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(54) **SUBSTITUTED PYRROLO-AMINOPYRIMIDINE COMPOUNDS**

(75) Inventors: **Yanbin Liu**, Acton, MA (US); **Nivedita Namdev**, Westford, MA (US); **Rocio Palma**, North Andover, MA (US); **Manish Tandon**, Framingham, MA (US); **Jianqiang Wang**, Acton, MA (US); **Hui Wu**, Malden, MA (US)

(73) Assignee: **ArQule, Inc.**, Woburn, MA (US)

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(57) **ABSTRACT**

The present invention relates to substituted pyrrolo-aminopyrimidine compounds and methods of synthesizing these compounds. The present invention also relates to pharmaceutical compositions containing substituted pyrrolo-aminopyrimidine compounds and methods of treating cell proliferative disorders, such as cancer, by administering these compounds and pharmaceutical compositions to subjects in need thereof.

SUBSTITUTED PYRROLO-AMINOPYRIMIDINE COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to, and the benefit of, U.S. Provisional Application No. 61/290,936, filed Dec. 30, 2009, the contents of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] Cancer is the second leading cause of death in the United States, exceeded only by heart disease. (*Cancer Facts and Figures* 2004, American Cancer Society, Inc.). Despite recent advances in cancer diagnosis and treatment, surgery and radiotherapy may be curative if a cancer is found early, but current drug therapies for metastatic disease are mostly palliative and seldom offer a long-term cure. Even with new chemotherapies entering the market, the need continues for new drugs effective in monotherapy or in combination with existing agents as first line therapy, and as second and third line therapies in treatment of resistant tumors.

[0003] Cancer cells are by definition heterogeneous. For example, within a single tissue or cell type, multiple mutational "mechanisms" may lead to the development of cancer. As such, heterogeneity frequently exists between cancer cells taken from tumors of the same tissue and same type that have originated in different individuals. Frequently observed mutational "mechanisms" associated with some cancers may differ between one tissue type and another (e.g., frequently observed mutational "mechanisms" leading to colon cancer may differ from frequently observed "mechanisms" leading to leukemias). It is therefore often difficult to predict whether a particular cancer will respond to a particular chemotherapeutic agent (*Cancer Medicine,* 5th edition, Bast et al., B. C. Decker Inc., Hamilton, Ontario).

[0004] Components of cellular signal transduction pathways that regulate the growth and differentiation of normal cells can, when dysregulated, lead to the development of cellular proliferative disorders and cancer. Mutations in cellular signaling proteins may cause such proteins to become expressed or activated at inappropriate levels or at inappropriate times during the cell cycle, which in turn may lead to uncontrolled cellular growth or changes in cell-cell attachment properties. For example, dysregulation of receptor tyrosine kinases by mutation, gene rearrangement, gene amplification, and overexpression of both receptor and ligand has been implicated in the development and progression of human cancers.

[0005] AKT protein family, which members are also called protein kinases B (PKB) plays an important role in mammalian cellular signaling. In humans, there are three genes in the AKT family: Akt1, Akt2, and Akt3. These genes code for enzymes that are members of the serine/threonine-specific protein kinase family. Akt1 is involved in cellular survival pathways, by inhibiting apoptotic processes. Akt1 is also able to induce protein synthesis pathways, and is therefore a key signaling protein in the cellular pathways that lead to skeletal muscle hypertrophy, and general tissue growth. Akt2 is an important signaling molecule in the Insulin signaling pathway and is required to induce glucose transport. The role of Akt3 is less clear, though it appears to be predominantly expressed in brain.

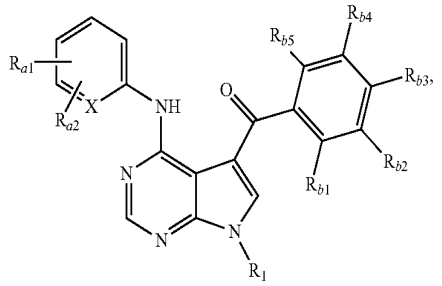
[0006] The AKT family regulates cellular survival and metabolism by binding and regulating many downstream effectors, e.g. Nuclear Factor-κB, Bcl-2 family proteins and murine double minute 2 (MDM2). Akt1 is known to play a role in the cell cycle. Moreover, activated Akt1 may enable proliferation and survival of cells that have sustained a potentially mutagenic impact and, therefore, may contribute to acquisition of mutations in other genes. Akt1 has also been implicated in angiogenesis and tumor development. Studies have shown that deficiency of Akt1 enhanced pathological angiogenesis and tumor growth associated with matrix abnormalities in skin and blood vessels. Since it can block apoptosis, and thereby promote cell survival, Akt1 is a major factor in many types of cancer

[0007] Accordingly, new compounds and methods for modulating AKT genes and treating proliferation disorders, including cancer, are needed. The present invention addresses these needs.

SUMMARY OF THE INVENTION

[0008] The present invention provides, in part, substituted pyrrolo-aminopyrimidine compounds of formula I, II, III or IV and methods of preparing the compounds of formula I, II, III or IV:

(I)



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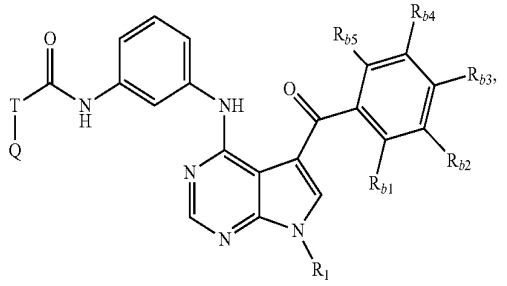

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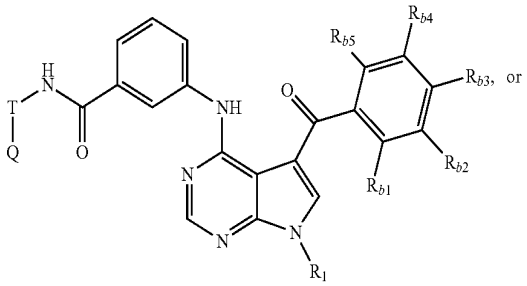

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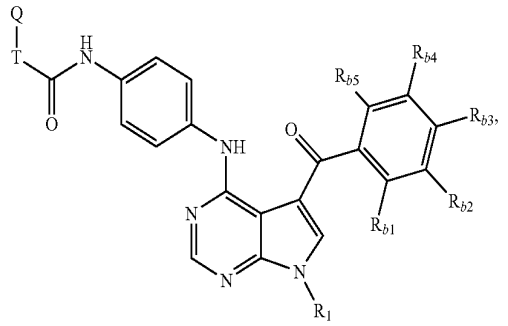


wherein:

[0009] X═CH or N;

[0010] R_1 is H or unsubstituted or substituted C_1-C_6 alkyl;

[0011] R_{a1} and R_{a2} are each independently H, —NHR_2, —$(CH_2)_mYR_2$, —$C(O)YR_2$, —$NHC(O)R_2$, halogen, —$NHC(O)NHR_2$, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, or

[0012] when adjacent, R_{a1} and R_{a2}, together with the carbon atoms to which they are attached, form an unsubstituted or substituted aryl comprising one or two 5- or 6-member rings, an unsubstituted or substituted C_3-C_8 carbocycle, an unsubstituted or substituted heteroaryl comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S, or an unsubstituted or substituted heterocycle comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S;

[0013] R_2 is H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_1-C_6 alkoxy, unsubstituted or substituted C_1-C_6 alkoxycarbonyl, unsubstituted or substituted aminocarbonyl, unsubstituted or substituted C_1-C_6 alkylcarbonylamino, unsubstituted or substituted di-C_1-C_6-alkylamino, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, or R_2 and Z, together with the nitrogen atom to which they are attached, form a 5- or 6-member ring which optionally comprises 1-3 additional heteroatoms selected from N, O and S and is optionally substituted;

[0014] Y is NH, NZ or O, provided that when Y is NZ, then Z and R_2, together with the nitrogen atom to which they are attached, form a 5- or 6-member ring which optionally comprises 1-3 additional heteroatoms selected from N, O and S and is optionally substituted;

[0015] m=0, 1, 2 or 3;

[0016] T is unsubstituted or substituted C_1-C_6 alkyl linker or a bond;

[0017] Q is H, halogen, cyano, nitro, unsubstituted or substituted C_1-C_6 alkyl, halogen substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, OR_5, NR_5R_6, $NR_6C(O)R_5$, $NR_6C(O)OR_5$, $NHC(O)NR_5R_6$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$ or $NHS(O)_2R_5$;

[0018] R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are each independently H, halogen, cyano, nitro, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, —$(CH_2)_pOR_3$, or

[0019] any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form an unsubstituted or substituted aryl comprising one or two 5- or 6-member rings, an unsubstituted or substituted C_3-C_8 carbocycle, an unsubstituted or substituted heteroaryl comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S, or an unsubstituted or substituted heterocycle comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S;

[0020] R_3, R_5 and R_6 are each independently H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, or R_5 and R_6, together with the nitrogen atom to which they are attached, form a 5- or 6-member ring which optionally comprises 1-3 additional heteroatoms selected from N, O and S and is optionally substituted; and

[0021] p is 0, 1, 2, 3, or 4,

and pharmaceutically acceptable salts, prodrugs, metabolites, analogs and derivatives thereof.

[0022] The present invention also provides pharmaceutical compositions comprising one or more compounds of each of the formulae described herein and one or more pharmaceutically acceptable carriers.

[0023] The present invention also provides methods of treating a cell proliferative disorder by administering to a subject in need thereof, a therapeutically effective amount of a compound of each of the formulae described herein, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof, in combination with a pharmaceutically acceptable carrier, such that the disorder is treated.

[0024] The present invention also provides methods of treating cancer by administering to a subject in need thereof, a therapeutically effective amount of a compound of each of the formulae described herein, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof, in combination with a pharmaceutically acceptable carrier, such that the cancer is treated.

[0025] The present invention also provides methods of selectively inducing cell death in precancerous or cancerous cells by contacting a cell with an effective amount of a compound of each of the formulae described herein, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof, in combination with a pharmaceutically

acceptable carrier, such that contacting the cell results in selective induction of cell death in the precancerous or cancer cells.

[0026] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference. The references cited herein are not admitted to be prior art to the claimed invention. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be limiting.

[0027] Other features and advantages of the invention will be apparent from the following detailed description and claims.

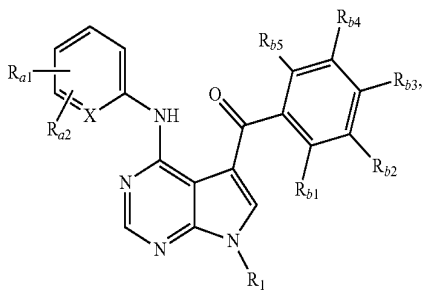
DETAILED DESCRIPTION OF THE INVENTION

1. Substituted Pyrrolo-Aminopyrimidine Compounds

[0028] The present invention provides novel substituted pyrrolo-aminopyrimidine compounds, synthetic methods for making the compounds, pharmaceutical compositions containing them and various uses of the disclosed compounds.

[0029] The present invention provides a compound of Formula I or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof:

(I)



wherein:

[0030] X=CH or N;

[0031] R_1 is H or unsubstituted or substituted C_1-C_6 alkyl;

[0032] R_{a1} and R_{a2} are each independently H, —NHR_2, —$(CH_2)_mYR_2$, —$C(O)YR_2$, —$NHC(O)R_2$, halogen, —$NHC(O)NHR_2$, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, or when adjacent, R_{a1} and R_{a2}, together with the carbon atoms to which they are attached, form an unsubstituted or substituted aryl comprising one or two 5- or 6-member rings, an unsubstituted or substituted C_3-C_8 carbocycle, an unsubstituted or substituted heteroaryl comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S, or an unsubstituted or substituted heterocycle comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S;

[0033] R_2 is H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_1-C_6 alkoxy, unsubstituted or substituted C_1-C_6 alkoxycarbonyl, unsubstituted or substituted aminocarbonyl, unsubstituted or substituted C_1-C_6 alkylcarbonylamino, unsubstituted or substituted di-C_1-C_6-alkylamino, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, or R_2 and Z, together with the nitrogen atom to which they are attached, form a 5- or 6-member ring which optionally comprises 1-3 additional heteroatoms selected from N, O and S and is optionally substituted;

[0034] Y is NH, NZ or O, provided that when Y is NZ, then Z and R_2, together with the nitrogen atom to which they are attached, form a 5- or 6-member ring which optionally comprises 1-3 additional heteroatoms selected from N, O and S and is optionally substituted;

[0035] m=0, 1, 2 or 3;

[0036] R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are each independently H, halogen, cyano, nitro, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, —$(CH_2)_pOR_3$, or

[0037] any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form an unsubstituted or substituted aryl comprising one or two 5- or 6-member rings, an unsubstituted or substituted C_3-C_8 carbocycle, an unsubstituted or substituted heteroaryl comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S, or an unsubstituted or substituted heterocycle comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S;

[0038] R_3 is H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, or unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S; and

[0039] p is 0, 1, 2, 3 or 4.

[0040] For example, X is N.

[0041] For example, X is CH.

[0042] For example, R_1 is H.

[0043] For example, R_1 is unsubstituted or substituted methyl, ethyl, or straight chain or branched propyl, butyl, pentyl, or hexyl.

[0044] For example, one of R_{a1} and R_{a2} is at the meta-position of the ring and the other is at the ortho-position of the ring relative to the nitrogen atom to which the ring is attached.

[0045] For example, one of R_{a1} and R_{a2} is at the meta-position of the ring and the other is at the meta-position of the ring relative to the nitrogen atom to which the ring is attached.

[0046] For example, one of R_{a1} and R_{a2} is at the meta-position of the ring and the other is at the para-position of the ring relative to the nitrogen atom to which the ring is attached.

[0047] For example, one of R_{a1} and R_{a2} is at the para-position of the ring and the other is at the ortho-position of the ring relative to the nitrogen atom to which the ring is attached.

[0048] For example, one of R_{a1} and R_{a2} is at the ortho-position of the ring and the other is at the ortho-position of the ring relative to the nitrogen atom to which the ring is attached.

[0049] For example, one of R_{a1} and R_{a2} is H.

[0050] For example, R_{a2} is H.

[0051] For example, R_{a1} is unsubstituted or substituted C_1-C_6 alkyl and R_{a2} is H.

[0052] For example, R_{a1} is unsubstituted or substituted methyl, ethyl, or straight chain or branched propyl, butyl, pentyl, or hexyl, each of which is optionally substituted.

[0053] For example, R_{a1} is straight chain or branched alkyl substituted with halogen (e.g., fluorine, chlorine, bromine and iodine) or aryl (e.g., phenyl).

[0054] For example, R_{a1} is C_1-C_6 alkyl substituted with unsubstituted or substituted phenyl and R_{a2} is H.

[0055] For example, R_{a1} is C_1-C_6 haloalkyl and R_{a2} is H.

[0056] For example, R_{a1} is CF_3 and R_{a2} is H.

[0057] For example, R_{a1} is C_1-C_6 haloalkyl and R_{a2} is —$(CH_2)_mYR_2$ wherein m is 0, Y is O and R_2 is unsubstituted or substituted C_1-C_6 alkyl.

[0058] For example, R_{a1} is C_1-C_6 haloalkyl and R_{a2} is —$(CH_2)_mYR_2$ wherein m is 0, Y is O and R_2 is CF_3.

[0059] For example, R_{a1} is H and R_{a2} is —$(CH_2)_mYR_2$ wherein m is 0, Y is O and R_2 is CF_3.

[0060] For example, R_{a1} is halogen (e.g., fluorine, chlorine, bromine and iodine) and R_{a2} is H.

[0061] For example, R_{a1} is unsubstituted or substituted phenyl and R_{a2} is H.

[0062] For example, R_{a1} is unsubstituted or substituted C_3-C_{10} carbocycle and R_{a2} is H.

[0063] For example, R_{a1} is carbocycle selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and is optionally substituted and R_{a2} is H.

[0064] For example, R_{a1} is —NHR_2.

[0065] For example, R_{a1} is —NHR_2 wherein R_2 is H and R_{a2} is H.

[0066] For example, R_{a1} is —NHR_2 wherein R_2 is H and R_{a2} is halogen.

[0067] For example, R_{a2} is halogen.

[0068] For example, R_{a2} is fluorine, chlorine, bromine or iodine.

[0069] For example, R_{a1} is unsubstituted or substituted C_1-C_6 alkoxycarbonylamino and R_{a2} is H.

[0070] For example, R_{a1} is C_1-C_6 alkyl substituted with unsubstituted or substituted C_1-C_6 alkoxycarbonylamino and R_{a2} is H.

[0071] For example, R_{a1} is —$C(O)YR_2$.

[0072] For example, R_{a1} is —$C(O)YR_2$ wherein Y is NZ, Z and R_2, together with the nitrogen atom to which they are attached, form a 5- or 6-member ring which optionally comprises 1-3 additional heteroatoms selected from N, O and S and is optionally substituted.

[0073] For example, R_{a1} is —$C(O)YR_2$ wherein Y is NZ, Z and R_2, together with the nitrogen atom to which they are attached, form a piperidinyl ring and R_{a2} is H.

[0074] For example, R_{a1} is —$C(O)YR_2$ wherein Y is O, R_2 is unsubstituted or substituted C_1-C_6 alkyl and R_{a2} is H.

[0075] For example, R_{a1} is —$C(O)YR_2$ wherein Y is O, R_2 is H and R_{a2} is H.

[0076] For example, one of R_{a1} and R_{a2} is —$C(O)NHR_2$.

[0077] For example, one of R_{a1} and R_{a2} is —$C(O)NHR_2$ wherein R_2 is unsubstituted or substituted phenyl.

[0078] For example, one of R_{a1} and R_{a2} is —$C(O)NHR_2$ wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted phenyl.

[0079] For example, one of R_{a1} and R_{a2} is —$C(O)NHR_2$ wherein R_2 is bound to Z to form a piperidinyl ring.

[0080] For example, one of R_{a1} and R_{a2} is —$C(O)NHR_2$ wherein R_2 is unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S.

[0081] For example, one of R_{a1} and R_{a2} is —$C(O)NHR_2$ wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S.

[0082] For example, one of R_{a1} and R_{a2} is —$C(O)NHR_2$ wherein R_2 is unsubstituted or substituted piperidinyl.

[0083] For example, one of R_{a1} and R_{a2} is —$C(O)NHR_2$ wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted piperidinyl.

[0084] For example, one of R_{a1} and R_{a2} is —$C(O)NHR_2$ wherein R_2 is unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S.

[0085] For example, one of R_{a1} and R_{a2} is —$C(O)NHR_2$ wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S.

[0086] For example, one of R_{a1} and R_{a2} is —$C(O)NHR_2$ wherein R_2 is unsubstituted or substituted pyridinyl.

[0087] For example, one of R_{a1} and R_{a2} is —$C(O)NHR_{2\ 2}$ wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted pyridinyl.

[0088] For example, one of R_{a1} and R_{a2} is —$C(O)NHR_2$ wherein R_2 is unsubstituted or substituted imidazolyl.

[0089] For example, one of R_{a1} and R_{a2} is —$C(O)NHR_2$ wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted imidazolyl.

[0090] For example, one of R_{a1} and R_{a2} is —$C(O)NHR_2$ wherein R_2 is unsubstituted or substituted indolyl.

[0091] For example, one of R_{a1} and R_{a2} is —$C(O)NHR_2$ wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted indolyl.

[0092] For example, one of R_{a1} and R_{a2} is —$C(O)NHR_2$ wherein R_2 is unsubstituted or substituted di-C_1-C_6-alkylamino.

[0093] For example, one of R_{a1} and R_{a2} is —$C(O)NHR_2$ wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted di-C_1-C_6-alkylamino.

[0094] For example, one of R_{a1} and R_{a2} is —$C(O)NHR_2$ wherein R_2 is unsubstituted or substituted C_1-C_6 alkyl.

[0095] For example, one of R_{a1} and R_{a2} is —$C(O)NHR_2$ wherein R_2 is unsubstituted or substituted C_1-C_6 alkoxy.

[0096] For example, one of R_{a1} and R_{a2} is —$C(O)NHR_2$ wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted C_1-C_6 alkoxy.

[0097] For example, R_{a1} is —$(CH_2)_mYR_2$.

[0098] For example, R_{a1} is —$(CH_2)_mYR_2$ wherein m is 0.

[0099] For example, R_{a1} is —$(CH_2)_mYR_2$ wherein m is 1.

[0100] For example, R_{a1} is —$(CH_2)_mYR_2$ wherein m is 2.

[0101] For example, R_{a1} is —$(CH_2)_mYR_2$ wherein m is 3.

[0102] For example, R_{a1} is —$(CH_2)_mYR_2$ wherein Y is NH.

[0103] For example, R_{a1} is —$(CH_2)_mYR_2$ wherein Y is O.

[0104] For example, R_{a1} is —$(CH_2)_mYR_2$ wherein m is 1 or 2, Y is O, R_2 is H and R_{a2} is H.

[0105] For example, R_{a1} is —$(CH_2)_mYR_2$ wherein m is 1, Y is NH, R_2 is H and R_{a2} is H.

[0106] For example, R_{a1} is —$(CH_2)_mYR_2$ wherein m is 2, Y is NZ, Z and R_2, together with the nitrogen atom to which they are attached, form a substituted piperazinyl ring and R_{a2} is H.

[0107] For example, R_{a1} is —$(CH_2)_mYR_2$ wherein m is 1, Y is NH, R_2 is unsubstituted or substituted C_1-C_6 alkoxycarbonyl and R_{a2} is H.

[0108] For example, R_{a1} is —$(CH_2)_mYR_2$ wherein m is 0, Y is O, R_2 is unsubstituted or substituted C_1-C_6 alkyl and R_{a2} is H.

[0109] For example, R_{a1} is —$(CH_2)_mYR_2$ wherein m is 0, Y is O, R_2 is C_1-C_6 haloalkyl and R_{a2} is H.

[0110] For example, R_{a1} is —$(CH_2)_mYR_2$ wherein m is 0, Y is O, R_2 is unsubstituted or substituted C_1-C_6 alkyl and R_{a2} is —$(CH_2)_mYR_2$ wherein m is 0, Y is O, R_2 is unsubstituted or substituted C_1-C_6 alkyl.

[0111] For example, R_{a1} is —$(CH_2)_mYR_2$ wherein m is 0, Y is O, R_2 is unsubstituted or substituted C_1-C_6 alkyl and R_{a2} unsubstituted or substituted C_1-C_6 alkyl.

[0112] For example, R_{a1} is —$(CH_2)_mYR_2$ wherein m is 0, Y is O, R_2 is unsubstituted or substituted phenyl and R_{a2} is H.

[0113] For example, R_{a1} is —$(CH_2)_mYR_2$ wherein m is 0, Y is O, R_2 is unsubstituted or substituted C_1-C_6 alkyl substituted with phenyl and R_{a2} is H.

[0114] For example, one of R_{a1} and R_{a2} is unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S.

[0115] For example, one of R_{a1} and R_{a2} is C_1-C_6 alkyl substituted with unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S.

[0116] For example, one of R_{a1} and R_{a2} is a heterocycle substituted with unsubstituted or substituted C_1-C_6 alkyl.

[0117] For example, one of R_{a1} and R_{a2} is C_1-C_6 alkyl substituted with a heterocycle substituted with unsubstituted or substituted C_1-C_6 alkyl.

[0118] For example, one of R_{a1} and R_{a2} is piperazinyl.

[0119] For example, one of R_{a1} and R_{a2} is C_1-C_6 alkyl substituted with piperazinyl.

[0120] For example, one of R_{a1} and R_{a2} is piperazinyl substituted with unsubstituted or substituted C_1-C_6 alkyl.

[0121] For example, one of R_{a1} and R_{a2} is C_1-C_6 alkyl substituted with piperazinyl substituted with unsubstituted or substituted C_1-C_6 alkyl.

[0122] For example, R_{a1} and R_{a2}, together with the carbon atoms to which they are attached, form a 5-member ring comprising at least one nitrogen atom.

[0123] For example, R_{a1} and R_{a2}, together with the carbon atoms to which they are attached, form a 5-member ring comprising at least one nitrogen atom, which is substituted with C_1-C_6 alkylcarbonyl.

[0124] For example, R_{a1} and R_{a2}, together with the carbon atoms to which they are attached, form a pyrazolyl ring.

[0125] For example, R_{a1} and R_{a2}, together with the carbon atoms to which they are attached, form a pyrrolyl ring.

[0126] For example, R_{a1} and R_{a2}, together with the carbon atoms to which they are attached, form a pyrrolidinyl ring.

[0127] For example, R_{a1} and R_{a2}, together with the carbon atoms to which they are attached, form a 5-member ring.

[0128] For example, R_{a1} and R_{a2}, together with the carbon atoms to which they are attached, form an unsubstituted 5-member carbocycle.

[0129] For example, R_{a1} and R_{a2}, together with the carbon atoms to which they are attached, form a substituted 5-member carbocycle.

[0130] For example, R_{a1} and R_{a2}, together with the carbon atoms to which they are attached, form a substituted 5-member carbocycle, which substituents, together with the atoms to which they are attached, form a phenyl ring.

[0131] For example, R_{a1} and R_{a2}, together with the carbon atoms to which they are attached, form an aryl comprising one or two 5- or 6-member rings.

[0132] For example, R_{a1} and R_{a2}, together with the carbon atoms to which they are attached, form an aryl comprising one 5-member ring and one 6-member ring.

[0133] For example, one of R_{a1} and R_{a2} is —$NHC(O)R_2$.

[0134] For example, one of R_{a1} and R_{a2} is —$NHC(O)R_2$ wherein R_2 is unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S.

[0135] For example, one of R_{a1} and R_{a2} is —$NHC(O)R_2$ wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S.

[0136] For example, one of R_{a1} and R_{a2} is —$NHC(O)R_2$ wherein R_2 is unsubstituted or substituted pyridinyl.

[0137] For example, one of R_{a1} and R_{a2} is —$NHC(O)R_2$ wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted pyridinyl.

[0138] For example, one of R_{a1} and R_{a2} is —$NHC(O)R_2$ wherein R_2 is unsubstituted or substituted imidazolyl.

[0139] For example, one of R_{a1} and R_{a2} is —$NHC(O)R_2$ wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted imidazolyl.

[0140] For example, one of R_{a1} and R_{a2} is —$NHC(O)R_2$ wherein R_2 is unsubstituted or substituted indolyl.

[0141] For example, one of R_{a1} and R_{a2} is —$NHC(O)R_2$ wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted indolyl.

[0142] For example, one of R_{a1} and R_{a2} is —$NHC(O)R_2$ wherein R_2 is unsubstituted or substituted C_1-C_6 alkylcarbonylamino.

[0143] For example, one of R_{a1} and R_{a2} is —$NHC(O)R_2$ wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted C_1-C_6 alkylcarbonylamino.

[0144] For example, one of R_{a1} and R_{a2} is —$NHC(O)R_2$ wherein R_2 is unsubstituted or substituted di-C_1-C_6-alkylamino.

[0145] For example, one of R_{a1} and R_{a2} is —$NHC(O)R_2$ wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted di-C_1-C_6-alkylamino.

[0146] For example, one of R_{a1} and R_{a2} is —$NHC(O)R_2$ wherein R_2 is unsubstituted or substituted C_1-C_6 alkyl.

[0147] For example, one of R_{a1} and R_{a2} is —$NHC(O)R_2$ wherein R_2 is unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S.

[0148] For example, one of R_{a1} and R_{a2} is —$NHC(O)R_2$ wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S.

[0149] For example, one of R_{a1} and R_{a2} is —$NHC(O)R_2$ wherein R_2 is unsubstituted or substituted pyrrolidinyl.

[0150] For example, one of R_{a1} and R_{a2} is —NHC(O)R_2 wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted pyrrolidinyl.

[0151] For example, one of R_{a1} and R_{a2} is —NHC(O)R_2 wherein R_2 is unsubstituted or substituted piperidinyl.

[0152] For example, one of R_{a1} and R_{a2} is —NHC(O)R_2 wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted piperidinyl.

[0153] For example, one of R_{a1} and R_{a2} is —NHC(O)R_2 wherein R_2 is unsubstituted or substituted aminocarbonyl.

[0154] For example, one of R_{a1} and R_{a2} is —NHC(O)R_2 wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted aminocarbonyl.

[0155] For example, one of R_{a1} and R_{a2} is —NHC(O)R_2 wherein R_2 is unsubstituted or substituted C_3-C_{10} carbocycle.

[0156] For example, one of R_{a1} and R_{a2} is —NHC(O)R_2 wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted C_3-C_{10} carbocycle.

[0157] For example, one of R_{a1} and R_{a2} is —NHC(O)R_2 wherein R_2 is unsubstituted or substituted cyclopentyl.

[0158] For example, one of R_{a1} and R_{a2} is —NHC(O)R_2 wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted cyclopentyl.

[0159] For example, one of R_{a1} and R_{a2} is —NHC(O)R_2 wherein R_2 is unsubstituted or substituted phenyl.

[0160] For example, one of R_{a1} and R_{a2} is —NHC(O)R_2 wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted phenyl.

[0161] For example, one of R_{a1} and R_{a2} is —NHC(O)R_2 wherein R_2 is unsubstituted or substituted C_1-C_6 alkoxy.

[0162] For example, one of R_{a1} and R_{a2} is —NHC(O)R_2 wherein R_2 is C_1-C_6 alkyl substituted with unsubstituted or substituted C_1-C_6 alkoxy.

[0163] For example, R_{a1} is —NHC(O)R_2 wherein R_2 is C_1-C_6 alkyl substituted with C_1-C_6 alkylcarbonylamino and R_{a2} is unsubstituted or substituted C_1-C_6 alkoxycarbonyl.

[0164] For example, R_{a1} is —NHC(O)R_2 wherein R_2 is C_1-C_6 alkyl substituted with C_1-C_6 alkylcarbonylamino and R_{a2} is halogen.

[0165] For example, R_{a1} is —NHC(O)NHR_2 and R_{a2} is H.

[0166] For example, R_{a1} is —NHC(O)NHR_2 wherein R_2 is unsubstituted or substituted C_1-C_6 alkyl and R_{a2} is H.

[0167] For example, R_{a1} is —NHC(O)NHR_2 wherein R_2 is unsubstituted or substituted C_6-C_{10} aryl and R_{a2} is H.

[0168] For example, R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are each H.

[0169] For example, four of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are H.

[0170] For example, three of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are H.

[0171] For example, two of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are H.

[0172] For example, one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is H.

[0173] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl including, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, and i-hexyl.

[0174] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is unsubstituted or substituted methyl.

[0175] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is fluorine, chlorine, bromine, or iodine.

[0176] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is unsubstituted or substituted phenyl or naphthyl.

[0177] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is heteroaryl selected from pyrrolyl, furanyl, thiophenyl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzoimidazolyl, benzothiophenyl, methylenedioxyphenyl, quinolinyl, isoquinolinyl, naphthrydinyl, indolyl, benzofuranyl, purinyl, deazapurinyl, indolizinyl, and the like, and is optionally substituted.

[0178] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is unsubstituted or substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.

[0179] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is heterocycle selected from pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, piperazinyl and morpholinyl, and the like, and is optionally substituted.

[0180] For example, any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form an unsubstituted or substituted phenyl.

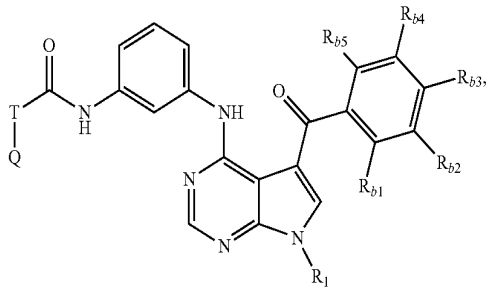
[0181] For example, any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form a heteroaryl selected from pyrrolyl, furanyl, thiophenyl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzoimidazolyl, benzothiophenyl, methylenedioxyphenyl, quinolinyl, isoquinolinyl, naphthrydinyl, indolyl, benzofuranyl, purinyl, deazapurinyl, indolizinyl, and the like, and is optionally substituted.

[0182] For example, any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form an unsubstituted or substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.

[0183] For example, any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form a heterocycle selected from pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, piperazinyl and morpholinyl, and the like, and is optionally substituted.

[0184] The present invention also provides a compound of Formula II or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof:

(II)



wherein:

[0185] R_1 is H or unsubstituted or substituted C_1-C_6 alkyl;

[0186] T is unsubstituted or substituted C_1-C_6 alkyl linker or a bond;

[0187] Q is H, halogen, cyano, nitro, unsubstituted or substituted C_1-C_6 alkyl, halogen substituted C_1-C_6 alkyl, unsub-

stituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, OR_5, NR_5R_6, $NR_6C(O)R_5$, $NR_6C(O)OR_5$, $NHC(O)NR_5R_6$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$ or $NHS(O)_2R_5$;

[0188] R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are each independently H, halogen, cyano, nitro, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, —$(CH_2)_pOR_3$, or

[0189] any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form an unsubstituted or substituted aryl comprising one or two 5- or 6-member rings, an unsubstituted or substituted C_3-C_8 carbocycle, an unsubstituted or substituted heteroaryl comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S, or an unsubstituted or substituted heterocycle comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S;

[0190] R_3, R_5 and R_6 are each independently H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, or R_5 and R_6, together with the nitrogen atom to which they are attached, form a 5- or 6-member ring which optionally comprises 1-3 additional heteroatoms selected from N, O and S and is optionally substituted; and

[0191] p is 0, 1, 2, 3 or 4.

[0192] For example, R_1 is H.

[0193] For example, R_1 is unsubstituted or substituted methyl, ethyl, or straight chain or branched propyl, butyl, pentyl, or hexyl.

[0194] For example, T is a bond.

[0195] For example, T is —CH_2—.

[0196] For example, T is —CH_2CH_2—.

[0197] For example, T is —$CH_2CH_2CH_2$—.

[0198] For example, T is —$CH_2CH_2CH_2CH_2$—.

[0199] For example, Q is unsubstituted or substituted heteroaryl selected from pyrrolyl, furanyl, thiophene, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzofuranyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzothiadiazolyl, benzoimidazolyl, benzothiophene, methylenedioxyphenyl, quinolinyl, isoquinolinyl, naphthrydinyl, indolyl and purinyl, and the like.

[0200] For example, Q is unsubstituted or substituted pyridinyl.

[0201] For example, Q is pyridinyl substituted with halogen (e.g., fluorine, chlorine, bromine and iodine).

[0202] For example, Q is unsubstituted or substituted imidazolyl.

[0203] For example, Q is unsubstituted or substituted indolyl.

[0204] For example, Q is indolyl substituted with unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl).

[0205] For example, Q is unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl, n-hexyl and 4-methylpentyl).

[0206] For example, Q is unsubstituted or substituted heterocycle selected from pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, piperidinone, piperazinyl and morpholinyl, and the like.

[0207] For example, Q is unsubstituted or substituted pyrrolidinyl.

[0208] For example, Q is unsubstituted or substituted piperidinyl.

[0209] For example, Q is piperidinyl substituted with unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl).

[0210] For example, Q is piperidinyl substituted with unsubstituted or substituted C_6-C_{10} aryl (e.g., phenyl).

[0211] For example, Q is piperidinyl substituted with heteroaryl selected from pyrrolyl, furanyl, thiophene, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyridinyl, pyrazinyl, pyridazinyl and pyrimidinyl, and the like.

[0212] For example, Q is piperidinyl substituted with pyridinyl.

[0213] For example, Q is unsubstituted or substituted C_3-C_{10} carbocycle selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

[0214] For example, Q is unsubstituted or substituted cyclopentyl.

[0215] For example, Q is unsubstituted or substituted phenyl.

[0216] For example, Q is phenyl substituted with unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl).

[0217] For example, Q is phenyl substituted a group selected from hydroxyl, nitro and cyano.

[0218] For example, Q is phenyl substituted with one, two or more halogen (e.g., fluorine, chlorine, bromine and iodine).

[0219] For example, Q is phenyl substituted with C_3-C_{10} carbocycle (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl).

[0220] For example, Q is phenyl substituted with unsubstituted or substituted heteroaryl selected from pyrrolyl, furanyl, thiophene, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzofuranyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzothiadiazolyl, benzoimidazolyl, benzothiophene, methylenedioxyphenyl, quinolinyl, isoquinolinyl, naphthrydinyl, indolyl and purinyl, and the like.

[0221] For example, Q is phenyl substituted with unsubstituted or substituted heterocycle selected from pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl,

triazolidinyl, tetrahyrofuranyl, piperidinyl, piperidinone, piperazinyl and morpholinyl, and the like.

[0222] For example, Q is phenyl substituted with unsubstituted or substituted C_1-C_6-alkylamino (e.g., methylamino, ethylamino, propylamino and butylamino).

[0223] For example, Q is phenyl substituted with unsubstituted or substituted di-C_1-C_6-alkylamino (e.g., dimethylamino, diethylamino, dipropylamino and dibutylamino).

[0224] For example, Q is phenyl substituted with unsubstituted or substituted C_1-C_6 alkoxy (e.g., methoxy, ethoxy, propyloxy, butoxy, t-butoxy and phenylmethoxy).

[0225] For example, Q is NR_5R_6.

[0226] For example, Q is NR_5R_6 wherein R_5 is unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl, each of which is optionally substituted with hydroxyl, halogen (e.g., fluorine (e.g., the substituted alkyl is —CF_3 or —CHF_2), chlorine, bromine and iodine), C_3-C_{10} carbocycle (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl)) and R_6 is H.

[0227] For example, Q is NR_5R_6 wherein R_5 is unsubstituted or substituted C_6-C_{10} aryl and R_6 is H.

[0228] For example, Q is NR_5R_6 wherein R_5 is unsubstituted or substituted phenyl and R_6 is H.

[0229] For example, Q is NR_5R_6 wherein R_5 is unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl, each of which is optionally substituted with hydroxyl, halogen (e.g., fluorine (e.g., the substituted alkyl is —CF_3 or —CHF_2), chlorine, bromine and iodine), C_3-C_{10} carbocycle (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl)) and R_6 is unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl, each of which is optionally substituted with hydroxyl, halogen (e.g., fluorine (e.g., the substituted alkyl is —CF_3 or —CHF_2), chlorine, bromine and iodine), C_3-C_{10} carbocycle (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl)).

[0230] For example, Q is OR_5 wherein R_5 is unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl).

[0231] For example, Q is OR_5 wherein R_5 is unsubstituted or substituted C_6-C_{10} aryl.

[0232] For example, Q is OR_5 wherein R_5 is unsubstituted or substituted phenyl.

[0233] For example, Q is $NR_6C(O)R_5$ wherein R_6 is H and R_5 is unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl).

[0234] For example, Q is $C(O)NR_5R_6$ wherein R_5 is H and R_6 is H.

[0235] For example, Q is $C(O)NR_5R_6$ wherein R_5 is H and R_6 is unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl).

[0236] For example, Q is NR_5R_6, $NHC(O)R_6$, $NHC(O)NR_5R_6$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$ or $NHS(O)_2R_5$.

[0237] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl including, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, and i-hexyl.

[0238] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with halogen, hydroxyl, unsubstituted or substituted C_1-C_6 alkoxyl, unsubstituted or substituted C_6-C_{10} aryloxyl, amino, unsubstituted or substituted C_1-C_6 alkylamino, unsubstituted or substituted di-C_1-C_6 alkylamino, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, and unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S.

[0239] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with fluorine, chlorine, bromine or iodine.

[0240] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with unsubstituted or substituted C_1-C_6 alkoxyl including, but not limited to, methoxyl, ethoxyl, propyloxyl, and i-propyloxyl.

[0241] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with unsubstituted or substituted phenoxyl.

[0242] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with unsubstituted or substituted methylamino, ethylamino, propylamino, butylamino, pentylamino, hexylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, dipentylamino, or dihexylamino.

[0243] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with unsubstituted or substituted phenyl.

[0244] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with heteroaryl selected from pyrrolyl, furanyl, thiophenyl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzoimidazolyl, benzothiophenyl, methylenedioxyphenyl, quinolinyl, isoquinolinyl, naphthrydinyl, indolyl, benzofuranyl, purinyl, deazapurinyl, indolizinyl, and the like, which is optionally substituted.

[0245] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with imidazolyl or pyrrolyl, which is optionally substituted.

[0246] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with heterocycle selected from pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, piperazinyl and morpholinyl, and the like, which is optionally substituted.

[0247] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with optionally substituted pyrrolidinyl.

[0248] For example, R_5 is unsubstituted or substituted phenyl or naphthyl.

[0249] For example, R_5 is phenyl substituted with one or more groups, each of which can the same of different, selected from hydroxyl, halogen, cyano, nitro, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_1-C_6 alkoxyl, unsubstituted or substituted C_6-C_{10} aryloxyl, amino, unsubstituted or substituted C_1-C_6 alkyl amino, and unsubstituted or substituted di-C_1-C_6 alkylamino.

[0250] For example, R_5 is phenyl substituted with one or more fluorine, chlorine, bromine, or iodine.

[0251] For example, R_5 is phenyl substituted with one or more unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl including, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, and i-hexyl.

[0252] For example, R_5 is phenyl substituted with one or more unsubstituted or substituted C_1-C_6 alkoxyl including, but not limited to, methoxyl, ethoxyl, propyloxyl, or i-propyloxyl.

[0253] For example, R_5 is phenyl substituted with one or more C_1-C_6 alkoxyl substituted with unsubstituted or substituted phenyl.

[0254] For example, R_5 is phenyl substituted with phenylmethoxyl.

[0255] For example, R_5 is phenyl substituted with one or more unsubstituted or substituted methylamino, ethylamino, propylamino, butylamino, pentylamino, hexylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, dipentylamino, or dihexylamino.

[0256] For example, R_5 is phenyl substituted with one or more heteroaryl selected from pyrrolyl, furanyl, thiophenyl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzoimidazolyl, benzothiophenyl, methylenedioxyphenyl, quinolinyl, isoquinolinyl, naphthrydinyl, indolyl, benzofuranyl, purinyl, deazapurinyl, indolizinyl, and the like, which is optionally substituted.

[0257] For example, R_5 is phenyl substituted with one or more heterocycle selected from pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, piperazinyl and morpholinyl, and the like, which is optionally substituted.

[0258] For example, R_5 is phenyl substituted with morpholinyl or piperidinyl.

[0259] For example, R_5 and R_6, together with the nitrogen atom to which they are attached, form a 5- or 6-member ring which optionally comprises 1-3 additional heteroatoms selected from N, O and S and is optionally substituted.

[0260] For example, R_5 and R_6, together with the nitrogen atom to which they are attached, form a heteroaryl which is optionally substituted.

[0261] For example, R_5 and R_6, together with the nitrogen atom to which they are attached, form a heterocycle which is optionally substituted.

[0262] For example, R_5 and R_6, together with the nitrogen atom to which they are attached, form an optionally substituted piperidinyl.

[0263] For example, when T is —CH_2CH_2—, Q is not unsubstituted or substituted amino, unsubstituted or substituted C_1-C_6 alkylamino, unsubstituted or substituted di-C_1-C_6-alkylamino, unsubstituted or substituted C_1-C_6 alkylcarbonylamino, unsubstituted or substituted C_1-C_6 alkoxycarbonylamino, —NR_5R_6, —$NR_6C(O)R_5$, —$NHC(O)NR_5R_6$, or —$NHS(O)_2R_5$.

[0264] For example, when Q is unsubstituted or substituted amino, unsubstituted or substituted C_1-C_6 alkylamino, unsubstituted or substituted di-C_1-C_6-alkylamino, unsubstituted or substituted C_1-C_6 alkylcarbonylamino, unsubstituted or substituted C_1-C_6 alkoxycarbonylamino, —NR_5R_6, —$NR_6C(O)R_5$, —$NHC(O)NR_5R_6$, or —$NHS(O)_2R_5$, T is not —CH_2CH_2—.

[0265] For example, R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are each H.

[0266] For example, four of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are H.

[0267] For example, three of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are H.

[0268] For example, two of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are H.

[0269] For example, one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is H.

[0270] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl including, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, and i-hexyl.

[0271] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is unsubstituted or substituted methyl.

[0272] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is fluorine, chlorine, bromine, or iodine.

[0273] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is unsubstituted or substituted phenyl or naphthyl.

[0274] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is heteroaryl selected from pyrrolyl, furanyl, thiophenyl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzoimidazolyl, benzothiophenyl, methylenedioxyphenyl, quinolinyl, isoquinolinyl, naphthrydinyl, indolyl, benzofuranyl, purinyl, deazapurinyl, indolizinyl, and the like, and is optionally substituted.

[0275] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is unsubstituted or substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.

[0276] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is heterocycle selected from pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, piperazinyl and morpholinyl, and the like, and is optionally substituted.

[0277] For example, any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form an unsubstituted or substituted phenyl.

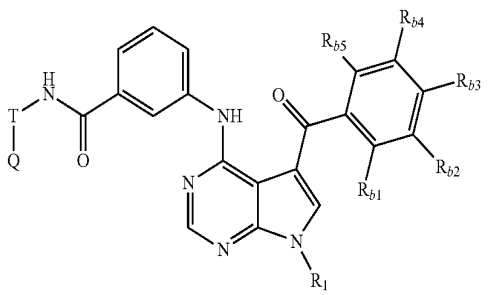
[0278] For example, any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form a heteroaryl selected from pyrrolyl, furanyl, thiophenyl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzoimidazolyl, benzothiophenyl, methylenedioxyphenyl, quinolinyl, isoquinolinyl, naphthrydinyl, indolyl, benzofuranyl, purinyl, deazapurinyl, indolizinyl, and the like, and is optionally substituted.

[0279] For example, any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form an unsubstituted or substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.

[0280] For example, any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form a heterocycle selected from pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, piperazinyl and morpholinyl, and the like, and is optionally substituted.

[0281] The present invention also provides a compound of Formula III or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof:

(III)



wherein:

[0282] R_1 is H or unsubstituted or substituted C_1-C_6 alkyl;

[0283] T is unsubstituted or substituted C_1-C_6 alkyl linker or a bond;

[0284] Q is H, halogen, cyano, nitro, unsubstituted or substituted C_1-C_6 alkyl, halogen substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, OR_5, NR_5R_6, $NR_6C(O)R_5$, $NR_6C(O)OR_5$, $NHC(O)NR_5R_6$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$ or $NHS(O)_2R_5$;

[0285] R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are each independently H, halogen, cyano, nitro, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, —$(CH_2)_pOR_3$, or any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form an unsubstituted or substituted aryl comprising one or two 5- or 6-member rings, an unsubstituted or substituted C_3-C_8 carbocycle, an unsubstituted or substituted heteroaryl comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S, or an unsubstituted or substituted heterocycle comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S;

[0286] R_3, R_5 and R_6 are each independently H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, or R_5 and R_6, together with the nitrogen atom to which they are attached, form a 5- or 6-member ring which optionally comprises 1-3 additional heteroatoms selected from N, O and S and is optionally substituted; and

[0287] p is 0, 1, 2, 3 or 4.

[0288] For example, R_1 is H.

[0289] For example, R_1 is unsubstituted or substituted methyl, ethyl, or straight chain or branched propyl, butyl, pentyl, or hexyl.

[0290] For example, T is a bond.

[0291] For example, T is —CH_2—.

[0292] For example, T is —CH_2CH_2—.

[0293] For example, T is —$CH_2CH_2CH_2$—.

[0294] For example, T is —$CH_2CH_2CH_2CH_2$—.

[0295] For example, Q is unsubstituted or substituted phenyl.

[0296] For example, Q is phenyl substituted with unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl).

[0297] For example, Q is phenyl substituted a group selected from hydroxyl, nitro and cyano.

[0298] For example, Q is phenyl substituted with one, two or more halogen (e.g., fluorine, chlorine, bromine and iodine).

[0299] For example, Q is phenyl substituted with C_3-C_{10} carbocycle (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl).

[0300] For example, Q is phenyl substituted with unsubstituted or substituted heteroaryl selected from pyrrolyl, furanyl, thiophene, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzofuranyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzothiadiazolyl, benzoimidazolyl, benzothiophene, methylenedioxyphenyl, quinolinyl, isoquinolinyl, naphthrydinyl, indolyl and purinyl, and the like.

[0301] For example, Q is phenyl substituted with unsubstituted or substituted heterocycle selected from pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, piperidinone, piperazinyl and morpholinyl, and the like.

[0302] For example, Q is phenyl substituted with morpholinyl.

[0303] For example, Q is phenyl substituted with piperidinyl.

[0304] For example, Q is phenyl substituted with unsubstituted or substituted C_1-C_6-alkylamino (e.g., methylamino, ethylamino, propylamino and butylamino).

[0305] For example, Q is phenyl substituted with unsubstituted or substituted di-C_1-C_6-alkylamino (e.g., dimethylamino, diethylamino, dipropylamino and dibutylamino).

[0306] For example, Q is phenyl substituted with unsubstituted or substituted C_1-C_6 alkoxy (e.g., methoxy, ethoxy, propyloxy, butoxy, t-butoxy and phenylmethoxy).

[0307] For example, Q is unsubstituted or substituted heteroaryl selected from pyrrolyl, furanyl, thiophene, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzofuranyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzothiadiazolyl, benzoimidazolyl, benzothiophene, methylenedioxyphenyl, quinolinyl, isoquinolinyl, naphthrydinyl, indolyl and purinyl, and the like.

[0308] For example, Q is imidazolyl.

[0309] For example, Q is unsubstituted or substituted heterocycle selected from pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, piperidinone, piperazinyl and morpholinyl, and the like.

[0310] For example, Q is unsubstituted or substituted piperidinyl.

[0311] For example, Q is unsubstituted or substituted pyrrolidinyl.

[0312] For example, Q is piperidinyl substituted with unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl).

[0313] For example, Q is unsubstituted or substituted C_3-C_{10} carbocycle selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

[0314] For example, Q is unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl, n-hexyl and 4-methylpentyl).

[0315] For example, Q is OR_5 wherein R_5 is unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl).

[0316] For example, Q is OR_5 wherein R_5 is unsubstituted or substituted C_6-C_{10} aryl.

[0317] For example, Q is OR_5 wherein R_5 is unsubstituted or substituted phenyl.

[0318] For example, R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are each H.

[0319] For example, four of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are H.

[0320] For example, three of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are H.

[0321] For example, two of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are H.

[0322] For example, one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is H.

[0323] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl including, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, and i-hexyl.

[0324] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is unsubstituted or substituted methyl.

[0325] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is fluorine, chlorine, bromine, or iodine.

[0326] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is unsubstituted or substituted phenyl or naphthyl.

[0327] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is heteroaryl selected from pyrrolyl, furanyl, thiophenyl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzoimidazolyl, benzothiophenyl, methylenedioxyphenyl, quinolinyl, isoquinolinyl, naphthrydinyl, indolyl, benzofuranyl, purinyl, deazapurinyl, indolizinyl, and the like, and is optionally substituted.

[0328] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is unsubstituted or substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.

[0329] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is heterocycle selected from pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, piperazinyl and morpholinyl, and the like, and is optionally substituted.

[0330] For example, any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form an unsubstituted or substituted phenyl.

[0331] For example, any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form a heteroaryl selected from pyrrolyl, furanyl, thiophenyl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzoimidazolyl, benzothiophenyl, methylenedioxyphenyl, quinolinyl, isoquinolinyl, naphthrydinyl, indolyl, benzofuranyl, purinyl, deazapurinyl, indolizinyl, and the like, and is optionally substituted.

[0332] For example, any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form an unsubstituted or substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.

[0333] For example, any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form a heterocycle selected from pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, piperazinyl and morpholinyl, and the like, and is optionally substituted.

[0334] For example, Q is OR_5, NR_5R_6, $NHC(O)R_5$, $NHC(O)NR_5R_6$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$ or $NHS(O)_2R_5$.

[0335] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl including, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, and i-hexyl.

[0336] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with halogen, hydroxyl, unsubstituted or substituted C_1-C_6 alkoxyl, unsubstituted or substituted C_6-C_{10} aryloxyl, amino, unsubstituted or substituted C_1-C_6 alkylamino, unsubstituted or substituted di-C_1-C_6 alkylamino, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, and unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S.

[0337] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with fluorine, chlorine, bromine or iodine.

[0338] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with unsubstituted or substituted C_1-C_6 alkoxyl including, but not limited to, methoxyl, ethoxyl, propyloxyl, and i-propyloxyl.

[0339] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with unsubstituted or substituted phenoxyl.

[0340] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with unsubstituted or substituted methylamino, ethylamino, propylamino, butylamino, pentylamino, hexylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, dipentylamino, or dihexylamino.

[0341] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with unsubstituted or substituted phenyl.

[0342] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with heteroaryl selected from pyrrolyl, furanyl, thiophenyl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzoimidazolyl, benzothiophenyl, methylenedioxyphenyl, quinolinyl, isoquinolinyl, naphthrydinyl, indolyl, benzofuranyl, purinyl, deazapurinyl, indolizinyl, and the like, which is optionally substituted.

[0343] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with imidazolyl or pyrrolyl, which is optionally substituted.

[0344] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with heterocycle selected from pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, piperazinyl and morpholinyl, and the like, which is optionally substituted.

[0345] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with optionally substituted pyrrolidinyl.

[0346] For example, R_5 is unsubstituted or substituted phenyl or naphthyl.

[0347] For example, R_5 is phenyl substituted with one or more groups, each of which can the same of different, selected from hydroxyl, halogen, cyano, nitro, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_1-C_6 alkoxyl, unsubstituted or substituted C_6-C_{10} aryloxyl, amino, unsubstituted or substituted C_1-C_6 alkyl amino, and unsubstituted or substituted di-C_1-C_6 alkylamino.

[0348] For example, R_5 is phenyl substituted with one or more fluorine, chlorine, bromine, or iodine.

[0349] For example, R_5 is phenyl substituted with one or more unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl including, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, and i-hexyl.

[0350] For example, R_5 is phenyl substituted with one or more unsubstituted or substituted C_1-C_6 alkoxyl including, but not limited to, methoxyl, ethoxyl, propyloxyl, or i-propyloxyl.

[0351] For example, R_5 is phenyl substituted with one or more C_1-C_6 alkoxyl substituted with unsubstituted or substituted phenyl.

[0352] For example, R_5 is phenyl substituted with phenylmethoxyl.

[0353] For example, R_5 is phenyl substituted with one or more unsubstituted or substituted methylamino, ethylamino, propylamino, butylamino, pentylamino, hexylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, dipentylamino, or dihexylamino.

[0354] For example, R_5 is phenyl substituted with one or more heteroaryl selected from pyrrolyl, furanyl, thiophenyl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzoimidazolyl, benzothiophenyl, methylenedioxyphenyl, quinolinyl, isoquinolinyl, naphthrydinyl, indolyl, benzofuranyl, purinyl, deazapurinyl, indolizinyl, and the like, which is optionally substituted.

[0355] For example, R_5 is phenyl substituted with one or more heterocycle selected from pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, piperazinyl and morpholinyl, and the like, which is optionally substituted.

[0356] For example, R_5 is phenyl substituted with morpholinyl or piperidinyl.

[0357] For example, R_5 and R_6, together with the nitrogen atom to which they are attached, form a 5- or 6-member ring which optionally comprises 1-3 additional heteroatoms selected from N, O and S and is optionally substituted.

[0358] For example, R_5 and R_6, together with the nitrogen atom to which they are attached, form an unsubstituted or substituted C_6-C_{10} aryl.

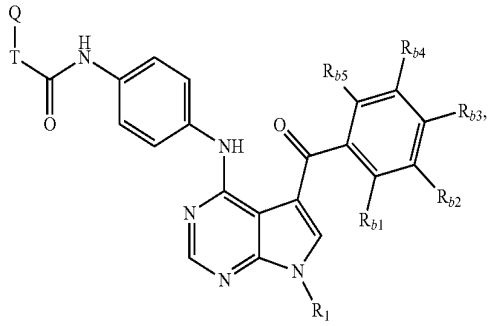
[0359] For example, R_5 and R_6, together with the nitrogen atom to which they are attached, form a heteroaryl which is optionally substituted.

[0360] For example, R_5 and R_6, together with the nitrogen atom to which they are attached, form a heterocycle which is optionally substituted.

[0361] For example, R_5 and R_6, together with the nitrogen atom to which they are attached, form an optionally substituted piperidinyl.

[0362] The present invention also provides a compound of Formula IV or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof:

(IV)



wherein:

[0363] R_1 is H or unsubstituted or substituted C_1-C_6 alkyl;

[0364] T is unsubstituted or substituted C_1-C_6 alkyl linker or a bond;

[0365] Q is H, halogen, cyano, nitro, unsubstituted or substituted C_1-C_6 alkyl, halogen substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, OR_5, NR_5R_6, $NR_6C(O)R_5$, $NR_6C(O)OR_5$, $NHC(O)NR_5R_6$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$ or $NHS(O)_2R_5$;

[0366] R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are each independently H, halogen, cyano, nitro, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, —$(CH_2)_pOR_3$, or

[0367] any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form an unsubstituted or substituted aryl comprising one or two 5- or 6-member rings, an unsubstituted or substituted C_3-C_8 carbocycle, an unsubstituted or substituted heteroaryl comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S, or an unsubstituted or substituted heterocycle comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S;

[0368] R_3, R_5 and R_6 are each independently H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, or R_5 and R_6, together with the nitrogen atom to which they are attached, form a 5- or 6-member ring which optionally comprises 1-3 additional heteroatoms selected from N, O and S and is optionally substituted; and

[0369] p is 0, 1, 2, 3 or 4.

[0370] For example, R_1 is H.

[0371] For example, R_1 is unsubstituted or substituted methyl, ethyl, or straight chain or branched propyl, butyl, pentyl, or hexyl.

[0372] For example, T is a bond.

[0373] For example, T is —CH_2—.

[0374] For example, T is —CH_2CH_2—.

[0375] For example, T is —$CH_2CH_2CH_2$—.

[0376] For example, T is —$CH_2CH_2CH_2CH_2$—.

[0377] For example, Q is unsubstituted or substituted heteroaryl selected from pyrrolyl, furanyl, thiophene, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzofuranyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzothiadiazolyl, benzoimidazolyl, benzothiophene, methylenedioxyphenyl, quinolinyl, isoquinolinyl, naphthrydinyl, indolyl and purinyl, and the like.

[0378] For example, Q is unsubstituted or substituted pyridinyl.

[0379] For example, Q is pyridinyl substituted with halogen (e.g., fluorine, chlorine, bromine and iodine).

[0380] For example, Q is unsubstituted or substituted imidazolyl.

[0381] For example, Q is unsubstituted or substituted indolyl.

[0382] For example, Q is indolyl substituted with unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl).

[0383] For example, Q is unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl, n-hexyl and 4-methylpentyl).

[0384] For example, Q is unsubstituted or substituted heterocycle selected from pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, piperidinone, piperazinyl and morpholinyl, and the like.

[0385] For example, Q is unsubstituted or substituted pyrrolidinyl.

[0386] For example, Q is unsubstituted or substituted piperidinyl.

[0387] For example, Q is piperidinyl substituted with unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl, n-hexyl).

[0388] For example, Q is piperidinyl substituted with unsubstituted or substituted C_6-C_{10} aryl (e.g., phenyl).

[0389] For example, Q is piperidinyl substituted with heteroaryl selected from pyrrolyl, furanyl, thiophene, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyridinyl, pyrazinyl, pyridazinyl and pyrimidinyl, and the like.

[0390] For example, Q is piperidinyl substituted with pyridinyl.

[0391] For example, Q is unsubstituted or substituted C_3-C_{10} carbocycle selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

[0392] For example, Q is unsubstituted or substituted cyclopentyl.

[0393] For example, Q is unsubstituted or substituted phenyl.

[0394] For example, Q is phenyl substituted with unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl).

[0395] For example, Q is phenyl substituted a group selected from hydroxyl, nitro and cyano.

[0396] For example, Q is phenyl substituted with one, two or more halogen (e.g., fluorine, chlorine, bromine and iodine).

[0397] For example, Q is phenyl substituted with C_3-C_{10} carbocycle (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl).

[0398] For example, Q is phenyl substituted with unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl, n-hexyl, each of which is optionally substituted with one or more groups selected from hydroxyl, halogen (e.g., fluorine, chlorine, fluorine and iodine), C_1-C_6 alkoxy (e.g., methoxy, ethoxy, propyloxy, butoxy, t-butoxy) and heterocycle (pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahydrofuranyl, piperidinyl, piperidinone, piperazinyl and morpholinyl)).

[0399] For example, Q is phenyl substituted with C_1-C_6 alkyl substituted with morpholinyl.

[0400] For example, Q is phenyl substituted with unsubstituted or substituted C_1-C_6 alkoxy (e.g., methoxy, ethoxy, propyloxy, butoxy, t-butoxy and phenylmethoxy).

[0401] For example, Q is NR_5R_6.

[0402] For example, Q is NR_5R_6 wherein R_5 is unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl, each of which is optionally substituted with hydroxyl, halogen (e.g., fluorine (e.g., the substituted alkyl is —CF_3 or —CHF_2), chlorine, bromine and iodine), C_3-C_{10} carbocycle (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl)) and R_6 is H.

[0403] For example, Q is NR_5R_6 wherein R_5 is unsubstituted or substituted C_6-C_{10} aryl and R_6 is H.

[0404] For example, Q is NR_5R_6 wherein R_5 is unsubstituted or substituted phenyl and R_6 is H.

[0405] For example, Q is NR_5R_6 wherein R_5 is unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl, each of which is optionally substituted with hydroxyl, halogen (e.g., fluorine (e.g., the substituted alkyl is —CF_3 or —CHF_2), chlorine, bromine and iodine), C_3-C_{10} carbocycle (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl)) and R_6 is unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl, each of which is optionally substituted with hydroxyl, halogen (e.g., fluorine (e.g., the substituted alkyl is —CF_3 or —CHF_2), chlorine,

bromine and iodine), C_3-C_{10} carbocycle (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl)).

[0406] For example, Q is OR_5 wherein R_5 is unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl).

[0407] For example, Q is OR_5 wherein R_5 is unsubstituted or substituted C_6-C_{10} aryl.

[0408] For example, Q is OR_5 wherein R_5 is unsubstituted or substituted phenyl.

[0409] For example, Q is $NR_6C(O)R_5$ wherein R_6 is H and R_5 is unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl).

[0410] For example, Q is $C(O)NR_5R_6$ wherein R_5 is H and R_6 is H.

[0411] For example, Q is $C(O)NR_5R_6$ wherein R_5 is H and R_6 is unsubstituted or substituted C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl).

[0412] For example, R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are each H.

[0413] For example, four of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are H.

[0414] For example, three of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are H.

[0415] For example, two of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are H.

[0416] For example, one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is H.

[0417] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl including, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, and i-hexyl.

[0418] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is unsubstituted or substituted methyl.

[0419] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is fluorine, chlorine, bromine, or iodine.

[0420] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is unsubstituted or substituted phenyl or naphthyl.

[0421] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is heteroaryl selected from pyrrolyl, furanyl, thiophenyl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzoimidazolyl, benzothiophenyl, methylenedioxyphenyl, quinolinyl, isoquinolinyl, naphthrydinyl, indolyl, benzofuranyl, purinyl, deazapurinyl, indolizinyl, and the like, and is optionally substituted.

[0422] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is unsubstituted or substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.

[0423] For example, at least one of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} is heterocycle selected from pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, piperazinyl and morpholinyl, and the like, and is optionally substituted.

[0424] For example, any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form an unsubstituted or substituted phenyl.

[0425] For example, any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form a heteroaryl selected from pyrrolyl, furanyl, thiophenyl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzoimidazolyl, benzothiophenyl, methylenedioxyphenyl, quinolinyl, isoquinolinyl, naphthrydinyl, indolyl, benzofuranyl, purinyl, deazapurinyl, indolizinyl, and the like, and is optionally substituted.

[0426] For example, any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form an unsubstituted or substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.

[0427] For example, any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form a heterocycle selected from pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, piperazinyl and morpholinyl, and the like, and is optionally substituted.

[0428] For example, Q is OR_5, NR_5R_6, $NHC(O)R_6$, $NHC(O)NR_5R_6$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$ or $NHS(O)_2R_5$.

[0429] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl including, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, and i-hexyl.

[0430] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with halogen, hydroxyl, unsubstituted or substituted C_1-C_6 alkoxyl, unsubstituted or substituted C_6-C_{10} aryloxyl, amino, unsubstituted or substituted C_1-C_6 alkylamino, unsubstituted or substituted di-C_1-C_6 alkylamino, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, and unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S.

[0431] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with fluorine, chlorine, bromine or iodine.

[0432] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with unsubstituted or substituted C_1-C_6 alkoxyl including, but not limited to, methoxyl, ethoxyl, propyloxyl, and i-propyloxyl.

[0433] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with unsubstituted or substituted phenoxyl.

[0434] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with unsubstituted or substituted methylamino, ethylamino, propylamino, butylamino, pentylamino, hexylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, dipentylamino, or dihexylamino.

[0435] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with unsubstituted or substituted phenyl.

[0436] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with heteroaryl selected from pyrrolyl, furanyl, thiophenyl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzoimidazolyl, benzothiophenyl, methylenedioxyphenyl, quinolinyl, isoquinolinyl, naphthrydinyl, indolyl, benzofuranyl, purinyl, deazapurinyl, indolizinyl, and the like, which is optionally substituted.

[0437] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with imidazolyl or pyrrolyl, which is optionally substituted.

[0438] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with heterocycle selected from pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, piperazinyl and morpholinyl, and the like, which is optionally substituted.

[0439] For example, R_5 is unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl substituted with optionally substituted pyrrolidinyl.

[0440] For example, R_5 is unsubstituted or substituted phenyl or naphthyl.

[0441] For example, R_5 is phenyl substituted with one or more groups, each of which can the same of different, selected from hydroxyl, halogen, cyano, nitro, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_1-C_6 alkoxyl, unsubstituted or substituted C_6-C_{10} aryloxyl, amino, unsubstituted or substituted C_1-C_6 alkyl amino, and unsubstituted or substituted di-C_1-C_6 alkylamino.

[0442] For example, R_5 is phenyl substituted with one or more fluorine, chlorine, bromine, or iodine.

[0443] For example, R_5 is phenyl substituted with one or more unsubstituted or substituted straight chain C_1-C_6 alkyl or branched C_3-C_6 alkyl including, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, and i-hexyl.

[0444] For example, R_5 is phenyl substituted with one or more unsubstituted or substituted C_1-C_6 alkoxyl including, but not limited to, methoxyl, ethoxyl, propyloxyl, or i-propyloxyl.

[0445] For example, R_5 is phenyl substituted with one or more C_1-C_6 alkoxyl substituted with unsubstituted or substituted phenyl.

[0446] For example, R_5 is phenyl substituted with phenylmethoxyl.

[0447] For example, R_5 is phenyl substituted with one or more unsubstituted or substituted methylamino, ethylamino, propylamino, butylamino, pentylamino, hexylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, dipentylamino, or dihexylamino.

[0448] For example, R_5 is phenyl substituted with one or more heteroaryl selected from pyrrolyl, furanyl, thiophenyl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzoimidazolyl, benzothiophenyl, methylenedioxyphenyl, quinolinyl, isoquinolinyl, naphthrydinyl, indolyl, benzofuranyl, purinyl, deazapurinyl, indolizinyl, and the like, which is optionally substituted.

[0449] For example, R_5 is phenyl substituted with one or more heterocycle selected from pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, piperazinyl and morpholinyl, and the like, which is optionally substituted.

[0450] For example, R_5 is phenyl substituted with morpholinyl or piperidinyl.

[0451] For example, R_5 and R_6, together with the nitrogen atom to which they are attached, form a 5- or 6-member ring which optionally comprises 1-3 additional heteroatoms selected from N, O and S and is optionally substituted.

[0452] For example, R_5 and R_6, together with the nitrogen atom to which they are attached, form an unsubstituted or substituted C_6-C_{10} aryl.

[0453] For example, R_5 and R_6, together with the nitrogen atom to which they are attached, form a heteroaryl which is optionally substituted.

[0454] For example, R_5 and R_6, together with the nitrogen atom to which they are attached, form a heterocycle which is optionally substituted.

[0455] For example, R_5 and R_6, together with the nitrogen atom to which they are attached, form optionally substituted piperidinyl.

[0456] Representative compounds of the present invention include compounds listed in Table 1.

TABLE 1

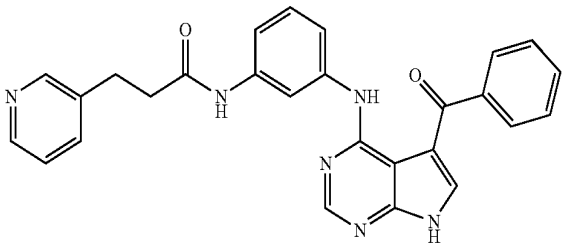
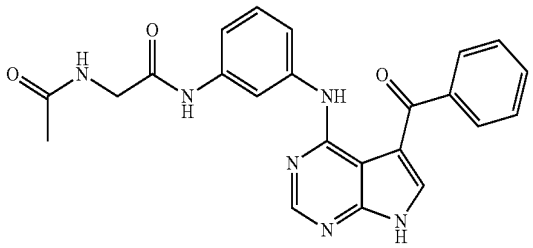
Compound No.	Structure	Chemical Name
1		N-(3-(3-benzoyl-1H-indol-4-ylamino)phenyl)-3-(pyridin-3-yl)propanamide
2		2-acetamido-N-(3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)acetamide

TABLE 1-continued

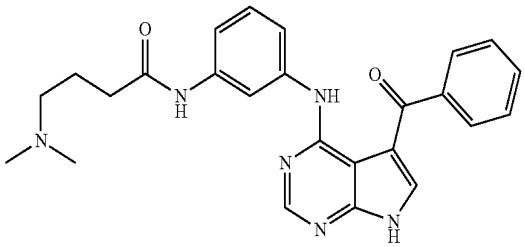
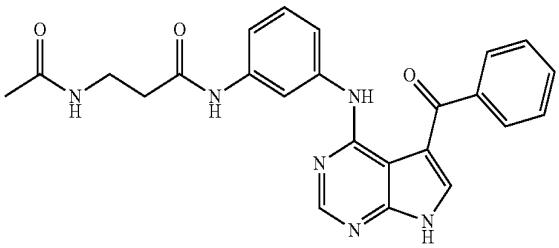
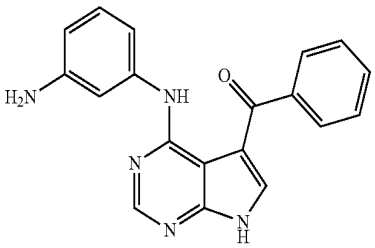
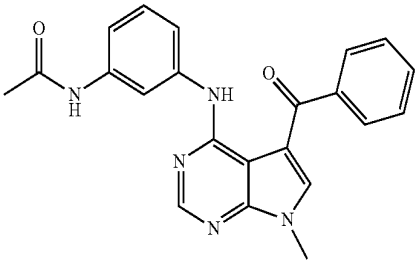
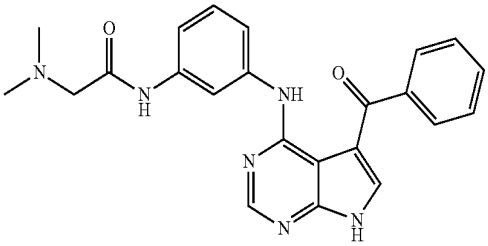
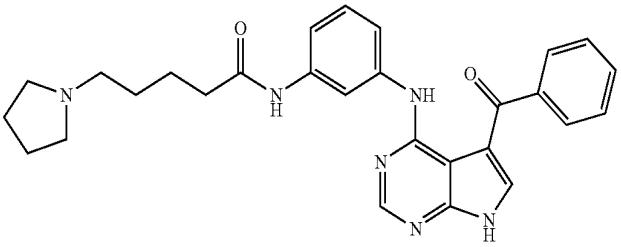
Compound No.	Structure	Chemical Name
3		N-(3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)-4-(dimethylamino)butanamide
4		3-acetamido-N-(3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)propanamide
5		(4-(3-aminophenylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone
6		N-(3-(5-benzoyl-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)acetamide
7		N-(3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)-2-(dimethylamino)acetamide
8		N-(3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)-5-(pyrrolidin-1-yl)pentanamide

TABLE 1-continued

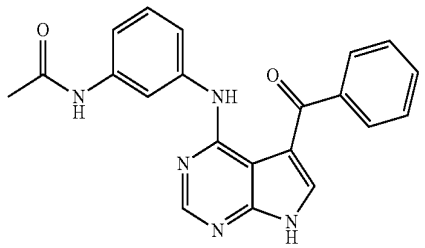
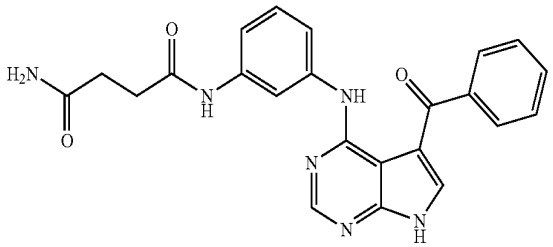
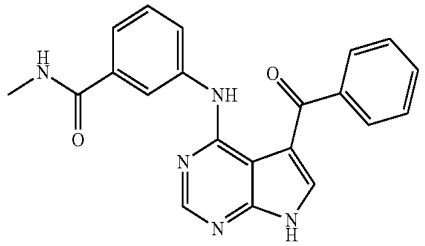
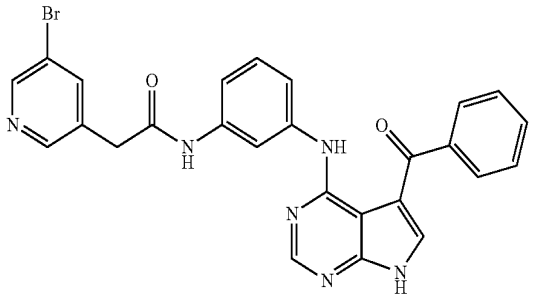
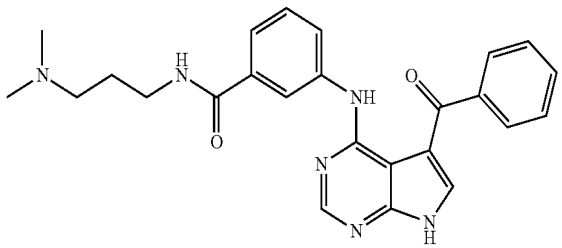
Compound No.	Structure	Chemical Name
9		N-(3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)acetamide
10		N^1-(3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)succinamide
11		3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-N-methylbenzamide
12		N-(3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)-2-(5-bromopyridin-3-yl)acetamide
13		3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-N-(3-(dimethylamino)propyl)benzamide

TABLE 1-continued

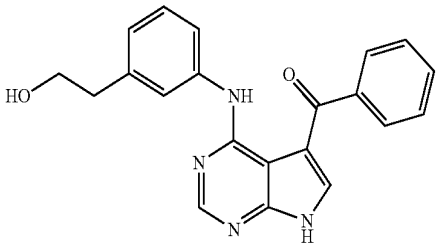
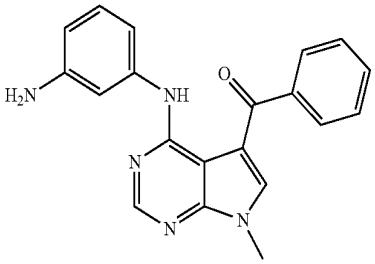
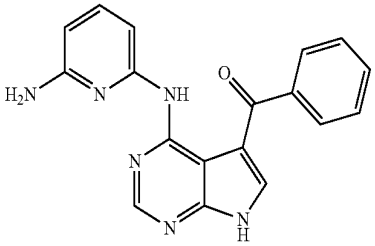
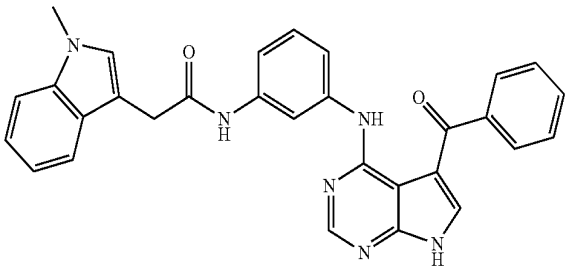
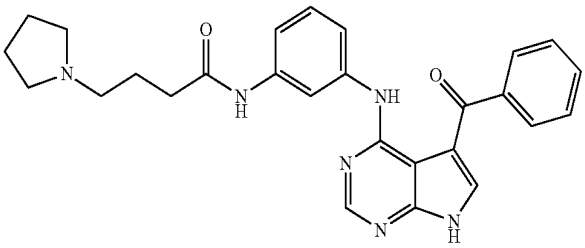
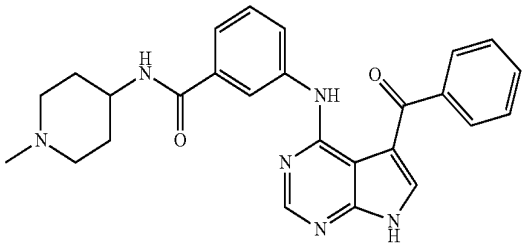
Compound No.	Structure	Chemical Name
14		(4-(3-(2-hydroxyethyl)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone
15		(4-(3-aminophenylamino)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone
16		(4-(6-aminopyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone
17		N-(3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)-2-(1-methyl-1H-indol-3-yl)acetamide
18		N-(3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)-4-(pyrrolidin-1-yl)butanamide
19		3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-N-(1-methylpiperidin-4-yl)benzamide

TABLE 1-continued

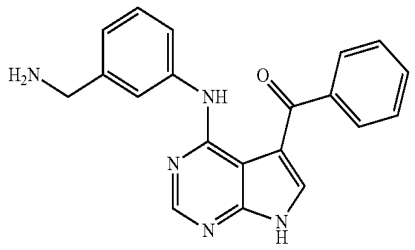
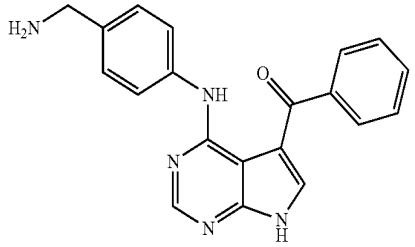
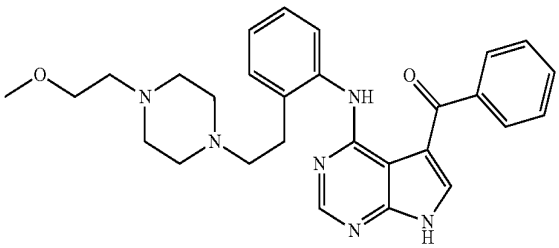
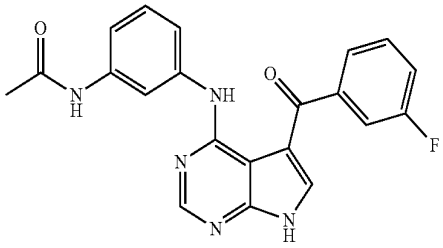
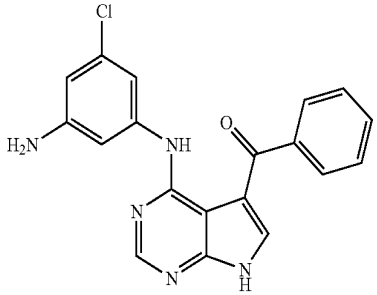
Compound No.	Structure	Chemical Name
20		(4-(3-(aminomethyl)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone
21		(4-(4-(aminomethyl)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone
22		(4-(2-(2-(4-(2-methoxyethyl)piperazin-1-yl)ethyl)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone
23		N-(3-(5-(3-fluorobenzoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)acetamide
24		(4-(3-amino-5-chlorophenylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone

TABLE 1-continued

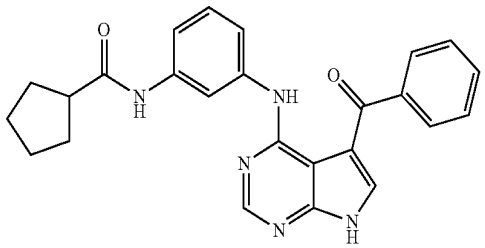
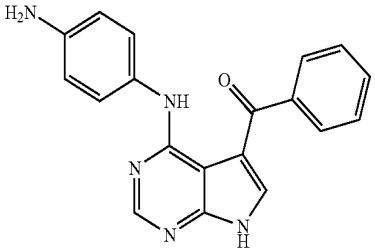
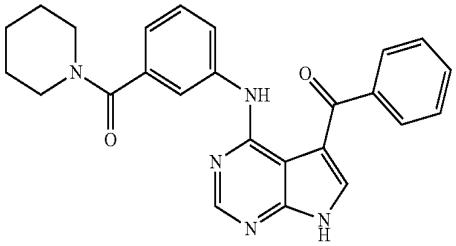
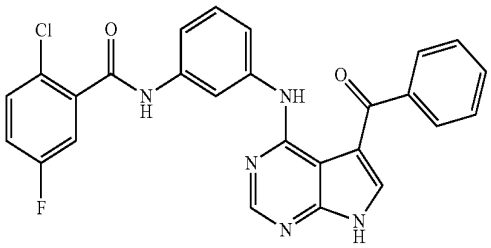
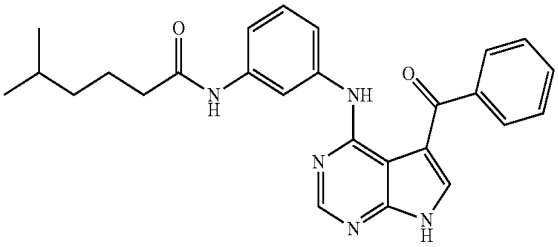
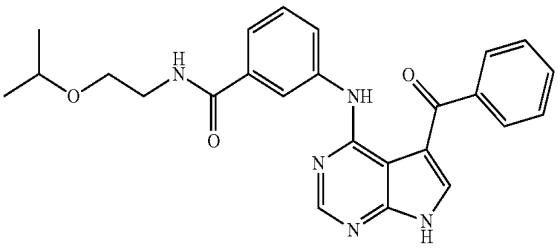
Compound No.	Structure	Chemical Name
25		N-(3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino) phenyl)cyclopentanecarboxamide
26		(4-(4-aminophenylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone
27		(3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)(piperidin-1-yl)methanone
28		N-(3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)-2-chloro-5-fluorobenzamide
29		N-(3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)-5-methylhexanamide
30		3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-N-(2-isopropoxyethyl)benzamide

TABLE 1-continued

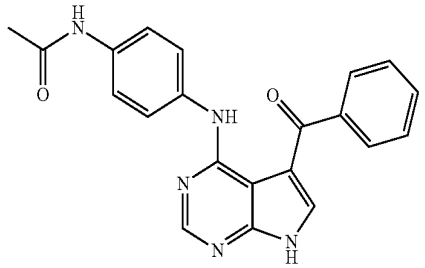
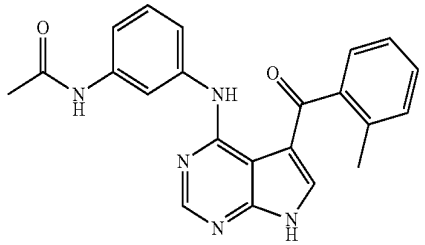
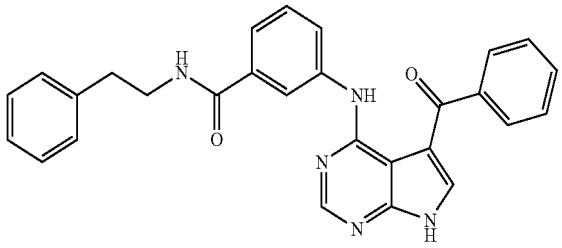
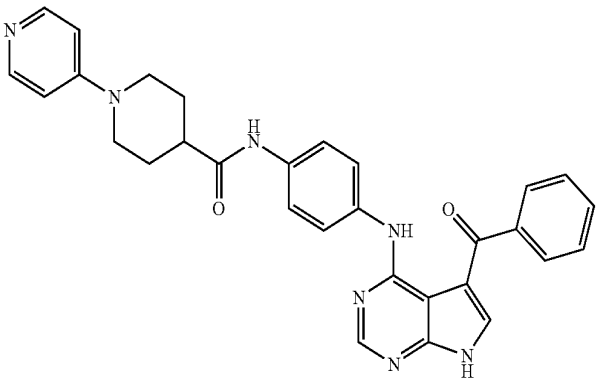
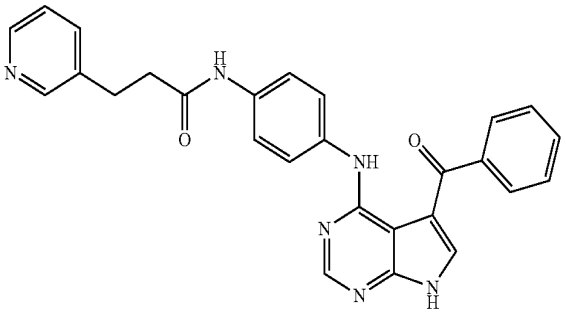
Compound No.	Structure	Chemical Name
31		N-(4-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)acetamide
32		N-(3-(5-(2-methylbenzoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)acetamide
33		3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-N-phenethylbenzamide
34		N-(4-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)-1-(pyridin-4-yl)piperidine-4-carboxamide
35		N-(4-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)-3-(pyridin-3-yl)propanamide

TABLE 1-continued

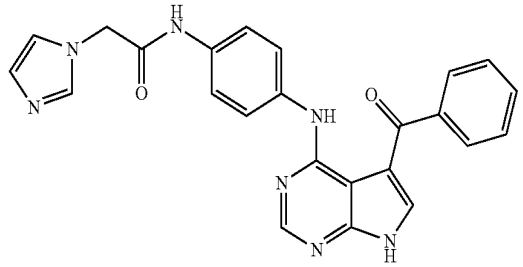
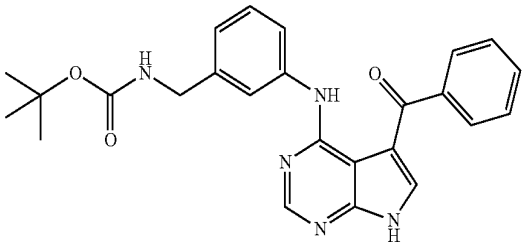
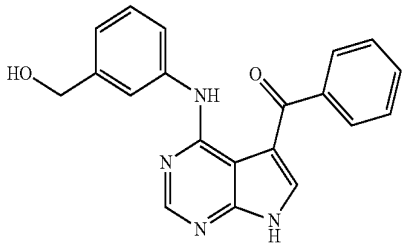
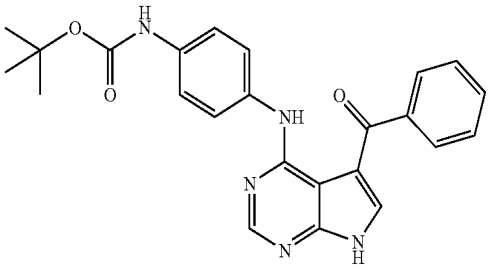
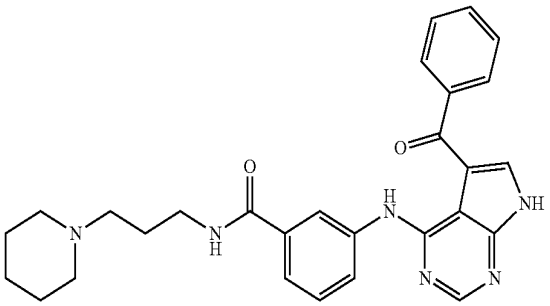
Compound No.	Structure	Chemical Name
36		N-(4-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)-2-(1H-imidazol-1-yl)acetamide
37		tert-butyl 3-(5-benzoyl-7H)-pyrrolo[2,3-d]pyrimidin-4-ylamino) benzylcarbamate
38		(4-(3-(hydroxymethyl)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone
39		tert-butyl 4-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenylcarbamate
40		3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-N-(3-(piperidin-1-yl)propyl)benzamide

TABLE 1-continued

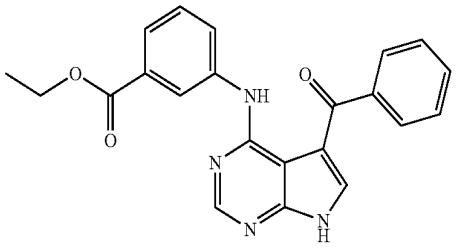
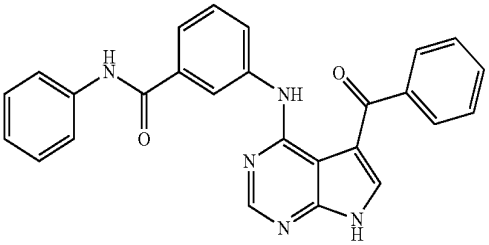
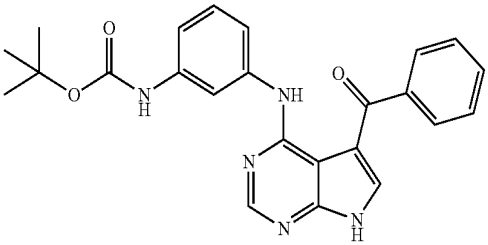
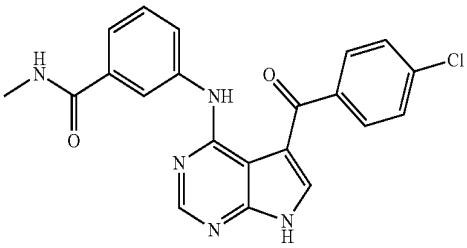
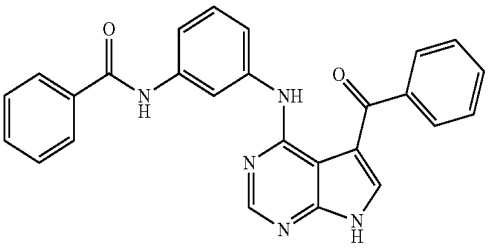
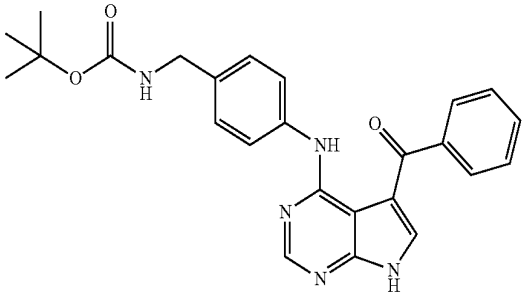
Compound No.	Structure	Chemical Name
41		ethyl 3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)benzoate
42		3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino-N-phenylbenzamide
43		tert-butyl(3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)phenyl)acetamide
44		3-((5-(4-chlorobenzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino-N-methylbenzamide
45		N-3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)phenyl)benzamide
46		tert-butyl 4-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)benzylcarbamate

TABLE 1-continued

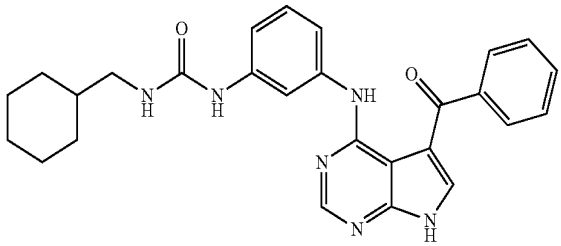
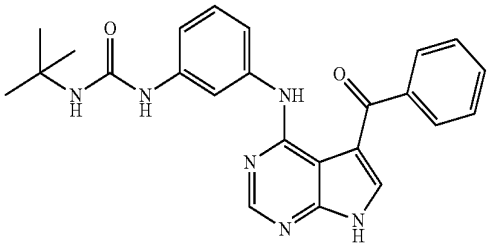
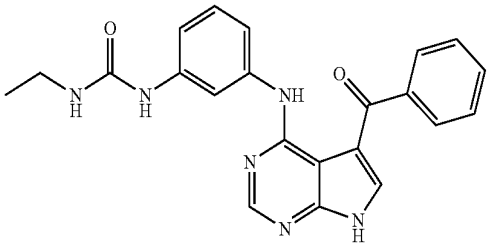
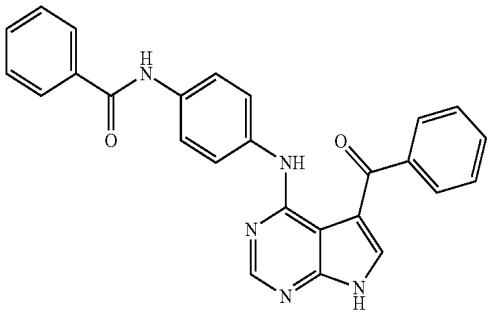
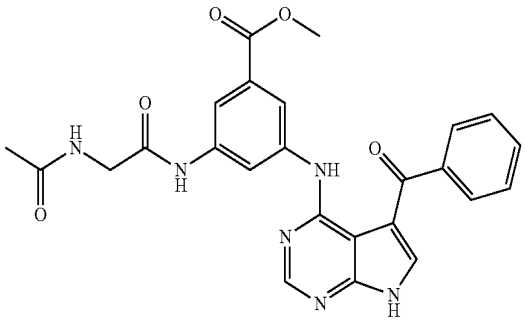
Compound No.	Structure	Chemical Name
47		1-3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)phenyl)-3-(cyclohexylmethyl)urea
48		1-3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)phenyl)-3-(tert-butyl)urea
49		1-3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)phenyl)-3-ethylurea
50		N-4-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)phenyl)benzamide
51		methyl 3-(2-acetamidoacetamido)-5-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)benzoate

TABLE 1-continued

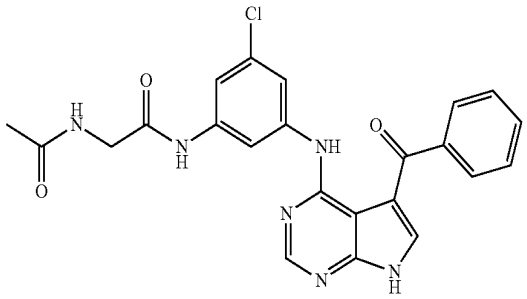
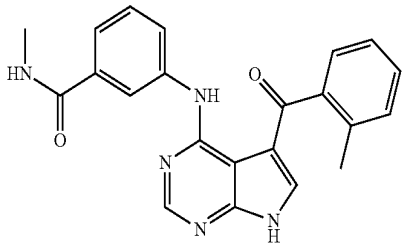
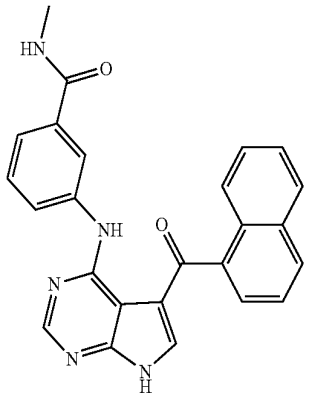
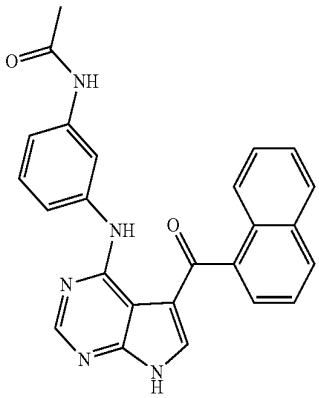
Compound No.	Structure	Chemical Name
52		2-acetamido-N-(3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-chlorophenyl)acetamide
53		N-methyl-3-((5-(2-methylbenzoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)benzamide
54		3-((5-(1-naphthoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-N-methylbenzamide
55		N-(3-((5-(1-naphthoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)acetamide

TABLE 1-continued

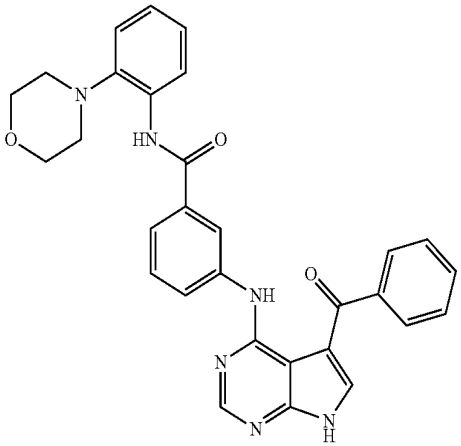
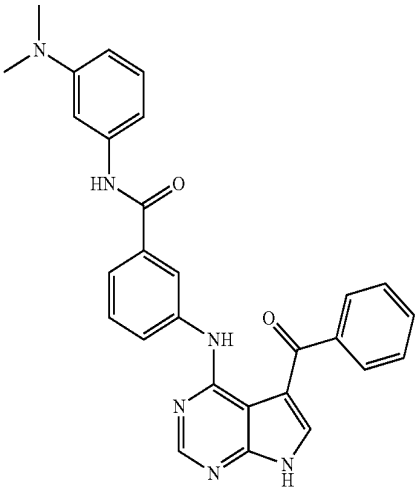
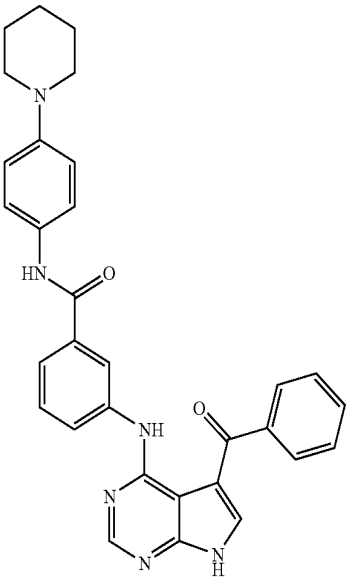
Compound No.	Structure	Chemical Name
56		3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(2-morpholin-4-ylphenyl)benzamide
57		3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-[3-(dimethylamino)phenyl]benzamide
58		3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(4-piperidin-1-ylphenyl)benzamide

TABLE 1-continued

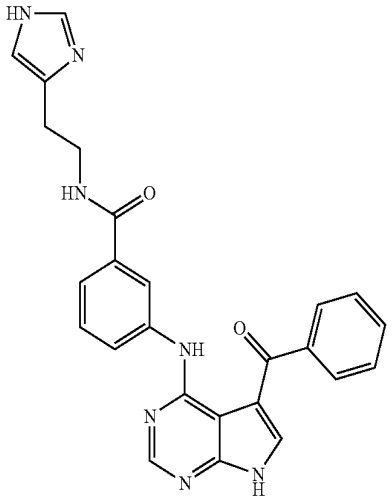
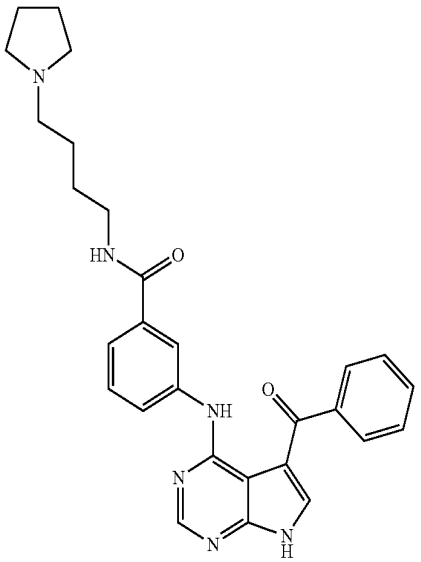
Compound No.	Structure	Chemical Name
59		3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-[2-(1H-imidazol-4-yl)ethyl]benzamide
60		3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(4-pyrrolidin-1-ylbutyl)benzamide

TABLE 1-continued

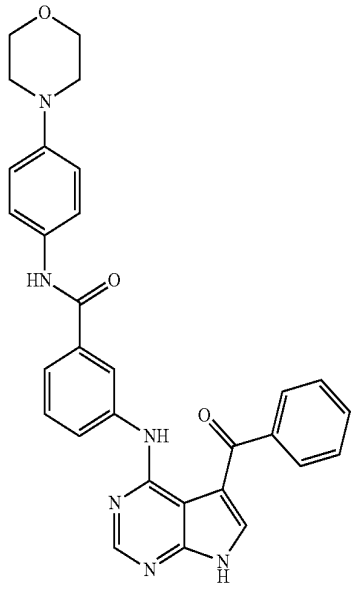
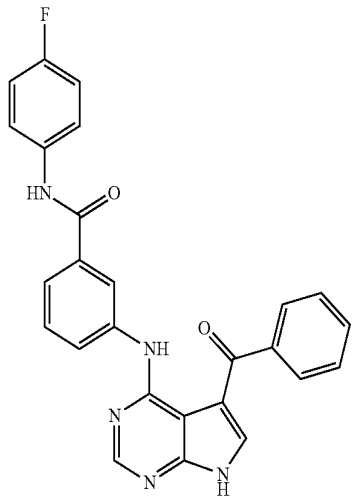
Compound No.	Structure	Chemical Name
61		3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(4-morpholin-4-ylphenyl)benzamide
62		3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(4-fluorophenyl)benzamide

TABLE 1-continued

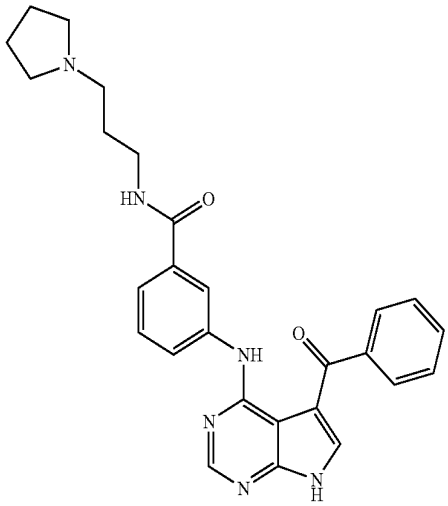
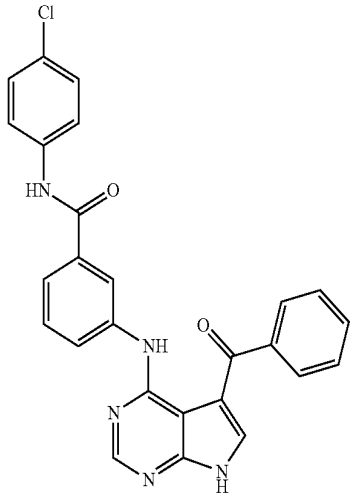
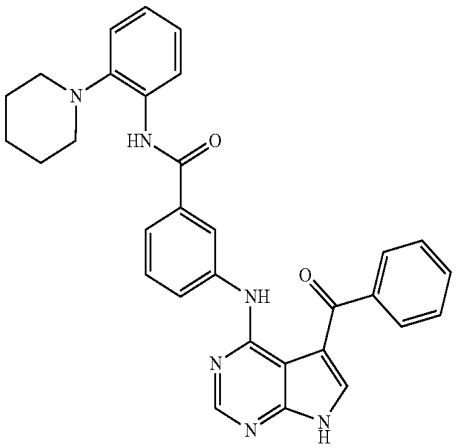
Compound No.	Structure	Chemical Name
63		3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(3-pyrrolidin-1-ylpropyl)benzamide
64		3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(4-chlorophenyl)benzamide
65		3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(2-piperidin-1-ylphenyl)benzamide

TABLE 1-continued

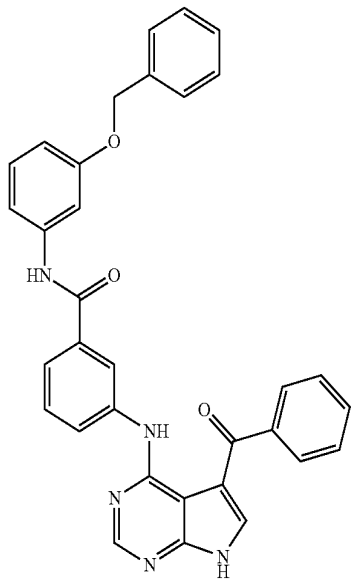
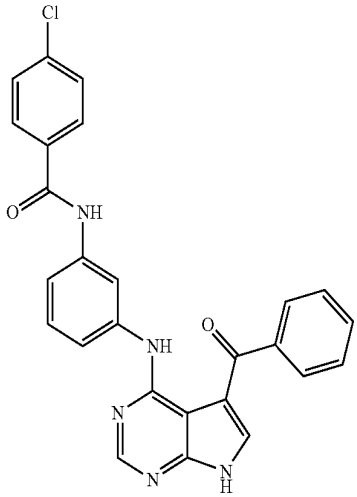
Compound No.	Structure	Chemical Name
66		3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-[3-(benzyloxy)phenyl]benzamide
67		4-chloro-N-(3-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)benzamide

TABLE 1-continued

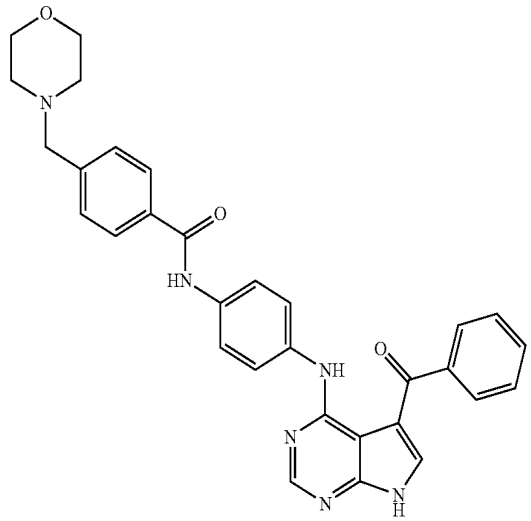
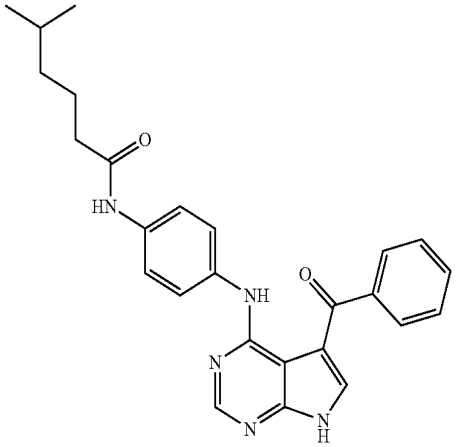
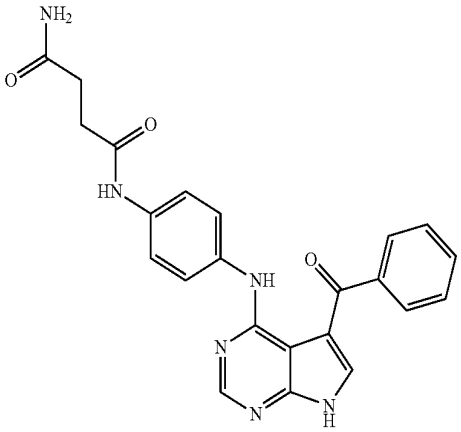
Compound No.	Structure	Chemical Name
68		4-(morpholin-4-ylmethyl)-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)benzamide
69		5-methyl-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)hexanamide
70		N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)butanediamide

TABLE 1-continued

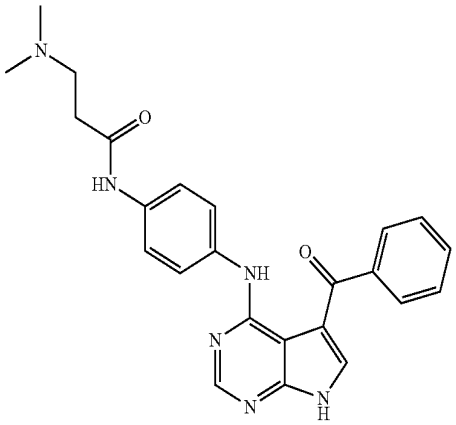
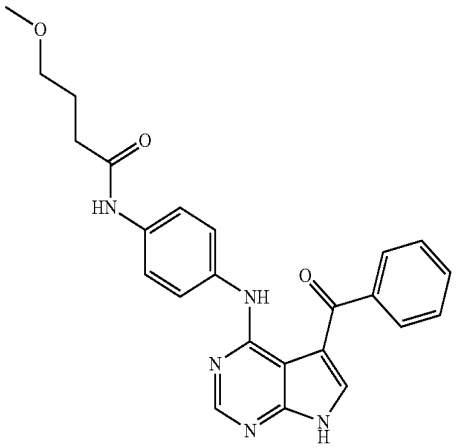
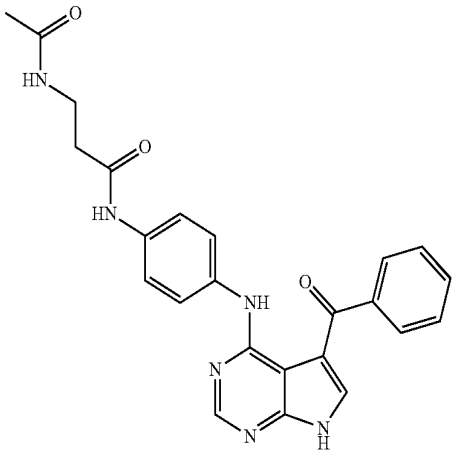
Compound No.	Structure	Chemical Name
71		N-(4-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)-3-(dimethylamino)propanamide
72		4-methoxy-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)butanamide
73		3-acetamido-N-(4-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)propanamide

TABLE 1-continued

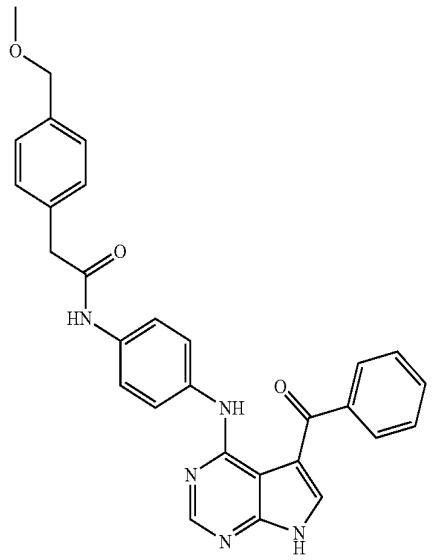
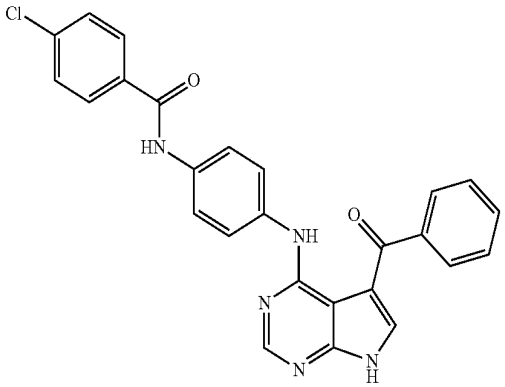
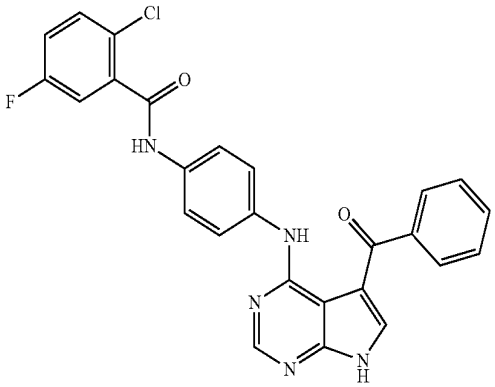
Compound No.	Structure	Chemical Name
74		2-[4-(methoxymethyl)phenyl]-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)acetamide
75		4-chloro-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)benzamide
76		2-chloro-5-fluoro-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)benzamide

TABLE 1-continued

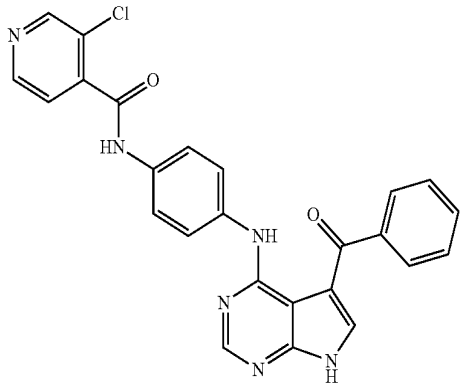
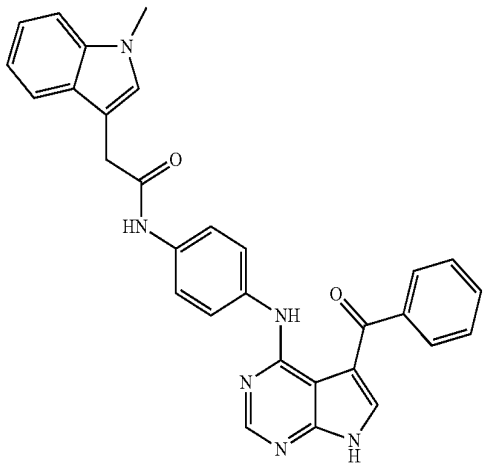
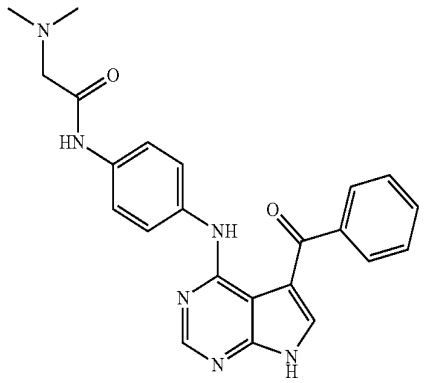
Compound No.	Structure	Chemical Name
77		3-chloro-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)pyridine-4-carboxamide
78		2-(1-methyl-1H-indol-3-yl)-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)acetamide
79		N-(4-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)-2-(dimethylamino)acetamide

TABLE 1-continued

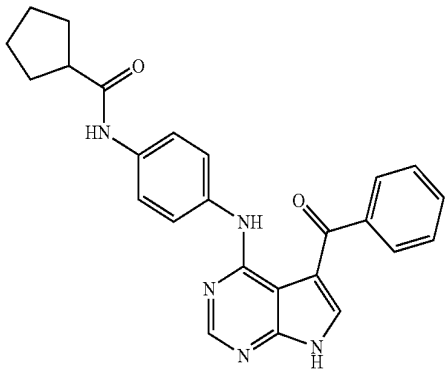
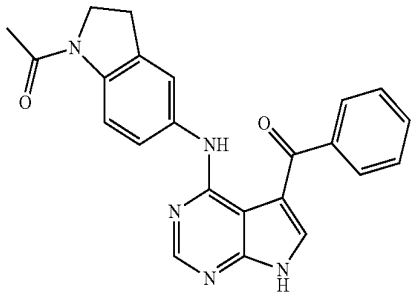
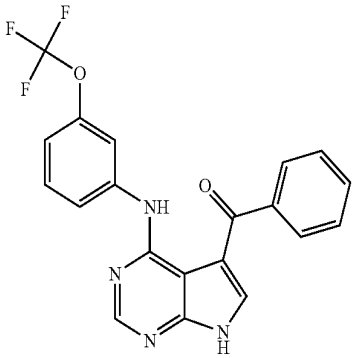
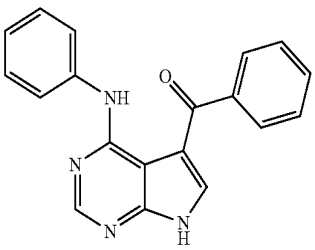
Compound No.	Structure	Chemical Name
80		N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)cyclopentanecarboxamide
81		1-(5-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)indolin-1-yl)ethanone
82		phenyl(4-((3-(trifluoromethoxy)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone
83		phenyl(4-(phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone

TABLE 1-continued

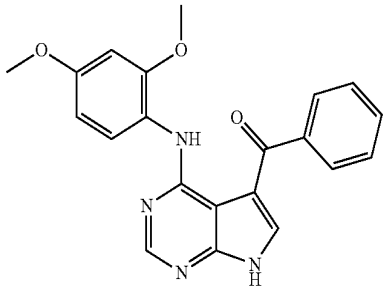
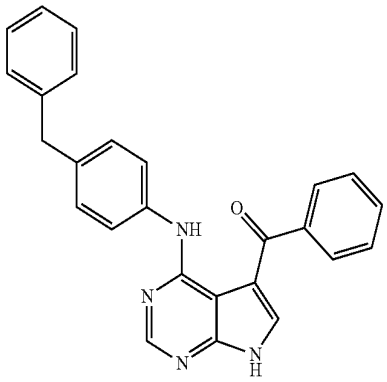
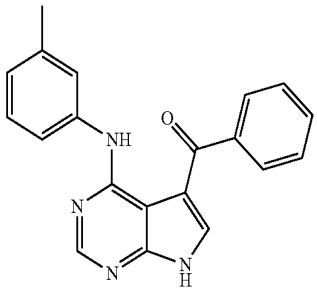
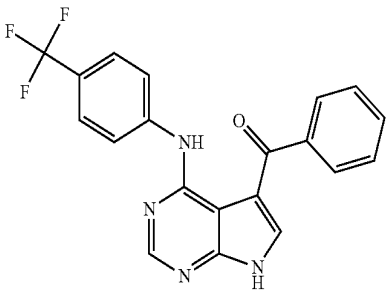
Compound No.	Structure	Chemical Name
84		(4-((2,4-dimethoxyphenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone
85		(4-((4-benzylphenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone
86		phenyl(4-(m-tolylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl) methanone
87		phenyl(4-((4-(trifluoromethyl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone

TABLE 1-continued

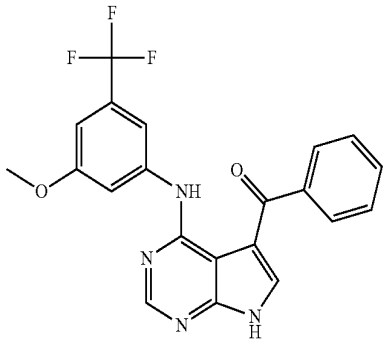
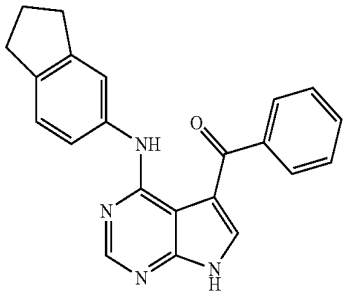
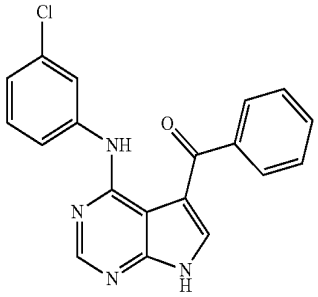
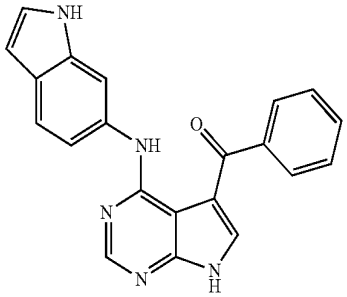
Compound No.	Structure	Chemical Name
88		(4-((3-methoxy-5-(trifluoromethyl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone
89		(4-((2,3-dihydro-1H-inden-5-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone
90		(4-((3-chlorophenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone
91		(4-((1H-indol-6-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone

TABLE 1-continued

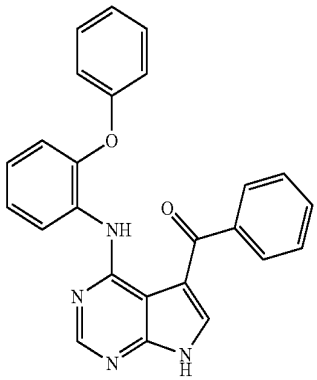
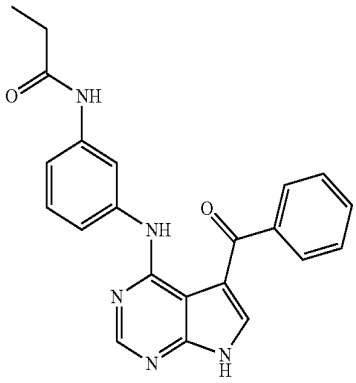
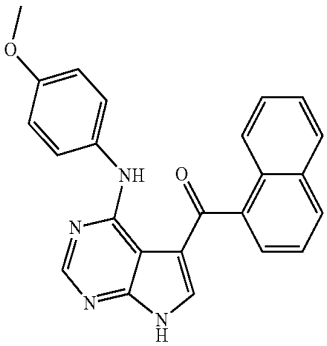
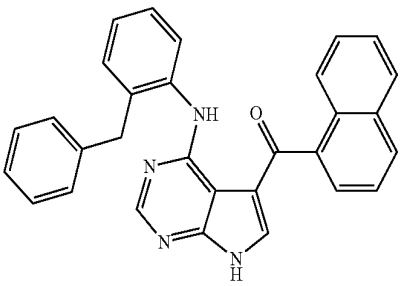
Compound No.	Structure	Chemical Name
92		(4-((2-phenoxyphenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone
93		N-(3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)propionamide
94		(4-((4-methoxyphenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone
95		(4-((2-benzylphenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone

TABLE 1-continued

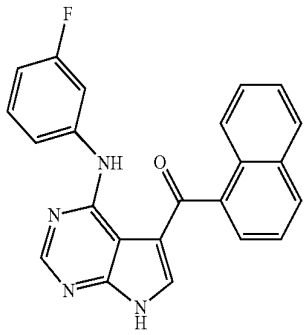
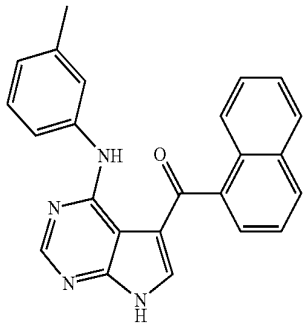
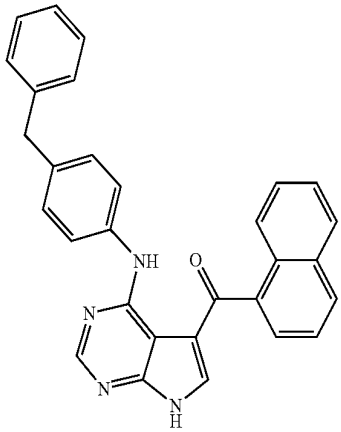
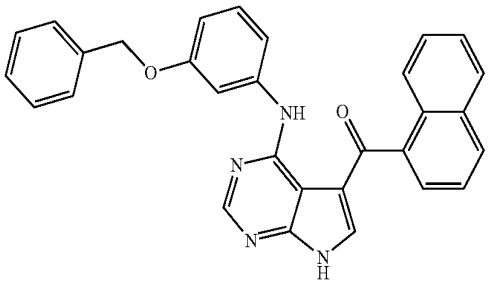
Compound No.	Structure	Chemical Name
96		(4-((3-fluorophenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone
97		naphthalen-1-yl(4-(m-tolylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone
98		(4-((4-benzylphenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone
99		(4-((3-(benzyloxy)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone

TABLE 1-continued

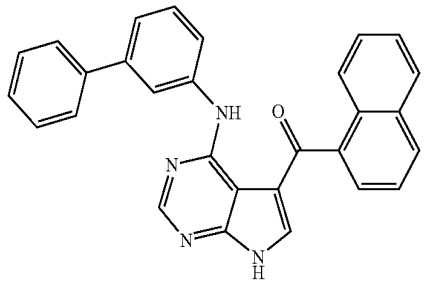
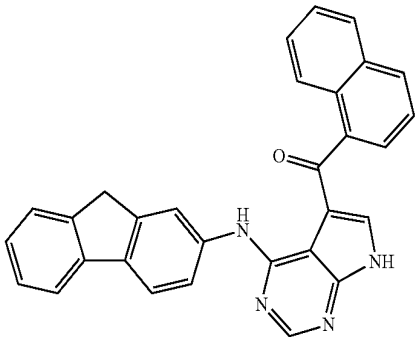
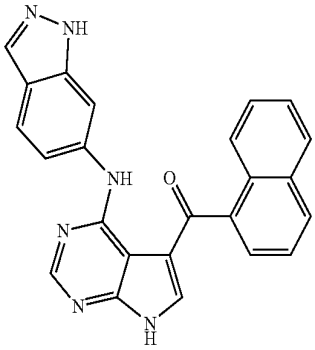
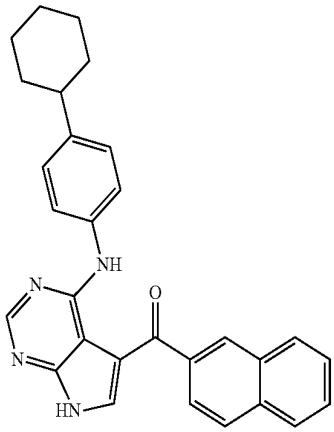
Compound No.	Structure	Chemical Name
100		(4-([1,1'-biphenyl]-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone
101		(4-((9H-fluoren-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone
102		(4-((1H-indazol-6-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone
103		(4-((4-cyclohexylphenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-2-yl)methanone

TABLE 1-continued

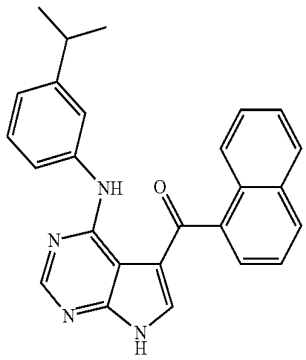
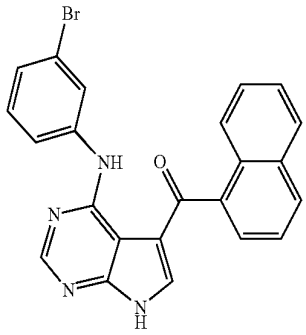
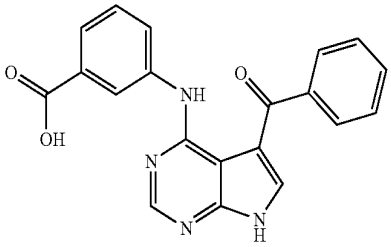
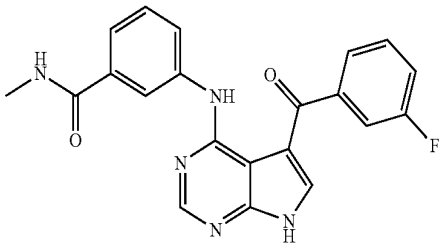
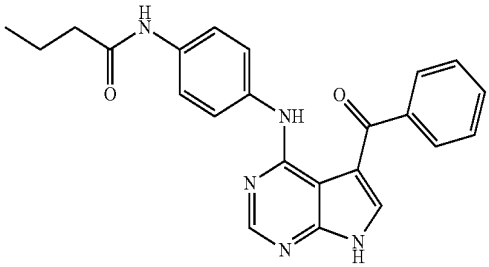
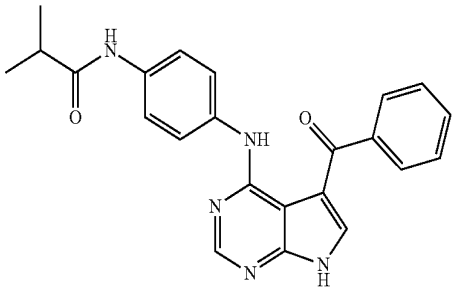
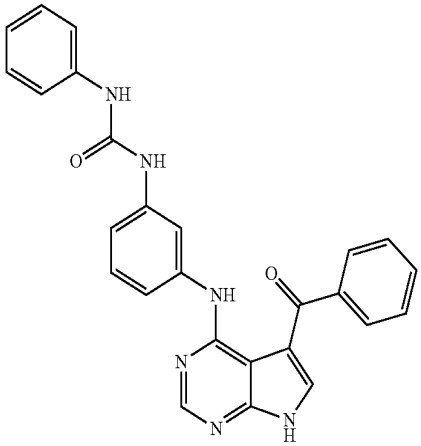
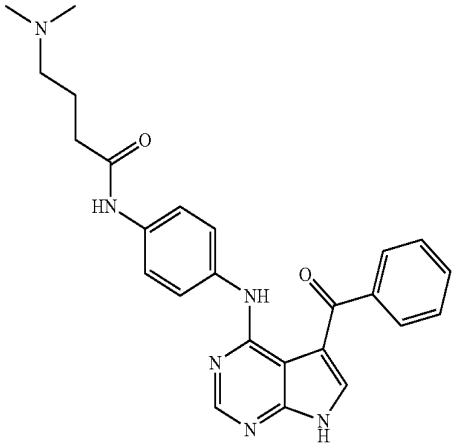
Compound No.	Structure	Chemical Name
104		(4-((3-isopropylphenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone
105		(4-((3-bromophenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone
106		3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]benzoic acid
107		3-{[5-(3-fluorobenzoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}-N-methylbenzamide
108		N-{4-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]phenyl}butanamide

TABLE 1-continued

Compound No.	Structure	Chemical Name
109		N-{4-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]phenyl}-2-methylpropanamide
110		1-phenyl-3-(3-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)urea
111		4-(dimethylamino)-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)butanamide

[0457] As used herein, "alkyl", "C_1, C_2, C_3, C_4, C_5 or C_6 alkyl" or "C_1-C_6 alkyl" is intended to include C_1, C_2, C_3, C_4, C_5 or C_6 straight chain (linear) saturated aliphatic hydrocarbon groups and C_3, C_4, C_5 or C_6 branched saturated aliphatic hydrocarbon groups.

[0458] For example, C_1-C_6 alkyl is intended to include C_1, C_2, C_3, C_4, C_5 and C_6 alkyl groups. Examples of alkyl include, moieties having from one to six carbon atoms, such as, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl or n-hexyl.

[0459] In certain embodiments, a straight chain or branched alkyl has six or fewer carbon atoms (e.g., C_1-C_6 for straight chain, C_3-C_6 for branched chain), and in another embodiment, a straight chain or branched alkyl has four or fewer carbon atoms.

[0460] "Heteroalkyl" groups are alkyl groups, as defined above, that have an oxygen, nitrogen, sulfur or phosphorous atom replacing one or more hydrocarbon backbone carbon atoms.

[0461] As used herein, the term "cycloalkyl", "C_3, C_4, C_5, C_6, C_7 or C_8 cycloalkyl" or "C_3-C_8 cycloalkyl" is intended to include hydrocarbon rings having from three to eight carbon atoms in their ring structure. In one embodiment, a cycloalkyl group has five or six carbons in the ring structure.

[0462] The term "substituted alkyl" refers to alkyl moieties having substituents replacing one or more hydrogen atoms on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen (i.e., haloalkyl), hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Cycloalkyls can be further substituted, e.g., with the substituents described above. An "alkylaryl" or an "aralkyl" moiety is an alkyl substituted with an aryl (e.g., phenylmethyl (benzyl)).

[0463] Unless the number of carbons is otherwise specified, "lower alkyl" includes an alkyl group, as defined above, having from one to six, or in another embodiment from one to four, carbon atoms in its backbone structure. "Lower alkenyl" and "lower alkynyl" have chain lengths of, for example, two to six or of two to four carbon atoms.

[0464] As used herein, "alkyl linker" is intended to include C_1, C_2, C_3, C_4, C_5 or C_6 straight chain (linear) saturated aliphatic hydrocarbon groups and C_3, C_4, C_5 or C_6 branched saturated aliphatic hydrocarbon groups. For example, C_1-C_6 alkyl linker is intended to include C_1, C_2, C_3, C_4, C_5 and C_6 alkyl linker groups. Examples of alkyl linker include, moieties having from one to six carbon atoms, such as, but not limited to, methyl (—CH_2—), ethyl (—CH_2CH_2—), n-propyl (—$CH_2CH_2CH_2$—), i-propyl (—$CHCH_3CH_2$—), n-butyl (—$CH_2CH_2CH_2CH_2$—), s-butyl (—$CHCH_3CH_2CH_2$—), i-butyl (—$C(CH_3)_2CH_2$—), n-pentyl (—$CH_2CH_2CH_2CH_2CH_2$—), s-pentyl (—$CHCH_3CH_2CH_2CH_2$—) or n-hexyl (—$CH_2CH_2CH_2CH_2CH_2CH_2$—).

[0465] "Alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond. For example, the term "alkenyl" includes straight chain alkenyl groups (e.g., ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl), branched alkenyl groups, cycloalkenyl (e.g., alicyclic) groups (e.g., cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), alkyl or alkenyl substituted cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkenyl groups. In certain embodiments, a straight chain or branched alkenyl group has six or fewer carbon atoms in its backbone (e.g., C_2-C_6 for straight chain, C_3-C_6 for branched chain). Likewise, cycloalkenyl groups may have from five to eight carbon atoms in their ring structure, and in one embodiment, cycloalkenyl groups have five or six carbons in the ring structure. The term "C_2-C_6" includes alkenyl groups containing two to six carbon atoms. The term "C_3-C_6" includes alkenyl groups containing three to six carbon atoms.

[0466] "Heteroalkenyl" includes alkenyl groups, as defined herein, having an oxygen, nitrogen, sulfur or phosphorous atom replacing one or more hydrocarbon backbone carbons.

[0467] The term "substituted alkenyl" refers to alkenyl moieties having substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0468] "Alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond. For example, "alkynyl" includes straight chain alkynyl groups (e.g., ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl), branched alkynyl groups, and cycloalkyl or cycloalkenyl substituted alkynyl groups. In certain embodiments, a straight chain or branched alkynyl group has six or fewer carbon atoms in its backbone (e.g., C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term "C_2-C_6" includes alkynyl groups containing two to six carbon atoms. The term "C_3-C_6" includes alkynyl groups containing three to six carbon atoms.

[0469] "Heteroalkynyl" includes alkynyl groups, as defined herein, having an oxygen, nitrogen, sulfur or phosphorous atom replacing one or more hydrocarbon backbone carbons.

[0470] The term "substituted alkynyl" refers to alkynyl moieties having substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0471] "Aryl" includes groups with aromaticity, including "conjugated", or multicyclic, systems with at least one aromatic ring. Examples include phenyl, benzyl, etc.

[0472] "Heteroaryl" groups are aryl groups, as defined above, having from one to four heteroatoms in the ring structure, and may also be referred to as "aryl heterocycles" or "heteroaromatics". As used herein, the term "heteroaryl" is intended to include a stable 5-, 6-, or 7-membered monocyclic or 7-, 8-, 9-, 10-, 11- or 12-membered bicyclic aromatic heterocyclic ring which consists of carbon atoms and one or more heteroatoms, e.g., 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen and sulfur. The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or other substituents, as defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (i.e., N→O and $S(O)_p$,

where p=one or two). It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1.

[0473] Examples of heteroaryl groups include pyrrole, furan, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isoxazole, pyridine, pyrazine, pyridazine, pyrimidine, and the like.

[0474] Furthermore, the terms "aryl" and "heteroaryl" include multicyclic aryl and heteroaryl groups, e.g., tricyclic, bicyclic, e.g., naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, methylenedioxyphenyl, quinoline, isoquinoline, naphthridine, indole, benzofuran, purine, benzofuran, deazapurine, indolizine.

[0475] In the case of multicyclic aromatic rings, only one of the rings needs to be aromatic (e.g., 2,3-dihydroindole), although all of the rings may be aromatic (e.g., quinoline). The second ring can also be fused or bridged.

[0476] The aryl or heteroaryl aromatic ring can be substituted at one or more ring positions with such substituents as described above, for example, alkyl, alkenyl, akynyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminocarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings, which are not aromatic so as to form a multicyclic system (e.g., tetralin, methylenedioxyphenyl).

[0477] As used herein, "carbocycle" or "carbocyclic ring" is intended to include any stable monocyclic, bicyclic or tricyclic ring having the specified number of carbons, any of which may be saturated, unsaturated, or aromatic. For example, a C_3-C_{14} carbocycle is intended to include a monocyclic, bicyclic or tricyclic ring having 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms. Examples of carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, fluorenyl, phenyl, naphthyl, indanyl, adamantyl and tetrahydronaphthyl. Bridged rings are also included in the definition of carbocycle, including, for example, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane and [2.2.2]bicyclooctane. A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. In one embodiment, bridge rings are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge. Fused (e.g., naphthyl, tetrahydronaphthyl) and spiro rings are also included.

[0478] As used herein, "heterocycle" includes any ring structure (saturated or partially unsaturated) which contains at least one ring heteroatom (e.g., N, O or S). Examples of heterocycles include, but are not limited to, morpholine, pyrrolidine, tetrahydrothiophene, piperidine, piperazine and tetrahydrofuran.

[0479] Examples of heterocyclic groups include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazol5(4H)-one, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl.

[0480] The term "substituted", as used herein, means that any one or more hydrogen atoms on the designated atom is replaced with a selection from the indicated groups, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogen atoms on the atom are replaced. Keto substituents are not present on aromatic moieties. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (e.g., C=C, C=N or N=N). "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[0481] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom in the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such formula. Combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0482] When any variable (e.g., R_5) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R_5 moieties, then the group may optionally be substituted with up to two R_5 moieties and R_5 at each occurrence is selected independently from the definition of R_5. Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0483] The term "hydroxy" or "hydroxyl" includes groups with an —OH or —O^-.

[0484] As used herein, "halo" or "halogen" refers to fluoro, chloro, bromo and iodo. The term "perhalogenated" generally refers to a moiety wherein all hydrogen atoms are replaced by halogen atoms.

[0485] The term "carbonyl" or "carboxy" includes compounds and moieties which contain a carbon connected with a double bond to an oxygen atom. Examples of moieties containing a carbonyl include, but are not limited to, aldehydes, ketones, carboxylic acids, amides, esters, anhydrides, etc.

[0486] "Acyl" includes moieties that contain the acyl radical (—C(O)—) or a carbonyl group. "Substituted acyl" includes acyl groups where one or more of the hydrogen atoms are replaced by, for example, alkyl groups, alkynyl groups, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0487] "Aroyl" includes moieties with an aryl or heteroaromatic moiety bound to a carbonyl group. Examples of aroyl groups include phenylcarboxy, naphthyl carboxy, etc.

[0488] "Alkoxyalkyl", "alkylaminoalkyl" and "thioalkoxyalkyl" include alkyl groups, as described above, wherein oxygen, nitrogen or sulfur atoms replace one or more hydrocarbon backbone carbon atoms.

[0489] The term "alkoxy" or "alkoxyl" includes substituted and unsubstituted alkyl, alkenyl and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups or alkoxyl radicals include, but are not limited to, methoxy, ethoxy, isopropyloxy, propoxy, butoxy and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy and trichloromethoxy.

[0490] The term "ether" or "alkoxy" includes compounds or moieties which contain an oxygen atom bonded to two carbon atoms or heteroatoms. For example, the term includes "alkoxyalkyl", which refers to an alkyl, alkenyl, or alkynyl group covalently bonded to an oxygen atom which is covalently bonded to an alkyl group.

[0491] The term "ester" includes compounds or moieties which contain a carbon or a heteroatom bound to an oxygen atom which is bonded to the carbon of a carbonyl group. The term "ester" includes alkoxycarboxy groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, etc.

[0492] The term "thioalkyl" includes compounds or moieties which contain an alkyl group connected with a sulfur atom. The thioalkyl groups can be substituted with groups such as alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, carboxyacid, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties.

[0493] The term "thiocarbonyl" or "thiocarboxy" includes compounds and moieties which contain a carbon connected with a double bond to a sulfur atom.

[0494] The term "thioether" includes moieties which contain a sulfur atom bonded to two carbon atoms or heteroatoms. Examples of thioethers include, but are not limited to alkthioalkyls, alkthioalkenyls and alkthioalkynyls. The term "alkthioalkyls" include moieties with an alkyl, alkenyl or alkynyl group bonded to a sulfur atom which is bonded to an alkyl group. Similarly, the term "alkthioalkenyls" refers to moieties wherein an alkyl, alkenyl or alkynyl group is bonded to a sulfur atom which is covalently bonded to an alkenyl group; and alkthioalkynyls" refers to moieties wherein an alkyl, alkenyl or alkynyl group is bonded to a sulfur atom which is covalently bonded to an alkynyl group.

[0495] As used herein, "amine" or "amino" includes moieties where a nitrogen atom is covalently bonded to at least one carbon or heteroatom. "Alkylamino" includes groups of compounds wherein nitrogen is bound to at least one alkyl group. Examples of alkylamino groups include benzylamino, methylamino, ethylamino, phenethylamino, etc. "Dialkylamino" includes groups wherein the nitrogen atom is bound to at least two additional alkyl groups. Examples of dialkylamino groups include, but are not limited to, dimethylamino and diethylamino. "Arylamino" and "diarylamino" include groups wherein the nitrogen is bound to at least one or two aryl groups, respectively. "Alkylarylamino", "alkylaminoaryl" or "arylaminoalkyl" refers to an amino group which is bound to at least one alkyl group and at least one aryl group. "Alkaminoalkyl" refers to an alkyl, alkenyl, or alkynyl group bound to a nitrogen atom which is also bound to an alkyl group. "Acylamino" includes groups wherein nitrogen is bound to an acyl group. Examples of acylamino include, but are not limited to, alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido groups.

[0496] The term "amide" or "aminocarboxy" includes compounds or moieties that contain a nitrogen atom that is bound to the carbon of a carbonyl or a thiocarbonyl group. The term includes "alkaminocarboxy" groups that include alkyl, alkenyl or alkynyl groups bound to an amino group which is bound to the carbon of a carbonyl or thiocarbonyl group. It also includes "arylaminocarboxy" groups that include aryl or heteroaryl moieties bound to an amino group

that is bound to the carbon of a carbonyl or thiocarbonyl group. The terms "alkylaminocarboxy", "alkenylaminocarboxy", "alkynylaminocarboxy" and "arylaminocarboxy" include moieties wherein alkyl, alkenyl, alkynyl and aryl moieties, respectively, are bound to a nitrogen atom which is in turn bound to the carbon of a carbonyl group. Amides can be substituted with substituents such as straight chain alkyl, branched alkyl, cycloalkyl, aryl, heteroaryl or heterocycle. Substituents on amide groups may be further substituted.

[0497] Compounds of the present invention that contain nitrogens can be converted to N-oxides by treatment with an oxidizing agent (e.g., 3-chloroperoxybenzoic acid (m-CPBA) and/or hydrogen peroxides) to afford other compounds of the present invention. Thus, all shown and claimed nitrogen-containing compounds are considered, when allowed by valency and structure, to include both the compound as shown and its N-oxide derivative (which can be designated as N→O or N^+—O^-). Furthermore, in other instances, the nitrogens in the compounds of the present invention can be converted to N-hydroxy or N-alkoxy compounds. For example, N-hydroxy compounds can be prepared by oxidation of the parent amine by an oxidizing agent such as m-CPBA. All shown and claimed nitrogen-containing compounds are also considered, when allowed by valency and structure, to cover both the compound as shown and its N-hydroxy (i.e., N—OH) and N-alkoxy (i.e., N—OR, wherein R is substituted or unsubstituted C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, 3-14-membered carbocycle or 3-14-membered heterocycle) derivatives.

[0498] In the present specification, the structural formula of the compound represents a certain isomer for convenience in some cases, but the present invention includes all isomers, such as geometrical isomers, optical isomers based on an asymmetrical carbon, stereoisomers, tautomers, and the like. In addition, a crystal polymorphism may be present for the compounds represented by the formula. It is noted that any crystal form, crystal form mixture, or anhydride or hydrate thereof is included in the scope of the present invention. Furthermore, so-called metabolite which is produced by degradation of the present compound in vivo is included in the scope of the present invention.

[0499] "Isomerism" means compounds that have identical molecular formulae but differ in the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereoisomers", and stereoisomers that are non-superimposable minor images of each other are termed "enantiomers" or sometimes optical isomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a "racemic mixture".

[0500] A carbon atom bonded to four nonidentical substituents is termed a "chiral center".

[0501] "Chiral isomer" means a compound with at least one chiral center. Compounds with more than one chiral center may exist either as an individual diastereomer or as a mixture of diastereomers, termed "diastereomeric mixture". When one chiral center is present, a stereoisomer may be characterized by the absolute configuration (R or S) of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under consideration are ranked in accordance with the *Sequence Rule* of Cahn, Ingold and Prelog. (Cahn et al., *Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511; Cahn et al., *Angew. Chem.* 1966, 78, 413; Cahn and Ingold, *J. Chem. Soc.* 1951 (London), 612; Cahn et al., *Experientia* 1956, 12, 81; Cahn, *J. Chem. Educ.* 1964, 41, 116).

[0502] "Geometric isomer" means the diastereomers that owe their existence to hindered rotation about double bonds. These configurations are differentiated in their names by the prefixes cis and trans, or Z and E, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

[0503] Furthermore, the structures and other compounds discussed in this invention include all atropic isomers thereof. "Atropic isomers" are a type of stereoisomer in which the atoms of two isomers are arranged differently in space. Atropic isomers owe their existence to a restricted rotation caused by hindrance of rotation of large groups about a central bond. Such atropic isomers typically exist as a mixture, however as a result of recent advances in chromatography techniques; it has been possible to separate mixtures of two atropic isomers in select cases.

[0504] "Tautomer" is one of two or more structural isomers that exist in equilibrium and is readily converted from one isomeric form to another. This conversion results in the formal migration of a hydrogen atom accompanied by a switch of adjacent conjugated double bonds. Tautomers exist as a mixture of a tautomeric set in solution. In solid form, usually one tautomer predominates. In solutions where tautomerization is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent and pH. The concept of tautomers that are interconvertable by tautomerizations is called tautomerism.

[0505] Of the various types of tautomerism that are possible, two are commonly observed. In keto-enol tautomerism a simultaneous shift of electrons and a hydrogen atom occurs. Ring-chain tautomerism arises as a result of the aldehyde group (—CHO) in a sugar chain molecule reacting with one of the hydroxy groups (—OH) in the same molecule to give it a cyclic (ring-shaped) form as exhibited by glucose.

[0506] Common tautomeric pairs are: ketone-enol, amide-nitrile, lactam-lactim, amide-imidic acid tautomerism in heterocyclic rings (e.g., in nucleobases such as guanine, thymine and cytosine), amine-enamine and enamine-enamine.

[0507] It is to be understood that the compounds of the present invention may be depicted as different tautomers. It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be included in the scope of the present invention, and the naming of the compounds does not exclude any tautomer form.

[0508] The term "crystal polymorphs", "polymorphs" or "crystal forms" means crystal structures in which a compound (or a salt or solvate thereof) can crystallize in different crystal packing arrangements, all of which have the same elemental composition. Different crystal forms usually have different X-ray diffraction patterns, infrared spectral, melting points, density hardness, crystal shape, optical and electrical properties, stability and solubility. Recrystallization solvent, rate of crystallization, storage temperature, and other factors

may cause one crystal form to dominate. Crystal polymorphs of the compounds can be prepared by crystallization under different conditions.

[0509] Additionally, the compounds of the present invention, for example, the salts of the compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. Nonlimiting examples of hydrates include monohydrates, dihydrates, etc. Nonlimiting examples of solvates include ethanol solvates, acetone solvates, etc.

[0510] "Solvate" means solvent addition forms that contain either stoichiometric or non stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate; and if the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one molecule of the substance in which the water retains its molecular state as H_2O.

[0511] As used herein, the term "analog" refers to a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group, or the replacement of one functional group by another functional group). Thus, an analog is a compound that is similar or comparable in function and appearance, but not in structure or origin to the reference compound.

[0512] As defined herein, the term "derivative" refers to compounds that have a common core structure, and are substituted with various groups as described herein. For example, all of the compounds represented by Formula I are pyrrolo-aminopyrimidine derivatives, and have Formula I as a common core.

[0513] The term "bioisostere" refers to a compound resulting from the exchange of an atom or of a group of atoms with another, broadly similar, atom or group of atoms. The objective of a bioisosteric replacement is to create a new compound with similar biological properties to the parent compound. The bioisosteric replacement may be physicochemically or topologically based. Examples of carboxylic acid bioisosteres include, but are not limited to, acyl sulfonimides, tetrazoles, sulfonates and phosphonates. See, e.g., Patani and LaVoie, *Chem. Rev.* 96, 3147-3176, 1996.

[0514] The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include C-13 and C-14.

2. Synthesis of Substituted Pyrrolo-Aminopyrimidine Compounds

[0515] The present invention provides methods for the synthesis of the compounds of each of the formulae described herein. The present invention also provides detailed methods for the synthesis of various disclosed compounds of the present invention according to the following schemes as shown in the Examples.

[0516] Throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated that compositions also consist essentially of, or consist of, the recited components. Similarly, where methods or processes are described as having, including, or comprising specific process steps, the processes also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions is immaterial so long as the invention remains operable. Moreover, two or more steps or actions can be conducted simultaneously.

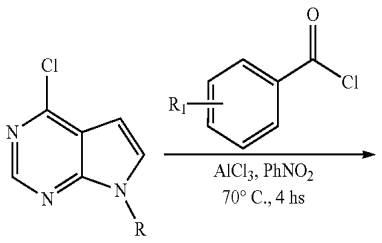
[0517] The synthetic processes of the invention can tolerate a wide variety of functional groups, therefore various substituted starting materials can be used. The processes generally provide the desired final compound at or near the end of the overall process, although it may be desirable in certain instances to further convert the compound to a pharmaceutically acceptable salt, ester or prodrug thereof.

[0518] Compounds of the present invention can be prepared in a variety of ways using commercially available starting materials, compounds known in the literature, or from readily prepared intermediates, by employing standard synthetic methods and procedures either known to those skilled in the art, or which will be apparent to the skilled artisan in light of the teachings herein. Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be obtained from the relevant scientific literature or from standard textbooks in the field. Although not limited to any one or several sources, classic texts such as Smith, M. B., March, J., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure,* 5th edition, John Wiley & Sons: New York, 2001; and Greene, T. W., Wuts, P. G. M., *Protective Groups in Organic Synthesis,* 3rd edition, John Wiley & Sons: New York, 1999, incorporated by reference herein, are useful and recognized reference textbooks of organic synthesis known to those in the art. The following descriptions of synthetic methods are designed to illustrate, but not to limit, general procedures for the preparation of compounds of the present invention.

[0519] Compounds of the present invention can be conveniently prepared by a variety of methods familiar to those skilled in the art. The compounds of each of the formulae described herein may be prepared according to the following procedures from commercially available starting materials or starting materials which can be prepared using literature procedures. These procedures show the preparation of representative compounds of this invention.

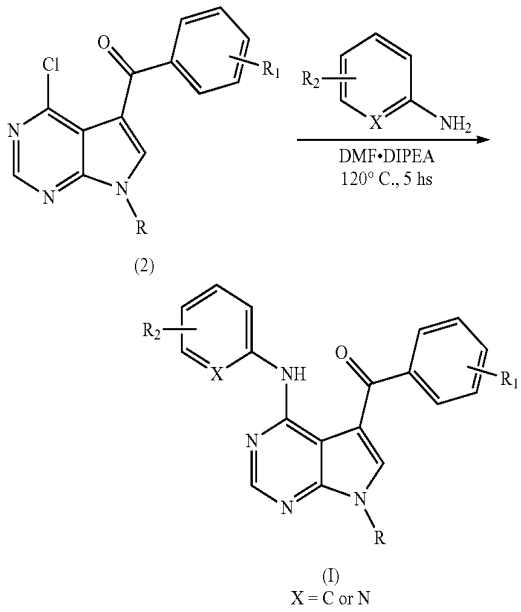
General Procedure A

[0520] One general procedure is illustrated below.



(1)
R = H or Me

-continued

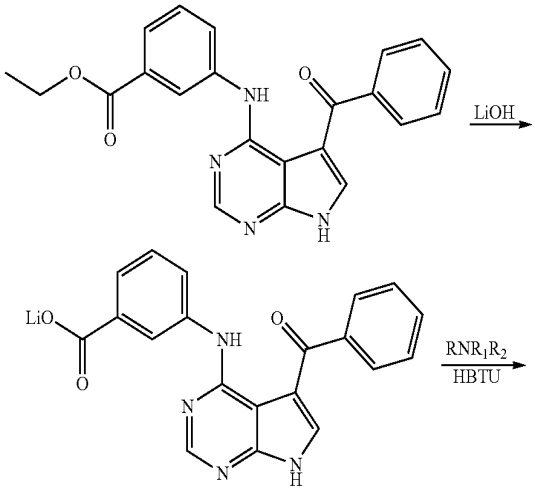


[0521] Step 1. To a solution of 4-chloro-7H-pyrrolo[2,3-d] pyrimidine in nitrobenzene was added aluminum trichloride (3.0 equivalents) and acid chloride (1.2 equivalents). The mixture was heated at 70° C. for 4 hours. After cooled to room temperature, the reaction mixture was quenched by adding water. Product was extracted with ethyl acetate, dried over sodium sulfate and concentrated. Product was purified by column chromatography on silica gel to afford the molecules of formula (2).

[0522] Step 2. A solution of molecules of formula (2), aryl amine and diisopropyl ethylamine (2 equivalents) In N,N-dimethylformamide was heated at 120° C. for 5 hours. After cooled to room temperature, dichloromethane was added to the mixture and the product was precipitated out and collected by filtration.

General Procedure B

[0523] Another general procedure is illustrated below.



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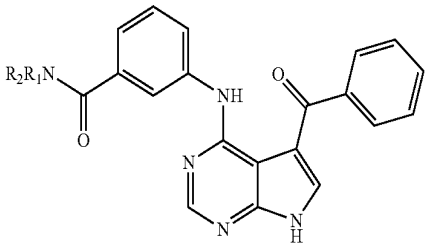
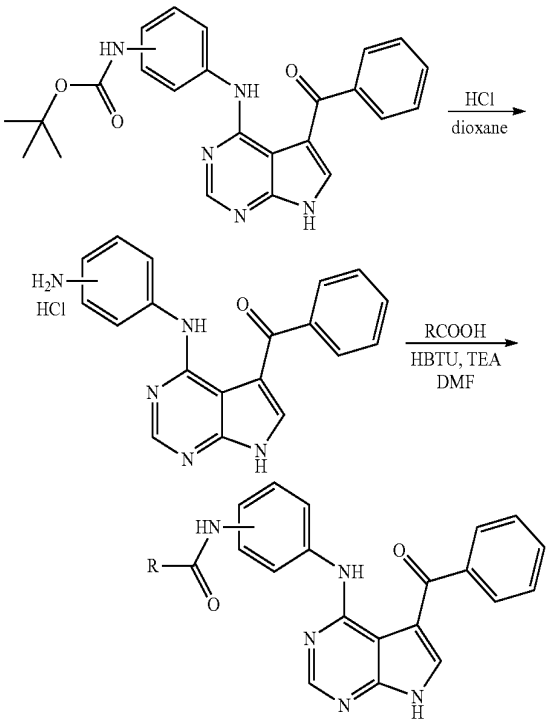


[0524] Step 1. A mixture of ethyl 3-(5-benzoyl-7H-pyrrolo [2,3-d]pyrimidin-4-ylamino)benzoate, lithium hydroxide (1.1 equivalents) in mixed solvent of THF-water-methanol (3:1:1) was stirred overnight. Solvent was removed. The lithium salt was used without further purification.

[0525] Step 2. A mixture of 3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)benzoate lithium salt, amines, HBTU (1.5 equivalents) and triethylamine (2 equivalents) in N,N-dimethylformate was stirred at room temperature overnight. Product was purified by reverse phase HPLC.

General Procedure C

[0526] Another general procedure is illustrated below.

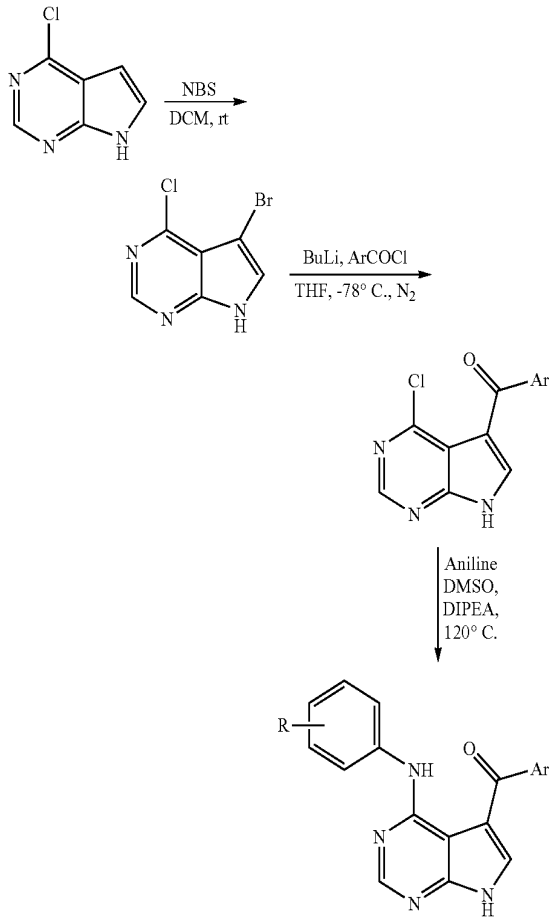


[0527] Step 1. To a solution of BOC protected aniline in dioxane was added 4.0 M HCl in dioxane, the mixture was stirred overnight. Solvent was removed. The HCL salt was used without further purification.

[0528] Step 2. A mixture of HCl salt, acids (1.2 equivalents), HBTU (1.5 equivalents) and triethylamine (2 equivalents) in N,N-dimethylformamide was stirred at room temperature overnight. Product was purified by reverse phase HPLC.

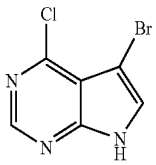
General Procedure D

[0529] Another general procedure is illustrated below.



Step 1. Synthesis of 5-bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine

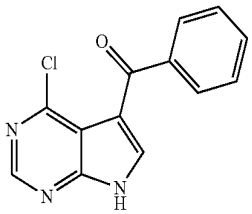
[0530]



[0531] To a suspension of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (5.91 g, 38 mmol) in DCM (250 mL) was added NBS (7.93 g, 44 mmol). The suspension was stirred at room temperature for 3 hours. Water (200 mL) was added to the reaction mixture. The mixture was sonicated for 5 min. The solid was collected by filtration and washed with water, then taken into 100 mL of MeOH. The suspension was sonicated for 3 min. The solid was collected by filtration as the desired product (6.47 g, 72%). LCMS[M+1]: 232.

Step 2. Synthesis of the (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone

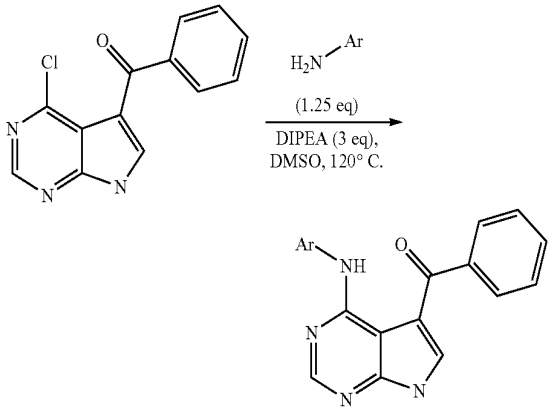
[0532]



[0533] To a solution of 5-bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (1.47 g, 6.38 mmol) in THF (60 mL) at −78° C. under N_2 was added n-BuLi (2.5 M in hexane, 5.74 mL, 14.36 mmol) dropwise. After completion of addition, the mixture was stirred at −78° C. for additional 40 min. PhCOCl (0.88 mL) was added and the reaction was stirred for an additional 1 hour. Water (1 mL) was added to quench the reaction. The reaction mixture was then poured into water (100 mL). EtOAc (200 mL) was added for extraction. The organic layer was separated, dried (Na_2SO_4), filtered and concentrated to a residue. The residue was dissolved into small amount of DCM and a little MeOH. It was loaded to silica gel column. The purification was down by eluent with 1/1 DCM/EtOAc. The (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone was obtained as a white solid (0.49 g, 29%). ^{1}H NMR (DMSO-d6, 400 MHz) 8.74 (s, 1H), 8.17 (s, 1H), 7.87 (m, 2H), 7.68 (m, 1H), 7.56 (m, 2H). LCMS [M+1]: 258.

General Procedure E

[0534] Another general procedure is illustrated below.



[0535] High throughput synthesis: To a solution of (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone (0.06 mmol) in DMSO (1.0 mL) was added 1.0 mL of the aniline (1.25 equivalents) and N,N-diisopropylethylamine (0.032 mL). The mixture was heated at 120° C. for 16 hours. After cooling to room temperature, 0.1 mL of 0.6 M NaOH solution was added. The resulting mixture was heated at 40° C. for 2 hours. Solvent was removed under Vacuum. The residue was dissolved in 1.0 mL of DMSO. Final products were purified by reverse phase chromatography on preparative LC/UV/MS system using a mass triggered fraction-

ation. Compounds were eluted from the HPLC column (Maccel 120-10-C18 SH 10 μm 20 mmID×50 mm) at 88 mL/min with acetonitrile/water gradient using 0.1% TFA as a modifier.

3. Methods of Treatment

[0536] The present invention provides methods for the treatment of a cell proliferative disorder in a subject in need thereof by administering to a subject in need of such treatment, a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof. The cell proliferative disorder can be cancer or a precancerous condition. The present invention further provides the use of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, for the preparation of a medicament useful for the treatment of a cell proliferative disorder.

[0537] The present invention also provides methods of protecting against a cell proliferative disorder in a subject in need thereof by administering a therapeutically effective amount of compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, to a subject in need of such treatment. The cell proliferative disorder can be cancer or a precancerous condition. The present invention also provides the use of compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, for the preparation of a medicament useful for the prevention of a cell proliferative disorder.

[0538] As used herein, a "subject in need thereof" is a subject having a cell proliferative disorder, or a subject having an increased risk of developing a cell proliferative disorder relative to the population at large. A subject in need thereof can have a precancerous condition. Preferably, a subject in need thereof has cancer. A "subject" includes a mammal. The mammal can be e.g., any mammal, e.g., a human, primate, bird, mouse, rat, fowl, dog, cat, cow, horse, goat, camel, sheep or a pig. Preferably, the mammal is a human.

[0539] As used herein, the term "cell proliferative disorder" refers to conditions in which unregulated or abnormal growth, or both, of cells can lead to the development of an unwanted condition or disease, which may or may not be cancerous. Exemplary cell proliferative disorders of the invention encompass a variety of conditions wherein cell division is deregulated. Exemplary cell proliferative disorder include, but are not limited to, neoplasms, benign tumors, malignant tumors, pre-cancerous conditions, in situ tumors, encapsulated tumors, metastatic tumors, liquid tumors, solid tumors, immunological tumors, hematological tumors, cancers, carcinomas, leukemias, lymphomas, sarcomas, and rapidly dividing cells. The term "rapidly dividing cell" as used herein is defined as any cell that divides at a rate that exceeds or is greater than what is expected or observed among neighboring or juxtaposed cells within the same tissue. A cell proliferative disorder includes a precancer or a precancerous condition. A cell proliferative disorder includes cancer. Preferably, the methods provided herein are used to treat or alleviate a symptom of cancer. The term "cancer" includes solid tumors, as well as, hematologic tumors and/or malignancies. A "precancer cell" or "precancerous cell" is a cell manifesting a cell proliferative disorder that is a precancer or a precancerous condition. A "cancer cell" or "cancerous cell" is a cell manifesting a cell proliferative disorder that is a cancer. Any reproducible means of measurement may be used to identify cancer cells or precancerous cells. Cancer cells or precancerous cells can be identified by histological typing or grading of a tissue sample (e.g., a biopsy sample). Cancer cells or precancerous cells can be identified through the use of appropriate molecular markers.

[0540] Exemplary non-cancerous conditions or disorders include, but are not limited to, rheumatoid arthritis; inflammation; autoimmune disease; lymphoproliferative conditions; acromegaly; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; asthma; adult respiratory distress syndrome; chronic obstructive pulmonary disease; chronic pulmonary inflammation; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; pancreatic fibrosis; hepatic fibrosis; acute and chronic renal disease; irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke and ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute and chronic pain; allergic rhinitis; allergic conjunctivitis; chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synovitis; muscle degeneration, bursitis; tendonitis; tenosynovitis; herniated, ruptures, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; restenosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis; graft-versus-host reaction; Multiple Sclerosis; lupus; fibromyalgia; AIDS and other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus and cytomegalovirus; and diabetes mellitus.

[0541] Exemplary cancers include, but are not limited to, adrenocortical carcinoma, AIDS-related cancers, AIDS-related lymphoma, anal cancer, anorectal cancer, cancer of the anal canal, appendix cancer, childhood cerebellar astrocytoma, childhood cerebral astrocytoma, basal cell carcinoma, skin cancer (non-melanoma), biliary cancer, extrahepatic bile duct cancer, intrahepatic bile duct cancer, bladder cancer, uringary bladder cancer, bone and joint cancer, osteosarcoma and malignant fibrous histiocytoma, brain cancer, brain tumor, brain stem glioma, cerebellar astrocytoma, cerebral astrocytoma/malignant glioma, ependymoma, medulloblastoma, supratentorial primitive neuroectodeimal tumors, visual pathway and hypothalamic glioma, breast cancer, bronchial adenomas/carcinoids, carcinoid tumor, gastrointestinal, nervous system cancer, nervous system lymphoma, central nervous system cancer, central nervous system lymphoma, cervical cancer, childhood cancers, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic myeloproliferative disorders, colon cancer, colorectal cancer, cutaneous T-cell lymphoma, lymphoid neoplasm, mycosis fungoides, Seziary Syndrome, endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, eye cancer, intraocular melanoma, retinoblastoma, gallbladder cancer, gastric (stomach) cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), germ cell tumor, ovarian germ cell tumor, gestational trophoblastic tumor glioma, head and neck cancer, hepatocellular (liver) cancer, Hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, ocular cancer, islet cell tumors (endocrine pancreas), Kaposi Sarcoma, kidney cancer, renal cancer, kidney cancer, laryngeal cancer, acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic

leukemia, chronic myelogenous leukemia, hairy cell leukemia, lip and oral cavity cancer, liver cancer, lung cancer, non-small cell lung cancer, small cell lung cancer, AIDS-related lymphoma, non-Hodgkin lymphoma, primary central nervous system lymphoma, Waldenstram macroglobulinemia, medulloblastoma, melanoma, intraocular (eye) melanoma, merkel cell carcinoma, mesothelioma malignant, mesothelioma, metastatic squamous neck cancer, mouth cancer, cancer of the tongue, multiple endocrine neoplasia syndrome, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/myeloproliferative diseases, chronic myelogenous leukemia, acute myeloid leukemia, multiple myeloma, chronic myeloproliferative disorders, nasopharyngeal cancer, neuroblastoma, oral cancer, oral cavity cancer, oropharyngeal cancer, ovarian cancer, ovarian epithelial cancer, ovarian low malignant potential tumor, pancreatic cancer, islet cell pancreatic cancer, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytoma, pineoblastoma and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleuropulmonary blastoma, prostate cancer, rectal cancer, renal pelvis and ureter, transitional cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, ewing family of sarcoma tumors, Kaposi Sarcoma, soft tissue sarcoma, uterine cancer, uterine sarcoma, skin cancer (non-melanoma), skin cancer (melanoma), merkel cell skin carcinoma, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, stomach (gastric) cancer, supratentorial primitive neuroectodermal tumors, testicular cancer, throat cancer, thymoma, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter and other urinary organs, gestational trophoblastic tumor, urethral cancer, endometrial uterine cancer, uterine sarcoma, uterine corpus cancer, vaginal cancer, vulvar cancer, and Wilm's Tumor.

[0542] A "cell proliferative disorder of the hematologic system" is a cell proliferative disorder involving cells of the hematologic system. A cell proliferative disorder of the hematologic system can include lymphoma, leukemia, myeloid neoplasms, mast cell neoplasms, myelodysplasia, benign monoclonal gammopathy, lymphomatoid granulomatosis, lymphomatoid papulosis, polycythemia vera, chronic myelocytic leukemia, agnogenic myeloid metaplasia, and essential thrombocythemia. A cell proliferative disorder of the hematologic system can include hyperplasia, dysplasia, and metaplasia of cells of the hematologic system. Preferably, compositions of the present invention may be used to treat a cancer selected from the group consisting of a hematologic cancer of the present invention or a hematologic cell proliferative disorder of the present invention. A hematologic cancer of the present invention can include multiple myeloma, lymphoma (including Hodgkin's lymphoma, non-Hodgkin's lymphoma, childhood lymphomas, and lymphomas of lymphocytic and cutaneous origin), leukemia (including childhood leukemia, hairy-cell leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, chronic myelogenous leukemia, and mast cell leukemia), myeloid neoplasms and mast cell neoplasms.

[0543] A "cell proliferative disorder of the lung" is a cell proliferative disorder involving cells of the lung. Cell proliferative disorders of the lung can include all forms of cell proliferative disorders affecting lung cells. Cell proliferative disorders of the lung can include lung cancer, a precancer or precancerous condition of the lung, benign growths or lesions of the lung, and malignant growths or lesions of the lung, and metastatic lesions in tissue and organs in the body other than the lung. Preferably, compositions of the present invention may be used to treat lung cancer or cell proliferative disorders of the lung. Lung cancer can include all forms of cancer of the lung. Lung cancer can include malignant lung neoplasms, carcinoma in situ, typical carcinoid tumors, and atypical carcinoid tumors. Lung cancer can include small cell lung cancer ("SCLC"), non-small cell lung cancer ("NSCLC"), squamous cell carcinoma, adenocarcinoma, small cell carcinoma, large cell carcinoma, adenosquamous cell carcinoma, and mesothelioma. Lung cancer can include "scar carcinoma", bronchioalveolar carcinoma, giant cell carcinoma, spindle cell carcinoma, and large cell neuroendocrine carcinoma. Lung cancer can include lung neoplasms having histologic and ultrastructual heterogeneity (e.g., mixed cell types).

[0544] Cell proliferative disorders of the lung can include all forms of cell proliferative disorders affecting lung cells. Cell proliferative disorders of the lung can include lung cancer, precancerous conditions of the lung. Cell proliferative disorders of the lung can include hyperplasia, metaplasia, and dysplasia of the lung. Cell proliferative disorders of the lung can include asbestos-induced hyperplasia, squamous metaplasia, and benign reactive mesothelial metaplasia. Cell proliferative disorders of the lung can include replacement of columnar epithelium with stratified squamous epithelium, and mucosal dysplasia. Individuals exposed to inhaled injurious environmental agents such as cigarette smoke and asbestos may be at increased risk for developing cell proliferative disorders of the lung. Prior lung diseases that may predispose individuals to development of cell proliferative disorders of the lung can include chronic interstitial lung disease, necrotizing pulmonary disease, scleroderma, rheumatoid disease, sarcoidosis, interstitial pneumonitis, tuberculosis, repeated pneumonias, idiopathic pulmonary fibrosis, granulomata, asbestosis, fibrosing alveolitis, and Hodgkin's disease.

[0545] A "cell proliferative disorder of the colon" is a cell proliferative disorder involving cells of the colon. Preferably, the cell proliferative disorder of the colon is colon cancer. Preferably, compositions of the present invention may be used to treat colon cancer or cell proliferative disorders of the colon. Colon cancer can include all forms of cancer of the colon. Colon cancer can include sporadic and hereditary colon cancers. Colon cancer can include malignant colon neoplasms, carcinoma in situ, typical carcinoid tumors, and atypical carcinoid tumors. Colon cancer can include adenocarcinoma, squamous cell carcinoma, and adenosquamous cell carcinoma. Colon cancer can be associated with a hereditary syndrome selected from the group consisting of hereditary nonpolyposis colorectal cancer, familial adenomatous polyposis, Gardner's syndrome, Peutz-Jeghers syndrome, Turcot's syndrome and juvenile polyposis. Colon cancer can be caused by a hereditary syndrome selected from the group consisting of hereditary nonpolyposis colorectal cancer, familial adenomatous polyposis, Gardner's syndrome, Peutz-Jeghers syndrome, Turcot's syndrome and juvenile polyposis.

[0546] Cell proliferative disorders of the colon can include all forms of cell proliferative disorders affecting colon cells. Cell proliferative disorders of the colon can include colon cancer, precancerous conditions of the colon, adenomatous polyps of the colon and metachronous lesions of the colon. A

cell proliferative disorder of the colon can include adenoma. Cell proliferative disorders of the colon can be characterized by hyperplasia, metaplasia, and dysplasia of the colon. Prior colon diseases that may predispose individuals to development of cell proliferative disorders of the colon can include prior colon cancer. Current disease that may predispose individuals to development of cell proliferative disorders of the colon can include Crohn's disease and ulcerative colitis. A cell proliferative disorder of the colon can be associated with a mutation in a gene selected from the group consisting of p53, ras, FAP and DCC. An individual can have an elevated risk of developing a cell proliferative disorder of the colon due to the presence of a mutation in a gene selected from the group consisting of p53, ras, FAP and DCC.

[0547] A "cell proliferative disorder of the pancreas" is a cell proliferative disorder involving cells of the pancreas. Cell proliferative disorders of the pancreas can include all forms of cell proliferative disorders affecting pancreatic cells. Cell proliferative disorders of the pancreas can include pancreas cancer, a precancer or precancerous condition of the pancreas, hyperplasia of the pancreas, and dysaplasia of the pancreas, benign growths or lesions of the pancreas, and malignant growths or lesions of the pancreas, and metastatic lesions in tissue and organs in the body other than the pancreas. Pancreatic cancer includes all forms of cancer of the pancreas. Pancreatic cancer can include ductal adenocarcinoma, adenosquamous carcinoma, pleomorphic giant cell carcinoma, mucinous adenocarcinoma, osteoclast-like giant cell carcinoma, mucinous cystadenocarcinoma, acinar carcinoma, unclassified large cell carcinoma, small cell carcinoma, pancreatoblastoma, papillary neoplasm, mucinous cystadenoma, papillary cystic neoplasm, and serous cystadenoma. Pancreatic cancer can also include pancreatic neoplasms having histologic and ultrastructual heterogeneity (e.g., mixed cell types).

[0548] A "cell proliferative disorder of the prostate" is a cell proliferative disorder involving cells of the prostate. Cell proliferative disorders of the prostate can include all forms of cell proliferative disorders affecting prostate cells. Cell proliferative disorders of the prostate can include prostate cancer, a precancer or precancerous condition of the prostate, benign growths or lesions of the prostate, and malignant growths or lesions of the prostate, and metastatic lesions in tissue and organs in the body other than the prostate. Cell proliferative disorders of the prostate can include hyperplasia, metaplasia, and dysplasia of the prostate.

[0549] A "cell proliferative disorder of the skin" is a cell proliferative disorder involving cells of the skin. Cell proliferative disorders of the skin can include all forms of cell proliferative disorders affecting skin cells. Cell proliferative disorders of the skin can include a precancer or precancerous condition of the skin, benign growths or lesions of the skin, melanoma, malignant melanoma and other malignant growths or lesions of the skin, and metastatic lesions in tissue and organs in the body other than the skin. Cell proliferative disorders of the skin can include hyperplasia, metaplasia, and dysplasia of the skin.

[0550] A "cell proliferative disorder of the ovary" is a cell proliferative disorder involving cells of the ovary. Cell proliferative disorders of the ovary can include all forms of cell proliferative disorders affecting cells of the ovary. Cell proliferative disorders of the ovary can include a precancer or precancerous condition of the ovary, benign growths or lesions of the ovary, ovarian cancer, malignant growths or lesions of the ovary, and metastatic lesions in tissue and organs in the body other than the ovary. Cell proliferative disorders of the skin can include hyperplasia, metaplasia, and dysplasia of cells of the ovary.

[0551] A "cell proliferative disorder of the breast" is a cell proliferative disorder involving cells of the breast. Cell proliferative disorders of the breast can include all forms of cell proliferative disorders affecting breast cells. Cell proliferative disorders of the breast can include breast cancer, a precancer or precancerous condition of the breast, benign growths or lesions of the breast, and malignant growths or lesions of the breast, and metastatic lesions in tissue and organs in the body other than the breast. Cell proliferative disorders of the breast can include hyperplasia, metaplasia, and dysplasia of the breast.

[0552] A cell proliferative disorder of the breast can be a precancerous condition of the breast. Compositions of the present invention may be used to treat a precancerous condition of the breast. A precancerous condition of the breast can include atypical hyperplasia of the breast, ductal carcinoma in situ (DCIS), intraductal carcinoma, lobular carcinoma in situ (LCIS), lobular neoplasia, and stage 0 or grade 0 growth or lesion of the breast (e.g., stage 0 or grade 0 breast cancer, or carcinoma in situ). A precancerous condition of the breast can be staged according to the TNM classification scheme as accepted by the American Joint Committee on Cancer (AJCC), where the primary tumor (T) has been assigned a stage of T0 or T is; and where the regional lymph nodes (N) have been assigned a stage of N0; and where distant metastasis (M) has been assigned a stage of M0.

[0553] The cell proliferative disorder of the breast can be breast cancer. Preferably, compositions of the present invention may be used to treat breast cancer. Breast cancer includes all forms of cancer of the breast. Breast cancer can include primary epithelial breast cancers. Breast cancer can include cancers in which the breast is involved by other tumors such as lymphoma, sarcoma or melanoma. Breast cancer can include carcinoma of the breast, ductal carcinoma of the breast, lobular carcinoma of the breast, undifferentiated carcinoma of the breast, cystosarcoma phyllodes of the breast, angiosarcoma of the breast, and primary lymphoma of the breast. Breast cancer can include Stage I, II, IIIA, IIIB, IIIC and IV breast cancer. Ductal carcinoma of the breast can include invasive carcinoma, invasive carcinoma in situ with predominant intraductal component, inflammatory breast cancer, and a ductal carcinoma of the breast with a histologic type selected from the group consisting of comedo, mucinous (colloid), medullary, medullary with lymphcytic infiltrate, papillary, scirrhous, and tubular. Lobular carcinoma of the breast can include invasive lobular carcinoma with predominant in situ component, invasive lobular carcinoma, and infiltrating lobular carcinoma. Breast cancer can include Paget's disease, Paget's disease with intraductal carcinoma, and Paget's disease with invasive ductal carcinoma. Breast cancer can include breast neoplasms having histologic and ultrastructual heterogeneity (e.g., mixed cell types).

[0554] Preferably, compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, may be used to treat breast cancer. A breast cancer that is to be treated can include familial breast cancer. A breast cancer that is to be treated can include sporadic breast cancer. A breast cancer that is to be treated can arise in a male subject. A breast cancer that is to be treated can arise in a female subject. A breast cancer that is to be treated

can arise in a premenopausal female subject or a postmenopausal female subject. A breast cancer that is to be treated can arise in a subject equal to or older than 30 years old, or a subject younger than 30 years old. A breast cancer that is to be treated has arisen in a subject equal to or older than 50 years old, or a subject younger than 50 years old. A breast cancer that is to be treated can arise in a subject equal to or older than 70 years old, or a subject younger than 70 years old.

[0555] A breast cancer that is to be treated can be typed to identify a familial or spontaneous mutation in BRCA1, BRCA2, or p53. A breast cancer that is to be treated can be typed as having a HER2/neu gene amplification, as overexpressing HER2/neu, or as having a low, intermediate or high level of HER2/neu expression. A breast cancer that is to be treated can be typed for a marker selected from the group consisting of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2, Ki-67, CA15-3, CA 27-29, and c-Met. A breast cancer that is to be treated can be typed as ER-unknown, ER-rich or ER-poor. A breast cancer that is to be treated can be typed as ER-negative or ER-positive. ER-typing of a breast cancer may be performed by any reproducible means. ER-typing of a breast cancer may be performed as set forth in Onkologie 27: 175-179 (2004). A breast cancer that is to be treated can be typed as PR-unknown, PR-rich or PR-poor. A breast cancer that is to be treated can be typed as PR-negative or PR-positive. A breast cancer that is to be treated can be typed as receptor positive or receptor negative. A breast cancer that is to be treated can be typed as being associated with elevated blood levels of CA 15-3, or CA 27-29, or both.

[0556] A breast cancer that is to be treated can include a localized tumor of the breast. A breast cancer that is to be treated can include a tumor of the breast that is associated with a negative sentinel lymph node (SLN) biopsy. A breast cancer that is to be treated can include a tumor of the breast that is associated with a positive sentinel lymph node (SLN) biopsy. A breast cancer that is to be treated can include a tumor of the breast that is associated with one or more positive axillary lymph nodes, where the axillary lymph nodes have been staged by any applicable method. A breast cancer that is to be treated can include a tumor of the breast that has been typed as having nodal negative status (e.g., node-negative) or nodal positive status (e.g., node-positive). A breast cancer that is to be treated can include a tumor of the breast that has metastasized to other locations in the body. A breast cancer that is to be treated can be classified as having metastasized to a location selected from the group consisting of bone, lung, liver, or brain. A breast cancer that is to be treated can be classified according to a characteristic selected from the group consisting of metastatic, localized, regional, local-regional, locally advanced, distant, multicentric, bilateral, ipsilateral, contralateral, newly diagnosed, recurrent, and inoperable.

[0557] A compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, may be used to treat or prevent a cell proliferative disorder of the breast, or to treat or prevent breast cancer, in a subject having an increased risk of developing breast cancer relative to the population at large. A subject with an increased risk of developing breast cancer relative to the population at large is a female subject with a family history or personal history of breast cancer. A subject with an increased risk of developing breast cancer relative to the population at large is a female subject having a germ-line or spontaneous mutation in BRCA1 or BRCA2, or both. A subject with an increased risk of developing breast cancer relative to the population at large is a female subject with a family history of breast cancer and a germ-line or spontaneous mutation in BRCA1 or BRCA2, or both. A subject with an increased risk of developing breast cancer relative to the population at large is a female who is greater than 30 years old, greater than 40 years old, greater than 50 years old, greater than 60 years old, greater than 70 years old, greater than 80 years old, or greater than 90 years old. A subject with an increased risk of developing breast cancer relative to the population at large is a subject with atypical hyperplasia of the breast, ductal carcinoma in situ (DCIS), intraductal carcinoma, lobular carcinoma in situ (LCIS), lobular neoplasia, or a stage 0 growth or lesion of the breast (e.g., stage 0 or grade 0 breast cancer, or carcinoma in situ).

[0558] A breast cancer that is to be treated can histologically graded according to the Scarff-Bloom-Richardson system, wherein a breast tumor has been assigned a mitosis count score of 1, 2, or 3; a nuclear pleiomorphism score of 1, 2, or 3; a tubule formation score of 1, 2, or 3; and a total Scarff-Bloom-Richardson score of between 3 and 9. A breast cancer that is to be treated can be assigned a tumor grade according to the International Consensus Panel on the Treatment of Breast Cancer selected from the group consisting of grade 1, grade 1-2, grade 2, grade 2-3, or grade 3.

[0559] A cancer that is to be treated can be staged according to the American Joint Committee on Cancer (AJCC) TNM classification system, where the tumor (T) has been assigned a stage of TX, T1, T1mic, T1a, T1b, T1c, T2, T3, T4, T4a, T4b, T4c, or T4d; and where the regional lymph nodes (N) have been assigned a stage of NX, N0, N1, N2, N2a, N2b, N3, N3a, N3b, or N3c; and where distant metastasis (M) can be assigned a stage of MX, M0, or M1. A cancer that is to be treated can be staged according to an American Joint Committee on Cancer (AJCC) classification as Stage I, Stage IIA, Stage IIB, Stage IIIA, Stage IIIB, Stage IIIC, or Stage IV. A cancer that is to be treated can be assigned a grade according to an AJCC classification as Grade GX (e.g., grade cannot be assessed), Grade 1, Grade 2, Grade 3 or Grade 4. A cancer that is to be treated can be staged according to an AJCC pathologic classification (pN) of pNX, pN0, PN0 (I−), PN0 (I+), PN0 (mol−), PN0 (mol+), PN1, PN1(mi), PN1a, PN1b, PN1c, pN2, pN2a, pN2b, pN3, pN3a, pN3b, or pN3c.

[0560] A cancer that is to be treated can include a tumor that has been determined to be less than or equal to about 2 centimeters in diameter. A cancer that is to be treated can include a tumor that has been determined to be from about 2 to about 5 centimeters in diameter. A cancer that is to be treated can include a tumor that has been determined to be greater than or equal to about 3 centimeters in diameter. A cancer that is to be treated can include a tumor that has been determined to be greater than 5 centimeters in diameter. A cancer that is to be treated can be classified by microscopic appearance as well differentiated, moderately differentiated, poorly differentiated, or undifferentiated. A cancer that is to be treated can be classified by microscopic appearance with respect to mitosis count (e.g., amount of cell division) or nuclear pleiomorphism (e.g., change in cells). A cancer that is to be treated can be classified by microscopic appearance as being associated with areas of necrosis (e.g., areas of dying or degenerating cells). A cancer that is to be treated can be classified as having an abnormal karyotype, having an abnormal number of chromosomes, or having one or more chro-

mosomes that are abnormal in appearance. A cancer that is to be treated can be classified as being aneuploid, triploid, tetraploid, or as having an altered ploidy. A cancer that is to be treated can be classified as having a chromosomal translocation, or a deletion or duplication of an entire chromosome, or a region of deletion, duplication or amplification of a portion of a chromosome.

[0561] A cancer that is to be treated can be evaluated by DNA cytometry, flow cytometry, or image cytometry. A cancer that is to be treated can be typed as having 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of cells in the synthesis stage of cell division (e.g., in S phase of cell division). A cancer that is to be treated can be typed as having a low S-phase fraction or a high S-phase fraction.

[0562] As used herein, a "normal cell" is a cell that cannot be classified as part of a "cell proliferative disorder". A normal cell lacks unregulated or abnormal growth, or both, that can lead to the development of an unwanted condition or disease. Preferably, a normal cell possesses normally functioning cell cycle checkpoint control mechanisms.

[0563] As used herein, "contacting a cell" refers to a condition in which a compound or other composition of matter is in direct contact with a cell, or is close enough to induce a desired biological effect in a cell.

[0564] As used herein, "candidate compound" refers to a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, that has been or will be tested in one or more in vitro or in vivo biological assays, in order to determine if that compound is likely to elicit a desired biological or medical response in a cell, tissue, system, animal or human that is being sought by a researcher or clinician. A candidate compound is a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof. The biological or medical response can be the treatment of cancer. The biological or medical response can be treatment or prevention of a cell proliferative disorder. In vitro or in vivo biological assays can include, but are not limited to, enzymatic activity assays, electrophoretic mobility shift assays, reporter gene assays, in vitro cell viability assays, and the assays described herein.

[0565] As used herein, "monotherapy" refers to the administration of a single active or therapeutic compound to a subject in need thereof. Preferably, monotherapy will involve administration of a therapeutically effective amount of an active compound. For example, cancer monotherapy with one of the compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof, to a subject in need of treatment of cancer. Monotherapy may be contrasted with combination therapy, in which a combination of multiple active compounds is administered, preferably with each component of the combination present in a therapeutically effective amount. In one aspect, monotherapy with a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, is more effective than combination therapy in inducing a desired biological effect.

[0566] As used herein, "treating" or "treat" describes the management and care of a patient for the purpose of combating a disease, condition, or disorder and includes the administration of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, to alleviate the symptoms or complications of a disease, condition or disorder, or to eliminate the disease, condition or disorder.

[0567] A compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, can also be used to prevent a disease, condition or disorder. As used herein, "preventing" or "prevent" describes reducing or eliminating the onset of the symptoms or complications of the disease, condition or disorder.

[0568] As used herein, the term "alleviate" is meant to describe a process by which the severity of a sign or symptom of a disorder is decreased. Importantly, a sign or symptom can be alleviated without being eliminated. In a preferred embodiment, the administration of pharmaceutical compositions of the invention leads to the elimination of a sign or symptom, however, elimination is not required. Effective dosages are expected to decrease the severity of a sign or symptom. For instance, a sign or symptom of a disorder such as cancer, which can occur in multiple locations, is alleviated if the severity of the cancer is decreased within at least one of multiple locations.

[0569] As used herein, the term "severity" is meant to describe the potential of cancer to transform from a precancerous, or benign, state into a malignant state. Alternatively, or in addition, severity is meant to describe a cancer stage, for example, according to the TNM system (accepted by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC)) or by other art-recognized methods. Cancer stage refers to the extent or severity of the cancer, based on factors such as the location of the primary tumor, tumor size, number of tumors, and lymph node involvement (spread of cancer into lymph nodes). Alternatively, or in addition, severity is meant to describe the tumor grade by art-recognized methods (see, National Cancer Institute, www.cancer.gov). Tumor grade is a system used to classify cancer cells in terms of how abnormal they look under a microscope and how quickly the tumor is likely to grow and spread. Many factors are considered when determining tumor grade, including the structure and growth pattern of the cells. The specific factors used to determine tumor grade vary with each type of cancer. Severity also describes a histologic grade, also called differentiation, which refers to how much the tumor cells resemble normal cells of the same tissue type (see, National Cancer Institute, www.cancer.gov). Furthermore, severity describes a nuclear grade, which refers to the size and shape of the nucleus in tumor cells and the percentage of tumor cells that are dividing (see, National Cancer Institute, www.cancer.gov).

[0570] In another aspect of the invention, severity describes the degree to which a tumor has secreted growth factors, degraded the extracellular matrix, become vascularized, lost adhesion to juxtaposed tissues, or metastasized. Moreover, severity describes the number of locations to which a primary tumor has metastasized. Finally, severity includes the difficulty of treating tumors of varying types and locations. For example, inoperable tumors, those cancers which have greater access to multiple body systems (hematological and immunological tumors), and those which are the most resistant to traditional treatments are considered most severe. In these situations, prolonging the life expectancy of the subject and/or reducing pain, decreasing the proportion of cancerous cells or restricting cells to one system, and improving cancer stage/tumor grade/histological grade/nuclear grade are considered alleviating a sign or symptom of the cancer.

[0571] As used herein the term "symptom" is defined as an indication of disease, illness, injury, or that something is not right in the body. Symptoms are felt or noticed by the individual experiencing the symptom, but may not easily be noticed by others. Others are defined as non-health-care professionals.

[0572] As used herein the term "sign" is also defined as an indication that something is not right in the body. But signs are defined as things that can be seen by a doctor, nurse, or other health care professional.

[0573] Cancer is a group of diseases that may cause almost any sign or symptom. The signs and symptoms will depend on where the cancer is, the size of the cancer, and how much it affects the nearby organs or structures. If a cancer spreads (metastasizes), then symptoms may appear in different parts of the body.

[0574] As a cancer grows, it begins to push on nearby organs, blood vessels, and nerves. This pressure creates some of the signs and symptoms of cancer. If the cancer is in a critical area, such as certain parts of the brain, even the smallest tumor can cause early symptoms.

[0575] But sometimes cancers start in places where it does not cause any symptoms until the cancer has grown quite large. Pancreas cancers, for example, do not usually grow large enough to be felt from the outside of the body. Some pancreatic cancers do not cause symptoms until they begin to grow around nearby nerves (this causes a backache). Others grow around the bile duct, which blocks the flow of bile and leads to a yellowing of the skin known as jaundice. By the time a pancreatic cancer causes these signs or symptoms, it has usually reached an advanced stage.

[0576] A cancer may also cause symptoms such as fever, fatigue, or weight loss. This may be because cancer cells use up much of the body's energy supply or release substances that change the body's metabolism. Or the cancer may cause the immune system to react in ways that produce these symptoms.

[0577] Sometimes, cancer cells release substances into the bloodstream that cause symptoms not usually thought to result from cancers. For example, some cancers of the pancreas can release substances which cause blood clots to develop in veins of the legs. Some lung cancers make hormone-like substances that affect blood calcium levels, affecting nerves and muscles and causing weakness and dizziness

[0578] Cancer presents several general signs or symptoms that occur when a variety of subtypes of cancer cells are present. Most people with cancer will lose weight at some time with their disease. An unexplained (unintentional) weight loss of 10 pounds or more may be the first sign of cancer, particularly cancers of the pancreas, stomach, esophagus, or lung.

[0579] Fever is very common with cancer, but is more often seen in advanced disease. Almost all patients with cancer will have fever at some time, especially if the cancer or its treatment affects the immune system and makes it harder for the body to fight infection. Less often, fever may be an early sign of cancer, such as with leukemia or lymphoma.

[0580] Fatigue may be an important symptom as cancer progresses. It may happen early, though, in cancers such as with leukemia, or if the cancer is causing an ongoing loss of blood, as in some colon or stomach cancers.

[0581] Pain may be an early symptom with some cancers such as bone cancers or testicular cancer. But most often pain is a symptom of advanced disease.

[0582] Along with cancers of the skin (see next section), some internal cancers can cause skin signs that can be seen. These changes include the skin looking darker (hyperpigmentation), yellow (jaundice), or red (erythema); itching; or excessive hair growth.

[0583] Alternatively, or in addition, cancer subtypes present specific signs or symptoms. Changes in bowel habits or bladder function could indicate cancer. Long-term constipation, diarrhea, or a change in the size of the stool may be a sign of colon cancer. Pain with urination, blood in the urine, or a change in bladder function (such as more frequent or less frequent urination) could be related to bladder or prostate cancer.

[0584] Changes in skin condition or appearance of a new skin condition could indicate cancer. Skin cancers may bleed and look like sores that do not heal. A long-lasting sore in the mouth could be an oral cancer, especially in patients who smoke, chew tobacco, or frequently drink alcohol. Sores on the penis or vagina may either be signs of infection or an early cancer.

[0585] Unusual bleeding or discharge could indicate cancer. Unusual bleeding can happen in either early or advanced cancer. Blood in the sputum (phlegm) may be a sign of lung cancer. Blood in the stool (or a dark or black stool) could be a sign of colon or rectal cancer. Cancer of the cervix or the endometrium (lining of the uterus) can cause vaginal bleeding. Blood in the urine may be a sign of bladder or kidney cancer. A bloody discharge from the nipple may be a sign of breast cancer.

[0586] A thickening or lump in the breast or in other parts of the body could indicate the presence of a cancer. Many cancers can be felt through the skin, mostly in the breast, testicle, lymph nodes (glands), and the soft tissues of the body. A lump or thickening may be an early or late sign of cancer. Any lump or thickening could be indicative of cancer, especially if the formation is new or has grown in size.

[0587] Indigestion or trouble swallowing could indicate cancer. While these symptoms commonly have other causes, indigestion or swallowing problems may be a sign of cancer of the esophagus, stomach, or pharynx (throat).

[0588] Recent changes in a wart or mole could be indicative of cancer. Any wart, mole, or freckle that changes in color, size, or shape, or loses its definite borders indicates the potential development of cancer. For example, the skin lesion may be a melanoma.

[0589] A persistent cough or hoarseness could be indicative of cancer. A cough that does not go away may be a sign of lung cancer. Hoarseness can be a sign of cancer of the larynx (voice box) or thyroid.

[0590] While the signs and symptoms listed above are the more common ones seen with cancer, there are many others that are less common and are not listed here. However, all art-recognized signs and symptoms of cancer are contemplated and encompassed by the instant invention.

[0591] Treating cancer can result in a reduction in size of a tumor. A reduction in size of a tumor may also be referred to as "tumor regression". Preferably, after treatment, tumor size is reduced by 5% or greater relative to its size prior to treatment; more preferably, tumor size is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75% or greater. Size of a tumor may be measured by any

reproducible means of measurement. The size of a tumor may be measured as a diameter of the tumor.

[0592] Treating cancer can result in a reduction in tumor volume. Preferably, after treatment, tumor volume is reduced by 5% or greater relative to its size prior to treatment; more preferably, tumor volume is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75% or greater. Tumor volume may be measured by any reproducible means of measurement.

[0593] Treating cancer results in a decrease in number of tumors. Preferably, after treatment, tumor number is reduced by 5% or greater relative to number prior to treatment; more preferably, tumor number is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75%. Number of tumors may be measured by any reproducible means of measurement. The number of tumors may be measured by counting tumors visible to the naked eye or at a specified magnification. Preferably, the specified magnification is 2×, 3×, 4×, 5×, 10×, or 50×.

[0594] Treating cancer can result in a decrease in number of metastatic lesions in other tissues or organs distant from the primary tumor site. Preferably, after treatment, the number of metastatic lesions is reduced by 5% or greater relative to number prior to treatment; more preferably, the number of metastatic lesions is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75%. The number of metastatic lesions may be measured by any reproducible means of measurement. The number of metastatic lesions may be measured by counting metastatic lesions visible to the naked eye or at a specified magnification. Preferably, the specified magnification is 2×, 3×, 4×, 5×, 10×, or 50×.

[0595] Treating cancer can result in an increase in average survival time of a population of treated subjects in comparison to a population receiving carrier alone. Preferably, the average survival time is increased by more than 30 days; more preferably, by more than 60 days; more preferably, by more than 90 days; and most preferably, by more than 120 days. An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with an active compound. An increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with an active compound.

[0596] Treating cancer can result in an increase in average survival time of a population of treated subjects in comparison to a population of untreated subjects. Preferably, the average survival time is increased by more than 30 days; more preferably, by more than 60 days; more preferably, by more than 90 days; and most preferably, by more than 120 days. An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with an active compound. An increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with an active compound.

[0597] Treating cancer can result in increase in average survival time of a population of treated subjects in comparison to a population receiving monotherapy with a drug that is not a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof. Preferably, the average survival time is increased by more than 30 days; more preferably, by more than 60 days; more preferably, by more than 90 days; and most preferably, by more than 120 days. An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with an active compound. An increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with an active compound.

[0598] Treating cancer can result in a decrease in the mortality rate of a population of treated subjects in comparison to a population receiving carrier alone. Treating cancer can result in a decrease in the mortality rate of a population of treated subjects in comparison to an untreated population. Treating cancer can result in a decrease in the mortality rate of a population of treated subjects in comparison to a population receiving monotherapy with a drug that is not a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof. Preferably, the mortality rate is decreased by more than 2%; more preferably, by more than 5%; more preferably, by more than 10%; and most preferably, by more than 25%. A decrease in the mortality rate of a population of treated subjects may be measured by any reproducible means. A decrease in the mortality rate of a population may be measured, for example, by calculating for a population the average number of disease-related deaths per unit time following initiation of treatment with an active compound. A decrease in the mortality rate of a population may also be measured, for example, by calculating for a population the average number of disease-related deaths per unit time following completion of a first round of treatment with an active compound.

[0599] Treating cancer can result in a decrease in tumor growth rate. Preferably, after treatment, tumor growth rate is reduced by at least 5% relative to number prior to treatment; more preferably, tumor growth rate is reduced by at least 10%; more preferably, reduced by at least 20%; more preferably, reduced by at least 30%; more preferably, reduced by at least 40%; more preferably, reduced by at least 50%; even more preferably, reduced by at least 50%; and most preferably, reduced by at least 75%. Tumor growth rate may be measured by any reproducible means of measurement. Tumor growth rate can be measured according to a change in tumor diameter per unit time.

[0600] Treating cancer can result in a decrease in tumor regrowth. Preferably, after treatment, tumor regrowth is less than 5%; more preferably, tumor regrowth is less than 10%; more preferably, less than 20%; more preferably, less than 30%; more preferably, less than 40%; more preferably, less

than 50%; even more preferably, less than 50%; and most preferably, less than 75%. Tumor regrowth may be measured by any reproducible means of measurement. Tumor regrowth is measured, for example, by measuring an increase in the diameter of a tumor after a prior tumor shrinkage that followed treatment. A decrease in tumor regrowth is indicated by failure of tumors to reoccur after treatment has stopped.

[0601] Treating or preventing a cell proliferative disorder can result in a reduction in the rate of cellular proliferation. Preferably, after treatment, the rate of cellular proliferation is reduced by at least 5%; more preferably, by at least 10%; more preferably, by at least 20%; more preferably, by at least 30%; more preferably, by at least 40%; more preferably, by at least 50%; even more preferably, by at least 50%; and most preferably, by at least 75%. The rate of cellular proliferation may be measured by any reproducible means of measurement. The rate of cellular proliferation is measured, for example, by measuring the number of dividing cells in a tissue sample per unit time.

[0602] Treating or preventing a cell proliferative disorder can result in a reduction in the proportion of proliferating cells. Preferably, after treatment, the proportion of proliferating cells is reduced by at least 5%; more preferably, by at least 10%; more preferably, by at least 20%; more preferably, by at least 30%; more preferably, by at least 40%; more preferably, by at least 50%; even more preferably, by at least 50%; and most preferably, by at least 75%. The proportion of proliferating cells may be measured by any reproducible means of measurement. Preferably, the proportion of proliferating cells is measured, for example, by quantifying the number of dividing cells relative to the number of nondividing cells in a tissue sample. The proportion of proliferating cells can be equivalent to the mitotic index.

[0603] Treating or preventing a cell proliferative disorder can result in a decrease in size of an area or zone of cellular proliferation. Preferably, after treatment, size of an area or zone of cellular proliferation is reduced by at least 5% relative to its size prior to treatment; more preferably, reduced by at least 10%; more preferably, reduced by at least 20%; more preferably, reduced by at least 30%; more preferably, reduced by at least 40%; more preferably, reduced by at least 50%; even more preferably, reduced by at least 50%; and most preferably, reduced by at least 75%. Size of an area or zone of cellular proliferation may be measured by any reproducible means of measurement. The size of an area or zone of cellular proliferation may be measured as a diameter or width of an area or zone of cellular proliferation.

[0604] Treating or preventing a cell proliferative disorder can result in a decrease in the number or proportion of cells having an abnormal appearance or morphology. Preferably, after treatment, the number of cells having an abnormal morphology is reduced by at least 5% relative to its size prior to treatment; more preferably, reduced by at least 10%; more preferably, reduced by at least 20%; more preferably, reduced by at least 30%; more preferably, reduced by at least 40%; more preferably, reduced by at least 50%; even more preferably, reduced by at least 50%; and most preferably, reduced by at least 75%. An abnormal cellular appearance or morphology may be measured by any reproducible means of measurement. An abnormal cellular morphology can be measured by microscopy, e.g., using an inverted tissue culture microscope. An abnormal cellular morphology can take the form of nuclear pleiomorphism.

[0605] As used herein, the term "selectively" means tending to occur at a higher frequency in one population than in another population. The compared populations can be cell populations. Preferably, a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, acts selectively on a cancer or precancerous cell but not on a normal cell. Preferably, a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, acts selectively to modulate one molecular target (e.g., a target kinase) but does not significantly modulate another molecular target (e.g., a non-target kinase). The invention also provides a method for selectively inhibiting the activity of an enzyme, such as a kinase. Preferably, an event occurs selectively in population A relative to population B if it occurs greater than two times more frequently in population A as compared to population B. An event occurs selectively if it occurs greater than five times more frequently in population A. An event occurs selectively if it occurs greater than ten times more frequently in population A; more preferably, greater than fifty times; even more preferably, greater than 100 times; and most preferably, greater than 1000 times more frequently in population A as compared to population B. For example, cell death would be said to occur selectively in cancer cells if it occurred greater than twice as frequently in cancer cells as compared to normal cells.

[0606] A compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, can modulate the activity of a molecular target (e.g., a target kinase). Modulating refers to stimulating or inhibiting an activity of a molecular target. Preferably, a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, modulates the activity of a molecular target if it stimulates or inhibits the activity of the molecular target by at least 2-fold relative to the activity of the molecular target under the same conditions but lacking only the presence of said compound. More preferably, a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, modulates the activity of a molecular target if it stimulates or inhibits the activity of the molecular target by at least 5-fold, at least 10-fold, at least 20-fold, at least 50-fold, at least 100-fold relative to the activity of the molecular target under the same conditions but lacking only the presence of said compound. The activity of a molecular target may be measured by any reproducible means. The activity of a molecular target may be measured in vitro or in vivo. For example, the activity of a molecular target may be measured in vitro by an enzymatic activity assay or a DNA binding assay, or the activity of a molecular target may be measured in vivo by assaying for expression of a reporter gene.

[0607] A compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, does not significantly modulate the activity of a molecular target if the addition of the compound does not stimulate or inhibit the activity of the molecular target by greater than 10% relative to the activity of the molecular target under the same conditions but lacking only the presence of said compound.

[0608] As used herein, the term "isozyme selective" means preferential inhibition or stimulation of a first isoform of an enzyme in comparison to a second isoform of an enzyme (e.g., preferential inhibition or stimulation of a kinase

isozyme alpha in comparison to a kinase isozyme beta). Preferably, a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, demonstrates a minimum of a four fold differential, preferably a ten fold differential, more preferably a fifty fold differential, in the dosage required to achieve a biological effect. Preferably, a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, demonstrates this differential across the range of inhibition, and the differential is exemplified at the IC_{50}, i.e., a 50% inhibition, for a molecular target of interest.

[0609] Administering a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, to a cell or a subject in need thereof can result in modulation (i.e., stimulation or inhibition) of an activity of a kinase of interest.

[0610] The present invention provides methods to assess biological activity of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof. In one method, an assay based on enzymatic activity can be utilized. In one specific enzymatic activity assay, the enzymatic activity is from a kinase. As used herein, "kinase" refers to a large class of enzymes which catalyze the transfer of the γ-phosphate from ATP to the hydroxyl group on the side chain of Ser/Thr or Tyr in proteins and peptides and are intimately involved in the control of various important cell functions, perhaps most notably: signal transduction, differentiation, and proliferation. There are estimated to be about 2,000 distinct protein kinases in the human body, and although each of these phosphorylates particular protein/peptide substrates, they all bind the same second substrate ATP in a highly conserved pocket. About 50% of the known oncogene products are protein tyrosine kinases (PTKs), and their kinase activity has been shown to lead to cell transformation. Preferably, the kinase assayed is a tyrosine kinase.

[0611] A change in enzymatic activity caused by a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, can be measured in the disclosed assays. The change in enzymatic activity can be characterized by the change in the extent of phosphorylation of certain substrates. As used herein, "phosphorylation" refers to the addition of phosphate groups to a substrate, including proteins and organic molecules; and, plays an important role in regulating the biological activities of proteins. Preferably, the phosphorylation assayed and measured involves the addition of phosphate groups to tyrosine residues. The substrate can be a peptide or protein.

[0612] In some assays, immunological reagents, e.g., antibodies and antigens, are employed. Fluorescence can be utilized in the measurement of enzymatic activity in some assays. As used herein, "fluorescence" refers to a process through which a molecule emits a photon as a result of absorbing an incoming photon of higher energy by the same molecule. Specific methods for assessing the biological activity of the disclosed compounds are described in the examples.

[0613] As used herein, an activity of c-Met refers to any biological function or activity that is carried out by c-Met. For example, a function of c-Met includes phosphorylation of downstream target proteins. Other functions of c-Met include autophosphorylation, binding of adaptor proteins such as Gab-1, Grb-2, Shc, SHP2 and c-Cbl, and activation of signal transducers such as Ras, Src, PI3K, PLC-γ, STATs, ERK1 and 2 and FAK.

[0614] Administering a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, to a cell or a subject in need thereof results in modulation (i.e., stimulation or inhibition) of an activity of an intracellular target (e.g., substrate). Several intracellular targets can be modulated with the compounds of the present invention, including, but not limited to, adaptor proteins such as Gab-1, Grb-2, Shc, SHP2 and c-Cbl, and signal transducers such as Ras, Src, PI3K, PLC-γ, STATs, ERK1 and 2 and FAK.

[0615] Activating refers to placing a composition of matter (e.g., protein or nucleic acid) in a state suitable for carrying out a desired biological function. A composition of matter capable of being activated also has an unactivated state. An activated composition of matter may have an inhibitory or stimulatory biological function, or both.

[0616] Elevation refers to an increase in a desired biological activity of a composition of matter (e.g., a protein or a nucleic acid). Elevation may occur through an increase in concentration of a composition of matter.

[0617] As used herein, "a cell cycle checkpoint pathway" refers to a biochemical pathway that is involved in modulation of a cell cycle checkpoint. A cell cycle checkpoint pathway may have stimulatory or inhibitory effects, or both, on one or more functions comprising a cell cycle checkpoint. A cell cycle checkpoint pathway is comprised of at least two compositions of matter, preferably proteins, both of which contribute to modulation of a cell cycle checkpoint. A cell cycle checkpoint pathway may be activated through an activation of one or more members of the cell cycle checkpoint pathway. Preferably, a cell cycle checkpoint pathway is a biochemical signaling pathway.

[0618] As used herein, "cell cycle checkpoint regulator" refers to a composition of matter that can function, at least in part, in modulation of a cell cycle checkpoint. A cell cycle checkpoint regulator may have stimulatory or inhibitory effects, or both, on one or more functions comprising a cell cycle checkpoint. A cell cycle checkpoint regulator can be a protein or not a protein.

[0619] Treating cancer or a cell proliferative disorder can result in cell death, and preferably, cell death results in a decrease of at least 10% in number of cells in a population. More preferably, cell death means a decrease of at least 20%; more preferably, a decrease of at least 30%; more preferably, a decrease of at least 40%; more preferably, a decrease of at least 50%; most preferably, a decrease of at least 75%. Number of cells in a population may be measured by any reproducible means. A number of cells in a population can be measured by fluorescence activated cell sorting (FACS), immunofluorescence microscopy and light microscopy. Methods of measuring cell death are as shown in Li et al., *Proc Natl Acad Sci USA.* 100(5): 2674-8, 2003. In an aspect, cell death occurs by apoptosis.

[0620] Preferably, an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, is not significantly cytotoxic to normal cells. A therapeutically effective amount of a compound is not significantly cytotoxic to normal cells if administration of the compound in a therapeutically effective amount does not induce cell death in greater than 10% of normal cells. A therapeutically effective

amount of a compound does not significantly affect the viability of normal cells if administration of the compound in a therapeutically effective amount does not induce cell death in greater than 10% of normal cells. In an aspect, cell death occurs by apoptosis.

[0621] Contacting a cell with a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, can induce or activate cell death selectively in cancer cells. Administering to a subject in need thereof a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, can induce or activate cell death selectively in cancer cells. Contacting a cell with a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, can induce cell death selectively in one or more cells affected by a cell proliferative disorder. Preferably, administering to a subject in need thereof a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, induces cell death selectively in one or more cells affected by a cell proliferative disorder.

[0622] The present invention relates to a method of treating or preventing cancer by administering a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, to a subject in need thereof, where administration of the compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, results in one or more of the following: accumulation of cells in G1 and/or S phase of the cell cycle, cytotoxicity via cell death in cancer cells without a significant amount of cell death in normal cells, antitumor activity in animals with a therapeutic index of at least 2, and activation of a cell cycle checkpoint. As used herein, "therapeutic index" is the maximum tolerated dose divided by the efficacious dose.

[0623] One skilled in the art may refer to general reference texts for detailed descriptions of known techniques discussed herein or equivalent techniques. These texts include Ausubel et al., *Current Protocols in Molecular Biology*, John Wiley and Sons, Inc. (2005); Sambrook et al., *Molecular Cloning, A Laboratory Manual* (3rd edition), Cold Spring Harbor Press, Cold Spring Harbor, N.Y. (2000); Coligan et al., *Current Protocols in Immunology*, John Wiley & Sons, N.Y.; Enna et al., *Current Protocols in Pharmacology*, John Wiley & Sons, N.Y.; Fingl et al., *The Pharmacological Basis of Therapeutics* (1975), *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pa., 18th edition (1990). These texts can, of course, also be referred to in making or using an aspect of the invention

[0624] As used herein, "combination therapy" or "co-therapy" includes the administration of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, and at least a second agent as part of a specific treatment regimen intended to provide the beneficial effect from the co-action of these therapeutic agents. The beneficial effect of the combination includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents. Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually minutes, hours, days or weeks depending upon the combination selected). "Combination therapy" may be, but generally is not, intended to encompass the administration of two or more of these therapeutic agents as part of separate monotherapy regimens that incidentally and arbitrarily result in the combinations of the present invention.

[0625] "Combination therapy" is intended to embrace administration of these therapeutic agents in a sequential manner, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single capsule having a fixed ratio of each therapeutic agent or in multiple, single capsules for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively, for example, all therapeutic agents may be administered orally or all therapeutic agents may be administered by intravenous injection. The sequence in which the therapeutic agents are administered is not narrowly critical.

[0626] "Combination therapy" also embraces the administration of the therapeutic agents as described above in further combination with other biologically active ingredients and non-drug therapies (e.g., surgery or radiation treatment). Where the combination therapy further comprises a non-drug treatment, the non-drug treatment may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents and non-drug treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved when the non-drug treatment is temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.

[0627] A compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof, may be administered in combination with a second chemotherapeutic agent. The second chemotherapeutic agent (also referred to as an anti-neoplastic agent or anti-proliferative agent) can be an alkylating agent; an antibiotic; an anti-metabolite; a detoxifying agent; an interferon; a polyclonal or monoclonal antibody; an EGFR inhibitor; a HER2 inhibitor; a histone deacetylase inhibitor; a hormone; a mitotic inhibitor; an MTOR inhibitor; a multi-kinase inhibitor; a serine/threonine kinase inhibitor; a tyrosine kinase inhibitors; a VEGF/VEGFR inhibitor; a taxane or taxane derivative, an aromatase inhibitor, an anthracycline, a microtubule targeting drug, a topoisomerase poison drug, an inhibitor of a molecular target or enzyme (e.g., a kinase inhibitor), a cytidine analogue drug or any chemotherapeutic, anti-neoplastic or anti-proliferative agent listed in www.cancer.org/docroot/cdg/cdg_0.asp.

[0628] Exemplary alkylating agents include, but are not limited to, cyclophosphamide (Cytoxan; Neosar); chlorambucil (Leukeran); melphalan (Alkeran); carmustine (BiCNU); busulfan (Busulfex); lomustine (CeeNU); dacarbazine (DTIC-Dome); oxaliplatin (Eloxatin); carmustine (Gliadel); Ifosfamide (Ifex); mechlorethamine (Mustargen); busulfan (Myleran); carboplatin (Paraplatin); cisplatin

(CDDP; Platinol); temozolomide (Temodar); thiotepa (Thioplex); bendamustine (Treanda); or streptozocin (Zanosar).

[0629] Exemplary antibiotics include, but are not limited to, doxorubicin (Adriamycin); doxorubicin liposomal (Doxil); mitoxantrone (Novantrone); bleomycin (Blenoxane); daunorubicin (Cerubidine); daunorubicin liposomal (DaunoXome); dactinomycin (Cosmegen); epirubicin (Ellence); idarubicin (Idamycin); plicamycin (Mithracin); mitomycin (Mutamycin); pentostatin (Nipent); or valrubicin (Valstar).

[0630] Exemplary anti-metabolites include, but are not limited to, fluorouracil (Adrucil); capecitabine (Xeloda); hydroxyurea (Hydrea); mercaptopurine (Purinethol); pemetrexed (Alimta); fludarabine (Fludara); nelarabine (Arranon); cladribine (Cladribine Novaplus); clofarabine (Clolar); cytarabine (Cytosar-U); decitabine (Dacogen); cytarabine liposomal (DepoCyt); hydroxyurea (Droxia); pralatrexate (Folotyn); floxuridine (FUDR); gemcitabine (Gemzar); cladribine (Leustatin); fludarabine (Oforta); methotrexate (MTX; Rheumatrex); methotrexate (Trexall); thioguanine (Tabloid); TS-1 or cytarabine (Tarabine PFS).

[0631] Exemplary detoxifying agents include, but are not limited to, amifostine (Ethyol) or mesna (Mesnex).

[0632] Exemplary interferons include, but are not limited to, interferon alfa-2b (Intron A) or interferon alfa-2a (Roferon-A).

[0633] Exemplary polyclonal or monoclonal antibodies include, but are not limited to, trastuzumab (Herceptin); ofatumumab (Arzerra); bevacizumab (Avastin); rituximab (Rituxan); cetuximab (Erbitux); panitumumab (Vectibix); tositumomab/iodine^{131} tositumomab (Bexxar); alemtuzumab (Campath); ibritumomab (Zevalin; In-111; Y-90 Zevalin); gemtuzumab (Mylotarg); eculizumab (Soliris) ordenosumab.

[0634] Exemplary EGFR inhibitors include, but are not limited to, gefitinib (Iressa); lapatinib (Tykerb); cetuximab (Erbitux); erlotinib (Tarceva); panitumumab (Vectibix); PKI-166; canertinib (CI-1033); matuzumab (Emd7200) or EKB-569.

[0635] Exemplary HER2 inhibitors include, but are not limited to, trastuzumab (Herceptin); lapatinib (Tykerb) or AC-480.

[0636] Histone Deacetylase Inhibitors include, but are not limited to, vorinostat (Zolinza).

[0637] Exemplary hormones include, but are not limited to, tamoxifen (Soltamox; Nolvadex); raloxifene (Evista); megestrol (Megace); leuprolide (Lupron; Lupron Depot; Eligard; Viadur); fulvestrant (Faslodex); letrozole (Femara); triptorelin (Trelstar LA; Trelstar Depot); exemestane (Aromasin); goserelin (Zoladex); bicalutamide (Casodex); anastrozole (Arimidex); fluoxymesterone (Androxy; Halotestin); medroxyprogesterone (Provera; Depo-Provera); estramustine (Emcyt); flutamide (Eulexin); toremifene (Fareston); degarelix (Firmagon); nilutamide (Nilandron); abarelix (Plenaxis); or testolactone (Teslac).

[0638] Exemplary mitotic inhibitors include, but are not limited to, paclitaxel (Taxol; Onxol; Abraxane); docetaxel (Taxotere); vincristine (Oncovin; Vincasar PFS); vinblastine (Velban); etoposide (Toposar; Etopophos; VePesid); teniposide (Vumon); ixabepilone (Ixempra); nocodazole; epothilone; vinorelbine (Navelbine); camptothecin (CPT); irinotecan (Camptosar); topotecan (Hycamtin); amsacrine or lamellarin D (LAM-D).

[0639] Exemplary MTOR inhibitors include, but are not limited to, everolimus (Afinitor) or temsirolimus (Torisel); rapamune, ridaforolimus; or AP23573.

[0640] Exemplary multi-kinase inhibitors include, but are not limited to, sorafenib (Nexavar); sunitinib (Sutent); BIBW 2992; E7080; Zd6474; PKC-412; motesanib; or AP24534.

[0641] Exemplary serine/threonine kinase inhibitors include, but are not limited to, ruboxistaurin; eril/easudil hydrochloride; flavopiridol; seliciclib (CYC202; Roscovitrine); SNS-032 (BMS-387032); Pkc412; bryostatin; KAI-9803; SF1126; VX-680; Azd1152; Arry-142886 (AZD-6244); SCIO-469; GW681323; CC-401; CEP-1347 or PD 332991.

[0642] Exemplary tyrosine kinase inhibitors include, but are not limited to, erlotinib (Tarceva); gefitinib (Iressa); imatinib (Gleevec); sorafenib (Nexavar); sunitinib (Sutent); trastuzumab (Herceptin); bevacizumab (Avastin); rituximab (Rituxan); lapatinib (Tykerb); cetuximab (Erbitux); panitumumab (Vectibix); everolimus (Afinitor); alemtuzumab (Campath); gemtuzumab (Mylotarg); temsirolimus (Torisel); pazopanib (Votrient); dasatinib (Sprycel); nilotinib (Tasigna); vatalanib (Ptk787; ZK222584); CEP-701; SU5614; MLN518; XL999; VX-322; Azd0530; BMS-354825; SKI-606 CP-690; AG-490; WHI-P154; WHI-P131; AC-220; or AMG888.

[0643] Exemplary VEGF/VEGFR inhibitors include, but are not limited to, bevacizumab (Avastin); sorafenib (Nexavar); sunitinib (Sutent); ranibizumab; pegaptanib; or vandetinib.

[0644] Exemplary microtubule targeting drugs include, but are not limited to, paclitaxel, docetaxel, vincristin, vinblastin, nocodazole, epothilones and navelbine.

[0645] Exemplary topoisomerase poison drugs include, but are not limited to, teniposide, etoposide, adriamycin, camptothecin, daunorubicin, dactinomycin, mitoxantrone, amsacrine, epirubicin and idarubicin.

[0646] Exemplary taxanes or taxane derivatives include, but are not limited to, paclitaxel and docetaxol.

[0647] Exemplary general chemotherapeutic, anti-neoplastic, anti-proliferative agents include, but are not limited to, altretamine (Hexylen); isotretinoin (Accutane; Amnesteem; Claravis; Sotret); tretinoin (Vesanoid); azacitidine (Vidaza); bortezomib (Velcade) asparaginase (Elspar); levamisole (Ergamisol); mitotane (Lysodren); procarbazine (Matulane); pegaspargase (Oncaspar); denileukin diftitox (Ontak); porfimer (Photofrin); aldesleukin (Proleukin); lenalidomide (Revlimid); bexarotene (Targretin); thalidomide (Thalomid); temsirolimus (Torisel); arsenic trioxide (Trisenox); verteporfin (Visudyne); mimosine (Leucenol); (1M tegafur—0.4 M 5-chloro-2,4-dihydroxypyrimidine-1 M potassium oxonate) or lovastatin.

[0648] In another aspect, the second chemotherapeutic agent can be a cytokine such as G-CSF (granulocyte colony stimulating factor). In another aspect, a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof, may be administered in combination with radiation therapy. Radiation therapy can also be administered in combination with a compound of the present invention and another chemotherapeutic agent described herein as part of a multiple agent therapy. In yet another aspect, a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof, may be administered in combination with standard chemotherapy combinations such as, but not

restricted to, CMF (cyclophosphamide, methotrexate and 5-fluorouracil), CAF (cyclophosphamide, adriamycin and 5-fluorouracil), AC (adriamycin and cyclophosphamide), FEC (5-fluorouracil, epirubicin, and cyclophosphamide), ACT or ATC (adriamycin, cyclophosphamide, and paclitaxel), rituximab, Xeloda (capecitabine), Cisplatin (CDDP), Carboplatin, TS-1 (tegafur, gimestat and otastat potassium at a molar ratio of 1:0.4:1), Camptothecin-11 (CPT-11, Irinotecan or Camptosar™) or CMFP (cyclophosphamide, methotrexate, 5-fluorouracil and prednisone).

[0649] In preferred embodiments, a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, may be administered with an inhibitor of an enzyme, such as a receptor or non-receptor kinase. Receptor and non-receptor kinases of the invention are, for example, tyrosine kinases or serine/threonine kinases. Kinase inhibitors of the invention are small molecules, polynucleic acids, polypeptides, or antibodies.

[0650] Exemplary kinase inhibitors include, but are not limited to, Bevacizumab (targets VEGF), BIBW 2992 (targets EGFR and Erb2), Cetuximab/Erbitux (targets Erb1), Imatinib/Gleevic (targets Bcr-Abl), Trastuzumab (targets Erb2), Gefitinib/Iressa (targets EGFR), Ranibizumab (targets VEGF), Pegaptanib (targets VEGF), Erlotinib/Tarceva (targets Erb1), Nilotinib (targets Bcr-Abl), Lapatinib (targets Erb1 and Erb2/Her2), GW-572016/lapatinib ditosylate (targets HER2/Erb2), Panitumumab/Vectibix (targets EGFR), Vandetinib (targets RET/VEGFR), E7080 (multiple targets including RET and VEGFR), Herceptin (targets HER2/Erb2), PKI-166 (targets EGFR), Canertinib/CI-1033 (targets EGFR), Sunitinib/SU-11464/Sutent (targets EGFR and FLT3), Matuzumab/Emd7200 (targets EGFR), EKB-569 (targets EGFR), Zd6474 (targets EGFR and VEGFR), PKC-412 (targets VEGR and FLT3), Vatalanib/Ptk787/ZK222584 (targets VEGR), CEP-701 (targets FLT3), SU5614 (targets FLT3), MLN518 (targets FLT3), XL999 (targets FLT3), VX-322 (targets FLT3), Azd0530 (targets SRC), BMS-354825 (targets SRC), SKI-606 (targets SRC), CP-690 (targets JAK), AG-490 (targets JAK), WHI-P154 (targets JAK), WHI-P131 (targets JAK), sorafenib/Nexavar (targets RAF kinase, VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, KIT, FLT-3, and RET), Dasatinib/Sprycel (BCR/ABL and Src), AC-220 (targets Flt3), AC-480 (targets all HER proteins, "panHER"), Motesanib diphosphate (targets VEGF1-3, PDGFR, and c-kit), Denosumab (targets RANKL, inhibits SRC), AMG888 (targets HER3), and AP24534 (multiple targets including Flt3).

[0651] Exemplary serine/threonine kinase inhibitors include, but are not limited to, Rapamune (targets mTOR/FRAP1), Deforolimus (targets mTOR), Certican/Everolimus (targets mTOR/FRAP1), AP23573 (targets mTOR/FRAP1), Eril/Fasudil hydrochloride (targets RHO), Flavopiridol (targets CDK), Seliciclib/CYC202/Roscovitrine (targets CDK), SNS-032/BMS-387032 (targets CDK), Ruboxistaurin (targets PKC), Pkc412 (targets PKC), Bryostatin (targets PKC), KAI-9803 (targets PKC), SF1126 (targets PI3K), VX-680 (targets Aurora kinase), Azd1152 (targets Aurora kinase), Arry-142886/AZD-6244 (targets MAP/MEK), SCIO-469 (targets MAP/MEK), GW681323 (targets MAP/MEK), CC-401 (targets JNK), CEP-1347 (targets JNK), and PD 332991 (targets CDK).

4. Pharmaceutical Compositions

[0652] The present invention also provides pharmaceutical compositions comprising a compound of each of the formulae described herein in combination with at least one pharmaceutically acceptable excipient or carrier.

[0653] A "pharmaceutical composition" is a formulation containing the compounds of the present invention in a form suitable for administration to a subject. In one embodiment, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler or a vial. The quantity of active ingredient (e.g., a formulation of the disclosed compound or salt, hydrate, solvate or isomer thereof) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In one embodiment, the active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers or propellants that are required.

[0654] As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0655] "Pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

[0656] A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), and transmucosal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0657] A compound or pharmaceutical composition of the invention can be administered to a subject in many of the

well-known methods currently used for chemotherapeutic treatment. For example, for treatment of cancers, a compound of the invention may be injected directly into tumors, injected into the blood stream or body cavities or taken orally or applied through the skin with patches. The dose chosen should be sufficient to constitute effective treatment but not so high as to cause unacceptable side effects. The state of the disease condition (e.g., cancer, precancer, and the like) and the health of the patient should preferably be closely monitored during and for a reasonable period after treatment.

[0658] The term "therapeutically effective amount", as used herein, refers to an amount of a pharmaceutical agent to treat, ameliorate, or prevent an identified disease or condition, or to exhibit a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician. In a preferred aspect, the disease or condition to be treated is cancer. In another aspect, the disease or condition to be treated is a cell proliferative disorder.

[0659] For any compound, the therapeutically effective amount can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. Therapeutic/prophylactic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., ED_{50} (the dose therapeutically effective in 50% of the population) and LD_{50} (the dose lethal to 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD_{50}/ED_{50}. Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

[0660] Dosage and administration are adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

[0661] The pharmaceutical compositions containing active compounds of the present invention may be manufactured in a manner that is generally known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

[0662] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0663] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0664] Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0665] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser, which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

[0666] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[0667] The active compounds can be prepared with pharmaceutically acceptable carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[0668] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved.

[0669] In therapeutic applications, the dosages of the pharmaceutical compositions used in accordance with the invention vary depending on the agent, the age, weight, and clinical condition of the recipient patient, and the experience and judgment of the clinician or practitioner administering the therapy, among other factors affecting the selected dosage. Generally, the dose should be sufficient to result in slowing, and preferably regressing, the growth of the tumors and also preferably causing complete regression of the cancer. Dosages can range from about 0.01 mg/kg per day to about 5000 mg/kg per day. In preferred aspects, dosages can range from about 1 mg/kg per day to about 1000 mg/kg per day. In an aspect, the dose will be in the range of about 0.1 mg/day to about 50 g/day; about 0.1 mg/day to about 25 g/day; about 0.1 mg/day to about 10 g/day; about 0.1 mg to about 3 g/day; or about 0.1 mg to about 1 g/day, in single, divided, or continuous doses (which dose may be adjusted for the patient's weight in kg, body surface area in m^2, and age in years). An effective amount of a pharmaceutical agent is that which provides an objectively identifiable improvement as noted by the clinician or other qualified observer. For example, regression of a tumor in a patient may be measured with reference to the diameter of a tumor. Decrease in the diameter of a tumor indicates regression. Regression is also indicated by failure of tumors to reoccur after treatment has stopped. As used herein, the term "dosage effective manner" refers to amount of an active compound to produce the desired biological effect in a subject or cell.

[0670] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0671] The compounds of the present invention are capable of further forming salts. All of these forms are also contemplated within the scope of the claimed invention.

[0672] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the compounds of the present invention wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, 1,2-ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicyclic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, e.g., glycine, alanine, phenylalanine, arginine, etc.

[0673] Other examples of pharmaceutically acceptable salts include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present invention also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

[0674] It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same salt.

[0675] The compounds of the present invention can also be prepared as esters, for example, pharmaceutically acceptable esters. For example, a carboxylic acid function group in a compound can be converted to its corresponding ester, e.g., a methyl, ethyl or other ester. Also, an alcohol group in a compound can be converted to its corresponding ester, e.g., an acetate, propionate or other ester.

[0676] The compounds of the present invention can also be prepared as prodrugs, for example, pharmaceutically acceptable prodrugs. The terms "pro-drug" and "prodrug" are used interchangeably herein and refer to any compound which releases an active parent drug in vivo. Since prodrugs are

known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.), the compounds of the present invention can be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers that release an active parent drug of the present invention in vivo when such prodrug is administered to a subject. Prodrugs in the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, sulfhydryl, carboxy or carbonyl group is bonded to any group that may be cleaved in vivo to form a free hydroxyl, free amino, free sulfhydryl, free carboxy or free carbonyl group, respectively.

[0677] Examples of prodrugs include, but are not limited to, esters (e.g., acetate, dialkylaminoacetates, formates, phosphates, sulfates and benzoate derivatives) and carbamates (e.g., N,N-dimethylaminocarbonyl) of hydroxy functional groups, esters (e.g., ethyl esters, morpholinoethanol esters) of carboxyl functional groups, N-acyl derivatives (e.g., N-acetyl) N-Mannich bases, Schiff bases and enaminones of amino functional groups, oximes, acetals, ketals and enol esters of ketone and aldehyde functional groups in compounds of the invention, and the like, See Bundegaard, H., *Design of Prodrugs, p* 1-92, Elesevier, New York-Oxford (1985).

[0678] The compounds, or pharmaceutically acceptable salts, esters or prodrugs thereof, are administered orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperintoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally and parenterally. In one embodiment, the compound is administered orally. One skilled in the art will recognize the advantages of certain routes of administration.

[0679] The dosage regimen utilizing the compounds is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

[0680] Techniques for formulation and administration of the disclosed compounds of the invention can be found in *Remington: the Science and Practice of Pharmacy,* 19th edition, Mack Publishing Co., Easton, Pa. (1995). In an embodiment, the compounds described herein, and the pharmaceutically acceptable salts thereof, are used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The compounds will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein.

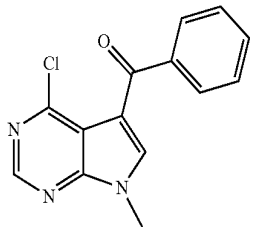
[0681] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present invention are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present invention. The examples do not limit the claimed invention. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present invention.

5. EXAMPLES

Example 1

Synthesis of (4-chloro-7-methyl-7H-pyrrolo[2,3-d] pyrimidin-5-yl)(phenyl)methanone

[0682]

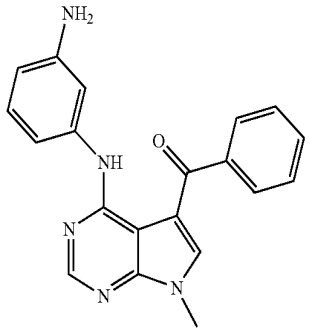


[0683] To a solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone (257 mg, 1.0 mmol) in tetrahydrofuran (5 mL) was added sodium hydride (36 mg, 1.5 mmol) at room temperature. After 5 min methyl iodide (0.06 mL, 1.5 mmol) was added via syringe. After 4 hours the reaction mixture was poured into water (50 mL), extracted with ethyl acetate (3×25 mL), washed with brine, and concentrated to obtain (4-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone (350 mg) as a yellow solid. LCMS [M+H]: 272.

Example 2

Synthesis of (4-((3-aminophenyl)amino)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone

[0684]



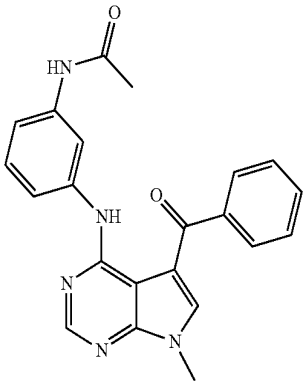
[0685] (4-((3-aminophenyl)amino)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone was synthesized according to general procedure A step 2 using 1,3-diaminobenzene and (4-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone. A white solid was obtained. M.p: 170-173° C.; 400 MHz ^{1}H NMR (DMSO-d_6) δ: 8.53 (s, 1H), 8.12 (s, 1H), 8.06 (s, 1H), 7.86 (d, J=6.6 Hz, 2H), 7.71 (d, J=4.3 Hz, 2H), 7.68 (d, J=4.3 Hz, 2H), 7.43 (d, J=7.8 Hz, 1H), 7.13 (t, J=7.8 Hz, 1H), 6.95 (d, J=5.8 Hz, 1H), 6.69 (s, 1H),

6.57 (d, J=1.9 Hz, 1H), 3.68 (s, 3H); LCMS [M+H]: 344; Calc. $C_{20}H_{17}N_5O$.1.6 trifluoroacetic acid.0.1 diethyl ether: C, 53.16; H, 3.70; N, 13.13. Found C, 50.79; H, 3.73; N, 12.93.

Example 3

Synthesis of N-(3-((5-benzoyl-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)acetamide

[0686]

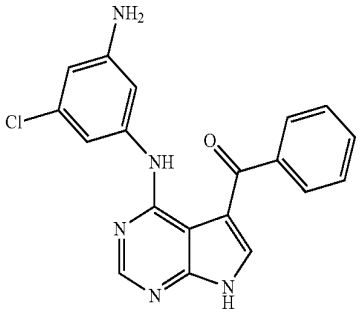


[0687] N-(3-((5-benzoyl-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)acetamide methanone was synthesized according to general procedure A step 2. A white solid was obtained. M.p: 140-142° C.; 400 MHz ^{1}H NMR (DMSO-d_6) δ: 11.38 (s, 1H), 10.01 (s, 1H), 8.49 (s, 1H), 8.09 (s, 1H), 8.03 (s, 1H), 7.86 (d, J=7.0 Hz, 2 H), 7.74-7.71 (m, 2H), 7.67 (t, J=7.0 Hz, 2H), 7.37 (d, J=8.2 Hz, 1H), 7.29 (t, J=8.2 Hz, 1H), 3.81 (s, 3H) 2.05 (s, 3H); LCMS [M+H]: 386.

Example 4

Synthesis of (4-((3-amino-5-chlorophenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone

[0688]

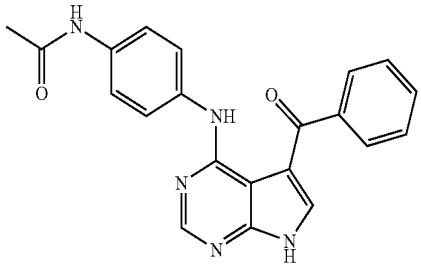


[0689] (4-((3-amino-5-chlorophenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone was synthesized according to general procedure A. A white solid was obtained. M.p: >300° C.; 400 MHz ^{1}H NMR (DMSO-d_6) δ: 12.99 (brs, 1H), 11.27 (s, 1H), 8.47 (s, 1H), 7.94 (s, 1H), 7.84 (d, J=7.0 Hz, 2H), 7.70-7.68 (m, 1H), 7.57 (d, J=7.4 Hz, 2H), 7.46 (s, 1H), 6.89 (s, 1H), 6.31 (s, 1H), 5.50 (brs, 2H); LCMS [M+H]: 364; Calc. $C_{19}H_{14}ClN_5O$ 0.3 water 0.1 dimethylacetamide: C, 61.66; H, 4.13; N, 18.90. Found C, 61.03; H, 3.80; N, 18.88.

Example 5

Synthesis of N-(4-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)acetamide

[0690]

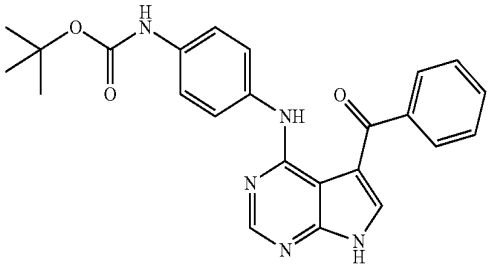


[0691] N-(4-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)acetamide was synthesized according to general procedure A. A yellow solid was obtained. M.p.=263-264° C.; ^{1}H NMR 400 MHz (DMSO-d_6) δ 11.22 (s, 1H), 9.91 (s, 1H), 8.42-8.41 (m, 1H), 7.91 (m, 1H), 7.85-7.79 (m, 4H), 7.68-7.66 (m, 2H), 7.60-7.75 (m, 4H), 2.04 (s, 3H); LCMS [M+H]=372.

Example 6

Synthesis of tert-butyl 4-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenylcarbamate

[0692]

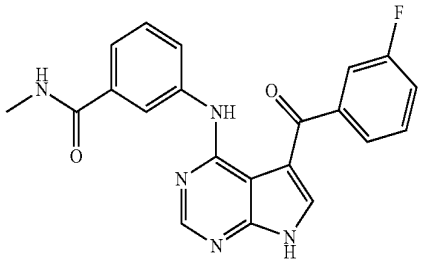


[0693] Tert-butyl 4-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenylcarbamate was synthesized according to general procedure A. A yellow solid was obtained. M.p. =274-280° C.; ^{1}H NMR 400 MHz (DMSO-d_6) δ 11.13 (s, 1H), 9.25 (s, 1H), 8.37-8.36 (m, 1H), 7.87-7.86 (m, 1H), 7.82-7.80 (m, 2H), 7.74-7.72 (m, 2H), 7.69-7.72 (m, 1H), 7.57-7.53 (m, 2H), 7.44-7.42 (m, 2H), 1.45 (s, 9H); LCMS [M+H]=430.

Example 7

Synthesis of 3-((5-(3-fluorobenzoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-N-methylbenzamide

[0694]



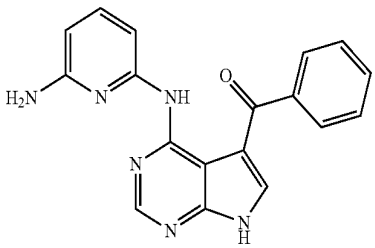
[0695] 3-((5-(3-fluorobenzoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-N-methylbenzamide was synthesized

according to general procedure A. An off-white solid was obtained. M.p.>300° C.; ^{1}H NMR 400 MHz (DMSO-d_6) δ 11.28 (s, 1H), 8.46-8.44 (m, 2 H), 8.20-8.14 (m, 2H), 8.02 (s, 1H), 7.68-7.59 (m, 3H), 7.52-7.42 (m, 3H), 2.77 (d, 3H); LCMS [M+H]=390.

Example 8

Synthesis of (4-(6-aminopyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone

[0696]

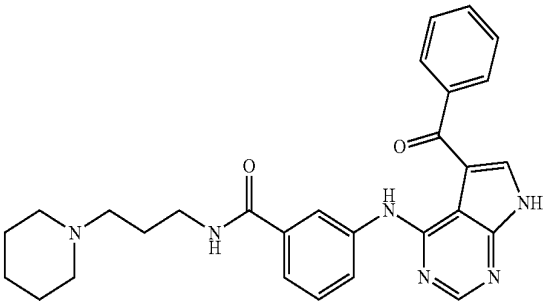


[0697] (4-(6-Aminopyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone was synthesized according to general procedure A. A tan solid was obtained. M.p. >300° C.; ^{1}H NMR 400 MHz (DMSO-d_6) δ 11.18 (s, 1H), 8.46 (s, 1H), 7.93 (s, 1H), 7.85-7.83 (m, 3H), 7.69-7.66 (m, 1H), 7.60-7.56 (m, 2H), 7.40 (t, J=8.4 Hz, 1H), 6.14 (d. J=8.0 Hz, 1H), 5.87 (s, 2H); LCMS [M+H]=331.

Example 9

Synthesis of 3-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-N-(3-(piperidin-1-yl)propyl)benzamide

[0698]

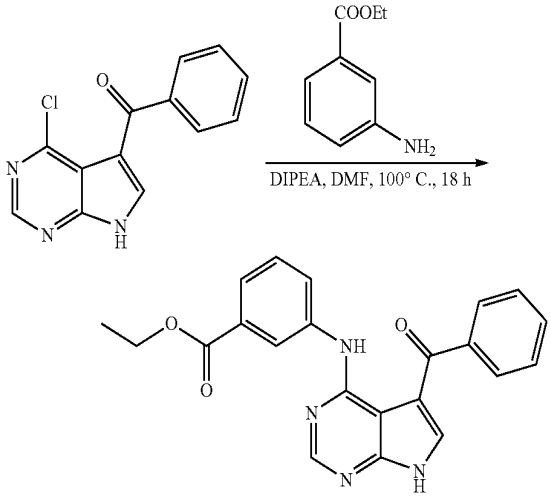


[0699] 3-(5-Benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-N-(3-(piperidin-1-yl)propyl)benzamide was synthesized according to general procedure B. A yellow solid was obtained. M.p.>300° C.; ^{1}H NMR 400 MHz (DMSO-d_6) δ 13.05 (s, 1H), 11.44 (s, 1H), 9.43 (s, 1H), 8.67 (t, J=6.0 Hz, 1H), 8.48 (s, 1H), 8.24-8.24 (m, 1H), 8.19 (s, 1H), 7.98 (d, J=2.4 Hz, 1H), 7.87-7.85 (m, 2H), 7.71-7.68 (m, 1H), 7.61-7.58 (m, 2H), 7.54-7.48 (m, 2H), 3.57-3.54 (m, 2H), 3.38-3.34 (m, 2H), 3.22-3.16 (m, 2H), 3.02-2.98 (m, 2H), 2.10-1.99 (m, 2H), 1.97-1.84 (m, 6H); LCMS [M+H]=483.

Example 10

Synthesis of ethyl 3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)benzoate

[0700]

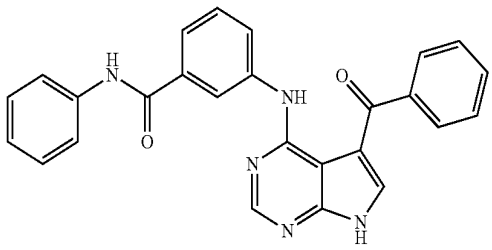


[0701] To a solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-yl)(phenyl)methanone (1.6 g, 6.23 mmol) in DMF (10 mL) were added ethyl 3-aminobenzoate (2.06 g, 12.46 mmol) and DIPEA (3.26 mL, 18.69 mmol). The reaction was heated at 100° C. for 18 hours. EtOAc (150 mL) and H_2O (30 mL) were added to the mixture. The precipitates were collected and washed with H_2O. The organic layer was separated, washed with brine (30 mL), dried over Na_2SO_4 and concentrated to dryness. The crude was purified by dry-packed flash column eluting with DCM/EtOAc (3:1) to give a pale yellow solid (1.5 g, 63%). M.p.=256-258° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 13.04 (s, 1H), 11.52 (s, 1H), 8.50 (s, 1H), 8.47 (t, J=2.0 Hz, 1H), 8.25-8.22 (m, 1H), 7.98 (s, 1H), 7.87 (d, J=7.6 Hz, 2H), 7.69-7.52 (m, 5H), 4.35 (q, J=7.2 Hz, 2H), 1.35 (t, J=7.6 Hz, 3 H); LCMS [M+H]=387.

Example 11

Synthesis of 3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino-N-phenylbenzamide

[0702]



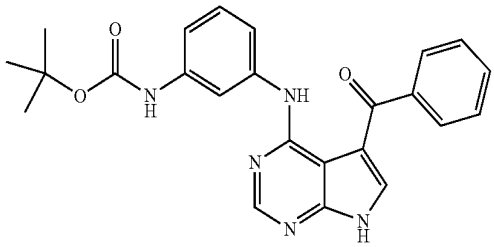
[0703] To a solution of 3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)benzoic acid (25 mg, 0.07 mmol) in DMF (1 mL) was added DIPEA (18 μL, 0.105 mmol), HBTU (32 mg, 0.084 mmol), and aniline (7.6 μL, 0.084 mmol). The reaction was stirred at room temperature for 18 hours. The

crude was purified by reverse phase preparative HPLC. M.p. >300° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 13.04 (s, 1H), 11.50 (s, 1H), 10.34 (s, 1H), 8.50 (s, 1H), 8.33 (t, J=1.6 Hz, 1H), 8.26-8.23 (d, J=8.0 Hz, 1H), 7.99 (d, J=2.4 Hz, 1H), 7.88 (d, J=6.8 Hz, 2H), 7.79 (d, J=7.6 Hz, 1H), 7.69-7.53 (m, 5H), 7.37 (t, J=7.6 Hz, 2H), 7.11 (t, J=6.8 Hz, 1H); LCMS [M+H] 434.

Example 12

Synthesis of tert-butyl(3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)phenyl)acetamide

[0704]

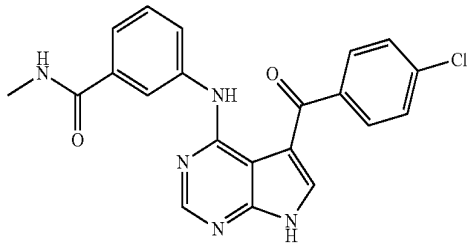


[0705] To 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-yl)(phenyl)methanone (1.6 g, 6.23 mmol) in DMF (10 mL) were added 3-boc-aminoaniline (1.3 g, 6.23 mmol) and DIPEA (3.3 mL, 18.69 mmol). The reaction was heated at 120° C. for 48 hours. After cooling down to room temperature, 40 mL of DCM was added to the mixture. The precipitates were collected, washed with DCM, and dried on high vacuum to give a yellow solid (2.0 g, 76%). M.p.=288-290° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 12.93 (s, 1H), 11.21 (s, 1H), 9.36 (s, 1H), 8.49 (s, 1H), 7.90-7.87 (m, 2H), 7.84-7.81 (m, 2H), 7.75-7.72 (dd, J=7.6 Hz, 1.2 Hz, 1H), 7.67-7.63 (m, 1H), 7.57 (t, J=7.6 Hz, 2H), 7.22 (t, J=8.4 Hz, 1H), 7.09 (d, J=8.4 Hz, 1H), 1.46 (s, 9H); LCMS [M+H] 430.

Example 13

Synthesis of 3-((5-(4-chlorobenzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino-N-methylbenzamide

[0706]

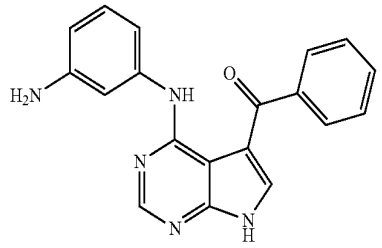


[0707] To a solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-yl)(4-chlorophenyl)methanone (500 mg, 1.72 mmol) in DMF (6 mL) were added 3-amino-N-methylbenzamide (516 mg, 3.44 mmol) and DIPEA (899 μL, 5.16 mmol). The reaction was heated at 120° C. for 18 hours. After cooling down to room temperature, 20 mL of DCM was added to the mixture. The precipitates were collected, washed with DCM, and dried on high vacuum to give a yellow solid (320 mg, 46%). M.p.>300° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 13.06 (s, 1H), 11.33 (s, 1H), 8.48 (s, 1H), 8.21 (d, J=7.6 Hz, 1H), 8.03 (s, 1H), 7.89 (d, J=8.4 Hz, 2H), 7.65 (d, J=8.0 Hz, 2H), 7.52-7.46 (m, 2H), 2.80 (d, J=4.0 Hz, 3H); LCMS [M+H] 406.

Example 14

Synthesis of (4-(3-aminophenylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone

[0708]

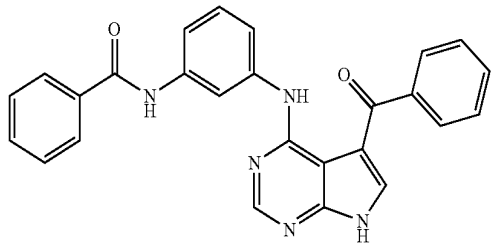


[0709] To a mixture of tert-butyl(3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)phenyl)carbamate (5.8 g, 13.5 mmol) in DCM (50 mL) was added 25 mL of TFA. The mixture was heated at 50° C. for 1 hour. Solvent was removed under reduced pressure. The residue was washed with DCM and dried on high vacuum to give an off-white solid. M.p. =280-282° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 13.11 (s, 1H), 11.56 (s, 1H), 8.51 (s, 1 H), 8.09 (s, 1H), 8.01 (s, 1H), 7.86 (d, J=7.6 Hz, 2H), 7.70 (t, J=10 Hz, 2H), 7.60 (t, J=7.2 Hz, 2H), 7.46 (t, J=8.0 Hz, 1H), 6.95 (d, J=7.2 Hz, 1H); LCMS [M+H] 330.

Example 15

Synthesis of N-3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)phenyl)benzamide

[0710]



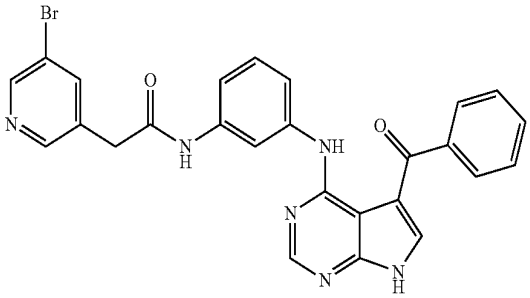
[0711] To a solution of 4-((3-aminophenyl)amino-7H-pyrrolo[2,3-d]pyrimidine-5-yl)amino)(phenyl)methanone (33 mg, 0.01 mmol) in DMF (1 mL) was added DIPEA (87 μL, 0.5 mmol), HBTU (45 mg, 0.12 mmol), and benzoic acid (13 mg, 0.11 mmol). The reaction was stirred at room temperature for 18 hours. The crude was purified by reverse phase preparative HPLC. M.p.>300° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 12.97 (s, 1H), 11.36 (s, 1H), 10.34 (s, 1H), 8.47 (s, 1H), 8.21 (s, 1H), 7.99 (d, J=7.2 Hz, 2H), 7.95 (s, 1 H), 7.90

(d, J=8.4 Hz, 1H), 7.86 (d, J=7.2 Hz, 2H), 7.69 (t, J=6.8 Hz, 1H), 7.62-7.52 (m, 6H), 7.36 (t, J=8.0 Hz, 1H); LCMS [M+H] 434.

Example 16

Synthesis of N-3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)phenyl)-2-(5-bromopyridin-3-yl) acetamide

[0712]

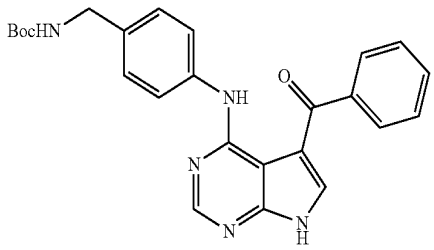


[0713] To a solution of 4-((3-aminophenyl)amino-7H-pyrrolo[2,3-d]pyrimidine-5-yl)amino)(phenyl)methanone (33 mg, 0.01 mmol) in DMF (1 mL) was added DIPEA (87 μL, 0.5 mmol), HBTU (45 mg, 0.12 mmol), and benzoic acid (13 mg, 0.11 mmol). The reaction was stirred at room temperature for 18 hours. The crude was purified by reverse phase preparative HPLC. M.p.>300° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 12.97 (s, 1H), 11.32 (s, 1H), 10.33 (s, 1H), 8.61 (d, J=2.0 Hz, 1H), 8.53 (d, J=2 Hz, 1H), 8.46 (s, 1H), 8.07 (s, 1H), 8.04 (s, 1H), 7.94 (s, 1H), 7.85 (d, J=7.2 Hz, 2H), 7.76 (d, J=8.0 Hz, 1H), 7.68 (t, J=7.2 Hz, 1H), 7.58 (t, J=8.0 Hz, 3H), 7.37 (d, J=8.0 Hz, 1H), 7.31 (t, J=8.4 Hz, 1H); LCMS [M+H] 527.

Example 17

Synthesis of tert-butyl 4-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)benzylcarbamate

[0714]

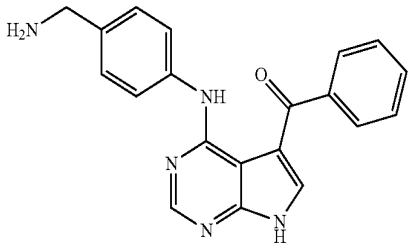


[0715] To a solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-yl)(phenyl)methanone (0.30 g, 1.17 mmol) in DMF (10 mL) was added 4-(N-Boc-aminomethyl)aniline (0.31 g, 1.40 mmol) and DIPEA (0.61 mL, 3.51 mmol). The reaction was heated at 120° C. for 48 hours. After cooling down to room temperature, half of the solvent was removed under reduced pressure. To the residue was added 20 mL of DCM. The precipitates were collected, washed with DCM, and dried on high vacuum to give a yellow solid (0.26 g, 50%). M.p. =256-258° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 12.95 (s, 1H), 11.29 (s, 1H), 8.44 (s, 1H), 7.92 (s, 1H), 7.86-7.82 (m, 4H), 7.70-7.66 (m, 1H), 7.58 (t, J=8.0 Hz, 2H), 7.37 (t, J=6.4 Hz, 1H), 7.25 (d, J=8.4 Hz, 1H), 4.11 (d, J=6.4 Hz, 2H), 1.40 (s, 9H); LCMS [M+H] 444.

Example 18

Synthesis of (4-(4-(aminomethyl)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone

[0716]

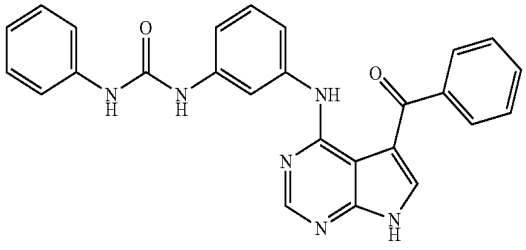


[0717] To a mixture of tert-butyl(4-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)benzyl)carbamate (0.18 g, 0.41 mmol) in DCM (1.5 mL) was added 0.5 mL of TFA. The mixture was heated at 50° C. for 1 hour. The solvent was removed under reduced pressure. The residue was washed with DCM and dried on high vacuum give a yellow solid. M.p.=255-257° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 13.05 (s, 1H), 11.43 (s, 1H), 8.48 (s, 1 H), 7.98-7.96 (m, 3H), 7.85 (d, J=8.4 Hz, 2H), 7.70 (t, J=7.6 Hz, 1H), 7.60 (t, J=7.6 Hz, 2H), 7.48 (d, J=8.4 Hz, 2H), 4.03 (q, J=5.2 Hz, 2H); LCMS [M+H] 344.

Example 19

Synthesis of 1-(3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)-3-phenylurea

[0718]



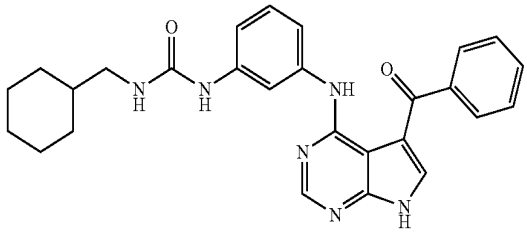
[0719] To a solution of 4-((3-aminophenyl)amino-7H-pyrrolo[2,3-d]pyrimidine-5-yl)amino)(phenyl)methanone (150 mg, 0.203 mmol) in DMF (2 mL) was added DIPEA (141 μL, 0.812 mmol) and phenyl isocyanate (24 μL, 0.203 mmol). The reaction was stirred at room temperature for 18 hours. The crude was purified by reverse phase preparative HPLC. M.p.>300° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 12.99 (s, 1H), 11.34 (s, 1H), 8.81 (s, 1H), 8.64 (s, 1H), 8.47 (s, 1H), 8.01 (t, J=2.0 Hz, 1H), 7.95 (s, 1H), 7.86 (d, J=8.4 Hz, 1H),

7.69 (t, J=7.2 Hz, 1H), 7.60 (q, J=8.8 Hz, 3H), 7.46 (d, J=7.6 Hz, 2H), 7.31-7.22 (m, 4 H), 6.98 (t, J=7.2 Hz, 1H); LCMS [M+H] 449.

Example 20

Synthesis of 1-3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)phenyl)-3-(cyclohexylmethyl) urea

[0720]

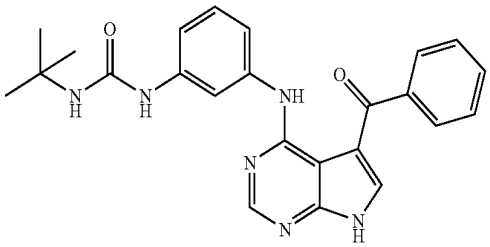


[0721] To a solution of 4-((3-aminophenyl)amino-7H-pyrrolo[2,3-d]pyrimidine-5-yl)amino)(phenyl)methanone (150 mg, 0.203 mmol) in DMF (2 mL) was added DIPEA (141 μL, 0.812 mmol) and cyclohexanmethyl isocyanate (29 μL, 0.203 mmol). The reaction was stirred at room temperature for 18 hours. The crude was purified by reverse phase preparative HPLC. M.p.=180-182° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 11.18 (s, 1H), 9.54 (t, J=5.6 Hz, 1H), 8.64 (s, 1H), 8.09 (s, 1H), 7.89 (d, J=5.2 Hz, 2H), 7.75 (t, J=7.2 Hz, 1H), 7.64 (t, J=7.6 Hz, 2H), 7.57 (s, 1H), 7.45 (d, J=8.0 Hz, 1H), 7.28 (t, J=8.0 Hz, 1H), 6.69 (d, J=8.8 Hz, 1H), 3.30 (t, J=6.4 Hz, 2H), 1.78-1.69 (m, 4H), 1.65-1.56 (m, 2H), 1.24-1.12 (m, 3H), 1.05-0.96 (m, 2H); LCMS [M+H] 469.

Example 21

Synthesis of 1-3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)phenyl)-3-(tert-butyl)urea

[0722]

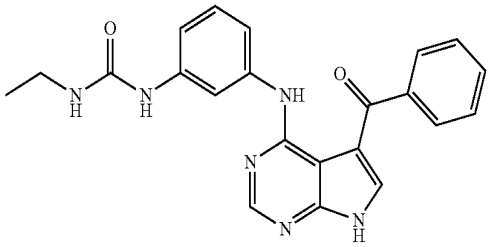


[0723] To a solution of 4-((3-aminophenyl)amino-7H-pyrrolo[2,3-d]pyrimidine-5-yl)amino)(phenyl)methanone (150 mg, 0.203 mmol) in DMF (2 mL) was added DIPEA (141 μL, 0.812 mmol) and tert-butyl isocyanate (26 μL, 0.203 mmol). The reaction was stirred at room temperature for 18 hours. The crude was purified by reverse phase preparative HPLC. M.p.=185-187° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 11.21 (s, 1H), 9.56 (s, 1H), 8.63 (s, 1 H), 8.10 (s, 1H), 7.89 (d, J=7.2 Hz, 2H), 7.75 (t, J=7.6 Hz, 1H), 7.64 (t, J=7.6 Hz, 2H), 7.59 (s, 1H), 7.45 (d, J=9.6 Hz, 1H), 7.28 (t, J=8.4 Hz, 1H), 6.69 (d, J=8.0 Hz, 1H), 1.47 (s, 9H); LCMS [M+H] 429.

Example 22

Synthesis of 1-3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)phenyl)-3-ethylurea

[0724]

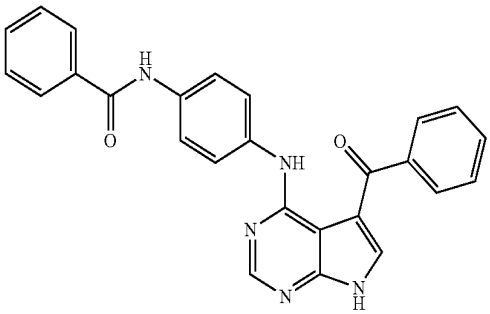


[0725] To a solution of 4-((3-aminophenyl)amino-7H-pyrrolo[2,3-d]pyrimidine-5-yl)amino)(phenyl)methanone (150 mg, 0.203 mmol) in DMF (2 mL) was added DIPEA (141 μL, 0.812 mmol) and phenyl isocyanate (16 μL, 0.203 mmol). The reaction was stirred at room temperature for 18 hours. The crude was purified by reverse phase preparative HPLC. M.p.=183-185° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 11.18 (s, 1H), 9.47 (t, J=6.0 Hz, 1H), 8.63 (s, 1H), 8.10 (s, 1H), 7.89 (d, J=7.6 Hz, 2H), 7.75 (t, J=7.2 Hz, 1H), 7.64 (t, J=7.6 Hz, 2H), 7.45 (d, J=8.8 Hz, 1H), 7.28 (t, J=8.4 Hz, 1H), 6.70 (d, J=8.0 Hz, 1H), 3.49-3.42 (m, 2H), 1.23 (t, J=7.6 Hz, 3H); LCMS [M+H] 401.

Example 23

Synthesis of N-4-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)phenyl)benzamide

[0726]



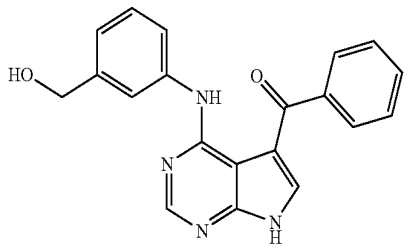
[0727] To a solution of 4-((4-aminophenyl)amino-7H-pyrrolo[2,3-d]pyrimidine-5-yl)amino)(phenyl)methanone (33 mg, 0.01 mmol) in DMF (1 mL) was added DIPEA (87 μL, 0.5 mmol), HBTU (49 mg, 0.13 mmol), and benzoic acid (16 mg, 0.13 mmol). The reaction was stirred at room temperature for 18 hours. The crude was purified by reverse phase preparative HPLC. M.p.>300° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 12.98 (s, 1H), 11.32 (s, 1H), 10.26 (s, 1H), 8.45

(s, 1H), 7.99-7.94 (m, 3H), 7.87 (t, J=9.2 Hz, 3H), 7.81 (d, J=8.8 Hz, 2H), 7.68 (d, J=8.0 Hz, 1H), 7.61-7.52 (m, 5H); LCMS [M+H] 434.

Example 24

Synthesis of (4-(3-(hydroxymethyl)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone

[0728]

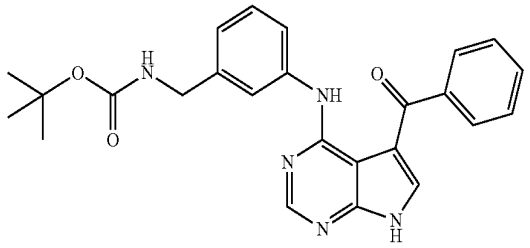


[0729] To a solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-yl)(phenyl)methanone (0.50 g, 1.95 mmol) in DMF (10 mL) was added 3-aminobenzyl alcohol (0.36 g, 2.92 mmol) and DIPEA (0.68 mL, 3.89 mmol). The reaction was heated at 120° C. for 48 hours. After cooling down to room temperature, 20 mL of DCM was added to the mixture. The precipitates were collected, washed with DCM, and dried on high vacuum to give a light grey solid (0.32 g, 76%). M.p. =273-275° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 12.94 (s, 1H), 11.32 (s, 1H), 8.43 (s, 1H), 7.91-7.89 (m, 2H), 7.82 (d, J=76.8 Hz, 2H), 7.73 (s, 1H), 7.66 (t, J=7.6 Hz, 1H), 7.56 (t, J=7.6 Hz, 2H), 7.31 (t, J=8.0 Hz, 1H), 6.98 (d, J=7.6 Hz, 1H), 4.51 (s, 2H), 3.30 (s, 1H); LCMS [M+H] 345.

Example 25

Synthesis of tert-butyl 3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)benzylcarbamate

[0730]

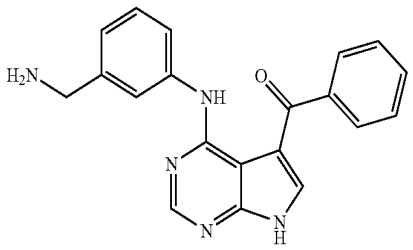


[0731] To a solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-yl)(phenyl)methanone (0.20 g, 0.78 mmol) in DMF (5 mL) was added tert-butyl 3-aminobenzylcarbamate (0.26 g, 1.17 mmol) and DIPEA (0.27 mL, 1.56 mmol). The reaction was heated at 120° C. for 48 hours. After cooling down to room temperature, 20 mL of DCM was added to the mixture. The precipitates were collected, washed with DCM, and dried on high vacuum to give a yellow solid (0.20 g, 59%). M.p. =210-212° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 12.97 (s, 1.H), 11.34 (s, 1.H), 8.44 (s, 1.H), 7.97-7.94 (m, 2.H), 7.85 (d, J=7.8 Hz, 2.H), 7.70 (t, J=4.8 Hz, 1.H), 7.63-7.56 (m, 3.H), 7.45 (t, J=6.4 Hz, 2.H), 7.33 (t, J=7.6 Hz, 1.H), 6.93 (d, J=7.6 Hz, 1.H), 4.16 (d, J=6.4 Hz, 2.H), 1.41 (s, 9.H); LCMS [M+H] 444.

Example 26

Synthesis of (4-((3-(aminomethyl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone

[0732]

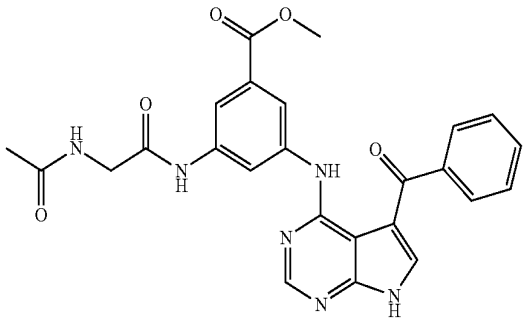


[0733] To a mixture of tert-butyl(3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)benzyl)carbamate (30 mg, 0.068 mmol) in dioxane (0.5 mL) was added 0.5 mL of 4 M HCl in dioxane. The mixture was heated at 50° C. for 1 hour. The solvent was removed under reduced pressure. The residue was washed with DCM and dried on high vacuum to give an off-white solid. M.p.=210-212° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 13.19 (s, 1H), 11.44 (s, 1H), 8.48 (s, 1H), 8.11 (d, J=8.4 Hz, 2H), 7.98 (s, 1H), 7.87-7.84 (m, 3H), 7.69 (t, J=6.4 Hz, 2H), 7.56 (t, J=7.6 Hz, 2H), 7.46 (t, J=7.6 Hz, 1H), 7.22 (d, J=7.6 Hz, 1H), 5.44 (s, 2H), 4.06 (d, J=6.4 Hz, 2H); LCMS [M+H] 344.

Example 27

Synthesis of methyl 3-(2-acetamidoacetamido)-5-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino) benzoate

[0734]

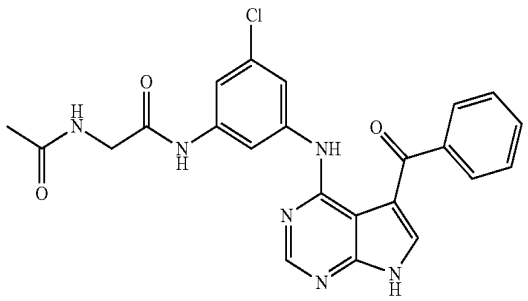


[0735] Methyl 3-(2-acetamidoacetamido)-5-(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)benzoate was synthesized using 2-acetamidoacetic acid and methyl 3-amino-5-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino) benzoate according to the procedure for the synthesis of N-3-((5-benzoyl-7H-pyrrolo[2,3-d]pyridine-4-yl)amino)phenyl) benzamide. A white solid was obtained. M.p.>300° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 11.53 (s, 1H), 10.28 (s, 1H), 8.51 (s, 1H), 8.42-8.41 (m, 1H), 8.31-8.30 (m, 1H), 8.23 (t, J=5.6 Hz, 1H), 8.03-8.02 (m, 1H), 7.98 (s, 1H), 7.88 (s, 1H), 7.86 (d, J=0.8 Hz, 1H), 7.69-7.67 (m, 1H), 7.61-7.51 (m, 2H), 3.89 (s, 3H), 3.87 (d, 2H), 1.90 (s, 3H); LCMS [M+H] 487.

Example 28

Synthesis of 2-acetamido-N-(3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-chlorophenyl) acetamide

[0736]

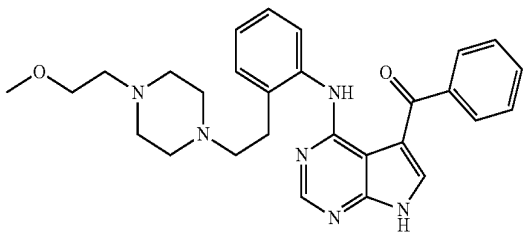


[0737] 2-Acetamido-N-(3-((5-benzoyl-7H-pyrrolo[2,3-d] pyrimidin-4-yl)amino)-5-chlorophenyl)acetamide was synthesized using 2-acetamidoacetic acid and (4-((3-amino-5-chlorophenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl) (phenyl)methanone according to the procedure for the synthesis of N-3-((5-benzoyl-7H-pyrrolo[2,3-d]pyridine-4-yl)amino)phenyl)benzamide. A white solid was obtained. M.p.>300° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 11.53 (s, 1H), 10.24 (s, 1H), 8.53 (s, 1H), 8.25-8.22 (m, 1H), 8.11-8.10 (m, 1 H), 8.00 (d, J=2.0 Hz, 1H), 7.87 (s, 1H), 7.86-7.85 (m, 1H), 7.81-7.81 (m, 1H), 7.69-7.67 (m, 1H), 7.61-7.57 (m, 2H), 7.51-7.50 (m, 1H), 3.87 (d, J=6.0 Hz, 2H), 1.90 (s, 3H); LCMS [M+H] 463.

Example 29

Synthesis of (4-((2-(2-(4-(2-methoxyethyl)piperazin-1-yl)ethyl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone

[0738]

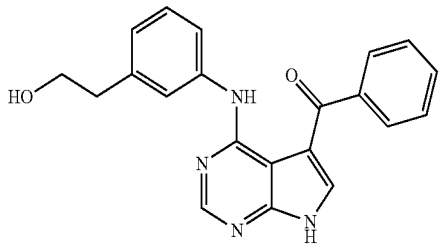


[0739] (4-((2-(2-(4-(2-Methoxyethyl)piperazin-1-yl) ethyl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl) (phenyl)methanone was synthesized using 2-(2-(4-(2-methoxyethyl)piperazin-1-yl)ethyl)aniline and (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone according to the general procedure A. A white solid was obtained. M.p. =192-193° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 10.66 (s, 1H), 8.31 (s, 1H), 7.98-7.94 (m, 2H), 7.84-7.82 (m, 2H), 7.70-7.66 (m, 1H), 7.60-7.57 (m, 2H), 7.30-7.25 (m, 2H), 7.13-7.09 (m, 1H), 3.33 (t, J=6.0 Hz, 4H), 3.32 (s, 3H), 2.90 (d, J=8.0 Hz, 2H), 2.51-2.46 (m, 4H), 2.36-2.33 (m, 4H), 2.24 (bs, 2H); LCMS [M+H] 463.

Example 30

Synthesis of (4-((3-(2-hydroxyethyl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone

[0740]

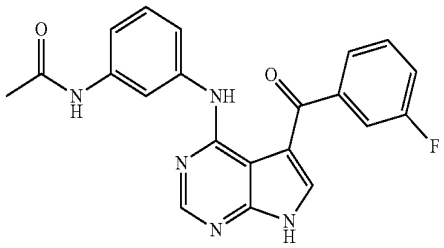


[0741] (4-((3-(2-Hydroxyethyl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone was synthesized using 2-(3-aminophenyl)ethanol and (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone according to the general procedure A. A white solid was obtained. M.p. >300° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 11.25 (s, 1H), 8.42 (s, 1H), 7.90-7.81 (m, 4H), 7.65-7.55 (m, 4H), 7.26 (m, 1H), 6.90 (d, J=7.2 Hz, 1H), 4.63 (s, 1H), 3.61-3.60 (m, 2H), 2.74-2.70 (m, 2H); LCMS [M+H] 359.

Example 31

Synthesis of N-(3-((5-(3-fluorobenzoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)acetamide

[0742]

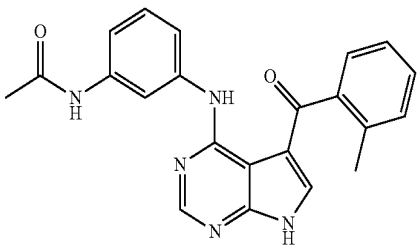


[0743] N-(3-((5-(3-Fluorobenzoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)acetamide was synthesized using N-(3-aminophenyl)acetamide and (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone according to the general procedure A. An off-white solid was obtained. M.p.>300° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 11.17 (s, 1H), 9.97 (s, 1H), 8.42 (s, 1H), 8.00-7.99 (m, 2H), 7.71-7.57 (m, 4H), 7.52-7.49 (m, 1H), 7.35 (d, J=8.8 Hz, 1H), 7.28-7.24 (m, 1H), 2.02 (s, 3H); LCMS [M+H] 390.

Example 32

Synthesis of N-(3-((5-(2-methylbenzoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)acetamide

[0744]

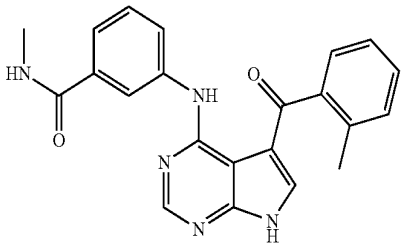


[0745] N-(3-((5-(2-Methylbenzo yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)acetamide was synthesized using N-(3-aminophenyl)acetamide and ((4-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(o-tolyl)methanone according to the general procedure A. An off-white solid was obtained. M.p.>300° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 11.36 (s, 1H), 10.01 (s, 1H), 8.46 (s, 1H), 8.06 (s, 1H), 7.73 (d, J=7.6 Hz, 1H), 7.57 (s, 1H), 7.49-7.45 (m, 2H), 7.39-7.28 (m, 4H), 2.34 (s, 3H), 2.02 (s, 3H); LCMS [M+H] 386.

Example 33

Synthesis of N-methyl-3-((5-(2-methylbenzoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)benzamide

[0746]

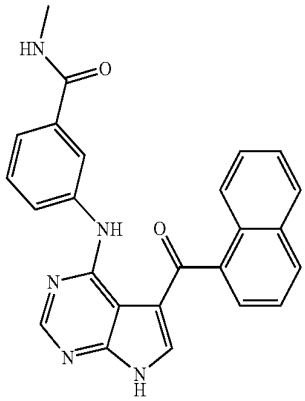


[0747] N-Methyl-3-((5-(2-methylbenzoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)benzamide was synthesized using 3-amino-N-methylbenzamide and ((4-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(o-tolyl)methanone according to the general procedure A. An off-white solid was obtained. M.p.>300° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 11.47 (s, 1H), 8.48-8.47 (m, 2H), 8.24-8.20 (m, 2H), 7.60 (s, 1H), 7.52-7.45 (m, 4H), 7.40-7.32 (m, 2H), 2.86 (d, J=4.4 Hz, 3H), 2.34 (s, 3H); LCMS [M+H] 386.

Example 34

Synthesis of 3-((5-(1-naphthoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-N-methylbenzamide

[0748]

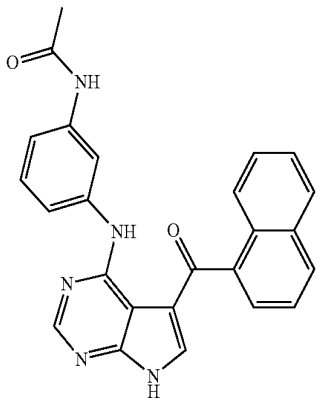


[0749] 3-((5-(1-Naphthoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-N-methylbenzamide was synthesized using 3-amino-N-methylbenzamide and (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone according to the general procedure A. A yellow solid was obtained. M.p.>300° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 11.53 (s, 1H), 8.48-8.44 (m, 2H), 8.24-8.20 (m, 2H), 8.14 (d, J=8.0 Hz, 1H), 8.06-8.03 (m, 2H), 7.80-7.78 (m, 1H), 7.70 (d, J=2.4 Hz, 1H), 7.64-7.53 (m, 3 H), 7.50-7.44 (m, 2H), 2.77 (d, J=4.4 Hz, 3H); LCMS [M+H] 422.

Example 35

Synthesis of N-(3-((5-(1-naphthoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)acetamide

[0750]



[0751] N-(3-((5-(1-Naphthoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)acetamide was synthesized using N-(3-aminophenyl)acetamide and (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone according to the general procedure A. A yellow solid was obtained. M.p.>300° C.; 400 MHz ^{1}HNMR (DMSO-d_6) δ 11.42 (s, 1H), 9.98 (s, 1H), 8.45 (s, 1H), 8.13 (d, J=8.4 Hz, 1H), 8.05-8.02 (m, 3H), 7.79-7.73 (m, 2H), 7.67 (s, 1H), 7.63-7.53 (m, 4H), 7.38-7.35 (m, 1H), 7.29-7.25 (m, 1H), 2.02 (s, 3H); LCMS [M+H] 422.

[0752] The following compounds (Table 2) were synthesized by using ethyl 3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)benzoate and different amines according to the procedure described in general procedure B.

TABLE 2

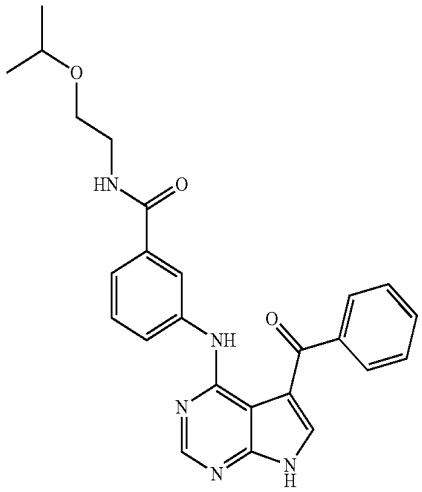
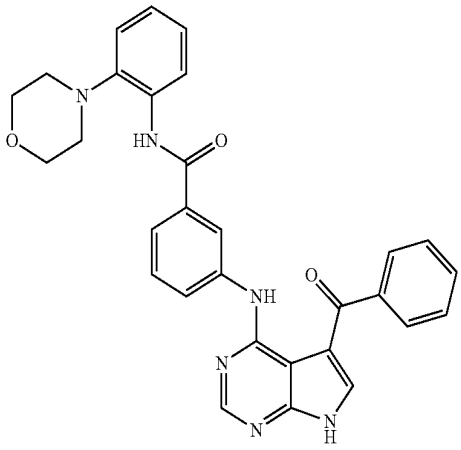
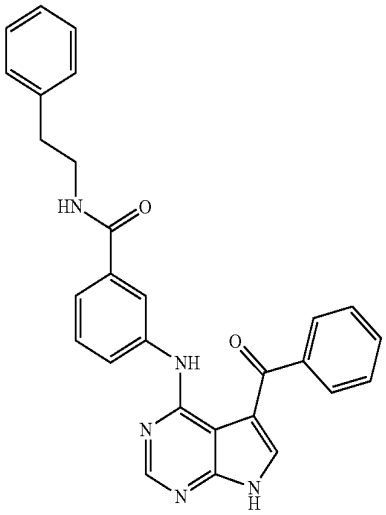
Structure	Chemical Name	LCMS [M + 1]
	3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(2-isopropoxyethyl)benzamide	445
	3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(2-morpholin-4-ylphenyl)benzamide	520
	3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(2-phenylethyl)benzamide	463

TABLE 2-continued

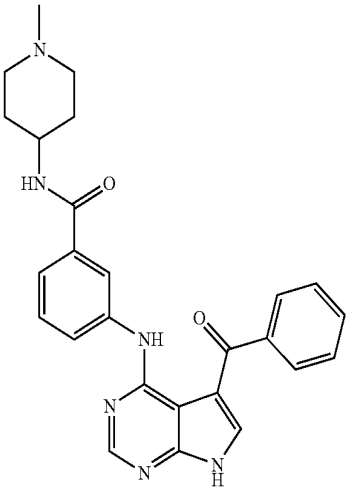
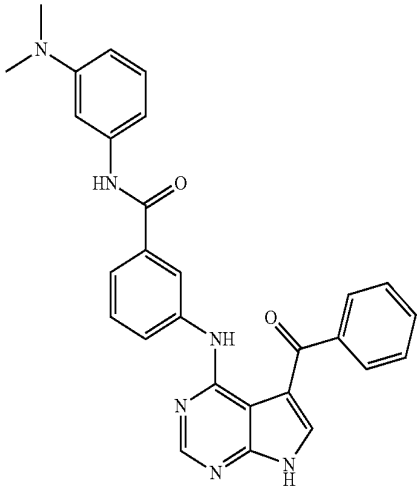
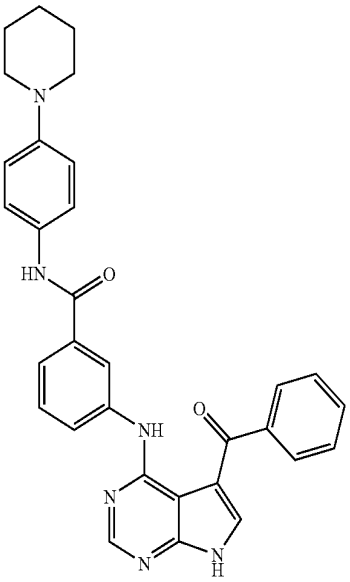
Structure	Chemical Name	LCMS [M + 1]
	3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(1-methylpiperidin-4-yl)benzamide	456
	3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-[3-(dimethylamino)phenyl]benzamide	478
	3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(4-piperidin-1-ylphenyl)benzamide	518

TABLE 2-continued

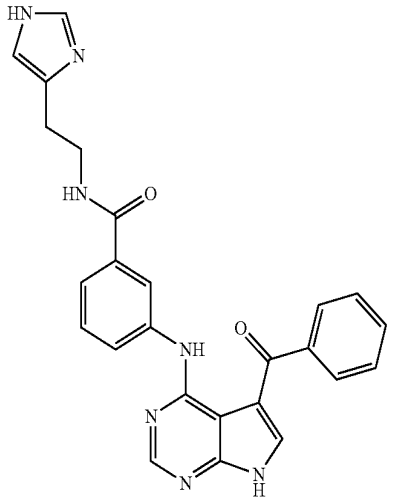
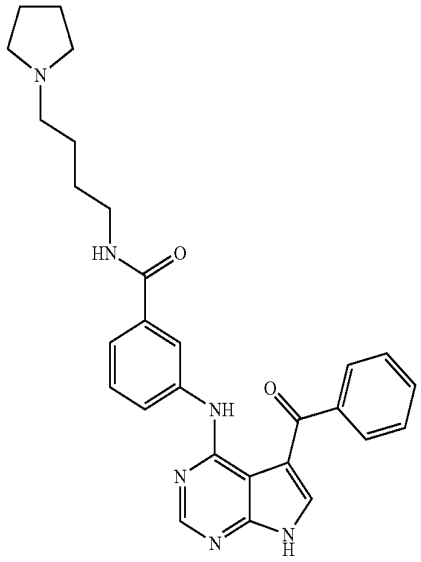
Structure	Chemical Name	LCMS [M + 1]
	3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-[2-(1H-imidazol-4-yl)ethyl]benzamide	452
	3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(4-pyrrolidin-1-ylbutyl)benzamide	484

TABLE 2-continued

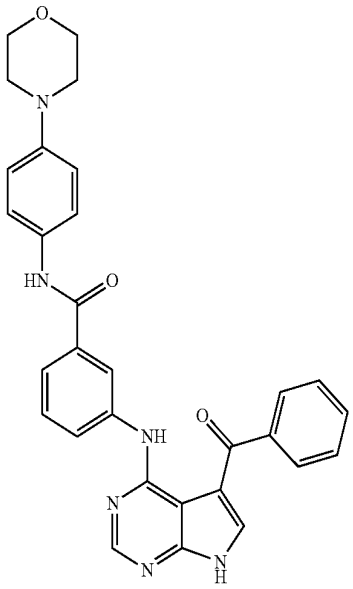
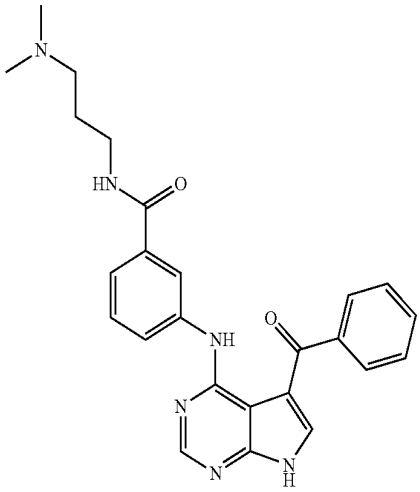
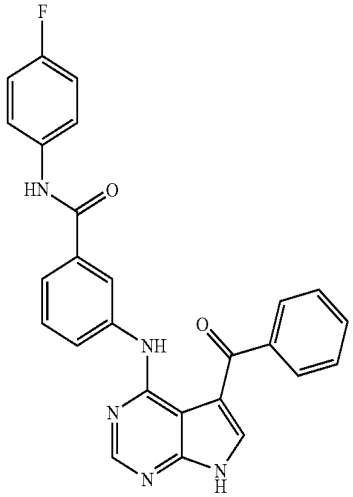
Structure	Chemical Name	LCMS [M + 1]
	3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(4-morpholin-4-ylphenyl)benzamide	520
	3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-[3-(dimethylamino)propyl]benzamide	444
	3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(4-fluorophenyl)benzamide	452

TABLE 2-continued

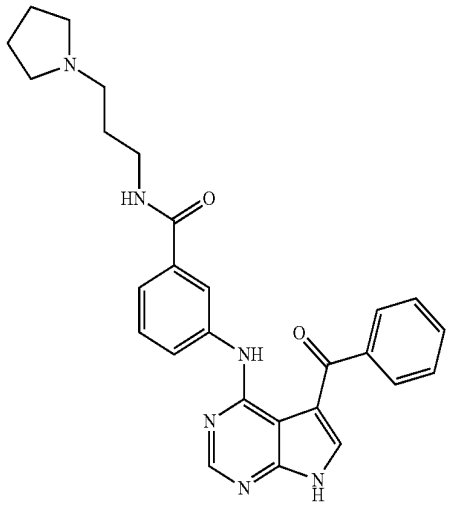
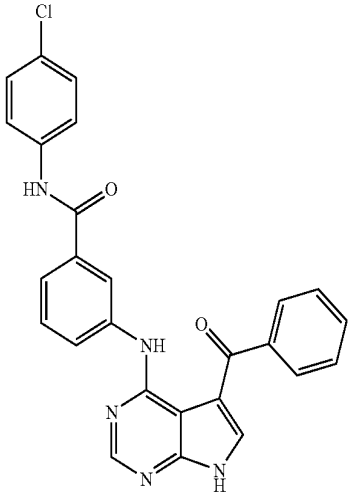
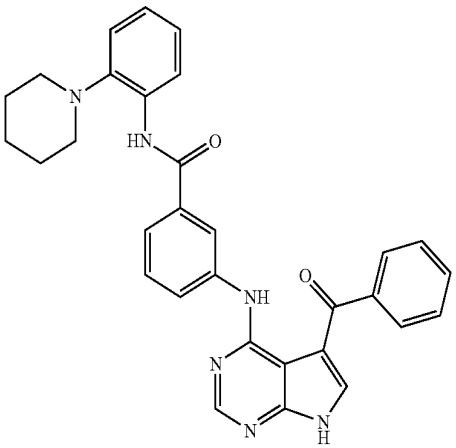
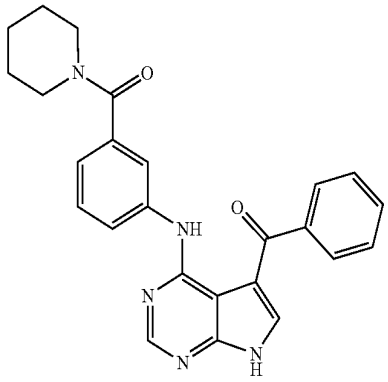
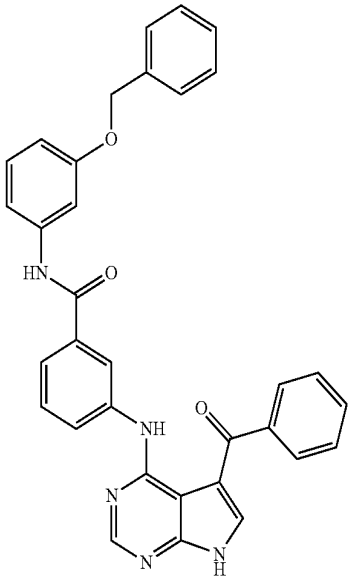
Structure	Chemical Name	LCMS [M + 1]
	3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(3-pyrrolidin-1-ylpropyl)benzamide	470
	3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(4-chlorophenyl)benzamide	469
	3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(2-piperidin-1-ylphenyl)benzamide	518

TABLE 2-continued

Structure	Chemical Name	LCMS [M + 1]
	phenyl(4-{[3-(piperidin-1-ylcarbonyl)phenyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone	426
	3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-[3-(benzyloxy)phenyl]benzamide	541

[0753] The following compounds (Table 3) were synthesized by using tert-butyl (4-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)carbamate or tert-butyl (3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)carbamate with different acids according to the procedure described in general procedure C.

TABLE 3

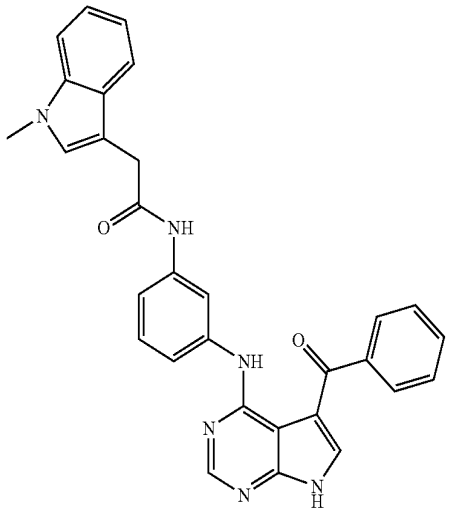
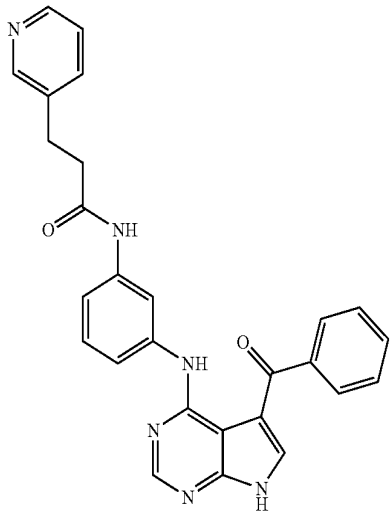
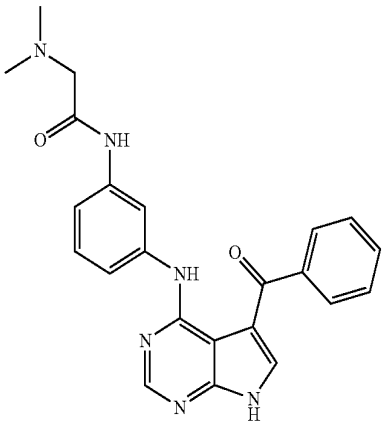
Structure	Chemical Name	LC/MS [M + 1]
	2-(1-methyl-1H-indol-3-yl)-N-(3-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)acetamide	502
	N-(3-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)-3-pyridin-3-ylpropanamide	464
	N,N-dimethyl-N-(3-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)glycinamide	415

TABLE 3-continued

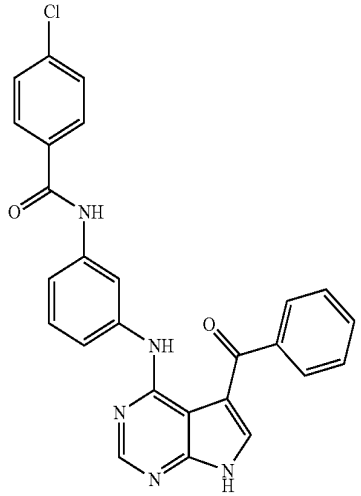
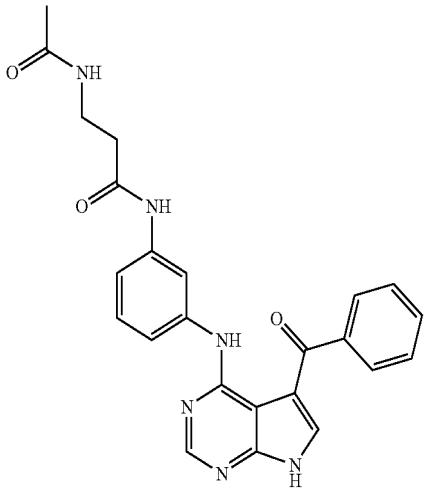
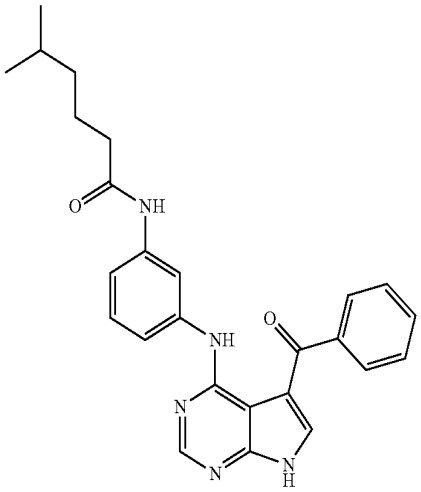
Structure	Chemical Name	LC/MS [M + 1]
	4-chloro-N-(3-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)benzamide	469
	3-acetamido-N-(3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)propanamide	443
	5-methyl-N-(3-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)hexanamide	443

TABLE 3-continued

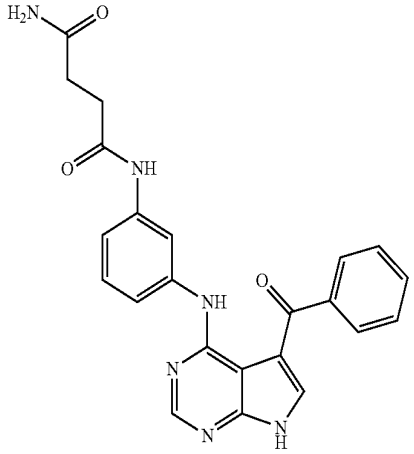
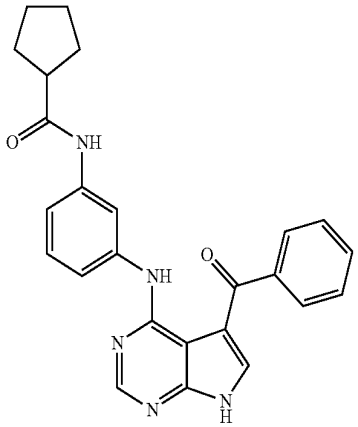
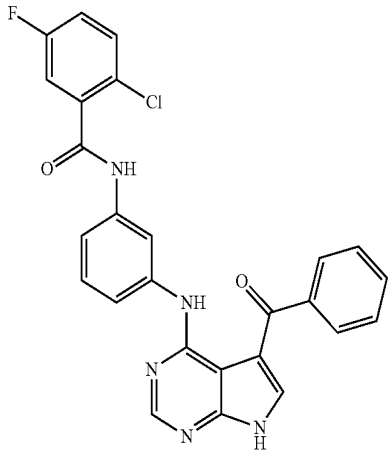
Structure	Chemical Name	LC/MS [M + 1]
	N-(3-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)butanediamide	429
	N-(3-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)cyclopentanecarboxamide	426
	2-chloro-5-fluoro-N-(3-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)benzamide	487

TABLE 3-continued

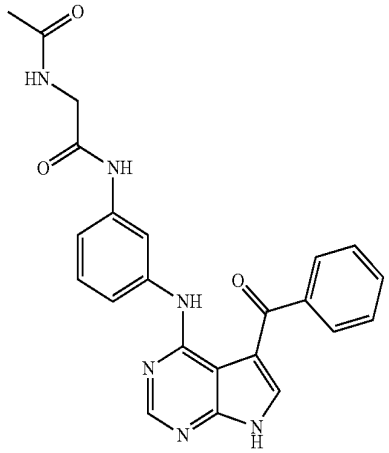
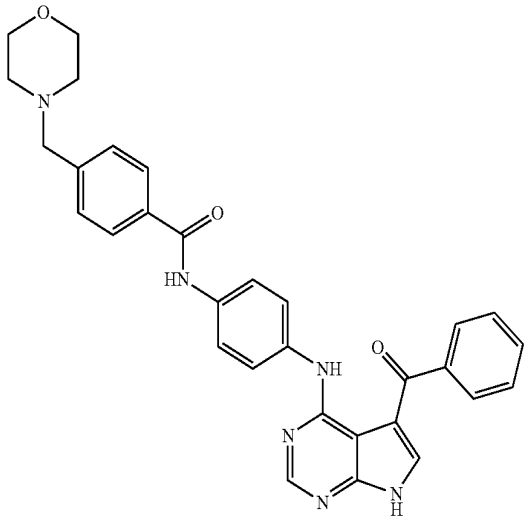
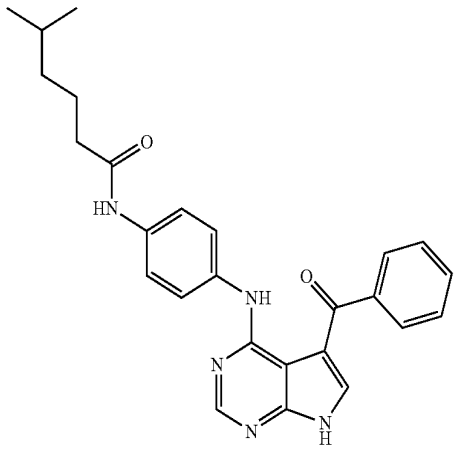
Structure	Chemical Name	LC/MS [M + 1]
	2-acetamido-N-(3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)acetamide	429
	4-(morpholin-4-ylmethyl)-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)benzamide	534
	5-methyl-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)hexanamide	443

TABLE 3-continued

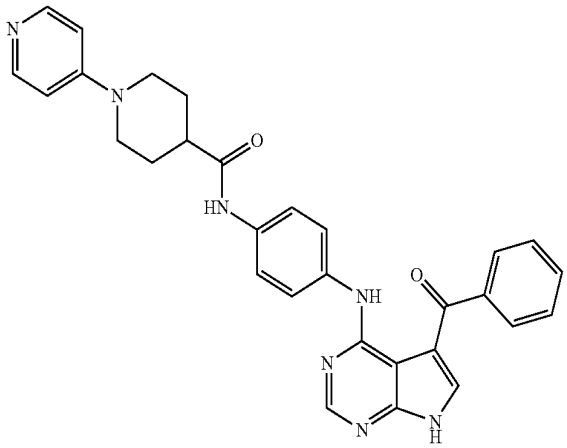
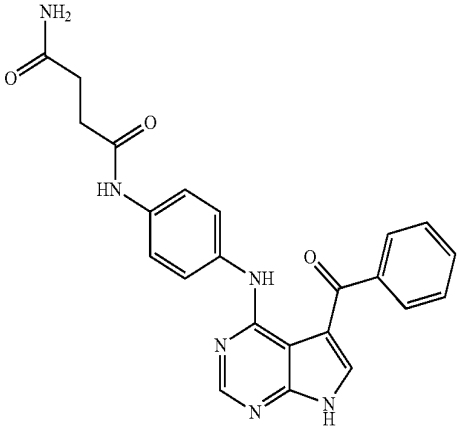
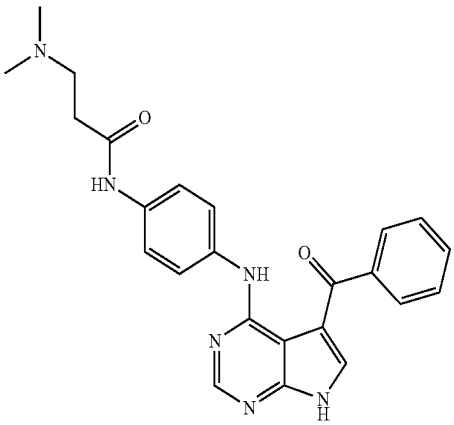
Structure	Chemical Name	LC/MS [M + 1]
	N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)-1-pyridin-4-ylpiperidine-4-carboxamide	519
	N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)butanediamide	429
	N-(4-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)-3-(dimethylamino)propanamide	429

TABLE 3-continued

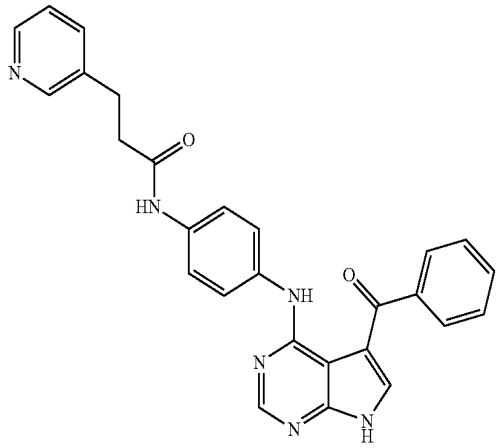
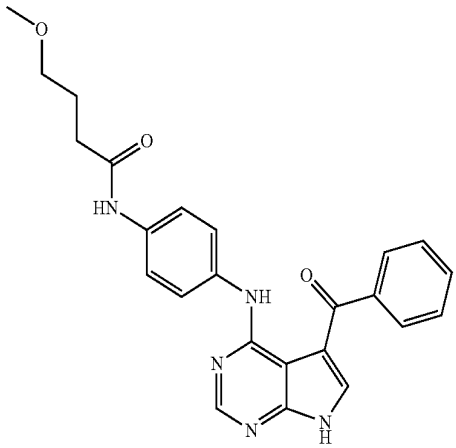
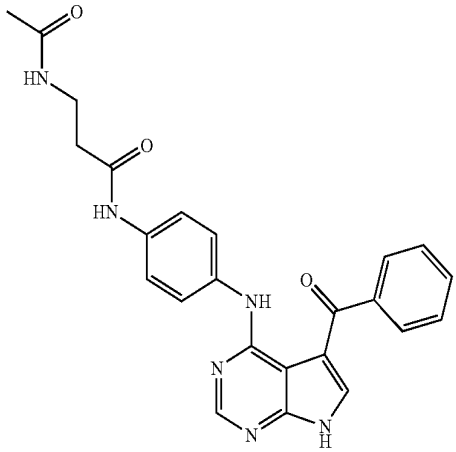
Structure	Chemical Name	LC/MS [M + 1]
	N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)-3-pyridin-3-ylpropanamide	464
	4-methoxy-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)butanamide	430
	3-acetamido-N-(4-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)propanamide	443

TABLE 3-continued

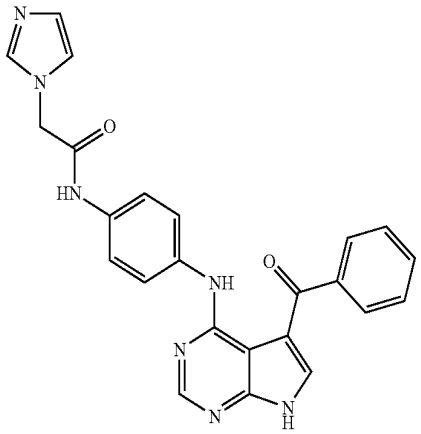
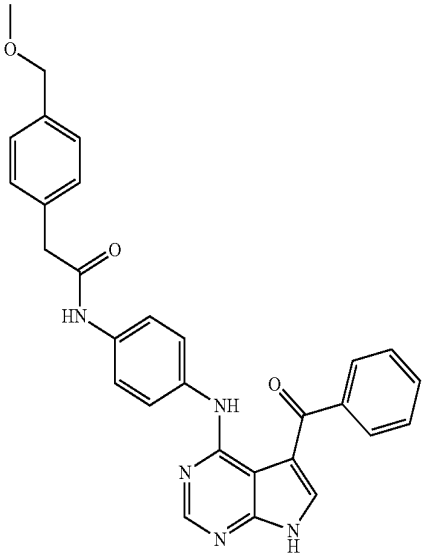
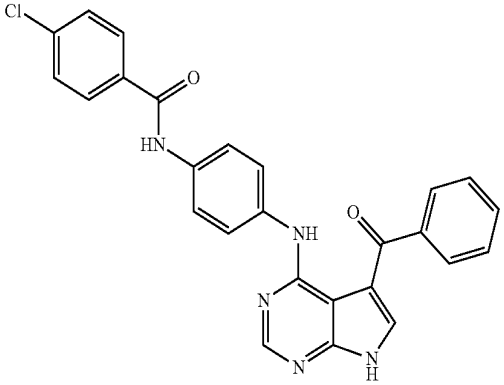
Structure	Chemical Name	LC/MS [M + 1]
	2-(1H-imidazol-1-yl)-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)acetamide	438
	2-[4-(methoxymethyl)phenyl]-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)acetamide	493
	4-chloro-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)benzamide	469

TABLE 3-continued

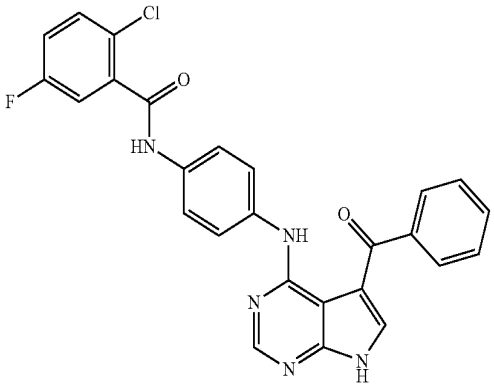
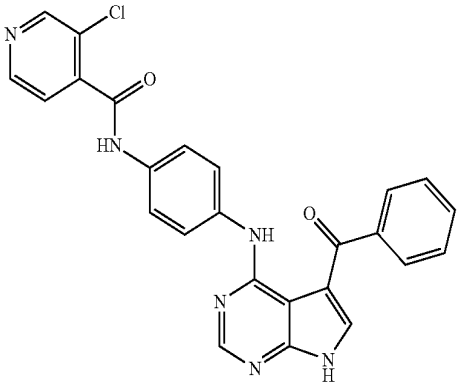
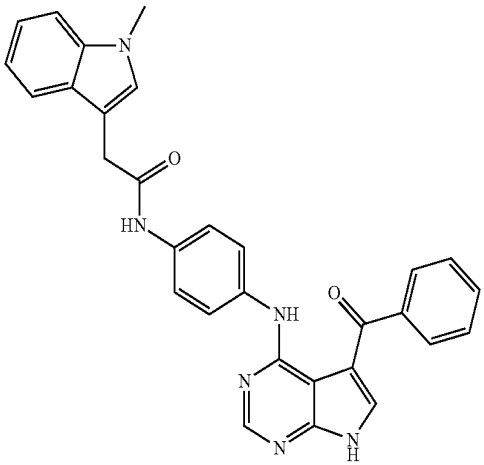
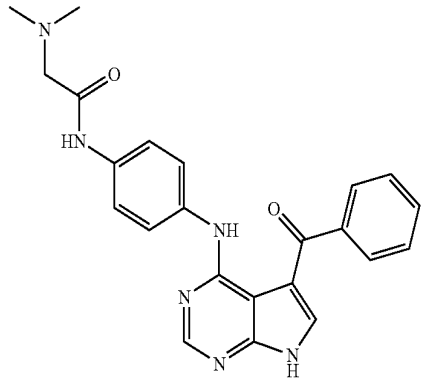
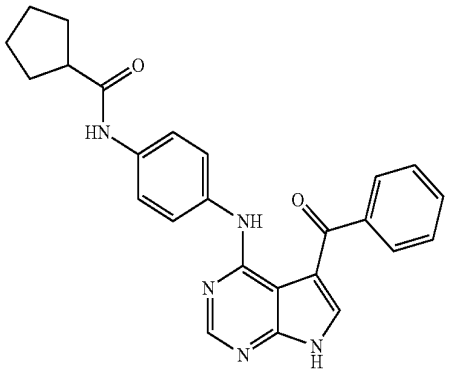
Structure	Chemical Name	LC/MS [M + 1]
	2-chloro-5-fluoro-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)benzamide	487
	3-chloro-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)pyridine-4-carboxamide	470
	2-(1-methyl-1H-indol-3-yl)-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)acetamide	502

TABLE 3-continued

Structure	Chemical Name	LC/MS [M + 1]
	N-(4-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)-2-(dimethylamino)acetamide	415
	N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)cyclopentanecarboxamide	426

[0754] The following compounds (Table 4) were synthesized by using (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone and different amines as described in general procedure E.

TABLE 4

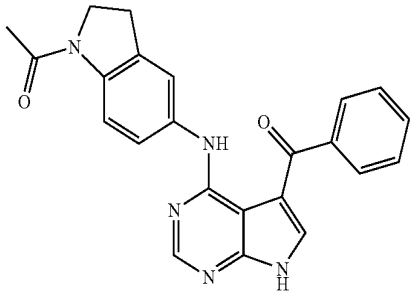
Structure	Chemical Name	LCMS [M + 1]
	1-(5-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)indolin-1-yl)ethanone	398

TABLE 4-continued

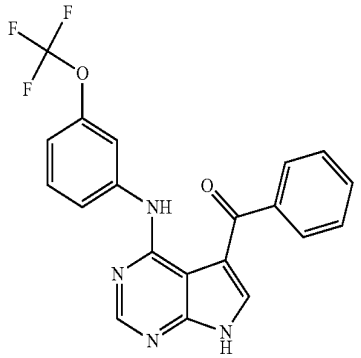
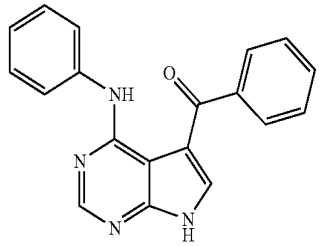
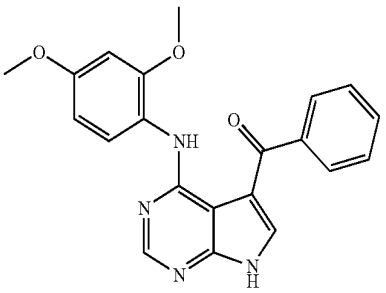
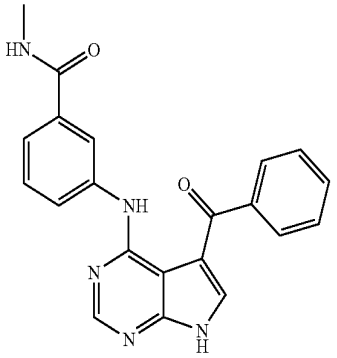
Structure	Chemical Name	LCMS [M + 1]
	phenyl(4-((3-(trifluoromethoxy)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone	399
	phenyl(4-(phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone	315
	(4-((2,4-dimethoxyphenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone	375
	3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-N-methylbenzamide	372

TABLE 4-continued

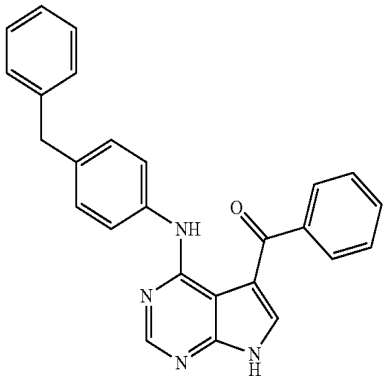
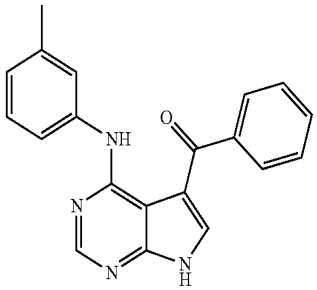
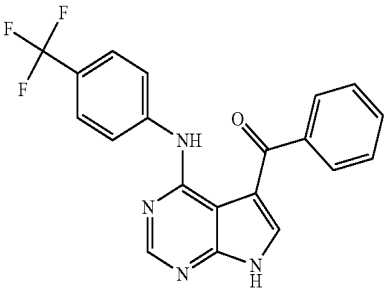
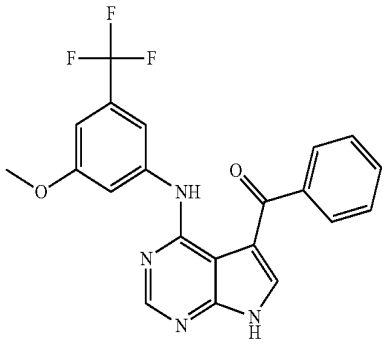
Structure	Chemical Name	LCMS [M + 1]
	(4-((4-benzylphenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone	405
	phenyl(4-(m-tolylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone	329
	phenyl(4-((4-(trifluoromethyl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone	383
	(4-((3-methoxy-5-(trifluoromethyl) phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone	413

TABLE 4-continued

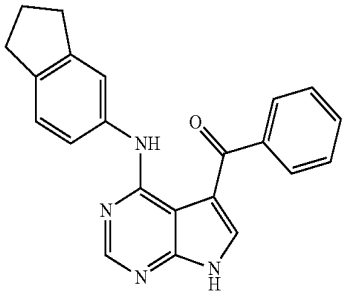
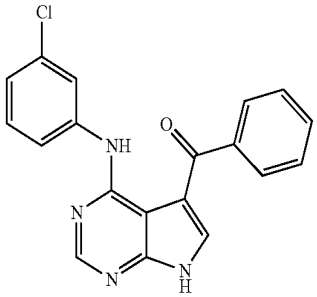
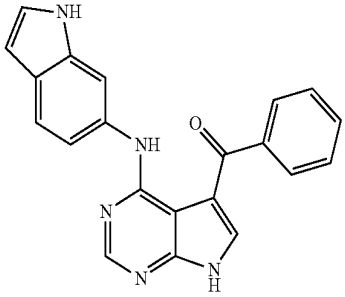
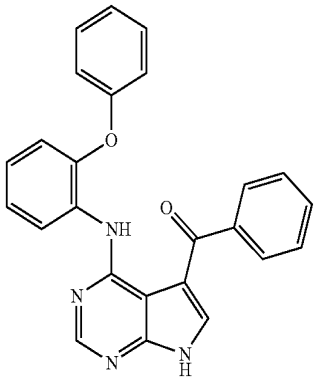
Structure	Chemical Name	LCMS [M + 1]
	(4-((2,3-dihydro-1H-inden-5-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone	355
	(4-((3-chlorophenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone	349
	(4-((1H-indol-6-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone	354
	(4-((2-phenoxyphenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone	407

TABLE 4-continued

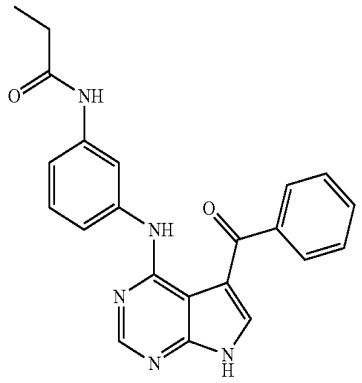
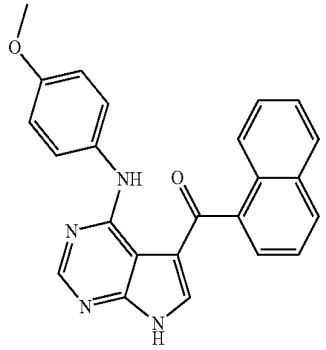
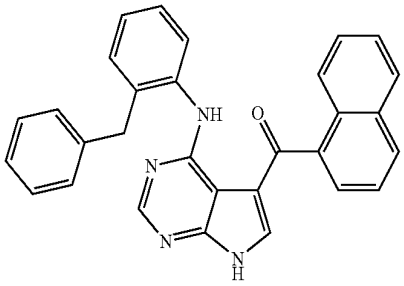
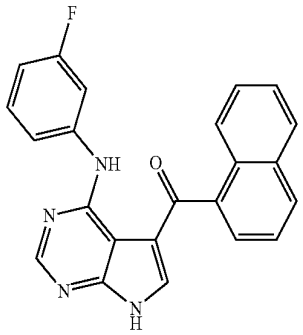
Structure	Chemical Name	LCMS [M + 1]
	N-(3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)propionamide	386
	(4-((4-methoxyphenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone	395
	(4-((2-benzylphenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone	455
	(4-((3-fluorophenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone	383

TABLE 4-continued

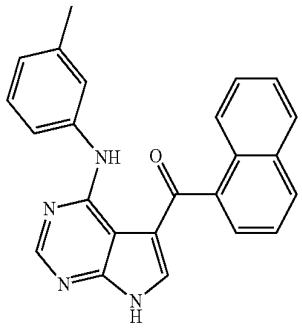
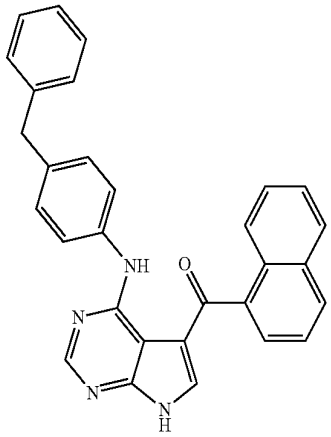
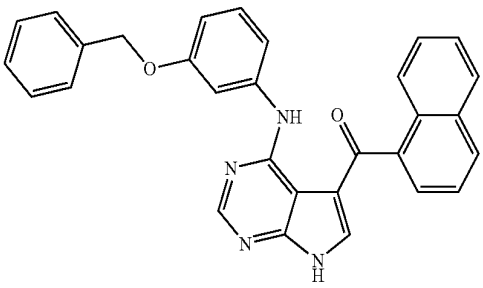
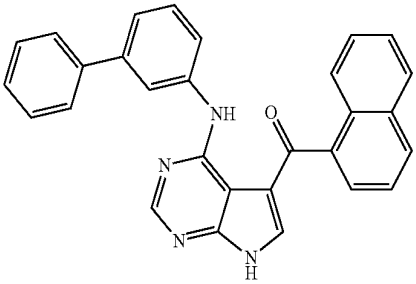
Structure	Chemical Name	LCMS [M + 1]
	naphthalen-1-yl(4-(m-tolylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone	379
	(4-((4-benzylphenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone	455
	(4-((3-(benzyloxy)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone	471
	(4-([1,1'-biphenyl]-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone	441

TABLE 4-continued

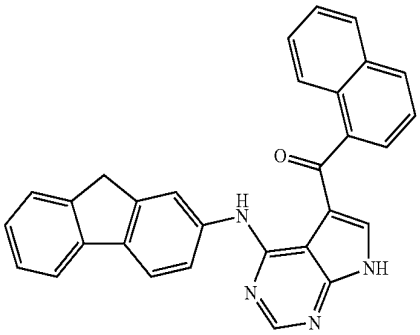
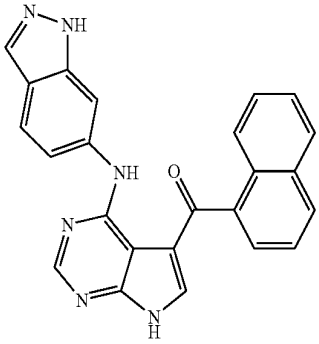
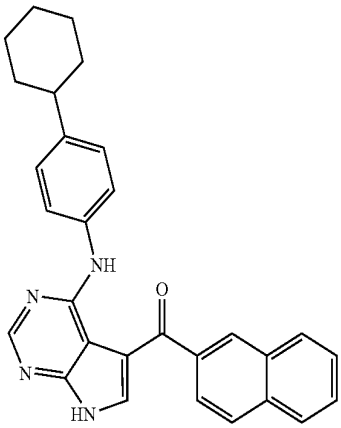
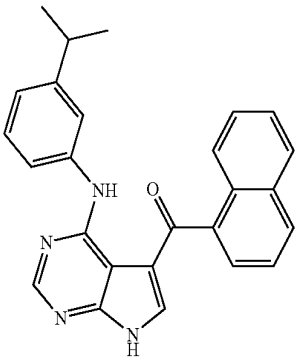
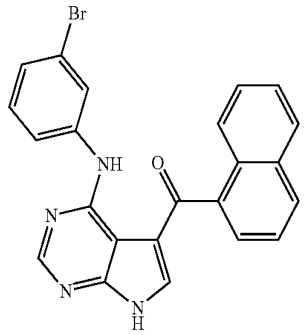
Structure	Chemical Name	LCMS [M + 1]
	(4-((9H-fluoren-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone	453
	(4-((1H-indazol-6-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone	405
	(4-((4-cyclohexylphenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-2-yl)methanone	447
	(4-((3-isopropylphenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone	407

TABLE 4-continued

Structure	Chemical Name	LCMS [M + 1]
	(4-((3-bromophenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(naphthalen-1-yl)methanone	443

Example 36

ACK1 Activity Assay

[0755] ACK1 activity was assayed by using a PYK2-derived biotinylated peptide substrate (biotin-AGAGSIESDIYAEIPDETC-NH2) and AlphaScreen™ (Amplified Luminescent Proximity Homogeneous Assay) technology. The extent of peptide phosphorylation was determined by using acceptor beads conjugated to phosphotyrosine antibody that recognizes the phosphorylated peptide and donor beads conjugated to streptavidin that binds to the biotin on the peptide. Excitation of the donor beads converted ambient oxygen to excited singlet oxygen which when in close proximity to acceptor beads, reacted with acceptor beads where the signal was amplified.

[0756] Test inhibitors and controls (N-(2,6-dimethylphenyl)-4-(2-ethoxyphenoxy)-2-[(4-piperazin-1-ylphenyl) amino]pyrimidine-5-carboxamide) were prepared in 10% DMSO at 10× the desired final concentration. Test compound (2.5 μl) and ACK1 110-489 (12.5 μl) were added to each well of a reaction plate (Corning 96-well half-area solid white nonbinding surface plate). The ACK1 was diluted in assay buffer (50 mM Tris, 0.02 mg/ml BSA, 10 mM $MgCl_2$, 1 mM EGTA, 10% glycerol, 0.1 mM Na_3VO_4, and 1 mM DTT) and the final concentration in the 25 μl reaction was 33 nM. After a 20-min incubation at room temperature, the kinase reaction was initiated by the addition of 10 μl of PYK2/ATP mixture. The PYK2 and ATP were diluted in assay buffer and the final concentrations in the 25 μl reaction were 35 nM and 50 μM, respectively. The plates were incubated for 60 min at room temperature. The reaction was stopped by the addition of 10 μl stop/detection mixture which contains EDTA (final concentration is 10 mM), AlphaScreen™ Streptavidin Donor beads (final concentration is 500 ng/well) and AlphaScreen™ Phospho-tyrosine (P-Tyr-100) Acceptor beads (final concentration is 500 ng/well) were diluted in assay buffer. This reagent addition step was performed in the dark because the AlphaScreen™ beads are light-sensitive. The plate was incubated for 60 min at room temperature in the dark and the plates were read on the Perkin Elmer Envision Multilabel plate reader (excitation wavelength: 640 nm, emission wavelength: 570 nm). Biological activities of representative compounds of the invention are shown in Table 5.

Example 37

AKT Kinase Activity Assay

[0757] AKT1 activity was assayed using the GSK3-derived biotinylated peptide substrate, crosstide (biotin-GRPRTSSFAEG), and AlphaScreen™ (Amplified Luminescent Proximity Homogeneous Assay) technology. AKT1 activation was achieved by the addition of the activating kinases PDK1 and MAPKAPK2, lipid vesicles, and ATP. The extent of peptide phosphorylation was determined using a phospho-AKT substrate antibody and acceptor beads conjugated to Protein A and donor beads conjugated to streptavidin that bind to the biotin on the peptide. Excitation of the donor beads converted ambient oxygen to excited singlet oxygen which, when in close proximity to acceptor beads, reacted with acceptor beads resulting in signal amplification.

[0758] Test inhibitors and controls (Abbott inhibitor, Merck pre-clinical inhibitor, and Merck clinical inhibitor) were prepared in 10% DMSO at 10-fold the desired final concentration, and added to each well of a reaction plate (Corning 96-well half-area solid white nonbinding surface plate) in a volume of 2.5 μL. Full-length inactive AKT1 was diluted in assay buffer (50 mM Tris, pH 8.0, 0.02 mg/mL BSA, 10 mM $MgCl_2$, 1 mM EGTA, 10% glycerol, 0.2 mM Na_3VO_4, 1 mM DTT, 0.1 mM β-glycerophosphate, and 0.2 mM NaF) and added to each well in a volume of 17.5 μL for a final concentration in the 25 μL reaction of 8 nM (Aka). After a 20 minute pre-incubation at room temperature, the kinase reaction was initiated by the addition of 5 μL of an activation mixture diluted in assay buffer containing biotinylated crosstide, PDK1, MAPKAPK2, DOPS/DOPC, PtdIns (3,4,5)P3, and ATP for final concentrations of 60 nM biotinylated crosstide, 0.1 nM PDK1, 0.7 nM MK2, 5.5 μM DOPS, 5.5 μM DOPC, 0.5 μM PtdIns(3,4,5)P3, and 50 μM ATP. The plates were incubated for 30 minutes at room temperature, and then stopped in the dark by the addition of 10 μL stop/detection mixture prepared in assay buffer containing EDTA, AlphaScreen™ Streptavidin Donor and Protein A Acceptor beads, and phospho-AKT substrate antibody for final concentrations of 10 mM EDTA, 500 ng/well of both AlphaScreen™ Streptavidin Donor beads and Protein A Acceptor beads, and phospho-AKT substrate antibody at a final dilution of 1:350. Assay plates were incubated for 90 minutes at room temperature in the dark, and the plates were read on a Perkin Elmer Envision Multilabel plate reader (excitation wavelength: 640 nm, emission wavelength: 570 nm). Biological activities of representative compounds of the invention are shown in Table 5.

TABLE 5

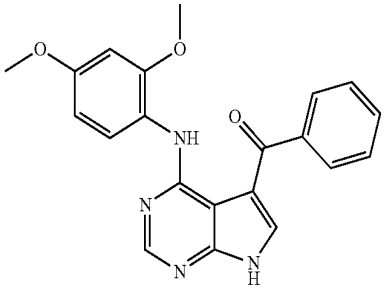
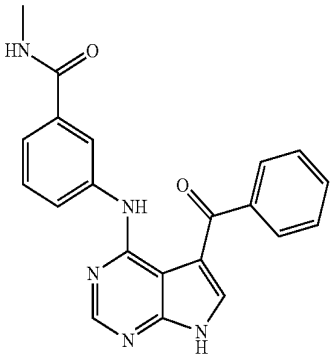
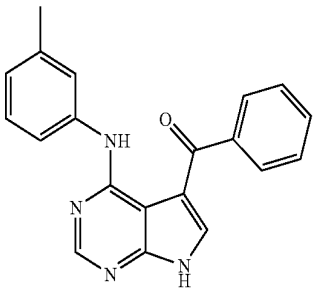
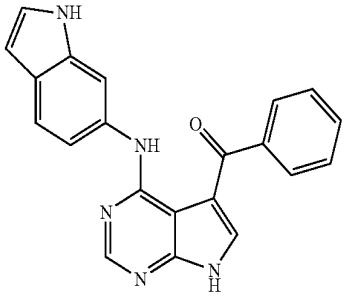
Structure	Chemical Name	AKT1 IC_{50}[1] (μM)	ACK1 (110-489) IC_{50}[2] (μM)
	(4-((2,4-dimethoxy-phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone	NA	4.53
	3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-N-methylbenzamide	5.12	NA
	phenyl(4-(m-tolylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone	NA	55.4
	(4-((1H-indol-6-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone	NA	61.5

TABLE 5-continued

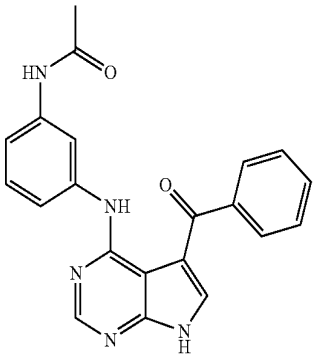
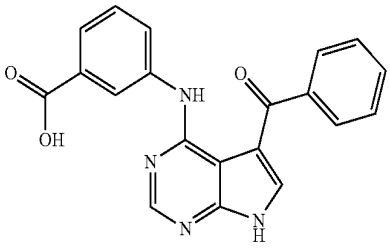
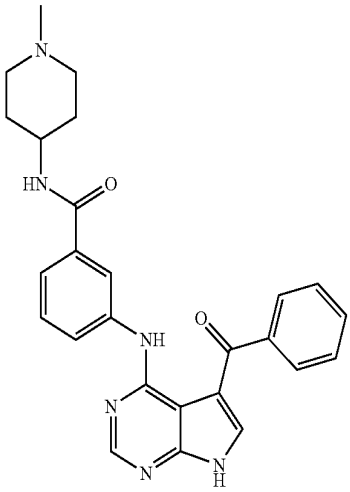
Structure	Chemical Name	AKT1 IC_{50}[1] (μM)	ACK1 (110-489) IC_{50}[2] (μM)
	N-{3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]phenyl}acetamide	2.17	3.87
	3-[(5-benzo-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]benzoic acid	3	2.19
	3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(1-methylpiperidin-4-yl)benzamide	1.44	0.592

TABLE 5-continued

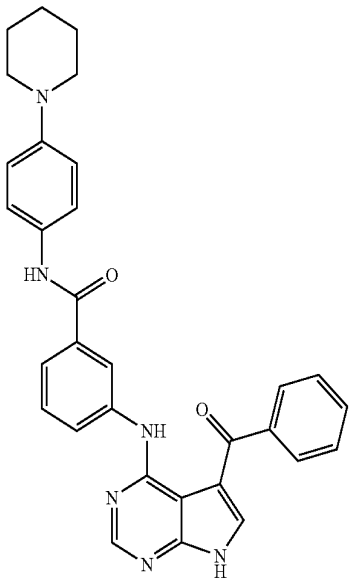
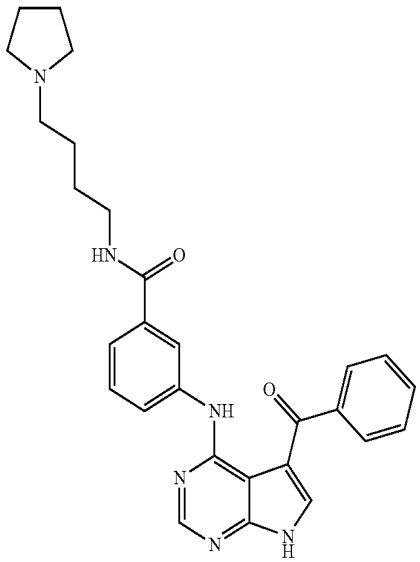
Structure	Chemical Name	AKT1 IC_{50}[1] (μM)	ACK1 (110-489) IC_{50}[2] (μM)
	3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(4-piperidin-1-ylphenyl)benzamide	NA	31.4
	3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(4-pyrrolidin-1-ylbutyl)benzamide	0.676	2.17

TABLE 5-continued

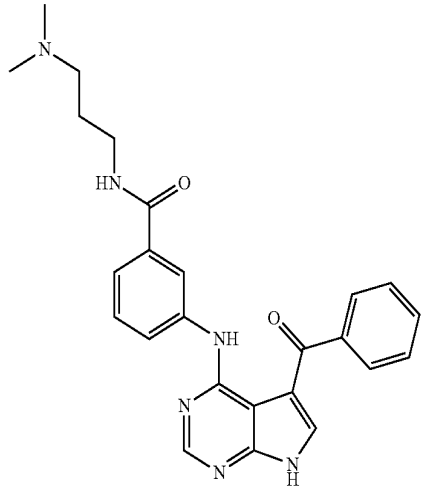
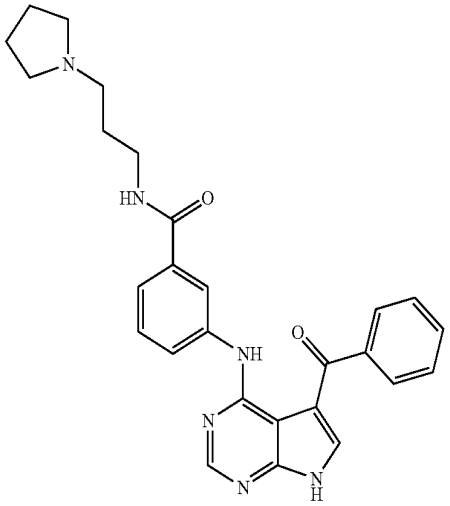
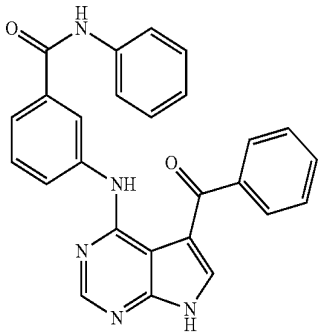
Structure	Chemical Name	AKT1 IC_{50}[1] (μM)	ACK1 (110-489) IC_{50}[2] (μM)
	3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-[3-(dimethylamino)propyl]benzamide	0.674	0.486
	3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-(3-pyrrolidin-1-ylpropyl)benzamide	0.899	1.2
	3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-N-phenylbenzamide	1.4	NA

TABLE 5-continued

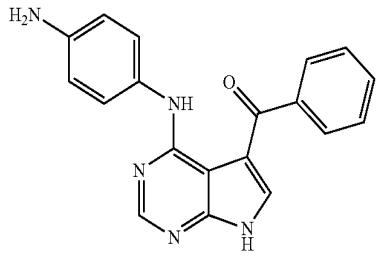
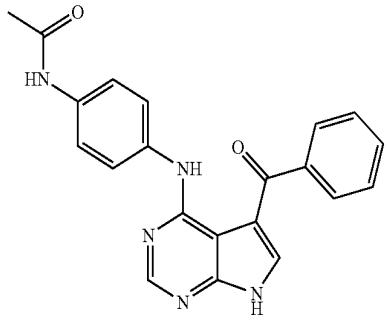
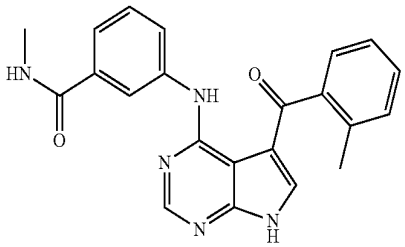
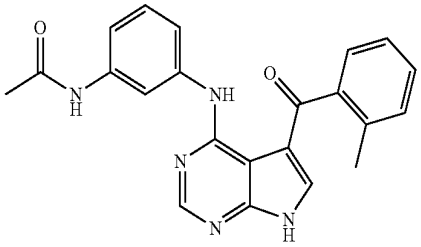
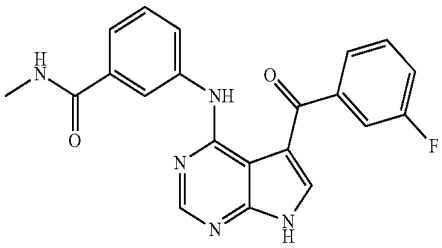
Structure	Chemical Name	AKT1 IC_{50}[1] (μM)	ACK1 (110-489) IC_{50}[2] (μM)
	{4-[(4-aminophenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}(phenyl)methanone	2.57	0.338
	N-{4-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]phenyl}acetamide	NA	1.43
	N-methyl-3-{[5-(2-methylbenzoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}benzamide	NA	0.189
	N-(3-{[5-(2-methylbenzoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)acetamide	NA	1.26
	3-{[5-(3-fluorobenzoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}-N-methylbenzamide	NA	0.914

TABLE 5-continued

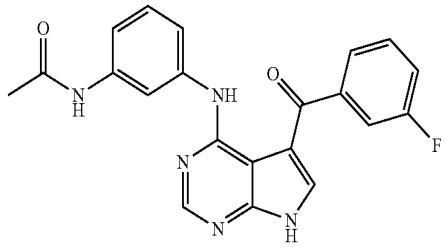
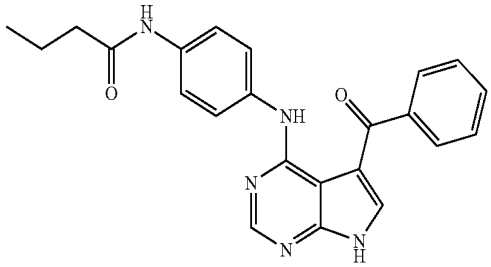
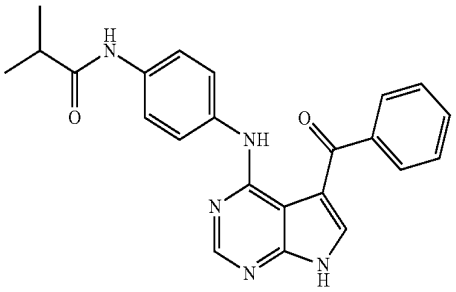
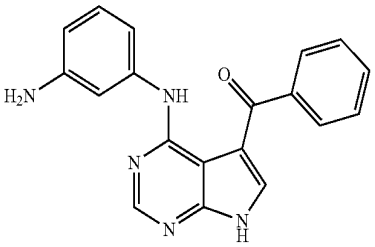
Structure	Chemical Name	AKT1 IC_{50}[1] (μM)	ACK1 (110-489) IC_{50}[2] (μM)
	N-(3-{[5-(3-fluorobenzoyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)acetamide	NA	2.29
	N-{4-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]phenyl}butanamide	NA	3.77
	N-{4-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]phenyl}-2-methylpropanamide	NA	4.77
	{4-[(3-aminophenyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}(phenyl)methanone	1.25	0.415

TABLE 5-continued

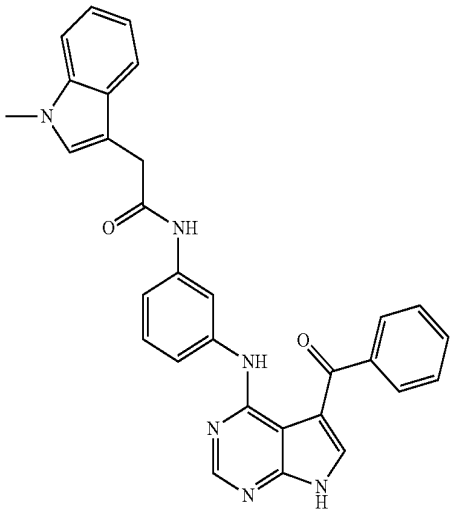
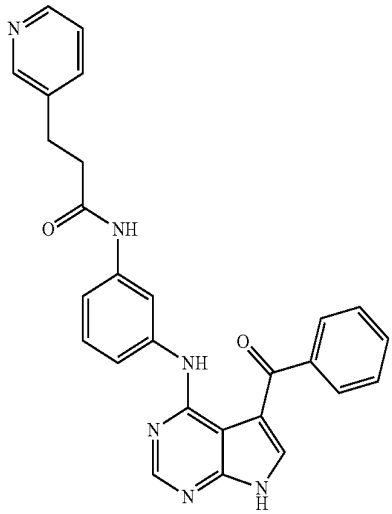
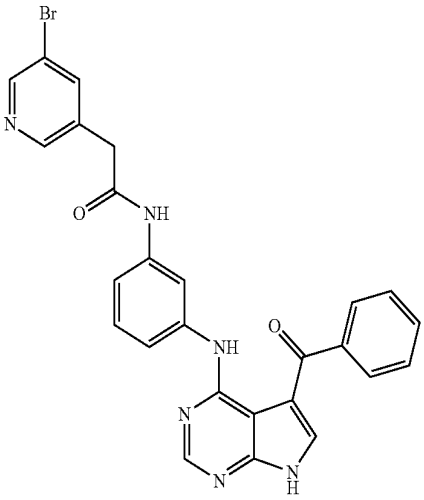
Structure	Chemical Name	AKT1 IC_{50}[1] (μM)	ACK1 (110-489) IC_{50}[2] (μM)
	2-(1-methyl-1H-indol-3-yl)-N-(3-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)acetamide	3.09	NA
	N-(3-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)-3-pyridin-3-ylpropanamide	0.288	1.07
	N-{3-[(5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]phenyl}-2-(5-bromopyridin-3-yl)acetamide	NA	1.47

TABLE 5-continued

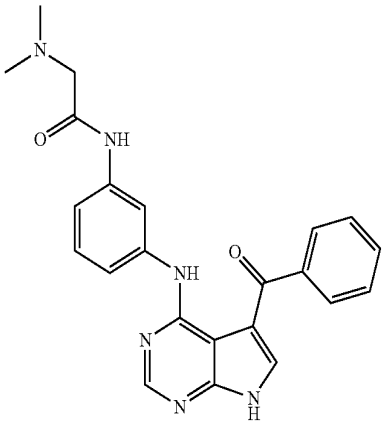
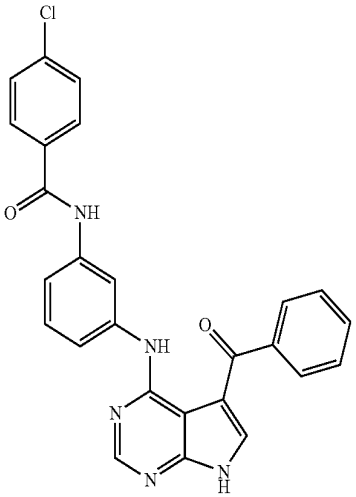
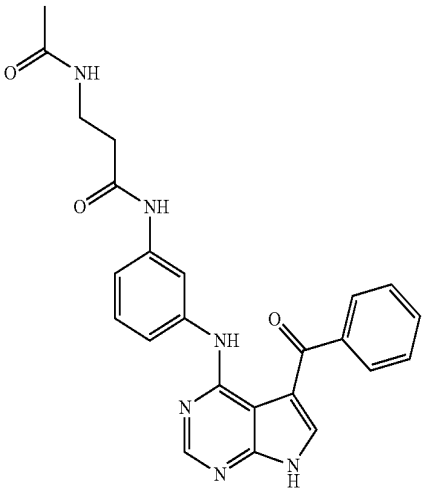
Structure	Chemical Name	AKT1 IC_{50}[1] (μM)	ACK1 (110-489) IC_{50}[2] (μM)
	N,N-dimethyl-N-(3-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)glycinamide	1.12	0.672
	4-chloro-N-(3-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)benzamide	5.13	15.7
	3-acetamido-N-(3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)propanamide	0.264	1.34

TABLE 5-continued

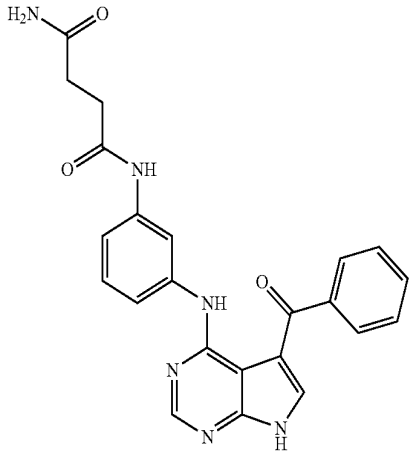
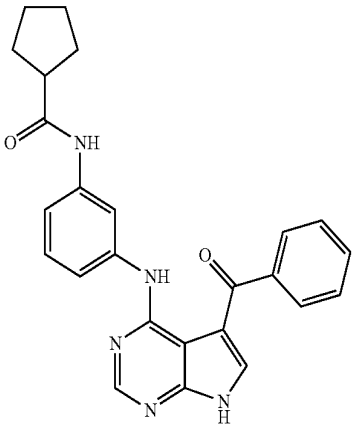
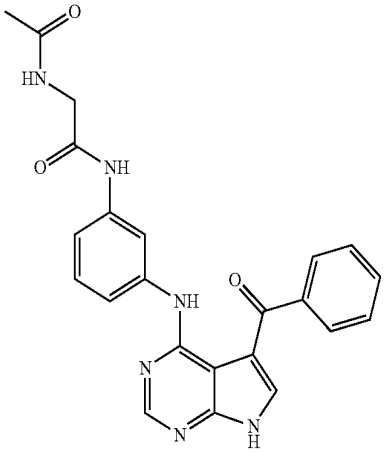
Structure	Chemical Name	AKT1 IC_{50}[1] (μM)	ACK1 (110-489) IC_{50}[2] (μM)
	N-(3-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)butanediamide	1.21	0.876
	N-(3-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl) cyclopentanecarboxamide	7.01	19
	2-acetamido-N-(3-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)acetamide	0.0949	0.666

TABLE 5-continued

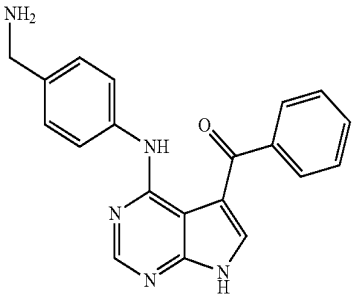
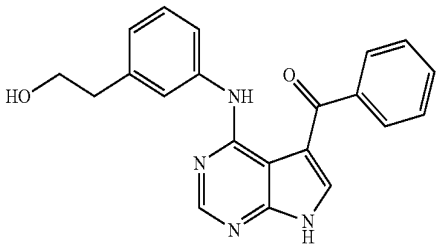
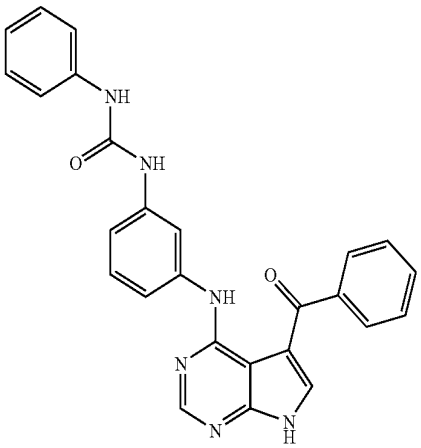
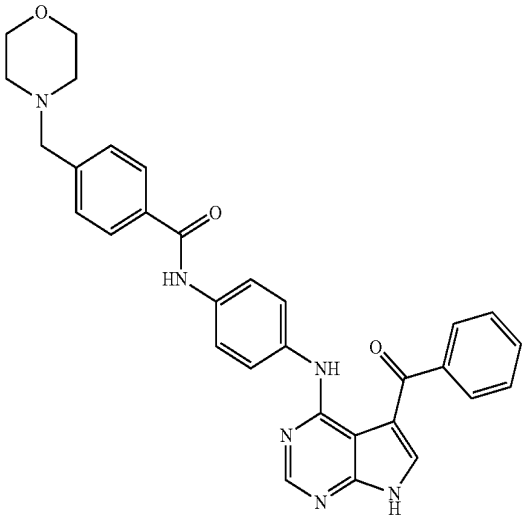
Structure	Chemical Name	AKT1 IC_{50}[1] (μM)	ACK1 (110-489) IC_{50}[2] (μM)
	(4-{[4-(aminomethyl)phenyl] amino}-7H-pyrrolo[2,3-d] pyrimidin-5-yl)(phenyl)methanone	NA	0.446
	(4-{[3-(2-hydroxyethyl)phenyl] amino}-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone	NA	5.14
	1-phenyl-3-(3-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)urea	NA	28.1
	4-(morpholin-4-ylmethyl)-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)benzamide	NA	10.9

TABLE 5-continued

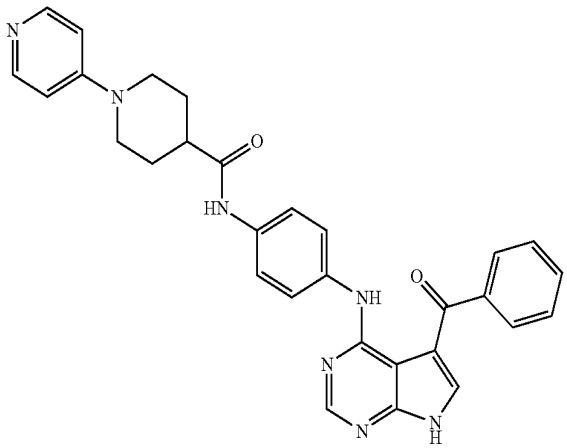
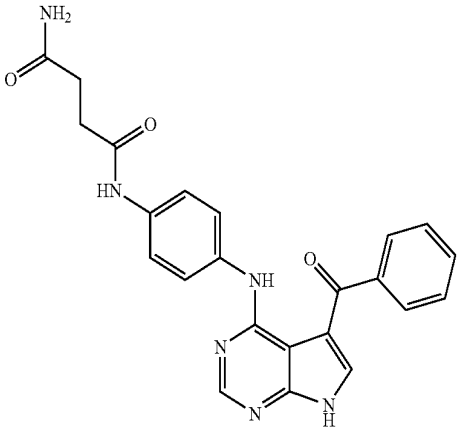
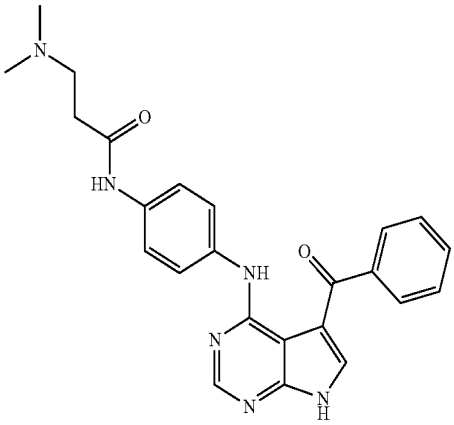
Structure	Chemical Name	AKT1 IC_{50}[1] (μM)	ACK1 (110-489) IC_{50}[2] (μM)
	N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)-1-pyridin-4-ylpiperidine-4-carboxamide	NA	1.27
	N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)butanediamide	NA	0.646
	N-(4-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)-3-(dimethylamino)propanamide	NA	0.415

TABLE 5-continued

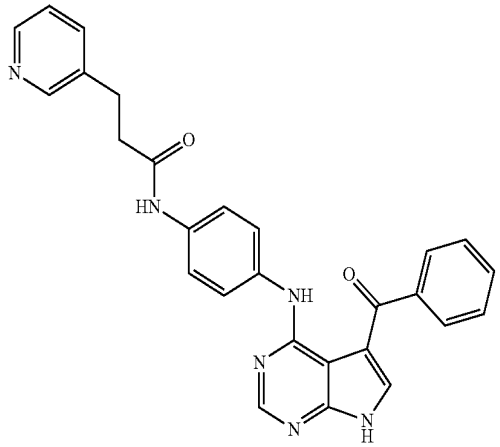
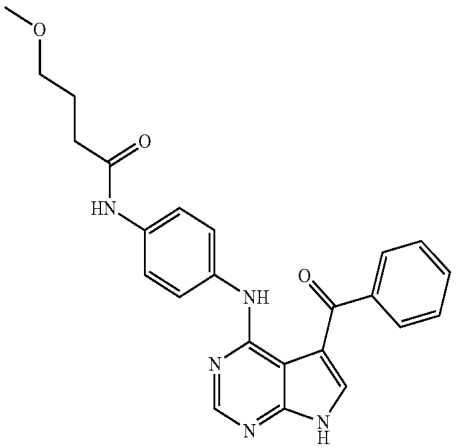
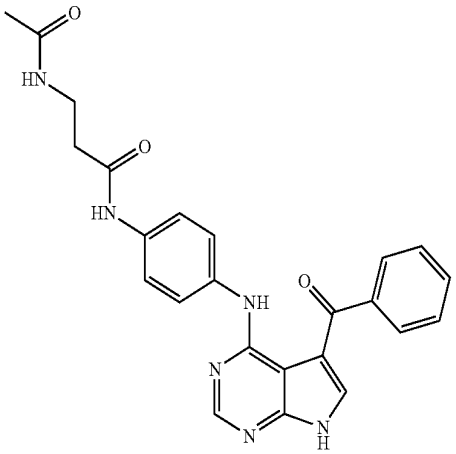
Structure	Chemical Name	AKT1 IC_{50}[1] (μM)	ACK1 (110-489) IC_{50}[2] (μM)
	N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)-3-pyridin-3-ylpropanamide	NA	4.39
	4-methoxy-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)butanamide	NA	1.02
	3-acetamido-N-(4-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)propanamide	NA	0.776

TABLE 5-continued

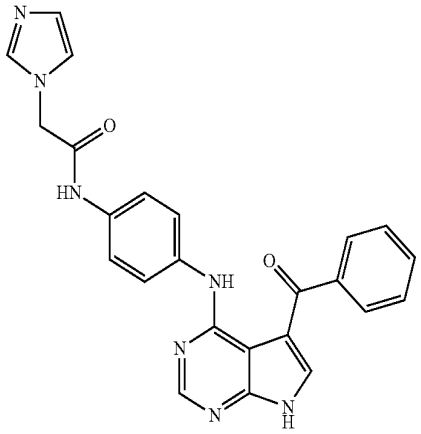
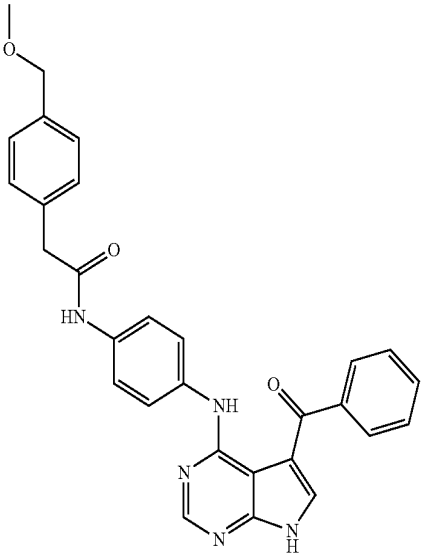
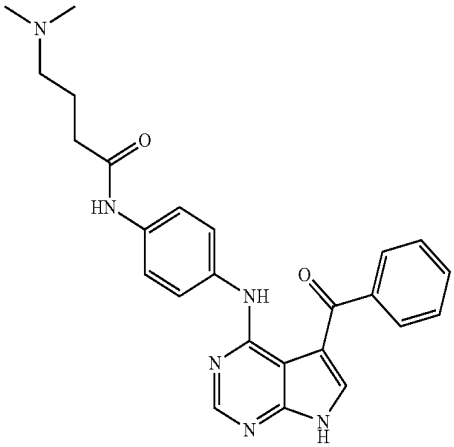
Structure	Chemical Name	AKT1 IC_{50}[1] (μM)	ACK1 (110-489) IC_{50}[2] (μM)
	2-(1H-imidazol-1-yl)-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)acetamide	NA	0.798
	2-[4-(methoxymethyl)phenyl]-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)acetamide	NA	69
	4-(dimethylamino)-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)butanamide	NA	2.57

TABLE 5-continued

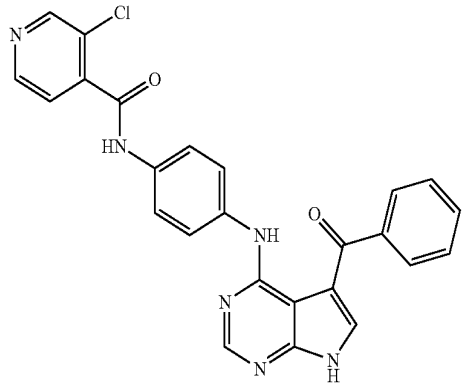
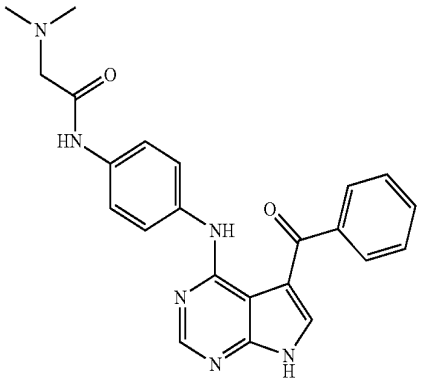
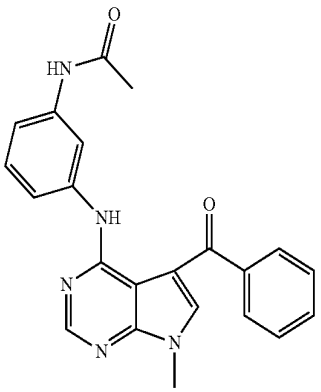
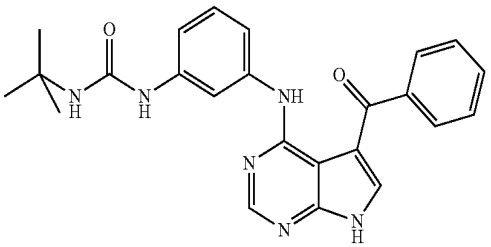
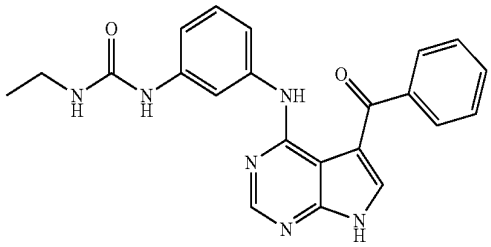
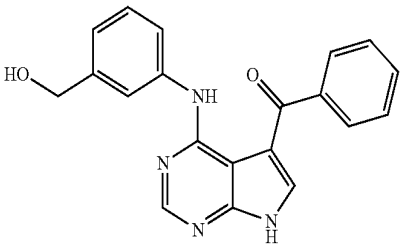
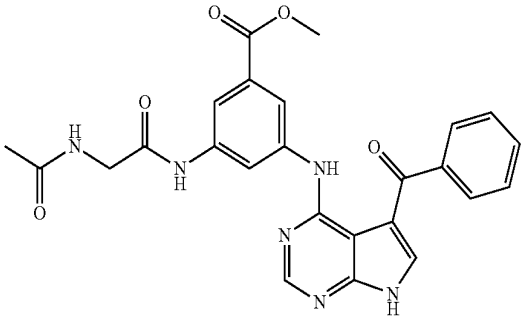
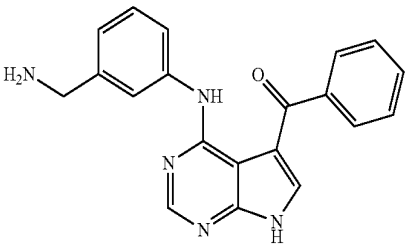
Structure	Chemical Name	AKT1 IC_{50}[1] (μM)	ACK1 (110-489) IC_{50}[2] (μM)
	3-chloro-N-(4-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)pyridine-4-carboxamide	NA	28.9
	N-(4-((5-benzoyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)phenyl)-2-(dimethylamino)acetamide	NA	0.241
	N-(3-{[7-methyl-5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)acetamide	2.51	NA
	1-tert-butyl-3-(3-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)urea	NA	6.65

TABLE 5-continued

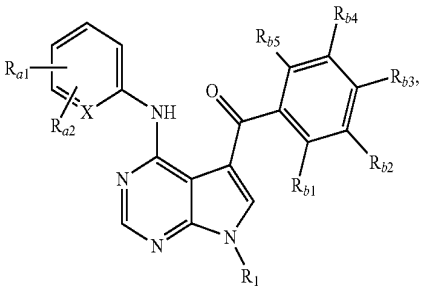
Structure	Chemical Name	AKT1 IC_{50}[1] (μM)	ACK1 (110-489) IC_{50}[2] (μM)
	1-ethyl-3-(3-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}phenyl)urea	NA	1.81
	(4-{[3-(hydroxymethyl)phenyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone	NA	0.24
	methyl 3-[(N-acetylglycyl)amino]-5-{[5-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}benzoate	NA	2
	(4-{[3-(aminomethyl)phenyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(phenyl)methanone	0.186	NA

[1]Average of Akt1 biochemical assay, IC_{50}, AlphaScreen (crosstide)
[2]Average of ACK1(110-489), IC_{50}, AlphaScreen (Pyk2)

What is claimed is:

1. A compound of Formula I or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof:

(I)



wherein:

X═CH or N;

R_1 is H or unsubstituted or substituted C_1-C_6 alkyl;

R_{a1} and R_{a2} are each independently H, —NHR_2, —$(CH_2)_mYR_2$, —C(O)YR_2, —NHC(O)R_2, halogen, —NHC(O)NHR_2, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, or

when adjacent, R_{a1} and R_{a2}, together with the carbon atoms to which they are attached, form an unsubstituted or substituted aryl comprising one or two 5- or 6-member rings, an unsubstituted or substituted C_3-C_8 carbocycle, an unsubstituted or substituted heteroaryl comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S, or an unsubstituted or substituted heterocycle comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S;

R_2 is H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_1-C_6 alkoxy, unsubstituted or substituted C_1-C_6 alkoxycarbonyl, unsubstituted or substituted aminocarbonyl, unsubstituted or substituted C_1-C_6 alkylcarbonylamino, unsubstituted or substituted di-C_1-C_6-alkylamino, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, or R_2 and Z, together with the nitrogen atom to which they are attached, form a 5- or 6-member ring which optionally comprises 1-3 additional heteroatoms selected from N, O and S and is optionally substituted;

Y is NH, NZ or O, provided that when Y is NZ, then Z and R_2, together with the nitrogen atom to which they are attached, form a 5- or 6-member ring which optionally comprises 1-3 additional heteroatoms selected from N, O and S and is optionally substituted;

m=0, 1, 2 or 3;

R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are each independently H, halogen, cyano, nitro, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, —$(CH_2)_pOR_3$, or

any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form an unsubstituted or substituted aryl comprising one or two 5- or 6-member rings, an unsubstituted or substituted C_3-C_8 carbocycle, an unsubstituted or substituted heteroaryl comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S, or an unsubstituted or substituted heterocycle comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S;

R_3 is H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, or unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S; and

p is 0, 1, 2, 3 or 4.

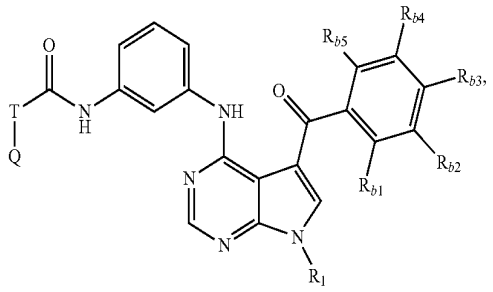
2. The compound of claim **1**, wherein X is CH and R_1 is H.

3. The compound of claim **2**, wherein R_{a1} is —NHC(O)R_2.

4. The compound of claim **2**, wherein R_{a1} is —C(O)YR_2.

5. The compound of claim **1**, having Formula II, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof:

(II)



wherein:

R_1 is H or unsubstituted or substituted C_1-C_6 alkyl;

T is unsubstituted or substituted C_1-C_6 alkyl linker or a bond;

Q is H, halogen, cyano, nitro, unsubstituted or substituted C_1-C_6 alkyl, halogen substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, OR_5, NR_5R_6, $NR_6C(O)R_5$, $NR_6C(O)OR_5$, $NHC(O)NR_5R_6$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$ or $NHS(O)_2R_5$;

R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are each independently H, halogen, cyano, nitro, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, —$(CH_2)_pOR_3$, or

any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form an unsubstituted or substituted aryl comprising one or two 5- or 6-member rings, an unsubstituted or substituted C_3-C_8 carbocycle, an unsubstituted or substituted heteroaryl comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S, or an unsubstituted or substituted heterocycle comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S;

R_3, R_5 and R_6 are each independently H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, or R_5 and R_6, together with the nitrogen atom to which they are attached, form a 5- or 6-member ring which optionally comprises 1-3 additional heteroatoms selected from N, O and S and is optionally substituted; and

p is 0, 1, 2, 3 or 4.

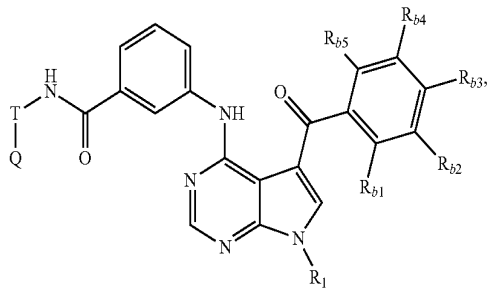
6. The compound of claim **5**, wherein R_1 is H.

7. The compound of claim **6**, wherein Q is unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S.

8. The compound of claim **6**, wherein Q is unsubstituted or substituted C_1-C_6 alkyl.

9. The compound of claim **1**, having Formula III, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof:

(III)



wherein:

R_1 is H or unsubstituted or substituted C_1-C_6 alkyl;

T is unsubstituted or substituted C_1-C_6 alkyl linker or a bond;

Q is H, halogen, cyano, nitro, unsubstituted or substituted C_1-C_6 alkyl, halogen substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, OR_5, NR_5R_6, $NR_6C(O)R_5$, $NR_6C(O)OR_5$, $NHC(O)NR_5R_6$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$ or $NHS(O)_2R_5$;

R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are each independently H, halogen, cyano, nitro, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, —$(CH_2)_pOR_3$, or

any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form an unsubstituted or substituted aryl comprising one or two 5- or 6-member rings, an unsubstituted or substituted C_3-C_8 carbocycle, an unsubstituted or substituted heteroaryl comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S, or an unsubstituted or substituted heterocycle comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S;

R_3, R_5 and R_6 are each independently H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, or R_5 and R_6, together with the nitrogen atom to which they are attached, form a 5- or 6-member ring which optionally comprises 1-3 additional heteroatoms selected from N, O and S and is optionally substituted; and

p is 0, 1, 2, 3 or 4.

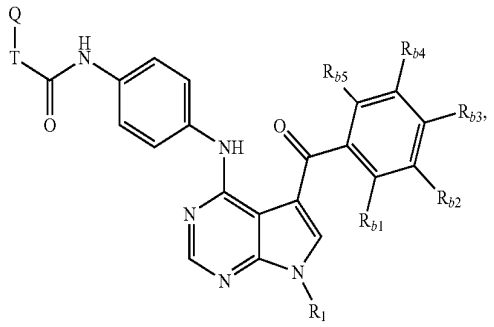
10. The compound of claim **9**, wherein R_1 is H.

11. The compound of claim **10**, wherein Q is unsubstituted or substituted phenyl.

12. The compound of claim **10**, wherein Q is unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S.

13. The compound of claim **1**, having Formula IV, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof:

(IV)



wherein:

R_1 is H or unsubstituted or substituted C_1-C_6 alkyl;

T is unsubstituted or substituted C_1-C_6 alkyl linker or a bond;

Q is H, halogen, cyano, nitro, unsubstituted or substituted C_1-C_6 alkyl, halogen substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, OR_5, NR_5R_6, $NR_6C(O)R_5$, $NR_6C(O)OR_5$, $NHC(O)NR_5R_6$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$ or $NHS(O)_2R_5$;

R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5} are each independently H, halogen, cyano, nitro, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, —$(CH_2)_pOR_3$, or

any two adjacent of R_{b1}, R_{b2}, R_{b3}, R_{b4} and R_{b5}, together with the carbon atoms to which they are attached, form an unsubstituted or substituted aryl comprising one or two 5- or 6-member rings, an unsubstituted or substituted C_3-C_8 carbocycle, an unsubstituted or substituted heteroaryl comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O

and S, or an unsubstituted or substituted heterocycle comprising one or two 5- to 6-member rings which comprises 1-4 heteroatoms selected from N, O and S;

R_3, R_5 and R_6 are each independently H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_6-C_{10} aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C_3-C_{10} carbocycle, unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, or R_5 and R_6, together with the nitrogen atom to which they are attached, form a 5- or 6-member ring which optionally comprises 1-3 additional heteroatoms selected from N, O and S and is optionally substituted; and

p is 0, 1, 2, 3 or 4.

14. The compound of claim **13**, wherein R_1 is H.

15. The compound of claim **14**, wherein Q is unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S.

16. The compound of claim **14**, wherein Q is unsubstituted or substituted di-C_1-C_6-alkylamino.

17. A pharmaceutical composition comprising a compound of claim **1** and a pharmaceutically acceptable carrier.

18. A method of treating a cell proliferative disorder by administering to a subject in need thereof, a therapeutically effective amount of a compound of claim **1**, in combination with a pharmaceutically acceptable carrier, such that the disorder is treated.

19. The method of claim **18**, further comprising administering to the subject in need thereof, a second anti-proliferative agent.

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