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Description

BACKGROUND

Field of Invention

[0001] This invention relates to the field of compounds, pharmaceutical compositions, and methods of using the compounds and compositions containing them. This invention relates more particularly to the field of pyrimidoisoquinolone compounds and pharmaceutical compositions thereof, methods of inhibiting one or more kinases, such as one or more of the TAM (Tyro 3, Axl and Mer) receptor family with the compounds, and methods of treating and/or preventing disease with the compounds.

Technical Background

[0002] In recent years, inhibition of specific cancer-associated tyrosine kinases has emerged as an important approach for cancer therapy. Tyrosine kinases as mediators of cell signaling, play a role in many diverse physiological pathways including cell growth and differentiation. Deregulation of tyrosine kinases activity can result in cellular transformation leading to the development of cancer.

[0003] Tyro 3 has been implicated in several malignant diseases, and its expression is upregulated in AML, CML, multiple myeloma, endometrial cancer and melanoma. Tyro 3 has also been shown to have transforming abilities, and may function as a prosurvival factor in tumorigenesis. In melanoma cells, Tyro 3 knockdown inhibits proliferation and leads to increased sensitivity to chemotherapeutic agents in vitro.

[0004] The Axl receptor tyrosine kinase (Axl) is overexpressed in a number of different tumor cell types. Axl signaling has been shown to favor tumor growth through activation of proliferative and anti-apoptotic signaling pathways, as well as through promotion of angiogenesis and tumor invasiveness. Axl is associated with the development and maintenance of various cancers including lung cancer, myeloid leukemia, uterine cancer, ovarian cancer, gliomas, melanoma, prostate cancer, breast cancer, gastric cancer, osteosarcoma, renal cell carcinoma, and thyroid cancer. In some type of cancers, particularly non-small cell lung cancer (NSCLC), myeloid leukemia, and gastric cancers, the overexpression of this cell signaling molecule indicates a poor prognosis for the patient.

[0005] Mer is a transmembrane receptor tyrosine kinase composed of two immunoglobulin domains and two fibronectin III domains in the extracellular portion, and a tyrosine kinase domain in the intracellular portion. Mer overexpression has been linked to a number of different cancers including subsets of B and T cell leukemia, lymphoma, pituitary adenoma, gastric cancer, and rhabdomyosarcoma.

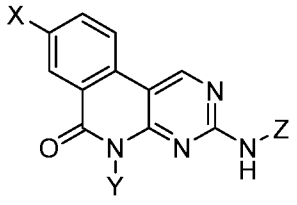
[0006] WO 2012/135800 describes substituted N-phenylpyrimidin-2-amine analogs, derivatives thereof, and related compounds, which are said to be useful as inhibitors of Axl kinase; synthetic methods for making the compounds; pharmaceutical compositions comprising the compounds; and methods of using the compounds and compositions for treating disorders associated with dysfunction of Axl kinase.

SUMMARY

[0007] In view of the foregoing, we recognized that new therapeutic agents that inhibit one or more kinases, in particular tyrosine receptor kinases of the TAM (Tyro 3, Axl and Mer) receptor family may be useful and therefore desirable for the treatment of proliferative disorders, in particular hematological neoplasms, such as acute myeloid leukemia (AML).

[0008] Accordingly, the present invention provides compounds, pharmaceutical compositions, and compounds or pharmaceutical compositions for use in methods of using them to treat hematological neoplasms. The invention is defined in claim 1. Further aspects and preferred embodiments are defined in the dependent claims. Any aspects, embodiments and examples of the present disclosure which do not fall under the scope of the appended claims do not form part of the invention and are merely provided for illustrative purposes.

[0009] The invention provides compounds having structural formula (I):



(I)

and pharmaceutically acceptable salts and *N*-oxides thereof (and solvates and hydrates thereof), wherein X, Y, and Z are as described herein.

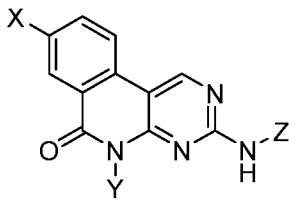
[0010] The invention also provides pharmaceutical compositions. Examples of such compositions include those having at least one pharmaceutically acceptable carrier, diluent, or excipient; and a compound, pharmaceutically acceptable salt, or *N*-oxide (or solvate or hydrate) as described herein.

[0011] The invention also provides the presently disclosed compounds or pharmaceutical compositions for use in methods for treating hematological neoplasms.

DETAILED DESCRIPTION

[0012] In one aspect, compounds of the invention may inhibit one or more of the TAM (Tyro 3, Ax1 and Mer) receptor family.

[0013] In embodiment I_1 of this first aspect, the compounds have structural formula (I):



(I)

or a pharmaceutically acceptable salt or *N*-oxide thereof, or a solvate or hydrate thereof, wherein

X is hydrogen, Cak(C_0-C_6alkyl), Hca(C_0-C_6alkyl), Ar(C_0-C_6alkyl) or Het(C_0-C_6alkyl),
wherein Ar, Het, Cak, Hca and the alkyl group is optionally substituted by one to four -R^{X1} groups, wherein

each -R^{X1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, -$C(O)NR_2$, -$S(O)_2NR_2$, -$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -$OC(O)NR_2$, -N(R)C(O)OR, -$N(R)C(O)NR_2$, -$N(R)S(O)_2$R, -$OP(O)(OR)_2$, -CH_2-OP(O)(OR), Ar(Co-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl),
or two -R^{X1} groups taken together, when attached to adjacent atoms, form a Cak, Hca or Het, wherein the Cak Hca and the Het comprise a 3-8 membered ring optionally substituted with one or two -R^{X2} groups,
or two -R^{X1} groups taken together, when attached to the same carbon atom, form a Hca, wherein the Hca comprises a 3-8 membered ring optionally substituted with one or two -R^{X2} groups,
or two -R^{X1} groups taken together, when attached to non-adjacent atoms, and combined with X, form a bridged Hca optionally substituted with one or two -R^{X2} groups,
wherein each -R^{X2} is independently halogen, cyano, nitro, oxo, -OR, -SR, - NR_2, -C(O)OR, -$C(O)NR_2$, -C(O)R, -S(O)R, -$S(O)_2$R, -S(O)OR, - $S(O)_2$OR, -$S(O)NR_2$, -$S(O)_2NR_2$,-OC(O)R, -OC(O)OR, -$OC(O)NR_2$, -N(R)C(O)R, -N(R)C(O)OR, -$N(R)C(O)NR_2$, -N(R)S(O)R, -$N(R)S(O)_2$R, C_1-C_6alkyl, or C_1-C_6haloalkyl;

Y is Cak(C_0-C_6alkyl) optionally substituted by one or two -R^{Y1} groups;
wherein each -R^{Y1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, C(O)NR_2, -$S(O)_2NR_2$,-$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -$OC(O)NR_2$, -N(R)C(O)OR, -$N(R)C(O)NR_2$, -$N(R)S(O)_2$R, -$OP(O)(OR)_2$ or -CH_2-OP(O)(OR);
Z is C_1-C_6alkyl or Cak(C_0-C_6alkyl), each optionally substituted by one to three -R^{Z1} groups;
wherein each -R^{Z1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, -$C(O)NR_2$, -$S(O)_2NR_2$,-$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -$OC(O)NR_2$, -N(R)C(O)OR, -$N(R)C(O)NR_2$, -$N(R)S(O)_2$R, -$OP(O)(OR)_2$ or -CH_2-OP(O)(OR); and
each R is independently hydrogen or C_1-C_6alkyl,
wherein

Hca is a 3-15 membered ring or ring system comprising at least one ring, 1-4 O, S, or N atoms, provided no O or S is adjacent to another O or S;
Het is a 5-15 membered aromatic ring or ring system comprising at least one ring and 1-4 O, S, or N atoms, provided no O or S is adj acent to another O or S;
Cak is a 3-8 membered non-aromatic carbocyclic ring or ring system, which may be saturated or partially

unsaturated ; and
Ar is a 6-16 membered aromatic ring or ring system having at least one carbocyclic aromatic ring optionally fused one or more aromatic or non-aromatic rings.

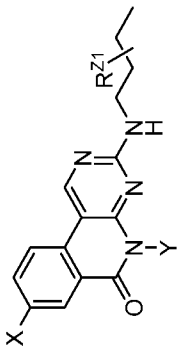
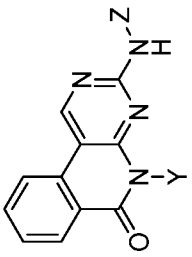
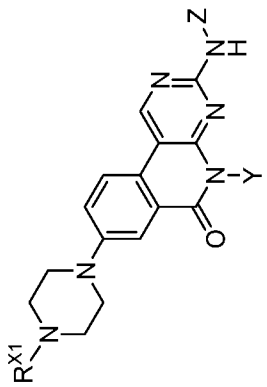
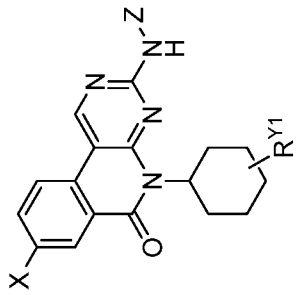
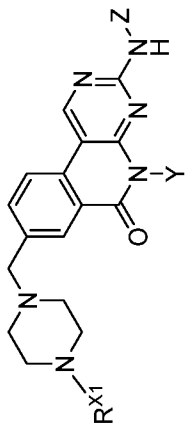
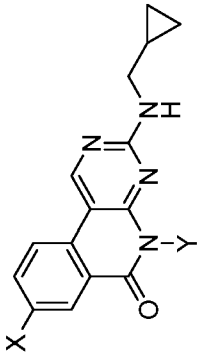
[0014] In embodiment I_2, the compounds are of embodiment I_1, wherein X is hydrogen, Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl), wherein each Cak, Hca and alkyl group is optionally substituted by one to three -R^{X1} groups.

[0015] In embodiment I_3, the compounds are of embodiment I_1, wherein X is hydrogen or Hca(C_0-C_6alkyl), wherein each Hca and alkyl group is optionally substituted by one to three -R^{X1} groups.

[0016] In embodiment I_4, the invention further comprises subgenera of formula (I) in which structural formula (I), X, Y and Z are any group or combinations of groups as defined sections I^a - I^d immediately below (*e.g.*, wherein the compound is of structural formula (I) as defined in any of the above embodiments and Z is piperazine optionally substituted with one R^{X1} group, wherein R^{X1} is methyl; or the compound is of formula (Ib), X is group (**1jj**), Y is group (**2r**), and Z is group (**3h**)):

I^a - Structural Formula (I) is one of formulae (Ia) - (If):

[0017]

	(Ic)		(If)
	(Ib)		(Ie)
	(Ia)		(Id)

I^b - X is selected from one of the following groups (1a) - (1pp):

[0018]

(1a) X is hydrogen, Cak(C_0-C_6alkyl), Hca(C_0-C_6alkyl), Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), wherein Ar, Het, Cak, Hca and the alkyl group is optionally substituted by one to four -R^{X1} groups, wherein each -R^{X1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, -C(O)NR_2, -$S(O)_2NR_2$,-$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)$S(O)_2$R, -OP(O)$(OR)_2$, -CH_2-OP(O)(OR), Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(1b) X is Cak(C_0-C_6alkyl), Hca(C_0-C_6alkyl), Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), wherein Ar, Het, Cak, Hca and the alkyl group is optionally substituted by one to four-R^{X1} groups.

(1c) X is Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl), wherein Cak, Hca and the alkyl group is optionally substituted by one to four -R^{X1} groups.

(1d) X is Cak(C_0-C_6alkyl), wherein Cak and the alkyl group is optionally substituted by one to four -R^{X1} groups.

(1e) X is Hca(C_0-C_6alkyl), wherein the Hca and the alkyl group is optionally substituted by one to four -R^{X1} groups.

(1f) X is any of groups **(1a) - (1e)**, wherein each -R^{X1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, -C(O)NR_2, -$S(O)_2NR_2$, -$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)$S(O)_2$R, -OP(O)$(OR)_2$, -CH_2-OP(O)(OR), Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl), or two -R^{X1} groups taken together, when attached to adjacent atoms, form a Cak, Hca or Het, wherein the Cak Hca and the Het comprise a 3-8 membered ring optionally substituted with one or two -R^{X2} groups, or two -R^{X1} groups taken together, when attached to the same carbon atom, form a Hca, wherein the Hca comprises a 3-8 membered ring optionally substituted with one or two -R^{X2} groups, or two -R^{X1} groups taken together, when attached to non-adjacent atoms, and combined with X, form a bridged Hca optionally substituted with one or two -R^{X2} groups, wherein each -R^{X2} is independently halogen, cyano, nitro, oxo, -OR,-SR, -NR_2, -C(O)OR, -C(O)NR_2, -C(O)R, -S(O)R, -$S(O)_2$R,-S(O)OR, -$S(O)_2$OR, -S(O)NR_2, -$S(O)_2NR_2$,-OC(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)R, -N(R)C(O)OR, -N(R)C(O)NR_2,-N(R)S(O)R, -N(R)$S(O)_2$R, C_1-C_6alkyl, or C_1-C_6haloalkyl.

(1g) X is any of groups **(1a) - (1e)**, wherein each -R^{X1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, -C(O)NR_2, -$S(O)_2NR_2$, -$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)$S(O)_2$R, -OP(O)$(OR)_2$, -CH_2-OP(O)(OR), Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl), or two -R^{X1} groups taken together, when attached to adjacent atoms, form a Cak, Hca or Het, wherein the Cak Hca and the Het comprise a 3-8 membered ring optionally substituted with one or two -R^{X2} groups, or two -R^{X1} groups taken together, when attached to the same carbon atom, form a Hca, wherein the Hca comprises a 3-8 membered ring optionally substituted with one or two -R^{X2} groups.

(1h) X is any of groups **(1a) - (1e)**, wherein each -R^{X1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, -C(O)NR_2, -$S(O)_2NR_2$, -$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)$S(O)_2$R, -OP(O)$(OR)_2$, -CH_2-OP(O)(OR), Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl), or two -R^{X1} groups taken together, when attached to adjacent atoms, form a Cak, Hca or Het, wherein the Cak Hca and the Het comprise a 3-8 membered ring optionally substituted with one or two -R^{X2} groups.

(1i) X is any of groups **(1a) - (1e)**, wherein each -R^{X1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, -C(O)NR_2, -$S(O)_2NR_2$, -$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)$S(O)_2$R, -OP(O)$(OR)_2$, -CH_2-OP(O)(OR), Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl), or two -R^{X1} groups taken together, when attached to the same carbon atom, form a Hca, wherein the Hca comprises a 3-8 membered ring optionally substituted with one or two -R^{X2} groups.

(1j) X is any of groups **(1a) - (1e)**, wherein each -R^{X1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, -C(O)NR_2, -$S(O)_2NR_2$, -$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)$S(O)_2$R, -OP(O)$(OR)_2$, -CH_2-OP(O)(OR), Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl), or two -R^{X1} groups taken together, when attached to non-adjacent atoms, and combined with X, form a bridged Hca optionally substituted with one or two -R^{X2} groups, wherein each -R^{X2} is independently halogen, cyano, nitro, oxo, -OR,-SR, -NR_2, -C(O)OR, -C(O)NR_2, -C(O)R, -S(O)R, -$S(O)_2$R,-S(O)OR, -$S(O)_2$OR, -S(O)NR_2, -$S(O)_2NR_2$,-OC(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)R, -N(R)C(O)OR, -N(R)C(O)NR_2,-N(R)S(O)R, -N(R)$S(O)_2$R, C_1-C_6alkyl, or C_1-C_6haloalkyl.

(1k) X is any of groups **(1a) - (1e)**, wherein two -R^{X1} groups taken together, when attached to adjacent atoms,

form a Cak, Hca or Het, wherein the Cak Hca and the Het comprise a 3-8 membered ring optionally substituted with one or two -R^{X2} groups, or two -R^{X1} groups taken together, when attached to the same carbon atom, form a Hca, wherein the Hca comprises a 3-8 membered ring optionally substituted with one or two -R^{X2} groups, or two -R^{X1} groups taken together, when attached to non-adjacent atoms, and combined with X, form a bridged Hca optionally substituted with one or two -R^{X2} groups, wherein each -R^{X2} is independently halogen, cyano, nitro, oxo, -OR,-SR, -NR_2, -C(O)OR, -$C(O)NR_2$, -C(O)R, -S(O)R, -$S(O)_2$R,-S(O)OR, -$S(O)_2$OR, -$S(O)NR_2$, -$S(O)_2NR_2$,-OC(O)R, -OC(O)OR, -$OC(O)NR_2$, -N(R)C(O)R, -N(R)C(O)OR, -$N(R)C(O)NR_2$,-N(R)S(O)R, -$N(R)S(O)_2$R, C_1-C_6alkyl, or C_1-C_6haloalkyl.

(1l) X is any of groups **(1a) - (1e)**, wherein two -R^{X1} groups taken together, when attached to adjacent atoms, form a Cak, Hca or Het, wherein the Cak Hca and the Het comprise a 3-8 membered ring optionally substituted with one or two -R^{X2} groups, or two -R^{X1} groups taken together, when attached to the same carbon atom, form a Hca, wherein the Hca comprises a 3-8 membered ring optionally substituted with one or two -R^{X2} groups.

(1m) X is any of groups **(1a) - (1e)**, wherein two -R^{X1} groups taken together, when attached to adjacent atoms, form a Cak, Hca or Het, wherein the Cak Hca and the Het comprise a 3-8 membered ring optionally substituted with one or two -R^{X2} groups, or two -R^{X1} groups taken together, when attached to non-adjacent atoms, and combined with X, form a bridged Hca optionally substituted with one or two -R^{X2} groups, wherein each -R^{X2} is independently halogen, cyano, nitro, oxo, -OR,-SR, -NR_2, -C(O)OR, -$C(O)NR_2$, -C(O)R, -S(O)R, -$S(O)_2$R,-S(O)OR, -$S(O)_2$OR, -$S(O)NR_2$, -$S(O)_2NR_2$,-OC(O)R, -OC(O)OR, -$OC(O)NR_2$, -N(R)C(O)R, -N(R)C(O)OR, -$N(R)C(O)NR_2$,-N(R)S(O)R, -$N(R)S(O)_2$R, C_1-C_6alkyl, or C_1-C_6haloalkyl.

(1n) X is any of groups **(1a) - (1e)**, wherein two -R^{X1} groups taken together, when attached to the same carbon atom, form a Hca, wherein the Hca comprises a 3-8 membered ring optionally substituted with one or two -R^{X2} groups, or two -R^{X1} groups taken together, when attached to non-adjacent atoms, and combined with X, form a bridged Hca optionally substituted with one or two -R^{X2} groups, wherein each -R^{X2} is independently halogen, cyano, nitro, oxo, -OR,-SR, -NR_2, -C(O)OR, -$C(O)NR_2$, -C(O)R, -S(O)R, -$S(O)_2$R,-S(O)OR, -$S(O)_2$OR, -$S(O)NR_2$, -$S(O)_2NR_2$,-OC(O)R, -OC(O)OR, -$OC(O)NR_2$, -N(R)C(O)R, -N(R)C(O)OR, -$N(R)C(O)NR_2$,-N(R)S(O)R, -$N(R)S(O)_2$R, C_1-C_6alkyl, or C_1-C_6haloalkyl.

(1o) X is any of groups **(1a) - (1e)**, wherein each -R^{X1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, -$C(O)NR_2$, -$S(O)_2NR_2$, -$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -$OC(O)NR_2$, -N(R)C(O)OR, -$N(R)C(O)NR_2$, -$N(R)S(O)_2$R, -OP(O)$(OR)_2$, -CH_2-OP(O)(OR), Ar(Co-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(1p) X is any of groups **(1a) - (1e)**, wherein two -R^{X1} groups taken together, when attached to adjacent atoms, form a Cak, Hca or Het, wherein the Cak Hca and the Het comprise a 3-8 membered ring optionally substituted with one or two -R^{X2} groups.

(1q) X is any of groups **(1a) - (1e)**, wherein two -R^{X1} groups taken together, when attached to the same carbon atom, form a Hca, wherein the Hca comprises a 3-8 membered ring optionally substituted with one or two -R^{X2} groups.

(1r) X is any of groups **(1a) - (1e)**, wherein two -R^{X1} groups taken together, when attached to non-adjacent atoms, and combined with X, form a bridged Hca optionally substituted with one or two -R^{X2} groups, wherein each -R^{X2} is independently halogen, cyano, nitro, oxo, -OR, - SR, -NR_2, -C(O)OR, -$C(O)NR_2$, -C(O)R, -S(O)R, -$S(O)_2$R, - S(O)OR, -$S(O)_2$OR, -$S(O)NR_2$, -$S(O)_2NR_2$,-OC(O)R, -OC(O)OR, -$OC(O)NR_2$, -N(R)C(O)R, -N(R)C(O)OR, -$N(R)C(O)NR_2$, - N(R)S(O)R, -$N(R)S(O)_2$R, C_1-C_6alkyl, or C_1-C_6haloalkyl.

(1s) X is any of groups **(1b) - (1r)**, wherein each -R^{X1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, -$C(O)NR_2$, -$S(O)_2NR_2$, -$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -$N(R)C(O)NR_2$, -$N(R)S(O)_2$R, -OP(O)$(OR)_2$, -CH_2-OP(O)(OR), Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(1t) X is any of groups **(1b) - (1r)**, wherein each -R^{X1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, -$C(O)NR_2$, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -$N(R)C(O)NR_2$, -$N(R)S(O)_2$R, -OP(O)$(OR)_2$, -CH_2-OP(O)(OR), Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(1u) X is any of groups **(1b) - (1r)**, wherein each -R^{X1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, -$C(O)NR_2$, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -$N(R)C(O)NR_2$, -$N(R)S(O)_2$R, Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(1v) X is any of groups **(1b) - (1r)**, wherein each -R^{X1} is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, -$C(O)NR_2$, -OC(O)R,-N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -$N(R)C(O)NR_2$,-$N(R)S(O)_2$R, Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(1w) X is any of groups **(1b) - (1r)**, wherein each -R^{X1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl,

$-C_1$-C_6alkoxy, oxo, -C(O)R, -C(O)OR, -C(O)NR_2, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)S(O)$_2$R, Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(1x) X is any of groups **(1b) - (1r)**, wherein each -R^{X1} is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, oxo, -C(O)R, -C(O)OR, -C(O)NR_2, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)S(O)$_2$R, Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(1y) X is any of groups **(1b) - (1r)**, wherein each -R^{X1} is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, oxo, -C(O)R, -C(O)OR, -C(O)NR_2, -N(R)C(O)R, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)S(O)$_2$R, Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(1z) X is any of groups **(1b) - (1r)**, wherein each -R^{X1} is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, oxo, -C(O)R, -C(O)OR, -C(O)NR_2, -OC(O)R, -OC(O)OR, -OC(O)NR_2, Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(1aa) X is any of groups **(1b) - (1r)**, wherein each -R^{X1} is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, oxo, -C(O)R, -C(O)OR, -C(O)NR_2, Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(1bb) X is any of groups **(1b) - (1r)**, wherein each -R^{X1} is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, oxo, -C(O)OR, Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(1cc) X is any of groups **(1b) - (1r)**, wherein each -R^{X1} is independently C_1-C_6alkyl, C_1-C_6haloalkyl, oxo, -C(O)OR, Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(1dd) X is any of groups **(1b) - (1r)**, wherein each -R^{X1} is independently C_1-C_6alkyl, C_1-C_6haloalkyl.

(1ee) X is any of groups **(1b) - (1r)**, wherein each -R^{X1} is independently oxo, -C(O)OR, Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(1ff) X is any of groups **(1b) - (1r)**, wherein each -R^{X1} is independently C_1-C_6alkyl, C_1-C_6haloalkyl, Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(1gg) X is any of groups **(1b) - (1r)**, wherein each -R^{X1} is independently Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(1hh) X is any of groups **(1b) - (1r)**, wherein each -R^{X1} is independently C_1-C_6alkyl, C_1-C_6haloalkyl, oxo, -C(O)OR or Hca(C_0-C_6alkyl).

(1ii) X is any of groups **(1b) - (1r)**, wherein each -R^{X1} is independently C_1-C_6alkyl, C_1-C_6haloalkyl, oxo, -C(O)OR or Cak(C_0-C_6alkyl).

(1jj) X is any of groups **(1b) - (1r)**, wherein each -R^{X1} is independently C_1-C_6alkyl, C_1-C_6haloalkyl, -C(O)OR, Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(1kk) X is any of groups **(1b) - (1jj)**, wherein -R^{X1} is C_1-C_6alkyl.

(1ll) X is any of groups **(1b) - (1jj)**, wherein -R^{X1} is C_1-C_6haloalkyl.

(1mm) X is any of groups **(1b) - (1jj)**, wherein -R^{X1} is oxo.

(1nn) X is any of groups **(1b) - (1jj)**, wherein -R^{X1} is -C(O)OR.

(1oo) X is any of groups **(1b) - (1jj)**, wherein -R^{X1} is Cak(C_0-C_6alkyl).

(1pp) X is any of groups **(1b) - (1jj)**, wherein -R^{X1} is Hca(C_0-C_6alkyl).

I^c - Y is selected from one of the following groups (2a) - (211):

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(2a) Y is Cak(C_0-C_6alkyl) optionally substituted by one or two -R^{Y1} groups, wherein each -R^{Y1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, C(O)NR_2, -S(O)$_2$$NR_2$,-S(O)$_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)S(O)$_2$R, -OP(O)(OR)$_2$ or -CH_2-OP(O)(OR).

(2b) Y is Cak(C_0-C_6alkyl) optionally substituted by one -R^{Y1} group; wherein each -R^{Y1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, C(O)NR_2, -S(O)$_2$$NR_2$,-S(O)$_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)S(O)$_2$R, -OP(O)(OR)$_2$ or -CH_2-OP(O)(OR).

(2c) Y is Cak(C_0-C_6alkyl) optionally substituted by two -R^{Y1} group; wherein each -R^{Y1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, C(O)NR_2, -S(O)$_2$$NR_2$,-S(O)$_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)S(O)$_2$R, -OP(O)(OR)$_2$ or -CH_2-OP(O)(OR).

(2d) Y is unsubstituted Cak(C_0-C_6alkyl).

(2e) Y is Cak optionally substituted by one or two -R^{Y1} groups, wherein each -R^{Y1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, C(O)NR_2, -S(O)$_2$$NR_2$,-S(O)$_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)S(O)$_2$R, -OP(O)(OR)$_2$ or -CH_2-OP(O)(OR).

(2f) Y is Cak optionally substituted by one -R^{Y1} group, wherein each -R^{Y1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, C(O)NR_2, -$S(O)_2NR_2$,-$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)$S(O)_2$R, -OP(O)$(OR)_2$ or -CH_2-OP(O)(OR).

(2g) Y is Cak optionally substituted by two -R^{Y1} group, wherein each -R^{Y1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, C(O)NR_2, -$S(O)_2NR_2$,-$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)$S(O)_2$R, -OP(O)$(OR)_2$ or -CH_2-OP(O)(OR).

(2h) Y is unsubstituted Cak.

(2i) Y is Cak(C_1alkyl) optionally substituted by one or two -R^{Y1} groups, wherein each -R^{Y1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, C(O)NR_2, -$S(O)_2NR_2$,-$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)$S(O)_2$R, -OP(O)$(OR)_2$ or -CH_2-OP(O)(OR).

(2j) Y is Cak(C_1alkyl) optionally substituted by one -R^{Y1} group; wherein each -R^{Y1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, C(O)NR_2, -$S(O)_2NR_2$,-$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)$S(O)_2$R, -OP(O)$(OR)_2$ or -CH_2-OP(O)(OR).

(2k) Y is Cak(C_1alkyl) optionally substituted by two -R^{Y1} group; wherein each -R^{Y1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, C(O)NR_2, -$S(O)_2NR_2$,-$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)$S(O)_2$R, -OP(O)$(OR)_2$ or -CH_2-OP(O)(OR).

(2l) Y is unsubstituted Cak(C_1alkyl).

(2m) Y is Cak(C_0-C_6alkyl) optionally substituted by one or two -R^{Y1} groups, wherein each -R^{Y1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, C(O)NR_2, -$S(O)_2NR_2$, -$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)$S(O)_2$R, -OP(O)$(OR)_2$ or -CH_2-OP(O)(OR).

(2n) Y is Cak(C_0-C_6alkyl) optionally substituted by one or two -R^{Y1} groups, wherein each -R^{Y1} is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, C(O)NR_2, -$S(O)_2NR_2$, -$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)$S(O)_2$R, -OP(O)$(OR)_2$or -CH_2-OP(O)(OR).

(2o) Y is Cak(C_0-C_6alkyl) optionally substituted by one or two -R^{Y1} groups, wherein each -R^{Y1} is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, C(O)NR_2, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)$S(O)_2$R, -OP(O)$(OR)_2$or -CH_2-OP(O)(OR).

(2p) Y is Cak(C_0-C_6alkyl) optionally substituted by one or two -R^{Y1} groups, wherein each -R^{Y1} is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, C(O)NR_2, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2 or -N(R)$S(O)_2$R.

(2q) Y is Cak(C_0-C_6alkyl) optionally substituted by one or two -R^{Y1} groups, wherein each -R^{Y1} is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2 or -N(R)$S(O)_2$R.

(2r) Y is Cak(C_0-C_6alkyl) optionally substituted by one or two -R^{Y1} groups, wherein each -R^{Y1} is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2 or -N(R)$S(O)_2$R.

(2s) Y is Cak(C_0-C_6alkyl) optionally substituted by one or two -R^{Y1} groups, wherein each -R^{Y1} is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -OC(O)NR_2 or -N(R)C(O)OR.

(2t) Y is Cak(C_0-C_6alkyl) optionally substituted by one or two -R^{Y1} groups, wherein each -R^{Y1} is independently C_1-C_6alkyl, C_1-C_6haloalkyl, oxo, -OR,-SR, -NR_2, -OC(O)NR_2 or -N(R)C(O)OR

(2u) Y is Cak(C_0-C_6alkyl) optionally substituted by one or two -R^{Y1} groups, wherein each -R^{Y1} is independently C_1-C_6alkyl, oxo, -OR, -NR_2, -OC(O)NR_2 or -N(R)C(O)OR.

(2v) Y is Cak(C_0-C_6alkyl) optionally substituted by one -R^{Y1} group, wherein each -R^{Y1} is independently C_1-C_6alkyl, oxo, -OR, -NR_2, -OC(O)NR_2 or -N(R)C(O)OR.

(2w) Y is Cak(C_0-C_6alkyl) optionally substituted by one -R^{Y1} groups, wherein -R^{Y1} is oxo.

(2x) Y is Cak(C_0-C_6alkyl) optionally substituted by one -R^{Y1} groups, wherein -R^{Y1} is-OR.

(2y) Y is Cak(C_0-C_6alkyl) optionally substituted by one -R^{Y1} groups, wherein -R^{Y1} is-NR_2.

(2z) Y is Cak(C_0-C_6alkyl) optionally substituted by one -R^{Y1} groups, wherein -R^{Y1} is -OC(O)NR_2.

(2aa) Y is Cak(C_0-C_6alkyl) optionally substituted by one -R^{Y1} groups, wherein -R^{Y1} is -N(R)C(O)OR.

(2bb) Y is Cak(C_0-C_6alkyl) optionally substituted by one -R^{Y1} group, wherein -R^{Y1} is C_1-C_6alkyl.

(2cc) Y is Cak(C_0-C_6alkyl) optionally substituted by two -R^{Y1} groups, wherein each-R^{Y1} is independently C_1-C_6alkyl,

oxo, -OR, -NR_2, -$OC(O)NR_2$ or-N(R)C(O)OR.

(2dd) Y is Cak(C_0-C_6alkyl) optionally substituted by two -R^{Y1} groups, wherein each-R^{Y1} is independently C_1-C_6alkyl or -N(R)C(O)OR.

(2ee) Y is Cak(C_0-C_6alkyl) optionally substituted by two -R^{Y1} groups, wherein each-R^{Y1} is independently C_1-C_6alkyl or -$OC(O)NR_2$.

(2ff) Y is Cak(C_0-C_6alkyl) optionally substituted by two -R^{Y1} groups, wherein each-R^{Y1} is independently C_1-C_6alkyl or oxo.

(2gg) Y is Cak(C_0-C_6alkyl) optionally substituted by two -R^{Y1} groups, wherein each-R^{Y1} is independently C_1-C_6alkyl or -OR.

(2hh) Y is Cak(C_0-C_6alkyl) optionally substituted by two -R^{Y1} groups, wherein each-R^{Y1} is independently C_1-C_6alkyl or -NR_2.

(2ii) Y is Cak(C_0-C_6alkyl) optionally substituted by two -R^{Y1} groups, wherein each-R^{Y1} is independently C_1-C_6alkyl or -$OC(O)NR_2$.

(2jj) Y is any of groups **(2m) - (2ii),** wherein Cak(C_0-C_6alkyl) is Cak.

(2kk) Y is any of groups **(2m) - (2ii),** wherein Cak(C_0-C_6alkyl) is Cak(C_1alkyl).

(2ll) Y is any of groups **(2m) - (2ii),** wherein Cak(C_0-C_6alkyl) is Cak(C_2alkyl).

I^d - Z is selected from one of the following groups (3a) - (3xx):

[0020]

(3a) Z is unsubstituted C_1-C_6alkyl or Cak(C_0-C_6alkyl).

(3b) Z is C_1-C_6alkyl or Cak(C_0-C_6alkyl), each optionally substituted by one to three-R^{Z1} groups, wherein each -R^{Z1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, -$C(O)NR_2$, -$S(O)_2NR_2$, -$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -$OC(O)NR_2$, -N(R)C(O)OR, -$N(R)C(O)NR_2$, -$N(R)S(O)_2$R, -$OP(O)(OR)_2$ or -CH_2-OP(O)(OR).

(3c) Z is group **(3b),** wherein C_1-C_6alkyl and Cak(C_0-C_6alkyl) are each optionally substituted by one or two -R^{Z1} groups.

(3d) Z is group **(3b),** wherein C_1-C_6alkyl and Cak(C_0-C_6alkyl) are each optionally substituted by two or three -R^{Z1} groups.

(3e) Z is group **(3b),** wherein C_1-C_6alkyl and Cak(C_0-C_6alkyl) are each optionally substituted by one -R^{Z1} group.

(3f) Z is group **(3b),** wherein C_1-C_6alkyl and Cak(C_0-C_6alkyl) are each optionally substituted by two -R^{Z1} groups.

(3g) Z is group **(3b),** wherein C_1-C_6alkyl and Cak(C_0-C_6alkyl) are each optionally substituted by three -R^{Z1} groups.

(3h) Z is any of groups **(3b) - (3g),** wherein Z is C_1-C_6alkyl.

(3i) Z is any of groups **(3b) - (3g),** wherein Z is methyl, ethyl, propyl, butyl or pentyl.

(3j) Z is any of groups **(3b) - (3g),** wherein Z is methyl, ethyl, propyl or butyl.

(3k) Z is any of groups **(3b) - (3g),** wherein Z is methyl, ethyl or propyl.

(3l) Z is any of groups **(3b) - (3g),** wherein Z is methyl or ethyl.

(3m) Z is any of groups **(3b) - (3g),** wherein Z is methyl or butyl.

(3n) Z is any of groups **(3b) - (3g),** wherein Z is methyl.

(3o) Z is any of groups **(3b) - (3g),** wherein Z is butyl.

(3p) Z is any of groups **(3b) - (3g),** wherein Z is Cak(C_0-C_6alkyl).

(3q) Z is any of groups **(3b) - (3g),** wherein Z is Cak.

(3r) Z is any of groups **(3b) - (3g),** wherein Z is Cak(C_1alkyl).

(3s) Z is any of groups **(3b) - (3g),** wherein Z is Cak(C_2alkyl).

(3t) Z is any of groups **(3a) - (3s),** wherein Cak is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

(3u) Z is any of groups **(3a) - (3s),** wherein Cak is cyclopropyl, cyclobutyl or cyclopentyl.

(3v) Z is any of groups **(3a) - (3s),** wherein Cak is cyclopropyl or cyclobutyl.

(3w) Z is any of groups **(3a) - (3s),** wherein Cak is cyclopropyl.

(3x) Z is any of groups **(3a) - (3s),** wherein Cak is cyclobutyl.

(3y) Z is any of groups **(3a) - (3s),** wherein Cak is cyclopentyl.

(3z) Z is any of groups **(3a) - (3s),** wherein Cak is cyclohexyl.

(3aa) Z is any of groups **(3b) - (3z),** wherein each -R^{Z1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R,-C(O)OR, -$C(O)NR_2$, -$S(O)_2NR_2$, -$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -$OC(O)NR_2$, -N(R)C(O)OR, -$N(R)C(O)NR_2$, -$N(R)S(O)_2$R, -$OP(O)(OR)_2$or -CH_2-OP(O)(OR).

(3bb) Z is any of groups **(3b) - (3z),** wherein each -R^{Z1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, -C(O)R, -C(O)OR, -$C(O)NR_2$, -$S(O)_2NR_2$, -$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR,

$-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)(OR)_2$ or $-CH_2-OP(O)(OR)$.

(3cc) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, $-C_1$-C_6alkoxy, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$,$-OC(O)R$, $-N(R)C(O)R$, $-OC(O)OR$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)(OR)_2$or $-CH_2-OP(O)(OR)$.

(3dd) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, $-C_1$-C_6alkoxy, $-OC(O)R$, $-N(R)C(O)R$, $-OC(O)OR$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)(OR)_2$or $-CH_2-OP(O)(OR)$.

(3ee) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, $-C_1$-C_6alkoxy,$-OC(O)R$,$-N(R)C(O)R$,$-OC(O)OR$,$-OC(O)NR_2$,$-N(R)C(O)OR$,$-N(R)C(O)NR_2$ or $-N(R)S(O)_2R$.

(3ff) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, $-C_1$-C_6alkoxy, $-N(R)C(O)R$, $-N(R)C(O)OR$,$-N(R)C(O)NR_2$ or $-N(R)S(O)_2R$.

(3gg) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl or $-C_1$-C_6alkoxy.

(3hh) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl or $-C_1$-C_6alkoxy.

(3ii) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is independently halogen, C_1-C_6alkyl or C_1-C_6haloalkyl.

(3jj) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is independently halogen or C_1-C_6haloalkyl.

(3kk) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is independently halogen.

(3ll) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is independently fluro or chloro.

(3mm) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is chloro.

(3nn) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is fluro.

(3oo) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is independently C_1-C_6haloalkyl.

(3pp) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is independently fluoromethyl, difluoromethyl or trifluoromethyl.

(3qq) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is independently trifluoromethyl.

(3rr) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is independently C_1-C_6alkyl.

(3ss) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is independently methyl, ethyl, propyl, butyl or pentyl.

(3tt) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is independently methyl, ethyl, propyl, or butyl.

(3uu) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is independently methyl, ethyl or propyl.

(3vv) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is independently methyl or ethyl.

(3ww) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is independently methyl.

(3xx) Z is any of groups **(3b) - (3z),** wherein each $-R^{Z1}$ is independently ethyl.

[0021] Particular embodiments of this aspect of the invention comprise compounds of any one of the formulae (I) and (Ia) - (If), each as defined in each of the following rows (or a pharmaceutically acceptable salt, or *N*-oxide thereof, or a solvate or hydrate thereof), wherein each entry is a group number as defined above (e.g., **(2h)** refers to Y is unsubstituted Cak, and a dash "-" indicates that the variable is as defined in embodiment I_1 or defined according to any one of the applicable variable definitions **(1a)-(3xx)** [*e.g.*, when Z is a dash, it can be either as defined in any of embodiments I_1 - I_4 or any one of definitions **(3a)-(3xx)**]):

	(I)	X	Y	Z
(1)-1	(Ia)	(1a)	(2a)	(3a)
(1)-2	(Ia)	(1f)	(2d)	(3b)
(1)-3	(Ia)	(1g)	(2e)	(3c)
(1)-4	(Ia)	(1h)	(2h)	(3f)
(1)-5	(Ia)	(1i)	(2i)	(3h)
(1)-6	(Ia)	(1j)	(2l)	(3j)
(1)-7	(Ia)	(1k)	(2m)	(3m)
(1)-8	(Ia)	(1o)	(2r)	(3n)
(1)-9	(Ia)	(1p)	(2v)	(3o)
(1)-10	(Ia)	(1q)	(2aa)	(3p)
(1)-11	(Ia)	(1r)	(2bb)	(3q)
(1)-12	(Ia)	(1v)	(2cc)	(3v)
(1)-13	(Ia)	(1y)	(2ff)	(3w)
(1)-14	(Ia)	(1aa)	(2gg)	(3x)
(1)-15	(Ia)	(1dd)	(2hh)	(3aa)
(1)-16	(Ia)	(1ii)	(2ii)	(3ee)
(1)-17	(Ia)	(1kk)	(2jj)	(3ii)
(1)-18	(Ia)	(1ll)	(2kk)	(3kk)
(1)-19	(Ia)	(1mm)	(2ll)	(3oo)
(1)-20	(Ia)	(1nn)	(2i)	(3rr)
(1)-21	(Ia)	(1oo)	(2l)	(3v)
(1)-22	(Ia)	(1pp)	(2m)	(3w)
(1)-23	(Ia)	(1i)	(2r)	(3x)
(1)-24	(Ia)	(1j)	(2v)	(3aa)
(1)-25	(Ia)	(1k)	(2aa)	(3n)

	(I)	X	Y	Z
(1)-26	(Ia)	(1dd)	(2m)	(3aa)
(1)-27	(Ia)	(1ii)	(2r)	(3n)
(1)-28	(Ia)	(1kk)	(2v)	(3o)
(1)-29	(Ia)	(1f)	(2aa)	(3p)
(1)-30	(Ia)	(1g)	(2aa)	(3aa)
(1)-31	(Ia)	(1h)	(2m)	(3n)
(1)-32	(Ia)	(1i)	(2r)	(3o)
(1)-33	(Ia)	(1j)	(2e)	(3p)
(1)-34	(Ia)	(1k)	(2h)	(3m)
(1)-35	(Ia)	(1o)	(2i)	(3n)
(1)-36	(Ia)	(1y)	(2l)	(3o)
(1)-37	(Ia)	(1aa)	(2m)	(3p)
(1)-38	(Ia)	(1dd)	(2m)	(3q)
(1)-39	(Ia)	(1ii)	(2r)	(3v)
(1)-40	(Ia)	(1kk)	(2v)	(3w)
(1)-41	(Ia)	(1r)	(2aa)	(3x)
(1)-42	(Ia)	(1v)	(2m)	(3aa)
(1)-43	(Ia)	(1y)	(2r)	(3n)
(1)-44	(Ia)	(1aa)	(2v)	(3o)
(1)-45	(Ia)	(1dd)	(2aa)	(3p)
(1)-46	(Ia)	(1ii)	(2i)	(3q)
(1)-47	(Ia)	(1i)	(2l)	(3aa)
(1)-48	(Ia)	(1j)	(2m)	(3n)
(1)-49	(Ia)	(1k)	(2r)	(3o)
(1)-50	(Ia)	(1g)	(2v)	(3p)

	(I)	X	Y	Z
(1)-51	(Ib)	(1h)	(2aa)	(3b)
(1)-52	(Ib)	(1i)	(2aa)	(3c)
(1)-53	(Ib)	(1j)	(2m)	(3f)
(1)-54	(Ib)	(1k)	(2r)	(3h)
(1)-55	(Ib)	(1o)	(2e)	(3j)
(1)-56	(Ib)	(1i)	(2h)	(3m)
(1)-57	(Ib)	(1j)	(2i)	(3n)
(1)-58	(Ib)	(1k)	(2l)	(3o)
(1)-59	(Ib)	(1o)	(2m)	(3p)
(1)-60	(Ib)	(1p)	(2r)	(3q)
(1)-61	(Ib)	(1q)	(2v)	(3v)
(1)-62	(Ib)	(1r)	(2aa)	(3w)
(1)-63	(Ib)	(1v)	(2aa)	(3x)
(1)-64	(Ib)	(1y)	(2m)	(3aa)
(1)-65	(Ib)	(1aa)	(2r)	(3ee)
(1)-66	(Ib)	(1dd)	(2aa)	(3ii)
(1)-67	(Ib)	(1ii)	(2bb)	(3kk)
(1)-68	(Ib)	(1kk)	(2cc)	(3oo)
(1)-69	(Ib)	(1ll)	(2e)	(3rr)
(1)-70	(Ib)	(1mm)	(2h)	(3a)
(1)-71	(Ib)	(1nn)	(2i)	(3b)
(1)-72	(Ib)	(1oo)	(2l)	(3c)
(1)-73	(Ib)	(1pp)	(2m)	(3f)
(1)-74	(Ib)	(1a)	(2r)	(3h)
(1)-75	(Ib)	(1f)	(2m)	(3j)

	(I)	X	Y	Z
(1)-76	(Ib)	(1g)	(2r)	(3m)
(1)-77	(Ib)	(1h)	(2v)	(3n)
(1)-78	(Ib)	(1i)	(2aa)	(3o)
(1)-79	(Ib)	(1j)	(2m)	(3p)
(1)-80	(Ib)	(1k)	(2r)	(3q)
(1)-81	(Ib)	(1o)	(2v)	(3v)
(1)-82	(Ib)	(1y)	(2aa)	(3w)
(1)-83	(Ib)	(1aa)	(2h)	(3x)
(1)-84	(Ib)	(1dd)	(2i)	(3aa)
(1)-85	(Ib)	(1ii)	(2l)	(3ee)
(1)-86	(Ib)	(1kk)	(2m)	(3ii)
(1)-87	(Ib)	(1i)	(2r)	(3kk)
(1)-88	(Ib)	(1j)	(2r)	(3oo)
(1)-89	(Ib)	(1k)	(2v)	(3rr)
(1)-90	(Ib)	(1o)	(2aa)	(3v)
(1)-91	(Ib)	(1y)	(2h)	(3w)
(1)-92	(Ib)	(1aa)	(2i)	(3x)
(1)-93	(Ib)	(1dd)	(2l)	(3aa)
(1)-94	(Ib)	(1ii)	(2m)	(3o)
(1)-95	(Ib)	(1kk)	(2r)	(3p)
(1)-96	(Ib)	(1a)	(2l)	(3q)
(1)-97	(Ib)	(1f)	(2m)	(3v)
(1)-98	(Ib)	(1g)	(2r)	(3w)
(1)-99	(Ib)	(1h)	(2v)	(3x)
(1)-100	(Ib)	(1i)	(2aa)	(3aa)

	(I)	X	Y	Z
(1)-101	(Ic)	(1j)	(2e)	(3v)
(1)-102	(Ic)	(1k)	(2h)	(3w)
(1)-103	(Ic)	(1o)	(2i)	(3x)
(1)-104	(Ic)	(1p)	(2l)	(3aa)
(1)-105	(Ic)	(1q)	(2m)	(3b)
(1)-106	(Ic)	(1r)	(2r)	(3c)
(1)-107	(Ic)	(1v)	(2v)	(3f)
(1)-108	(Ic)	(1y)	(2aa)	(3h)
(1)-109	(Ic)	(1aa)	(2aa)	(3j)
(1)-110	(Ic)	(1dd)	(2aa)	(3m)
(1)-111	(Ic)	(1ii)	(2bb)	(3n)
(1)-112	(Ic)	(1kk)	(2cc)	(3o)
(1)-113	(Ic)	(1ll)	(2e)	(3p)
(1)-114	(Ic)	(1mm)	(2r)	(3q)
(1)-115	(Ic)	(1nn)	(2v)	(3v)
(1)-116	(Ic)	(1oo)	(2aa)	(3w)
(1)-117	(Ic)	(1pp)	(2bb)	(3x)
(1)-118	(Ic)	(1y)	(2cc)	(3aa)
(1)-119	(Ic)	(1aa)	(2e)	(3ee)
(1)-120	(Ic)	(1dd)	(2h)	(3ii)
(1)-121	(Ic)	(1ii)	(2i)	(3kk)
(1)-122	(Ic)	(1kk)	(2l)	(3oo)
(1)-123	(Ic)	(1v)	(2m)	(3rr)
(1)-124	(Ic)	(1y)	(2r)	(3aa)
(1)-125	(Ic)	(1aa)	(2v)	(3n)

	(I)	X	Y	Z
(1)-126	(Ic)	(1dd)	(2aa)	(3o)
(1)-127	(Ic)	(1ii)	(2bb)	(3p)
(1)-128	(Ic)	(1a)	(2cc)	(3aa)
(1)-129	(Ic)	(1f)	(2ff)	(3a)
(1)-130	(Ic)	(1g)	(2gg)	(3b)
(1)-131	(Ic)	(1h)	(2hh)	(3c)
(1)-132	(Ic)	(1i)	(2ii)	(3f)
(1)-133	(Ic)	(1j)	(2jj)	(3h)
(1)-134	(Ic)	(1k)	(2kk)	(3j)
(1)-135	(Ic)	(1o)	(2ll)	(3m)
(1)-136	(Ic)	(1f)	(2i)	(3n)
(1)-137	(Ic)	(1g)	(2l)	(3o)
(1)-138	(Ic)	(1h)	(2m)	(3p)
(1)-139	(Ic)	(1i)	(2i)	(3q)
(1)-140	(Ic)	(1j)	(2l)	(3v)
(1)-141	(Ic)	(1k)	(2m)	(3w)
(1)-142	(Ic)	(1o)	(2r)	(3x)
(1)-143	(Ic)	(1h)	(2v)	(3aa)
(1)-144	(Ic)	(1i)	(2aa)	(3ee)
(1)-145	(Ic)	(1j)	(2aa)	(3ii)
(1)-146	(Ic)	(1k)	(2bb)	(3kk)
(1)-147	(Ic)	(1o)	(2cc)	(3oo)
(1)-148	(Ic)	(1p)	(2e)	(3rr)
(1)-149	(Ic)	(1q)	(2h)	(3aa)
(1)-150	(Ic)	(1r)	(2i)	(3n)

	(I)	X	Y	Z
(1)-151	(Id)	(1v)	(2l)	(3o)
(1)-152	(Id)	(1y)	(2m)	(3p)
(1)-153	(Id)	(1aa)	(2r)	(3m)
(1)-154	(Id)	(1dd)	(2v)	(3n)
(1)-155	(Id)	(1ii)	(2aa)	(3o)
(1)-156	(Id)	(1kk)	(2bb)	(3p)
(1)-157	(Id)	(1ll)	(2cc)	(3q)
(1)-158	(Id)	(1mm)	(2ff)	(3v)
(1)-159	(Id)	(1nn)	(2gg)	(3w)
(1)-160	(Id)	(1oo)	(2hh)	(3x)
(1)-161	(Id)	(1pp)	(2ii)	(3aa)
(1)-162	(Id)	(1y)	(2jj)	(3aa)
(1)-163	(Id)	(1aa)	(2kk)	(3n)
(1)-164	(Id)	(1dd)	(2ll)	(3o)
(1)-165	(Id)	(1ii)	(2cc)	(3p)
(1)-166	(Id)	(1kk)	(2ff)	(3a)
(1)-167	(Id)	(1f)	(2gg)	(3b)
(1)-168	(Id)	(1g)	(2hh)	(3c)
(1)-169	(Id)	(1h)	(2r)	(3f)
(1)-170	(Id)	(1i)	(2v)	(3h)
(1)-171	(Id)	(1j)	(2aa)	(3j)
(1)-172	(Id)	(1k)	(2bb)	(3m)
(1)-173	(Id)	(1o)	(2cc)	(3n)
(1)-174	(Id)	(1r)	(2ff)	(3o)
(1)-175	(Id)	(1v)	(2l)	(3p)

	(I)	X	Y	Z
(1)-176	(Id)	(1y)	(2m)	(3q)
(1)-177	(Id)	(1aa)	(2r)	(3v)
(1)-178	(Id)	(1dd)	(2v)	(3w)
(1)-179	(Id)	(1ii)	(2aa)	(3x)
(1)-180	(Id)	(1kk)	(2m)	(3aa)
(1)-181	(Id)	(1dd)	(2r)	(3ee)
(1)-182	(Id)	(1ii)	(2v)	(3ii)
(1)-183	(Id)	(1kk)	(2aa)	(3kk)
(1)-184	(Id)	(1r)	(2bb)	(3oo)
(1)-185	(Id)	(1v)	(2cc)	(3rr)
(1)-186	(Id)	(1y)	(2m)	(3v)
(1)-187	(Id)	(1aa)	(2r)	(3w)
(1)-188	(Id)	(1dd)	(2v)	(3x)
(1)-189	(Id)	(1ii)	(2aa)	(3aa)
(1)-190	(Id)	(1kk)	(2bb)	(3ee)
(1)-191	(Id)	(1y)	(2cc)	(3o)
(1)-192	(Id)	(1aa)	(2l)	(3p)
(1)-193	(Id)	(1dd)	(2m)	(3a)
(1)-194	(Id)	(1ii)	(2r)	(3b)
(1)-195	(Id)	(1kk)	(2v)	(3v)
(1)-196	(Id)	(1i)	(2aa)	(3w)
(1)-197	(Id)	(1j)	(2bb)	(3x)
(1)-198	(Id)	(1k)	(2cc)	(3aa)
(1)-199	(Id)	(1i)	(2ff)	(3o)
(1)-200	(Id)	(1j)	(2gg)	(3p)

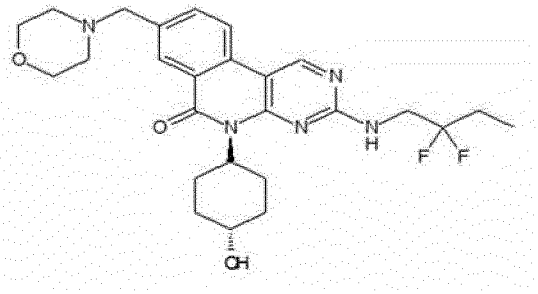
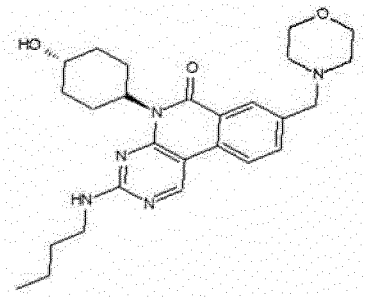
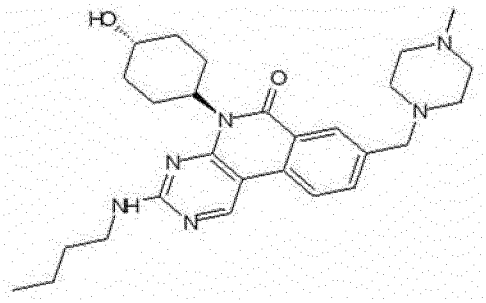
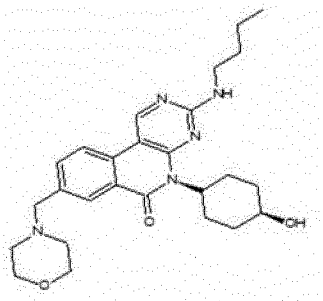
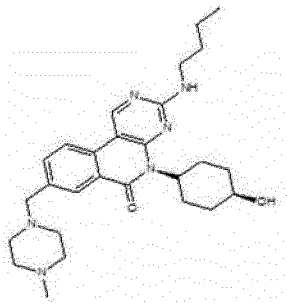
	(I)	X	Y	Z
(1)-201	(Ie)	(1k)	(2hh)	(3q)
(1)-202	(Ie)	(1f)	(2ii)	(3v)
(1)-203	(Ie)	(1g)	(2jj)	(3w)
(1)-204	(Ie)	(1h)	(2kk)	(3x)
(1)-205	(Ie)	(1i)	(2ll)	(3aa)
(1)-206	(Ie)	(1j)	(2e)	(3o)
(1)-207	(Ie)	(1k)	(2h)	(3p)
(1)-208	(Ie)	(1o)	(2i)	(3a)
(1)-209	(Ie)	(1p)	(2l)	(3b)
(1)-210	(Ie)	(1q)	(2m)	(3b)
(1)-211	(Ie)	(1r)	(2cc)	(3c)
(1)-212	(Ie)	(1v)	(2ff)	(3f)
(1)-213	(Ie)	(1y)	(2e)	(3h)
(1)-214	(Ie)	(1aa)	(2h)	(3j)
(1)-215	(Ie)	(1dd)	(2i)	(3m)
(1)-216	(Ie)	(1ii)	(2l)	(3n)
(1)-217	(Ie)	(1r)	(2m)	(3o)
(1)-218	(Ie)	(1v)	(2r)	(3p)
(1)-219	(Ie)	(1y)	(2v)	(3q)
(1)-220	(Ie)	(1aa)	(2aa)	(3v)
(1)-221	(Ie)	(1aa)	(2bb)	(3w)
(1)-222	(Ie)	(1dd)	(2cc)	(3x)
(1)-223	(Ie)	(1ii)	(2ff)	(3aa)
(1)-224	(Ie)	(1kk)	(2gg)	(3ee)
(1)-225	(Ie)	(1g)	(2hh)	(3ii)

	(I)	X	Y	Z
(1)-226	(Ie)	(1h)	(2ii)	(3kk)
(1)-227	(Ie)	(1i)	(2jj)	(3oo)
(1)-228	(Ie)	(1j)	(2kk)	(3rr)
(1)-229	(Ie)	(1k)	(2ll)	(3m)
(1)-230	(Ie)	(1o)	(2e)	(3n)
(1)-231	(Ie)	(1p)	(2h)	(3o)
(1)-232	(Ie)	(1q)	(2i)	(3p)
(1)-233	(Ie)	(1r)	(2l)	(3q)
(1)-234	(Ie)	(1v)	(2m)	(3v)
(1)-235	(Ie)	(1y)	(2cc)	(3w)
(1)-236	(Ie)	(1aa)	(2ff)	(3x)
(1)-237	(Ie)	(1dd)	(2e)	(3aa)
(1)-238	(Ie)	(1ii)	(2h)	(3o)
(1)-239	(Ie)	(1kk)	(2i)	(3p)
(1)-240	(Ie)	(1ll)	(2l)	(3q)
(1)-241	(Ie)	(1mm)	(2m)	(3v)
(1)-242	(Ie)	(1nn)	(2aa)	(3w)
(1)-243	(Ie)	(1oo)	(2bb)	(3x)
(1)-244	(Ie)	(1pp)	(2cc)	(3aa)
(1)-245	(Ie)	(1r)	(2ff)	(3ee)
(1)-246	(Ie)	(1v)	(2e)	(3ii)
(1)-247	(Ie)	(1y)	(2h)	(3kk)
(1)-248	(Ie)	(1aa)	(2i)	(3oo)
(1)-249	(Ie)	(1f)	(2l)	(3rr)
(1)-250	(Ie)	(1g)	(2m)	(3o)

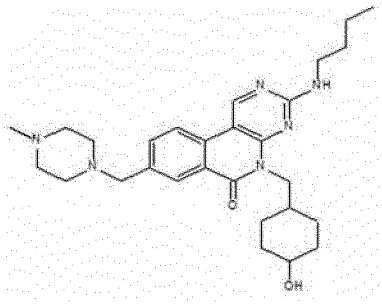
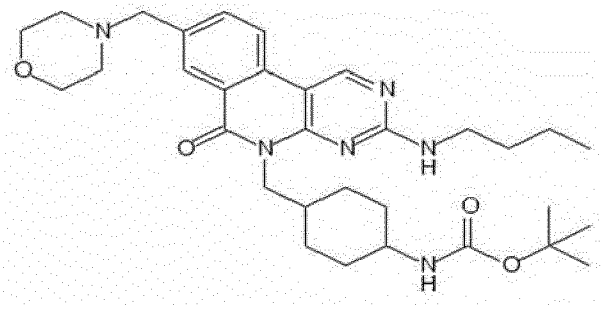
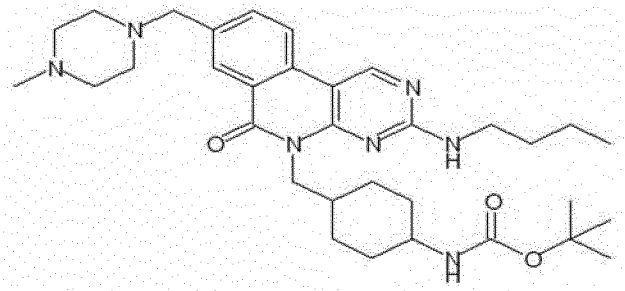
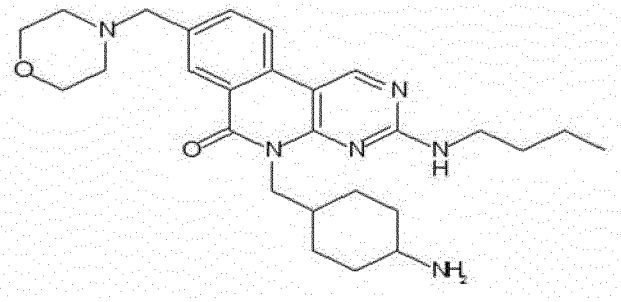
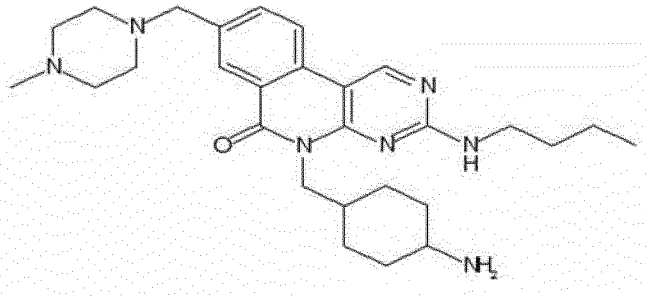
	(I)	X	Y	Z
(1)-251	(If)	(1h)	(2r)	(3p)
(1)-252	(If)	(1i)	(2v)	(3a)
(1)-253	(If)	(1j)	(2aa)	(3b)
(1)-254	(If)	(1k)	(2bb)	(3o)
(1)-255	(If)	(1o)	(2cc)	(3p)
(1)-256	(If)	(1v)	(2ff)	(3q)
(1)-257	(If)	(1y)	(2gg)	(3v)
(1)-258	(If)	(1aa)	(2hh)	(3w)
(1)-259	(If)	(1dd)	(2ii)	(3x)
(1)-260	(If)	(1ii)	(2jj)	(3aa)
(1)-261	(If)	(1r)	(2kk)	(3n)
(1)-262	(If)	(1v)	(2ll)	(3o)
(1)-263	(If)	(1y)	(2cc)	(3p)
(1)-264	(If)	(1aa)	(2ff)	(3q)
(1)-265	(If)	(1dd)	(2gg)	(3v)
(1)-266	(If)	(1ii)	(2hh)	(3w)
(1)-267	(If)	(1kk)	(2e)	(3x)
(1)-268	(If)	(1h)	(2h)	(3aa)
(1)-269	(If)	(1i)	(2i)	(3ee)
(1)-270	(If)	(1j)	(2l)	(3ii)
(1)-271	(If)	(1k)	(2m)	(3kk)
(1)-272	(If)	(1o)	(2d)	(3oo)
(1)-273	(If)	(1p)	(2e)	(3rr)
(1)-274	(If)	(1q)	(2h)	(3v)
(1)-275	(If)	(1r)	(2i)	(3w)

	(I)	X	Y	Z
(1)-276	(If)	(1v)	(2l)	(3x)
(1)-277	(If)	(1y)	(2m)	(3aa)
(1)-278	(If)	(1aa)	(2r)	(3m)
(1)-279	(If)	(1dd)	(2v)	(3n)
(1)-280	(If)	(1ii)	(2aa)	(3o)
(1)-281	(If)	(1kk)	(2bb)	(3p)
(1)-282	(If)	(1ll)	(2cc)	(3q)
(1)-283	(If)	(1mm)	(2ff)	(3v)
(1)-284	(If)	(1nn)	(2gg)	(3w)
(1)-285	(If)	(1oo)	(2hh)	(3x)
(1)-286	(If)	(1pp)	(2ii)	(3aa)
(1)-287	(If)	(1r)	(2jj)	(3b)
(1)-288	(If)	(1v)	(2kk)	(3c)
(1)-289	(If)	(1y)	(2ll)	(3f)
(1)-290	(If)	(1aa)	(2cc)	(3h)
(1)-291	(If)	(1dd)	(2ff)	(3j)
(1)-292	(If)	(1ii)	(2gg)	(3m)
(1)-293	(If)	(1kk)	(2hh)	(3n)
(1)-294	(If)	(1aa)	(2h)	(3o)
(1)-295	(If)	(1dd)	(2i)	(3p)
(1)-296	(If)	(1ii)	(2l)	(3q)
(1)-297	(If)	(1r)	(2m)	(3v)
(1)-298	(If)	(1v)	(2v)	(3w)
(1)-299	(If)	(1y)	(2aa)	(3x)
(1)-300	(If)	(1aa)	(2bb)	(3aa)

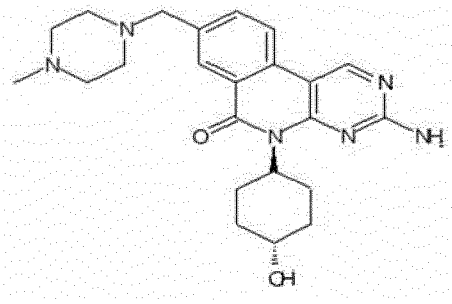
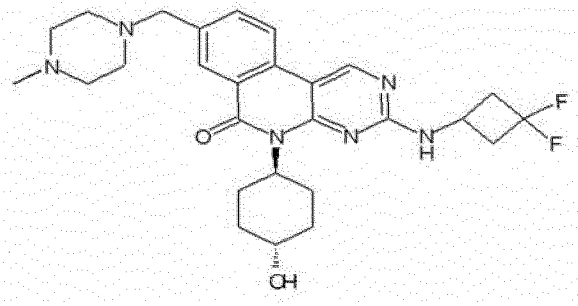
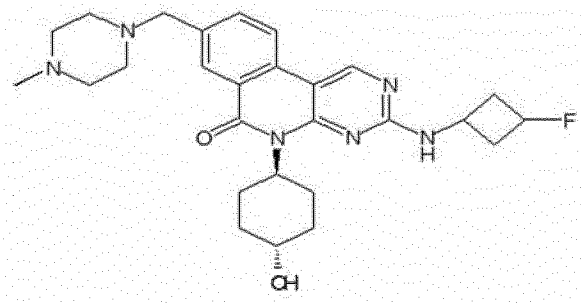
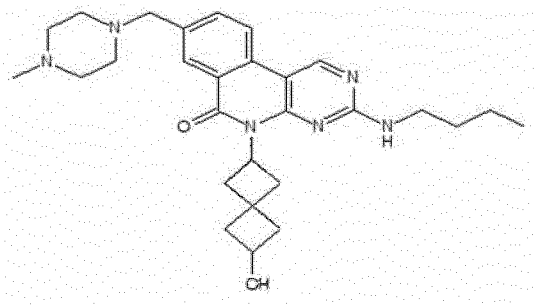
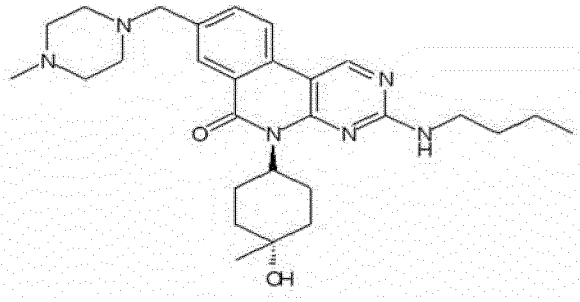
[0022] In some embodiments, the compound of formulae (I) or (Ia) - (If) is one of the following compounds (or a pharmaceutically acceptable salt, or N-oxide thereof, or a solvate or hydrate thereof):

No.	Structure	Name
1		trans-3-((2,2-Difluorobutyl)amino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one
2		trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one
3		*trans*-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido [4,5-c]isoquinolin-6(5H)-one
4		cis-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one
5		cis-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido [4,5-c]isoquinolin-6(5H)-one

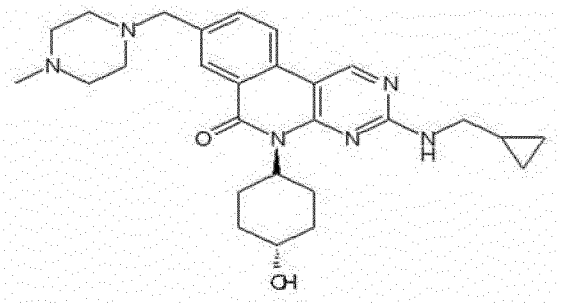
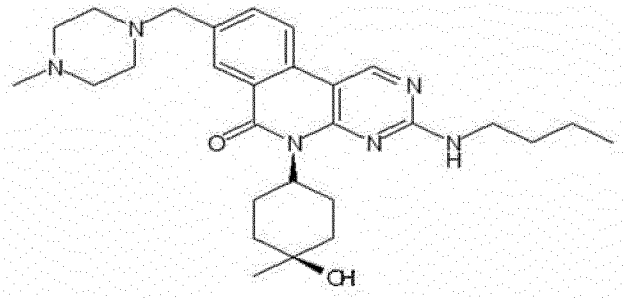
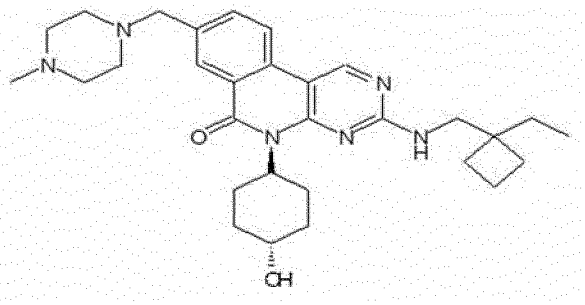
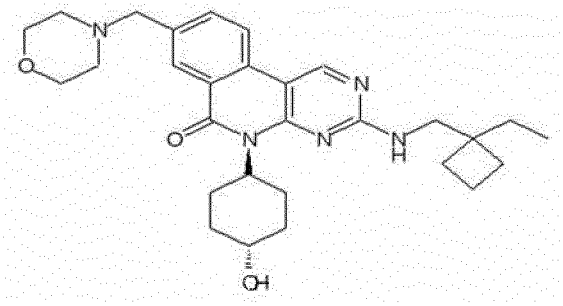
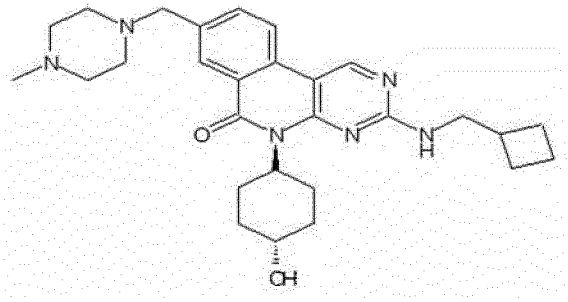
(continued)

No.	Structure	Name
6		3-(Butylamino)-5-((4-hydroxycyclohexyl)methyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido [4,5-c]isoquinolin-6(5H)-one
7		tert-Butyl (4-((3-(butylamino)-8-(morpholinomethyl)-6-oxopyrimido [4,5-c]isoquinolin-5(6H)-yl)methyl) cyclohexyl)carbamat e
8		tert-Butyl (4-((3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5 (6H)-yl) methyl)cyclohexyl)carbamat e
9		5-((4-Aminocyclohexyl)methyl)-3-(butylamino)-8-(morpholinomethyl) pyrimido[4, 5-c]isoquinolin-6(5H)-one
10		5-((4-Aminocyclohexyl)methyl)-3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6 (5H)-one

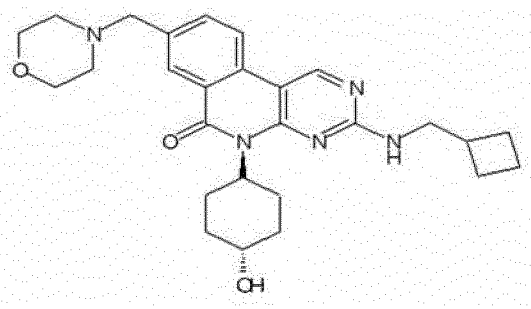
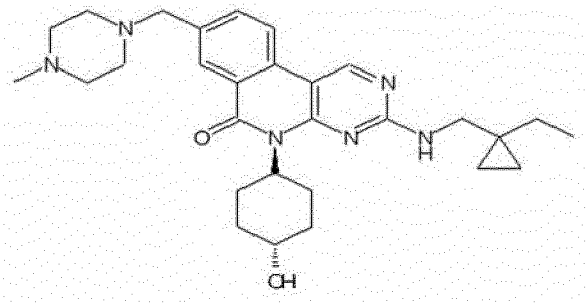
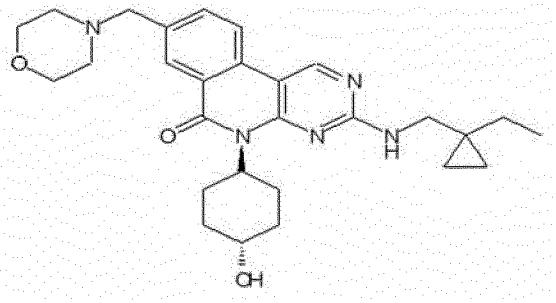
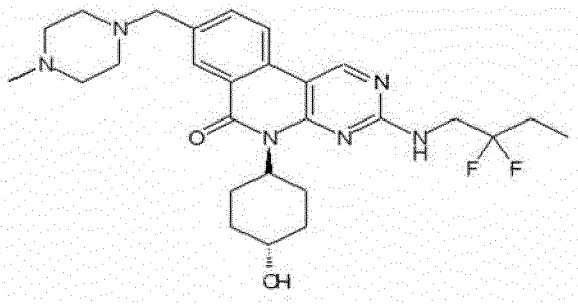
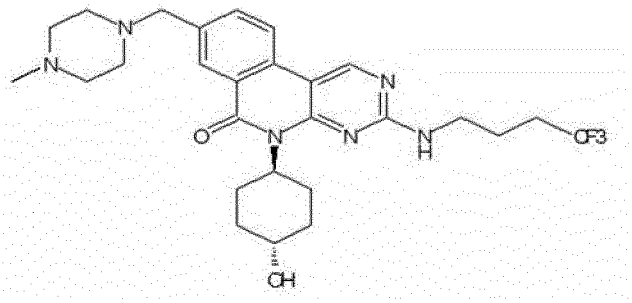
(continued)

No.	Structure	Name
11		trans-3-Amino-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one
12		trans-3-((3,3-Difluorocyclobutyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one
13		trans-3-((3-Fluorocyclobutyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one
14		3 -(Butyl amino)-5 -(6-hydroxyspiro[3.3]heptan-2-yl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one
15		trans-3-(Butylamino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

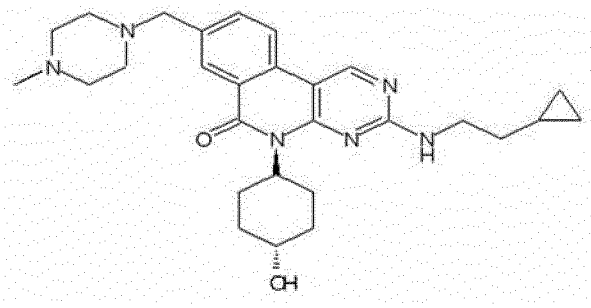
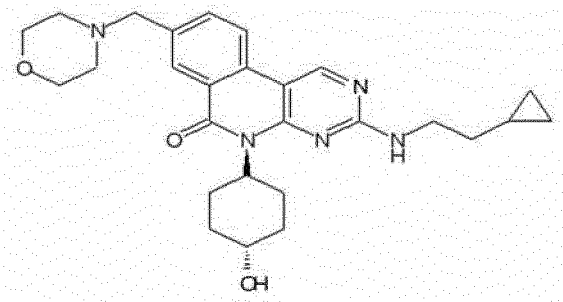
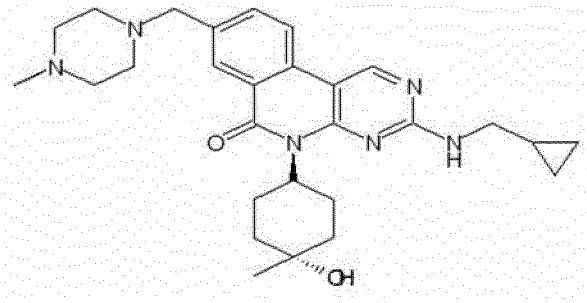
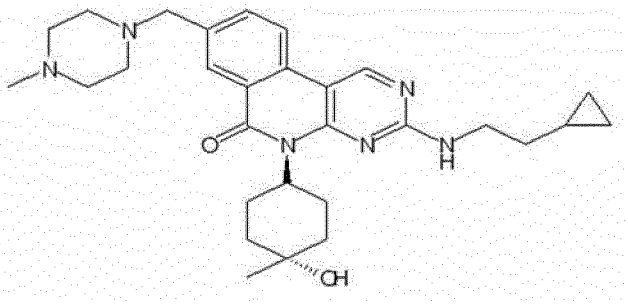
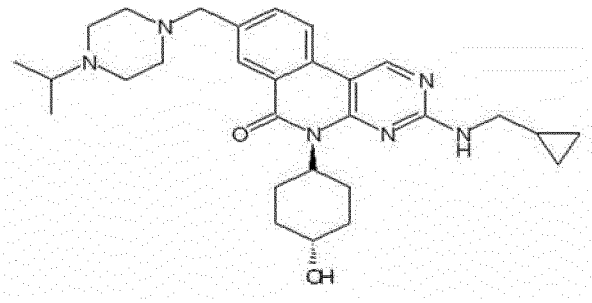
(continued)

No.	Structure	Name
16		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one
17		cis-3-(Butylamino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one
18		trans-3-(((1-Ethylcyclobutyl)methyl) amino) -5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one
19		trans-3-(((1-Ethylcyclobutyl)methyl) amino) -5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one
20		trans-3-(((1-Ethylcyclobutyl)methyl) amino) -5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one

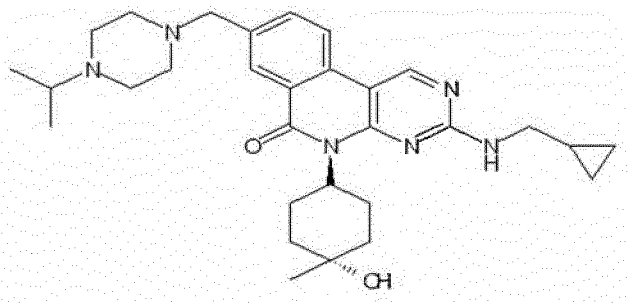
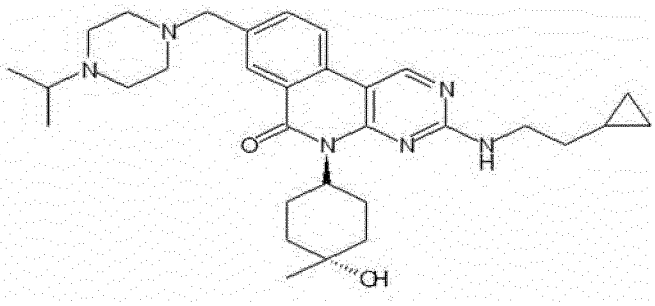
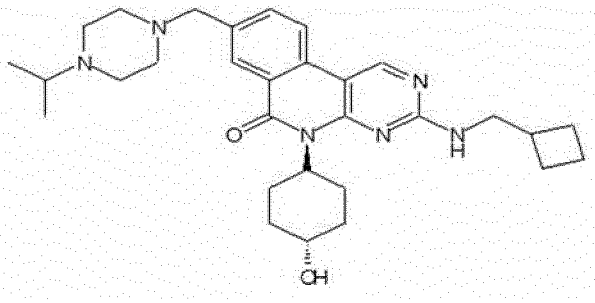
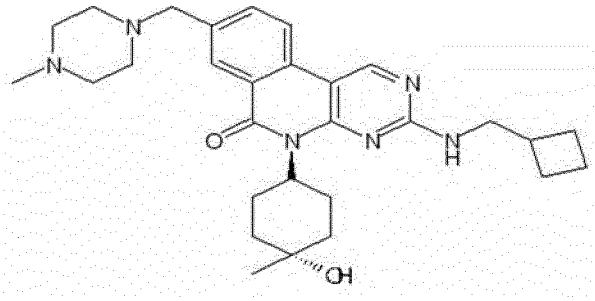
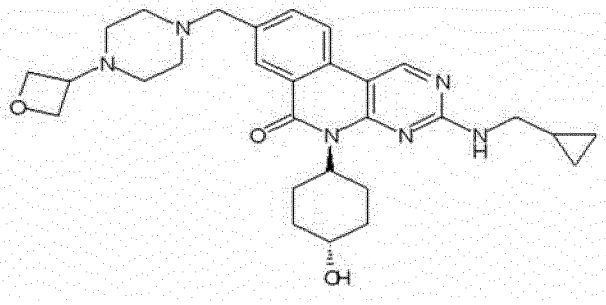
(continued)

No.	Structure	Name
21		trans-3-((Cyclobutylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one
22		trans-3-(((1-Ethylcyclopropyl)methyl) amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido [4,5-c]isoquinolin-6(5H)-one
23		trans-3-(((1-Ethylcyclopropyl)methyl) amino)-5-((4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one
24		trans-3-((2,2-Difluorobutyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido [4,5-c]isoquinolin-6(5H)-one
25		trans-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)-3 -((4,4,4-trifluorobutyl)amino)pyrimido[4,5-c] isoquinolin-6(5H)-one

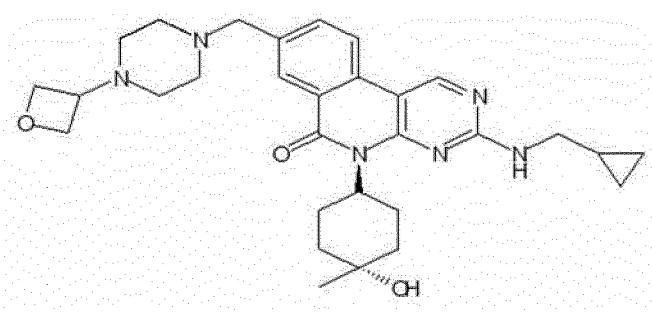
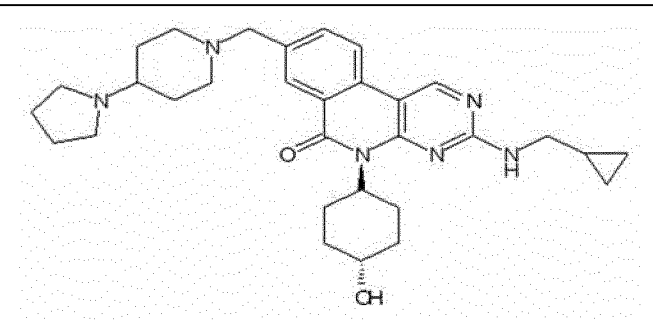
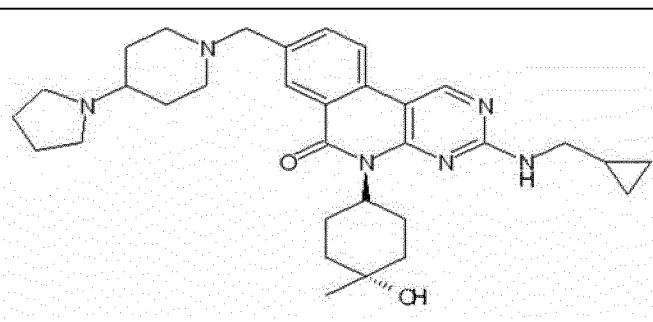
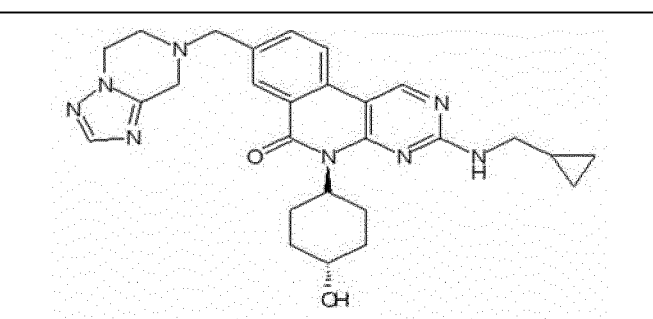
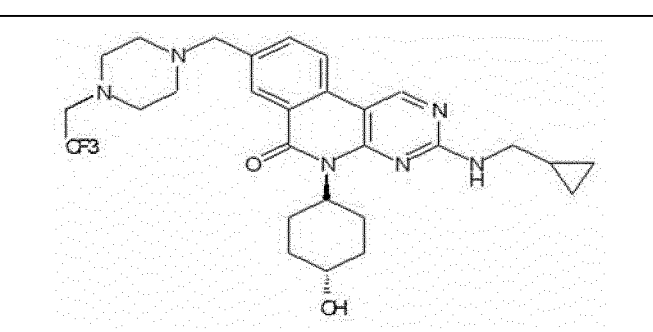
(continued)

No.	Structure	Name
26		trans-3-((2-Cyclopropylethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one
27		trans-3-((2-Cyclopropylethyl)amino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4, 5-c]isoquinolin-6(5H)-one
28		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one
29		trans-3-((2-Cyclopropylethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one
30		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-isopropylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

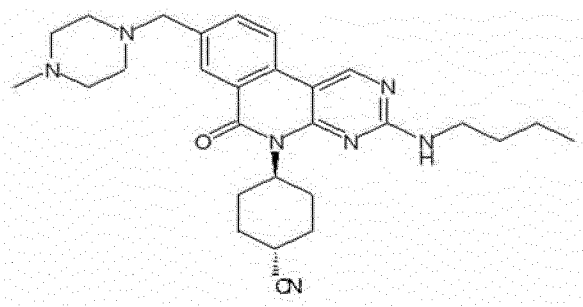
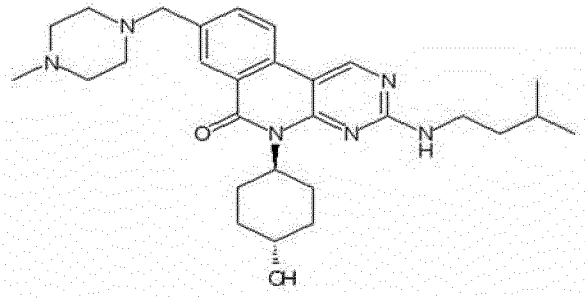
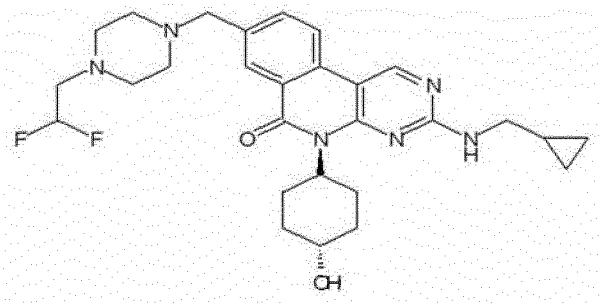
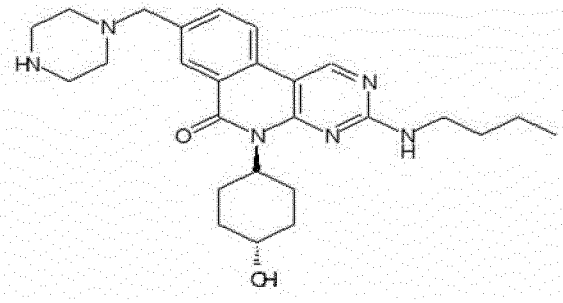
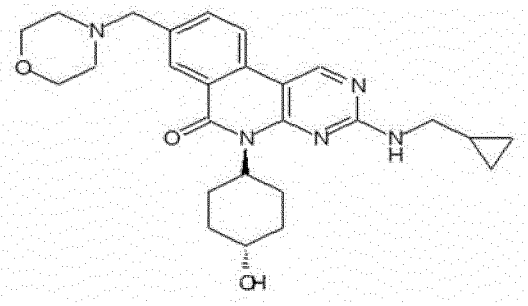
(continued)

No.	Structure	Name
31		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-isopropylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one
32		trans-3-((2-Cyclopropylethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-isopropylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one
33		trans-3-((Cyclobutylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-isopropylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one
34		trans-3-((Cyclobutylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one
35		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-(oxetan-3-yl)piperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

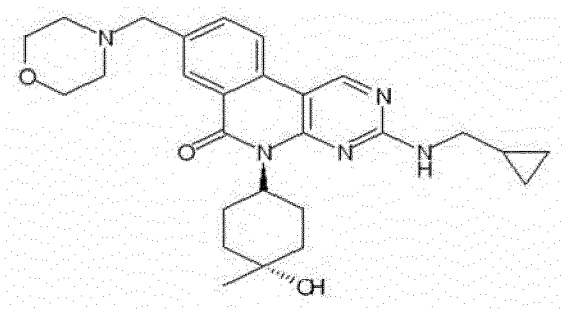
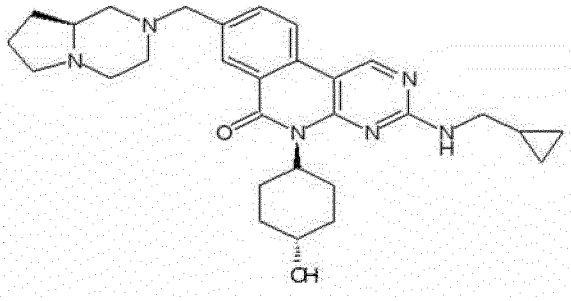
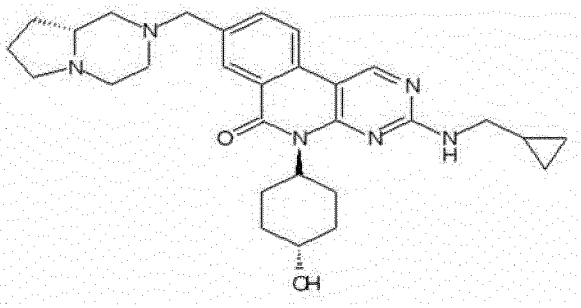
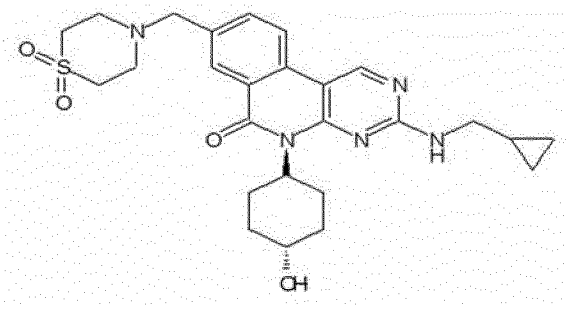
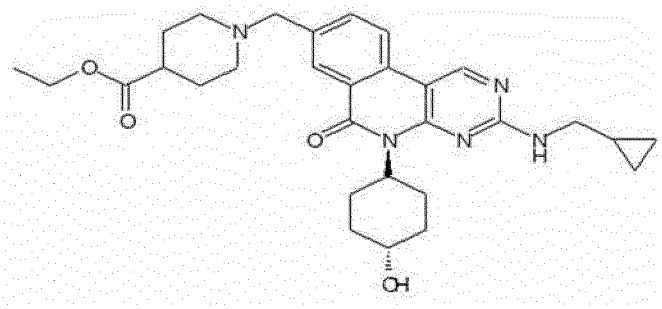
(continued)

No.	Structure	Name
36		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-(oxetan-3-yl)piperazin-1-yl) methyl)pyrimido[4,5-c]isoquinolin-6 (5H)-one
37		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-(pyrrolidin-1-yl)piperidin-1-yl) methyl)pyrimido[4,5-c]isoquinolin-6 (5H)-one
38		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-(pyrrolidin-1-yl)piperidin-1-yl) methyl)pyrimido[4,5-c]isoquinolin-6 (5H)-one
39		trans-3-((Cyclopropylmethyl)amino)-8-((5,6-dihydro-[1,2,4]triazolo[1,5-a] pyrazin-7(8H)-yl)methyl)-5-(4-hydroxycyclohexyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one
40		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-(2,2,2-trifluoroethyl)piperazin-1-yl)methyl) pyrimido[4,5-c]isoquinolin-6(5H)-one

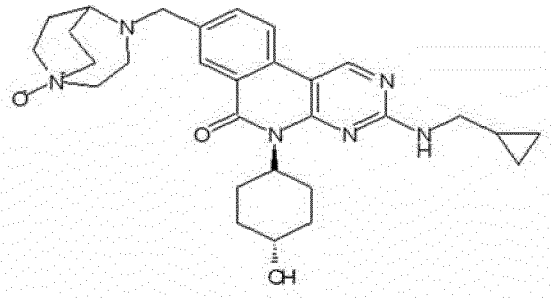
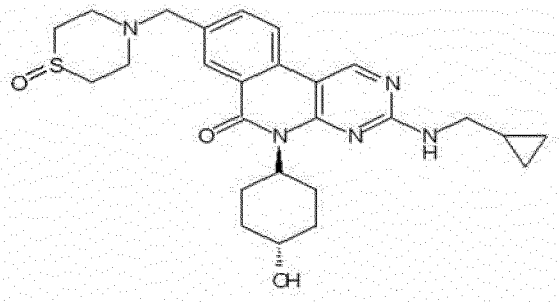
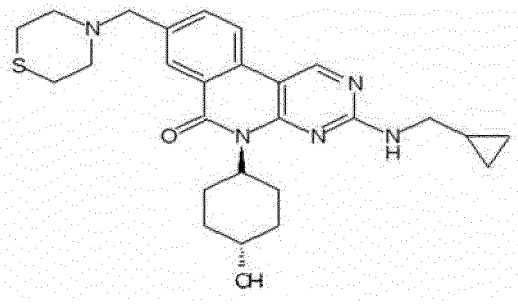
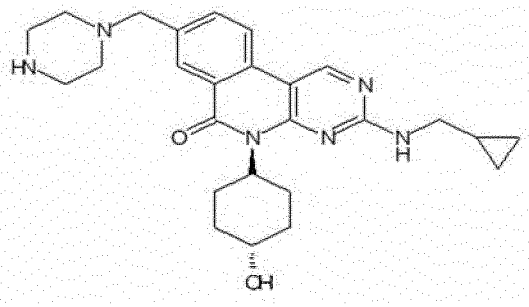
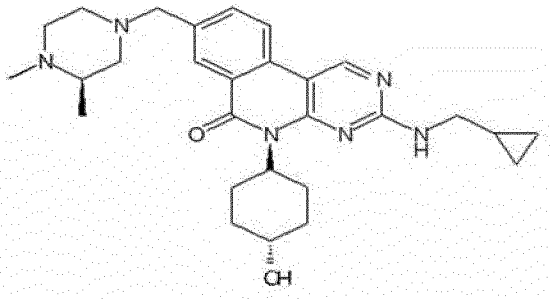
(continued)

No.	Structure	Name
41		trans-(3 -(butylamino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl) cyclohexane-1-carbonitrile
42		trans-5-(4-hydroxycyclohexyl)-3-(isopentylamino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido [4,5-c]isoquinolin-6(5H)-one
43		trans-3-((Cyclopropylmethyl)amino)-8-((4-(2,2-difluoroethyl)piperazin-1-yl) methyl)-5-(4-hydroxycyclohexyl) pyrimido[4, 5-c]isoquinolin-6(5H)-one
44		trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(piperazin-1-ylmethyl)pyrimido[4,5-c]isoquinolin-6 (5H)-one
45		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one

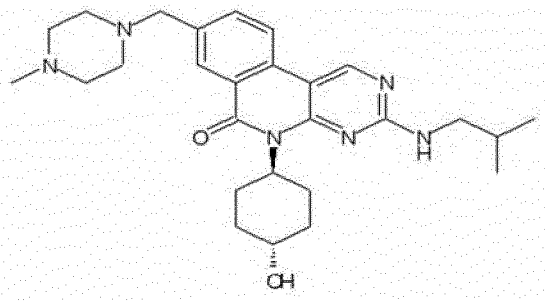
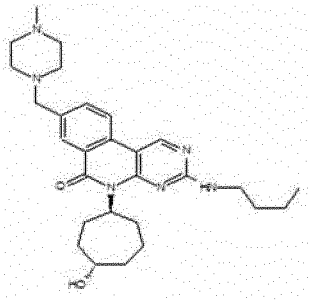
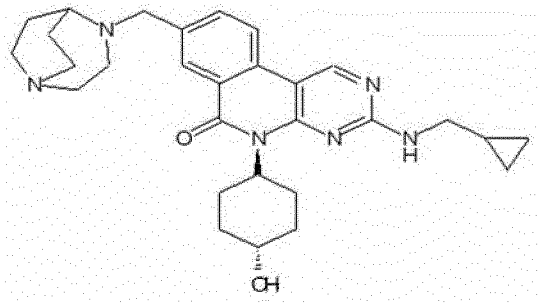
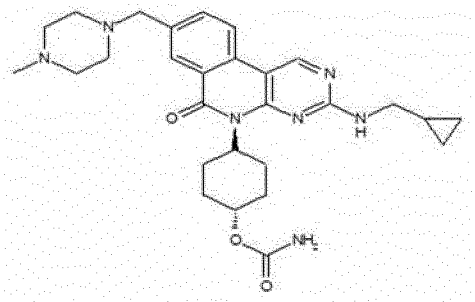
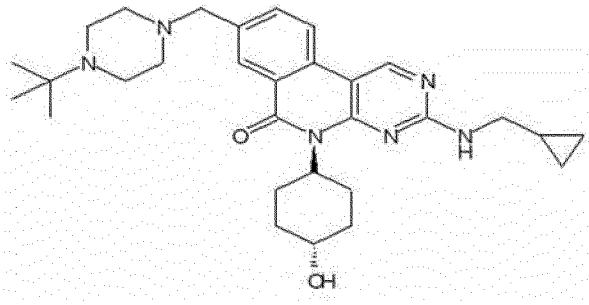
(continued)

No.	Structure	Name
46		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-(morpholinomethyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one
47		trans-3-((Cyclopropylmethyl)amino)-8-(((S)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)methyl)-5-(4-hydroxycyclohexyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one
48		trans-3-((Cyclopropylmethyl)amino)-8-(((R)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)methyl)-5-(4-hydroxycyclohexyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one
49		trans-3-((Cyclopropylmethyl)amino)-8-((1,1-dioxidothiomorpholino)methyl)-5-(4-hydroxycyclohexyl)pyrimido[4, 5-c]isoquinolin-6(5H)-one
50		trans-Ethyl 1-((3-((Cyclopropylmethyl) amino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methyl)piperidine-4-carboxylate

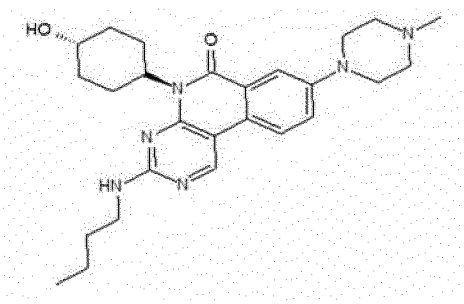
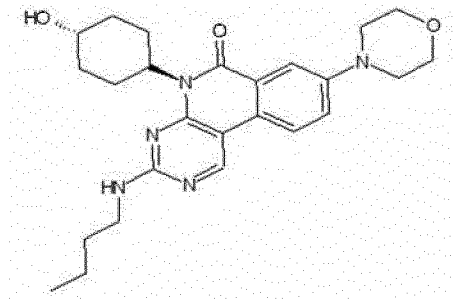
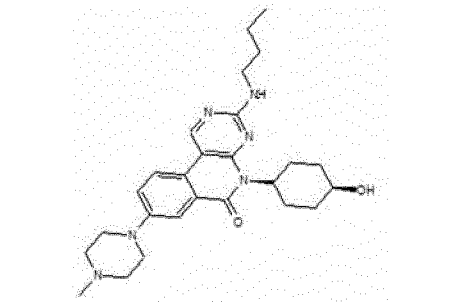
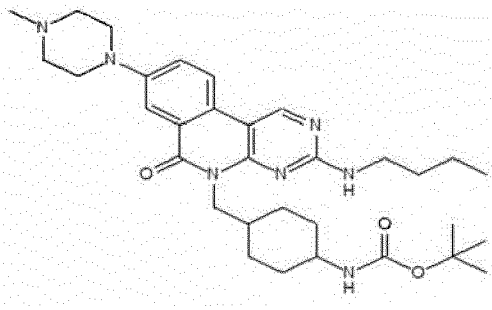
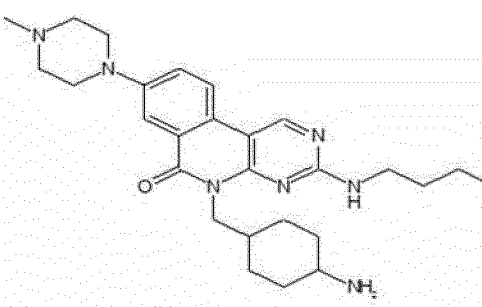
(continued)

No.	Structure	Name
51		trans-4-((3-((Cyclopropylmethyl) amino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methyl)-1,4-diazabicyclo[3.2.2] nonane 1-oxide
52		trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((1-oxidothiomorpholino)methyl)py rimido [4,5-c]isoquinolin-6(5H)-one
53		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(thiomorpholinomethyl)pyrimid o[4,5-c]isoquinolin-6(5H)-one
54		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(piperazin-1-ylmethyl)pyrimido[4,5-c]isoquinolin-6 (5H)-one
55		trans-3-((Cyclopropylmethyl)amino)-8-(((R)-3,4-dimethylpiperazin-1-yl) methyl)-5-(4-hydroxycyclohexyl) pyrimido[4, 5-c]isoquinolin-6(5H)-one

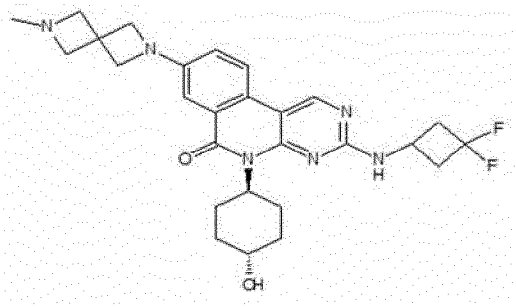
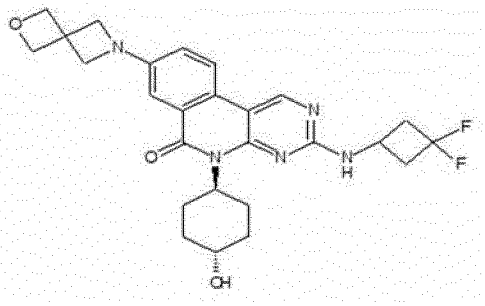
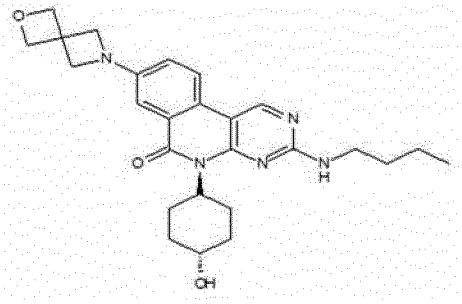
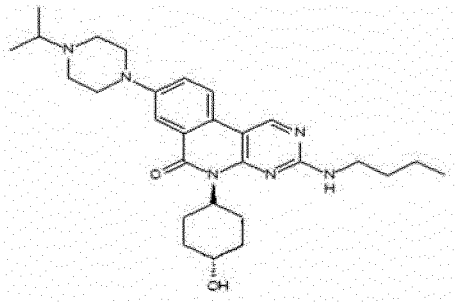
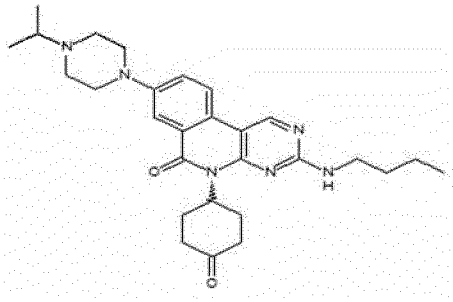
(continued)

No.	Structure	Name
56		trans-5-(4-Hydroxycyclohexyl)-3-(isobutylamino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one
57		3-(Butylamino)-5-((1S,4S)-4-hydroxycycloheptyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one
58		trans-8-((1,4-Diazabicyclo[3.2.2]nonan-4-yl)methyl)-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4, 5-c]isoquinolin-6(5H)-one
59		trans-4-(3-((Cyclopropylmethyl)amino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5 (6H)-yl) cyclohexyl carbamate
60		trans-8-((4-(tert-butyl)piperazin-1-yl)methyl)-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4, 5-c]isoquinolin-6(5H)-one

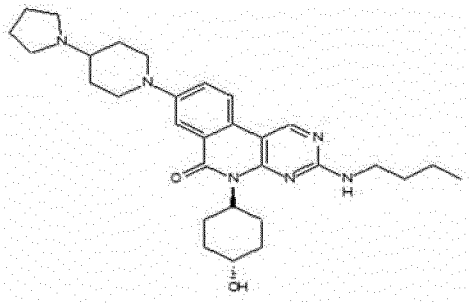
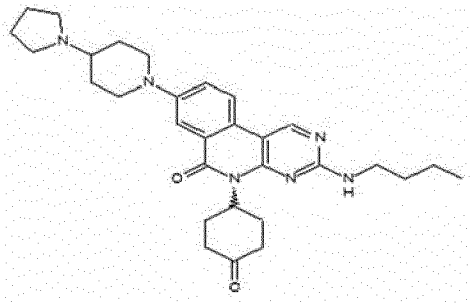
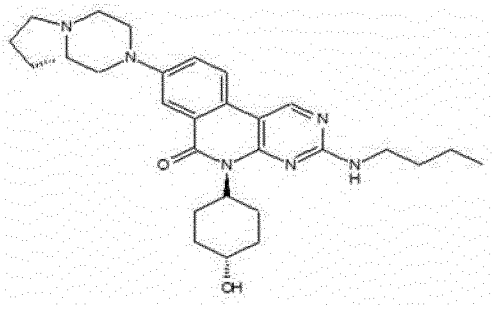
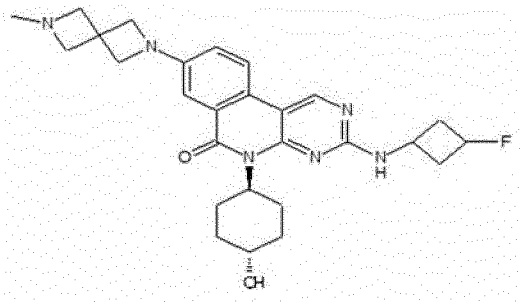
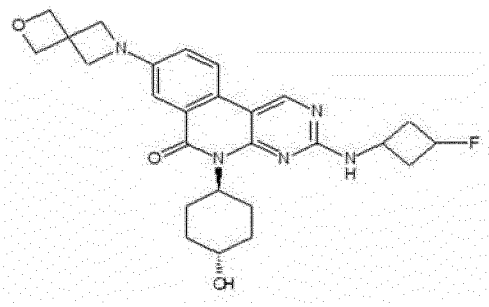
(continued)

No.	Structure	Name
61		trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c] isoquinolin-6(5H)-one
62		trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-morpholinopyrimido[4,5-c]isoquinolin-6 (5H)-one
63		cis-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c] isoquinolin-6(5H)-one
64		tert-Butyl(4-((3-(Butylamino)-8-(4-methylpiperazin-1-yl)-6-oxopyrimido [4,5-c]isoquinolin-5(6H)-yl)methyl) cyclohexyl)carbamat e
65		5-((4-Aminocyclohexyl)methyl)-3-(butylamino)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

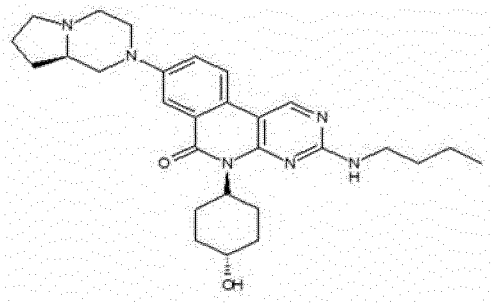
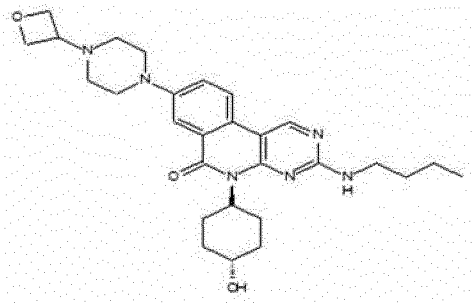
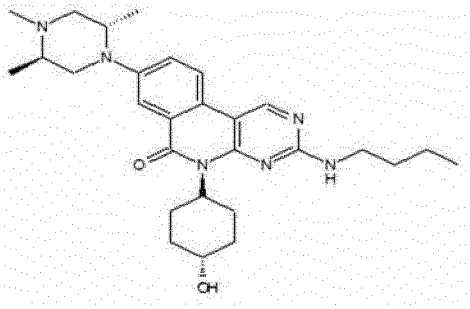
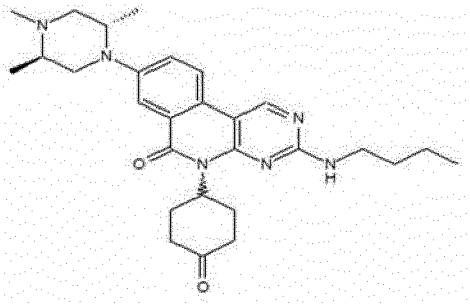
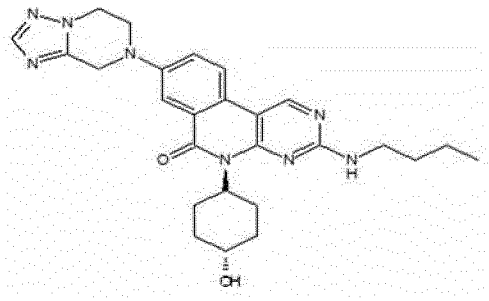
(continued)

No.	Structure	Name
66		trans-3-((3,3-Difluorocyclobutyl)amino)-5-(4-hydroxycyclohexyl)-8-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one
67		trans-3-((3,3-difluorocyclobutyl)amino)-5-(4-hydroxycycl ohexyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one
68		trans-3-(Butylamino)-5-(4-hydroxycycl ohexyl)-8-(2-oxa-6-azaspiro[3.3] heptan-6-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one
69		trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(4-isopropylpiperazin-1-yl)pyrimido[4,5-c] isoquinolin-6(5H)-one
70		3-(Butylamino)-8-(4-isopropylpiperazin-1-yl)-5-(4-oxocyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

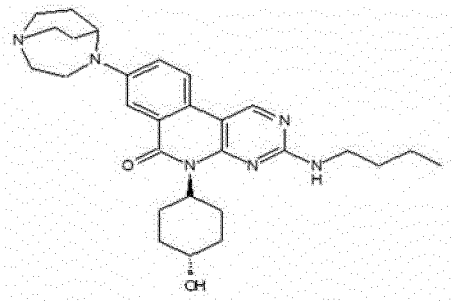
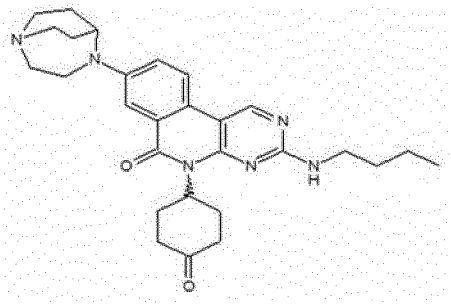
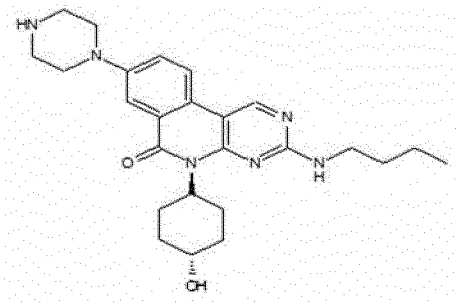
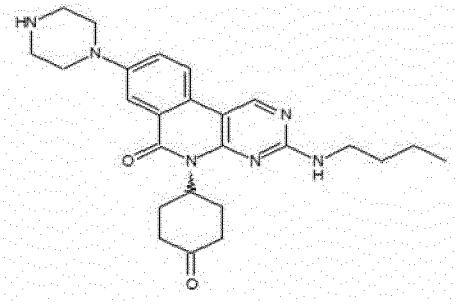
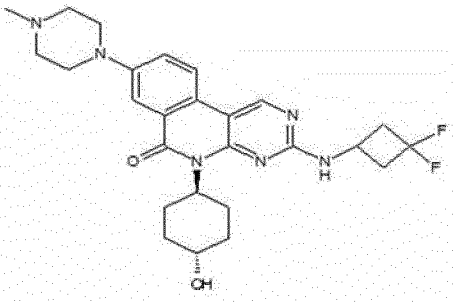
(continued)

No.	Structure	Name
71		trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(4-(pyrrolidin-1-yl)piperidin-1-yl)pyrimido[4,5-c] isoquinolin-6(5H)-one
72		3-(Butylamino)-5-(4-oxocyclohexyl)-8-(4-(pyrrolidin-1-yl)piperidin-1-yl) pyrimido[4,5-c]isoquinolin-6(5H)-one
73		trans-3-(Butylamino)-8-((S)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-5-((1r,4S)-4-hydroxycyclohexyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one
74		trans-3-((3-Fluorocyclobutyl)amino)-5-(4-hydroxycyclohexyl)-8-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)pyrimido [4,5-c]isoquinolin-6(5H)-one
75		trans-3-((3-Fluorocyclobutyl)amino)-5-(4-hydroxycyclohexyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

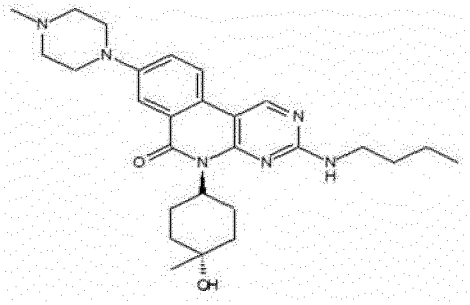
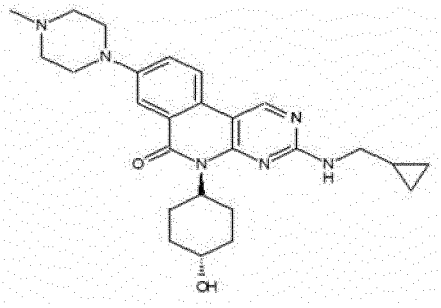
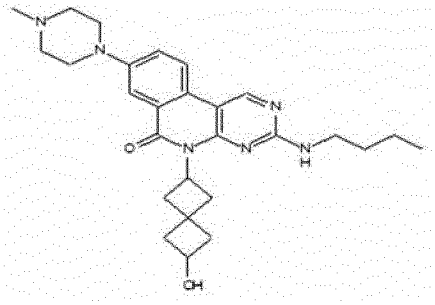
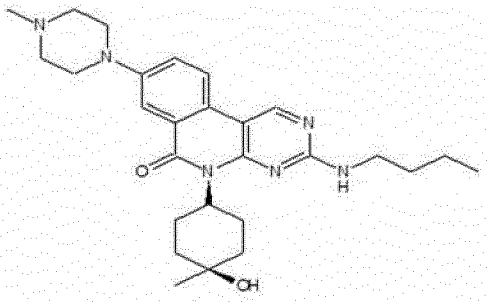
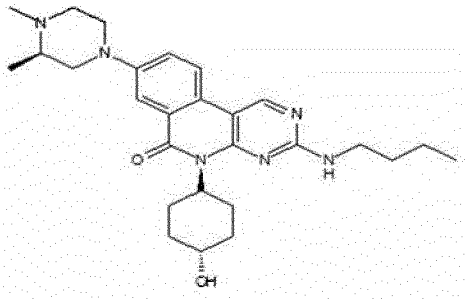
(continued)

No.	Structure	Name
76		trans-3-(Butylamino)-8-((R)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-5-(4-hydroxycyclohexyl) pyrimido[4, 5-c]isoquinolin-6(5H)-one
77		trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(4-(oxetan-3-yl) piperazin-1-yl)pyrimido[4,5-c] isoquinolin-6(5H)-one
78		trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-((2S,5R)-2,4,5-trimethylpiperazin-1-yl)pyrimido[4,5-c] isoquinolin-6(5H)-one
79		3-(Butylamino)-5-(4-oxocyclohexyl)-8-((2S, 5R)-2,4,5-trimethylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one
80		trans-3-(Butylamino)-8-(5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazin-7 (8H)-yl)-5-(4-hydroxycyclohexyl) pyrimido[4, 5-c]isoquinolin-6(5H)-one

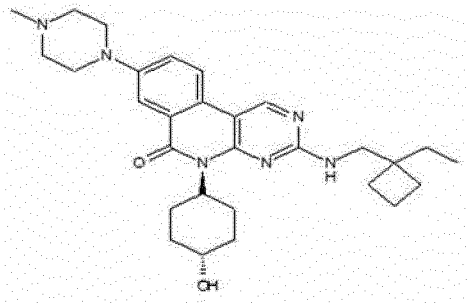
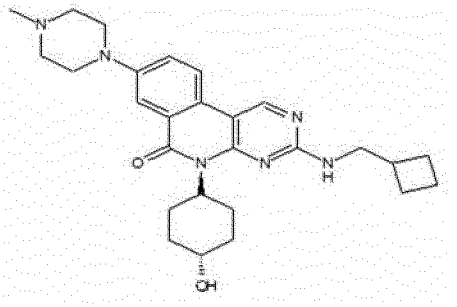
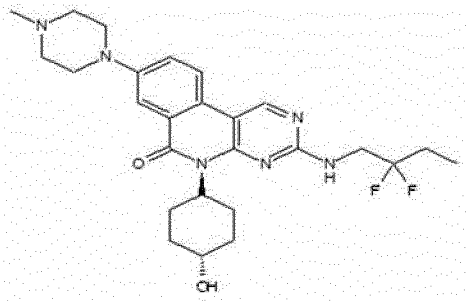
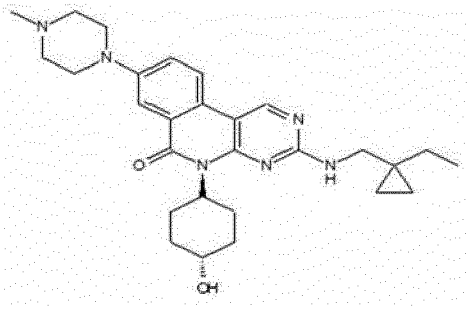
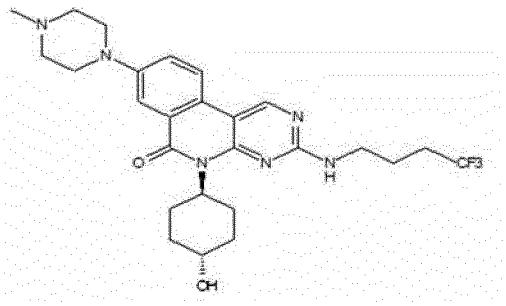
(continued)

No.	Structure	Name
81		trans-8-(1,4-Diazabicyclo[3.2.2]nonan-4-yl)-3-(butylamino)-5-(4-hydroxycyclohexyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one
82		8-(1,4-Diazabicyclo[3.2.2]nonan-4-yl)-3-(butylamino)-5-(4-oxocyclohexyl) pyrimido[4,5-c]isoquinolin-6(5H)-one
83		trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(piperazin-1-yl) pyrimido[4,5-c]isoquinolin-6(5H)-one
84		3-(Butylamino)-5-(4-oxocyclohexyl)-8-(piperazin-1-yl)pyrimido[4,5-c] isoquinolin-6(5H)-one
85		trans-3-((3,3-Difluorocyclobutyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c] isoquinolin-6(5H)-one

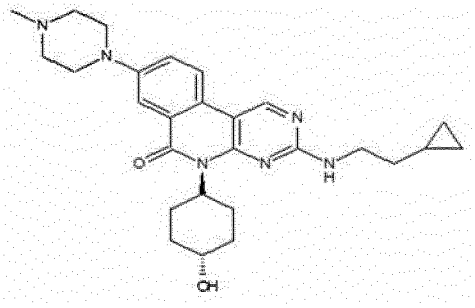
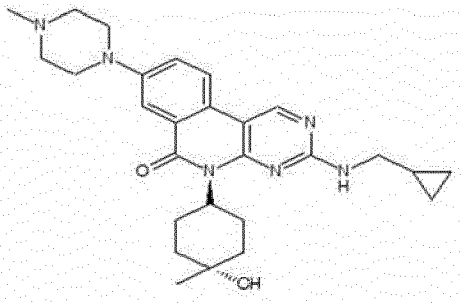
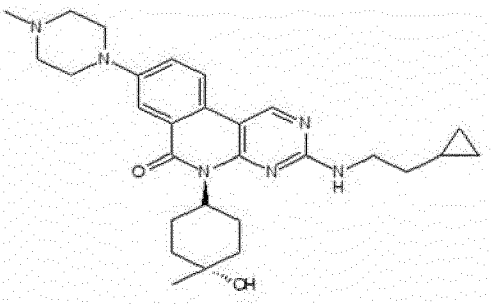
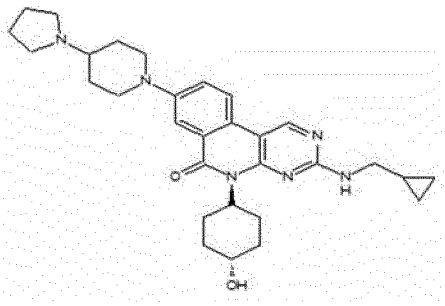
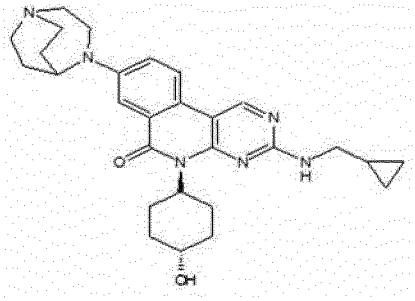
(continued)

No.	Structure	Name
86		trans-3-(Butylamino)-5-(4-hydroxy-4-methylcyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c] isoquinolin-6(5H)-one
87		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c] isoquinolin-6(5H)-one
88		3 -(Butyl amino)-5 -(6-hydroxyspiro[3.3] heptan-2-yl)-8-(4-methylpiperazin-1-yl) pyrimido[4,5-c]isoquinolin-6(5H)-one
89		cis-3-(Butylamino)-5-(4-hydroxy-4-methylcyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c] isoquinolin-6(5H)-one
90		trans-3-(Butylamino)-8-((R)-3,4-dimethylpiperazin-1-yl)-5-(4-hydroxycyclohexyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one

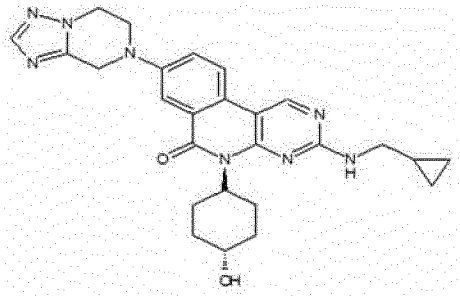
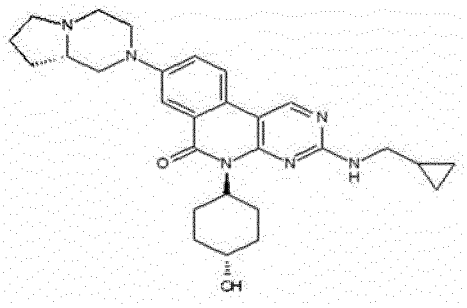
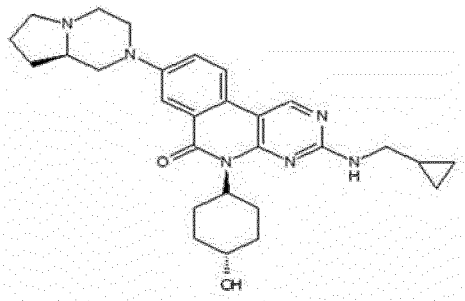
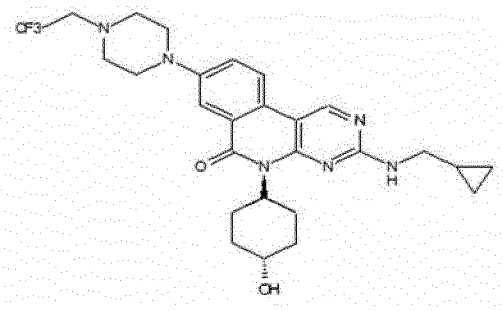
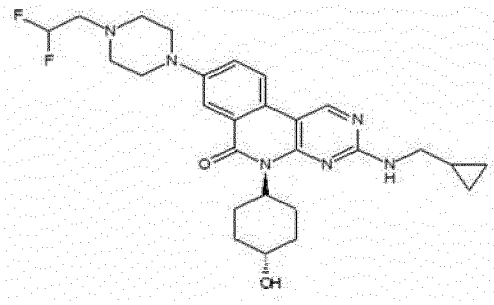
(continued)

No.	Structure	Name
91		trans-3-(((1-Ethylcyclobutyl)methyl) amino) -5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c] isoquinolin-6(5H)-one
92		trans-3-((Cyclobutylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c] isoquinolin-6(5H)-one
93		trans-3-((2,2-Difluorobutyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c] isoquinolin-6(5H)-one
94		trans-3-(((1-Ethylcyclopropyl)methyl) amino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c] isoquinolin-6(5H)-one
95		trans-5-(4-Hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)-3-((4,4,4-trifluorobutyl)amino)pyrimido[4,5-c] isoquinolin-6(5H)-one

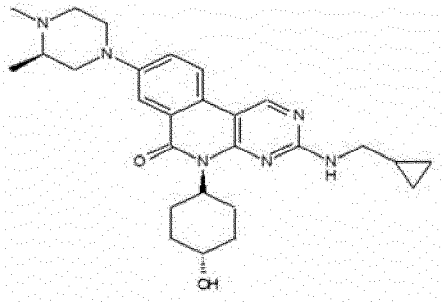
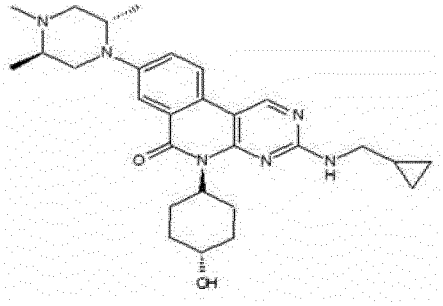
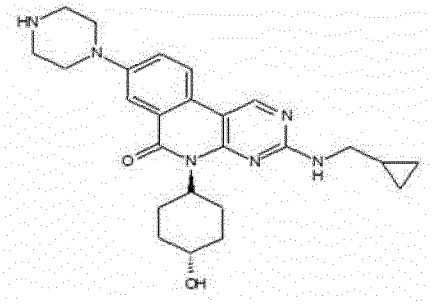
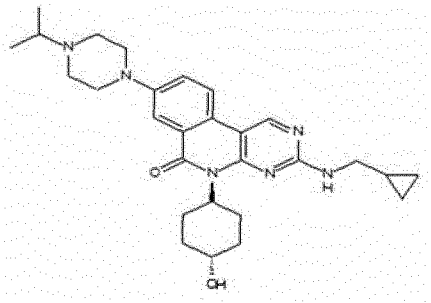
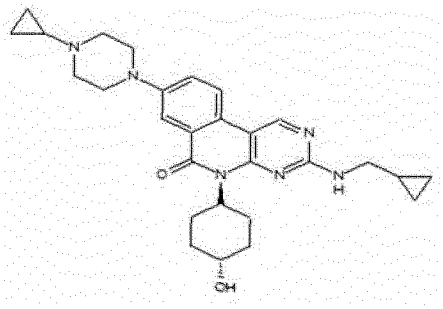
(continued)

No.	Structure	Name
96		trans-3-((2-Cyclopropylethyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c] isoquinolin-6(5H)-one
97		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c] isoquinolin-6(5H)-one
98		trans-3-((2-Cyclopropylethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c] isoquinolin-6(5H)-one
99		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-(pyrrolidin-1-yl)piperidin-1-yl) pyrimido[4,5-c]isoquinolin-6(5H)-one
100		trans-8-(1,4-diazabicyclo[3 .2.2]nonan-4-yl)-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one

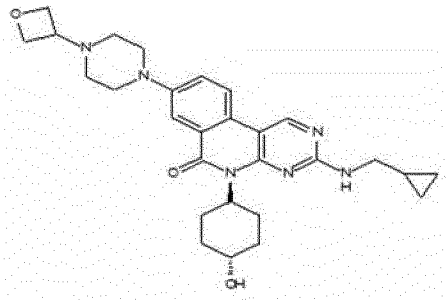
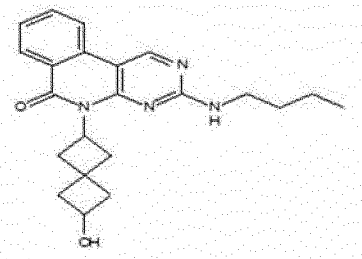
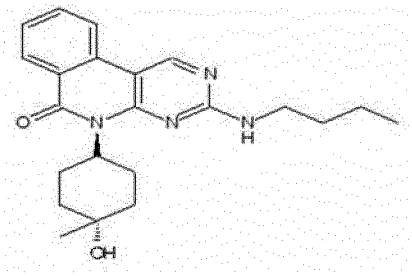
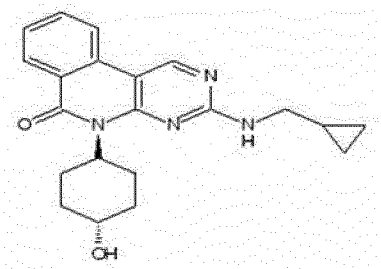
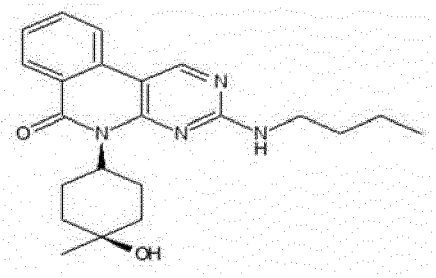
(continued)

No.	Structure	Name
101		trans-3-((Cyclopropylmethyl)amino)-8-(5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazin-7(8H)-yl)-5-(4-hydroxycyclohexyl)pyrimido[4, 5-c]isoquinolin-6(5H)-one
102		trans-3-((Cyclopropylmethyl)amino)-8-((S)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-5-(4-hydroxycyclohexyl)pyrimido[4, 5-c]isoquinolin-6(5H)-one
103		trans-3-((Cyclopropylmethyl)amino)-8-((R)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-5-(4-hydroxycyclohexyl)pyrimido[4, 5-c]isoquinolin-6(5H)-one
104		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one
105		trans-3-((Cyclopropylmethyl)amino)-8-(4-(2,2-difluoroethyl)piperazin-1-yl)-5-(4-hydroxycyclohexyl)pyrimido[4, 5-c]isoquinolin-6(5H)-one

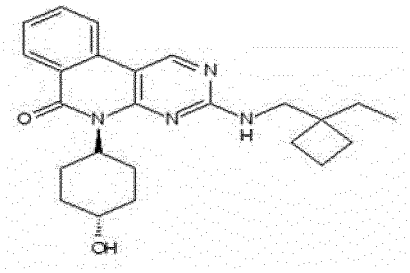
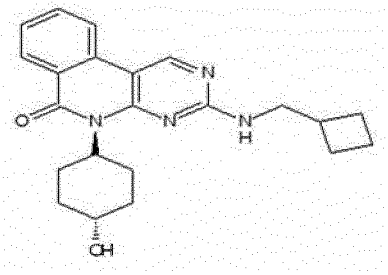
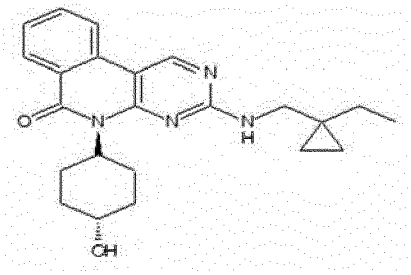
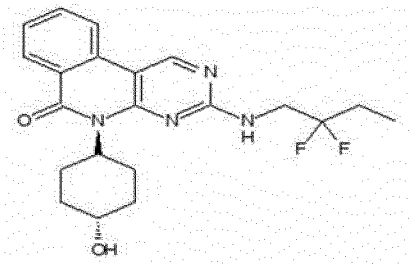
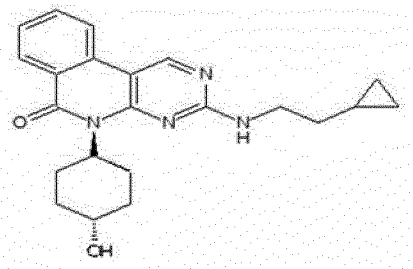
(continued)

No.	Structure	Name
106		trans-3-((Cyclopropylmethyl)amino)-8-((R)-3,4-dimethylpiperazin-1-yl)-5-(4-hydroxycyclohexyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one
107		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((2S,5R)-2,4,5-trimethylpiperazin-1-yl)pyrimido [4,5-c]isoquinolin-6(5H)-one
108		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(piperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one
109		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-isopropylpiperazin-1-yl)pyrimido[4,5-c] isoquinolin-6(5H)-one
110		trans-3-((Cyclopropylmethyl)amino)-8-(4-cyclopropylpiperazin-1-yl)-5-(4-hydroxycyclohexyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one

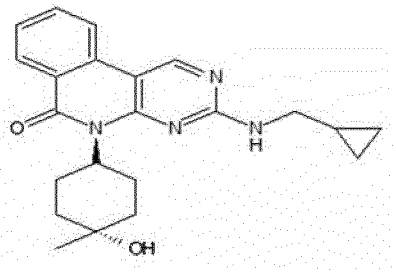
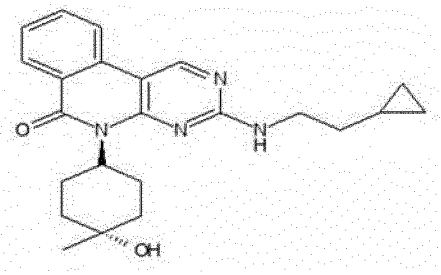
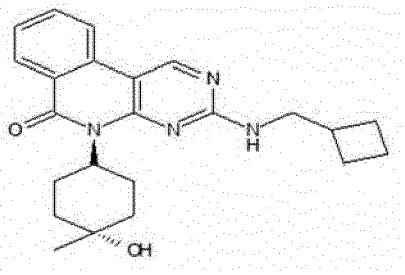
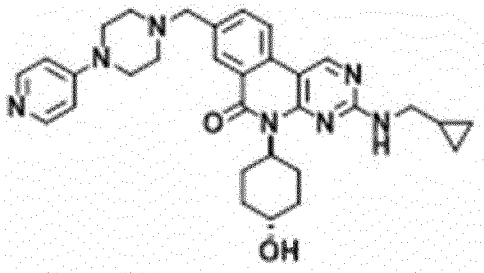
(continued)

No.	Structure	Name
111		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-(oxetan-3-yl)piperazin-1-yl)pyrimido[4,5-c] isoquinolin-6(5H)-one
112		3 -(Butyl amino)-5 -(6-hydroxyspiro[3.3] heptan-2-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one
113		trans-3-(Butylamino)-5-(4-hydroxy-4-methylcyclohexyl)pyrimido[4,5 -c] isoquinolin-6(5H)-one
114		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one
115		cis-3-(Butylamino)-5-(4-hydroxy-4-methylcyclohexyl)pyrimido[4,5 -c] isoquinolin-6(5H)-one

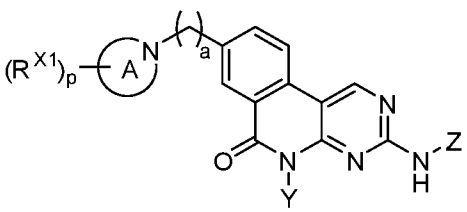
(continued)

No.	Structure	Name
116		trans-3-(((1-Ethylcyclobutyl)methyl) amino) -5-(4-hydroxycyclohexyl) pyrimido[4, 5-c]isoquinolin-6(5H)-one
117		trans-3-((Cyclobutylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one
118		3-(((1-Ethylcyclopropyl)methyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one
119		trans-3-((2,2-difluorobutyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one
120		trans-3-((2-Cyclopropylethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4, 5-c] isoquinolin-6(5H)-one

(continued)

No.	Structure	Name
121		trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl) pyrimido[4,5 -c]isoquinolin-6(5H)-one
122		trans-3-((2-Cyclopropylethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl) pyrimido[4,5 -c]isoquinolin-6(5H)-one
123		trans-3-((Cyclobutylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl) pyrimido[4,5 -c]isoquinolin-6(5H)-one
124		*trans*-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-(pyridin-4-yl)piperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

[0023] In embodiment II_1 of this aspect, the invention comprises compounds having the structure of formula (II):



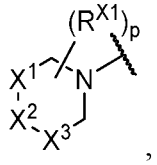
(II)

or a pharmaceutically acceptable salt or *N*-oxide thereof, or solvate or hydrate thereof, wherein

ring A is Hca;
a is 0 or 1;
p is 1, 2, 3 or 4; and
each -R^{X1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, -$C(O)NR_2$, -$S(O)_2NR_2$, -$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -$OC(O)NR_2$, -N(R)C(O)OR, -$N(R)C(O)NR_2$, -$N(R)S(O)_2$R, -$OP(O)(OR)_2$, -CH_2-OP(O)(OR), Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

[0024] In embodiment II_2 of this aspect, the invention comprises compounds of embodiment H_1, wherein

(a) ring A is

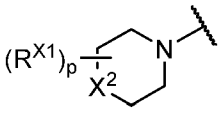


,

wherein

p is 0, 1, 2, 3 or 4;
X^1 is -O-, -S-, -S(O)-, -$S(O)_2$-, -CR^2-, -C(R)(R^{X1})-, -$C(R^{X1})_2$-, -N(R)- or -N(R^{X1})-;
X^2 is -O-, -S-, -S(O)-, -$S(O)_2$-, -CR^2-, -C(R)(R^{X1})-, -$C(R^{X1})_2$-, -N(R)- or -N(R^{X1})-; and
X^3 is -O-, -S-, -S(O)-, -$S(O)_2$-, -CR^2-, -C(R)(R^{X1})-, -$C(R^{X1})_2$-, -N(R)- or -N(R^{X1})-;

(b) ring A is

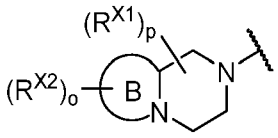


,

wherein

p is 0, 1, 2, 3 or 4;
X^2 is -O-, -S-, -S(O)-, -$S(O)_2$-, -CR^2-, -C(R)(R^{X1})-, -$C(R^{X1})_2$-, -N(R)- or -N(R^{X1})-;

(c) ring A is

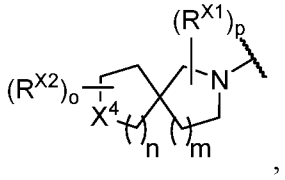


,

wherein

p is 0, 1 or 2;
o is 0, 1 or 2; and
ring B is Hca or Het, each comprising a 3-8 membered ring optionally substituted with one or two -R^{X2} groups;

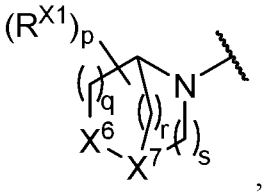
(d) ring A is



wherein

p is 0, 1 or 2;
o is 0, 1 or 2;
n is 0, 1 or 2;
m is 0, 1 or 2; and
X^4 is -O-, -S-, -S(O)-, $-S(O)_2$-, $-CR^2$-, $-C(R)(R^{X1})$-, $-C(R^{X1})_2$-, -N(R)- or $-N(R^{X1})$-;

(e) ring A is

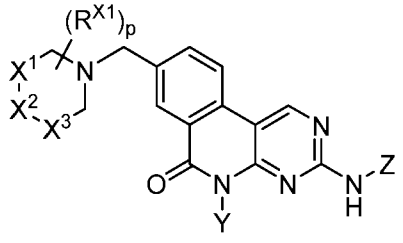
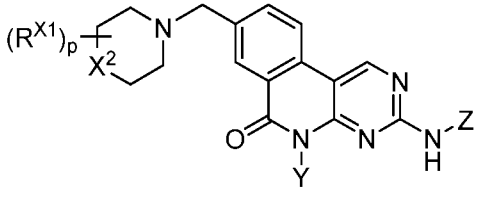


wherein

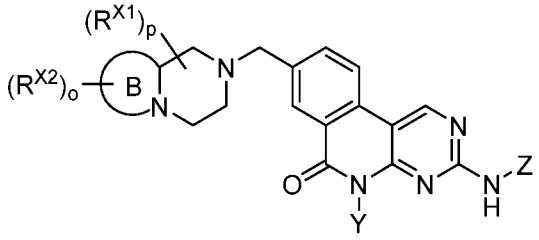
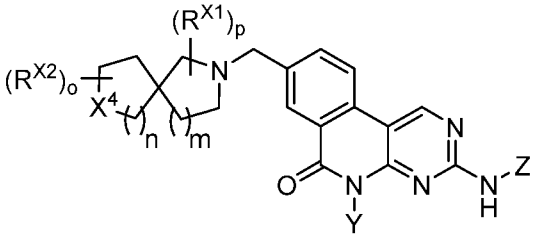
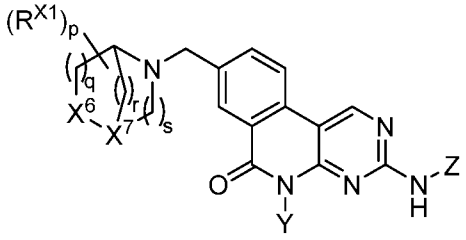
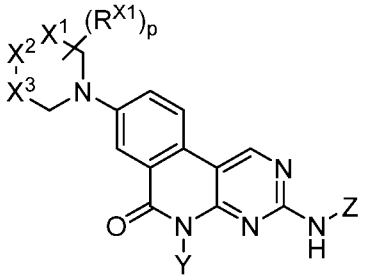
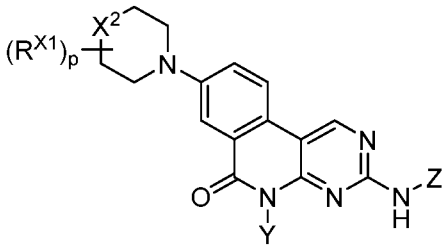
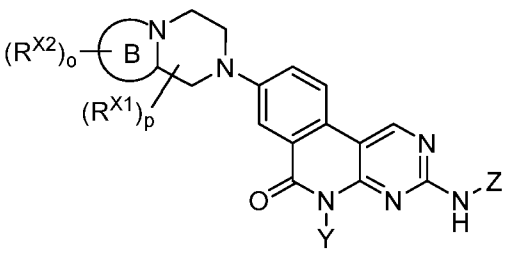
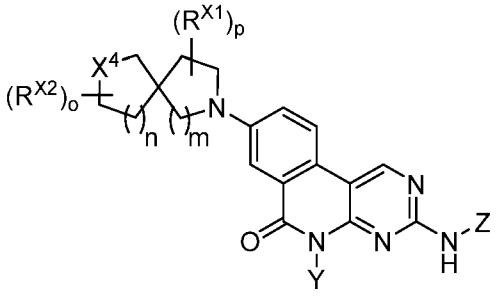
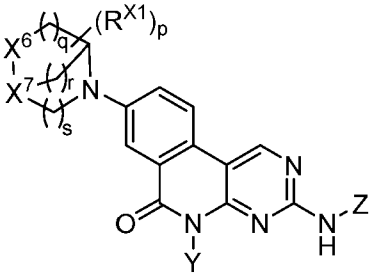
X^6 is -O-, -S-, -S(O)-, $-S(O)_2$-, $-CR^2$-, $-C(R)(R^{X1})$-, $-C(R^{X1})_2$-, -N(R)- or $-N(R^{X1})$-; and
X^7 is -CR-, $-C(R^{X1})$- or -N-;
p is 0, 1 or 2;
q is 0, 1 or 2;
r is 0, 1 or 2; and
s is 0, 1 or 2.

[0025] In embodiment II_3, the compounds are of embodiment I_1 or II_2, wherein a is 0.
[0026] In embodiment II_4, the compounds are of embodiment I_1 or II_2, wherein a is 1.
[0027] In embodiment II_5, the compounds are of embodiment I_1 - II_4, wherein Y is any of groups **(2a) - (2ll).**
[0028] In embodiment II_6, the compounds are of embodiment I_1 - II_4, wherein Z is any of groups **(3a) - (3xx).**
[0029] In embodiment II_7, the compounds of the invention are one of formulae (IIa) - (IIj), wherein ring A, ring B, a, p, o, n, m, q, r, s, X^1, X^2, X^4, X^6, X^7, R^{X1}, R^{X2}, Y and Z are as defined in embodiments II_1 - II_6 above:

Structural Formula (II) is one of formulae (IIa) - (IIj):

	
(IIa)	(IIb)

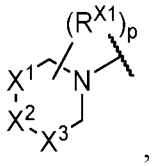
(continued)

	
(IIc)	(IId)
	
(IIe)	(IIf)
	
(IIg)	(IIh)
	
(IIi)	(IIj)

Ring A is selected from one of the following groups (4a) - (4ffff):

[0030]

(4a) Ring A is



,

wherein

p is 0, 1, 2, 3 or 4;
X^1 is -O-, -S-, -S(O)-, $-S(O)_2$-, $-CR^2$-, $-C(R)(R^{X1})$-, $-C(R^{X1})_2$-, -N(R)- or - $N(R^{X1})$-;
X^2 is -O-, -S-, -S(O)-, $-S(O)_2$-, $-CR^2$-, $-C(R)(R^{X1})$-, $-C(R^{X1})_2$-, -N(R)- or - $N(R^{X1})$-; and
X^3 is -O-, -S-, -S(O)-, $-S(O)_2$-, $-CR^2$-, $-C(R)(R^{X1})$-, $-C(R^{X1})_2$-, -N(R)- or - $N(R^{X1})$-;

(4b) Ring A is group (4a), wherein

X^1 is -O-, $-CR^2$-, $-C(R)(R^{X1})$-, $-C(R^{X1})_2$-, -N(R)- or $-N(R^{X1})$-;
X^2 is -O-, $-CR^2$-, $-C(R)(R^{X1})$-, $-C(R^{X1})_2$-, -N(R)- or $-N(R^{X1})$-; and
X^3 is -O-, $-CR^2$-, $-C(R)(R^{X1})$-, $-C(R^{X1})_2$-, -N(R)- or $-N(R^{X1})$-.

(4c) Ring A is group **(4a),** wherein

X^1 is $-CR^2$-, $-C(R)(R^{X1})$- or $-C(R^{X1})_2$;
X^2 is -O-, $-CR^2$-, $-C(R)(R^{X1})$-, $-C(R^{X1})_2$-, -N(R)- or $-N(R^{X1})$-; and
X^3 is $-CR^2$-, $-C(R)(R^{X1})$- or $-C(R^{X1})_2$-.

(4d) Ring A is group **(4a),** wherein

X^1 is $-CR^2$-, $-C(R)(R^{X1})$- or $-C(R^{X1})_2$;
X^2 is -O-, -S(O)-, $-S(O)_2$-, -N(R)- or $-N(R^{X1})$-; and
X^3 is $-CR^2$-, $-C(R)(R^{X1})$- or $-C(R^{X1})_2$-.

(4e) Ring A is group **(4a),** wherein

X^1 is $-CR^2$-, $-C(R)(R^{X1})$- or $-C(R^{X1})_2$;
X^2 is -O-, -N(R)- or $-N(R^{X1})$-; and
X^3 is $-CR^2$-, $-C(R)(R^{X1})$- or $-C(R^{X1})_2$-.

(4f) Ring A is group **(4a),** wherein

X^1 is $-CR^2$-, $-C(R)(R^{X1})$- or $-C(R^{X1})_2$;
X^2 is -S(O)-, $-S(O)_2$-; and
X^3 is $-CR^2$-, $-C(R)(R^{X1})$- or $-C(R^{X1})_2$-.

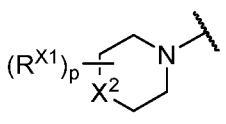
(4g) Ring A is group **(4a),** wherein

X^1 is $-CR^2$-, $-C(R)(R^{X1})$- or $-C(R^{X1})_2$;
X^2 is -O-; and
X^3 is $-CR^2$-, $-C(R)(R^{X1})$- or $-C(R^{X1})_2$-.

(4h) Ring A is group **(4a),** wherein

X^1 is $-CR^2$-, $-C(R)(R^{X1})$- or $-C(R^{X1})_2$;
X^2 is -N(R)- or $-N(R^{X1})$-; and
X^3 is $-CR^2$-, $-C(R)(R^{X1})$- or $-C(R^{X1})_2$-.

(4i) Ring A is

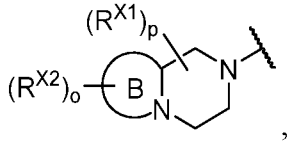


,

wherein

p is 0, 1, 2, 3 or 4;
X^2 is -O-, -S-, -S(O)-, $-S(O)_2$-, $-CR^2$-, $-C(R)(R^{X1})$-, $-C(R^{X1})_2$-, -N(R)- or - $N(R^{X1})$-.

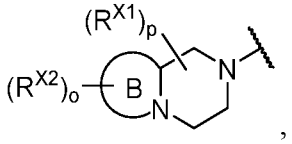
(4j) Ring A is group **(4i),** wherein X^2 is -O-, $-CR^2$-, $-C(R)(R^{X1})$-, $-C(R^{X1})_2$-, -N(R)- or - $N(R^{X1})$-.
(4k) Ring A is group **(4i),** wherein X^2 is $-CR^2$- or $-C(R)(R^{X1})$-.
(41) Ring A is group **(4i),** wherein X^2 is -O-.
(4m) Ring A is group **(4i),** wherein X^2 is $-S(O)_2$-.
(4n) Ring A is group **(4i),** wherein X^2 is -N(R)- or $-N(R^{X1})$-.
(4o) Ring A is



wherein

p is 0, 1 or 2;
o is 0, 1 or 2; and
Ring B is Hca or Het, each comprising a 3-8 membered ring optionally substituted with one or two $-R^{X2}$ groups.

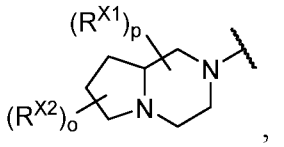
(4p) Ring A is



wherein

p is 0, 1 or 2;
o is 0, 1 or 2; and

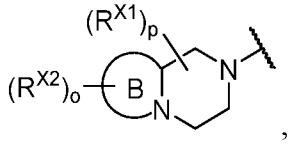
Ring B is Hca, each comprising a 3-8 membered ring optionally substituted with one or two $-R^{X2}$ groups.
(4q) Ring A is group **(4o)** or **(4p),** wherein Hca is a 3-6 membered ring.
(4r) Ring A is group **(4o)** or **(4p),** wherein Hca is a 5-6 membered ring.
(4s) Ring A is



wherein

p is 0, 1 or 2; and
o is 0, 1 or 2.

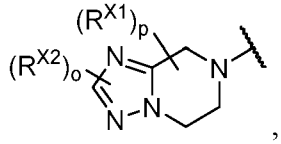
(4t) Ring A is



wherein

p is 0, 1 or 2;
o is 0, 1 or 2; and

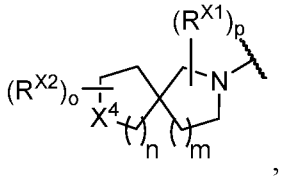
Ring B is Het, each comprising a 3-8 membered ring optionally substituted with one or two -R^{X2} groups.
(4u) Ring A is group **(4t),** wherein Het is a 3-6 membered ring.
(4v) Ring A is group **(4t),** wherein Het is a 5-6 membered ring.
(4w) Ring A is



wherein

p is 0, 1 or 2; and
o is 0, 1 or 2.

(4x) Ring A is



wherein

p is 0, 1 or 2;
o is 0, 1 or 2;
n is 0, 1 or 2;
m is 0, 1 or 2; and
X^4 is -O-, -S-, -S(O)-, -$S(O)_2$-, -CR^2-, -C(R)(R^{X1})-, -$C(R^{X1})_2$-, -N(R)- or -N(R^{X1})-.

(4y) Ring A is group **(4x),** wherein X^4 is -O-, -$S(O)_2$-, -CR^2-, -C(R)(R^{X1})-, -$C(R^{X1})_2$-, - N(R)- or -N(R^{X1})-.
(4z) Ring A is group **(4x),** wherein X^4 is -O-, -$S(O)_2$-, -N(R)- or -N(R^{X1})-.
(4aa) Ring A is group **(4x),** wherein X^4 is -O-, -N(R)- or -N(R^{X1})-.
(4bb) Ring A is group **(4x),** wherein X^4 is -O-, -CR^2-, -C(R)(R^{X1})- or -$C(R^{X1})_2$-.
(4cc) Ring A is group **(4x),** wherein X^4 is -CR^2-, -C(R)(R^{X1})-, -$C(R^{X1})_2$-, -N(R)- or - N(R^{X1})-.
(4dd) Ring A is group **(4x),** wherein X^4 is -$S(O)_2$-, -CR^2-, -C(R)(R^{X1})- or -$C(R^{X1})_2$-.
(4ee) Ring A is group **(4x),** wherein X^4 is -O-.
(4ff) Ring A is group **(4x),** wherein X^4 is -CR^2-, -C(R)(R^{X1})- or -$C(R^{X1})_2$-.
(4gg) Ring A is group **(4x),** wherein X^4 is -N(R)- or -N(R^{X1})-.
(4hh) Ring A is any of **(4x) - (4gg),** wherein

n is 0, 1 or 2; and
m is 0, 1 or 2.

(4ii) Ring A is any of **(4x) - (4gg),** wherein

n is 0; and
m is 0.

(4jj) Ring A is any of **(4x) - (4gg),** wherein

n is 1; and
m is 1.

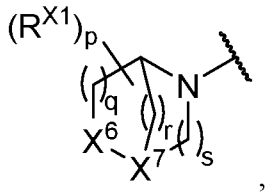
(4kk) Ring A is any of **(4x) - (4gg),** wherein

n is 0; and
m is 1.

(4ll) Ring A is any of **(4x) - (4gg),** wherein

n is 1; and
m is 0.

(4mm) Ring A is



,

wherein

X^6 is -O-, -S-, -S(O)-, -$S(O)_2$-, -CR^2-, -C(R)(R^{X1})-, -$C(R^{X1})_2$-, -N(R)- or -N(R^{X1})-; and
X^7 is -CR-, -C(R^{X1})- or -N-;

p is 0, 1 or 2;
q is 0, 1 or 2;
r is 1 or 2; and
s is 0, 1 or 2.

(4nn) Ring A is group **(4mm),** wherein X^6 is -O-, -$S(O)_2$-, -CR^2-, -C(R)(R^{X1})-, -$C(R^{X1})_2$-, - N(R)- or -N(R^{X1})-.
(4oo) Ring A is group **(4mm),** wherein X^6 is -O-, -CR^2-, -C(R)(R^{X1})-, -$C(R^{X1})_2$-, -N(R)- or -N(R^{X1})-.
(4pp) Ring A is group **(4mm),** wherein X^6 is -O-, -N(R)- or -N(R^{X1})-.
(4qq) Ring A is group **(4mm),** wherein X^6 is -O.
(4rr) Ring A is group **(4mm),** wherein X^6 is -$S(O)_2$-.
(4ss) Ring A is group **(4mm),** wherein X^6 is -CR^2-, -C(R)(R^{X1})- or -$C(R^{X1})_2$-.
(4tt) Ring A is group **(4mm),** wherein X^6 is -N(R)- or -N(R^{X1})-.
(4uu) Ring A is any of groups **(4mm) - (4tt),** wherein X^7 is -CR- or -C(R^{X1})-.
(4vv) Ring A is any of groups **(4mm) - (4tt),** wherein X^7 is -N-.
(4ww) Ring A is any of **(4mm) - (4vv),** wherein

q is 0, 1 or 2;
r is 1 or 2; and
s is 0, 1 or 2.

(4xx) Ring A is any of **(4mm) - (4vv),** wherein

q is 0 or 1;
r is 1 or 2; and
s is 0 or 1.

(4yy) Ring A is any of **(4mm) - (4vv),** wherein

q is 0;
r is 1 or 2; and

s is 0.

(4zz) Ring A is any of **(4mm) - (4vv),** wherein

q is 1;
r is 1 or 2; and
s is 1.

(4aaa) Ring A is any of **(4mm) - (4vv),** wherein

q is 0;
r is 1 or 2; and
s is 0.

(4bbb) Ring A is any of **(4mm) - (4vv),** wherein

q is 1;
r is 1; and
s is 1.

(4ccc) Ring A is any of **(4mm) - (4vv),** wherein

q is 0;
r is 1 or 2; and
s is 0.

(4ddd) Ring A is any of **(4mm) - (4vv),** wherein

q is 1;
r is 1; and
s is 1.

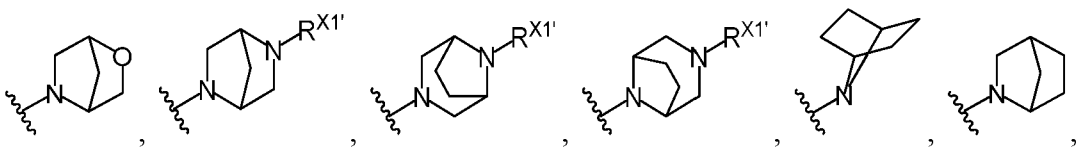
(4eee) Ring A is any of **(4mm) - (4vv),** wherein

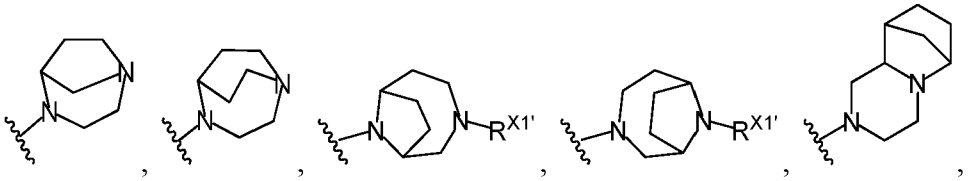
q is 1;
r is 2; and
s is 1.

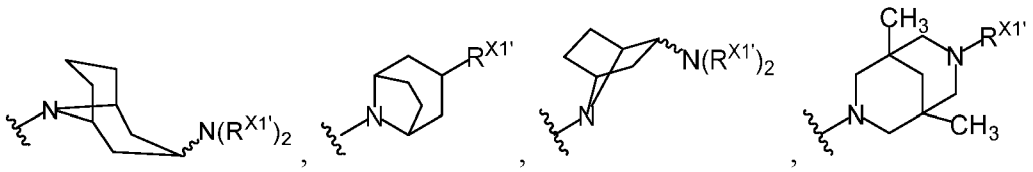
(4fff) Ring A is any of **(4mm) - (4vv),** wherein

q is 2;
r is 2; and
s is 2.

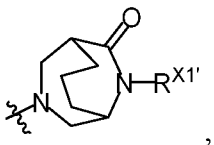
(4ggg) Ring A is





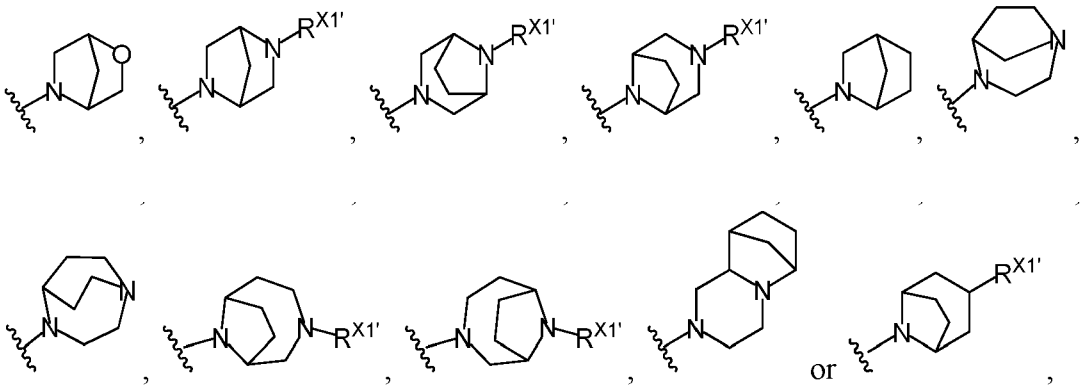


or



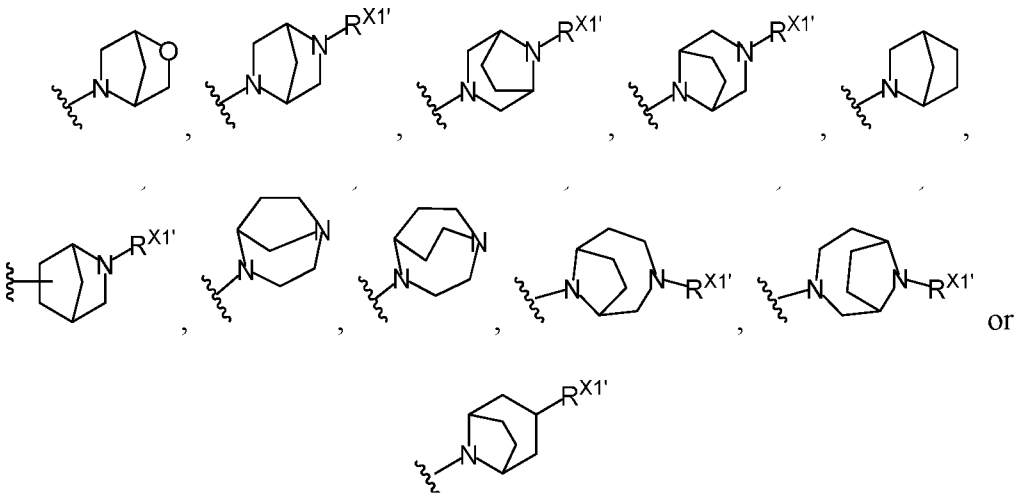
each optionally substituted with one, two or three R^{X1} groups, wherein -$R^{X1'}$ is hydrogen or R^{X1}.

(4hhh) Ring A is



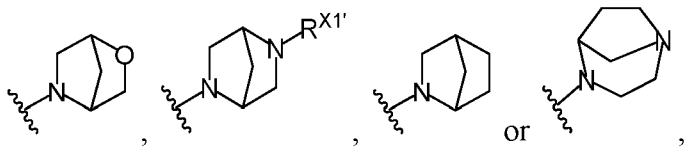
each optionally substituted with one, two or three R^{X1} groups, wherein -$R^{X1'}$ is hydrogen or R^{X1}.

(4iii) Ring A is



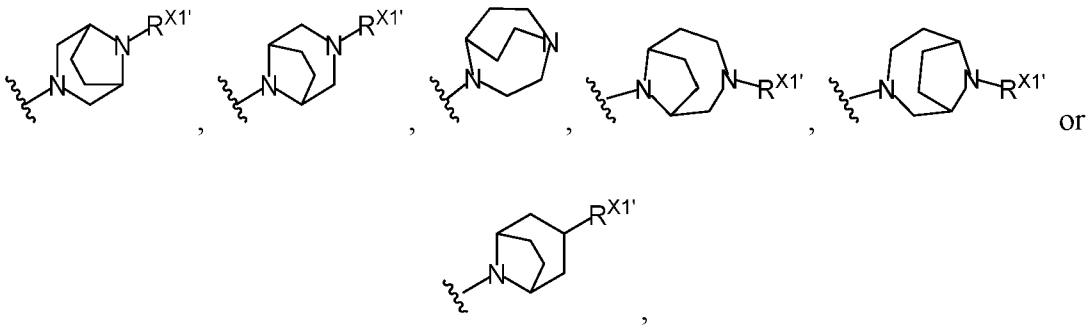
each optionally substituted with one, two or three R^{X1} groups, wherein -$R^{X1'}$ is hydrogen or R^{X1}.

(4jjj) Ring A is



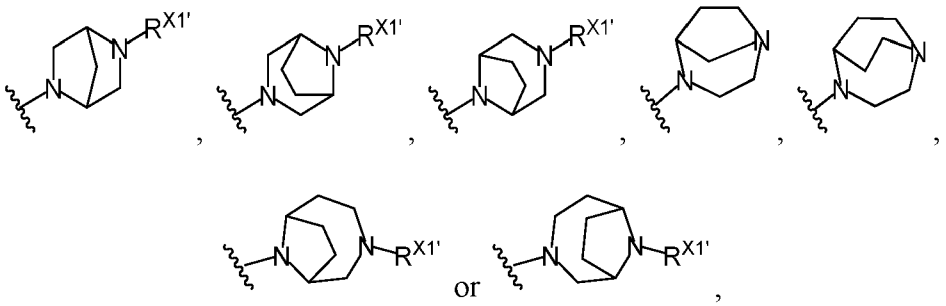
each optionally substituted with one, two or three R^{X1} groups, wherein $-R^{X1'}$ is hydrogen or R^{X1}.

(4kkk) Ring A is



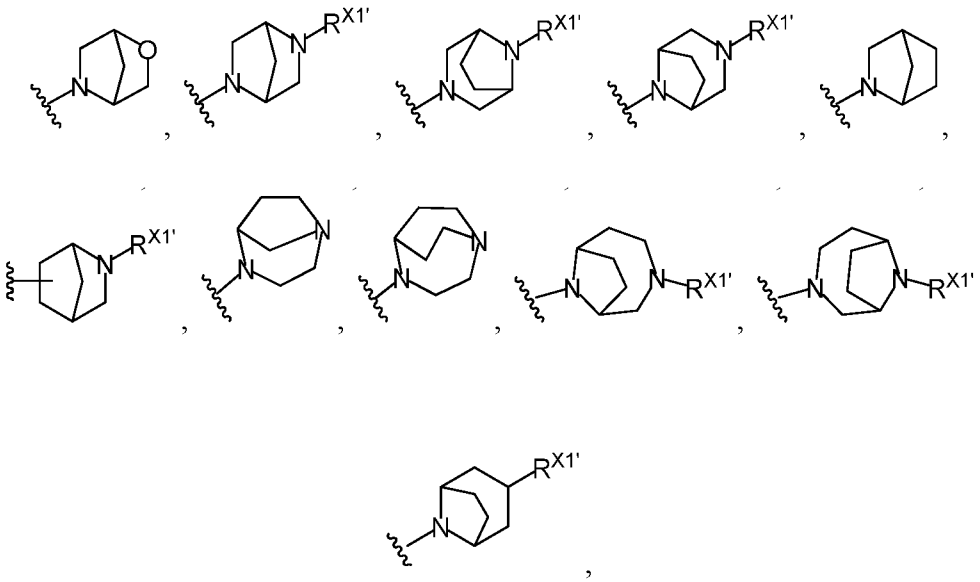
each optionally substituted with one, two or three R^{X1} groups, wherein $-R^{X1'}$ is hydrogen or R^{X1}.

(4lll) Ring A is



each optionally substituted with one, two or three R^{X1} groups, wherein $-R^{X1'}$ is hydrogen or R^{X1}.

(4mmm) Ring A is



each optionally substituted with one, two or three R^{X1} groups, wherein -$R^{X1'}$ is hydrogen or R^{X1}.

(4nnn) Ring A is any of groups **(4a) - (4fff),** wherein p is 0, 1 or 2.

(4ooo) Ring A is any of groups **(4a) - (4fff),** wherein p is 0 or 1.

(4ppp) Ring A is any of groups **(4a) - (4fff),** wherein p is 2.

(4qqq) Ring A is any of groups **(4a) - (4fff),** wherein p is 1.

(4rrr) Ring A is any of groups **(4a) - (4qqq),** each -R^{X1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, -C(O)R, -C(O)OR, -C(O)NR_2, -S(O)$_2$$NR_2$, -S(O)$_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)S(O)$_2$R, -OP(O)(OR)$_2$, -CH_2-OP(O)(OR), Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(4sss) Ring A is any of groups **(4a) - (4qqq),** each -R^{X1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, -C(O)R, -C(O)OR, -C(O)NR_2, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)S(O)$_2$R, -OP(O)(OR)$_2$, -CH_2-OP(O)(OR), Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(4ttt) Ring A is any of groups **(4a) - (4qqq),** each -R^{X1} is independently halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, -C(O)R, -C(O)OR, -C(O)NR_2, -N(R)C(O)R, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)S(O)$_2$R, -OP(O)(OR)$_2$, -CH_2-OP(O)(OR), Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(4uuu) Ring A is any of groups **(4a) - (4qqq),** each -R^{X1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, -C(O)R, -C(O)OR, -C(O)NR_2, -OC(O)R, -OP(O)(OR)$_2$, -CH_2-OP(O)(OR), Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(4vvv) Ring A is any of groups **(4a) - (4qqq),** each -R^{X1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, -C(O)R, -C(O)OR, -C(O)NR_2, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -OC(O)NR_2, -N(R)C(O)OR, -N(R)C(O)NR_2, -N(R)S(O)$_2$R, Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(4www) Ring A is any of groups **(4a) - (4qqq),** each -R^{X1} is independently halogen, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkoxy, -C(O)R, -C(O)OR, -C(O)NR_2, -OC(O)NR_2, Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(4xxx) Ring A is any of groups **(4a) - (4qqq),** each -R^{X1} is independently C_1-C_6alkyl, C_1-C_6haloalkyl, -C(O)OR, Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(Co-C_6alkyl).

(4yyy) Ring A is any of groups **(4a) - (4qqq),** each -R^{X1} is independently C_1-C_6alkyl, C_1-C_6haloalkyl, Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(4zzz) Ring A is any of groups **(4a) - (4qqq),** each -R^{X1} is independently Cak(C_0-C_6alkyl) or Hca(C_0-C_6alkyl).

(4aaaa) Ring A is any of groups **(4a) - (4qqq),** each -R^{X1} is independently Cak(C_0-C_6alkyl).

(4bbbb) Ring A is any of groups **(4a) - (4qqq),** each -R^{X1} is independently Hca(C_0-C_6alkyl).

(4cccc) Ring A is any of groups **(4a) - (4qqq),** each -R^{X1} is independently C_1-C_6alkyl or C_1-C_6haloalkyl.

(4dddd) Ring A is any of groups **(4a) - (4qqq),** each -R^{X1} is independently Cak(C_0-C_6alkyl).

(4eeee) Ring A is any of groups **(4a) - (4qqq),** each -R^{X1} is independently C_1-C_6haloalkyl.

(4ffff) Ring A is any of groups **(4a) - (4fff),** wherein p is 0.

[0031] Particular embodiments of this aspect of the invention comprise compounds of any one of the formulae (II), and (IIa) - (IIj), each as defined in each of the following rows (or a pharmaceutically acceptable salt, or *N*-oxide thereof, or a solvate or hydrate thereof), wherein each entry is a group number as defined above (e.g., **(4ffff)** refers to Ring A being any of groups (4a) - (4fff), wherein p is 0, and a dash "-" indicates that the variable is as defined in embodiment II or defined according to any one of the applicable variable definitions **(4a)-(4ffff), (2a)-(211)** and **(3a)-(3xx)** [*e.g.*, when Ring A is a dash, it can be either as defined in any of embodiments II_1 - II_7 or any one of the applicable definitions **(4a)-(4ffff)]):**

	(II)	Ring A	Y	Z
(2)-1	(IIa)	(4a)	(2a)	(3a)
(2)-2	(IIa)	(4c)	(2d)	(3b)
(2)-3	(IIa)	(4e)	(2e)	(3c)
(2)-4	(IIa)	(4g)	(2h)	(3f)
(2)-5	(IIa)	(4h)	(2i)	(3h)
(2)-6	(IIa)	(4b)	(2l)	(3j)
(2)-7	(IIa)	(4d)	(2m)	(3m)
(2)-8	(IIa)	(4f)	(2r)	(3n)
(2)-9	(IIa)	(4nnn)	(2v)	(3o)
(2)-10	(IIa)	(4ooo)	(2aa)	(3p)
(2)-11	(IIa)	(4ppp)	(2bb)	(3q)
(2)-12	(IIa)	(4qqq)	(2cc)	(3v)
(2)-13	(IIa)	(4ttt)	(2ff)	(3w)
(2)-14	(IIa)	(4vvv)	(2gg)	(3x)
(2)-15	(IIa)	(4yyy)	(2hh)	(3aa)
(2)-16	(IIa)	(4zzz)	(2ii)	(3ee)
(2)-17	(IIa)	(4cccc)	(2jj)	(3ii)
(2)-18	(IIa)	(4dddd)	(2kk)	(3kk)
(2)-19	(IIa)	(4d)	(2ll)	(3oo)
(2)-20	(IIa)	(4a)	(2i)	(3rr)
(2)-21	(IIa)	(4c)	(2l)	(3v)
(2)-22	(IIa)	(4e)	(2m)	(3w)
(2)-23	(IIa)	(4g)	(2r)	(3x)
(2)-24	(IIa)	(4h)	(2v)	(3aa)

	(II)	Ring A	Y	Z
(2)-25	(IIa)	(4nnn)	(2aa)	(3n)
(2)-26	(IIa)	(4cccc)	(2m)	(3aa)
(2)-27	(IIa)	(4vvv)	(2r)	(3n)
(2)-28	(IIa)	(4cccc)	(2v)	(3o)
(2)-29	(IIa)	(4vvv)	(2aa)	(3p)
(2)-30	(IIa)	(4nnn)	(2aa)	(3aa)
(2)-31	(IIb)	(4i)	(2m)	(3n)
(2)-32	(IIb)	(4j)	(2r)	(3o)
(2)-33	(IIb)	(4k)	(2e)	(3p)
(2)-34	(IIb)	(4l)	(2h)	(3m)
(2)-35	(IIb)	(4n)	(2i)	(3n)
(2)-36	(IIb)	(4nnn)	(2l)	(3o)
(2)-37	(IIb)	(4cccc)	(2m)	(3p)
(2)-38	(IIb)	(4j)	(2m)	(3q)
(2)-39	(IIb)	(4k)	(2r)	(3v)
(2)-40	(IIb)	(4l)	(2v)	(3w)
(2)-41	(IIb)	(4n)	(2aa)	(3x)
(2)-42	(IIb)	(4j)	(2m)	(3aa)
(2)-43	(IIb)	(4k)	(2r)	(3n)
(2)-44	(IIb)	(4l)	(2v)	(3o)
(2)-45	(IIb)	(4n)	(2aa)	(3p)
(2)-46	(IIb)	(4nnn)	(2i)	(3q)
(2)-47	(IIb)	(4cccc)	(2l)	(3aa)
(2)-48	(IIb)	(4i)	(2m)	(3n)

	(II)	Ring A	Y	Z
(2)-49	(IIb)	(4i)	(2r)	(3o)
(2)-50	(IIb)	(4j)	(2v)	(3p)
(2)-51	(IIb)	(4k)	(2aa)	(3b)
(2)-52	(IIb)	(4l)	(2aa)	(3c)
(2)-53	(IIb)	(4n)	(2m)	(3f)
(2)-54	(IIb)	(4nnn)	(2r)	(3h)
(2)-55	(IIb)	(4cccc)	(2e)	(3j)
(2)-56	(IIb)	(4vvv)	(2h)	(3m)
(2)-57	(IIb)	(4cccc)	(2i)	(3n)
(2)-58	(IIb)	(4l)	(2l)	(3o)
(2)-59	(IIb)	(4n)	(2m)	(3p)
(2)-60	(IIb)	(4nnn)	(2r)	(3q)
(2)-61	(IIc)	(4o)	(2v)	(3v)
(2)-62	(IIc)	(4p)	(2aa)	(3w)
(2)-63	(IIc)	(4s)	(2aa)	(3x)
(2)-64	(IIc)	(4t)	(2m)	(3aa)
(2)-65	(IIc)	(4w)	(2r)	(3ee)
(2)-66	(IIc)	(4p)	(2aa)	(3ii)
(2)-67	(IIc)	(4s)	(2bb)	(3kk)
(2)-68	(IIc)	(4o)	(2cc)	(3oo)
(2)-69	(IIc)	(4o)	(2e)	(3rr)
(2)-70	(IIc)	(4p)	(2h)	(3a)
(2)-71	(IIc)	(4s)	(2i)	(3b)
(2)-72	(IIc)	(4o)	(2l)	(3c)
(2)-73	(IIc)	(4p)	(2m)	(3f)
(2)-74	(IIc)	(4s)	(2r)	(3h)

	(II)	Ring A	Y	Z
(2)-75	(IIc)	(4t)	(2m)	(3j)
(2)-76	(IIc)	(4w)	(2r)	(3m)
(2)-77	(IIc)	(4o)	(2v)	(3n)
(2)-78	(IIc)	(4p)	(2aa)	(3o)
(2)-79	(IIc)	(4s)	(2m)	(3p)
(2)-80	(IIc)	(4t)	(2r)	(3q)
(2)-81	(IIc)	(4w)	(2v)	(3v)
(2)-82	(IIc)	(4ooo)	(2aa)	(3w)
(2)-83	(IIc)	(4ppp)	(2h)	(3x)
(2)-84	(IIc)	(4qqq)	(2i)	(3aa)
(2)-85	(IIc)	(4ttt)	(2l)	(3ee)
(2)-86	(IIc)	(4vvv)	(2m)	(3ii)
(2)-87	(IIc)	(4yyy)	(2r)	(3kk)
(2)-88	(IIc)	(4zzz)	(2r)	(3oo)
(2)-89	(IIc)	(4cccc)	(2v)	(3rr)
(2)-90	(IIc)	(4dddd)	(2aa)	(3v)
(2)-91	(IId)	(4x)	(2h)	(3w)
(2)-92	(IId)	(4aa)	(2i)	(3x)
(2)-93	(IId)	(4ee)	(2l)	(3aa)
(2)-94	(IId)	(4ff)	(2m)	(3o)
(2)-95	(IId)	(4gg)	(2r)	(3p)
(2)-96	(IId)	(4jj)	(2l)	(3q)
(2)-97	(IId)	(4ff)	(2m)	(3v)
(2)-98	(IId)	(4gg)	(2r)	(3w)
(2)-99	(IId)	(4jj)	(2v)	(3x)
(2)-100	(IId)	(4ee)	(2aa)	(3aa)

	(II)	Ring A	Y	Z
(2)-101	(IId)	(4aa)	(2e)	(3v)
(2)-102	(IId)	(4ee)	(2h)	(3w)
(2)-103	(IId)	(4ff)	(2i)	(3x)
(2)-104	(IId)	(4gg)	(2l)	(3aa)
(2)-105	(IId)	(4jj)	(2m)	(3b)
(2)-106	(IId)	(4ee)	(2r)	(3c)
(2)-107	(IId)	(4ff)	(2v)	(3f)
(2)-108	(IId)	(4gg)	(2aa)	(3h)
(2)-109	(IId)	(4jj)	(2aa)	(3j)
(2)-110	(IId)	(4aa)	(2aa)	(3m)
(2)-111	(IId)	(4nnn)	(2bb)	(3n)
(2)-112	(IId)	(4ooo)	(2cc)	(3o)
(2)-113	(IId)	(4ppp)	(2e)	(3p)
(2)-114	(IId)	(4qqq)	(2r)	(3q)
(2)-115	(IId)	(4ttt)	(2v)	(3v)
(2)-116	(IId)	(4vvv)	(2aa)	(3w)
(2)-117	(IId)	(4yyy)	(2bb)	(3x)
(2)-118	(IId)	(4zzz)	(2cc)	(3aa)
(2)-119	(IId)	(4cccc)	(2e)	(3ee)
(2)-120	(IId)	(4dddd)	(2h)	(3ii)
(2)-121	(IIe)	(4mm)	(2i)	(3kk)
(2)-122	(IIe)	(4ss)	(2l)	(3oo)
(2)-123	(IIe)	(4uu)	(2m)	(3rr)
(2)-124	(IIe)	(4ggg)	(2r)	(3aa)
(2)-125	(IIe)	(4jjj)	(2v)	(3n)
(2)-126	(IIe)	(4lll)	(2aa)	(3o)

	(II)	Ring A	Y	Z
(2)-127	(IIe)	(4ss)	(2bb)	(3p)
(2)-128	(IIe)	(4uu)	(2cc)	(3aa)
(2)-129	(IIe)	(4ggg)	(2ff)	(3a)
(2)-130	(IIe)	(4mm)	(2gg)	(3b)
(2)-131	(IIe)	(4ss)	(2hh)	(3c)
(2)-132	(IIe)	(4uu)	(2ii)	(3f)
(2)-133	(IIe)	(4ggg)	(2jj)	(3h)
(2)-134	(IIe)	(4jjj)	(2kk)	(3j)
(2)-135	(IIe)	(4lll)	(2ll)	(3m)
(2)-136	(IIe)	(4mmm)	(2i)	(3n)
(2)-137	(IIe)	(4uu)	(2l)	(3o)
(2)-138	(IIe)	(4ggg)	(2m)	(3p)
(2)-139	(IIe)	(4jjj)	(2i)	(3q)
(2)-140	(IIe)	(4lll)	(2l)	(3v)
(2)-141	(IIe)	(4mmm)	(2m)	(3w)
(2)-142	(IIe)	(4ooo)	(2r)	(3x)
(2)-143	(IIe)	(4ppp)	(2v)	(3aa)
(2)-144	(IIe)	(4qqq)	(2aa)	(3ee)
(2)-145	(IIe)	(4ttt)	(2aa)	(3ii)
(2)-146	(IIe)	(4vvv)	(2bb)	(3kk)
(2)-147	(IIe)	(4yyy)	(2cc)	(3oo)
(2)-148	(IIe)	(4zzz)	(2e)	(3rr)
(2)-149	(IIe)	(4cccc)	(2h)	(3aa)
(2)-150	(IIe)	(4dddd)	(2i)	(3n)
(2)-151	(IIf)	(4a)	(2l)	(3o)
(2)-152	(IIf)	(4c)	(2m)	(3p)

	(II)	Ring A	Y	Z
(2)-153	(IIf)	(4e)	(2r)	(3m)
(2)-154	(IIf)	(4g)	(2v)	(3n)
(2)-155	(IIf)	(4h)	(2aa)	(3o)
(2)-156	(IIf)	(4b)	(2bb)	(3p)
(2)-157	(IIf)	(4d)	(2cc)	(3q)
(2)-158	(IIf)	(4f)	(2ff)	(3v)
(2)-159	(IIf)	(4nnn)	(2gg)	(3w)
(2)-160	(IIf)	(4ooo)	(2hh)	(3x)
(2)-161	(IIf)	(4ppp)	(2ii)	(3aa)
(2)-162	(IIf)	(4qqq)	(2jj)	(3aa)
(2)-163	(IIf)	(4ttt)	(2kk)	(3n)
(2)-164	(IIf)	(4vvv)	(2ll)	(3o)
(2)-165	(IIf)	(4yyy)	(2cc)	(3p)
(2)-166	(IIf)	(4zzz)	(2ff)	(3a)
(2)-167	(IIf)	(4cccc)	(2gg)	(3b)
(2)-168	(IIf)	(4dddd)	(2hh)	(3c)
(2)-169	(IIf)	(4d)	(2r)	(3f)
(2)-170	(IIf)	(4a)	(2v)	(3h)
(2)-171	(IIf)	(4c)	(2aa)	(3j)
(2)-172	(IIf)	(4e)	(2bb)	(3m)
(2)-173	(IIf)	(4g)	(2cc)	(3n)
(2)-174	(IIf)	(4h)	(2ff)	(3o)
(2)-175	(IIf)	(4nnn)	(2l)	(3p)
(2)-176	(IIf)	(4cccc)	(2m)	(3q)
(2)-177	(IIf)	(4vvv)	(2r)	(3v)
(2)-178	(IIf)	(4cccc)	(2v)	(3w)

	(II)	Ring A	Y	Z
(2)-179	(IIf)	(4vvv)	(2aa)	(3x)
(2)-180	(IIf)	(4nnn)	(2m)	(3aa)
(2)-181	(IIg)	(4i)	(2r)	(3ee)
(2)-182	(IIg)	(4j)	(2v)	(3ii)
(2)-183	(IIg)	(4k)	(2aa)	(3kk)
(2)-184	(IIg)	(4l)	(2bb)	(3oo)
(2)-185	(IIg)	(4n)	(2cc)	(3rr)
(2)-186	(IIg)	(4nnn)	(2m)	(3v)
(2)-187	(IIg)	(4cccc)	(2r)	(3w)
(2)-188	(IIg)	(4j)	(2v)	(3x)
(2)-189	(IIg)	(4k)	(2aa)	(3aa)
(2)-190	(IIg)	(4l)	(2bb)	(3ee)
(2)-191	(IIg)	(4n)	(2cc)	(3o)
(2)-192	(IIg)	(4j)	(2l)	(3p)
(2)-193	(IIg)	(4k)	(2m)	(3a)
(2)-194	(IIg)	(4l)	(2r)	(3b)
(2)-195	(IIg)	(4n)	(2v)	(3v)
(2)-196	(IIg)	(4nnn)	(2aa)	(3w)
(2)-197	(IIg)	(4cccc)	(2bb)	(3x)
(2)-198	(IIg)	(4i)	(2cc)	(3aa)
(2)-199	(IIg)	(4i)	(2ff)	(3o)
(2)-200	(IIg)	(4j)	(2gg)	(3p)
(2)-201	(IIg)	(4k)	(2hh)	(3q)
(2)-202	(IIg)	(4l)	(2ii)	(3v)
(2)-203	(IIg)	(4n)	(2jj)	(3w)
(2)-204	(IIg)	(4nnn)	(2kk)	(3x)

	(II)	Ring A	Y	Z
(2)-205	(IIg)	(4cccc)	(2ll)	(3aa)
(2)-206	(IIg)	(4vvv)	(2e)	(3o)
(2)-207	(IIg)	(4cccc)	(2h)	(3p)
(2)-208	(IIg)	(4l)	(2i)	(3a)
(2)-209	(IIg)	(4n)	(2l)	(3b)
(2)-210	(IIg)	(4nnn)	(2m)	(3b)
(2)-211	(IIh)	(4o)	(2cc)	(3c)
(2)-212	(IIh)	(4p)	(2ff)	(3f)
(2)-213	(IIh)	(4s)	(2e)	(3h)
(2)-214	(IIh)	(4t)	(2h)	(3j)
(2)-215	(IIh)	(4w)	(2i)	(3m)
(2)-216	(IIh)	(4p)	(2l)	(3n)
(2)-217	(IIh)	(4s)	(2m)	(3o)
(2)-218	(IIh)	(4o)	(2r)	(3p)
(2)-219	(IIh)	(4o)	(2v)	(3q)
(2)-220	(IIh)	(4p)	(2aa)	(3v)
(2)-221	(IIh)	(4s)	(2bb)	(3w)
(2)-222	(IIh)	(4o)	(2cc)	(3x)
(2)-223	(IIh)	(4p)	(2ff)	(3aa)
(2)-224	(IIh)	(4s)	(2gg)	(3ee)
(2)-225	(IIh)	(4t)	(2hh)	(3ii)
(2)-226	(IIh)	(4w)	(2ii)	(3kk)
(2)-227	(IIh)	(4o)	(2jj)	(3oo)
(2)-228	(IIh)	(4p)	(2kk)	(3rr)
(2)-229	(IIh)	(4s)	(2ll)	(3m)
(2)-230	(IIh)	(4t)	(2e)	(3n)

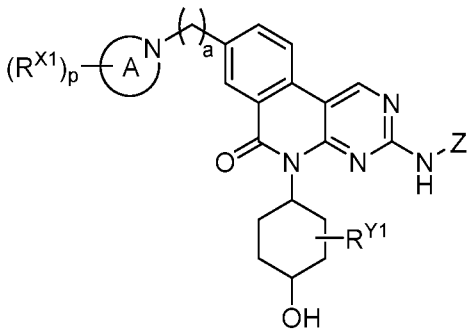
	(II)	Ring A	Y	Z
(2)-231	(IIh)	(4nnn)	(2h)	(3o)
(2)-232	(IIh)	(4ooo)	(2i)	(3p)
(2)-233	(IIh)	(4ppp)	(2l)	(3q)
(2)-234	(IIh)	(4qqq)	(2m)	(3v)
(2)-235	(IIh)	(4ttt)	(2cc)	(3w)
(2)-236	(IIh)	(4vvv)	(2ff)	(3x)
(2)-237	(IIh)	(4yyy)	(2e)	(3aa)
(2)-238	(IIh)	(4zzz)	(2h)	(3o)
(2)-239	(IIh)	(4cccc)	(2i)	(3p)
(2)-240	(IIh)	(4dddd)	(2l)	(3q)
(2)-241	(IIi)	(4x)	(2m)	(3v)
(2)-242	(IIi)	(4aa)	(2aa)	(3w)
(2)-243	(IIi)	(4ee)	(2bb)	(3x)
(2)-244	(IIi)	(4ff)	(2cc)	(3aa)
(2)-245	(IIi)	(4gg)	(2ff)	(3ee)
(2)-246	(IIi)	(4jj)	(2e)	(3ii)
(2)-247	(IIi)	(4ff)	(2h)	(3kk)
(2)-248	(IIi)	(4gg)	(2i)	(3oo)
(2)-249	(IIi)	(4jj)	(2l)	(3rr)
(2)-250	(IIi)	(4ee)	(2m)	(3o)
(2)-251	(IIi)	(4aa)	(2r)	(3p)
(2)-252	(IIi)	(4ee)	(2v)	(3a)
(2)-253	(IIi)	(4ff)	(2aa)	(3b)
(2)-254	(IIi)	(4gg)	(2bb)	(3o)
(2)-255	(IIi)	(4jj)	(2cc)	(3p)
(2)-256	(IIi)	(4ee)	(2ff)	(3q)

	(II)	Ring A	Y	Z
(2)-257	(IIi)	(4ff)	(2gg)	(3v)
(2)-258	(IIi)	(4gg)	(2hh)	(3w)
(2)-259	(IIi)	(4jj)	(2ii)	(3x)
(2)-260	(IIi)	(4aa)	(2jj)	(3aa)
(2)-261	(IIi)	(4nnn)	(2kk)	(3n)
(2)-262	(IIi)	(4ooo)	(2ll)	(3o)
(2)-263	(IIi)	(4ppp)	(2cc)	(3p)
(2)-264	(IIi)	(4qqq)	(2ff)	(3q)
(2)-265	(IIi)	(4ttt)	(2gg)	(3v)
(2)-266	(IIi)	(4vvv)	(2hh)	(3w)
(2)-267	(IIi)	(4yyy)	(2e)	(3x)
(2)-268	(IIi)	(4zzz)	(2h)	(3aa)
(2)-269	(IIi)	(4cccc)	(2i)	(3ee)
(2)-270	(IIi)	(4dddd)	(2l)	(3ii)
(2)-271	(IIj)	(4mm)	(2m)	(3kk)
(2)-272	(IIj)	(4ss)	(2d)	(3oo)
(2)-273	(IIj)	(4uu)	(2e)	(3rr)
(2)-274	(IIj)	(4ggg)	(2h)	(3v)
(2)-275	(IIj)	(4jjj)	(2i)	(3w)
(2)-276	(IIj)	(4lll)	(2l)	(3x)
(2)-277	(IIj)	(4ss)	(2m)	(3aa)
(2)-278	(IIj)	(4uu)	(2r)	(3m)

	(II)	Ring A	Y	Z
(2)-279	(IIj)	(4ggg)	(2v)	(3n)
(2)-280	(IIj)	(4mm)	(2aa)	(3o)
(2)-281	(IIj)	(4ss)	(2bb)	(3p)
(2)-282	(IIj)	(4uu)	(2cc)	(3q)
(2)-283	(IIj)	(4ggg)	(2ff)	(3v)
(2)-284	(IIj)	(4jjj)	(2gg)	(3w)
(2)-285	(IIj)	(4lll)	(2hh)	(3x)
(2)-286	(IIj)	(4mmm)	(2ii)	(3aa)
(2)-287	(IIj)	(4uu)	(2jj)	(3b)
(2)-288	(IIj)	(4ggg)	(2kk)	(3c)
(2)-289	(IIj)	(4jjj)	(2ll)	(3f)
(2)-290	(IIj)	(4lll)	(2cc)	(3h)
(2)-291	(IIj)	(4mmm)	(2ff)	(3j)
(2)-292	(IIj)	(4ooo)	(2gg)	(3m)
(2)-293	(IIj)	(4ppp)	(2hh)	(3n)
(2)-294	(IIj)	(4qqq)	(2h)	(3o)
(2)-295	(IIj)	(4ttt)	(2i)	(3p)
(2)-296	(IIj)	(4vvv)	(2l)	(3q)
(2)-297	(IIj)	(4yyy)	(2m)	(3v)
(2)-298	(IIj)	(4zzz)	(2v)	(3w)
(2)-299	(IIj)	(4cccc)	(2aa)	(3x)
(2)-300	(IIj)	(4dddd)	(2bb)	(3aa)

[0032] In some embodiments, the compound of formulae (II) or (IIa) - (IIj) is one of the following compounds (or a pharmaceutically acceptable salt, prodrug, or *N*-oxide thereof, or a solvate or hydrate thereof): 2, 3, 5, 14, 15, 16, 17, 20, 21, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 42, 43, 44, 47, 48, 50, 53, 55, 56, 57, 60, 61, 62, 65, 68, 69, 71, 73, 76, 77, 78, 80, 81, 83, 86, 88, 90, 92, 96, 97, 98, 99, 106, 107, 109, 113 or 123.

[0033] In embodiment III_1 of this aspect, the invention comprises compounds having the structure of formula (III):

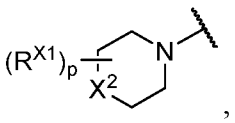


(III)

or a pharmaceutically acceptable salt, prodrug or *N*-oxide thereof, or solvate or hydrate thereof, wherein

a is 0 or 1;
ring A is

(a)

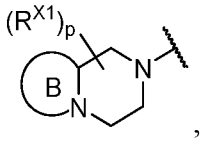


,

wherein

p is 0, 1, 2 or 3;
X^2 is -O-, -S-, $-CR^2-$, $-C(R)(R^{X1})-$, $-C(R^{X1})_2-$, -N(R)- or $-N(R^{X1})-$;

(b)

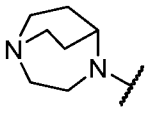


,

wherein

p is 0, 1 or 2;
ring B is 5-membered Hca or Het; or

(c)

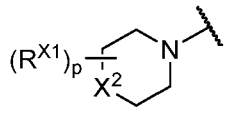


;

each $-R^{X1}$ is independently hydrogen, C_1-C_6alkyl, -C(O)OR, Cak(C_0-C_6alkyl) or Hca(Co-C_6alkyl);
$-R^{Y1}$ is hydrogen or C_1-C_6alkyl;
Z is C_1-C_6alkyl or Cak(C_1-C_6alkyl); and
each R is independently hydrogen or C_1-C_6alkyl.

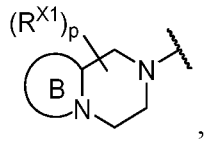
[0034] In embodiment III_2, the compounds are of embodiment I_1, wherein a is 0.
[0035] In embodiment III_3, the compounds are of embodiment I_1, wherein a is 1.

[0036] In embodiment III_4, the compounds are of embodiment I_1 - II_3, wherein ring A is



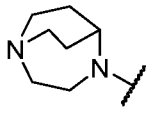
wherein p is 0, 1, 2 or 3; and X^2 is -O-, -S-, $-CR^2$-, $-C(R)(R^{X1})$-, $-C(R^{X1})_2$-, -N(R)- or $-N(R^{X1})$-.

[0037] In embodiment III_5, the compounds are of embodiment I_1 - II_3, wherein ring A is

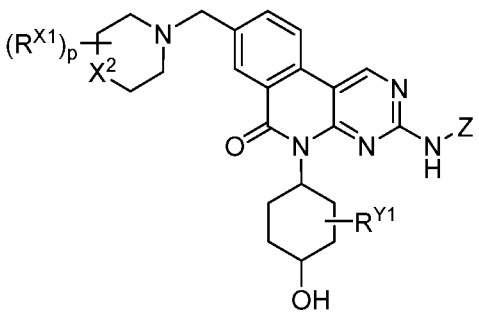
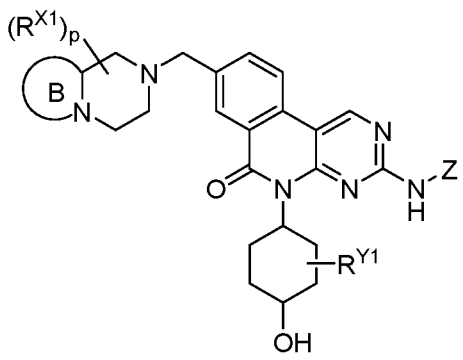
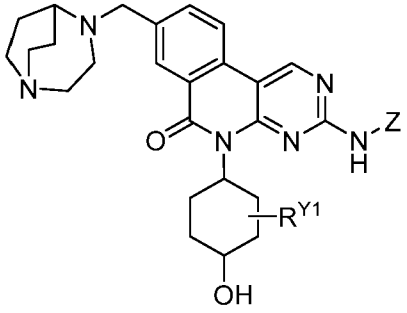
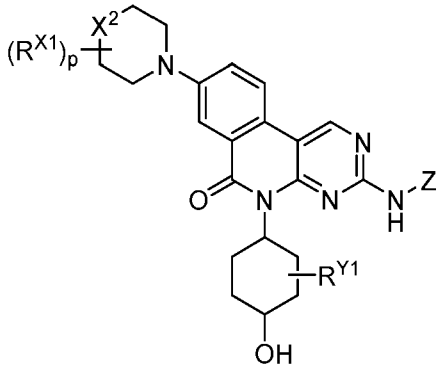


wherein p is 0, 1 or 2; and ring B is 5-membered Hca or Het.

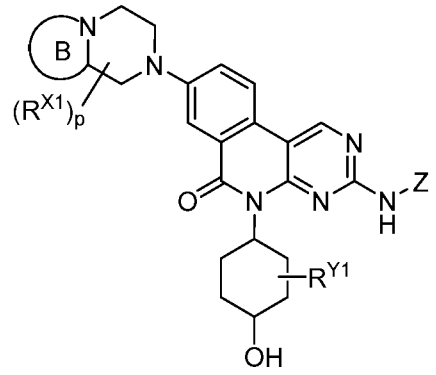
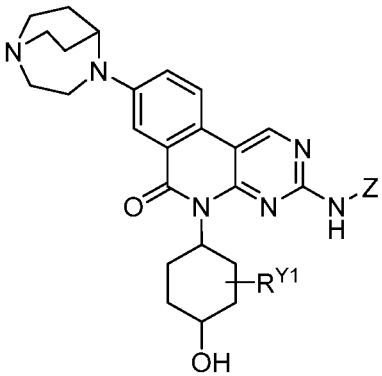
[0038] In embodiment III_6, the compounds are of embodiment I_1 - II_3, wherein ring A is



[0039] In embodiment III_7, the compounds of the invention are of one of formulae (IIIa) - (IIIf), wherein all labels are as defined in any of embodiments III_1 - III_6 above:

	
(IIIa)	(IIIb)
	
(IIIc)	(IIId)

(continued)

	
(IIIe)	(IIIf)

[0040] Particular embodiments of this aspect of the invention comprise compounds of any one of the formulae (III), and (IIIa) - (IIf), each as defined in each of the following rows (or a pharmaceutically acceptable salt, prodrug, or *N*-oxide thereof, or a solvate or hydrate thereof), wherein each entry is a group number as defined above (e.g., **(4ffff)** refers to Ring A being any of groups (4a) - (4fff), wherein p is 0, and a dash "-" indicates that the variable is as defined in embodiment III or defined according to any one of the applicable variable definitions **(4a)-(4ffff), (2a)-(211)** and **(3a)-(3xx)** [e.g., when Ring A is a dash, it can be either as defined in any of embodiments III_1 - III_7 or any one of the applicable definitions **(4a)-(4ffff)**]):

	(III)	Ring A	Z		(III)	Ring A	Z
(3)-1	(IIIa)	(4i)	(3a)	**(3)-6**	(IIIa)	(4nnn)	(3j)
(3)-2	(IIIa)	(4j)	(3b)	**(3)-7**	(IIIa)	(4cccc)	(3m)
(3)-3	(IIIa)	(4k)	(3c)	**(3)-8**	(IIIa)	(4j)	(3n)
(3)-4	(IIIa)	(4l)	(3f)	**(3)-9**	(IIIa)	(4k)	(3o)
(3)-5	(IIIa)	(4n)	(3h)	**(3)-10**	(IIIa)	(4l)	(3p)

	(III)	Ring A	Z
(3)-11	(IIIa)	(4n)	(3q)
(3)-12	(IIIa)	(4j)	(3v)
(3)-13	(IIIa)	(4k)	(3w)
(3)-14	(IIIa)	(4l)	(3x)
(3)-15	(IIIa)	(4n)	(3aa)
(3)-16	(IIIa)	(4nnn)	(3ee)
(3)-17	(IIIa)	(4cccc)	(3ii)
(3)-18	(IIIa)	(4i)	(3kk)
(3)-19	(IIIa)	(4i)	(3oo)
(3)-20	(IIIa)	(4j)	(3rr)
(3)-21	(IIIa)	(4k)	(3v)
(3)-22	(IIIa)	(4l)	(3w)
(3)-23	(IIIa)	(4n)	(3x)
(3)-24	(IIIa)	(4nnn)	(3aa)
(3)-25	(IIIa)	(4cccc)	(3n)
(3)-26	(IIIa)	(4vvv)	(3aa)
(3)-27	(IIIa)	(4cccc)	(3n)
(3)-28	(IIIa)	(4l)	(3o)
(3)-29	(IIIa)	(4n)	(3p)
(3)-30	(IIIa)	(4nnn)	(3aa)
(3)-31	(IIIa)	(4i)	(3n)
(3)-32	(IIIa)	(4j)	(3o)
(3)-33	(IIIa)	(4k)	(3p)
(3)-34	(IIIa)	(4l)	(3m)
(3)-35	(IIIa)	(4n)	(3n)

	(III)	Ring A	Z
(3)-36	(IIIa)	(4nnn)	(3o)
(3)-37	(IIIa)	(4cccc)	(3p)
(3)-38	(IIIa)	(4j)	(3q)
(3)-39	(IIIa)	(4k)	(3v)
(3)-40	(IIIa)	(4l)	(3w)
(3)-41	(IIIa)	(4n)	(3x)
(3)-42	(IIIa)	(4j)	(3aa)
(3)-43	(IIIa)	(4k)	(3n)
(3)-44	(IIIa)	(4l)	(3o)
(3)-45	(IIIa)	(4n)	(3p)
(3)-46	(IIIa)	(4nnn)	(3q)
(3)-47	(IIIa)	(4cccc)	(3aa)
(3)-48	(IIIa)	(4i)	(3n)
(3)-49	(IIIa)	(4i)	(3o)
(3)-50	(IIIa)	(4j)	(3p)
(3)-51	(IIIb)	(4o)	(3b)
(3)-52	(IIIb)	(4p)	(3c)
(3)-53	(IIIb)	(4s)	(3f)
(3)-54	(IIIb)	(4t)	(3h)
(3)-55	(IIIb)	(4w)	(3j)
(3)-56	(IIIb)	(4p)	(3m)
(3)-57	(IIIb)	(4s)	(3n)
(3)-58	(IIIb)	(4o)	(3o)
(3)-59	(IIIb)	(4o)	(3p)
(3)-60	(IIIb)	(4p)	(3q)

	(III)	Ring A	Z
(3)-61	(IIIb)	(4s)	(3v)
(3)-62	(IIIb)	(4o)	(3w)
(3)-63	(IIIb)	(4p)	(3x)
(3)-64	(IIIb)	(4s)	(3aa)
(3)-65	(IIIb)	(4t)	(3ee)
(3)-66	(IIIb)	(4w)	(3ii)
(3)-67	(IIIb)	(4o)	(3kk)
(3)-68	(IIIb)	(4p)	(3oo)
(3)-69	(IIIb)	(4s)	(3rr)
(3)-70	(IIIb)	(4t)	(3a)
(3)-71	(IIIb)	(4w)	(3b)
(3)-72	(IIIb)	(4ooo)	(3c)
(3)-73	(IIIb)	(4ppp)	(3f)
(3)-74	(IIIb)	(4qqq)	(3h)
(3)-75	(IIIb)	(4ttt)	(3j)
(3)-76	(IIIb)	(4vvv)	(3m)
(3)-77	(IIIb)	(4yyy)	(3n)
(3)-78	(IIIb)	(4zzz)	(3o)
(3)-79	(IIIb)	(4cccc)	(3p)
(3)-80	(IIIb)	(4ooo)	(3q)
(3)-81	(IIIb)	(4o)	(3v)
(3)-82	(IIIb)	(4p)	(3w)
(3)-83	(IIIb)	(4s)	(3x)
(3)-84	(IIIb)	(4t)	(3aa)
(3)-85	(IIIb)	(4w)	(3ee)

	(III)	Ring A	Z
(3)-86	(IIIb)	(4p)	(3ii)
(3)-87	(IIIb)	(4s)	(3kk)
(3)-88	(IIIb)	(4o)	(3oo)
(3)-89	(IIIb)	(4o)	(3rr)
(3)-90	(IIIb)	(4p)	(3v)
(3)-91	(IIIb)	(4s)	(3w)
(3)-92	(IIIb)	(4o)	(3x)
(3)-93	(IIIb)	(4p)	(3aa)
(3)-94	(IIIb)	(4s)	(3o)
(3)-95	(IIIb)	(4t)	(3p)
(3)-96	(IIIb)	(4w)	(3q)
(3)-97	(IIIb)	(4o)	(3v)
(3)-98	(IIIb)	(4p)	(3w)
(3)-99	(IIIb)	(4s)	(3x)
(3)-100	(IIIb)	(4t)	(3aa)
(3)-101	(IIIc)	-	(3v)
(3)-102	(IIIc)	-	(3w)
(3)-103	(IIIc)	-	(3x)
(3)-104	(IIIc)	-	(3aa)
(3)-105	(IIIc)	-	(3b)
(3)-106	(IIIc)	-	(3c)
(3)-107	(IIIc)	-	(3f)
(3)-108	(IIIc)	-	(3h)
(3)-109	(IIIc)	-	(3j)
(3)-110	(IIIc)	-	(3m)

	(III)	Ring A	Z
(3)-111	(IIIc)	-	(3n)
(3)-112	(IIIc)	-	(3o)
(3)-113	(IIIc)	-	(3p)
(3)-114	(IIIc)	-	(3q)
(3)-115	(IIIc)	-	(3v)
(3)-116	(IIIc)	-	(3w)
(3)-117	(IIIc)	-	(3x)
(3)-118	(IIIc)	-	(3aa)
(3)-119	(IIIc)	-	(3ee)
(3)-120	(IIIc)	-	(3ii)
(3)-121	(IIIc)	-	(3kk)
(3)-122	(IIIc)	-	(3oo)
(3)-123	(IIIc)	-	(3rr)
(3)-124	(IIIc)	-	(3aa)
(3)-125	(IIIc)	-	(3n)
(3)-126	(IIIc)	-	(3o)
(3)-127	(IIIc)	-	(3p)
(3)-128	(IIIc)	-	(3aa)
(3)-129	(IIIc)	-	(3a)
(3)-130	(IIIc)	-	(3b)
(3)-131	(IIIc)	-	(3c)
(3)-132	(IIIc)	-	(3f)
(3)-133	(IIIc)	-	(3h)
(3)-134	(IIIc)	-	(3j)
(3)-135	(IIIc)	-	(3m)

	(III)	Ring A	Z
(3)-136	(IIIc)	-	(3n)
(3)-137	(IIIc)	-	(3o)
(3)-138	(IIIc)	-	(3p)
(3)-139	(IIIc)	-	(3q)
(3)-140	(IIIc)	-	(3v)
(3)-141	(IIIc)	-	(3w)
(3)-142	(IIIc)	-	(3x)
(3)-143	(IIIc)	-	(3aa)
(3)-144	(IIIc)	-	(3ee)
(3)-145	(IIIc)	-	(3ii)
(3)-146	(IIIc)	-	(3kk)
(3)-147	(IIIc)	-	(3oo)
(3)-148	(IIIc)	-	(3rr)
(3)-149	(IIIc)	-	(3aa)
(3)-150	(IIIc)	-	(3n)
(3)-151	(IIId)	(4i)	(3o)
(3)-152	(IIId)	(4j)	(3p)
(3)-153	(IIId)	(4k)	(3m)
(3)-154	(IIId)	(4l)	(3n)
(3)-155	(IIId)	(4n)	(3o)
(3)-156	(IIId)	(4nnn)	(3p)
(3)-157	(IIId)	(4cccc)	(3q)
(3)-158	(IIId)	(4j)	(3v)
(3)-159	(IIId)	(4k)	(3w)
(3)-160	(IIId)	(4l)	(3x)

	(III)	Ring A	Z
(3)-161	(IIId)	(4n)	(3aa)
(3)-162	(IIId)	(4j)	(3aa)
(3)-163	(IIId)	(4k)	(3n)
(3)-164	(IIId)	(4l)	(3o)
(3)-165	(IIId)	(4n)	(3p)
(3)-166	(IIId)	(4nnn)	(3a)
(3)-167	(IIId)	(4cccc)	(3b)
(3)-168	(IIId)	(4i)	(3c)
(3)-169	(IIId)	(4i)	(3f)
(3)-170	(IIId)	(4j)	(3h)
(3)-171	(IIId)	(4k)	(3j)
(3)-172	(IIId)	(4l)	(3m)
(3)-173	(IIId)	(4n)	(3n)
(3)-174	(IIId)	(4nnn)	(3o)
(3)-175	(IIId)	(4cccc)	(3p)
(3)-176	(IIId)	(4vvv)	(3q)
(3)-177	(IIId)	(4cccc)	(3v)
(3)-178	(IIId)	(4l)	(3w)
(3)-179	(IIId)	(4n)	(3x)
(3)-180	(IIId)	(4nnn)	(3aa)
(3)-181	(IIId)	(4i)	(3ee)
(3)-182	(IIId)	(4j)	(3ii)
(3)-183	(IIId)	(4k)	(3kk)
(3)-184	(IIId)	(4l)	(3oo)
(3)-185	(IIId)	(4n)	(3rr)

	(III)	Ring A	Z
(3)-186	(IIId)	(4nnn)	(3v)
(3)-187	(IIId)	(4cccc)	(3w)
(3)-188	(IIId)	(4j)	(3x)
(3)-189	(IIId)	(4k)	(3aa)
(3)-190	(IIId)	(4l)	(3ee)
(3)-191	(IIId)	(4n)	(3o)
(3)-192	(IIId)	(4j)	(3p)
(3)-193	(IIId)	(4k)	(3a)
(3)-194	(IIId)	(4l)	(3b)
(3)-195	(IIId)	(4n)	(3v)
(3)-196	(IIId)	(4nnn)	(3w)
(3)-197	(IIId)	(4cccc)	(3x)
(3)-198	(IIId)	(4i)	(3aa)
(3)-199	(IIId)	(4i)	(3o)
(3)-200	(IIId)	(4j)	(3p)
(3)-201	(IIIe)	(4o)	(3q)
(3)-202	(IIIe)	(4p)	(3v)
(3)-203	(IIIe)	(4s)	(3w)
(3)-204	(IIIe)	(4t)	(3x)
(3)-205	(IIIe)	(4w)	(3aa)
(3)-206	(IIIe)	(4p)	(3o)
(3)-207	(IIIe)	(4s)	(3p)
(3)-208	(IIIe)	(4o)	(3a)
(3)-209	(IIIe)	(4o)	(3b)
(3)-210	(IIIe)	(4p)	(3b)

	(III)	Ring A	Z
(3)-211	(IIIe)	(4s)	(3c)
(3)-212	(IIIe)	(4o)	(3f)
(3)-213	(IIIe)	(4p)	(3h)
(3)-214	(IIIe)	(4s)	(3j)
(3)-215	(IIIe)	(4t)	(3m)
(3)-216	(IIIe)	(4w)	(3n)
(3)-217	(IIIe)	(4o)	(3o)
(3)-218	(IIIe)	(4p)	(3p)
(3)-219	(IIIe)	(4s)	(3q)
(3)-220	(IIIe)	(4t)	(3v)
(3)-221	(IIIe)	(4w)	(3w)
(3)-222	(IIIe)	(4ooo)	(3x)
(3)-223	(IIIe)	(4ppp)	(3aa)
(3)-224	(IIIe)	(4qqq)	(3ee)
(3)-225	(IIIe)	(4ttt)	(3ii)
(3)-226	(IIIe)	(4vvv)	(3kk)
(3)-227	(IIIe)	(4yyy)	(3oo)
(3)-228	(IIIe)	(4zzz)	(3rr)
(3)-229	(IIIe)	(4cccc)	(3m)
(3)-230	(IIIe)	(4ooo)	(3n)
(3)-231	(IIIe)	(4o)	(3o)
(3)-232	(IIIe)	(4p)	(3p)
(3)-233	(IIIe)	(4s)	(3q)
(3)-234	(IIIe)	(4t)	(3v)
(3)-235	(IIIe)	(4w)	(3w)

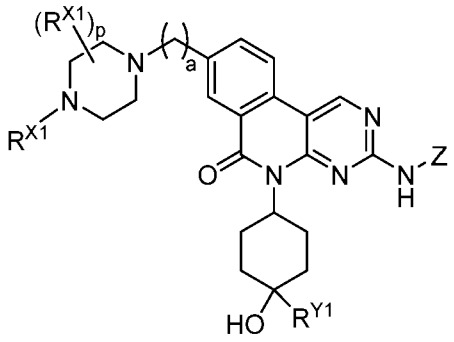
	(III)	Ring A	Z
(3)-236	(IIIe)	(4p)	(3x)
(3)-237	(IIIe)	(4s)	(3aa)
(3)-238	(IIIe)	(4o)	(3o)
(3)-239	(IIIe)	(4o)	(3p)
(3)-240	(IIIe)	(4p)	(3q)
(3)-241	(IIIe)	(4s)	(3v)
(3)-242	(IIIe)	(4o)	(3w)
(3)-243	(IIIe)	(4p)	(3x)
(3)-244	(IIIe)	(4s)	(3aa)
(3)-245	(IIIe)	(4t)	(3ee)
(3)-246	(IIIe)	(4w)	(3ii)
(3)-247	(IIIe)	(4o)	(3kk)
(3)-248	(IIIe)	(4p)	(3oo)
(3)-249	(IIIe)	(4s)	(3rr)
(3)-250	(IIIe)	(4t)	(3o)
(3)-251	(IIIf)	-	(3p)
(3)-252	(IIIf)	-	(3a)
(3)-253	(IIIf)	-	(3b)
(3)-254	(IIIf)	-	(3o)
(3)-255	(IIIf)	-	(3p)
(3)-256	(IIIf)	-	(3q)
(3)-257	(IIIf)	-	(3v)
(3)-258	(IIIf)	-	(3w)
(3)-259	(IIIf)	-	(3x)
(3)-260	(IIIf)	-	(3aa)

	(III)	Ring A	Z
(3)-261	(IIIf)	-	(3n)
(3)-262	(IIIf)	-	(3o)
(3)-263	(IIIf)	-	(3p)
(3)-264	(IIIf)	-	(3q)
(3)-265	(IIIf)	-	(3v)
(3)-266	(IIIf)	-	(3w)
(3)-267	(IIIf)	-	(3x)
(3)-268	(IIIf)	-	(3aa)
(3)-269	(IIIf)	-	(3ee)
(3)-270	(IIIf)	-	(3ii)
(3)-271	(IIIf)	-	(3kk)
(3)-272	(IIIf)	-	(3oo)
(3)-273	(IIIf)	-	(3rr)
(3)-274	(IIIf)	-	(3v)
(3)-275	(IIIf)	-	(3w)
(3)-276	(IIIf)	-	(3x)
(3)-277	(IIIf)	-	(3aa)
(3)-278	(IIIf)	-	(3m)
(3)-279	(IIIf)	-	(3n)
(3)-280	(IIIf)	-	(3o)

	(III)	Ring A	Z
(3)-281	(IIIf)	-	(3p)
(3)-282	(IIIf)	-	(3q)
(3)-283	(IIIf)	-	(3v)
(3)-284	(IIIf)	-	(3w)
(3)-285	(IIIf)	-	(3x)
(3)-286	(IIIf)	-	(3aa)
(3)-287	(IIIf)	-	(3b)
(3)-288	(IIIf)	-	(3c)
(3)-289	(IIIf)	-	(3f)
(3)-290	(IIIf)	-	(3h)
(3)-291	(IIIf)	-	(3j)
(3)-292	(IIIf)	-	(3m)
(3)-293	(IIIf)	-	(3n)
(3)-294	(IIIf)	-	(3o)
(3)-295	(IIIf)	-	(3p)
(3)-296	(IIIf)	-	(3q)
(3)-297	(IIIf)	-	(3v)
(3)-298	(IIIf)	-	(3w)
(3)-299	(IIIf)	-	(3x)
(3)-300	(IIIf)	-	(3aa)

[0041] In some embodiments, the compound of formulae (III) or (IIIa) - (IIIf) is one of the following compounds (or a pharmaceutically acceptable salt, prodrug, or *N*-oxide thereof, or a solvate or hydrate thereof): 2, 3, 15, 20, 21, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 38, 42, 47, 48, 50, 53, 55, 60, 61, 69, 71, 73, 76, 77, 78, 80, 81, 83, 86, 90, 92, 96, 98 or 113.

[0042] In embodiment IV_1 of this aspect, the invention comprises compounds having the structure of formula (IV):



(IV)

or a pharmaceutically acceptable salt, prodrug or *N*-oxide thereof, or solvate or hydrate thereof, wherein

a is 0 or 1;
each -R^{X1} is independently hydrogen or C_1-C_6alkyl;
-R^{Y1} is hydrogen or C_1-C_6alkyl; and
Z is C_1-C_6alkyl or Cak(C_1-C_6alkyl).

[0043] In embodiment IV_2, the compounds are of embodiment IV_1, wherein a is 0.
[0044] In embodiment IV_3, the compounds are of embodiment IV_1, wherein a is 1.
[0045] In embodiment IV_4, the compounds are of any of embodiments IV_1 - IV_3, wherein Z is C_1-C_6alkyl.
[0046] In embodiment IV_5, the compounds are of any of embodiments IV_1 - IV_3, wherein Z is Cak(C_1-C_6alkyl).
[0047] In some embodiments, the compound of formulae (IV) is one of the following compounds (or a pharmaceutically acceptable salt, prodrug, or *N*-oxide thereof, or a solvate or hydrate thereof): 15, 29, 32, 33, 34, 60 or 78.
[0048] In another aspect, the present invention comprises pharmaceutical compositions comprising a compound according to any one of the preceding aspects of the invention or any embodiment thereof, together with a pharmaceutically acceptable excipient, diluent, or carrier.
[0049] A compound described by any one of the preceding aspects of the invention or any embodiment thereof, may be useful for the preparation of a medicament for the treatment of medical diseases or conditions that benefit from the inhibition of cytokine signaling. Medical conditions contemplated in this regard include all diseases and conditions described herein.
[0050] The compounds of formulae (I), (Ia) - (If), (II), (IIa) - (IIj), (III), (IIIa) - (IIIf) and (IV) described above are useful as tyrosine kinase inhibitors. Tyrosine kinases are characterized by a conserved sequence within the kinase domain and adhesion molecule-like extracellular domains. Tyrosine kinases regulate a number of biological processes, including cell proliferation/survival, cell adhesion and migration, blood clot stabilization, and regulation of inflammatory cytokine release. Genetic or experimental alteration of tyrosine kinase function, specifically of the TAM (Tyro 3, Axl and Mer) receptor family, can contribute to a number of disease states, including coagulopathy, autoimmune disease, retinitis pigmentosa, and cancer. Thus, tyrosine kinases, specifically the TAM (Tyro 3, Axl and Mer) receptor family play a role in oncogenic mechanisms as family members are overexpressed in a spectrum of human cancers and have prognostic significance in some. In one aspect the present compounds are selective for one or more tyrosine kinase. For example, exemplary compounds inhibit one or more of the TAM (Tyro 3, Axl and Mer) receptor family. In certain examples, the present compounds inhibit Mer from about 5-fold less potently to about equipotently with Axl. In other examples, the present compounds inhibit Mer selectively over Axl.
[0051] In particular, it is disclosed that the present compounds can be useful in treating disorders, such as pulmonary hypertension, chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcers, ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, peritoneal and sub-dermal adhesion, kidney fibrosis, lung fibrosis, including idiopathic pulmonary fibrosis, and liver fibrosis, hepatitis B, hepatitis C, alcohol-induced hepatitis, cancer, haemochromatosis, primary biliary cirrhosis, restenosis, retroperitoneal fibrosis, mesenteric fibrosis, endometriosis, keloids, cancer, abnormal bone function, inflammatory disorders, scarring and photoaging of the skin.
[0052] Particular proliferative diseases also disclosed herein that can be treated with the present compounds include those selected from a benign or malignant tumor, carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina or thyroid, sarcoma, glioblastomas, multiple myeloma or gastrointestinal cancer, especially colon carcinoma or colorectal adenoma or a tumor of the neck and head, an epidermal hyperproliferation, melanoma, psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of

epithelial character, leukemias and lymphomas, a mammary carcinoma or a leukemia. Other diseases include Cowden syndrome, Lhermitte-Dudos disease and Bannayan-Zonana syndrome, or diseases in which the PI3K/PKB pathway is aberrantly activated.

[0053] The compounds described herein also include isotopically labeled compounds where one or more atoms have an atomic mass different from the atomic mass conventionally found in nature. Examples of isotopes that may be incorporated into the compounds disclosed herein include, but are not limited to, ^{2}H , ^{3}H , ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{18}F etc. Thus, the disclosed compounds may be enriched in one or more of these isotopes relative to the natural abundance of such isotope. As is known to those of skill in the art, such isotopically enriched compounds are useful for a variety of purposes. For example, substitution with heavier isotopes such as deuterium (^{2}H) may afford certain therapeutic advantages that result from greater metabolic stability. Substitution with positron emitting isotopes, such as 18F can be useful in Positron Emission Tomography (PET) studies. By way of example, deuterium (^{2}H) has a natural abundance of about 0.015%. Accordingly, for approximately every 6,500 hydrogen atoms occurring in nature, there is one deuterium atom. Specifically contemplated herein are compounds enriched in deuterium at one or more positions. Thus, deuterium containing compounds of the disclosure have deuterium at one or more positions (as the case may be) in an abundance of greater than 0.015%.

[0054] In another aspect, the invention comprises a present compound or pharmaceutical composition in combination with one or more chemotherapeutic agents for use in the treatment of hematological neoplasms. The compounds disclosed herein may be used in combination with standard of care anti-proliferative treatments of cancer. The amount of a compound disclosed herein for use in the combination therapy is an amount sufficient to inhibit one or more of the TAM (Tyro 3, Axl and Mer) receptor family. Treatment with the present compounds thus blocks the ability of cancer stem cells to recapitulate a tumor destroyed by treatment with standard of care. Efficacy of treatment can be determined by any art recognized method generally empolyed for the particular cancer being treated and includes, for example, retardation, inhibition, or regression of tumor growth.

[0055] Reference to "combination therapy" and treatment with a compound dislcosed herein "in conjunction with" another therapeutic treatment means that the compound and other therapeutic treatment can be administered simultaneously or sequentially such that the resultant treatment is more efficacious than either treatment alone.

[0056] The one or more chemotherapeutic agents may be selected from the group consisting of antimetabolites, alkylating agents, coordination compounds, platinum complexes, DNA crosslinking compounds, inhibitors of transcription enzymes, tyrosine kinase inhibitors, protein kinase inhibitors, topoisomerase inhibitors, DNA minor-groove binding compounds, vinca alkyloids, taxanes, antitumor antibiotics, hormones, aromatase inhibitors, enzymes, growth factor receptors antibodies, cytokines, cell surface markers antibodies, HDAC inhibitors, HSP 90 inhibitors, BCL-2 inhibitors, B-raf inhibitors, MEK inhibitors, mTOR inhibitors, proteasome inhibitors and monoclonal antibodies.

[0057] Among the BCL-2 inhibitors useful in the invention is ABT-199.

[0058] The one or more chemotherapeutic agents may be independently selected from the group consisting of mechlorothamine, cyclophosphamide, ifosfamide, melphalan, chlorambucil, ethyleneimines, methylmelamines, procarbazine, dacarbazine, temozolomide, busulfan, carmustine, lomustine, methotrexate, fluorouracil, capecitabine, cytarabine, gemcitabine, cytosine arabinoside, mecaptopurine, fludarabine, cladribine, thioguanine, azathioprine, vinblastine, vincristine, paclitaxel, docetaxel, colchicine, actinomycin D, daunorubicin, bleomycin,L-asparaginase, cisplatin, carboplatin, oxaliplatin, prednisone, dexamethasone, amino glutethimide, formestane, anastrozole, hydroxyprogesterone caproate, medroxyprogesterone, tamoxifen, amsacrine, mitoxantrone, topotecan, irinotecan, camptothecin, afatinib, axitinib, bosutinib, bortezomib, carfilzomib, cabozantinib, cediranib, crizotinib, dasatinib, dabrafenib, evorolimus, ibrutinib, LDK378, LGX818, MEK162, regorafenib, ruxolitinib, selumetinib, sorafenib, trametinib, vemurafenib, erlotinib, gefitinib, imatinib, lapatinib, lestaurtinib, nilotinib, palbociclib, pazopanib, pomatinib, semaxanib, sirolimus, sunitinib, temsirolimus, vatalanib, vandetanib, anti Her2 antibodies, interferon-α, interferon-γ, interleukin 2, GM CSF, anti CTLA 4 antibodies, rituximab, anti CD33 antibodies, MGCD0103, vorinostat, 17-AAG, thalidomide, lenalidomide, rapamycin, CCI-779, doxorubicine, gemcitabine, melphalan, NPI052, gemtuzumab, alemtuzumab, cetuximab, ibritumomab tiuxaetan, tositumomab, iodine-131 tositumomab, trastuzumab, ado-trastuzumab emtansine, obinutuzumab, bevacizumab, rituximab, and anti-TRAIL death receptor antibodies.

[0059] In particular, the presently disclosed compounds are useful in combination with immunooncology agents, such as checkpoint inhibitors. Examples of such agents include anti-CTLA 4 agents, anti-PD1 and anti PD-L1 agents. Among the CTLA 4 antibodies that can be used in the present invention is ipilimumab, marketed as YERVOY® by Bristol-Myers Squibb.

[0060] Other checkpoint pathway inhibitors include PD-1 inhibitors, such as nivolumab and lambrolizumab, and PD-L1 inhibitors, such as pembrolizumab, MEDI-4736 and MPDL3280A/RG7446. Additional checkpoint inhibitors for combination with the compounds disclosed herein include, Anti-LAG-3 agents, such as BMS-986016 (MDX-1408).

[0061] Further chemotherapeutic agents for combination with the presently disclosed TAM receptor family inhibitors include Anti-SLAMF7 agents, such as the humanized monoclonal antibody elotuzumab (BMS-901608), anti-KIR agents, such as the anti-KIR monoclonal antibody lirilumab (BMS-986015), and anti-CD137 agents, such as the fully human

monoclonal antibody urelumab (BMS-663513).

[0062] The following table displays exemplary cancers treatable in combination therapies that are further disclosed and the therapeutic drug and/or other treatment for use with the compounds disclosed herein:

Cancer	Drug or Treatment
Glioma	lomustine, temozolide and/or radiation
hepatocellular carcinoma	sorafenib, regorafenib
myelodysplastic syndromes	decitabine or azacytidine
pancreatic cancer	Gemcitabine
ovarian cancer, such as epithelial ovarian carcinoma	carboplatin, cisplatin, doxorubicin, gemcitabine, paclitaxel
breast cancer	Trastuzumab
basal and squamous skin carcinomas	5-fluorouracil, imiquimod, photodynamic therapy (e.g. with 5-aminolevulinic acid),
head and neck carcinoma	bleomycin, cisplatin, cetuximab, docetaxel, fluorouracil, methotrexate
triple negative breast cancer	Paclitaxel
Prostate	abiraterone, enzalutamide

[0063] Further disclosed is a method of determining and measuring the ability of the compounds disclosed herein to inhibit TAM (Tyro 3, Axl and Mer) receptor family, in order to identify cancers and, more specifically, tumors. Neoplasms susceptible to such combination therapy can be identified by testing for TAM (Tyro 3, Axl and Mer) receptor family activity using techniques known to those skilled in the art. Optionally, where the tested compound is found to inhibit one or more of the TAM (Tyro 3, Axl and Mer) receptor family in the tested neoplasm, the compound may be subsequently used in a combination therapy for treatment of the neoplasm, as described herein.

Definitions

[0064] The names of the chemical structures disclosed herein are generated from the structures by ChemDraw Profession version 16.

[0065] Terms used herein may be preceded and/or followed by a single dash, "-", or a double dash, "=", to indicate the bond order of the bond between the named substituent and its parent moiety; a single dash indicates a single bond and a double dash indicates a double bond or a pair of single bonds in the case of a spiro-substituent. In the absence of a single or double dash it is understood that a single bond is formed between the substituent and its parent moiety; further, substituents are intended to be read "left to right" unless a dash indicates otherwise. For example, arylalkyl, arylalkyl-, and -alkylaryl indicate the same functionality.

[0066] For simplicity, chemical moieties are defined and referred to throughout primarily as univalent chemical moieties (e.g., alkyl, aryl, etc.). Nevertheless, such terms are also used to convey corresponding multivalent moieties under the appropriate structural circumstances clear to those skilled in the art. For example, while an "alkyl" moiety can refer to a monovalent radical (*e.g.* CH_3-CH_2-), in some circumstances a bivalent linking moiety can be "alkyl," in which case those skilled in the art will understand the alkyl to be a divalent radical (*e.g.*, -CH_2-CH_2-), which is equivalent to the term "alkylene." (Similarly, in circumstances in which a divalent moiety is required and is stated as being "aryl," those skilled in the art will understand that the term "aryl" refers to the corresponding divalent moiety, arylene). All atoms are understood to have their normal number of valences for bond formation (*i.e.,* 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S). Nitrogens in the presently disclosed compounds can be hypervalent, e.g., an N-oxide or tetrasubstituted ammonium salt. On occasion a moiety may be defined, for example, as $(A)_a$-B-, wherein a is 0 or 1. In such instances, when a is 0 the moiety is B- and when a is 1 the moiety is A-B-.

[0067] As used herein, the term "alkyl" includes alkyl, alkenyl and alkynyl groups of a designed number of carbon atoms, such as 1 to 6 carbons (i.e., inclusive of 1 and 6), 1 to 6 carbons, 1 to 3 carbons, or 1, 2, 3, 4, 5 or 6. The term "C_m-$C_n$alkyl" means an alkyl group having from m to n carbon atoms (i.e., inclusive of m and n). The term "C_m-$C_n$alkyl" means an alkyl group having from m to n carbon atoms. For example, "C_1-C_6alkyl" is an alkyl group having from one to six carbon atoms. Alkyl and alkyl groups may be straight or branched and depending on context, may be a monovalent radical or a divalent radical (i.e., an alkylene group). In the case of an alkyl or alkyl group having zero carbon atoms (i.e.,

"Coalkyl"), the group is simply a single covalent bond if it is a divalent radical or is a hydrogen atom if it is a monovalent radical. For example, the moiety "-(C_0-C_6alkyl)-Ar" signifies connection of an optionally substituted aryl through a single bond or an alkylene bridge having from 1 to 6 carbons. Examples of "alkyl" include, for example, methyl, ethyl, propyl, isopropyl, butyl, iso-, sec- and tert-butyl, pentyl, hexyl, heptyl, 3-ethylbutyl, 3-hexenyl and propargyl. If the number of carbon atoms is not specified, the subject "alkyl" or "alkyl" moiety has from 1 to 6 carbons.

[0068] The term "haloalkyl" is an alkyl group substituted with one or more halogen atoms, e.g. F, Cl, Br and I. A more specific term, e.g., "fluoroalkyl" is an alkyl group substituted with one or more fluorine atoms. Examples of "fluoroalkyl" include fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, hexafluoroisopropyl and the like. In certain embodiments of the compounds disclosed herein, each haloalkyl is a fluoroalkyl.

[0069] The term "aryl" or "Ar" represents an aromatic ring system having a single ring (e.g., phenyl) which is optionally fused to other aromatic hydrocarbon rings or non-aromatic hydrocarbon rings. "Aryl" includes ring systems having multiple condensed rings or 6-16 members, in which at least one is carbocyclic and aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl). Examples of aryl groups include phenyl, 1-naphthyl, 2-naphthyl, indanyl, indenyl, dihydronaphthyl, fluorenyl, tetralinyl, and 6,7,8,9-tetrahydro-5*H*-benzo[a]cycloheptenyl. In certain examples, aryl groups include those having a first carbocyclic, aromatic ring fused to an aromatic or aliphatic heterocycle, for example, 2,3-dihydrobenzofuranyl.. The aryl groups herein are unsubstituted or, when specified as "optionally substituted", can unless stated otherwise be substituted in one or more substitutable positions with various groups, as described below.

[0070] The term "heteroaryl" or "Het" refers to an aromatic ring system containing 5-15 members and at least one heteroatom selected from nitrogen, oxygen and sulfur in an aromatic ring. Heteroaryl groups will have 1-4 O, S, or N atoms, provided no O or S is adjacent to another O or S. Most commonly, the heteroaryl groups will have 1, 2, 3, or 4 heteroatoms. The heteroaryl may be fused to one or more non-aromatic ring, for example, cycloalkyl or heterocycloalkyl rings, wherein the cycloalkyl (Cak) and heterocycloalkyl (Hca) rings are described herein. In one embodiment of the present compounds the heteroaryl group is bonded to the remainder of the structure through an atom in a heteroaryl group aromatic ring. In another embodiment, the heteroaryl group is bonded to the remainder of the structure through a non-aromatic ring atom. Examples of heteroaryl groups include, for example, pyridyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl, indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, benzo[1,4]oxazinyl, triazolyl, tetrazolyl, isothiazolyl, naphthyridinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl, chromonyl, chromanonyl, pyridinyl-*N*-oxide, tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl, dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, pyrrolyl *N*-oxide, pyrimidinyl *N*-oxide, pyridazinyl *N*-oxide, pyrazinyl *N*-oxide, quinolinyl *N*-oxide, indolyl *N*-oxide, indolinyl *N*-oxide, isoquinolyl *N*-oxide, quinazolinyl *N*-oxide, quinoxalinyl *N*-oxide, phthalazinyl *N*-oxide, imidazolyl *N*-oxide, isoxazolyl *N*-oxide, oxazolyl *N*-oxide, thiazolyl *N*-oxide, indolizinyl *N*-oxide, indazolyl *N*-oxide, benzothiazolyl *N*-oxide, benzimidazolyl *N*-oxide, pyrrolyl *N*-oxide, oxadiazolyl *N*-oxide, thiadiazolyl *N*-oxide, triazolyl *N*-oxide, tetrazolyl *N*-oxide, benzothiopyranyl S-oxide, benzothiopyranyl S,S-dioxide. Preferred heteroaryl groups include pyridyl, pyrimidyl, quinolinyl, indolyl, pyrrolyl, furanyl, thienyl and imidazolyl, pyrazolyl, indazolyl, thiazolyl and benzothiazolyl. In certain embodiments, each heteroaryl is selected from pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, isothiazolyl, pyridinyl-*N*-oxide, pyrrolyl *N*-oxide, pyrimidinyl *N*-oxide, pyridazinyl *N*-oxide, pyrazinyl *N*-oxide, imidazolyl *N*-oxide, isoxazolyl *N*-oxide, oxazolyl *N*-oxide, thiazolyl *N*-oxide, pyrrolyl *N*-oxide, oxadiazolyl *N*-oxide, thiadiazolyl *N*-oxide, triazolyl *N*-oxide, and tetrazolyl *N*-oxide. Preferred heteroaryl groups include pyridyl, pyrimidyl, quinolinyl, indolyl, pyrrolyl, furanyl, thienyl, imidazolyl, pyrazolyl, indazolyl, thiazolyl and benzothiazolyl. The heteroaryl groups herein are unsubstituted or, when specified as "optionally substituted", can unless stated otherwise be substituted in one or more substitutable positions with various groups, as described below.

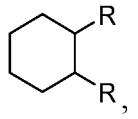
[0071] The term "heterocycloalkyl" or "Hca" refers to a non-aromatic ring or ring system containing at least one heteroatom that is preferably selected from nitrogen, oxygen and sulfur, wherein said heteroatom is in a non-aromatic ring. The heterocycloalkyl may have 1-4 O, S, or N atoms, provided no O or S is adjacent to another O or S. The heterocycloalkyl may have 1, 2, 3 or 4 heteroatoms. The heterocycloalkyl may be saturated (i.e., a heterocycloalkyl) or partially unsaturated (i.e., a heterocycloalkenyl). Heterocycloalkyl includes monocyclic groups of three to eight annular atoms as well as bicyclic and polycyclic ring systems, including bridged and fused systems, wherein each ring includes three to eight annular atoms, or the ring system includes 3-15 members. The heterocycloalkyl ring is optionally fused to other heterocycloalkyl rings and/or non-aromatic hydrocarbon rings and/or phenyl rings. In certain embodiments, the heterocycloalkyl groups have from 3 to 8 members in a single ring. In other embodiments, heterocycloalkyl groups have 5 or 6 members in a single ring. In some embodiments, the heterocycloalkyl groups have 3, 4, 5, 6, 7 or 8 members in a single ring. Examples of heterocycloalkyl groups include, for example, azabicyclo[2.2.2]octyl (in each case also "quinuclidinyl" or a

quinuclidine derivative), azabicyclo[3.2.1]octyl, 2,5-diazabicyclo[2.2.1]heptyl, morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, 2-oxazolidonyl, piperazinyl, homopiperazinyl, piperazinonyl, pyrrolidinyl, azepanyl, azetidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl, tetrahydrofuranyl, tetrahydrothienyl, 3,4-dihydroisoquinolin-2(1*H*)-yl, isoindolindionyl, homopiperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, imidazolidonyl, tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide and homothiomorpholinyl S-oxide. Especially desirable heterocycloalkyl groups include morpholinyl, 3,4-dihydroisoquinolin-2(1*H*)-yl, tetrahydropyranyl, piperidinyl, aza-bicyclo[2.2.2]octyl, γ-butyrolactonyl (i.e., an oxo-substituted tetrahydrofuranyl), γ-butryolactamyl (i.e., an oxo-substituted pyrrolidine), pyrrolidinyl, piperazinyl, azepanyl, azetidinyl, thiomorpholinyl, thiomorpholinyl S,S-dioxide, 2-oxazolidonyl, imidazolidonyl, isoindolindionyl, piperazinonyl. The heterocycloalkyl groups herein are unsubstituted or, when specified as "optionally substituted", can unless stated otherwise be substituted in one or more substitutable positions with various groups, as described below.

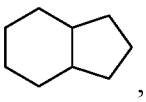
[0072] The term "cycloalkyl" or "Cak" refers to a non-aromatic carbocyclic ring or ring system, which may be saturated (i.e., a cycloalkyl) or partially unsaturated (i.e., a cycloalkenyl). The cycloalkyl ring optionally fused to or otherwise attached (e.g., spiro or bridged systems) to other cycloalkyl rings. Certain examples of cycloalkyl groups present in the disclosed compounds have from 3 to 8 members in a single ring, such as having 5 or 6 members in a single ring. In some embodiments, the cycloalkyl groups have 3, 4, 5, 6, 7 or 8 members in a single ring. Examples of cycloalkyl groups include, for example, cyclohexyl, cyclopentyl, cyclobutyl, cyclopropyl, tetrahydronaphthyl and bicyclo[2.2.1]heptane. The cycloalkyl groups herein are unsubstituted or, when specified as "optionally substituted", may be substituted in one or more substitutable positions with various groups.

[0073] The term "ring system" encompasses monocycles, as well as fused, spiro and/or bridged polycycles.

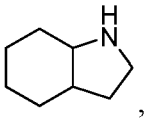
[0074] The term "fused" as used herein refers to a cyclic moiety formed by two adjacent atoms and two available substitutable postions on those atoms. Each of the rings in the fused system is independently aromatic or non-aromatic. For example, a moiety such as



wherein two R groups attached to the adjacent atoms form a fused-Cak group, which includes compounds such as

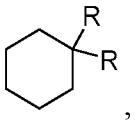


where the fused-cyclopentyl group is formed from the two R groups attached to the parent cyclohexyl ring by two single bonds. Similarly, a fused-Hca group can be formed, including such compounds as

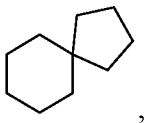


where the fused pyrrolidinyl ring is formed from the two R groups attached to the parent cyclohexyl ring by two single bonds.

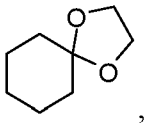
[0075] The term "spiro" as used herein refers to a cyclic moiety formed by an atom and two available substitutable postions on that same atom. For example, a moiety such as



wherein two R groups attached to the same atom form a spiro-Cak group, which includes compounds such as

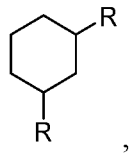


where the spiro-cyclopentyl group is formed from the two R groups attached to the parent cyclohexyl ring by two single bonds. Similarly, a spiro-Hca group can be formed, including such compounds as



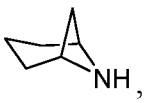
where the spiro-1,3-dioxolanyl ring is formed from the two R groups attached to the parent cyclohexyl ring by two single bonds.

[0076] The term "bridged" as used herein refers to a cyclic moiety formed by two non-adjacent atoms and two available substitutable postions on those atoms. For example, a moiety such as



wherein two R groups attached to the adjacent atoms form a fused-Cak group, which includes compounds such as

where the bridged portion is formed from the two R groups attached to the parent cyclohexyl ring by two single bonds. Similarly, a bridged-Hca group can be formed, including such compounds as



where the bridged portion is formed from the two R groups attached to the parent cyclohexyl ring by two single bonds.

[0077] The term "oxa" means a divalent oxygen radical in a chain, sometimes designated as -O-.

[0078] The term "oxo" means a doubly bonded oxygen, sometimes designated as =O or for example in describing a carbonyl "C(O)" may be used to show an oxo substituted carbon.

[0079] The term "electron withdrawing group" means a group that withdraws electron density from the structure to which it is attached than would a similarly-attached hydrogen atom. For example, electron withdrawing groups can be selected from the group consisting of halo (*e.g.,* fluoro, chloro, bromo, and iodo), cyano, -(C_1-C_4 fluoroalkyl), -O-(C_1-C_4 fluoroalkyl), - C(O)-(C_0-C_4alkyl), -C(O)O-(C_0-C_4alkyl), -C(O)N(C_0-C_4alkyl)(C_0-C_4alkyl), -S(O)$_2$O-(C_0-C_4alkyl), NO_2 and -C(O)-Hca in which the Hca includes a nitrogen atom to which the -C(O)- is bound, in which no alkyl, fluoroalkyl or heterocycloalkyl is substituted with an aryl, heteroaryl, cycloalkyl or heterocycloalkyl-containing group.

[0080] The term "substituted," when used to modify a specified group or radical, means that one or more hydrogen atoms of the specified group or radical are each, independently of one another, replaced with the same or different substituent groups as defined below, unless specified otherwise.

[0081] Substituent groups for substituting for hydrogens on saturated carbon atoms in the specified group or radical are, unless otherwise specified, -R^{60}, halo, -O^-M^+, =O, -OR^{70}, -SR^{70}, -S^-M^+, =S, -$NR^{80}R^{80}$, =NR^{70}, =N-OR^{70}, trihalomethyl, -CF_3, -CN, -OCN, -SCN, -NO, -NO_2, =N_2, -N_3, -SO_2R^{70}, -$SO_2O^-M^+$, -SO_2OR^{70}, -OSO_2R^{70}, -$OSO_2O^-M^+$, -OSO_2OR^{70}, -$P(O)(O^-)_2(M^+)_2$, -$P(O)(OR^{70})O^-M^+$, -$P(O)(OR^{70})_2$, -$C(O)R^{70}$, -$C(S)R^{70}$, -$C(NR^{70})R^{70}$, -$C(O)O^-M^+$, -$C(O)OR^{70}$, -$C(S)OR^{70}$, -$C(O)NR^{80}R^{80}$, -$C(NR^{70})NR^{80}R^{80}$, -$OC(O)R^{70}$, -$OC(S)R^{70}$, -$OC(O)O^-M^+$, -$OC(O)OR^{70}$,

-OC(S)OR^{70}, -NR^{70}C(O)R^{70}, -NR^{70}C(S)R^{70}, -$Nk^{70}CO_2$-M^+, -$NR^{70}CO_2R^{70}$, -NR^{70}C(S)OR^{70}, -NR^{70}C(O)$NR^{80}R^{80}$, -NR^{70}C(NR^{70})R^{70} and -NR^{70}C(NR^{70})$NR^{80}R^{80}$. Each R^{60} is independently selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl, each of which is optionally substituted with 1, 2, 3, 4 or 5 groups selected from the group consisting of halo, -O-M^+, =O, -OR^{71}, -SR^{71}, -S-M^+, =S, -$NR^{81}R^{81}$, =NR^{71}, =N-OR^{71}, trihalomethyl, -CF_3, -CN, -OCN, -SCN, -NO, -NO_2, =N_2, -N_3, -SO_2R^{71}, -SO_2O-M^+, -SO_2OR^{71}, -OSO_2R^{71}, -OSO_2O-M^+, -OSO_2OR^{71}, -P(O)(O-)$_2$(M^+)$_2$, -P(O)(OR^{71})O-M^+, -P(O)(OR^{71})$_2$, -C(O)R^{71}, -C(S)R^{71}, -C(NR^{71})R^{71}, -C(O)O- M^+, -C(O)OR^{71}, -C(S)OR^{71}, -C(O)$NR^{81}R^{81}$, -C(NR^{71})$NR^{81}R^{81}$, -OC(O)R^{71}, -OC(S)R^{71}, -OC(O)O -M^+, -OC(O)OR^{71}, -OC(S)OR^{71}, -NR^{71}C(O)R^{71}, -NR^{71}C(S)R^{71}, -$NR^{71}CO_2$-M^+, -$NR^{71}CO_2R^{71}$, -NR^{71}C(S)OR^{71}, -NR^{71}C(O)$NR^{81}R^{81}$, -NR^{71}C(NR^{71})R^{71} and -NR^{71}C(NR^{71})$NR^{81}R^{81}$. Each R^{70} is independently hydrogen or R^{60}; each R^{80} is independently R^{70} or alternatively, two R^{80}'s, taken together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7-membered heterocycloalkyl which may optionally include from 1 to 4 of the same or different additional heteroatoms selected from the group consisting of O, N and S, of which N may have -H or C_1-C_3alkyl substitution; and each M^+ is a counter ion with a net single positive charge. Each R^{71} is independently hydrogen or R^{61}, in which R^{61} is alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl, each of which is optionally substituted with 1, 2, 3, 4 or 5 groups selected from the group consisting of halo, -O-M^+, =O, -OR^{72}, -SR^{72}, -S-M^+, =S, -$NR^{82}R^{82}$, =NR^{72}, =N-OR^{72}, trihalomethyl, -CF_3, -CN, -OCN, -SCN, -NO, -NO_2, =N_2, -N_3, -SO_2R^{71}, -SO_2O-M^+, -SO_2OR^{72}, -OSO_2R^{72}, -OSO_2O-M^+, -OSO_2OR^{72}, -P(O)(O-)$_2$(M^+)$_2$, -P(O)(OR^{72})O-M^+, -P(O)(OR^{72})$_2$, -C(O)R^{72}, -C(S)R^{72}, -C(NR^{72})R^{72}, -C(O)O-M^+, -C(O)OR^{72}, -C(S)OR^{72}, -C(O)$NR^{82}R^{82}$, -C(NR^{72})$NR^{82}R^{82}$, -OC(O)R^{72}, -OC(S)R^{72}, -OC(O)O-M^+, -OC(O)OR^{72}, -OC(S)OR^{72}, -NR^{72}C(O)R^{72}, -NR^{72}C(S)R^{72}, -$NR^{72}CO_2$-M^+, -$NR^{72}CO_2R^{72}$, -NR^{72}C(S)OR^{72}, -NR^{72}C(O)$NR^{82}R^{82}$, -NR^{72}C(NR^{72})R^{72} and -NR^{72}C(NR^{72})$NR^{82}R^{82}$; and each R^{81} is independently R^{71} or alternatively, two R^{81}s, taken together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7-membered heterocycloalkyl which may optionally include from 1 to 4 of the same or different additional heteroatoms selected from the group consisting of O, N and S, of which N may have -H or C_1-C_3 alkyl substitution. Each R^{72} is independently hydrogen, (C_1-C_6alkyl) or (C_1-C_6fluoroalkyl); each R^{82} is independently R^{72} or alternatively, two R^{82}s, taken together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7-membered heterocycloalkyl which may optionally include 1, 2, 3 or 4 of the same or different additional heteroatoms selected from the group consisting of O, N and S, of which N may have -H or C_1-C_3alkyl substitution. Each M^+ may independently be, for example, an alkali ion, such as K^+, Na^+, Li^+; an ammonium ion, such as $^+N(R^{60})_4$; or an alkaline earth ion, such as $[Ca^{2+}]_{0.5}$, $[Mg^{2+}]_{0.5}$, or $[Ba^{2+}]_{0.5}$ ("subscript 0.5 means e.g. that one of the counter ions for such divalent alkali earth ions can be an ionized form of a presently disclosed compound and the other a typical counter ion such as chloride, or two ionized presently disclosed molecules can serve as counter ions for such divalent alkali earth ions, or a doubly ionized compound can serve as the counter ion for such divalent alkali earth ions). As specific examples, -$NR^{80}R^{80}$ is meant to include -NH_2, -NH-alkyl, *N*-pyrrolidinyl, *N*-piperazinyl, 4-methyl-piperazin-1-yl and *N*-morpholinyl.

[0082] Substituent groups for hydrogens on unsaturated carbon atoms in "substituted" alkene, alkyne, aryl and heteroaryl groups are, unless otherwise specified, -R^{60}, halo, -O-M^+, -OR^{70}, -SR^{70}, -S-M^+, -$NR^{80}R^{80}$, trihalomethyl, -CF_3, -CN, -OCN, -SCN, -NO, -NO_2, -N_3, -SO_2R^{70}, -SO_3-M^+, -SO_3R^{70}, -OSO_2R^{70}, -OSO_3-M^+, -OSO_3R^{70}, -PO_3-^{2}(M^+)$_2$, -P(O)(OR^{70})O- M^+, -P(O)(OR^{70})$_2$, -C(O)R^{70}, -C(S)R^{70}, -C(NR^{70})R^{70}, -CO_2-M^+, -CO_2R^{70}, -C(S)OR^{70}, -C(O)$NR^{80}R^{80}$, -C(NR^{70})$NR^{80}R^{80}$, -OC(O)R^{70}, -OC(S)R^{70}, -OCO_2-M^+, -OCO_2R^{70}, -OC(S)OR^{70}, -NR^{70}C(O)R^{70}, -NR^{70}C(S)R^{70}, -$NR^{70}CO_2$-M^+, -$NR^{70}CO_2R^{70}$, -NR^{70}C(S)OR^{70}, -NR^{70}C(O)$NR^{80}R^{80}$, -NR^{70}C(NR^{70})R^{70} and -NR^{70}C(NR^{70})$NR^{80}R^{80}$, where R^{60}, R^{70}, R^{80} and M^+ are as previously defined.

[0083] Substituent groups for hydrogens on nitrogen atoms in "substituted" heteroalkyl and heterocycloalkyl groups are, unless otherwise specified, -R^{60}, -O-M^+, -OR^{70}, -SR^{70}, -S-M^+, -$NR^{80}R^{80}$, trihalomethyl, -CF_3, -CN, -NO, -NO_2, -S(O)$_2R^{70}$, -S(O)$_2$O-M^+, -S(O)$_2OR^{70}$, -OS(O)$_2R^{70}$, -OS(O)$_2$O-M^+, -OS(O)$_2OR^{70}$, -P(O)(O-)$_2$(M^+)$_2$, -P(O)(OR^{70})O-M^+, -P(O)(OR^{70})(OR^{70}), -C(O)R^{70}, -C(S)R^{70}, -C(NR^{70})R^{70}, -C(O)OR^{70}, -C(S)OR^{70}, -C(O)$NR^{80}R^{80}$, -C(NR^{70})$NR^{80}R^{80}$, -OC(O)-R^{70}, -OC(S)R^{70}, -OC(O)OR^{70}, -OC(S)OR^{70}, -NR^{70}C(O)R^{70}, -NR^{70}C(S)R^{70}, -NR^{70}C(O)OR^{70}, -NR^{70}C(S)OR^{70}, -NR^{70}C(O)$NR^{80}R^{80}$, -NR^{70}C(NR^{70})R^{70} and -NR^{70}C(NR^{70})$NR^{80}R^{80}$, where R^{60}, R^{70}, R^{80} and M^+ are as previously defined.

[0084] In certain embodiments of the compounds disclosed herein, a group that is substituted has 1, 2, 3, or 4 substituents, 1, 2, or 3 substituents, 1 or 2 substituents, or 1 substituent.

[0085] In certain embodiments, substituent groups on "substituted" alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups are -halo, -OH, -O-(C_1-C_4alkyl), -O-(C_1 -C_4haloalkyl), -N(C_0-C_4 alkyl)(C_0-C_4alkyl), -SH, -S(O)$_{0-2}$-(C_1-C_4alkyl), -(C_1-C_4alkyl), -(C_1-C_4haloalkyl), -C(O)-(C_0-C_4alkyl), -C(O)N(C_0-C_4alkyl)(C_0-C_4alkyl), -N(C_0-C_4alkyl)C(O)(C_0-C_4alkyl)(C_0-C_4alkyl), -C(O)O-(C_0-C_4alkyl), -OC(O)-(C_0-C_4alkyl), S(O)$_2$-O(C_O-C_4alkyl), and -NO_2, in which no alkyl is further substituted.

[0086] The compounds disclosed herein can also be provided as pharmaceutically acceptable salts. The term "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic acids and bases and organic acids and bases. If the

compound is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids. Such salts may be, for example, acid addition salts of at least one of the following acids: benzenesulfonic acid, citric acid, α-glucoheptonic acid, D-gluconic acid, glycolic acid, lactic acid, malic acid, malonic acid, mandelic acid, phosphoric acid, propanoic acid, succinic acid, sulfuric acid, tartaric acid (d, 1, or dl), tosic acid (toluenesulfonic acid), valeric acid, palmitic acid, pamoic acid, sebacic acid, stearic acid, lauric acid, acetic acid, adipic acid, carbonic acid, 4-chlorobenzenesulfonic acid, ethanedisulfonic acid, ethylsuccinic acid, fumaric acid, galactaric acid (mucic acid), D-glucuronic acid, 2-oxo-glutaric acid, glycerophosphoric acid, hippuric acid, isethionic acid (ethanolsulfonic acid), lactobionic acid, maleic acid, 1,5-naphthalene-disulfonic acid, 2-naphthalene-sulfonic acid, pivalic acid, terephthalic acid, thiocyanic acid, cholic acid, n-dodecyl sulfate, 3-hydroxy-2-naphthoic acid, 1-hydroxy-2-naphthoic acid, oleic acid, undecylenic acid, ascorbic acid, (+)-camphoric acid, d-camphorsulfonic acid, dichloroacetic acid, ethanesulfonic acid, formic acid, hydriodic acid, hydrobromic acid, hydrochloric acid, methanesulfonic acid, nicotinic acid, nitric acid, orotic acid, oxalic acid, picric acid, L-pyroglutamic acid, saccharine, salicylic acid, gentisic acid, and/or 4-acetamidobenzoic acid.

[0087] While not envisaged as part of the invention, the compounds described herein can also be provided in prodrug form. "Prodrug" refers to a derivative of an active compound (drug) that undergoes a transformation under the conditions of use, such as within the body, to release the active drug. Prodrugs are frequently, but not necessarily, pharmacologically inactive until converted into the active drug. Prodrugs are typically obtained by masking a functional group in the drug believed to be in part required for activity with a progroup (defined below) to form a promoiety which undergoes a transformation, such as cleavage, under the specified conditions of use to release the functional group, and hence the active drug. The cleavage of the promoiety can proceed spontaneously, such as by way of a hydrolysis reaction, or it can be catalyzed or induced by another agent, such as by an enzyme, by light, by acid, or by a change of or exposure to a physical or environmental parameter, such as a change of temperature. The agent can be endogenous to the conditions of use, such as an enzyme present in the cells to which the prodrug is administered or the acidic conditions of the stomach, or it can be supplied exogenously. A wide variety of progroups, as well as the resultant promoieties, suitable for masking functional groups in the active drugs to yield prodrugs are well-known in the art. For example, a hydroxyl functional group can be masked as a sulfonate, ester or carbonate promoiety, which can be hydrolyzed *in vivo* to provide the hydroxyl group. An amino functional group can be masked as an amide, carbamate, imine, urea, phosphenyl, phosphoryl or sulfenyl promoiety, which can be hydrolyzed *in vivo* to provide the amino group. A carboxyl group can be masked as an ester (including silyl esters and thioesters), amide or hydrazide promoiety, which can be hydrolyzed *in vivo* to provide the carboxyl group. Specific examples of suitable progroups and their respective promoieties will be apparent to those of skill in the art.

[0088] The compounds disclosed herein can also be provided as *N*-oxides.

[0089] The presently disclosed compounds, salts, prodrugs and *N*-oxides can be provided, for example, in solvate or hydrate form.

[0090] One of ordinary skill in the art of medicinal chemistry also will appreciate that the disclosed structures are intended to include isotopically enriched forms of the present compounds. As used herein "isotopes" includes those atoms having the same atomic number but different mass numbers. As is known to those of skill in the art, certain atoms, such as hydrogen occur in different isotopic forms. For example, hydrogen includes three isotopic forms, protium, deuterium and tritium. As will be apparent to those of skill in the art upon consideration of the present compounds, certain compounds can be enriched at a given position with a particular isotope of the atom at that position. For example, compounds having a fluorine atom, may be synthesized in a form enriched in the radioactive fluorine isotope ^{18}F. Similarly, compounds may be enriched in the heavy isotopes of hydrogen: deuterium and tritium; and similarly can be enriched in a radioactive isotope of carbon, such as ^{13}C. Such isotopic variant compounds undergo different metabolic pathways and can be useful, for example, in studying the ubiquitination pathway and its role in disease.

[0091] As used herein, the term "cell" is meant to refer to a cell that is *in vitro,* ex vivo or *in vivo.* In some embodiments, an ex vivo cell can be part of a tissue sample excised from an organism such as a mammal. In some embodiments, an *in vitro* cell can be a cell in a cell culture. In some embodiments, an *in vivo* cell is a cell living in an organism such as a mammal.

[0092] As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" an enzyme with a compound includes the administration of a compound described herein to an individual or patient, such as a human, as well as, for example, introducing a compound into a sample containing a cellular or purified preparation containing the enzyme.

[0093] As used herein, the terms "individual," "patient," or "subject" are used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

[0094] As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician.

[0095] In certain embodiments, a therapeutically effective amount can be an amount suitable for

(1) preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed or otherwise susceptible to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;
(2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder; or
(3) ameliorating the disease (including a symptom thereof); for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.,* reversing the pathology and/or symptomatology) such as decreasing the severity of disease.

[0096] As used here, the terms "treatment" and "treating" means (i) ameliorating the referenced disease state, condition, or disorder (or a symptom thereof), such as, for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.,* reversing or improving the pathology and/or symptomatology) such as decreasing the severity of disease or symptom thereof; or (ii) eliciting the referenced biological effect (e.g., modulation or inhibition of one or more of the TAM (Tyro 3, Axl and Mer) receptor family).

[0097] Manifestation of amelioration of a disease condition by inhibiting one or more of the TAM (Tyro 3, Axl and Mer) receptor family may require the concomitant or sequential administration of additional therapeutic agents, such as antineoplastic agents in the case of cancer, or antiretroviral agents in the case of viral diseases. For example, administration of inhibitors of one or more of the TAM (Tyro 3, Axl and Mer) receptor family for the treatment of cancer does not always produce a direct antitumor effect when used as a single agent. However, when combined with chemotherapeutic drugs (antineoplastic) the antitumor effect observed is higher than the sum of effects of each agent alone.

[0098] As used herein, the terms "catalytic pocket", "catalytic site", "active site" collectively and indistinctly refer to a region of the enzyme that contains amino acid residues responsible for the substrate binding (charge, hydrophobicity, steric hindrance) and catalytic amino acid residues which act as proton donors or acceptors or are responsible for binding a cofactor and participate in the catalysis of a chemical reaction.

[0099] As used herein, the phrase "pharmaceutically acceptable salt" refers to both pharmaceutically acceptable acid and base addition salts and solvates. Such pharmaceutically acceptable salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC-$(CH_2)_n$-COOH where n is 0-4, and the like. Non-toxic pharmaceutical base addition salts include salts of bases such as sodium, potassium, calcium, ammonium, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

Pharmaceutical Formulations and Dosage Forms

[0100] The compounds of structural formulae (I) - (IV) can be administered, for example, orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing one or more pharmaceutically acceptable carriers, diluents or excipients. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (e.g., intravenous), intramuscular, or intrathecal injection or infusion techniques and the like.

[0101] Pharmaceutical compositions can be made using the presently disclosed compounds. For example, in one embodiment, a pharmaceutical composition includes a pharmaceutically acceptable carrier, diluent or excipient, and compound as described above with reference to structural formulae (I) - (IV).

[0102] In the pharmaceutical compositions disclosed herein, one or more compounds of structural formulae (I) - (IV) may be present in association with one or more pharmaceutically acceptable carriers, diluents or excipients, and, if desired, other active ingredients. The pharmaceutical compositions containing compounds of structural formulae (I) - (IV) may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

[0103] Compositions intended for oral use can be prepared according to any suitable method for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preservative agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients can be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets can be uncoated or they can be coated by known techniques. In some cases such coatings can be prepared by suitable techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed.

[0104] Formulations for oral use can also be presented as hard gelatin capsules, wherein the active ingredient is mixed

with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

[0105] Formulations for oral use can also be presented as lozenges.

[0106] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients can be suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0107] Oily suspensions can be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

[0108] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, can also be present.

[0109] Pharmaceutical compositions can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents can be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions can also contain sweetening and flavoring agents.

[0110] In some embodiments, the pharmaceutically acceptable carrier, diluent, or excipient is not water. In other embodiments, the water comprises less than 50% of the composition. In some embodiments, composiitons comprising less than 50% water have at least 1%, 2%, 3%, 4% or 5% water. In other embodiments, the water content is present in the composition in a trace amount.

[0111] In some embodiments, the pharmaceutically acceptable carrier, diluent, or excipient is not alcohol. In other embodiments, the alcohol comprises less than 50% of the composition. In some embodiments, composiitons comprising less than 50% alcohol have at least 1%, 2%, 3%, 4% or 5% alcohol. In other embodiments, the alcohol content is present in the composition in a trace amount.

[0112] Syrups and elixirs can be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations can also contain a demulcent, a preservative, flavoring, and coloring agents. The pharmaceutical compositions can be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils can be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0113] Compounds of structural formulae (I) - (IV) can also be administered in the form of suppositories, e.g., for rectal administration of the drug. These compositions can be prepared by mixing the compound with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

[0114] Compounds of structural formula (I) - (IV) can also be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

[0115] The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharma-

ceutical excipient.

[0116] The active compound can be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[0117] For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound described herein. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of a compound described herein.

[0118] The tablets or pills can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

[0119] The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

[0120] The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

[0121] The therapeutic dosage of the compounds can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound described herein in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (e.g., hydrophobicity), and the route of administration. For example, the compounds described herein can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 μg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0122] The compounds described herein can also be formulated in combination with one or more additional active ingredients which can include any pharmaceutical agent such as anti-viral agents, vaccines, antibodies, immune enhancers, immune suppressants, anti-inflammatory agents and the like.

Examples

General Synthetic Methodologies

[0123] Many general references providing commonly known chemical synthetic schemes and conditions useful for synthesizing the disclosed compounds are available (see, e.g., Smith and March, March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Fifth Edition, Wiley-Interscience, 2001; or Vogel, A Textbook of Practical Organic Chemistry, Including Qualitative Organic Analysis, Fourth Edition, New York: Longman, 1978).

[0124] Compounds as described herein can be purified by any of the means known in the art, including chromatographic means, such as HPLC, preparative thin layer chromatography, flash column chromatography and ion exchange chro-

matography. Any suitable stationary phase can be used, including normal and reversed phases as well as ionic resins. Most typically the disclosed compounds are purified via silica gel and/or alumina chromatography. See, e.g., Introduction to Modern Liquid Chromatography, 2nd Edition, ed. L. R. Snyder and J. J. Kirkland, John Wiley and Sons, 1979; and Thin Layer Chromatography, ed E. Stahl, Springer-Verlag, New York, 1969.

[0125] During any of the processes for preparation of the subject compounds, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups as described in standard works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry," Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis," Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie," Houben-Weyl, 4.sup.th edition, Vol. 15/1, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jescheit, "Aminosauren, Peptide, Proteine," Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and/or in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide and Derivate," Georg Thieme Verlag, Stuttgart 1974. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

[0126] The compounds disclosed herein can be made using procedures familiar to the person of ordinary skill in the art and as described herein. For example, compounds of structural formula (I) can be prepared according to Schemes 1-3, or analogous synthetic schemes.

[0127] One of skill in the art can adapt the reaction sequences of Schemes 1-3 to fit the desired target molecule. Of course, in certain situations one of skill in the art will use different reagents to affect one or more of the individual steps or to use protected versions of certain of the substituents. Additionally, one skilled in the art would recognize that compounds of structural formulae (I) - (IV) can be synthesized using different routes altogether.

[0128] Compounds suitable for use in the presently disclosed pharmaceutical compositions include compounds described herein. These compounds can be made according to the general schemes described above, for example using a procedure similar to that described below in the Examples.

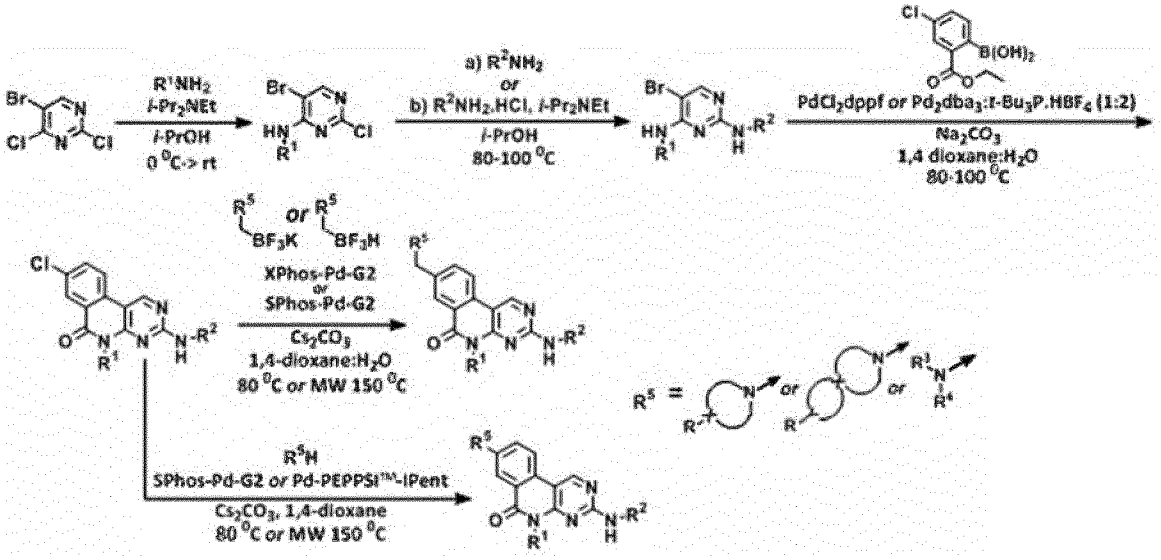
[0129] The following examples are intended to further illustrate certain embodiments and are not intended to limit the scope of the presently disclosed compounds. Examples falling outside the scope of the claims are included for reference purposes.

EXAMPLES

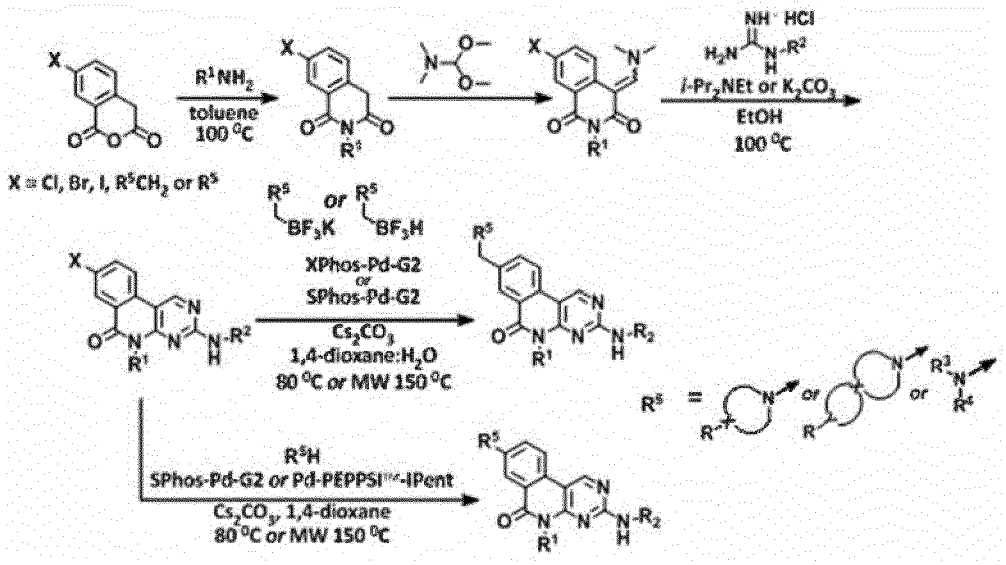
Example 1: Synthesis and Characterization

[0130]

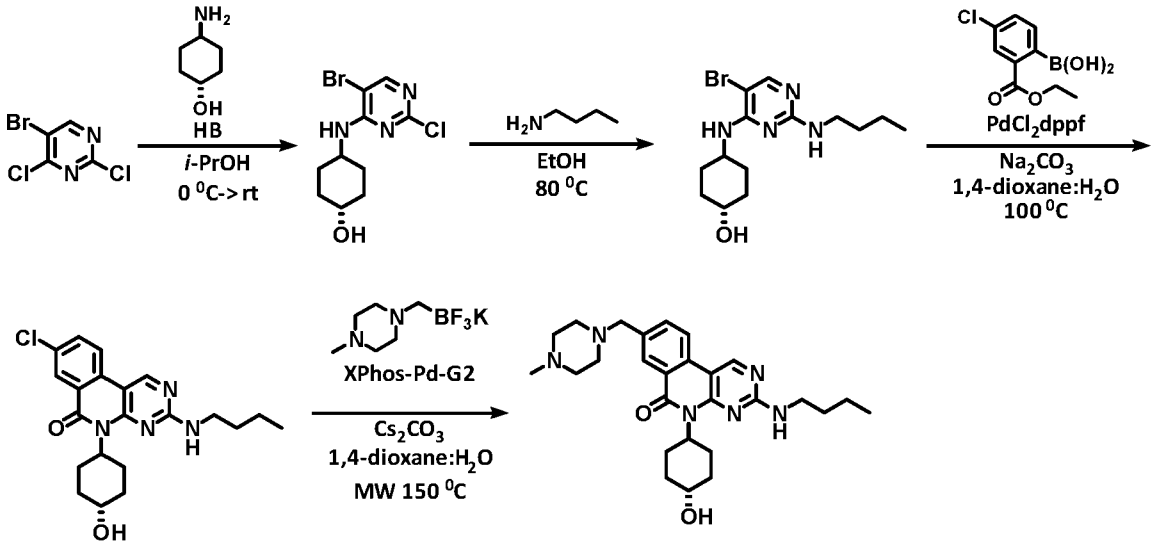
Scheme 1: General Synthesis 1



Scheme 2: General Synthesis 2



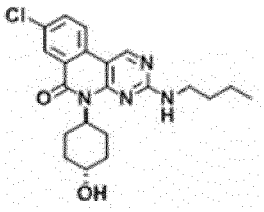
Scheme3: General Synthesis 3



General procedure for the preparation of 3-(alkylamino)-8-chloro-5-(4-alky)pyrimido[4,5-c]isoquinolin-6(5H)-ones is described in the preparation of *trans*-3-(butylamino)-8-chloro-5-(4-hydroxycyclohexyl)pyrimido [4,5-c] isoquinolin-6(5H)-one

trans-3-(Butylamino)-8-chloro-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

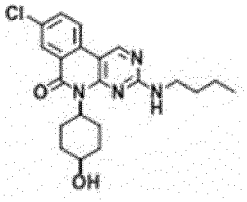
[0131]



[0132] A two-neck round-bottom flask was charged with trans-4-((5-bromo-2-(butylamino)pyrimidin-4-yl)amino)cyclohexan-1-ol (1.1 g, 3.20 mmol), 4-chloro-2-ethoxycarbonylphenylboronic acid (1.25 g, 5.47 mmol), Na_2CO_3 (1.22 g, 11.5 mmol), 1,4-dioxane (30 mL), water (10 mL) and a stir bar. One of the reaction flask necks was fitted with a three-way stopcock attached reflux condenser and closed other neck with a rubber septum. Aargon filled balloon was attached to stopcock and degassing was done by evacuating air from the closed reaction system under vacuum and subsequently back filled with argon while stirring the reaction contents. Heating with an oil bath was also initiated simultaneously during the degassing procedure. Following three cycles of degassing in the space of 15 minutes and oil bath temperature at 35 °C, $PdCl_2$(dppf) (0.26 g, 0.32 mmol) was added to stirred heterogeneous mixture through rubber septum stoppered neck. Rubber septum was fitted back to reaction flask after the catalyst addition, degassing cycle repeated (3 times, 15 minutes) and the stirred reaction mixture was heated further to 100 °C under argon. Initial red heterogeneous reaction mixture transformed to dark biphasic solution upon heating at 90 °C (oil-bath) under argon for 14h. LC/MS analysis of reaction mixture aliquot indicated unreacted *trans*-4-((5-bromo-2-(butylamino)pyrimidin-4-yl)amino)cyclohexan-1-ol (11.89%) still present. Upon no change in the peak composition of reaction mixture after 22h of heating, hot dark reaction mixture suction filtered through sintered glass funnel loaded with Celite® (14 g) and reaction flask was rinsed with 1,4-dioxane (2 X 25 mL) and filtered. The filter cake was further washed with additional 1,4-dioxane (30 mL) until no material was detected by silica gel TLC plate analysis. Resulting homogenous brown filtrate (120 mL) was concentrated by rotary evaporator under vacuum to dryness. The crude dark solid was diluted with EtOAc/THF (150 mL/75 mL), water (75 mL), stirred at room temperature for 20 min, transfered to separatory funnel and aqueous layer was separated. Subequently, organic layer was washed with saturated aq. NaCl solution (20 mL) and separated organic layer. Previously separated aq.layer was further extracted with EtOAc/THF (150 mL/75 mL) and washed with aq. NaCl solution (20 mL). Combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated by rotary evaporator under vacuum. The dark crude solid thus obtained was dissolved in 4% MeOH/CH_2Cl_2 (30 mL), adsorbed on silica gel (22g) and purified by by flash chromatography [Combiflash Torrent® with RediSep® silica gel column 40 g and eluted with 30-50-70% EtOAc/hexane solvent gradient]. Upon analyzing off-white solid obtained after concentrating fractions eluted with 50-70% EtOAc/hexane indicated mixture of *trans*-4-((5-bromo-2-(butylamino)pyrimidin-4-yl)amino)cyclohexan-1-ol (12%) and *trans*-3-(butylamino)-8-chloro-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (87%). Subsequently, above solid was heated in EtOAc/hexane (25mL / 6 mL), cooled to room temperature, sution filtered and dried to obtain 800 mg *of trans*-3-(butylamino)-8-chloro-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (LC/MS: purity 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.33 (d, J = 8.7 Hz, 1H), 8.10 (d, J = 2.5 Hz, 1H), 7.82 (br s, 0.7H), 7.76 (dd, J = 8.7, 2.4 Hz, 1H), 7.62 (br s, 0.3H), 5.37 (br s, 1H), 4.65 (d, J = 4.2 Hz, 1H), 3.49 (br s, 1H), 3.34 (q, J = 6.8 Hz, 2H), 2.72 (br s, 2H), 1.95 (d, J = 9.6 Hz, 2H), 1.60-1.51 (m, 4H), 1.44 - 1.22 (m, 4H), 0.91 (t, J = 7.3 Hz, 3H). LCMS: Purity 98%, MS (m/e) 401 (MH^+).

cis-3-(Butylamino)-8-chloro-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

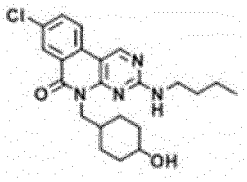
[0133]



[0134] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.33 (d, J = 8.7 Hz, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.76 (dd, J = 8.7, 2.4 Hz, 1H), 7.72 (br s, 0.7H) 7.52 (br s, 0.3H), 5.39 (s, 1H), 4.33 (app d, J = 1.8 Hz, 1H), 3.92-3.86 (m, 1H), 3.41 (br s, 1H), 3.11 (br s, 2H), 1.81 (d, J = 13.0 Hz, 2H), 1.54 (p, J = 7.9, 7.3 Hz, 4H), 1.41 - 1.27 (m, 4H), 0.89 (t, J = 7.3 Hz, 3H). LCMS: Purity 97%, MS (m/e) 401 (MH^+).

3-(Butylamino)-8-chloro-5-((4-hydroxycyclohexyl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

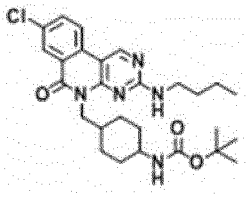
[0135]



[0136] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.37 (d, *J* = 8.7 Hz, 1H), 8.13 (d, *J* = 2.3 Hz, 1H), 7.84 (t, *J* = 6.0 Hz, 1H), 7.79 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.44 (d, *J* = 4.5 Hz, 1H), 4.20 (d, *J* = 6.9 Hz, 2H), 3.37 - 3.28 (overlapped m, 3H), 1.90-1.74 (app m 3H), 1.60-1.50 (m, 4H), 1.36 (p, *J* = 7.4 Hz, 2H), 1.19 - 0.94 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 3H). LCMS: Purity 98%, MS (m/e) 415 (MH^+).

tert-Butyl-(4-((3-(butylamino)-8-chloro-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)methyl)cyclohexyl)carbamate

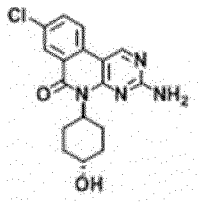
[0137]



[0138] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.36 (d, *J* = 8.7 Hz, 1H), 8.12 (d, *J* = 2.0 Hz, 1H), 7.90 - 7.81 (m, 1H), 7.78 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.63 (d, *J* = 7.7 Hz, 1H), 4.19 (d, *J* = 6.4 Hz, 2H), 3.32 (overlapped m, 2H), 3.13 (br s, 1H), 1.80 (br s, 1H), 1.72 (d, *J* = 10.7 Hz, 2H), 1.62 - 1.51 (m, 4H), 1.33 (overlapped s, 11H), 1.15-0.99 (m, 4H), 0.92 (t, *J* = 7.4 Hz, 3H). LCMS: Purity 96%, MS (m/e) 515 (MH^+).

trans-3-Amino-8-chloro-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

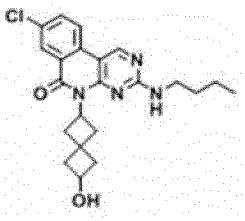
[0139]



[0140] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.34 (d, *J* = 8.9 Hz, 1H), 8.10 (d, *J* = 2.4 Hz, 1H), 7.75 (d, *J* = 2.4 Hz, 1H), 7.15 (s, 2H), 5.38 (s, 1H), 4.60 (d, *J* = 4.4 Hz, 1H), 3.56 (s, 1H), 2.71 (s, 2H), 1.93 (d, *J* = 10.6 Hz, 2H), 1.53 (d, *J* = 10.7 Hz, 2H), 1.29 (q, *J* = 13.7 Hz, 2H). LCMS: Purity 99%, MS (m/e) 345 (MH^+).

3-(Butylamino)-8-chloro-5-(6-hydroxyspiro[3.3]heptan-2-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

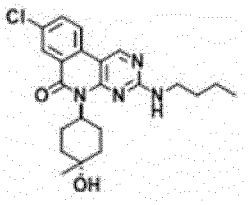
[0141]



[0142] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.29 (d, *J* = 8.7 Hz, 1H), 8.07 (d, *J* = 2.4 Hz, 1H), 7.77 (br s, 0.7H), 7.74 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.58 (br s, 0.3H), 5.65 (p, *J* = 9.0 Hz, 1H), 4.93 (d, *J* = 6.2 Hz, 1H), 4.07 - 3.93 (m, 1H), 3.41 - 3.29 (m, 2H), 3.20 -3.19 (m, 2H), 2.48 - 2.38 (m, 1H), 2.31 - 2.18 (m, 3H), 1.90 (ddd, *J* = 11.3, 7.7, 4.1 Hz, 2H), 1.55 (t, *J* = 7.3 Hz, 2H), 1.44 - 1.31 (m, 2H), 0.92 (t, *J* = 7.6 Hz, 3H).). LCMS: Purity 97%, MS (m/e) 413 (MH^+).

trans-3-(Butylamino)-8-chloro-5-(4-hydroxy-4-methylcyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

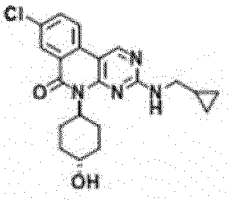
[0143]



[0144] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.33 (d, *J* = 9.0 Hz, 1H), 8.11 (d, *J* = 2.4 Hz, 1H), 7.81 (s, 0.7H), 7.76 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.56 (s, 0.3H), 5.46 (br s, 1H), 4.42 (s, 1H), 3.35 (app q, *J* = 6.8 Hz, 2H), 2.76-2.69 (app m, 2H), 1.67 (d, *J* = 10.9 Hz, 2H), 1.60 - 1.46 (m, 6H), 1.35 (q, *J* = 7.3 Hz, 2H), 1.28 (s, 3H), 0.90 (t, *J* = 7.3 Hz, 3H). LCMS: Purity 97%, MS (m/e) 415 (MH^+).

trans-8-Chloro-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

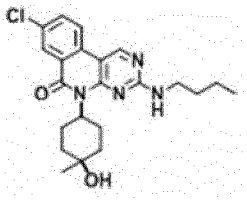
[0145]



[0146] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (s, 1H), 8.34 (d, *J* = 8.8 Hz, 1H), 8.11 (d, *J* = 2.3 Hz, 1H), 7.94 - 7.86 (m, 1H), 7.77 (dd, *J* = 8.7, 2.4 Hz, 1H), 5.37 (br s, 1H), 4.65 (app d, *J* = 4.3 Hz, 1H), 3.75 - 3.42 (br s, 1H), 3.25 (t, *J* = 6.5 Hz, 2H), 2.74 (br s, 2H), 1.94 (app d, *J* = 13.7 Hz, 2H), 1.57 (d, *J* = 11.1 Hz, 2H), 1.37 - 1.25 (q, *J* = 13.3 Hz, 2H), 1.15-1.05 (m, 1H), 0.45 (q, *J*= 5.2 Hz, 2H), 0.25 (q, *J* = 4.9 Hz, 2H). LCMS: Purity 99%, MS (m/e) 399 (MH^+).

cis-3-(Butylamino)-8-chloro-5-(4-hydroxy-4-methylcyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

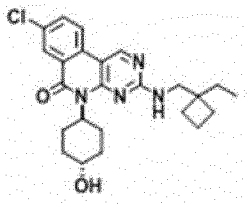
[0147]



[0148] LCMS: Purity 98%, MS (m/e) 415 (MH^+).

trans-8-Chloro-3-(((1-ethylcyclobutyl)methyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

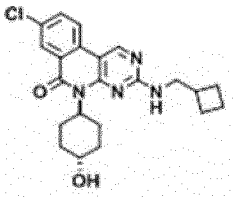
[0149]



[0150] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.34 (d, *J* = 8.8 Hz, 1H), 8.09 (d, *J* = 2.4 Hz, 1H), 7.82 (br s, 0.7H), 7.76 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.53 (br s, 0.3H), 5.42 (br s, 1H), 4.66 (d, *J* = 4.2 Hz, 1H), 3.52 - 3.42 (m, 3H), 2.70 (br s, 2H), 1.95 - 1.75 (m, 6H), 1.79 (app q, *J* = 6.9 Hz, 2H), 1.70 - 1.48 (m, 4H), 1.36 - 1.25 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H). LCMS: Purity 98%, MS (m/e) 441(MH$^+$).

trans-8-Chloro-3-((cyclobutylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

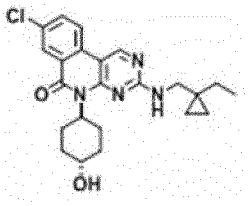
[0151]



[0152] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.33 (d, *J* = 8.8 Hz, 1H), 8.10 (d, *J* = 2.4 Hz, 1H), 7.87 (app s, 0.7H), 7.76 (d, *J* = 8.8, 2.4 Hz, 1H), 7.64 (br s, 0.3H), 5.37 (br s, 1H), 4.66 (d, *J* = 4.4 Hz, 1H), 3.49 (br s, 1H), 3.40 (t, *J* = 6.6 Hz, 2H), 2.90 - 2.52 (m, 3H), 2.10 - 1.89 (m, 4H), 1.84 (p, *J* = 6.8, 6.3 Hz, 2H), 1.74 (q, *J* = 8.1 Hz, 2H), 1.57 (app d, *J* = 11.4 Hz, 2H), 1.30 (app q, *J* = 14.0 Hz, 2H). LCMS: Purity 98%, MS (m/e) 413 (MH$^+$).

trans-8-Chloro-3-(((1-ethylcyclopropyl)methyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

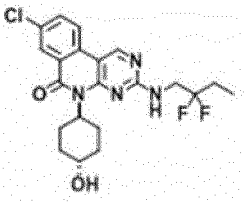
[0153]



[0154] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 - 9.20 (m, 1H), 8.33 (d, *J* = 8.7 Hz, 1H), 8.09 (d, *J* = 2.3 Hz, 1H), 7.81 (br s, 0.7H), 7.76 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.60 (br s, 0.3H), 5.41 (br s, 1H), 4.65 (d, *J* = 4.1 Hz, 1H), 3.52 (br s, 1H), 3.39 (app t, *J* = 7.0 Hz, 2H), 2.72 (br s, 2H), 1.94 (d, *J* = 10.7 Hz, 2H), 1.55 (d, *J* = 10.4 Hz, 2H), 1.36 - 1.26 (m, 4H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.49 - 0.43 (app m, 2H), 0.29 - 0.22 (m, 2H). LCMS: Purity 98%, MS (m/e) 427 (MH$^+$).

trans-8-Chloro-3-((2,2-difluorobutyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

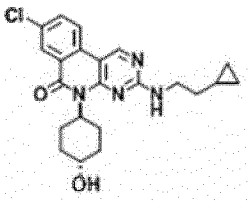
[0155]



[0156] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.30 (s, 1H), 8.37 (d, *J* = 8.7 Hz, 1H), 8.12 (d, *J* = 2.4 Hz, 1H), 8.09 (br s, 0.7H), 7.97 (br s,0.3H), 7.80 (dd, *J* = 8.7, 2.4 Hz, 1H), 5.38 (s, 1H), 4.65 (s, 1H), 3.93 - 3.82 (app m, 2H), 3.51 (s, 1H), 2.72 (br s, 2H), 2.01 - 1.83 (m, 4H), 1.56 (d, *J* = 10.5 Hz, 2H), 1.30 (q, *J* = 11.5 Hz, 2H), 0.99 (t, *J* = 7.5 Hz, 3H). LCMS: Purity 98%, MS (m/e) 437 (MH$^+$).

trans-8-Chloro-3-((2-cyclopropylethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

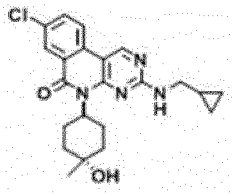
[0157]



[0158] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.33 (d, *J* = 8.7 Hz, 1H), 8.10 (d, *J* = 2.3 Hz, 1H), 7.80 (s, 0.7H), 7.76 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.63 (s, 0.3H), 5.37 (br s, 1H), 4.64 (d, *J* = 4.2 Hz, 1H), 3.52 (br s, 1H), 3.43 (q, *J* = 6.5 Hz, 2H), 2.73 (br s, 2H), 1.95 (d, *J* = 11.1 Hz, 2H), 1.58 (d, *J* = 10.7 Hz, 2H), 1.48 (q, *J* = 7.2 Hz, 2H), 1.30 (q, *J* = 10.7 Hz, 2H), 0.81 - 0.66 (m, 1H), 0.41 (app d, *J* = 7.7 Hz, 2H), 0.06 (app d, *J* = 5.0 Hz, 2H). LCMS: Purity 99%, MS (m/e) 413 (MH$^+$).

trans-8-Chloro-3-((cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

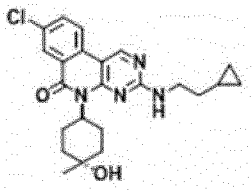
[0159]



[0160] LCMS: Purity 99%, MS (m/e) 413 (MH$^+$).

trans-8-Chloro-3-((2-cyclopropylethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

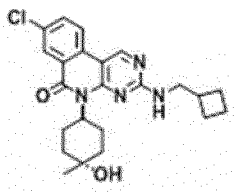
[0161]



[0162] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.33 (d, *J* = 8.8 Hz, 1H), 8.11 (d, *J* = 2.3 Hz, 1H), 7.79 (br s, 0.7H), 7.76 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.53 (br s, 03H), 5.44 (br s, 1H), 4.41 (br s, 1H), 3.43 (q, *J* = 6.3 Hz, 2H), 2.80-2.68 (app m, 2H), 1.67 (app d, *J* = 8.8 Hz, 2H), 1.58 - 1.42 (m, 6H), 1.29 (s, 3H), 0.80 - 0.67 (m, 1H), 0.45 - 0.35 (m, 2H), 0.06 (q, *J* = 5.0 Hz, 2H). LCMS: Purity 99%, MS (m/e) 427 (MH$^+$).

trans-8-Chloro-3-((cyclobutylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

[0163]



[0164] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.32 (d, *J* = 8.8 Hz, 1H), 8.11 (d, *J*= 2.4 Hz, 1H), 7.84 (br s, 0.7H), 7.75 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.57 (br s 0.3H), 5.44 (br s, 1H), 4.43 (s, 1H), 3.41 (t, *J* = 6.5 Hz, 2H), 2.69 (s, 2H), 2.65 - 2.52 (m, 1H), 2.06 - 1.93 (m, 2H), 1.90 - 1.77 (m, 2H), 1.70 (dd, *J* = 20.6, 11.8 Hz, 4H), 1.58 - 1.41 (m, 4H), 1.28 (s, 3H). LCMS: Purity 98%, MS (m/e) 427 (MH^+).

trans-8-Chloro-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

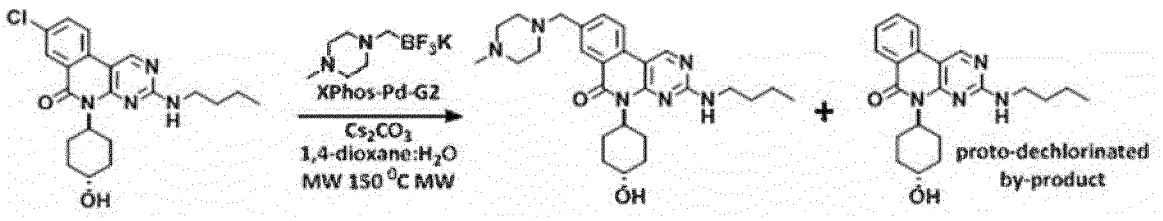
[0165] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (s, 1H), 9.11 (s, 1H), 8.66 (d, *J* = 8.8 Hz, 1H), 8.25 (d, *J* = 2.3 Hz, 1H), 7.97 (dd, *J* = 8.6, 2.3 Hz, 1H), 5.47 (br s, 1H), 4.63 (d, *J* = 4.5 Hz, 1H), 3.59 - 3.46 (m, 1H), 2.70 (dd, *J* = 27.3, 15.3 Hz, 2H), 1.95 (d, *J* = 10.7 Hz, 2H), 1.62 (d, *J* = 11.2 Hz, 2H), 1.40 - 1.25 (m, 2H). LCMS: Purity 96%, MS (m/e) 330 (MH^+).

[0166] General procedure for the preparation of 3-(alkylamino)-5-(substituedalkyl)-8-((substitutedamino)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-ones is described in the preparation of *trans*-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one.

[0167] The crude concentrate obtained after processing end reaction mixture was purified by preparative HPLC (reverse phase column, CH_3CN:H_2O as eluting solvent containing either formic acid or CF_3COOH as a modifier) or silica gel flash column chromatography to provide corresponding product as salt/solvates or free base respectively.

trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

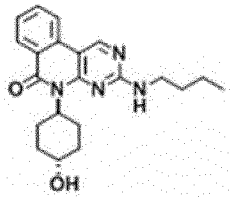
[0168]



[0169] A microwave vial was charged with *trans*-3-(butylamino)-8-chloro-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (125 mg, 0.31 mmol), potassium 1-methyl-4-trifluoroboratomethyl piperazine (97 mg, 0.44 mmol), Cs_2CO_3 (300 mg, 0.94 mmol), XPhos-Pd-G2 (9 mg, 0.011 mmol), 1,4-dioxane (3 mL), water (0.3 mL) and a stirbar. After bubbling nitrogen through suspension for 3 min, reaction mixture was capped and heated in a microwave at 150 °C for 45 min. LC/MC analysis reaction aliquot indicated desried *trans*-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (AUC 70%) and proto-dechlorinated by-product [*trans*-3-(butylamino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (AUC 16%)] with complete consumption of *trans*-3-(butylamino)-8-chloro-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one. At this stage, pale yellow heterogeneous reaction mixture was diluted with THF (3 mL) and filtered through Celite®. Upon rinsing microwave vial with additional amount of THF (2 X 5 mL), flitering through Celite® homogeneous yellow filtrate was dried over $MgSO_4$, filtered and concentrated to dryness. The crude concentrated semi-solid was dissolved in 5% 7N NH_3 MeOH/CH_2Cl_2 (12 mL), adsorbed on silica gel (4 g), dried and purified by flash chromatography [Combiflash Torrent® with RediSep® silica gel column 12 g and eluted with 30-50% 5% 7N NH_3 MeOH in CH_2Cl_2:CH_2Cl_2 solvent gradient]. Solid that was obtained upon concentrating product fractions was heated in EtOAc (6 mL), cooled to room temperature and filtered to provide desired *trans*-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (78 mg) as a white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.04 (s, 1H), 8.19 (s, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.69 (dd, *J* = 8.3, 1.9 Hz, 1H), 5.68 - 5.31 (m, 1H), 3.68 (app dd, *J* = 11.4, 4.4 Hz, 1H), 3.61 (s, 2H), 3.45 (t, *J* = 7.2 Hz, 2H), 3.10 - 2.70 (br s, 2H), 2.53 - 2.48 (m, 8H), 2.26 (s, 3H), 2.09 (app d, *J* = 11.1 Hz, 2H), 1.72 - 1.62 (m, 4H), 1.47 (app dt, *J* = 15.3, 8.8 Hz, 4H), 0.99 (t, *J* = 7.3 Hz, 3H). LCMS: Purity 99%, MS (m/e) 479 (MH^+).

trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

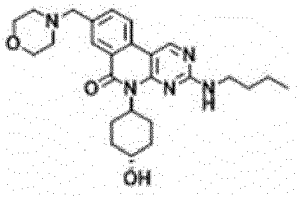
[0170]



[0171] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.72 (t, *J* = 8.3 Hz, 1H), 7.54 (br s, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 5.39 (s, 1H), 4.64 (app d, *J* = 4.3 Hz, 1H), 3.50 (s, 1H), 3.35 (q, *J* = 6.7 Hz, 2H), 2.76 (s, 2H), 1.95 (d, *J* = 13.0 Hz, 2H), 1.69 - 1.46 (m, 4H), 1.46 - 1.18 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 3H). LCMS: Purity 98%, MS (m/e) 367 (MH^+).

trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

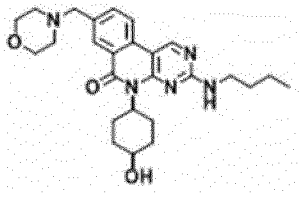
[0172]



[0173] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.09 (s, 1H), 8.24 (app d, *J* = 1.9 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 7.74 (dd, *J* = 8.3, 1.9 Hz, 1H), 5.75 - 5.42 (br s, 1H), 3.74-3.70 (m, 1H),
[0174] 3.69 (t, *J* = 4.7 Hz, 4H), 3.63 (s, 2H), 3.47 (t, *J* = 7.2 Hz, 2H), 3.09 - 2.71 (br s, 2H), 2.48 (t, *J* = 4.7 Hz, 4H), 2.10 (app d, *J* = 11.6 Hz, 2H), 1.79 - 1.58 (m, 4H), 1.58 - 1.36 (m, 4H), 1.00 (t, *J* = 7.4 Hz, 3H). LCMS: Purity 98%, MS (m/e) 479 (MH^+).

cis-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

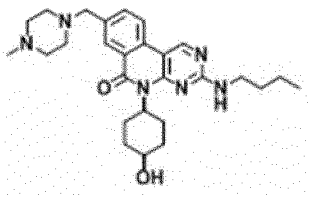
[0175]



[0176] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.06 (s, 1H), 8.23 (d, *J* = 1.4 Hz, 1H), 8.14 (d, *J* = 8.3 Hz, 1H), 7.72 (dd, *J* = 8.4, 1.9 Hz, 1H), 5.51 (br s, 1H), 4.05 (app s, 1H), 3.69 (app t, *J* = 4.7 Hz, 4H), 3.61 (s, 2H), 3.59 - 3.39 (br s, 2H), 3.28 - 3.06 (br s, 2H), 2.47 (app t, J = 4.7 Hz, 4H), 1.97 (d, *J* = 14.0 Hz, 2H), 1.78 - 1.54 (m, 4H), 1.46 (app td, *J* = 14.6, 14.1, 7.1 Hz, 4H), 0.98 (t, *J* = 7.4 Hz, 3H). LCMS: Purity 97%, MS (m/e) 479 (MH^+).

cis-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

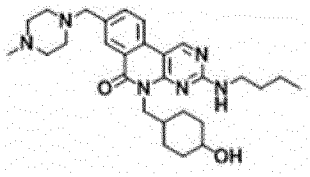
[0177]



[0178] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.06 (s, 1H), 8.22 (s, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 5.68 - 5.28 (m, 1H), 4.05 (s, 1H), 3.63 (s, 2H), 3.51 (br s, 2H), 3.23-3.16 (m, 2H), 2.64-2.34 (br s, 8H), 2.26 (s, 3H), 1.97 (d, *J* = 12.6 Hz, 2H), 1.75 - 1.58 (m, 4H), 1.51 - 1.40 (m, 4H), 0.98 (t, *J* = 7.3 Hz, 3H). LCMS: Purity 97%, MS (m/e) 479 (MH^+).

3-(Butylamino)-5-((4-hydroxycyclohexyl)methyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

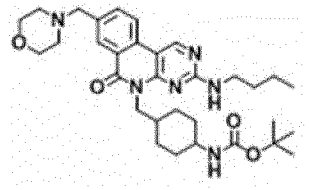
[0179]



[0180] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.09 (s, 1H), 8.25 (d, *J* = 1.7 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.74 (dd, *J* = 8.3, 1.9 Hz, 1H), 4.33 (d, *J* = 7.5 Hz, 2H), 3.65 (s, 2H), 3.54 - 3.41 (m, 3H), 2.61 - 2.44 (m, 8H), 2.28 (s, 3H), 2.0-1.92 (app m, 3H), 1.67 (app td, *J* = 15.0, 14.2, 7.2 Hz, 4H), 1.46 (app dt, *J* = 15.0, 7.4 Hz, 2H), 1.31 - 1.09 (m, 4H), 0.99 (t, *J* = 7.4 Hz, 3H). LCMS: Purity 97%, MS (m/e) 479 (MH^+).

tert-Butyl (4-((3-(butylamino)-8-(morpholinomethyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)methyl)cyclohexyl)carbamate

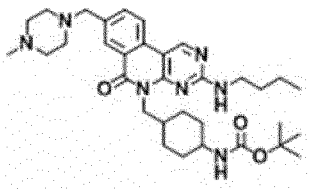
[0181]



[0182] LCMS: Purity 98%, MS (m/e) 579 (MH^+).

tert-Butyl (4-((3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)methyl)cyclohexyl)carbamate

[0183]

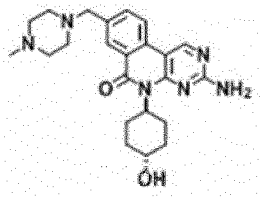


[0184] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.10 (s, 1H), 8.25 (s, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.74 (dd, *J* = 8.3, 1.9

Hz, 1H), 4.35 (d, *J* = 6.9 Hz, 2H), 3.65 (s, 2H), 3.45 (t, *J* = 7.2 Hz, 2H), 2.87 - 2.32 (m, 8H), 2.27 (s, 3H), 2.06 - 1.75 (m, 4H), 1.75 - 1.54 (m, 4H), 1.48-1.39 (m, 2H), 1.40 (s, 9H), 1.31-1.19 (app m, 2H), 1.09 (q, *J* = 15.4, 14.0 Hz, 2H), 0.99 (t, *J* = 7.5 Hz, 3H). LCMS: Purity 98%, MS (m/e) 592 (MH^+).

trans-3-Amino-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

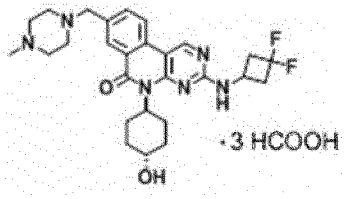
[0185]



[0186] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.09 (s, 1H), 8.22 (d, *J* = 1.7 Hz, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.72 (dd, *J* = 8.3, 1.9 Hz, 1H), 5.57 (br s, 1H), 3.80 - 3.67 (app m, 1H), 3.64 (s, 2H), 2.94-2.70 (br m , 2H), 2.59-2.39 (br m, 8H), 2.27 (s, 3H), 2.08 (d, J = 11.7 Hz, 2H), 1.67 (d, *J* = 11.0 Hz, 2H), 1.55 - 1.40 (m, 2H). LCMS: Purity 97%, MS (m/e) 423 (MH^+).

trans-3-((3,3-Difluorocyclobutyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one triformate salt or solvate

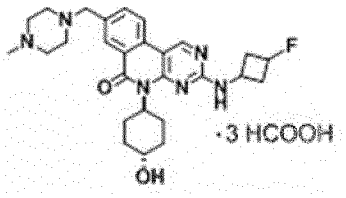
[0187]



[0188] ^{1}H NMR (300 MHz, Methanol-d_4) δ 9.17 (s, 1H), 8.27 (s, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 5.56 (br s, 1H), 4.36 (br s, 1H), 3.77 (s, 2H), 3.72 (br s, 1H), 3.35-3.29 (m, 4H), 3.06-3.02 (m, 4H), 2.88 (s, 3H), 2.86-2.65 (m, 8H), 2.14-2.10 (m, 2H), 1.72-1.68 (m, 2H), 1.56-1.47 (m, 2H). LCMS: Purity 99%, MS (m/e) 513 (MH^+ - 3 HCOOH).

trans-3-((3-Fluorocyclobutyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one triformate salt or solvate

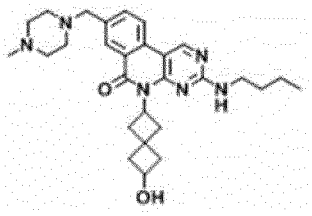
[0189]



[0190] ^{1}H NMR (300 MHz, Methanol-d_4) δ 9.13 (s, 1H), 8.28 (s, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 5.52 (br s, 1H), 5.35-5.16 (m, 1H), 4.65 (br s, 1H), 3.84 (s, 2H), 3.73 (br s, 1H), 3.30-3.28 (m, 6H), 2.89 (s, 3H), 2.86-2.45 (m, 1H), 2.13-2.09 (m, 2H), 1.72-1.68 (m, 2H), 1.54-1.46 (m, 2H). LCMS: Purity 99%, MS (m/e) 495 (MH^+ - 3 HCOOH).

3-(Butylamino)-5-(6-hydroxyspiro[3.3]heptan-2-yl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

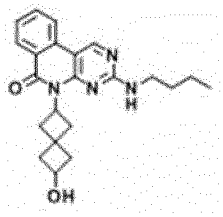
[0191]



[0192] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.99 (s, 1H), 8.15 (s, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 1H), 5.76 (p, *J* = 8.9 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 1H), 3.60 (s, 2H), 3.44 (t, *J* = 7.2 Hz, 2H), 3.17 (br s, 2H), 2.60-2.31 (br m, 12H), 2.26 (s, 3H), 2.08 - 1.97 (m, 2H), 1.64 (dt, *J* = 14.5, 7.3 Hz, 2H), 1.46 (p, *J* = 7.2 Hz, 2H), 0.99 (t, *J* = 7.3 Hz, 3H). LCMS: Purity 99%, MS (m/e) 491 (MH^+).

3-(Butylamino)-5-(6-hydroxyspiro[3.3]heptan-2-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

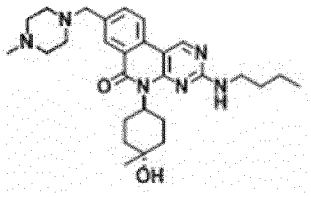
[0193]



[0194] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 9.1 Hz, 1H), 7.79 - 7.65 (m, 2H), 7.45 (t, *J* = 7.6 Hz, 1H), 5.69 (p, *J* = 9.0 Hz, 1H), 4.93 (d, *J* = 6.3 Hz, 1H), 4.01 (dq, *J* = 14.8, 7.7, 7.3 Hz, 1H), 3.43 - 3.32 (m, 2H), 3.25 - 3.08 (m, 2H), 2.99 (br s, 1H), 2.39 - 2.12 (m, 3H), 2.01 - 1.81 (m, 2H), 1.70 - 1.49 (m, 2H), 1.49 - 1.29 (m, 2H), 0.93 (d, *J* = 7.0 Hz, 3H). LCMS: Purity 95%, MS (m/e) 379 (MH^+).

trans-3-(Butylamino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

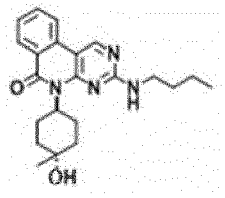
[0195]



[0196] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.07 (s, 1H), 8.21 (d, *J* = 1.6 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.71 (dd, *J* = 8.3, 1.9 Hz, 1H), 5.65 (app br s, 1H), 3.63 (s, 2H), 3.47 (t, *J* = 7.1 Hz, 2H), 2.88 (app qt, *J* = 12.6 Hz, 2H), 2.62-2.41 (br s, 8H), 2.27 (s, 3H), 1.82 (d, *J* = 12.2 Hz, 2H), 1.74 - 1.57 (m, 6H), 1.47 (app q, J = 7.2 Hz, 2H)), 1.44 (s, 3H), 0.99 (t, *J* = 7.3 Hz, 3H). LCMS: Purity 99%, MS (m/e) 493 (MH^+).

trans-3-(Butylamino)-5-(4-hydroxy-4-methylcyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

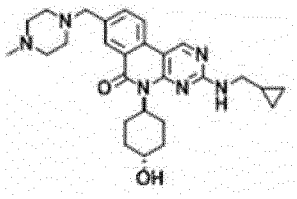
[0197]



[0198] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.29 (d, *J* = 8.1 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.72 (app t, *J* = 7.6 Hz, 2H), 7.45 (app t, *J* = 7.6 Hz, 1H), 5.46 (s, 1H), 4.41 (s, 1H), 3.36 (q, *J* = 6.8 Hz, 2H), 2.91 - 2.57 (m, 2H), 1.67 (d, *J* = 12.4 Hz, 2H), 1.63 - 1.44 (m, 6H), 1.35 (q, *J* = 7.3 Hz, 2H), 1.29 (s, 3H), 0.91 (t, *J* = 7.3 Hz, 3H). LCMS: Purity 95%, MS (m/e) 381 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

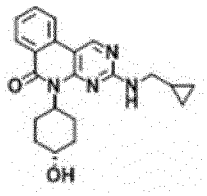
[0199]



[0200] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.05 (s, 1H), 8.20 (d, *J* = 1.5 Hz, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 7.69 (dd, *J* = 8.3, 1.9 Hz, 1H), 5.54 (br s, 1H), 3.71 (tt, *J* = 10.2, 4.2 Hz, 1H), 3.62 (s, 2H), 3.34 (d, *J* = 6.9 Hz, 2H), 2.99-2.72 (br s, 2H), 2.68-2.35 (br s, 8H), 2.26 (s, 3H), 2.09 (d, *J* = 11.3 Hz, 2H), 1.68 (d, *J* = 11.5 Hz, 2H), 1.48 (q, *J* = 13.3 Hz, 2H), 1.22 - 1.12 (m, 1H), 0.59 - 0.50 (m, 2H), 0.31 (q, *J* = 4.8 Hz, 2H). LCMS: Purity 98%, MS (m/e) 477 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

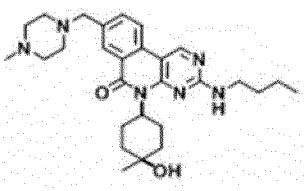
[0201]



[0202] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (s, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 8.18 (d, *J* = 8.2 Hz, 1H), 7.81 (br s, 0.7H), 7.73 (t, *J* = 7.6 Hz, 1H), 7.66 (br s, 0.3H), 7.45 (t, *J* = 7.9 Hz, 1H), 5.40 (s, 1H), 4.65 (s, 1H), 3.75 - 3.42 (br, 1H), 3.25 (t, *J* = 6.3 Hz, 2H), 2.80 (br s, 2H), 1.95 (app d, *J* = 11.8 Hz, 2H), 1.55 (d, *J* = 11.1 Hz, 2H), 1.31 (q, *J* = 13.3 Hz, 2H), 1.20 (app br s , 1H), 0.45 (q, *J* = 5.2 Hz, 2H), 0.25 (q, *J* = 4.8 Hz, 2H). LCMS: Purity 94%, MS (m/e) 365 (MH^+).

cis-3-(Butylamino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

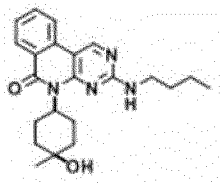
[0203]



[0204] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.05 (s, 1H), 8.21 (s, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 7.69 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.47 (s, 1H), 3.61 (s, 2H), 3.49 (br s, 2H), 3.20 (br s, 2H), 2.69-2.30 (s, 8H), 2.26 (s, 3H), 1.83 (d, *J* = 13.4 Hz, 2H), 1.69 - 1.52 (m, 4H), 1.51 - 1.41 (m, 4H), 1.25 (s, 3H), 0.98 (t, *J* = 7.3 Hz, 3H). LCMS: Purity 99%, MS (m/e) 493 (MH^+).

cis-3-(Butylamino)-5-(4-hydroxy-4-methylcyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

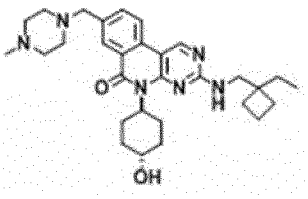
[0205]



[0206] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.28 (d, *J* = 8.1 Hz, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.66 - 7.57 (m , 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 5.37 (s, 1H), 4.00 (s, 1H), 3.39 (br s, 2H), 3.22 - 2.85 (m, 2H), 1.69 (d, *J* = 12.9 Hz, 2H), 1.54 (dt, *J* = 14.7, 7.2 Hz, 2H), 1.46 - 1.27 (m, 6H), 1.14 (s, 3H), 0.89 (q, *J* = 7.1 Hz, 3H). LCMS: Purity 95%, MS (m/e) 381 (MH^+).

trans-3-(((1-Ethyl cyclobutyl)methyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

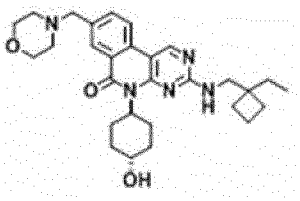
[0207]



[0208] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.09 (m, 1H), 8.21 (s, 1H), 8.15 (d, *J* = 8.3 Hz, 1H), 7.71 (dd, *J* = 8.3, 2.1 Hz, 1H), 5.60 (br s, 1H), 3.74 - 3.66 (m, 1H), 3.63 (s, 2H), 3.58 (s, 2H), 3.00-2.72 (br s, 2H), 2.2.7-2.33 (br s, 8H), 2.27 (s, 3H), 2.09 (d, *J* = 11.7 Hz, 2H), 1.94-1.88 (m 4H), 1.85 - 1.75 (m, 2H), 1.68 (d, *J* = 12.1 Hz, 2H), 1.61 (q, *J* = 7.1, 6.6 Hz, 2H), 1.48 (q, *J* = 12.0 Hz, 2H), 0.93 (t, *J* = 7.2 Hz, 3H). LCMS: Purity 99%, MS (m/e) 519 (MH^+).

trans-3-(((1-Ethylcyclobutyl)methyl)amino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

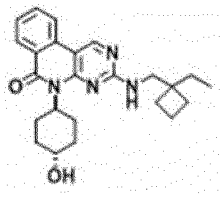
[0209]



[0210] LCMS: Purity 99%, MS (m/e) 506 (MH^+).

trans-3-(((1-Ethylcyclobutyl)methyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

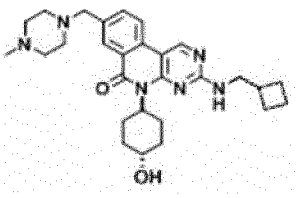
[0211]



[0212] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (s, 1H), 8.30 (d, *J* = 8.1 Hz, 1H), 8.18 (d, *J* = 7.9 Hz, 1H), 7.72 (t, *J* = 8.3 Hz, 1H), 7.66-7.61 (app m, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 5.43 (br s, 1H), 4.65 (s, 1H), 3.60 - 3.45 (unresolved m, 3H), 2.97 - 2.58 (br s, 2H), 1.99 - 1.75 (m, 6H), 1.84 - 1.75 (m, 2H), 1.70 - 1.48 (m, 4H), 1.36 - 1.25 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H). LCMS: Purity 96%, MS (m/e) 407 (MH^+).

trans-3-(((1-Ethyl cyclobutyl)methyl)amino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

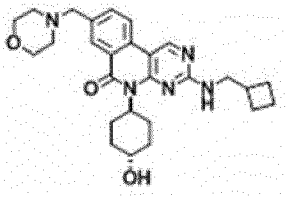
[0213]



[0214] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.06 (s, 1H), 8.21 (s, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.70 (dd, *J* = 8.3, 1.9 Hz, 1H), 5.56 (br s, 1H), 3.76 - 3.64 (m, 1H), 3.63 (s, 2H), 3.50 (d, *J* = 7.1 Hz, 2H), 3.09-2.76 (br s, 2H), 2.69 (p, *J* = 7.6 Hz, 1H), 2.58-2.35 (br s, 8H), 2.27 (s, 3H), 2.19 - 2.06 (m, 4H), 2.01 - 1.89 (m, 2H), 1.82 (dt, *J* = 18.4, 8.4 Hz, 2H), 1.69 (d, *J* = 11.2 Hz, 2H), 1.48 (qd, *J* = 12.9, 12.5, 3.5 Hz, 2H). LCMS: Purity 98%, MS (m/e) 490 (MH^+).

trans-3-((Cyclobutylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

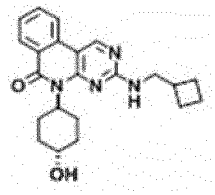
[0215]



[0216] LCMS: Purity 99%, MS (m/e) 478 (MH^+).

trans-3-((Cyclobutylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

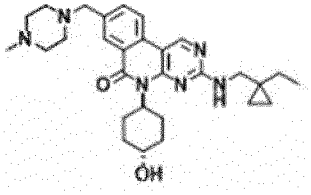
[0217]



[0218] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 8.19 (d, *J* = 8.2 Hz, 1H), 7.84 - 7.75 (br s m, 1H), 7.73 (t, *J* = 8.3 Hz, 1H), 7.45 (t, *J* = 7.9 Hz, 1H), 5.39 (br s, 1H), 4.65 (s, 1H), 3.49 (br s, 1H), 3.41 (t, *J* = 6.5 Hz, 2H), 2.85 - 2.70 (br s, 2H), 2.68 - 2.56 (m, 1H), 2.07 - 1.92 (m, 4H), 1.87 (p, *J* = 6.9, 6.3 Hz, 2H), 1.74 (q, *J* = 7.9 Hz, 2H), 1.58 (d, *J* = 14.7 Hz, 2H), 1.37 - 1.28 (m, 2H). LCMS: Purity 97%, MS (m/e) 379 (MH^+).

trans-3-(((1-Ethyl cyclopropyl)methyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

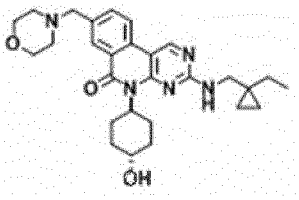
[0219]



[0220] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.08 (s, 1H), 8.21 (s, 1H), 8.14 (d, *J* = 8.9 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 5.59 (br s, 1H), 3.77 - 3.66 (m, 1H), 3.63 (s, 2H), 3.48 (s, 2H), 2.87 (br s, 2H), 2.51 (br s, 8H), 2.27 (s, 3H), 2.09 (d, *J* = 12.0 Hz, 2H), 1.68 (d, *J* = 11.9 Hz, 2H), 1.52-1.41 (app m, 4H), 0.99 (app t, *J* = 14.4 Hz, 3H), 0.51 (s, 2H), 0.36 (s, 2H). LCMS: Purity 99%, MS (m/e) 505 (MH^+).

trans-3-(((1-Ethyl cyclopropyl)methyl)amino)-5-((4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

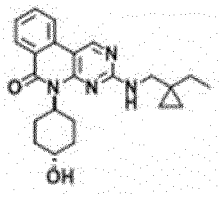
[0221]



[0222] LCMS: Purity 99%, MS (m/e) 492 (MH^+).

3-(((1-Ethylcyclopropyl)methyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

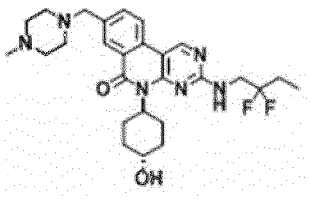
[0223]



[0224] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.29 (d, J = 8.1 Hz, 1H), 8.18 (d, J = 7.8 Hz, 1H), 7.72 (overlapped t, J = 7.6 Hz, 2H), 7.45 (t, J = 7.6 Hz, 1H), 5.43 (s, 1H), 4.65 (s, 1H), 3.50 (br s, 1H), 3.40 (app d, J = 5.3 Hz, 2H), 2.73 (br s, 2H), 1.95 (d, J = 10.8 Hz, 2H), 1.55 (d, J = 11.9 Hz, 2H), 1.36 - 1.26 (m, 4H), 0.92 (t, J = 7.3 Hz, 3H), 0.46 (app t, J = 2.7 Hz, 2H), 0.27 - 0.24 (app m, 2H). LCMS: Purity 97%, MS (m/e) 393 (MH^+).

trans-3-((2,2-Difluorobutyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

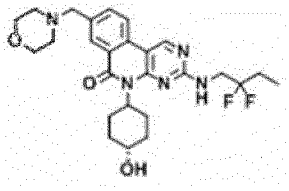
[0225]



[0226] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.15 (s, 1H), 8.23 (s, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 5.56 (br s, 1H), 3.96 (t, J = 13.9 Hz, 2H), 3.75-3.69 (app m, 1H), 3.64 (s, 2H), 3.00-2.78 (br s, 2H), 2.72-2.35 (br s , 8H), 2.27 (s, 3H), 2.09 (d, J = 11.5 Hz, 2H), 1.97 (dq, J = 16.4, 8.1 Hz, 2H), 1.69 (d, J = 12.1 Hz, 2H), 1.48 (app qt, J = 12.1 Hz, 2H), 1.08 (t, J = 7.5 Hz, 3H). LCMS: Purity 99%, MS (m/e) 515 (MH^+).

trans-3-((2,2-Difluorobutyl)amino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

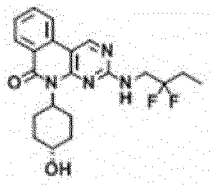
[0227]



[0228] LCMS: Purity 99%, MS (m/e) 502 (MH^+).

trans-3-((2,2-difluorobutyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

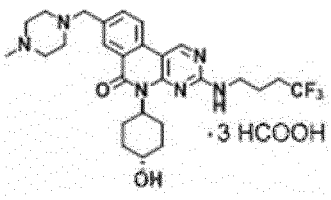
[0229]



[0230] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.30 (s, 1H), 8.33 (d, J = 8.1 Hz, 1H), 8.20 (d, J = 7.7 Hz, 1H), 8.02 (br s, 1H), 7.75 (t, J = 7.6 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 5.38 (br s, 1H), 4.64 (s, 1H), 3.95 - 3.82 (app m, 2H), 3.89 (br s, 1H), 2.76 (br s, 2H), 2.03 - 1.84 (m, 4H), 1.56 (d, J = 10.9 Hz, 2H), 1.31 (q, J = 11.1 Hz, 2H), 0.99 (t, J = 7.5 Hz, 3H). LCMS: Purity 97%, MS (m/e) 403 (MH^+).

trans-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)-3-((4,4,4-trifluorobutyl)amino)pyrimido[4,5-c]isoquinolin-6(5H)-one triformate salt or solvate

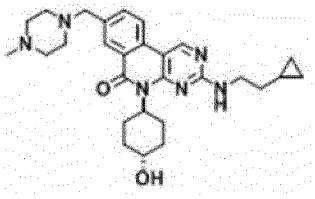
[0231]



[0232] ^{1}H NMR (300 MHz, Methanol-d_4) δ 9.13 (s, 1H), 8.46 (br s, 1H), 8.25 (s, 1H), 8.20 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 5.53 (br s, 1H), 3.71 (s, 3H), 3.55 (t, *J* = 6.9 Hz, 2H), 3.29 (br s, 2H), 2.93 (br s, 6H), 2.78-2.63 (m, 4H), 2.60 (s, 2H), 2.33-2.24 (m, 2H), 2.12-2.08 (m, 2H), 1.95-1.93 (m, 2H), 1.72-1.68 (m, 2H), 1.54-1.46 (m, 2H). LCMS: Purity 99%, MS (m/e) 533 (MH^+ - 3HCOOH).

trans-3-((2-Cyclopropylethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

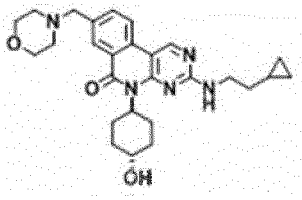
[0233]



[0234] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.08 (s, 1H), 8.22 (s, 1H), 8.15 (d, *J* = 8.3 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 5.57 (br s, 1H), 3.71 (dq, *J* = 11.0, 5.7, 4.6 Hz, 1H), 3.63 (s, 2H), 3.56 (t, *J* = 7.3 Hz, 2H), 2.91 (br s, 2H), 2.51 (br s, 8H), 2.27 (s, 3H), 2.10 (d, *J* = 11.2 Hz, 2H), 1.69 (d, *J* = 12.2 Hz, 2H), 1.62 - 1.42 (overlapped m, 4H), 0.79 (app dq, *J* = 14.4, 7.4 Hz, 1H), 0.49 (app d, *J* = 8.2 Hz, 2H), 0.12 (app d, *J* = 4.9 Hz, 2H). LCMS: Purity 99%, MS (m/e) 491 (MH^+).

trans-3-((2-Cyclopropylethyl)amino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

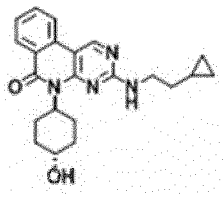
[0235]



[0236] LCMS: Purity 99%, MS (m/e) 478 (MH^+).

trans-3-((2-Cyclopropylethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

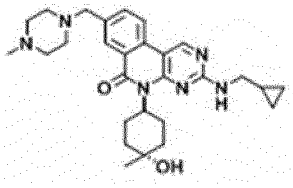
[0237]



[0238] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.29 (d, *J* = 8.1 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.72 (t, *J* = 8.2 Hz, 1H), 7.55 (br s, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 5.39 (br s, 1H), 4.64 (d, *J* = 4.1 Hz, 1H), 3.53 (br s, 1H), 3.44 (q, *J* = 6.4 Hz, 2H), 2.77 (br s, 2H), 1.96 (d, *J* = 10.1 Hz, 2H), 1.58 (d, *J* = 10.7 Hz, 2H), 1.48 (q, *J* = 7.2 Hz, 2H), 1.33 (q, *J* = 10.7 Hz, 2H), 0.82 - 0.67 (m, 1H), 0.42 (q, *J* = 4.8 Hz, 2H), 0.07 (dt, *J* = 5.0, 2.6 Hz, 2H). LCMS: Purity 97%, MS (m/e) 379 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

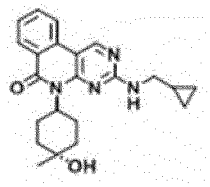
[0239]



[0240] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.08 (s, 1H), 8.21 (s, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 5.63 (br s, 1H), 3.63 (s, 2H), 3.35 (d, *J* = 6.7 Hz, 2H), 2.89 (app qt, *J* = 13.0 Hz, 2H), 2.51 (br s, 8H), 2.27 (s, 3H), 1.82 (d, *J* = 12.7 Hz, 2H), 1.70 (d, *J* = 12.8 Hz, 2H), 1.60 (d, *J* = 12.8 Hz, 2H), 1.44 (s, 3H), 1.17 (tt, *J* = 13.8, 7.0 Hz, 1H), 0.53 (dt, *J* = 7.5, 4.9 Hz, 2H), 0.30 (d, *J* = 4.5 Hz, 2H). LCMS: Purity 99%, MS (m/e) 491 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

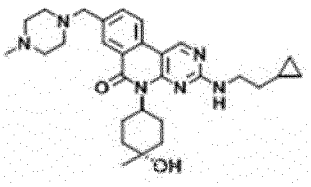
[0241]



[0242] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.30 (d, *J* = 8.1 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.81 (br s, 1H), 7.73 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 5.46 (br s, 1H), 4.41 (s, 1H), 3.26 (t, *J* = 6.4 Hz, 2H), 2.75 (app br s, 2H), 1.68 (d, *J* = 12.4 Hz, 2H), 1.56 - 1.48 (m, 4H), 1.30 (s, 3H), 1.12 - 1.08 (app m, 1H), 0.44 (app q, *J* = 5.6 Hz, 2H), 0.24 (app q, *J* = 5.1 Hz, 2H).). LCMS: Purity 99%, MS (m/e) 379 (MH^+).

trans-3-((2-Cyclopropylethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

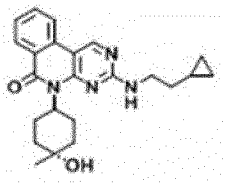
[0243]



[0244] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.23 (d, *J*= 8.4 Hz, 1H), 8.08 (s, 1H), 7.66 (br s, 0.7H), 7.62 (d, *J*= 8.4 Hz, 1H), 7.41 (br s, 0.3H), 5.45 (br s, 1H), 4.39 (s, 1H), 3.52 (s, 2H), 3.42 (q, *J* = 6.3 Hz, 2H), 3.30 - 3.24 (m, 1H), 2.74 (app d, *J* = 11.6 Hz, 2H), 2.35 (s, 3H), 2.30 (s, 3H), 2.11 (s, 3H), 1.66 (d, *J* = 10.0 Hz, 2H), 1.58 - 1.43 (m, 6H), 1.29 (s, 3H), 0.72 (td, *J* = 13.7, 13.2, 5.8 Hz, 1H), 0.39 (app dtd, *J*= 7.7, 5.6, 3.1 Hz, 2H), 0.05 (app d, *J*= 4.6 Hz, 2H). LCMS: Purity 99%, MS (m/e) 505 (MH^+).

trans-3-((2-Cyclopropylethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

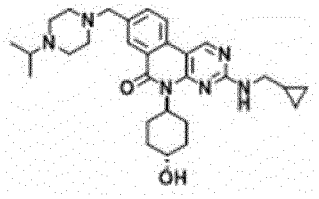
[0245]



[0246] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.29 (d, *J* = 8.1 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.73 (overlapped t, *J*= 7.6 Hz, 2H), 7.45 (t, *J*= 7.6 Hz, 1H), 5.46 (br s, 1H), 4.41 (s, 1H), 3.44 (q, *J* = 6.4 Hz, 2H), 2.84 - 2.71 (m, 2H), 1.68 (app d, *J* = 10.6 Hz, 2H), 1.59 - 1.43 (m, 6H), 1.30 (s, 3H), 0.80 - 0.68 (m, 1H), 0.45 - 0.36 (m, 2H), 0.06 (q, *J*= 5.2 Hz, 2H). LCMS: Purity 95%, MS (m/e) 393 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-isopropylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

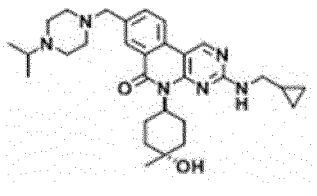
[0247]



[0248] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.09 (d, *J*= 1.8 Hz, 1H), 8.23 (s, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.72 (d, *J* = 8.3 Hz, 1H), 5.57 (br s, 1H), 3.71 (tt, *J* = 10.2, 4.2 Hz, 1H), 3.63 (s, 2H), 3.35 (d, *J* = 6.5 Hz, 2H), 2.90 (br s, 2H), 2.67-2.55 (m, 9H), 2.10 (d, *J* = 12.4 Hz, 2H), 1.69 (d, *J*= 12.4 Hz, 2H), 1.48 (q, *J*= 12.4 Hz, 2H), 1.25 - 1.14 (m, 1H), 1.07 (dd, *J* = 6.6, 1.9 Hz, 6H), 0.54 (app q, *J* = 5.5, 4.8 Hz, 2H), 0.31 (app q, *J* = 4.8 Hz, 2H). LCMS: Purity 97%, MS (m/e) 505 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-isopropylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

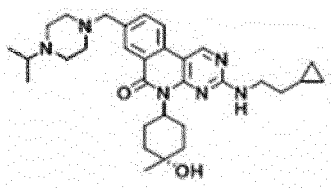
[0249]



[0250] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.09 (s, 1H), 8.22 (s, 1H), 8.15 (d, *J*= 8.1 Hz, 1H), 7.72 (d, *J*= 8.3 Hz, 1H), 5.63 (s, 1H), 3.63 (s, 2H), 3.35 (d, *J*= 6.5 Hz, 2H), 2.89 (app m, 2H), 2.69 - 2.57 (m, 9H), 1.82 (d, *J* = 12.3 Hz, 2H), 1.75 - 1.57 (m, 4H), 1.44 (s, 3H), 1..25 - 1.14 (app m, 1H), 1.06 (d, *J*= 6.5 Hz, 6H), 0.54 (app q, *J*= 5.5, 4.8 Hz, 2H), 0.30 (app q, *J*= 5.0 Hz, 2H). LCMS: Purity 98%, MS (m/e) 519 (MH^+).

trans-3-((2-Cyclopropylethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-isopropylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

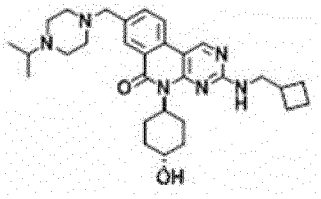
[0251]



[0252] LCMS: Purity 97%, MS (m/e) 533 (MH^+).

trans-3-((Cyclobutylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-isopropylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

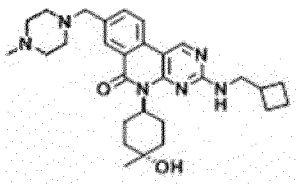
[0253]



[0254] LCMS: Purity 99%, MS (m/e) 519 (MH^+).

trans-3-((Cyclobutylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

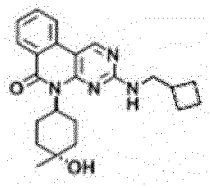
[0255]



[0256] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.23 (d, *J*= 8.3 Hz, 1H), 8.08 (s, 1H), 7.72 (br s, 0.7H), 7.62 (d, *J*= 8.3 Hz, 1H), 7.47 (br s, 0.3H), 5.45 (br s, 1H), 4.40 (s, 1H), 3.52 (s, 2H), 3.40 (t, *J*= 6.4 Hz, 2H), 3.27 (app d, *J*= 2.7 Hz, 1H), 2.72-2.56 (m, 4H), 2.35 (br s, 3H), 2.30 (br s, 3H), 2.11 (s, 3H), 2.04 - 1.93 (m, 2H), 1.89 - 1.77 (m, 2H), 1.76-1.60 (m, 4H), 1.57 - 1.46 (m, 4H), 1.28 (s, 3H). LCMS: Purity 99%, MS (m/e) 505 (MH^+).

trans-3-((Cyclobutylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

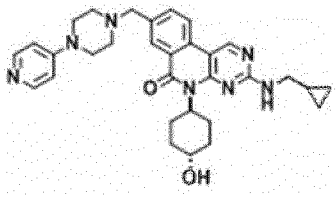
[0257]



[0258] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.29 (d, *J*= 8.2 Hz, 1H), 8.19 (d, *J* = 7.9 Hz, 1H), 7.74 (br s, 1H), 7.72 (t, *J*= 7.6 Hz, 1H), 7.45 (t, *J*= 7.6 Hz, 1H), 5.46 (br s, 1H), 4.42 (s, 1H), 3.42 (t, *J* = 6.5 Hz, 2H), 2.74 (app m, 2H), 2.60 (p, *J* = 7.3 Hz, 1H), 2.07 - 1.94 (m, 2H), 1.84 (dt, *J*= 14.1, 6.7 Hz, 2H), 1.80-1.70 (m, 4H), 1.56 - 1.50 (m, 4H), 1.29 (s, 3H). LCMS: Purity 95%, MS (m/e) 393 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-(pyridin-4-yl)piperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

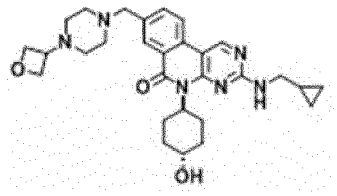
[0259]



[0260] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.10 (s, 1H), 8.26 (d, *J* = 1.3 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 8.09 (dd, *J* = 5.2, 1.7 Hz, 2H), 7.76 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.82 (dd, *J* = 5.2, 1.7 Hz, 2H), 5.58 (br s, 1H), 3.75-3.71 (m, 1H), 3.68 (s, 2H), 3.41 (app t, *J*= 5.0 Hz, 4H), 3.38 - 3.33 (m, 2H), 2.92 (br s, 2H), 2.61 (t, *J* = 5.1 Hz, 4H), 2.14 - 2.04 (m, 2H), 1.70 (d, *J* = 11.3 Hz, 2H), 1.56 - 1.39 (m, 2H), 1.22 - 1.12 (m, 1H), 0.59 - 0.44 (m, 2H), 0.31 (app q, *J* = 4.7 Hz, 2H). LCMS: Purity 98%, MS (m/e) 540 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-(oxetan-3-yl)piperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

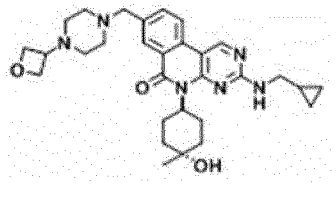
[0261]



[0262] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (s, 1H), 8.23 (d, *J*= 8.4 Hz, 1H), 8.08 (s, 1H), 7.77 (s, 1H), 7.63 (d, *J*= 8.3 Hz, 1H), 5.37 (br s, 1H), 4.63 (s, 1H), 4.48 (t, *J*= 6.5 Hz, 2H), 4.37 (t, *J*= 6.5 Hz, 2H), 3.55(s, 2H), 3.41 - 3.33 (m, 2H), 3.25-3.22 (app m, 2H), 2.76 (br s, 2H), 2.39 (br s, 4H), 2.24 (br s, 4H), 1.94 (app d, *J* = 13.5 Hz, 2H), 1.54 (app s, 2H), 1.30 (*q, J*= 12.1, 11.3 Hz, 2H), 1.15-1.15 (m, 1H), 0.44 (d, *J*= 7.8 Hz, 2H), 0.23 (app d, *J*= 5.0 Hz, 2H). LCMS: Purity 99%, MS (m/e) 519 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-(oxetan-3-yl)piperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

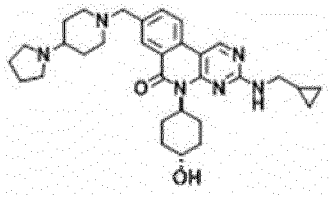
[0263]



[0264] LCMS: Purity 99%, MS (m/e) 533 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

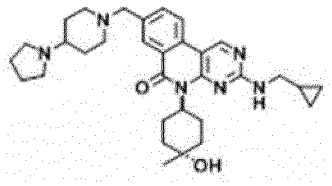
[0265]



[0266] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.10 (s, 1H), 8.20 (s, 1H), 8.16 (d, *J*= 8.3 Hz, 1H) 7.73 (d, *J* = 8.3 Hz, 1H), 5.56 (br s, 1H), 3.72 (m, 1H), 3.60 (s, 2H), 3.35 (d, *J* = 6.8 Hz, 2H), 2.92 (d, *J* = 11.2 Hz, 4H), 2.61 (s, 4H), 2.12 - 2.01 (m, 5H), 1.93 (d, *J* = 12.3 Hz, 2H), 1.79 (s, 4H), 1.69 (d, *J* = 11.3 Hz, 2H), 1.60-1.43 (app m, 4H), 1.18 (br s, 1H), 0.58 - 0.49 (m, 2H), 0.31 (app d, *J* = 5.1 Hz, 2H). LCMS: Purity 97%, MS (m/e) 531 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

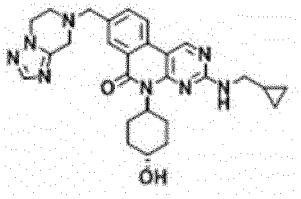
[0267]



[0268] LCMS: Purity 98%, MS (m/e) 545 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-8-((5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazin-7(8H)-yl)methyl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

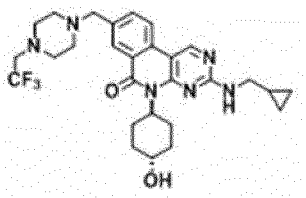
[0269]



[0270] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.28 (d, *J*= 8.4 Hz, 1H), 8.15 (s, 1H), 7.87 (s, 1H), 7.87 (br s, 0.6H), 7.72 (d, *J*= 8.2 Hz, 1H), 7.64 (br s, 0.3H), 5.37 (br s, 1H), 4.63 (s, 1H), 4.09 (t, *J*= 4.9 Hz, 2H), 4.00 (tt, *J*= 1.6, 0.9 Hz, 1H), 3.85 (s, 2H), 3.70 (s, 2H), 3.50 (br s, 1H), 3.30 - 3.22 (m, 2H), 2.96 (t, *J* = 5.6 Hz, 2H), 2.76 (br s, 1H), 1.94 (d, *J* = 12.7 Hz, 2H), 1.56 (app d, *J* = 11.1 Hz, 2H), 1.30 (q, *J* = 11.2 Hz, 2H), 1.10 (m, 1H), 0.44 (d, *J* = 7.8 Hz, 2H), 0.24 (d, *J* = 4.9 Hz, 2H). LCMS: Purity 97%, MS (m/e) 501 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-(2,2,2-trifluoroethyl)piperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

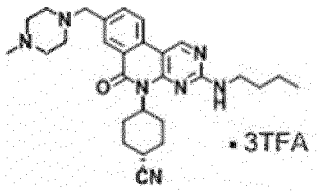
[0271]



[0272] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (s, 1H), 8.23 (d, *J* = 8.3 Hz, 1H), 8.08 (s, 1H), 7.77 (s, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 5.38 (s, 1H), 4.63 (s, 1H), 3.54 (app s, 3H), 3.32 - 3.20 (m, 2H), 3.11 (q, *J* = 10.4 Hz, 2H), 2.76 (br s, 2H), 2.60 (s, 4H), 2.37 (s, 4H), 1.94 (app d, *J* = 9.7 Hz, 2H), 1.55 (app d, *J* = 8.6 Hz, 2H), 1.30 (q, *J* = 11.8 Hz, 2H), 1.10 (app br s, 1H), 0.44 (app d, *J* = 7.8 Hz, 2H), 0.24 (app d, *J* = 4.4 Hz, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -67.84 (t, *J* = 10.1 Hz). LCMS: Purity 98%, MS (m/e) 545 (MH^+).

trans-(3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclohexane-1-carbonitrile tris trifluoroacetic acid salt or solvate

[0273]

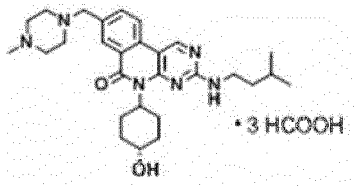


[0274] ^{1}H NMR (300 MHz, Methanol-d_4) δ 9.12 (s, 1H), 8.29 (s, 1H), 8.20 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 5.52 (br s, 1H), 3.81 (s, 2H), 3.51 (br s, 2H), 3.36-3.24 (m, 5H),

[0275] 2.89 (s, 3H), 2.85-2.65 (m, 6H), 2.32-2.29 (m, 2H), 1.83-1.68 (m, 6H), 1.52-1.45 (m, 2H), 1.02 (t, *J* = 7.5 Hz, 3H). LCMS: Purity 98%, MS (m/e) 488 (MH^+-3TFA).

trans-5-(4-hydroxycyclohexyl)-3-(isopentylamino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one triformate salt or solvate

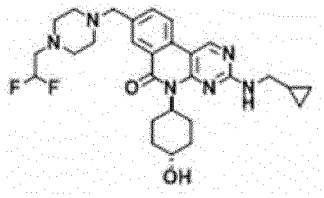
[0276]



[0277] LCMS: Purity 99%, MS (m/e) 493 (MH^+-3 HCOOH).

trans-3-((Cyclopropylmethyl)amino)-8-((4-(2,2-difluoroethyl)piperazin-1-yl)methyl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

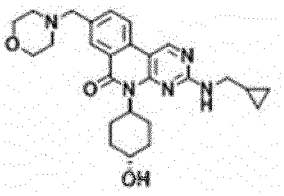
[0278]



[0279] LCMS: Purity 98%, MS (m/e) 527 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

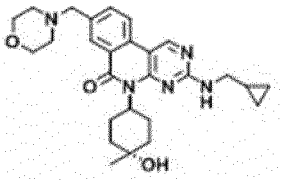
[0280]



[0281] LCMS: Purity 97%, MS (m/e) 464 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

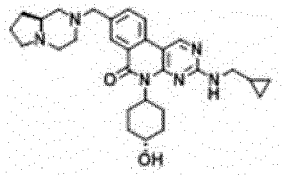
[0282]



[0283] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.10 (s, 1H), 8.23 (s, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.74 (dd, *J* = 8.4, 1.8 Hz, 1H), 5.64 (br s, 1H), 3.70 (t, *J* = 4.6 Hz, 4H), 3.63 (s, 2H), 3.36 (d, *J* = 7.0 Hz, 2H), 2.90 (qt, *J* = 11.9 Hz, 2H), 2.48 (t, *J*= 4.6 Hz, 4H), 1.83 (d, *J* = 12.2 Hz, 2H), 1.70 (td, *J* = 13.1, 3.9 Hz, 2H), 1.62 (d, *J* = 11.2 Hz, 2H), 1.45 (s, 3H), 1.25-1.15 (m, 1H), 0.59 - 0.49 (m, 2H), 0.31 (q, *J* = 5.1 Hz, 2H). LCMS: Purity 99%, MS (m/e) 478 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-8-(((S)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)methyl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

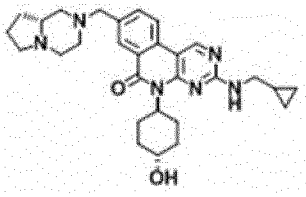
[0284]



[0285] LCMS: Purity 97%, MS (m/e) 503 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-8-(((R)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)methyl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

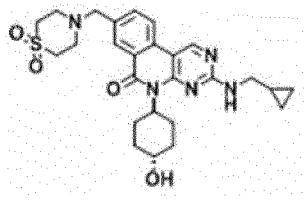
[0286]



[0287] LCMS: Purity 96%, MS (m/e) 503 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-8-((1,1-dioxidothiomorpholino)methyl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

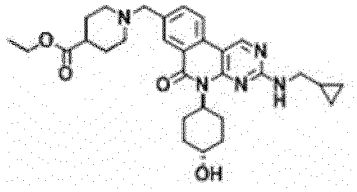
[0288]



[0289] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 8.12 (s, 1H), 7.80 (br s, 0.7H), 7.70 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.65 (br s, 0.3 H), 5.38 (br s, 1H), 4.64 (s, 1H), 3.77 (s, 2H), 3.51 (br s, 1H), 3.27-3.23 (app m, 3H), 3.09 (t, *J* = 4.6 Hz, 4H), 2.88 (app d, *J* = 5.5 Hz, 4H), 2.76 (br s, 1H), 1.95 (d, *J* = 10.8 Hz, 2H), 1.56 (d, *J* = 9.9 Hz, 2H), 1.30 (q, *J* = 11.0 Hz, 2H), 1.11 (app br s, 1H), 0.45 (d, *J* = 7.6 Hz, 2H), 0.25 (q, *J* = 5.1 Hz, 2H). LCMS: Purity 96%, MS (m/e) 512 (MH^+).

trans-Ethyl 1-((3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methyl)piperidine-4-carboxylate

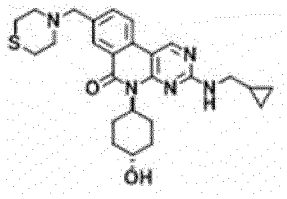
[0290]



[0291] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.11 (s, 1H), 8.22 (s, 1H), 8.17 (s, *J* = 8.3 Hz, 1H), 7.73 (dd, *J* = 8.3, 1.9 Hz, 1H), 5.57 (br s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.76-3.67 (m, 1H), 3.63 (s, 2H), 3.36 (d, *J* = 6.8 Hz, 2H), 2.88 (app d, *J* = 11.5 Hz, 4H), 2.34 (ddt, *J* = 11.1, 8.1, 4.0 Hz, 1H), 2.13 (dd, *J* = 19.4, 10.4 Hz, 4H), 1.89 (d, *J* = 10.6 Hz, 2H), 1.80 - 1.66 (m, 4H), 1.56 - 1.41 (app m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.21-1.15 (m, 1H), 0.55 (app ddd, *J* = 8.0, 5.8, 4.4 Hz, 2H), 0.32 (q, *J* = 5.1 Hz, 2H). LCMS: Purity 96%, MS (m/e) 534 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(thiomorpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

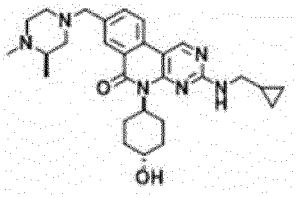
[0292]



[0293] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.24 (d, *J* = 8.3 Hz, 1H), 8.08 (s, 1H), 7.78 (br s, 0.7H), 7.64 (app dd, *J* = 8.2, 1.9 Hz, 1.3H), 5.39 (br s, 1H), 4.64 (s, 1H), 3.58 (s, 2H), 3.51 (br s, 1H), 3.27 (t, *J* = 6.4 Hz, 2H), 2.76 (br s, 2H), 2.61 (app q, *J* = 6.4 Hz, 8H), 1.95 (d, *J* = 9.9 Hz, 2H), 1.56 (d, *J* = 9.6 Hz, 2H), 1.30 (q, *J* = 11.2 Hz, 2H), 1.11 (app br s, 1H), 0.44 (dd, *J* = 7.7, 4.8 Hz, 2H), 0.24 (q, *J* = 4.9 Hz, 2H). LCMS: Purity 97%, MS (m/e) 480 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-8-(((R)-3,4-dimethylpiperazin-1-yl)methyl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

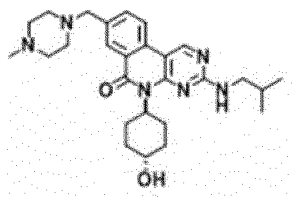
[0294]



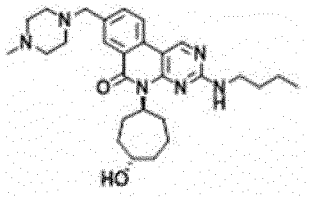
[0295] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.10 (s, 1H), 8.23 (s, 1H), 8.17 (d, J = 8.3 Hz, 1H), 7.73 (dd, J = 8.3, 1.9 Hz, 1H), 5.57 (br s, 1H), 3.78 - 3.67 (m, 1H), 3.62 (s, 2H), 3.36 (d, J = 6.7 Hz, 2H), 3.10-2.85 (br s , 2H), 2.83 - 2.71 (m, 3H), 2.42 - 2.22 (m, 6H), 2.10 (d, J = 10.6 Hz, 2H), 1.94 (t, J = 10.8 Hz, 1H), 1.70 (d, J = 11.0 Hz, 2H), 1.51 (d, J = 10.6 Hz, 2H), 1.11 (m, 1H), 1.04 (d, J = 6.3 Hz, 3H), 0.54 (app ddd, J = 8.0, 5.8, 4.4 Hz, 2H), 0.32 (q, J = 4.9 Hz, 2H). LCMS: Purity 97%, MS (m/e) 491 (MH^+).

trans-5-(4-Hydroxycyclohexyl)-3-(isobutylamino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

[0296]



[0297] ^{1}H NMR (300 MHz, Methanol-d_4) δ 9.09 (s, 1H), 8.22 (s, 1H), 8.16 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 5.53 (br s, 1H), 3.72 (br s, 1H), 3.64 (s, 2H), 3.29 (br s, 4H), 2.89 (br s, 2H), 2.52 (br s, 8H), 2.27 (s, 3H), 2.12-1.98 (m, 3H), 1.71-1.67 (m, 2H), 1.55-1.46 (m, 2H), 1.01 (d, J = 6.6 Hz, 6H). LCMS: Purity 98%, MS (m/e) 479 (MH^+).

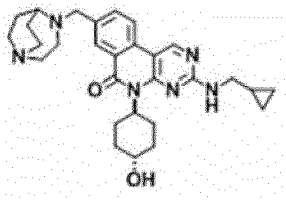


3-(Butylamino)-5-((1*S*,4*S*)-4-hydroxycycloheptyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

[0298] LCMS: Purity 97%, MS (m/e) 492 (MH^+).

trans-8-((1,4-Diazabicyclo[3.2.2]nonan-4-yl)methyl)-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

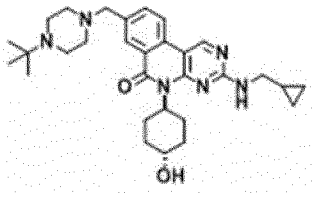
[0299]



[0300] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.09 (s, 1H), 8.24 (s, 1H), 8.15 (d, *J* = 8.3 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 5.57 (br s, 1H), 3.80 (s, 2H), 3.79-3.69 (app m , 2H), 3.35 (app d, *J* = 8.5 Hz, 2H), 3.03 - 2.79 (m, 8H), 2.80 (t, *J* = 5.6 Hz, 2H), 2.10 (d, *J* = 11.2 Hz, 2H), 2.03 - 1.98 (m, 2H), 1.70 (d, *J* = 11.3 Hz, 2H), 1.62 (tt, *J* = 9.6, 5.1 Hz, 2H), 1.48 (qd, *J* = 13.7, 3.3 Hz, 2H). 1.28 - 1.16 (m, 1H), 0.55 (app dt, *J* = 7.5, 5.0 Hz, 2H), 0.31 (q, *J* = 5.1 Hz, 2H). LCMS: Purity 98%, MS (m/e) 503 (MH^+).

trans-8-((4-(tert-butyl)piperazin-1-yl)methyl)-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

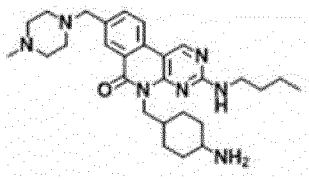
[0301]



[0302] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.10 (s, 1H), 8.23 (s, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 7.73 (dd, *J* = 8.3, 1.8 Hz, 1H), 5.58 (br s, 1H), 3.76 - 3.68 (m, 1H), 3.64 (s, 2H), 3.36 (d, *J* = 6.8 Hz, 2H), 3.10-2.80 (br s, 2H), 2.67 (s, 4H), 2.55 (s, 4H), 2.10 (d, *J* = 11.3 Hz, 2H), 1.70 (d, *J* = 11.1 Hz, 2H), 1.49 (qd, *J* = 13.7, 3.3 Hz, 2H), 1.09 (s, 9H), 0.54 (app dt, *J* = 7.5, 5.0 Hz, 2H), 0.31 (q, *J* = 4.9 Hz, 2H). LCMS: Purity 98%, MS (m/e) 519 (MH^+).

5-((4-Aminocyclohexyl)methyl)-3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

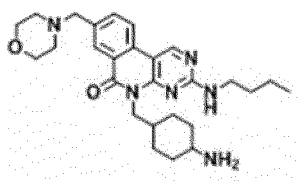
[0303]



[0304] *tert*-Butyl (4-((3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)methyl)cyclohexyl)carbamate (70 mg, 0.118 mmol) was stirred in 4.0 N HCl in 1,4-dioxane (3mL) and MeOH (2 mL) at room temperature. After 2h, reaction mixure was concentrated to dryness, upon analyzing by LC/MS which indicated complete consumption of tert-butyl (4-((3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)methyl)cyclohexyl)carbamate to desired 5-((4-aminocyclohexyl)methyl)-3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one, neutralized with aq. $NaHCO_3$ suction filtered and dried. Thus collected off-white solid (78 mg) upon heating in MeOH (7 mL), was polish filtered. The resulting off-white solid thus obtained after concentration of filtreate was heated in EA (7 mL), cooled to room temperature, filtered, washed with water on the funnel and dried to provide 5-((4-aminocyclohexyl)methyl)-3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (38 mg) as a white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.07 (s, 1H), 8.23 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 4.32 (d, *J* = 7.2 Hz, 2H), 3.64 (s, 2H), 3.44 (t, *J* = 7.2 Hz, 2H), 2.52-2.38 (m, 9H), 2.27 (d, *J* = 1.8 Hz, 3H), 1.97 (app s, 1H), 1.87 (d, *J* = 12.1 Hz, 2H), 1.73 - 1.61 (m, 4H), 1.46 (p, *J* = 7.3 Hz, 2H), 1.24 (q, *J* = 12.4 Hz, 2H), 1.05 (app q, *J* = 12.7 Hz, 2H), 0.99 (t, *J* = 7.3 Hz, 3H). LCMS: Purity 99%, MS (m/e) 492 (MH^+).

5-((4-Aminocyclohexyl)methyl)-3-(butylamino)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

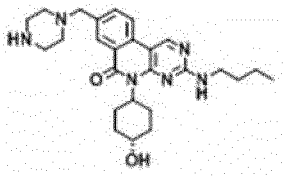
[0305]



[0306] 5-((4-Aminocyclohexyl)methyl)-3-(butylamino)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one was prepared analogous to the preparation of 5-((4-aminocyclohexyl)methyl)-3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one from tert-butyl (4-((3-(butylamino)-8-(morpholinomethyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)methyl)cyclohexyl)carbamate. LCMS: Purity 98%, MS (m/e) 479 (MH^+).

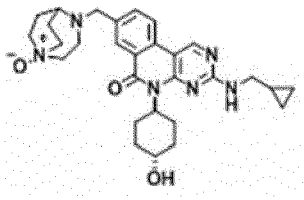
trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(piperazin-1-ylmethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

[0307]



[0308] Analogous to the preparation of *trans*-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one, *trans-tert-butyl* 4-((3-(butylamino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methyl)piperazine-1-carboxylate was prepared and hydrolysed similar to the preparation of 5-((4-aminocyclohexyl)methyl)-3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one. The crude concentrated semi-solid obtained after concentration of reaction solution was dissolved in 7% 7N NH_3 MeOH/CH_2Cl_2 (16 mL), adsorbed on silica gel (4 g), dried, purified by flash chromatography [Combiflash Torrent® with RediSep® silica gel column 12 g and eluted with 30-100% 10% 7N NH_3 MeOH in CH_2Cl_2 :CH_2Cl_2 solvent gradient]. Upon concentrating product fractions, the resulting solid (purity 98%) was heated in EtOAc (10 mL), cooled to room temperature, filtered and dried to provide *trans*-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-(piperazin-1-ylmethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.23 (d, J = 8.3 Hz, 1H), 8.08 (s, 1H), 7.70 (s, 0.7H), 7.63 (dd, J = 8.3, 1.9 Hz, 1H), 7.51 (s, 0.3H), 5.38 (br s, 1H), 4.64 (s, 1H), 3.50 (app s, 3H), 3.39 - 3.27 (m, 3H), 2.76 (br s, 2H), 2.66 (t, J = 4.9 Hz, 4H), 2.27 (s, 4H), 1.94 (app d, J = 9.7 Hz, 2H), 1.56 (app dt, J = 14.1, 6.6 Hz, 4H), 1.44 - 1.23 (m, 4H), 0.91 (t, J = 7.3 Hz, 3H). LCMS: Purity 99%, MS (m/e) 465 (MH^+).

[0309] *trans*-4-((3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methyl)-1,4-diazabicyclo[3.2.2]nonane 1-oxide

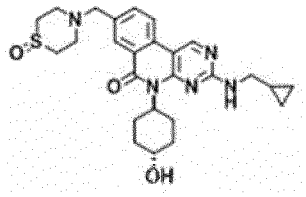


[0310] A microwave vial was charged with *trans*-3-(butylamino)-8-chloro-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (100 mg, 0.25 mmol), ((1,4-diazabicyclo[3.2.2]nonan-4-ium-4-yl)methyl)trifluoroborate (73 mg, 0.35 mmol), Cs_2CO_3 (245 mg, 0.74 mmol), SPhos-Pd-G2 (5 mg, 0.007 mmol), 1,4-dioxane (3 mL), water (0.3 mL) and a stirbar. After bubbling nitrogen through suspension for 3 min, reaction mixture was capped and heated in a microwave for 45 min at 150 °C. Pale yellow heterogeneous reaction mixture was diluted with THF (3 mL) and filtered through Celite®. Upon rinsing microwave vial with additional amount of THF (2 X 5 mL), flitering through Celite®, homogeneous yellow filtrate was dried over $MgSO_4$, filtered and concentrated to dryness. The crude concentrated semi-solid was

dissolved in 5% 7N NH3 MeOH/CH_2Cl_2 (12 mL) and adsorbed on silica gel (4 g). The resulting material was dried by slow stream of house nitrogen and purified by flash chromatography [Combiflash Torrent® with RediSep® silica gel column 12 g and eluted with 30-50-100% 10% 7N NH_3 MeOH in CH_2Cl_2:CH_2Cl_2 solvent gradient. Major peak on chromatogram was identified by LC/MS as an oxidized product of *trans*-8-((1,4-diazabicyclo[3.2.2]nonan-4-yl)methyl)-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one. The resulting white solid obtained after concentration of major peak fractions heated in EtOAc (9 mL), cooled to room temperature, filtered to provide *trans*-4-((3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methyl)-1,4-diazabicyclo[3.2.2]nonane 1-oxide (62 mg, purity 99%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.10 (s, 1H), 8.27 (s, 1H), 8.16 (d, J = 8.3 Hz, 1H), 7.76 (dd, J = 8.3, 1.9 Hz, 1H), 5.58 (br s, 1H), 3.80 (s, 2H), 3.73-3.65 (m, 5H), 3.45 - 3.27 (m, 4H), 3.09 (t, J = 5.6 Hz, 1H), 2.96 (app t, J = 5.6 Hz, 4H), 2.37-2.30 (m, 2H), 2.11-2.02 (m, 4H), 1.69 (d, J = 11.5 Hz, 2H), 1.55 - 1.41 (app m, 2H), 1.21 - 1.12 (m, 1H), 0.54 (ddd, J = 8.0, 5.8, 4.4 Hz, 2H), 0.31 (q, J = 5.1 Hz, 2H). LCMS: Purity 99%, MS (m/e) 519 (MH^+).

trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyc1ohexyl)-8-((1-oxidothiomorpholino)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

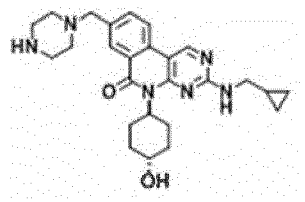
[0311]



[0312] *trans*-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((1-oxidothiomorpholino)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one was obtained after following reaction and work-up procedures analogous to the preparation of *trans*-4-((3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methyl)-1,4-diazabicyclo[3.2.2]nonane 1-oxide. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.26 (d, J = 8.3 Hz, 1H), 8.12 (s, 1H), 7.79 (br s, 0.6H), 7.67 (dd, J = 8.2, 1.9 Hz, 1.4H), 5.39 (br s, 1H), 4.64 (s, 1H), 3.66 (s, 2H), 3.50 (br s, 1H), 3.27 - 3.23 (m, 3H), 2.93 - 2.80 (m, 4H), 2.79 - 2.67 (m, 3H), 2.62 (app dd, J = 9.6, 5.3 Hz, 2H), 1.95 (d, J = 11.9 Hz, 2H), 1.57 (d, J = 11.9 Hz, 2H), 1.30 (q, J = 11.2 Hz, 2H), 1.11 (app br s, 1H), 0.48 (ddd, J = 8.0, 5.8, 4.4 Hz, 2H), 0.25 (q, J = 4.7 Hz, 2H). LCMS: Purity 99%, MS (m/e) 496 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(piperazin-1-ylmethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

[0313]

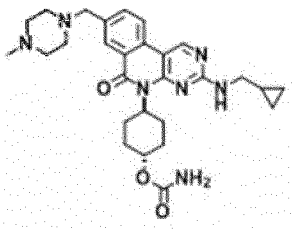


[0314] *trans-tert*-Butyl 4-((3-(cyclopropylamino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methyl)piperazine-1-carboxylate (170 mg), prepared in the similar manner to the preparation of *trans*-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one, was stirred in conc. HCl (3 mL), THF (3 mL) and EtOH (3 mL) for 36h. Upon removing volatiles from reaction solution, the concentrate was cooled in ice-bath, basified with solid K_2CO_3, warmed to room temperature, diluted with CH_2Cl_2 (75 mL) and sepearated the organic layer. Upon further extraction of aqueous layer with CH_2Cl_2 (75 mL X 2), combined organic layers were stirred over anhydrous Na_2SO_4, filtered and concentrated. The crude viscous liquid was purified by flash chromatography [Combiflash Torrent® with RediSep® silica gel column 12 g and eluted with 50-100% 10% 7N NH_3 MeOH in CH_2Cl_2 :CH_2Cl_2 solvent gradient]. Upon concentrating product fractions, the resulting white solid was heated in EtOAc (10 mL), cooled to room temperature, filtered and dried provide *trans*-3-((cyclopropylmethyl)amino)-5-(4-hy-

droxycyclohexyl)-8-(piperazin-1-ylmethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (120 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.24 (d, *J* = 8.3 Hz, 1H), 8.08 (s, 1H), 7.77 (s, 0.7H), 7.64 (dd, *J* = 8.3, 1.9 Hz, 1.3H), 5.39 (brs, 1H), 4.64 (s, 1H), 3.51 (app s, 3H), 3.25 (t, *J* = 6.4 Hz, 2H), 2.77 (br s, 2H), 2.66 (t, *J* = 4.8 Hz, 4H), 2.28 (s, 4H), 1.95 (d, *J* = 10.9 Hz, 2H), 1.56 (d, *J* = 10.6 Hz, 2H), 1.30 (q, *J* = 11.2 Hz, 2H), 1.11 (m, 1H), 0.44 (ddd, *J* = 8.0, 5.8, 4.4 Hz, 2H), 0.24 (q, *J* = 4.9 Hz, 2H). LCMS: Purity 97%, MS (m/e) 463 (MH^+).

trans-4-(3-((Cyclopropylmethyl)amino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclohexyl carbamate

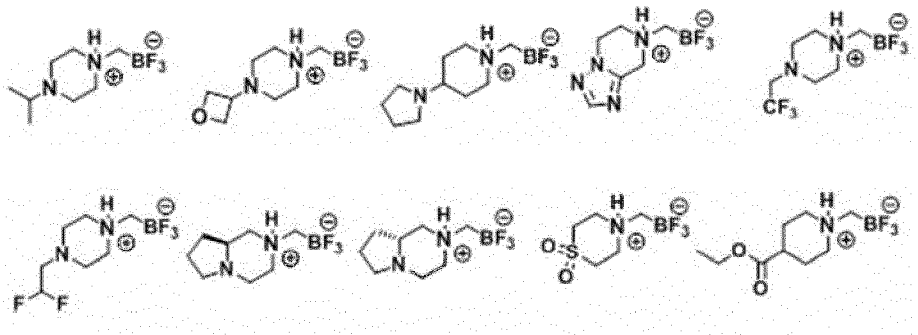
[0315]

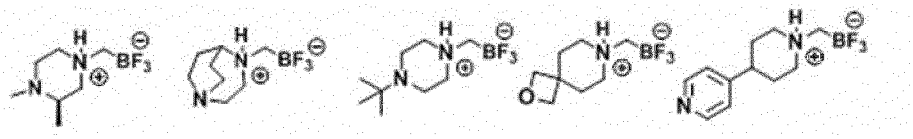


[0316] Trichloroacetyl isocyanate (25 □L, 40 mg, 0.21 mmol) was added slowly over a period of 3 min to a stirred heterogeneous solution of *trans*-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (100 mg, 0.21 mmol) in anhydrous CH_2Cl_2 at -78 °C under argon. The resulting pale yellow homogeneous solution was stirred for 2h and warmed to room temperature. LC/MS analysis after 2h indicated complete consumption of *trans*-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one. At this stage, reaction mixture was quenched with MeOH (4 mL) and concentrated to dryness. The resulting solid was stirred in MeOH (6 mL) and K_2CO_3 (116 mg, 0.83 mmol) at room temperature. After 2h, heterogeneous reaction mixture was concentrated to dryness, diluted with water (10 mL) and filtered. Thus collected white solid after drying was purified by flash chromatography [Combiflash Torrent® with RediSep® silica gel column 12 g and eluted with 30-70% 7% 7N NH_3 MeOH in CH_2Cl_2 :CH_2Cl_2 solvent gradient] and obtained *trans-4-(3*-((cyclopropylmethyl)amino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclohexyl carbamate as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.25 (d, *J* = 8.1 Hz, 1H), 8.09 (s, 1H), 7.81 (br s, 1H), 7.65 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.43 (br s, 2H), 5.42 (br s, 1H), 4.54 (br s, 1H), 4.00 (br s, 1H), 3.54 (s, 2H), 3.31 - 3.22 (m, 2H), 2.84 (br s, 2H), 2.36-2.31 (overlapped br s, 8H), 2.13 (s, 3H), 2.05 (app d, *J* = 10.2 Hz, 2H), 1.64 (app s, 2H), 1.43 (app q, *J* = 12.1 Hz, 2H), 1.16 - 1.07 (m, 1H), 0.45 (q, *J* = 5.5 Hz, 2H), 0.25 (q, *J*= 6.1, 5.6 Hz, 2H). LCMS: Purity 99%, MS (m/e) 520 (MH^+).

[0317] General procedure for the preparation of 3-((alkylamino)-8-((cycloaminomethyl)-5-4-alkyl)pyrimido[4,5-c]isoquinolin-6(5H)-one is described in the preparation of *trans*-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

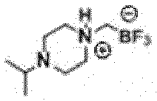
[0318] Preparation of aminomethyltrifluoroborates: (JOC 2008, 73, 2052-2057, JOC 2011, 76, 2762-2769). Aminomethyltrifluoroborates which are not available commerically were prepared according to literature procedure. Trifluoro((4-isopropylpiperazin-1-ium-1-yl)methyl)borate preparation describes reaction procedure and isolation of synthesized respective aminomethyltrifluoroborates represented below.





Trifluoro((4-isopropylpiperazin-1-ium-1-yl)methyl)borate

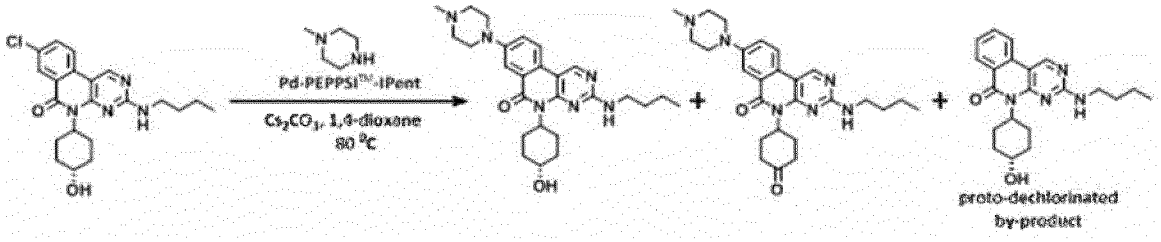
[0319]



[0320] A mixture of potassium(bromomethyl)trifluoroborate (1.28 g, 6.37 mmol) and N-isopropylpiperazine (0.84 g, 6.55 mol) was stirred in dry THF (20 ml) at 70 °C overnight under argon, cooled to room temperature and concentrated to dryness. The resulting white solid was stirred again at 70 °C in dry acetone (75 mL) under argon for 3h. Upon filtering heterogeneous slurry through Celite®, filtrate was concentrated to drynesss, heated in acetone (3 mL), diluted with dry Et_2O (15 mL) and heated at 30 °C for 20 min, and cooled to room temperature. The resulting off-white crystalline solid was filtered through a fritted Teflon tube under nitrogen and dried under high vauum to provide trifluoro((4-isopropylpiperazin-1-ium-1-yl)methyl)borate (1.0 g). ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 6.10 (s, 1H), 3.48 (d, J = 12.6 Hz, 2H), 2.92 (app t, J = 10.7 Hz, 4H), 2.74 (hept, J = 6.6 Hz, 1H), 2.53 (app t, J = 12.9 Hz, 2H), 2.12 (s, 2H), 1.02 (d, J = 6.6 Hz, 6H). ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -142.02 (q, J = 47.3 Hz).

[0321] General procedure for the preparation of 3-((alkylamino)-5-(substitutedalkyl)-8-(substitutedaminyl)pyrimido[4,5-c]isoquinolin-6(5H)-ones is described in the preparation of *trans*-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one. The crude concentrate obtained after processing end reaction mixture was purified by preparative HPLC (reverse phase column, CH_3CN:H_2O as eluting solvent containing either formic acid or CF_3COOH as a modifier) or silica gel flash column chromatography to provide corresponding product as salt/solvates or free base respectively.

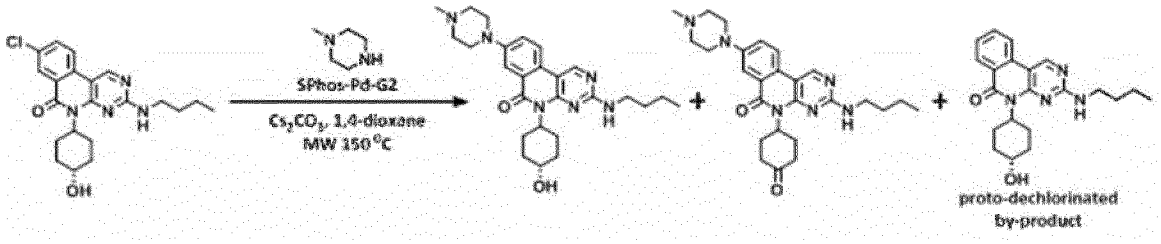
[0322] Procedure-A: *trans*-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one



[0323] *trans*-3-(Butylamino)-8-chloro-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (200 mg, 0.49 mmol), N-methylpiperazine (80 mg, 0.79 mmol), Cs_2CO_3 (320 mg, 0.98 mmol), Pd-PEPPSI™-IPent (40 mg, 0.05 mmol) and a stir bar were transferred to a screwcapped vial (20 mL). The vial was sealed with a cap containing PTFE septum and air was removed from vial by vacuum. Dry 1,4-Dioxane (4 mL) was added to vial under vacuum by a syringe. Air was removed from the closed reaction system by vacuum, back filled with argon while stirring the reaction contents. After 3-4 cycles of repeated degassing cycles, reaction mixture was stirred at 80 °C and progress was monitored by LC/MS. Initial reaction mixture turned to yellow after 30 min of heating and eventually to an organge. After 5h, LC/MS analysis of reaction aliquot indicated the desired *trans*-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one (AUC 66%) formation along with proto-dechlorinated by-product [*trans*-3-(butylamino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (AUC 14%] and 3-(butylamino)-8-(4-methylpiperazin-1-yl)-5-(4-oxocyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (AUC 9%) with complete consumption of *trans*-3-(butylamino)-8-chloro-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one At this stage, orange heterogeneous reaction mixture was diluted with THF (3 mL) and filtered through Celite®. Upon rinsing vial with additional amount of THF (2 X 5 mL), flitering through Celite®, homogeneous yellow filtrate was concentrated to dryness. The crude concentrated semi-solid was dissolved in 5% 7N NH3 MeOH/CH_2Cl_2 (12 mL), adsorbed on silica gel (10 g), dried and purified by flash chromatography [Combiflash Torrent® with RediSep® silica gel column 12 g (pre-conditioned with

CH_2Cl_2) and eluted with 30-70% CH_2Cl_2:7% 7N NH3 MeOH in CH_2Cl_2 solvent gradient. Off-white solid obtained upon concentrating product fractions was heated in EtOAc (6 mL), cooled to room temperature and filtered to provide desired *trans*-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (113 mg) as a off-white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.98 (s, 1H), 8.06 (d, *J* = 9.0 Hz, 1H), 7.71 (d, *J* = 2.4 Hz, 1H), 7.46 (dd, *J* = 8.9, 2.8 Hz, 1H), 5.58 (br s, 1H), 3.75 - 3.68 (m, 1H), 3.46 (t, *J* = 7.2 Hz, 2H), 3.36 - 3.29 (app m, 4H), 2.91 (br s, 2H), 2.65 (t, *J* = 5.1 Hz, 4H), 2.37 (s, 3H), 2.10 (d, *J* = 11.6 Hz, 2H), 1.73 - 1.60 (m, 4H), 1.53-1.42 (app m, 4H), 1.00 (t, *J* = 7.4 Hz, 3H). LCMS: Purity 97%, MS (m/e) 465 (MH^+).

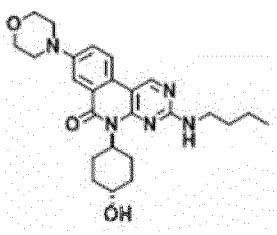
[0324] Procedure-B: *trans*-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one



[0325] *trans*-3-(Butylamino)-8-chloro-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (100 mg, 0.25 mmol), *N*-methylpiperazine (75 mg, 0.75 mmol), Cs_2CO_3 (163 mg, 0.50 mmol), SPhos-Pd-G2 (18 mg, 0.025 mmol) and a stir bar were transferred to a microwave vial. The vial was tightly capped with a rubber septum and air was removed from vial by vacuum. Dry 1,4-Dioxane (4 mL) was added to vial under vacuum by a syringe. Air was removed from the closed reaction system by vacuum, back filled with argon while stirring the reaction contents. After 3-4 cycles of repeated degassing cycles, reaction mixture was heated in a microwave at 150 °C for 60 min. LC/MS analysis of reaction aliquot indicated partial consumption *trans*-3-(butylamino)-8-chloro-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (AUC 24%). At this stage additional amounts of *N*-methylpiperazine (75 mg, 0.75 mmol), Cs_2CO_3 (163 mg, 0.50 mmol) and SPhos-Pd-G2 (18 mg, 0.025 mmol) were transferred to previously heated above reaction mixture and heated again in microwave at 150 °C for 45 min. LC/MS analysis of reaction aliquot indicated the desired *trans*-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one (AUC 46%) formation along with proto-dechlorinated by-product [*trans*-3-(butylamino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (AUC 24%] and 3-(butylamino)-8-(4-methylpiperazin-1-yl)-5-(4-oxocyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (AUC 12%) with complete consumption of *trans*-3-(butylamino)-8-chloro-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one. At this stage, dark heterogeneous reaction mixture was diluted with THF (3 mL) and filtered through Celite®. Upon rinsing microwave vial with additional amount of THF (2 X 3 mL), flitering through Celite®, homogeneous yellow filtrate was concentrated to dryness. The crude concentrated semi-solid was dissolved in 5% 7N NH3 MeOH/CH_2Cl_2 (12 mL), adsorbed on silica gel (10 g), dried and purified by flash chromatography [Combiflash Torrent® with RediSep® silica gel column 12 g (pre-conditioned with CH_2Cl_2) and eluted with 30-70% CH_2Cl_2:7% 7N NH3 MeOH in CH_2Cl_2 solvent gradient. Off-white solid obtained upon concentrating product fractions was heated in EtOAc (6 mL), cooled to room temperature and filtered to provide desired *trans*-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (38 mg, purity 98%) as a off-white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.98 (s, 1H), 8.06 (d, *J* = 9.0 Hz, 1H), 7.71 (d, *J* = 2.4 Hz, 1H), 7.46 (dd, *J* = 8.9, 2.8 Hz, 1H), 5.58 (br s, 1H), 3.75 - 3.68 (m, 1H), 3.46 (t, *J* = 7.2 Hz, 2H), 3.36 - 3.29 (app m, 4H), 2.91 (br s, 2H), 2.65 (t, *J* = 5.1 Hz, 4H), 2.37 (s, 3H), 2.10 (d, *J* = 11.6 Hz, 2H), 1.73 - 1.60 (m, 4H), 1.53-1.42 (app m, 4H), 1.00 (t, *J* = 7.4 Hz, 3H). LCMS: Purity 99%, MS (m/e) 465 (MH^+).

trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-morpholinopyrimido[4,5-c]isoquinolin-6(5H)-one

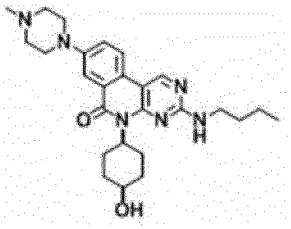
[0326]



[0327] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.00 (s, 1H), 8.08 (d, *J* = 9.0 Hz, 1H), 7.72 (d, *J* = 2.7 Hz, 1H), 7.47 (dd, *J* = 8.9, 2.8 Hz, 1H), 5.58 (br s, 1H), 3.90 - 3.83 (m, 4H), 3.75 - 3.68 (m, 1H), 3.46 (t, *J* = 7.2 Hz, 2H), 3.29 - 3.21 (m, 4H), 2.91 (br s, 2H), 2.10 (d, *J* = 11.8 Hz, 2H), 1.74 - 1.60 (m, 4H), 1.53-1.42 (app m, 4H), 1.00 (t, *J* = 7.3 Hz, 3H). LCMS: Purity 95%, MS (m/e) 452 (MH^+).

cis-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

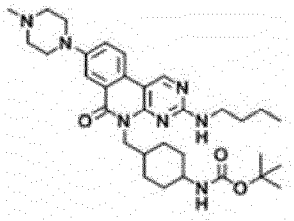
[0328]



[0329] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.98 (s, 1H), 8.06 (d, *J* = 8.9 Hz, 1H), 7.73 (d, *J* = 2.8 Hz, 1H), 7.46 (dd, *J* = 8.9, 2.8 Hz, 1H), 5.54 (br s, 1H), 4.09 - 4.03 (app m, 1H), 3.50 (s, 2H), 3.36 - 3.29 (app m, 4H), 3.26 - 3.15 (app m, 2H), 2.69 - 2.61 (app m, 4H), 2.36 (s, 3H), 1.98 (d, *J* = 14.2 Hz, 2H), 1.75 - 1.58 (m, 4H), 1.53-1.42 (app m, 4H), 0.98 (t, *J* = 7.4 Hz, 3H). LCMS: Purity 97%, MS (m/e) 401 (MH^+).

tert-Butyl (4-((3-(Butylamino)-8-(4-methylpiperazin-1-yl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)methyl)cyclohexyl)carbamate

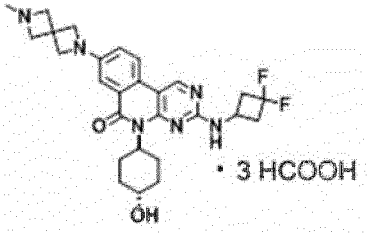
[0330]



[0331] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 1H), 8.18 (d, *J* = 8.9 Hz, 1H), 7.58 (d, *J* = 2.7 Hz, 1H), 7.50 (br s, 1H), 7.49 (dd, *J* = 9.0, 2.8 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 4.22 (d, *J* = 6.9 Hz, 2H), 3.26 - 3.18 (m, 3H), 3.16-3.13 (br s, 1H), 2.22 (s, 3H), 1.81-1.70 (m, 3H), 1.61 - 1.49 (m, 4H), 1.33 (s, 9H), 1.15 - 0.97 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 3H). LCMS: Purity 98%, MS (m/e) 578 (MH^+).

trans-3-((3,3-Difluorocyclobutyl)amino)-5-(4-hydroxycyclohexyl)-8-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one triformic acid salt or solvate

[0332]

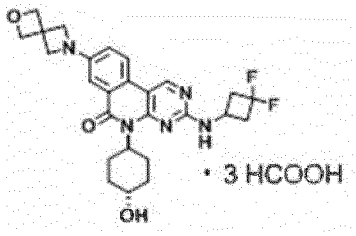


[0333] ^{1}H NMR (300 MHz, Methanol-d_4) δ 9.03 (s, 1H), 8.10 (d, *J* = 9.0 Hz, 1H), 7.28 (s, 1H), 7.01 (d, *J* = 9.0 Hz, 1H), 5.52 (br s, 1H), 4.57-4.53 (m, 2H), 4.30-4.26 (m, 4H), 4.20 (brs, 2H), 4.14 (brs, 2H), 3.04 (m, 2H), 3.01 (s, 3H), 2.91-2.82

(m, 2H), 2.78-2.63 (m, 3H), 2.14-2.10 (m, 2H), 1.72-1.67 (m, 2H), 1.51-1.47 (m, 2H). LCMS: Purity 99%, MS (m/e) 511 (MH^+ - 3HCOOH).

trans-3-((3,3-difluorocyclobutyl)amino)-5-(4-hydroxycyclohexyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one triformic acid salt or solvate

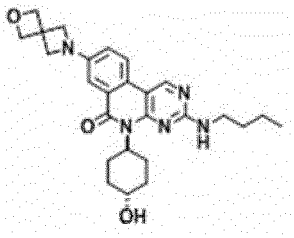
[0334]



[0335] LCMS: Purity 99%, MS (m/e) 498 (MH^+ - 3HCOOH).

trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

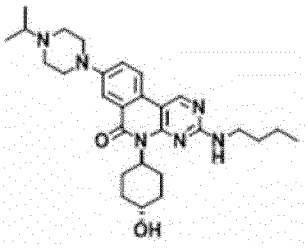
[0336]



[0337] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 1H), 8.12 (d, *J* = 8.7 Hz, 1H), 7.47 (s, 1H), 7.10 (d, *J* = 2.5 Hz, 1H), 6.91 (dd, *J* = 8.7, 2.6 Hz, 1H), 5.39 (br s, 1H), 4.72 (s, 4H), 4.62 (s, 1H), 4.07 (s, 4H), 4.03-4.00 (app s, 1H), 3.49 (app s, 1H), 3.35-3.31 (hidden m, 1H), 2.98-2.58 (br s, 2H), 1.94 (d, *J* = 10.7 Hz, 2H), 1.58-1.51 (app m, 4H), 1.43 - 1.21 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 3H). LCMS: Purity 98%, MS (m/e) 464 (MH^+).

trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(4-isopropylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

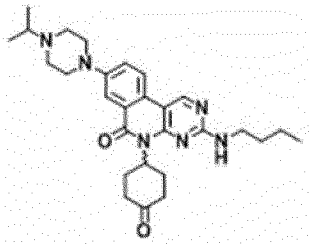
[0338]



[0339] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.00 (s, 1H), 8.09 (d, *J* = 8.9 Hz, 1H), 7.74 (d, *J* = 2.5 Hz, 1H), 7.49 (dd, *J* = 8.9, 2.8 Hz, 1H), 5.59 (br s, 1H), 3.75 - 3.68 (m, 1H), 3.46 (t, *J* = 7.2 Hz, 2H), 3.42 - 3.31 (app m, 4H), 2.99 - 2.92 (app m, 7H), 2.10 (d, *J* = 10.9 Hz, 2H), 1.71-1.63 (app m, 4H), 1.54-1.42 (m, 4H), 1.22 (d, *J* = 6.5 Hz, 6H), 1.00 (t, *J* = 7.4 Hz, 3H). LCMS: Purity 99%, MS (m/e) 493 (MH^+).

3-(Butylamino)-8-(4-isopropylpiperazin-1-yl)-5-(4-oxocyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

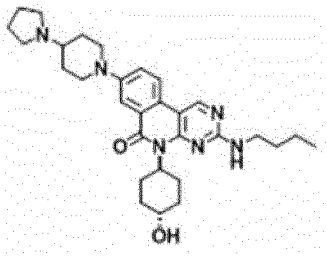
[0340]



[0341] LCMS: Purity 99%, MS (m/e) 491 (MH^+).

trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(4-(pyrrolidin-1-yl)piperidin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

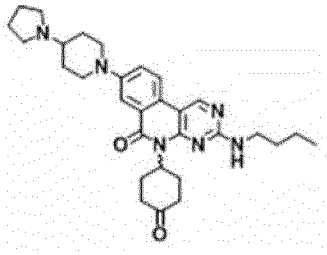
[0342]



[0343] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.11 (d, J = 9.2 Hz, 1H), 7.55 (d, J = 2.5 Hz, 1H), 7.50 (b s, 0.7H), 7.45 (dd, J = 8.9, 2.7 Hz, 1.3 H), 5.39 (br s, 1H), 4.62 (s, 1H), 3.69 (d, J = 12.8 Hz, 2H), 3.49 (br s, 1H), 3.33 - 3.32 (m, 3H), 3.27 (app s, 4H), 2.79 (app t, J = 11.2 Hz, 3H), 2.13-2.09 (app m, 1H), 1.91 (app br s, 4H), 1.68 - 1.62 (m, 4H), 1.56-1.50 (m, 6H), 1.42 - 1.24 (m, 4H), 0.90 (t, J = 7.3 Hz, 3H). LCMS: Purity 99%, MS (m/e) 519 (MH^+).

3-(Butylamino)-5-(4-oxocyclohexyl)-8-(4-(pyrrolidin-1-yl)piperidin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

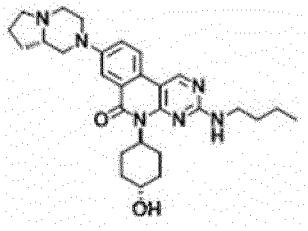
[0344]



[0345] LCMS: Purity 98%, MS (m/e) 517 (MH^+).

trans-3-(Butylamino)-8-((S)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-5-((1r,4S)-4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

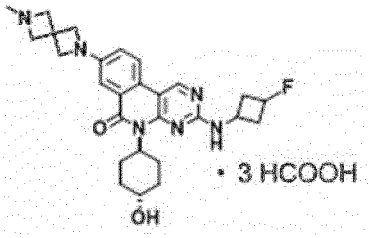
[0346]



[0347] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.95 (s, 1H), 8.01 (d, *J* = 9.0 Hz, 1H), 7.69 (d, *J* = 2.4 Hz, 1H), 7.44 (dd, *J* = 8.9, 2.7 Hz, 1H), 5.56 (br s, 1H), 3.89 (app d, *J* = 10.2 Hz, 1H), 3.79 - 3.65 (m, 2H), 3.44 (t, *J* = 7.2 Hz, 2H), 3.22 - 3.08 (m, 2H), 2.93 (app td, *J* = 11.8, 3.2 Hz, 3H), 2.59 (t, *J* = 10.1Hz, 1H), 2.42 (td, *J* = 11.3, 3.3 Hz, 1H), 2.29-2.21 (m, 2H), 2.09 (d, *J* = 11.0 Hz, 2H), 2.04 - 1.92 (m, 1H), 1.92 - 1.79 (m, 2H), 1.69-1.61 (m, 4H), 1.57-1.41(m, 5H) 0.99 (t, *J* = 7.4 Hz, 3H). LCMS: Purity 98%, MS (m/e) 491 (MH^+).

trans-3-((3-Fluorocyclobutyl)amino)-5-(4-hydroxycyclohexyl)-8-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one triformic acid salt or solvate

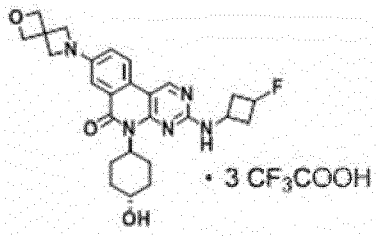
[0348]



[0349] ^{1}H NMR (300 MHz, Methanol-d_4) δ 8.95 (s, 1H), 9.49 (br s, 1H), 8.02 (d, *J* = 8.7 Hz, 1H), 7.22 (s, 1H), 6.96 (d, *J* = 8.7 Hz, 1H), 5.53 (br s, 1H), 5.36-5.14 (m, 1H), 4.60 (m, 1H), 4.31 (brs, 4H), 4.12 (brs, 4H), 3.73 (m, 1H), 2.88 (s, 3H), 2.68-2.39 (m, 4H), 2.12-2.09 (m, 2H), 1.68-1.65 (m, 2H), 1.51-1.46 (m, 2H). LCMS: Purity 99%, MS (m/e) 493 (MH^+ - 3HCOOH).

trans-3-((3-Fluorocyclobutyl)amino)-5-(4-hydroxycyclohexyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one tris trifluoroacetic acid salt or solvate

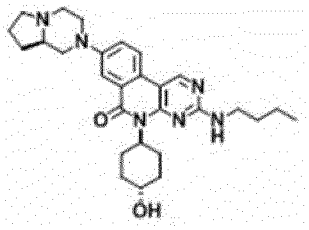
[0350]



[0351] ^{1}H NMR (300 MHz, Methanol-d_4) δ 8.95 (s, 1H), 9.49 (br s, 1H), 8.03 (d, *J* = 8.7 Hz, 1H), 7.27 (s, 1H), 6.97 (d, *J* = 8.7 Hz, 1H), 5.53 (br s, 1H), 5.36-5.14 (m, 1H), 4.88 (brs, 4H), 4.80 (m, 1H), 4.64 (m, 1H), 4.16 (brs, 3H), 3.79 (m, 2H), 2.85 (m, 2H), 2.66 (brs, 2H), 2.60-2.42 (m, 2H), 2.15-2.11 (m, 2H), 1.74-1.71 (m, 2H), 1.52-1.47 (m, 2H).
[0352] LCMS: Purity 99%, MS (m/e) 480 (MH^+ - 3TFA).

trans-3-(Butylamino)-8-((R)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

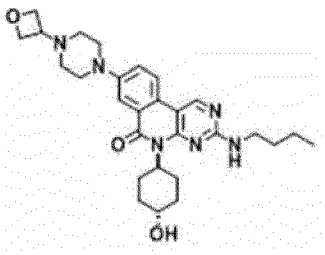
[0353]



[0354] LCMS: Purity 99%, MS (m/e) 491 (MH^+).

trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(4-(oxetan-3-yl)piperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

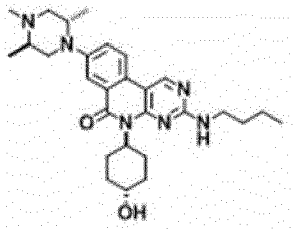
[0355]



[0356] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (s, 1H), 8.14 (d, *J* = 8.9 Hz, 1H), 7.56 (d, *J* = 2.5 Hz, 1H), 7.52 (s, 0.7H), 7.47 (dd, *J* = 9.0, 2.8 Hz, 1H), 7.36 (s, 0.3H), 5.40 (br s, 1H), 4.62 (s, 1H), 4.56 (t, *J* = 6.5 Hz, 2H), 4.46 (t, *J* = 6.1 Hz, 2H), 3.53 - 3.38 (m, 2H), 3.38 - 3.32 (app m, 2H), 3.25-3.22 (m, 4H), 2.76 (br s, 2H), 2.46 - 2.38 (m, 4H), 1.94 (d, *J* = 11.0 Hz, 2H), 1.62 - 1.51 (m, 4H), 1.43 - 1.23 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 3H). LCMS: Purity 99%, MS (m/e) 507 (MH^+).

trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-((2S,5R)-2,4,5-trimethylpiperazin-1-yl)pyrimido 4,5-c]isoquinolin-6(5H)-one

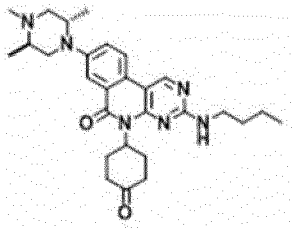
[0357]



[0358] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.96 (s, 1H), 8.03 (d, *J* = 9.0 Hz, 1H), 7.67 (d, *J* = 2.3 Hz, 1H), 7.44 (dd, *J* = 8.9, 2.8 Hz, 1H), 5.57 (br s, 1H), 3.75-3.72 (app m, 1H), 3.67 (d, *J* = 11.9 Hz, 2H), 3.45 (t, *J* = 7.2 Hz, 2H), 2.90 (br s, 2H), 2.60 (t, *J* = 11.5 Hz, 2H), 2.50-2.42 (app m, 2H), 2.37 (s, 3H), 2.10 (d, *J* = 10.7 Hz, 2H), 1.70-1.62 (app m, 4H), 1.53 - 1.39 (m, 4H), 1.23 (d, *J*= 6.2 Hz, 6H), 0.99 (t, *J* = 7.4 Hz, 3H). LCMS: Purity 99%, MS (m/e) 493 (MH^+).

3-(Butylamino)-5-(4-oxocyclohexyl)-8-((2S,5R)-2,4,5-trimethylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

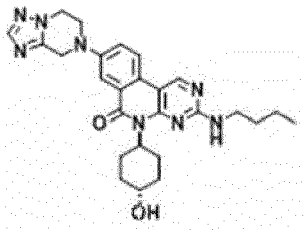
[0359]



[0360] LCMS: Purity 97%, MS (m/e) 401 (MH^+).

trans-3-(Butylamino)-8-(5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazin-7(8H)-yl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

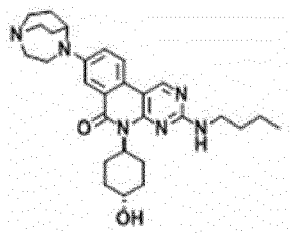
[0361]



[0362] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.01 (s, 1H), 8.16 (d, J = 9.1 Hz, 1H), 7.99 (s, 1H), 7.87 (d, J = 3.0 Hz, 1H), 7.64 (dd, J = 9.0, 2.7 Hz, 1H), 5.54 (br s, 1H), 4.68 (s, 2H), 4.37 (t, J = 5.2 Hz, 2H), 3.99 (t, J = 5.2 Hz, 2H), 3.78 - 3.68 (m, 1H), 3.56 - 3.44 (m, 2H), 2.11 (d, J = 11.4 Hz, 2H), 1.73-1.66 (m, 5H), 1.53-1.44 (m, 5H), 1.01 (t, J = 7.4 Hz, 3H). LCMS: Purity 99%, MS (m/e) 489 (MH^+).

trans-8-(1,4-Diazabicyclo[3.2.2]nonan-4-yl)-3-(butylamino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

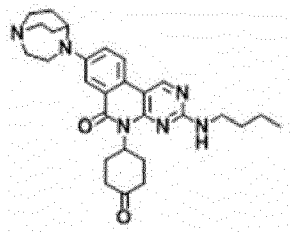
[0363]



[0364] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.08 (d, J = 8.9 Hz, 1H), 7.43 (d, J = 2.9 Hz, 1H), 7.35 (br s, 0.7H), 7.28 (dd, J = 9.1, 2.9 Hz, 1H), 7.07 (br s, 0.3 H), 5.40 (br s, 1H), 4.62 (s, 1H), 4.09 (s, 1H), 3.56 (t, J = 5.7 Hz, 2H), 3.50 (br s, 1H), 2.99 - 2.89 (m, 4H), 2.85-2.78 (m, 4H), 2.02-1.93 (m 4H), 1.70-1.63 (m, 2H), 1.55 (app p, J = 7.4 Hz, 4H), 1.43 - 1.22 (m, 4H), 0.91 (t, J = 7.3 Hz, 3H). LCMS: Purity 99%, MS (m/e) 491 (MH^+).

8-(1,4-Diazabicyclo[3.2.2]nonan-4-yl)-3-(butylamino)-5-(4-oxocyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

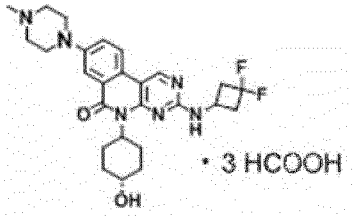
[0365]



[0366] LCMS: Purity 97%, MS (m/e) 489

trans-3-((3,3-Difluorocyclobutyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one triformate salt or solvate

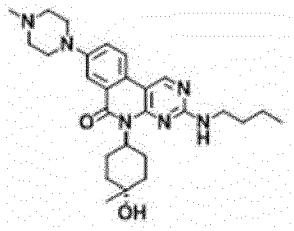
[0367]



[0368] ^{1}H NMR (300 MHz, Methanol-d_4) δ 9.09 (s, 1H), 8.19 (d, J = 9.0 Hz, 1H), 7.80 (s, 1H), 7.57 (d, J = 90 Hz, 1H), 5.56 (br s, 1H), 4.35 (m, 1H), 3.99 (m, 2H), 3.76-3.74 (m, 4H), 3.12-3.02 (m, 6H), 2.99 (s, 3H), 2.89 (br s, 2H), 2.74-2.64 (m, 2H), 2.14-2.10 (m, 2H), 1.72-1.68 (m, 2H), 1.51-1.47 (m, 2H). LCMS: Purity 98%, MS (m/e) 499 (MH^+ - 3HCOOH).

trans-3-(Butylamino)-5-(4-hydroxy-4-methylcyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

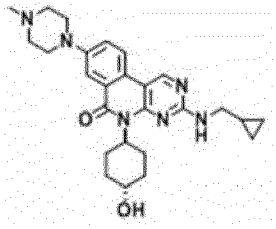
[0369]



[0370] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (s, 1H), 8.14 (d, J = 8.9 Hz, 1H), 7.56 (d, J = 2.6 Hz, 1H), 7.50 (br s, 0.7H), 7.46 (dd, J = 9.0, 2.7 Hz, 1H), 7.07 (br s, 0.3 H), 5.48 (br s, 1H), 4.40 (s, 1H), 3.35 - 3.30 (m, 1H), 3.27 (s, 1H), 3.21 (t, J = 4.9 Hz, 4H), 2.74 (app q, J = 12.9 Hz, 2H), 2.45 (t, J = 4.9 Hz, 4H), 2.21 (s, 3H), 1.66 (d, J = 12.3 Hz, 2H), 1.61 - 1.43 (m, 6H), 1.42 - 1.26 (m, 2H), 1.35 (h, J = 7.3 Hz, 1H), 0.90 (t, J = 7.3 Hz, 3H). LCMS: Purity 97%, MS (m/e) 479 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

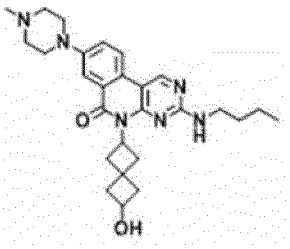
[0371]



[0372] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.12 (s, 1H), 8.13 (d, *J* = 8.9 Hz, 1H), 7.58 (br s, 1H) 7.56 (d, *J* = 2.6 Hz, 1H), 7.45 (dd, *J* = 9.0, 2.8 Hz, 1H), 5.39 (br s, 1H), 4.61 (s, 1H), 3.50 (s, 1H), 3.26 - 3.15 (m, 6H), 2.75 (br s, 2H), 2.44 (app t, *J* = 5.0 Hz, 4H), 2.20 (s, 3H), 1.98 - 1.89 (m, 2H), 1.53 (d, *J* = 10.6 Hz, 2H), 1.29 (q, *J* = 13.0 Hz, 2H), 1.14-1.10 (m, 1H), 0.47 - 0.38 (m, 2H), 0.23 (q, *J* = 4.8 Hz, 2H). LCMS: Purity 99%, MS (m/e) 463 (MH^+).

3-(Butylamino)-5-(6-hydroxyspiro[3.3]heptan-2-yl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

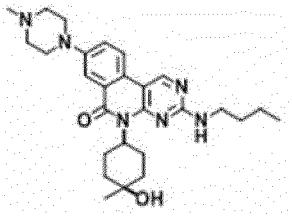
[0373]



[0374] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.11 (d, *J* = 9.0 Hz, 1H), 7.54 (d, *J* = 2.6 Hz, 1H), 7.47 (br s, 1H), 7.44 (dd, *J* = 9.0, 2.7 Hz, 1H), 5.73 (p, *J* = 9.1 Hz, 1H), 4.92 (s, 1H), 4.00 (dt, *J* = 13.5, 5.6 Hz, 1H), 3.39 - 3.33 (app m, 2H), 3.20 (t, *J* = 5.1 Hz, 4H), 3.10 (br s, 2H), 2.45 (t, *J* = 5.1 Hz, 4H), 2.42-2.41 (m, 2H), 2.29 (br s, 2H), 2.21 (s, 3H), 1.95 - 1.85 (m, 2H), 1.54 (dt, *J* = 14.0, 6.7 Hz, 2H), 1.36 (app *q*, *J* = 11.0, 7.4 Hz, 2H), 0.91 (t, *J* = 7.2 Hz, 3H). LCMS: Purity 96%, MS (m/e) 477 (MH^+).

cis-3-(Butylamino)-5-(4-hydroxy-4-methylcyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

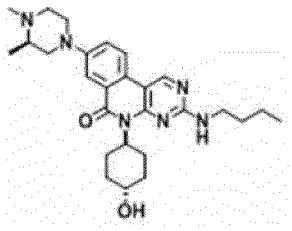
[0375]



[0376] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.98 (s, 1H), 8.06 (d, *J* = 8.9 Hz, 1H), 7.73 (d, *J* = 2.7 Hz, 1H), 7.46 (dd, *J* = 8.9, 2.8 Hz, 1H), 5.52 (br s, 1H), 3.48 (br s, *J* = 7.7 Hz, 2H), 3.32 (app m, *J* = 5.2 Hz, 4H), 3.25-3.12 (br s, 2H), 2.69 - 2.61 (m, 4H), 2.36 (s, 3H), 1.84 (d, *J* = 13.0 Hz, 2H), 1.69 - 1.55 (m, 4H), 1.51-1.42 (m, 4H), 1.26 (s, 3H), 0.98 (t, *J* = 7.4 Hz, 3H). LCMS: Purity 99%, MS (m/e) 479 (MH^+).

trans-3-(Butylamino)-8-((R)-3,4-dimethylpiperazin-1-yl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

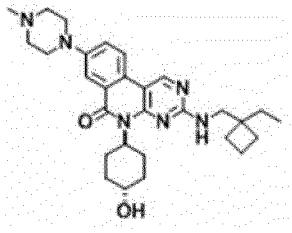
[0377]



[0378] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.95 (s, 1H), 8.02 (d, *J* = 9.0 Hz, 1H), 7.68 (d, *J* = 2.5 Hz, 1H), 7.43 (dd, *J* = 8.9, 2.7 Hz, 1H), 5.56 (br s, 1H), 3.73 - 3.60 (m, 3H), 3.44 (t, *J* = 7.2 Hz, 2H), 3.01 - 2.87 (m, 4H), 2.56 (dd, *J* = 12.0, 10.2 Hz, 1H), 2.46 (td, *J* = 12.6, 12.0, 3.2 Hz, 1H), 2.36 (s, 3H), 2.35-2.31 (m, 1H), 2.09(d, *J* = 11.1 Hz, 2H), 1.72 - 1.59 (m, 4H), 1.52-1.42 (m, 4H), 1.19 (d, *J* = 6.3 Hz, 3H), 0.99 (t, *J* = 7.3 Hz, 3H). LCMS: Purity 98%, MS (m/e) 479 (MH^+).

trans-3-(((1-Ethylcyclobutyl)methyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

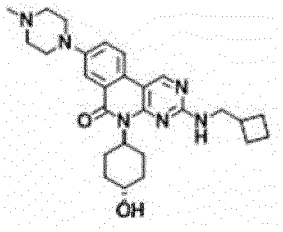
[0379]



[0380] LCMS: Purity 98%, MS (m/e) 505 (MH^+).

trans-3-((Cyclobutylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

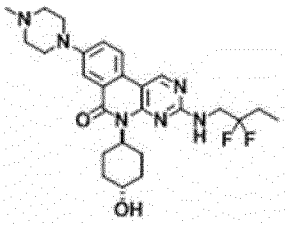
[0381]



[0382] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.98 (s, 1H), 8.06 (d, *J* = 9.0 Hz, 1H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.46 (dd, *J* = 8.9, 2.8 Hz, 1H), 5.58 (br s, 1H), 3.74 - 3.67 (m, 1H), 3.50 (d, *J* = 7.1 Hz, 2H), 3.33 - 3.31 (overlapped m, 4H), 2.91 (br s, 2H), 2.73-2.65 (app m, 1H), 2.66 - 2.64 (app m, 4H), 2.37 (s, 3H), 2.19 - 2.06 (m, 4H), 1.99 - 1.89 (m, 2H), 1.86-1.78 (m, 2H), 1.69 (d, *J* = 11.2 Hz, 2H), 1.48 (app qd, *J* = 13.3, 12.9, 3.4 Hz, 2H). LCMS: Purity 98%, MS (m/e) 477 (MH^+).

trans-3-((2,2-Difluorobutyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

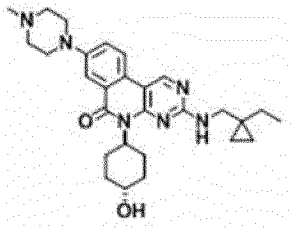
[0383]



[0384] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 (s, 1H), 8.18 (d, *J* = 9.0 Hz, 1H), 7.80 (br s, 1H), 7.56 (d, *J* = 2.6 Hz, 1H), 7.48 (dd, *J* = 8.9, 2.7 Hz, 1H), 5.40 (br s, 1H), 4.62 (s, 1H), 3.86 (td, *J* = 14.0, 6.5 Hz, 2H), 3.52 (br s, 1H), 3.23 - 3.21 (app m, 4H), 2.75 (br s, 2H), 2.47 - 2.45 (overlapped m, 4H), 2.21 (s, 3H), 2.00 - 1.85 (m, 4H), 1.53 (d, *J* = 10.9 Hz, 2H), 1.30 (q, *J* = 10.9 Hz, 2H), 0.99 (t, *J* = 7.5 Hz, 3H). LCMS: Purity 98%, MS (m/e) 501 (MH^+).

trans-3-(((1-Ethylcyclopropyl)methyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

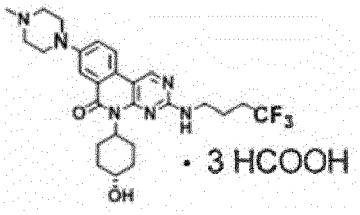
[0385]



[0386] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (s, 1H), 8.14 (d, *J* = 9.0 Hz, 1H), 7.55 (d, *J* = 2.6 Hz, 1H), 7.46 (app dd, *J* = 8.9, 2.6 Hz, 2H), 5.44 (br s, 1H), 4.63 (s, 2H), 3.51 (br s, 1H), 3.37 (d, *J* = 6.2 Hz, 2H), 3.24 - 3.16 (m, 4H), 2.74 (br s, 2H), 2.47-2.45 (overlapped m, 4H), 2.21 (s, 3H), 1.94 (d, *J* = 11.3 Hz, 2H), 1.53 (d, *J* = 12.0 Hz, 2H), 1.36 - 1.26 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 3H), 0.45 (app s, 2H), 0.28 - 0.21 (app m, 2H). LCMS: Purity 99%, MS (m/e) 491 (MH^+).

trans-5-(4-Hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)-3-((4,4,4-trifluorobutyl)amino)pyrimido[4,5-c]isoquinolin-6(5H)-one triformic acid salt or solvate

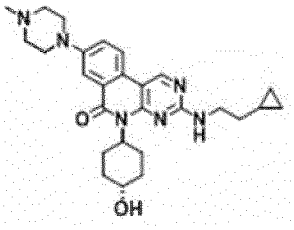
[0387]



[0388] ^{1}H NMR (300 MHz, Methanol-d_4) δ 9.03 (s, 1H), 8.42 (br s, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.75 (s, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 5.53 (br s, 1H), 3.71 (m, 1H), 3.55 (t, *J* = 7.2 Hz, 2H), 3.43 (m, 4H), 3.02 (m, 4H), 2.78-2.68 (m, 2H), 2.64 (s, 3H), 2.33-2.24 (m, 2H), 2.13-2.08 (m, 2H), 1.98-1.91 (m, 2H), 1.72-1.68 (m, 2H), 1.51-1.46 (m, 2H). LCMS: Purity 98%, MS (m/e) 519 (MH^+ - 3HCOOH).

trans-3-((2-Cyclopropylethyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

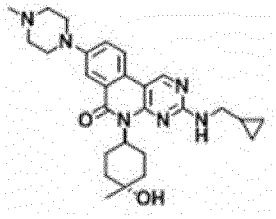
[0389]



[0390] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.97 (s, 1H), 8.04 (d, *J* = 8.9 Hz, 1H), 7.71 (d, *J* = 2.6 Hz, 1H), 7.45 (dd, *J* = 8.9, 2.7 Hz, 1H), 5.57 (br s, 1H), 3.72 (ddd, *J* = 15.2, 7.4, 4.2 Hz, 1H), 3.55 (t, *J* = 7.2 Hz, 2H), 3.32 - 3.31 (overlapped m, 4H), 2.91 (br s 2H), 2.65 (t, *J* = 5.1 Hz, 4H), 2.37 (s, 3H), 2.10 (d, *J* = 11.2 Hz, 2H), 1.69 (d, *J* = 11.1 Hz, 2H), 1.56 (q, *J* = 7.1 Hz, 2H), 1.53 - 1.44 (app m, 2H), 0.86 - 0.76 (m, 1H), 0.49 (dt, *J* = 8.0, 5.0 Hz, 2H), 0.12 (q, *J* = 5.0 Hz, 2H). LCMS: Purity 98%, MS (m/e) 477 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

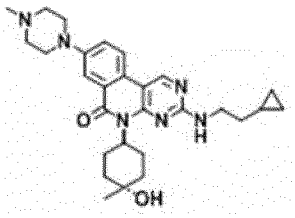
[0391]



[0392] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.01 (s, 1H), 8.08 (d, *J* = 8.9 Hz, 1H), 7.72 (d, *J* = 2.7 Hz, 1H), 7.48 (dd, *J* = 8.9, 2.8 Hz, 1H), 5.65 (br s, 1H), 3.36-3.33 (overlapped m, 4H), 2.91 (dd, *J* = 24.4, 12.4 Hz, 2H), 2.65 (t, *J* = 5.1 Hz, 4H), 2.37 (s, 3H), 1.83 (d, *J* = 12.2 Hz, 2H), 1.70 (td, *J* = 13.3, 3.8 Hz, 2H), 1.61 (d, *J* = 11.4 Hz, 2H), 1.45 (s, 3H), 1.20 - 1.14 (m, 2H), 0.54 (ddd, *J* = 8.0, 5.8, 4.4 Hz, 2H), 0.30 (q, *J* = 5.0 Hz, 2H). LCMS: Purity 99%, MS (m/e) 477 (MH^+).

trans-3-((2-Cyclopropylethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

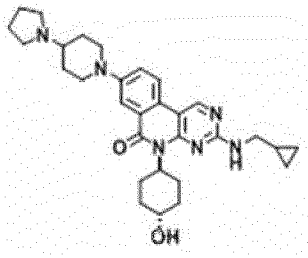
[0393]



[0394] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 1H), 8.14 (d, *J* = 8.9 Hz, 1H), 7.56 (d, *J* = 2.7 Hz, 1H), 7.46 (overlapped dd, *J* = 9.0, 2.7 Hz, 1H), 5.48 (br s, 1H), 4.40 (s, 1H), 3.44-3.39 (m, 2H), 3.28 (app s, 1H), 3.24 - 3.17 (m, 4H), 2.75 (app dd, *J* = 25.8, 14.2 Hz, 2H), 2.46 - 2.44 (overlapped m, 4H), 2.21 (s, 3H), 1.67 (d, *J* = 12.1 Hz, 2H), 1.58 - 1.42 (m, 6H), 1.29 (s, 3H), 0.80 - 0.68 (m, 1H), 0.40 (dt, *J* = 8.0, 5.0 Hz, 2H), 0.06 (q, *J* = 5.3 Hz, 2H). LCMS: Purity 99%, MS (m/e) 491 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-(pyrrolidin-1-yl)piperidin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

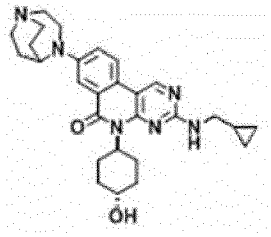
[0395]



[0396] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (s, 1H), 8.13 (d, *J* = 8.9 Hz, 1H), 7.56 (d, *J* = 2.7 Hz, 1H), 7.46 (dd, *J* = 9.0, 2.8 Hz, 1H), 5.40 (br s, 1H), 4.62 (s, 1H), 3.69 (dd, *J* = 12.3, 4.7 Hz, 2H), 3.51 (br s, 1H), 3.27 (app s, 1H), 3.22 (d, *J* = 12.0 Hz, 2H), 2.79 (app t, *J* = 11.2 Hz, 3H), 2.15-2.10 (app m, 1H), 1.97-1.90 (m, 4H), 1.65 (app s, 4H), 1.57- 1.44 (m, 4H), 1.30 (q, *J* = 11.5 Hz, 2H), 1.15 - 1.07 (m, 1H), 0.43 (dt, *J* = 8.0, 5.0 Hz, 2H), 0.24 (q, *J* = 5.0 Hz, 2H). LCMS: Purity 96%, MS (m/e) 517 (MH^+).

trans-8-(1,4-diazabicyclo[3.2.2]nonan-4-yl)-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

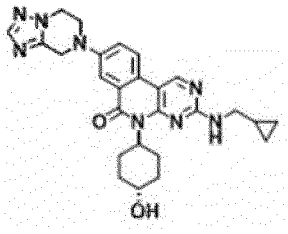
[0397]



[0398] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (s, 1H), 8.08 (d, *J* = 9.0 Hz, 1H), 7.48 (br s, 1H), 7.43 (d, *J* = 2.8 Hz, 1H), 7.28 (dd, *J* = 9.1, 2.9 Hz, 1H), 5.40 (br s, 1H), 4.62 (s, 1H), 4.09 (s, 1H), 3.56 (t, *J* = 5.8 Hz, 2H), 3.50 (br s, 1H), 3.22 (d, *J* = 6.6 Hz, 2H), 2.99 - 2.89 (m, 4H), 2.85 - 2.78 (m, 4H), 2.02-1.93 (m, 4H), 1.70-1.63 (m, 2H), 1.53 (d, *J* = 11.7 Hz, 2H), 1.30 (q, *J* = 11.0 Hz, 2H), 1.13 - 1.04 (m, 1H), 0.43 (dt, *J* = 8.0, 5.0 Hz, 2H), 0.24 (q, *J* = 5.0 Hz, 2H). LCMS: Purity 97%, MS (m/e) 401 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-8-(5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazin-7(8H)-yl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

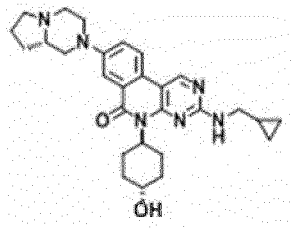
[0399]



[0400] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (s, 1H), 8.23 (d, *J* = 8.8 Hz, 1H), 7.97 (s, 1H), 7.69 (d, *J* = 2.8 Hz, 1H), 7.65 (dd, *J* = 9.1, 2.9 Hz, 1H), 7.63 (overlapped s, 1H), 5.41 (br s, 1H), 4.62 (app s, 3H), 4.26 (t, *J* = 5.4 Hz, 2H), 3.95 - 3.87 (t, *J* = 5.4 Hz, 2H), 3.51 (br s, 1H), 3.24 (t, *J* = 6.2 Hz, 2H), 2.88 (br s, 2H), 1.95 (d, *J* = 10.5 Hz, 2H), 1.55 (d, *J* = 9.4 Hz, 2H), 1.31 (q, *J* = 11.0 Hz, 2H), 1.17-1.11 (m, 1H), 0.44 (dt, *J* = 8.0, 5.0 Hz, 2H), 0.24 (q, *J* = 5.0 Hz, 2H). LCMS: Purity 97%, MS (m/e) 487 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-8-((S)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

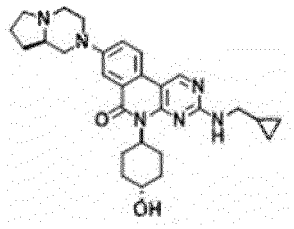
[0401]



[0402] H NMR (400 MHz, Methanol-d_4) δ 9.00 (s, 1H), 8.07 (d, J = 9.0 Hz, 1H), 7.73 (d, J = 2.3 Hz, 1H), 7.49 (dd, J = 8.9, 2.8 Hz, 1H), 5.58 (br s, 1H), 3.93 (d, J = 10.5 Hz, 1H), 3.82 - 3.67 (m, 2H), 3.34 (app d, J = 6.8 Hz, 2H), 3.23 - 3.09 (m, 2H), 2.95 (app td, J = 11.8, 3.3 Hz, 3H), 2.61 (t, J = 10.9 Hz, 1H), 2.44 (td, J = 11.4, 3.3 Hz, 1H), 2.29 - 2.22 (m, 2H), 2.10 (d, J = 11.3 Hz, 2H), 1.99 - 1.93 (m, 1H), 1.93 - 1.79 (m, 2H), 1.69 (d, J = 11.5 Hz, 2H), 1.61 - 1.42 (m, 3H), 1.20-1.14 (m, 1H), 0.54 (ddd, J = 8.0, 5.8, 4.4 Hz, 2H), 0.30 (q, J = 5.0 Hz, 2H). LCMS: Purity 97%, MS (m/e) 489 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-8-((*R*)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

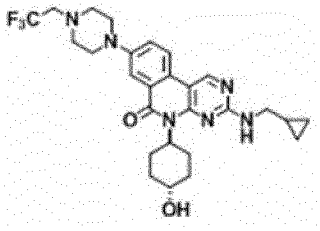
[0403]



[0404] LCMS: Purity 97%, MS (m/e) 489 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

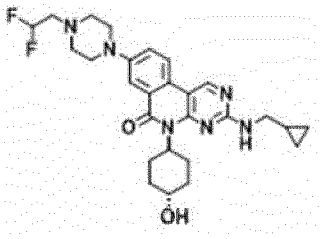
[0405]



[0406] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 1H), 8.15 (d, J = 8.9 Hz, 1H), 7.62 (br s, 1H), 7.56 (d, J = 2.7 Hz, 1H), 7.47 (dd, J = 9.0, 2.8 Hz, 1H), 5.40 (br s, 1H), 4.62 (s, 1H), 3.51 (br s, 1H), 3.31 - 3.17 (app m, 8H), 2.78 (app t, J = 5.1 Hz, 6H), 1.94 (d, J = 10.6 Hz, 2H), 1.54 (d, J = 10.3 Hz, 2H), 1.30 (q, J = 11.0 Hz, 2H), 1.17-1.11 (m, 1H), 0.43 (dt, J = 8.0, 5.0 Hz, 2H), 0.23 (q, J = 5.0 Hz, 2H). LCMS: Purity 97%, MS (m/e) 531(MH^+).

trans-3-((Cyclopropylmethyl)amino)-8-(4-(2,2-difluoroethyl)piperazin-1-yl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

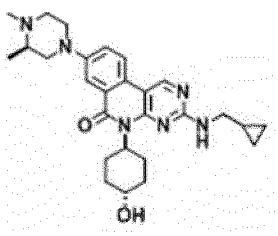
[0407]



[0408] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 1H), 8.14 (d, *J* = 8.9 Hz, 1H), 7.60 (br s, 1H), 7.56 (d, *J* = 2.7 Hz, 1H), 7.46 (dd, *J* = 9.0, 2.8 Hz, 1H), 6.17 (tt, *J* = 55.7, 4.3 Hz, 1H), 5.40 (br s, 1H), 4.62 (s, 1H), 3.51 (app br s, 1H), 3.28 - 3.17 (m, 6H), 2.78 (app td, *J* = 15.7, 4.3 Hz, 4H), 2.69 (app t, *J* = 4.8 Hz, 4H),1.94 (d, *J* = 10.6 Hz, 2H), 1.54 (d, *J* = 10.3 Hz, 2H), 1.30 (q, *J* = 11.0 Hz, 2H), 1.17-1.11 (m, 1H), 0.43 (dt, *J* = 8.0, 5.0 Hz, 2H), 0.23 (q, *J* = 5.0 Hz, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -118.56 (dt, *J* = 55.8, 15.7 Hz). LCMS: Purity 97%, MS (m/e) 513 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-8-((R)-3,4-dimethylpiperazin-1-yl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

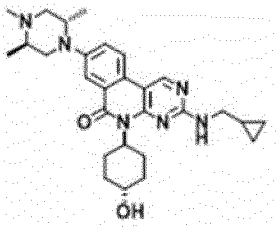
[0409]



[0410] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.98 (s, 1H), 8.05 (d, *J* = 9.0 Hz, 1H), 7.69 (d, *J* = 2.4 Hz, 1H), 7.46 (dd, *J* = 9.0, 2.8 Hz, 1H), 5.57 (br s, 1H), 3.78 - 3.61 (m, 3H), 3.34 (app d, *J* = 6.9 Hz, 2H), 3.03 - 2.88 (m, 3H), 2.56 (dd, *J* = 12.0, 10.2 Hz, 1H), 2.46 (td, *J* = 12.6, 12.0, 3.2 Hz, 1H), 2.36 (s, 3H), 2.35-2.31 (m, 1H), 2.10 (d, *J* = 11.4 Hz, 2H), 1.69 (d, *J* = 11.1 Hz, 2H), 1.48 (q, *J* = 11.6, 10.5 Hz, 2H), 1.20-1.14 (m, 1H), 1.19 (overlapped app d, *J* = 6.3 Hz, 4H), 0.54 (ddd, *J* = 8.0, 5.8, 4.4 Hz, 2H), 0.30 (q, *J*= 5.0 Hz, 2H). LCMS: Purity 97%, MS (m/e) 477 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((2S,*5R*)-2,4,5-trimethylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

[0411]

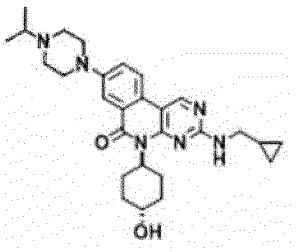


[0412] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 1H), 8.13 (d, *J* = 8.9 Hz, 1H), 7.58 (br s, 1H), 7.53 (d, *J* = 2.7 Hz, 1H), 7.47 (dd, *J* = 9.0, 2.8 Hz, 1H), 5.42 (br s, 1H), 4.62 (s, 1H), 3.63 (d, *J* = 11.4 Hz, 2H), 3.50 (br s, 1H), 3.23 (d, *J* = 6.6 Hz, 2H), 2.75 (br s, 2H), 2.43 (t, *J* = 11.3 Hz, 2H), 2.29 - 2.22 (m, 2H), 2.18 (s, 3H), 1.94 (d, *J* = 11.5 Hz, 2H), 1.54 (d, *J* = 10.8 Hz, 2H), 1.30 (q, *J* = 10.9 Hz, 2H), 1.08 (overlapped d, *J* = 6.1 Hz, 7H), 0.43 (dt, *J* = 8.0, 5.0 Hz, 2H), 0.23 (q,

J = 5.0 Hz, 2H). LCMS: Purity 98%, MS (m/e) 491 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-isopropylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

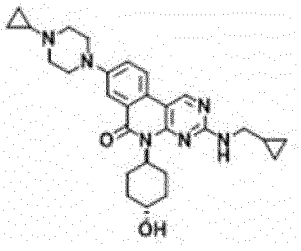
[0413]



[0414] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 1H), 8.14 (d, *J* = 8.9 Hz, 1H), 7.58 (br s, 1H), 7.54 (d, *J* = 2.8 Hz, 1H), 7.45 (dd, *J* = 9.0, 2.8 Hz, 1H), 5.73 (br s, 1H), 4.62 (s, 1H), 3.51 (br s, 1H), 3.27 - 3.15 (m, 6H), 2.75 (br s, 2H), 2.69 (p, *J* = 6.7 Hz, 1H) 2.59 - 2.54 (m, 4H), 1.94 (d, *J* = 11.1 Hz, 2H), 1.54(d, *J* = 11.4 Hz, 2H), 1.30 (q, *J* = 11.3 Hz, 2H), 1.17 - 1.06 (m, 1H), 0.99 (d, *J* = 6.5 Hz, 6H), 0.43 (dt, *J* = 8.0, 5.0 Hz, 2H), 0.23 (q, *J* = 5.0 Hz, 2H). LCMS: Purity 97%, MS (m/e) 491 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-8-(4-cyclopropylpiperazin-1-yl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

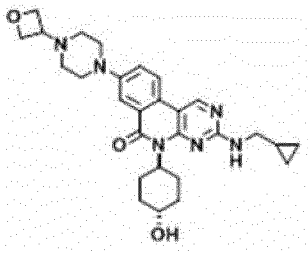
[0415]



[0416] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 1H), 8.14 (d, *J* = 8.9 Hz, 1H), 7.55 (d, *J* = 2.7 Hz, 1H), 7.58 (br s, 1H), 7.46 (dd, *J* = 9.0, 2.8 Hz, 1H), 5.42 (s, 1H), 4.62 (s, 1H), 3.52 (br s, 1H), 3.23 (t, *J* = 6.4 Hz, 2H), 3.20 - 3.12 (m, 4H), 2.75 (br s, 2H), 2.73 - 2.63 (m, 4H), 1.94 (d, *J* = 11.7 Hz, 2H), 1.72 - 1.60 (m, 1H), 1.54 (d, *J* = 10.5 Hz, 2H), 1.30 (q, *J* = 11.4 Hz, 2H), 1.20 - 1.02 (m, 1H), 0.52 - 0.37 (m, 4H), 0.34 (dt, *J* = 6.9, 4.0 Hz, 2H), 0.24 (q, *J* = 4.9 Hz, 2H). LCMS: Purity 97%, MS (m/e) 489 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-(oxetan-3-yl)piperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

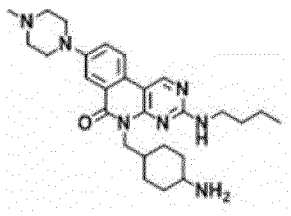
[0417]



[0418] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 1H), 8.15 (d, *J* = 8.9 Hz, 1H), 7.62 (br s, 1H), 7.56 (d, *J* = 2.7 Hz, 1H), 7.47 (dd, *J* = 9.0, 2.8 Hz, 1H), 5.40 (br s, 1H), 4.63 (s, 1H), 4.56 (t, *J* = 6.5 Hz, 2H), 4.46 (t, *J* = 6.1 Hz, 2H), 3.52 (br s, 1H), 3.44 (p, *J* = 6.5 Hz, 1H), 3.27-3.19 (m, 6H), 2.77 (br s, 2H), 2.45 - 2.37 (m, 4H), 1.94 (d, *J* = 11.4 Hz, 2H), 1.54 (d, *J* = 11.8 Hz, 2H), 1.30 (q, *J* = 11.5 Hz, 2H), 1.21 - 0.95 (m, 1H), 0.43 (dt, *J* = 8.0, 5.0 Hz, 2H), 0.23 (q, *J* = 5.0 Hz, 2H). LCMS: Purity 97%, MS (m/e) 505 (MH^+).

5-((4-Aminocyclohexyl)methyl)-3-(butylamino)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

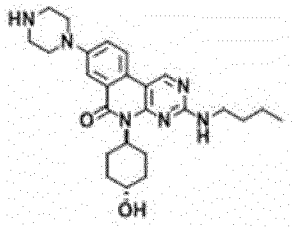
[0419]



[0420] 5-((4-Aminocyclohexyl)methyl)-3-(butylamino)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one was prepared by the acid hydrolysis of *tert*-butyl (4-((3-(butylamino)-8-(4-methylpiperazin-1-yl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)methyl)cyclohexyl)carbamate analogous to the preparation of 5-((4-aminocyclohexyl)methyl)-3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.98 (s, 1H), 8.08 (d, *J* = 8.8 Hz, 1H), 7.73 (d, *J* = 2.6 Hz, 1H), 7.48 (dd, *J* = 9.0, 2.6 Hz, 1H), 4.33 (d, *J* = 7.3 Hz, 2H), 3.48 - 3.39 (m, 2H), 3.36 - 3.29 (hidden m, 4H), 2.65 (t, *J*= 5.0 Hz, 4H), 2.61-2.58 (m, 1H), 2.37 (s, 3H), 2.01-1.86 (m, 1H), 1.99 (d, *J* = 14.5 Hz, 2H), 1.73 - 1.59 (m, 4H), 1.46 (p, *J* = 7.4 Hz, 2H), 1.28 - 1.17 (m, 2H), 1.12 - 0.95 (m, 5H). LCMS: Purity 98%, MS (m/e) 478 (MH^+).

trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(piperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

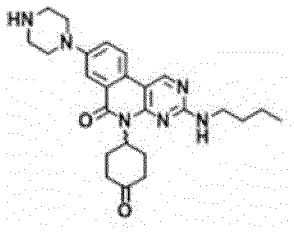
[0421]



[0422] Analogous to the preparation of *trans*-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(piperazin-1-ylmethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one, *trans*-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-(piperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one was obtained after acidic hydrolysis of *trans-tert*-butyl 4-(3-(butylamino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)piperazine-1-carboxylate. The crude reaction mixture was purified by preparative HPLC on reverse phase column by CH_3CN:H_2O an an eluting solvent containing formic acid modifier. Upon neutralizing concentrated fraction with aq. $NaHCO_3$, the resulting white solid was collected by filtration and suction dried to obtain *trans-3*-(butylamino)-5-(4-hydroxycyclohexyl)-8-(piperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (s, 1H), 8.14 (d, *J* = 8.8 Hz, 1H), 7.54 (d, *J* = 2.7 Hz, 1H), 7.50 (br s, 0.7H), 7.45 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.07 (br s, 0.3 H), 5.40 (br s, 1H), 4.63 (s, 1H), 3.50 (s, 1H), 3.34-3.39 (app m, 2H), 3.12 (t, *J* = 5.1 Hz, 4H), 2.85 (t, *J* = 4.9 Hz, 4H), 2.74 (br s, 2H), 1.94 (d, *J* = 12.1 Hz, 2H), 1.60 - 1.51 (m, 4H), 1.40-1.21 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 3H). LCMS: Purity 99%, MS (m/e) 451 (MH^+).

3-(Butylamino)-5-(4-oxocyclohexyl)-8-(piperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

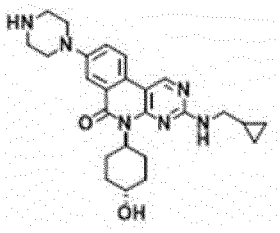
[0423]



[0424] LCMS: Purity 97%, MS (m/e) 449 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(piperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

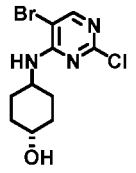
[0425]



[0426] Analogous to the preparation of *trans*-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-(piperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one, trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(piperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one was obtained after acidic hydrolysis of *trans-tert-butyl* 4-(3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)piperazine-1-carboxylate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (s, 1H), 8.14 (d, *J*= 9.0 Hz, 1H), 7.57 (br s, 1H), 7.54 (d, *J* = 2.7 Hz, 1H), 7.45 (dd, *J* = 8.9, 2.8 Hz, 1H), 5.40 (br s, 1H), 4.62 (s, 1H), 3.51 (br s, 1H), 3.23 (t, *J* = 6.3 Hz, 2H), 3.15 - 3.07 (m, 4H), 2.88 - 2.77 (m, 6H), 2.41 9app br s, 1H), 1.94 (d, *J* = 11.4 Hz, 2H), 1.54 (d, *J* = 11.8 Hz, 2H), 1.30 (q, *J* = 11.4 Hz, 2H), 1.17- 1.06 (m, 1H), 0.43 (dt, *J*= 8.0, 5.0 Hz, 2H), 0.23 (q, *J* = 5.0 Hz, 2H). LCMS: Purity 98%, MS (m/e) 449 (MH^+).

trans-4-((5-Bromo-2-chloropyrimidin-4-yl)amino)cyclohexan-1-ol

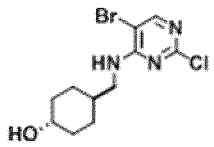
[0427]



[0428] *i*-Pr_2NEt (15 mL, 11 g, 86.6 mmol) was added to a stirring ice-salt bath cooled solution of 5-bromo-2,4-dichloropyrimidine (10 g, 43.9 mmol) in *i*-PrOH (20 mL) over a period of 20 min. Subsequently, a solution of *trans*-4-aminocyclohexan-1-ol (5 g, 43.4 mmol) dissolved in *i*-PrOH (25 mL) was added over a period of 2h. Upon complete addition of *trans*-4-aminocyclohexan-1-ol, reaction mixture was maintained at the same temperature for additional period (2h) and allowed to warm to room temperature. After 18 h, reaction solution was concentrated under reduced pressure, diluted with aq. $NaHCO_3$ and extracted into EtOAc (3 X 100 mL). Combined organic layers were washed with water (75 mL), aq. NaCl (70 mL), stirred over $MgSO_4$, and fitered through Celite®. Upon concentrating filtrate, the resulting pale yellow crystalline solid (12G) was stirred in 20%EtOAc/hexanes (60 mL) at 90 °C for 20 min, cooled to room temperature and suction filtered. The crystalline white solid on the funnel was further washed with 20%EtOAc/hexanes (15 mL) to provide trans-4-((5-bromo-2-chloropyrimidin-4-yl)amino)cyclohexan-1-ol (9g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 4.55 (d, *J* = 4.5 Hz, 1H), 3.84 (tdt, *J* = 11.9, 8.1, 4.1 Hz, 1H), 3.36 (app ddt, *J* = 15.0, 10.8, 4.2 Hz, 1H), 1.82 (app d, *J* = 12.4 Hz, 2H), 1.74 (app d, *J* = 12.5 Hz, 2H)., 1.50 (app qd, *J* = 12.9, 3.3 Hz, 2H), 1.21 (app qd, *J* = 13.3, 3.4 Hz, 2H). LCMS: Purity 99%, MS (m/e) 307 (MH^+).

trans-4-(((5-Bromo-2-chloropyrimidin-4-yl)amino)methyl)cyclohexan-1-ol

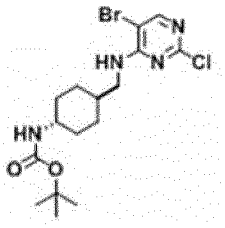
[0429]



[0430] *trans*-(4-Aminomethyl)cyclohexan-1-ol (2.0 g, 12 mmol) was added all at once to a stirring heterogeneous mixture of 5-bromo-2,4-dichloropyrimidine (3.85 g, 16.9 mmol), Na_2CO_3 (2.6 g, 24.5 mmol) in 2-propanol (10 mL) and water (10 mL). After stirring heterogeneous reaction mixture at room temperature for 18h, reaction mixture was concentrated and diluted with water (30 mL) followed by EtOAc (150 mL). Upon separating organic layer and further extraction of aqueous layer with EtOAc (2 X 100 mL), combined organic layers were washed with water (30 mL), saturated aq. NaCl solution (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Subsequent purification of crude concentrate by silica gel flash column chromatography [Combiflash Torrent® with RediSep® silica gel column 80 g and eluted with 30-50% EtOAc/hexanes solvent gradient], concentrating the desired product fractions, the resulting white solid was heated in 20%EtOAc/hexanes (15 mL) for 5 min, cooled to room temperature, filtered and dried to obtain trans-4-(((5-bromo-2-chloropyrimidin-4-yl)amino)methyl)cyclohexan-1-ol (1.6 g, 41%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.65 (t, *J* = 5.8 Hz, 1H), 4.44 (s, 1H), 3.33 (overlapped m 1H), 3.19 (t, *J* = 6.5 Hz, 2H), 1.79 (d, *J* = 12.3, 3.1 Hz, 2H), 1.62 (d, *J* = 12.3 Hz, 2H), 1.58 - 1.45 (m, 1H), 1.13 - 0.99 (m, 2H), 0.99 - 0.81 (m, 2H). LCMS: Purity 97%, MS (m/e) 321 (MH^+).

trans-tert-Butyl (4-(((5-bromo-2-chloropyrimidin-4-yl)amino)methyl)cyclohexyl)carbamate

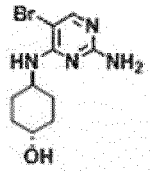
[0431]



[0432] *trans-tert-Butyl* (4-(((5-bromo-2-chloropyrimidin-4-yl)amino)methyl)cyclohexyl)carbamate was obtained in an analogous manner to the preparation of *trans*-4-(((5-bromo-2-chloropyrimidin-4-yl)amino)methyl)cyclohexan-1-ol. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.67 (t, *J* = 5.8 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 3.18 (t, *J* = 6.4 Hz, 2H), 3.14 - 3.08 (m, 1H)., 1.74 (d, *J* = 11.0 Hz, 2H), 1.64 (d, *J* = 12.2 Hz, 2H), 1.56 - 1.47 (m, 1H), 1.35 (s, 9H), 1.07 (q, *J* = 12.1, 11.5 Hz, 2H), 0.93 (q, *J* = 12.4, 11.5 Hz, 2H). LCMS: Purity 99%, MS (m/e) 419 (MH^+).

trans-4-((2-Amino-5-bromopyrimidin-4-yl)amino)cyclohexan-1-ol

[0433]

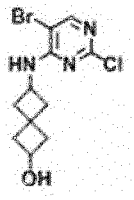


[0434] *trans*-4-aminocyclohexan-1-ol (1.6g, 13.8 mmol), 5-bromo-2,4-dichloropyrimidine (2.5 g, 11.9 mmol) and *i*-Pr_2NEt (3.1 mL, 2.3 g, 17.7 mmol) in 2-propanol were stirred in a sealed tube at 100 °C. After 16h, reaction mixture was cooled to room temperature, concentrated and purified silica gel flash column chromatography [Combiflash Torrent® with RediSep® silica gel column 40 g and eluted with 0-5% MeOH/CH_2Cl_2 solvent gradient] to obtain off-white solid of

trans-4-((2-Amino-5-bromopyrimidin-4-yl)amino)cyclohexan-1-ol (2.1 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (s, 1H), 6.61 (s, 2H), 6.44 (d, *J* = 8.3 Hz, 1H), 4.55 (s, 1H), 3.94 - 3.84 (m, 1H), 3.38- 3.33 (app m, 1H), 1.82 (d, *J* = 11.6 Hz, 2H), 1.74 (d, *J* = 10.3 Hz, 2H), 1.44 (q, *J* = 11.6, 10.1 Hz, 2H), 1.23 - 1.07 (m, 2H). LCMS: Purity 99%, MS (m/e) 287 (MH^+).

6-((5-Bromo-2-chloropyrimidin-4-yl)amino)spiro[3.3]heptan-2-ol

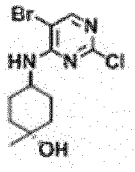
[0435]



[0436] *tert*-Butyl (6-hydroxyspiro[3.3]heptan-2-yl)carbamate (2.0 g, 8.79 mmol) in EtOAc (50 mL) was treated 4.0 N HCl in dioxane (20 mL, 80 mmol) at room temperature and stirred under nitrogen 2h. Upon concentrating heterogeneous reaction, the resulting 6-aminospiro[3.3]heptan-2-ol hydrochloride was sitrrred in 2-propanol (10 mL)/ water (10 mL) at 0 °C, treated with solid Na_2CO_3 (2.8 g, 26.40 mmol) followed by 5-bromo-2,4-dichloropyrimidine (3.4 g, 14.9 mmol) portion-wise over a period of 20 min under nitrogen and allowed to warm to room tempeurature. After overnight, reaction mixture was concentrated and diluted with water (30 mL)/EtOAc (150 mL). Upon separating organic layer and further extraction of aqueous layer with EtOAc (2 X 100 mL), combined organic layers were washed with water (30 mL), saturated aq. NaCl solution (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Subsequent purification of crude visclous liquid by silica gel column chromatography [Combiflash Torrent® with RediSep® silica gel column 80 g and eluted with 30-50-70% EtOAc/hexanes solvent gradient] provided 6-((5-Bromo-2-chloropyrimidin-4-yl)amino)spiro[3.3]heptan-2-ol. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.69 (d, *J* = 7.2 Hz, 1H), 4.33 (app h, *J* = 8.1 Hz, 2H), 3.94 (p, *J* = 7.3 Hz, 1H), 2.42 - 2.32 (m, 1H), 2.30 - 2.24 (m, 1H), 2.23 - 2.09 (m, 4H), 1.81 (ddd, *J* = 13.5, 10.8, 7.7 Hz, 2H). LCMS: Purity 99%, MS (m/e) 318 (MH^+).

trans-4-((5-Bromo-2-chloropyrimidin-4-yl)amino)-1-methylcyclohexan-1-ol

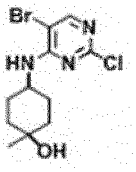
[0437]



[0438] *t*rans-4-((5-Bromo-2-chloropyrimidin-4-yl)amino)-1-methylcyclohexan-1-ol was obtained as a white solid after following analogous reaction procedure and isolation described for *trans*-4-((5-bromo-2-chloropyrimidin-4-yl)amino)cyclohexan-1-ol. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (d, *J* = 0.8 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 4.30 (br s, 1H), 3.96 - 3.82 (m, 1H), 1.71 - 1.49 (m, 6H), 1.42 (td, *J* = 12.7, 4.9 Hz, 2H), 1.15 (s, 3H). LCMS: Purity 99%, MS (m/e) 320 (MH^+).

cis-4-((5-Bromo-2-chloropyrimidin-4-yl)amino)-1-methyl cyclohexan-1-ol

[0439]

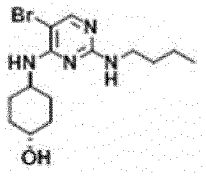


[0440] *cis*-4-((5-Bromo-2-chloropyrimidin-4-yl)amino-methylcyclohexan-1-ol was prepared analogous to *trans*-4-((5-

bromo-2-chloropyrimidin-4-yl)amino)cyclohexan-1-ol to obtain a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, *J* = 0.8 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 1H), 4.03 (s, 1H), 3.87 - 3.83 (app m, 1H), 1.87 - 1.77 (m, 2H), 1.59 - 1.48 (m, 4H), 1.35 (td, *J*= 14.5, 13.8, 4.2 Hz, 2H), 1.10 (s, 3H). LCMS: Purity 98%, MS (m/e) 320 (MH^+).

trans-4-((5-Bromo-2-(butylamino)pyrimidin-4-yl)amino)cyclohexan-1-ol

[0441]

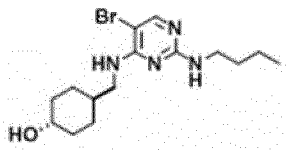


[0442] A solution of *trans*-4-((5-bromo-2-chloropyrimidin-4-yl)amino)cyclohexan-1-ol (6.3 g, 20.5 mmol), *n*-butylamine (6.1 mL, 4.5 g, 61.5 mmol) and ethanol (10 ml) was stirred and heated in a sealed tube at 90 °C. After 16h, pale yellow reaction solution was cooled to room temperature and progress of reaction was analyzed by LC/MS which indicated complete consumption of *trans*-4-((5-bromo-2-chloropyrimidin-4-yl)amino)cyclohexan-1-ol to *trans-4*-((5-bromo-2-(butylamino)pyrimidin-4-yl)amino)cyclohexan-1-ol quantitatively. The crude yellow semi-solid obtained after concentration of reaction solution was diluted with diluted with aq. $NaHCO_3$ (30 ml) and extracted into EtOAc (3 X 75 mL). Combined organic layers were washed with water (35 mL), aq. NaCl (30 mL), stirred over $MgSO_4$, and fitered through Celite®. Upon concentrating filtrate, the resulting pale yellow crystalline solid (8G) was purified by silica gel flash column chromatography [Combiflash Torrent® with RediSep® silica gel column 80 g and eluted with 30-65% EtOAc/hexanes solvent gradient] and obtained *trans*-4-((5-bromo-2-(butylamino)pyrimidin-4-yl)amino)cyclohexan-1-ol (5.9 g) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (s, 1H), 6.70 (s, 1H), 5.98 (s, 1H), 4.52 (d, *J* = 4.4 Hz, 1H), 3.89 - 3.78 (m, 1H), 3.41 - 3.32 (m, 1H), 3.14 (q, *J* = 6.9 Hz, 2H), 1.86 - 1.77 (m, 4H), 1.51 - 1.33 (m, 4H), 1.33 - 1.24 (m, 2H), 1.24 - 1.11 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H). LCMS: Purity 98%, MS (m/e) 344 (MH^+).

[0443] The following compounds were prepared and isolated by the reaction of respective amine and corresponding 5-bromo-4-amino(substituted)pyrimidines in similar manner to *trans*-4-((5-bromo-2-(butylamino)pyrimidin-4-yl)amino)cyclohexan-1-ol

trans-4-(((5-Bromo-2-(butylamino)pyrimidin-4-yl)amino)methyl)cyclohexan-1-ol

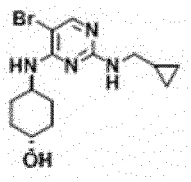
[0444]



[0445] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (s, 1H), 6.66 (br s, 2H), 4.44 (d, *J* = 4.4 Hz, 1H), 3.36-3.22 (m, 1H), 3.13 (app q, *J* = 6.7 Hz, 4H), 1.84 - 1.75 (m, 2H), 1.63 (d, *J* = 11.9 Hz, 2H), 1.53 (ddt, *J* = 11.4, 7.7, 4.1 Hz, 1H), 1.44 (p, *J* = 7.4 Hz, 2H), 1.27 (dq, *J* = 14.4, 7.3 Hz, 2H), 1.13 - 0.97 (m, 2H), 0.97 - 0.84 (app m, 5H). LCMS: Purity 99%, MS (m/e) 357 (MH^+).

trans-4-((5-Bromo-2-((cyclopropylmethyl)amino)pyrimidin-4-yl)amino)cyclohexan-1-ol

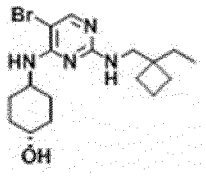
[0446]



[0447] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (s, 1H), 6.76 (s, 1H), 5.99 (app d, *J* = 7.5 Hz, 1H), 4.52 (d, *J* = 4.5 Hz, 1H), 3.88 - 3.74 (m, 1H), 3.41-3.22 (m, 1H), 3.04 (t, *J* = 6.4 Hz, 2H), 1.80 (t, *J* = 12.5 Hz, 4H), 1.48 - 1.32 (m, 2H), 1.26 - 1.12 (m, 2H), 1.05 - 0.96 (m, 1H), 0.41 - 0.30 (m, 2H), 0.16 (q, *J* = 4.9 Hz, 2H). LCMS: Purity 97%, MS (m/e) 341 (MH^+).

trans-4-((5-Bromo-2-(((1-ethylcyclobutyl)methyl)amino)pyrimidin-4-yl)amino)cyclohexan-1-ol

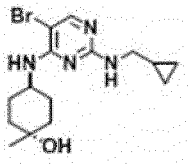
[0448]



[0449] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (s, 1H), 6.74 (br s, 1H), 5.99 (br s, 1H), 4.52 (d, *J*= 4.4 Hz, 1H), 3.91 - 3.84 (m, 1H), 3.43 - 3.32 (m, 1H), 3.28 (d, *J*= 6.4 Hz, 2H), 1.88 - 1.67 (m, 8H), 1.57 (app qd, *J* = 8.2, 7.6, 2.6 Hz, 2H), 1.47 - 1.32 (m, 4H), 1.25 - 1.10 (m, 2H), 0.79 (t, *J* = 7.4 Hz, 3H). LCMS: Purity 99%, MS (m/e) 384 (MH^+).

trans-4-((5-Bromo-2-((cyclopropylmethyl)amino)pyrimidin-4-yl)amino)-1-methylcyclohexan-1-ol

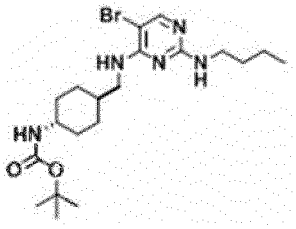
[0450]



[0451] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (s, 1H), 6.75 (br s, 1H), 6.04 (d, *J* = 8.0 Hz, 1H), 4.26 (s, 1H), 3.94 - 3.86 (m, 1H), 3.03 (t, *J* = 6.4 Hz, 2H), 1.70 (app d, *J* = 7.8 Hz, 2H), 1.58 - 1.34 (m, 6H), 1.14 (s, 3H), 1.06 - 0.93 (m, 1H), 0.41 - 0.31 (m, 2H), 0.15 (q, *J* = 4.8 Hz, 2H). LCMS: Purity 99%, MS (m/e) 355 (MH^+).

trans-tert-butyl-4-(((5-bromo-2-(butylamino)pyrimidin-4-yl)amino)methyl)cyclohexyl)carbamate

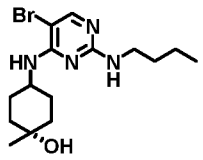
[0452]



[0453] *trans-tert*-butyl-4-(((5-bromo-2-(butylamino)pyrimidin-4-yl)amino)methyl)cyclohexyl)carbamate was prepared analogous to the preparation of *trans*-4-((5-bromo-2-(butylamino)pyrimidin-4-yl)amino)cyclohexan-1-ol. The resulting white solid obtained after reaction solution concentration followed by treating with aq. $NaHCO_3$ was filtered. *trans-tert*-Butyl-4-(((5-bromo-2-(butylamino)pyrimidin-4-yl)amino)methyl)cyclohexyl)carbamate thus obtained was used in next step with no further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (s, 1H), 6.65 (app br d, *J* = 8.1 Hz, 3H), 3.13 (app q, *J* = 6.7 Hz, 5H), 1.74 (d, *J* = 10.9 Hz, 2H), 1.66 (d, *J* = 12.8 Hz, 2H), 1.56 - 1.49 (m, 1H), 1.49 - 1.38 (m, 2H), 1.35 (s, 9H), 1.32 - 1.19 (app m, 2H), 1.06 (q, *J* = 11.8 Hz, 2H), 0.97 - 0.82 (app m, 5H). LCMS: Purity 98%, MS (m/e) 457 (MH^+).

trans-4-((5-Bromo-2-(butylamino)pyrimidin-4-yl)amino)-1-methylcyclohexan-1-ol

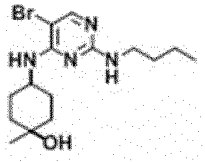
[0454]



[0455] *trans*-4-((5-Bromo-2-(butylamino)pyrimidin-4-yl)amino)-1-methylcyclohexan-1-ol was prepared and purified analogous to the preparation of *trans-tert*-butyl-4-(((5-bromo-2-(butylamino)pyrimidin-4-yl)amino)methyl)cyclohexyl)carbamate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (s, 1H), 6.70 (br s, 1H), 6.02 (d, J = 7.2 Hz, 1H), 4.26 (s, 1H), 3.89 (app br s, 1H), 3.14 (q, J = 6.6 Hz, 2H), 1.78 - 1.67 (m, 2H), 1.58 - 1.47 (m, 4H), 1.47 - 1.34 (m, 4H), 1.27 (h, J = 7.3 Hz, 2H), 1.14 (s, 3H), 0.86 (t, J = 7.3 Hz, 3H). LCMS: Purity 98%, MS (m/e) 358 (MH^+).

cis-4-((5-Bromo-2-(butyl amino)pyrimidin-4-yl)amino)-1-methylcyclohexan-1-ol

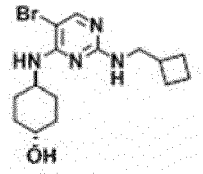
[0456]



[0457] *cis*-4-((5-Bromo-2-(butylamino)pyrimidin-4-yl)amino)-1-methyl cyclohexan-1-ol was prepared and isolated analogously to the preparation of *trans-tert*-butyl-4-(((5-bromo-2-(butylamino)pyrimidin-4-yl)amino)methyl)cyclohexyl)carbamate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (s, 1H), 6.69 (br s, 1H), 5.90 (s, 1H), 4.02 (s, 1H), 3.85 - 3.76 (m, 1H), 3.14 (q, J = 6.6 Hz, 2H), 1.74 - 1.64 (m, 2H), 1.63 - 1.51 (m, 4H), 1.51 - 1.38 (m, 4H), 1.27 (h, J = 7.3 Hz, 2H), 1.09 (s, 3H), 0.86 (t, J = 7.3 Hz, 3H). LCMS: Purity 96%, MS (m/e) 358 (MH^+).

trans-4-((5-Bromo-2-((cyclobutylmethyl)amino)pyrimidin-4-yl)amino)cyclohexan-1-ol

[0458]

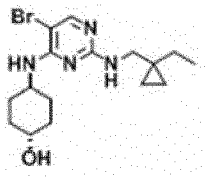


[0459] A solution of *trans*-4-((5-bromo-2-chloropyrimidin-4-yl)amino)cyclohexan-1-ol (2.0 g, 6.5 mmol), cyclobutylmethanamine hydrochloride (2.0 g, 16.4 mmol), *i*-Pr_2NEt (8.5 mL, 6.3 g, 48.9 mmol) and ethanol (10 ml) was stirred and heated in a sealed tube at 90 °C till complete consumption of *trans*-4-((5-bromo-2-chloropyrimidin-4-yl)amino)cyclohexan-1-ol. Upon completion of reaction, reaction solution was processed and isolated in an identical manner as described in the preparation of *trans*-4-((5-bromo-2-(butylamino)pyrimidin-4-yl)amino)cyclohexan-1-ol. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (s, 1H), 6.72 (br s, 1H), 5.99 (br s, 1H), 4.52 (d, J = 4.2 Hz, 1H), 3.86 - 3.77 (m, 1H), 3.37 (app tt, J = 10.7, 3.6 Hz, 2H), 3.20 (t, J = 6.5 Hz, 2H), 1.98 - 1.90 (m, 2H), 1.83 - 1.76 (m, 6H), 1.71 - 1.58 (m, 2H), 1.45 - 1.35 (m, 2H), 1.26 - 1.11 (m, 2H). LCMS: Purity 99%, MS (m/e) 356 (MH^+).

[0460] The following analogs were also prepared analogous to the preparation of *trans*-4-((5-bromo-2-((cyclobutylmethyl)amino)pyrimidin-4-yl)amino)cyclohexan-1-ol from corresponding amine hydrochloride salts and 5-bromo-4-amino(substituted)pyrimidines

trans-4-((5-Bromo-2-(((1-ethyl cyclopropyl)methyl)amino)pyrimidin-4-yl)amino)cyclohexan-1-ol

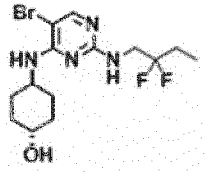
[0461]



[0462] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (s, 1H), 6.67 (br s, 1H), 5.99 (br s, 1H), 4.52 (d, *J* = 4.4 Hz, 1H), 3.91 - 3.81 (m, 1H), 3.40 - 3.32 (m, 1H), 3.18 (d, *J* = 5.9 Hz, 2H), 1.80 (app t, *J* = 12.2 Hz, 4H), 1.40 (qd, *J* = 13.6, 12.3, 3.4 Hz, 2H), 1.27 (q, *J* = 7.4 Hz, 2H), 1.23 - 1.11 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.42 - 0.34 (m, 2H), 0.20 - 0.13 (m, 2H). LCMS: Purity 99%, MS (m/e) 370 (MH^+).

trans-4-((5-Bromo-2-((2,2-difluorobutyl)amino)pyrimidin-4-yl)amino)cyclohexan-1-ol

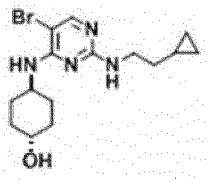
[0463]



[0464] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (s, 1H), 7.02 (br s, 1H), 6.15 (d, *J* = 8.3 Hz, 1H), 4.53 (d, *J* = 4.5 Hz, 1H), 3.91 - 3.78 (m, 1H), 3.68 (td, *J* = 14.2, 6.6 Hz, 2H), 3.36 (tq, *J* = 11.1, 4.2 Hz, 1H), 1.94 - 1.74 (m, 6H), 1.49 1.33 (m, 2H), 1.26 - 1.11 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -103.62 (app q, *J* = 14.5 Hz). LCMS: Purity 97%, MS (m/e) 380 (MH^+).

trans-4-((5-Bromo-2-((2-cyclopropylethyl)amino)pyrimidin-4-yl)amino)cyclohexan-1-ol

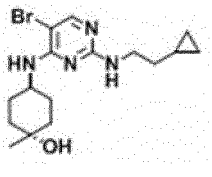
[0465]



[0466] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (s, 1H), 6.71 (br s, 1H), 5.98 (br s, 1H), 4.53 (d, *J* = 4.3 Hz, 1H), 3.88 - 3.79 (m, 1H), 3.43 - 3.26 (m, 1H), 3.26 - 3.16 (app m, 2H), 1.87 - 1.77 (m, 4H), 1.47- 1.32 (m, 4H), 1.19 (qd, *J* = 14.2, 13.0, 3.7 Hz, 2H), 0.74 - 0.59 (m, 1H), 0.37 (q, *J* = 5.1 Hz, 2H), 0.01 (q, *J* = 4.8 Hz, 2H). LCMS: Purity 99%, MS (m/e) 356 (MH^+).

trans-4-((5-Bromo-2-((2-cyclopropylethyl)amino)pyrimidin-4-yl)amino)-1-methylcyclohexan-1-ol

[0467]



[0468] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (s, 1H), 6.69 (br s, 1H), 6.02 (d, J = 7.9 Hz, 1H), 4.26 (s, 1H), 3.96 - 3.86 (m, 1H), 3.26 - 3.16 (app m, 2H), 1.70 (br s, 2H), 1.59 - 1.31 (m, 8H), 1.14 (s, 3H), 0.69 - 0.63 (m, 1H), 0.42 - 0.32 (m, 2H), 0.00 (q, J = 4.8 Hz, 2H). LCMS: Purity 99%, MS (m/e) 370 (MH^+).

[0469] **General scheme for the preparation of 3-heteroaryl-2,2'-bipyridine** :

Catalyst 1: $Pd(PPh_3)_4$ or $Pd_2(dba)_3$/2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) or $Pd(OAc)_2$/2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) or $Pd_2(dba)_3$/2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (Xphos), $Pd(OAc)_2$/2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (Xphos) or Chloro(2-dicyclohexylphosphino-2',6'-dimethoxy-1, 1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (SPhos-Pd-G2) or Chloro(2-dicyclohexylphosphino-2',4'-6'-triisopropyl-1,1'-biphenyl) [2-2'-amino-1, 1'-biphenyl)]palladium(II) (XPhos-Pd-G2) or $Pd_2(dba)_3$/sodium 2'-dicyclohexylphosphino-2,6-dimethoxy-1,1'-biphenyl-3-sulfonate hydrate or $Pd(OAc)_2$/sodium 2'-dicyclohexylphosphino-2,6-dimethoxy-1,1'-biphenyl-3-sulfonate hydrate

Catalyst 2: $Pd(PPh_3)_4$ or $Pd_2(dba)_3$/2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) or $Pd(OAc)_2$/2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) or $Pd_2(dba)_3$/2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (Xphos), $Pd(OAc)_2$/2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (Xphos) or Chloro(2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (SPhos-Pd-G2) or Chloro(2-dicyclohexylphosphino-2',4'-6'-triisopropyl-1,1'-biphenyl)[2-2'-amino-1,1'-biphenyl)]palladium(II) (XPhos-Pd-G2)

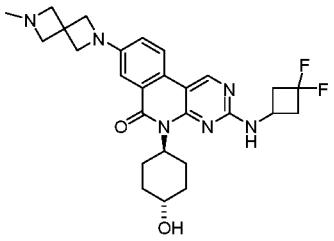
LC/MS: rt (Method A or Method B)

Method A: Column: Luna 5 □m C8 (100 X 4.6 mm), Flow rate 1.0 mL/min, Mobile phase: A: H_2O 0.05% TFA, B: CH_3CN 0.05% TFA

Method B: Column: Gemini 5□m C18 (100 X 4.6 mm), Flow rate 1.5 mL/min, Mobile phase: A: H_2O 0.05% HCOOH, B: CH_3CN 0.05% HCOOH

3-((3,3-difluorocyclobutyl)amino)-5-(trans-4-hydroxycyclohexyl)-8-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

[0470]

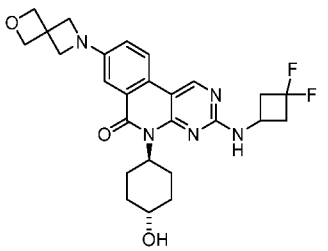


[0471] LCMS: rt 3.17 min (B), MS (m/e) 511 MH^+.

[0472] ^{1}H NMR (300 MHz, Methanol-d_4) δ 9.03 (s, 1H), 8.10 (d, J = 9.0 Hz, 1H), 7.28 (s, 1H), 7.01 (d, J= 9.0 Hz, 1H), 5.52 (br s, 1H), 4.57-4.53 (m, 2H), 4.30-4.26 (m, 4H), 4.20 (brs, 2H), 4.14 (brs, 2H), 3.04 (m, 2H), 3.01 (s, 3H), 2.91-2.82 (m, 2H), 2.78-2.63 (m, 3H), 2.14-2.10 (m, 2H), 1.72-1.67 (m, 2H), 1.51-1.47 (m, 2H).

3-((3,3-difluorocyclobutyl)amino)-5-(trans-4-hydroxycyclohexyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

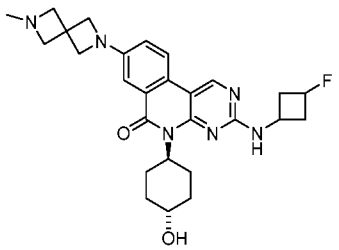
[0473]



[0474] LCMS: rt 5.13 min (B), MS (m/e) 498 MH^+.

3-((3-fluorocyclobutyl)amino)-5-(trans-4-hydroxycyclohexyl)-8-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

[0475]

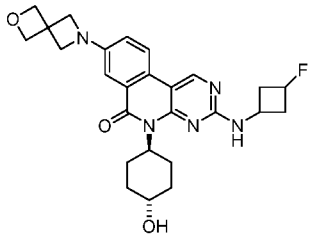


[0476] LCMS: rt 4.30 min (A), MS (m/e) 493 MH^+.

[0477] ^1H NMR (300 MHz, Methanol-d_4) δ 8.95 (s, 1H), 9.49 (br s, 1H), 8.02 (d, *J*= 8.7 Hz, 1H), 7.22 (s, 1H), 6.96 (d, *J* = 8.7 Hz, 1H), 5.53 (br s, 1H), 5.36-5.14 (m, 1H), 4.60 (m, 1H), 4.31 (brs, 4H), 4.12 (brs, 4H), 3.73 (m, 1H), 2.88 (s, 3H), 2.68-2.39 (m, 4H), 2.12-2.09 (m, 2H), 1.68-1.65 (m, 2H), 1.51-1.46 (m, 2H).

3-((3-fluorocyclobutyl)amino)-5-(trans-4-hydroxycyclohexyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

[0478]

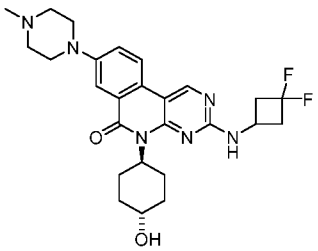


[0479] LCMS: rt 5.35 min (A), MS (m/e) 480 MH^+.

[0480] ^1H NMR (300 MHz, Methanol-d_4) δ 8.95 (s, 1H), 9.49 (br s, 1H), 8.03 (d, *J*= 8.7 Hz, 1H), 7.27 (s, 1H), 6.97 (d, *J* = 8.7 Hz, 1H), 5.53 (br s, 1H), 5.36-5.14 (m, 1H), 4.88 (brs, 4H), 4.80 (m, 1H), 4.64 (m, 1H), 4.16 (brs, 3H), 3.79 (m, 2H), 2.85 (m, 2H), 2.66 (brs, 2H), 2.60-2.42 (m, 2H), 2.15-2.11 (m, 2H), 1.74-1.71 (m, 2H), 1.52-1.47 (m, 2H).

3-((3,3-difluorocyclobutyl)amino)-5-(trans-4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-one

[0481]

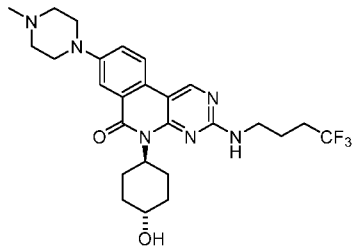


[0482] LCMS: rt 4.66 min (A), MS (m/e) 499 MH^+.

[0483] ^1H NMR (300 MHz, Methanol-d_4) δ 9.09 (s, 1H), 8.19 (d, *J*= 9.0 Hz, 1H), 7.80 (s, 1H), 7.57 (d, *J* = 90 Hz, 1H), 5.56 (br s, 1H), 4.35 (m, 1H), 3.99 (m, 2H), 3.76-3.74 (m, 4H), 3.12-3.02 (m, 6H), 2.99 (s, 3H), 2.89 (br s, 2H), 2.74-2.64 (m, 2H), 2.14-2.10 (m, 2H), 1.72-1.68 (m, 2H), 1.51-1.47 (m, 2H).

5-(Trans-4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)-3-((4,4,4-trifluorobutyl)amino)pyrimido[4,5-c]isoquinolin-6(5H)-one

[0484]

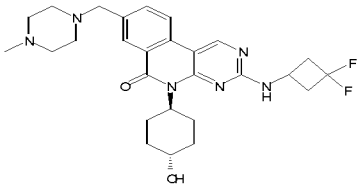


[0485] LCMS: rt 3.19 min (A), MS (m/e) 519 MH^+.

[0486] ^1H NMR (300 MHz, Methanol-d_4) δ 9.03 (s, 1H), 8.42 (br s, 1H), 8.12 (d, J= 7.8 Hz, 1H), 7.75 (s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 5.53 (br s, 1H), 3.71 (m, 1H), 3.55 (t, J = 7.2 Hz, 2H), 3.43 (m, 4H), 3.02 (m, 4H), 2.78-2.68 (m, 2H), 2.64 (s, 3H), 2.33-2.24 (m, 2H), 2.13-2.08 (m, 2H), 1.98-1.91 (m, 2H), 1.72-1.68 (m, 2H), 1.51-1.46 (m, 2H).

3-((3,3-difluorocyclobutyl)amino)-5-((trans-4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

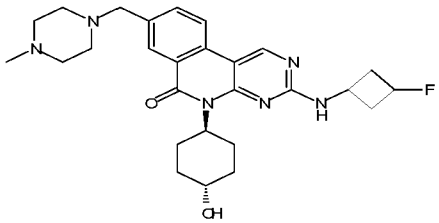
[0487]



[0488] LCMS: rt 3.03 min (B), MS (m/e) 513 MH^+.

[0489] ^1H NMR (300 MHz, Methanol-d_4) δ 9.17 (s, 1H), 8.27 (s, 1H), 8.22 (d, J= 8.4 Hz, 1H), 7.75 (d, J= 8.4 Hz, 1H), 5.56 (br s, 1H), 4.36 (br s, 1H), 3.77 (s, 2H), 3.72 (br s, 1H), 3.35-3.29 (m, 4H), 3.06-3.02 (m, 4H), 2.88 (s, 3H), 2.86-2.65 (m, 8H), 2.14-2.10 (m, 2H), 1.72-1.68 (m, 2H), 1.56-1.47 (m, 2H).

[0490] 3-((3-fluorocyclobutyl)amino)-5-((trans-4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

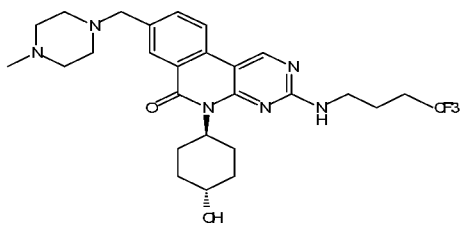


[0491] LCMS: rt 2.85 min (B), MS (m/e) 495 MH^+.

[0492] ^1H NMR (300 MHz, Methanol-d_4) δ 9.13 (s, 1H), 8.28 (s, 1H), 8.21 (d, J= 8.4 Hz, 1H), 7.77 (d, J= 8.4 Hz, 1H), 5.52 (br s, 1H), 5.35-5.16 (m, 1H), 4.65 (br s, 1H), 3.84 (s, 2H), 3.73 (br s, 1H), 3.30-3.28 (m, 6H), 2.89 (s, 3H), 2.86-2.45 (m, 1H), 2.13-2.09 (m, 2H), 1.72-1.68 (m, 2H), 1.54-1.46 (m, 2H).

5-((Trans-4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)-3-((4,4,4-trifluorobutyl)amino)pyrimido[4,5-c]isoquinolin-6(5H)-one

[0493]

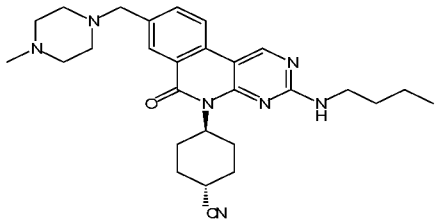


[0494] LCMS: rt 3.17 min (B), MS (m/e) 533 MH^+.

[0495] ^1H NMR (300 MHz, Methanol-d_4) δ 9.13 (s, 1H), 8.46 (br s, 1H), 8.25 (s, 1H), 8.20 (d, J= 7.8 Hz, 1H), 7.74 (d, J= 7.8 Hz, 1H), 5.53 (br s, 1H), 3.71 (s, 3H), 3.55 (t, J= 6.9 Hz, 2H), 3.29 (br s, 2H), 2.93 (br s, 6H), 2.78-2.63 (m, 4H), 2.60 (s, 2H), 2.33-2.24 (m, 2H), 2.12-2.08 (m, 2H), 1.95-1.93 (m, 2H), 1.72-1.68 (m, 2H), 1.54-1.46 (m, 2H).

trans-4-(3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclohexane-1-carbonitrile

[0496]



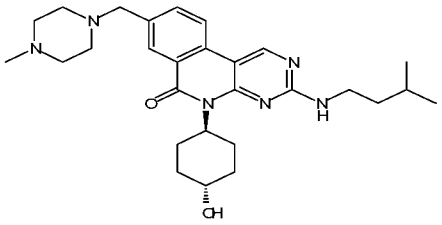
[0497] LCMS: rt 5.43 min (A), MS (m/e) 488 MH^+.

[0498] ^1H NMR (300 MHz, Methanol-d_4) δ 9.12 (s, 1H), 8.29 (s, 1H), 8.20 (d, J= 8.1 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 5.52 (br s, 1H), 3.81 (s, 2H), 3.51 (br s, 2H), 3.36-3.24 (m, 5H),

[0499] 2.89 (s, 3H), 2.85-2.65 (m, 6H), 2.32-2.29 (m, 2H), 1.83-1.68 (m, 6H), 1.52-1.45 (m, 2H), 1.02 (t, J = 7.5 Hz, 3H).

5-((trans-4-hydroxycyclohexyl)-3-(isopentylamino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

[0500]

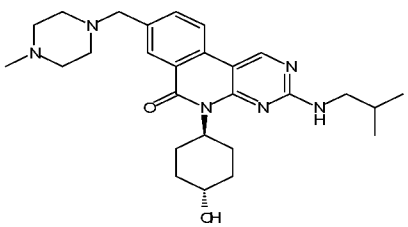


[0501] LCMS: rt 3.28 min (B), MS (m/e) 493 MH^+.

[0502] ^1H NMR (300 MHz, Methanol-d_4) δ 9.09 (s, 1H), 8.31 (br s, 1H), 8.24 (s, 1H), 8.18 (d, J= 8.1 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1H), 5.54 (br s, 1H), 3.74 (s, 2H), 3.71 (br s, 1H), 3.50 (t, J= 7.5 Hz, 2H), 3.20 (br s, 4H), 2.86 (br s, 2H), 2.80 (s, 3H), 2.74 (br s, 4H), 2.12-2.08 (m, 2H), 1.76-1.42 (m, 8H), 1.01 (d, J = 6.6 Hz, 6H).

5-(trans-4-hydroxycyclohexyl)-3-(isobutylamino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

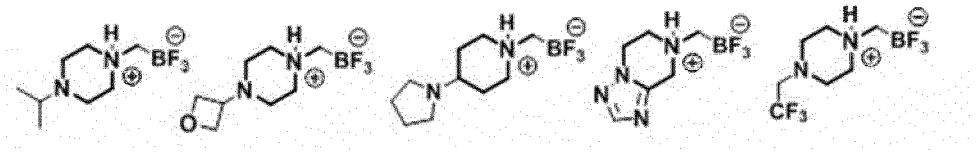
[0503]

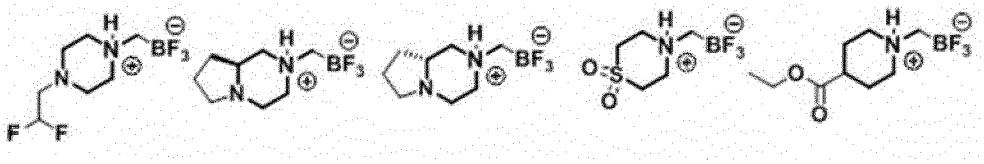


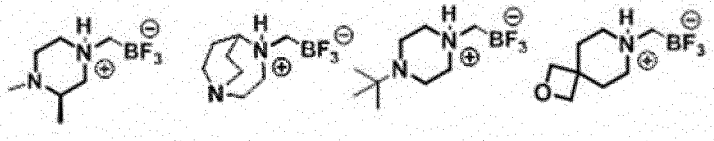
[0504] LCMS: rt 4.33 min (A), MS (m/e) 479 MH^+.

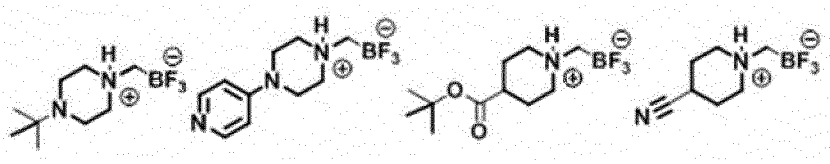
[0505] ^1H NMR (300 MHz, Methanol-d_4) δ 9.09 (s, 1H), 8.22 (s, 1H), 8.16 (d, J = 8.1 Hz, 1H), 7.72 (d, J= 8.1 Hz, 1H), 5.53 (br s, 1H), 3.72 (br s, 1H), 3.64 (s, 2H), 3.29 (br s, 4H), 2.89 (br s, 2H), 2.52 (br s, 8H), 2.27 (s, 3H), 2.12-1.98 (m, 3H), 1.71-1.67 (m, 2H), 1.55-1.46 (m, 2H), 1.01 (d, J = 6.6 Hz, 6H).

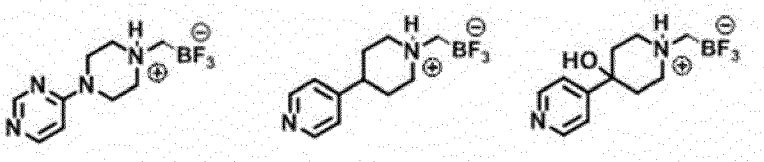
[0506] Preparation of aminomethyltrifluoroborates: (JOC 2008, 73, 2052-2057, JOC 2011, 76, 2762-2769). Aminomethyltrifluoroborates which are not available commerically were prepared according to literature procedure. Trifluoro((4-isopropylpiperazin-1-ium-1-yl)methyl)borate preparation describes reaction procedure and isolation of synthesized respective aminomethyltrifluoroborates represented below.

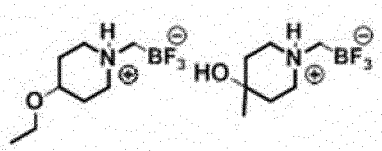






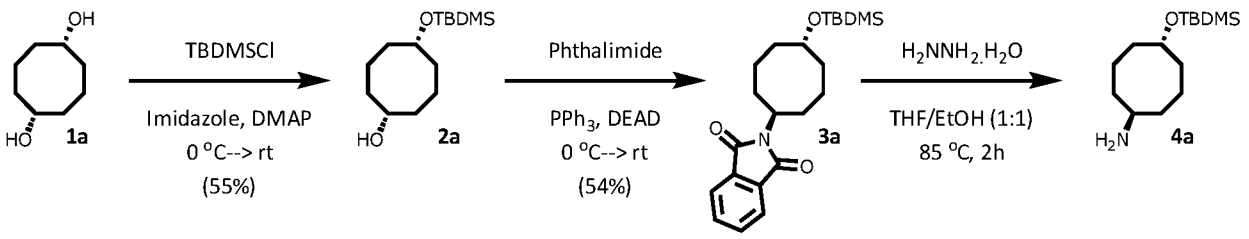






Example 2: Synthesis of **(1r,5r)-5-((*tert*-Butyldimethylsilyl)oxy)cyclooctan-1-amine** (5)

[0507]



Step 1-1: **Synthesis of (1s,5s)-5-((*tert*-Butyldimethylsilyl)oxy)cyclooctan-1-ol (2a)**

[0508] To an ice-cold solution of (1s,5s)-cyclooctane-1,5-diol (10 g, 69.3 mmol) in THF (200 mL), imidazole (6.6 g, 97 mmol), tert-butylchlorodimethylsilane (10.5 g, 69.7 mmol) and DMAP (30 mg, 24.6 μmol) were added successively (Plettenburg, O. et al. PCT Int. Appl. WO2008077551). A white precipitate was observed and the reaction mixture was allowed to stir and warm up to room temperature over 18 h. LC/MS traces show no starting material, and hence the reaction mixture was poured over ice-water (100 mL). The layers were separated, aqueous layer extracted with ethyl acetate (3x50 mL) and the combined organic layer was dried ($MgSO_4$), filtered and concentrated to give a colorless oil. Column chromatography purification using 10-20% ethyl acetate/hexanes as the eluent provided 9.9 g (55%) of a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.88 - 3.73 (m, 2H), 1.91 - 1.59 (m, 10H), 1.47 - 1.35 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H). MS *m/e:* 259 $(M+H)^+$.

Step 2: Synthesis of 2-((1r,5r)-5-((*tert*-Butyldimethylsilyl)oxy)cyclooctyl)isoindoline-1,3-dione (3a)

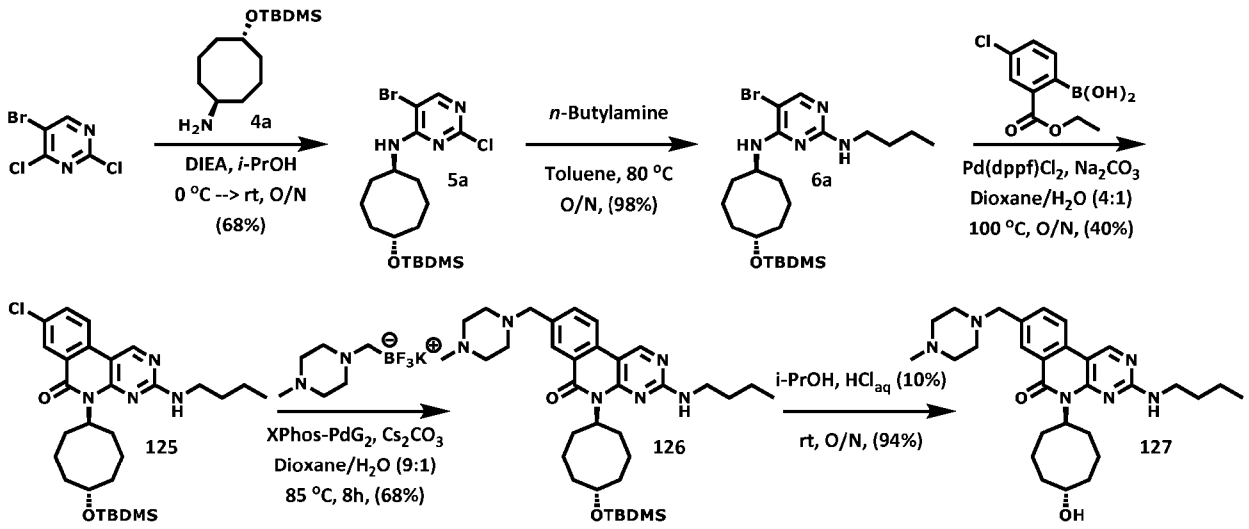
[0509] To an ice-cold solution of (1s,5s)-5-((tert-butyldimethylsilyl)oxy)cyclooctan-1-ol (2a, 0.5 g, 1.9 mmol), phthalimide (0.31 g, 2.1 mmol) and triphenylphosphine (0.57 g, 2.2 mmol) in THF (10 mL), diethyl azodicaboxylate (40%wt. in toluene, 0.95 mL, 0.36 g, 2.1 mmol) was added dropwise (Inoue, T. et al. PCT Int. Appl. WO2007077949). The resulting colorless reaction mixture was allowed to stir and warm up to room temperature overnight. LC/MS traces show starting material has been consumed. The reaction mixture was then concentrated and purified by column chromatography, eluting with neat hexanes initially and increasing the polarity to 20% ethyl acetate/hexanes, to provide 407 mg (54%) of 2-((1r,5r)-5-((*tert*butyldimethylsilyl)oxy)cyclooctyl)-isoindoline-1,3-dione (3a) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 - 7.77 (m, 2H), 7.70 - 7.65 (m, 2H), 4.37 (tt, *J* = 11.2, 2.8 Hz, 1H), 3.90 (td, *J* = 7.2, 4.2 Hz, 1H), 2.30 (dddd, *J* = 14.1, 11.0, 8.2, 4.4 Hz, 2H), 1.85 - 1.62 (m, 10H), 0.90 (s, 9H), 0.07 (s, 6H). MS *m/e:* 388 $(M+H)^+$.

Step 3: Synthesis of (1r,5r)-5-((*tert*-Butyldimethylsilyl)oxy)cyclooctan-1-amine (4a)

[0510] A solution of 2-((1r,5r)-5-((*tert*-butyldimethylsilyl)oxy)cyclooctyl)-isoindoline-1,3-dione (**3a**, 0.4 g, 1.0 mmol), hydrazine hydrate (64%, 0.5 mL, 0.33 g, 10.3 mmol) in THF/EtOH (1:1) solution was allowed to stir at 85 °C for 12h (Inoue, T. et al. PCT Int. Appl. WO2007077949). The resulting reaction mixture was then concentrated, diluted with dichloromethane (20 mL) and extracted with 1N NaOH solution (3x10 mL) to give 0.26 g (98%) of (1r,5r)-5-((*tert*-butyldimethylsilyl)oxy)cyclooctan-1-amine (**4a**) as a colorless oil upon drying ($MgSO_4$), filtration and concentration. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.79 (septet, *J* = 3.9 Hz, 1H), 2.95 (tt, *J*= 9.4, 3.3 Hz, 1H), 1.80 - 1.52 (m, 10H), 1.45 - 1.36 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H). MS *m/e:* 258 $(M+H)^+$.

Example 3: Synthesis of 3-(Butylamino)-5-((1r,5r)-5-hydroxycyclooctyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-*c*]isoquinolin-6(5*H*)-one (127

[0511]



Step 2-1: Synthesis of 5-Bromo-*N*-((1r,5r)-5-((*tert*-butyldimethylsilyl)oxy)cyclooctyl)-2-chloropyrimidin-4-amine (5a)

[0512] To an ice-cold solution of 5-bromo-2,4-dichloropyrimidine (0.215 g, 0.94 mmol) and *N,N*-diisopropylethylamine (0.22 mL, 0.16 g, 1.3 mmol) in isopropanol (5 mL), (1r,5r)-5-((*tert*butyldimethylsilyl)oxy)cyclooctan-1-amine (**4a,** 260 mg, 1.0 mmol) was added dropwise (Zhang, W. et al. J. Med. Chem.2014, 57(16), 7031). The resulting reaction mixture was allowed to stir and warm up to room temperature overnight, concentrated, diluted with ethyl acetate (20 mL) and water (20 mL). The layers were separated and the aqueous solution was extracted with ethyl acetate (3x10 mL) and the combined organic layer was dried ($MgSO_4$), filtered and concentrated to give a yellow oil. Column chromatography purification using 0-20% ethyl acetate/hexanes as the eluent provided 0.286 g (68%) of 5-bromo-*N*-((1r,5r)-5-((*tert*-butyldimethylsilyl)oxy)-cyclooctyl)-2-chloropyrimidin-4-amine (5a) as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d)* δ 8.08 (s, 1H), 5.39 (d, *J* = 7.7 Hz, 1H), 4.25 - 4.17 (m, 1H), 3.87 - 3.81 (m, 1H), 1.99 - 1.92 (m, 2H), 1.80 - 1.75 (m, 6H), 1.65 - 1.54 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H). MS *m/e:* 448 $(M+H)^+$.

Step 2-2: Synthesis of 5-Bromo-N^2-butyl-N^4-((1r,5r)-5-((*tert*-butyldimethylsilyl)oxy)cyclooctyl)pyrimidine-2,4-diamine (6a)

[0513] A solution of 5-bromo-*N*-((1r,5r)-5-((*tert*-butyldimethylsilyl)oxy)-cyclooctyl)-2-chloropyrimidin-4-amine (5a, 0.286 g, 0.64 mmol) and *n*-butylamine (0.65 mL, 0.48 g, 6.6 mmol) in toluene (10 mL) was allowed to stir at 80 °C under N_2 atmosphere for 12h (Zhang, W. et al. J. Med. Chem.2013, 56(23), 9683). LC/MS traces indicated less than 50% of starting material was consumed, and hence additional amounts (1 mL, 2x2 mL) of *n*-butylamine were added with continued heating until only the product was detected by LC/MS traces. The resulting reaction mixture was concentrated, diluted with ethyl acetate (30 mL) and brine (20 mL) and the layers were separated. The organic layer was washed with brine (2x10 mL), dried ($MgSO_4$), filtered and concentrated to provide 0.30 g (98%) of 5-bromo-N^2-butyl-N^4-((1r,5r)-5-((*tert*-butyldimethylsilyl)oxy)cyclooctyl)pyrimidine-2,4-diamine (**6a**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 (s, 1H), 5.00 (d, *J* = 7.8 Hz, 1H), 4.88 (s, 1H), 4.21 - 4.14 (m, 1H), 3.83 - 3.77 (m, 1H), 3.33 (td, *J* = 7.1, 5.8 Hz, 2H), 1.98 - 1.89 (m, 2H), 1.80 - 1.70 (m, 6H), 1.65 - 1.48 (m, 6H), 1.44 - 1.35 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H). MS *m/e:* 485 $(M+H)^+$.

Step 2-3: Synthesis of 3-(Butylamino)-5-((1r,5r)-5-((*tert*-butyldimethylsilyl)oxy)cyclooctyl)-8-chloropyrimido[4,5-*c*]isoquinolin-6(5*H*)-one (125)

[0514] The orange degassed (3x) solution of 5-bromo-N^2-butyl-N^4-((1r,5r)-5-((*tert*butyldimethylsilyl)oxy)cyclooctyl)pyrimidine-2,4-diamine (**6a**, 0.3 g, 0.62 mmol), 4-chloro-2-ethoxycarbonylphenylboronic acid (0.215 g, 0.94 mmol), $Pd(dppf)Cl_2$ (55 mg, 67 μmol), Na_2CO_3 (0.2 g, 1.9 mmol) in dioxane/H_2O (4:1, 20 mL) was allowed to stir at 100 °C under N_2 atmosphere for 19h. Additional amounts of boronic acid (2x100 mg), palladium catalyst (2x25 mg) and Na_2CO_3 were added and the reaction mixture was allowed to stir at 100 °C overnight. The reaction mixture was cooled down to room temperature, concentrated and diluted with dichloromethane and water. The layers were separated and the aqueous layer was extracted with dichloromethane (3x20 mL). The combined organic layer was dried ($MgSO_4$), filtered and concentrated to provide a black residue. Column chromatography purification using 0-20% ethyl acetate/hexanes as

the eluent provided 0.135 g (40%) of 3-(butylamino)-5-((1r,5r)-5-((*tert*butyldimethylsilyl)oxy)cyclooctyl)-8-chloropyrimido[4,5-*c*]isoquinolin-6(5*H*)-one (125) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.95 (s, 1H), 8.36 (d, *J* = 19.8 Hz, 1H), 7.94 (d, *J* = 8.7 Hz, 1H), 7.61 (dd, *J* = 8.6, 2.4 Hz, 1H), 3.88 (s, 1H), 3.53 (q, *J* = 6.8 Hz, 2H), 2.70 - 2.54 (m, 2H), 1.95 - 1.64 (m, 13H), 1.47 (q, *J* = 7.7 Hz, 2H), 0.98 (t, *J* = 7.5 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H). MS *m/e:* 543 $(M+H)^+$.

Step 2-4: Synthesis of 3-(Butylamino)-5-((1r,5r)-5-((*tert*-butyldimethylsilyl)oxy)cyclooctyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-*c*]isoquinolin-6(5*H*)-one (126)

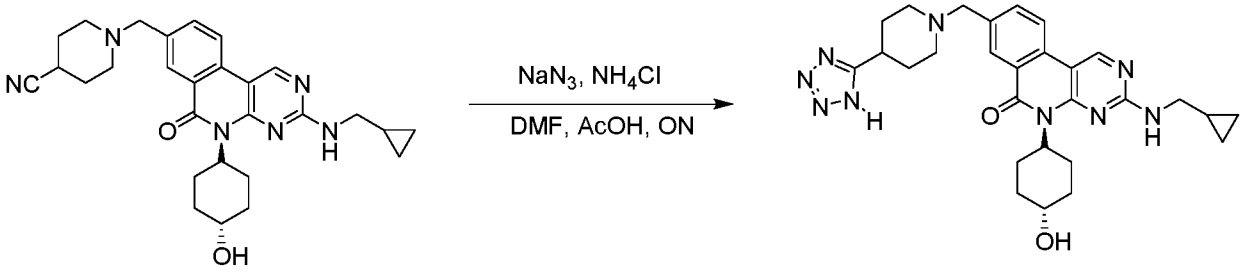
[0515] A degassed (3x) solution of 3-(butylamino)-5-((1r,5r)-5-((*tert*butyldimethylsilyl)oxy)cyclooctyl)-8-chloropyrimido[4,5-*c*]isoquinolin-6(5*H*)-one (7, 0.13 g, 0.24 mmol), potassium 1-methyl-4-trifluoroboratomethylpiperzine (0.08 g, 0.36 mmol), XPhos Palladacycle G2 (0.02 g, 0.25 mmol), Cs_2CO_3 (0.235 g, 0.72 mmol) in dioxane/H_2O (9:1, 10 mL) was allowed to stir at 85 °C under N_2 atmosphere for 8h. Since starting material was still present (LC/MS traces), additional amounts of the borate (0.16 g), palladium catalyst (0.02 g), and Cs_2CO_3 (0.235 g) were added to the cooled down reaction mixture, vessel degassed (3x), and the reaction mixture was allowed to stir at 85 °C overnight. The reaction mixture was cooled down to room temperature, concentrated and diluted with dichloromethane (20 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3x10 mL) and the combined organic layer was dried ($MgSO_4$), filtered and concentrated to provide a brown residue. Column chromatography purification using 0-10% methanol/dichloromethane as the eluent provided, upon trituration with hexanes, 0.101 g (68%) of 3-(butylamino)-5-((1r,5r)-5-((*tert*-butyldimethylsilyl)oxy)cyclooctyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-*c*]isoquinolin-6(5*H*)-one (126) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.99 (s, 1H), 8.30 (d, *J* = 22.7 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.69 (dd, *J* = 8.2, 1.9 Hz, 1H), 5.92 (s, 1H), 5.68 (s, 1H). 5.37 (s, 1H), 3.88 (s, 1H), 3.61 (s, 2H), 3.52 (p, *J*= 6.4, 6.0 Hz, 2H), 2.74 - 2.35 (m, 9H), 2.28 (s, 3H), 1.97 - 1.64 (m, 12H), 1.47 (dq, *J*= 14.2, 7.1 Hz, 2H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H). MS *m/e:* 621 $(M+H)^+$.

Step 2-5: Synthesis of of 3-(Butylamino)-5-((1r,5r)-5-hydroxycyclooctyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-*c*]isoquinolin-6(5*H*)-one (127)

[0516] A solution of 3-(butylamino)-5-((1r,5r)-5-((*tert*-butyldimethylsilyl)oxy)cyclooctyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-*c*]isoquinolin-6(5*H*)-one (**126**, 0.075 g, 0.12 mmol) in a mixture of *i*-PrOH (0.5 mL) and 10% HCl aqueous solution (0.5 mL) was allowed to stir at room temperature overnight (Plettenburg, O. et al. PCT Int. Appl. WO2008077551). LC/MS traces indicated only product was present, and hence the reaction mixture was concentrated to provide, upon trituration with ethyl ether, 62 mg (94%) of 3-(butylamino)-5-((1r,5r)-5-hydroxycyclooctyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-*c*]isoquinolin-6(5*H*)-one (**127**) as a white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.20 (s, 1H), 8.50 (d, *J* = 27.6 Hz, 1H), 8.32 (d, *J* = 8.3 Hz, 1H), 8.04 (dd, *J* = 8.2, 1.9 Hz, 1H), 5.75 (d, *J*= 50.9 Hz, 1H), 4.37 (s, 2H), 3.90 (s, 2H), 3.81 - 3.35 (m, 9H), 2.98 (s, 3H), 2.75 - 2.52 (m, 2H), 2.03 - 1.68 (m, 13H), 1.60 - 1.44 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H). MS *m/e:* 507 $(M+H)^+$.

Synthesis of 143:

[0517]



7a **143**

Synthesis of 8-((4-(1H-tetrazol-5-yl)piperidin-1-yl)methyl)-3-((cyclopropylmethyl)amino)-5-((1s,4s)-4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (143):

[0518] To a solution of 1-((3-((cyclopropylmethyl)amino)-5-((1s,4s)-4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methyl)piperidine-4-carbonitrile (0.1g, 0.21 mmol) in DMF (2 mL), was added NH_4Cl (0.107g,

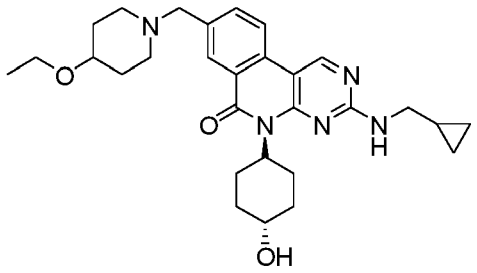
2.0 mmol) at room temperature followed by NaN_3 (0.078g, 1.2 mmol) and a drop of acetic acid. The resulting reaction mixture was stirred at room temperature for over night. Crude reaction mixture was diluted with few drops of water and the resulting white solid was filtered off to get the desired product in 45% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 1.7 Hz, 1H), 7.62 - 7.49 (m, 1H), 7.44 (dd, *J* = 8.3, 1.9 Hz, 1H), 5.15 (s, 1H), 3.41 (s, 4H), 2.86 - 2.53 (m, 5H), 1.96 (td, *J* = 11.1, 10.6, 2.5 Hz, 2H), 1.71 (dd, *J* = 10.2, 5.9 Hz, 4H), 1.63 - 1.41 (m, 1H), 1.32 (d, *J* = 11.4 Hz, 2H), 1.07 (d, *J* = 12.7 Hz, 2H), 0.87 (d, *J* = 9.3 Hz, 1H), 0.35 - 0.11 (m, 2H), 0.01 (q, *J* = 3.1, 1.7 Hz, 2H). MS m/e: 530 $(M+H)^+$.

Synthesis of 144 & 145:

Synthesis of 3-((cyclopropylmethyl)amino)-8-((4-ethoxypiperidin-1-yl)methyl)-5-((1s,4s)-4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (144):

See general experimental procedure from Sekhar's experimental section.

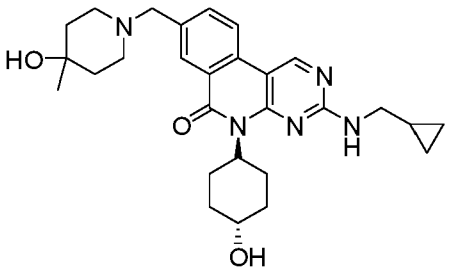
[0519]



[0520] ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 1.8 Hz, 1H), 7.55 (s, 1H), 7.42 (dd, *J* = 8.3, 1.9 Hz, 1H), 5.17 (s, 1H), 4.42 (d, *J* = 4.8 Hz, 1H), 3.31 (s, 3H), 3.18 (q, *J* = 7.0 Hz, 2H), 3.04 (d, *J* = 7.4 Hz, 3H), 2.64 - 2.36 (m, 4H), 1.85 (t, *J* = 10.6 Hz, 2H), 1.78 - 1.66 (m, 2H), 1.64 - 1.48 (m, 2H), 1.42 - 1.26 (m, 2H), 1.28 - 0.95 (m, 4H), 0.84 (t, *J* = 7.0 Hz, 3H), 0.29 - 0.15 (m, 2H), 0.10 - -0.02 (m, 2H). MS m/e: 506 $(M+H)^+$.

Synthesis of 3-((cyclopropylmethyl)amino)-8-((4-hydroxy-4-methylpiperidin-1-yl)methyl)-5-((1s,4s)-4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (145):

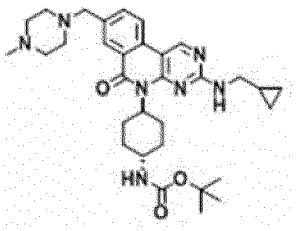
[0521]



[0522] ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.01 (d, *J* = 8.3 Hz, 1H), 7.86 (s, 1H), 7.54 (s, 1H), 7.41 (dd, *J* = 8.3, 1.9 Hz, 1H), 5.16 (s, 1H), 4.41 (s, 1H), 3.83 (d, *J* = 4.4 Hz, 1H), 3.78 (t, *J* = 7.1 Hz, 1H), 3.31 (s, 2H), 3.07 - 2.96 (m, 3H), 2.55 (s, 2H), 2.14 (s, 4H), 1.75 (s, 1H), 1.33 (s, 2H), 1.22 (t, *J* = 5.5 Hz, 4H), 1.09 (d, *J* = 12.2 Hz, 1H), 0.93 (t, *J* = 7.1 Hz, 1H), 0.86 (s, 3H), 0.29 - 0.16 (m, 2H), 0.02 (d, *J* = 5.2 Hz, 2H). MS m/e: 492 $(M+H)^+$.

trans-tert-Butyl (4-(3-((cyclopropylmethyl)amino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclohexyl)carbamate (184)

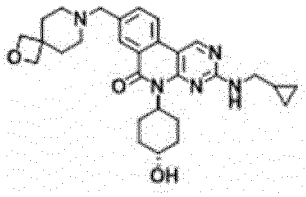
[0523]



[0524] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.24 (d, *J* = 8.3 Hz, 1H), 8.19 - 8.01 (m, 1H), 7.78 (s, 1H), 7.64 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.36 (s, 1H), 3.54 (s, 2H), 3.28 - 3.21 (m, 2H), 2.98 - 2.66 (m, 3H), 2.45 - 2.17 (m, 8H), 2.13 (s, 3H), 1.89 (app d, *J* = 11.8 Hz, 2H), 1.63- 1.52 (app m, 2H), 1.38 (s, 10H), 1.18 - 1.06 (m, 1H), 0.67 - 0.38 (m, 2H), 0.38 - 0.13 (m, 2H). LCMS: Purity 96%, MS (m/e) 576 (MH^+).

trans-8-((2-Oxa-7-azaspiro[3.5]nonan-7-yl)methyl)-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (**186**)

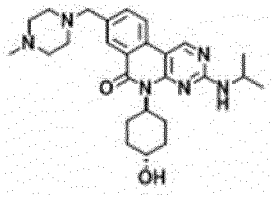
[0525]



[0526] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.11 (s, 1H), 8.22 (d, *J* = 1.8 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 7.72 (dd, *J* = 8.3, 1.9 Hz, 1H), 5.58 (s, 1H), 4.41 (s, 4H), 3.79 - 3.65 (m, 1H), 3.59 (s, 2H), 3.36 (d, *J* = 6.8 Hz, 2H), 2.92 (br s, 2H), 2.40 (br s, 4H), 2.10 (d, *J* = 12.2 Hz, 2H), 1.89 (t, *J* = 5.3 Hz, 4H), 1.70 (d, *J* = 12.1 Hz, 2H), 1.49 (q, *J* = 12.6, 11.8 Hz, 2H), 1.34 - 1.07 (m, 1H), 0.70 - 0.49 (m, 2H), 0.42 - 0.07 (m, 2H). LCMS: Purity 96%, MS (m/e) 504 (MH^+).

trans-5-(4-Hydroxycyclohexyl)-3-(isopropylamino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (**195**)

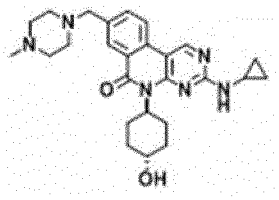
[0527]



[0528] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.10 (s, 1H), 8.23 (d, *J* = 1.9 Hz, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.73 (dd, *J* = 8.3, 1.9 Hz, 1H), 5.58 (s, 1H), 4.20 (dt, *J* = 13.9, 7.2 Hz, 1H), 3.71 (td, *J* = 10.8, 5.3 Hz, 1H), 3.65 (s, 2H), 2.90 (s, 2H), 2.52 (s, 8H), 2.28 (s, 3H), 2.10 (d, *J* = 11.6 Hz, 2H), 1.70 (d, *J* = 12.3 Hz, 2H), 1.48 (q, *J* = 12.9 Hz, 2H), 1.31 (d, *J* = 6.5 Hz, 6H). LCMS: Purity 98%, MS (m/e) 465 (MH^+).

trans-3-(Cyclopropylamino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (**196**)

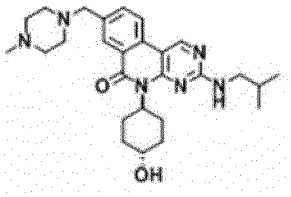
[0529]



[0530] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.11 (s, 1H), 8.29 - 8.22 (m, 1H), 8.18 (d, *J* = 8.3 Hz, 1H), 7.74 (dd, *J* = 8.3, 1.9 Hz, 1H), 5.54 (d, *J* = 44.7 Hz, 1H), 3.78 - 3.67 (m, 1H), 3.65 (s, 2H), 2.98 (s, 2H), 2.81 (tt, *J*= 7.1, 3.8 Hz, 1H), 2.53 (s, 8H), 2.28 (s, 3H), 2.10 (d, *J* = 11.7 Hz, 2H), 1.70 (d, *J* = 11.7 Hz, 2H), 1.60 - 1.40 (m, 2H), 0.93 - 0.78 (m, 2H), 0.69 - 0.53 (m, 2H). LCMS: Purity 95%, MS (m/e) 463 (MH^+).

trans-5-(4-hydroxycyclohexyl)-3-(isobutylamino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one **(130)**

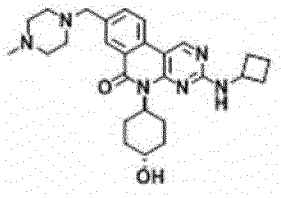
[0531]



[0532] LCMS: Purity 98%, MS (m/e) 479 (MH^+).

trans-3-(cyclobutylamino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (137)

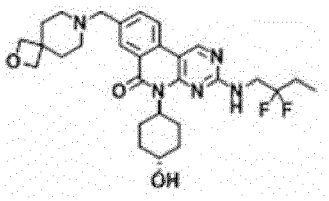
[0533]



[0534] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.24 (d, *J* = 8.3 Hz, 1H), 8.09 (d, *J* = 1.8 Hz, 1H), 8.05 - 7.90 (m, 1H), 7.64 (dd, *J* = 8.3, 1.8 Hz, 1H), 5.38 (br s, 1H), 4.66 (s, 1H), 4.33 (s, 1H), 3.53 (s, 2H), 2.98 - 2.61 (m, 2H), 2.39 - 2.22 (m,11H), 2.13 (s, 3H), 2.10- 1.88 (m, 4H), 1.72 (s, 2H), 1.55 (s, 2H), 1.32 (q, *J*= 12.1, 11.6 Hz, 2H). LCMS: Purity 98%, MS (m/e) 477 (MH^+).

trans-8-((2-Oxa-7-azaspiro[3.5]nonan-7-yl)methyl)-3-((2,2-difluorobutyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (197)

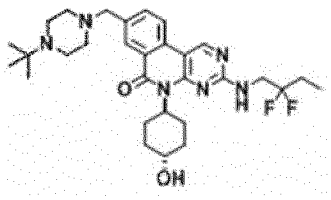
[0535]



[0536] LCMS: Purity 98%, MS (m/e) 542 (MH^+).

trans-8-((4-(*tert*-Butyl)piperazin-1-yl)methyl)-3-((2,2-difluorobutyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (198)

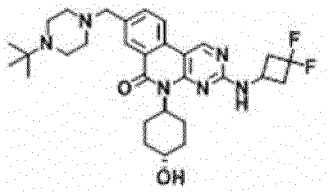
[0537]



[0538] LCMS: Purity 98%, MS (m/e) 557 (MH^+).

trans-8-((4-(tert-Butyl)piperazin-1-yl)methyl)-3-((3,3-difluorocyclobutyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one **(199)**

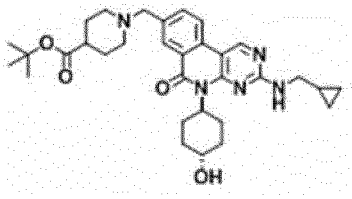
[0539]



[0540] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.15 (s, 1H), 8.25 (s, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.74 (dd, J = 8.3, 1.8 Hz, 1H), 5.52 (s, 1H), 4.35 (br s, 1H), 3.73 (dt, J = 11.1, 6.5 Hz, 1H), 3.65 (s, 2H), 3.15 - 2.78 (m, 4H), 2.79 - 2.38 (m, 10H), 2.12 (d, J = 12.2 Hz, 2H), 1.70 (d, J = 12.2 Hz, 2H), 1.49 (q, J = 10.6 Hz, 2H), 1.09 (s, 9H). LCMS: Purity 95%, MS (m/e) 555 (MH^+).

trans-tert-Butyl 1-((3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methyl)piperidine-4-carboxylate (201)

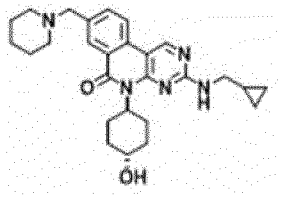
[0541]



[0542] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.11 (s, 1H), 8.22 (s, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.74 (dd, J= 8.4, 1.9 Hz, 1H), 5.58 (s, 1H), 3.77 - 3.68 (app m, 1H), 3.63 (s, 2H), 3.36 (d, J = 6.8 Hz, 2H), 3.06 - 2.74 (m, 3H), 2.31 - 2.19 (m, 1H), 2.15 - 2.06 (m, 5H), 1.89 - 1.80 (m, 4H), 1.79 - 1.64 (m, 4H), 1.53- 1.44 (m, 2H), 1.43 (s, 9H), 1.29 - 1.08 (m, 1H), 0.67 - 0.48 (m, 2H), 0.31 (q, J= 4.9 Hz, 2H). LCMS: Purity 96%, MS (m/e) 562 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(piperidin-1-ylmethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one **(202)**

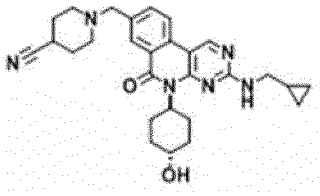
[0543]



[0544] LCMS: Purity 97%, MS (m/e) 462 (MH^+).

trans-1-((3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methyl)piperidine-4-carbonitrile **(204)**

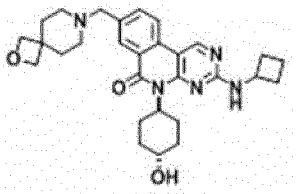
[0545]



[0546] ^1H NMR (400 MHz, Methanol-d_4) δ 9.11 (s, 1H), 8.22 (s, 1H), 8.17 (d, J = 8.3 Hz, 1H), 7.73 (dd, J = 8.3, 1.9 Hz, 1H), 5.53 (br s, 1H), 3.77 - 3.68 (m, 1H), 3.64 (s, 2H), 3.36 (d, J = 6.8 Hz, 2H), 3.06 - 2.60 (m, 5H), 2.38 (app s, 2H), 2.10 (app d, J = 12.4 Hz, 2H), 2.00 - 1.92 (m, 2H), 1.86 - 1.78 (m, 2H), 1.70 (d, J = 12.5 Hz, 2H), 1.54 - 1.43 (m, 2H), 1.29 - 1.08 (m, 1H), 0.63 - 0.46 (m, 2H), 0.41 - 0.23 (m, 2H). LCMS: Purity 97%, MS (m/e) 487 (MH^+).

trans-8-((2-Oxa-7-azaspiro[3.5]nonan-7-yl)methyl)-3-(cyclobutylamino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (209)

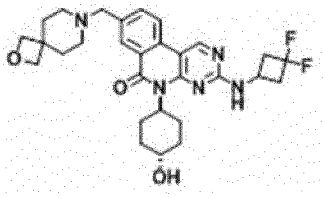
[0547]



[0548] LCMS: Purity 97%, MS (m/e) 504 (MH^+).

trans-8-((2-Oxa-7-azaspiro[3.5]nonan-7-yl)methyl)-3 -((3,3 - difluorocyclobutyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (210)

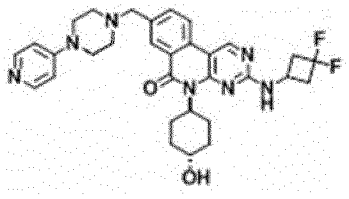
[0549]



[0550] LCMS: Purity 97%, MS (m/e) 540 (MH^+).

trans-3-((3,3-Difluorocyclobutyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-(pyridin-4-yl)piperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one **(212)**

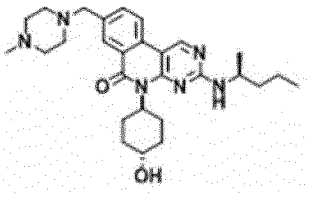
[0551]



[0552] LCMS: Purity 96%, MS (m/e) 576 (MH^+).

trans-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)-3-(((*S*)-pentan-2-yl)amino)pyrimido[4,5-c]isoquinolin-6(5H)-one **(213)**

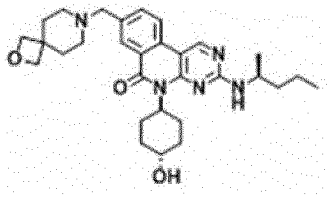
[0553]



[0554] LCMS: Purity 94%, MS (m/e) 493 (MH^+).

trans-8-((2-oxa-7-azaspiro[3.5]nonan-7-yl)methyl)-5-(4-hydroxycyclohexyl)-3-(((*S*)-pentan-2-yl)amino)pyrimido[4,5-c]isoquinolin-6(5H)-one **(214)**

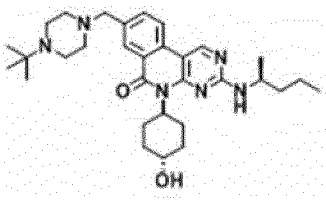
[0555]



[0556] LCMS: Purity 94%, MS (m/e) 520 (MH^+).

trans-8-((4-(*tert*-Butyl)piperazin-1-yl)methyl)-5-(4-hydroxycyclohexyl)-3-(((*S*)-pentan-2-yl)amino)pyrimido[4,5-c]isoquinolin-6(5H)-one **(215)**

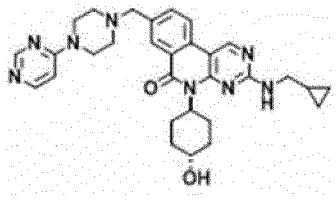
[0557]



[0558] LCMS: Purity 94%, MS (m/e) 535 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-(pyiimidin-4-yl)piperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one **(216)**

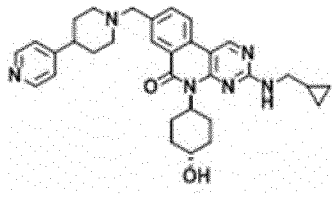
[0559]



[0560] ^1H NMR (400 MHz, Methanol-d_4) δ 9.11 (s, 1H), 8.43 (dd, J = 1.2, 0.7 Hz, 1H), 8.27 (d, J = 1.7 Hz, 1H), 8.19 (d, J = 8.3 Hz, 1H), 8.09 (dd, J = 6.5, 0.7 Hz, 1H), 7.77 (dd, J = 8.3, 1.9 Hz, 1H), 6.75 (dd, J = 6.5, 1.3 Hz, 1H), 5.53 (br s, 1H), 3.79 - 3.70 (m, 5H), 3.69 (s, 2H), 3.36 (d, J= 6.9 Hz, 2H), 2.92 (br s, 2H), 2.56 (t, J = 5.1 Hz, 4H), 2.10 (d, J= 12.0 Hz, 2H), 1.70 (d, J = 12.5 Hz, 2H), 1.49(q, J = 12.3, 11.1 Hz, 2H), 1.32 - 1.10 (m, 1H), 0.63 - 0.49 (m, 2H), 0.38-0.25 (m, 2H). LCMS: Purity 97%, MS (m/e) 541 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-(pyridin-4-yl)piperidin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one **(217)**

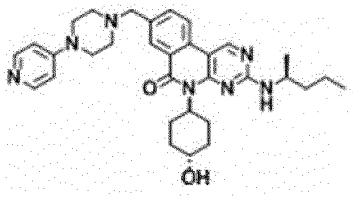
[0561]



[0562] ^1H NMR (400 MHz, Methanol-d_4) δ 9.11 (s, 1H), 8.47 - 8.36 (m, 2H), 8.26 (s, 1H), 8.18 (d, J = 8.3 Hz, 1H), 7.76 (dd, J = 8.4, 1.9 Hz, 1H), 7.41 - 7.16 (m, 2H), 5.58 (s, 1H), 3.76 - 3.70 (m, 1H), 3.69 (s, 2H), 3.36 (d, J = 6.8 Hz, 2H), 3.05 (d, J = 11.5 Hz, 2H), 2.92 (br s, 2H), 2.62 (app ddt, J = 11.5, 8.6, 4.4 Hz, 1H), 2.22 (td, J = 11.9, 3.3 Hz, 2H), 2.10 (d, J = 11.9 Hz, 2H), 1.94 - 1.74 (m, 4H), 1.70 (d, J = 11.9 Hz, 2H), 1.49 (app q, J = 12.2, 11.0 Hz, 2H), 1.35 - 1.08 (m, 1H), 0.62 - 0.47 (m, 2H), 0.45 - 0.22 (m, 2H). LCMS: Purity 97%, MS (m/e) 539 (MH^+).

trans-5-(4-Hydroxycyclohexyl)-3-(((*S*)-pentan-2-yl)amino)-8-((4-(pyridin-4-yl)piperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one **(219)**

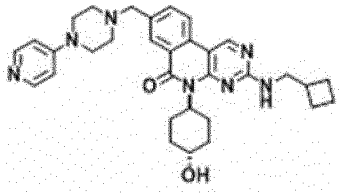
[0563]



[0564] ^1H NMR (400 MHz, Methanol-d_4) δ 9.10 (s, 1H), 8.26 (s, 1H), 8.18 (d, J = 8.3 Hz, 1H), 8.10 (dd, J = 5.2, 1.7 Hz, 2H), 7.77 (dd, J = 8.3, 1.9 Hz, 1H), 6.82 (dd, J = 5.3, 1.4 Hz, 2H), 5.58 (br s, 1H), 4.15 (app td, J = 15.0, 14.1, 7.4 Hz, 1H), 3.75 - 3.71 (m, 1H), 3.69 (s, 2H), 3.42 (t, J = 5.1 Hz, 4H), 2.90 (br s, 2H), 2.61 (t, J = 5.1 Hz, 4H), 2.10 (d, J = 12.6 Hz, 2H), 1.70 (app d, J = 13.0 Hz, 4H), 1.58 - 1.41 (m, 4H), 1.28 (d, J = 6.5 Hz, 3H), 0.97 (t, J = 7.2 Hz, 3H). LCMS: Purity 97%, MS (m/e) 556 (MH^+).

trans-3-((Cyclobutylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-(pyridin-4-yl)piperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one **(220)**

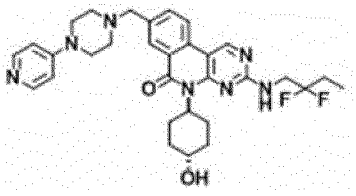
[0565]



[0566] LCMS: Purity 97%, MS (m/e) 554 (MH^+).

trans-3-((2,2-Difluorobutyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-(pyridin-4-yl)piperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one **(221)**

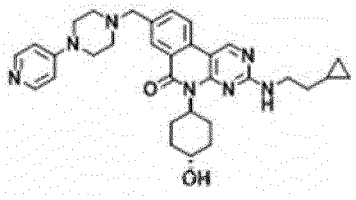
[0567]



[0568] LCMS: Purity 97%, MS (m/e) 578 (MH^+).

trans-3-((2-Cyclopropylethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-(pyridin-4-yl)piperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one **(222)**

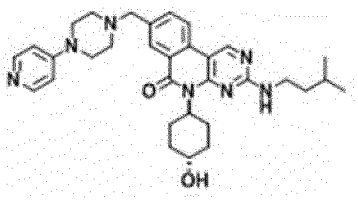
[0569]



[0570] LCMS: Purity 97%, MS (m/e) 554 (MH^+).

trans-5-(4-Hydroxycyclohexyl)-3-(isopentylamino)-8-((4-(pyridin-4-yl)piperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one **(223)**

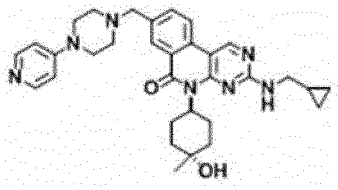
[0571]



[0572] LCMS: Purity 97%, MS (m/e) 555 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-(pyridin-4-yl)piperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one **(224)**

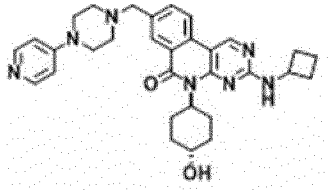
[0573]



[0574] LCMS: Purity 97%, MS (m/e) 554 (MH^+).

trans-3-(Cyclobutylamino)-5-(4-hydroxycyclohexyl)-8-((4-(pyridin-4-yl)piperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one **(225)**

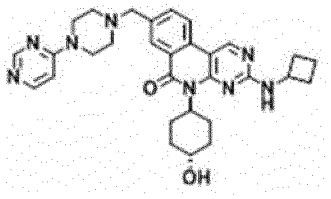
[0575]



[0576] LCMS: Purity 98%, MS (m/e) 540 (MH^+).

trans-3-(Cyclobutylamino)-5-(4-hydroxycyclohexyl)-8-((4-(pyrimidin-4-yl)piperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one **(226)**

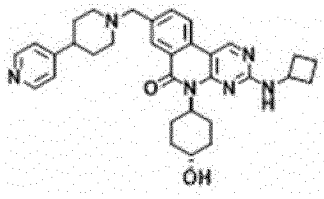
[0577]



[0578] LCMS: Purity 99%, MS (m/e) 541 (MH^+).

trans-3-(Cyclobutylamino)-5-(4-hydroxycyclohexyl)-8-((4-(pyridin-4-yl)piperidin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one **(227)**

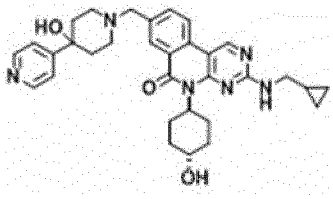
[0579]



[0580] LCMS: Purity 97%, MS (m/e) 539 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-8-((4-hydroxy-4-(pyridin-4-yl)piperidin-1-yl)methyl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one **(228)**

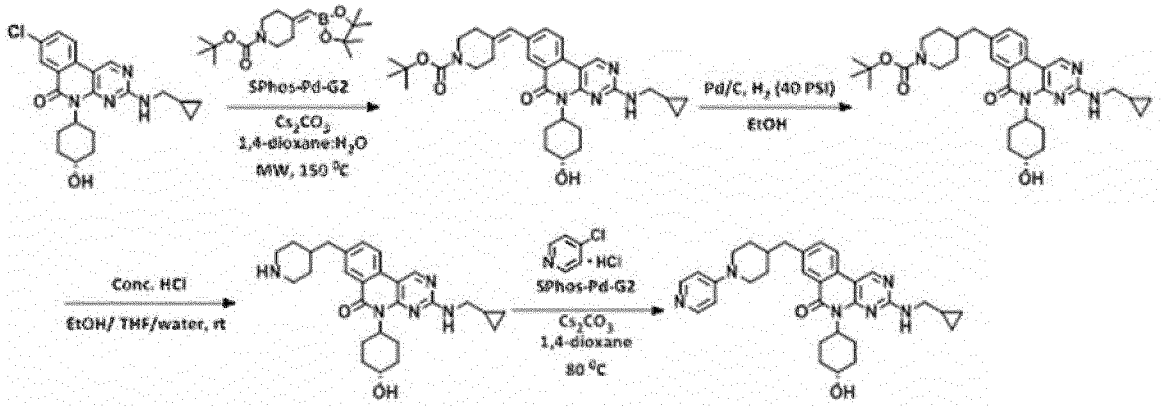
[0581]



[0582] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.57 - 8.42 (app m, 2H), 8.26 (d, J = 8.3 Hz, 1H), 8.13 (d, J = 1.6 Hz, 1H), 7.78 (s, 1H), 7.69 (dd, J = 8.3, 1.8 Hz, 1H), 7.52 - 7.40 (app m, 2H), 5.38 (br s, 1H), 5.04 (s, 1H), 4.64 (br s, 1H), 3.62 (s, 2H), 3.52 (br s, 1H), 3.25 (t, J = 6.4 Hz, 2H), 2.77 (br s, 2H), 2.71 - 2.55 (m, 2H), 2.43 (app d, J = 11.0 Hz, 2H), 1.99 - 1.87 (m, 4H), 1.61 - 1.49 (m, 4H), 1.46 - 1.22 (m, 2H), 1.22 - 1.01 (m, 1H), 0.54 - 0.35 (m, 2H), 0.35 - 0.14 (m, 2H). LCMS: Purity 98%, MS (m/e) 555 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((1-(pyridin-4-yl)piperidin-4-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one **(218)**

[0583]

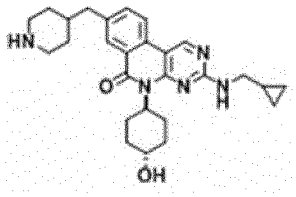


[0584] *trans*-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(piperidin-4-ylmethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (75 mg, 0.16 mmol), 4-chloropyridine hydrochloride (34 mg, 0.23 mmol), Cs_2CO_3 (150 mg, 0.46 mmol), SPhos-Pd-G2 (6 mg, 0.008 mmol) and dry 1,4-dioxane (4 mL) were transferred successively to a Teflon screw capped vial (18 mg, 0.025 mmol) containing a stir bar. Air was removed from the closed reaction system by vacuum, back filled with argon while stirring the reaction contents. After three repeated degassing cycles, reaction mixture was stirred at 80 °C. After 6h, dark reaction mixture was cooled to room temperature and analyzed the progress of reaction. LC/MS analysis of reaction aliquot indicated complete consumption of *trans*-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(piperidin-4-ylmethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one. Subsequently, dark heterogeneous reaction mixture was diluted with THF (10 mL) and filtered through Celite®. Reaction vial was further rinsed with THF (10 mL) and

filtered through Celite®. Upon concentrating the combined homogeneous filtrates, the crude concentrated semi-solid was dissolved in 5% 7N NH_3 MeOH/CH_2Cl_2 (6 mL), adsorbed on silica gel, dried and purified by flash chromatography [Combiflash with RediSep® silica gel column 12 g (pre-conditioned with CH_2Cl_2) and eluted with 0-5% 7N NH_3 MeOH in CH_2Cl_2:CH_2Cl_2 solvent gradient. Off-white solid obtained upon concentrating product fractions was stirred in EtOAc (3 mL), sonicated and filtered. The resulting off-white solid was dried to provide *trans*-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((1-(pyridin-4-yl)piperidin-4-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (62 mg). ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.09 (s, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 8.10 (s, 1H), 8.08 - 8.01 (app m, 2H), 7.60 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.83 - 6.73 (app m, 2H), 5.58 (br s, 1H), 3.98 (d, *J* = 13.2 Hz, 2H), 3.81 - 3.62 (m, 1H), 3.36 (d, *J* = 6.8 Hz, 2H), 3.08 - 2.79 (app m, 3H), 2.71 (d, *J* = 7.2 Hz, 2H), 2.10 (d, *J* = 11.9 Hz, 2H), 1.96 - 1.86 (m, 1H), 1.78 - 1.66 (app m, 5H), 1.49 (app q, *J* = 11.2, 10.7 Hz, 2H), 1.41 - 1.13 (m, 3H), 0.65 - 0.46 (m, 2H), 0.42 - 0.25 (m, 2H). LCMS: Purity 98%, MS (m/e) 539 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(piperidin-4-ylmethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one **(207)**

[0585]



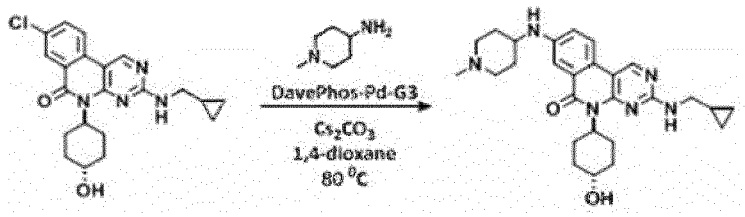
[0586] A microwave vial (35 mL) containing a stir bar was charged with *trans*-8-chloro-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (300 mg, 0.75 mmol), tert-butyl 4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)piperidine-1-carboxylate (310 mg, 0.96 mmol), SPhos-Pd-G2 (16 mg, 0.02 mmol), Cs_2CO_3 (610 mg, 1.87 mmol), 1,4-dioxane (18 mL) and water (2 mL) successively. The resulting heterogeneous suspension was degassed by bubbling nitrogen for 10 min, capped and heated at 150 °C in microwave for 90 min. At this stage, LC/MS of the reaction aliquot indicated 15% unreacted *trans*-8-chloro-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one. Subsequently, additional amounts of tert-butyl 4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)piperidine-1-carboxylate (100 mg), SPhos-Pd-G2 (7 mg) and Cs_2CO_3 (1.87 mmol) were added to reaction mixture, degassed by nitrogen and stoppered. Upon heating at 150 °C in the microwave for 1h, LC/MS of the reaction aliquot indicated the complete consumption of *trans*-8-chloro-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one, dark reaction mixture was diluted with THF (15 mL) filtered through Celite®. The Celite® pad was further washed with THF rinses (2 x 10 ml) of reaction vial. Combined filtrates were stirred over anhydrous $MgSO_4$ for 15 min, filtered and concentrated. The resulting semi-solid crude concentrate was diluted with CH_2Cl_2(4 mL), adsorbed on silica gel, purified by flash column chromatography [Combiflash with RediSep® silica gel column 40g (pre-conditioned with 50% EtOAc/hexanes) and eluted with 50-100% EtOAc/hexanes solvent gradient). Thus obtained semi white solid of *trans-tert-butyl* 4-((3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methylene)piperidine-1-carboxylate (380 mg) was hydrogenated over Pd/C (30 mg, 10 wt.% loading, Degussa type E101 NE/W) at 40 PSI for 2 days in EtOH in a par vessel on a par shaker. The reaction mixture was filtered through Celite®, concentrated, adsorbed on silica gel after dissolving in 3% 7N NH_3 MeOH in CH_2Cl_2, dried, purified by flash chromatography [Combiflash with RediSep® silica gel column 12g (pre-conditioned with CH_2Cl_2) and eluted with 0-3% 7N NH_3 MeOH in CH_2Cl_2:CH_2Cl_2 solvent gradient] and obtained *trans-tert-butyl* 4-((3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methyl)piperidine-1-carboxylate (340 mg) as a white solid.

[0587] *trans-tert*-butyl 4-((3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methyl)piperidine-1-carboxylate (300 mg) was stirred in a solution of conc. HCl (2 mL), THF (4 mL), EtOH (2 mL) and water (3 mL) at room temperature. After 2d, reaction mixture was concentrated, cooled in ice-bath, basified with solid Na_2CO_3 and warmed to room temperature. The resulting semi-suspension was extracted into 0.5% MeOH/CH_2Cl_2 (5 X 75 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude concentrate was dissolved in 10% 7N NH_3 MeOH/CH_2Cl_2, adsorbed onto silica gel, dried, purified by flash chromatography [Combiflash with RediSep® silica gel column 24 g and eluted with 0-10% 7N NH_3 MeOH in CH_2Cl_2:CH_2Cl_2 solvent gradient] and obtained *trans*-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(piperidin-4-ylmethyl)pyrimido[4,5-c]isoquinolin-6(5H)-one as a white solid (182 mg). ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.08 (s, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 8.07 (s, 1H), 7.57 (dd, *J* = 8.3, 1.9 Hz, 1H), 5.58 (br s, 1H), 3.75 - 3.67 (app m, 1H),

3.35 (d, *J* = 6.8 Hz, 2H), 3.01 (app dt, *J* = 12.5, 3.2 Hz, 2H), 2.91 (br s, 2H), 2.67 (d, *J* = 7.1 Hz, 2H), 2.54 (td, *J* = 12.5, 2.6 Hz, 2H), 2.10 (d, *J* = 12.1 Hz, 2H), 1.87 - 1.57 (m, 5H), 1.57 - 1.34 (m, 2H), 1.28 - 1.15 (m, 3H), 0.62 - 0.47 (m, 2H), 0.31 (app q, *J* = 4.8 Hz, 2H). LCMS: Purity 97%, MS (m/e) 462 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((1-methylpiperidin-4-yl)amino)pyrimido[4,5-c]isoquinolin-6(5H)-one **(189)**

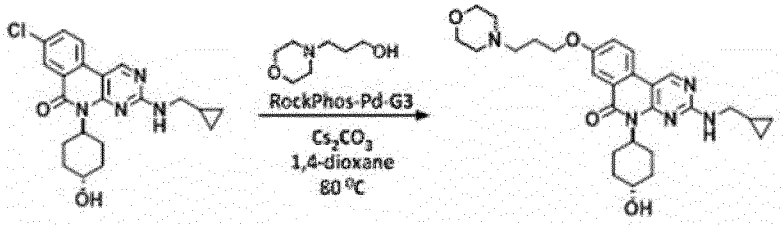
[0588]



[0589] *trans*-8-Chloro-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (100 mg, 025 mmol), 4-amino-1-methylpiperidine (60 mg, 0.52 mmol), Cs_2CO_3 (163 mg, 0.50 mmol), DavePhos-Pd-G3 (20 mg , 26 mmol) and dry 1,4-dioxane (4 mL) were transferred successively to a Teflon stoppered vial (18 mg, 0.025 mmol) containing a stir bar. Air was removed from the closed reaction system by vacuum, back filled with argon while stirring the reaction contents. After three degassing cycles, reaction mixture was heated at 80 °C under argon atmosphere for 4h. LC/MS analysis of reaction aliquot indicated complete consumption of *trans-8-Chloro-3-*((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one resulting in the quantitative formation of product after 4h. Subsequently, dark heterogeneous reaction mixture was diluted with THF (10 mL) and filtered through Celite®. Upon rinsing the reaction vial with additional THF (10 mL) followed by filtration through Celite®, combined homogeneous filtrates were concentrated. The resulting dark semi-solid was dissolved in 5% 7N NH_3 MeOH/CH_2Cl_2 (12 mL), adsorbed on silica gel (10 g), dried and purified by flash chromatography [Combiflash with RediSep® silica gel column 12 g (pre-conditioned with CH_2Cl_2) and eluted with 0-5% 7N NH_3 MeOH in CH_2Cl_2:CH_2Cl_2 solvent gradient. Off-white solid obtained upon concentrating product fractions was stirred in EtOAc (3 mL), sonicated, filtered and suction dried. Thus collected off-white solid was further dried under high vacuum and obtained *trans*-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((1-methylpiperidin-4-yl)amino)pyrimido[4,5-c]isoquinolin-6(5H)-one (63 mg). ^1H NMR (400 MHz, DMSO-d_6) δ 9.04 (s, 1H), 8.00 (d, *J* = 8.8 Hz, 1H), 7.43 (s, 1H), 7.24 (d, *J* = 2.1 Hz, 1H), 7.06 (dd, *J* = 8.8, 2.6 Hz, 1H), 5.95 (d, *J* = 7.8 Hz, 1H), 5.39 (s, 1H), 4.62 (d, *J* = 4.3 Hz, 1H), 3.52 (s, 1H), 3.22 (t, *J* = 6.4 Hz, 3H), 3.02 - 2.62 (m, 3H), 2.16 (s, 3H), 2.12 - 1.75 (m, 6H), 1.56-1.24 m, 7H), 1.15 - 1.05 (m, 1H), 0.51 - 0.33 (m, 2H), 0.23 (dt, *J* = 5.9, 4.4 Hz, 2H). LCMS: Purity 96%, MS (m/e) 477 (MH^+).

trans-3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(3-morpholinopropoxy)pyrimido[4,5-c]isoquinolin-6(5H)-one **(208)**

[0590]

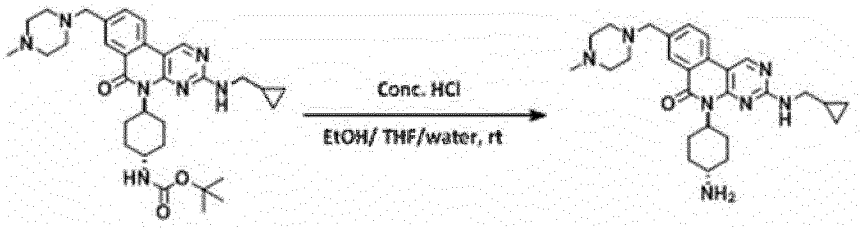


[0591] *trans*-8-Chloro-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (100 mg, 025 mmol), 3-morpholinopropanol (72 mg, 0.49 mmol), Cs_2CO_3 (160 mg, 0.49 mmol), RockPhos-Pd-G3 (6 mg , 0.006 mmol) and dry 1,4-dioxane (4 mL) were transferred successively to a Teflon stoppered vial containing a stir bar. Air was removed from the closed reaction system by vacuum, back filled with argon while stirring the reaction contents. After 3-4 cycles of repeated degassing cycles, reaction mixture was heated at 80 °C. LC/MS analysis of reaction aliquot indicated complete consumption of *trans*-8-chloro-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one resulting in the quantitative formation of product after 24h. Reaction mixture was diluted

with THF (5 mL) and filtered through Celite®. Upon rinsing reaction vial further with THF (5 mL) followed by filtration through Celite®, combined homogeneous filtrates were concentrated under reduced pressure. The resulting the crude concentrate was dissolved in 5% 7N NH3 MeOH/CH_2Cl_2 (12 mL), adsorbed on silica gel (10 g), dried and purified by flash chromatography [Combiflash with RediSep® silica gel column 12 g (pre-conditioned with CH_2Cl_2) and eluted with 0-5% 7N NH_3 MeOH in CH_2Cl_2:CH_2Cl_2 solvent gradient. Pale yellow solid thus obtained after concentrating product fractions was stirred in EtOAc (3 mL), sonicated, filtered and dried to provide 78 mg of *trans*-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(3-morpholinopropoxy)pyrimido[4,5-c]isoquinolin-6(5H)-one. LCMS: Purity 98%, MS (m/e) 508 (MH^+).

trans-5-(4-aminocyclohexyl)-3-((cyclopropylmethyl)amino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one **(185)**

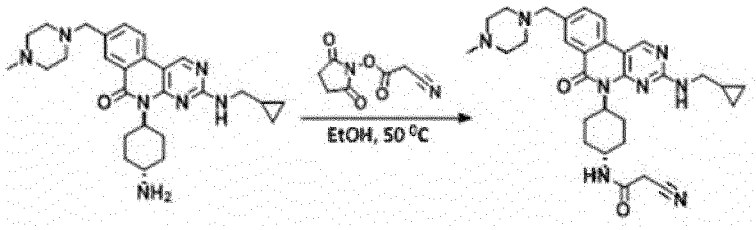
[0592]



[0593] *trans-tert-Butyl* (4-(3-((cyclopropylmethyl)amino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclohexyl)carbamate (500 mg), was stirred in conc. HCl (3 mL), THF (3 mL), EtOH (3 mL) and water (2 mL). After 36 h, LC/MS analysis of reaction aliquot indicated partial (50%) progress, additional conc. HCl (3 mL), EtOH (2 mL) and water (3 mL) were added to reaction mixture and allowed to stir at room temperature for 3 days (90% conversion). Upon removing volatiles from reaction solution, the concentrate was cooled in ice-bath, basified with solid Na_2CO_3 and warmed to room temperature. The resulting white solid was collected by filtration, washed with water, suction dried and purified by flash chromatography [Combiflash with RediSep® silica gel column 12 g and eluted with 0-5% 7N NH_3 MeOH in CH_2Cl_2:CH_2Cl_2 solvent gradient]. Upon concentrating product fractions, the resulting white solid was stirred in EtOAc (6 mL), filtered and dried provide *trans-5-(4*-aminocyclohexyl)-3-((cyclopropylmethyl)amino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (280 mg). ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.08 (s, 1H), 8.22 (d, J = 2.0 Hz, 1H), 8.15 (d, J = 8.3 Hz, 1H), 7.71 (dd, J = 8.3, 1.9 Hz, 1H), 5.55 (d, J = 17.1 Hz, 1H), 3.63 (s, 2H), 3.35 (d, J = 6.9 Hz, 2H), 3.01 - 2.75 (m, 3H), 2.51 (s, 9H), 2.27 (s, 3H), 2.06 (app d, J = 12.4 Hz, 2H), 1.79 - 1.60 (m, 2H), 1.40 (qd, J = 12.9, 3.6 Hz, 2H), 1.29 - 0.93 (m, 1H), 0.65 - 0.45 (m, 2H), 0.44 - 0.13 (m, 2H). LCMS: Purity 98%, MS (m/e) 476 (MH^+).

trans-2-Cyano-N-(4-(3-((cyclopropylmethyl)amino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclohexyl)acetamide **(190)**

[0594]

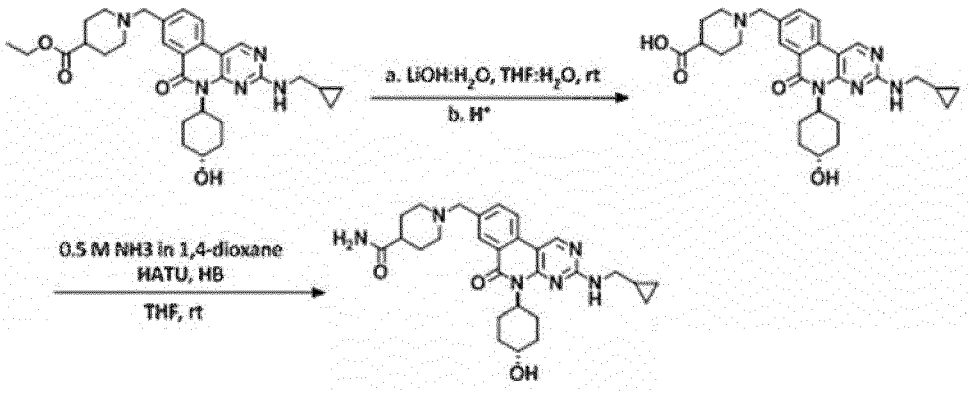


[0595] *trans*-5-(4-Aminocyclohexyl)-3-((cyclopropylmethyl)amino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (25 mg, 52 mmol) and succinimidyl cyanoacetate (10 mg, 55 mmol) were stirred in EtOH at 50 °C under nitrogen overnight. Reaction mixture was concentrated and purified by flash chromatography [Combiflash with RediSep® silica gel column 12 g (pre-conditioned with CH_2Cl_2) and eluted with 0-7% 7N NH_3 MeOH in CH_2Cl_2:CH_2Cl_2 solvent gradient) to obtain *trans*-2-Cyano-N-(4-(3-((cyclopropylmethyl)amino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclohexyl)acetamide (18 mg) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ

9.22 (s, 1H), 8.27 - 8.19 (m, 2H), 8.10 (d, *J* = 1.8 Hz, 1H), 7.80 (s, 1H), 7.65 (dd, *J* = 8.4, 1.8 Hz, 1H), 5.39 (s, 1H), 3.70 - 3.54 (app m, 4H), 3.29 - 3.22 (m, 1H), 2.99 - 2.72 (br m, 3H), 2.42 - 2.20 (m, 8H), 2.13 (s, 3H), 1.95 (d, *J* = 12.1 Hz, 2H), 1.71 - 1.52 (m, 3H), 1.46 - 1.25 (m, 2H), 1.19 - 1.05 (m, 1H), 0.46 (d, *J*= 7.7 Hz, 2H), 0.26 (d, *J*= 4.9 Hz, 2H). LCMS: Purity 97%, MS (m/e) 543 (MH^+).

trans-1-((3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methyl)piperidine-4-carboxamide **(203)**

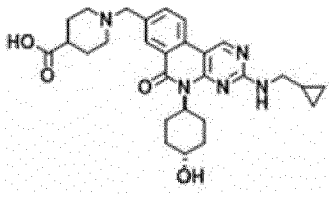
[0596]



[0597] *i*-Pr_2NEt (0.08 mL, 58 mg, 0.57 mmol) followed by 0.5 M NH_3 in 1,4-dioxane (1.48 mL, 0.74 mmol) were added successively to a stirring suspension of *trans*-1-((3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methyl)piperidine-4-carboxylic acid (75 mg, 0.15 mmol) and HATU (84 mg, 0.22 mmol) in THF (5 mL), under nitrogen. After 14 h, reaction mixture was concentrated, diluted with water and filtered. Thus collected solid upon suction drying was dissolved in 5% 7N NH_3 MeOH/CH_2Cl_2, adsorbed on silica gel, dried and purified by flash silica gel column chromatography [Combiflash with RediSep® silica gel column 4g (pre-conditioned with CH_2Cl_2) and eluted with 0-7% 7N NH_3 MeOH in CH_2Cl_2:CH_2Cl_2 solvent gradient) and obtained *trans*-1-((3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methyl)piperidine-4-carboxamide as a white solid (38 mg) ^1H NMR (400 MHz, Methanol-d_4) δ 9.11 (s, 1H), 8.22 (d, *J* = 1.6 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 7.74 (dd, *J* = 8.3, 1.9 Hz, 1H), 5.58 (s, 1H), 3.83 - 3.66 (m, 1H), 3.63 (s, 2H), 3.36 (d, *J* = 6.8 Hz, 2H), 3.07 - 2.80 (app m, 3H), 2.26 - 2.18 m, 1H), 2.14 - 2.04 2.09 (m, 4H), 1.88 - 1.56 (m, 6H), 1.62 - 1.36 (m, 2H), 1.36 - 1.09 (m, 1H), 0.60 - 0.44 (m, 2H), 0.44 - 0.19 (m, 2H). LCMS: Purity 97%, MS (m/e) 505 (MH^+).

trans-1-((3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methyl)piperidine-4-carboxylic acid (200)

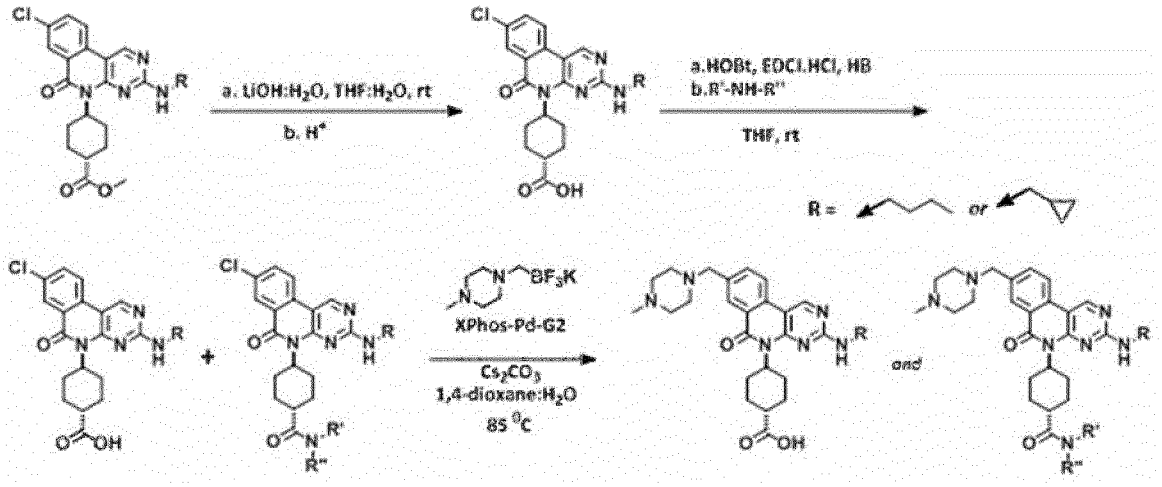
[0598]



[0599] trans-ethyl 1-((3-((Cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methyl)piperidine-4-carboxylate (160 mg, 0.3 mmol) and LiOH.H_2O (25 mg, 0.59 mmol) was stirred in THF (2 mL) and water (1 mL) at room temperature. LC/MS analysis of reaction aliquot indicated quantitative conversion of ester to acid after 4h. Subsequently, reaction mixture was concentrated under reduce pressure and acidified with 1N aq. HCl to pH 7.0. The resulting homogeneous solution was extracted into EtOAc (3 X 30 mL). Combined organic layers were dried over anhydrous Na_2SO_4, polish filtered and concentrated. The resulting white solid was diluted with water, stirred, filtered, dried and obtained *trans*-1-((3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methyl)piperidine-4-carboxylic acid (114 mg) ^1H NMR (400 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.24

(d, *J* = 8.3 Hz, 1H), 8.08 (d, *J* = 1.8 Hz, 1H), 7.77 (s, 1H), 7.64 (dd, *J* = 8.3, 1.9 Hz, 1H), 5.41 (s, 1H), 4.63 (s, 1H), 4.02 (s, 1H), 3.53 (s, 2H), 3.21 - 3.22 (app m, 4H), 2.85 - 2.64 (m, 2H), 2.20 - 2.13 (m, 1H), 2.02 - 1.89 (m, 4H), 1.80 - 1.69 (m, 2H), 1.60 - 1.47 (m, 4H), 1.38 - 1.23 (m, 2H), 1.14 - 1.07 (m, 1H), 0.44 (dt, *J* = 8.2, 2.9 Hz, 2H), 0.37 - 0.12 (m, 2H). LCMS: Purity 98%, MS (m/e) 506 (MH^+).

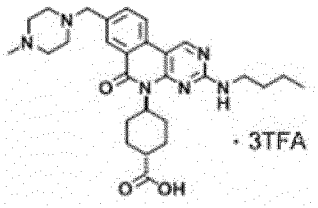
[0600] Procedure for the preparation of *trans*-4-(3-(alkylamino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclohexane-1-carboxylic acids and *trans*-4-(3-(alkylamino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclohexane-1-carboxamides



[0601] *trans-methyl* 4-(3-(butylamino)-8-chloro-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclohexane-1-carboxylate (600 mg, 1.35 mmol) dissolved in THF (10 mL):H_2O (5 mL) was added LiOH:H_2O (65 mg, 2.7 mmol). Upon stirring at room temperature overnight, reaction solution was concentrated under reduced pressure and neutralized with 1N aq. HCl (pH 6). The resulting solid was filtered and dried to provide crude *trans*-4-(3-(butylamino)-8-chloro-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclohexane-1-carboxylic acid (300 mg) [LCMS: Purity 96%, MS (m/e) 443]. A stirring mixture of *trans*-4-(3-(butylamino)-8-chloro-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclohexane-1-carboxylic acid (300 mg, 0.7 mmol), HOBt (142 mg, 1.0 mmol), EDCI.HCl (202 mg, 1.0 mmol) and dry THF (7 mL) under nitrogen was treated with *i*-Pr_2NEt (0.35 mL, 260 mg, 2.1 mL). After 1h, 28% ammonia solution (2.5 mL) was added to the stirring reaction mixture and concentrated after 16h. Upon diluting the concentrate with water, the resulting white solid (200 mg), a 1:1 mixture of acid and amide, was filtered, suction dried and used in the next step of Suzuki reaction with no further purification. Thus, 1:1 mixture of acid:amide (200 mg, 0.47 mmol), potassium 1-methyl-4-trifluoroboratomethyl piperazine (150 mg, 0.75 mmol), Cs_2CO_3 (350 mg, 1.1 mmol), XPhos-Pd-G2 (30 mg, 0.04 mmol), 1,4-dioxane (3 mL) and water were added successively to a Teflon screw cap vial containing a stir bar. Following three degassing cycles of vacuum and argon purge, reaction mixture was stirred at 85 °C for 17h. Subsequently, reaction mixture was diluted with THF (7 mL) and filtered through Celite®. Upon concentration of the filtrate, the crude residue was purified (preparative reverse phase HPLC using acetonitrile:water containing TFA modifier) to obtain acid and amide separately either as tris trifluoroacetic acid salt or solvates.

trans-4-(3-(Butyl amino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclohexane-1-carboxylic acid tris trifluoroacetic acid salt or solvate (132)

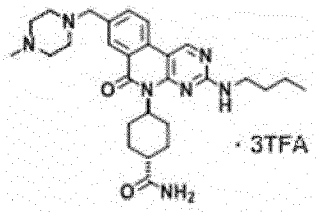
[0602]



[0603] LCMS: Purity 98%, MS (m/e) 507 (MH^+-3TFA).

trans-4-(3-(Butylamino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclohexane-1-carboxamide tris trifluoroacetic acid salt or solvate **(131)**

[0604]

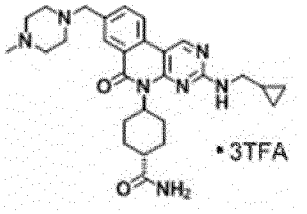


[0605] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.13 (s, 1H), 8.31 (s, 1H), 8.21 (d, *J* = 8.3 Hz, 1H), 7.81 (dd, *J* = 8.3, 1.9 Hz, 1H), 5.54 (s, 1H), 3.86 (s, 2H), 3.47 - 3.37 (m, 4H), 3.38 -3.33 (m, 4H), 2.90 (s, 3H), 2.87 - 2.76 (br s, 4H), 2.39 (app t, *J* = 12.3 Hz, 1H), 2.06 (d, *J* = 12.7 Hz, 2H), 1.85 - 1.62 (m, 4H), 1.27 - 1.16 (m, 1H), 0.65 - 0.55 (m, 2H), 0.37 (q, *J* = 5.1 Hz, 2H). LCMS: Purity 99%, MS (m/e) 504 (MH^+-3TFA).

[0606] The following amides were prepared in the similar manner to the preparation of *trans*-4-(3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclohexane-1-carboxamide and purified by either reverse phase HPLC using acetonitrile:water containing TFA / formic acid as modifier or flash silica gel column chromatography [Combiflash with RediSep® silica gel column 12g and eluted with 0-5% 7N NH_3 MeOH:CH_2Cl_2 solvent gradient).

trans-4-(3-((Cyclopropylmethyl)amino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclohexane-1-carboxamide (tris trifluoroacetic acid salt or solvate (134)

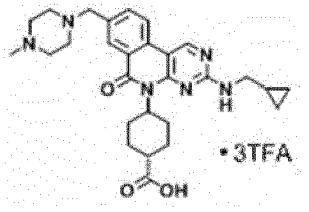
[0607]



[0608] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.13 (s, 1H), 8.31 (s, 1H), 8.21 (d, *J*= 8.3 Hz, 1H), 7.81 (dd, *J*= 8.3, 1.9 Hz, 1H), 5.54 (s, 1H), 3.86 (s, 2H), 3.47 - 3.37 (m, 4H), 3.38 -3.33 (m, 4H), 2.90 (s, 3H), 2.87 - 2.76 (br s, 4H), 2.39 (app t, *J*= 12.3 Hz, 1H), 2.06 (d, *J*= 12.7 Hz, 2H), 1.85 - 1.62 (m, 4H), 1.27 - 1.16 (m, 1H), 0.65 - 0.55 (m, 2H), 0.37 (q, *J* = 5.1 Hz, 2H). LCMS: Purity 99%, MS (m/e) 504 (MH^+-3TFA).

trans-4-(3-((Cyclopropylmethyl)amino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclohexane-1-carboxylic acid tris trifluoroacetic acid salt or solvate **(135)**

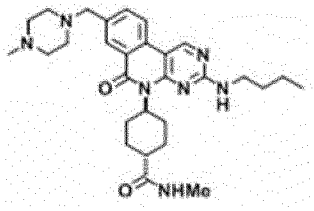
[0609]



[0610] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.12 (s, 1H), 8.29 (d, *J* = 1.7 Hz, 1H), 8.21 (d, *J* = 8.3 Hz, 1H), 7.78 (dd, *J* = 8.4, 1.8 Hz, 1H), 5.56 (s, 1H), 3.80 (s, 2H), 3.39 (s, 4H), 3.98 - 2.62 (app m, 11H), 2.46 - 2.39 (m, 1H), 2.19 (app d, *J* = 13.0 Hz, 2H), 1.79 (d, *J* = 12.2 Hz, 2H), 1.71 - 1.55 (m, 2H), 1.26 - 1.19 (m, 1H), 0.63 - 0.53 (m, 2H), 0.35 (t, *J* = 4.9 Hz, 2H). LCMS: Purity 99%, MS (m/e) 505 (MH^+-3TFA).

trans-4-(3-(Butylamino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)-N-methylcyclohexane-1-carboxamide **(138)**

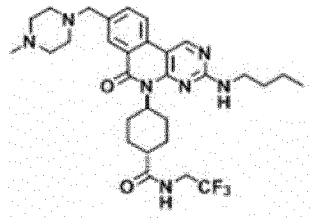
[0611]



[0612] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (s, 1H), 8.24 (d, *J*= 8.3 Hz, 1H), 8.08 (s, 1H), 7.73 (app q, *J* = 5.5, 5.0 Hz, 2H), 7.64 (dd, *J* = 8.3, 1.8 Hz, 1H), 5.46 (s, 1H), 3.53 (s, 2H), 3.35 (q, *J* = 6.7 Hz, 2H), 2.56 (d, *J* = 4.5 Hz, 3H), 2.42-2.22 (br m, 9H), 2.13 (s, 3H), 1.85 (d, *J* = 12.6 Hz, 2H), 1.68 - 1.44 (m, 7H), 1.42 - 1.31 (m, 2H), 0.91 (t, *J*= 7.3 Hz, 3H). LCMS: Purity 99%, MS (m/e) 520 (MH^+).

trans-4-(3-(Butylamino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)-N-(2,2,2-trifluoroethyl)cyclohexane-1-carboxamide **(139)**

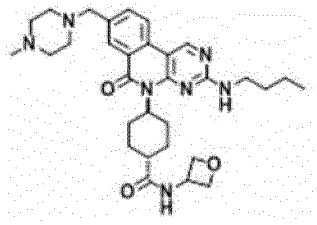
[0613]



[0614] ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.10 (s, 1H), 8.23 (d, *J* = 1.6 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.73 (dd, *J* = 8.3, 1.9 Hz, 1H), 5.65 (br s, 1H), 3.91 (q, *J* = 9.4 Hz, 2H), 3.65 (s, 2H), 3.57 - 3.38 (m, 2H), 2.98 - 2.35 (m, 10H), 2.29 (s, 3H), 2.02 (d, *J* = 12.9 Hz, 2H), 1.88 - 1.58 (m, 7H), 1.48 (dt, *J*= 14.9, 7.4 Hz, 2H), 0.99 (t, *J*= 7.3 Hz, 3H). LCMS: Purity 97%, MS (m/e) 586 (MH^+).

trans-4-(3-(Butylamino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)-N-(oxetan-3-yl)cyclohexane-1-carboxamide **(140)**

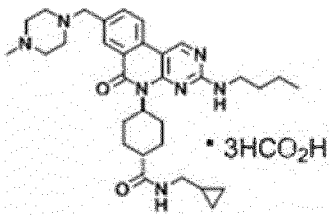
[0615]



[0616] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (s, 1H), 8.55 (d, *J*= 6.7 Hz, 1H), 8.24 (d, *J* = 8.2 Hz, 1H), 8.08 (d, *J* = 1.7 Hz, 1H), 7.72 (s, 1H), 7.64 (dd, *J* = 8.3, 1.8 Hz, 1H), 5.46 (s, 1H), 4.78 (dq, *J*= 13.1, 6.5 Hz, 1H), 4.69 (dd, *J* = 7.5, 6.0 Hz, 2H), 4.40 (t, *J* = 6.2 Hz, 2H), 3.54 (s, 2H), 3.35 (q, *J* = 6.7 Hz, 2H), 2.67 (br s, 1H), 2.43 - 2.18 (m, 9H), 2.13 (s, 3H), 1.96 - 1.80 (m,2H), 1.75 - 1.27 (m, 9H), 0.90 (t, *J* = 7.3 Hz, 3H). LCMS: Purity 97%, MS (m/e) 562 (MH^+).

trans-4-(3-(Butylamino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)-N-(cyclopropyl-methyl)cyclohexane-1-carboxamide tris formic acid salt or solvate **(141)**

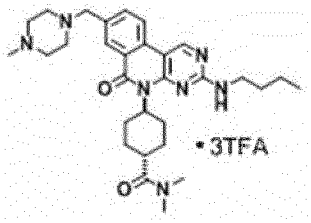
[0617]



[0618] LCMS: Purity 99%, MS (m/e) 560 (MH^+-3HCO_2H).

trans-4-(3-(Butyl amino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)-N,N-dimethylcy-clohexane-1-carboxamide tris trifluoroacetic acid salt or solvate **(142)**

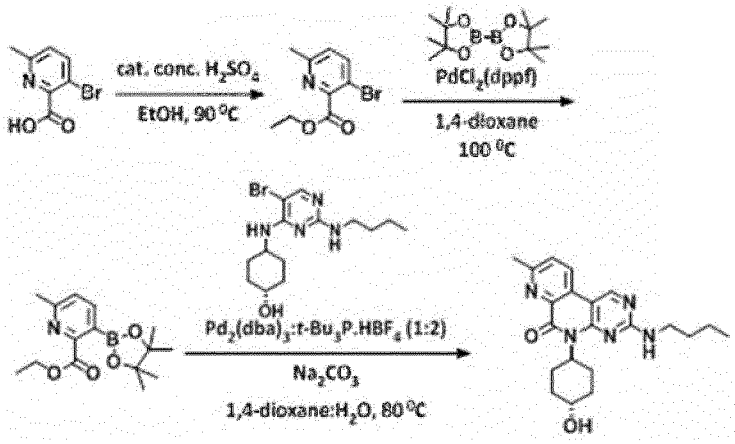
[0619]



[0620] LCMS: Purity 99%, MS (m/e) 534 (MH^+-3TFA).

trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-methylpyrimido[5,4-f][1,7]naphthyridin-6(5H)-one tris trifluoroacetic ac-id salt or solvate **(8a)**

[0621]

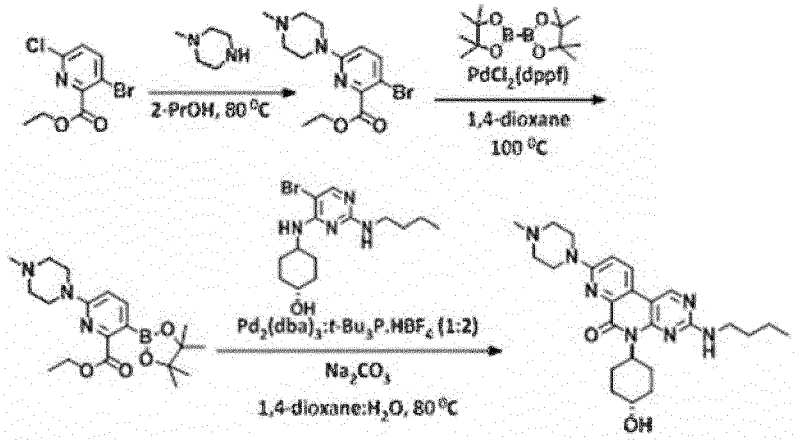


[0622] A solution of 6-bromo-6-methylpicolinic acid (2g), EtOH (40 mL) and conc. H_2SO_4 was heated to reflux for three days under nitrogen, cooled to room temperature and concentrated. Crude residue was neutralized with aq. $NaHCO_3$ in an ice-bath and extracted into EtOAc (3 X 80 mL). Combined organic layers were stirred over anhydrous $MgSO_4$, filtered, concentrated, dried under high vacuum, purified by silica gel column chromatography with 50% EtOAc/hexanes as an eluent and obtained 1.5 g of ethyl 3-bromo-6-methylpicolinate as viscous liquid. LCMS: Purity 98%, MS (m/e) 245 (MH^+). A stirring mixture of 3-bromo-6-methylpicolinate (1.5 g, 6.14 mmol), bis(pinacolato)diboron (2.0 g, 7.99 mmol),

KOAc (1.8 g, 18.4 mmol) and 1,4-dioxane (30 mL) was degassed under high vacuum, back filled with argon successively in three degassing cycles over a period of 10 min. $PdCl_2(dppf)$ (0.5 g, 0.61 mmol) was added to degassed reaction mixture, repeated degassing cycles and heated at 100 °C. After 17 h, dark reaction mixture was cooled to room temperature, diluted with EtOAc (50 mL) and filtered through Celite®. The crude ethyl 6-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinate (LC/MS: Purity 72%) obtained after concentration of the filtrate to dryness was used in the next step with no further purification. Similar to the general reaction conditions described for the preparation of *trans*-3-(butylamino)-8-chloro-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-one, ethyl 6-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinate (400 mg) was reacted with *trans*-4-((5-bromo-2-(butylamino)pyrimidin-4-yl)amino)cyclohexan-1-ol (200 mg, 0.58 mmol) and Na_2CO_3 (216 mg, 2.0 mmol) in 1,4-dioxane:H_2O (2.5 mL:0.5 mL) in the presence of $Pd_2(dba)_3$:*t*-$BuP_3.HBF_4$ (1:2) (22 mg, 0.014 mmol) [instead of previously described $PdCl_2(dppf)$] as a catalyst at 80 °C under argon after degassing cycles. After overnight heating, reaction mixture was diluted with THF (8 mL), filtered through Celite®. Upon concentration of the filtrate, the crude residue was purified on preparative reverse phase HPLC using acetonitrile:water containing TFA modifier and obtained *trans*-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-methylpyrimido[5,4-f][1,7]naphthyridin-6(5H)-one tris trifluoroacetic acid salt or solvate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.15 (s, 1H), 8.82 (d, *J*= 8.5 Hz, 1H), 7.84 (d, *J*= 8.5 Hz, 1H), 5.53 (d, *J*= 37.1 Hz, 1H), 3.71 (td, *J* = 10.9, 10.2, 5.0 Hz, 1H), 3.64 - 3.42 (m, 2H), 3.13 - 2.83 (m, 2H), 2.78 (s, 3H), 2.12 (d, *J*= 12.1 Hz, 2H), 1.92 - 1.60 (m, 4H), 1.60 - 1.33 (m, 4H), 1.00 (t, *J*= 7.4 Hz, 3H). LCMS: Purity 97%, MS (m/e) 382 (MH^+-3TFA).

trans-3-(Butylamino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[5,4-f][1,7]naphthyridin-6(5H)-one **(9a)**

[0623]

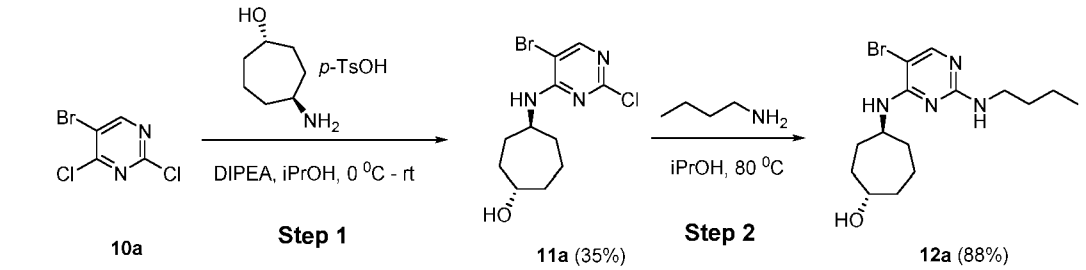


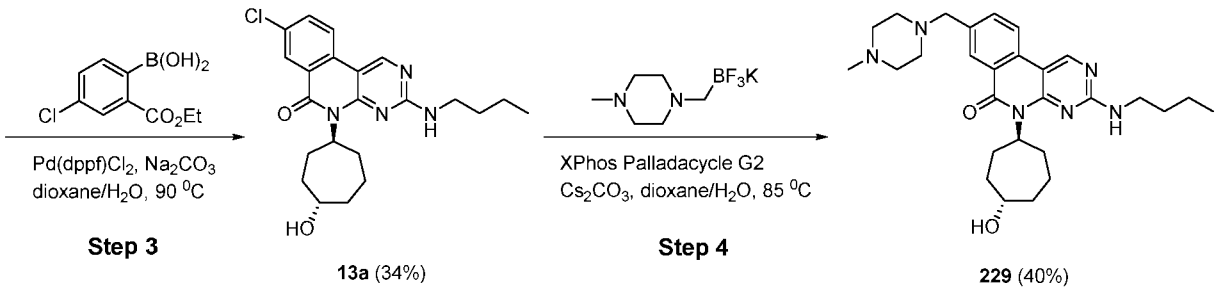
[0624] A solution of ethyl 3-bromo-6-chloropicolinate (900 mg, 3.4 mmol), 1-methylpiperazine (600 mg, 6 mmol) and 2-propanol (10 mL) was stirred at 80 °C in a sealed tube. After 48 h, reaction solution was cooled to room temperature and concentrated under reduced pressure. The crude orange viscous liquid was purified by silica gel column chromatography by eluting with 5-8% 7N NH_3 MeOH/EtOAc and obtained 400 mg of ethyl 3-bromo-6-(4-methylpiperazin-1-yl)picolinate (LCMS: Purity 90%). A stirring mixture of 3-bromo-6-(4-methylpiperazin-1-yl)picolinate (400 mg, 1.2 mmol), bis(pinacolato)diboron (418 mg, 1.6 mmol), KOAc (360 mg, 3.6 mmol) and 1,4-dioxane (10 mL) was degassed under high vacuum, back filled with argon successively in three degassing cycles over a period of 10 min. $PdCl_2(dppf)$ (100 mg, 0.12 mmol) was added to degassed reaction mixture, degassed and heated at 95 °C under argon. After overnight, dark reaction mixture was cooled to room temperature, diluted with EtOAc (50 mL) and filtered through Celite®. The resulting dark filtrated was concentrated, diluted with water (15 mL) and extracted into EtOAc (2 x 75 mL). Upon stirring and filtration of the combined organic layers over anhydrous $MgSO_4$, filtrate was concentrated to dryness and obtained ethyl 6-(4-methylpiperazin-1-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinate (280 mg, LCMS: Purity 77%) Thus obtained crude ethyl 6-(4-methylpiperazin-1-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinate (150 mg) was reacted with *trans*-4-((5-bromo-2-(butylamino)pyrimidin-4-yl)amino)cyclohexan-1-ol (83 mg, 0.24 mmol), $Pd_2(dba)_3$:*t*-$BuP_3.HBF_4$ (1:2) (13 mg, 0.008 mmol) and Na_2CO_3 (90 mg, 0.84 mmol) in 1,4-dioxane:H_2O (2.5 mL:0.5 mL) at 85 °C under argon after degassing cycles. After overnight heating, reaction mixture was diluted with THF (8 mL) and filtered through Celite®. Upon concentration of the filtrate, the crude residue was dissolved in 7% 7N NH_3 MeOH/CH_2Cl_2, adsorbed on silica gel, dried and purified by flash silica gel column chromatography [Combiflash with RediSep® silica gel column 12g (pre-conditioned with CH_2Cl_2) and eluted with 0-10% 7N NH_3 MeOH:CH_2Cl_2 solvent

gradient) and obtained *trans*-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[5,4-f][1,7]naphthyridin-6(5H)-one (23 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.46 (d, *J*= 9.1 Hz, 1H), 7.52 (s, 1H), 7.32 (d, *J*= 9.1 Hz, 1H), 5.42 (br s, 1H), 4.63 (d, *J*= 4.2 Hz, 1H), 3.73 - 3.57 (m, 5H), 3.50 (s, 1H), 3.41 - 3.19 (m, 1H), 2.98 - 2.62 (br s, 2H), 2.39 *(t, J*= 5.1 Hz, 4H), 2.21 (s, 3H), 1.94 (app d, *J* = 12.1 Hz, 2H), 1.55 (app p, J= 7.4 Hz, 4H), 1.47 - 1.19 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 3H). LCMS: Purity 97%, MS (m/e) 466 (MH^+).

Synthesis of 3-(butylamino)-5-((1*S*,4*S*)-4-hydroxycycloheptyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5*H*)-one (229)

[0625]





Step 1.

[0626] To a solution of 2,4-dichloro-5-bromopyrimidine (0.46 g, 2.00 mmol) and *N,N*-diisopropylethylamine (0.44 ml, 2.59 mmol) in anhydrous isopropyl alcohol (1 mL) was slowly added (1S,4S)-4-aminocycloheptan-1-ol *p*-TsOH (1:1) (0.61 g, 2.03 mmol) in anhydrous isopropyl alcohol (1 mL) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 4 h, then stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by chromatography eluting with ethyl acetate/hexanes (3/7) to provide (1S,4S)-4-((5-bromo-2-chloropyrimidin-4-yl)amino)cycloheptan-1-ol (0.22 g, 35%). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.10 (s, 1H), 5.39 (m, 1H), 4.24 (m, 1H), 3.91 (m, 1H), 2.09 (m, 5H), 1.74 (m, 6H) ppm; MS *m/e*: 321.9 $(M+H)^+$.

Step 2.

[0627] A mixture of (1S,4S)-4-((5-bromo-2-chloropyrimidin-4-yl)amino)cycloheptan-1-ol (0.30 g, 0.94 mmol), n-butylamine (0.46 mL, 4.70 mmol) and DIEA (0.25 mL, 1.41 mmol) in anhydrous isopropyl alcohol (1 mL) was stirred at 80 °C overnight. The reaction mixture was then concentrated under reduced pressure to give a residue, which was purified by chromatography eluting with ethyl acetate/hexanes (8/2) to (1S,4S)-4-((5-bromo-2-(butylamino)pyrimidin-4-yl)amino)cycloheptan-1-ol (0.29 g, 88%). MS *m/e*: 357.1 $(M+H)^+$.

Step 3.

[0628] A mixture of (1S,4S)-4-((5-bromo-2-(butylamino)pyrimidin-4-yl)amino)cycloheptan-1-ol (0.29 g, 0.81 mmol), (4-chloro-2-(ethoxycarbonyl)phenyl)boronic acid (0.22 g, 0.97 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.03 g, 0.04 mmol), and Na_2CO_3 (0.14 g, 1.62 mmol) in dioxane (3.2 mL) and water (0.4 mL) was stirred at 90 °C for 18 h. The mixture was then concentrated under reduced pressure to give a residue, which was purified by

chromatography eluting with ethyl acetate/hexanes (7/3) to provide 3-(butylamino)-8-chloro-5-((1S,4S)-4-hydroxycycloheptyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (0.11 g, 34%). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.96 (s, 1H), 8.34 (s, 1H), 7.94 (m, 1H), 7.62 (m, 1H), 5.77 (bs, 1H), 5.38 (bs, 1H), 3.95 (m, 1H), 3.51 (m, 2H), 2.64 (m, 1H), 2.39 (m, 1H), 2.19 (m, 1H), 2.04 (m, 1H), 1.74 (m, 8H), 1.47 (m, 3H), 0.99 (m, 3H) ppm; MS *m/e:* 415.1 $(M+H)^+$.

Step 4.

[0629] A mixture of 3-(butylamino)-8-chloro-5-((1S,4S)-4-hydroxycycloheptyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (0.04 g, 0.09 mmol), potassium 1-methyl-4-trifluoroboratomethylpiperazine (0.03 g, 0.14 mmol), XPhos-Pd-G2 (0.01 g, 0.01 mmol), and Cs_2CO_3 (0.58 g, 0.18 mmol) in dioxane (1 mL) and water (0.2 mL) was stirred at 85 °C for 18 h. The mixture was then concentrated under reduced pressure to give a residue, which was purified by reversed phase HPLC to provide 229 3-(butylamino)-5-((1S,4S)-4-hydroxycycloheptyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one (0.02 g, 40%).

229 3-(butylamino)-5-((1S,4S)-4-hydroxycycloheptyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

[0630] ^{1}H NMR (CD_3OD, 400 MHz) 9.10 (s, 1H), 8.22 (bs, 1H), 8.17 (m, 1H), 7.73 (m, 1H), 3.85 (m, 1H), 3.65 (s, 2H), 3.48 (m, 2H), 2.53 (m, 9H), 2.29 (s, 3H), 2.17 (m, 1H), 2.02 (m, 2H), 1.75 (m, 7H), 1.55 (m, 4H), 0.99 (m, 3H) ppm; MS *m/e:* 493.4 $(M+H)^+$.

230 3-((cyclopropylmethyl)amino)-5-((1S,4S)-4-hydroxycycloheptyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

[0631] ^{1}H NMR (DMSO-d_6, 400 MHz) 9.21 (s, 1H), 8.24 (m, 1H), 8.38 (m, 1H), 8.07 (m, 1H), 7.79 (m, 1H), 7.63 (m, 1H), 5.74 (m, 1H), 5.42 (bs, 1H), 4.49 (m, 1H), 3.68 (m, 1H), 3.54 (s, 2H), 3.25 (m, 2H), 2.33 (m, 8H), 2.13 (s, 3H), 1.66 (m, 10H), 1.11 (m, 1H), 0.44 (m, 2H), 0.25 (m, 2H) ppm; MS *m/e*: 491.5 $(M+H)^+$.

231 tert-butyl ((1S,3S)-3-(3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclopentyl)carbamate

[0632] MS *m/e*: 564.3 $(M+H)^+$.

232 5-((1S,3S)-3-aminocyclopentyl)-3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

[0633] ^{1}H NMR (CD_3OD, 400 MHz) 9.02 (s, 1H), 8.28 (s, 1H), 7.97 (m, 1H), 7.70 (m, 1H), 6.32 (m, 1H), 5.31 (bs, 1H), 4.00 (m, 1H), 3.61 (s, 2H), 3.51 (m, 2H), 2.52 (m, 10H), 2.29 (s, 3H), 2.08 (m, 2H), 1.69 (m, 4H), 1.49 (m, 4H), 0.99 (m, 3H) ppm; MS *m/e*: 464.3 $(M+H)^+$.

233 N-((1S,3S)-3-(3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclopentyl)acetamide

[0634] MS *m/e*: 506.3 $(M+H)^+$.

234 3-(butylamino)-8-chloro-5-((1R,3R)-3-hydroxycyclopentyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

[0635] ^{1}H NMR (CD_3OD, 400 MHz) 9.25 (m, 1H), 8.35 (m, 1H), 8.12 (m, 1H), 7.77 (m, 1H), 7.66 (bs, 1H), 6.24 (m, 1H), 4.57 (bs, 1H), 4.37 (bs, 1H), 3.34 (m, 2H), 2.21 (m, 2H), 1.96 (m, 2H), 1.64 (m, 4H), 1.35 (m, 2H), 0.90 (m, 3H) ppm; MS *m/e*: 387.2 $(M+H)^+$.

235 3-(butylamino)-5-((1R,3R)-3-hydroxycyclopentyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

[0636] ^{1}H NMR (CD_3OD, 400 MHz) 9.11 (s, 1H), 8.23 (bs, 1H), 8.18 (m, 1H), 7.74 (m, 1H), 6.44 (m, 1H), 4.64 (m, 1H), 3.65 (s, 2H), 3.47 (m, 2H), 2.53 (m, 10H), 2.29 (s, 3H), 2.14 (m, 2H), 1.88 (m, 1H), 1.77 (m, 1H), 1.67 (m, 2H), 1.45 (m, 2h), 0.99 (m, 3H) ppm; MS *m/e*: 465.3 $(M+H)^+$.

236 3-(butylamino)-5-((1S,3S)-3-(dimethylamino)cyclopentyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

[0637] MS *m/e:* 492.3 $(M+H)^+$.

237 2-(((1S,3S)-3-(3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclopentyl)amino)acetamide

[0638] MS *m/e:* 521.3 (M+H)

238 3-(butylamino)-5-((1S,3S)-3-((2-hydroxyethyl)amino)cyclopentyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-one

[0639] MS *m/e*: 508.2 $(M+H)^+$.

239 1-((1S,3S)-3-(3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclopentyl)guanidine

[0640] MS *m/e*: 506.3 $(M+H)^+$.

Example 4: PAKT HTRF-HUVEC Assay

Materials

[0641]

Dimethyl Sulfoxide (DMSO) (Sigma-Aldrich, D2650)
Corning™ Costar™ 96-Well White Clear-Bottom Plates (Fisher Scientific, 07-200-587) ProxiPlate-384 Plus, White 384-shallow well Microplate (Perkin Elmer, 6008280) Phospho Akt (Ser473) Assay kit-10,000 tests (Cisbio US, 64AKSPEH)
HUVEC cells (Lonza, CC-2519)
EGM-2 BulletKit (Lonza, CC-3162)
EBM-2 Basal Medium (Lonza, CC-3156)
Biotin-SP-conjugated Anti-mouse IgG (Jackson Immunoresearch Labs, 115-065-003) Anti-human MerTK antibody (Clone 125518) (R&D Systems, MAB8912)

Equipment

[0642] SpectraMax Paradigm Multi-Mode Microplate Reader (Molecular Devices)

Method

[0643] Seed HUVECs (10K cells/well) in EBM-2 complete media (EBM-2 basal medium plus EGM-2 BulletKit supplements) overnight at 37°C, 5 % CO_2 in Costar 96-well white clear-bottom plates. Remove culture media and starve cells for 3-4 hours in 50 μL/well EBM-2 basal medium. Perform serial dilution of compounds in DMSO from 2.5 mM in 4-fold dilutions, and then dilute 1:125 in EBM-2 basal media. Mix 50 μL/well 2x compounds with 50 μL/well HUVECs in duplicate in Costar 96-well white clear-bottom plates. Incubate plates for 1 hour at 37°C, 5 % CO_2. Cross-link anti-human MerTK antibody to Biotin-SP-conjugated anti-mouse IgG antibody (1:1) to give final concentrations of 5ug/mL of anti-human MerTK-XL. Stimulate HUVECs with 25 μL/well 5x anti-human MerTK-XL to give final concentrations of 1ug/mL for 10 minutes at 37°C, 5 % CO_2. Completely remove media and lyse HUVECs with 40uL/WELL per well of Cisbio HTRF 1x lysis buffer. Performed pAkt(Ser473) HTRF assay in ProxiPlate-384 Plus, white 384-shallow well microplate according to the vendor protocol and read plates with a SpectralMax Paradigm plate reader. Enter the HTRF values into Athena (Rigel) for curve fitting, EC_{50} calculation, and database storage.

[0644] Representative results for inhibition of MerTK (μM)) is shown in **Table 1:**

No.	MerTK
1	0.2471
2	0.0442
3	0.0288
4	0.1743
5	0.098
6	2.043
7	N/A
8	N/A
9	0.1165
10	0.1456
11	N/A
12	0.1165
13	0.1442
14	0.0564
15	0.0059
16	0.0639

No.	MerTK
17	0.068
18	0.2773
19	0.6972
20	0.0182
21	0.0307
22	0.5893
23	1.177
24	0.2208
25	1.679
26	0.0167
27	0.0459
28	0.0366
29	0.0062
30	0.0183
31	0.0125
32	0.0065

No.	MerTK
33	0.0046
34	0.0074
35	0.0467
36	0.0168
37	0.0538
38	0.0333
39	0.0646
40	0.0507
41	0.1263
42	0.0459
43	0.0513
44	0.066
45	0.1495
46	0.1165
47	0.0497
48	0.0487

No.	MerTK
49	0.2207
50	0.0259
51	11.9
52	0.4007
53	0.0363
54	0.309
55	0.0364
56	0.0512
57	0.072
58	0.1146
59	0.2924
60	0.0042
61	0.0231
62	0.0952
63	0.1385
64	N/A

No.	MerTK
65	0.0783
66	0.2978
67	8.03
68	0.0784
69	0.0204
70	0.184
71	0.0334
72	0.2201
73	0.021
74	0.2181
75	1.076
76	0.0115
77	0.0219
78	0.009
79	0.1556
80	0.0345
81	0.0139
82	0.2163
83	0.0318
84	0.2881
85	0.2211
86	0.0199
87	0.1148
88	0.051
89	0.152
90	0.0131
91	3.911
92	0.0388

No.	MerTK
93	0.3581
94	1.104
95	3.924
96	0.0414
97	0.0691
98	0.0357
99	0.0948
100	0.1126
101	0.2957
102	0.1232
103	0.129
104	0.2893
105	0.3538
106	0.0704
107	0.0582
108	0.17
109	0.0975
110	0.4829
111	0.3795
112	0.4717
113	0.0449
114	0.7434
115	0.5543
116	4.619
117	0.3257
118	N/A
119	15.75
120	0.3523

No.	MerTK
121	0.6202
122	0.1651
123	0.0765
124	0.0362
125	9999
126	9999
127	0.0891
128	0.1263
129	0.0459
130	0.0512
131	0.0546
132	1.555
133	1.672
134	0.3471
135	4.04
136	0.3197
137	0.0196
138	0.0688
139	0.1343
140	0.1474
141	0.1873
142	0.1146
143	13.47
144	0.0573
145	0.0257
146	0.0074
147	0.0467
148	0.0168

No.	MerTK
149	0.0538
150	0.0333
151	0.0646
152	0.0507
153	0.0513
154	0.066
155	0.1495
156	0.1165
157	0.0497
158	0.0948
159	0.0487
160	0.2207
161	0.0259
162	11.9
163	0.1126
164	0.2957
165	0.4007
166	0.1232
167	0.129
168	0.2893
169	0.3538
170	0.0363
171	0.309
172	0.0704
173	0.0582
174	0.17
175	0.0364
176	0.0975

No.	MerTK
177	0.4829
178	0.3795
179	0.1146
180	9999
181	0.2924
182	0.0076
183	13.77
184	5.138
185	0.0287
186	0.0454
187	9999
188	11.32
189	0.0764
190	0.073
191	0.8752
192	4.04

No.	MerTK
193	0.9572
194	0.0336
195	0.0721
196	0.2396
197	0.0977
198	0.0132
199	0.0108
200	11.26
201	0.0725
202	0.0473
203	0.1667
204	0.0577
205	0.2926
206	1.279
207	0.5374
208	0.4153

No.	MerTK
209	0.0139
210	0.0856
211	9999
212	0.0636
213	0.0304
214	0.0105
215	0.0037
216	0.0225
217	0.0041
218	0.0242
219	0.0183
220	0.0112
221	0.0861
222	0.0145
223	0.0143
224	0.0283

No.	MerTK
225	0.021
226	0.0109
227	0.0024
228	0.0266
229	0.072
230	0.1397
231	1.907
232	0.043
233	0.5118
234	9999
235	0.2642
236	0.1301
237	0.2203
238	0.16
239	0.9468

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

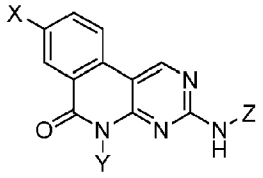
- WO 2012135800 A **[0006]**
- WO 2008077551 PCT, Plettenburg, O. **[0508] [0516]**
- WO 2007077949 PCT, Inoue, T. **[0509] [0510]**

Non-patent literature cited in the description

- **SMITH ; MARCH.** March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure. Wiley-Interscience, 2001 **[0123]**
- **VOGEL.** A Textbook of Practical Organic Chemistry, Including Qualitative Organic Analysis. Longman, 1978 **[0123]**
- Introduction to Modern Liquid Chromatography. John Wiley and Sons, 1979 **[0124]**
- Thin Layer Chromatography. Springer-Verlag, 1969 **[0124]**
- **J. F. W. MCOMIE.** Protective Groups in Organic Chemistry. Plenum Press, 1973 **[0125]**
- **T. W. GREENE ; P. G. M. WUTS.** Protective Groups in Organic Synthesis. Wiley, 1999 **[0125]**
- The Peptides. Academic Press, 1981, vol. 3 **[0125]**
- **HOUBEN-WEYL.** Methoden der organischen Chemie. Georg Thieme Verlag, 1974, vol. 15/1 **[0125]**
- **H.-D. JAKUBKE ; H. JESCHEIT.** Aminosauren, Peptide, Proteine. Verlag Chemie, 1982 **[0125]**
- **JOCHEN LEHMANN.** Chemie der Kohlenhydrate: Monosaccharide and Derivate. Georg Thieme Verlag, 1974 **[0125]**
- *JOC,* 2008, vol. 73, 2052-2057 **[0318] [0506]**
- *JOC,* 2011, vol. 76, 2762-2769 **[0318] [0506]**
- **ZHANG, W. et al.** *J. Med. Chem.,* 2014, vol. 57 (16), 7031 **[0512]**
- **ZHANG, W. et al.** *J. Med. Chem.,* 2013, vol. 56 (23), 9683 **[0513]**

Patentkrav

1. Forbindelse med strukturformel (I):



(I)

eller et farmaceutisk acceptabelt salt eller en farmaceutisk acceptabel *N*-oxid deraf eller et solvat eller hydrat deraf, hvor X er hydrogen, Cak(C_0-C_6alkyl), Hca(C_0-C_6alkyl), Ar(C_0-C_6alkyl) eller Het(C_0-C_6alkyl), hvor Ar, Het, Cak, Hca og alkylgruppen er eventuelt substitueret med en til fire -R^{X1}-grupper, hvor
hver -R^{X1} uafhængigt er halogen, cyano, C_1-C_6alkyl, C_1-C_6halogenalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, -$C(O)NR_2$, -$S(O)_2NR_2$, -$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -OC(O)OR, -$OC(O)NR_2$, -N(R)C(O)OR, -$N(R)C(O)NR_2$, -$N(R)S(O)_2$R, -$OP(O)(OR)_2$, -CH_2-OP(O)(OR), Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) eller Hca(C_0-C_6alkyl),
eller to -R^{X1}-grupper sammen, når de er bundet til tilstødende atomer, danner en Cak, Hca eller Het, hvor Cak Hca og Het omfatter en 3-8-leddet ring, der eventuelt er substitueret med en eller to -R^{X2}-grupper,
eller to -R^{X1}-grupper sammen, når de er bundet til det samme carbonatom, danner en Hca, hvor Hca omfatter en 3-8-leddet ring, der eventuelt er substitueret med en eller to -R^{X2}-grupper,
eller to -R^{X1}-grupper sammen, når de er bundet til ikke-tilstødende atomer, og kombineret med X danner en broforbundet Hca, der eventuelt er substitueret med en eller to -R^{X2}-grupper,
hvor hver -R^{X2} uafhængigt er halogen, cyano, nitro, oxo, -OR, -SR, -NR_2, -C(O)OR, -$C(O)NR_2$, -C(O)R, -S(O)R, -$S(O)_2$R, -S(O)OR, -$S(O)_2$OR, -S(O)NR_2, -$S(O)_2NR_2$, -OC(O)R, -OC(O)OR, -$OC(O)NR_2$, -N(R)C(O)R, -N(R)C(O)OR, -$N(R)C(O)NR_2$, -N(R)S(O)R, -$N(R)S(O)_2$R, C_1-C_6alkyl eller C_1-C_6halogenalkyl;
Y er Cak(C_0-C_6alkyl) eventuelt substitueret med en eller to -R^{Y1}-grupper;
hvor hver -R^{Y1} uafhængigt er halogen, cyano, C_1-C_6alkyl, C_1-C_6halogenalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, -NR_2, -C(O)R, -C(O)OR, C(O)NR_2, -$S(O)_2NR_2$, -$S(O)_2$R, -OC(O)R, -N(R)C(O)R, -

$OC(O)OR$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)(OR)_2$ eller $-CH_2-OP(O)(OR)$;
Z er C_1-C_6alkyl eller Cak(C_0-C_6alkyl), der hver eventuelt er substitueret med en til tre $-R^{Z1}$-grupper;
hvor hver $-R^{Z1}$ uafhængigt er halogen, cyano, C_1-C_6alkyl, C_1-C_6halogenalkyl, $-C_1$-C_6alkoxy, oxo, -OR, -SR, $-NR_2$, -C(O)R, -C(O)OR, $-C(O)NR_2$, $-S(O)_2NR_2$, $-S(O)_2R$, -OC(O)R, -N(R)C(O)R, -OC(O)OR, $-OC(O)NR_2$, -N(R)C(O)OR, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)(OR)_2$ eller $-CH_2-OP(O)(OR)$; og
hver R uafhængigt er hydrogen eller C_1-C_6alkyl,
hvor
Hca er en/et 3-15-leddet ring eller ringsystem, der omfatter mindst én ring og 1-4 O-, S- eller N-atomer, forudsat at intet O eller S er tilstødende et andet O eller S;
Het er en/et 5-15-leddet aromatisk ring eller ringsystem, der omfatter mindst én ring og 1-4 O-, S- eller N-atomer, forudsat at intet O eller S er tilstødende et andet O eller S;
Cak er en/et 3-8-leddet ikke-aromatisk carbocyklisk ring eller ringsystem, der kan være mættet eller delvist umættet; og
Ar er en/et 6-16-leddet aromatisk ring eller ringsystem, der har mindst én carbocyklisk aromatisk ring og eventuelt fusioneret én eller flere aromatiske eller ikke-aromatiske ringe.

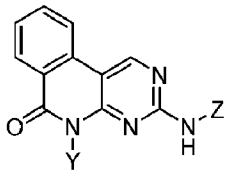
2. Forbindelse ifølge krav 1, der har strukturen med formel (Ie):

(Ie).

3. Forbindelse ifølge krav 2, hvor m er 1, og R^{Y1} er -OH.

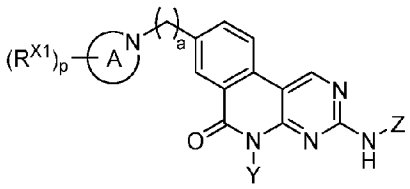
4. Forbindelse ifølge et hvilket som helst af kravene 1-3, hvor X er hydrogen, Cak(C_0-C_6alkyl) eller Hca(C_0-C_6alkyl), hvor hver Cak, Hca og alkylgruppe er eventuelt substitueret med en til tre $-R^{X1}$-grupper.

5. Forbindelse ifølge krav 1, der har strukturen med formel (If):



(If).

6. Forbindelse ifølge krav 1, der har strukturen med formel (II):



(II)

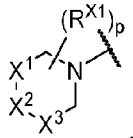
eller et farmaceutisk acceptabelt salt eller en farmaceutisk acceptabel N-oxid deraf eller et solvat eller hydrat deraf, hvor ring A er Hca;

a er 0 eller 1; og

p er 1, 2, 3 eller 4; og

hver $-R^{X1}$ uafhængigt er halogen, cyano, C_1-C_6alkyl, C_1-C_6halogenalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, $-NR_2$, -C(O)R, -C(O)OR, $-C(O)NR_2$, $-S(O)_2NR_2$, $-S(O)_2R$, -OC(O)R, -N(R)C(O)R, -OC(O)OR, $-OC(O)NR_2$, -N(R)C(O)OR, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)(OR)_2$, $-CH_2-OP(O)(OR)$, Ar(C_0-C_6alkyl), Het(C_0-C_6alkyl), Cak(C_0-C_6alkyl) eller Hca(C_0-C_6alkyl).

7. Forbindelse ifølge krav 6, hvor

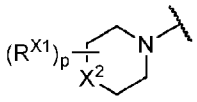
(a) ring A er  , hvor

p er 0, 1, 2, 3 eller 4;

X^1 er -O-, -S-, -S(O)-, $-S(O)_2-$, $-CR^2-$, $-C(R)(R^{X1})-$, $-C(R^{X1})_2-$, -N(R)- eller $-N(R^{X1})-$;

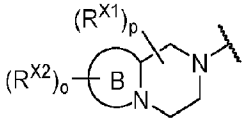
X^2 er -O-, -S-, -S(O)-, $-S(O)_2-$, $-CR^2-$, $-C(R)(R^{X1})-$, $-C(R^{X1})_2-$, -N(R)- eller $-N(R^{X1})-$; og

X^3 er -O-, -S-, -S(O)-, $-S(O)_2-$, $-CR^2-$, $-C(R)(R^{X1})-$, $-C(R^{X1})_2-$, -N(R)- eller $-N(R^{X1})-$;

(b) ring A er  , hvor

p er 0, 1, 2, 3 eller 4;

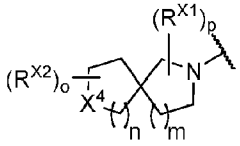
X^2 er -O-, -S-, -S(O)-, $-S(O)_2$-, $-CR^2$-, $-C(R)(R^{X1})$-, $-C(R^{X1})_2$-, -N(R)- eller $-N(R^{X1})$-;

(c) ring A er  , hvor

p er 0, 1 eller 2;

o er 0, 1 eller 2; og

ring B er Hca eller Het, der hver omfatter en 3-8-leddet ring, der eventuelt er substitueret med en eller to $-R^{X2}$-grupper;

(d) ring A er  , hvor

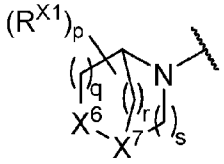
p er 0, 1 eller 2;

o er 0, 1 eller 2;

n er 0, 1 eller 2;

m er 0, 1 eller 2; og

X^4 er -O-, -S-, -S(O)-, $-S(O)_2$-, $-CR^2$-, $-C(R)(R^{X1})$-, $-C(R^{X1})_2$-, -N(R)- eller $-N(R^{X1})$-;

(e) ring A er  , hvor

X^6 er -O-, -S-, -S(O)-, $-S(O)_2$-, $-CR^2$-, $-C(R)(R^{X1})$-, $-C(R^{X1})_2$-, -N(R)- eller $-N(R^{X1})$-; og

X^7 er -CR-, $-C(R^{X1})$- eller -N-;

p er 0, 1 eller 2;

q er 0, 1 eller 2;

r er 0, 1 eller 2; og

s er 0, 1 eller 2.

8. Forbindelse ifølge et hvilket som helst af kravene 1-7, hvor

(a) Z er C_1-C_6alkyl eventuelt substitueret med en til tre $-R^{Z1}$-grupper;

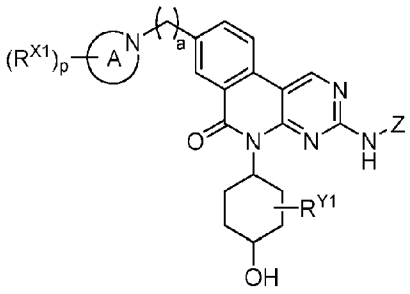
hvor hver $-R^{Z1}$ uafhængigt er halogen, C_1-C_6alkyl eller C_1-C_6halogenalkyl;
eller Z er C_1-C_6alkyl eventuelt substitueret med en til tre $-R^{Z1}$-grupper;
hvor hver $-R^{Z1}$ uafhængigt er halogen, cyano, C_1-C_6alkyl, C_1-C_6halogenalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, $-NR_2$, -C(O)R, -C(O)OR, $C(O)NR_2$, $-S(O)_2NR_2$, $-S(O)_2R$, -OC(O)R, -N(R)C(O)R, -OC(O)OR, $-OC(O)NR_2$, -N(R)C(O)OR, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)(OR)_2$ eller $-CH_2$-OP(O)(OR);
eller Z er C_1-C_6alkyl eventuelt substitueret med en til tre $-R^{Z1}$-grupper;
hvor hver $-R^{Z1}$ uafhængigt er halogen, C_1-C_6alkyl eller C_1-C_6halogenalkyl;
(b) Z er Cak(C_0-C_6alkyl) eventuelt substitueret med en til tre $-R^{Z1}$-grupper;
hvor hver $-R^{Z1}$ uafhængigt er halogen, cyano, C_1-C_6alkyl, C_1-C_6halogenalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, $-NR_2$, -C(O)R, -C(O)OR, -$C(O)NR_2$, $-S(O)_2NR_2$, $-S(O)_2R$, -OC(O)R, -N(R)C(O)R, -OC(O)OR, $-OC(O)NR_2$, -N(R)C(O)OR, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)(OR)_2$ eller $-CH_2$-OP(O)(OR)
eller Z er Cak(C_0-C_6alkyl) eventuelt substitueret med en til tre $-R^{Z1}$-grupper;
hvor hver $-R^{Z1}$ uafhængigt er halogen, C_1-C_6alkyl eller C_1-C_6halogenalkyl;
(c) Z er Cak eventuelt substitueret med en til tre $-R^{Z1}$-grupper;
hvor hver $-R^{Z1}$ uafhængigt er halogen, cyano, C_1-C_6alkyl, C_1-C_6halogenalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, $-NR_2$, -C(O)R, -C(O)OR, -$C(O)NR_2$, $-S(O)_2NR_2$, $-S(O)_2R$, -OC(O)R, -N(R)C(O)R, -OC(O)OR, $-OC(O)NR_2$, -N(R)C(O)OR, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)(OR)_2$ eller $-CH_2$-OP(O)(OR);
eller Z er Cak eventuelt substitueret med en til tre $-R^{Z1}$-grupper;
hvor hver $-R^{Z1}$ uafhængigt er halogen, C_1-C_6alkyl eller C_1-C_6halogenalkyl; eller
(d) Z er Cak(C_1alkyl) eventuelt substitueret med en til tre $-R^{Z1}$-grupper;
hvor hver $-R^{Z1}$ uafhængigt er halogen, cyano, C_1-C_6alkyl, C_1-C_6halogenalkyl, -C_1-C_6alkoxy, oxo, -OR, -SR, $-NR_2$, -C(O)R, -

$C(O)OR$, $-C(O)NR_2$, $-S(O)_2NR_2$, $-S(O)_2R$, $-OC(O)R$, $-N(R)C(O)R$, $-OC(O)OR$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)(OR)_2$ eller $-CH_2-OP(O)(OR)$;

eller Z er Cak(C_1alkyl) eventuelt substitueret med en til tre $-R^{Z1}$-grupper;

hvor hver $-R^{Z1}$ uafhængigt er halogen, C_1-C_6alkyl eller C_1-C_6halogenalkyl.

9. Forbindelse ifølge krav 1, der har strukturen med formel (III):

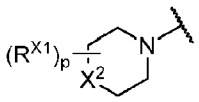


(III)

eller et farmaceutisk acceptabelt salt eller en farmaceutisk acceptabel N-oxid deraf eller et solvat eller hydrat deraf, hvor

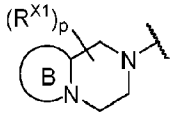
a er 0 eller 1;

ring A er

(a)  , hvor

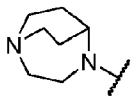
p er 0, 1, 2 eller 3;

X^2 er $-O-$, $-S-$, $-CR_2-$, $-C(R)(R^{X1})-$, $-C(R^{X1})_2-$, $-N(R)-$ eller $-N(R^{X1})-$;

(b)  , hvor

p er 0, 1 eller 2;

ring B er 5-leddet Hca eller Het; eller

(c)  ;

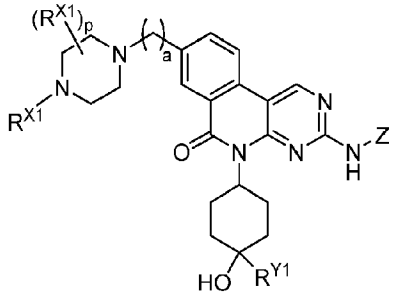
hver $-R^{X1}$ uafhængigt er hydrogen, C_1-C_6alkyl, $-C(O)OR$, Cak(C_0-C_6alkyl) eller Hca(C_0-C_6alkyl);

$-R^{Y1}$ er hydrogen eller C_1-C_6alkyl;

Z er C_1-C_6alkyl eller Cak(C_1-C_6alkyl); og

hver R uafhængigt er hydrogen eller C_1-C_6alkyl.

10. Forbindelse ifølge krav 1, der har strukturen med formel (IV):



(IV)

eller et farmaceutisk acceptabelt salt eller en farmaceutisk acceptabel N-oxid deraf eller et solvat eller hydrat deraf, hvor a er 0 eller 1;
hver $-R^{X1}$ uafhængigt er hydrogen eller C_1-C_6alkyl;
$-R^{Y1}$ er hydrogen eller C_1-C_6alkyl; og
Z er C_1-C_6alkyl eller Cak(C_1-C_6alkyl).

11. Forbindelse ifølge krav 1, som er:
trans-3-((2,2-difluorbutyl)amino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
cis-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
cis-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
3-(butylamino)-5-((4-hydroxycyclohexyl)methyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
tert-butyl(4-((3-(butylamino)-8-(morpholinomethyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)methyl)cyclohexyl)carbamat;

tert-butyl(4-((3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)methyl)cyclohexyl)carbamat;
5-((4-aminocyclohexyl)methyl)-3-(butylamino)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
5-((4-aminocyclohexyl)methyl)-3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-amino-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((3,3-difluorcyclobutyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((3-fluorcyclobutyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
3-(butylamino)-5-(6-hydroxyspiro[3.3]heptan-2-yl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(butylamino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
cis-3-(butylamino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(((1-ethylcyclobutyl)methyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(((1-ethylcyclobutyl)methyl)amino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(((1-ethylcyclobutyl)methyl)amino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;

trans-3-((cyclobutylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(((1-ethylcyclopropyl)methyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(((1-ethylcyclopropyl)methyl)amino)-5-((4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((2,2-difluorbutyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)-3-((4,4,4-trifluorbutyl)amino)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((2-cyclopropylethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((2-cyclopropylethyl)amino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((2-cyclopropylethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-isopropylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-isopropylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((2-cyclopropylethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-isopropylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclobutylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-isopropylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;

trans-3-((cyclobutylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-(oxetan-3-yl)piperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-(oxetan-3-yl)piperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-8-((5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazin-7(8H)-yl)methyl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-(2,2,2-trifluorethyl)piperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-(3-(butylamino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclohexan-1-carbonitril;
trans-5-(4-hydroxycyclohexyl)-3-(isopentylamino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-8-((4-(2,2-difluorethyl)piperazin-1-yl)methyl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-(piperazin-1-ylmethyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-(morpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;

trans-3-((cyclopropylmethyl)amino)-8-(((S)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)methyl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-8-(((R)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)methyl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-8-((1,1-dioxidothiomorpholino)methyl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-ethyl-1-((3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methyl)piperidin-4-carboxylat;
trans-4-((3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-6-oxo-5,6-dihydropyrimido[4,5-c]isoquinolin-8-yl)methyl)-1,4-diazabicyclo[3.2.2]nonan-1-oxid;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((1-oxidothiomorpholino)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(thiomorpholinomethyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(piperazin-1-ylmethyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-8-(((R)-3,4-dimethylpiperazin-1-yl)methyl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-5-(4-Hydroxycyclohexyl)-3-(isobutylamino)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
3-(butylamino)-5-((1*S*,4*S*)-4-hydroxycycloheptyl)-8-((4-methylpiperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-8-((1,4-diazabicyclo[3.2.2]nonan-4-yl)methyl)-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-4-(3-((cyclopropylmethyl)amino)-8-((4-methylpiperazin-1-yl)methyl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)cyclohexylcarbamat;

trans-8-((4-(tert-butyl)piperazin-1-yl)methyl)-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-morpholinopyrimido[4,5-c]isoquinolin-6(5H)-on;
cis-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
tert-butyl(4-((3-(butylamino)-8-(4-methylpiperazin-1-yl)-6-oxopyrimido[4,5-c]isoquinolin-5(6H)-yl)methyl)cyclohexyl)carbamat;
5-((4-aminocyclohexyl)methyl)-3-(butylamino)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((3,3-difluorcyclobutyl)amino)-5-(4-hydroxycyclohexyl)-8-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((3,3-difluorcyclobutyl)amino)-5-(4-hydroxycyclohexyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-(4-isopropylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
3-(butylamino)-8-(4-isopropylpiperazin-1-yl)-5-(4-oxocyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-(4-(pyrrolidin-1-yl)piperidin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
3-(butylamino)-5-(4-oxocyclohexyl)-8-(4-(pyrrolidin-1-yl)piperidin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(butylamino)-8-((S)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-5-((1r,4S)-4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((3-fluorcyclobutyl)amino)-5-(4-hydroxycyclohexyl)-8-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;

trans-3-((3-fluorcyclobutyl)amino)-5-(4-hydroxycyclohexyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(butylamino)-8-((R)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-(4-(oxetan-3-yl)piperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-((2S,5R)-2,4,5-trimethylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
3-(butylamino)-5-(4-oxocyclohexyl)-8-((2S,5R)-2,4,5-trimethylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(butylamino)-8-(5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazin-7(8H)-yl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-8-(1,4-diazabicyclo[3.2.2]nonan-4-yl)-3-(butylamino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
8-(1,4-diazabicyclo[3.2.2]nonan-4-yl)-3-(butylamino)-5-(4-oxocyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(butylamino)-5-(4-hydroxycyclohexyl)-8-(piperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
3-(butylamino)-5-(4-oxocyclohexyl)-8-(piperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((3,3-difluorcyclobutyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(butylamino)-5-(4-hydroxy-4-methylcyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
3-(butylamino)-5-(6-hydroxyspiro[3.3]heptan-2-yl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
cis-3-(butylamino)-5-(4-hydroxy-4-methylcyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(butylamino)-8-((R)-3,4-dimethylpiperazin-1-yl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;

trans-3-(((1-ethylcyclobutyl)methyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclobutylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((2,2-difluorbutyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(((1-ethylcyclopropyl)methyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)-3-((4,4,4-trifluorbutyl)amino)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((2-cyclopropylethyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((2-cyclopropylethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)-8-(4-methylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-(pyrrolidin-1-yl)piperidin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-8-(1,4-diazabicyclo[3.2.2]nonan-4-yl)-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-8-(5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazin-7(8H)-yl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-8-((S)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-8-((*R*)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;

trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-(2,2,2-trifluorethyl)piperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-8-(4-(2,2-difluorethyl)piperazin-1-yl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-8-((*R*)-3,4-dimethylpiperazin-1-yl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((2*S*,5*R*)-2,4,5-trimethylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(piperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-isopropylpiperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-8-(4-cyclopropylpiperazin-1-yl)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-(4-(oxetan-3-yl)piperazin-1-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
3-(butylamino)-5-(6-hydroxyspiro[3.3]heptan-2-yl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(butylamino)-5-(4-hydroxy-4-methylcyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
cis-3-(butylamino)-5-(4-hydroxy-4-methylcyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-(((1-ethylcyclobutyl)methyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclobutylmethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
3-(((1-ethylcyclopropyl)methyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;

trans-3-((2,2-difluorbutyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((2-cyclopropylethyl)amino)-5-(4-hydroxycyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((2-cyclopropylethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclobutylmethyl)amino)-5-(4-hydroxy-4-methylcyclohexyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
trans-3-((cyclopropylmethyl)amino)-5-(4-hydroxycyclohexyl)-8-((4-(pyridin-4-yl)piperazin-1-yl)methyl)pyrimido[4,5-c]isoquinolin-6(5H)-on;
eller et farmaceutisk acceptabelt salt eller en farmaceutisk acceptabel N-oxid deraf eller et solvat eller hydrat deraf.

12. Farmaceutisk sammensætning, som omfatter et farmaceutisk acceptabelt fortyndingsmiddel, bæremateriale eller hjælpestof og en forbindelse ifølge et hvilket som helst af kravene 1-11.

13. Forbindelse ifølge et hvilket som helst af kravene 1-11 eller sammensætning ifølge krav 12 til anvendelse til behandling af hæmatologiske neoplasmer, fortrinsvis akut myeloid leukæmi AML, eventuelt i kombination med administration af en terapeutisk effektiv mængde af et eller flere kemoterapeutiske midler.