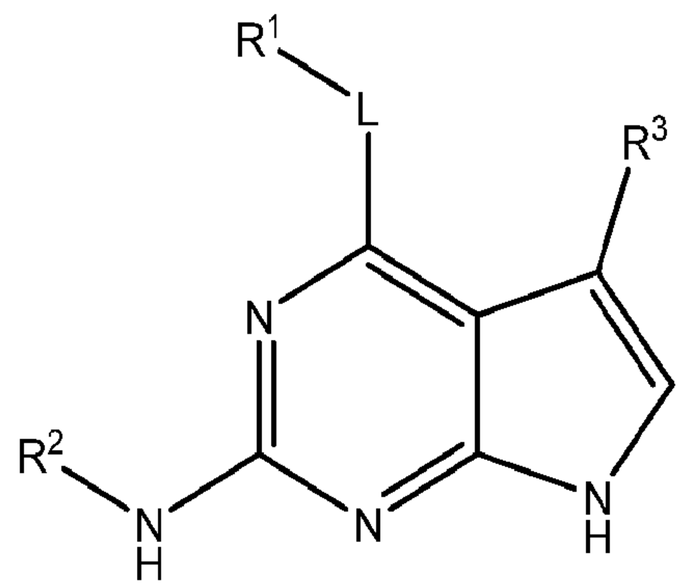
22. The method of claim 21, wherein the leukemia is selected from acute lymphocytic

leukemia (ALL), chronic myeloid leukemia (CML), acute T-cell leukemia, B cell precursor leukemia, acute promyelocytic leukemia (APML), plasma cell leukemia, myelomonoblastic/T-ALL, B myelomonocytic leukemia, erythroleukemia, and acute myeloid leukemia (AML).

23. The method of claim 21, wherein the lymphoma is selected from Hodgkin's lymphoma, non Hodgkin's lymphoma (NHL), Burkitt's lymphoma (BL), B cell lymphoma, lymphoblastic lymphoma, follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and large cell immunoblastic lymphoma).

24. The method of claim 21, wherein the the hematological cancer is multiple myeloma.

25. The method of claim 12 or claim 17, wherein the compound that inhibits TTK, CLK1, and CLK2 kinase activity is a compound of formula (I)



(I)

and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, and isotopologues thereof,

wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, or substituted or unsubstituted non-aromatic heterocyclyl;

R^2 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is substituted or unsubstituted heterocyclyl or substituted or unsubstituted aryl, and

L is NH or O;

provided

R^3 is not pyridyl when L is NH or when R^2 is pyrazolyl; and

the compound is not

N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-4-yl)-2-[(1-methyl-1H-pyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]-2-propenamide; or

N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-3-yl)-2-[(1-methyl-1H-pyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]-2-propenamide.

26. The method of any one of claim 1, 8, 9, 10, 11, or claim 25, wherein L is O.

27. The method of claim 1, 8, 9, 10, 11, or claim 25, wherein R^1 is substituted or unsubstituted alkyl.

28. The method of claim 1, 8, 9, 10, 11, or claim 25, wherein R^1 is substituted or unsubstituted methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, sec-pentyl, tert-pentyl, or 2,2-dimethylpropyl.

29. The method of claim 1, 8, 9, 10, 11, or claim 25, wherein R^1 is substituted or unsubstituted methyl, ethyl, isopropyl, sec-butyl, t-butyl, or 2,2-dimethylpropyl.

30. The method of claim 27, wherein the alkyl is substituted with one or more -OR or $-NR_2$, wherein each R is independently -H or substituted or unsubstituted (C_{1-4})alkyl.

31. The method of claim 1, 8, 9, 10, 11, or claim 25, wherein R^1 is substituted or unsubstituted C_{3-8} cycloalkyl.

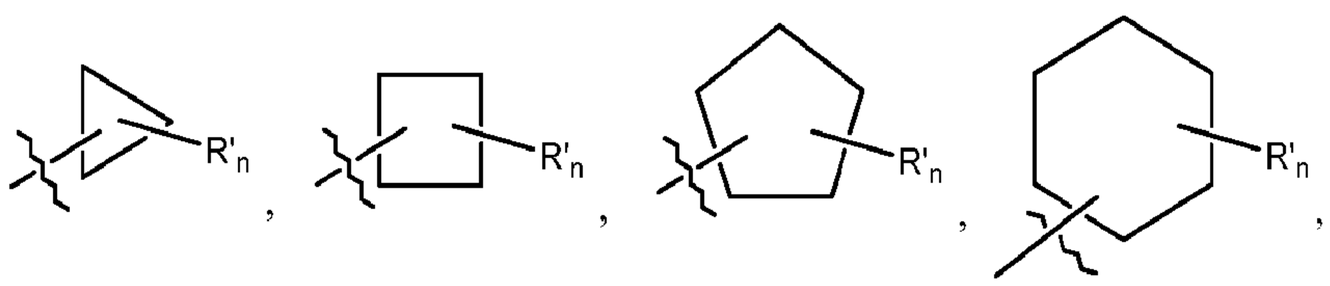
32. The method of claim 1, 8, 9, 10, 11, or claim 25, wherein R^1 is substituted or unsubstituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.

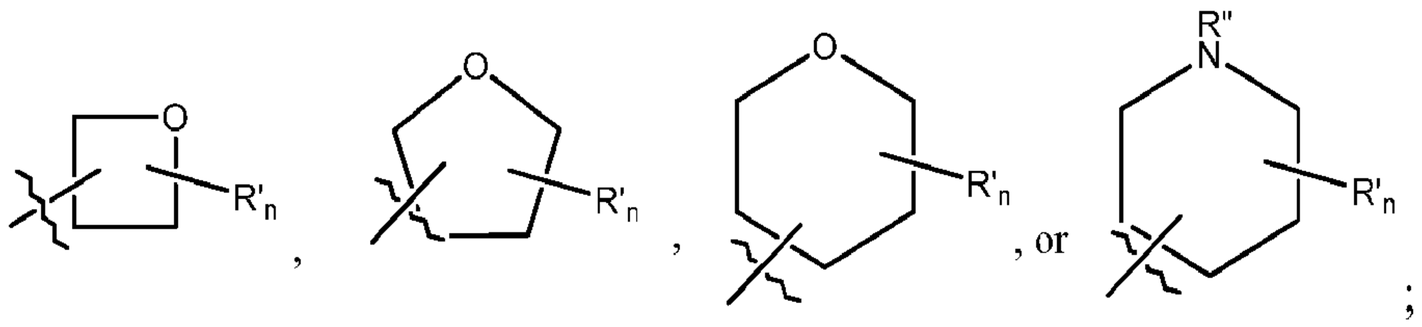
33. The method of claim 31, wherein the cycloalkyl is substituted with one or more -CN, halogen, -OR or a substituted or unsubstituted C_{1-3} alkyl, wherein each R is independently -H or substituted or unsubstituted (C_{1-4})alkyl.

34. The method of claim 1, 8, 9, 10, 11, or claim 25, wherein R^1 is substituted or unsubstituted non-aromatic heterocyclyl.

35. The method of claim 1, 8, 9, 10, 11, or claim 25, wherein R^1 is substituted or unsubstituted oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, or piperidinyl.

36. The method of claim 1, 8, 9, 10, 11, or claim 25, wherein R^1 is substituted or unsubstituted C_{1-8} alkyl,





wherein

each R' is independently -CN, halogen, -OR or C_{1-3} alkyl;

R" is -H or C_{1-3} alkyl;

each R is independently –H or substituted or unsubstituted (C_{1-4})alkyl; and

n is 0-2.

37. The method of claim 1, 8, 9, 10, 11, or claim 25, wherein R^2 is substituted phenyl.

38. The method of claim 37, wherein R^2 is phenyl, substituted with one or more substituted or unsubstituted C_{1-6} alkyl, halogen, -CN, $-OR^5$, $-C(=O)NR^5_2$, -C(=O)(substituted or unsubstituted heterocyclyl), -C(=O)(substituted or unsubstituted alkylheterocyclyl), $-NHC(=O)R^5$, $-SO_2NR^5_2$, or substituted or unsubstituted heteroaryl, wherein each R^5 is independently -H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted alkylheterocyclyl.

39. The method of claim 37, wherein R^2 is phenyl, substituted with one or more $-(C_{1-3}$ alkyl), $-(C_{1-3}$ alkyl)NR_2, $-CF_3$, -Cl, -F, -CN, $-OCH_3$, $-OCF_3$, $-C(=O)NR_2$, -C(=O)NR(substituted or unsubstituted cycloalkyl), $-C(=O)NR(CH_2)_{0-2}CR_2(CH_2)_{0-2}OR$, $-C(=O)NR(CH_2)_{0-2}CR_2(CH_2)_{0-2}NR_2$, $-C(=O)NR(CH_2)_{0-2}CR_2(CH_2)_{0-2}C(=O)NR_2$, -C(=O)N(substituted or unsubstituted cycloalkyl)$(CH_2)_{0-2}OR$, $-C(=O)NR(CH_2)_{0-3}$(substituted or unsubstituted heterocyclyl), $-C(=O)(CH_2)_{0-3}$(substituted or unsubstituted heterocyclyl), $-C(=NR)NR_2$, $-NRC(=O)R$, $-SO_2NR_2$,

-SO_2R, or substituted or unsubstituted heterocyclyl, wherein each R is independently -H or substituted or unsubstituted (C_{1-4})alkyl.

40. The method of claim 39, wherein each R is independently -H or -CH_3.

41. The method of claim 37, wherein R^2 is phenyl, substituted with one or more -CH_3, -CH_2CH_3, -CH_2 CH_2CH_3, -$CH(CH_3)_2$, -CH_2NH_2, -CF_3, -Cl,- F, -CN, -OCH_3, -OCF_3, -C(=O)NH_2, -C(=O)$NHCH_3$, -C(=O)$N(CH_3)_2$, -C(=O)$NC(CH_3)_3$, -C(=O)$NHCH_2CH_2F$, -C(=O)$NHCH_2CHF_2$, -C(=O)$NHCH_2CF_3$, -C(=O)$NHCH_2CF_2CH_3$, -C(=O)$NHCH_2CN$, -C(=O)$N(CH_3)CH_2CN$, -C(=O)$NHCH_2CH_2CN$, -C(=O)$N(CH_3)CH_2CH_2CN$, -C(=O)NH-cyclobutyl, -C(=O)NH-(hydroxy-cyclobutyl), -C(=O)NH-cyclopentyl, -C(=O)NH-(hydroxy-cyclopentyl), -C(=O)$NHCH_2CH_2OH$, -C(=O)$NHCH_2CH_2OCH_3$, -C(=O)$N(CH_3)CH_2CH_2OH$, -C(=O)$N(CH_3)CH_2CH_2OCH_3$, -C(=O)$NHCH_2CH_2CH_2OH$, -C(=O)$N(CH_3)CH_2CH_2CH_2OH$, -C(=O)$N(CH_3)CH_2CH_2CH_2OCH_3$, -C(=O)$NHCH_2CH(CH_3)OH$, -C(=O)$NHCH_2C(CH_3)_2OH$, -C(=O)$NHCH(CH_3)CH_2OH$, -C(=O)$NHC(CH_3)_2CH_2OH$, -C(=O)$NHCH_2CH_2NH_2$, -C(=O)$NHCH_2CH_2NH(CH_3)$, -C(=O)$NHCH_2CH_2N(CH_3)_2$, -C(=O)$NHCH_2C(=O)NH_2$, -C(=O)$N(CH_3)CH_2C(=O)NH_2$, -C(=O)$NHCH_2CH_2C(=O)NH_2$, -C(=O)$N(CH_3)CH_2CH_2C(=O)NH_2$, -C(=O)N(cyclopropyl)CH_2CH_2OH, -C(=O)NH-oxetanyl, -C(=O)$N(CH_3)$-oxetanyl, -C(=O)NH-(methyl-oxetanyl), -C(=O)NH-azetidinyl, -C(=O)NH-(methylazetidinyl), -C(=O)NH-(1-acetylazetidinyl), -C(=O)NH-pyrrolidyl, -C(=O)NH-piperidyl, -C(=O)NH-tetrahydrofuranyl, -C(=O)$N(CH_3)$-tetrahydrofuranyl, -C(=O)NH-tetrahydropyranyl, -C(=O)$N(CH_3)$-tetrahydropyranyl, -C(=O)$NHCH_2$-oxetanyl, -C(=O)$N(CH_3)CH_2$-oxetanyl, -C(=O)$NHCH_2$-(methyl-oxetanyl), -C(=O)$N(CH_3)CH_2$-(methyl-oxetanyl), -C(=O)$NHCH_2$-tetrahydrofuranyl, -C(=O)$NHCH_2$-tetrahydropyranyl, -C(=O)$NHCH_2$-dioxanyl, -C(=O)aziridinyl, -C(=O)(methyl-aziridinyl), -C(=O)(dimethyl-aziridinyl), -C(=O)(hydroxymethyl-aziridinyl), -C(=O)azetidinyl, -C(=O)pyrrolidinyl, -C(=O)(hydroxyl-pyrrolidinyl), -C(=O)(hydroxyl,methoxypyrrolidinyl), -C(=O)(dimethoxypyrrolidinyl), -C(=O)morpholinyl, -C(=O)piperazinyl, -C(=O)(methylpiperazinyl), -C(=O)(hydroxy-piperidyl), -C(=O)(fluoropiperidinyl), -(C=O)(methoxy-piperidyl), -C(=NH)NH_2, -$NHC(=O)CH_3$, -SO_2NHCH_3, -SO_2CH_3, or substituted or unsubstituted pyrazolyl.

42. The method of claim 37, wherein R^2 is phenyl, substituted with one or more -CH_3, -CH_2CH_3, -CH_2 CH_2CH_3, -$CH(CH_3)_2$, -CH_2NH_2, -CF_3, -Cl,- F, -CN, -OCH_3, -OCF_3, -C(=O)NH_2, -C(=O)$NHCH_3$, -C(=O)$N(CH_3)_2$, -C(=O)$NC(CH_3)_3$, -C(=O)$NHCH_2CH_2F$, -C(=O)$NHCH_2CF_2CH_3$, -C(=O)$N(CH_3)CH_2CN$, -C(=O)$N(CH_3)CH_2CH_2CN$, -C(=O)NH-(3-hydroxy-cyclobutyl), -C(=O)NH-cyclopentyl, -C(=O)NH-(2-hydroxycyclopentyl),-C(=O)$NHCH_2CH_2OH$, -C(=O)$NHCH_2CH_2OCH_3$, -C(=O)$N(CH_3)CH_2CH_2OH$, -C(=O)$N(CH_3)CH_2CH_2OCH_3$, -C(=O)$NHCH_2CH_2CH_2OH$, -C(=O)$N(CH_3)CH_2CH_2CH_2OH$, -C(=O)$NHCH_2CH(CH_3)OH$, -C(=O)$NHCH_2C(CH_3)_2OH$, -C(=O)$NHCH(CH_3)CH_2OH$, -C(=O)$NHC(CH_3)_2CH_2OH$, -C(=O)$NHCH_2CH_2NH_2$, -C(=O)$NHCH_2CH_2NH(CH_3)$, -C(=O)$NHCH_2CH_2N(CH_3)_2$, -C(=O)$N(CH_3)CH_2C(=O)NH_2$, -C(=O)$N(CH_3)CH_2CH_2C(=O)NH_2$, -C(=O)N(cyclopropyl)CH_2CH_2OH, -C(=O)NH-oxetanyl, -C(=O)$N(CH_3)$-oxetanyl, -C(=O)NH-(3-methyl-oxetanyl), -C(=O)NH-(1-methylazetidinyl), -C(=O)NH-(1-acetylazetidinyl), -C(=O)NH-piperidyl, -C(=O)NH-tetrahydrofuranyl, -C(=O)NH-tetrahydropyranyl, -C(=O)$N(CH_3)$-tetrahydropyranyl, -C(=O)$NHCH_2$-oxetanyl, -C(=O)$N(CH_3)CH_2$-(3-methyl-oxetanyl), -C(=O)$NHCH_2$-tetrahydrofuranyl, -C(=O)$NHCH_2$-tetrahydropyranyl, -C(=O)$NHCH_2$-dioxanyl, -C(=O)aziridinyl, -C(=O)(2-methyl-aziridinyl), -C(=O)(2,2-dimethyl-aziridinyl), -C(=O)(2-(hydroxymethyl)aziridinyl), -C(=O)azetidinyl, -C(=O)pyrrolidinyl, -C(=O)(3-hydroxy-4-methoxypyrrolidinyl), -C(=O)(3,4-dimethoxypyrrolidinyl), -C(=O)morpholinyl, -C(=O)piperazinyl, -C(=O)(4-methylpiperazinyl), -C(=O)(4-hydroxy-piperidyl), -C(=O)(4,4-difluoropiperidinyl), -(C=O)(4-methoxy-piperidyl), -C(=NH)NH_2,-$NHC(=O)CH_3$, -SO_2NHCH_3, -SO_2CH_3, or substituted or unsubstituted pyrazolyl.

43. The method of claim 1, 8, 9, 10, 11, or claim 25, wherein R^2 is substituted or unsubstituted pyrazolyl, substituted or unsubstituted pyridyl, substituted or unsubstituted indazolyl or substituted or unsubstituted isoindolinone.

44. The method of claim 43, wherein R^2 is substituted with one or more halogen, substituted or unsubstituted (C_{1-4})alkyl, -OR, -C(=O)NR_2, or substituted or unsubstituted heterocyclyl, wherein each R is independently –H or substituted or unsubstituted (C_{1-4})alkyl.

45. The method of claim 1, 8, 9, 10, 11, or claim 25, wherein R^3 is substituted or unsubstituted heterocyclyl.

46. The method of claim 45, wherein the heterocyclyl is substituted or unsubstituted pyrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, benztriazolyl, indazolyl, indolyl, benzoxazolyl, benzisoxazolyl, benzthiazolyl, benzoxazolonyl, benzoxadiazolyl, benzimidazolyl, or quinolyl.

47. The method of claim 45, wherein the heterocyclyl is substituted with one or more substituents selected from substituted or unsubstituted (C_{1-4})alkyl, halogen, -OR, -CN, $-NR_2$, $-C(=O)NR_2$, -NRC(=O)R, or substituted or unsubstituted triazolyl, wherein each R is independently –H or substituted or unsubstituted (C_{1-4})alkyl.

48. The method of claim 45, wherein the heterocyclyl is substituted with one or more substituents selected from $-CH_3$, $-CH(CH_3)_2$, -F, -Cl, -OH, $-OCH_3$, $-OCH_2CH_3$, -CN, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)NH(CH_3)$, $-NHC(=O)CH_3$, or substituted or unsubstituted triazolyl.

49. The method of claim 1, 8, 9, 10, 11, or claim 25, wherein R^3 is substituted or unsubstituted aryl.

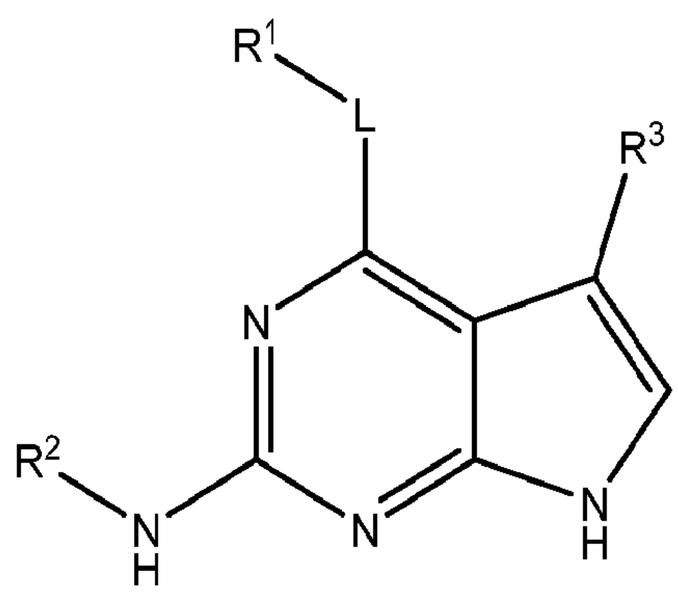
50. The method of claim 1, 8, 9, 10, 11, or claim 25, wherein R^3 is substituted or unsubstituted phenyl.

51. The method of claim 50, wherein the phenyl is substituted with one or more substituents selected from substituted or unsubstituted C_{1-4} alkyl, halogen, -CN, -OR, $-NR_2$, $-NRSO_2R'$, $-NR(C=O)NR_2$, -NR(C=O)R', -COOR, $-(C=O)NR_2$, $-C(=N)NR_2$, $-SO_2R'$, or substituted or unsubstituted heteroaryl, wherein each R is independently -H or substituted or unsubstituted (C_{1-4})alkyl, and R' is C_{1-3} alkyl.

52. The method of claim 50, wherein the phenyl is substituted with one or more substituents selected from $-CH_3$,- CH_2OH, $-CH(OH)CH_3$, $-C(CH_3)_2OH$, -CN, -F, -Cl, -OH, $-OCH_3$, $-NH_2$, $-N(CH_3)_2$, $-NHSO_2CH_3$, $-NH(C=O)NH_2$, $-NH(C=O)CH_3$, $-COOCH_3$, $-(C=O)NHCH_3$, $-C(=NH)NH_2$, $-SO_2CH_3$, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazolyl, or substituted or unsubstituted imidazolyl.

53. The method of claim 1, 8, 9, 10, 11, or claim 25, wherein the compound is selected from Table A, or a pharmaceutically acceptable salt, tautomer, stereoisomer, enantiomer, or isotopologue thereof.

54. A Pyrrolopyrimidine Compound for use in a method for treating or preventing a cancer, wherein the cancer is a solid tumor or a hematological cancer, and wherein the Pyrrolopyrimidine Compound is a compound of formula (I):



(I)

and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, and isotopologues thereof,

wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, or substituted or unsubstituted non-aromatic heterocyclyl;

R^2 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is substituted or unsubstituted heterocyclyl or substituted or unsubstituted aryl, and

L is NH or O;

provided

R^3 is not pyridyl when L is NH or when R^2 is pyrazolyl; and

the compound is not

N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-4-yl)-2-[(1-methyl-1H-pyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]-2-propenamide; or

N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-3-yl)-2-[(1-methyl-1H-pyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]-2-propenamide.

55. The Pyrrolopyrimidine Compound for use of claim 54, wherein the solid tumor is bladder cancer, breast cancer, central nervous system cancer, colorectal cancer, gastrointestinal cancer, endocrine cancer, eye cancer, female genitourinary cancer, head and neck cancer, liver cancer, lung cancer, skin cancer, soft tissue cancer, bone cancer, squamous cell cancer, pancreas cancer, kidney cancer, and prostate cancer; or

wherein the solid tumor is colon cancer, lung cancer or bladder cancer; or

wherein the hematological cancer is leukemia, lymphoma or multiple myeloma, preferably:

wherein the leukemia is selected from acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), acute T-cell leukemia, B cell precursor leukemia, acute promyelocytic leukemia (APML), plasma cell leukemia, myelomonoblastic/T-ALL, B myelomonocytic leukemia, erythroleukemia, and acute myeloid leukemia (AML); or

wherein the lymphoma is selected from Hodgkin's lymphoma, non Hodgkin's lymphoma (NHL), Burkitt's lymphoma (BL), B cell lymphoma, lymphoblastic lymphoma, follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and large cell immunoblastic lymphoma); or

wherein the hematological cancer is multiple myeloma.

56. A Pyrrolopyrimidine Compound for use in:

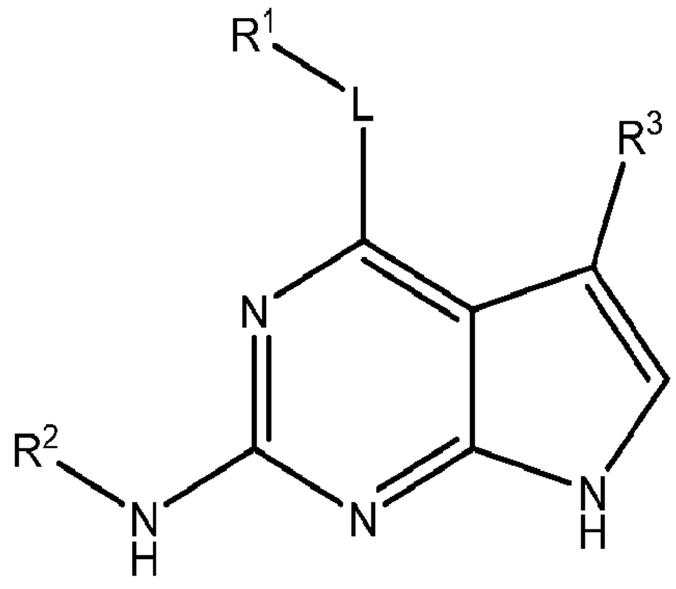
a method for preventing cancer metastasis,

a method of eradicating cancer stem cells in a subject,

a method of inducing differentiation in cancer stem cells in a subject, or

a method of inducing cancer stem cell death in a subject

wherein the Pyrrolopyrimidine Compound is a compound of formula (I):



(I)

and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, and isotopologues thereof,

wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, or substituted or unsubstituted non-aromatic heterocyclyl;

R^2 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is substituted or unsubstituted heterocyclyl or substituted or unsubstituted aryl, and

L is NH or O;

provided

R^3 is not pyridyl when L is NH or when R^2 is pyrazolyl; and

the compound is not

N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-4-yl)-2-[(1-methyl-1H-pyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]-2-propenamide; or

N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-3-yl)-2-[(1-methyl-1H-pyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]-2-propenamide.

57. The Pyrrolopyrimidine Compound for use of claim 56, wherein the cancer is a solid tumor or a hematological cancer, optionally

wherein the solid tumor is bladder cancer, breast cancer, central nervous system cancer, colorectal cancer, gastrointestinal cancer, endocrine cancer, eye cancer, female genitourinary cancer, head and neck cancer, liver cancer, lung cancer, skin cancer, soft tissue cancer, bone cancer, squamous cell cancer, pancreas cancer, kidney cancer, and prostate cancer; preferably wherein the solid tumor is a central nervous system cancer or breast cancer; or

wherein the hematological cancer is leukemia.

58. A compound for use in a method for treating or preventing a cancer, wherein the compound is a compound that inhibits TTK, CLK1, and CLK2 kinase activity, and optionally CAMKK2 kinase activity.

59. A compound for use in a method for treating or preventing a cancer associated with the pathways involving TTK, CLK1, and CLK2 and mutants or isoforms thereof, wherein the compound is a compound that inhibits TTK, CLK1, and CLK2 kinase activity, and optionally CAMKK2 kinase activity.

60. The compound for use of claim 57 or claim 59, wherein the solid tumor is bladder cancer, breast cancer, central nervous system cancer, colorectal cancer, gastrointestinal cancer, endocrine cancer, eye cancer, female genitourinary cancer, head and neck cancer, liver cancer, lung cancer, skin cancer, soft tissue cancer, bone cancer, squamous cell cancer, pancreas cancer, kidney cancer, and prostate cancer; or

wherein the solid tumor is colon cancer, lung cancer or bladder cancer; or

wherein the hematological cancer is leukemia, lymphoma or multiple myeloma; preferably

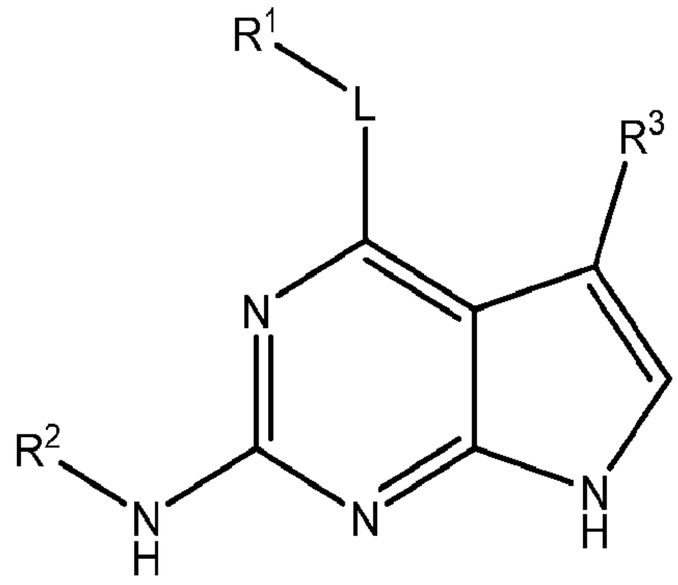
wherein the leukemia is selected from acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), acute T-cell leukemia, B cell precursor leukemia, acute promyelocytic leukemia (APML), plasma cell leukemia, myelomonoblastic/T-ALL, B myelomonocytic leukemia, erythroleukemia, and acute myeloid leukemia (AML); or

wherein the lymphoma is selected from Hodgkin's lymphoma, non Hodgkin's lymphoma (NHL), Burkitt's lymphoma (BL), B cell lymphoma, lymphoblastic lymphoma, follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and large cell immunoblastic

lymphoma); or

wherein the the hematological cancer is multiple myeloma.

61. The compound for use of claim 57 or claim 59, wherein the compound that inhibits TTK, CLK1, and CLK2 kinase activity is a compound of formula (I)



(I)

and pharmaceutically acceptable salts, tautomers, stereoisomers, enantiomers, and isotopologues thereof,

wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{3-8} cycloalkyl, or substituted or unsubstituted non-aromatic heterocyclyl;

R^2 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is substituted or unsubstituted heterocyclyl or substituted or unsubstituted aryl, and

L is NH or O;

provided

R^3 is not pyridyl when L is NH or when R^2 is pyrazolyl; and

the compound is not

N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-4-yl)-2-[(1-methyl-1H-pyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]-2-propenamide; or

N-methyl-N-[trans-3-[[5-(1-methyl-1H-pyrazol-3-yl)-2-[(1-methyl-1H-pyrazol-4-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]cyclobutyl]-2-propenamide.

62. The compound for use of any one of claim 54, 56, or claim 61, wherein L is O.

63. The compound for use of claim 54, 56, or claim 61, wherein R^1 is substituted or unsubstituted alkyl, preferably wherein the alkyl is substituted with one or more -OR or $-NR_2$, wherein each R is independently -H or substituted or unsubstituted (C_{1-4})alkyl;

wherein R^1 is substituted or unsubstituted methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, sec-pentyl, tert-pentyl, or 2,2-dimethylpropyl; or

wherein R^1 is substituted or unsubstituted methyl, ethyl, isopropyl, sec-butyl, t-butyl, or 2,2-dimethylpropyl; or

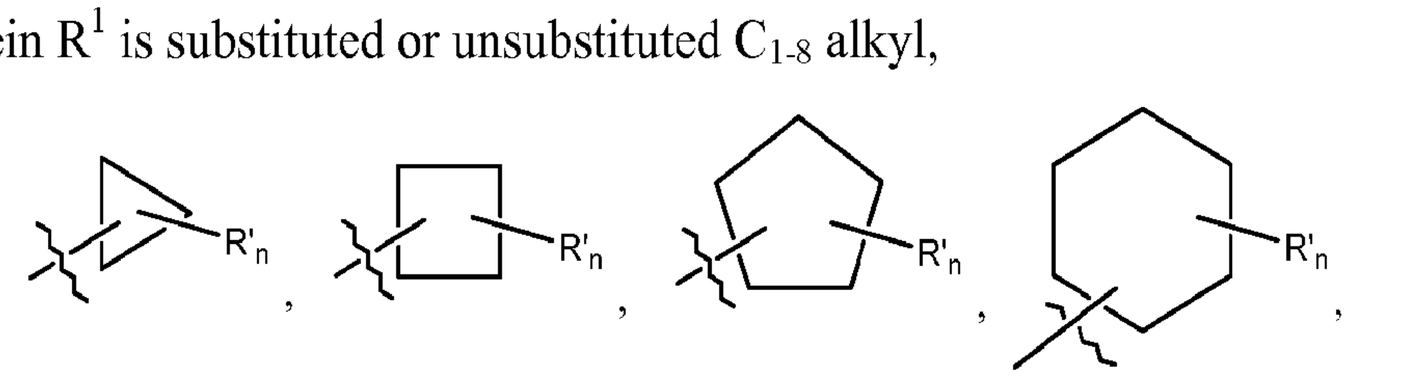
wherein R^1 is substituted or unsubstituted C_{3-8} cycloalkyl, preferably wherein the cycloalkyl is substituted with one or more -CN, halogen, -OR or a substituted or unsubstituted C_{1-3} alkyl, wherein each R is independently -H or substituted or unsubstituted (C_{1-4})alkyl; or

wherein R^1 is substituted or unsubstituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl; or

wherein R^1 is substituted or unsubstituted non-aromatic heterocyclyl; or

wherein R^1 is substituted or unsubstituted oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, or piperidinyl; or

wherein R^1 is substituted or unsubstituted C_{1-8} alkyl,



, or ;

wherein

each R' is independently -CN, halogen, -OR or C_{1-3} alkyl;

R" is -H or C_{1-3} alkyl;

each R is independently –H or substituted or unsubstituted (C_{1-4})alkyl; and

n is 0-2.

64. The compound for use of claim 54, 56, or claim 61, wherein R^2 is substituted phenyl.

65. The compound for use of claim 64, wherein R^2 is phenyl, substituted with one or more substituted or unsubstituted C_{1-6} alkyl, halogen, -CN, $-OR^5$, $-C(=O)NR^5_2$, -C(=O)(substituted or unsubstituted heterocyclyl), -C(=O)(substituted or unsubstituted alkylheterocyclyl), $-NHC(=O)R^5$, $-SO_2NR^5_2$, or substituted or unsubstituted heteroaryl, wherein each R^5 is independently -H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted alkylheterocyclyl; or

wherein R^2 is phenyl, substituted with one or more -(C_{1-3} alkyl), -(C_{1-3} alkyl)NR_2, $-CF_3$, -Cl, -F, -CN, $-OCH_3$, $-OCF_3$, $-C(=O)NR_2$, -C(=O)NR(substituted or unsubstituted cycloalkyl), $-C(=O)NR(CH_2)_{0-2}CR_2(CH_2)_{0-2}OR$, $-C(=O)NR(CH_2)_{0-2}CR_2(CH_2)_{0-2}NR_2$, $-C(=O)NR(CH_2)_{0-2}CR_2(CH_2)_{0-2}C(=O)NR_2$, -C(=O)N(substituted or unsubstituted cycloalkyl)$(CH_2)_{0-2}OR$, $-C(=O)NR(CH_2)_{0-3}$(substituted or unsubstituted heterocyclyl), $-C(=O)(CH_2)_{0-3}$(substituted or unsubstituted heterocyclyl), $-C(=NR)NR_2$, $-NRC(=O)R$, $-SO_2NR_2$, $-SO_2R$, or substituted or unsubstituted heterocyclyl, wherein each R is independently -H or substituted or unsubstituted (C_{1-4})alkyl, preferably wherein each R is independently -H or $-CH_3$; or

wherein R^2 is phenyl, substituted with one or more $-CH_3$, $-CH_2CH_3$, $-CH_2\ CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2NH_2$, $-CF_3$, -Cl,- F, -CN, $-OCH_3$, $-OCF_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-C(=O)NC(CH_3)_3$, $-C(=O)NHCH_2CH_2F$, $-C(=O)NHCH_2CHF_2$, $-C(=O)NHCH_2CF_3$, $-C(=O)NHCH_2CF_2CH_3$, $-C(=O)NHCH_2CN$, $-C(=O)N(CH_3)CH_2CN$, $-C(=O)NHCH_2CH_2CN$, $-C(=O)N(CH_3)CH_2CH_2CN$, -C(=O)NH-cyclobutyl, -C(=O)NH-(hydroxy-cyclobutyl), -C(=O)NH-cyclopentyl, -C(=O)NH-(hydroxy-cyclopentyl), $-C(=O)NHCH_2CH_2OH$, $-C(=O)NHCH_2CH_2OCH_3$, $-C(=O)N(CH_3)CH_2CH_2OH$, $-C(=O)N(CH_3)CH_2CH_2OCH_3$, $-C(=O)NHCH_2CH_2CH_2OH$, $-C(=O)N(CH_3)CH_2CH_2CH_2OH$, $-C(=O)N(CH_3)CH_2CH_2CH_2OCH_3$, $-C(=O)NHCH_2CH(CH_3)OH$, $-C(=O)NHCH_2C(CH_3)_2OH$, $-C(=O)NHCH(CH_3)CH_2OH$, $-C(=O)NHC(CH_3)_2CH_2OH$, $-C(=O)NHCH_2CH_2NH_2$, $-C(=O)NHCH_2CH_2NH(CH_3)$, $-C(=O)NHCH_2CH_2N(CH_3)_2$, $-C(=O)NHCH_2C(=O)NH_2$, $-C(=O)N(CH_3)CH_2C(=O)NH_2$, $-C(=O)NHCH_2CH_2C(=O)NH_2$, $-C(=O)N(CH_3)CH_2CH_2C(=O)NH_2$, $-C(=O)N(cyclopropyl)CH_2CH_2OH$, -C(=O)NH-oxetanyl, $-C(=O)N(CH_3)$-oxetanyl, -C(=O)NH-(methyl-oxetanyl), -C(=O)NH-azetidinyl, -C(=O)NH-(methylazetidinyl), -C(=O)NH-(1-acetylazetidinyl), -C(=O)NH-pyrrolidyl, -C(=O)NH-piperidyl, -C(=O)NH-tetrahydrofuranyl, $-C(=O)N(CH_3)$-tetrahydrofuranyl,

-C(=O)NH-tetrahydropyranyl, -C(=O)N(CH_3)-tetrahydropyranyl, -C(=O)NHCH_2-oxetanyl, -C(=O)N(CH_3)CH_2-oxetanyl, -C(=O)NHCH_2-(methyl-oxetanyl), -C(=O)N(CH_3)CH_2-(methyl-oxetanyl), -C(=O)NHCH_2-tetrahydrofuranyl, -C(=O)NHCH_2-tetrahydropyranyl, -C(=O)NHCH_2-dioxanyl, -C(=O)aziridinyl, -C(=O)(methyl-aziridinyl), -C(=O)(dimethyl-aziridinyl), -C(=O)(hydroxymethyl-aziridinyl), -C(=O)azetidinyl, -C(=O)pyrrolidinyl, -C(=O)(hydroxyl-pyrrolidinyl), -C(=O)(hydroxyl,methoxypyrrolidinyl), -C(=O)(dimethoxypyrrolidinyl), -C(=O)morpholinyl, -C(=O)piperazinyl, -C(=O)(methylpiperazinyl), -C(=O)(hydroxy-piperidyl), -C(=O)(fluoropiperidinyl), -(C=O)(methoxy-piperidyl), -C(=NH)NH_2, -NHC(=O)CH_3, -SO_2NHCH_3, -SO_2CH_3, or substituted or unsubstituted pyrazolyl, or

wherein R^2 is phenyl, substituted with one or more -CH_3, -CH_2CH_3, -CH_2 CH_2CH_3, -$CH(CH_3)_2$, -CH_2NH_2, -CF_3, -Cl,- F, -CN, -OCH_3, -OCF_3, -C(=O)NH_2, -C(=O)NHCH_3, -C(=O)N$(CH_3)_2$, -C(=O)N$C(CH_3)_3$, -C(=O)NHCH_2CH_2F, -C(=O)NH$CH_2CF_2CH_3$, -C(=O)N(CH_3)CH_2CN, -C(=O)N(CH_3)CH_2CH_2CN, -C(=O)NH-(3-hydroxy-cyclobutyl), -C(=O)NH-cyclopentyl, -C(=O)NH-(2-hydroxycyclopentyl),-C(=O)NHCH_2CH_2OH, -C(=O)NH$CH_2CH_2OCH_3$, -C(=O)N(CH_3)CH_2CH_2OH, -C(=O)N(CH_3)$CH_2CH_2OCH_3$, -C(=O)NH$CH_2CH_2CH_2$OH, -C(=O)N(CH_3)$CH_2CH_2CH_2$OH, -C(=O)NH$CH_2CH(CH_3)$OH, -C(=O)NH$CH_2C(CH_3)_2$OH, -C(=O)NHCH(CH_3)CH_2OH, -C(=O)NH$C(CH_3)_2CH_2$OH, -C(=O)NH$CH_2CH_2NH_2$, -C(=O)NHCH_2CH_2NH(CH_3), -C(=O)NH$CH_2CH_2N(CH_3)_2$, -C(=O)N(CH_3)CH_2C(=O)NH_2, -C(=O)N(CH_3)CH_2CH_2C(=O)NH_2, -C(=O)N(cyclopropyl)CH_2CH_2OH, -C(=O)NH-oxetanyl, -C(=O)N(CH_3)-oxetanyl, -C(=O)NH-(3-methyl-oxetanyl), -C(=O)NH-(1-methylazetidinyl), -C(=O)NH-(1-acetylazetidinyl), -C(=O)NH-piperidyl, -C(=O)NH-tetrahydrofuranyl, -C(=O)NH-tetrahydropyranyl, -C(=O)N(CH_3)-tetrahydropyranyl, -C(=O)NHCH_2-oxetanyl, -C(=O)N(CH_3)CH_2-(3-methyl-oxetanyl), -C(=O)NHCH_2-tetrahydrofuranyl, -C(=O)NHCH_2-tetrahydropyranyl, -C(=O)NHCH_2-dioxanyl, -C(=O)aziridinyl, -C(=O)(2-methyl-aziridinyl), -C(=O)(2,2-dimethyl-aziridinyl), -C(=O)(2-(hydroxymethyl)aziridinyl), -C(=O)azetidinyl, -C(=O)pyrrolidinyl, -C(=O)(3-hydroxy-4-methoxypyrrolidinyl), -C(=O)(3,4-dimethoxypyrrolidinyl), -C(=O)morpholinyl, -C(=O)piperazinyl, -C(=O)(4-methylpiperazinyl),

-C(=O)(4-hydroxy-piperidyl), -C(=O)(4,4-difluoropiperidinyl), -(C=O)(4-methoxy-piperidyl), -C(=NH)NH_2,-NHC(=O)CH_3, -SO_2NHCH_3, -SO_2CH_3, or substituted or unsubstituted pyrazolyl.

66. The compound for use of claim 54, 56, or claim 61, wherein R^2 is substituted or unsubstituted pyrazolyl, substituted or unsubstituted pyridyl, substituted or unsubstituted indazolyl or substituted or unsubstituted isoindolinone, preferably

wherein R^2 is substituted with one or more halogen, substituted or unsubstituted (C_{1-4})alkyl, -OR, -C(=O)NR_2, or substituted or unsubstituted heterocyclyl, wherein each R is independently –H or substituted or unsubstituted (C_{1-4})alkyl.

67. The compound for use of claim 54, 56, or claim 61, wherein R^3 is substituted or unsubstituted heterocyclyl, preferably

wherein the heterocyclyl is substituted or unsubstituted pyrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, benztriazolyl, indazolyl, indolyl, benzoxazolyl, benzisoxazolyl, benzthiazolyl, benzoxazolonyl, benzoxadiazolyl, benzimidazolyl, or quinolyl; or

wherein the heterocyclyl is substituted with one or more substituents selected from substituted or unsubstituted (C_{1-4})alkyl, halogen, -OR, -CN, -NR_2, -C(=O)NR_2, -NRC(=O)R, or substituted or unsubstituted triazolyl, wherein each R is independently –H or substituted or unsubstituted (C_{1-4})alkyl; or

wherein the heterocyclyl is substituted with one or more substituents selected from -CH_3, -$CH(CH_3)_2$, -F, -Cl, -OH, -OCH_3, -OCH_2CH_3, -CN, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -C(=O)$NH(CH_3)$, -NHC(=O)CH_3, or substituted or unsubstituted triazolyl; or

wherein R^3 is substituted or unsubstituted aryl; or

wherein R^3 is substituted or unsubstituted phenyl, preferably

wherein the phenyl is substituted with one or more substituents selected from substituted or unsubstituted C_{1-4} alkyl, halogen, -CN, -OR, -NR_2, -$NRSO_2R'$, -NR(C=O)NR_2, -NR(C=O)R', -COOR, -(C=O)NR_2, -C(=N)NR_2, -SO_2R', or substituted or unsubstituted heteroaryl, wherein each R is independently -H or substituted or unsubstituted (C_{1-4})alkyl, and R' is C_{1-3} alkyl; or

wherein the phenyl is substituted with one or more substituents selected from -CH_3,- CH_2OH, -$CH(OH)CH_3$, -$C(CH_3)_2OH$, -CN, -F, -Cl, -OH, -OCH_3, -NH_2, -$N(CH_3)_2$, -$NHSO_2CH_3$, -$NH(C=O)NH_2$, -$NH(C=O)CH_3$, -$COOCH_3$, -$(C=O)NHCH_3$, -$C(=NH)NH_2$, -SO_2CH_3, substituted or unsubstituted triazolyl, substituted or unsubstituted pyrazolyl, or substituted or unsubstituted imidazolyl.

68. The compound for use of claim 54, 56, or claim 61, wherein the compound is selected from Table A, or a pharmaceutically acceptable salt, tautomer, stereoisomer, enantiomer, or isotopologue thereof.

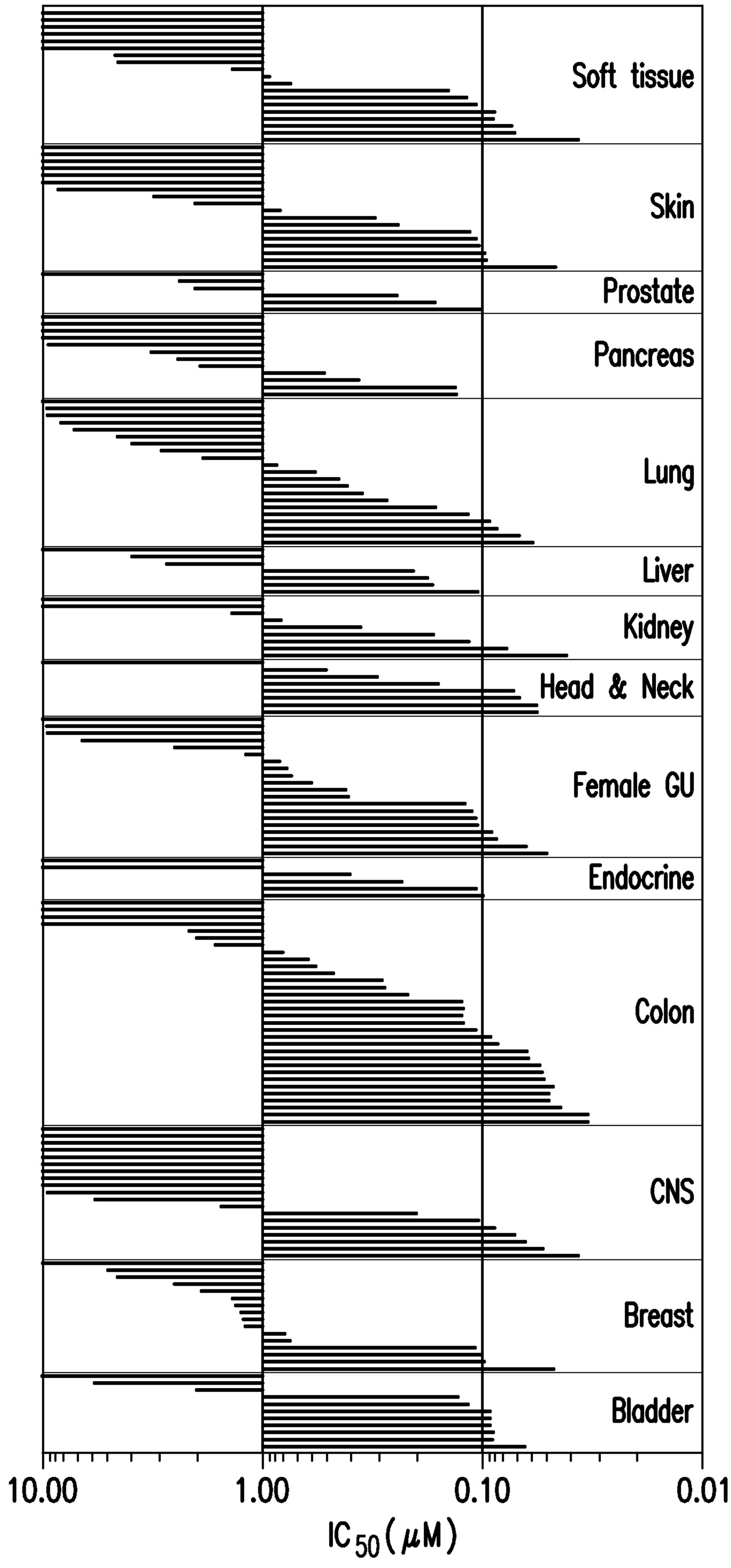

Soft tissue
Skin
Prostate
Pancreas
Lung
Liver
Kidney
Head & Neck
Female GU
Endocrine
Colon
CNS
Breast
Bladder
10.00
1.00
0.10
0.01
IC50 (μM)

FIG. 1

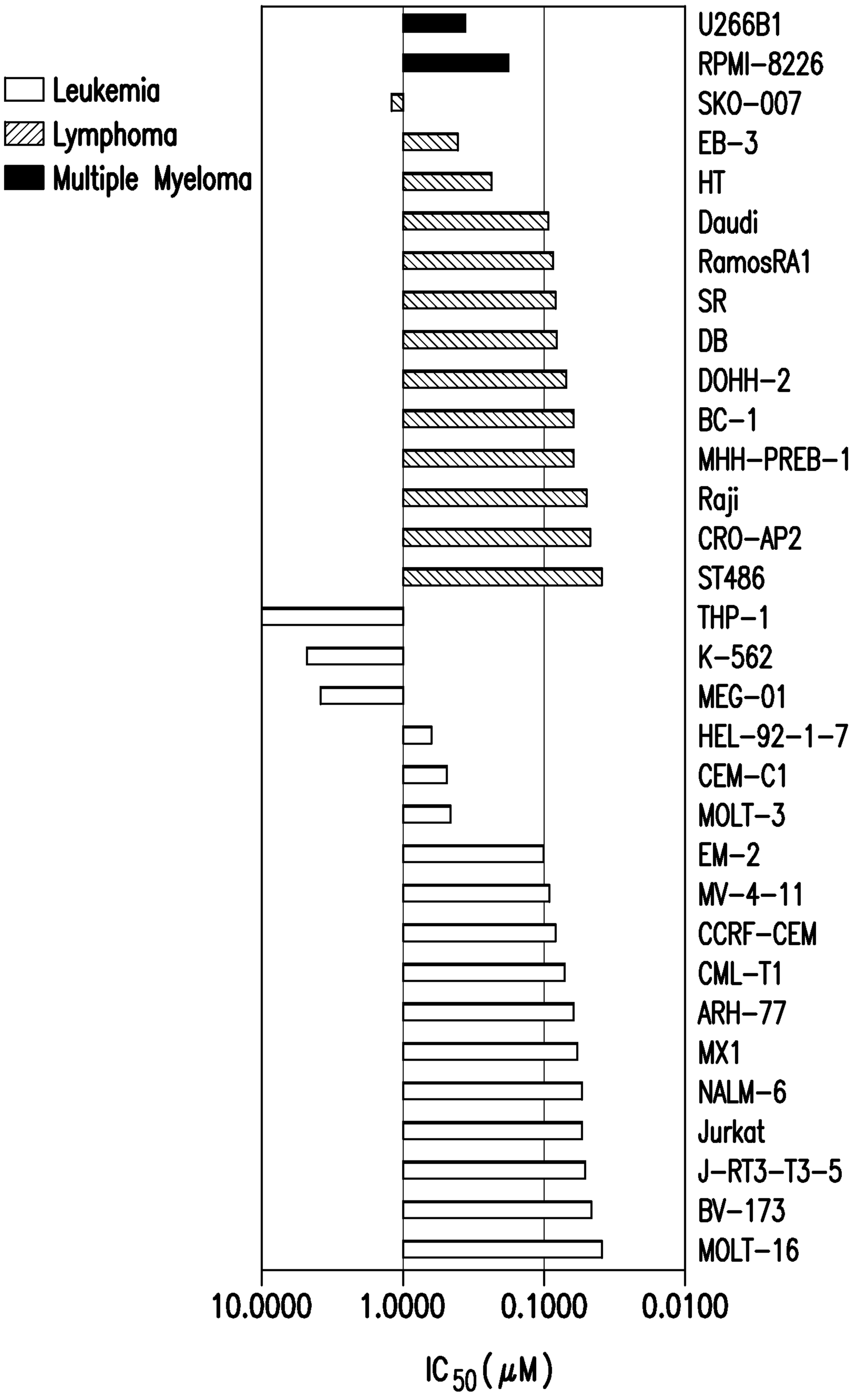

Leukemia
Lymphoma
Multiple Myeloma
U266B1
RPMI-8226
SKO-007
EB-3
HT
Daudi
RamosRA1
SR
DB
DOHH-2
BC-1
MHH-PREB-1
Raji
CRO-AP2
ST486
THP-1
K-562
MEG-01
HEL-92-1-7
CEM-C1
MOLT-3
EM-2
MV-4-11
CCRF-CEM
CML-T1
ARH-77
MX1
NALM-6
Jurkat
J-RT3-T3-5
BV-173
MOLT-16
10.0000
1.0000
0.1000
0.0100
IC50(μM)

FIG. 2

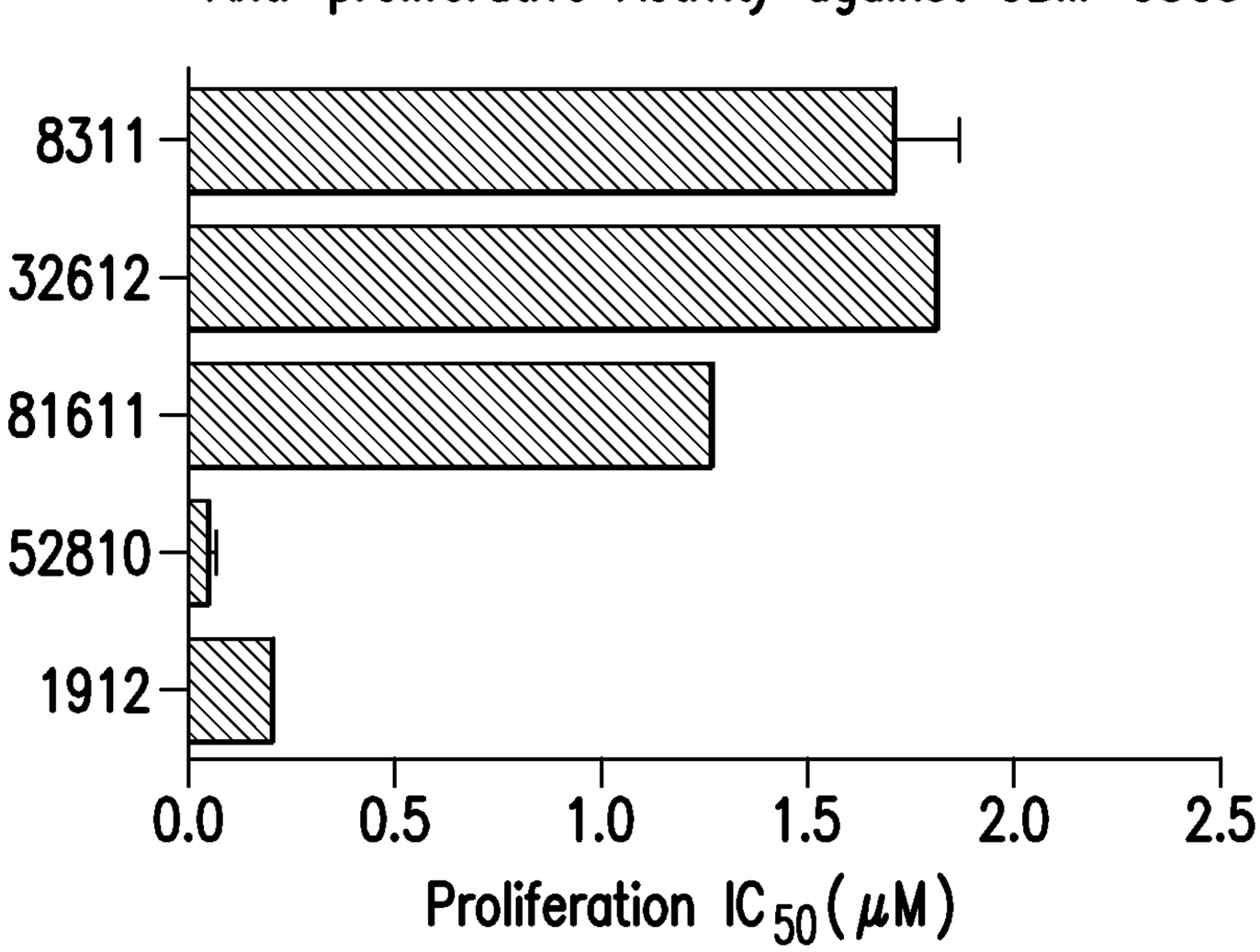

Anti-proliferative Activity against GBM-CSCs
8311
32612
81611
52810
1912
0.0
0.5
1.0
1.5
2.0
2.5
Proliferation IC50 (μM)

FIG. 3

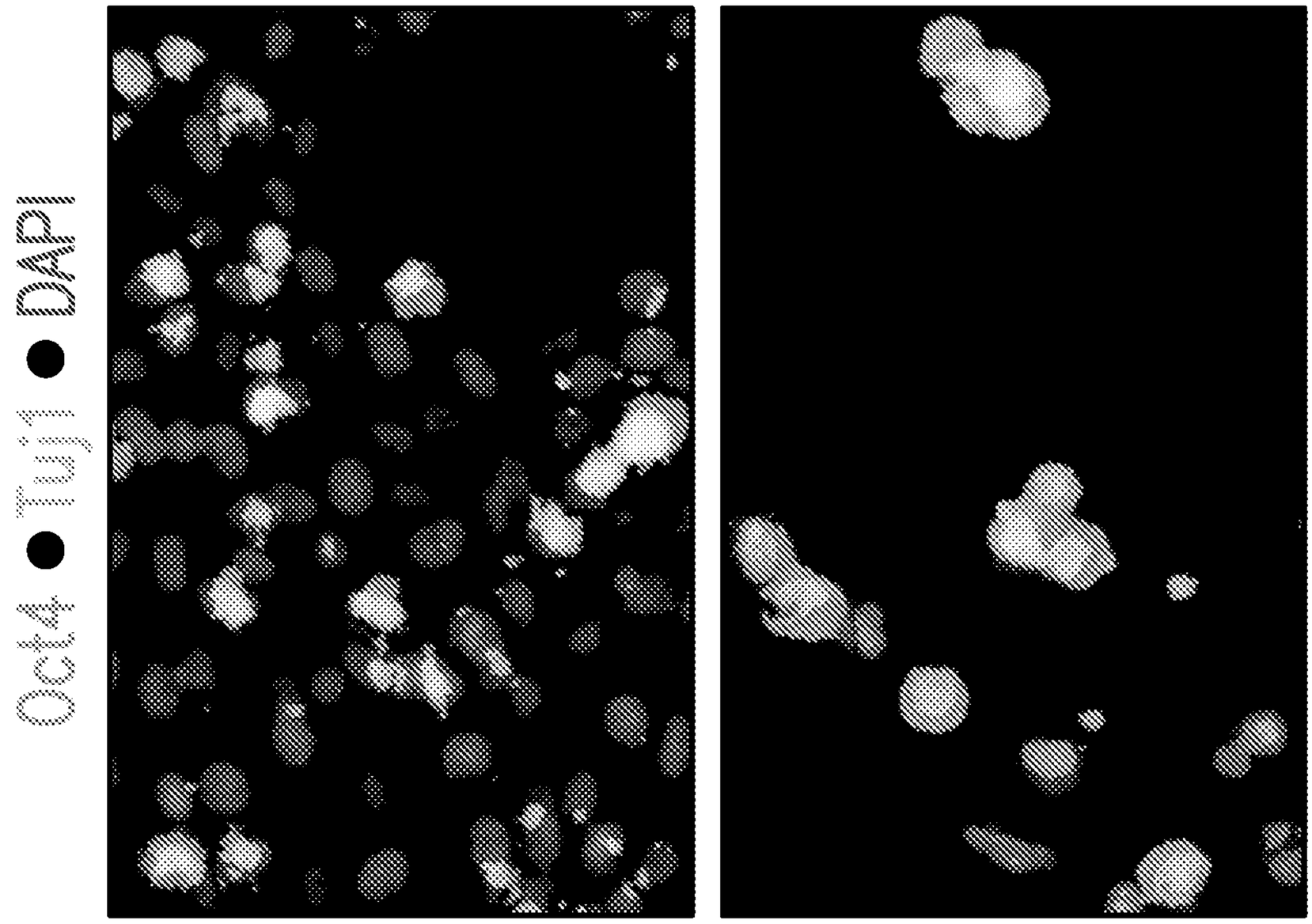
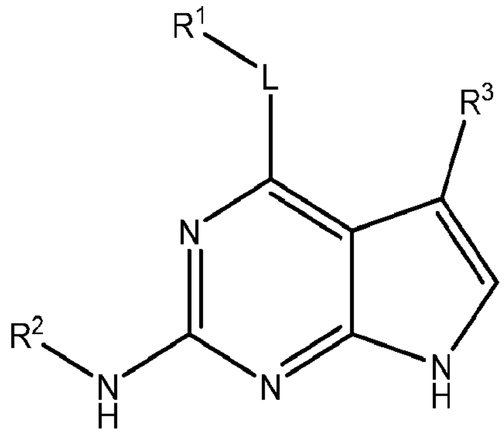


FIG. 4


R1
L
R3
N
R2
N
H
N
N
H

(I)

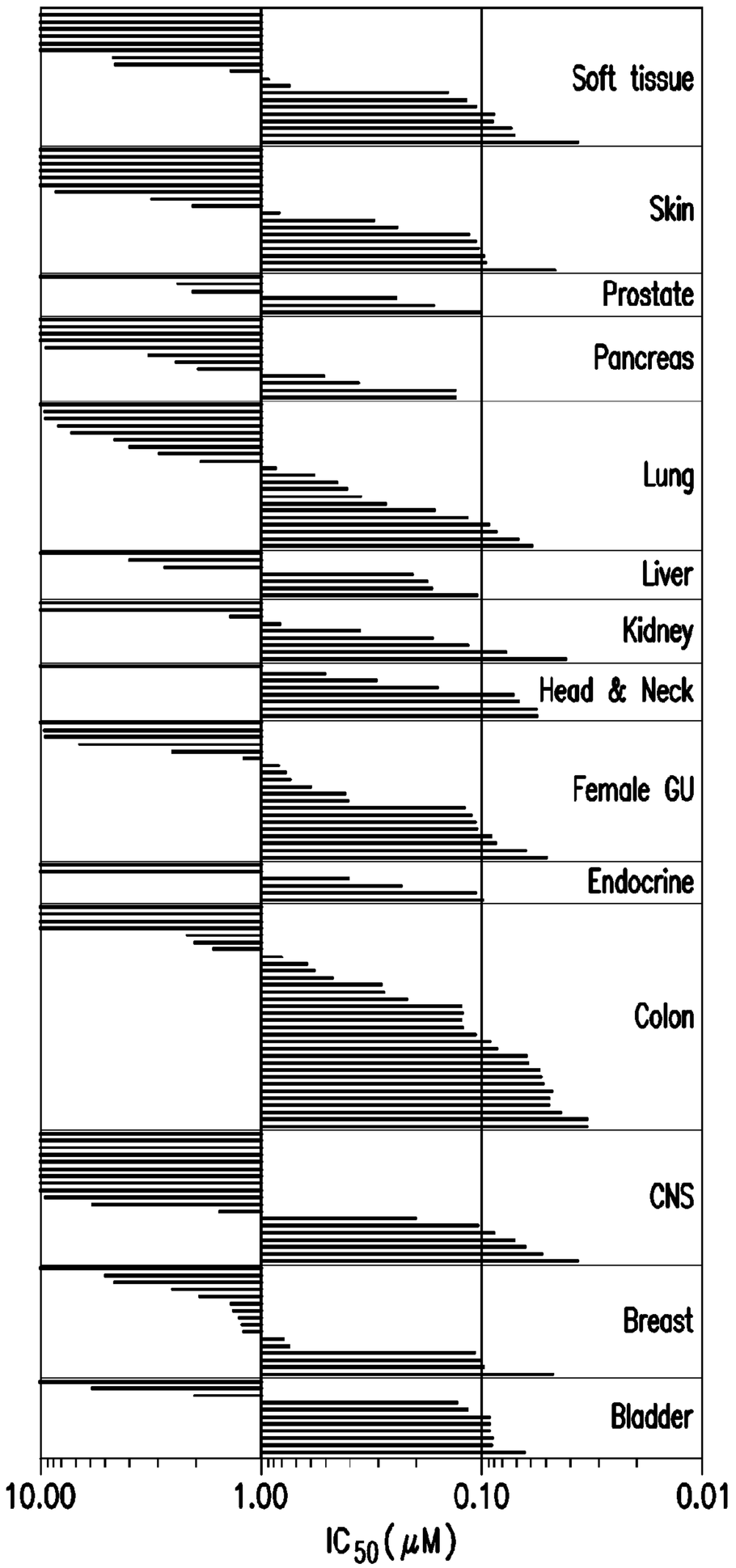

Soft tissue
Skin
Prostate
Pancreas
Lung
Liver
Kidney
Head & Neck
Female GU
Endocrine
Colon
CNS
Breast
Bladder
10.00
1.00
0.10
0.01
IC50 (μM)

FIG. 1