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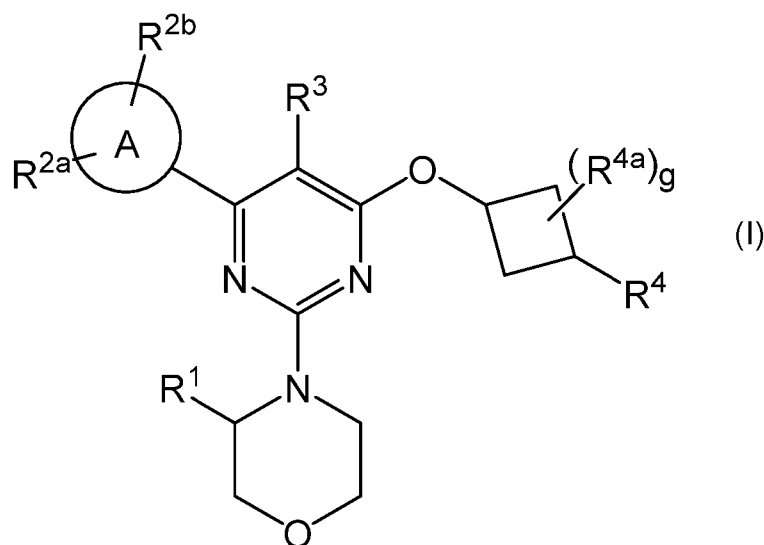
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Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i))
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

[Continued on next page]

(54) Title: PYRIMIDINE DERIVATIVES AS PI3K INHIBITORS FOR USE IN THE TREATMENT OF CANCER



(57) Abstract: The present inventions relates to compounds of formula (I) or pharmaceutically acceptable salts thereof, wherein ring A, R¹, R^{2a}, R^{2b}, R³, R⁴, R^{4a}, R⁵-R²³, g, j, m, n, x, y, and z are defined herein. The novel pyrimidine derivatives are useful in the treatment of abnormal cell growth, such as cancer, in mammals. Additional embodiments relate to pharmaceutical compositions containing the compounds and to methods of using the compounds and compositions in the treatment of abnormal cell growth in mammals.

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PYRIMIDINE DERIVATIVES

This application claims the benefit of U. S. Provisional Application No. 62/019,380 filed on June 30, 2014 and U. S. Provisional Application No. 62/163,947 filed on May 19, 2015, the contents of which is hereby incorporated by reference in its entirety.

Field of the Invention

The present invention relates to novel pyrimidine derivatives that are useful in the treatment of abnormal cell growth, such as cancer, in mammals. The present invention also relates to pharmaceutical compositions containing the compounds and to methods of using the compounds and compositions in the treatment of abnormal cell growth in mammals.

Background of the Invention

Phosphoinositide 3-kinases ("PI3Ks") comprise a family of lipid kinases that catalyze the synthesis of the phosphatidylinositol ("PI") second messengers PI(3)P ("PIP"), PI(3,4)P₂ ("PIP₂"), and PI(3,4,5)P₃ ("PIP₃"). (Fruman *et al.*, "Phosphoinositide kinases", *Annu. Rev. Biochem.* **67** (1998), pp. 481-507; Knight *et al.*, "A Pharmacological Map of the PI3-K Family Defines a Role for p110α in Insulin Signaling", *Cell* **125** (2006), pp. 733-747.) In the appropriate cellular context, these lipids mediate diverse physiological processes including cell growth, survival, differentiation, and chemotaxis. (Katso *et al.*, "Cellular function of phosphoinositide 3-kinases: implications for development, homeostasis, and cancer", *Annu. Rev. Cell Dev. Biol.* **17** (2001), pp. 615 - 675.) The PI3K family comprises at least 15 different lipid and serine/threonine kinases, sub-classified by structural homology, with distinct substrate specificities, expression patterns, and mode of regulation. Class I PI3Kα is the main PI3-kinase isoform in cancer, and consists of catalytic (p110α) and adapter (p85) subunits. (Stirdivant *et al.*, "Cloning and mutagenesis of the p110α subunit of human phosphoinositide 3'-hydroxykinase", *Bioorg. Med. Chem.* **5** (1997), pp. 65-74.)

The 3-phosphorylated phospholipid, PIP₃, acts as a second messenger recruiting kinases with lipid binding domains (including plekstrin homology ("PH") regions), such as Akt, the product of the human homologue of the viral oncogene *v-Akt*, and

phosphoinositide-dependent kinase-1 ("PDK1"). (Vivanco & Sawyers, "The Phosphatidylinositol 3-Kinase-Akt Pathway In Human Cancer", *Nature Reviews Cancer* **2** (2002), pp. 489-501.) Binding of Akt to PIP₃ induces Akt to translocate to the plasma membrane, bringing Akt into contact with PDK1, which activates Akt. The tumor-suppressor phosphatase, PTEN, dephosphorylates PIP₃, and therefore acts as a negative regulator of Akt activation. The PI3Ks, Akt and PDK1 are important in the regulation of many cellular processes including cell cycle regulation, proliferation, survival, apoptosis and motility and are significant components of the molecular mechanisms of diseases such as cancer, diabetes and immune inflammation.

Functional loss of PTEN (the most commonly mutated tumor-suppressor gene in cancer after p53), oncogenic mutations in the PIK3CA gene encoding PI3K α , amplification of the PIK3CA gene and overexpression of Akt have been established in many malignancies (see, for example, Samuels, *et al.*, "High frequency of mutations of the PIK3CA gene in human cancers", *Science* **304** (2004), p. 554; Broderick *et al.*, "Mutations in PIK3CA in anaplastic oligodendrogliomas, high-grade astrocytomas, and medulloblastomas", *Cancer Research* **64** (2004), pp.5048-5050). Therefore, the deregulation of PI3k and the upstream and downstream components of this signaling pathway is one of the most common deregulations associated with human cancers and proliferative diseases. (Parsons *et al.*, *Nature*, **436** (2005), p. 792; Hennessey *et al.*, *Nature Rev. Drug Disc.* **4** (2005) 988-1004.)

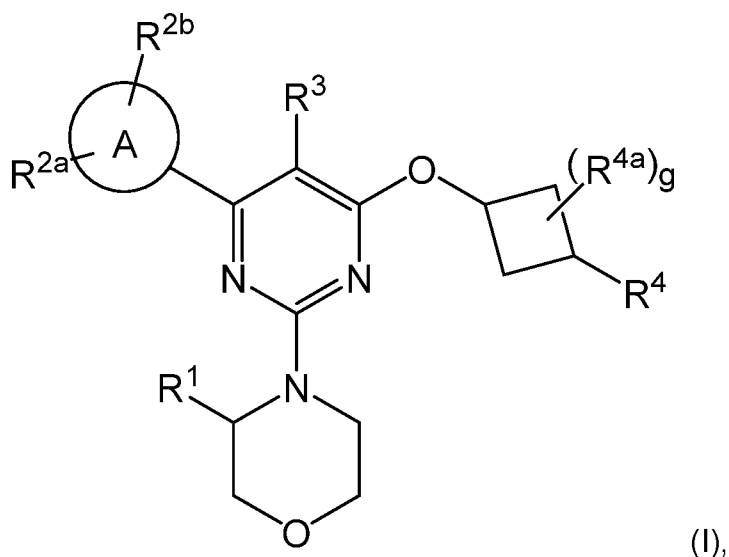
PI3K α is thus an attractive target for cancer drug development because PI3K α inhibitors would be expected to inhibit proliferation and summon resistance to cytotoxic agents in cancer cells.

Summary of the Invention

Each of the embodiments described below can be combined with any other embodiment described herein not inconsistent with the embodiment with which it is combined. Furthermore, each of the embodiments described herein envisions within its scope the pharmaceutically acceptable salts of the compounds described herein.

Accordingly, the phrase "or a pharmaceutically acceptable salt thereof" is implicit in the description of all compounds described herein.

Embodiments described herein relate to a compound of formula (I)



or a pharmaceutically acceptable salt thereof,
wherein

R^1 is hydrogen or methyl;

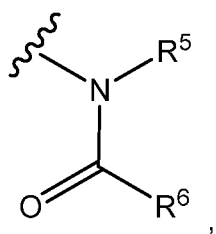
5 ring A is 6 membered heteroaryl;

R^{2a} and R^{2b} are each independently hydrogen, halogen, -CN, C_1 - C_4 alkyl, -CHF₂, -CF₃, hydroxy, methoxy, -NH₂, or C_3 - C_4 cycloalkyl;

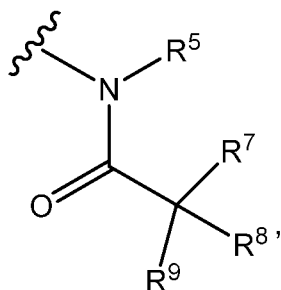
R^3 is hydrogen, halogen, -CN, C_1 - C_3 alkyl, -CF₃, or methoxy;

R^4 is

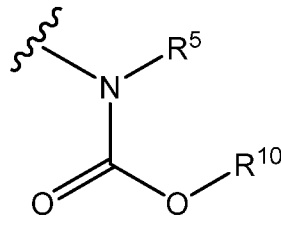
(a)



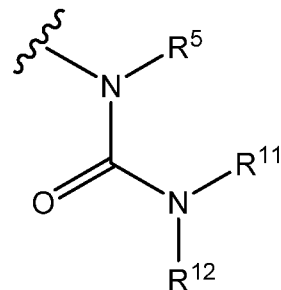
(b)



(c)

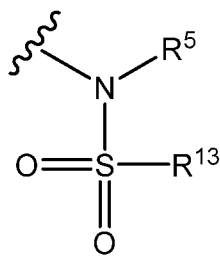


(d)

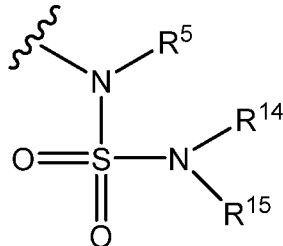


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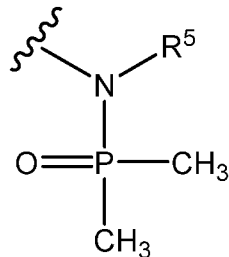
(e)



(f)



(g)



, or (CH₂)_j-

N(R¹⁶)(R¹⁷);

each R^{4a} is independently fluorine, -CN, methyl, hydroxy, or methoxy;

R^5 is hydrogen, C_1 - C_3 alkyl, or C_3 - C_4 cycloalkyl;

R^6 is hydrogen, phenyl, or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl is optionally substituted by methyl, $-(CH_2)_2OH$, or $-(CH_2)_2CN$;

5 R^7 is hydrogen, -CN, C_1 - C_4 alkyl, $-CF_3$, $-N(R^{18})(R^{19})$, $-SO_2(C_1$ - C_3 alkyl), C_3 - C_6 cycloalkyl, 4-6 membered heterocycloalkyl, $-(CH_2)_m$ -(phenyl), or $-(CH_2)_n$ -(5-10 membered heteroaryl), wherein the C_1 - C_4 alkyl is optionally substituted by hydroxy, further wherein the C_3 - C_6 cycloalkyl and the 4-6 membered heterocycloalkyl are each independently optionally substituted by one or two R^{20} groups, even further wherein the
10 $-(CH_2)_m$ -(phenyl) and the $-(CH_2)_n$ -(5-10 membered heteroaryl) are each independently optionally substituted by one or two substituents selected from the group consisting of halogen, -CN, methyl, $-CF_3$, C_1 - C_3 alkoxy, $-NH_2$, and cyclopropyl;

R^8 is hydrogen, methyl, hydroxy, methoxy, or NH_2 ,

provided that R^8 cannot be hydroxy, methoxy or NH_2 , when R^7 is $-N(R^{18})(R^{19})$;

15 R^9 is hydrogen or C_1 - C_6 alkyl,

provided that R^7 may form a 5-6 membered heterocycloalkyl ring with R^5 , R^7 may form a C_3 - C_6 cycloalkyl ring or a 4-8 membered heterocycloalkyl ring with R^9 , or R^8 may form a C_3 - C_6 cycloalkyl ring with R^9 , wherein the 5-6 membered heterocycloalkyl ring, the C_3 - C_6 cycloalkyl ring, and the 4-8 membered heterocycloalkyl ring formed are each
20 independently optionally substituted by one or two R^{20} groups;

R^{10} and R^{11} are each independently C_1 - C_4 alkyl, $-(CH_2)_x$ -(C_3 - C_5 cycloalkyl), $-(CH_2)_y$ -(4-6 membered heterocycloalkyl), or $-(CH_2)_z$ -(5-6 membered heteroaryl), wherein the C_1 - C_4 alkyl is optionally substituted by one or two substituents selected from the group consisting of fluorine, -CN, $-CF_3$, C_1 - C_3 alkoxy, and $-N(R^{18})(R^{19})$, further
25 wherein the $-(CH_2)_x$ -(C_3 - C_5 cycloalkyl) is optionally substituted by one or two fluorine atoms, even further wherein the $-(CH_2)_y$ -(4-6 membered heterocycloalkyl) and the $-(CH_2)_z$ -(5-6 membered heteroaryl) are each independently optionally substituted by one or two substituents selected from the group consisting of fluorine, -CN, methyl, hydroxy, methoxy, and $-N(R^{18})(R^{19})$,

30 provided that R^{10} or R^{11} may form a 4-7 membered heterocycloalkyl ring with R^5 , wherein the 4-7 membered heterocycloalkyl ring formed is optionally substituted by one or two R^{20} groups;

R^{12} is hydrogen or C_1 - C_4 alkyl,

provided that R^{11} and R^{12} may form a 4-8 membered heterocycloalkyl ring, wherein the 4-8 membered heterocycloalkyl ring formed is optionally substituted by one or two R^{21} groups, further wherein a carbon atom of the 4-8 membered heterocycloalkyl ring formed is optionally replaced by a nitrogen atom or an oxygen atom;

5 R^{13} is C_1 - C_4 alkyl or C_3 - C_6 cycloalkyl,

provided that R^{13} may form a 5-6 membered heterocycloalkyl ring with R^5 , wherein the 5-6 membered heterocycloalkyl ring formed is optionally substituted by one or two R^{20} groups;

10 R^{14} and R^{15} are each independently hydrogen, C_1 - C_3 alkyl, or C_3 - C_4 cycloalkyl, provided that R^{14} may form a 5-6 membered heterocycloalkyl ring with R^5 or R^{14} and R^{15} may form a 4-8 membered heterocycloalkyl ring, wherein the 5-6 membered heterocycloalkyl ring formed is optionally substituted by one or two R^{20} groups, further wherein the 4-8 membered heterocycloalkyl ring formed is optionally substituted by one or two R^{21} groups, even further wherein a carbon atom of the 4-8 membered
15 heterocycloalkyl ring formed is optionally replaced by a nitrogen atom or an oxygen atom;

R^{16} and R^{17} are each independently hydrogen or C_1 - C_3 alkyl,

provided that R^{16} and R^{17} may form a 4-6 membered heterocycloalkyl ring, wherein the 4-6 membered heterocycloalkyl ring formed is optionally substituted by one
20 or two R^{20} groups, further wherein one carbon of the 4-6 membered heterocycloalkyl ring formed may be optionally replaced with an oxygen atom;

each R^{18} and R^{19} is independently hydrogen or methyl,

provided that R^{18} and R^{19} may form a 4-8 membered heterocycloalkyl ring, wherein the 4-8 membered heterocycloalkyl ring formed is optionally substituted by one
25 or two substituents selected from the group consisting of =O, fluorine, -CN, methyl, -CF₃, hydroxy, methoxy, and -N(R^{22})(R^{23}), further wherein a carbon atom of the 4-8 membered heterocycloalkyl ring formed is optionally replaced by a nitrogen atom or an oxygen atom;

each R^{20} is independently fluorine, -CN, methyl, -CF₃, hydroxy, and methoxy;

30 each R^{21} is independently =O, fluorine, -CN, methyl, -CF₃, hydroxy, methoxy, and -N(R^{18})(R^{19});

each R^{22} and R^{23} is independently hydrogen or methyl,

provided that R^{22} and R^{23} may form a 4-8 membered heterocycloalkyl ring, wherein the 4-8 membered heterocycloalkyl ring formed is optionally substituted by one or two substituents selected from the group consisting of =O, fluorine, -CN, methyl, -CF₃, hydroxy, methoxy, -NH₂, -NHCH₃ and -N(CH₃)₂, further wherein a carbon atom of the 4-8 membered heterocycloalkyl ring formed is optionally replaced by a nitrogen atom or an oxygen atom;

g is 0, 1, 2, 3, or 4;

j is 0, 1, or 2;

m is 0, 1, or 2;

n is 0 or 1;

x is 0 or 1;

y is 0, 1, or 2; and

z is 0 or 1.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 is methyl.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein ring A is 6-membered heteroaryl.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein ring A is pyridine.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein ring A is pyrimidine.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^{2a} is hydrogen.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^{2a} is -NH₂.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^{2b} is hydrogen, halogen, C₁-C₄ alkyl, -CHF₂, or -CF₃.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^{2b} is hydrogen.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein g is 0.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein g is 1.

5 Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R⁵ is hydrogen or C₁-C₃ alkyl.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R⁵ is hydrogen.

10 Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R⁵ is methyl.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R⁶ is hydrogen.

15 Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R⁶ is 5-6 membered heteroaryl optionally substituted by methyl, -(CH₂)₂OH, or -(CH₂)₂CN.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R⁷ is hydrogen, -CN, C₁-C₄ alkyl, -CF₃, -NH₂, or -SO₂CH₃.

20 Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R⁷ is C₃-C₆ cycloalkyl.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R⁷ is -(CH₂)_m-(phenyl) or -(CH₂)_n-(5-10 membered heteroaryl), wherein the -(CH₂)_n-(5-10 membered heteroaryl) is optionally substituted by one or two substituents selected from the group consisting of halogen and methyl.

25 Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R⁷ is hydrogen.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R⁷ is C₁-C₄ alkyl.

30 Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R⁷ is methyl.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R⁸ is hydrogen, methyl, hydroxy, or methoxy.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^8 is hydrogen.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^8 is methyl.

5 Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^8 is hydroxy.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^9 is hydrogen.

10 Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^9 is methyl.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^9 is ethyl.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^7 is hydrogen, R^8 is hydrogen, and R^9 is hydrogen.

15 Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^7 is hydrogen, R^8 is hydroxy, and R^9 is hydrogen.

Some embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^7 is C_1 - C_4 alkyl, R^8 is hydroxy, and R^9 is hydrogen.

20 Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^7 and R^9 form a C_3 - C_6 cycloalkyl ring optionally substituted by one or two fluorine groups.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^7 and R^9 form a 4-6 membered heterocycloalkyl ring.

25 Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^8 and R^9 form a C_3 - C_6 cycloalkyl ring optionally substituted by one or two substituents selected from the group consisting of fluorine, -CN, and methyl.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^{10} is C_1 - C_4 alkyl.

30 Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^{10} is methyl.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^{10} is C_3 - C_5 cycloalkyl.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^{10} and R^5 form a 5-6 membered heterocycloalkyl ring.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^{11} is C_1 - C_4 alkyl or $-(CH_2)_x$ -(C_3 - C_5 cycloalkyl), further
 5 wherein the C_1 - C_4 alkyl is optionally substituted by one or two substituents selected from the group consisting of fluorine, -CN, $-CF_3$, C_1 - C_3 alkoxy, and $-N(CH_3)_2$, even further wherein the $-(CH_2)_x$ -(C_3 - C_5 cycloalkyl) is optionally substituted by one or two fluorine atoms.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^{11} is $-(CH_2)_y$ -(4-6 membered heterocycloalkyl) optionally substituted by methyl.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^{11} is $-(CH_2)_z$ -(5-6 membered heteroaryl) optionally substituted by methyl.

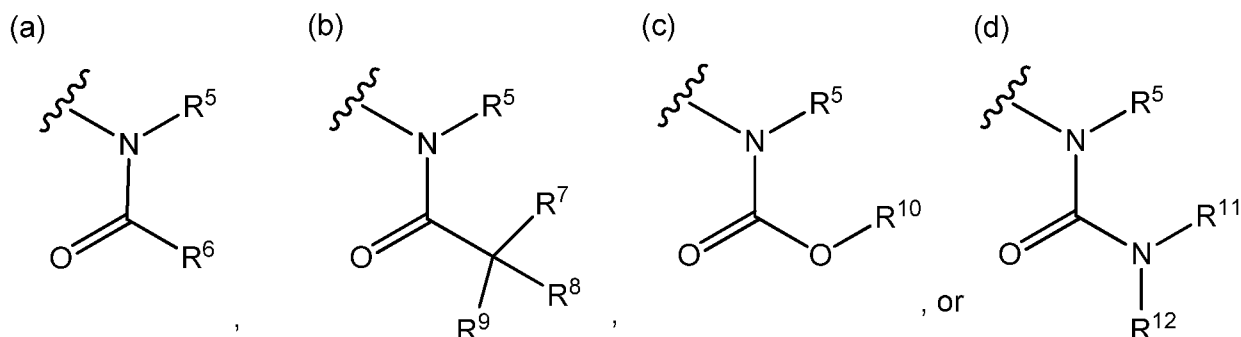
15 Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^{12} is hydrogen.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^{12} is methyl.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^{11} and R^{12} form a 4-6 membered heterocycloalkyl ring optionally substituted by one or two substituents selected from the group consisting of fluorine, -CN, methyl, and hydroxy.

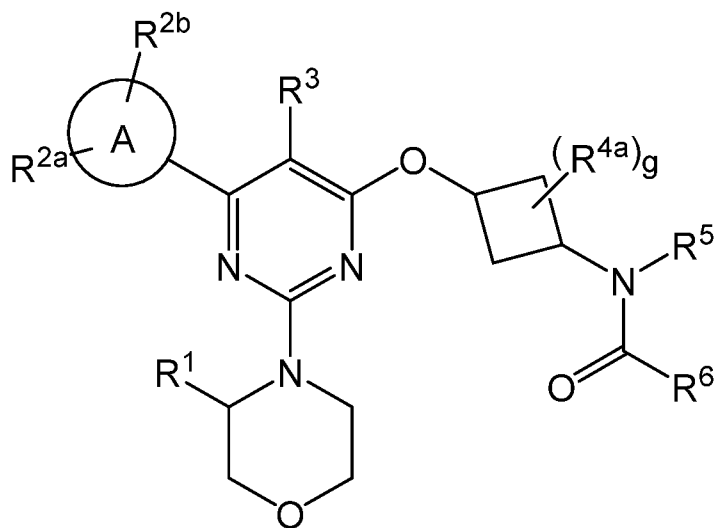
Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^{11} and R^5 form a 5-6 membered heterocycloalkyl ring.

25 Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^4 is



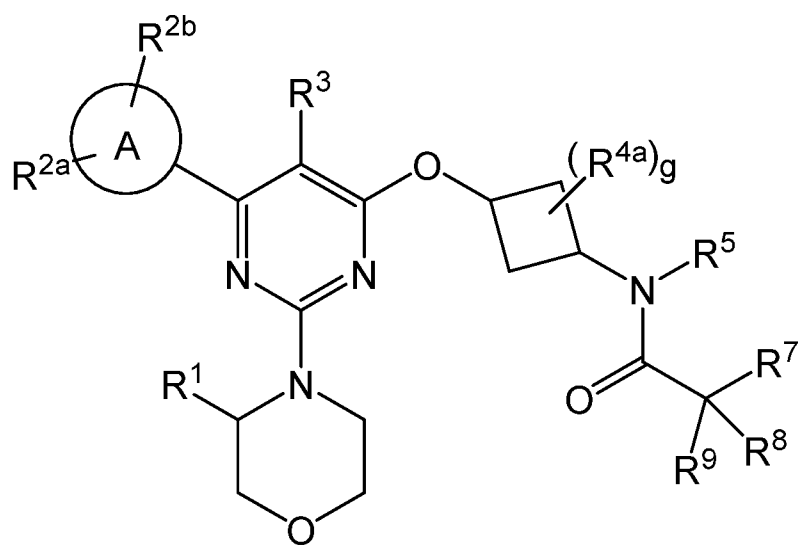
Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^4 is $-(CH_2)_j-N(R^{16})(N^{17})$.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, having formula (Ia)



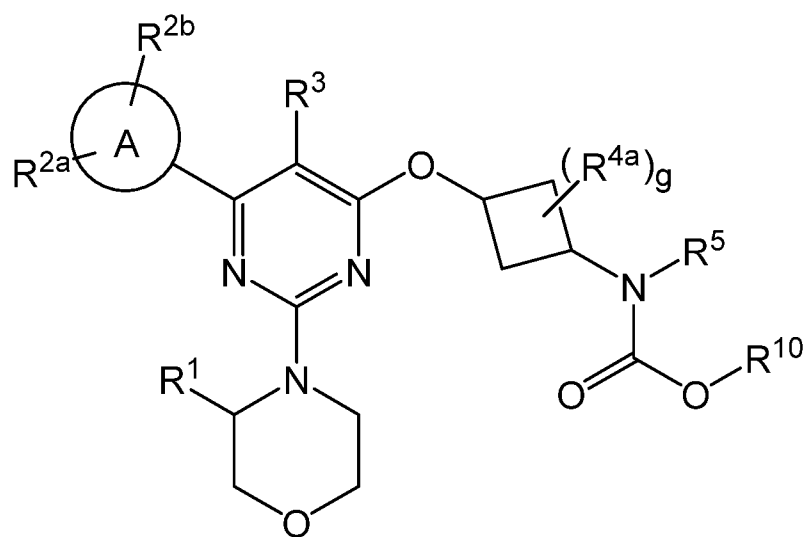
(Ia).

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, having formula (Ib)

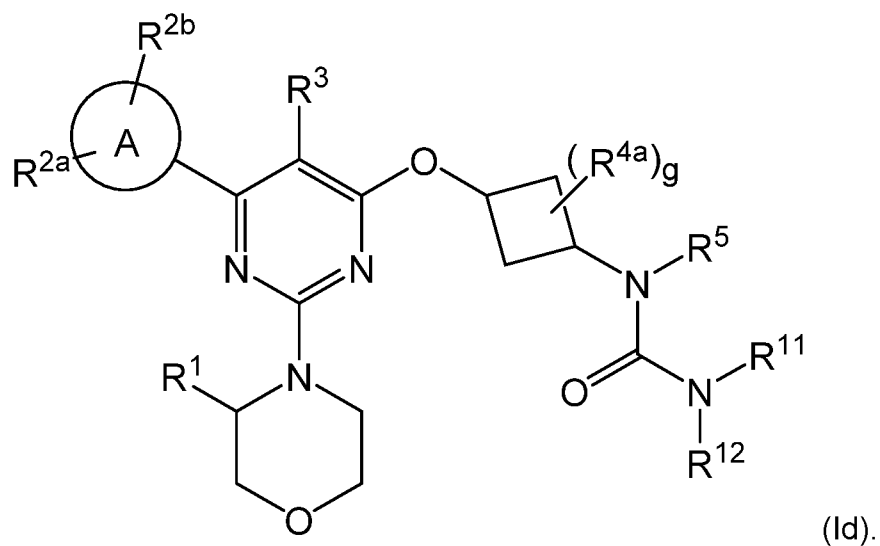


(Ib).

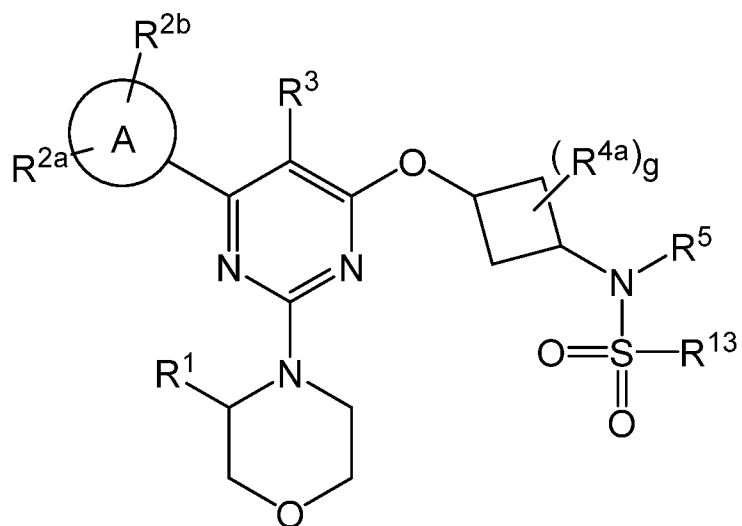
Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, having formula (Ic)



Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, having formula (Id)

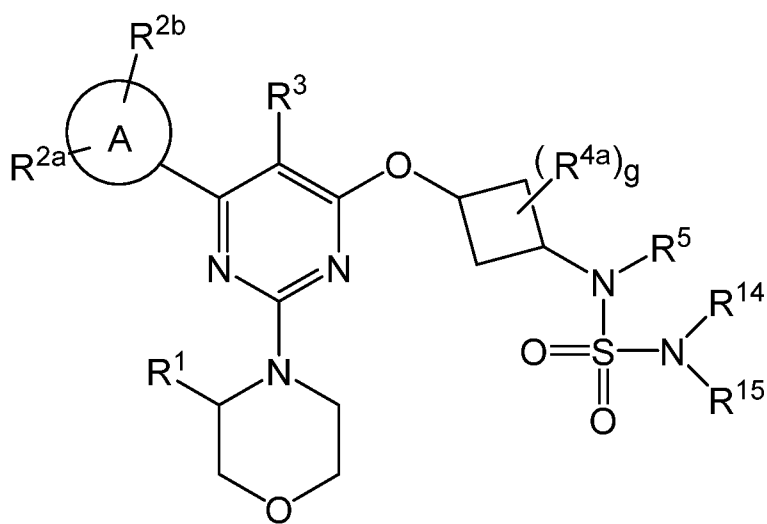


5 Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, having formula (Ie)



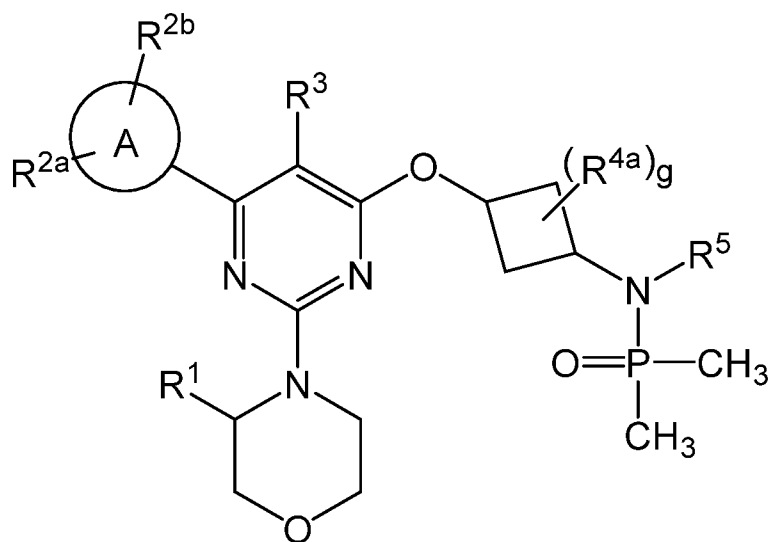
(Ie).

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, having formula (If)



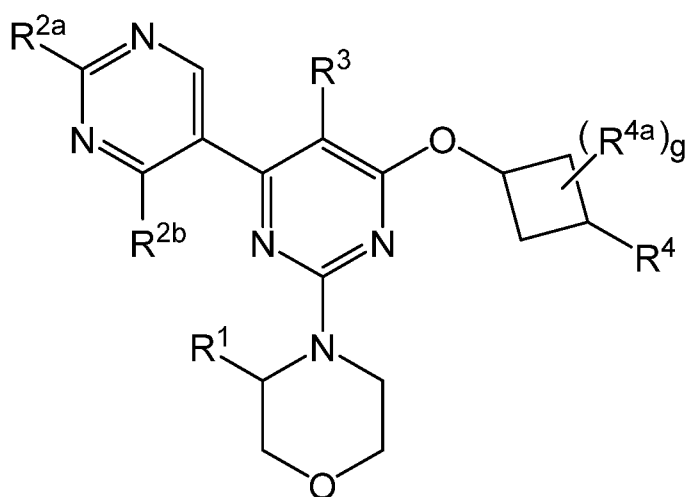
(If).

- 5 Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, having formula (Ig)



(Ig).

Embodiments described herein relate to a compound of formula (II)



(II)

or a pharmaceutically acceptable salt thereof,

5 wherein

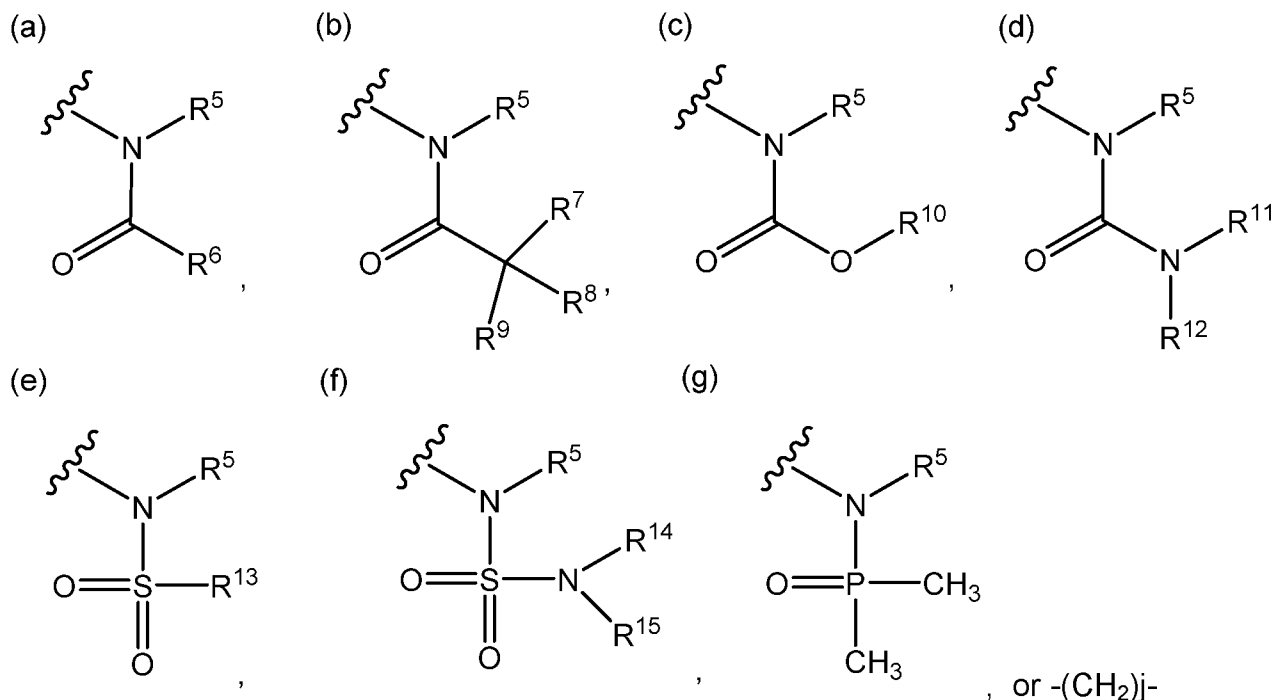
R¹ is hydrogen or methyl;

R^{2a} and R^{2b} are each independently hydrogen, halogen, -CN, C₁-C₄ alkyl, -CHF₂, -CF₃, hydroxy, methoxy, -NH₂, or C₃-C₄ cycloalkyl;

R³ is hydrogen, halogen, -CN, C₁-C₃ alkyl, -CF₃, or methoxy;

R⁴ is

10



$N(R^{16})(R^{17})$;

each R^{4a} is independently fluorine, -CN, methyl, hydroxy, or methoxy;

5 R^5 is hydrogen, C_1 - C_3 alkyl, or C_3 - C_4 cycloalkyl;

R^6 is hydrogen, phenyl, or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl is optionally substituted by methyl, $-(CH_2)_2OH$, or $-(CH_2)_2CN$;

10 R^7 is hydrogen, -CN, C_1 - C_4 alkyl, $-CF_3$, $-N(R^{18})(R^{19})$, $-SO_2(C_1$ - C_3 alkyl), C_3 - C_6 cycloalkyl, 4-6 membered heterocycloalkyl, $-(CH_2)_m$ -(phenyl), or $-(CH_2)_n$ -(5-10 membered heteroaryl), wherein the C_1 - C_4 alkyl is optionally substituted by hydroxy, further wherein the C_3 - C_6 cycloalkyl and the 4-6 membered heterocycloalkyl are each independently optionally substituted by one or two R^{20} groups, even further wherein the $-(CH_2)_m$ -(phenyl) and the $-(CH_2)_n$ -(5-10 membered heteroaryl) are each independently optionally substituted by one or two substituents selected from the group consisting of

15 halogen, -CN, methyl, $-CF_3$, C_1 - C_3 alkoxy, $-NH_2$, and cyclopropyl;

R^8 is hydrogen, methyl, hydroxy, methoxy, or NH_2 ,

provided that R^8 cannot be hydroxy, methoxy or NH_2 , when R^7 is $-N(R^{18})(R^{19})$;

R^9 is hydrogen or C_1 - C_6 alkyl,

20 provided that R^7 may form a 5-6 membered heterocycloalkyl ring with R^5 , R^7 may form a C_3 - C_6 cycloalkyl ring or a 4-8 membered heterocycloalkyl ring with R^9 , or R^8 may form a C_3 - C_6 cycloalkyl ring with R^9 , wherein the 5-6 membered heterocycloalkyl ring,

the C₃-C₆ cycloalkyl ring, and the 4-8 membered heterocycloalkyl ring formed are each independently optionally substituted by one or two R²⁰ groups;

R¹⁰ and R¹¹ are each independently C₁-C₄ alkyl, -(CH₂)_x-(C₃-C₅ cycloalkyl), -(CH₂)_y-(4-6 membered heterocycloalkyl), or -(CH₂)_z-(5-6 membered heteroaryl),

5 wherein the C₁-C₄ alkyl is optionally substituted by one or two substituents selected from the group consisting of fluorine, -CN, -CF₃, C₁-C₃ alkoxy, and -N(R¹⁸)(R¹⁹), further wherein the -(CH₂)_x-(C₃-C₅ cycloalkyl) is optionally substituted by one or two fluorine atoms, even further wherein the -(CH₂)_y-(4-6 membered heterocycloalkyl) and the -(CH₂)_z-(5-6 membered heteroaryl) are each independently optionally substituted by one
10 or two substituents selected from the group consisting of fluorine, -CN, methyl, hydroxy, methoxy, and -N(R¹⁸)(R¹⁹),

provided that R¹⁰ or R¹¹ may form a 4-7 membered heterocycloalkyl ring with R⁵, wherein the 4-7 membered heterocycloalkyl ring formed is optionally substituted by one or two R²⁰ groups;

15 R¹² is hydrogen or C₁-C₄ alkyl,

provided that R¹¹ and R¹² may form a 4-8 membered heterocycloalkyl ring, wherein the 4-8 membered heterocycloalkyl ring formed is optionally substituted by one or two R²¹ groups, further wherein a carbon atom of the 4-8 membered heterocycloalkyl ring formed is optionally replaced by a nitrogen atom or an oxygen atom;

20 R¹³ is C₁-C₄ alkyl or C₃-C₆ cycloalkyl,

provided that R¹³ may form a 5-6 membered heterocycloalkyl ring with R⁵, wherein the 5-6 membered heterocycloalkyl ring formed is optionally substituted by one or two R²⁰ groups;

R¹⁴ and R¹⁵ are each independently hydrogen, C₁-C₃ alkyl, or C₃-C₄ cycloalkyl,

25 provided that R¹⁴ may form a 5-6 membered heterocycloalkyl ring with R⁵ or R¹⁴ and R¹⁵ may form a 4-8 membered heterocycloalkyl ring, wherein the 5-6 membered heterocycloalkyl ring formed is optionally substituted by one or two R²⁰ groups, further wherein the 4-8 membered heterocycloalkyl ring formed is optionally substituted by one or two R²¹ groups, even further wherein a carbon atom of the 4-8 membered
30 heterocycloalkyl ring formed is optionally replaced by a nitrogen atom or an oxygen atom;

R¹⁶ and R¹⁷ are each independently hydrogen or C₁-C₃ alkyl,

provided that R^{16} and R^{17} may form a 4-6 membered heterocycloalkyl ring, wherein the 4-6 membered heterocycloalkyl ring formed is optionally substituted by one or two R^{20} groups, further wherein one carbon of the 4-6 membered heterocycloalkyl ring formed may be optionally replaced with an oxygen atom;

5 each R^{18} and R^{19} is independently hydrogen or methyl, provided that R^{18} and R^{19} may form a 4-8 membered heterocycloalkyl ring, wherein the 4-8 membered heterocycloalkyl ring formed is optionally substituted by one or two substituents selected from the group consisting of =O, fluorine, -CN, methyl, -CF₃, hydroxy, methoxy, and -N(R^{22})(R^{23}), further wherein a carbon atom of the 4-8
10 membered heterocycloalkyl ring formed is optionally replaced by a nitrogen atom or an oxygen atom;

each R^{20} is independently fluorine, -CN, methyl, -CF₃, hydroxy, and methoxy;

each R^{21} is independently =O, fluorine, -CN, methyl, -CF₃, hydroxy, methoxy, and -N(R^{18})(R^{19});

15 each R^{22} and R^{23} is independently hydrogen or methyl, provided that R^{22} and R^{23} may form a 4-8 membered heterocycloalkyl ring, wherein the 4-8 membered heterocycloalkyl ring formed is optionally substituted by one or two substituents selected from the group consisting of =O, fluorine, -CN, methyl, -CF₃, hydroxy, methoxy, -NH₂, -NHCH₃ and -N(CH₃)₂, further wherein a carbon atom of
20 the 4-8 membered heterocycloalkyl ring formed is optionally replaced by a nitrogen atom or an oxygen atom;

g is 0, 1, 2, 3, or 4;

j is 0, 1, or 2;

m is 0, 1, or 2;

25 n is 0 or 1;

x is 0 or 1;

y is 0, 1, or 2; and

z is 0 or 1.

Embodiments described herein relate to a compound of formula (II), or a
30 pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^1 is methyl.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^{2a} is hydrogen.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^{2a} is $-NH_2$.

5 Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^{2b} is hydrogen, halogen, C_1 - C_4 alkyl, $-CHF_2$, or $-CF_3$.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^{2b} is hydrogen.

10 Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein g is 0.

15 Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein g is 1.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen or C_1 - C_3 alkyl.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen.

20 Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^5 is methyl.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^6 is hydrogen.

25 The compound or salt of any of claims 57-69, wherein R^6 is 5-6 membered heteroaryl optionally substituted by methyl, $-(CH_2)_2OH$, or $-(CH_2)_2CN$.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^7 is hydrogen, $-CN$, C_1 - C_4 alkyl, $-CF_3$, $-NH_2$, or $-SO_2CH_3$.

30 Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^7 is C_3 - C_6 cycloalkyl.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^7 is $-(CH_2)_m$ -(phenyl) or $-(CH_2)_n$ -(5-10 membered heteroaryl), wherein the $-(CH_2)_n$ -(5-10 membered heteroaryl) is optionally

substituted by one or two substituents selected from the group consisting of halogen and methyl.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^7 is hydrogen.

5 Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^7 is C_1 - C_4 alkyl.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^7 is methyl.

10 Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^8 is hydrogen, methyl, hydroxy, or methoxy.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^8 is hydrogen.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^8 is methyl.

15 Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^8 is hydroxy.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^9 is hydrogen.

20 Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^9 is methyl.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^9 is ethyl.

25 Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^7 is hydrogen, R^8 is hydrogen, and R^9 is hydrogen.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^7 is hydrogen, R^8 is hydroxy, and R^9 is hydrogen.

30 Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^7 is C_1 - C_4 alkyl, R^8 is hydroxy, and R^9 is hydrogen.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^7 and R^9 form a C_3 - C_6 cycloalkyl ring optionally substituted by one or two fluorine groups.

5 Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^7 and R^9 form a 4-6 membered heterocycloalkyl ring.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^8 and R^9 form a C_3 - C_6 cycloalkyl ring optionally substituted by one or two substituents selected from the group consisting of
10 fluorine, -CN, and methyl.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^{10} is C_1 - C_4 alkyl.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^{10} is methyl.

15 Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^{10} is C_3 - C_5 cycloalkyl.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^{10} and R^5 form a 5-6 membered heterocycloalkyl ring.

20 Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^{11} is C_1 - C_4 alkyl or $-(CH_2)_x-(C_3-C_5$ cycloalkyl), further wherein the C_1 - C_4 alkyl is optionally substituted by one or two substituents selected from the group consisting of fluorine, -CN, -CF₃, C_1 - C_3 alkoxy, and $-N(CH_3)_2$, even further wherein the $-(CH_2)_x-(C_3-C_5$ cycloalkyl) is optionally substituted by
25 one or two fluorine atoms.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^{11} is $-(CH_2)_y$ -(4-6 membered heterocycloalkyl) optionally substituted by methyl.

30 Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^{11} is $-(CH_2)_z$ -(5-6 membered heteroaryl) optionally substituted by methyl.

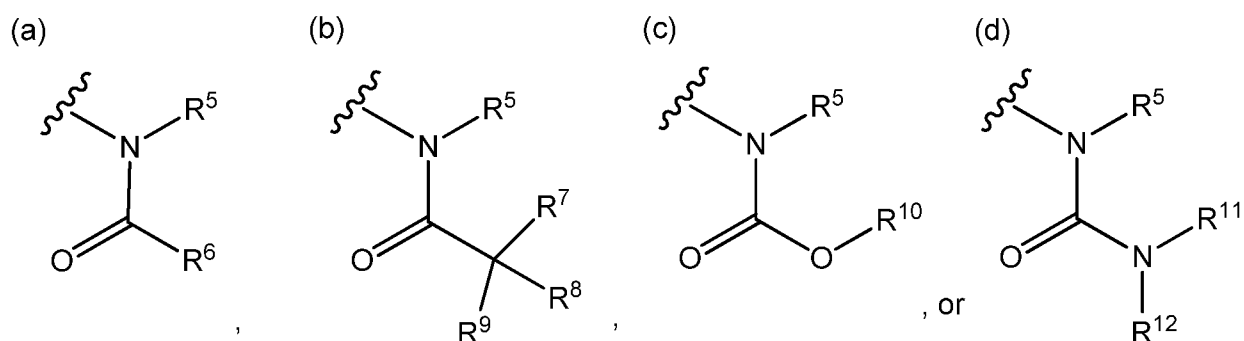
Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^{12} is hydrogen.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^{12} is methyl.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^{11} and R^{12} form a 4-6 membered heterocycloalkyl ring optionally substituted by one or two substituents selected from the group consisting of fluorine, -CN, methyl, and hydroxy.

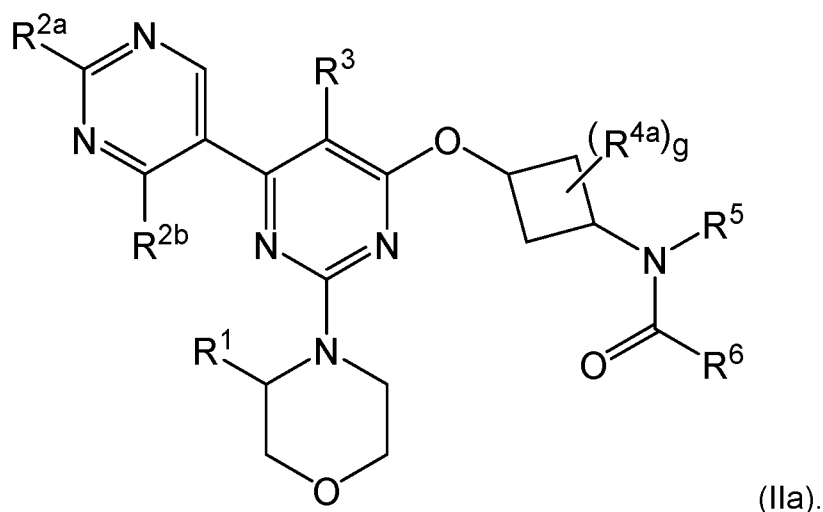
Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^{11} and R^5 form a 5-6 membered heterocycloalkyl ring.

Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^4 is

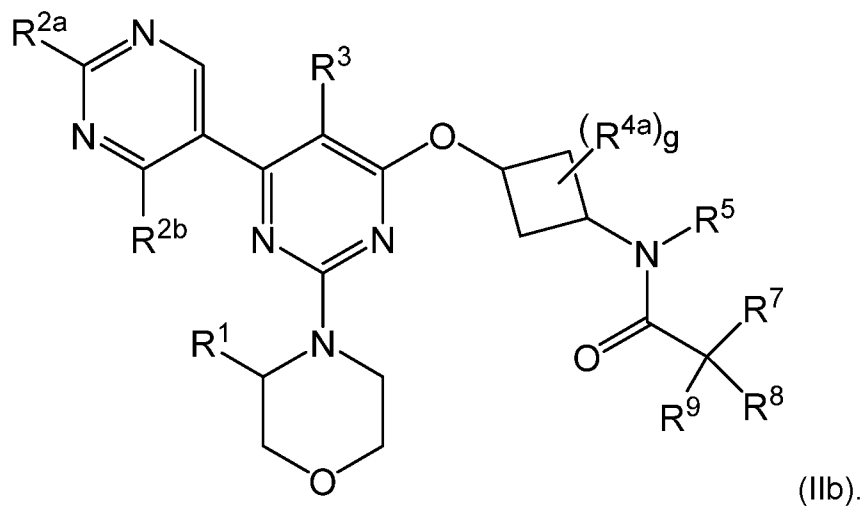


Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein R^4 is $-(CH_2)_j-N(R^{16})(N^{17})$.

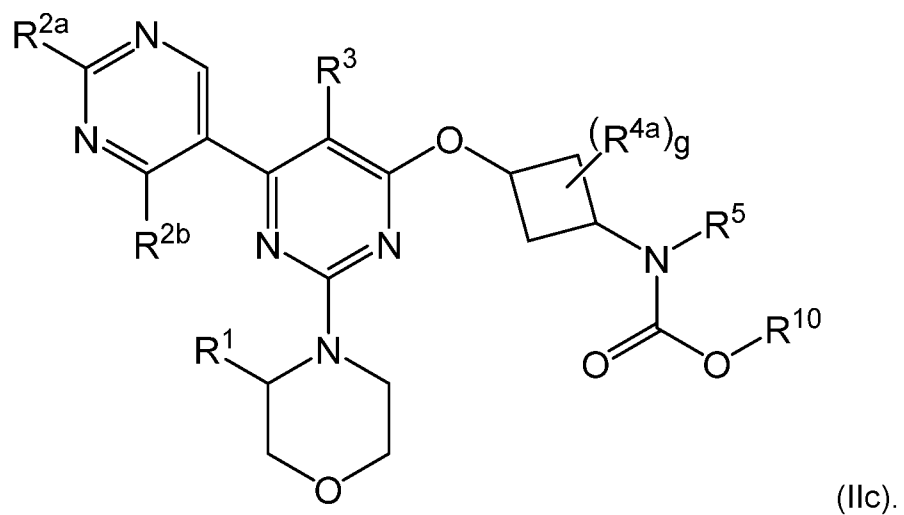
Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, having formula (IIa)



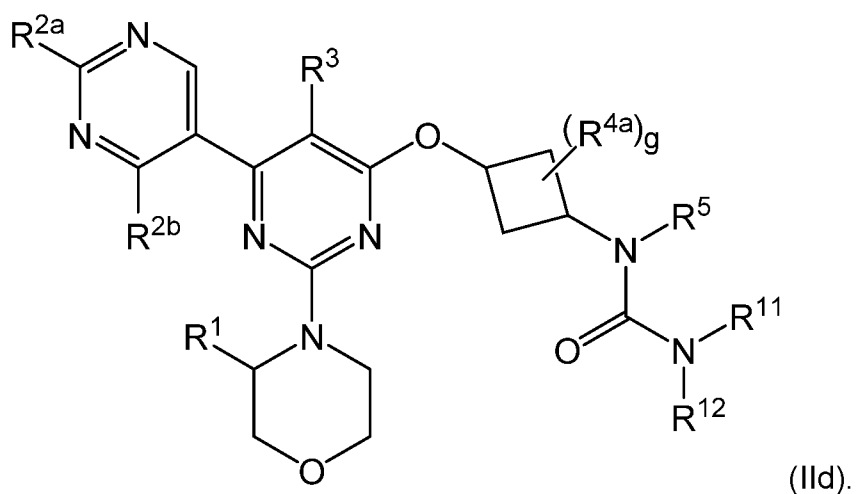
Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, having formula (IIb)



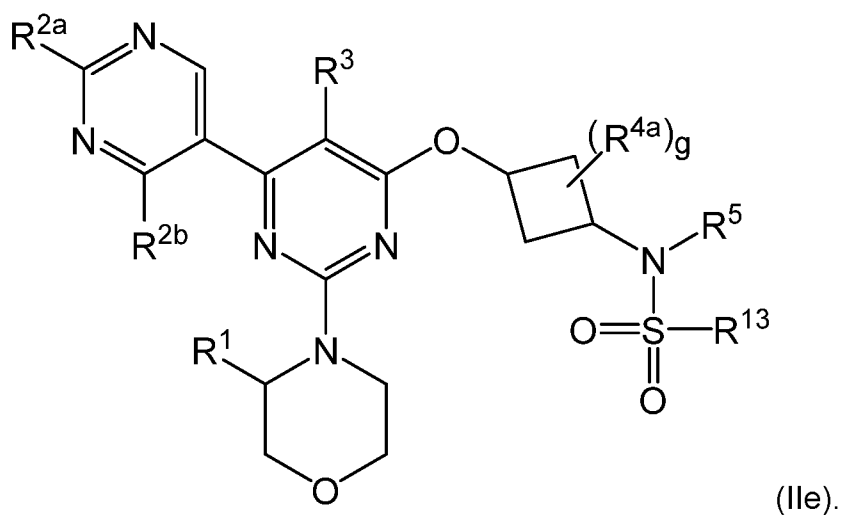
Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, having formula (IIc)



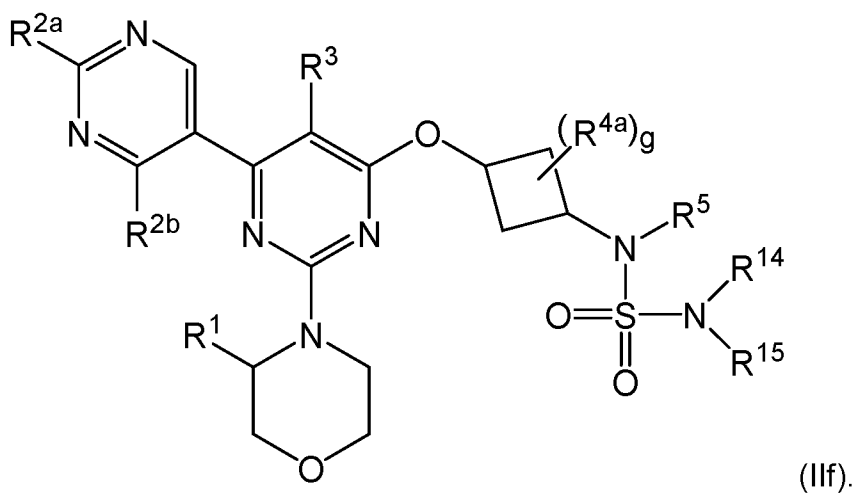
Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, having formula (IId)



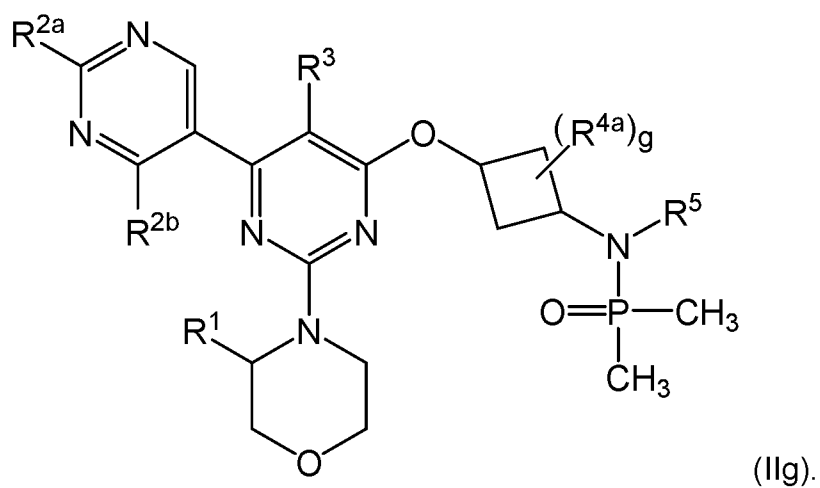
Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, having formula (IIe)



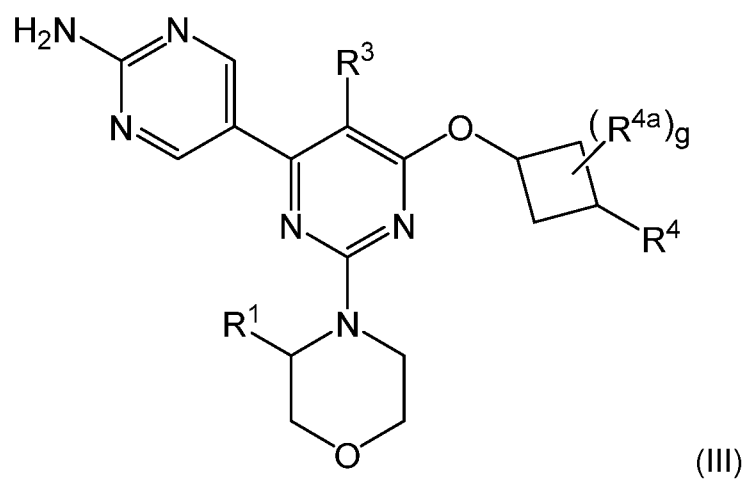
5 Embodiments described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof, having formula (IIf)



Embodiments described herein relate to a having formula (IIg)



Embodiments described herein relate to a compound formula (III)



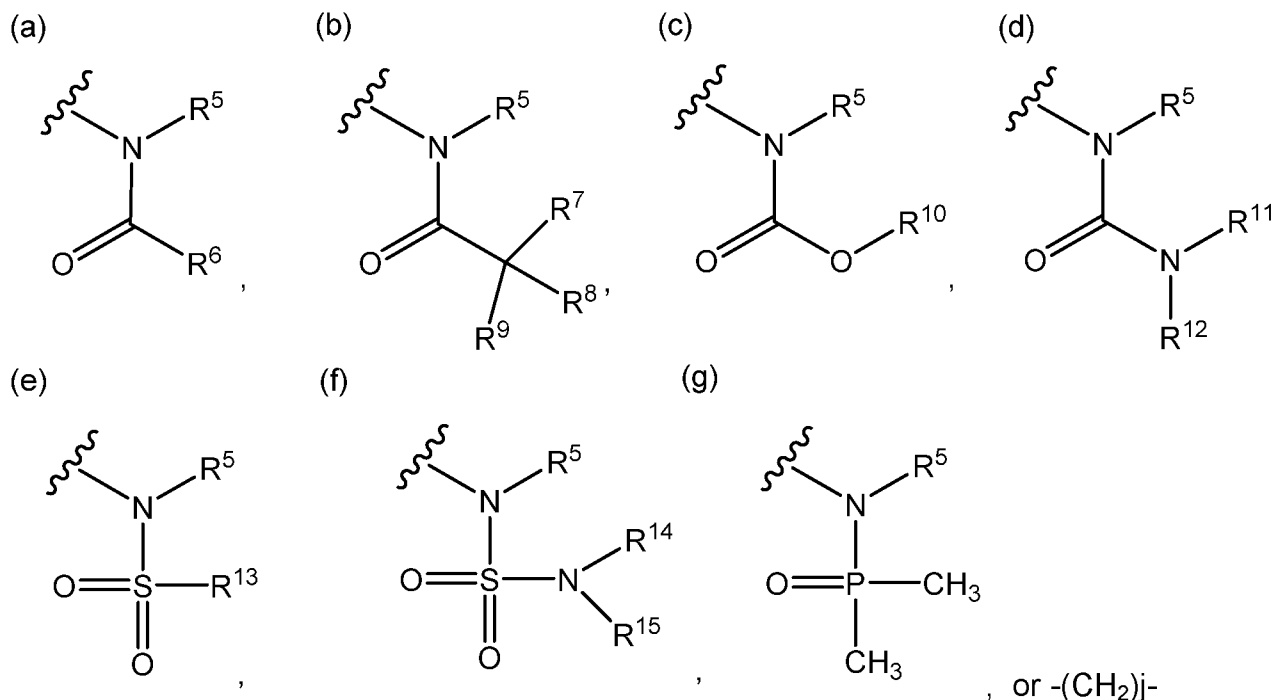
or a pharmaceutically acceptable salt thereof,

5 wherein

R^1 is hydrogen or methyl;

R^3 is hydrogen, halogen, $-CN$, C_1 - C_3 alkyl, $-CF_3$, or methoxy;

R^4 is



$N(R^{16})(R^{17})$;

each R^{4a} is independently fluorine, -CN, methyl, hydroxy, or methoxy;

5 R^5 is hydrogen, C_1 - C_3 alkyl, or C_3 - C_4 cycloalkyl;

R^6 is hydrogen, phenyl, or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl is optionally substituted by methyl, $-(CH_2)_2OH$, or $-(CH_2)_2CN$;

10 R^7 is hydrogen, -CN, C_1 - C_4 alkyl, $-CF_3$, $-N(R^{18})(R^{19})$, $-SO_2(C_1$ - C_3 alkyl), C_3 - C_6 cycloalkyl, 4-6 membered heterocycloalkyl, $-(CH_2)_m$ -(phenyl), or $-(CH_2)_n$ -(5-10 membered heteroaryl), wherein the C_1 - C_4 alkyl is optionally substituted by hydroxy, further wherein the C_3 - C_6 cycloalkyl and the 4-6 membered heterocycloalkyl are each independently optionally substituted by one or two R^{20} groups, even further wherein the $-(CH_2)_m$ -(phenyl) and the $-(CH_2)_n$ -(5-10 membered heteroaryl) are each independently optionally substituted by one or two substituents selected from the group consisting of

15 halogen, -CN, methyl, $-CF_3$, C_1 - C_3 alkoxy, $-NH_2$, and cyclopropyl;

R^8 is hydrogen, methyl, hydroxy, methoxy, or NH_2 ,

provided that R^8 cannot be hydroxy, methoxy or NH_2 , when R^7 is $-N(R^{18})(R^{19})$;

R^9 is hydrogen or C_1 - C_6 alkyl,

20 provided that R^7 may form a 5-6 membered heterocycloalkyl ring with R^5 , R^7 may form a C_3 - C_6 cycloalkyl ring or a 4-8 membered heterocycloalkyl ring with R^9 , or R^8 may form a C_3 - C_6 cycloalkyl ring with R^9 , wherein the 5-6 membered heterocycloalkyl ring,

the C₃-C₆ cycloalkyl ring, and the 4-8 membered heterocycloalkyl ring formed are each independently optionally substituted by one or two R²⁰ groups;

R¹⁰ and R¹¹ are each independently C₁-C₄ alkyl, -(CH₂)_x-(C₃-C₅ cycloalkyl), -(CH₂)_y-(4-6 membered heterocycloalkyl), or -(CH₂)_z-(5-6 membered heteroaryl),

5 wherein the C₁-C₄ alkyl is optionally substituted by one or two substituents selected from the group consisting of fluorine, -CN, -CF₃, C₁-C₃ alkoxy, and -N(R¹⁸)(R¹⁹), further wherein the -(CH₂)_x-(C₃-C₅ cycloalkyl) is optionally substituted by one or two fluorine atoms, even further wherein the -(CH₂)_y-(4-6 membered heterocycloalkyl) and the -(CH₂)_z-(5-6 membered heteroaryl) are each independently optionally substituted by one
10 or two substituents selected from the group consisting of fluorine, -CN, methyl, hydroxy, methoxy, and -N(R¹⁸)(R¹⁹),

provided that R¹⁰ or R¹¹ may form a 4-7 membered heterocycloalkyl ring with R⁵, wherein the 4-7 membered heterocycloalkyl ring formed is optionally substituted by one or two R²⁰ groups;

15 R¹² is hydrogen or C₁-C₄ alkyl,

provided that R¹¹ and R¹² may form a 4-8 membered heterocycloalkyl ring, wherein the 4-8 membered heterocycloalkyl ring formed is optionally substituted by one or two R²¹ groups, further wherein a carbon atom of the 4-8 membered heterocycloalkyl ring formed is optionally replaced by a nitrogen atom or an oxygen atom;

20 R¹³ is C₁-C₄ alkyl or C₃-C₆ cycloalkyl,

provided that R¹³ may form a 5-6 membered heterocycloalkyl ring with R⁵, wherein the 5-6 membered heterocycloalkyl ring formed is optionally substituted by one or two R²⁰ groups;

R¹⁴ and R¹⁵ are each independently hydrogen, C₁-C₃ alkyl, or C₃-C₄ cycloalkyl,

25 provided that R¹⁴ may form a 5-6 membered heterocycloalkyl ring with R⁵ or R¹⁴ and R¹⁵ may form a 4-8 membered heterocycloalkyl ring, wherein the 5-6 membered heterocycloalkyl ring formed is optionally substituted by one or two R²⁰ groups, further wherein the 4-8 membered heterocycloalkyl ring formed is optionally substituted by one or two R²¹ groups, even further wherein a carbon atom of the 4-8 membered
30 heterocycloalkyl ring formed is optionally replaced by a nitrogen atom or an oxygen atom;

R¹⁶ and R¹⁷ are each independently hydrogen or C₁-C₃ alkyl,

provided that R^{16} and R^{17} may form a 4-6 membered heterocycloalkyl ring, wherein the 4-6 membered heterocycloalkyl ring formed is optionally substituted by one or two R^{20} groups, further wherein one carbon of the 4-6 membered heterocycloalkyl ring formed may be optionally replaced with an oxygen atom;

5 each R^{18} and R^{19} is independently hydrogen or methyl, provided that R^{18} and R^{19} may form a 4-8 membered heterocycloalkyl ring, wherein the 4-8 membered heterocycloalkyl ring formed is optionally substituted by one or two substituents selected from the group consisting of =O, fluorine, -CN, methyl, -CF₃, hydroxy, methoxy, and -N(R^{22})(R^{23}), further wherein a carbon atom of the 4-8
10 membered heterocycloalkyl ring formed is optionally replaced by a nitrogen atom or an oxygen atom;

each R^{20} is independently fluorine, -CN, methyl, -CF₃, hydroxy, and methoxy;

each R^{21} is independently =O, fluorine, -CN, methyl, -CF₃, hydroxy, methoxy, and -N(R^{18})(R^{19});

15 each R^{22} and R^{23} is independently hydrogen or methyl, provided that R^{22} and R^{23} may form a 4-8 membered heterocycloalkyl ring, wherein the 4-8 membered heterocycloalkyl ring formed is optionally substituted by one or two substituents selected from the group consisting of =O, fluorine, -CN, methyl, -CF₃, hydroxy, methoxy, -NH₂, -NHCH₃ and -N(CH₃)₂, further wherein a carbon atom of
20 the 4-8 membered heterocycloalkyl ring formed is optionally replaced by a nitrogen atom or an oxygen atom;

g is 0, 1, 2, 3, or 4;

j is 0, 1, or 2;

m is 0, 1, or 2;

25 n is 0 or 1;

x is 0 or 1;

y is 0, 1, or 2; and

z is 0 or 1.

Embodiments described herein relate to a compound of formula (III), or a
30 pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^1 is methyl.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein g is 0.

5 Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein g is 1.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen or C_1 - C_3 alkyl.

10 Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^5 is methyl.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^6 is hydrogen.

15 Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^6 is 5-6 membered heteroaryl optionally substituted by methyl, $-(CH_2)_2OH$, or $-(CH_2)_2CN$.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^7 is hydrogen, $-CN$, C_1 - C_4 alkyl, $-CF_3$, $-NH_2$, or $-SO_2CH_3$.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^7 is C_3 - C_6 cycloalkyl.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^7 is $-(CH_2)_m$ -(phenyl) or $-(CH_2)_n$ -(5-10 membered heteroaryl), wherein the $-(CH_2)_n$ -(5-10 membered heteroaryl) is optionally substituted by one or two substituents selected from the group consisting of halogen and methyl.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^7 is hydrogen.

30 Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^7 is C_1 - C_4 alkyl.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^7 is methyl.

Embodiments relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^8 is hydrogen, methyl, hydroxy, or methoxy.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^8 is hydrogen.

5 Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^8 is methyl.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^8 is hydroxy.

10 Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^9 is hydrogen.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^9 is methyl.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^9 is ethyl.

15 Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^7 is hydrogen, R^8 is hydrogen, and R^9 is hydrogen.

20 Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^7 is hydrogen, R^8 is hydroxy, and R^9 is hydrogen.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^7 is C_1 - C_4 alkyl, R^8 is hydroxy, and R^9 is hydrogen.

25 Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^7 and R^9 form a C_3 - C_6 cycloalkyl ring optionally substituted by one or two fluorine groups.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^7 and R^9 form a 4-6 membered heterocycloalkyl ring.

30 Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^8 and R^9 form a C_3 - C_6 cycloalkyl ring optionally substituted by one or two substituents selected from the group consisting of fluorine, -CN, and methyl.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^{10} is C_1 - C_4 alkyl.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^{10} is methyl.

5 Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^{10} is C_3 - C_5 cycloalkyl.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^{10} and R^5 form a 5-6 membered heterocycloalkyl ring.

10 Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^{11} is C_1 - C_4 alkyl or $-(CH_2)_x$ -(C_3 - C_5 cycloalkyl), further wherein the C_1 - C_4 alkyl is optionally substituted by one or two substituents selected from the group consisting of fluorine, $-CN$, $-CF_3$, C_1 - C_3 alkoxy, and $-N(CH_3)_2$, even further wherein the $-(CH_2)_x$ -(C_3 - C_5 cycloalkyl) is optionally substituted by
15 one or two fluorine atoms.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^{11} is $-(CH_2)_y$ -(4-6 membered heterocycloalkyl) optionally substituted by methyl.

Embodiments described herein relate to a compound of formula (III), or a
20 pharmaceutically acceptable salt thereof, wherein R^{11} is $-(CH_2)_z$ -(5-6 membered heteroaryl) optionally substituted by methyl.

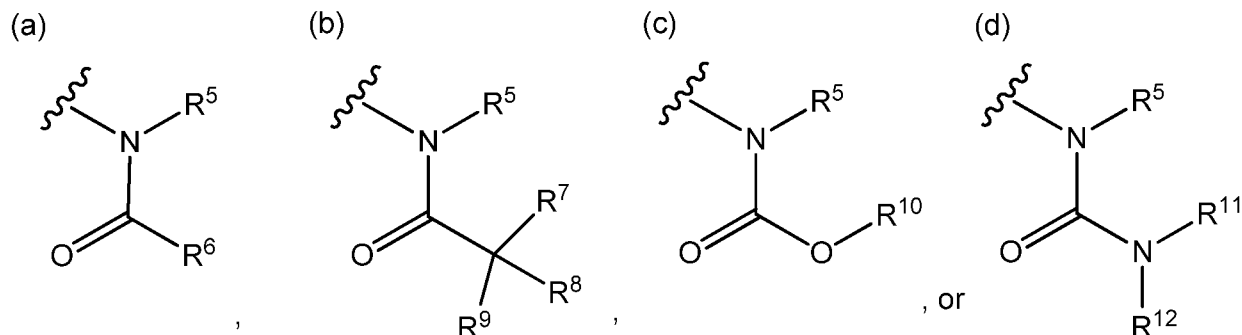
Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^{12} is hydrogen.

Embodiments described herein relate to a compound of formula (III), or a
25 pharmaceutically acceptable salt thereof, wherein R^{12} is methyl.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^{11} and R^{12} form a 4-6 membered heterocycloalkyl ring optionally substituted by one or two substituents selected from the group consisting of fluorine, $-CN$, methyl, and hydroxy.

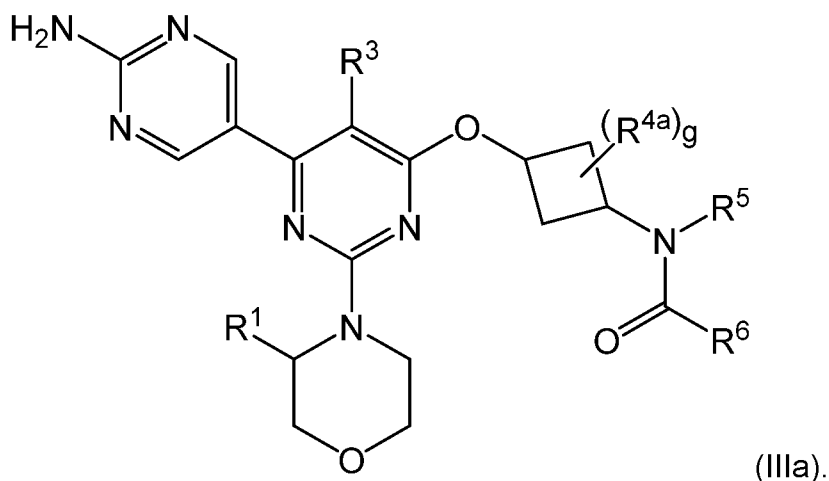
30 Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^{11} and R^5 form a 5-6 membered heterocycloalkyl ring.

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^4 is

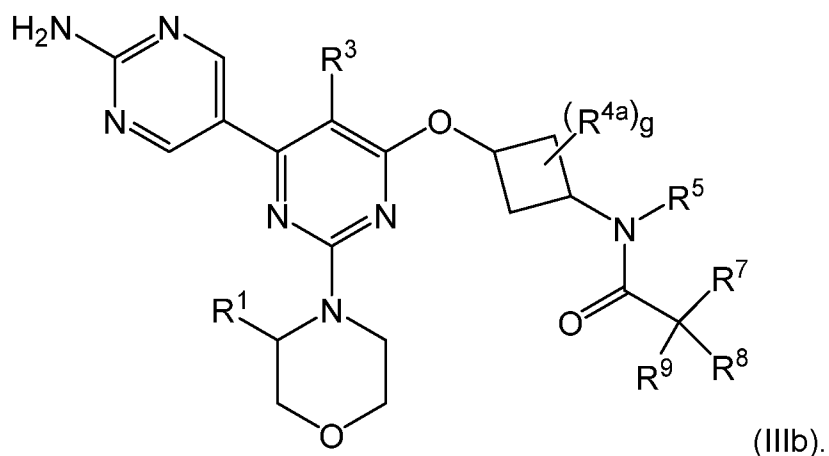


Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein R^4 is $-(CH_2)_j-N(R^{16})(N^{17})$.

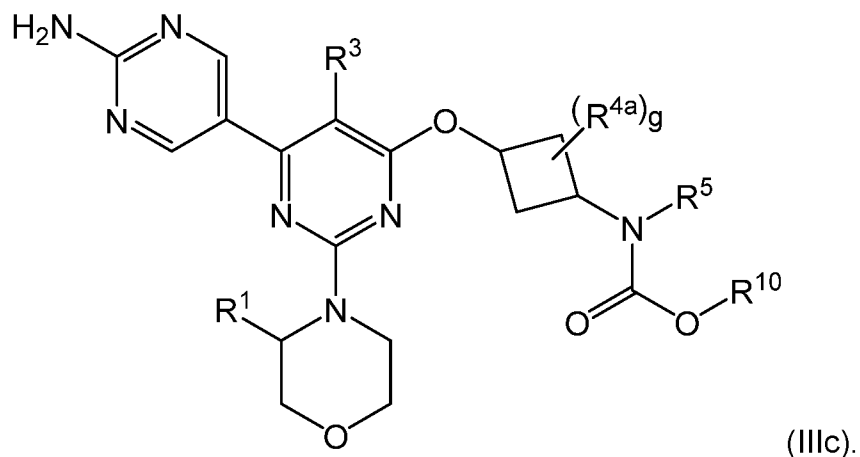
Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, having formula (IIIa)



Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, having formula (IIIb)

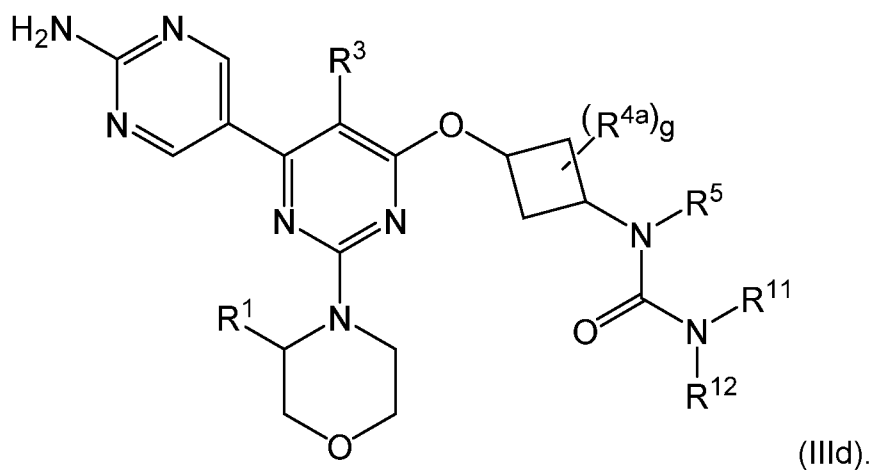


Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, having formula (IIIc)



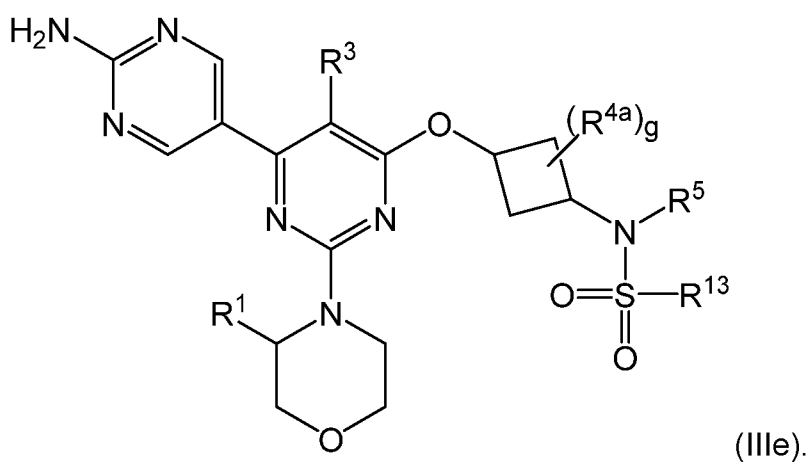
(IIIc).

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, having formula (IIIId)



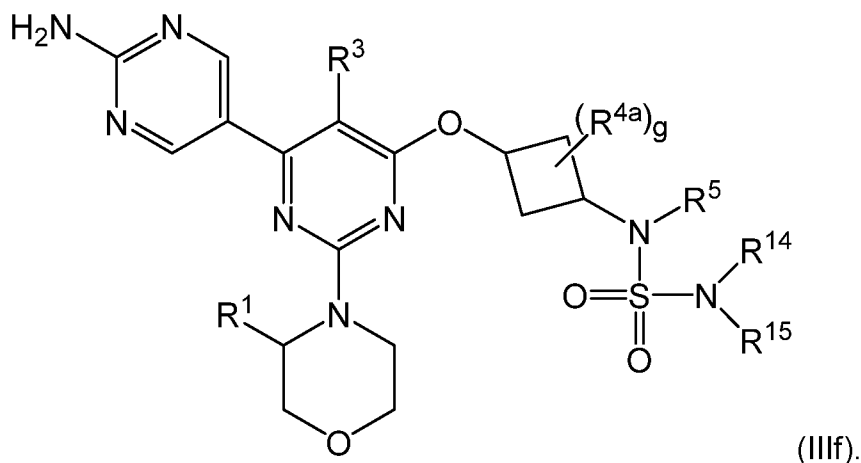
(IIIId).

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, having formula (IIIe)

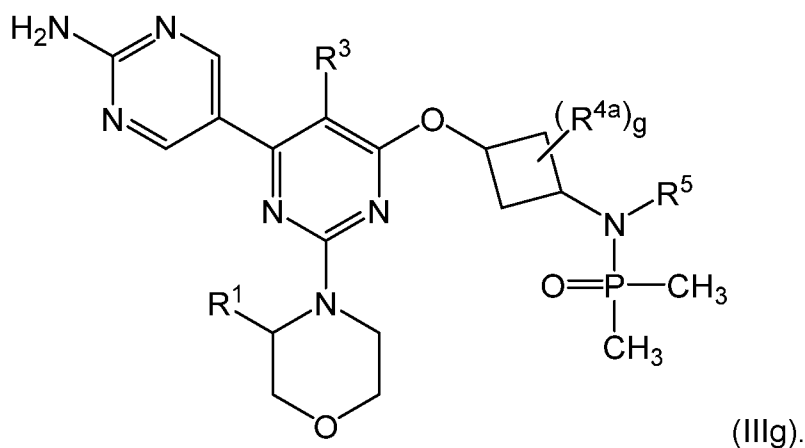


(IIIe).

Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, having formula (III_f)



Embodiments described herein relate to a compound of formula (III), or a pharmaceutically acceptable salt thereof, having formula (III_g)



In some embodiments, the compound is selected from:

N-(*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-*N*-methylacetamide;

1-(*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-1,3-dimethylurea;

N-[*trans*-3-([2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl]-*N*-methylacetamide;

N-(*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-*N*-methylacetamide;

methyl (*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)carbamate;

N-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-2-hydroxyacetamide;

N-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)acetamide;

5 1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-methylurea;

N-(*trans*-3-{[6-(6-aminopyridin-3-yl)-2-(morpholin-4-yl)pyrimidin-4-yl]oxy}cyclobutyl)-2-hydroxy-*N*-methylacetamide;

10 *N*-(*trans*-3-{[6-(6-aminopyridin-3-yl)-2-(morpholin-4-yl)pyrimidin-4-yl]oxy}cyclobutyl)-*N*-methylacetamide;

(2*S*)-*N*-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-2-hydroxy-*N*-methylpropanamide;

(2*S*)-*N*-(*trans*-3-{[6-(6-aminopyridin-3-yl)-2-(morpholin-4-yl)pyrimidin-4-yl]oxy}cyclobutyl)-2-hydroxy-*N*-methylpropanamide;

15 methyl (*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)methylcarbamate;

(2*R*)-*N*-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-2-hydroxy-*N*-methylpropanamide;

20 *N*-(*trans*-3-{[6-(6-aminopyridin-3-yl)-2-(morpholin-4-yl)pyrimidin-4-yl]oxy}cyclobutyl)-2-hydroxyacetamide;

N-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-*N*-methyl-L-alaninamide;

N-(*trans*-3-{[2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-*N*-methylacetamide;

25 2-hydroxy-*N*-methyl-*N*-(*trans*-3-{[2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)acetamide;

N-(*trans*-3-{[2'-amino-5-methoxy-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-*N*-methylacetamide;

30 2-hydroxy-*N*-methyl-*N*-(*trans*-3-{[2-(morpholin-4-yl)-6-(pyridin-3-yl)pyrimidin-4-yl]oxy}cyclobutyl)acetamide;

N-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-2-hydroxy-*N*,2-dimethylpropanamide;

(2*S*)-*N*-(*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-*N*,2-dimethylbutanamide;

(2*R*)-*N*-(*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-*N*,2-dimethylbutanamide;

5 (2*S*)-*N*-(*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-*N*-methyl-2-phenylethanamide;

N-[*trans*-3-({6-[6-amino-4-(trifluoromethyl)pyridin-3-yl]-2-(morpholin-4-yl)pyrimidin-4-yl]oxy)cyclobutyl]-2-hydroxy-*N*-methylacetamide;

10 *N*-[*trans*-3-({6-[6-amino-4-(trifluoromethyl)pyridin-3-yl]-2-(morpholin-4-yl)pyrimidin-4-yl]oxy)cyclobutyl]-*N*-methylacetamide;

methyl [*trans*-3-({6-[6-amino-4-(trifluoromethyl)pyridin-3-yl]-2-(morpholin-4-yl)pyrimidin-4-yl]oxy)cyclobutyl]methylcarbamate;

(2*R*)-*N*-(*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-3,3,3-trifluoro-2-hydroxy-*N*,2-dimethylpropanamide;

15 (2*S*)-*N*-(*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-3,3,3-trifluoro-2-hydroxy-*N*,2-dimethylpropanamide;

N-(*trans*-3-([2'-amino-5-methyl-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-*N*-methylacetamide;

20 *N*-(*trans*-3-([2'-amino-5-ethyl-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-*N*-methylacetamide;

(2*R*)-*N*-(*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-*N*-methyl-2-phenylethanamide;

N-(*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-1-hydroxy-*N*-methylcyclobutanecarboxamide;

25 (2*R*)-*N*-(*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-*N*,3-dimethylbutanamide;

N-(*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-*N*,*P*,*P*-trimethylphosphinic amide;

30 (2*R*)-*N*-(*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-*N*,3,3-trimethylbutanamide;

(2*S*)-*N*-(*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-*N*,3,3-trimethylbutanamide;

1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-cyclopropyl-1-methylurea;

(2*S*)-*N*-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-2-hydroxy-*N*,3-dimethylbutanamide;

5 (2*R*)-*N*-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-2-hydroxy-*N*,4-dimethylpentanamide;

(2*S*)-*N*-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-2-hydroxy-*N*,4-dimethylpentanamide;

10 1-[*trans*-3-({6-amino-4-(trifluoromethyl)pyridin-3-yl}-2-(morpholin-4-yl)pyrimidin-4-yl]oxy)cyclobutyl]-1,3-dimethylurea;

(2*R*)-*N*-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-2-hydroxy-*N*-methyl-2-(trifluoromethyl)butanamide;

1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-ethyl-1-methylurea;

15 1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1-methyl-3-propan-2-ylurea;

1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1,3,3-trimethylurea;

20 (2*S*)-*N*-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-2-hydroxy-*N*-methyl-2-(trifluoromethyl)butanamide;

1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1-ethyl-3-methylurea;

1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-(3,3-difluorocyclobutyl)-1-methylurea;

25 *N*-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-*N*-ethyl-2-hydroxyacetamide;

1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-(cyanomethyl)-1-methylurea;

30 1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-cyclopropyl-1,3-dimethylurea;

(2*R*)-*N*-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-*N*-methyltetrahydrofuran-2-carboxamide;

ethyl (*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)carbamate;

1-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1-methyl-3-(1-methyl-1*H*-pyrazol-4-yl)urea;

5 1-(*trans*-3-[[2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1,3-dimethylurea;

propan-2-yl (*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)carbamate;

10 *N*-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-2-hydroxy-*N*-(propan-2-yl)acetamide;

N-(*trans*-3-[[2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-*N*,5-dimethyl-1,2-oxazole-3-carboxamide;

N-(*trans*-3-[[2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-*N*,1-dimethyl-1*H*-1,2,3-triazole-4-carboxamide;

15 *N*-(*trans*-3-[[2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-2-hydroxy-*N*-methylacetamide;

N-(*trans*-3-[[2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-*N*,1-dimethyl-1*H*-pyrazole-3-carboxamide;

20 *N*-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-*N*-methylmorpholine-4-carboxamide;

N-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-*N*-methylazetidine-1-carboxamide;

N-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-cyano-*N*-methylazetidine-1-carboxamide;

25 *N*-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-*N*-methyl-1-(1*H*-pyrazol-1-yl)cyclopropanecarboxamide;

N-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-fluoro-*N*-methylazetidine-1-carboxamide;

30 1-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)imidazolidin-2-one;

N-(*cis*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-2-hydroxy-3-(1*H*-imidazol-4-yl)-*N*-methylpropanamide;

(2R)-N-(*trans*-3-[[2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-2-hydroxy-N,3-dimethylbutanamide;

(2S)-N-(*trans*-3-[[2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-2-hydroxy-N,3-dimethylbutanamide;

5 methyl (*trans*-3-[[2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)methylcarbamate;

1-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-1-methyl-3-oxetan-3-ylurea;

10 N-(*trans*-3-[[2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-N-methylformamide;

(2S)-N-(*trans*-3-[[2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-2-hydroxy-N,3,3-trimethylbutanamide;

methyl (*trans*-3-[[2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)carbamate;

15 1-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-1-methyl-3-(1-methylazetidin-3-yl)urea;

1-(*trans*-3-[[6-(6-amino-5-fluoropyridin-3-yl)-2-(morpholin-4-yl)pyrimidin-4-yl]oxy]cyclobutyl)-1,3-dimethylurea;

20 (2R)-N-(*trans*-3-[[2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-2-hydroxy-N,3,3-trimethylbutanamide;

cyclobutyl (*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)carbamate;

2-(morpholin-4-yl)-6-[[cis-3-(morpholin-4-yl)cyclobutyl]oxy]-4,5'-bipyrimidin-2'-amine;

25 N-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-N-methylformamide;

1-(*trans*-3-[[2'-amino-4'-methyl-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-1,3-dimethylurea;

30 3-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-1,3-oxazolidin-2-one;

(3R)-N-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-3-hydroxy-N-methylpyrrolidine-1-carboxamide;

N-(*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-*N,N'*-dimethylsulfuric diamide;

(3*S*)-*N*-(*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-3-hydroxy-*N*-methylpyrrolidine-1-carboxamide;

5 propan-2-yl (*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)methylcarbamate;

N-[(1*R*,2*R*)-2-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl]acetamide;

10 ethyl (*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)methylcarbamate;

1-(*trans*-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-1-methyl-3-propan-2-ylurea;

1-[(1*R*,2*R*)-2-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl]-3-methylurea;

15 methyl [(1*R*,2*R*)-2-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl]carbamate;

cyclobutyl (*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)methylcarbamate;

20 1-(*trans*-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-1-methyl-3-[2-(pyrrolidin-1-yl)ethyl]urea;

N-(*trans*-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-*N*,4-dimethylpiperazine-1-carboxamide;

N-(*trans*-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-*N*-methylpiperazine-1-carboxamide;

25 (2*S*)-*N*-(*trans*-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-3,3-dimethylbutanamide;

1-(*trans*-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-3-[2-(dimethylamino)ethyl]-1-methylurea;

30 *N*-(*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-cyclopropyl-2-hydroxy-*N*-methylacetamide;

N-[*trans*-3-([2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl]-*N*-methylmethanesulfonamide;

methyl [*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]methylcarbamate;

N-(*trans*-3-{{2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy}cyclobutyl)acetamide;

5 (2*R*)-*N*-(*trans*-3-{{2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy}cyclobutyl)-2-hydroxy-3-methylbutanamide;

(2*S*)-*N*-(*trans*-3-{{2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy}cyclobutyl)tetrahydrofuran-2-carboxamide;

10 (2*R*)-*N*-(*trans*-3-{{2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy}cyclobutyl)-2-cyclopropyl-2-hydroxy-*N*-methylethanamide;

(2*S*)-*N*-(*trans*-3-{{2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy}cyclobutyl)-2-cyclopropyl-2-hydroxy-*N*-methylethanamide;

1-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-1,3-dimethylurea;

15 1-(*trans*-3-{{2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy}cyclobutyl)-1-methyl-3-[(3*S*)-tetrahydrofuran-3-yl]urea;

6-{{*trans*-3-(methylamino)cyclobutyl}oxy}-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-2'-amine;

20 1-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-3-methylurea;

N-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]methanesulfonamide;

methyl [*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]carbamate;

25 *N*-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]acetamide;

1-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-1-methyl-3-[2-(pyrrolidin-1-yl)ethyl]urea;

30 *N*-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-*N*-methylpiperazine-1-carboxamide;

1-(*trans*-3-{{2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy}cyclobutyl)-1-methyl-3-[(3*R*)-tetrahydrofuran-3-yl]urea;

N-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-4-methylpiperazine-1-carboxamide;

6-[(*trans*-3-aminocyclobutyl)oxy]-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-2'-amine;

5 *N*-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-*N*-methylpiperazine-1-carboxamide;

1-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-3-(2-methoxyethyl)-1-methylurea;

10 1-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-1-methyl-3-(1-methyl-1*H*-pyrazol-4-yl)urea;

1-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-1-methyl-3-[(3*S*)-tetrahydrofuran-3-yl]urea;

N-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-*N*-methylsulfuric diamide;

15 *N*-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-*N,N'*-dimethylsulfuric diamide;

tert-butyl [*trans*-3-({2'-amino-5-bromo-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]methylcarbamate;

20 (3*R*)-*N*-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-3-hydroxy-*N*-methylpyrrolidine-1-carboxamide;

1-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-1-methyl-3-[(3*R*)-tetrahydrofuran-3-yl]urea;

N-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-*N*,4-dimethylpiperazine-1-carboxamide;

25 1-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-3-(cyanomethyl)-1-methylurea;

N-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-3-cyano-*N*-methylazetidine-1-carboxamide;

30 (3*S*)-*N*-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-3-hydroxy-*N*-methylpyrrolidine-1-carboxamide;

N-[*trans*-3-({2'-amino-5-cyano-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-*N*-methylacetamide;

1-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]imidazolidin-2-one;

N-(*trans*-3-{{2'-amino-5-fluoro-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl)-*N*-methylethylacetamide;

5 1-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]tetrahydropyrimidin-2(1*H*)-one;

methyl [*trans*-3-({2'-amino-5-fluoro-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]carbamate;

10 *N*-[*trans*-3-({2'-amino-5-fluoro-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]methanesulfonamide;

1-[*trans*-3-({2'-amino-5-fluoro-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-3-methylurea;

N-[*trans*-3-({2'-amino-5-fluoro-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]acetamide;

15 6-{{*trans*-3-(1,1-dioxido-1,2-thiazolidin-2-yl)cyclobutyl}oxy}-2-(morpholin-4-yl)-4,5'-bipyrimidin-2'-amine;

1-[*trans*-3-({2'-amino-5-fluoro-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-1,3-dimethylurea;

20 1-[*trans*-3-({2'-amino-5-fluoro-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-1-methyl-3-[2-(pyrrolidin-1-yl)ethyl]urea;

N-[*trans*-3-({2'-amino-5-fluoro-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-*N*-methylmethanesulfonamide;

6-{{*trans*-3-(1,1-dioxido-1,2,5-thiadiazolidin-2-yl)cyclobutyl}oxy}-2-(morpholin-4-yl)-4,5'-bipyrimidin-2'-amine;

25 methyl [*trans*-3-({2'-amino-5-fluoro-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]methylcarbamate;

N-[*trans*-3-({2'-amino-5-fluoro-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-*N*-methylpiperazine-1-carboxamide;

30 (2*R*)-*N*-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-2-hydroxy-*N*,3-dimethylbutanamide;

N-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-*N*-methylmorpholine-4-carboxamide;

(2S)-*N*-[trans-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-2-hydroxy-*N*-methyl-2-phenylethanamide;

N-[trans-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-*N*-methyl-2-(methylsulfonyl)acetamide;

5 *N*-(trans-3-{{2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy})-3-methylcyclobutyl)methanesulfonamide;

N-(trans-3-{{2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy})-3-methylcyclobutyl)-*N*-methylmethanesulfonamide;

10 *N*-(trans-3-{{2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy})cyclobutyl)-*N*-methylpyridine-3-carboxamide;

N-(trans-3-{{2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy})cyclobutyl)-*N*,1-dimethyl-1*H*-pyrazole-3-carboxamide;

N-(trans-3-{{2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy})cyclobutyl)-3,3,3-trifluoro-*N*-methylpropanamide;

15 (2*R*)-*N*-(trans-3-{{2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy})cyclobutyl)-2-hydroxy-*N*-methyl-4-phenylbutanamide;

N-(trans-3-{{2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy})cyclobutyl)-2-(4-fluoro-1*H*-pyrazol-1-yl)-*N*-methylpropanamide;

20 *N*-(trans-3-{{2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy})cyclobutyl)-*N*,2-dimethyl-2-(1*H*-pyrazol-1-yl)propanamide;

N-(trans-3-{{2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy})cyclobutyl)-*N*,5-dimethyl-1,2-oxazole-4-carboxamide;

N-(trans-3-{{2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy})cyclobutyl)-2,2-difluoro-*N*-methylcyclopropanecarboxamide;

25 (2*R*)-*N*-(trans-3-{{2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy})cyclobutyl)-2-cyclohexyl-2-hydroxy-*N*-methylethanamide;

N-(trans-3-{{2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy})cyclobutyl)-*N*-methyl-1-(1*H*-pyrazol-1-yl)cyclobutanecarboxamide;

30 (2S)-*N*-(trans-3-{{2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy})cyclobutyl)-2-hydroxy-*N*-methyl-2-phenylpropanamide;

N-(trans-3-{{2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy})cyclobutyl)-1-(2-hydroxyethyl)-*N*-methyl-1*H*-pyrazole-4-carboxamide;

N-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-2-(2,3-dihydro-1-benzofuran-5-yl)-2-hydroxy-*N*-methylacetamide;

N-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-*N*,5-dimethyl-1,2-oxazole-3-carboxamide;

5 *N*-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-1-(2-cyanoethyl)-*N*-methyl-1*H*-pyrazole-4-carboxamide;

(2*S*)-*N*-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-2-hydroxy-3-(1*H*-imidazol-4-yl)-*N*-methylpropanamide;

10 *N*-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-*N*,5-dimethyl-1*H*-imidazole-4-carboxamide;

N-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-*N*-methylacetamide;

N-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-1-(4-chloro-1*H*-pyrazol-1-yl)-*N*-methylcyclopropanecarboxamide;

15 1-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-1-methyl-3-[(3-methyloxetan-3-yl)methyl]urea;

N-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-4-cyano-*N*-methylpiperidine-1-carboxamide;

20 1-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-3-(2-methoxyethyl)-1-methylurea;

1-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-1-methyl-3-propylurea;

(1*S*,4*S*)-*N*-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-*N*-methyl-6-oxo-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide;

25 *N*-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-4,4-difluoro-*N*-methylpiperidine-1-carboxamide;

N-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-*N*,4-dimethylpiperazine-1-carboxamide;

30 1-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-3-[(3,3-difluorocyclobutyl)methyl]-1-methylurea;

1-(*trans*-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-1-methyl-3-[(2*S*)-tetrahydrofuran-2-ylmethyl]urea;

1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1-methyl-3-(pyridin-2-ylmethyl)urea;

1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-[(2*R*)-1-methoxypropan-2-yl]-1-methylurea;

5 1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-bicyclo[1.1.1]pent-1-yl-1-methylurea;

1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1-methyl-3-[2-(pyrrolidin-1-yl)ethyl]urea;

10 1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1-methyl-3-[(2*R*)-tetrahydrofuran-2-ylmethyl]urea;

1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-(cyclopropylmethyl)-1-methylurea;

1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-(2,2-difluoropropyl)-1-methylurea;

15 1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-(2-ethoxyethyl)-1-methylurea;

1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1-methyl-3-[(1*R*,5*S*,6*r*)-3-oxabicyclo[3.1.0]hex-6-yl]urea;

20 1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1-methyl-3-(tetrahydro-2*H*-pyran-3-yl)urea;

1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1-methyl-3-(tetrahydrofuran-3-yl)urea;

1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-[(2*S*)-1-methoxypropan-2-yl]-1-methylurea;

25 1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1-methyl-3-(tetrahydro-2*H*-pyran-4-ylmethyl)urea;

1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-(3-methoxypropyl)-1-methylurea;

30 1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1,3-dimethyl-3-(2,2,2-trifluoroethyl)urea;

1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1-methyl-3-(2,2,2-trifluoroethyl)urea;

6-[[*trans*-3-(1,1-dioxido-1,2,5-thiadiazolidin-2-yl)cyclobutyl]oxy}-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-2'-amine;

(2*R*)-*N*-[[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-2-cyclopropyl-2-hydroxy-*N*-methylethanamide;

5 (2*S*)-*N*-[[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-2-cyclopropyl-2-hydroxy-*N*-methylethanamide;

(3*R*)-*N*-[[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-*N*-methylpiperidine-3-carboxamide;

10 (3*S*)-*N*-[[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-*N*-methylpiperidine-3-carboxamide;

6-[[*trans*-3-(1,1-dioxido-1,2-thiazolidin-2-yl)cyclobutyl]oxy}-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-2'-amine;

N-[[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-*N*-methylpiperidine-4-carboxamide;

15 (3*S*)-*N*-[[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-*N*,3-dimethylpiperazine-1-carboxamide;

(3*R*)-*N*-[[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-*N*,3-dimethylpiperazine-1-carboxamide;

20 (2*R*)-*N*-[[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-*N*,2-dimethylpiperazine-1-carboxamide;

(2*S*)-*N*-[[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-*N*,2-dimethylpiperazine-1-carboxamide;

6-[[*cis*-3-(1,1-dioxido-1,2-thiazolidin-2-yl)-3-methylcyclobutyl]oxy}-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-2'-amine;

25 6-[[*trans*-3-(1,1-dioxido-1,2-thiazolidin-2-yl)-3-methylcyclobutyl]oxy}-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-2'-amine;

tert-butyl [[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]carbamate;

30 1-[[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]pyrrolidin-2-one;

(2*R*)-*N*-[[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-2-hydroxy-2-phenylethanamide;

(2S)-N-[*trans*-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-2-hydroxy-2-phenylethanamide;

(2S)-N-[*trans*-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-2-hydroxy-N,3-dimethylbutanamide;

5 (2R)-N-[*trans*-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-2-hydroxy-N-methyl-2-phenylethanamide;

(2R)-2-amino-N-[*trans*-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-N-methyl-2-phenylethanamide;

10 N-[*trans*-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-2-phenylacetamide;

N-[*trans*-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-3,3,3-trifluoropropanamide;

(2S)-2-amino-N-[*trans*-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-N-methyl-2-phenylethanamide;

15 N-[*trans*-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-N-methyl-2-phenylacetamide;

N-[*trans*-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-1-fluorocyclopropanecarboxamide;

20 N-[*trans*-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-N-methylpropanamide;

(2S)-N-[*trans*-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]tetrahydrofuran-2-carboxamide;

N-[*trans*-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-2-hydroxy-N-methyl-2-(pyridin-2-yl)acetamide;

25 N-[*trans*-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-1-fluoro-N-methylcyclopropanecarboxamide;

N-[*trans*-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-3,3,3-trifluoro-N-methylpropanamide;

30 (2S)-N-[*trans*-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-N-methyltetrahydrofuran-2-carboxamide; and

N-[*trans*-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]propanamide,

or a pharmaceutically acceptable salt thereof.

Embodiments relate to a pharmaceutical composition comprising a compound of any of the embodiments of the compounds of formula (I), formula (II), or formula (III), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

5 Embodiments relate to a combination of a compound of any of the embodiments of the compounds of formula (I), formula (II), or formula (III), or a pharmaceutically acceptable salt thereof, with an anti-tumor agent or with radiation therapy, for the treatment of cancer.

10 Embodiments relate to a combination of a compound of any of the embodiments of the compounds of formula (I), formula (II), or formula (III), or a pharmaceutically acceptable salt thereof, with an anti-tumor agent, for the treatment of cancer.

15 Embodiments relate to a method of treating abnormal cell growth in a mammal comprising administering to the mammal an amount of a compound of any of the embodiments of the compounds of formula (I), formula (II), or formula (III), or a pharmaceutically acceptable salt thereof, that is effective in treating abnormal cell growth.

Embodiments relate to the method of treating abnormal cell growth, wherein the abnormal cell growth is cancer.

20 Embodiments relate to the method of treating cancer, wherein the cancer is selected from the group consisting of basal cell cancer, medulloblastoma cancer, liver cancer, rhabdomyosarcoma, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the
25 endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the
30 bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system, primary central nervous system lymphoma, spinal axis tumors, brain stem glioma and pituitary adenoma, or a combination of one or more of the foregoing cancers.

Embodiments relate to the method of treating cancer, wherein the cancer is selected from the group consisting of lung cancer, cancer of the head or neck, colon cancer, breast cancer, and ovarian cancer, or a combination of one or more of the foregoing cancers.

5

Detailed Description of the Invention

The following abbreviations may be used herein: AcOH (acetic acid); Boc (*tert*-butoxycarbonyl); CBZ (carboxybenzyl); cDNA (complementary DNA); CDI (1,1'-carbonyldiimidazole); DBU (1,8-diazabicyclo[5.4.0]undec-7-ene); DIPEA (*N,N*-diisopropylethylamine); DMF (*N,N*-dimethylformamide); DMSO (dimethylsulfoxide); dppf [1,1'-bis(diphenylphosphanyl)ferrocene]; DTT ((2*S*,3*S*)-1,4-bis(sulfanyl)butane-2,3-diol); EDTA (2-({2-[bis(carboxymethyl)amino]ethyl}(carboxymethyl)amino)acetic acid); EtOH (ethanol); EtOAc (ethyl acetate); eq (equivalent); h (hour or hours); HATU (2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate); HEPES (2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid); HPLC (high-performance liquid chromatography); iPrOH (isopropyl alcohol); KHMDS (potassium bis(trimethylsilyl)amide); LCMS (liquid chromatography-mass spectrometry); Me (methyl); MeCN (acetonitrile); MeOH (methanol); min (minute or minutes); NaHCO₃ (sodium bicarbonate); NaHMDS (sodium bis(trimethylsilyl)amide); N/A (not available); N/D (not determined); OAc (acetate); Pd/C (palladium on carbon); SEC (size exclusion chromatography); SFC (supercritical fluid chromatography); TBAF (tetrabutylammonium fluoride); TCEP (*tris*(2-carboxyethyl)phosphine); TFA (trifluoroacetate); THF (tetrahydrofuran); TLC (thin layer chromatography); TMS-Cl (trimethylsilyl chloride); TMSI (trimethylsilyl iodide); and Tris (tris(hydroxymethyl)aminomethane).

The term "halogen", as used herein, refers to a fluorine, chlorine, bromine, or iodine atom or fluoro, chloro, bromo, or iodo. Additionally, the term "halogen" refers to F, Cl, Br, or I. The terms fluorine, fluoro and F, for example, are understood to be equivalent herein.

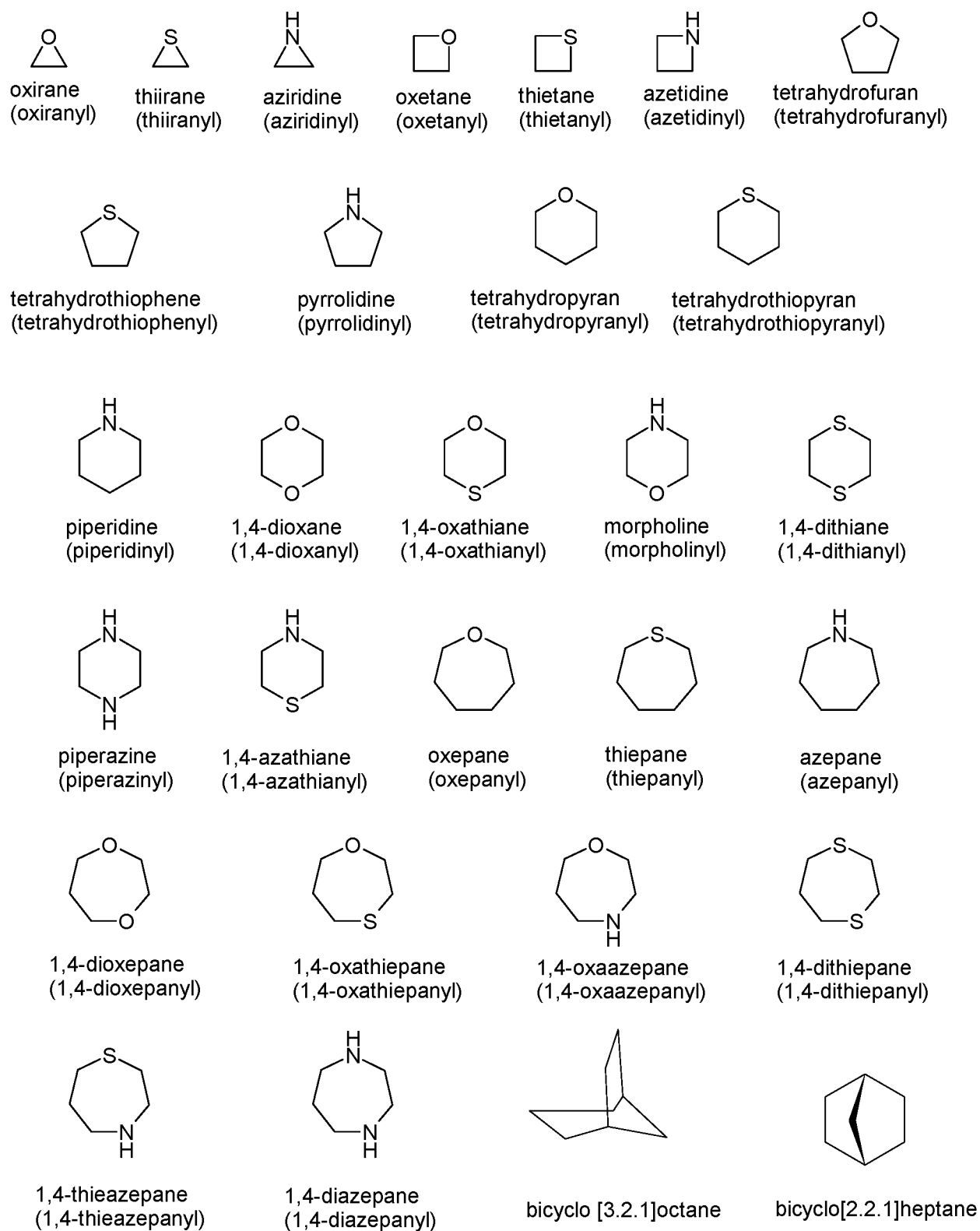
The term "alkyl", as used herein, refers to saturated monovalent hydrocarbon radicals containing, in certain embodiments, from one to six, or from one to three carbon atoms, having straight or branched moieties. The term "C₁-C₆ alkyl" refers to an alkyl radical containing from one to six carbon atoms, having straight or branched

moieties. The term "C₁-C₆ alkyl" includes within its definition the terms "C₁-C₃ alkyl" and "C₁-C₄ alkyl". Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, 2-pentyl, 3-pentyl, isopentyl, neopentyl, (*R*)-2-methylbutyl, (*S*)-2-methylbutyl, 3-methylbutyl,

5 2,3-dimethylpropyl, 2,3-dimethylbutyl, hexyl, and the like. Optional substitutions, unless otherwise specified, occur off any available carbon of the alkyl moiety.

The term "cycloalkyl", as used herein, refers to a monocyclic, fused or bridged bicyclic or tricyclic carbocyclic ring group containing, in certain embodiments, from three to ten carbon atoms. The term "cycloalkyl" also includes spirocyclic cycloalkyl groups, including multi-ring systems joined by a single atom. The terms "C₃-C₁₀ cycloalkyl", "C₃-C₇ cycloalkyl", "C₃-C₆ cycloalkyl", "C₃-C₅ cycloalkyl", "C₃-C₄ cycloalkyl", and "C₅-C₇ cycloalkyl" contain from three to ten, from three to seven, from three to six, from three to five, from three to four, and from five to seven carbon atoms, respectively. Cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, bicyclo[2.2.1]heptanyl, bicyclo[3.2.1]octanyl, bicyclo[5.2.0]nonanyl, adamantanyl, and the like.

The term "heterocycloalkyl", as used herein, refers to a non-aromatic, monocyclic, fused or bridged bicyclic or tricyclic or spirocyclic ring group containing, in certain embodiments, a total of three to ten ring atoms, in which one to four ring atoms are heteroatoms independently selected from nitrogen, oxygen, and sulfur, and wherein the sulfur atom may be optionally oxidized with one or two oxygen atoms, the remaining ring atoms being carbon, with the proviso that such ring systems may not contain two adjacent oxygen atoms or two adjacent sulfur atoms. Furthermore, such groups may be bonded to the remainder of the compounds of embodiments disclosed herein through either a carbon atom or a heteroatom, if possible. The terms "3-10 membered heterocycloalkyl", "3-7 membered heterocycloalkyl", "4-8 membered heterocycloalkyl", "4-7 membered heterocycloalkyl", "4-6 membered heterocycloalkyl", and "5-6 membered heterocycloalkyl" contain from three to ten, from three to seven, from four to eight, from four to seven, from four to six carbon atoms, and from five to six carbon atoms, respectively. Examples of saturated heterocycloalkyl groups include, but are not limited to:



The term "aryl", as used herein, refers to a group derived from an aromatic hydrocarbon containing in certain embodiments, from five to ten carbon atoms. The term "C₅-C₁₀ aryl" contains from five to ten carbon atoms. Examples of such groups include, but are not limited to, phenyl and naphthyl. The term "aryl" also includes fused

polycyclic aromatic ring systems in which an aromatic ring is fused to one or more rings. Examples include, but are not limited to, 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl. Also included within the scope of the term “aryl”, as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as in an indanyl, phenanthridinyl, or tetrahydronaphthyl, where the radical or point of attachment is on the aromatic ring.

The term “heteroaryl, as used herein, refers to an aromatic monocyclic or bicyclic heterocyclic group having a total of from 5 to 12 atoms in its ring, and containing from 2 to 9 carbon atoms and from one to four heteroatoms each independently selected from nitrogen, oxygen, and sulfur, with the proviso that the ring of said group does not contain two adjacent oxygen atoms or two adjacent sulfur atoms. The terms “5-12 membered heteroaryl”, “5-10 membered heteroaryl”, “5-6 membered heteroaryl”, and “4-6 membered heteroaryl” contain from five to twelve, from five to ten, from five to six, and from four to six ring atoms, respectively. The heteroaryl groups include benzo-fused ring systems. Examples of heteroaryl groups include, but are not limited to, pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, furazanyl, thiadiazolyl, thiazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, indolyl, isoindolyl, indolizinyl, benzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, benzoxazolyl, furo[3,2-*b*]pyridinyl, benzothiazolyl, benzofurazanyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, cinnolinyl, phthalazinyl, pyrido[3,4-*d*]pyrimidinyl, pteridinyl, and the like.

Also included within the scope of the term “5-12 membered heteroaryl”, as used herein, are benzo-fused unsaturated oxygen or nitrogen heterocycles, which refer to a heterocyclic group in which a heteroatomic ring is fused to one or more aromatic rings. Examples include, but are not limited to, 2,3-dihydrobenzofuran, indolinyl, 1,3-dihydroisobenzofuran, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

The term “treating”, as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term “treatment”, as used herein, unless otherwise indicated, refers to the act of treating as “treating” is defined immediately above.

As used herein, an "effective" amount refers to an amount of a substance, agent, compound, or composition that is of sufficient quantity to result in a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction - either as a single dose or according to a multiple dose regimen, alone or in combination with other agents or substances. One of ordinary skill in the art would be able to determine such amounts based on such factors as the subject's size, the severity of the subject's symptoms, and the particular composition or route of administration selected. The subject may be a human or non-human mammal (e.g., rabbit, rat, mouse, monkey or other lower-order primate).

Embodiments disclosed herein include isotopically-labeled compounds, which are identical to those recited in formula (I), formula (II), or formula (III), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes that can be incorporated into compounds of the embodiments disclosed herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as, but not limited to, ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds described herein and pharmaceutically acceptable salts of said compounds which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present embodiments. Certain isotopically-labeled compounds of the embodiments disclosed herein, for example, those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically-labeled compounds of embodiments disclosed herein can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically-labeled reagent for a non-isotopically-labeled reagent.

Some embodiments relate to the pharmaceutically acceptable salts of the compounds described herein. Pharmaceutically acceptable salts of the compounds described herein include the acid addition and base addition salts thereof.

Some embodiments also relate to the pharmaceutically acceptable acid addition salts of the compounds described herein. Suitable acid addition salts are formed from acids which form non-toxic salts. Non-limiting examples of suitable acid addition salts, i.e., salts containing pharmacologically acceptable anions, include, but are not limited to, the acetate, acid citrate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, bitartrate, borate, camsylate, citrate, cyclamate, edisylate, esylate, ethanesulfonate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methanesulfonate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, p-toluenesulfonate, tosylate, trifluoroacetate and xinofoate salts.

Additional embodiments relate to base addition salts of the compounds described herein. Suitable base addition salts are formed from bases which form non-toxic salts. Non-limiting examples of suitable base salts include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

The compounds described herein that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds described herein are those that form non-toxic acid addition salts, e.g., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts. The compounds described herein that include a basic moiety,

such as an amino group, may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above.

The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of the compounds described herein that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

The compounds of the embodiments described herein include all stereoisomers (e.g., *cis* and *trans* isomers) and all optical isomers of compounds described herein (e.g., *R* and *S* enantiomers), as well as racemic, diastereomeric and other mixtures of such isomers. While all stereoisomers are encompassed within the scope of our claims, one skilled in the art will recognize that particular stereoisomers may be preferred.

In some embodiments, the compounds described herein can exist in several tautomeric forms, including the enol and imine form, and the keto and enamine form and geometric isomers and mixtures thereof. All such tautomeric forms are included within the scope of the present embodiments. Tautomers exist as mixtures of a tautomeric set in solution. In solid form, usually one tautomer predominates. Even though one tautomer may be described, the present embodiments includes all tautomers of the present compounds.

The present embodiments also include atropisomers of the compounds described herein. Atropisomers refer to compounds that can be separated into rotationally restricted isomers.

Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, 2002). Methods for making pharmaceutically acceptable salts of compounds described herein are known to one of skill in the art.

The term "solvate" is used herein to describe a molecular complex comprising a compound described herein and one or more pharmaceutically acceptable solvent molecules, for example, ethanol.

5 The compounds described herein may also exist in unsolvated and solvated forms. Accordingly, some embodiments relate to the hydrates and solvates of the compounds described herein.

Compounds described herein containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound described herein contains an alkenyl or alkenylene group, geometric cis/trans (or Z/E) isomers are possible.
10 Where structural isomers are interconvertible via a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in compounds described herein containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds which contain an aromatic moiety. A single compound may exhibit more than one type of isomerism.

15 Included within the scope of the present embodiments are all stereoisomers, geometric isomers and tautomeric forms of the compounds described herein, including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, d-lactate or l-lysine, or racemic, for example, dl-tartrate or dl-
20 arginine.

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the
25 racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC) or SFC.

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where a compound described herein contains an acidic or basic moiety, a base or acid such as
30 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

“Abnormal cell growth”, as used herein, unless otherwise indicated, refers to cell growth that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) that proliferate by expressing a mutated tyrosine kinase or overexpression of a receptor tyrosine kinase; (2) benign and malignant cells of other proliferative diseases in which aberrant tyrosine kinase activation occurs; (3) any tumors that proliferate by receptor tyrosine kinases; (4) any tumors that proliferate by aberrant serine/threonine kinase activation; (5) benign and malignant cells of other proliferative diseases in which aberrant serine/threonine kinase activation occurs; (6) any tumors that proliferate by aberrant signaling, metabolic, epigenetic and transcriptional mechanism; and (7) benign and malignant cells of other proliferative diseases in which aberrant signaling, metabolic, epigenetic and transcriptional mechanism.

Further embodiments relate to methods of treating abnormal cell growth in a mammal. Additional embodiments relate to a method of treating abnormal cell growth in a mammal comprising administering to the mammal an amount of a compound described herein that is effective in treating abnormal cell growth.

In other embodiments, the abnormal cell growth is cancer.

In some embodiments, the cancer is selected from the group consisting of lung cancer, mesothelioma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, hepatic carcinoma, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin’s disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, hematology malignancy, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, glioblastoma, brain stem glioma, pituitary adenoma, or a combination of two or more of the foregoing cancers.

Additional embodiments relate to methods of treating cancer solid tumors in a mammal. Some embodiments relate to the treatment of cancer solid tumor in a

mammal comprising administering to the mammal an amount of a compound described herein that is effective in treating said cancer solid tumor.

In other embodiments, the cancer solid tumor is breast, lung, colon, brain, prostate, stomach, pancreatic, ovarian, skin (melanoma), endocrine, uterine, testicular, or bladder.

Further embodiments relate to methods of treating abnormal cell growth in a mammal which comprises administering to said mammal an amount of a compound described herein that is effective in treating abnormal cell growth in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, radiation, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.

More embodiments relate to pharmaceutical compositions for treating abnormal cell growth in a mammal comprising an amount of a compound described herein that is effective in treating abnormal cell growth, and a pharmaceutically acceptable carrier.

Additional embodiments relate to a method of treating abnormal cell growth in a mammal, including a human, comprising administering to the mammal an amount of a compound described herein, or a pharmaceutically acceptable salt, solvate, hydrate or prodrug thereof, that is effective in treating abnormal cell growth. In one embodiment of this method, the abnormal cell growth is cancer, including, but not limited to, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers. In one embodiment the method comprises administering to a mammal an amount

of a compound described herein that is effective in treating said cancer solid tumor. In one preferred embodiment the solid tumor is breast, lung, colon, brain, prostate, stomach, pancreatic, ovarian, skin (melanoma), endocrine, uterine, testicular, and bladder cancer.

5 In another embodiment of said method, said abnormal cell growth is a benign proliferative disease, including, but not limited to, psoriasis, benign prostatic hypertrophy or restinosis.

 Some embodiments relate to a method of treating abnormal cell growth in a mammal which comprises administering to said mammal an amount of a compound
10 described herein, or a pharmaceutically acceptable salt, solvate, hydrate or prodrug thereof, that is effective in treating abnormal cell growth in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies,
15 cytotoxics, anti-hormones, and anti-androgens.

 Additional embodiments relate to a pharmaceutical composition for treating abnormal cell growth in a mammal, including a human, comprising an amount of a compound described herein, or a pharmaceutically acceptable salt, solvate, hydrate or prodrug thereof, that is effective in treating abnormal cell growth, and a
20 pharmaceutically acceptable carrier. In one embodiment of said composition, said abnormal cell growth is cancer, including, but not limited to, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian
25 tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic
30 lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers. In another embodiment of said

pharmaceutical composition, said abnormal cell growth is a benign proliferative disease, including, but not limited to, psoriasis, benign prostatic hypertrophy or restinosis.

Further embodiments relate to a method of treating abnormal cell growth in a mammal which comprises administering to said mammal an amount of a compound
5 described herein, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, that is effective in treating abnormal cell growth in combination with another anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies,
10 cytotoxics, anti-hormones, and anti-androgens. Some embodiments contemplate a pharmaceutical composition for treating abnormal cell growth wherein the composition includes a compound described herein, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, that is effective in treating abnormal cell growth, and another anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents,
15 anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.

Yet more embodiments relate to a method of treating a disorder associated with angiogenesis in a mammal, including a human, comprising administering to said
20 mammal an amount of a compound described herein, as defined above, or a pharmaceutically acceptable salt, solvate, hydrate or prodrug thereof, that is effective in treating said disorder in combination with one or more anti-tumor agents listed above. Such disorders include cancerous tumors such as melanoma; ocular disorders such as age-related macular degeneration, presumed ocular histoplasmosis syndrome, and
25 retinal neovascularization from proliferative diabetic retinopathy; rheumatoid arthritis; bone loss disorders such as osteoporosis, Paget's disease, humoral hypercalcemia of malignancy, hypercalcemia from tumors metastatic to bone, and osteoporosis induced by glucocorticoid treatment; coronary restenosis; and certain microbial infections including those associated with microbial pathogens selected from adenovirus,
30 hantaviruses, *Borrelia burgdorferi*, *Yersinia* spp., *Bordetella pertussis*, and group A *Streptococcus*.

Some embodiments relate to a method of (and to a pharmaceutical composition for) treating abnormal cell growth in a mammal which comprise an amount of a

compound described herein, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, in combination with an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors inhibitor (e.g., inhibiting the means by which regulatory molecules that govern the fundamental processes of cell growth, differentiation, and survival communicated within the cell), and antiproliferative agents, which amounts are together effective in treating said abnormal cell growth.

Anti-angiogenesis agents, such as MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloproteinase 9) inhibitors, and COX-II (cyclooxygenase II) inhibitors, can be used in conjunction with a compound described herein in the methods and pharmaceutical compositions described herein. Examples of useful COX-II inhibitors include CELEBREXTM (celecoxib), Bextra (valdecoxib), paracoxib, Vioxx (rofecoxib), and Arcoxia (etoricoxib). Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24, 1996), WO 96/27583 (published March 7, 1996), European Patent Application No. 97304971.1 (filed July 8, 1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26, 1998), WO 98/03516 (published January 29, 1998), WO 98/34918 (published August 13, 1998), WO 98/34915 (published August 13, 1998), WO 98/33768 (published August 6, 1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13, 1994), European Patent Publication 931,788 (published July 28, 1999), WO 90/05719 (published May 31, 1990), WO 99/52910 (published October 21, 1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17, 1999), PCT International Application No. PCT/IB98/01113 (filed July 21, 1998), European Patent Application No. 99302232.1 (filed March 25, 1999), Great Britain patent application number 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12, 1999), United States Patent 5,863,949 (issued January 26, 1999), United States Patent 5,861,510 (issued January 19, 1999), and European Patent Publication 780,386 (published June 25, 1997), all of which are herein incorporated by reference in their entirety. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or MMP-9 relative to the other matrix-metalloproteinases (i.e. MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13).

Some specific examples of MMP inhibitors useful in combination with the compounds described herein are AG-3340, RO 32-3555, RS 13-0830, and the following compounds:

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclopentyl)-amino]-propionic acid;

3-exo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide;

(2R, 3R) 1-[4-(2-chloro-4-fluoro-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

4-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide;

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclobutyl)-amino]-propionic acid;

4-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide;

3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-3-carboxylic acid hydroxyamide;

(2R, 3R) 1-[4-(4-fluoro-2-methyl-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-1-methyl-ethyl)-amino]-propionic acid;

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(4-hydroxycarbamoyl-tetrahydro-pyran-4-yl)-amino]-propionic acid;

3-exo-3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide;

3-endo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; and

3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-furan-3-carboxylic acid hydroxyamide;

and pharmaceutically acceptable salts and solvates of said compounds.

VEGF inhibitors, for example, sutent and axitinib, can also be combined with a compound described herein. VEGF inhibitors are described in, for example in WO 99/24440 (published May 20, 1999), PCT International Application PCT/IB99/00797

(filed May 3, 1999), in WO 95/21613 (published August 17, 1995), WO 99/61422 (published December 2, 1999), United States Patent 5,834,504 (issued November 10, 1998), WO 98/50356 (published November 12, 1998), United States Patent 5,883,113 (issued March 16, 1999), United States Patent 5,886,020 (issued March 23, 1999),
5 United States Patent 5,792,783 (issued August 11, 1998), U.S. Patent No. US 6,653,308 (issued November 25, 2003), WO 99/10349 (published March 4, 1999), WO 97/32856 (published September 12, 1997), WO 97/22596 (published June 26, 1997), WO 98/54093 (published December 3, 1998), WO 98/02438 (published January 22, 1998), WO 99/16755 (published April 8, 1999), and WO 98/02437 (published January
10 22, 1998), all of which are herein incorporated by reference in their entirety. Other examples of some specific VEGF inhibitors are IM862 (Cytran Inc. of Kirkland, Washington, USA); Avastin, an anti-VEGF monoclonal antibody of Genentech, Inc. of South San Francisco, California; and angiozyme, a synthetic ribozyme from Ribozyme (Boulder, Colorado) and Chiron (Emeryville, California).

15 ErbB2 receptor inhibitors, such as GW-282974 (Glaxo Wellcome plc), and the monoclonal antibodies AR-209 (Aronex Pharmaceuticals Inc. of The Woodlands, Texas, USA) and 2B-1 (Chiron), may be administered in combination with a compound described herein. Such erbB2 inhibitors include Herceptin, 2C4, and pertuzumab. Such erbB2 inhibitors include those described in WO 98/02434 (published January 22, 1998),
20 WO 99/35146 (published July 15, 1999), WO 99/35132 (published July 15, 1999), WO 98/02437 (published January 22, 1998), WO 97/13760 (published April 17, 1997), WO 95/19970 (published July 27, 1995), United States Patent 5,587,458 (issued December 24, 1996), and United States Patent 5,877,305 (issued March 2, 1999), each of which is herein incorporated by reference in its entirety. ErbB2 receptor inhibitors useful in the
25 embodiments described herein are also described in United States Provisional Application No. 60/117,341, filed January 27, 1999, and in United States Provisional Application No. 60/117,346, filed January 27, 1999, both of which are herein incorporated by reference in their entirety. Other erbb2 receptor inhibitors include TAK-165 (Takeda) and GW-572016 (Glaxo-Wellcome).

30 Various other compounds, such as styrene derivatives, have also been shown to possess tyrosine kinase inhibitory properties, and some of tyrosine kinase inhibitors have been identified as erbB2 receptor inhibitors. More recently, five European patent publications, namely EP 0 566 226 A1 (published October 20, 1993), EP 0 602 851 A1

(published June 22, 1994), EP 0 635 507 A1 (published January 25, 1995), EP 0 635 498 A1 (published January 25, 1995), and EP 0 520 722 A1 (published December 30, 1992), refer to certain bicyclic derivatives, in particular quinazoline derivatives, as possessing anti-cancer properties that result from their tyrosine kinase inhibitory properties. Also, World Patent Application WO 92/20642 (published November 26, 1992), refers to certain bis-mono and bicyclic aryl and heteroaryl compounds as tyrosine kinase inhibitors that are useful in inhibiting abnormal cell proliferation. World Patent Applications WO96/16960 (published June 6, 1996), WO 96/09294 (published March 6, 1996), WO 97/30034 (published August 21, 1997), WO 98/02434 (published January 22, 1998), WO 98/02437 (published January 22, 1998), and WO 98/02438 (published January 22, 1998), also refer to substituted bicyclic heteroaromatic derivatives as tyrosine kinase inhibitors that are useful for the same purpose. Other patent applications that refer to anti-cancer compounds are World Patent Application WO00/44728 (published August 3, 2000), EP 1029853A1 (published August 23, 2000), and WO01/98277 (published December 12, 2001) all of which are incorporated herein by reference in their entirety.

Epidermal growth factor receptor (EGFR) inhibitors may be administered in combination with a compound of the presentation invention. Such EGFR inhibitors include gefinitib, erlotinib, icotinib, afatinib and dacomitinib. Monoclonal antibody inhibitors of EGFR, such as cetuximab, may also be combined with a compound of the present invention.

PI3K inhibitors, such as PI3K beta inhibitors, may be administered in combination with a compound of the presentation invention.

Mammalian target of rapamycin (mTOR) inhibitors may be administered in combination with a compound of the presentation invention. Such mTOR inhibitors include rapamycin analogs and ATP competitive inhibitors.

c-Met inhibitors may be administered in combination with a compound of the presentation invention. Such c-Met inhibitors include crizotinib and ARQ-197. Monoclonal antibody inhibitors of c-Met, such as METMab, may also be combined with a compound of the present invention.

CDK inhibitors may be administered in combination with a compound of the presentation invention. Such mTOR inhibitors include palbociclib.

MEK inhibitors may be administered in combination with a compound of the presentation invention. Such MEK inhibitors include PD-325901.

PARP inhibitors may be administered in combination with a compound of the presentation invention.

5 JAK inhibitors may be administered in combination with a compound of the presentation invention.

An antagonist of a Programmed Death 1 protein (PD-1) may be administered in combination with a compound of the presentation invention.

Other antiproliferative agents that may be used with the compounds described
10 herein include inhibitors of the enzyme farnesyl protein transferase and inhibitors of the receptor tyrosine kinase PDGFr, including the compounds disclosed and claimed in the following United States patent applications: 09/221946 (filed December 28, 1998); 09/454058 (filed December 2, 1999); 09/501163 (filed February 9, 2000); 09/539930 (filed March 31, 2000); 09/202796 (filed May 22, 1997); 09/384339 (filed August 26,
15 1999); and 09/383755 (filed August 26, 1999); and the compounds disclosed and claimed in the following United States provisional patent applications: 60/168207 (filed November 30, 1999); 60/170119 (filed December 10, 1999); 60/177718 (filed January 21, 2000); 60/168217 (filed November 30, 1999), and 60/200834 (filed May 1, 2000). Each of the foregoing patent applications and provisional patent applications is herein
20 incorporated by reference in their entirety.

A compound described herein may also be used with other agents useful in treating abnormal cell growth or cancer, including, but not limited to, agents capable of enhancing antitumor immune responses, such as CTLA4 (cytotoxic lymphocyte antigen 4) antibodies, and other agents capable of blocking CTLA4; and anti-proliferative agents
25 such as other farnesyl protein transferase inhibitors, for example the farnesyl protein transferase inhibitors described in the references cited in the "Background" section, supra. Specific CTLA4 antibodies that can be used in the present embodiments include those described in United States Provisional Application 60/113,647 (filed December 23, 1998) which is herein incorporated by reference in its entirety.

30 A compound described herein may be applied as a sole therapy or may involve one or more other anti-tumor substances, for example those selected from, for example, mitotic inhibitors, for example vinblastine; alkylating agents, for example cis-platin, oxaliplatin, carboplatin and cyclophosphamide; anti-metabolites, for example 5-

fluorouracil, capecitabine, cytosine arabinoside and hydroxyurea, or, for example, one of the preferred anti-metabolites disclosed in European Patent Application No. 239362 such as N-(5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid; growth factor inhibitors; cell cycle inhibitors; intercalating
5 antibiotics, for example adriamycin and bleomycin; enzymes, for example interferon; and anti-hormones, for example anti-estrogens such as Nolvadex (tamoxifen) or, for example anti-androgens such as Casodex (4'-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide).

The compounds described herein may be used alone or in combination with one
10 or more of a variety of anti-cancer agents or supportive care agents. For example, the compounds described herein may be used with cytotoxic agents, e.g., one or more selected from the group consisting of a camptothecin, irinotecan HCl (Camptosar), edotecarin, SU-11248, epirubicin (Ellence), docetaxel (Taxotere), paclitaxel, rituximab (Rituxan) bevacizumab (Avastin), imatinib mesylate (Gleevec), Erbitux, gefitinib (Iressa),
15 and combinations thereof. Some embodiments also contemplate the use of the compounds described herein together with hormonal therapy, e.g., exemestane (Aromasin), Lupron, anastrozole (Arimidex), tamoxifen citrate (Nolvadex), Trelstar, and combinations thereof. Further, some embodiments provide a compound described herein alone or in combination with one or more supportive care products, e.g., a
20 product selected from the group consisting of Filgrastim (Neupogen), ondansetron (Zofran), Fragmin, Procrit, Aloxi, Emend, or combinations thereof. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment.

The compounds described herein may be used with antitumor agents, alkylating
25 agents, antimetabolites, antibiotics, plant-derived antitumor agents, camptothecin derivatives, tyrosine kinase inhibitors, antibodies, interferons, and/or biological response modifiers. In this regard, the following is a non-limiting list of examples of secondary agents that may be used with the compounds described herein.

Alkylating agents include, but are not limited to, nitrogen mustard N-oxide,
30 cyclophosphamide, ifosfamide, melphalan, busulfan, mitobronitol, carboquone, thiotepa, ranimustine, nimustine, temozolomide, AMD-473, altretamine, AP-5280, apaziquone, brostallicin, bendamustine, carmustine, estramustine, fotemustine, glufosfamide, ifosfamide, KW-2170, mafosfamide, and mitolactol; platinum-coordinated alkylating

compounds include but are not limited to, cisplatin, carboplatin, eptaplatin, lobaplatin, nedaplatin, oxaliplatin or satrplatin.

Antimetabolites include but are not limited to, methotrexate, 6-mercaptopurine riboside, mercaptopurine, 5-fluorouracil (5-FU) alone or in combination with leucovorin, tegafur, UFT, doxifluridine, carmofur, cytarabine, cytarabine ocfosfate, enocitabine, S-1, gemcitabine, fludarabin, 5-azacitidine, capecitabine, cladribine, clofarabine, decitabine, eflornithine, ethynylcytidine, cytosine arabinoside, hydroxyurea, TS-1, melphalan, nelarabine, nolatrexed, ocfosfate, disodium premetrexed, pentostatin, pelitrexol, raltitrexed, triapine, trimetrexate, vidarabine, vincristine, vinorelbine; or for example, one of the preferred anti-metabolites disclosed in European Patent Application No. 239362 such as N-(5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid.

Antibiotics include but are not limited to: aclarubicin, actinomycin D, amrubicin, annamycin, bleomycin, daunorubicin, doxorubicin, elsamitrucin, epirubicin, galarubicin, idarubicin, mitomycin C, nemorubicin, neocarzinostatin, peplomycin, pirarubicin, rebeccamycin, stimalamer, streptozocin, valrubicin or zinostatin.

Hormonal therapy agents, e.g., exemestane (Aromasin), Lupron, anastrozole (Arimidex), doxercalciferol, fadrozole, formestane, anti-estrogens such as tamoxifen citrate (Nolvadex) and fulvestrant, Trelstar, toremifene, raloxifene, lasofoxifene, letrozole (Femara), or anti-androgens such as bicalutamide, flutamide, mifepristone, nilutamide, Casodex® (4'-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide) and combinations thereof.

Plant derived anti-tumor substances include for example those selected from mitotic inhibitors, for example vinblastine, docetaxel (Taxotere) and paclitaxel.

Cytotoxic topoisomerase inhibiting agents include one or more agents selected from the group consisting of aclarubicin, amonafide, belotecan, camptothecin, 10-hydroxycamptothecin, 9-aminocamptothecin, diflomotecan, irinotecan HCl (Camptosar), edotecarin, epirubicin (Ellence), etoposide, exatecan, gimatecan, lurtotecan, mitoxantrone, pirarubicin, pixantrone, rubitecan, sobuzoxane, SN-38, tafluposide, and topotecan, and combinations thereof.

Immunologicals include interferons and numerous other immune enhancing agents. Interferons include interferon alpha, interferon alpha-2a, interferon, alpha-2b, interferon beta, interferon gamma-1a or interferon gamma-n1. Other agents include

PF3512676, filgrastim, lentinan, sizofilan, TheraCys, ubenimex, WF-10, aldesleukin, alemtuzumab, BAM-002, dacarbazine, daclizumab, denileukin, gemtuzumab, ozogamicin, ibritumomab, imiquimod, lenograstim, lentinan, melanoma vaccine (Corixa), molgramostim, OncoVAX-CL, sargramostim, tasonermin, tecleukin, thymalasin, tositumomab, Virulizin, Z-100, epratuzumab, mitumomab, oregovomab, pemtumomab, Provenge.

Biological response modifiers are agents that modify defense mechanisms of living organisms or biological responses, such as survival, growth, or differentiation of tissue cells to direct them to have anti-tumor activity. Such agents include krestin, lentinan, sizofiran, picibanil, or ubenimex.

Other anticancer agents include alitretinoin, ampligen, atrasentan, bexarotene, bortezomib, Bosentan, calcitriol, exisulind, finasteride, fotemustine, ibandronic acid, miltefosine, mitoxantrone, L-asparaginase, procarbazine, dacarbazine, hydroxycarbamide, pegaspargase, pentostatin, tazarotene, TLK-286, Velcade, Tarceva, or tretinoin.

Other anti-angiogenic compounds include acitretin, fenretinide, thalidomide, zoledronic acid, angiostatin, aplidine, cilengitide, combretastatin A-4, endostatin, halofuginone, rebimastat, removab, Revlimid, squalamine, ukrain and Vitaxin.

Platinum-coordinated compounds include but are not limited to, cisplatin, carboplatin, nedaplatin, or oxaliplatin.

Camptothecin derivatives include but are not limited to camptothecin, 10-hydroxycamptothecin, 9-aminocamptothecin, irinotecan, SN-38, edotecarin, and topotecan.

Tyrosine kinase inhibitors include, for example, Iressa and SU5416.

Antibodies include, for example, Herceptin, Erbitux, Avastin, and Rituximab.

Interferons include, for example, interferon alpha, interferon alpha-2a, interferon, alpha-2b, interferon beta, interferon gamma-1a and interferon gamma-n1.

Biological response modifiers include agents that modify defense mechanisms of living organisms or biological responses, such as survival, growth, or differentiation of tissue cells to direct them to have anti-tumor activity. Such agents include, for example, krestin, lentinan, sizofiran, picibanil, and ubenimex.

Other antitumor agents include, for example, mitoxantrone, L-asparaginase, procarbazine, dacarbazine, hydroxycarbamide, pentostatin, and tretinoin. Additionally,

PI3K inhibitors and RAS-targeted cancer treatments may be combined with the compounds described herein.

Some embodiments also relate to a pharmaceutical composition comprising a compound of formula (I), formula (II), or formula (III), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

Further embodiments relate to a pharmaceutical composition which comprises mixing a compound of formula (I), formula (II), or formula (III), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound formula (I), formula (II), or formula (III), or pharmaceutically acceptable salt thereof, may be in the range from 1 mg to 1 gram, preferably 1 mg to 250 mg, more preferably 10 mg to 100 mg.

The present embodiments also encompass sustained release compositions.

Administration of the compounds described herein (hereinafter the "active compound(s)") can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), topical, and rectal administration.

The active compound may be applied as a sole therapy or may involve one or more other anti-tumor substances, for example those selected from, for example, mitotic inhibitors, for example vinblastine; alkylating agents, for example cis-platin, carboplatin and cyclophosphamide; anti-metabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea, or, for example, one of the preferred anti-metabolites disclosed in European Patent Application No. 239362 such as N-(5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid; growth factor inhibitors; cell cycle inhibitors; intercalating antibiotics, for example adriamycin and bleomycin; enzymes, for example interferon; and anti-hormones, for example anti-estrogens such as Nolvadex® (tamoxifen) or, for example anti-androgens such as Casodex® (4'-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-

(trifluoromethyl)propionanilide). Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment.

5 The pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition
10 will include a conventional pharmaceutical carrier or excipient and a compound described herein as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

Exemplary parenteral administration forms include solutions or suspensions of active compounds in sterile aqueous solutions, for example, aqueous propylene glycol
15 or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents. The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various excipients, such as citric acid may be
20 employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Preferred materials, therefor,
25 include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

30 The examples and preparations provided below further illustrate and exemplify the compounds described herein and methods of preparing such compounds. The scope of the embodiments described herein is not limited in any way by the following examples and preparations. In the following examples, molecules with a single chiral

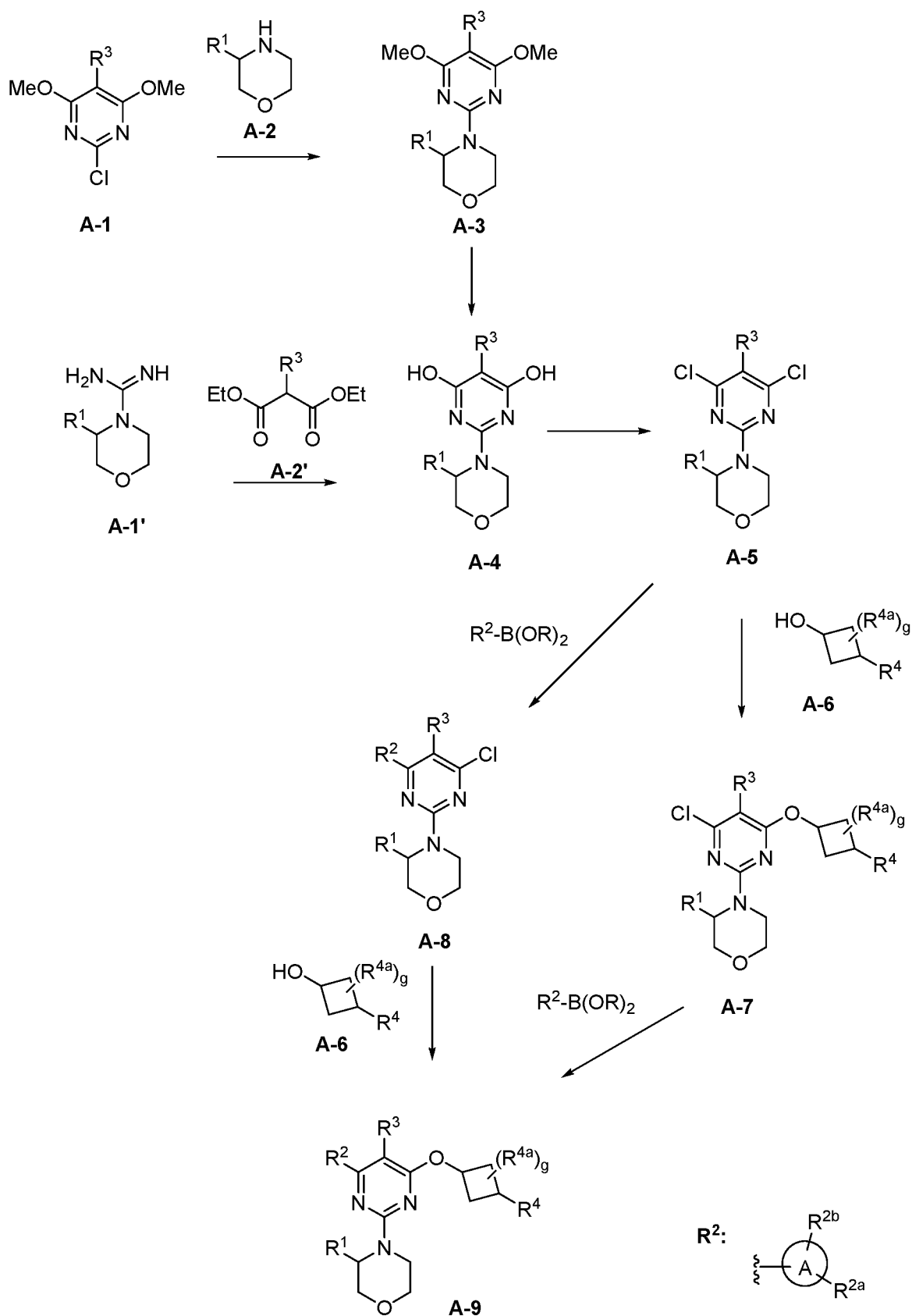
center, unless otherwise noted, exist as a racemic mixture. Those molecules with two or more chiral centers, unless otherwise noted, exist as a racemic mixture of diastereomers. Single enantiomers/diastereomers may be obtained by methods known to those skilled in the art.

5 In the examples shown, salt forms were occasionally isolated as a consequence of the mobile phase additives during HPLC based chromatographic purification. In these cases, salts such as formate, trifluoroacetate and acetate were isolated and tested without further processing. It will be recognized that one of ordinary skill in the art will be able to realize the free base form by standard methodology (such as using ion
10 exchange columns, or performing simple basic extractions using a mild aqueous base).

 In general, the compounds described herein may be prepared by processes known in the chemical arts, particularly in light of the description contained herein. Certain processes for the manufacture of the compounds described herein are provided as further features of the embodiments and are illustrated in the reaction schemes
15 provided below and in the experimental section.

 Unless stated otherwise, the variables in Schemes A and B have the same meanings as defined herein.

20 **Scheme A:**



As exemplified in **Scheme A**, a pyrimidine **A-1** is subjected to chlorine displacement with an amine **A-2** in the presence of a suitable base (such as DIPEA,

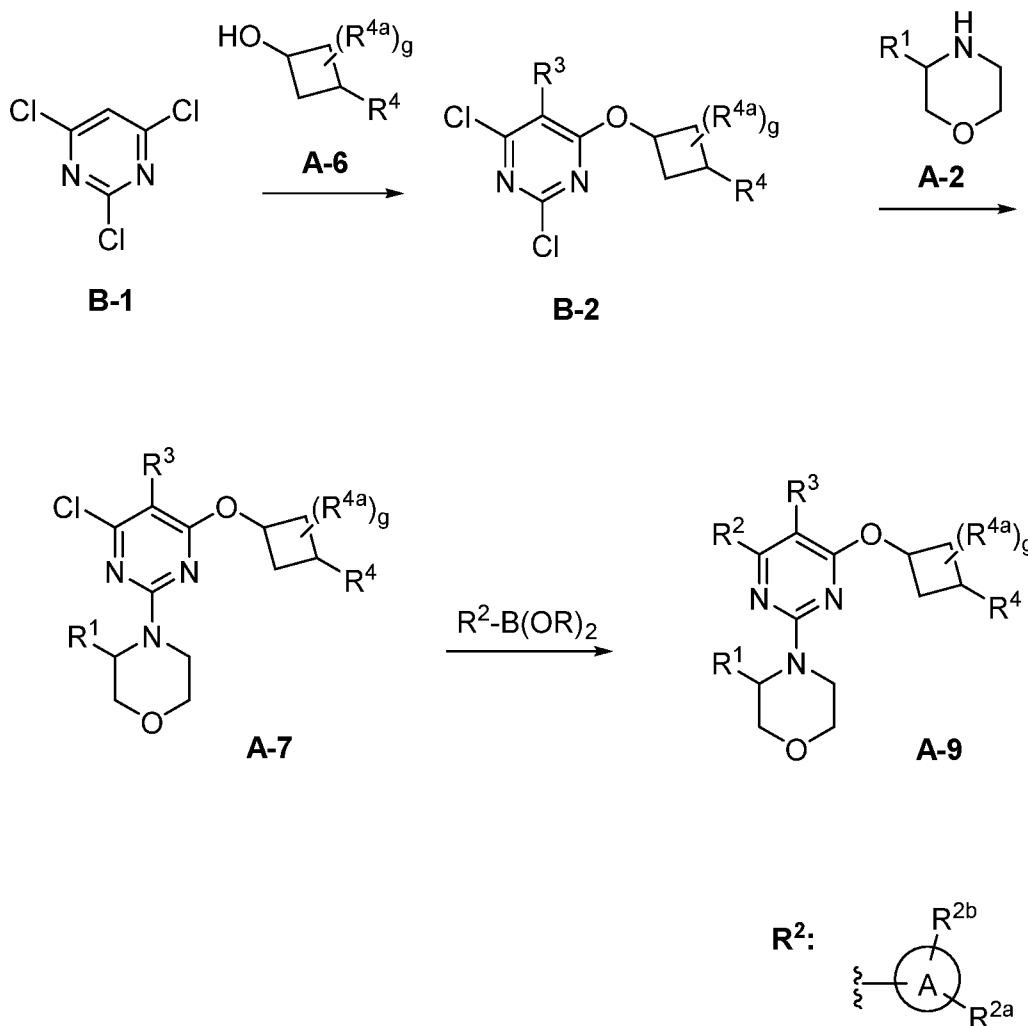
NaH, K₂CO₃, or CsF) in a suitable solvent (such as DMSO, MeCN, NMP, THF, or DMF) to afford **A-3**. **A-3** is treated under demethylation conditions known in the art with sodium iodide and TMS-Cl in MeCN to provide **A-4**. Alternatively, as exemplified in **Scheme A**, a guanidine **A-1'** and a malonate **A-2'** are subjected to a condensation to afford **A-4**. **A-4** is treated with POCl₃ to afford **A-5**. **A-5** is subjected to selective chlorine displacement with an alkoxide **A-6** (using parent alcohol in the presence of a suitable base {NaH, NaHMDS, KHMDS, K₂CO₃ or DIPEA}) in a suitable solvent (such as iPrOH, MeCN, THF or DMF) to afford **A-7**. **A-7** is treated under Suzuki cross-coupling conditions known in the literature with a boronic acid or a boronic ester to yield **A-9**.

Alternatively, the intermediate **A-5** is treated under Suzuki cross-coupling conditions known in the literature with a boronic acid or a boronic ester to yield **A-8**. **A-8** is subjected to chlorine displacement with an alkoxide **A-6** (using parent alcohol in the presence of a suitable base {NaH, NaHMDS, KHMDS, K₂CO₃ or DIPEA}) in a suitable solvent (such as iPrOH, MeCN, THF or DMF) to afford **A-9**.

Furthermore, if the R⁴ group contains an amine protecting group, such as a Boc group or a CBZ group, the protecting group may be deprotected under procedures known to one of skill in the art. For example, the Boc group may be deprotected under acidic conditions (such as HCl or TFA) and the CBZ group may be deprotected under hydrogenation conditions. The resultant amine may be subjected to amide, carbamate, urea, sulfonamide, sulfamide or phosphinic amide formation. Amide formation can be achieved using a suitable amide coupling agent (such as CDI, EDCI, HATU) in the presence of a suitable base (such as DIPEA, TEA) and an appropriate carboxylic acid. Carbamate formation can be achieved using an appropriate chloroformate in the presence of a suitable base (such as DIPEA or TEA). Urea formation can be achieved by using an appropriate isocyanate in the presence of a suitable base (such as TEA), or in the presence of triphosgene or phosgene and an amine in the presence of a suitable base (such as sodium carbonate, sodium bicarbonate, or TEA). Sulfonamide formation can be achieved with a sulfonyl chloride in the presence of a suitable base (such as DIPEA or TEA). Sulfamide formation can be achieved with sulfamoyl chloride or sulfamoylcarbamate in the presence of a suitable base (such as DIPEA or TEA). Phosphinic amide formation can be achieved with phosphinic chloride in the presence

of a suitable base (such as DIPEA or TEA). These amine functionalizations may be performed either before or after the Suzuki cross-coupling step.

Scheme B:



5

As exemplified in **Scheme B**, trichloropyrimidine **B-1** is subjected to a selective chlorine displacement with an alkoxide **A-6** (using parent alcohol in the presence of a suitable base {NaH, NaHMDS, KHMDS, K₂CO₃ or DIPEA}) in a suitable solvent (such as iPrOH, MeCN, THF or DMF) to afford **B-2**. **B-2** is subjected to another selective chlorine displacement with amine **A-2** in the presence of a suitable base {NaH, NaHMDS, KHMDS, K₂CO₃ or DIPEA}) in a suitable solvent (such as iPrOH, MeCN, THF or DMF) to afford **A-7**. **A-7** is treated under Suzuki cross-coupling conditions known in the literature with a boronic acid or a boronic ester to yield **A-9**.

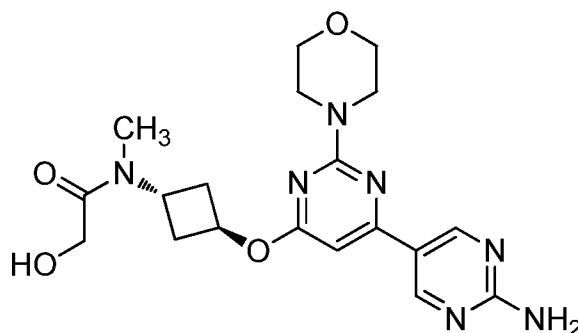
Furthermore, if the R⁴ group contains an N-Boc group or an N-CBZ group, it may be suitably deprotected and subjected to amide, carbamate, urea, sulfonamide,

15

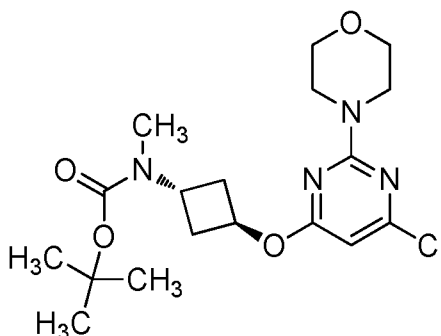
sulfamide, or phosphinic amide formation either before or after the Suzuki cross-coupling step as described above in Scheme A.

Examples

5 **Example 1 (Scheme A): Preparation of *N*-(*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-*N*-methylacetamide**



Step 1: Preparation of *tert*-butyl(*trans*-3-{[6-chloro-2-(morpholin-4-yl)pyrimidin-4-yl]oxy}cyclobutyl)methylcarbamate



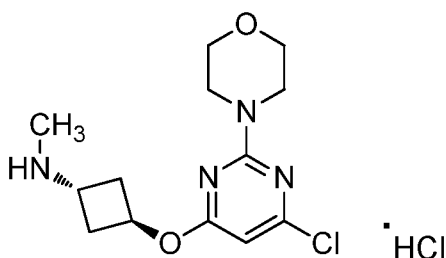
10 To a solution of *tert*-butyl (*trans*-3-hydroxycyclobutyl)methylcarbamate (1.55 g, 7.69 mmol) in tetrahydrofuran (30 mL) at 0 °C under nitrogen, was added sodium hydride (256 mg, 6.41 mmol, 60 % in mineral oil). After stirring for ~10 min, a solution of 4-(4,6-dichloropyrimidin-2-yl)morpholine (1.5 g, 6.41 mmol) in tetrahydrofuran (30 mL)

15 was added via an addition funnel. The solution was stirred for 20 hours while letting the ice bath warm to room temperature. The reaction mixture was quenched with water (0.5 mL), and washed with brine (75 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL), and the combined organic layers were washed with brine (25 mL), dried (MgSO₄), and concentrated. The residue solidified upon standing and was triturated

20 with methyl *tert*-butyl ether to give 1.35 g (53 % yield) of the title compound as a white solid. The filtrate was purified by Biotage (40+S cartridge) using a gradient of 10-50 % EtOAc/heptane to give another 783 mg (31 % yield) of the title compound. ¹H NMR (400

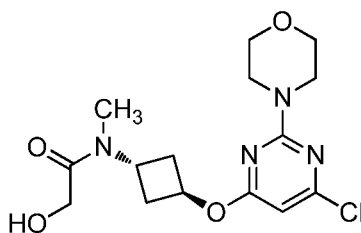
MHz, CD₃CN) δ ppm 6.06 (s, 1 H) 5.20 - 5.14 (m, 1 H) 4.69 (br s, 1 H) 3.71 - 3.63 (m, 8 H) 2.82 (s, 3 H) 2.66 - 2.58 (m, 2 H) 2.39 - 2.30 (m, 2 H) 1.42 (s, 9 H). m/z (APCI+) for C₁₈H₂₇ClN₄O₄ 399.1 (M+H)⁺.

5 Step 2: Preparation of *trans*-3-[[6-chloro-2-(morpholin-4-yl)pyrimidin-4-yl]oxy]-*N*-methylcyclobutanamine hydrochloride



tert-Butyl (*trans*-3-[[6-chloro-2-(morpholin-4-yl)pyrimidin-4-yl]oxy]cyclobutyl)methylcarbamate (305 mg, 0.76 mmol) was dissolved in methylene chloride (4 mL) and treated with HCl solution (4 mL, 4 M in dioxane). The mixture was stirred at room temperature for 1 hour. The resulting suspension was diluted with toluene and concentrated under reduced pressure. The residue was concentrated a second time from toluene to give a white solid which was carried directly into the next reaction. ¹H NMR (400 MHz, D₂O) δ ppm 6.23 (s, 1H) 5.38 - 5.31 (m, 1 H) 4.02 - 3.93 (m, 1 H) 3.82 - 3.78 (m, 4 H) 3.77 - 3.73 (m, 4 H) 2.80 - 2.64 (m, 7 H). m/z (APCI+) for C₁₃H₁₉ClN₄O₂ 299.1 (M+H)⁺.

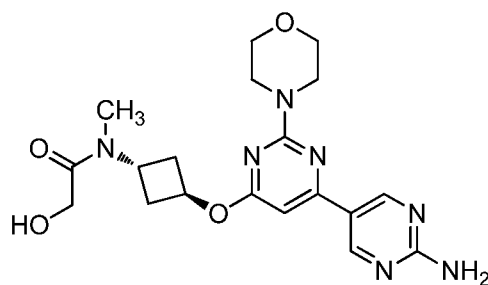
Step 3: Preparation of *N*-(*trans*-3-[[6-chloro-2-(morpholin-4-yl)pyrimidin-4-yl]oxy]cyclobutyl)-2-hydroxy-*N*-methylacetamide



To a solution of crude *trans*-3-[[6-chloro-2-(morpholin-4-yl)pyrimidin-4-yl]oxy]-*N*-methylcyclobutanamine hydrochloride (~0.76 mmol) in DMSO (8 mL) was added glycolic acid (88 mg, 1.2 mmol), DIPEA (0.66 mL, 3.8 mmol), and HATU (440 mg, 1.1 mmol). The mixture was stirred at room temperature for 1.5 hours. The mixture was partitioned between EtOAc (50 mL) and saturated aqueous NaHCO₃ (80 mL). The

aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organics were washed with water (25 mL) and brine (25 mL), dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by Biotage (25+M cartridge) using a gradient of 50-100 % EtOAc/heptanes to give 172 mg (63 % yield) of the title compound as a white solid. ¹H NMR (400 MHz, 80 °C, DMSO-d₆) δ ppm 6.15 (s, 1 H) 5.28 - 5.21 (m, 1 H) 4.83 (br s, 1 H) 4.16 (br s, 1 H) 4.06 (d, J=4.5 Hz, 2 H) 3.70 - 3.63 (m, 8 H) 2.91 (s, 3 H) 2.75 - 2.65 (m, 2 H) 2.45 - 2.36 (m, 2 H). *m/z* (APCI+) for C₁₅H₂₁ClN₄O₄ 357.1 (M+H)⁺.

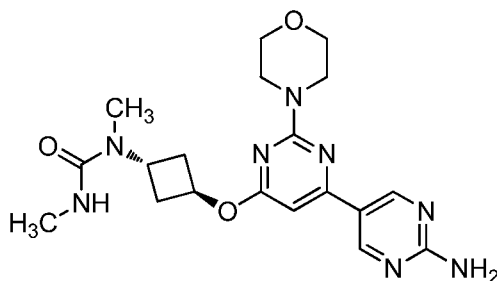
Step 4: Preparation of *N*-(*trans*-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-*N*-methylacetamide



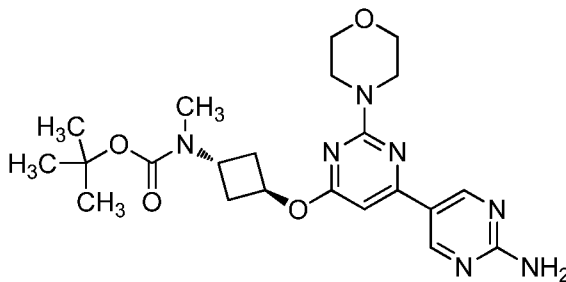
In a microwavable vial equipped with a stir bar, *N*-(*trans*-3-([6-chloro-2-(morpholin-4-yl)pyrimidin-4-yl]oxy)cyclobutyl)-2-hydroxy-*N*-methylacetamide (593 mg, 1.66 mmol) and 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrimidin-2-ylamine (514 mg, 2.33 mmol) were dissolved in DMSO (15 mL). Cesium fluoride (765 mg, 4.99 mmol) was added and the mixture was sparged with a nitrogen bubbler for 5 min. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) 1:1 complex with dichloromethane (68 mg, 0.083 mmol) was added and the vessel was sealed. The mixture was heated in the microwave at 140 °C for 15 min. The mixture was filtered through a 0.45 micron syringe filter, and the filtrate was poured to a brine solution (150 mL) and the resulting precipitate was collected by filtration and rinsed with water. The filtrate was extracted with EtAOc (3 x 50 mL). The solids were washed with methylene chloride, the washings were combined with the EtOAc extracts, dried (MgSO₄) and reduced under reduced pressure. The residue was dissolved in 10 % MeOH in methylene chloride (25 mL) and treated with silica gel thiol (1 g, 1.34 mmol/g) and the suspension was stirred at room temperature for 1 hour. The mixture was filtered and the solids washed with 10% MeOH in methylene chloride until clear solution was observed.

The filtrate was concentrated under reduced pressure, and the residue purified on a Biotage 40+S cartridge using a gradient of 0-10% MeOH/EtOAc. The product was dissolved in 10 % MeOH in methylene chloride (25 mL), treated with silica gel thiol (1 g, 1.34 mmol/g) and the resulting suspension was stirred for 3 hours. The mixture was filtered through a 0.45 micron syringe filter, the filtrate was concentrated to ~10 mL volume and diluted with EtOAc. The solution was concentrated to a 1-2 mL volume and the resulting suspension was filtered. The solids were rinsed with EtOAc and dried under vacuum to give 394 mg (57 % yield) of the title compound as a beige solid. ¹H NMR (400 MHz, 80 °C, DMSO-d₆) δ ppm 8.89 (s, 2 H) 6.76 (br s, 2 H) 6.53 (s, 1 H) 5.33 - 5.26 (m, 1 H) 4.86 (br s, 1 H) 4.17 (br s, 1 H) 4.07 (d, J=5.0 Hz, 2 H) 3.78 - 3.73 (m, 4 H) 3.72 - 3.66 (m, 4 H) 2.93 (s, 3 H) 2.76 - 2.66 (m, 2 H) 2.45 - 2.37 (m, 2 H). *m/z* (APCI+) for C₁₉H₂₅N₇O₄ 416.1 (M+H)⁺.

Example 2 (Scheme A): Preparation of 1-(*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1,3-dimethylurea



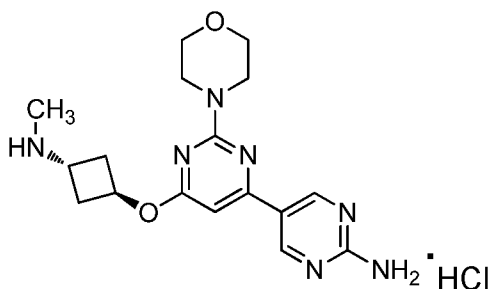
Step 1: Preparation of *tert*-butyl (*trans*-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)methylcarbamate



A suspension of *tert*-butyl (*trans*-3-{[6-chloro-2-(morpholin-4-yl)pyrimidin-4-yl]oxy}cyclobutyl)methylcarbamate (200 mg, 0.50 mmol), 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrimidin-2-ylamine (150 mg, 0.68 mmol) and sodium carbonate (60 mg, 0.71 mmol) in MeCN (2 mL) and water (0.22 mL, 12.3 mmol) was

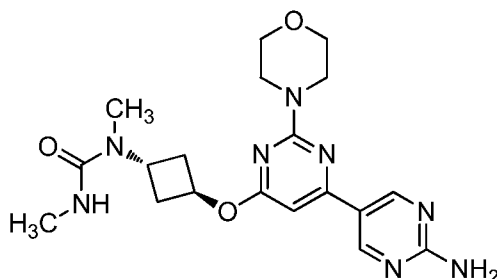
purged with nitrogen for 10 min. Dichlorobis[di-*tert*-butyl(4-dimethylaminophenyl)phosphino]palladium(II)55 (40 mg, 0.056 mmol) was added and the reaction was sealed and heated at 100 °C for 30 min. The reaction mixture was concentrated under reduced pressure and the resulting brown residue was purified on silica gel (Biotage SNAP, HP-Sil, 10g, 0-50 % EtOAc in methylene chloride) to give 201 mg (88 % yield) of the title compound as a tan solid. ¹H NMR (600 MHz, DMSO-d₆) δ ppm 8.92 (s, 2 H) 7.11 (s, 2 H) 6.61 (s, 1 H) 5.22 - 5.18 (m, 1 H) 4.69 (br s, 1 H), 3.74 - 3.71 (m, 4 H) 3.67 - 3.64 (m, 4 H) 2.80 (s, 3 H) 2.66 - 2.60 (m, 2 H) 2.33 - 2.27 (m, 2 H) 1.39 (s, 9 H). *m/z* (APCI+) for C₂₂H₃₁N₇O₄ 458.2 (M+H)⁺.

Step 2: Preparation of 6-{{*trans*-3-(methylamino)cyclobutyl}oxy}-2-(morpholin-4-yl)-4,5'-bipyrimidin-2'-amine hydrochloride



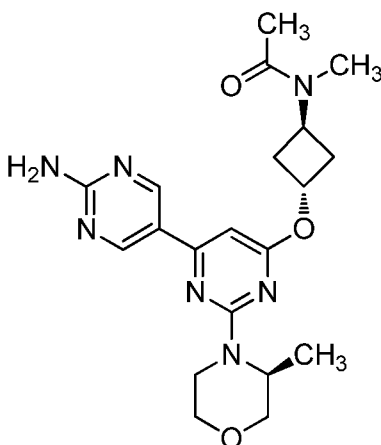
tert-Butyl (*trans*-3-{{2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy}cyclobutyl)methylcarbamate (250 mg, 0.55 mmol) was dissolved in methylene chloride (3 mL) and treated with a HCl solution (3 mL, 4 M in dioxane) at room temperature and the mixture was stirred for 18 hours. The mixture was diluted with toluene and concentrated under reduced pressure. The residue was concentrated a second time from toluene to give 276 mg of a foamy solid which was used directly in the next reaction. ¹H NMR (400 MHz, D₂O) δ ppm 8.86 (s, 2 H) 6.48 - 6.45 (m, 1 H) 5.42 - 5.36 (m, 1 H) 4.00 - 3.91 (m, 1 H) 3.81 (s, 8 H) 2.78 - 2.63 (m, 7 H). *m/z* (APCI+) for C₁₇H₂₃N₇O₂ 358.1 (M+H)⁺.

Step 3: Preparation of 1-(*trans*-3-{{2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl}oxy}cyclobutyl)-1,3-dimethylurea

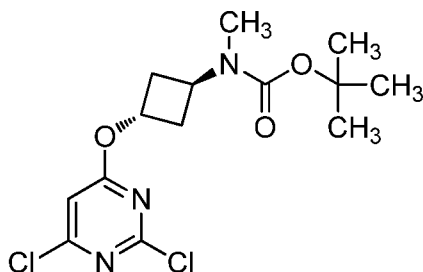


To a mixture of 6-[[*trans*-3-(methylamino)cyclobutyl]oxy]-2-(morpholin-4-yl)-4,5'-bipyrimidin-2'-amine hydrochloride (40 mg, 0.086 mmol) and DIPEA (0.075 mL, 0.43 mmol) in DMSO (1 mL) was added methyl isocyanate (0.008 mL, 0.129 mmol) at room temperature, and the mixture was stirred for 18 hours. The mixture was purified by SFC column (SFC/ZymorSpher HADP 150 x 21.2 mm; with 15-30 % MeOH at 3%/min, 140 bar, 55 mL/min) to give 20.5 mg (57 % yield) of the title compound as a white solid. ¹H NMR (400 MHz, CD₃CN) δ ppm 8.91 (s, 2 H) 6.39 (s, 1 H) 5.74 (br s, 2 H) 5.24 - 5.19 (m, 1 H) 5.03 - 4.97 (m, 1 H) 4.86 (p, *J*=8.4 Hz, 1 H) 3.80 - 3.76 (m, 4 H) 3.70 - 3.65 (m, 4 H) 2.81 (s, 3 H) 2.64 (d, *J*=4.5 Hz, 3 H) 2.63 - 2.55 (m, 2 H) 2.41 - 2.32 (m, 2 H). *m/z* (APCI+) for C₁₉H₂₆N₈O₃ 415.1 (M+H)⁺.

Example 3 (Scheme B): Preparation of *N*-[*trans*-3-{2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy]cyclobutyl]-*N*-methylacetamide

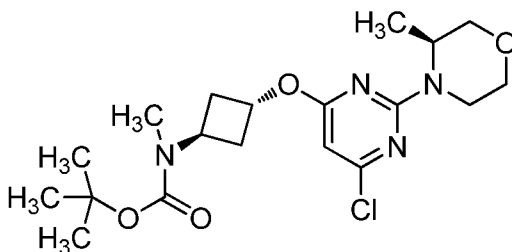


Step 1: Preparation of *tert*-butyl [trans-3-[(2,6-dichloropyrimidin-4-yl)oxy]cyclobutyl]methylcarbamate



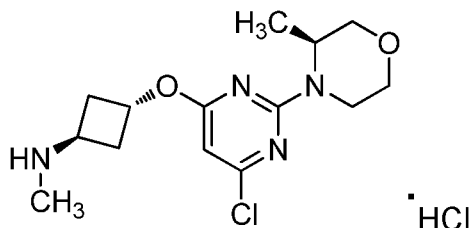
To a mixture of 2,4,6-trichloropyrimidine (1.1 g, 6 mmol) and NaH (0.288 g, 12 mmol, 60 % in mineral oil) in THF (10 mL) was added a solution of *tert*-butyl (*trans*-3-hydroxycyclobutyl)methylcarbamate (0.9 g, 4.5 mmol) in THF (10 mL) at -10 °C under nitrogen atmosphere over 30 min. The cooling bath was removed and the mixture was stirred at room temperature for 18 hours. Ice-water (50 mL) was added while keeping the reaction mixture below 10 °C and the resultant mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by silica gel chromatography using a gradient of petroleum ether/EtOAc (20:1 to 10:1) to give 1.37 g (88 % yield) of the title compound as a colorless oil, which was used in the next step without further purification.

Step 2: Preparation of *tert*-butyl [(*trans*-3-((6-chloro-2-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl)oxy)cyclobutyl)methylcarbamate



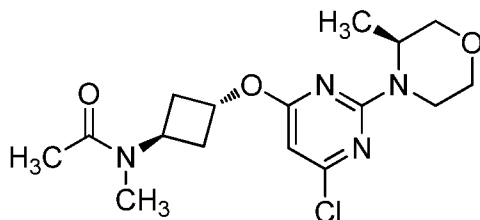
A solution of *tert*-butyl [(*trans*-3-[(2,6-dichloropyrimidin-4-yl)oxy]cyclobutyl)methylcarbamate (0.68 g, 1.97 mmol), (3*S*)-3-methylmorpholine (0.24 g, 2.36 mmol) and DIPEA (0.76 g, 5.91 mmol) in dry THF (10 mL) was heated at 60 °C for 18 hours. The mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography using a gradient of petroleum ether/EtOAc (6:1) to give 0.35 g (43 % yield) of the title compound as a colorless gum, which was used in the next step without further purification.

Step 3: Preparation of *trans*-3-({6-chloro-2-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl}oxy)-*N*-methylcyclobutanamine hydrochloride



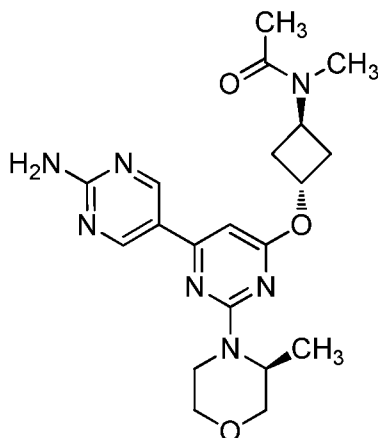
To a solution of *tert*-butyl [*trans*-3-({6-chloro-2-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl}oxy)cyclobutyl]methylcarbamate (350 mg, 0.85 mmol) in EtOAc (10 mL) was added HCl in EtOAc (2 mL, 4 M) at 0 °C. The mixture was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure to give 280 mg (100 % yield) of the title compound as a white solid, which was used in the next step without further purification.

Step 4: Preparation of *N*-[*trans*-3-({6-chloro-2-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl}oxy)cyclobutyl]-*N*-methylacetamide



To a mixture of *trans*-3-({6-chloro-2-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl}oxy)-*N*-methylcyclobutanamine hydrochloride (280 mg, 0.85 mmol) and triethylamine (257 mg, 2.55 mmol) in THF (20 mL) was added acetic anhydride (130 mg, 1.28 mmol) at room temperature and the mixture was stirred for 3 hours. MeOH (1 mL) was added and the mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography using a gradient of methylene chloride/MeOH, (20:1) to give 270 mg (89 % yield) of the title compound as a yellow gum. ¹H NMR (400 MHz, CDCl₃) δ ppm 6.02 - 6.01 (m, 1 H) 5.23 - 4.75 (m, 2 H) 4.61 - 4.55 (m, 1 H) 4.26 - 4.22 (m, 1 H) 3.96 - 3.94 (m, 1 H) 3.77 - 3.72 (m, 1 H) 3.67 - 3.64 (m, 1 H) 3.50 (td, J=12, 2.6 Hz, 1 H) 2.99 - 2.95 (m, 3 H) 2.69 - 2.49 (m, 4 H) 2.68 - 2.10 (m, 3 H) 1.28 - 1.26 (m, 3 H).

Step 5: Preparation of *N*-[*trans*-3-({2'-amino-2-[(3*S*)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-*N*-methylacetamide



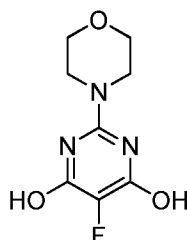
A mixture of *N*-[*trans*-3-({6-chloro-2-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl}oxy)cyclobutyl]-*N*-methylacetamide (50 mg, 0.14 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-amine (46 mg, 0.21 mmol), Pd(dppf)Cl₂ (11.4 mg, 0.014 mmol) and saturated aqueous Na₂CO₃ (1 mL) in dioxane (3 mL) was degassed with nitrogen and stirred at 120 °C in a microwave reactor for 30 min. The mixture was concentrated and the residue was purified by silica gel chromatography using a gradient of methylene chloride/methanol (20:1) to give 18.1 mg (31 % yield) of the title compound as a light brown solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.90 (s, 2 H) 6.30 (s, 1 H) 5.25 (br s, 3 H) 4.78 - 4.66 (m, 2 H) 4.37 (d, J=15.6 Hz, 1 H) 4.00 (d, J=12.8 Hz, 1 H) 3.81-3.70 (m, 2 H) 3.59 - 3.54 (m, 1 H) 3.30 - 3.27 (m, 1 H) 3.01-2.97 (m, 3 H) 2.68 - 2.52 (m, 4 H) 2.12 (s, 3 H) 1.29 (t, J=6.8 Hz, 3 H). *m/z* (ESI+) for C₂₀H₂₇N₇O₃ 414.1 (M+H)⁺.

Enantiomeric excess: 98.41 % (Chiralcel OZ-3 150×4.6 mm I.D., 3 μm, retention time: 9.72 min, mobile phase: 25 % MeOH (0.05 % diethylamine) in CO₂, flow rate: 2.35 mL/min).

Experimental Procedures for Intermediates

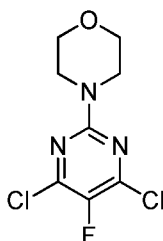
Preparation 1: Preparation of 4-(4,6-dichloro-5-fluoropyrimidin-2-yl)morpholine

Step 1: Preparation of 5-fluoro-2-(morpholin-4-yl)pyrimidine-4,6-diol



A solution of potassium ethoxide (8.90 g, 25 mmol, 24 % weight in EtOH) was diluted with EtOH (35 mL) and morpholine-4-carboxamide hydrobromide (2.69 g, 12.8 mmol) was added. The suspension was treated with diethyl fluoromalonate (2.00 mL, 12.8 mmol) and heated at 75 °C for 18 hours. The reaction mixture was cooled to room temperature, concentrated under vacuum, and the resulting yellow solids were dissolved in hot water (15 mL). The pH was adjusted to ~3 with 6 N HCl, and the flask was cooled on ice for 10 min and let sit at room temperature for 30 min. The precipitate was collected by filtration, washed with water, and dried under vacuum to afford the title compound (0.402 g, 15 % yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 3.65 - 3.57 (m, 4 H) 3.53 - 3.46 (m, 4 H). *m/z* (APCI-) for C₈H₁₀FN₃O₃ 214.1 (M-H)⁻.

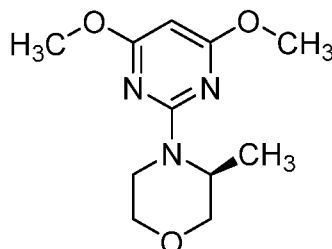
Step 2: Preparation of 4-(4,6-dichloro-5-fluoropyrimidin-2-yl)morpholine



A suspension of 5-fluoro-2-(morpholin-4-yl)pyrimidine-4,6-diol (0.384 g, 1.78 mmol) in phosphorous oxychloride (6.0 mL) was heated at 100 °C for 1.5 hours. The reaction mixture was cooled to room temperature and concentrated under vacuum. The resulting residue was sonicated with ice water. The resulting suspension was kept cool with the addition of ice and brought to pH~6 with 2 N aqueous NaOH. The remaining solids were collected by filtration and dried under vacuum to afford the title compound (0.074 g, 16 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 3.71 - 3.60 (m, 8H).

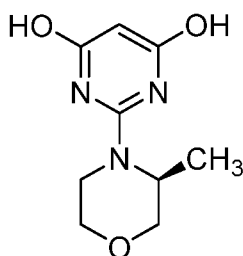
Preparation 2: Preparation of (3S)-4-(4,6-dichloropyrimidin-2-yl)-3-methylmorpholine:

Step 1: Preparation of (3S)-4-(4,6-dimethoxypyrimidin-2-yl)-3-methylmorpholine



A solution of (S)-3-methylmorpholine (4.86 g, 48.0 mmol), 2-chloro-4,6-dimethoxypyrimidine (6.98 g, 40 mmol) and DIPEA (8.36 mL, 48.0 mmol) in DMSO (40 mL) was heated at 100 °C in a sealed flask for 22 hours, and then allowed to cool to room temperature. The reaction mixture was placed in an ice bath, and water (120 mL) was added drop-wise. The mixture was decanted and the gummy precipitate was dissolved in ethyl acetate. The ethyl acetate solution was washed with brine, dried with MgSO₄, filtered and concentrated by rotary evaporation to give the title compound (8.58 g, 90%). ¹H NMR (400 MHz, CDCl₃) δ 5.40 (s, 1 H), 4.69 (qd, *J* = 6.8, 3.1 Hz, 1 H), 4.33 (dd, *J* = 13.7, 2.9 Hz, 1 H), 4.01 - 3.93 (m, 1 H), 3.86 (s, 6 H), 3.78 - 3.73 (m, 1 H), 3.73 - 3.66 (m, 1 H), 3.54 (ddd, *J* = 12.2, 11.4, 3.1 Hz, 1 H), 3.25 (ddd, *J* = 13.5, 12.4, 3.8 Hz, 1 H), 1.29 (d, *J* = 6.8 Hz, 3 H). *m/z* (APCI+) for C₁₁H₁₇N₃O₃ 240.0 (M+H)⁺.

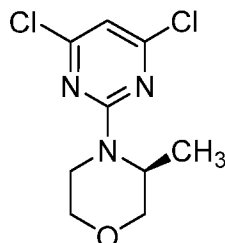
Step 2: Preparation of 2-[(3S)-3-methylmorpholin-4-yl]pyrimidine-4,6-diol



(3S)-4-(4,6-Dimethoxypyrimidin-2-yl)-3-methylmorpholine (6.3 g, 26.3 mmol) was dissolved in MeCN (88 mL). Argon was bubbled into the solution and sodium iodide (11.8 g, 79.0 mmol) and TMS-Cl (10.3 mL, 79.0 mmol) were added. The reaction was heated under reflux for 2 hours, and then allowed to cool to room temperature. Water (50 mL) and sodium bisulfite (2.74 g, 26.3 mmol) was added. MeCN was removed by rotary evaporation and the resulting slurry was filtered. The precipitate was suspended in ethanol and concentrated to dryness by rotary evaporation to give the title compound (3.81 g, 68%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.61 (br s, 2 H), 4.80 (br s, 1 H), 4.40 (d, *J* = 5.9 Hz, 1 H), 3.98 (d, *J* = 12.7 Hz, 1 H), 3.85 (dd, *J* = 11.3, 3.5 Hz, 1 H), 3.68 -

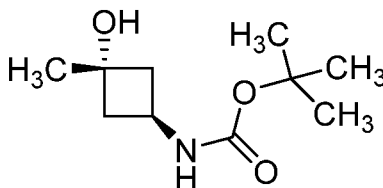
3.62 (m, 1 H), 3.56 - 3.50 (m, 1 H), 3.38 (td, $J = 11.8, 3.0$ Hz, 1 H), 3.16 - 3.04 (m, 1 H), 1.16 (d, $J = 6.7$ Hz, 3 H).

Step 3: Preparation of (3S)-4-(4,6-dichloropyrimidin-2-yl)-3-methylmorpholine



5 2-[(3S)-3-methylmorpholin-4-yl]pyrimidine-4,6-diol (4.06 g, 19.2 mmol) was suspended in MeCN (38.4 mL) and phosphorous oxychloride (14.3 mL, 154 mmol) was added. The reaction mixture was heated in a sealed vial for 2 hours and then concentrated by rotary evaporation. A 1:1 mixture of MeCN and water (10 mL) was added dropwise with stirring keeping the temperature below 40 °C. Additional water (20 mL) was added and the MeCN was removed by rotary evaporation. The resulting slurry was cooled to 0 °C and filtered. The precipitate was dissolved in dichloromethane, dried with Na₂SO₄, filtered and concentrated by rotary evaporation to give the title compound (4.38 g, 92%). ¹H NMR (400 MHz, CDCl₃) δ 6.56 (s, 1 H), 4.68 (qd, $J = 6.8, 3.1$ Hz, 1 H), 4.33 (dd, $J = 13.7, 2.9$ Hz, 1 H), 3.97 (dd, $J = 11.5, 3.7$ Hz, 1 H), 3.79 - 3.73 (m, 1 H), 3.69 - 3.64 (m, 1 H), 3.51 (td, $J = 11.9, 3.0$ Hz, 1 H), 3.30 (ddd, $J = 13.6, 12.4, 3.8$ Hz, 1 H), 1.32 (d, $J = 6.5$ Hz, 3 H). m/z (APCI+) for C₉H₁₁Cl₂N₃O 247.9 (M+H)⁺.

Preparation 3: Preparation of tert-butyl (trans-3-hydroxy-3-methylcyclobutyl)carbamate:

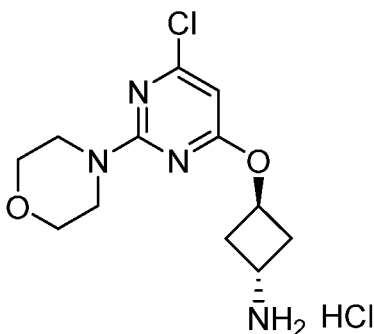


To a rapidly stirring suspension of *trans*-3-amino-1-methylcyclobutan-1-ol hydrochloride (100 mg, 0.727 mmol) in dioxane (2.8 mL) and water (0.28 mL) was added potassium carbonate (201 mg, 1.45 mmol) and boc anhydride (180 mg, 0.800 mmol) at ambient temperature. The reaction was stirred for 48 hours at which time the heterogeneous mixture was diluted with water and ethyl acetate. The layers were

separated and the aqueous phase was extracted with ethyl acetate (3 x 5 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated to furnish 121 mg (83%) of the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 4.67 (br s, 1H), 3.81 - 3.64 (m, 2H), 2.50 (t, *J* = 8.8 Hz, 2H), 1.98 (t, *J* = 10.0 Hz, 2H), 1.45 (s, 9H), 1.37 (s, 3H).

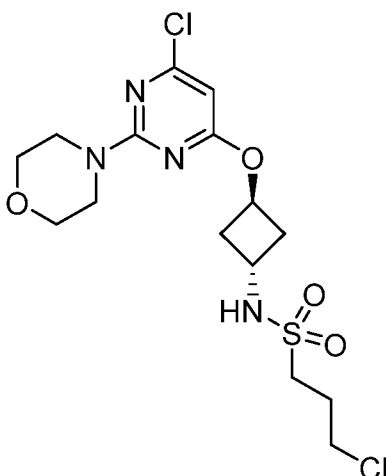
Preparation 4: Preparation of 4-(4-chloro-6-[[*trans*-3-(1,1-dioxido-1,2-thiazolidin-2-yl)cyclobutyl]oxy]pyrimidin-2-yl)morpholine

Step 1: Preparation of *trans*-3-[[6-chloro-2-(morpholin-4-yl)pyrimidin-4-yl]oxy]cyclobutanamine hydrochloride



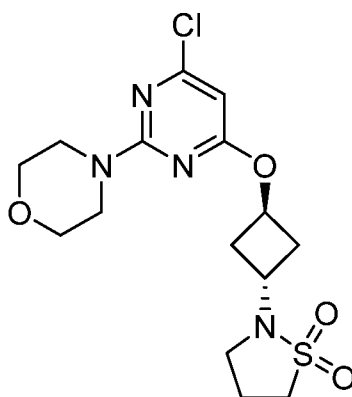
To a solution of *tert*-butyl (*trans*-3-[[6-chloro-2-(morpholin-4-yl)pyrimidin-4-yl]oxy]cyclobutyl)carbamate (prepared analogously to Example 1, step 1 by replacing *tert*-butyl (*trans*-3-hydroxycyclobutyl)methylcarbamate with *tert*-butyl (*trans*-3-hydroxycyclobutyl)carbamate) (3 g, 7.812 mmol) in EtOAc/dichloromethane (12 mL, 5:1) was added dropwise HCl(g)/dioxane (4N, 20 mL) at 10 °C. The resulting mixture was stirred at room temperature for 12 hours. The mixture was concentrated under reduced pressure to obtain the title compound (2.5 g, 100%) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 6.09 (s, 1 H), 5.44-5.41 (m, 1 H), 3.97-3.93 (m, 1 H), 3.76-3.66 (m, 8 H), 2.65-2.62 (m, 4 H).

Step 2: Preparation of 3-chloro-*N*-(*trans*-3-[[6-chloro-2-(morpholin-4-yl)pyrimidin-4-yl]oxy]cyclobutyl)propane-1-sulfonamide



To a solution of *trans*-3-[[6-chloro-2-(morpholin-4-yl)pyrimidin-4-yl]oxy}cyclobutanamine hydrochloride (0.4 g, 1.248 mmol) in dichloromethane (30 mL) was added 3-chloropropane-1-sulfonyl chloride (0.26 g, 1.49 mmol) and triethylamine (0.43 mL, 3.12 mmol) at 10 °C. The resulting mixture was allowed to warm to room temperature and stirring was continued for 12 hours. The mixture was washed with saturated aqueous NaHCO₃ (8 mL) and brine (5 mL), dried over Na₂SO₄ and concentrated under reduced pressure to give a crude title compound, which was used in the next step without further purification.

Step 3: Preparation of 4-(4-chloro-6-[[*trans*-3-(1,1-dioxido-1,2-thiazolidin-2-yl)cyclobutyl]oxy}pyrimidin-2-yl)morpholine

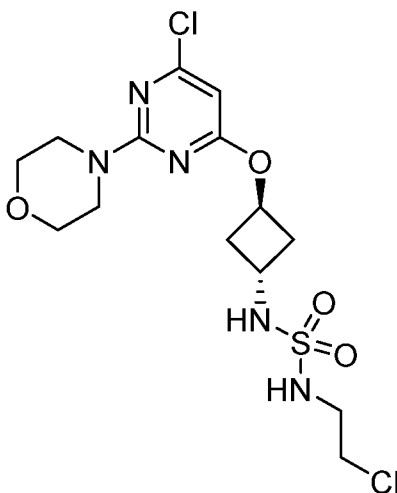


To a suspension of NaH (0.2 g, 4.99 mmol, 60% in mineral oil) in anhydrous THF (40 mL) was added dropwise a solution of compound 3-chloro-*N*-(*trans*-3-[[6-chloro-2-(morpholin-4-yl)pyrimidin-4-yl]oxy}cyclobutyl)propane-1-sulfonamide (0.53 g, 1.25 mmol) in THF (10 mL) at 10 °C. The resulting mixture was stirred at room temperature for 1 hour and then heated under reflux for 12 hours. The mixture was quenched with

water (5 mL) at 10 °C and then extracted with EtOAc (3 x 15 mL). The organic layers were combined, washed with brine (8 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography eluting with petroleum ether/EtOAc (1:1) to give the title compound (0.25 g, 51%) as yellow oil. *m/z* (APCI+) for C₁₅H₂₁ClN₄O₄S 389.1 (M+H)⁺.

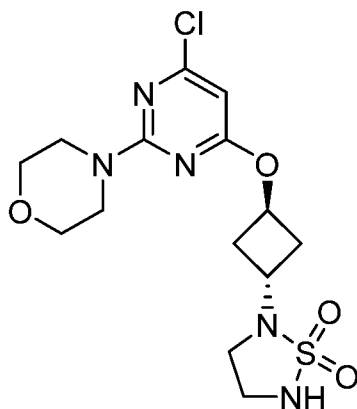
Preparation 5: Preparation of 4-(4-chloro-6-{[*trans*-3-(1,1-dioxido-1,2,5-thiadiazolidin-2-yl)cyclobutyl]oxy}pyrimidin-2-yl)morpholine

Step 1: Preparation of *N*-(2-chloroethyl)-*N'*-(*trans*-3-{[6-chloro-2-(morpholin-4-yl)pyrimidin-4-yl]oxy}cyclobutyl)sulfuric diamide



To a solution of *trans*-3-{[6-chloro-2-(morpholin-4-yl)pyrimidin-4-yl]oxy}cyclobutanamine hydrochloride (0.35 g, 1.09 mmol) in anhydrous dichloromethane (30 mL) was added TEA (0.44 g, 0.6 mL) and an ether solution of (2-chloroethyl)sulfamyl chloride (3 mL, 2.18 mmol, 0.718 M) via a syringe at -70 °C. The resulting mixture was allowed to stir at room temperature for 1 hour. The mixture was washed with saturated aqueous NaHCO₃ (5 mL), water (5 mL) and brine (5 mL), dried over Na₂SO₄ and concentrated under reduced pressure to give the title compound (1.09 mmol), which was used in the next step without further purification. *m/z* (APCI+) for C₁₄H₂₁Cl₂N₅O₄S 426.1(M+H)⁺.

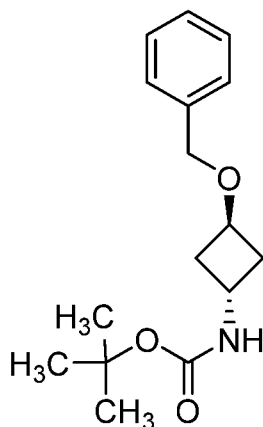
Step 2: Preparation of 4-(4-chloro-6-{[*trans*-3-(1,1-dioxido-1,2,5-thiadiazolidin-2-yl)cyclobutyl]oxy}pyrimidin-2-yl)morpholine



To a solution of *N*-(2-chloroethyl)-*N'*-(*trans*-3-[[6-chloro-2-(morpholin-4-yl)pyrimidin-4-yl]oxy]cyclobutyl)sulfuric diamide (0.463 g, 1.09 mmol) in DMSO (10 mL) was added K_2CO_3 (0.3 g, 2.18 mmol), and the resulting mixture was stirred at room temperature for 30 min and then heated at 50-60 °C for 1 hour. The mixture was cooled to 10 °C whereupon water (10 mL) was added. The mixture was extracted with EtOAc (4 x 15 mL). The organic layers were combined, washed with water (3 x 8 mL), brine (5 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with a gradient of petroleum ether/EtOAc (3:1 to 1:1) to give the title compound (0.18 g, 42%) as a white solid. m/z (APCI+) for $C_{14}H_{20}ClN_5O_4S$ 390.0 ($M+H$)⁺.

Preparation 6: Preparation of 1-(*trans*-3-hydroxycyclobutyl)imidazolidin-2-one

Step 1: Preparation of *tert*-butyl [trans-3-(benzyloxy)cyclobutyl]carbamate

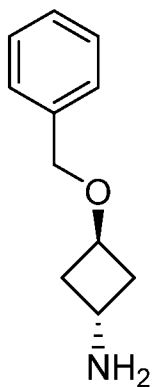


15

To a solution of *tert*-butyl (*trans*-3-hydroxycyclobutyl)carbamate (3 g, 16 mmol) in anhydrous THF (50 mL) was added NaH (640 mg, 16 mmol, 60% in oil) at 0 °C under nitrogen atmosphere, and the reaction mixture was stirred at room temperature for 30 min. Benzyl bromide (4.1 g, 24 mmol) was added dropwise and the resulting mixture

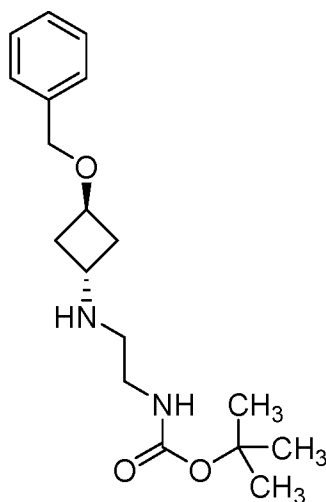
was stirred at room temperature for 12 hours. The mixture was quenched with H₂O (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to give a residue, which was purified by column chromatography eluting with petroleum ether/EtOAc (10:1) to give the title compound (2.92 g, 66%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.27 (m, 5 H), 4.68 (br s, 1 H), 4.40 (s, 2 H), 4.21-4.17 (m, 2 H), 2.44-2.42 (m, 2 H), 2.14-2.11 (m, 2 H), 1.43 (s, 9 H).

Step 2: Preparation of *trans*-3-(benzyloxy)cyclobutanamine



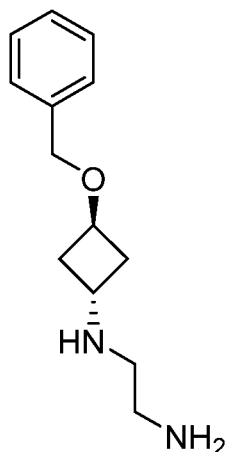
To a solution of *tert*-butyl [*trans*-3-(benzyloxy)cyclobutyl]carbamate (2.92 g, 10.5 mmol) in dichloromethane (50 mL) was added TFA (20 mL), and the resulting mixture was stirred at room temperature for 12 hours. The mixture was concentrated under reduced pressure, and saturated aqueous NaHCO₃ solution (10 mL) was added. The mixture was extracted with dichloromethane/MeOH (10:1) (5 x 150 mL), the combined organic layers were washed with brine (3 x 100 mL), dried over Na₂SO₄ and concentrated to give the title compound (1.8 g, 97%) as an oil. ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.27 (m, 5 H), 4.40 (s, 2 H), 4.27-4.23 (m, 1 H), 3.71-3.70 (m, 1 H), 2.36-2.32 (m, 2 H), 2.00-1.97 (m, 2 H).

Step 3: Preparation of *tert*-butyl (2-[[*trans*-3-(benzyloxy)cyclobutyl]amino]ethyl)carbamate



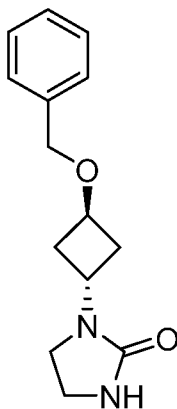
To a mixture of *trans*-3-(benzyloxy)cyclobutanamine (824 mg, 4.65 mmol) and *tert*-butyl (2-oxoethyl)carbamate (740 mg, 4.65 mmol) in 1,2-dichloroethane (100 mL) was added AcOH (279 mg, 4.65 mmol) and the reaction mixture was stirred at 0 °C for 30 min. To the mixture was added NaBH(OAc)₃ (2.46 g, 11.6 mmol) portionwise at 0 °C and the resulting mixture was stirred at room temperature for 12 hours. Saturated aqueous NaHCO₃ solution (20 mL) was added to adjust pH to ~ 8. The organic layer was separated and the aqueous layer was extracted with dichloromethane (100 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to give a residue, which was purified by column chromatography eluting with dichloromethane/MeOH (10:1) to give the title compound (240 mg, 16%) as an oil. ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.27 (m, 5 H), 4.90 (s, 1 H), 4.41 (m, 2 H), 4.26-4.24 (m, 1 H), 3.47-3.45 (m, 1 H), 3.23-3.22 (m, 2 H), 2.68-2.65 (m, 2 H), 2.27-2.24 (m, 2 H), 2.07-2.05 (m, 2 H), 1.45 (s, 9 H).

Step 4: Preparation of *N*-[*trans*-3-(benzyloxy)cyclobutyl]ethane-1,2-diamine



To a solution of *tert*-butyl (2-[[*trans*-3-(benzyloxy)cyclobutyl]amino]ethyl)carbamate (320 mg, 1 mmol) in dichloromethane (10 mL) was added TFA (10 mL) and the resulting mixture was stirred at room temperature for 4 hours. The mixture was concentrated to remove the solvent, and saturated aqueous NaHCO₃ solution (10 mL) was added to adjust the pH to ~ 8. The mixture was extracted with dichloromethane/MeOH (10:1) (3 x 100 mL), the combined organic layers were washed with brine (2 x 50 mL), dried over Na₂SO₄ and concentrated to give the title compound (190 g, 86.4%) as an oil. This material was used directly in the next step.

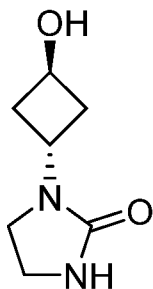
Step 5: Preparation of 1-[*trans*-3-(benzyloxy)cyclobutyl]imidazolidin-2-one



To a solution of *N*-[*trans*-3-(benzyloxy)cyclobutyl]ethane-1,2-diamine (190 mg, 0.86 mmol) in MeCN (10 mL) was added DBU (392 mg, 2.58 mmol) and then CDI (156 mg, 0.95 mmol) and the resulting mixture was stirred at room temperature for 12 hours.

The mixture was concentrated to give a residue, which was dissolved in dichloromethane (80 mL) and washed with citric acid (1 N, 10 mL), brine (10 mL) and dried over Na₂SO₄, filtered and concentrated to give a residue, which was purified by column chromatography eluting with dichloromethane/MeOH (10:1) to give the title compound (120 mg, 56.7%) as a solid. ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.28 (m, 5 H), 4.64-4.60 (m, 1 H), 4.42 (s, 2 H), 4.17-4.15 (m, 1 H), 3.52-3.48 (m, 2 H), 3.44-3.41 (m, 2 H), 2.45-2.37 (m, 4 H).

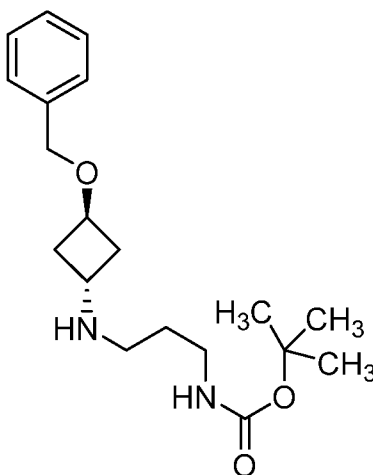
Step 6: Preparation of 1-(*trans*-3-hydroxycyclobutyl)imidazolidin-2-one



To a solution of 1-[(*trans*-3-(benzyloxy)cyclobutyl)]imidazolidin-2-one (120 mg, 0.49 mmol) in MeOH (50 mL) was added Pd/C (10 mg) at room temperature. The resulting mixture was purged with hydrogen gas three times and stirred at 40 °C at 40
 5 Psi of hydrogen for 12 hours. The mixture was filtered and washed with MeOH (20 mL). The filtrate was concentrated to give the title compound (50 mg, 65.4%) as an oil. ¹H NMR (400 MHz, CDCl₃) δ 4.67-4.65 (m, 1 H), 4.46-4.43 (m, 2 H), 3.49-3.37 (m, 4 H), 2.51-2.47 (m, 2 H), 2.26-2.23 (m, 2 H).

10 **Preparation 7: Preparation of 1-[(*trans*-3-hydroxycyclobutyl)]tetrahydropyrimidin-2(1*H*)-one**

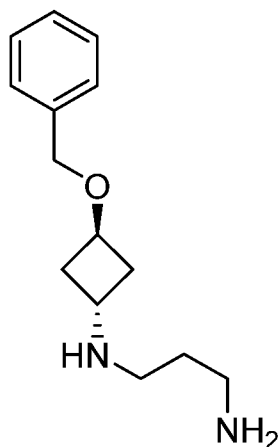
Step 1: Preparation of *tert*-butyl (3-[(*trans*-3-(benzyloxy)cyclobutyl)]amino}propyl)carbamate



15 To a mixture of *trans*-3-(benzyloxy)cyclobutanamine (400 mg, 2.26 mmol) and *tert*-butyl (3-oxopropyl)carbamate (391 mg, 2.26 mmol) in 1,2-dichloroethane (30 mL) was added AcOH (136 mg, 2.26 mmol) and the reaction mixture was stirred at 0 °C for 30 min. NaBH(OAc)₃ (1.2 g, 5.65 mmol) was added portionwise at 0 °C and the resulting mixture was stirred at room temperature for 12 hours. Saturated aqueous
 20 NaHCO₃ solution (20 mL) was added to adjust pH to ~ 8. The organic layer was

separated and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over Na₂SO₄ and concentrated to give a residue, which was purified by column chromatography eluting with dichloromethane/MeOH (10:1) to give the title compound (200 mg, 26.5%) as an oil. This material was used directly in the next step.

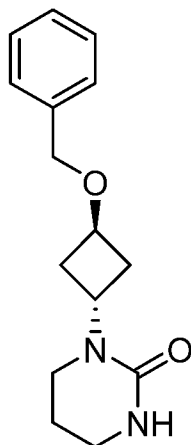
Step 2: Preparation of *N*-[*trans*-3-(benzyloxy)cyclobutyl]propane-1,3-diamine



To a solution of *tert*-butyl (3-[[*trans*-3-(benzyloxy)cyclobutyl]amino}propyl)carbamate (340 mg, 1.02 mmol) in dichloromethane (20 mL) was added TFA (20 mL) and the resulting mixture was stirred at room temperature for 2 hours. The mixture was concentrated to remove the solvent, and saturated aqueous NaHCO₃ solution (10 mL) was added to adjust the pH to ~ 8. The mixture was extracted with dichloromethane/MeOH (10:1) (4 x 100 mL), the combined organic layers were washed with brine (2 x 50 mL), dried over Na₂SO₄ and concentrated to give the title compound (150 mg, 63%) as an oil. This material was used directly in the next step.

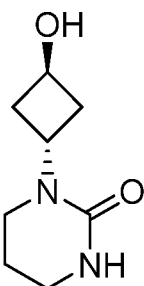
Step 3: Preparation of 1-[*trans*-3-(benzyloxy)cyclobutyl]tetrahydropyrimidin-2(1*H*)-

one



To a solution of *N*-[*trans*-3-(benzyloxy)cyclobutyl]propane-1,3-diamine (200 mg, 0.86 mmol) in MeCN (10 mL) was added DBU (392 mg, 2.58 mmol) and CDI (156 mg, 0.94 mmol) and the resulting mixture was stirred at room temperature for 12 hours. The mixture was concentrated to give a residue, which was dissolved in dichloromethane (50 mL) and washed with citric acid (1 N, 10 mL), brine (20 mL) and dried over Na₂SO₄, filtered and concentrated to give a residue, which was purified by column chromatography eluting with dichloromethane/MeOH (10:1) to give the title compound (100 mg, 44.7%) as a solid. ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.28 (m, 5 H), 5.12 (p, *J* = 8.0 Hz, 1 H), 4.76 (br s, 1 H), 4.42 (s, 2 H), 4.14-4.09 (m, 1 H), 3.29-3.26 (m, 4 H), 2.39-2.35 (m, 4 H), 1.97-1.93 (m, 2 H).

Step 4: Preparation of 1-(*trans*-3-hydroxycyclobutyl)tetrahydropyrimidin-2(1H)-one

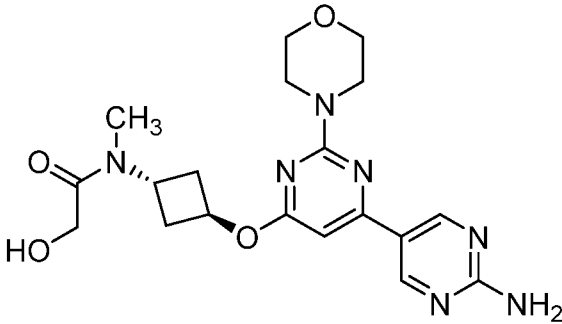
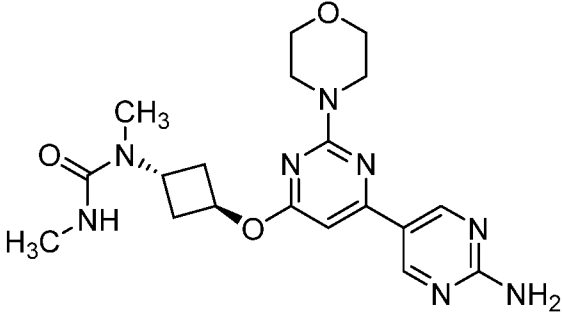


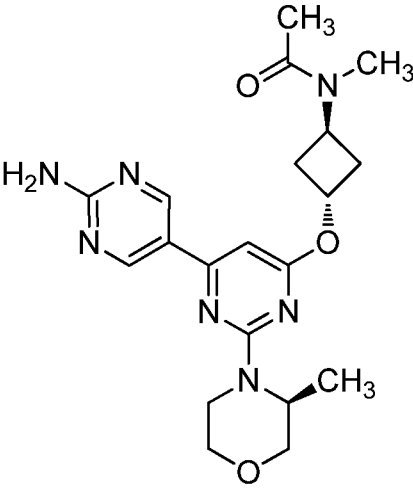
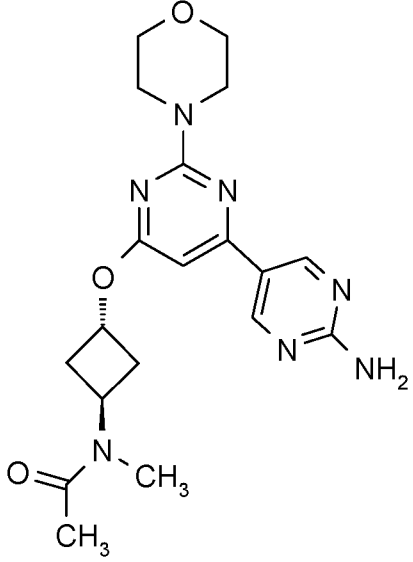
To a solution of 1-[*trans*-3-(benzyloxy)cyclobutyl]tetrahydropyrimidin-2(1H)-one (150 mg, 0.58 mmol) in MeOH (50 mL) was added Pd/C (15 mg) at room temperature. The resulting mixture was purged with hydrogen three times and stirred at 40 °C under 40 Psi of hydrogen for 12 hours. The mixture was filtered and washed with MeOH (20 mL). The filtrate was concentrated to give the title compound (90 mg, 91%) as a solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.17 (s, 1 H), 5.09 (p, *J* = 8.0 Hz, 1 H), 4.92 (br s, 1 H),

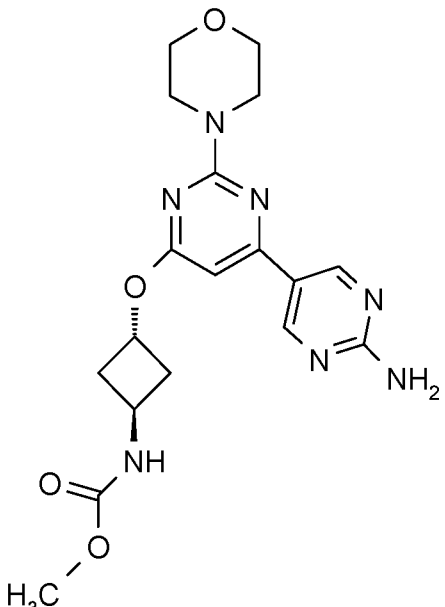
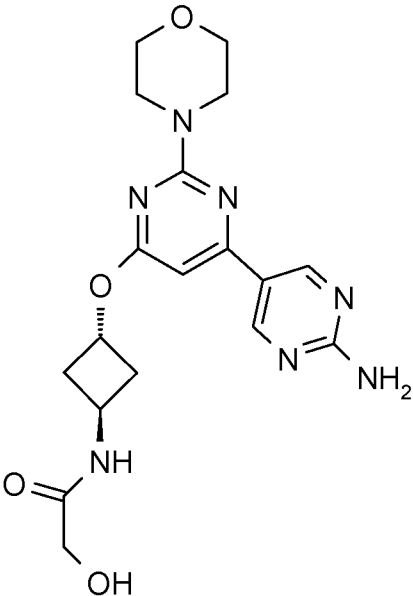
4.13 (br s, 1 H), 3.19-3.17 (m, 2 H), 3.07-3.05 (m, 2 H), 2.30-2.27 (m, 2 H), 1.91-1.88 (m, 2 H), 1.79-1.76 (m, 2 H).

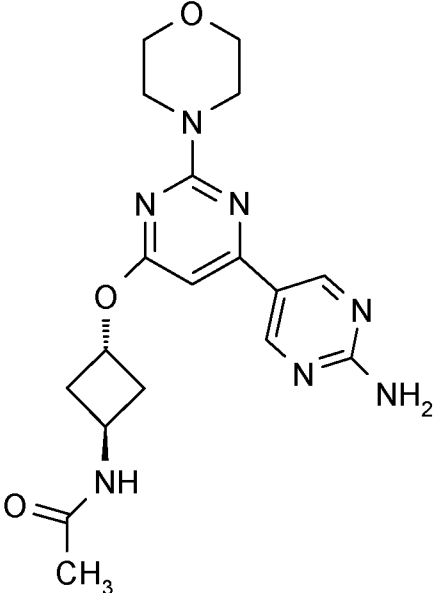
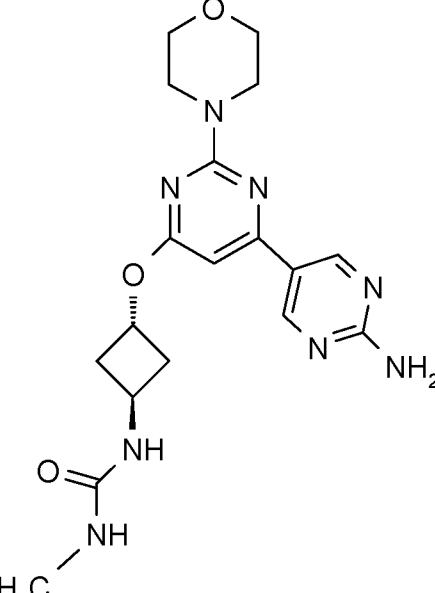
The following examples were made with non-critical changes or substitutions to the exemplified procedures that would be understood by one skilled in the art.

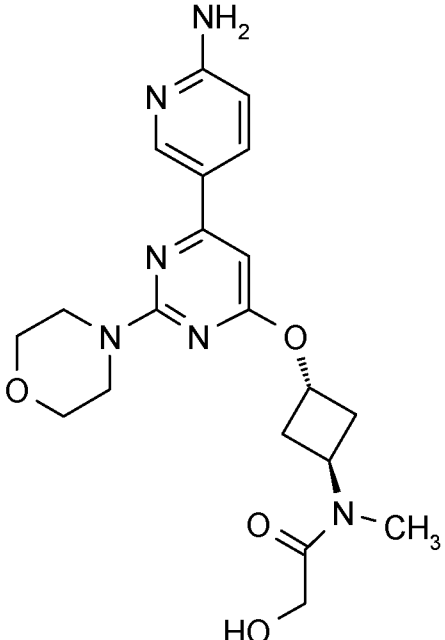
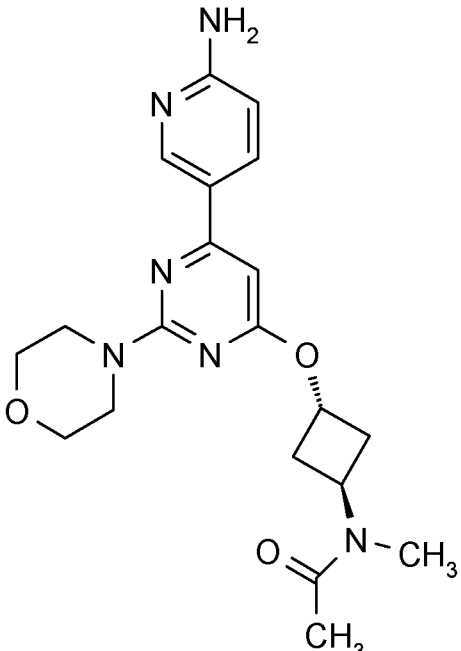
Table 1

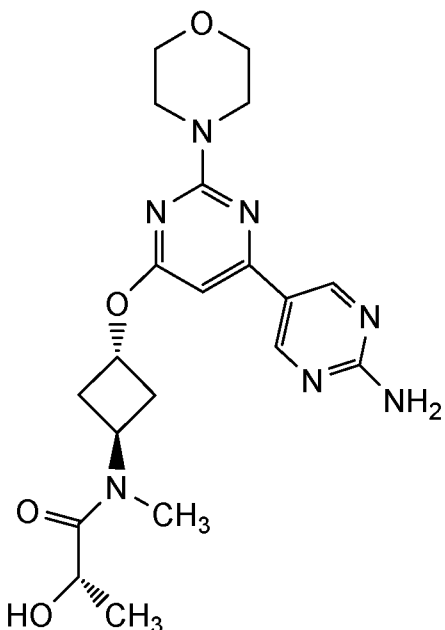
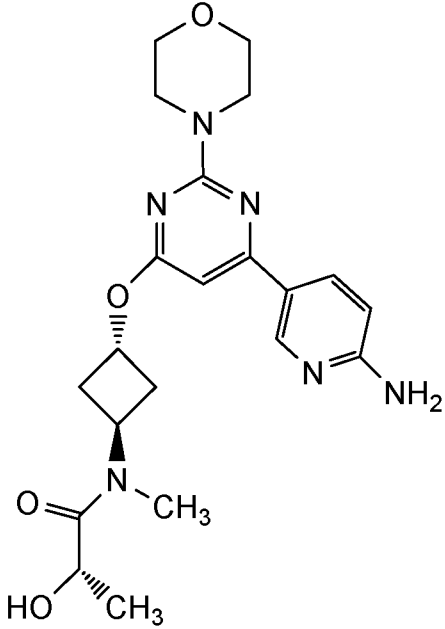
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
1	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-<i>N</i>-methylacetamide	416.1	1H NMR (400 MHz, 80 °C, DMSO- d_6) δ ppm 8.89 (s, 2 H) 6.76 (br s, 2 H) 6.53 (s, 1 H) 5.33-5.26 (m, 1 H) 4.86 (br s, 1 H) 4.17 (br s, 1 H) 4.07 (d, $J=5.0$ Hz, 2 H) 3.78-3.73 (m, 4 H) 3.72-3.66 (m, 4 H) 2.93 (s, 3 H) 2.76-2.66 (m, 2 H) 2.45-2.37 (m, 2 H).
2	 1-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-1,3-dimethylurea	436.9 $[M+23]^+$	1H NMR (400 MHz, CD $_3$ CN) δ ppm 8.91 (s, 2 H) 6.39 (s, 1 H) 5.74 (br s, 2 H) 5.24 - 5.19 (m, 1 H) 5.03 - 4.97 (m, 1 H) 4.86 (p, $J=8.4$ Hz, 1 H) 3.80 - 3.76 (m, 4 H) 3.70 - 3.65 (m, 4 H) 2.81 (s, 3 H) 2.64 (d, $J=4.5$ Hz, 3 H) 2.63 - 2.55 (m, 2 H) 2.41 - 2.32 (m, 2 H).

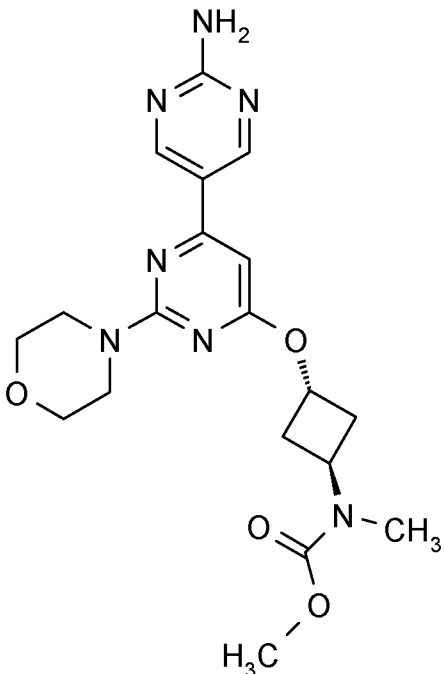
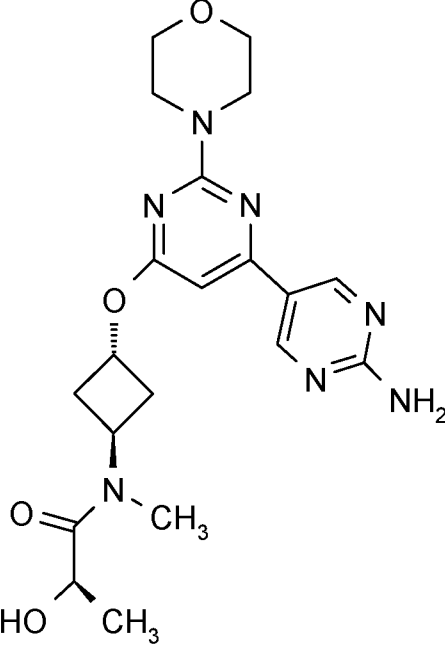
Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
3	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-<i>N</i>-methylacetamide	414.1	¹ H NMR (400 MHz, CDCl ₃) δ ppm 8.90 (s, 2 H) 6.30 (s, 1 H) 5.25 (br s, 3 H) 4.78-4.66 (m, 2 H) 4.37 (d, J=15.6 Hz, 1 H) 4.00 (d, J=12.8 Hz, 1 H) 3.81-3.70 (m, 2 H) 3.59-3.54 (m, 1 H) 3.30-3.27 (m, 1 H) 3.01-2.97 (m, 3 H) 2.68-2.52 (m, 4 H) 2.12 (s, 3 H) 1.29 (t, J=6.8 Hz, 3 H).
4	 <i>N</i>-(<i>trans</i>-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-<i>N</i>-methylacetamide	400.1	¹ H NMR (400 MHz, 80 °C, DMSO- <i>d</i> ₆) δ ppm 8.89 (s, 2 H) 6.75 (br s, 2 H) 6.53 (s, 1 H) 5.31-5.24 (m, 1 H) 4.89 (br s, 1 H) 3.77-3.73 (m, 4 H) 3.70-3.66 (m, 4 H) 2.93 (s, 3 H) 2.73-2.63 (m, 2 H) 2.41 (t, J=10.9 Hz, 2 H) 2.00 (s, 3 H).

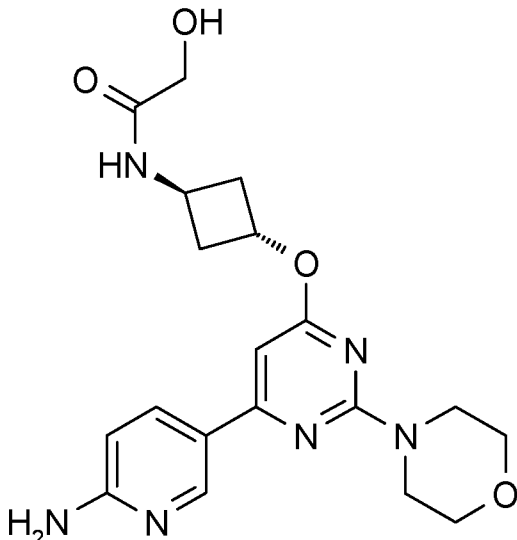
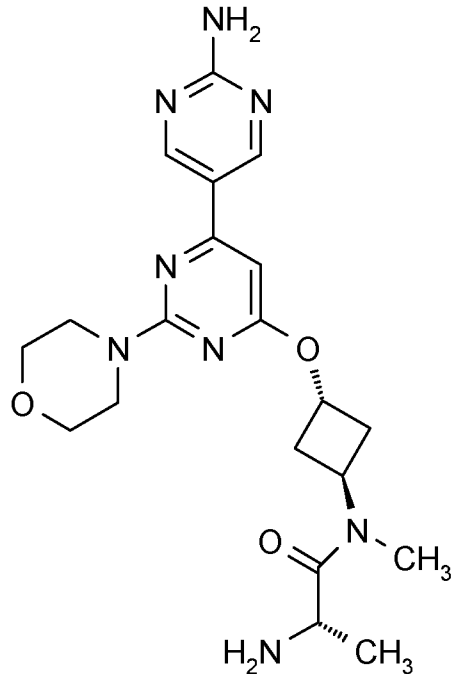
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	^1H NMR
5	 methyl (<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)carbamate	402.1	^1H NMR (600 MHz, DMSO- d_6) δ ppm 8.91 (s, 2 H) 7.62 (d, $J=6.9$ Hz, 1 H) 7.13-7.09 (m, 2 H) 6.58-6.55 (m, 1 H) 5.27 (p, $J=5.8$ Hz, 1 H) 4.13-4.06 (m, 1 H) 3.75-3.71 (m, 4 H) 3.68-3.65 (m, 4 H) 3.53 (s, 3 H) 2.41-2.33 (m, 4 H).
6	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxyacetamide	402.1	^1H NMR (400 MHz, DMSO- d_6) δ ppm 8.91 (s, 2 H) 8.13 (d, $J=7.2$ Hz, 1 H) 7.09 (s, 2 H) 6.58 (s, 1 H) 5.40 (t, $J=5.8$ Hz, 1 H) 5.35-5.28 (m, 1 H) 4.45-4.36 (m, 1 H) 3.80 (d, $J=5.8$ Hz, 2 H) 3.75-3.71 (m, 4 H) 3.70-3.64 (m, 4 H) 2.44-2.35 (m, 2 H).

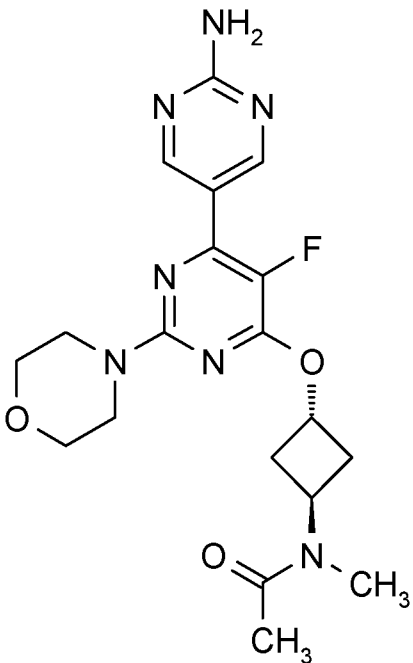
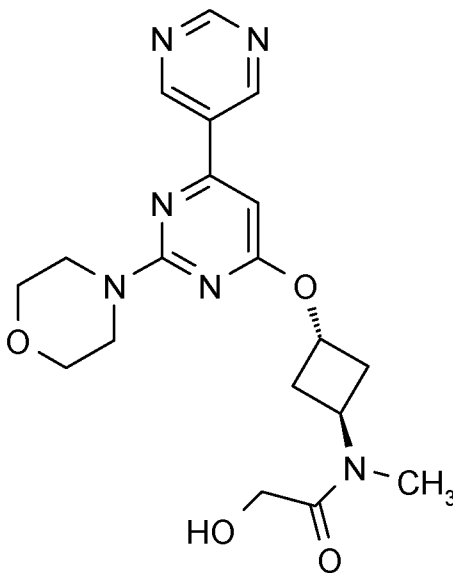
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	^1H NMR
7	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)acetamide	386.1	^1H NMR (600 MHz, DMSO- d_6) δ ppm 8.91 (s, 2 H) 8.27 (d, $J=6.9$ Hz, 1 H) 7.11 (s, 2 H) 6.58 (s, 1 H) 5.28 (p, $J=6.0$ Hz, 1 H) 4.29-4.22 (m, 1 H) 3.74-3.71 (m, 4 H) 3.69-3.65 (m, 4 H) 2.42-2.33 (m, 4 H) 1.81 (s, 3 H).
8	 1-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-3-methylurea	401.2	^1H NMR (600 MHz, DMSO- d_6) δ ppm 8.91 (s, 2 H) 7.11 (s, 2 H) 6.57 (s, 1 H) 6.34 (d, $J=6.9$ Hz, 1 H), 5.69 (p, $J=4.6$ Hz, 1 H) 5.27-5.22 (m, 1 H) 4.19-4.12 (m, 1 H) 3.74-3.71 (m, 4 H) 3.69-3.64 (m, 4 H) 2.53 (d, $J=4.6$ Hz, 3 H) 2.38-2.28 (m, 4 H).

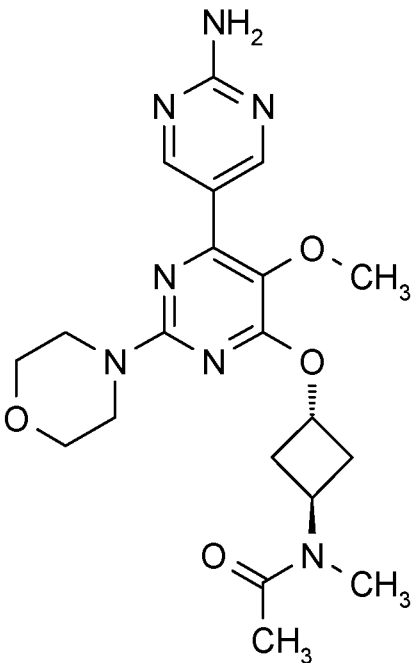
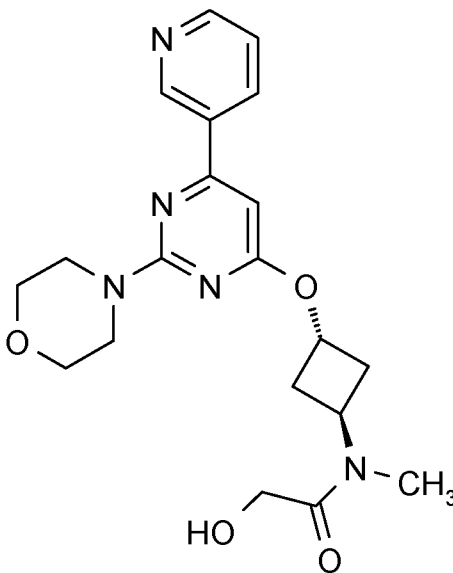
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
9	 <i>N</i>-(<i>trans</i>-3-([6-(6-aminopyridin-3-yl)-2-(morpholin-4-yl)pyrimidin-4-yl]oxy)cyclobutyl)-2-hydroxy-<i>N</i>-methylacetamide	415.0	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.73 (s, 1 H) 8.08 (d, $J=8.8$ Hz, 1 H) 6.55 (d, $J=8.4$ Hz, 1 H) 6.34 (s, 1 H) 5.28-5.22 (m, 1 H) 4.18-4.14 (m, 1 H) 4.68 (s, 2 H) 3.82-3.77 (m, 8 H) 3.75-3.70 (m, 1 H) 3.07-2.89 (m, 3 H) 2.69-2.54 (m, 4 H).
10	 <i>N</i>-(<i>trans</i>-3-([6-(6-aminopyridin-3-yl)-2-(morpholin-4-yl)pyrimidin-4-yl]oxy)cyclobutyl)-<i>N</i>-methylacetamide	399.0	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.72 (s, 1 H) 8.09 (d, $J=8.0$ Hz, 1 H) 6.57 (dd, $J=8.0$ Hz, 4.4 Hz, 1 H), 6.34 (d, $J=4.4$ Hz, 1 H) 5.28-5.24 (m, 2 H) 4.78-4.72 (m, 2 H) 3.82-3.78 (m, 8 H) 3.02-2.98 (m, 3 H) 2.67-2.54 (m, 4 H) 2.11 (s, 3 H).

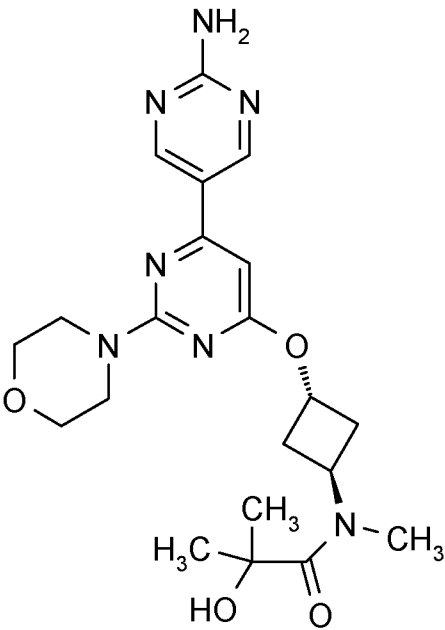
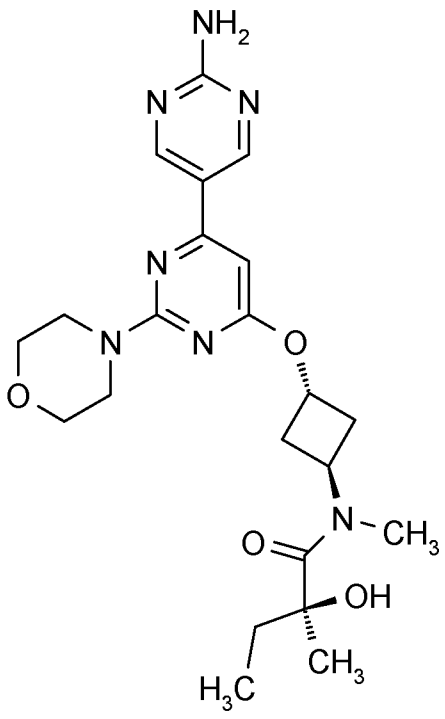
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	^1H NMR
11	 (2S)-N-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-N-methylpropanamide	430.1	^1H NMR (400 MHz, DMSO- d_6) δ ppm 8.90 (s, 2 H) 6.70-6.72 (m, 2 H) 6.54 (s, 1 H) 5.33-5.26 (m, 1 H) 4.98 (p, $J=8.1$ Hz, 1 H) 4.53-4.49 (m, 1 H) 4.43 (p, $J=6.4$ Hz, 1 H) 3.77-3.74 (m, 4 H) 3.71-3.66 (m, 4 H) 2.98 (s, partially overlapping with water, 3 H) 2.76-2.66 (m, 2 H) 2.45-2.37 (m, 2 H) 1.20 (d, $J=6.5$ Hz, 3 H).
12	 (2S)-N-(<i>trans</i>-3-([6-(6-aminopyridin-3-yl)-2-(morpholin-4-yl)pyrimidin-4-yl]oxy)cyclobutyl)-2-hydroxy-N-methylpropanamide	429.5	^1H NMR (400 MHz, DMSO- d_6) δ ppm 8.69 (br s, 1 H) 8.07 (d, 1 H) 6.56-6.44 (m, 2 H) 6.38 (s, 2 H) 5.24 (br s, 1 H) 5.17-4.89 (m, 1 H) 4.88-4.72 (m, 1 H) 4.42 (br s, 1 H) 3.79-3.59 (m, 8 H) 3.01-2.89 (m, 3 H) 2.82-2.60 (m, 2 H) 2.45-2.22 (m, 2 H) 1.20-1.10 (m, 3 H).

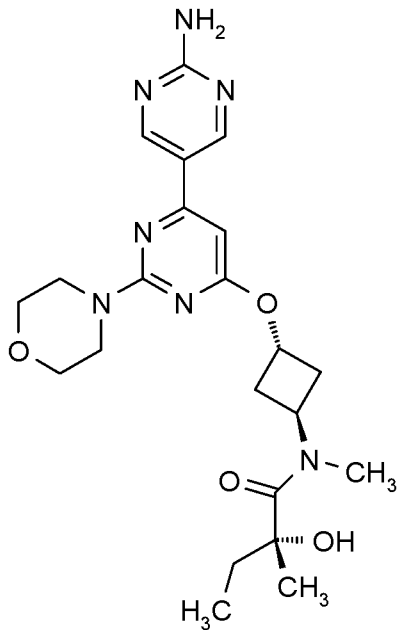
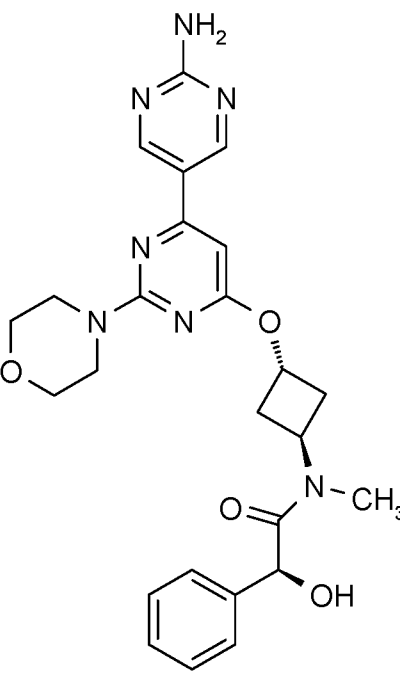
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
13	 methyl (<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)methylcarbamate	416.0	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.82 (s, 2 H) 6.23 (s, 1 H) 5.20-5.16 (m, 3 H) 4.80-4.79 (m, 1 H) 3.74-3.70 (m, 8 H) 3.63 (s, 3 H) 2.85 (s, 3 H) 2.55-2.54 (m, 2 H) 2.42-2.37 (m, 2 H).
14	 (2<i>R</i>)-<i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-<i>N</i>-methylpropanamide	430.1	1H NMR (400 MHz, 80 °C, $DMSO-d_6$) δ ppm 8.90 (s, 2 H) 6.76 (br s, 2 H) 6.54 (s, 1 H) 5.33-5.26 (m, 1 H) 5.02-4.93 (m, 1 H) 4.51 (d, $J=6.7$ Hz, 1 H) 4.43 (p, $J=6.5$ Hz, 1 H) 3.77-3.73 (m, 4 H) 3.71-3.66 (m, 4 H) 2.98 (s, 3 H) 2.76-2.68 (m, 2 H) 2.45-2.37 (m, 2 H) 1.20 (d, $J=6.5$ Hz, 3 H).

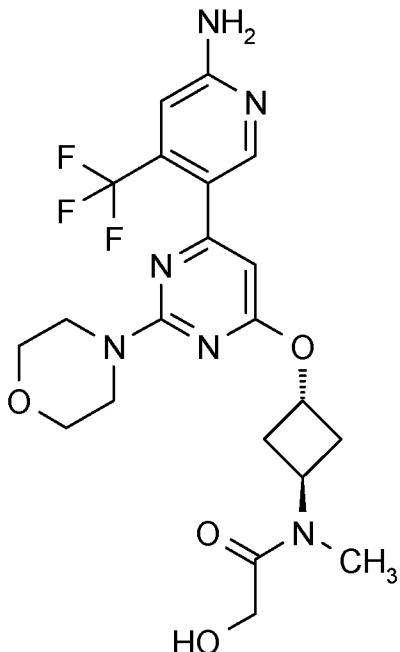
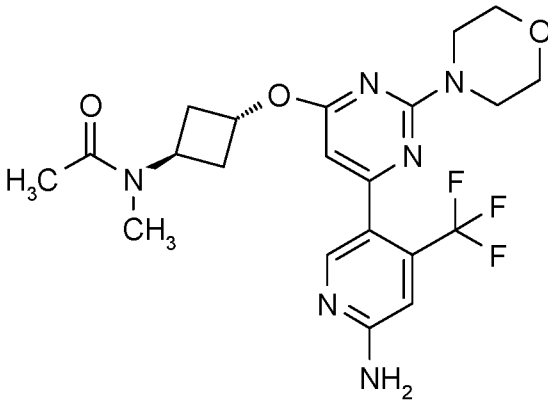
Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
15	 <i>N</i>-(<i>trans</i>-3-([6-(6-aminopyridin-3-yl)-2-(morpholin-4-yl)pyrimidin-4-yl]oxy)cyclobutyl)-2-hydroxyacetamide	400.9	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 8.68 (d, J=2 Hz, 1 H) 8.21 (d, J=7.6 Hz, 1 H) 8.06 (dd, J=8.8 Hz, 2.4 Hz, 1 H) 6.50-6.44 (m, 4 H) 5.52-5.49 (m, 1 H) 5.30-5.29 (m, 1 H) 3.81-3.66 (m, 10 H) 2.47-2.39 (m, 4 H).
16	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-<i>N</i>-methyl-L-alaninamide	429.1	¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.92 (s, 2 H) 6.49 (s, 1 H) 5.33 (s, 1 H) 5.17-5.12 (m, 1 H) 4.52-4.39 (m, 1 H) 3.83-3.76 (m, 8 H) 3.1 (d, J=14.6 Hz, 3 H) 2.91-2.78 (m, 2 H) 2.76-2.47 (m, 2 H) 1.50-1.37 (m, 3 H).

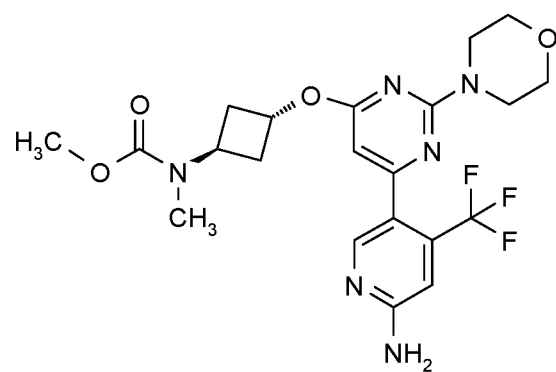
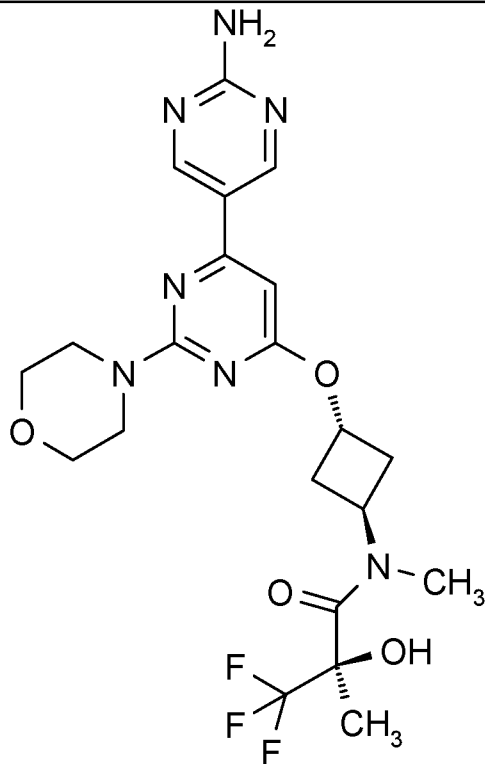
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
17	 <i>N</i>-(<i>trans</i>-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-<i>N</i>-methylacetamide	418.2	1H NMR (400 MHz, DMSO- d_6 , 80 °C) δ 8.83 (s, 2 H) 6.87 (br s, 2 H), 5.40-5.28 (m, 1 H) 4.91 (br s, 1 H) 3.68 (s, 8 H) 2.93 (s, 3 H) 2.78-2.64 (m, 2 H) 2.49-2.42 (m, 2 H) 2.00 (s, 3 H).
18	 2-hydroxy-<i>N</i>-methyl-<i>N</i>-(<i>trans</i>-3-([2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)acetamide	401.1	1H NMR (400 MHz, CDCl $_3$) δ ppm 9.27 (s, 3 H) 6.46 (d, J =2.4 Hz, 1 H) 5.31-5.21 (m, 1 H) 4.41 (d, J =16.8 Hz, 2 H) 3.84-3.78 (m, 8 H) 3.62 (s, 1 H) 3.07-2.72 (m, 3 H) 2.71-2.66 (m, 2 H) 2.57-2.54 (m, 2 H).

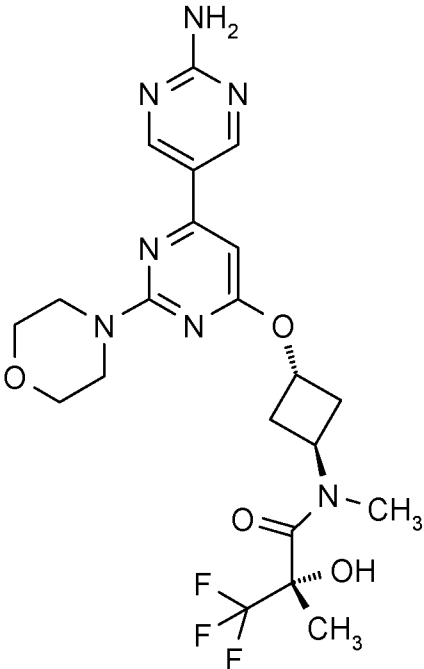
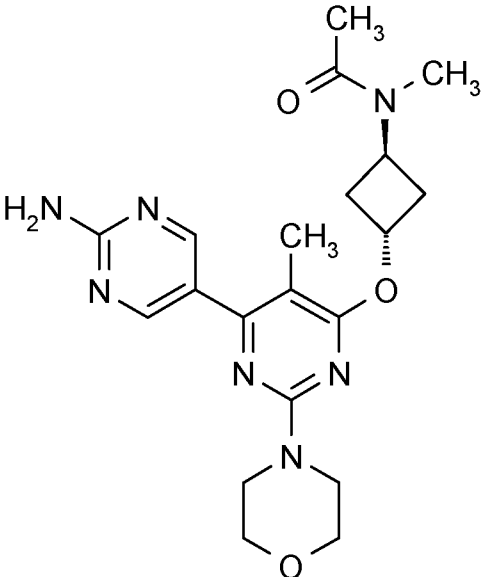
Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
19**	 <i>N</i>-(<i>trans</i>-3-([2'-amino-5-methoxy-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-<i>N</i>-methylacetamide	430.2	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 8.90 (s, 2H), 7.05 (s, 2H), 5.27 (br s, 1H), 5.23-5.12 (m, 0.5H), 4.79-4.66 (m, 0.5H), 3.68 (s, 3H), 3.67-3.60 (m, 8H), 2.97 (s, 1.5H), 2.85 (s, 1.5H), 2.79-2.28 (m, 4H), 2.01-1.99 (m, 3H).
20	 2-hydroxy-<i>N</i>-methyl-<i>N</i>-(<i>trans</i>-3-([2-(morpholin-4-yl)-6-(pyridin-3-yl)pyrimidin-4-yl]oxy)cyclobutyl)acetamide	400.0	¹ H NMR (400 MHz, CDCl ₃) δ ppm 9.20 (s, 1 H) 8.67 (s, 1 H) 8.28 (d, J=6 Hz, 1 H) 7.41-7.37 (m, 1 H) 6.47 (d, J=2.4 Hz, 1 H) 5.31-4.45 (m, 2 H) 4.16 (d, J=16.8 Hz, 2 H) 3.84-3.83 (m, 8 H) 3.78 (s, 1 H) 3.08-2.71 (m, 3 H) 2.69-2.68 (m, 2 H) 2.58-2.53 (m, 2 H).

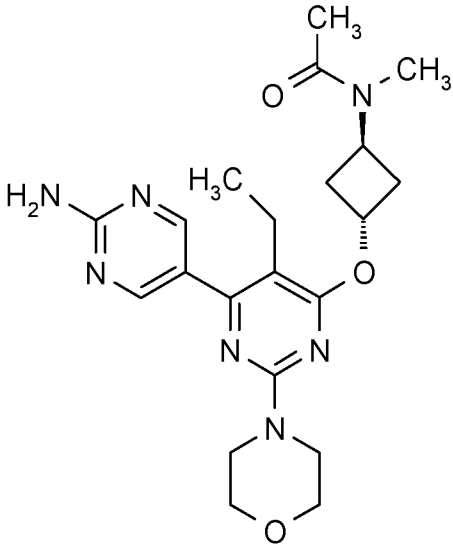
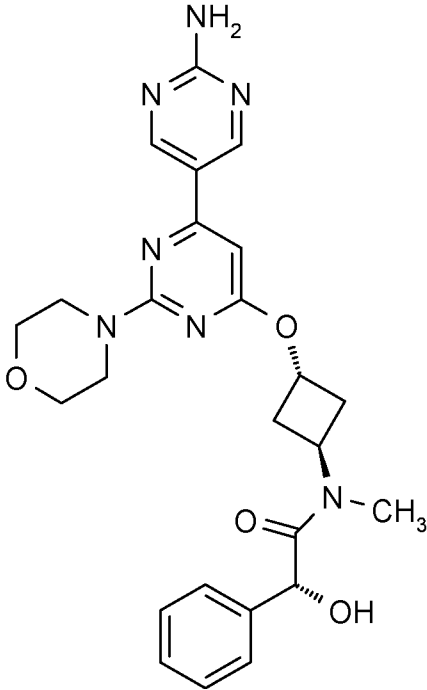
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
21	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-<i>N</i>,2-dimethylpropanamide	443.9	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.90 (s, 2 H) 6.35 (s, 1 H) 5.32-5.22 (m, 3 H) 5.13-5.12 (m, 1 H) 4.50 (s, 1 H) 3.75-3.71 (m, 8 H) 3.08 (s, 3 H) 2.56-2.70 (m, 2 H) 2.55-2.53 (m, 2 H) 1.49 (s, 6 H).
22*	 (2<i>S</i>)-<i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-<i>N</i>,2-dimethylbutanamide	458.1	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.89 (s, 2 H) 6.32 (s, 1 H) 5.27 (br s, 3 H) 5.07-5.03 (m, 1 H) 4.77 (br s, 1 H) 3.82-3.76 (m, 8 H) 3.07 (s, 3 H) 2.70-2.53 (m, 4 H) 1.84-1.77 (m, 2 H) 1.47 (s, 3 H) 0.85 (t, $J=7.2$ Hz, 3 H).

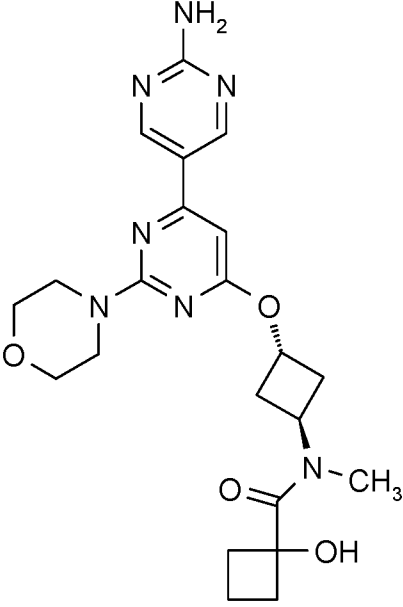
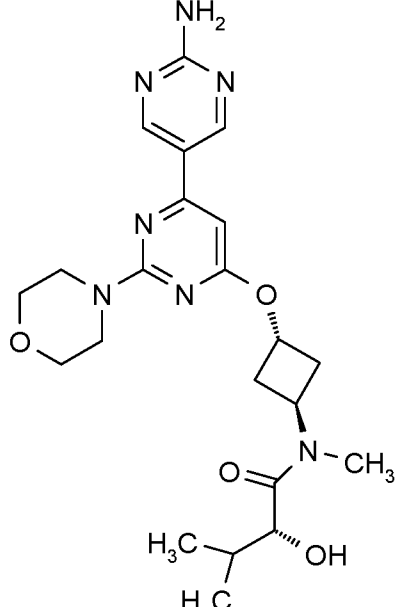
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
23*	 (2R)-N-(<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-2-hydroxy-N,2-dimethylbutanamide	458.1	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.89 (s, 2 H) 6.32 (s, 1 H) 5.29-5.27 (br s, 3 H) 5.07-5.03 (m, 1 H) 4.77 (br s, 1 H) 3.82-3.76 (m, 8 H) 3.07 (s, 3 H) 2.70-2.53 (m, 4 H) 1.83-1.77 (m, 2 H) 1.47 (s, 3 H) 0.85 (t, $J=7.2$ Hz, 3 H).
24	 (2S)-N-(<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-2-hydroxy-N-methyl-2-phenylethanamide	492.2	1H NMR (400 MHz, DMSO, $t=80$ °C) δ ppm 8.90 (s, 2 H) 7.35-7.27 (m, 5 H) 6.81 (s, 2 H) 6.52 (s, 1 H) 5.38 (d, $J=6.0$ Hz, 1 H) 5.28-5.20 (m, 2 H) 4.94 (br s, 1 H) 3.74-3.66 (m, 8 H) 2.91 (s, 3 H) 2.67-2.52 (m, 2 H) 2.51-2.33 (m, 2 H).

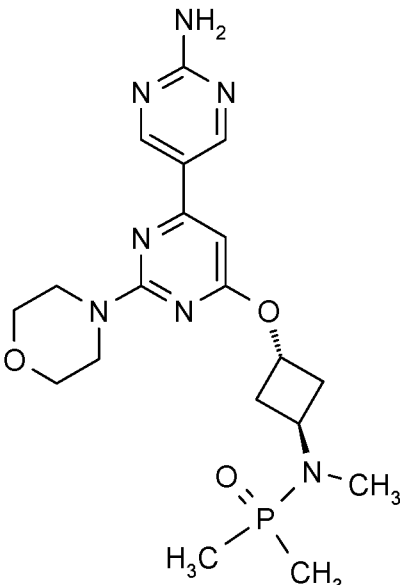
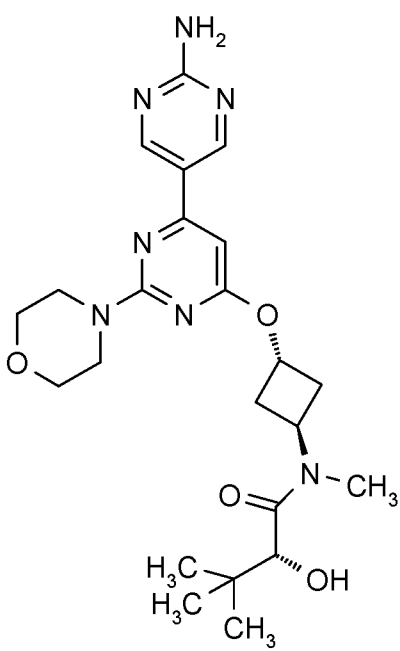
Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
25	 <i>N</i>-[<i>trans</i>-3-({6-[6-amino-4-(trifluoromethyl)pyridin-3-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)cyclobutyl]-2-hydroxy-<i>N</i>-methylacetamide	483.1	¹ H NMR (400 MHz, CDCl ₃) δ ppm 8.28 (s, 1 H) 6.81 (s, 1 H) 6.14 (s, 1 H) 5.28-5.26 (m, 1 H), 4.45-4.40 (m, 1 H) 4.85-4.80 (m, 2 H) 4.20-4.14 (m, 2 H) 3.77-3.76 (m, 8 H) 3.65-3.64 (m, 1 H) 3.08-2.90 (m, 3 H) 2.75-2.65 (m, 2 H) 2.57-2.56 (m, 2 H).
26	 <i>N</i>-[<i>trans</i>-3-({6-[6-amino-4-(trifluoromethyl)pyridin-3-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)cyclobutyl]-<i>N</i>-methylacetamide	467.1	¹ H NMR (400 MHz, CDCl ₃) δ ppm 8.28 (s, 1 H) 6.81 (s, 1 H) 6.14 (s, 1 H) 5.30-4.70 (m, 2 H) 4.85-4.75 (m, 2 H) 3.78-3.75 (m, 8 H) 3.01-2.98 (m, 3 H) 2.69-2.67 (m, 2 H) 2.59-2.53 (m, 2 H) 2.13-2.11 (m, 3 H).

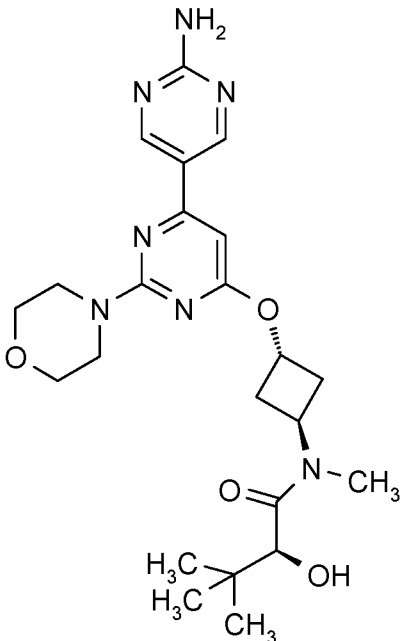
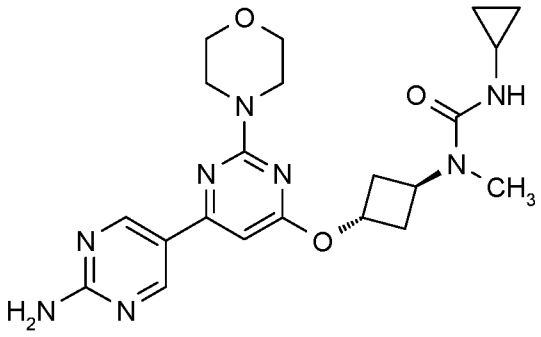
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
27	 methyl [<i>trans</i>-3-({6-[6-amino-4-(trifluoromethyl)pyridin-3-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)cyclobutyl]methylcarbamate	483.1	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.28 (s, 1 H) 6.81 (s, 1 H) 6.13 (s, 1 H) 5.30-4.85 (m, 2 H) 4.85-4.79 (m, 2 H) 3.78-3.75 (m, 8 H) 3.71 (s, 3 H) 2.93 (s, 3 H) 2.63-2.61 (m, 2 H) 2.52-2.49 (m, 2 H).
28*	 (2<i>R</i>)-<i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-3,3,3-trifluoro-2-hydroxy-<i>N</i>,2-dimethylpropanamide	497.8	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.89 (s, 2 H) 6.32 (s, 1 H) 5.31-5.28 (m, 4 H) 5.26 (br s, 1 H) 3.81-3.77 (m, 8 H) 3.13 (s, 3 H) 2.75-2.45 (m, 4 H) 1.73 (s, 3 H).

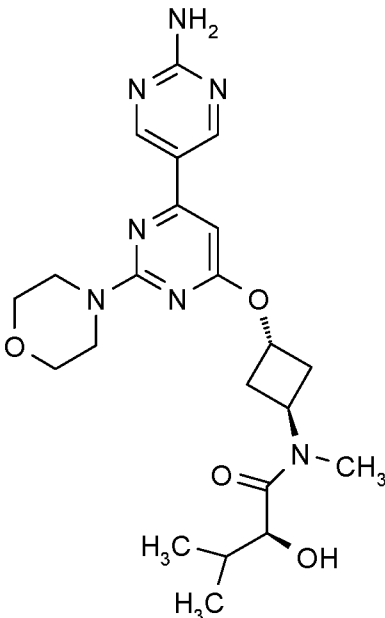
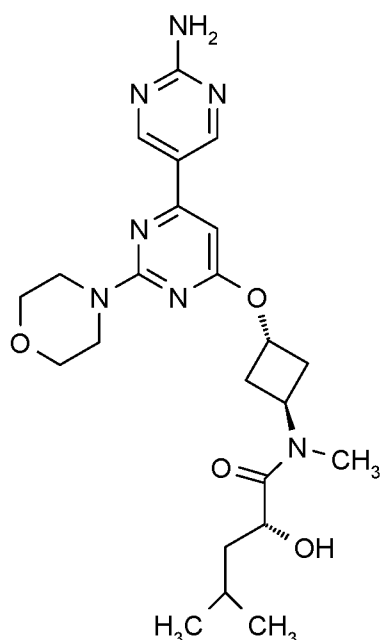
Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
29*	 (2S)-N-(trans-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-3,3,3-trifluoro-2-hydroxy-N,2-dimethylpropanamide	497.8	¹ H NMR (400 MHz, CDCl ₃) δ ppm 8.89 (s, 2 H) 6.32 (s, 1 H) 5.27 (br s, 4 H) 5.08 (br s, 1 H) 3.80-3.77 (m, 8 H) 3.13 (s, 3 H) 2.69-2.53 (m, 4 H) 1.71 (s, 3 H).
30	 N-(trans-3-([2'-amino-5-methyl-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-N-methylacetamide	435.0	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 8.51 (s, 2 H) 6.99 (s, 2 H) 5.21-4.21 (m, 2 H) 3.64-3.61 (m, 8 H) 2.97-2.86 (m, 3 H) 2.70-2.65 (m, 2 H) 2.53-2.42 (m, 2 H) 2.10 (s, 3 H) 2.01-1.99 (m, 3 H).

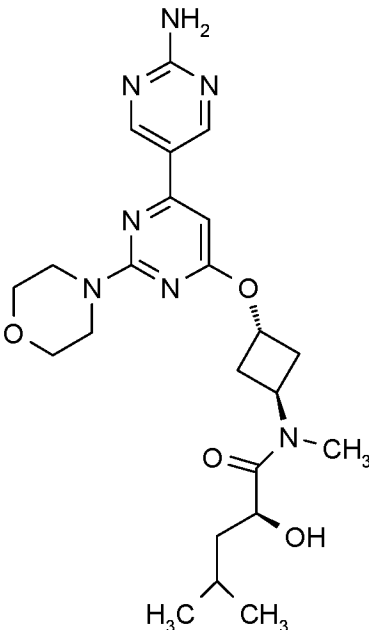
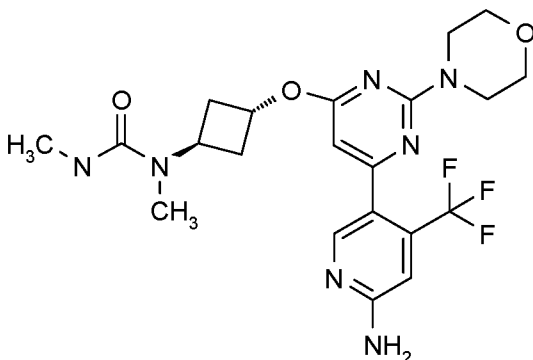
Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
31	 <i>N</i>-(<i>trans</i>-3-([2'-amino-5-ethyl-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-<i>N</i>-methylacetamide	451.0	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 8.39 (s, 2 H) 6.95 (s, 2 H) 5.23-4.65 (m, 2 H) 3.63-3.61 (m, 8 H) 2.95-2.84 (d, 3 H) 2.75-2.52 (m, 3 H) 2.45-2.23 (m, 3 H) 1.99-1.97 (m, 3 H) 1.10 (t, J= 7.4 Hz, 3 H).
32	 (2<i>R</i>)-<i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-<i>N</i>-methyl-2-phenylethanamide	492.3	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 8.91 (s, 2 H) 7.33-7.29 (m, 5 H) 7.11 (s, 2 H) 6.60-6.55 (m, 1 H) 5.54-5.44 (m, 1 H) 5.41-5.34 (m, 1 H) 5.19-4.82 (m, 2 H) 3.68-3.63 (m, 8 H) 2.86 (s, 3 H) 2.59-1.69 (m, 4 H).

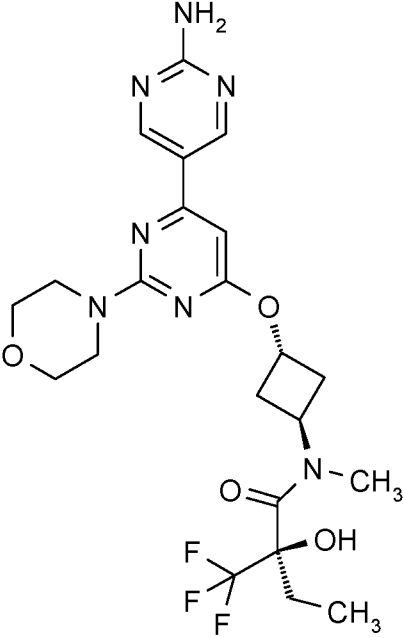
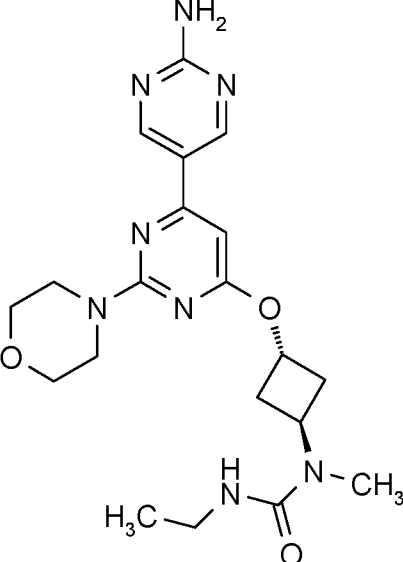
Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
33	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-1-hydroxy-<i>N</i>-methylcyclobutanecarboxamide	456.1	¹ H NMR (400 MHz, CDCl ₃) δ ppm 8.94 (s, 2 H) 7.13 (s, 2 H) 6.63 (s, 1 H) 5.89 (s, 1 H) 5.22-5.20 (m, 1 H) 5.11-5.07 (m, 1 H) 3.73-3.67 (m, 8 H) 3.00 (s, 3 H) 2.75-2.60 (m, 2 H) 2.55-2.40 (m, 2 H) 2.32-2.27 (m, 2 H) 2.05-2.03 (m, 2 H) 1.73-1.71 (m, 2 H) 1.43-1.39 (m, 1 H).
34	 (2<i>R</i>)-<i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-<i>N</i>,3-dimethylbutanamide	458.1	¹ H NMR (400 MHz, CDCl ₃) δ ppm 8.90 (s, 2 H) 6.30 (s, 1 H) 5.38 (s, 2 H) 5.28 (s, 1 H) 5.10-4.66 (m, 1 H) 4.30 (s, 1 H) 3.81-3.78 (m, 8 H) 3.00 (s, 3 H) 2.73-2.50 (m, 4 H) 1.91-1.76 (m, 2 H) 1.09-1.07 (m, 3 H) 0.81-0.76 (m, 3 H).

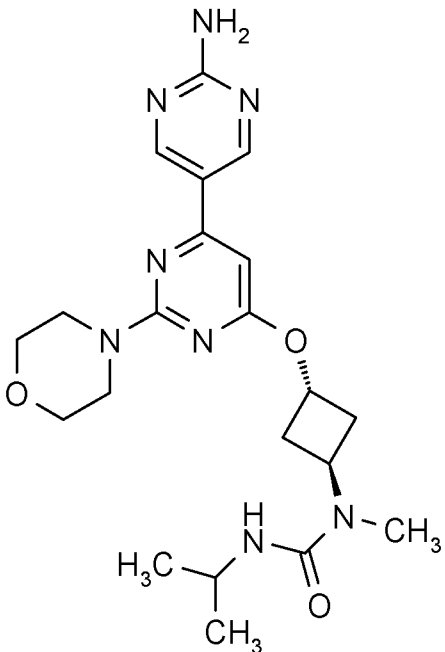
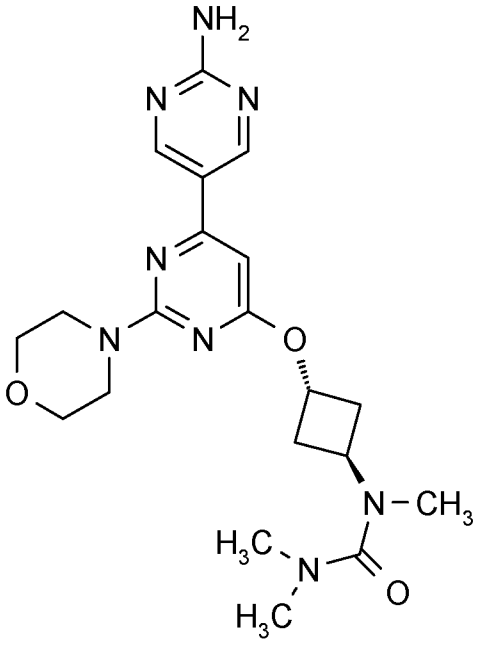
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
35	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-<i>N</i>,<i>P</i>,<i>P</i>-trimethylphosphinic amide	N/A	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.89 (s, 2 H) 6.29 (s, 1 H) 5.29 (s, 2 H) 5.22-5.19 (m, 1 H) 4.50-4.43 (m, 1 H) 3.82-3.76 (m, 8 H) 2.70-2.65 (m, 5 H) 2.40-2.35 (m, 2 H) 1.48 (s, 3 H) 1.45 (s, 3 H).
36*	 (2<i>R</i>)-<i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-<i>N</i>,3,3-trimethylbutanamide	472.2	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.89 (s, 2 H) 6.31 (d, $J=8.0$ Hz, 1 H) 5.27 (s, 3 H) 5.02-4.87 (m, 1 H) 4.28-4.16 (m, 1 H) 3.80-3.78 (m, 8 H) 3.41-3.36 (m, 1 H) 3.03 (s, 3 H) 2.71-2.52 (m, 4 H) 1.02-0.93 (m, 9 H).

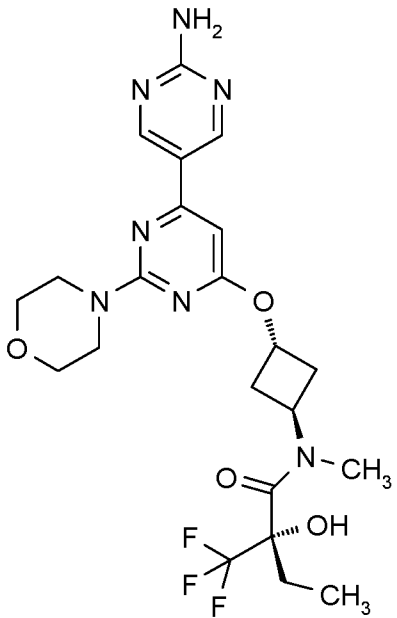
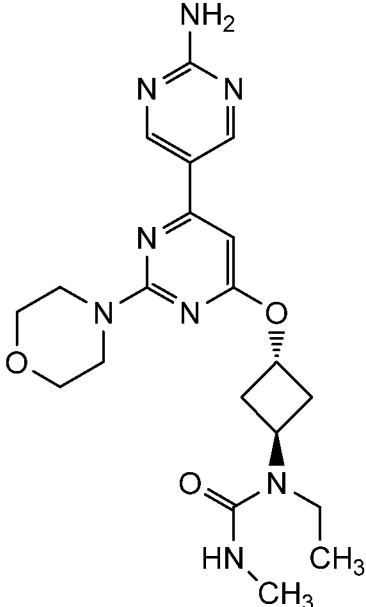
Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
37*	 (2S)-N-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-N,3,3-trimethylbutanamide	472.2	¹ H NMR (400 MHz, CDCl ₃) δ ppm 8.82 (s, 2 H) 6.24 (d, J=7.6 Hz, 1 H) 5.19 (s, 3 H) 4.95-4.81 (m, 1 H) 4.21-4.09 (m, 1 H) 3.74-3.71 (m, 8 H) 3.34-3.26 (m, 1 H) 2.96 (s, 3 H) 2.64-2.45 (m, 4 H) 0.91-0.87 (m, 9 H).
38	 1-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-3-cyclopropyl-1-methylurea	441.2	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 8.92 (s, 2 H) 7.10 (s, 2 H) 6.60 (s, 1 H) 6.36 (d, J=2.8 Hz, 1 H) 5.18 (t, J=7.1 Hz, 1 H) 4.93-4.84 (m, 1 H) 3.78-3.69 (m, 4 H) 3.66 (t, J=4.4 Hz, 4 H) 2.75 (s, 3 H) 2.61-2.52 (m, 3 H) 2.30-2.21 (m, 2 H) 0.55-0.45 (m, 2 H) 0.43-0.35 (m, 2 H).

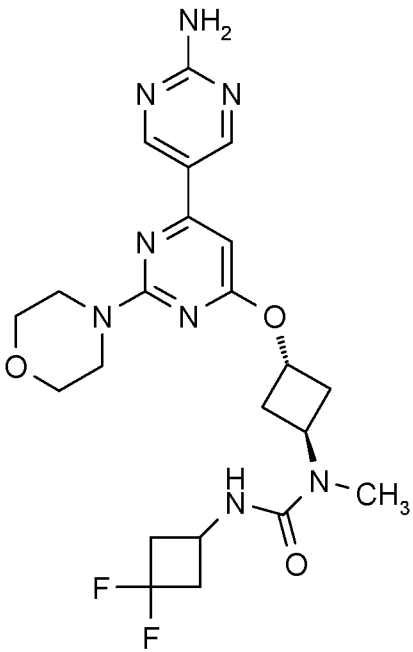
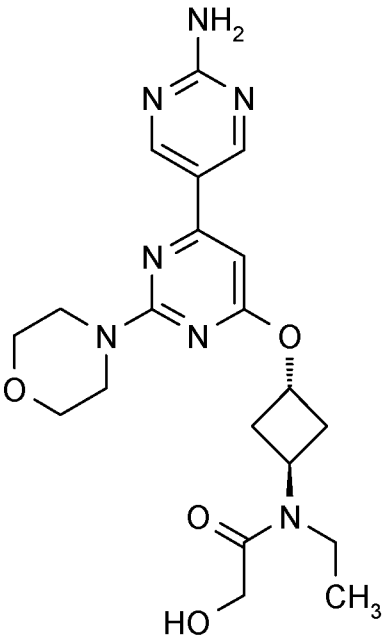
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
39	 (2S)-N-(trans-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-N,3-dimethylbutanamide	458.1	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.90 (s, 2 H), 6.31 (d, $J=8.0$ Hz, 1 H) 5.32 (br s, 2 H) 5.28 (br s, 1 H) 5.08-4.60 (m, 1 H) 4.31-4.23 (m, 1 H) 3.81-3.78 (m, 8 H) 3.66-3.59 (m, 1 H) 3.05-2.99 (m, 3 H) 2.73-2.62 (m, 2 H) 2.56-2.51 (m, 2 H) 1.91-1.75 (m, 1 H) 1.09-0.76 (m, 6 H).
40*	 (2R)-N-(trans-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-N,4-dimethylpentanamide	472.2	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.89 (s, 2 H) 6.30 (s, 1 H) 5.29 (s, 3 H) 5.18-4.60 (m, 1 H) 4.45-4.36 (m, 1 H) 3.82-3.78 (m, 8 H) 3.72-3.60 (m, 1 H) 3.04-2.97 (m, 3 H) 2.71-2.53 (m, 4 H) 1.99 (s, 1 H) 1.45-1.40 (m, 2 H) 1.02-0.93 (m, 6 H).

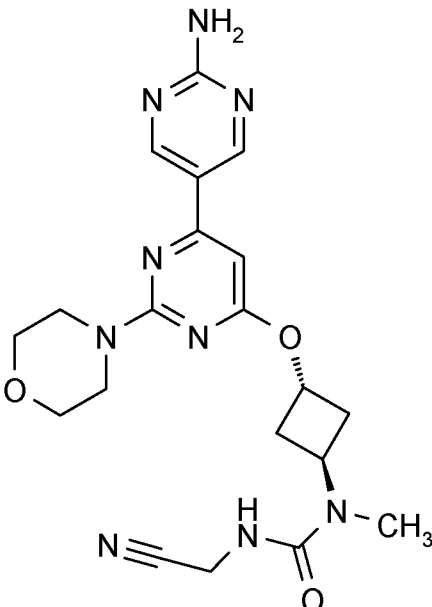
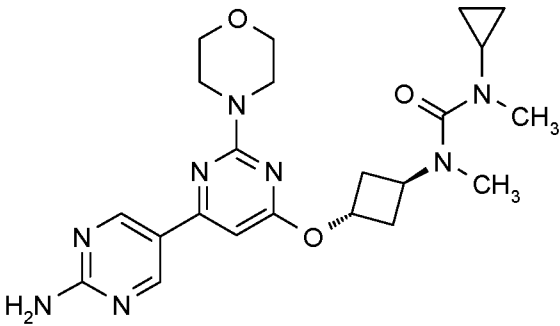
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
41*	 (2S)-N-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-N,4-dimethylpentanamide	472.2	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.89 (s, 2 H) 6.30 (s, 1 H) 5.29 (s, 3 H) 5.20-4.60 (m, 1 H) 4.45-4.30 (m, 1 H) 3.82-3.78 (m, 8 H) 3.65-3.55 (m, 1 H) 3.04-2.97 (m, 3 H) 2.71-2.53 (m, 4 H) 1.99 (s, 1 H) 1.45-1.40 (m, 2 H) 1.02-0.93 (m, 6 H).
42	 1-[<i>trans</i>-3-({6-[6-amino-4-(trifluoromethyl)pyridin-3-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)cyclobutyl]-1,3-dimethylurea	482.1	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.27 (s, 1 H) 6.81 (s, 1 H) 6.13 (s, 1 H) 5.30-4.81 (m, 2 H) 4.88-4.75 (m, 2 H) 4.34-4.33 (m, 1 H) 3.78-3.74 (m, 8 H) 2.89 (s, 3 H) 2.83-2.82 (m, 3 H) 2.61-2.59 (m, 2 H) 2.59-2.52 (m, 2 H).

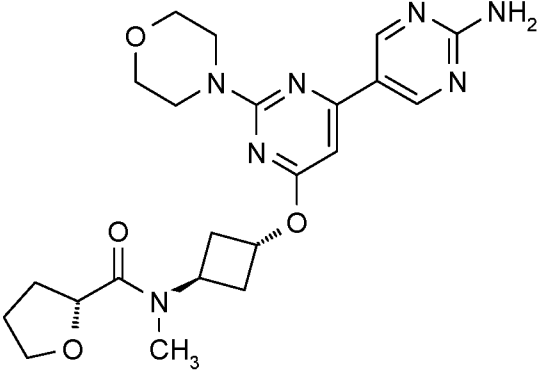
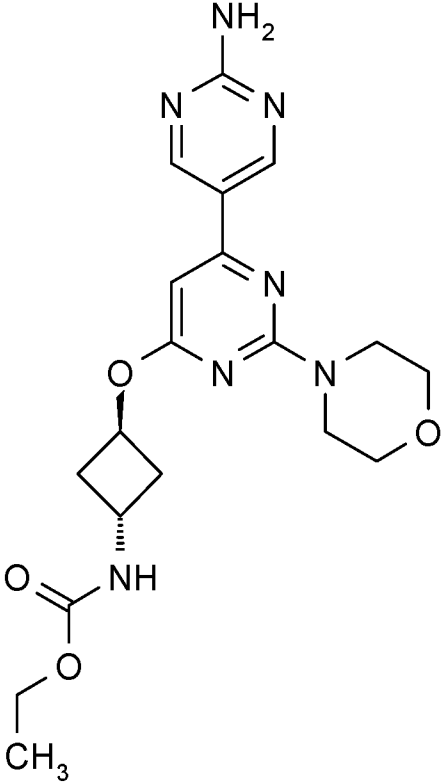
Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
43*	 (2R)-N-(trans-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-2-hydroxy-N-methyl-2-(trifluoromethyl)butanamide	512.1	¹ H NMR (400 MHz, CDCl ₃) δ ppm 8.90 (s, 2 H) 6.32 (s, 1 H) 5.60-5.30 (m, 2 H) 5.50-5.45 (m, 2 H) 5.05 (br s, 1 H) 3.81-3.78 (m, 8 H) 3.15 (s, 3 H) 2.75-2.60 (m, 2 H) 2.60-2.55 (m, 2 H) 2.20-2.07 (m, 2 H) 0.92 (t, J=7.2 Hz, 3 H).
44	 1-(trans-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-ethyl-1-methylurea	429.1	¹ H NMR (400 MHz, CDCl ₃) δ ppm 8.89 (s, 2 H) 6.30 (s, 1 H) 5.26-5.22 (m, 3 H) 4.87-4.80 (m, 1 H) 4.29-4.28 (m, 1 H) 3.82-3.76 (m, 8 H) 3.29-3.26 (m, 2 H) 2.88 (s, 3 H) 2.60-2.49 (m, 4 H) 1.14 (t, J=7.2 Hz, 3 H).

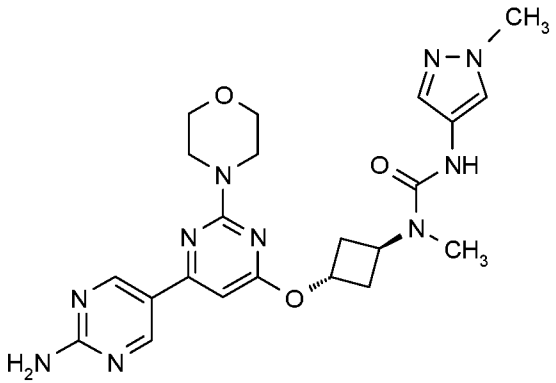
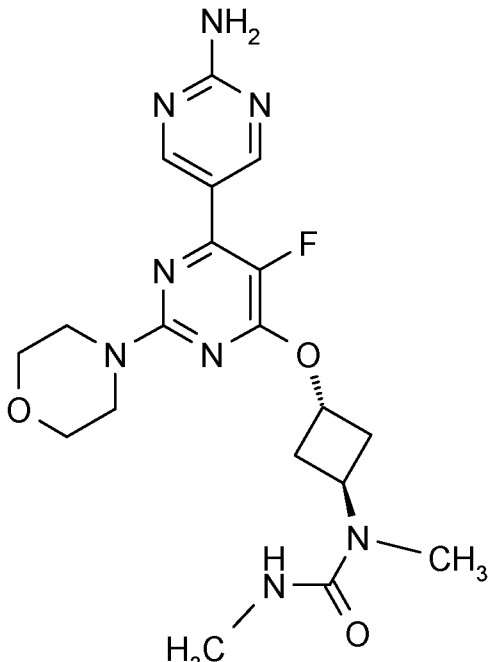
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	^1H NMR
45	 1-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-1-methyl-3-propan-2-ylurea	443.1	^1H NMR (400 MHz, CDCl_3) δ ppm 8.89 (s, 2 H) 6.30 (s, 1 H) 5.32 (s, 2 H) 5.26-5.23 (m, 1 H) 4.85-4.80 (m, 1 H) 4.11 (d, $J=2.8$ Hz, 1 H) 4.00-3.96 (m, 1 H) 3.82-3.76 (m, 8 H) 2.87 (s, 3 H) 2.60-2.49 (m, 4 H) 1.15 (d, $J=6.4$ Hz, 6 H).
46	 1-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-1,3,3-trimethylurea	429.0	^1H NMR (400 MHz, CDCl_3) δ ppm 8.89 (s, 2 H) 6.29 (s, 1 H) 5.30-5.22 (m, 3 H) 4.37-4.29 (m, 1 H) 3.82-3.76 (m, 8 H) 2.84 (s, 6 H) 2.76 (s, 3 H) 2.58-2.47 (m, 4 H).

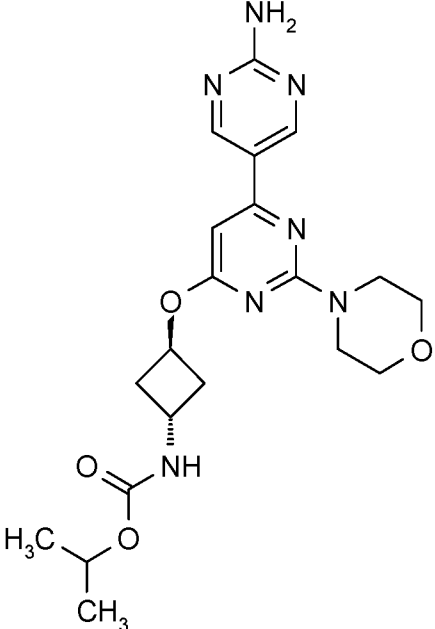
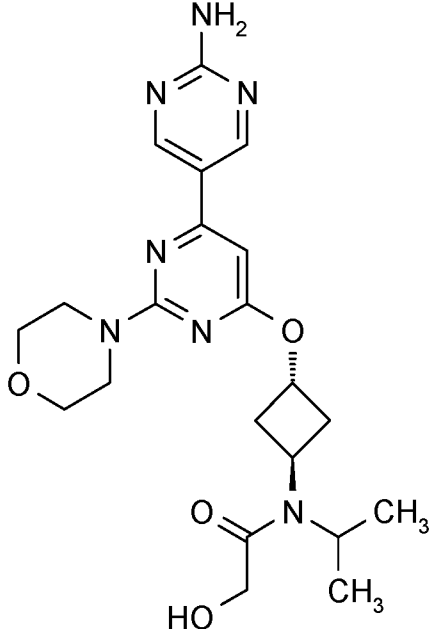
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	^1H NMR
47*	 (2S)-N-(trans-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-N-methyl-2-(trifluoromethyl)butanamide	512.1	^1H NMR (400 MHz, CDCl_3) δ ppm 8.90 (s, 2 H) 6.32 (s, 1 H) 5.55-5.25 (m, 2 H) 5.50-5.45 (m, 2 H) 5.05 (br s, 1 H) 3.81-3.78 (m, 8 H) 3.15 (s, 3 H) 2.75-2.60 (m, 2 H) 2.60-2.55 (m, 2 H) 2.20-2.07 (m, 2 H) 0.92 (t, $J=7.2$ Hz, 3 H).
48	 1-(trans-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-1-ethyl-3-methylurea	429.0	^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.92 (s, 2 H) 7.11 (br s, 2 H) 6.59 (s, 1 H) 6.11 (q, $J=4$ Hz, 1 H) 5.18 (t, $J=6.4$ Hz, 1 H) 4.62 (q, $J=8.47$ Hz, 1 H) 3.72-3.66 (m, 8 H) 3.26-3.23 (m, 3 H) 2.58-2.52 (m, 4 H) 2.35-2.30 (m, 2 H) 1.00 (t, $J=6.8$ Hz, 3 H).

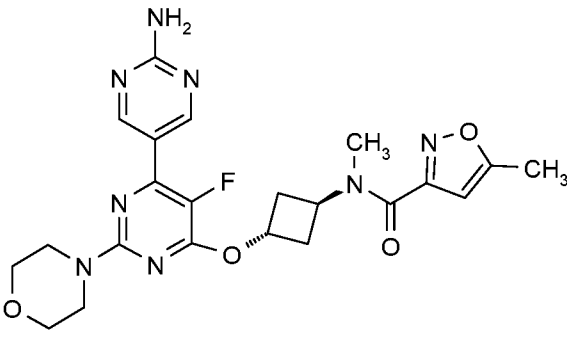
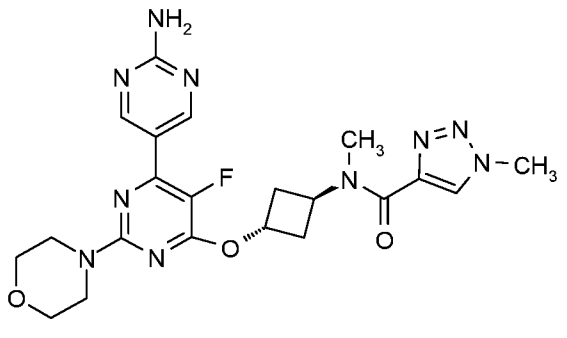
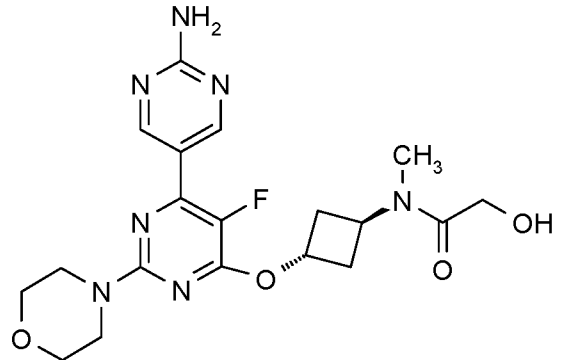
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
49	 1-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-3-(3,3-difluorocyclobutyl)-1-methylurea	491.2	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.90 (s, 2 H) 6.30 (s, 1 H) 5.40 (s, 2 H) 5.25-5.24 (m, 1 H) 4.86-4.81 (m, 1 H) 4.51 (d, $J=5.6$ Hz, 1 H) 4.19-4.17 (m, 1 H) 3.82-3.77 (m, 8 H) 3.03-2.97 (m, 2 H) 2.90 (s, 3 H) 2.61-2.46 (m, 6 H).
50	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-<i>N</i>-ethyl-2-hydroxyacetamide	430.0	1H NMR (400 MHz, $DMSO-d_6$) δ ppm 8.93 (s, 2 H) 7.13 (br s, 2 H) 6.61 (s, 1 H) 5.65-5.15 (m, 1 H) 4.67-4.47 (m, 2 H) 4.06 (d, $J=4.8$ Hz, 2 H) 3.72-3.66 (m, 8 H) 3.30-3.23 (m, 2 H) 2.74-2.61 (m, 2 H) 2.39-2.33 (m, 2 H) 1.06 (t, $J=7.0$ Hz, 3 H).

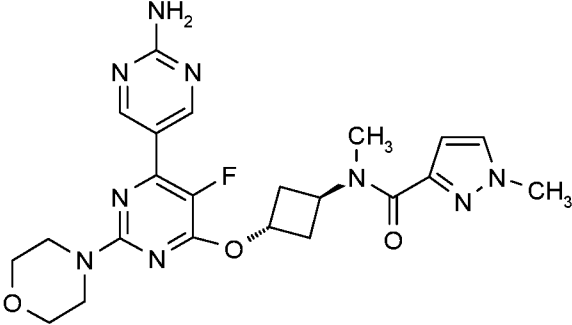
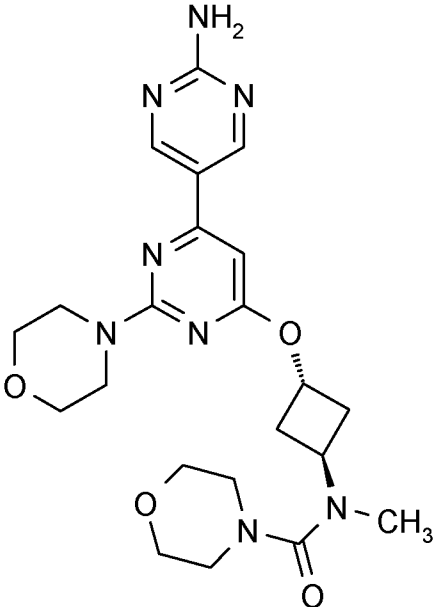
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
51	 1-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-3-(cyanomethyl)-1-methylurea	440.0	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.90 (s, 2 H) 6.30 (s, 1 H) 5.29-5.23 (m, 3 H) 4.87-4.81 (m, 1 H) 4.71-4.68 (m, 1 H) 4.18 (d, $J=5.6$ Hz, 2 H) 3.82-3.77 (m, 8 H) 2.93 (s, 3 H) 2.63-2.52 (m, 4 H).
52	 1-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-3-cyclopropyl-1,3-dimethylurea	455.3	1H NMR (400 MHz, $DMSO-d_6$) δ ppm 8.92 (s, 2 H) 7.09 (s, 2 H) 6.60 (s, 1 H) 5.23-5.17 (m, 1 H) 4.43-4.32 (m, 1 H) 3.72 (d, $J=4.8$ Hz, 4 H) 3.69-3.55 (m, 4 H) 2.76 (s, 3 H) 2.69 (s, 3 H) 2.62-2.53 (m, 3 H) 2.35-2.25 (m, 2 H) 0.68-0.58 (m, 2 H) 0.53-0.43 (m, 2 H).

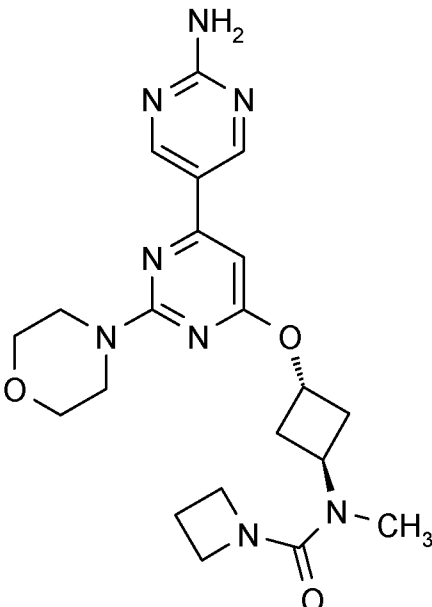
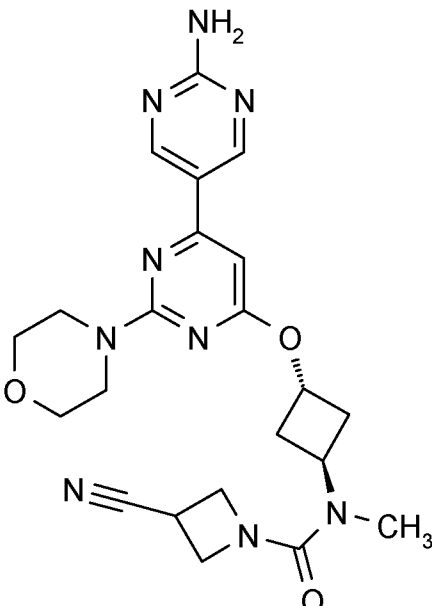
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	^1H NMR
53	 (2R)-N-(trans-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-N-methyltetrahydrofuran-2-carboxamide	456.2	^1H NMR (400 MHz, DMSO- d_6) δ ppm 8.94 (s, 2H) 7.13 (s, 2H) 6.63 (s, 1H) 5.22-4.92 (m, 2H) 4.69-4.63 (m, 1H) 3.78-3.67 (m, 10H) 3.03-2.87 (m, 3H) 2.80-2.60 (m, 2H) 2.40-2.20 (m, 2H) 2.01-1.98 (m, 2H) 1.85-1.79 (m, 2H).
54	 ethyl (trans-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)carbamate	416.1	^1H NMR (400 MHz, DMSO- d_6) δ ppm 8.92 (s, 2H) 7.62-7.60 (m, 1H) 7.13 (s, 2H) 6.59 (s, 1H) 5.30-5.27 (m, 1H) 4.11-4.09 (m, 1H) 4.02-3.96 (m, 2H) 3.74-3.67 (m, 8H) 2.40-2.34 (m, 4H) 1.17 (t, $J=4.8$ Hz, 3H).

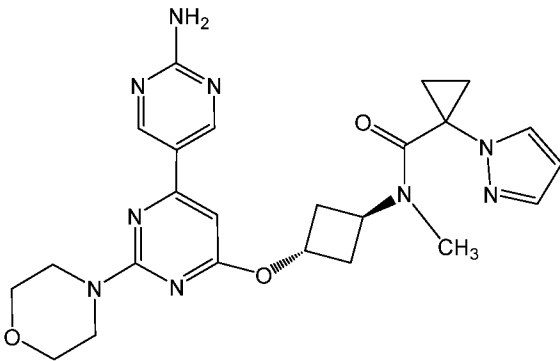
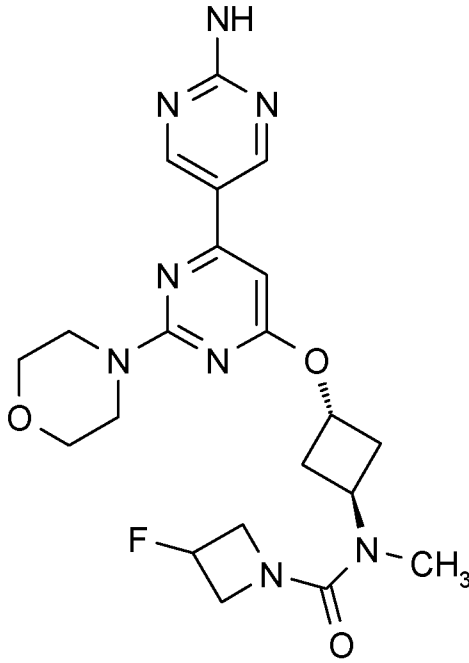
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
55	 1-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-1-methyl-3-(1-methyl-1<i>H</i>-pyrazol-4-yl)urea	481.0	1H NMR (400 MHz, CD_3OD) δ ppm 8.90 (s, 2H) 7.64 (s, 1H) 7.42 (s, 1H) 6.47 (s, 1H) 5.29 (t, $J=6.9$ Hz, 1H) 4.98 (t, $J=8.4$ Hz, 1H) 3.85-3.78 (m, 7H) 3.78-3.72 (m, 4H) 3.01 (s, 3H) 2.75-2.66 (m, 2H) 2.53-2.43 (m, 2H).
56	 1-(<i>trans</i>-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-1,3-dimethylurea	433.0	1H NMR (400 MHz, $DMSO-d_6$) δ ppm 8.82 (s, 2H) 7.23 (s, 2H) 6.24 (d, $J=4.4$ Hz, 1H) 5.24-5.23 (m, 1H) 4.92-4.89 (m, 1H) 3.65-3.64 (m, 8H) 2.77 (s, 3H) 2.59-2.55 (m, 2H) 2.54 (s, 3H) 2.36-2.33 (m, 2H).

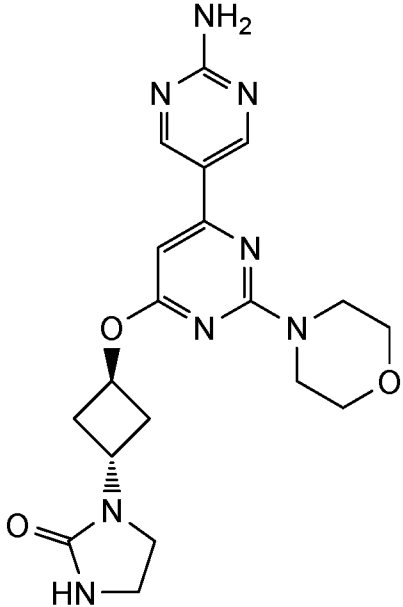
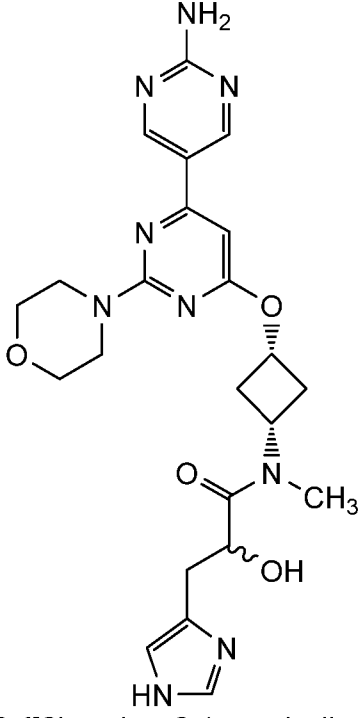
Example Number	Structure and Compound Name	LRMS <i>m/z</i> [M+H] ⁺	¹ H NMR
57	 propan-2-yl (<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)carbamate	430.0	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.92 (s, 2H) 7.55-7.54 (m, 1H) 7.12 (s, 2H) 6.58 (s, 1H) 5.29-5.26 (m, 1H) 4.78-4.72 (m, 1H) 4.11-4.10 (m, 1H) 3.73-3.67 (m, 8H) 2.39-2.36 (m, 4H) 1.18 (d, <i>J</i> =6.4 Hz, 6H).
58	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-<i>N</i>-(propan-2-yl)acetamide	444.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.93 (s, 2H) 7.14 (s, 2H) 6.60 (s, 1H) 5.44-5.34 (m, 1H) 4.48 (br s, 1H) 4.10 (br s, 2H) 3.81-3.77 (m, 1H) 3.72-3.67 (m, 8H) 3.20-3.10 (m, 2H) 2.40-2.30 (m, 2H) 2.02-1.98 (m, 1H) 1.25-1.10 (m, 6H).

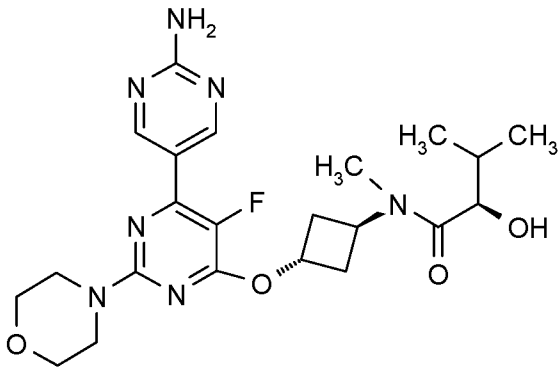
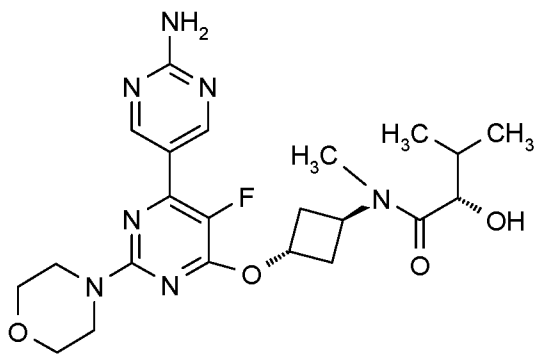
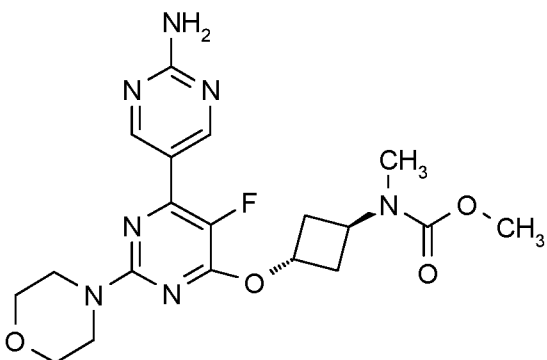
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
59	 <i>N</i>-(<i>trans</i>-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-<i>N</i>,5-dimethyl-1,2-oxazole-3-carboxamide	485.0	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.83-8.80 (m, 2H) 7.26 (s, 2H) 6.44 (d, $J=6.8$ Hz, 1H) 5.33-5.26 (m, 1H) 4.83-4.79 (m, 1H) 3.65-3.64 (m, 8H) 3.07 (s, 3H) 2.85-2.83 (m, 2H) 2.45 (s, 3H) 2.41-2.39 (m, 2H).
60	 <i>N</i>-(<i>trans</i>-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-<i>N</i>,1-dimethyl-1<i>H</i>-1,2,3-triazole-4-carboxamide	485.1	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.82 (s, 2H) 8.45 (s, 1H) 7.26 (s, 2H) 5.50-5.31 (m, 2H) 4.08 (s, 3H) 3.65-3.64 (m, 8H) 3.17 (s, 3H) 2.85-2.84 (m, 2H) 2.44-2.43 (m, 2H).
61	 <i>N</i>-(<i>trans</i>-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-<i>N</i>-methylacetamide	434.1	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.82 (s, 2H) 6.92 (s, 2H) 5.34-5.33 (m, 1H) 4.87-4.86 (m, 1H) 4.23 (s, 1H), 4.08-4.07 (d, $J=3.6$ Hz, 2H) 3.67-3.66 (m, 8H) 2.92 (s, 3H) 2.75-2.72 (m, 2H) 2.54-2.53 (m, 2H).

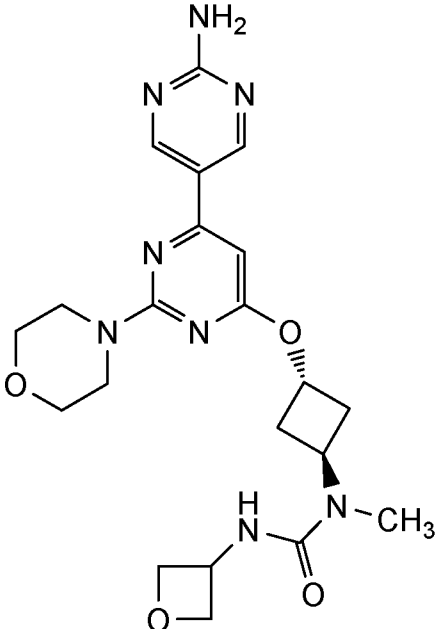
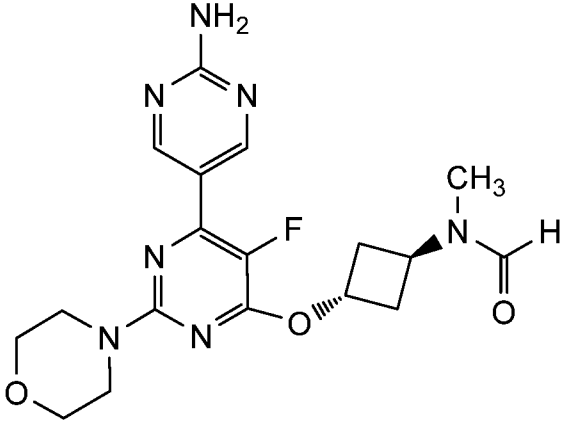
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
62	 <i>N</i>-(<i>trans</i>-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-<i>N</i>,1-dimethyl-1<i>H</i>-pyrazole-3-carboxamide	484.1	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.82 (s, 2H) 7.74 (d, J = 2 Hz, 1H) 7.25 (s, 2H) 6.49 (s, 1H) 5.75-5.31 (m, 2H) 3.87 (s, 3H) 3.65-3.64 (m, 8H) 3.44 (s, 3H) 2.79-2.78 (m, 2H) 2.33-2.32 (m, 2H).
63	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-<i>N</i>-methylmorpholine-4-carboxamide	471.1	1H NMR (400 MHz, CD $_3$ OD) δ ppm 8.92 (s, 2H) 6.49 (s, 1H) 5.37-5.28 (m, 1H) 4.43-4.39 (m, 1H) 3.84-3.68 (m, 12H) 3.30-3.28 (m, 4H) 2.87 (s, 3H) 2.65-2.63 (m, 2H) 2.49-2.44 (m, 2H).

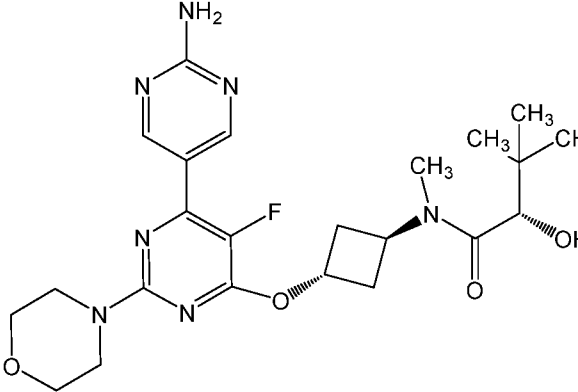
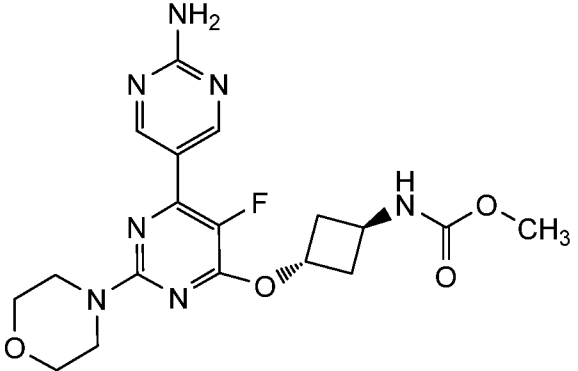
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
64	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-<i>N</i>-methylazetidine-1-carboxamide	444.1	1H NMR (400 MHz, CD_3OD) δ ppm 8.93 (s, 2H) 6.49 (s, 1H) 5.36-5.28 (m, 1H) 4.69-4.65 (m, 1H) 4.03 (t, $J=16.0$ Hz, 4H) 3.84-3.83 (m, 4H) 3.78-3.75 (m, 4H) 2.88 (s, 3H) 2.71-2.66 (m, 2H) 2.46-2.43 (m, 2H) 2.28-2.24 (m, 2H).
65	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-3-cyano-<i>N</i>-methylazetidine-1-carboxamide	466.1	1H NMR (400 MHz, CD_3OD) δ ppm 8.92 (s, 2H) 6.49 (s, 1H) 5.36-5.29 (m, 1H) 4.69-4.65 (m, 1H) 4.29 (t, $J = 20.0$ Hz, 2H) 4.16 (t, $J = 8.0$ Hz, 2H) 3.85-3.83 (m, 4H) 3.77-3.75 (m, 4H) 3.75-3.70 (m, 1H) 2.90 (s, 3H) 2.73-2.70 (m, 2H) 2.48-2.45 (m, 2H).

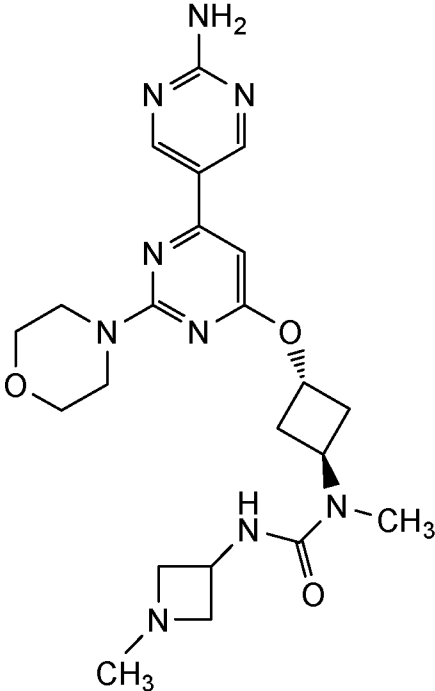
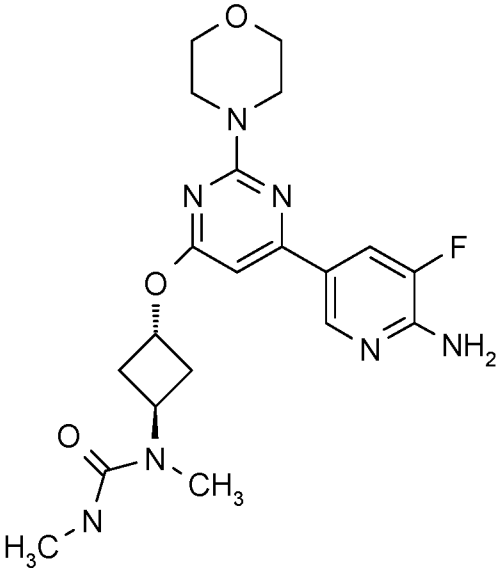
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	^1H NMR
66	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-<i>N</i>-methyl-1-(1<i>H</i>-pyrazol-1-yl)cyclopropanecarboxamide	492.1	^1H NMR (400 MHz, DMSO- d_6) δ ppm 8.95 (s, 2H) 7.83 (s, 1H) 7.49 (s, 1H) 7.15 (s, 2H) 6.62 (s, 1H) 6.29 (s, 1H) 5.16-4.99 (m, 2H) 3.72-3.66 (m, 8H) 2.82 (s, 3H) 2.60-2.45 (m, 2H) 2.20-2.00 (m, 2H) 1.51-1.46 (m, 4H).
67	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-3-fluoro-<i>N</i>-methylazetidine-1-carboxamide	462.3	^1H NMR (400 MHz, DMSO- d_6) δ ppm 8.89 (s, 2H) 7.04 (s, 2H) 6.81 (s, 2H) 6.03 (s, 1H) 3.94-3.82 (m, 2H) 3.72-3.59 (m, 8H) 3.54-3.46 (m, 2H) 3.19-3.17 (m, 2H) 2.61-2.55 (m, 2H) 2.18-2.15 (m, 2H) 1.86-1.83 (m, 2H).

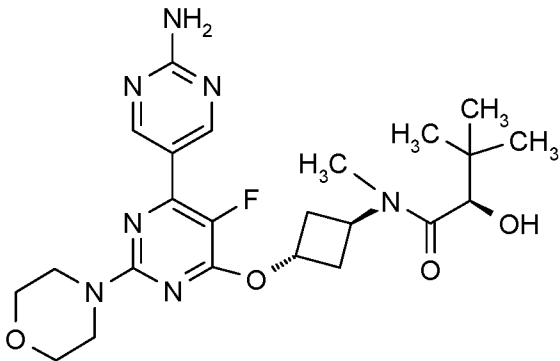
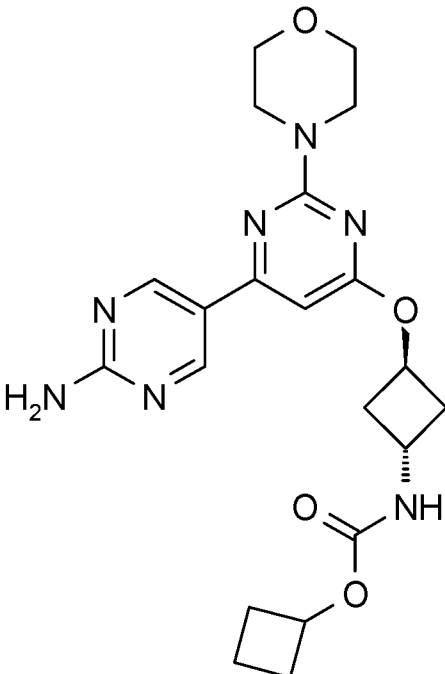
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
68	 1-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)imidazolidin-2-one	413.0	1H NMR (400 MHz, CD_3OD) δ ppm 8.92 (s, 2H) 7.13 (s, 2H) 6.61 (s, 1H) 6.37 (s, 1H) 5.28-5.20 (m, 1H) 4.55-4.45 (m, 1H) 3.72-3.66 (m, 8H) 3.47-3.44 (m, 2H) 3.27-3.25 (m, 2H) 2.67-2.64 (m, 2H) 2.33-2.27 (m, 2H).
69	 <i>N</i>-(<i>cis</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-3-(1<i>H</i>-imidazol-4-yl)-<i>N</i>-methylpropanamide	518.1	1H NMR (400 MHz, $DMSO-d_6$) δ ppm 8.93 (s, 2H) 8.16 (s, 1H) 7.60 (d, $J = 5.8$ Hz, 1H) 7.15 (s, 2H) 6.78 (d, $J = 5.8$ Hz, 1H) 6.60 (s, 1H) 4.93-4.87 (m, 1H) 4.61-4.38 (m, 2H) 3.76-3.36 (m, 8H) 2.92-2.84 (m, 3H) 2.84-2.79 (m, 2H) 2.71-2.65 (m, 3H) 2.28-2.17 (m, 2H).

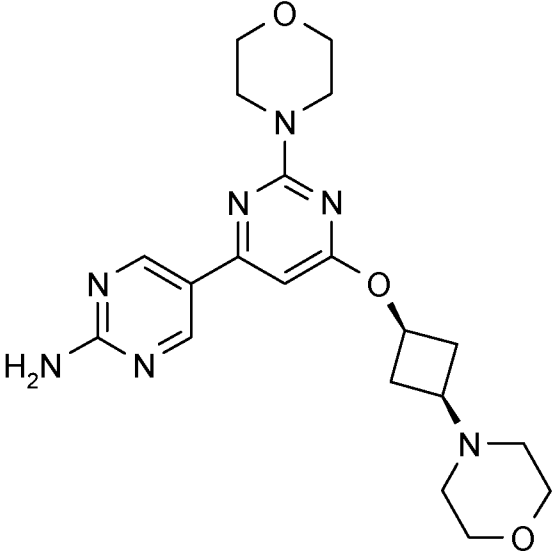
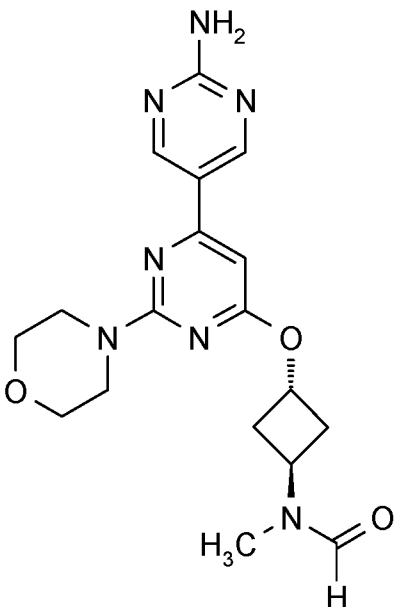
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
70	 (2R)-N-(<i>trans</i>-3-{[2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-2-hydroxy-N,3-dimethylbutanamide	498.1	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.83 (s, 2H) 7.27 (s, 2H) 5.30 (br s, 1H) 5.08-5.06 (m, 1H) 4.69-4.54 (m, 1H) 4.07 (br s, 1H) 3.70-3.64 (m, 8H) 3.02-2.92 (m, 3H) 2.80-2.61 (m, 2H) 2.38-2.32 (m, 2H) 1.88-1.79 (m, 1H) 0.88-0.78 (m, 6H).
71	 (2S)-N-(<i>trans</i>-3-{[2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-2-hydroxy-N,3-dimethylbutanamide	498.1	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.83 (s, 2H) 7.27 (s, 2H) 5.31 (br s, 1H) 5.08-5.06 (m, 1H) 4.70-4.68 (m, 1H) 4.07 (br s, 1H) 3.68-3.64 (m, 8H) 3.02-2.92 (m, 3H) 2.80-2.68 (m, 2H) 2.51-2.34 (m, 2H) 1.88-1.77 (m, 1H) 0.88-0.78 (m, 6H).
72	 methyl (<i>trans</i>-3-{[2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)methylcarbamate	434.0	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.82 (s, 2H) 7.25 (s, 2H) 5.26-4.81 (m, 2H) 3.65-3.64 (m, 8H) 3.58 (s, 3H) 2.86 (s, 3H) 2.67-2.66 (m, 2H) 2.37-2.33 (m, 2H).

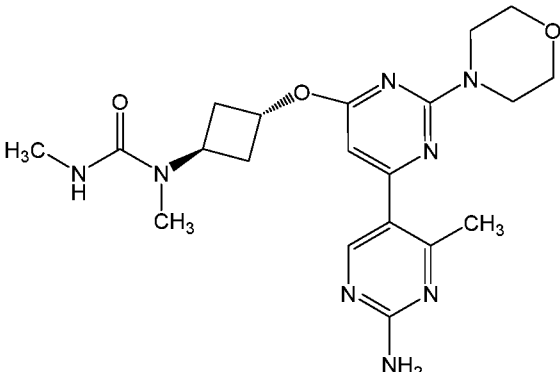
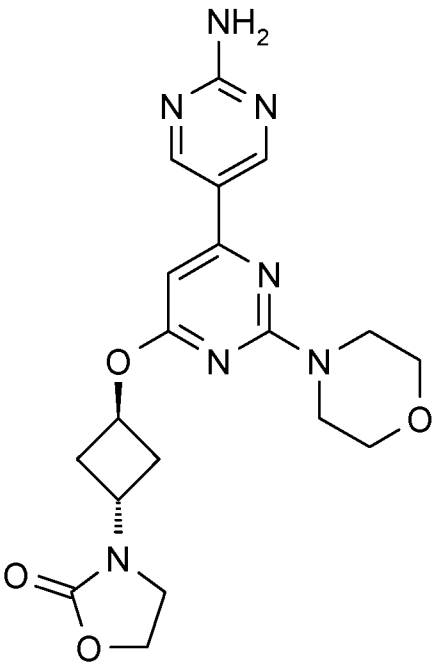
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
73	 1-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-1-methyl-3-oxetan-3-ylurea	479.1	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.98 (s, 2H) 8.13 (s, 1H) 7.14 (s, 2H) 6.61 (s, 1H) 5.20 (br s, 1H) 4.70-4.45 (m, 2H) 4.27-4.25 (m, 1H) 4.10-4.00 (m, 1H) 3.91-3.90 (m, 1H) 3.73-3.67 (m, 8H) 3.22-3.21 (m, 1H) 2.85-2.83 (m, 3H) 2.68-2.67 (m, 2H) 2.32-2.31 (m, 2H).
74	 <i>N</i>-(<i>trans</i>-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-<i>N</i>-methylformamide	404.0	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.82 (s, 2H) 8.11-8.01 (m, 1H) 7.27 (s, 2H) 5.32-4.56 (m, 2H) 3.65-3.64 (m, 8H) 2.97-2.81 (m, 3H) 2.91-2.77 (m, 2H) 2.45-2.42 (m, 2H).

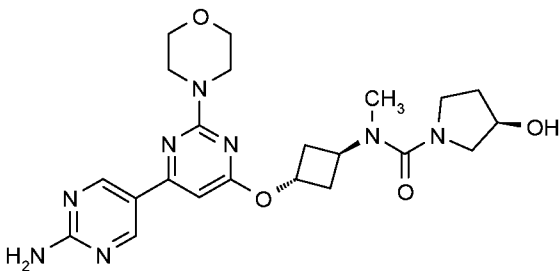
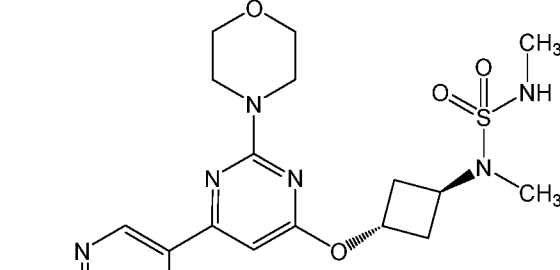
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
75	 (2S)-N-(trans-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-N,3,3-trimethylbutanamide	490.0	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.82 (s, 2H) 7.26 (s, 2H) 5.29 (br s, 1H) 5.13-5.02 (m, 1H) 4.63-4.52 (m, 1H) 4.17-4.11 (m, 1H) 3.66-3.64 (m, 8H) 3.04-2.90 (m, 3H) 2.77-2.67 (m, 2H) 2.40-2.33 (m, 2H) 0.88 (d, J=12.8 Hz, 9H).
76	 methyl (trans-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)carbamate	420.1	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.32 (s, 2H) 7.62 (s, 1H) 7.24 (s, 2H) 5.34-4.11 (m, 2H) 3.75-3.72 (m, 8H) 3.55 (s, 3H) 2.49-2.40 (m, 4H).

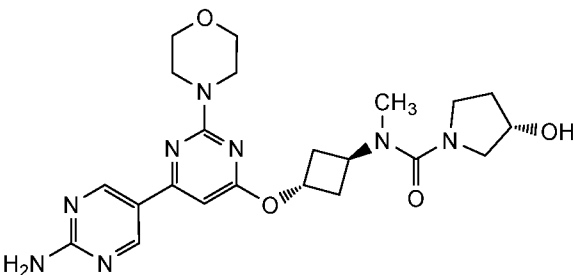
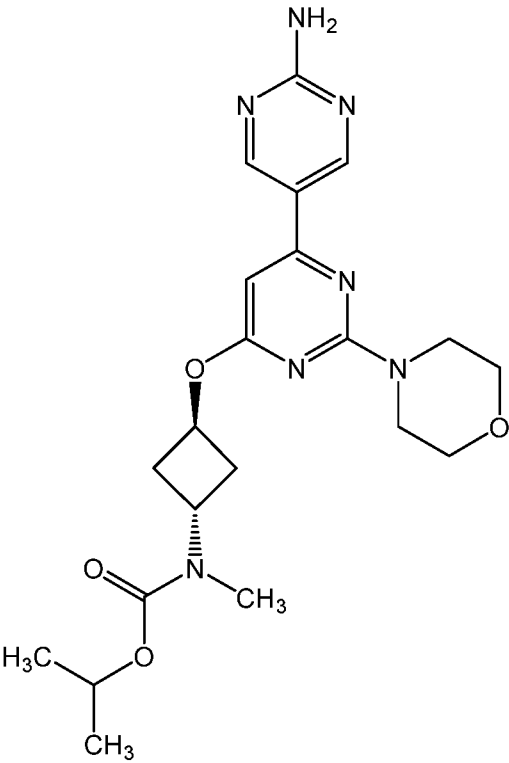
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
77	 1-(<i>trans</i>-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-1-methyl-3-(1-methylazetidin-3-yl)urea	492.1	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.93 (s, 2H) 7.13 (s, 2H) 6.61 (s, 1H) 6.58-6.56 (m, 1H) 5.18-5.17 (m, 1H) 4.92-4.88 (m, 1H) 4.15-4.10 (m, 1H) 3.73-3.67 (m, 8H) 3.46-3.43 (m, 2H) 2.83-2.79 (m, 5H) 2.53-2.52 (m, 2H) 2.32-2.27 (m, 2H) 2.21 (s, 3H).
78	 1-(<i>trans</i>-3-[[6-(6-amino-5-fluoropyridin-3-yl)-2-(morpholin-4-yl)pyrimidin-4-yl]oxy]cyclobutyl)-1,3-dimethylurea	432.2	1H NMR (600 MHz, DMSO- d_6) δ 8.57 (s, 1H) 8.00 (d, $J=11.0$ Hz, 1H) 6.70 (br s, 2H) 6.60 (s, 1H) 6.21 (q, $J=4.0$ Hz, 1H) 5.20-5.16 (m, 1H) 4.90 (p, $J=8.4$ Hz, 1H) 3.74-3.70 (m, 4H) 3.68-3.64 (m, 4H) 2.77 (s, 3H) 2.59-2.53 (m, 5H) 2.29-2.23 (m, 2H).

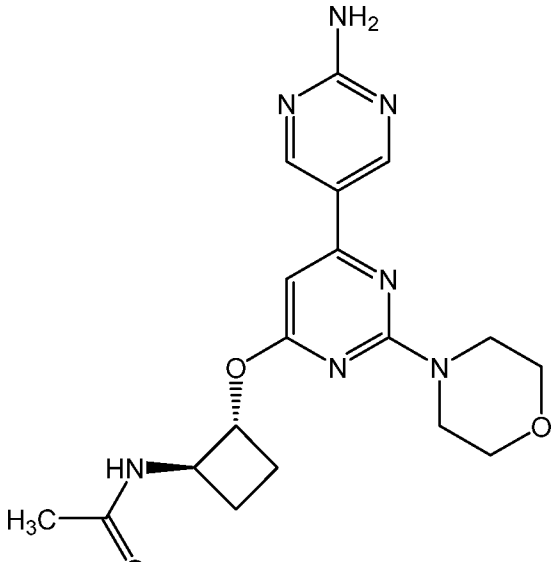
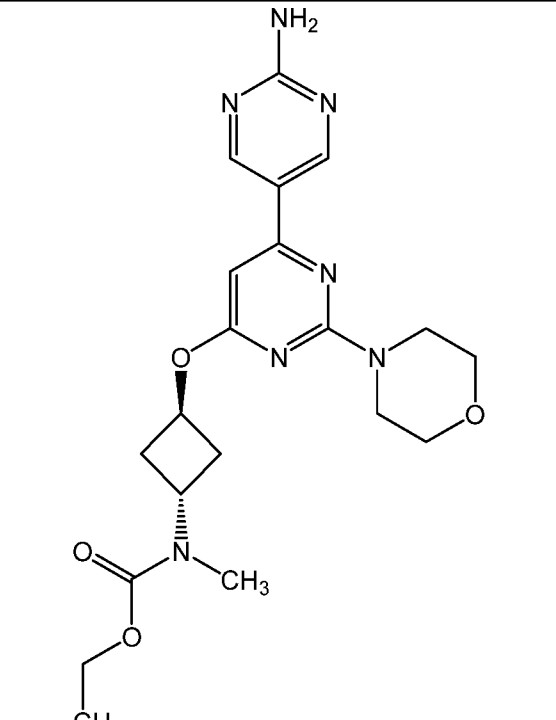
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
79	 (2R)-N-(trans-3-{[2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-2-hydroxy-N,3,3-trimethylbutanamide	490.0	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.82 (s, 2H) 7.26 (s, 2H) 5.30 (br s, 1H) 5.09-5.04 (m, 1H) 4.63-4.52 (m, 1H) 4.17-4.11 (m, 1H) 3.66-3.64 (m, 8H) 3.04-2.90 (m, 3H) 2.76-2.67 (m, 2H) 2.43-2.32 (m, 2H) 0.88 (d, J= 12.8 Hz, 9H).
80	 cyclobutyl (trans-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)carbamate	442.1	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.92 (s, 2H) 7.63-7.62 (m, 1H) 7.12 (s, 2H) 6.58 (s, 1H) 5.29-5.26 (m, 1H) 4.83-4.80 (m, 1H) 4.10-4.05 (m, 1H) 3.74-3.67 (m, 8H) 2.39-2.34 (m, 4H) 2.24-2.21 (m, 2H) 1.99-1.93 (m, 2H) 1.68-1.55 (m, 2H).

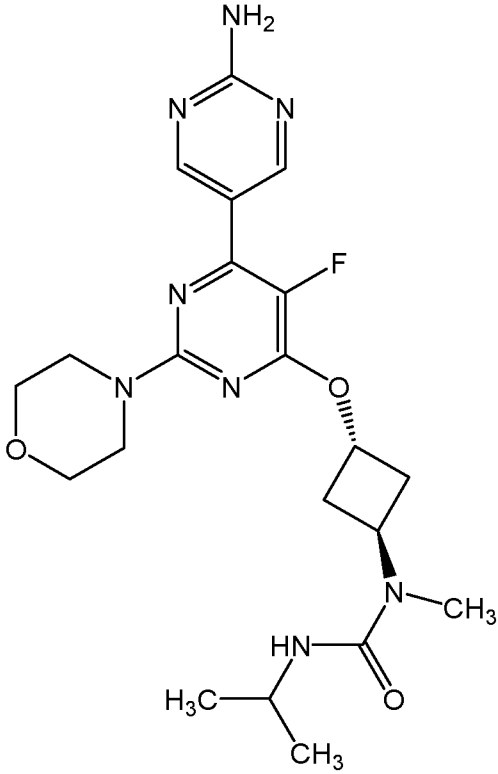
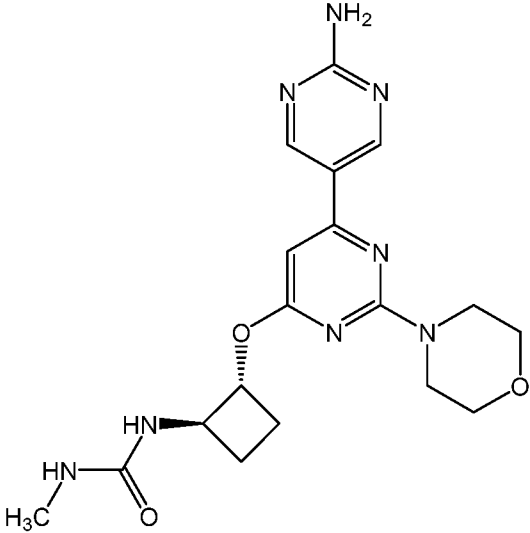
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
81	 2-(morpholin-4-yl)-6-([cis-3-(morpholin-4-yl)cyclobutyl]oxy)-4,5'-bipyrimidin-2'-amine	414.5	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.91 (s, 2 H) 7.09 (s, 2 H) 6.55 (s, 1 H) 4.93 (t, $J=7.34$ Hz, 1 H) 3.70 - 3.77 (m, 4 H) 3.63 - 3.69 (m, 4 H) 3.54 - 3.60 (m, 4 H) 2.57 - 2.67 (m, 4 H) 2.42 - 2.48 (m, 2 H) 2.23 - 2.30 (m, 1 H) 1.82 - 1.91 (m, 4 H) 1.82 - 1.91 (m, 2 H).
82	 <i>N</i>-(trans-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-<i>N</i>-methylformamide	386.2	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.94 (s, 2H) 8.18-7.81 (m, 1H) 7.11 (s, 2H) 6.71-6.53 (m, 1H) 5.31-4.83 (m, 1H) 4.65-4.45 (m, 1H) 3.79-3.54 (m, 8H) 3.04-2.78 (m, 3H) 2.79-2.61 (m, 2H) 2.42-2.21 (m, 2H).

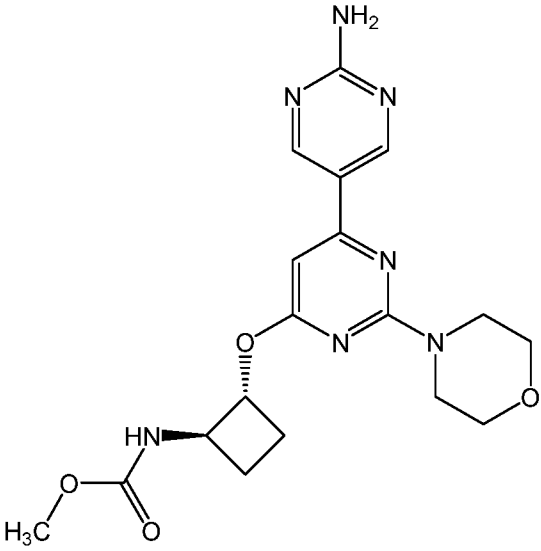
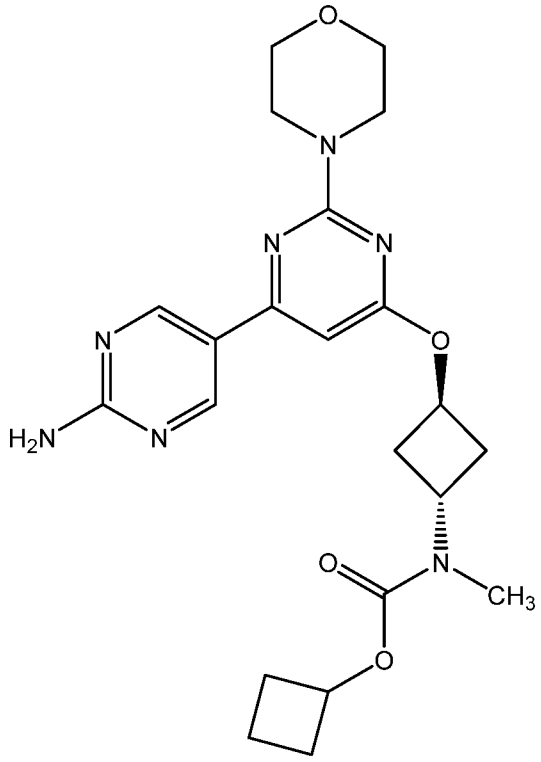
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
83	 1-(<i>trans</i>-3-([2'-amino-4'-methyl-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-1,3-dimethylurea	429.1	1H NMR (400 MHz, CD_3OD) δ ppm 8.34 (s, 1H) 6.21 (s, 1H) 5.28-5.25 (m, 1H) 4.94-4.92 (m, 1H) 3.79-3.72 (m, 8H) 2.89 (s, 3H) 2.71 (s, 3H) 2.66-2.64 (m, 2H) 2.50 (s, 3H) 2.44-2.40 (m, 2H).
84	 3-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-1,3-oxazolidin-2-one	414.0	1H NMR (400 MHz, $DMSO-d_6$) δ ppm 8.93 (s, 2H) 7.14 (s, 2H) 6.62 (s, 1H) 5.25-5.27 (m, 1H) 4.50-4.40 (m, 1H) 4.32-4.28 (m, 2H) 3.73-3.72 (m, 2H) 3.72-3.67 (m, 8H) 2.77-2.72 (m, 2H) 2.41-2.35 (m, 2H).

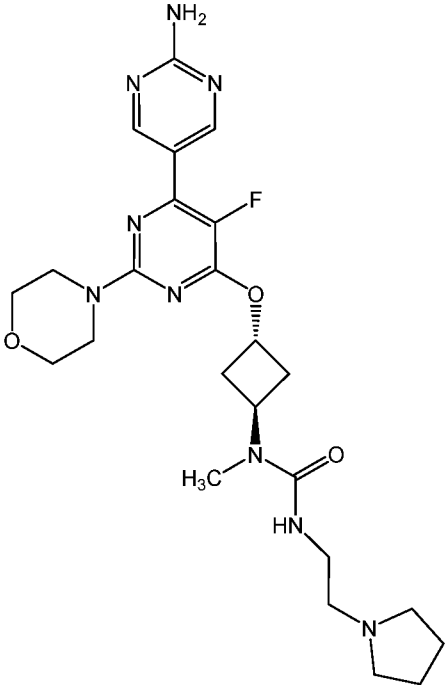
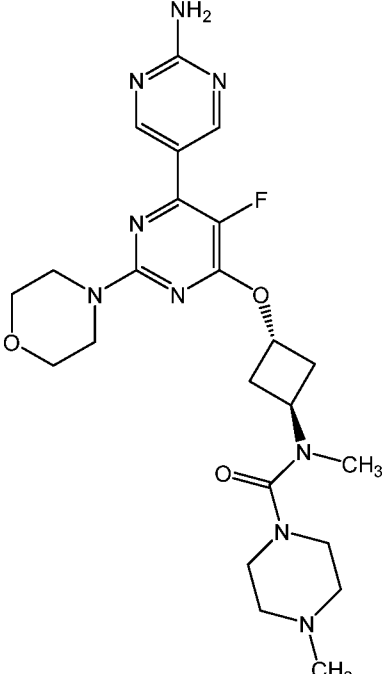
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
85	 (3R)-N-(trans-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-hydroxy-N-methylpyrrolidine-1-carboxamide	471.2	1H NMR (400 MHz, CDOD ₃) δ ppm 8.91 (s, 2H) 6.48 (s, 1H) 5.35-5.12 (m, 1H) 4.43 (t, $J=7.9$ Hz, 1H) 4.38 (tt, $J=4.3, 2.35$ Hz, 1H) 3.86-3.79 (m, 4H) 3.79-3.73 (m, 4H) 3.67-3.60 (m, 1H) 3.57 (dd, $J=11.3, 4.4$ Hz, 1H) 3.42-3.37 (m, 1H) 3.36 (s, 1H) 3.28-3.22 (m, 1H) 2.85 (s, 3H) 2.65 (dt, $J=14.3, 7.2$ Hz, 2H) 2.49-2.39 (m, 2H) 2.02-1.94 (m, 1H) 1.94-1.86 (m, 1H).
86	 N-(trans-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-N,N'-dimethylsulfuric diamide	450.9	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.92 (s, 2H) 7.09 (s, 2H) 7.00 (q, $J=4.7$ Hz, 1H) 6.60 (s, 1H) 5.21-5.16 (m, 1H) 4.46-4.38 (m, 1H) 3.72 (d, $J=4.6$ Hz, 4H) 3.67 (d, $J=4.9$ Hz, 4H) 2.72 (s, 3H) 2.71-2.64 (m, 2H) 2.45 (d, $J=5.0$ Hz, 3H) 2.34-2.24 (m, 2H).

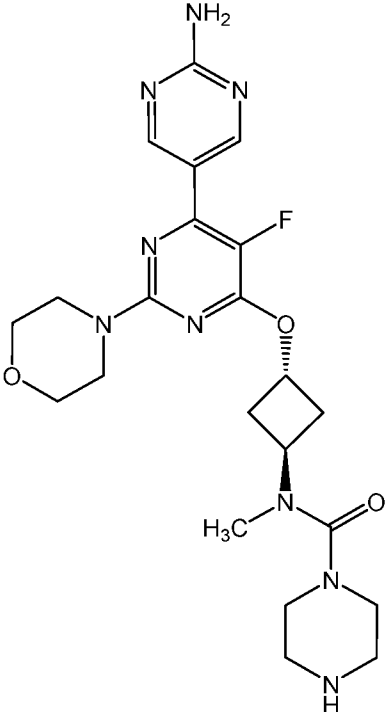
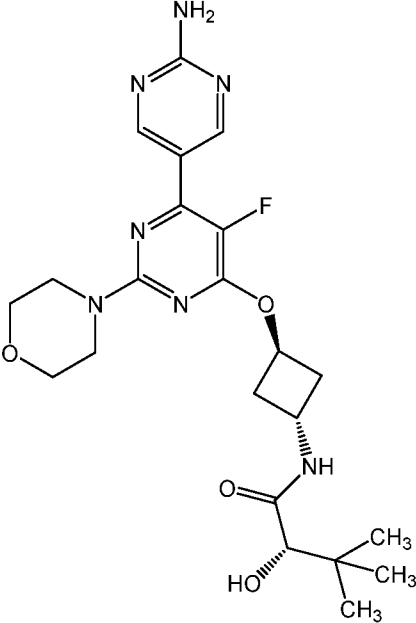
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
87	 (3S)-N-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-3-hydroxy-N-methylpyrrolidine-1-carboxamide	470.9	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.92 (s, 2H) 7.08 (s, 2H) 6.60 (s, 1H) 5.23-5.17 (m, 1H) 4.83 (d, $J=3.4$ Hz, 1H) 4.40-4.29 (m, 1H) 4.20 (d, $J=2.2$ Hz, 1H) 3.72 (d, $J=4.5$ Hz, 4H) 3.67 (d, $J=4.9$ Hz, 4H) 3.46-3.36 (m, 2H) 3.27-3.18 (m, 1H) 3.03 (d, $J=11.0$ Hz, 1H) 2.72 (s, 3H) 2.59 (dt, $J=14.4$, 7.3 Hz, 2H) 2.35-2.24 (m, 2H) 1.85-1.75 (m, 1H) 1.74-1.66 (m, 1H).
88	 propan-2-yl (<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)methylcarbamate	444.1	1H NMR (400 MHz, DMSO- d_6) δ 8.94 (s, 2H), 7.14 (s, 2H), 6.63 (s, 1H), 5.30-5.20 (m, 1H), 4.79-4.75 (m, 2H), 3.73-3.67 (m, 8H), 2.85 (s, 3H), 2.68-2.64 (m, 2H), 2.34-2.31 (m, 2H), 1.24-1.18 (m, 6H).

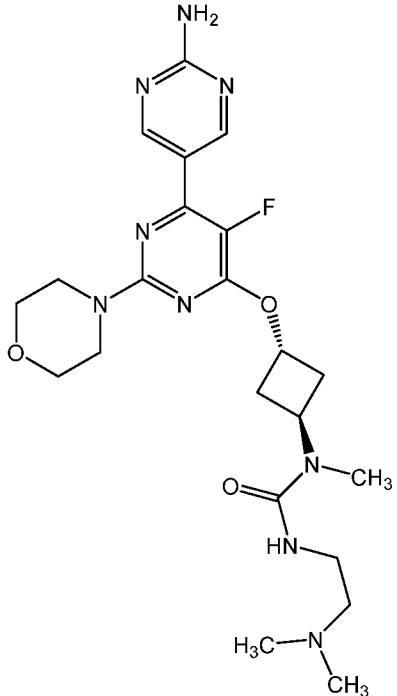
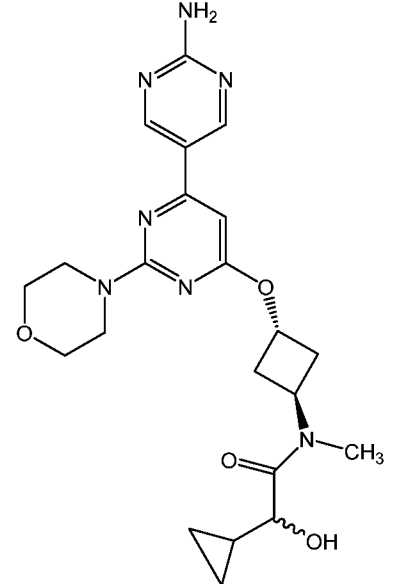
Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
89	 <i>N</i>-[(1<i>R</i>,2<i>R</i>)-2-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl]acetamide	386.0	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.91 (s, 2H), 8.30 (d, <i>J</i> =8.4 Hz, 1H), 7.11 (s, 2H), 6.56 (s, 1H), 5.13-5.09 (m, 1H), 4.31-4.29 (m, 1H), 3.74-3.67 (m, 8H), 2.33-2.21 (m, 1H), 2.08-2.05 (m, 1H), 1.77 (s, 3H), 1.61-1.52 (m, 1H), 1.52-1.50 (m, 1H).
90	 ethyl (<i>trans</i>-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)methylcarbamate	430.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.93 (s, 2H), 7.12 (s, 2H), 6.62 (s, 1H), 5.25-5.21 (m, 1H), 4.80-4.75 (m, 1H), 4.03 (q, <i>J</i> =7.2 Hz, 2H), 3.73-3.66 (m, 8H), 2.86 (s, 3H), 2.70-2.60 (m, 2H), 2.35-2.20 (m, 2H), 1.18 (t, <i>J</i> =7.2 Hz, 3H).

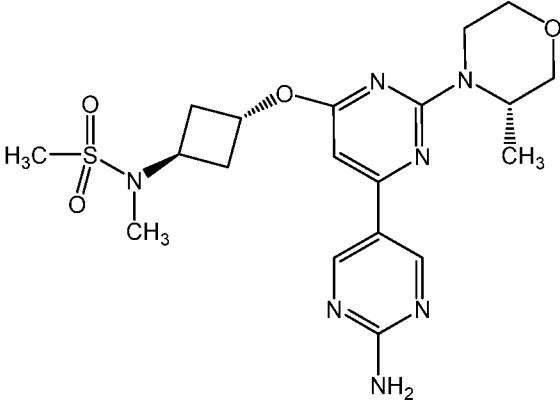
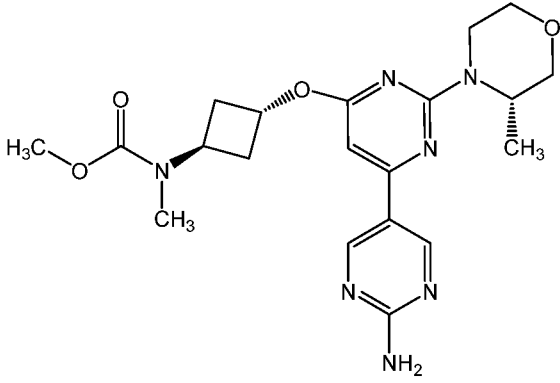
Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
91	 1-(<i>trans</i>-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-1-methyl-3-propan-2-ylurea	483.1 [M+23] ⁺	¹ H NMR (400 MHz, CDCl ₃) δ ppm 8.99 (s, 2H), 5.33-5.27 (m, 3H), 4.86-4.78 (m, 1H), 4.13-4.11 (m, 1H), 4.01-3.93 (m, 1H), 3.77-3.72 (m, 8H), 2.88 (s, 3H), 2.66-2.57 (m, 4H), 1.17-1.15 (m, 6H).
92	 1-[(1<i>R</i>,2<i>R</i>)-2-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl]-3-methylurea	401.0	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.89 (s, 2H), 7.06 (s, 2H), 6.53 (s, 1H), 6.43-6.38 (m, 1H), 5.74-5.70 (m, 1H), 5.14-5.05 (m, 1H), 4.18-4.09 (m, 1H), 3.73-3.65 (m, 8H), 2.18-2.16 (m, 1H), 2.07-2.03 (m, 1H), 1.57-1.45 (m, 2H).

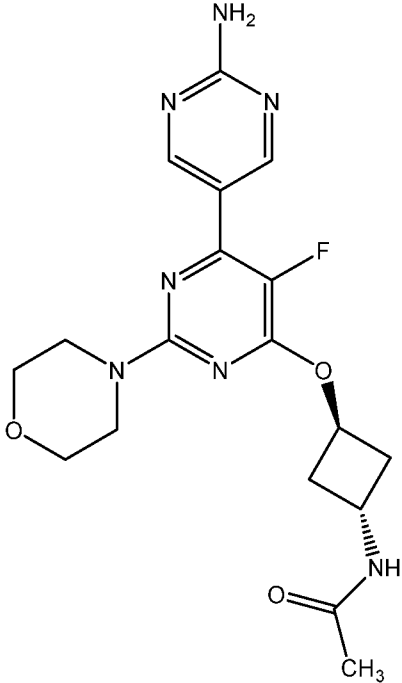
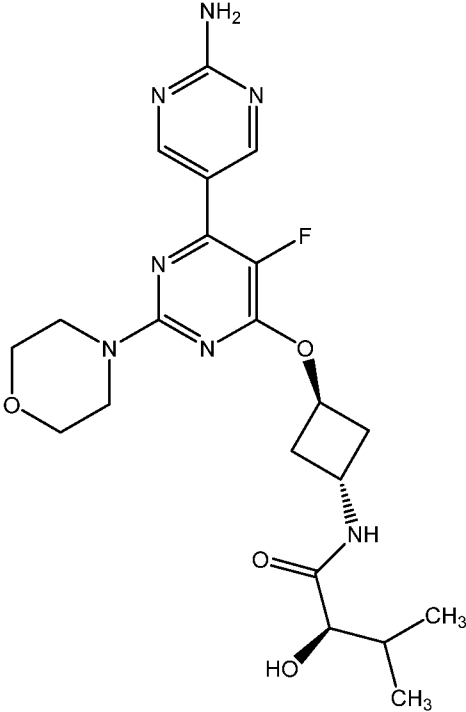
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	^1H NMR
93	 methyl [(1<i>R</i>,2<i>R</i>)-2-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl]carbamate	401.9	^1H NMR (400 MHz, DMSO- d_6) δ 8.92 (s, 2H), 7.64 (d, $J=8.8$ Hz, 1H), 7.14 (s, 2H), 6.62 (s, 1H), 5.22-5.04 (m, 1H), 4.09-3.96 (m, 1H), 3.74-3.62 (m, 8H), 3.51 (s, 3H), 2.26-2.06 (m, 2H), 1.64-1.53 (m, 2H).
94	 cyclobutyl (<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)methylcarbamate	456.0	^1H NMR (400 MHz, DMSO- d_6) δ 8.93 (s, 2H), 7.13 (s, 2H), 6.62 (s, 1H), 5.25-5.15 (m, 1H), 4.85-4.75 (m, 2H), 3.72-3.66 (m, 8H), 2.84 (s, 3H), 2.67-2.65 (m, 3H), 2.49-2.21 (m, 3H), 2.00-1.97 (m, 2H), 1.71-1.52 (m, 2H).

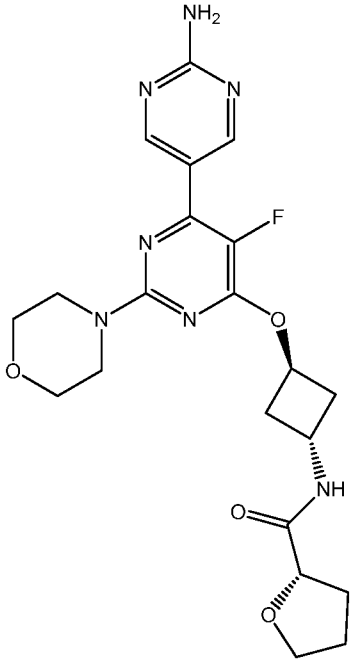
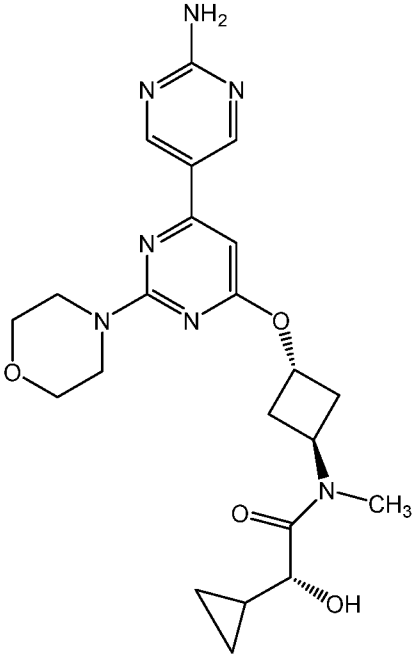
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	^1H NMR
95	 1-(<i>trans</i>-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-1-methyl-3-[2-(pyrrolidin-1-yl)ethyl]urea	516.1	^1H NMR (400 MHz, CD_3OD) δ 8.91 (s, 2H), 5.32-5.30 (m, 1H), 5.00-4.96 (m, 1H), 3.80-3.70 (m, 8H), 3.48-3.45 (m, 2H), 3.31-3.30 (m, 4H), 3.17-3.14 (m, 2H), 2.94 (s, 3H), 2.72-2.70 (m, 2H), 2.52-2.49 (m, 2H), 2.05-1.95 (m, 4H).
96	 <i>N</i>-(<i>trans</i>-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-<i>N</i>,4-dimethylpiperazine-1-carboxamide	524.1 $[M+23]^+$	^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.82 (s, 2H), 7.25 (s, 2H), 5.30-5.20 (m, 1H), 4.31-4.27 (m, 1H), 3.75-3.60 (m, 8H), 3.15-3.10 (m, 4H), 2.73 (s, 3H), 2.59-2.57 (m, 2H), 2.37-2.33 (m, 2H), 2.30-2.20 (m, 4H), 2.16 (s, 3H).

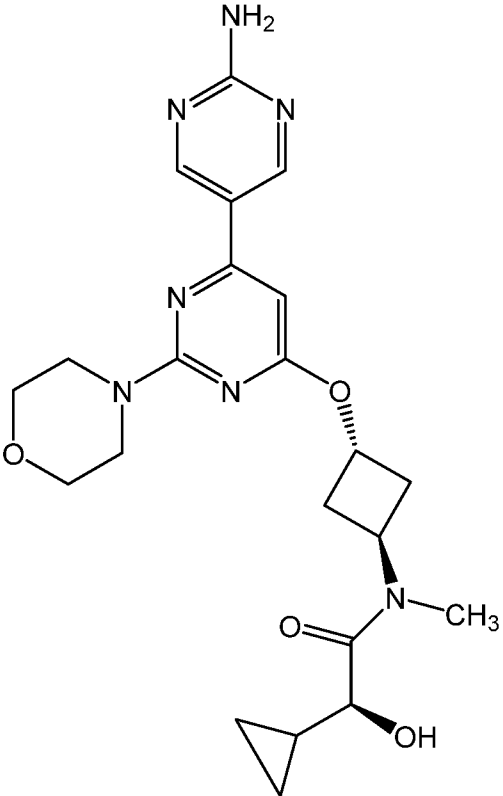
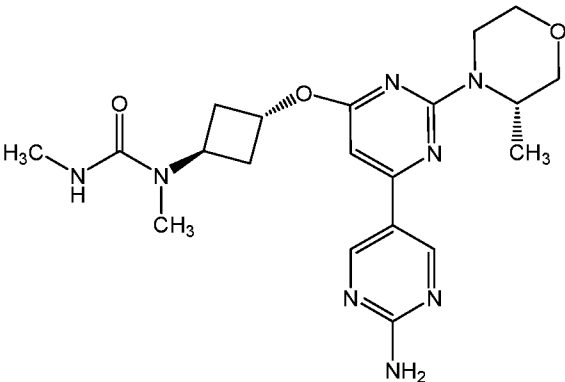
Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
97	 <i>N</i>-(<i>trans</i>-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-<i>N</i>-methylpiperazine-1-carboxamide	510.1 [M+23] ⁺	¹ H NMR (400 MHz, CD ₃ OD) δ ppm 9.19 (s, 2H), 5.40-5.30 (m, 1H), 4.50-4.40 (m, 1H), 3.80-3.70 (m, 8H), 3.50-3.48 (m, 4H), 3.26-3.25 (m, 4H), 2.91 (s, 3H), 2.74-2.70 (m, 2H), 2.56-2.51 (m, 2H).
98	 (2<i>S</i>)-<i>N</i>-(<i>trans</i>-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-3,3-dimethylbutanamide	476.1	¹ H NMR (400 MHz, CDCl ₃) δ ppm 8.99 (s, 2H), 6.50-6.47 (m, 1H), 5.39-5.37 (m, 3H), 4.56-4.52 (m, 1H), 3.77-3.72 (m, 10H), 2.72-2.69 (m, 2H), 2.53-2.51 (m, 2H), 1.02-1.00 (m, 9H).

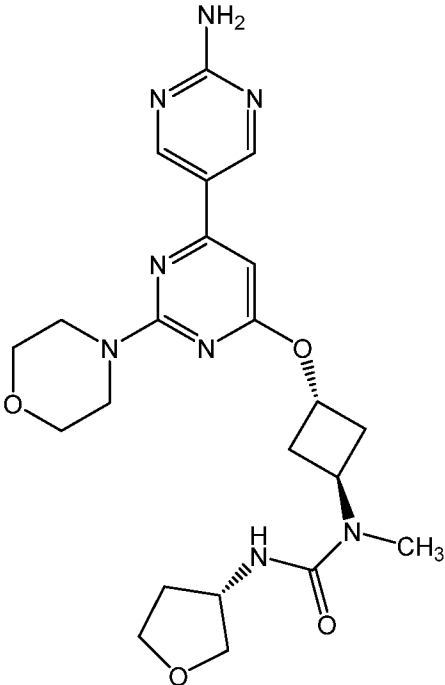
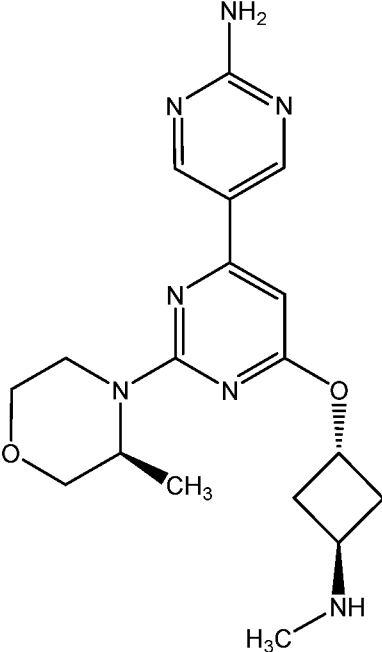
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
99	 1-(<i>trans</i>-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-3-[2-(dimethylamino)ethyl]-1-methylurea	490.1	1H NMR (400 MHz, DMSO- d_6) δ 8.82 (s, 2H), 7.26 (s, 2H), 6.30-6.20 (m, 1H), 5.30-5.20 (m, 1H), 4.92-4.88 (m, 1H), 3.75-3.65 (m, 8H), 3.12-3.10 (m, 2H), 2.78 (s, 3H), 2.65-2.55 (m, 2H), 2.35-2.34 (m, 4H), 2.19 (s, 6H).
100	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-cyclopropyl-2-hydroxy-<i>N</i>-methylacetamide	456.2	1H NMR (400 MHz, CD $_3$ OD) δ ppm 8.92 (s, 2H), 6.49 (s, 1H), 5.34-5.31 (m, 1H), 5.12-5.10 (m, 1H), 4.10-4.09 (m, 1H), 3.83-3.75 (m, 8H), 3.15-3.04 (m, 3H), 2.82-2.74 (m, 2H), 2.52-2.51 (m, 2H), 1.20-1.11 (m, 1H), 0.53-0.43 (m, 4H).

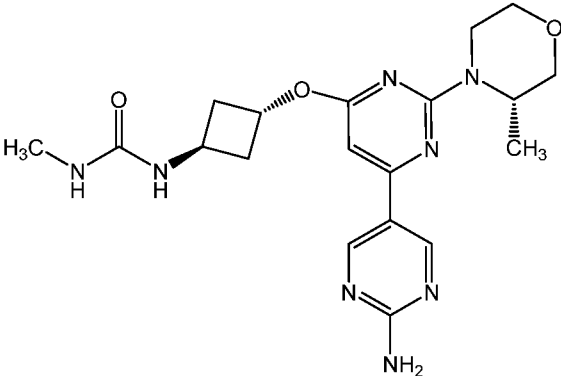
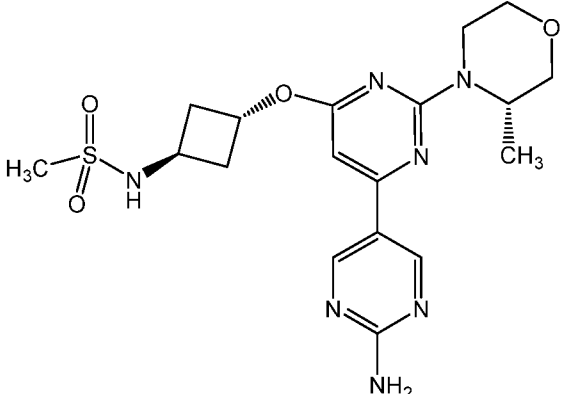
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
101	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-<i>N</i>-methylmethanesulfonamide	450.0	1H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 2H), 6.29 (s, 1H), 5.35 (s, 2H), 5.23-5.22 (m, 1H), 4.70-4.60 (m, 1H), 4.59-4.54 (m, 1H), 4.40-4.30 (m, 1H), 4.00-3.97 (m, 1H), 3.80-3.77 (m, 1H), 3.72-3.69 (m, 1H), 3.56-3.55 (m, 1H), 3.30-3.20 (m, 1H), 2.88 (s, 3H), 2.78 (s, 3H), 2.70-2.60 (m, 2H), 2.52-2.48 (m, 2H), 1.29 (d, $J=6.8$ Hz, 3H).
102	 methyl [<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]methylcarbamate	430.1	1H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 2H), 6.30 (s, 1H), 5.27-5.23 (m, 3H), 4.89-4.86 (m, 1H), 4.75-4.65 (m, 1H), 4.40-4.36 (m, 1H), 4.01-3.98 (m, 1H), 3.80-3.70 (m, 5H), 3.56-3.55 (m, 1H), 3.28-3.25 (m, 1H), 2.93 (s, 3H), 2.64-2.60 (m, 2H), 2.50-2.46 (m, 2H), 1.29 (d, $J=6.8$ Hz, 3H).

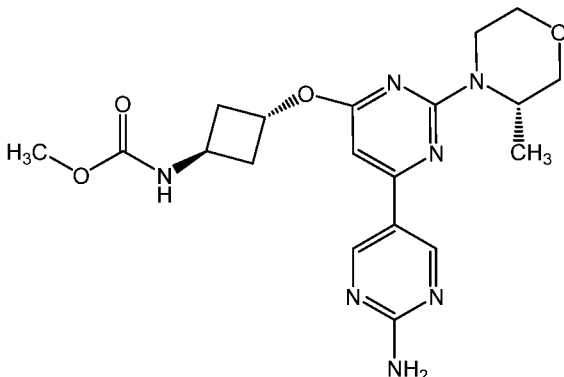
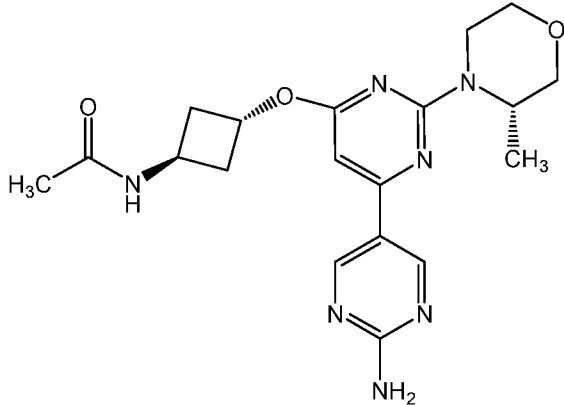
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
103	 <i>N</i>-(<i>trans</i>-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)acetamide	404.0	1H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 2H), 5.37-5.34 (m, 1H), 5.29-5.27 (m, 1H), 3.75-3.73 (m, 8H), 2.76-2.70 (m, 2H), 2.49-2.46 (m, 2H), 2.04-2.01 (m, 3H).
104	 (2<i>R</i>)-<i>N</i>-(<i>trans</i>-3-([2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-3-methylbutanamide	462.1	1H NMR (400 MHz, $DMSO-d_6$) δ 8.83 (s, 2H), 8.17 (d, $J=8.0$ Hz, 1H), 7.27 (s, 2H), 5.38-5.36 (m, 1H), 4.38-4.36 (m, 1H), 3.70-3.62 (m, 10H), 2.48-2.46 (m, 2H), 2.45-2.42 (m, 2H), 1.99-1.95 (m, 1H), 0.91 (d, $J=8.0$ Hz, 3H), 0.79 (d, $J=4.0$ Hz, 3H).

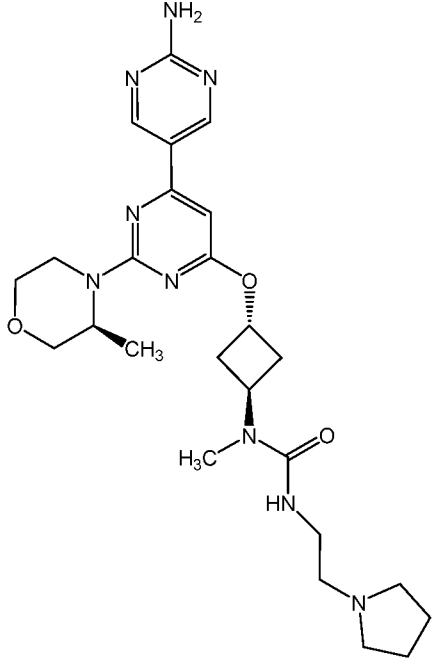
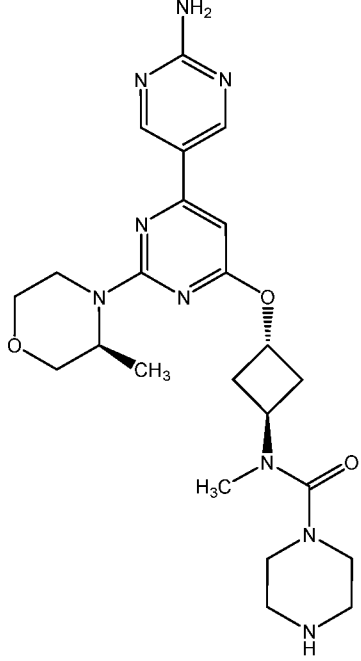
Example Number	Structure and Compound Name	LRMS <i>m/z</i> [M+H] ⁺	¹ H NMR
105	 (2S)-N-(trans-3-{[2'-amino-5-fluoro-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)tetrahydrofuran-2-carboxamide	482.0 [M+23] ⁺	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.83 (s, 2H), 8.23 (d, J=8.0 Hz, 1H), 7.29 (s, 2H), 5.39-5.33 (m, 1H), 4.42-4.39 (m, 1H), 4.22-4.19 (m, 1H), 3.92-3.90 (m, 1H), 3.81-3.77 (m, 1H), 3.70-3.64 (m, 1H), 2.57-2.55 (m, 9H), 2.48-2.44 (m, 2H), 2.13-2.09 (m, 2H), 1.86-1.79 (m, 1H), 1.86-1.79 (m, 3H).
106*	 (2R)-N-(trans-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-2-cyclopropyl-2-hydroxy-N-methylethanamide	456.1	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.94 (s, 2H), 7.14 (s, 2H), 6.63 (s, 1H), 5.24 (br s, 1H), 5.13-5.03 (m, 1H), 4.86-4.75 (m, 1H), 3.95-3.92 (m, 1H), 3.73-3.67 (m, 8H), 3.05-2.91 (m, 3H), 2.68-2.53 (m, 2H), 2.39-2.33 (m, 2H), 1.15-1.02 (m, 1H), 0.39-0.30 (m, 4H).

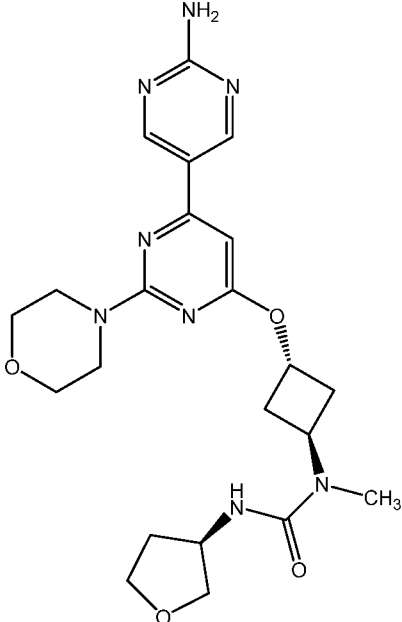
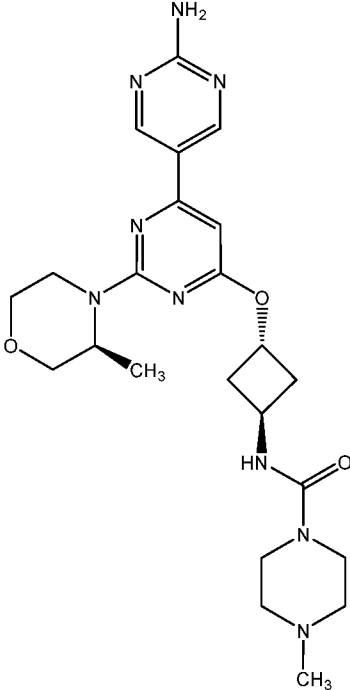
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	^1H NMR
107*	 (2S)-N-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-cyclopropyl-2-hydroxy-N-methylethanamide	478.1 $[M+23]^+$	^1H NMR (400 MHz, DMSO- d_6) δ 8.94 (s, 2H), 7.14 (s, 2H), 6.63 (s, 1H), 5.24 (br s, 1H), 5.13-5.02 (m, 1H), 4.85-4.74 (m, 1H), 3.95-3.91 (m, 1H), 3.73-3.67 (m, 8H), 3.05-2.91 (m, 3H), 2.68-2.53 (m, 2H), 2.39-2.33 (m, 2H), 1.15-1.02 (m, 1H), 0.39-0.30 (m, 4H).
108	 1-[<i>trans</i>-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-1,3-dimethylurea	429.2	^1H NMR (400 MHz, DMSO- d_6) δ 8.92 (s, 2H), 7.12 (s, 2H), 6.60 (s, 1H), 6.24-6.23 (m, 1H), 5.19-5.15 (m, 1H), 4.93-4.89 (m, 1H), 4.65-4.55 (m, 1H), 4.32-4.29 (m, 1H), 3.93-3.90 (m, 1H), 3.74-3.71 (m, 1H), 3.60-3.57 (m, 1H), 3.28-3.25 (m, 1H), 2.78 (s, 3H), 2.59-2.51 (m, 6H), 2.27-2.26 (m, 2H), 1.19 (d, $J=6.8$ Hz, 3H).

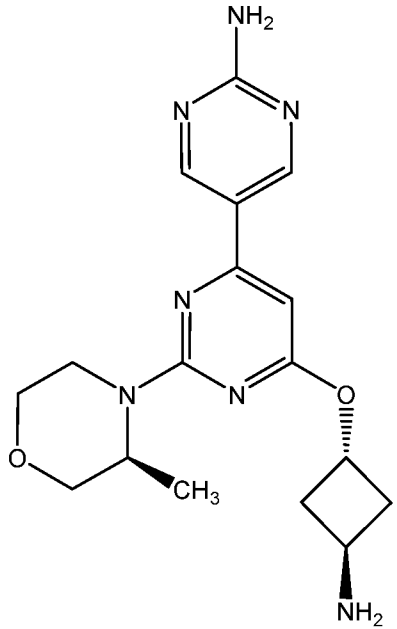
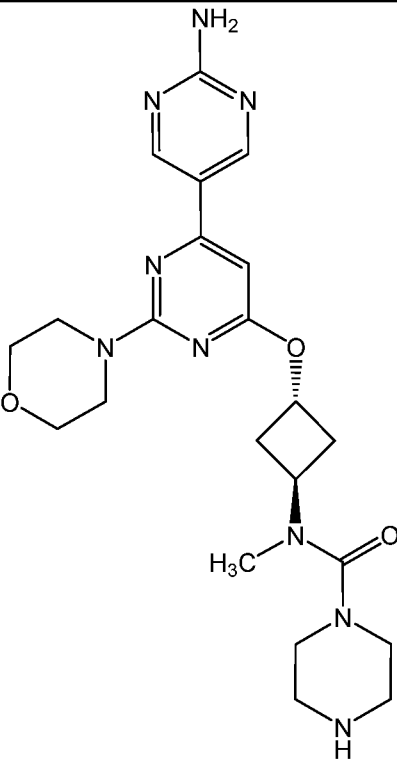
Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
109	 1-(<i>trans</i>-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-1-methyl-3-[(3<i>S</i>)-tetrahydrofuran-3-yl]urea	493.1 [M+23] ⁺	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.93 (s, 2H), 7.12 (s, 2H), 6.60 (s, 1H), 6.29-6.27 (m, 1H), 5.20-5.16 (m, 1H), 4.94-4.90 (m, 1H), 4.14-4.12 (m, 1H), 3.77-3.65 (m, 12H), 2.80 (s, 3H), 2.60-2.55 (m, 2H), 2.27-2.24 (m, 2H), 2.03-2.01 (m, 1H), 1.81-1.79 (m, 1H).
110	 6-[[<i>trans</i>-3-(methylamino)cyclobutyl]oxy]-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-2'-amine	372.0	¹ H NMR (400 MHz, CDCl ₃) δ 8.89 (s, 2H), 6.27 (s, 1H), 5.40-5.29 (m, 1H), 5.29 (s, 2H), 4.74-4.72 (m, 1H), 4.42-4.39 (m, 1H), 4.00-3.97 (m, 1H), 3.80-3.72 (m, 2H), 3.59-3.52 (m, 1H), 3.45-3.41 (m, 1H), 3.28-3.27 (m, 1H), 2.40-2.37 (m, 5H), 2.32-2.27 (m, 2H), 1.29 (d, <i>J</i> =8.0 Hz, 3H), 1.26-1.24 (m, 1H).

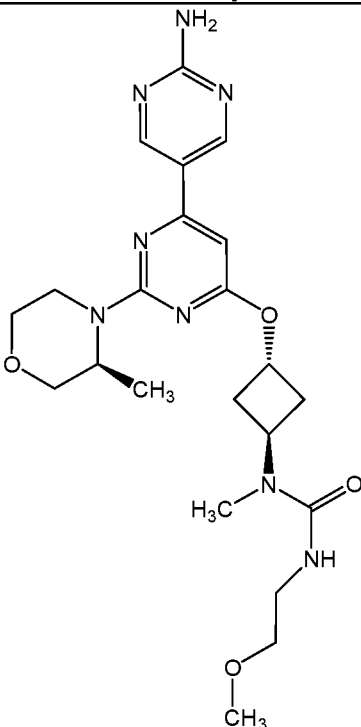
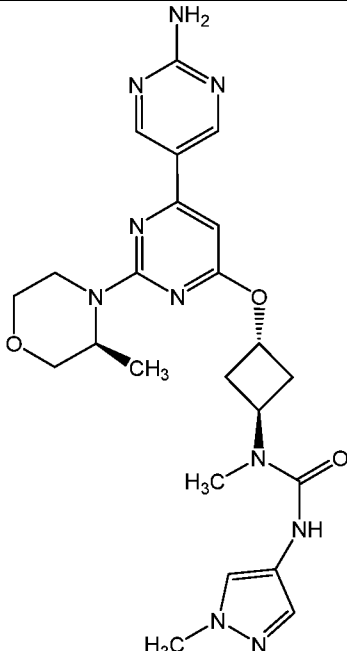
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
111	 1-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-3-methylurea	415.1	1H NMR (400 MHz, DMSO- d_6) δ 8.90 (s, 2H), 7.11 (s, 2H), 6.55 (s, 1H), 6.40-6.35 (m, 1H), 5.75-5.65 (m, 1H), 5.25-5.15 (m, 1H), 4.65-4.55 (m, 1H), 4.31-4.28 (m, 1H), 4.20-4.15 (m, 1H), 3.91-3.90 (m, 1H), 3.74-3.71 (m, 1H), 3.60-3.55 (m, 1H), 3.39-3.34 (m, 1H), 3.15-3.10 (m, 1H), 2.53-2.51 (m, 3H), 2.37-2.33 (m, 4H), 1.19-1.18 (m, 3H).
112	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]methanesulfonamide	436.0	1H NMR (400 MHz, DMSO- d_6) δ 8.91 (s, 2H), 7.56-7.54 (m, 1H), 7.12 (s, 2H), 6.57 (s, 1H), 5.27-5.25 (m, 1H), 4.65-4.61 (m, 1H), 4.32-4.29 (m, 1H), 3.99-3.91 (m, 2H), 3.74-3.71 (m, 1H), 3.60-3.58 (m, 1H), 3.43-3.41 (m, 1H), 3.19-3.10 (m, 1H), 2.88 (s, 3H), 2.45-2.40 (m, 4H), 1.20-1.18 (m, 3H).

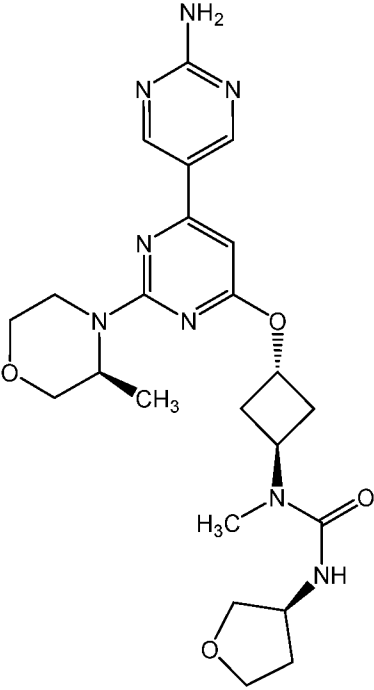
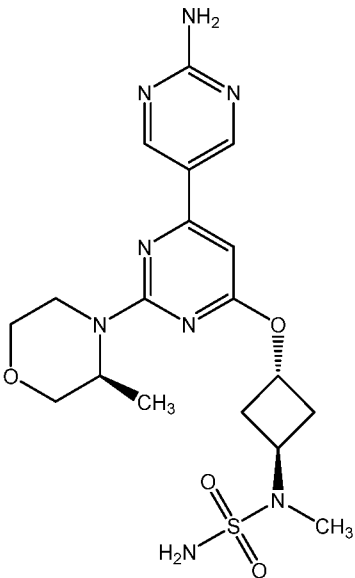
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
113	 methyl [<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]carbamate	416.3	1H NMR (400 MHz, DMSO- d_6) δ 8.90 (s, 2H), 7.63-7.62 (m, 1H), 7.11 (s, 2H), 6.56 (s, 1H), 5.27-5.24 (m, 1H), 4.65-4.55 (m, 1H), 4.32-4.29 (m, 1H), 4.15-4.05 (m, 1H), 3.93-3.90 (m, 1H), 3.73-3.70 (m, 1H), 3.60-3.58 (m, 1H), 3.57-3.43 (m, 3H), 3.35-3.34 (m, 1H), 3.14-3.13 (m, 1H), 2.38-2.33 (m, 4H), 1.19-1.18 (m, 3H).
114	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]acetamide	400.1	1H NMR (400 MHz, DMSO- d_6) δ 8.90 (s, 2H), 8.28-8.26 (m, 1H), 7.11 (s, 2H), 6.57 (s, 1H), 5.28-5.25 (m, 1H), 4.63-4.62 (m, 1H), 4.32-4.26 (m, 2H), 3.95-3.90 (m, 1H), 3.74-3.71 (m, 1H), 3.61-3.60 (m, 1H), 3.44-3.43 (m, 1H), 3.15-3.10 (m, 1H), 2.41-2.37 (m, 4H), 1.81 (s, 3H), 1.20-1.18 (m, 3H).

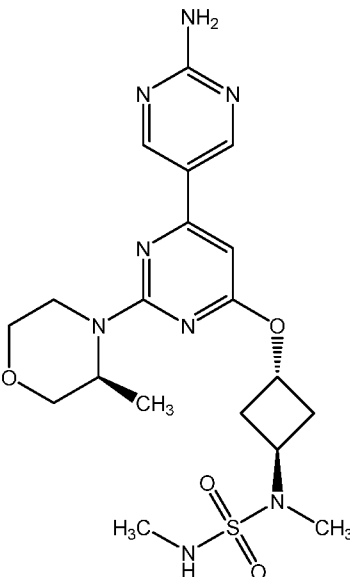
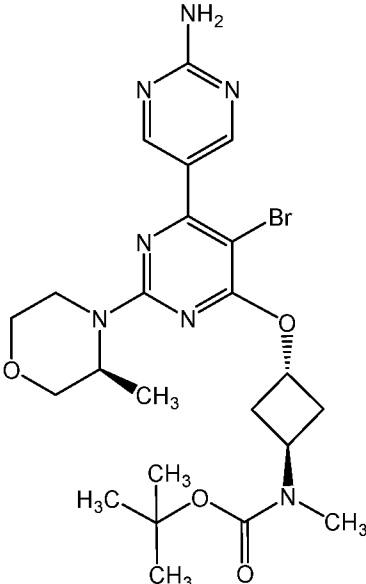
Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
115	 1-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-1-methyl-3-[2-(pyrrolidin-1-yl)ethyl]urea	512.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.92 (s, 2H), 7.11 (s, 2H), 6.59 (s, 1H), 6.35-6.33 (m, 1H), 5.17-5.15 (m, 1H), 4.91-4.89 (m, 1H), 4.62-4.55 (m, 1H), 4.32-4.28 (m, 1H), 3.93-3.91 (m, 1H), 3.73-3.71 (m, 1H), 3.57-3.56 (m, 1H), 3.15-3.11 (m, 4H), 2.78 (s, 3H), 2.60-2.51 (m, 8H), 2.28-2.27 (m, 2H), 1.71-1.70 (m, 4H), 1.19 (d, <i>J</i> =6.8 Hz, 3H).
116	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-<i>N</i>-methylpiperazine-1-carboxamide	484.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.92 (s, 2H), 7.12 (s, 2H), 6.59 (s, 1H), 5.21-5.20 (m, 1H), 4.65-4.62 (m, 1H), 4.39-4.35 (m, 2H), 3.93-3.90 (m, 1H), 3.74-3.71 (m, 1H), 3.60-3.59 (m, 1H), 3.39-3.37 (m, 1H), 3.36-3.09 (m, 10H), 2.79 (s, 3H), 2.61-2.59 (m, 2H), 2.33-2.27 (m, 2H), 1.20 (d, <i>J</i> =6.8 Hz, 3H).

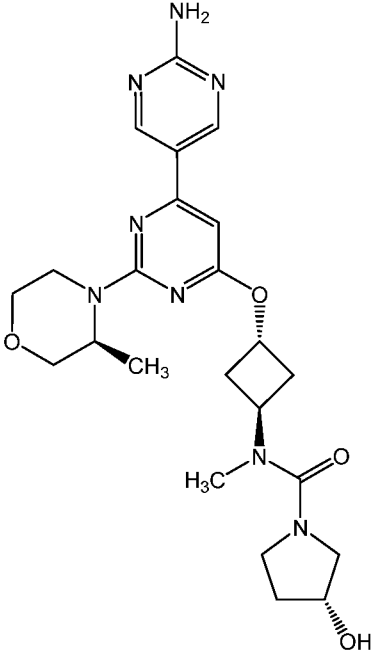
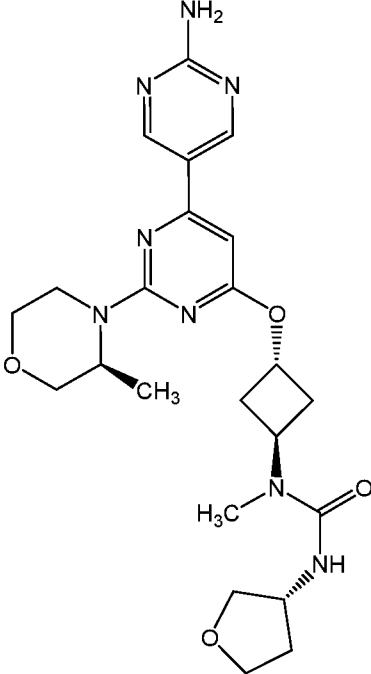
Example Number	Structure and Compound Name	LRMS <i>m/z</i> [M+H] ⁺	¹ H NMR
117	 1-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-1-methyl-3-[(3<i>R</i>)-tetrahydrofuran-3-yl]urea	493.2 [M+23] ⁺	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.93 (s, 2H), 7.12 (s, 2H), 6.60 (s, 1H), 6.29-6.27 (m, 1H), 5.20-5.16 (m, 1H), 4.94-4.90 (m, 1H), 4.14-4.12 (m, 1H), 3.79-3.63 (m, 12H), 2.80 (s, 3H), 2.59-2.51 (m, 2H), 2.28-2.25 (m, 2H), 2.01-2.00 (m, 1H), 1.79-1.78 (m, 1H).
118	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-4-methylpiperazine-1-carboxamide	484.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.90 (s, 2H), 7.11 (s, 2H), 6.82-6.81 (m, 1H), 6.57 (s, 1H), 5.25-5.23 (m, 1H), 4.65-4.61 (m, 1H), 4.32-4.25 (m, 2H), 3.95-3.85 (m, 1H), 3.73-3.71 (m, 1H), 3.60-3.58 (m, 1H), 3.46-3.42 (m, 2H), 3.15-3.10 (m, 2H), 2.40-2.32 (m, 10H), 2.23 (s, 3H), 1.19-1.18 (m, 3H).

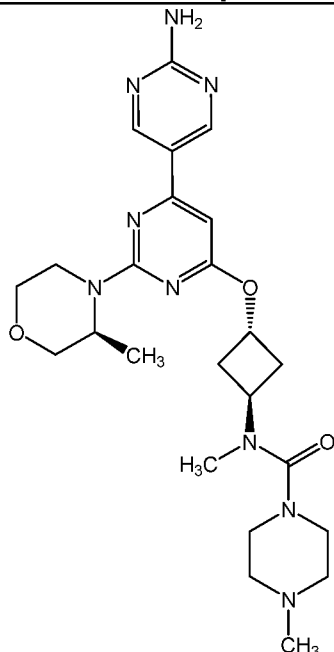
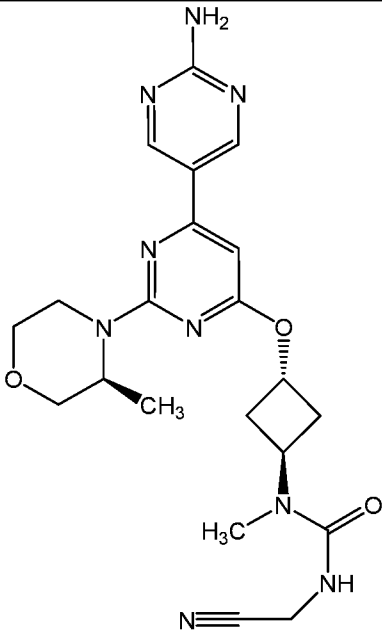
Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
119	 6-[(<i>trans</i>-3-aminocyclobutyl)oxy]-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-2'-amine	358.0	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.91 (s, 2H), 7.13 (s, 2H), 6.57 (s, 1H), 5.48-5.45 (m, 1H), 4.66-4.64 (m, 1H), 4.35-4.31 (m, 1H), 3.95-3.92 (m, 1H), 3.77-3.72 (m, 3H), 3.61-3.58 (m, 2H), 3.19-3.16 (m, 2H), 2.56-2.55 (m, 2H), 2.48-2.44 (m, 2H), 1.20 (d, <i>J</i> =6.8 Hz, 3H).
120	 <i>N</i>-(<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-<i>N</i>-methylpiperazine-1-carboxamide	492.3 [M+23] ⁺	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.93 (s, 2H), 7.14 (s, 2H), 6.61 (s, 1H), 5.25-5.20 (m, 1H), 4.39-4.35 (m, 1H), 3.73-3.67 (m, 8H), 3.25-3.15 (m, 5H), 3.05-3.00 (m, 4H), 2.79 (s, 3H), 2.63-2.60 (m, 2H), 2.37-2.32 (m, 2H).

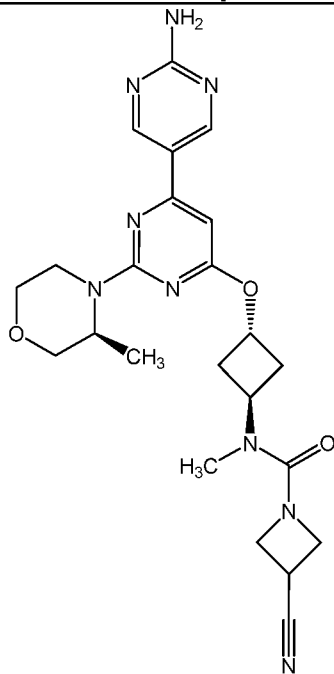
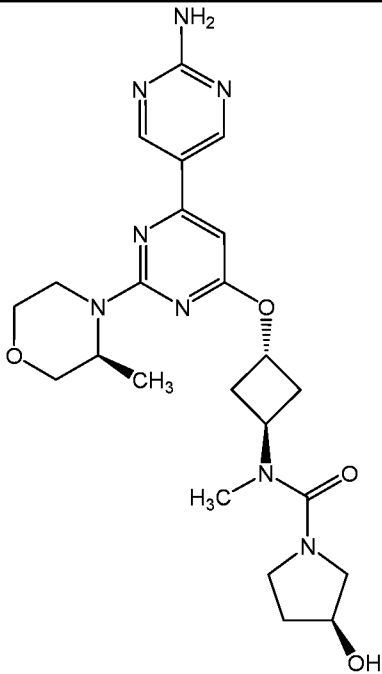
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
121	 1-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-3-(2-methoxyethyl)-1-methylurea	473.2	1H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 2H), 6.30 (s, 1H), 5.43 (s, 2H), 5.26-5.21 (m, 1H), 4.90-4.82 (m, 1H), 4.78-4.69 (m, 2H), 4.39-4.35 (m, 1H), 4.01-3.97 (m, 1H), 3.80-3.78 (m, 2H), 3.59-3.42 (m, 5H), 3.37 (s, 3H), 3.30-3.23 (m, 1H), 2.90 (s, 3H), 2.64-2.46 (m, 4H), 1.30 (d, $J=8.0$ Hz, 3H).
122	 1-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-1-methyl-3-(1-methyl-1<i>H</i>-pyrazol-4-yl)urea	495.2	1H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 2H), 7.71 (s, 1H), 7.32 (s, 1H), 6.30 (s, 1H), 6.10 (s, 1H), 5.36 (s, 2H), 5.28-5.24 (m, 1H), 4.93-4.87 (m, 1H), 4.71-4.69 (m, 1H), 4.39-4.36 (m, 1H), 4.01-3.97 (m, 1H), 3.84 (s, 3H), 3.80-3.77 (m, 1H), 3.73-3.69 (m, 1H), 3.65-3.56 (m, 1H), 3.28-3.26 (m, 1H), 3.00 (s, 3H), 2.68-2.54 (m, 4H), 1.29 (d, $J=8.0$ Hz, 3H).

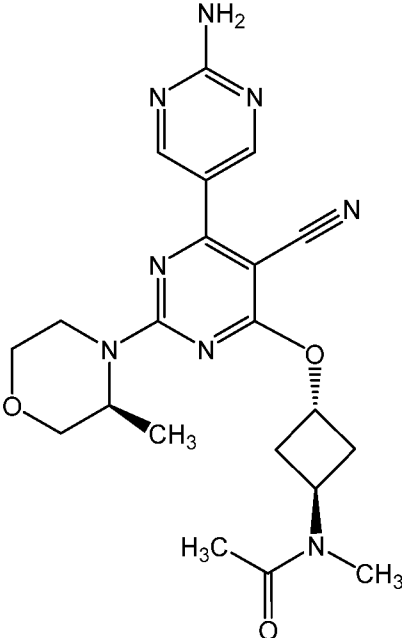
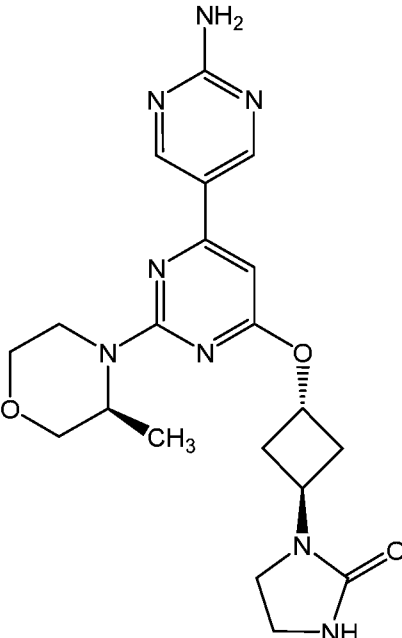
Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
123	 1-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-1-methyl-3-[(3<i>S</i>)-tetrahydrofuran-3-yl]urea	485.2	¹ H NMR (400 MHz, CDCl ₃) δ ppm 8.89-8.13 (m, 2H), 7.26 (m, 1H), 6.30 (s, 1H), 5.37 (s, 2H), 5.25-5.21 (m, 1H), 4.88-4.81 (m, 1H), 4.71-4.67 (m, 1H), 4.51-4.35 (m, 3H), 4.01-3.91 (m, 2H), 3.84-3.66 (m, 5H), 3.59-3.52 (m, 1H), 3.30-3.23 (m, 1H), 2.88 (s, 3H), 2.62-2.48 (m, 4H), 2.30-2.22 (m, 1H), 1.29 (d, J = 8Hz, 3H).
124	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-<i>N</i>-methylsulfuric diamide	451.0	¹ H NMR (400 MHz, CD ₃ OD) δ 8.92 (s, 2H), 6.47 (s, 1H), 5.25 (t, J=6.8 Hz, 1H), 4.80-4.70 (m, 1H), 4.41 (dd, J=13.4, 2.1 Hz, 1H), 4.31 (p, J=8.2 Hz, 1H), 3.99 (dd, J=11.2, 3.4 Hz, 1H), 3.80 (d, J=11.4 Hz, 1H), 3.71 (dd, J=11.4, 3.2 Hz, 1H), 3.56 (dt, J=11.9, 2.9 Hz, 1H), 3.31-3.23 (m, 1H), 2.76 (s, 3H), 2.74-2.68 (m, J=6.9 Hz, 2H), 2.50-2.41 (m, 2H), 1.30 (d, J=6.7 Hz, 3H).

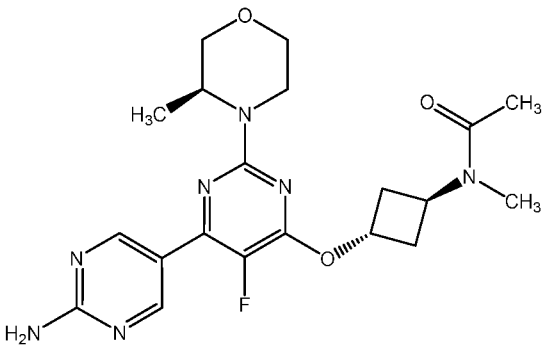
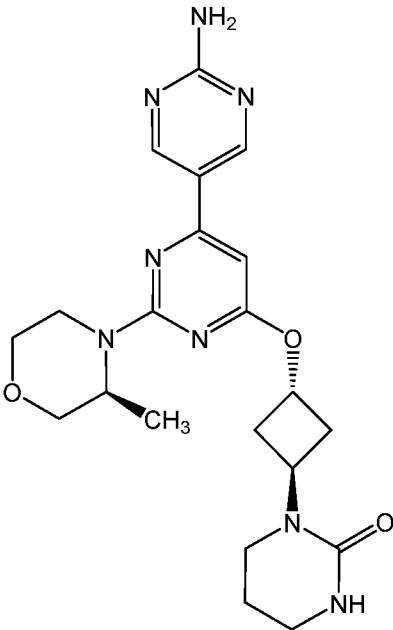
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
125	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-<i>N,N'</i>-dimethylsulfuric diamide	465.0	1H NMR (400 MHz, CD_3OD) δ 8.92 (s, 2H), 6.48 (s, 1H), 5.26 (t, $J=6.7$ Hz, 1H), 4.79-4.72 (m, 1H), 4.51 (p, $J=8.2$ Hz, 1H), 4.41 (dd, $J=14.1, 2.6$ Hz, 1H), 3.99 (dd, $J=11.4, 3.5$ Hz, 1H), 3.81 (d, $J=11.2$ Hz, 1H), 3.72 (dd, $J=11.2, 3.18$ Hz, 1H), 3.56 (dt, $J=11.9, 2.9$ Hz, 1H), 3.29-3.24 (m, 1H), 2.82 (s, 3H), 2.80-2.70 (m, 2H), 2.61 (s, 3H), 2.47-2.39 (m, 2H), 1.31 (d, $J=6.8$ Hz, 3H).
126	 <i>tert</i>-butyl [<i>trans</i>-3-({2'-amino-5-bromo-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]methylcarbamate	550, 552	1H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 0.5H), 8.86 (s, 1.5H), 5.49 (br s, 2H), 5.30-5.22 (m, 1H), 4.82 (br s, 1H), 4.66-4.57 (m, 1H), 4.28 (dd, $J=13.7, 2.2$ Hz, 1H), 3.99 (dd, $J=11.2, 3.4$ Hz, 1H), 3.82-3.76 (m, 1H), 3.74-3.66 (m, 1H), 3.60-3.50 (m, 1H), 3.25 (dt, $J=13.0, 3.8$ Hz, 1H), 2.90 (s, 3H), 2.71-2.62 (m, 2H), 2.61-2.49 (m, 2H), 1.49 (s, 9H), 1.30 (d, $J=6.8$ Hz, 3H).

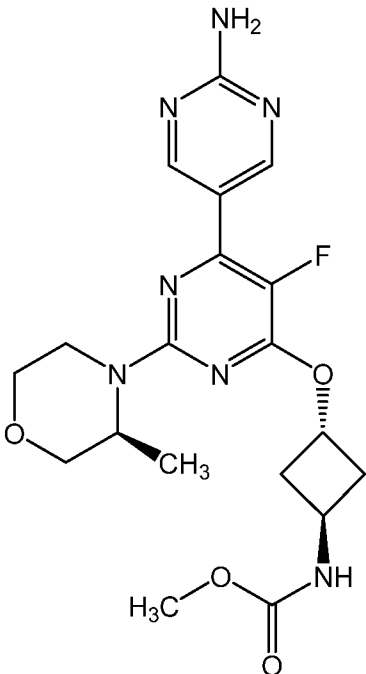
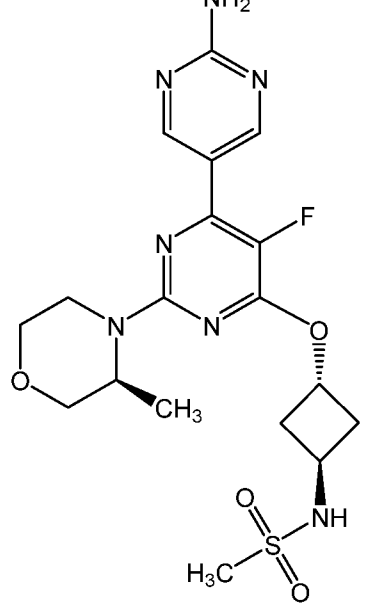
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
127	 (3R)-N-[trans-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-3-hydroxy-N-methylpyrrolidine-1-carboxamide	507.3 $[M+23]^+$	1H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 2H), 6.29 (s, 1H), 5.34 (s, 2H), 5.24-5.20 (m, 1H), 4.72-4.69 (m, 1H), 4.51-4.46 (m, 2H), 4.39-4.36 (m, 1H), 4.01-3.97 (m, 1H), 3.80-3.53 (m, 6H), 3.44-3.24 (m, 3H), 2.83 (s, 3H), 2.61-2.47 (m, 4H), 2.00-1.94 (m, 2H), 1.29 (d, $J=8.0$ Hz, 3H).
128	 1-[trans-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-1-methyl-3-[(3R)-tetrahydrofuran-3-yl]urea	485.2	1H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 2H), 6.30 (s, 1H), 5.41 (s, 2H), 5.25-5.21 (m, 1H), 4.88-4.81 (m, 1H), 4.71-4.67 (m, 1H), 4.51-4.35 (m, 3H), 4.01-3.91 (m, 2H), 3.84-3.66 (m, 5H), 3.59-3.52 (m, 1H), 3.31-3.23 (m, 1H), 2.89 (s, 3H), 2.62-2.48 (m, 4H), 2.31-2.22 (m, 1H), 1.30 (d, $J=8.0$ Hz, 3H).

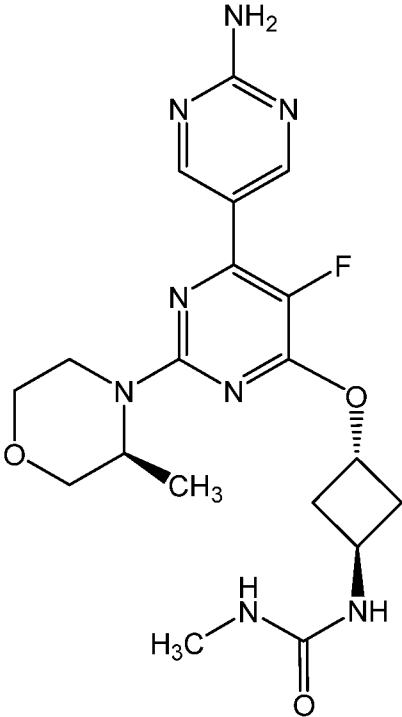
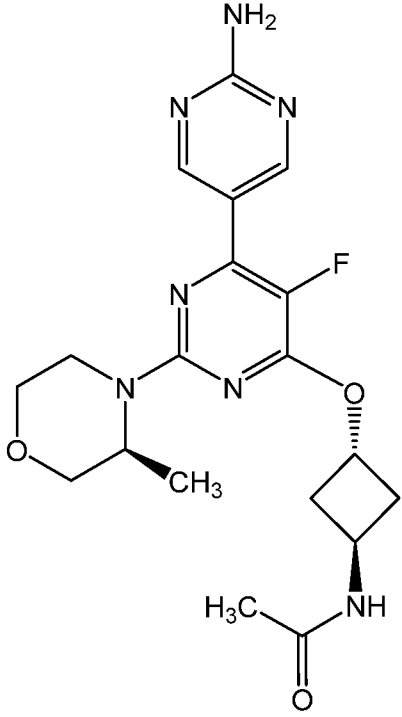
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
129	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-<i>N</i>,4-dimethylpiperazine-1-carboxamide	520.3 $[M+23]^+$	1H NMR (400 MHz, DMSO- d_6) δ 11.12 (s, 1H), 9.12 (s, 2H), 6.70 (s, 1H), 5.24-5.20 (m, 1H), 4.65-4.61 (m, 1H), 4.40-4.30 (m, 2H), 3.95-3.91 (m, 1H), 3.75-3.72 (m, 2H), 3.63-3.60 (m, 4H), 3.46-3.41 (m, 1H), 3.36-3.32 (m, 2H), 3.24-3.13 (m, 3H), 3.03-2.94 (m, 2H), 2.80 (s, 3H), 2.75 (d, $J=4.0$ Hz, 3H), 2.64-2.61 (m, 2H), 2.36-2.33 (m, 2H), 1.20 (d, $J=8.0$ Hz, 3H).
130	 1-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-3-(cyanomethyl)-1-methylurea	454.1	1H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 2H), 6.30 (s, 1H), 5.38 (s, 2H), 5.26-5.23 (m, 1H), 4.87-4.67 (m, 3H), 4.39-4.36 (m, 1H), 4.18 (d, $J=8.0$ Hz, 2H), 4.01-3.97 (m, 1H), 3.81-3.69 (m, 2H), 3.59-3.53 (m, 1H), 3.31-3.24 (m, 1H), 2.94 (s, 3H), 2.66-2.54 (m, 4H), 1.30 (d, $J=8.0$ Hz, 3H).

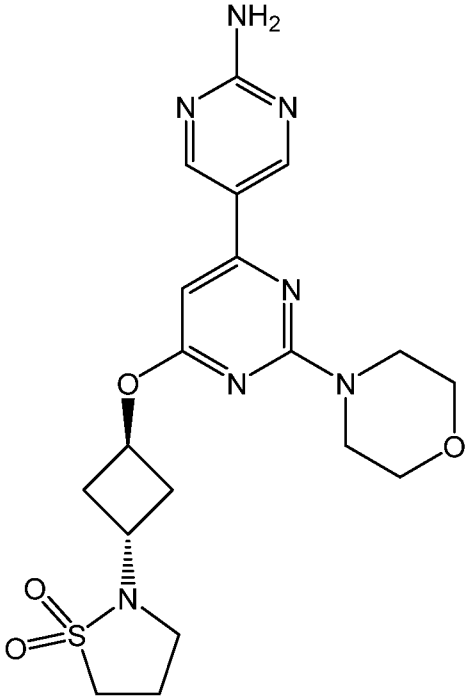
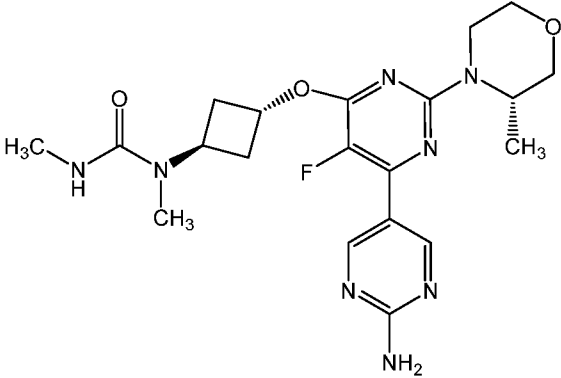
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
131	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-3-cyano-<i>N</i>-methylazetidine-1-carboxamide	502.3 $[M+23]^+$	1H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 2H), 6.31 (s, 1H), 5.38 (s, 2H), 5.24-5.21 (m, 1H), 4.69-4.62 (m, 2H), 4.39-4.35 (m, 1H), 4.26-4.17 (m, 4H), 4.01-3.98 (m, 1H), 3.80-3.69 (m, 2H), 3.59-3.53 (m, 1H), 3.47-3.41 (m, 1H), 3.30-3.23 (m, 1H), 2.86 (s, 3H), 2.66-2.58 (m, 2H), 2.49-2.46 (m, 2H), 1.29 (d, $J=8.0$ Hz, 3H).
132	 (3<i>S</i>)-<i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-3-hydroxy-<i>N</i>-methylpyrrolidine-1-carboxamide	485.4	1H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 2H), 6.29 (s, 1H), 5.40 (s, 2H), 5.24-5.20 (m, 1H), 4.72-4.69 (m, 1H), 4.54-4.46 (m, 2H), 4.39-4.36 (m, 1H), 4.01-3.97 (m, 1H), 3.80-3.53 (m, 6H), 3.43-3.23 (m, 3H), 2.83 (s, 3H), 2.61-2.47 (m, 4H), 2.00-1.94 (m, 2H), 1.29 (d, $J=8.0$ Hz, 3H).

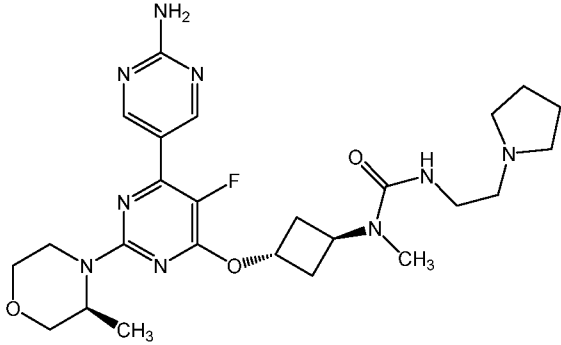
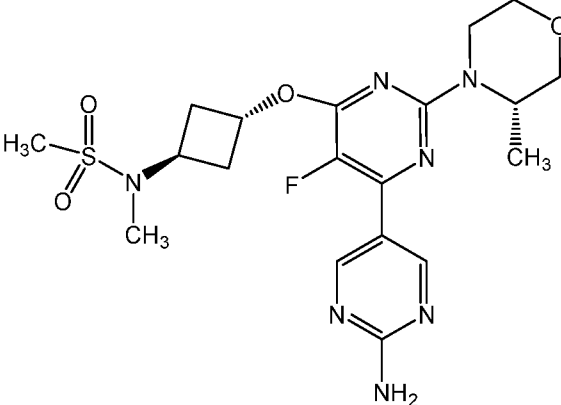
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
133**	 <i>N</i>-[<i>trans</i>-3-({2'-amino-5-cyano-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-<i>N</i>-methylacetamide	439.0	1H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 2H), 5.91-5.65 (m, 2H), 5.34 (br s, 1H), 5.09-4.21 (m, 3H), 4.02 (d, $J=10.5$ Hz, 1H), 3.81 (dd, $J=11.1, 4.3$ Hz, 1H), 3.69 (d, $J=9.8$ Hz, 1H), 3.54 (t, $J=12.1$ Hz, 1H), 3.40-3.28 (m, 1H), 3.01 (s, 1.5H), 2.98 (s, 1.5H), 2.79-2.69 (m, 2H), 2.69-2.57 (m, 2H), 2.13 (br s, 1.5H), 2.11 (br s, 1.5H), 1.34 (br s, 3H)
134	 1-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]imidazolidin-2-one	449.1 $[M+23]^+$	1H NMR (400 MHz, $DMSO-d_6$) δ 8.93 (s, 2H), 7.13 (s, 2H), 6.61 (s, 1H), 6.39 (s, 1H), 5.25-5.18 (m, 1H), 4.67-4.58 (m, 1H), 4.53-4.46 (m, 1H), 4.31 (d, $J=13.6$ Hz, 1H), 3.92 (d, $J=10.3$ Hz, 1H), 3.73 (d, $J=11.3$ Hz, 1H), 3.59 (d, $J=8.5$ Hz, 1H), 3.49-3.44 (m, 2H), 3.26 (t, $J=7.8$ Hz, 2H), 3.20-3.11 (m, 1H), 2.99 (br s, 1H), 2.71-2.62 (m, 2H), 2.36-2.23 (m, 2H), 1.20 (d, $J=6.8$ Hz, 3H).

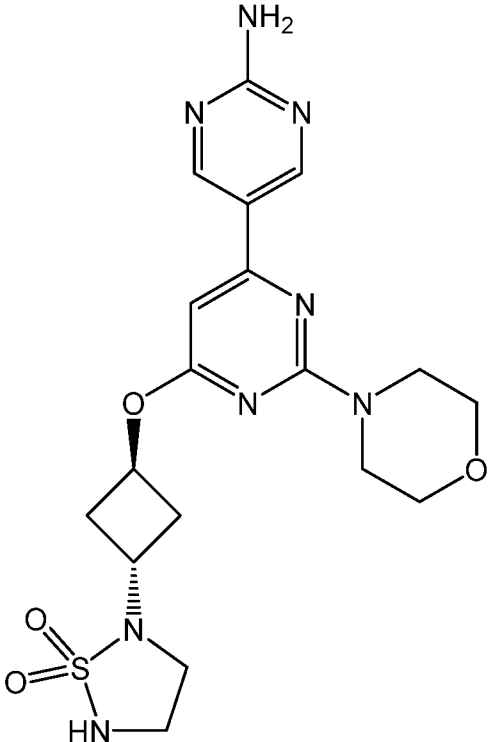
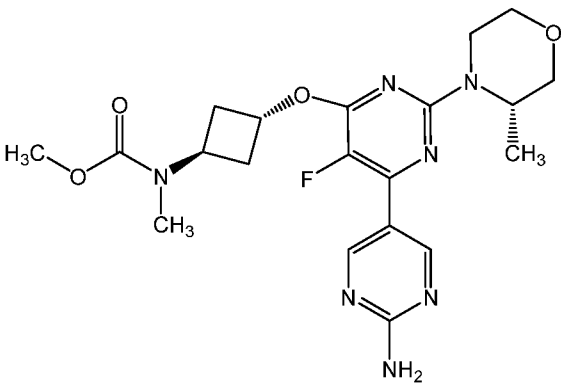
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
135	 <i>N</i>-(<i>trans</i>-3-((2'-amino-5-fluoro-2-((<i>S</i>)-3-methylmorpholin-4-yl)-4,5'-bipyrimidin-6-yl)oxy)cyclobutyl)-<i>N</i>-methylacetamide	432.0	1H NMR (600 MHz, DMSO- d_6) δ 8.81 (s, 2H) 7.22 (s, 2H) 5.30-5.23 (m, 1H) 5.20-5.11 (m, 0.5H) 4.77-4.68 (m, 0.5H) 4.49 (br s, 1H) 4.16 (d, $J=13.4$ Hz, 1H) 3.94-3.88 (m, 1H) 3.71 (d, $J=11.4$ Hz, 1H) 3.57 (dd, $J=11.4, 3.1$ Hz, 1H) 3.46-3.38 (m, 2H) 3.17-3.08 (m, 1H) 2.96 (s, 1.5H) 2.84 (s, 1.5H) 2.77-2.70 (m, 1H) 2.68-2.60 (m, 1H) 2.41-2.30 (m, 1H) 2.00 (s, 3H) 1.17 (d, $J=6.8$ Hz, 3H).
136	 1-[<i>trans</i>-3-((2'-amino-2-((3<i>S</i>)-3-methylmorpholin-4-yl)-4,5'-bipyrimidin-6-yl)oxy)cyclobutyl]tetrahydropyrimidin-2(1<i>H</i>)-one	441.1 $[M+23]^+$	1H NMR (400 MHz, DMSO- d_6) δ 8.93 (s, 2H), 7.13 (s, 2H), 6.62 (s, 1H), 6.26 (s, 1H), 5.21-5.15 (m, 1H), 5.14-5.07 (m, 1H), 4.66-4.59 (m, 1H), 4.32 (d, $J=12.8$ Hz, 1H), 3.93 (d, $J=10.3$ Hz, 1H), 3.73 (d, $J=11.8$ Hz, 1H), 3.59 (d, $J=8.3$ Hz, 1H), 3.48-3.40 (m, 1H), 3.29-3.25 (m, 2H), 3.18-3.15 (m, 1H), 3.12-3.06 (m, 2H), 2.66-2.61 (m, 2H), 2.26-2.16 (m, 2H), 1.85-1.77 (m, 2H), 1.20 (d, $J=6.5$ Hz, 3H).

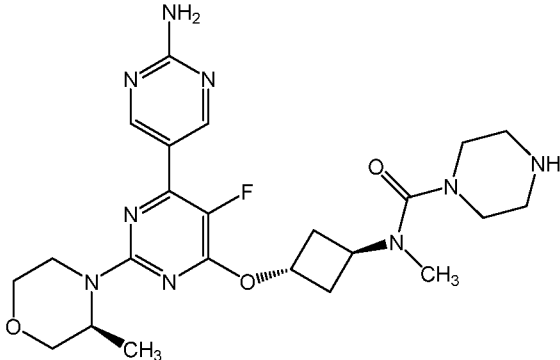
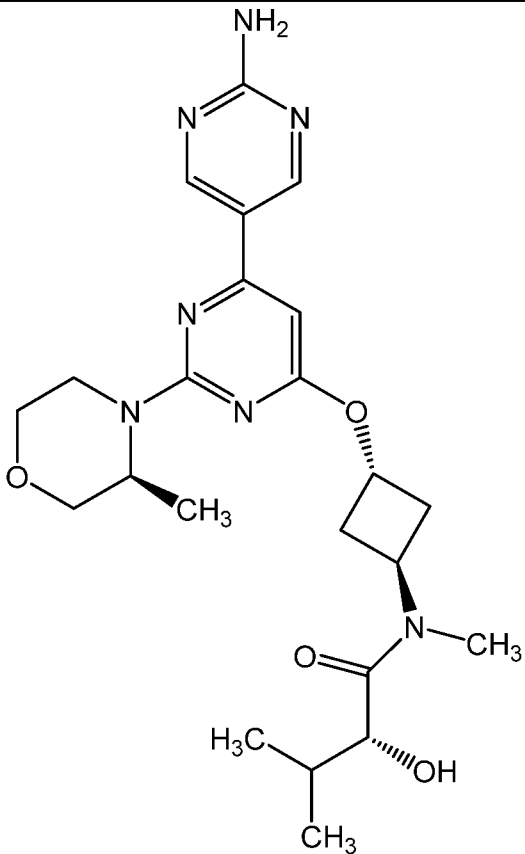
Example Number	Structure and Compound Name	LRMS <i>m/z</i> [M+H] ⁺	¹ H NMR
137	 methyl [<i>trans</i>-3-({2'-amino-5-fluoro-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]carbamate	434.0	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ 8.80 (s, 2H), 7.64 (d, <i>J</i> =6.9 Hz, 1H), 7.22 (s, 2H), 5.31 (td, <i>J</i> =12.1, 6.0 Hz, 1H), 4.53-4.47 (m, 1H), 4.17 (dd, <i>J</i> =13.6, 2.2 Hz, 1H), 4.15-4.07 (m, 1H), 3.91 (dd, <i>J</i> =11.4, 3.7 Hz, 1H), 3.71 (d, <i>J</i> =11.4 Hz, 1H), 3.58 (dd, <i>J</i> =11.2, 3.1 Hz, 1H), 3.53 (s, 3H), 3.42 (dt, <i>J</i> =11.9, 2.9 Hz, 1H), 3.12 (dt, <i>J</i> =12.9, 3.8 Hz, 1H), 2.48-2.37 (m, 4H), 1.17 (d, <i>J</i> =6.6 Hz, 3H).
138	 <i>N</i>-[<i>trans</i>-3-({2'-amino-5-fluoro-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]methanesulfonamide	454.0	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ 8.82 (s, 2H), 7.58 (br s, 1H), 7.24 (s, 2H), 5.36-5.28 (m, 1H), 4.54-4.46 (m, 1H), 4.18 (d, <i>J</i> =13.2 Hz, 1H), 4.08-3.99 (m, 1H), 3.93 (dd, <i>J</i> =11.2, 3.5 Hz, 1H), 3.73 (d, <i>J</i> =11.4 Hz, 1H), 3.59 (dd, <i>J</i> =11.4, 2.9 Hz, 1H), 3.13 (dt, <i>J</i> =12.8, 3.7 Hz, 1H), 2.90 (s, 3H), 2.61-2.52 (m, 2H), 2.49 (d, <i>J</i> =2.6 Hz, 2H), 1.19 (d, <i>J</i> =6.6 Hz, 3H).

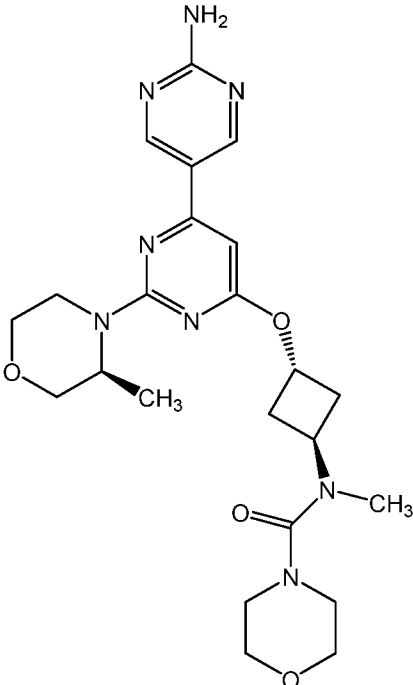
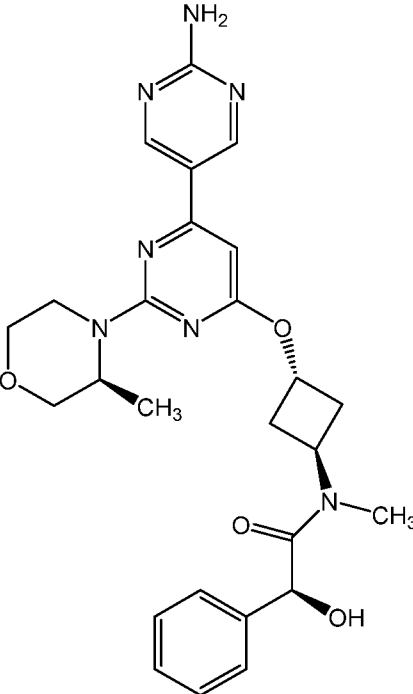
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
139	 1-[<i>trans</i>-3-({2'-amino-5-fluoro-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-3-methylurea	433.0	1H NMR (600 MHz, DMSO- d_6) δ 8.80 (s, 2H), 7.21 (s, 2H), 6.41 (d, $J=6.9$ Hz, 1H), 5.75 (q, $J=4.4$ Hz, 1H), 5.32-5.24 (m, 1H), 4.54-4.45 (m, 1H), 4.22-4.12 (m, 2H), 3.91 (dd, $J=11.0$, 3.3 Hz, 1H), 3.71 (d, $J=11.4$ Hz, 1H), 3.58 (dd, $J=11.5$, 3.1 Hz, 1H), 3.12 (dt, $J=12.8$, 3.7 Hz, 1H), 2.53 (d, $J=4.4$ Hz, 3H), 2.48-2.39 (m, 2H), 2.39-2.30 (m, 2H), 1.17 (d, $J=6.9$ Hz, 3H).
140	 <i>N</i>-[<i>trans</i>-3-({2'-amino-5-fluoro-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]acetamide	418.0	1H NMR (600 MHz, DMSO- d_6) δ 8.81 (s, 2H), 8.30 (d, $J=6.9$ Hz, 1H), 7.23 (s, 2H), 5.36-5.30 (m, 1H), 4.54-4.48 (m, 1H), 4.34-4.25 (m, 1H), 4.18 (dd, $J=13.4$, 2.4 Hz, 1H), 3.93 (dd, $J=11.2$, 3.5 Hz, 1H), 3.73 (d, $J=11.0$ Hz, 1H), 3.59 (dd, $J=11.5$, 3.1 Hz, 1H), 3.16-3.11 (m, 1H), 2.50-2.45 (m, 2H), 2.45-2.36 (m, 2H), 1.83 (s, 3H), 1.18 (d, $J=6.9$ Hz, 3H).

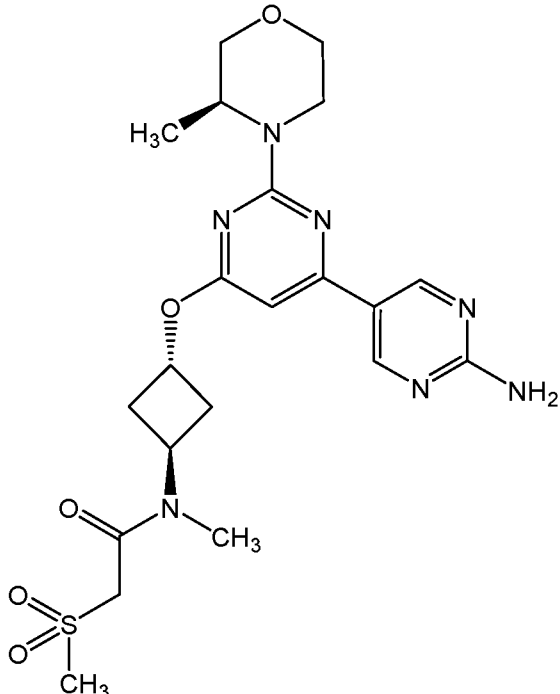
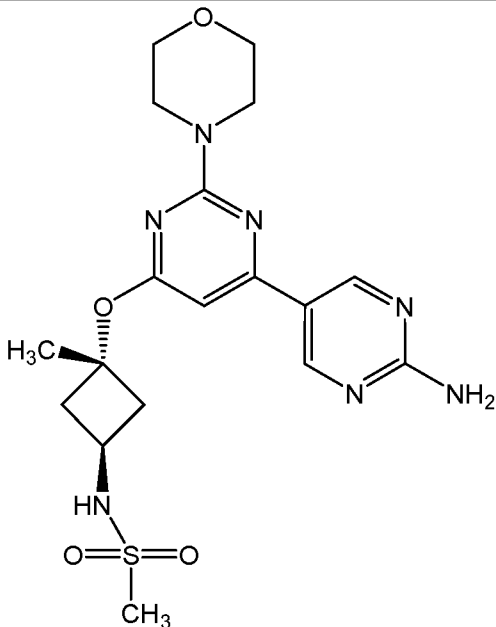
Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
141	 6-[[<i>trans</i>-3-(1,1-dioxido-1,2-thiazolidin-2-yl)cyclobutyl]oxy}-2-(morpholin-4-yl)-4,5'-bipyrimidin-2'-amine	448.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.92 (s, 2H), 7.14 (s, 2H), 6.60 (s, 1H), 5.26-5.24 (m, 1H), 3.90-3.71 (m, 1H), 3.70-3.66 (m, 8H), 3.26-3.21 (m, 4H), 2.72-2.70 (m, 2H), 2.35-2.33 (m, 2H), 2.24-2.20 (m, 2H).
142	 1-[<i>trans</i>-3-({2'-amino-5-fluoro-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-1,3-dimethylurea	447.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.83 (s, 2H), 7.23 (s, 2H), 6.27 (d, <i>J</i> =4.4 Hz, 1H), 5.27-5.20 (br s, 1H), 4.92 (t, <i>J</i> =8.4 Hz, 1H), 4.50 (d, <i>J</i> =4.4 Hz, 1H), 4.18 (d, <i>J</i> =12.8 Hz, 1H), 3.92 (d, <i>J</i> =8.4 Hz, 1H), 3.72 (d, <i>J</i> =11.6 Hz, 1H), 3.60-3.55 (m, 1H), 3.46-3.43 (m, 1H), 3.10 (t, <i>J</i> =12.0 Hz, 1H), 2.79 (s, 3H), 2.63-2.62 (m, 2H), 2.60-2.56 (m, 3H), 2.40-2.30 (m, 2H), 1.18 (d, <i>J</i> =6.4 Hz, 3H).

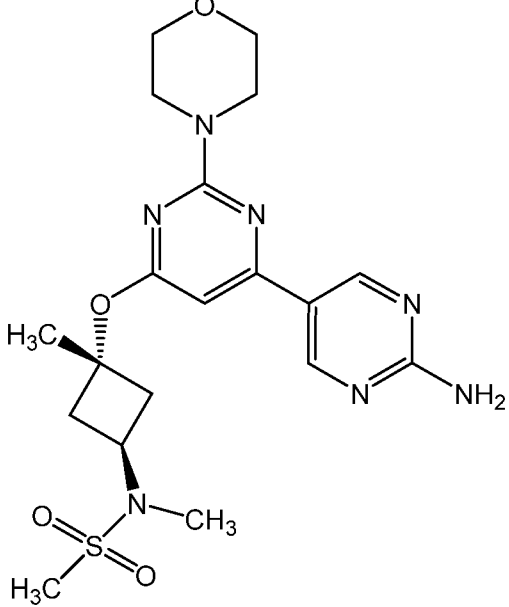
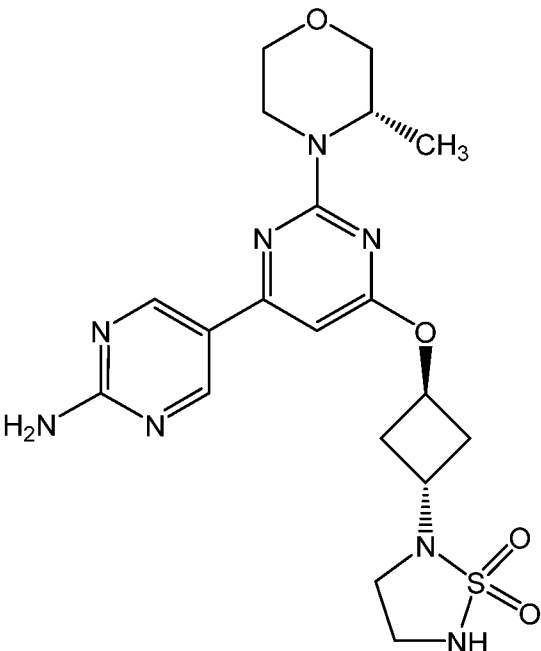
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
143	 1-[<i>trans</i>-3-({2'-amino-5-fluoro-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-1-methyl-3-[2-(pyrrolidin-1-yl)ethyl]urea	530.4	1H NMR (400 MHz, DMSO- d_6) δ 8.81 (s, 2H), 7.23 (s, 2H), 6.35 (t, $J=5.4$ Hz, 1H), 5.22 (t, $J=7.0$ Hz, 1H), 4.91-4.85 (m, 1H), 4.50-4.48 (m, 1H), 4.18-4.14 (m, 1H), 3.90-3.89 (m, 1H), 3.72-3.69 (m, 1H), 3.59-3.57 (m, 1H), 3.16-3.12 (m, 4H), 2.78 (s, 3H), 2.63-2.55 (m, 8H), 2.36-2.34 (m, 2H), 1.71-1.69 (m, 4H), 1.17 (d, $J=6.8$ Hz, 3H).
144	 <i>N</i>-[<i>trans</i>-3-({2'-amino-5-fluoro-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-<i>N</i>-methylmethanesulfonamide	468.1	1H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 2H), 5.35 (s, 2H), 5.26 (t, $J=6.8$ Hz, 1H), 4.58-4.54 (m, 2H), 4.21-4.18 (m, 1H), 3.99-3.96 (m, 1H), 3.79-3.76 (m, 1H), 3.71-3.70 (m, 1H), 3.60-3.54 (m, 1H), 3.26-3.24 (m, 1H), 2.87 (s, 3H), 2.78 (s, 3H), 2.74-2.71 (m, 2H), 2.60-2.57 (m, 2H), 1.26 (d, $J=6.8$ Hz, 3H).

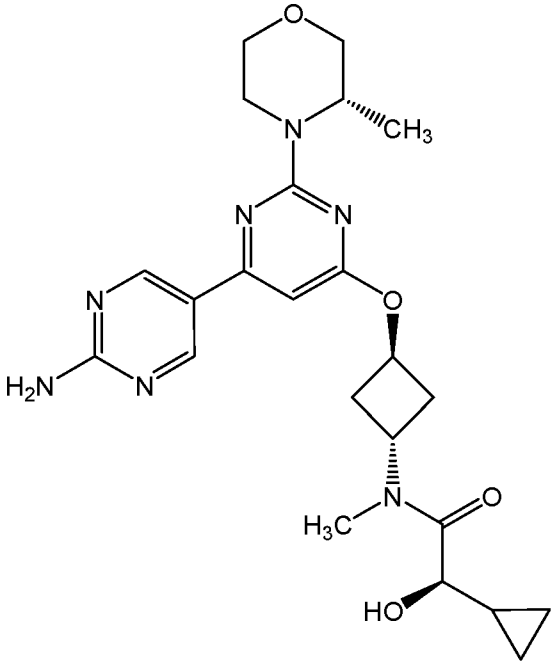
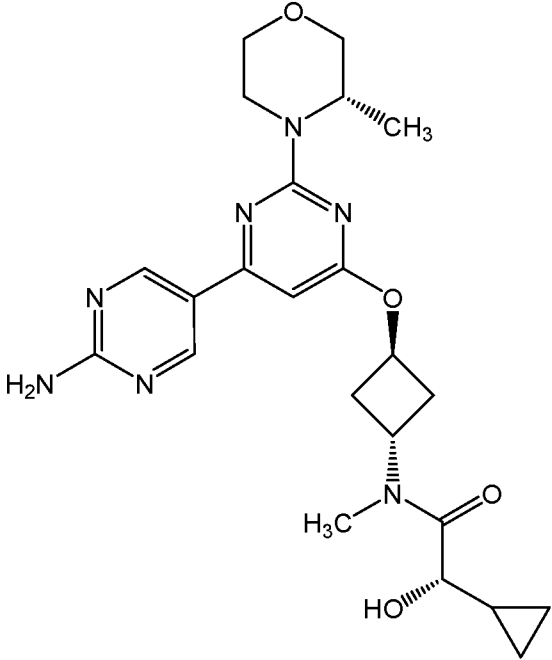
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
145	 6-([<i>trans</i>-3-(1,1-dioxido-1,2,5-thiadiazolidin-2-yl)cyclobutyl]oxy)-2-(morpholin-4-yl)-4,5'-bipyrimidin-2'-amine	449.1	1H NMR (400 MHz, DMSO- d_6) δ 8.91 (s, 2H), 7.12 (s, 2H), 6.58 (s, 1H), 5.29-5.24 (m, 1H), 4.03-3.95 (m, 1H), 3.72-3.66 (m, 10H), 2.46-2.42 (m, 2H), 2.17 (s, 4H).
146	 methyl [<i>trans</i>-3-({2'-amino-5-fluoro-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]methylcarbamate	448.1	1H NMR (400 MHz, CDCl $_3$) δ 8.92 (s, 2H), 5.27 (s, 2H), 5.25-5.20 (m, 1H), 4.85-4.75 (m, 1H), 4.55-4.45 (m, 1H), 4.16-4.12 (m, 1H), 3.93-3.89 (m, 1H), 3.71 (d, J=11.2 Hz, 1H), 3.67-3.60 (m, 4H), 3.48-3.45 (m, 1H), 3.18-3.15 (m, 1H), 2.86 (s, 3H), 2.65-2.55 (m, 2H), 2.52-2.45 (m, 2H), 1.19 (d, J=6.8 Hz, 3H).

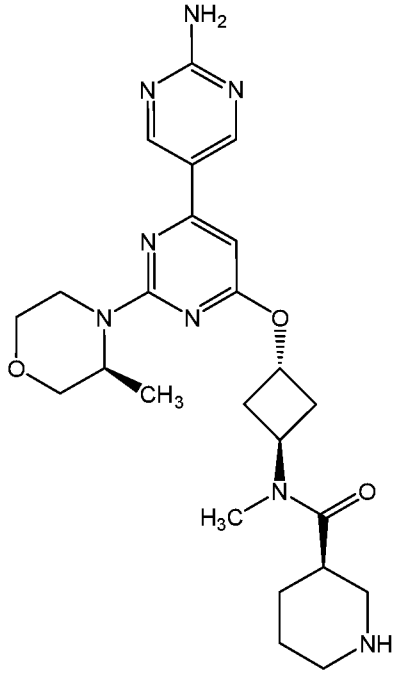
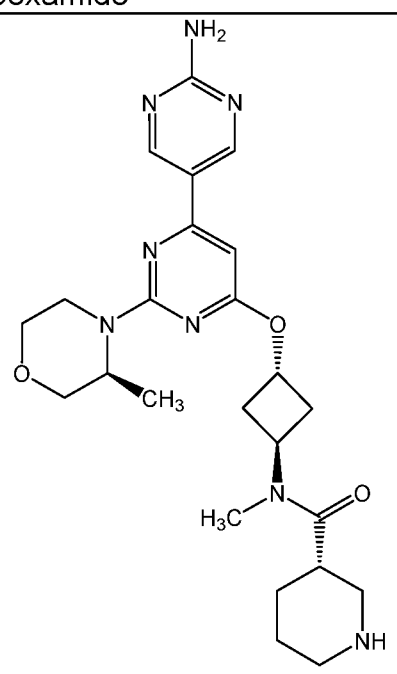
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
147	 <i>N</i>-[<i>trans</i>-3-({2'-amino-5-fluoro-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-<i>N</i>-methylpiperazine-1-carboxamide	524.2 $[M+23]^+$	1H NMR (400 MHz, CD_3OD) δ 9.21 (d, $J=2.8$ Hz, 2H), 5.43-5.35 (s, 1H), 4.69-4.60 (s, 1H), 4.59-4.45 (s, 1H), 4.30 (d, $J=13.2$ Hz, 1H), 3.99 (d, $J=10.8$ Hz, 1H), 3.80 (d, $J=11.6$ Hz, 1H), 3.70 (d, $J=11.6$ Hz, 1H), 3.60-3.47 (m, 5H), 3.35-3.25 (m, 5H), 2.93 (s, 3H), 3.80-3.70 (s, 3H), 3.27-3.26 (s, 2H), 1.29 (d, $J=3.6$ Hz, 3H).
148	 (2<i>R</i>)-<i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-2-hydroxy-<i>N</i>,3-dimethylbutanamide	472.3	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.92 (s, 2H), 6.32 (d, $J=8.0$ Hz, 1H), 5.41 (s, 2H), 5.30-5.26 (m, 1H), 5.11-5.07 (m, 1H), 4.71-4.70 (m, 1H), 4.39-4.26 (m, 2H), 4.02-3.99 (m, 1H), 3.82-3.71 (m, 2H), 3.57 (t, $J=12.0$ Hz, 1H), 3.28 (t, $J=12.0$ Hz, 1H), 3.06-3.00 (m, 3H), 3.74-3.55 (m, 4H), 1.80-1.73 (m, 1H), 1.32-1.26 (m, 4H), 1.08 (d, $J=8.0$ Hz, 3H), 0.82-0.79 (m, 3H).

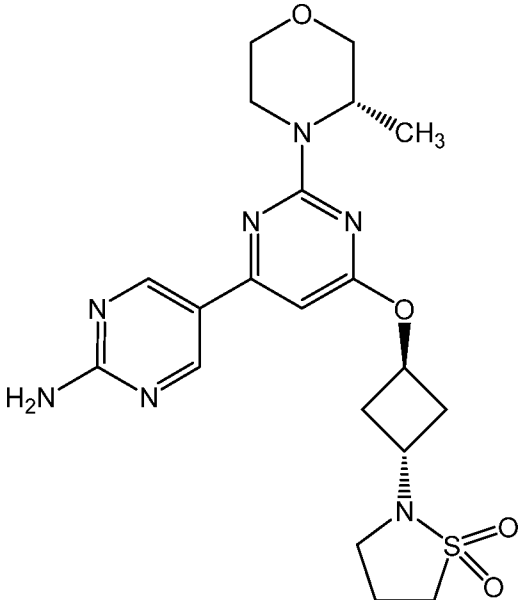
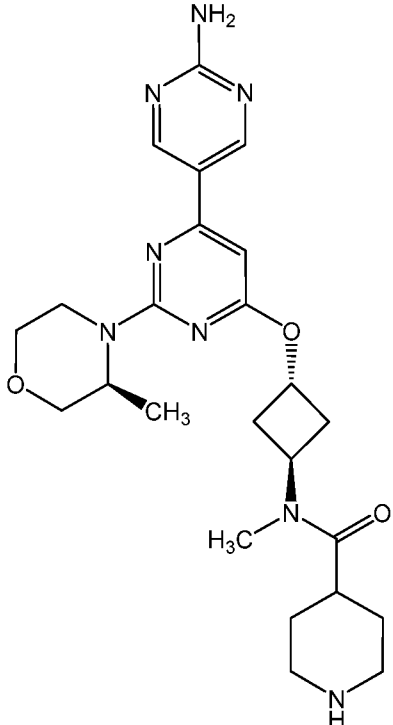
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
149	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-<i>N</i>-methylmorpholine-4-carboxamide	485.3	1H NMR (400 MHz, DMSO- d_6) δ 8.92 (s, 2H), 7.12 (s, 2H), 6.60 (s, 1H), 5.21-5.17 (m, 1H), 4.63-4.59 (m, 1H), 4.34-4.30 (m, 2H), 3.93-3.90 (m, 1H), 3.73-3.70 (m, 1H), 3.60-3.55 (m, 5H), 3.46-3.39 (m, 1H), 3.13-3.10 (m, 5H), 2.75 (s, 3H), 2.60-2.56 (m, 2H), 2.34-2.30 (m, 2H), 1.18 (d, $J=8.0$ Hz, 3H).
150	 (2<i>S</i>)-<i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-2-hydroxy-<i>N</i>-methyl-2-phenylethanamide	528.1 $[M+23]^+$	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.89 (s, 2H), 7.38-7.28 (m, 5H), 6.27 (d, $J=8.0$ Hz, 1H), 5.39 (s, 2H), 5.28-5.11 (m, 3H), 4.64-4.59 (m, 1H), 4.33 (t, $J=12.0$ Hz, 1H), 4.00-3.97 (m, 1H), 3.79-3.70 (m, 2H), 3.54 (t, $J=12.0$ Hz, 1H), 3.26-3.23 (m, 1H), 3.07 (s, 2H), 2.77 (s, 1H), 2.67-2.52 (m, 3H), 2.19-2.15 (m, 1H), 2.55-1.39 (m, 1H), 1.28 (d, $J=8.0$ Hz, 3H).

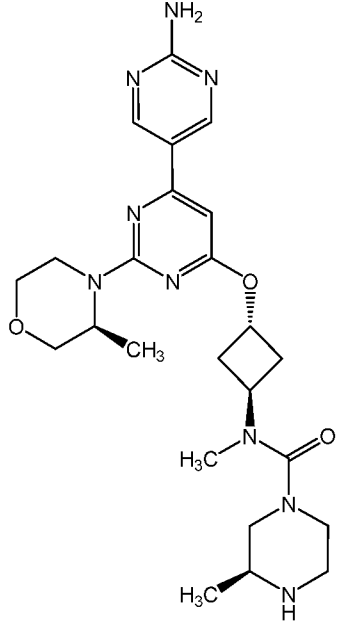
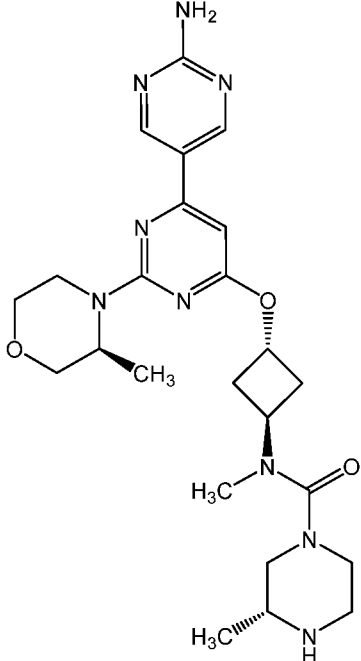
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
151	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-<i>N</i>-methyl-2-(methylsulfonyl)acetamide	492.1	1H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, $J=8.0$ Hz, 2H), 6.32 (d, $J=16.0$ Hz, 1H), 5.33-5.17 (m, 4H), 4.91-4.87 (m, 1H), 4.71-4.67 (m, 1H), 4.38-4.36 (m, 1H), 4.11 (d, $J=12.0$ Hz, 2H), 4.01-3.98 (m, 1H), 3.81-3.73 (m, 2H), 3.59-3.53 (m, 1H), 3.31-3.23 (m, 1H), 3.17 (s, 1H), 3.16-3.14 (m, 3H), 3.07 (s, 1H), 2.71-2.58 (m, 4H), 1.31-1.26 (m, 3H).
152	 <i>N</i>-(<i>trans</i>-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]-3-methylcyclobutyl)methanesulfonamide	436.1	1H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 2H), 6.25 (s, 1H), 5.87 (s, 2H), 5.63-5.49 (m, 1H), 3.78 (br s, 9H), 2.96 (s, 3H), 2.88 (t, $J=9.7$ Hz, 2H), 2.41 (t, $J=10.3$ Hz, 2H), 1.67 (s, 3H).

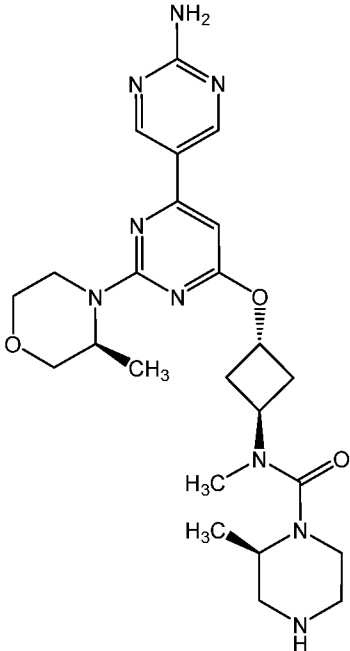
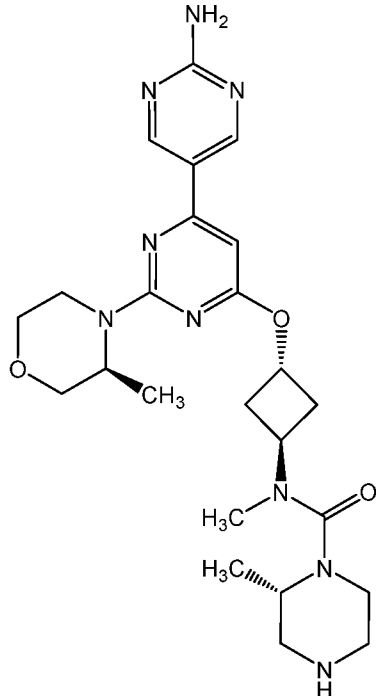
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	^1H NMR
153	 <i>N</i>-(<i>trans</i>-3-({[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}-3-methylcyclobutyl)-<i>N</i>-methylmethanesulfonamide	450.2	^1H NMR (600 MHz, DMSO- d_6) δ 8.84 (s, 2H), 6.43 (d, $J=1.5$ Hz, 1H), 3.70-3.60 (m, 9H), 2.79 (s, 3H), 2.65 (s, 3H), 2.58-2.52 (m, 2H), 2.48-2.42 (m, 2H), 1.59 (s, 3H).
154	 6-([<i>trans</i>-3-(1,1-dioxido-1,2,5-thiadiazolidin-2-yl)cyclobutyl]oxy)-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-2'-amine	463.1	^1H NMR (400 MHz, DMSO- d_6) δ ppm 8.90 (s, 2H), 8.05-7.95 (m, 1H), 7.11 (s, 2H), 6.60 (s, 1H), 5.30-5.20 (m, 1H), 4.65-4.55 (m, 1H), 4.32-4.29 (m, 1H), 4.10-4.03 (m, 1H), 3.95-3.91 (m, 1H), 3.75-3.55 (m, 2H), 3.46-3.44 (m, 2H), 3.34-3.15 (m, 4H), 2.20-2.17 (m, 4H), 1.20-1.18 (m, 3H).

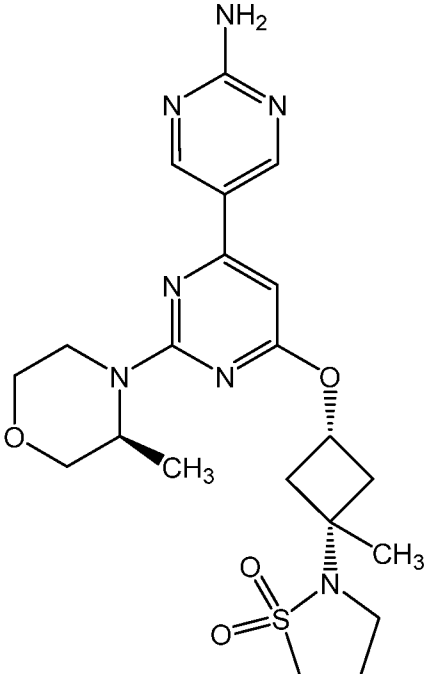
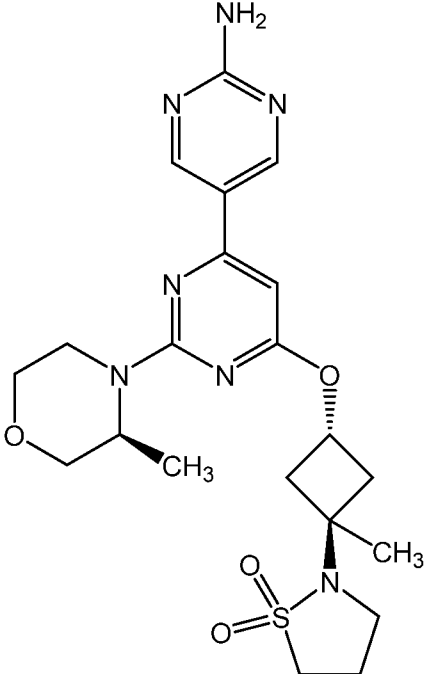
Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
155	 (2R)-N-[trans-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-2-cyclopropyl-2-hydroxy-N-methylethanamide	470.2	¹ H NMR (400 MHz, CDCl ₃) δ ppm 8.91 (s, 2H), 6.33 (s, 1H), 5.33 (s, 2H), 5.29-4.85 (m, 2H), 4.75-4.68 (m, 1H), 4.39-4.36 (m, 2H), 4.01-3.99 (m, 1H), 3.81-3.70 (m, 2H), 3.63-3.53 (m, 2H), 3.31-3.25 (m, 1H), 3.07 (s, 3H), 2.75-2.65 (m, 2H), 2.51 (m, 2H), 1.30 (d, J=4.8 Hz, 3H), 1.04-0.94 (m, 1H), 0.56-0.47 (m, 4H).
156	 (2S)-N-[trans-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-2-cyclopropyl-2-hydroxy-N-methylethanamide	470.2	¹ H NMR (400 MHz, CDCl ₃) δ ppm 8.91 (s, 2H), 6.33-6.31 (m, 1H), 5.33-5.30 (m, 3H), 5.29-4.85 (m, 2H), 4.73-4.67 (m, 1H), 4.39-4.36 (m, 2H), 3.99-3.81 (m, 1H), 3.78-3.70 (m, 2H), 3.57-3.53 (m, 1H), 3.28-3.25 (m, 1H), 3.08 (s, 3H), 2.74-2.66 (m, 2H), 2.57-2.54 (m, 2H), 1.29 (t, J=12.6 Hz, 3H), 1.04-0.94 (m, 1H), 0.58-0.43 (m, 4H).

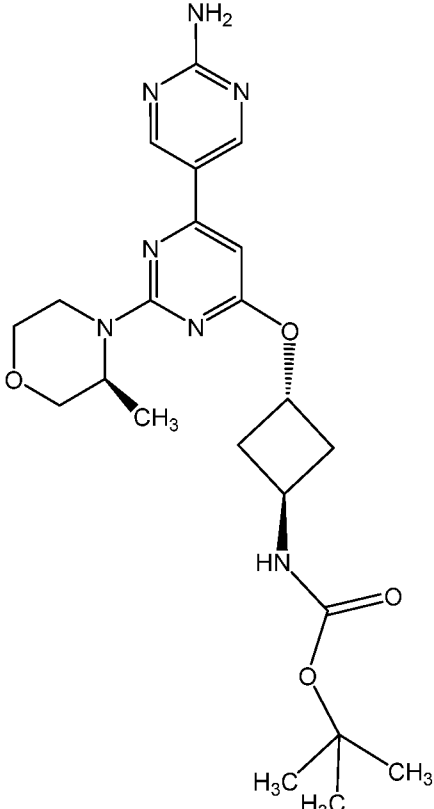
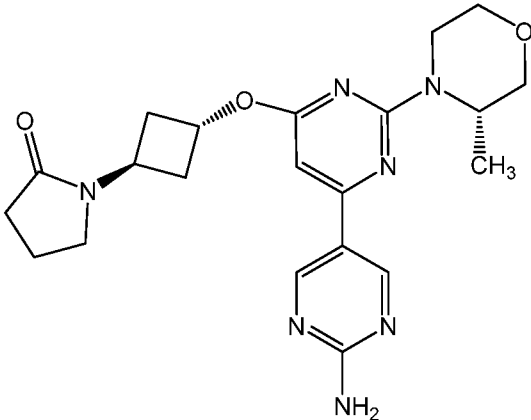
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
157	 (3R)-N-[<i>trans</i>-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-N-methylpiperidine-3-carboxamide	483.1	1H NMR (400 MHz, D_2O) δ ppm 8.85 (d, $J=9.6$ Hz, 2H), 6.47 (d, $J=11.6$ Hz, 1H), 5.29-5.28 (m, 1H), 5.02-5.00 (m, 2H), 4.68-4.65 (m, 1H), 4.20-4.16 (m, 1H), 4.06-4.04 (m, 1H), 3.87-3.73 (m, 2H), 3.61-3.60 (m, 1H), 3.44-3.29 (m, 1H), 3.26-3.14 (m, 4H), 3.10-2.97 (m, 3H), 2.54-2.20 (m, 4H), 1.92-1.70 (m, 4H), 1.31 (d, $J=6.8$ Hz, 3H).
158	 (3S)-N-[<i>trans</i>-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-N-methylpiperidine-3-carboxamide	483.1	1H NMR (400 MHz, D_2O) δ ppm 8.89 (d, $J=8.0$ Hz, 2H), 6.44 (d, $J=9.2$ Hz, 1H), 5.26-5.24 (m, 1H), 4.95-4.70 (m, 1H), 4.64-4.60 (m, 2H), 4.14-4.11 (m, 1H), 4.00-3.98 (m, 1H), 3.81-3.71 (m, 2H), 3.56-3.52 (m, 1H), 3.40-3.38 (m, 1H), 3.23-3.14 (m, 4H), 3.04-2.91 (m, 3H), 2.69-2.67 (m, 1H), 2.65-2.47 (m, 3H), 1.93-1.64 (m, 4H), 1.26 (d, $J=6.8$ Hz, 3H).

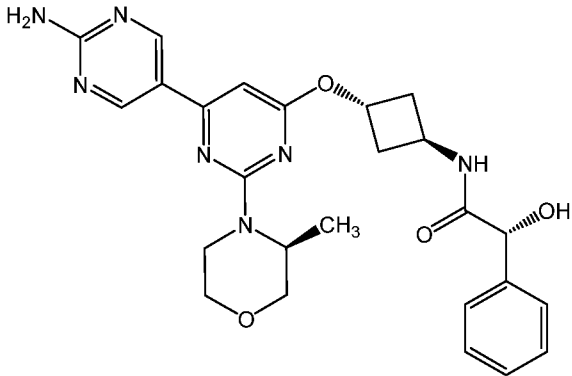
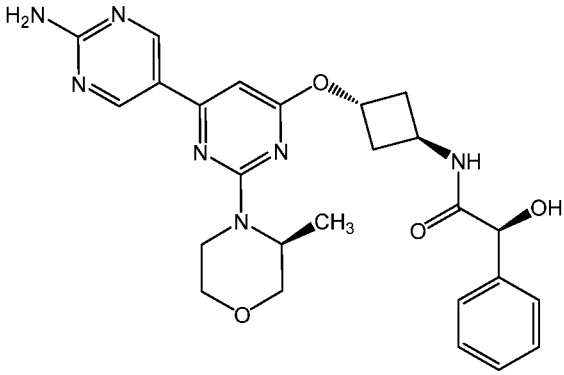
Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
159	 6-[[<i>trans</i>-3-(1,1-dioxido-1,2-thiazolidin-2-yl)cyclobutyl]oxy}-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-2'-amine	462.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.90 (s, 2H), 7.09 (s, 2H), 6.58 (s, 1H), 5.30-5.20 (m, 1H), 4.65-4.55 (m, 1H), 4.31-4.29 (m, 1H), 3.92-3.90 (m, 2H), 3.75-3.70 (m, 1H), 3.59-3.57 (m, 1H), 3.45-3.40 (m, 1H), 3.25-3.24 (m, 4H), 3.22-3.21 (m, 1H), 2.73-2.72 (m, 2H), 2.35-2.32 (m, 2H), 2.24-2.21 (m, 2H), 1.20-1.18 (m, 3H).
160	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-<i>N</i>-methylpiperidine-4-carboxamide	483.3	¹ H NMR (400 MHz, D ₂ O) δ ppm 8.85 (d, <i>J</i> =7.2 Hz, 2H), 6.47 (d, <i>J</i> =7.2 Hz, 1H), 5.31-5.28 (m, 1H), 4.99-4.95 (m, 1H), 4.68-4.64 (m, 1H), 4.14-4.04 (m, 1H), 4.04-4.01 (m, 1H), 3.85-3.73 (m, 2H), 3.60-3.57 (m, 1H), 3.47-3.44 (m, 3H), 3.09-2.69 (m, 7H), 2.67-2.52 (m, 3H), 1.97-1.77 (m, 4H), 1.30 (d, <i>J</i> =6.8 Hz, 3H).

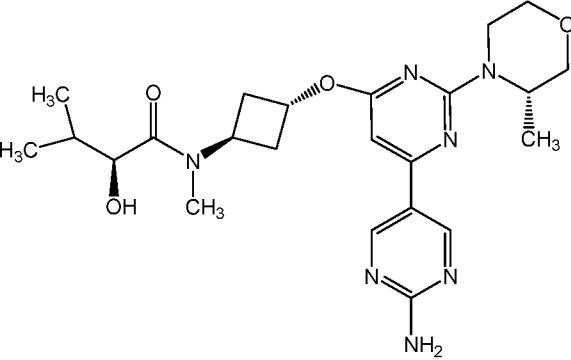
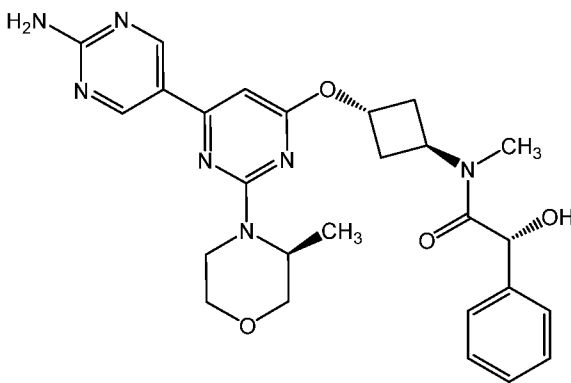
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
161	 (3S)-N-[<i>trans</i>-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-N,3-dimethylpiperazine-1-carboxamide	520.2 $[M+23]^+$	1H NMR (400 MHz, D_2O) δ ppm 8.85 (s, 2H), 6.51 (s, 1H), 5.35-5.25 (m, 1H), 4.70-4.62 (m, 1H), 4.45-4.35 (m, 1H), 4.25-4.03 (m, 2H), 3.90-3.71 (m, 4H), 3.67-3.42 (m, 4H), 3.30-3.01 (m, 3H), 2.84 (s, 3H), 2.72-2.65 (m, 2H), 2.60-2.45 (m, 2H), 1.32-1.29 (m, 6H).
162	 (3R)-N-[<i>trans</i>-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-N,3-dimethylpiperazine-1-carboxamide	520.1 $[M+23]^+$	1H NMR (400 MHz, D_2O) δ ppm 8.87 (s, 2H), 6.49 (s, 1H), 5.29-5.26 (m, 1H), 4.70-4.64 (m, 1H), 4.40-4.39 (m, 1H), 4.18-4.17 (m, 1H), 4.05-4.02 (m, 1H), 3.87-3.74 (m, 4H), 3.64-3.62 (m, 1H), 3.46-3.41 (m, 3H), 3.26-3.14 (m, 2H), 3.05-3.00 (m, 1H), 2.87 (s, 3H), 2.69-2.66 (m, 2H), 2.54-2.52 (m, 2H), 1.33 (d, $J=6.8$ Hz, 6H).

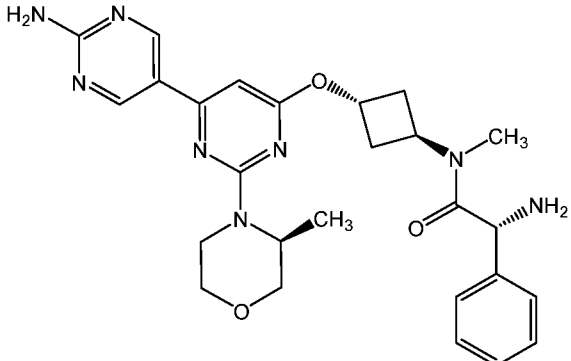
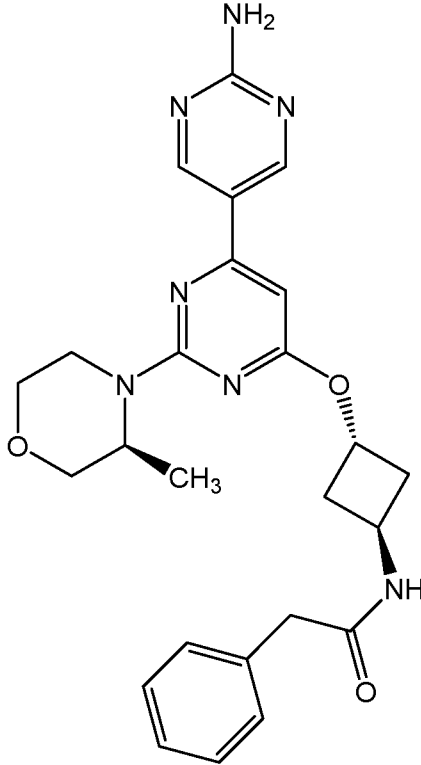
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
163	 (2R)-N-[trans-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-N,2-dimethylpiperazine-1-carboxamide	498.1	1H NMR (400 MHz, D_2O) δ ppm 8.83 (s, 2H), 6.50 (s, 1H), 5.29 (brs, 1H), 4.38 (t, $J=8.2$ Hz, 1H), 4.18-4.01 (m, 3H), 3.85-3.81 (m, 1H), 3.76-3.73 (m, 1H), 3.62-3.21 (m, 8H), 3.13-3.07 (m, 1H), 2.85 (s, 3H), 2.69-2.59 (m, 2H), 2.54-2.46 (m, 2H), 1.31-1.28 (m, 6H).
164	 (2S)-N-[trans-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-N,2-dimethylpiperazine-1-carboxamide	520.1 $[M+23]^+$	1H NMR (400 MHz, D_2O) δ ppm 8.84 (s, 2H), 6.50 (s, 1H), 5.29 (brs, 1H), 4.39 (t, $J=7.5$ Hz, 1H), 4.18-4.01 (m, 3H), 3.85-3.82 (m, 1H), 3.76-3.72 (m, 1H), 3.63-3.21 (m, 8H), 3.14-3.08 (m, 1H), 2.86 (s, 3H), 2.71-2.58 (m, 2H), 2.54-2.46 (m, 2H), 1.31-1.28 (m, 6H).

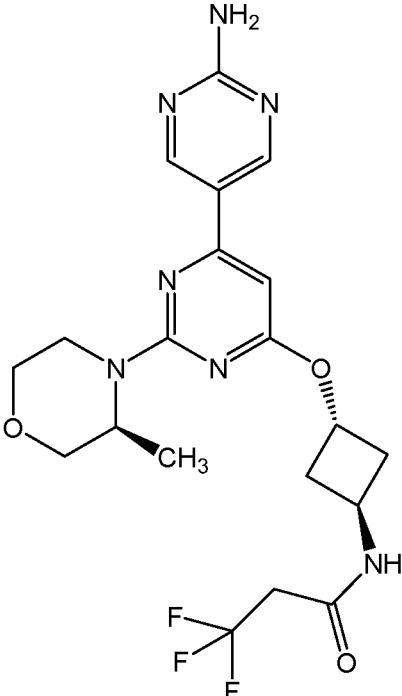
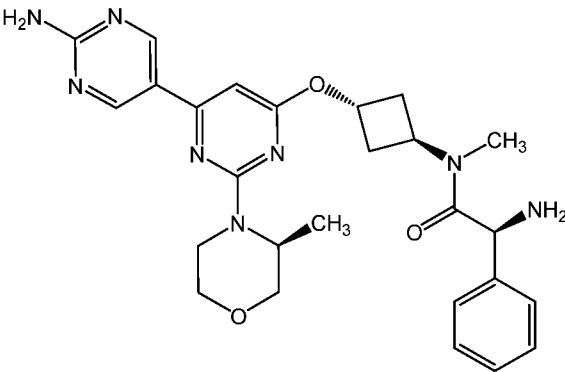
Example Number	Structure and Compound Name	LRMS <i>m/z</i> [M+H] ⁺	¹ H NMR
165	 6-[[<i>cis</i>-3-(1,1-dioxido-1,2-thiazolidin-2-yl)-3-methylcyclobutyl]oxy]-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-2'-amine	476.3	¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>) δ ppm 9.25-8.84 (m, 2H), 6.26 (s, 1H), 6.07 (br s, 2H), 5.08 (t, <i>J</i> =7.2 Hz, 1H), 4.69 (br s, 1H), 4.35 (d, <i>J</i> =13.1 Hz, 1H), 4.05-3.97 (m, 1H), 3.84-3.76 (m, 1H), 3.75-3.67 (m, 1H), 3.62-3.50 (m, 1H), 3.35-3.22 (m, 3H), 3.14 (t, <i>J</i> =7.6 Hz, 2H), 2.80-2.58 (m, 4H), 2.40-2.30 (m, 2H), 1.62-1.54 (m, 3H), 1.34-1.27 (m, 3H).
166	 6-[[<i>trans</i>-3-(1,1-dioxido-1,2-thiazolidin-2-yl)-3-methylcyclobutyl]oxy]-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-2'-amine	476.3	¹ H NMR (700 MHz, DMSO- <i>d</i> ₆) δ ppm 8.90 (s, 2H), 7.10 (s, 2H), 6.56 (s, 1H), 5.19 (t, <i>J</i> =6.5 Hz, 1H), 4.62 (br s, 1H), 4.31 (d, <i>J</i> =13.0 Hz, 1H), 3.96-3.83 (m, 1H), 3.72-3.66 (m, 1H), 3.58 (dd, <i>J</i> =11.1, 2.5 Hz, 1H), 3.47-3.39 (m, 1H), 3.30-3.18 (m, 4H), 3.18-2.97 (m, 3H), 2.23-2.16 (m, 2H), 2.08-1.99 (m, 2H), 1.48 (s, 3H), 1.19 (d, <i>J</i> =6.6 Hz, 3H).

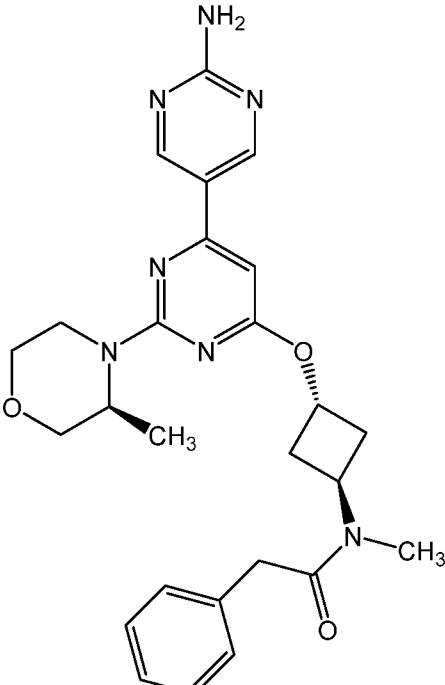
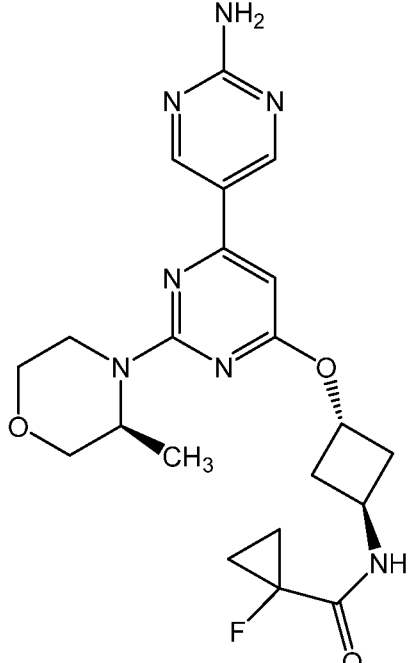
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
167	 <i>tert</i>-butyl [<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]carbamate	458.2	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.90 (s, 2H), 7.33-7.27 (m, 1H), 7.07 (s, 2H), 6.56 (s, 1H), 5.29-5.21 (m, 1H), 4.67-4.60 (m, 1H), 4.35-4.29 (m, 1H), 4.11-4.01 (m, 1H), 3.95-3.89 (m, 1H), 3.72 (d, $J=11.0$ Hz, 1H), 3.59 (dd, $J=3.1$, 11.2 Hz, 1H), 3.44 (dt, $J=3.2$, 11.7 Hz, 1H), 3.15 (dt, $J=3.9$, 13.0 Hz, 1H), 2.40-2.34 (m, 4H), 1.39 (s, 9H), 1.19 (d, $J=6.7$ Hz, 3H).
168	 1-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]pyrrolidin-2-one	426.1	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.89 (s, 2H), 6.29 (s, 1H), 5.46-5.22 (m, 3H), 4.98-4.88 (m, 1H), 4.73-4.65 (m, 1H), 4.37 (d, $J=16$ Hz, 1H), 4.03-3.95 (m, 1H), 3.82-3.67 (m, 2H), 3.61-3.48 (m, 3H), 3.31-3.21 (m, 1H), 2.72-2.61 (m, 2H), 2.58-2.39 (m, 4H), 2.13-2.02 (m, 2H), 1.29 (d, $J=6.8$ Hz, 3H).

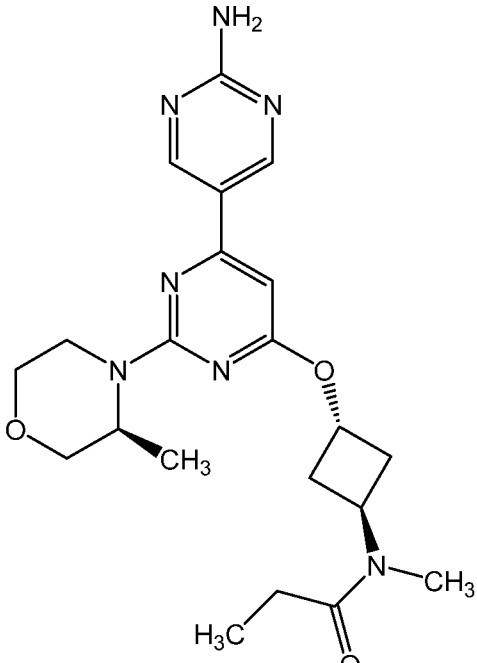
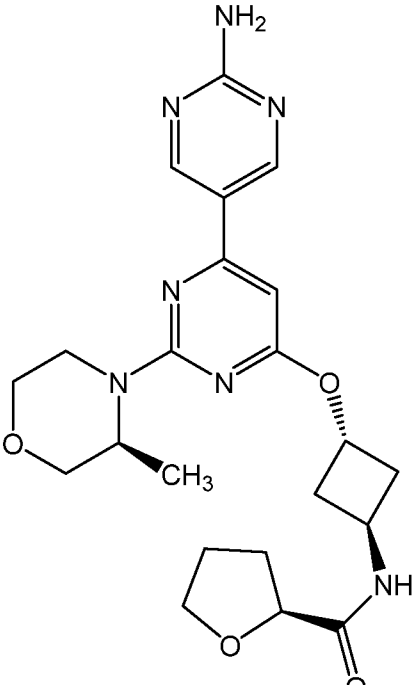
Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
169	 (2R)-N-[trans-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-2-hydroxy-2-phenylethanamide	492.0	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.91 (s, 2H), 8.45 (d, $J=7.6$ Hz, 1H), 7.44-7.42 (m, 2H), 7.35-7.27 (m, 3H), 7.12 (s, 2H), 6.58 (s, 1H), 6.18 (d, $J=4.8$ Hz, 1H), 5.25-5.35 (m, 1H), 4.91-4.90 (m, 1H), 4.65-4.62 (m, 1H), 4.36-4.232 (m, 2H), 3.94-3.91 (m, 1H), 3.74-3.71 (m, 1H), 3.61-3.59 (m, 1H), 3.46-3.41 (m, 3H), 3.20-3.09 (m, 1H), 2.41-2.36 (m, 2H), 1.18 (d, $J=6.8$, 3H).
170	 (2S)-N-[trans-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-2-hydroxy-2-phenylethanamide	492.0	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.91 (s, 2H), 8.46 (d, $J = 3.6$ Hz, 1H), 7.44-7.42 (m, 2H), 7.35-7.27 (m, 3H), 7.12 (s, 2H), 6.58 (s, 1H), 5.25-5.35 (m, 1H), 4.91 (s, 1H), 4.72-4.54 (m, 1H), 4.36-4.29 (m, 2H), 3.94-3.92 (m, 1H), 3.74-3.72 (m, 1H), 3.61-3.59 (m, 1H), 3.47-3.41 (m, 3H), 3.10-3.22 (m, 1H), 2.73-2.62 (m, 1H), 2.42-2.38 (m, 2H), 1.14 (d, $J=6.8$, 3H).

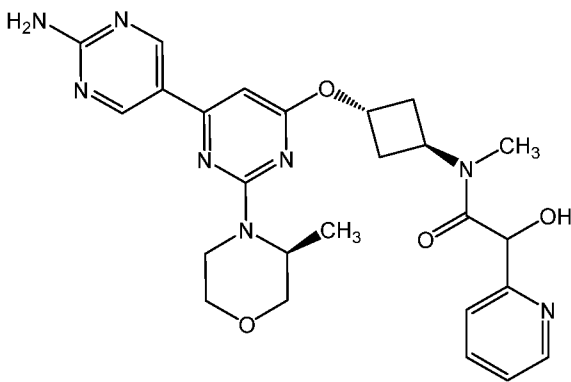
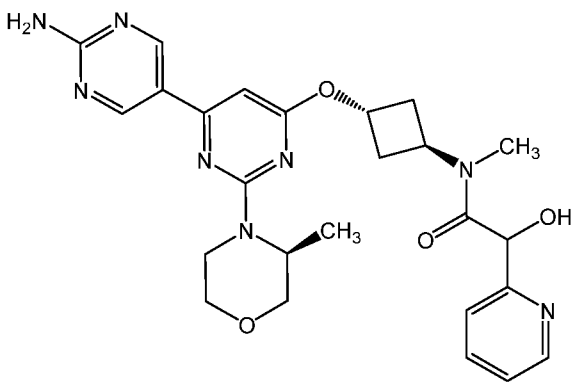
Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
171	 (2S)-N-[trans-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-2-hydroxy-N,3-dimethylbutanamide	472.2	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 8.93 (s, 2H), 7.12 (s, 2H), 6.62 (s, 1H), 5.25-5.23 (m, 1H), 5.05-4.93 (m, 1H), 4.65-4.52 (m, 2H), 4.33-4.30 (m, 1H), 4.07-4.05 (m, 1H), 3.94-3.91 (m, 1H), 3.74-3.71 (m, 1H), 3.60-3.58 (m, 1H), 3.44-3.41 (m, 1H), 3.18-3.15 (m, 1H), 3.02-2.92 (m, 3H), 2.75-2.65 (m, 2H), 2.45-2.40 (m, 1H), 1.85-1.78 (m, 2H), 1.20 (d, J=6.4 Hz, 3H), 0.88-0.84 (m, 3H), 0.79 (d, J=6.8 Hz, 3H).
172	 (2R)-N-[trans-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-2-hydroxy-N-methyl-2-phenylethanamide	506.3	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 8.92 (s, 2H), 7.35-7.25 (m, 5H), 7.12 (s, 2H), 6.61-6.57 (m, 1H), 5.55-5.36 (m, 2H), 5.20-5.09 (m, 2H), 4.85-4.81 (m, 1H), 4.60-4.56 (m, 1H), 4.31-4.27 (m, 1H), 3.92-3.90 (m, 1H), 3.72-3.70 (m, 1H), 3.59-3.56 (m, 1H), 3.43-3.39 (m, 1H), 3.15-3.11 (m, 1H), 2.92-2.86 (m, 3H), 2.72-2.63 (m, 1H), 2.24-2.20 (m, 1H), 1.71-1.67 (m, 1H), 1.16 (d, J=11.6 Hz, 3H).

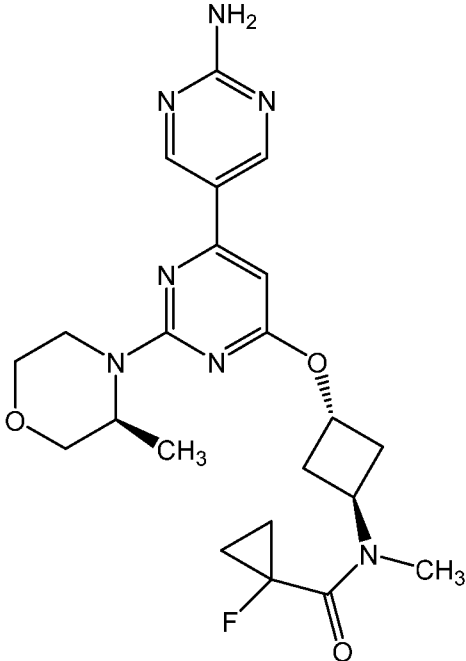
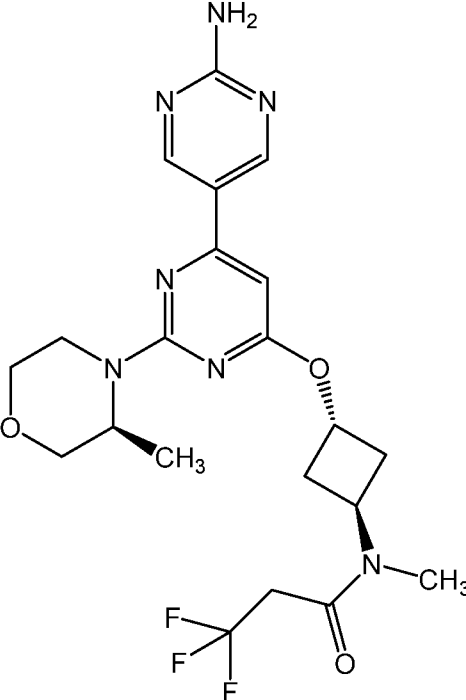
Example Number	Structure and Compound Name	LRMS <i>m/z</i> [M+H] ⁺	¹ H NMR
173	 (2<i>R</i>)-2-amino-<i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-<i>N</i>-methyl-2-phenylethanamide	505.3	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ ppm 9.22-9.21 (m, 2H), 7.53-7.47 (m, 5H), 6.67-6.63 (m, 1H), 5.63-5.46 (m, 1H), 5.35-5.16 (m, 2H), 4.71-4.67 (m, 1H), 4.41-4.38 (m, 1H), 4.01-3.98 (m, 1H), 3.82-3.70 (m, 2H), 3.56-3.53 (m, 1H), 3.28-3.25 (m, 1H), 3.08-2.89 (m, 3H), 2.86-2.23 (m, 4H), 1.35-1.23 (m, 3H).
174	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-2-phenylacetamide	476.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.90 (s, 2H), 8.55 (d, <i>J</i> =6.4 Hz, 1H), 7.32-7.19 (m, 5H), 7.08 (s, 2H), 6.56 (s, 1H), 5.33-5.23 (m, 1H), 4.60-4.53 (m, 1H), 4.32-4.19 (m, 2H), 3.93-3.90 (m, 1H), 3.74-3.70 (m, 1H), 3.60-3.58 (m, 1H), 3.18-3.09 (m, 4H), 2.44-2.31 (m, 4H), 1.23-1.18 (m, 3H).

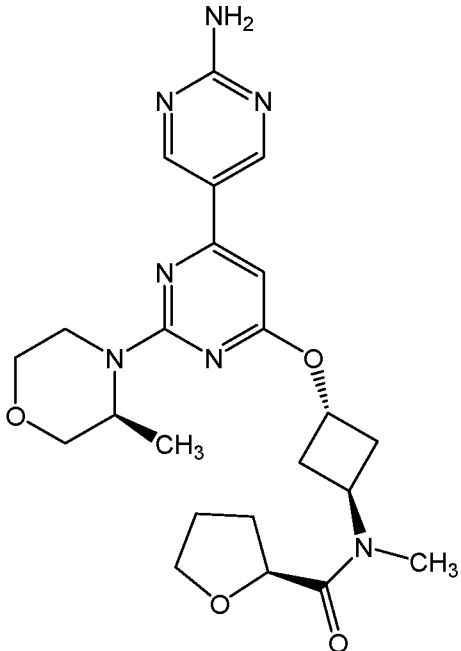
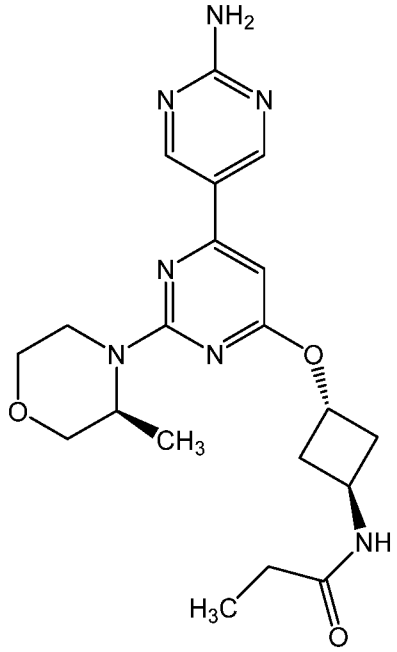
Example Number	Structure and Compound Name	LRMS <i>m/z</i> [M+H] ⁺	¹ H NMR
175	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-3,3,3-trifluoropropanamide	468.2	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ ppm 8.89 (s, 2H), 6.44 (s, 1H), 5.37-5.36 (m, 1H), 4.81-4.69 (m, 1H), 4.40 (d, <i>J</i> =13.2 Hz, 2H), 3.96-3.90 (m, 1H), 3.82-3.67 (m, 2H), 3.60-3.51 (m, 1H), 3.27-3.15 (m, 3H), 2.64-2.43 (m, 4H), 1.28 (d, <i>J</i> =6.8 Hz, 3H).
176	 (2<i>S</i>)-2-amino-<i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-<i>N</i>-methyl-2-phenylethanamide	527.2 [M+23] ⁺	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ ppm 9.2 (s, 2H), 7.53-7.50 (m, 5H), 6.66-6.62 (m, 1H), 5.61-5.45 (m, 1H), 5.33-5.12 (m, 2H), 4.71-4.69 (m, 1H), 4.40-4.34 (m, 1H), 4.01-3.97 (m, 1H), 3.81-3.78 (m, 1H), 3.71-3.69 (m, 1H), 3.55-3.53 (m, 1H), 3.08-2.88 (m, 3H), 2.76-2.48 (m, 4H), 2.28-2.26 (m, 1H), 1.31-1.29 (m, 3H).

Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
177	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-<i>N</i>-methyl-2-phenylacetamide	490.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.91 (s, 2H), 7.33-7.26 (m, 2H), 7.24-7.16 (m, 3H), 7.11 (s, 2H), 6.62-6.57 (m, 1H), 5.25-4.79 (m, 2H), 4.65-4.57 (m, 1H), 4.33-4.26 (m, 1H), 3.95-3.88 (m, 1H), 3.76-3.67 (m, 3H), 3.62-3.55 (m, 1H), 3.47-3.42 (m, 1H), 3.18-3.10 (m, 1H), 3.01-2.89 (m, 3H), 2.68-2.60 (m, 2H), 2.31-2.20 (m, 2H), 1.18 (d, <i>J</i> =6.4 Hz, 3H).
178	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-1-fluorocyclopropanecarboxamide	444.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.87 (s, 2H), 8.83 (d, <i>J</i> =7.6 Hz, 1H), 6.51 (s, 1H), 5.32-5.24 (m, 1H), 4.67-4.57 (m, 1H), 4.48-4.38 (m, 1H), 4.29-4.26 (m, 1H), 3.90-3.88 (m, 1H), 3.72-3.70 (m, 1H), 3.57-3.54 (m, 1H), 3.48-3.32 (m, 1H), 3.18-3.06 (m, 1H), 2.48-2.31 (m, 3H), 1.30-1.17 (m, 3H), 1.16 (d, <i>J</i> =6.4 Hz, 4H).

Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
179	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-<i>N</i>-methylpropanamide	428.2	1H NMR (400 MHz, Methanol- d_4) δ ppm 8.92 (s, 2H), 6.48 (s, 1H), 5.33-5.29 (m, 1H), 5.21-5.19 (m, 1H), 4.77-4.73 (m, 1H), 4.43-4.40 (m, 1H), 4.00-3.98 (m, 1H), 3.82-3.79 (m, 1H), 3.73-3.69 (m, 1H), 3.56-3.50 (m, 1H), 3.33-3.27 (m, 1H), 3.07-3.00 (m, 1H), 2.80-2.70 (m, 3H), 2.55-2.42 (m, 2H), 1.30 (d, $J=6.8$ Hz, 3H), 1.12 (t, $J=7.2$ Hz, 3H).
180	 (2<i>S</i>)-<i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]tetrahydrofuran-2-carboxamide	478.2 $[M+23]^+$	1H NMR (400 MHz, DMSO- d_6) δ ppm 8.91 (s, 2H), 8.21 (d, $J=8$ Hz, 1H), 7.12 (s, 2H), 6.58 (s, 1H), 5.30-5.23 (m, 1H), 4.62-4.55 (m, 1H), 4.42-4.30 (m, 1H), 4.20-4.16 (m, 2H), 3.98-3.87 (m, 1H), 3.80-3.70 (m, 2H), 3.65-3.57 (m, 2H), 3.50-3.37 (m, 1H), 3.20-3.07 (m, 2H), 2.40-3.37 (m, 1H), 2.20-2.05 (m, 2H), 1.85-1.78 (m, 1H), 1.19 (d, $J=6.8$ Hz, 3H).

Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
181*	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-2-hydroxy-<i>N</i>-methyl-2-(pyridin-2-yl)acetamide	507.1	1H NMR (400 MHz, Methanol- d_4) δ ppm 8.91-8.89 (m, 2H), 8.55-8.52 (m, 1H), 7.75-7.69 (m, 1H), 7.45-7.41 (m, 1H), 7.25-7.19 (m, 1H), 6.31-6.29 (m, 1H), 5.52-5.44 (m, 1H), 5.31-5.25 (m, 2H), 5.19-5.17 (m, 2H), 4.81-4.9 (m, 1H), 4.68-4.66 (m, 1H), 4.39-4.34 (m, 1H), 3.98-3.8 (m, 1H), 3.77-3.69 (m, 2H), 3.59-3.55 (m, 1H), 3.26-3.24 (m, 1H), 3.07-3.03 (m, 3H), 2.69-2.53 (m, 3H), 2.32-1.91 (m, 1H), 1.3-1.27 (m, 3H).
182*	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-2-hydroxy-<i>N</i>-methyl-2-(pyridin-2-yl)acetamide	529.1 $[M+23]^+$	1H NMR (400 MHz, Methanol- d_4) δ ppm 8.91-8.9 (m, 2H), 8.55-8.5 (m, 1H), 7.73-7.68 (m, 1H), 7.45-7.41 (m, 1H), 7.25-7.17 (m, 1H), 6.32-6.29 (m, 1H), 5.52-5.44 (m, 1H), 5.32-5.25 (m, 2H), 5.19-5.14 (m, 2H), 4.81-4.9 (m, 1H), 4.68-4.66 (m, 1H), 4.36-4.36 (m, 1H), 3.98-3.8 (m, 1H), 3.77-3.68 (m, 2H), 3.59-3.55 (m, 1H), 3.29-3.25 (m, 1H), 3.07-3.03 (m, 3H), 2.69-2.54 (m, 3H), 2.30-1.87 (m, 1H), 1.29-1.25 (m, 3H).

Example Number	Structure and Compound Name	LRMS m/z [M+H] ⁺	¹ H NMR
183	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-1-fluoro-<i>N</i>-methylcyclopropanecarboxamide	458.2	¹ H NMR (400 MHz, CDCl ₃) δ ppm 8.90 (s, 2H), 6.31 (s, 1H), 5.40-5.25 (m, 3H), 5.15-5.00 (m, 1H), 4.75-4.65 (m, 1H), 4.39-4.36 (m, 1H), 3.81-3.72 (m, 1H), 3.60-3.52 (m, 2H), 3.35-3.20 (m, 2H), 3.25-3.00 (m, 3H), 2.75-2.45 (m, 4H), 1.35-1.20 (m, 7H).
184	 <i>N</i>-[<i>trans</i>-3-({2'-amino-2-[(3<i>S</i>)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-3,3,3-trifluoro-<i>N</i>-methylpropanamide	482.2	¹ H NMR (400 MHz, CDCl ₃) δ ppm 8.90 (s, 2H), 6.31 (s, 1H), 5.43 (m, 2H), 5.27 (s, 1H), 5.25-4.40 (m, 2H), 4.36 (d, J=13.2 Hz, 1H), 4.00 (d, J=10.4 Hz, 1H), 3.83-3.70 (m, 2H), 3.56 (t, J=8.0 Hz, 1H), 3.35-3.17 (m, 3H), 3.04 (m, 3H), 2.80-2.50 (m, 4H), 1.30 (s, 3H).

Example Number	Structure and Compound Name	LRMS m/z $[M+H]^+$	1H NMR
185	 (2S)-N-[trans-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]-N-methyltetrahydrofuran-2-carboxamide	470.2	1H NMR (400 MHz, $CDCl_3$) δ ppm 8.90 (s, 2H), 6.31 (s, 1H), 5.40-5.22 (m, 3H), 5.15-5.00 (m, 1H), 4.70-4.55 (m, 2H), 4.37 (d, $J=12.8$ Hz, 1H), 4.02-3.65 (m, 5H), 3.60-3.50 (m, 1H), 3.30-3.20 (m, 1H), 3.09-2.99 (m, 3H), 2.75-2.45 (m, 4H), 2.25-1.85 (m, 4H), 1.29 (d, $J=6.8$ Hz, 3H).
186	 N-[trans-3-({2'-amino-2-[(3S)-3-methylmorpholin-4-yl]-4,5'-bipyrimidin-6-yl}oxy)cyclobutyl]propanamide	414.1	1H NMR (400 MHz, $DMSO-d_6$) δ ppm 8.92 (s, 2H), 8.20 (d, $J=6.8$ Hz, 1H), 7.13 (s, 2H), 6.59 (s, 1H), 5.31-5.24 (m, 1H), 4.66-4.58 (m, 1H), 4.34-4.25 (m, 2H), 3.95-3.85 (m, 1H), 3.74 (d, $J=11.2$ Hz, 1H), 3.63-3.59 (m, 1H), 3.49-3.39 (m, 1H), 3.18-3.09 (m, 1H), 2.43-2.30 (m, 4H), 2.09 (q, $J=7.6$ Hz, 2H), 1.20 (d, $J=6.8$ Hz, 3H), 1.00 (t, $J=7.6$ Hz, 3H).

*Compounds are single enantiomers; however, absolute stereochemistry is unknown.

**Compounds can exist as rotational isomers (rotamers)

The compounds provided in Table 2 were prepared via parallel synthesis, using the following general procedure that would be understood by one skilled in the art.

5 A solution of the product of Example 2, Step 2, 6-*[[trans-3-(methylamino)cyclobutyl]oxy]-2-(morpholin-4-yl)-4,5'-bipyrimidin-2'-amine* hydrochloride, (0.18 M) in anhydrous DMF was prepared. A solution of HATU (0.18 M) in anhydrous DMF was prepared. The carboxylic acid monomers (75 μ mol, 1.1 eq) were dispensed to 8 mL vials, followed by 383 μ L of the solution of the product of Example 2, Step 2 (69
10 μ mol, 1.0 eq). TEA (25.6 μ L, 177 μ mol, 2.6 eq) was dispensed to each vial, followed by 383 μ L of the HATU solution (69 μ mol, 1.0 eq). The vials were capped and shaken at 30 °C for 16 hours. The solvent was evaporated by Speedvac and the residues were purified by preparative HPLC to give the desired product.

15 Analytical HPLC methods:

PF-CD05: Column Xbridge C18 2.1 $\times$ 50mm 5 μ m; Temperature 40 °C; Mobile Phase A 0.05% NH₄OH in water; Mobile Phase B 100% MeCN; Gradient: 5% B to 100% B; Flow rate 0.8 mL / min; Agilent 1200 HPLC/1956 MSD/SEDEX 75 ELSD.

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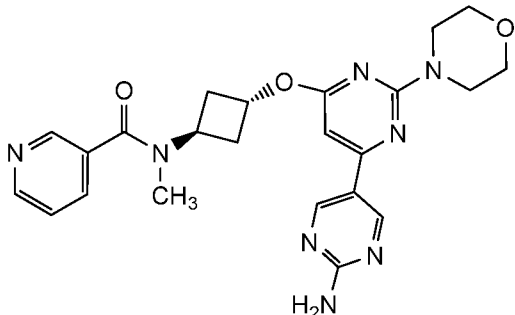
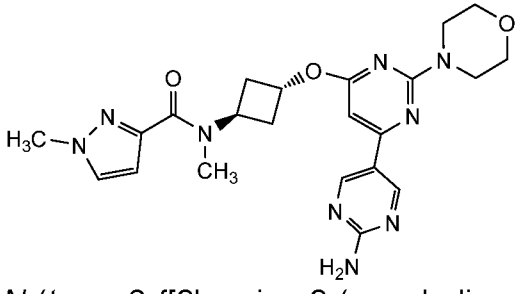
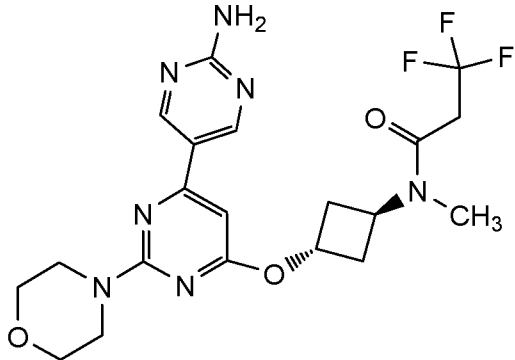
PF-AB01: Column Xbridge C18 2.1 $\times$ 50mm 5 μ m; Temperature 40 °C; Mobile Phase A 0.0375% TFA in water; Mobile Phase B 0.01875% TFA in MeCN; Gradient: 1% B to 100% B; Flow rate 0.8 mL / min; Agilent 1200 HPLC/1956 MSD/SEDEX 75 ELSD.

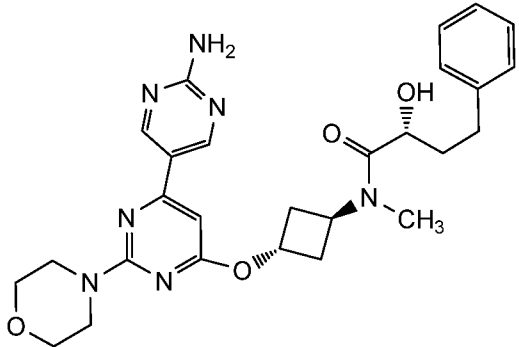
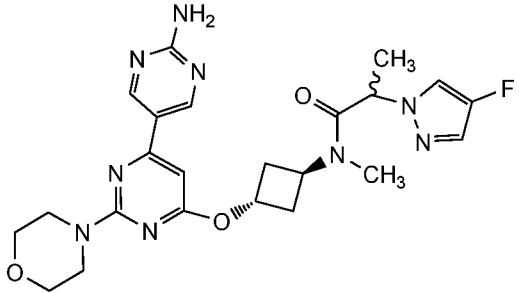
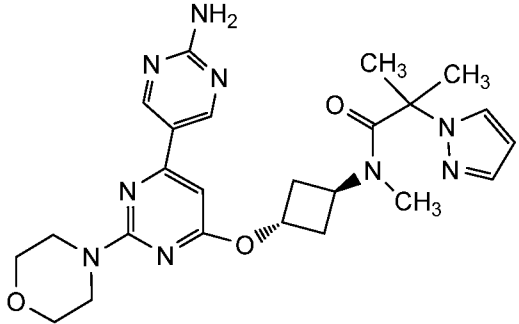
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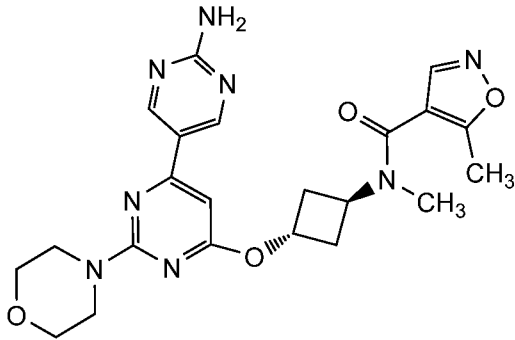
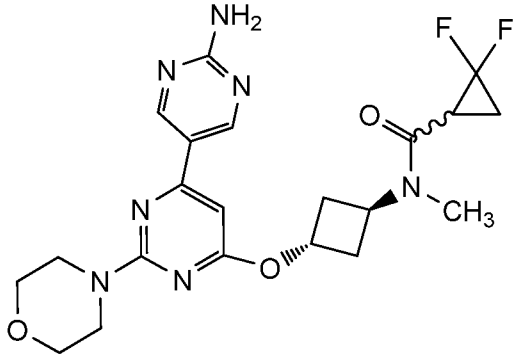
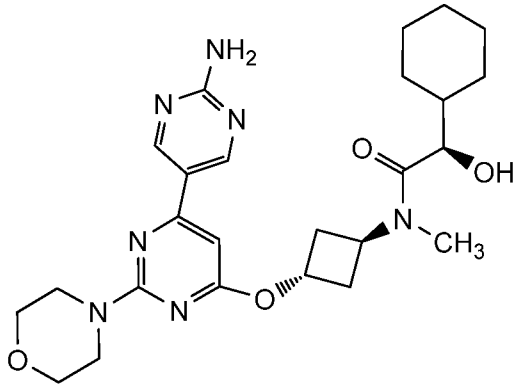
PF-AB10: Column Xbridge C18 2.1 $\times$ 50mm 5 μ m; Temperature 40 °C; Mobile Phase A 0.0375% TFA in water; Mobile Phase B 0.01875% TFA in MeCN; Gradient: 10% B to 100% B; Flow rate 0.8 mL / min; Agilent 1200 HPLC/1956 MSD/SEDEX 75 ELSD.

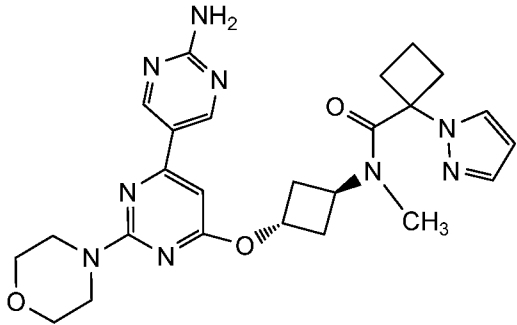
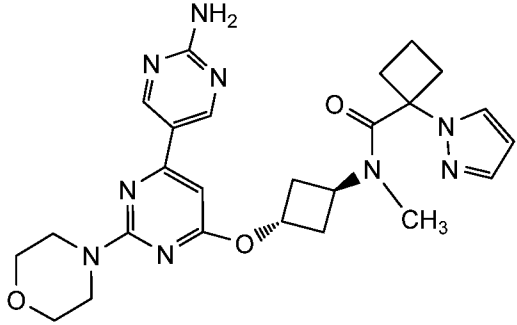
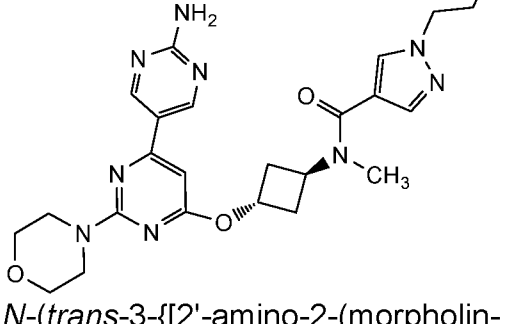
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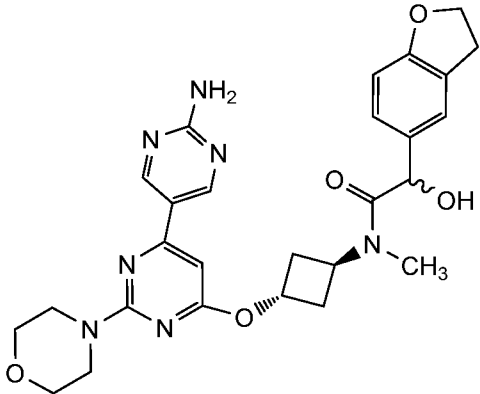
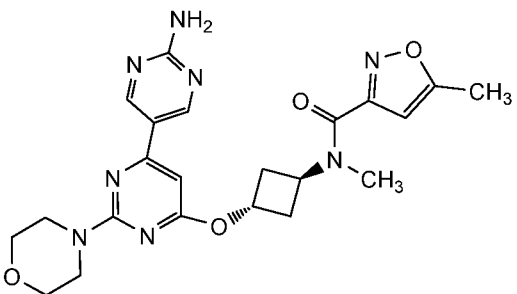
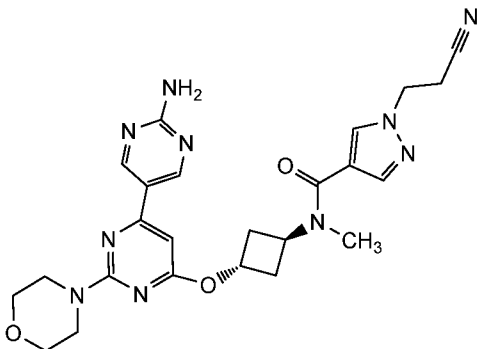
Table 2

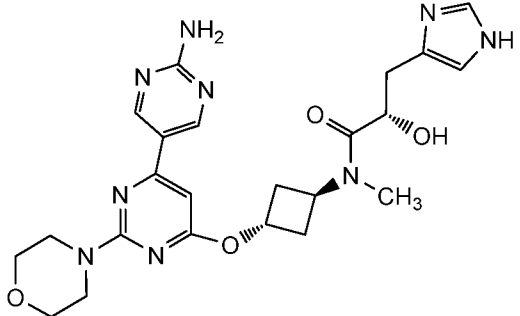
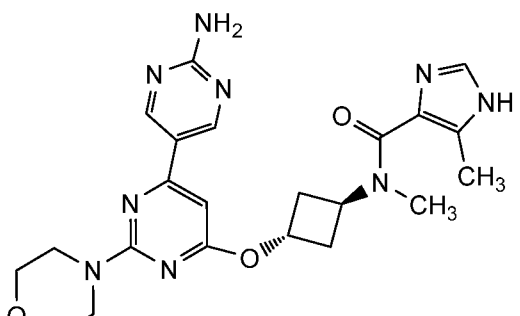
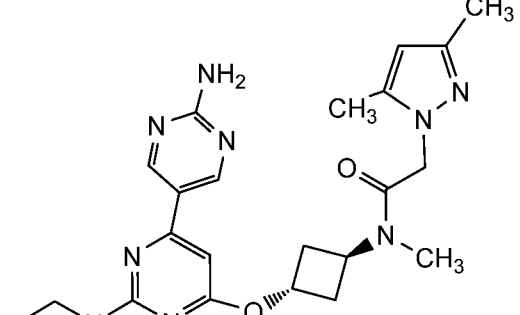
Example Number	Structure and Chemical Name	Observed MW	RT (min)	Method
187	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-<i>N</i>-methylpyridine-3-carboxamide	463	1.994	PF-AB01
188	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-<i>N</i>,1-dimethyl-1<i>H</i>-pyrazole-3-carboxamide	466	2.336	PF-CD05
189	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-3,3,3-trifluoro-<i>N</i>-methylpropanamide	468	2.747	PF-AB01

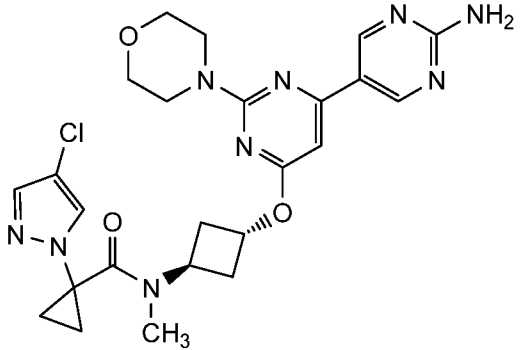
Example Number	Structure and Chemical Name	Observed MW	RT (min)	Method
190	 (2R)-N-(trans-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-2-hydroxy-N-methyl-4-phenylbutanamide	520	2.723	PF-AB10
191	 N-(trans-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-2-(4-fluoro-1H-pyrazol-1-yl)-N-methylpropanamide	498	2.731	PF-AB01
192	 N-(trans-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-N,2-dimethyl-2-(1H-pyrazol-1-yl)propanamide	494	2.709	PF-AB01

Example Number	Structure and Chemical Name	Observed MW	RT (min)	Method
193	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-<i>N</i>,5-dimethyl-1,2-oxazole-4-carboxamide	467	2.939	PF-AB01
194	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2,2-difluoro-<i>N</i>-methylcyclopropanecarboxamide	462	2.759	PF-AB01
195	 (2<i>R</i>)-<i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-cyclohexyl-2-hydroxy-<i>N</i>-methylethanamide	498	2.766	PF-AB10

Example Number	Structure and Chemical Name	Observed MW	RT (min)	Method
196	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-<i>N</i>-methyl-1-(1<i>H</i>-pyrazol-1-yl)cyclobutanecarboxamide	506	2.81	PF-AB01
197	 (2<i>S</i>)-<i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-<i>N</i>-methyl-2-phenylpropanamide	506	2.851	PF-AB01
198	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-1-(2-hydroxyethyl)-<i>N</i>-methyl-1<i>H</i>-pyrazole-4-carboxamide	496	2.383	PF-AB01

Example Number	Structure and Chemical Name	Observed MW	RT (min)	Method
199	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-(2,3-dihydro-1-benzofuran-5-yl)-2-hydroxy-<i>N</i>-methylacetamide	534	2.731	PF-AB01
200	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-<i>N</i>,5-dimethyl-1,2-oxazole-3-carboxamide	467	2.706	PF-AB01
201	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-1-(2-cyanoethyl)-<i>N</i>-methyl-1<i>H</i>-pyrazole-4-carboxamide	505	2.385	PF-CD05

Example Number	Structure and Chemical Name	Observed MW	RT (min)	Method
202	 (2S)-N-(trans-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-hydroxy-3-(1H-imidazol-4-yl)-N-methylpropanamide	496	2.772	PF-CD05
203	 N-(trans-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-N,5-dimethyl-1H-imidazole-4-carboxamide	466	2.239	PF-CD05
204	 N-(trans-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-2-(3,5-dimethyl-1H-pyrazol-1-yl)-N-methylacetamide	494	2.533	PF-AB01

Example Number	Structure and Chemical Name	Observed MW	RT (min)	Method
205	 <i>N</i>-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-1-(4-chloro-1<i>H</i>-pyrazol-1-yl)-<i>N</i>-methylcyclopropanecarboxamide	526	2.91	PF-AB01

The compounds provided in Table 3 were prepared via parallel synthesis, using the following general procedure that would be understood by one skilled in the art.

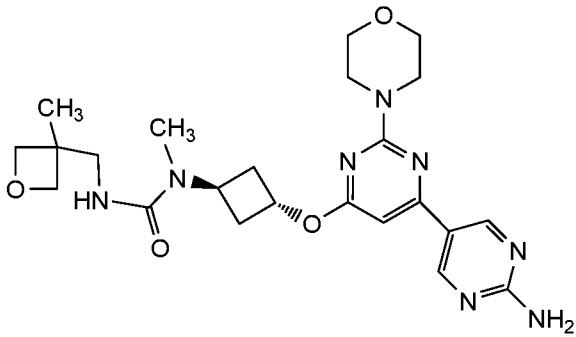
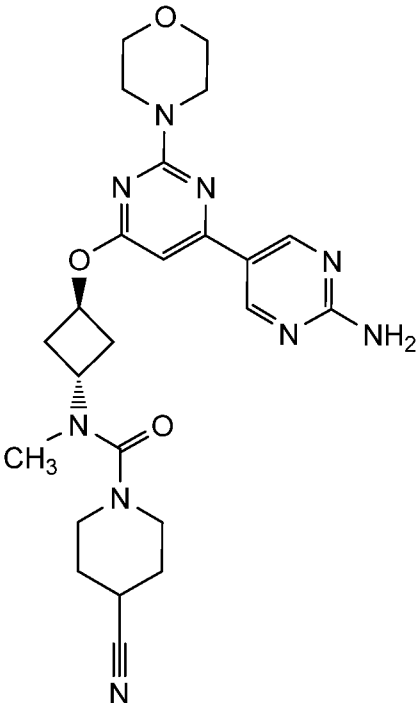
The product of Example 2, Step 2, 6-{{*trans*-3-(methylamino)cyclobutyl]oxy}-2-(morpholin-4-yl)-4,5'-bipyrimidin-2'-amine hydrochloride (75 μ mol, 1.0 eq) was dispensed to 8 mL vials. The amines monomers (75 μ mol, 1.0 eq), CDI (225 μ mol, 3.0 eq) and THF (600 μ L) were added, followed by triethylamine (450 μ mol, 6.0 eq). The vials were capped and stirred at 30 °C for 16 hours. The solvent was evaporated by Speedvac and the residues were purified by preparative HPLC to give the desired product.

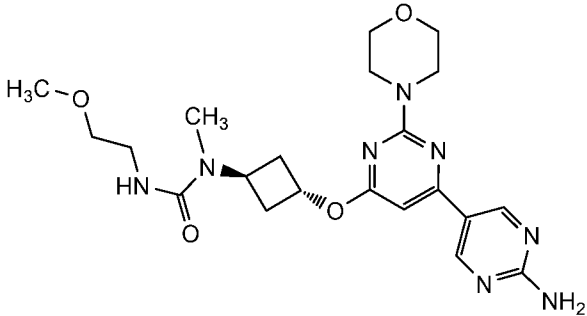
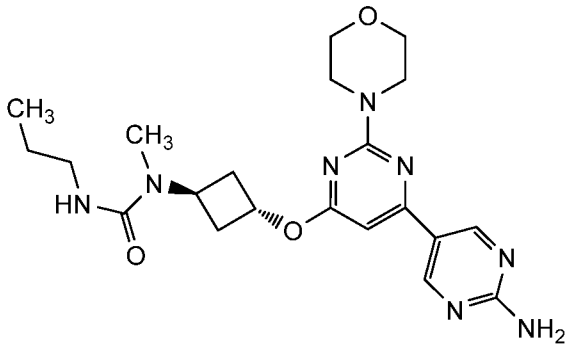
Analytical HPLC methods:

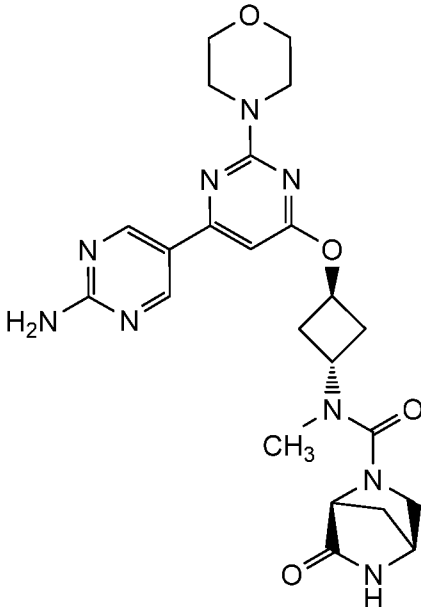
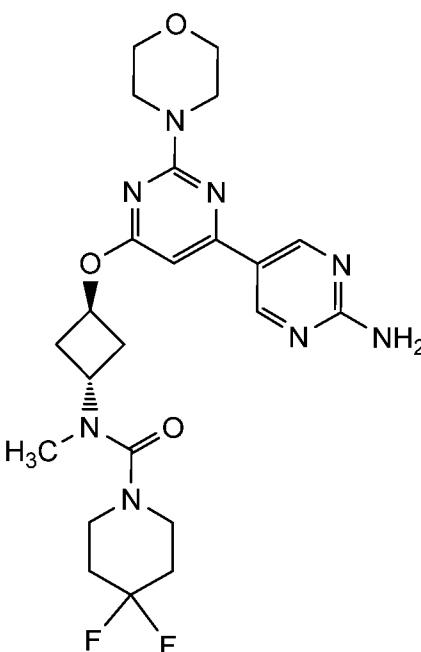
PF-CD05: Column Xbridge C18 2.1×50mm 5 μ m; Temperature 40 °C; Mobile Phase A 0.05% NH₄OH in water; Mobile Phase B 100% MeCN; Gradient: 5% B to 100% B; Flow rate 0.8 mL / min; Agilent 1200 HPLC/1956 MSD/SEDEX 75 ELSD.

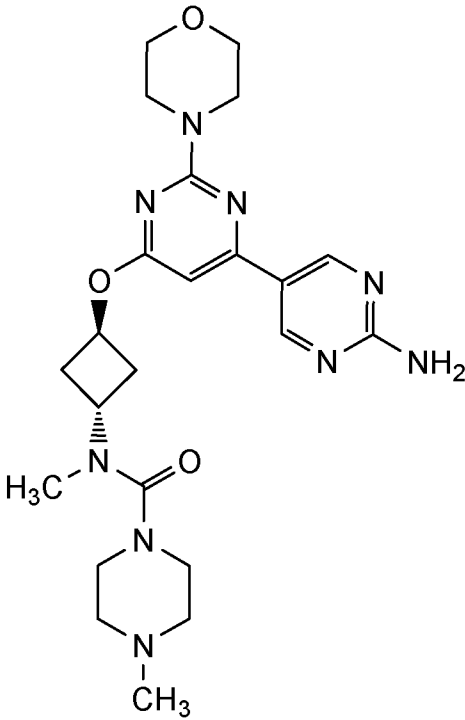
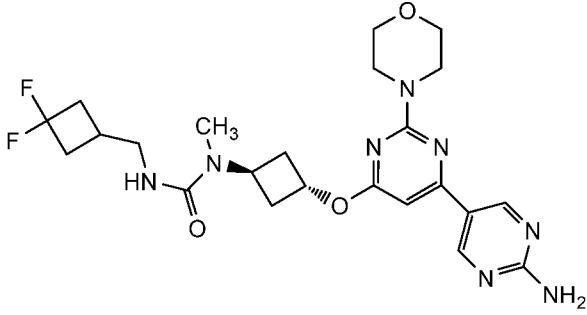
PF-AB01: Column Xbridge C18 2.1×50mm 5 μ m; Temperature 40 °C; Mobile Phase A 0.0375% TFA in water; Mobile Phase B 0.01875% TFA in MeCN; Gradient: 1% B to 100% B; Flow rate 0.8 mL / min; Agilent 1200 HPLC/1956 MSD/SEDEX 75 ELSD.

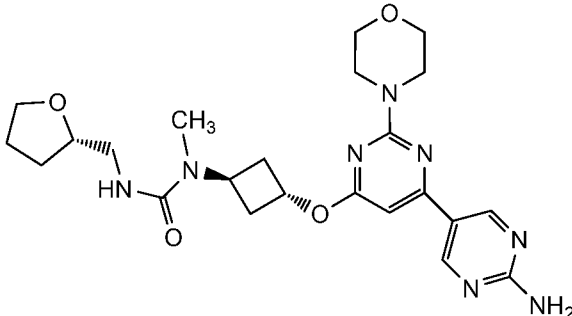
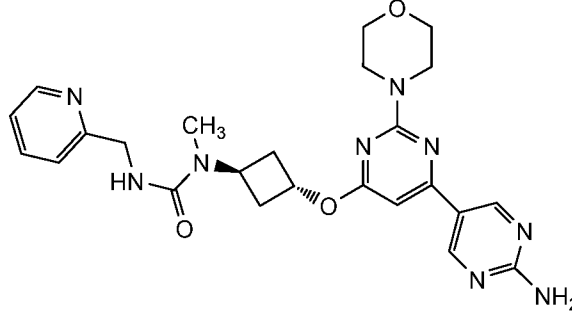
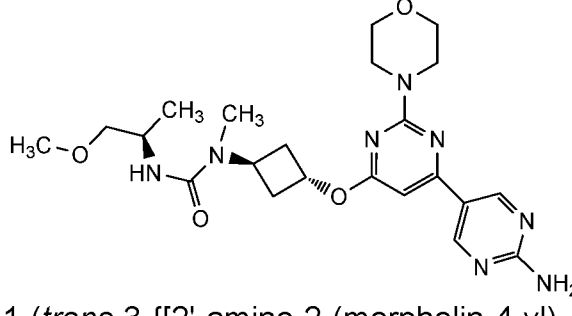
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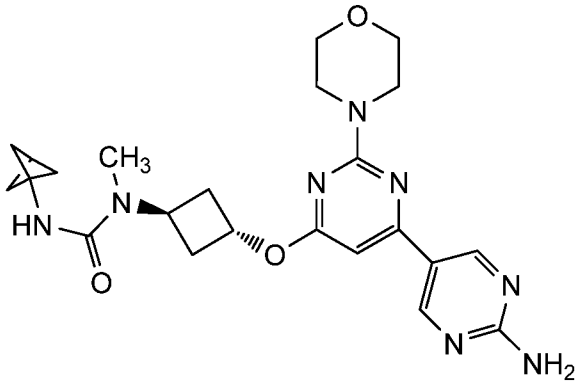
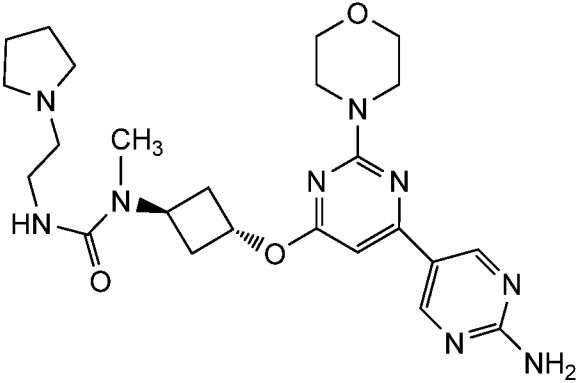
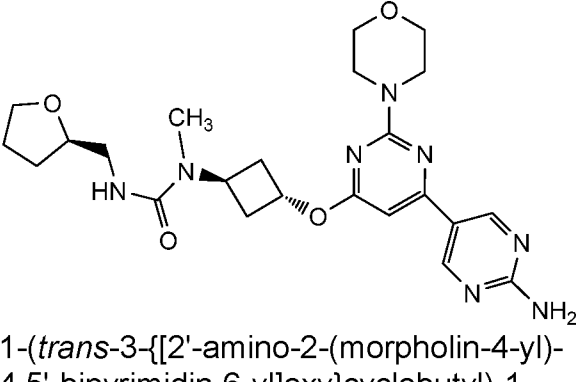
Example Number	Structure and Chemical Name	Observed MW	RT (min)	Method
206	 1-(<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1-methyl-3-[(3-methyloxetan-3-yl)methyl]urea	485	2.435	PF-CD05
207	 <i>N</i>-(<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-4-cyano-<i>N</i>-methylpiperidine-1-carboxamide	494	2.413	PF-AB01

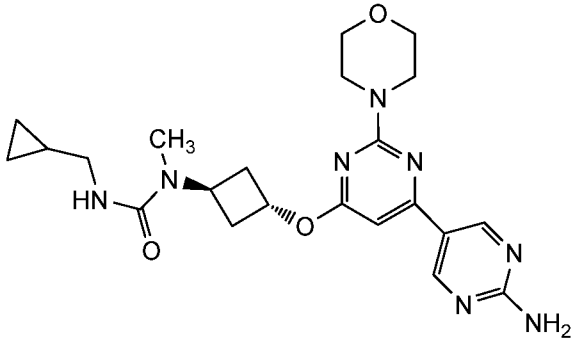
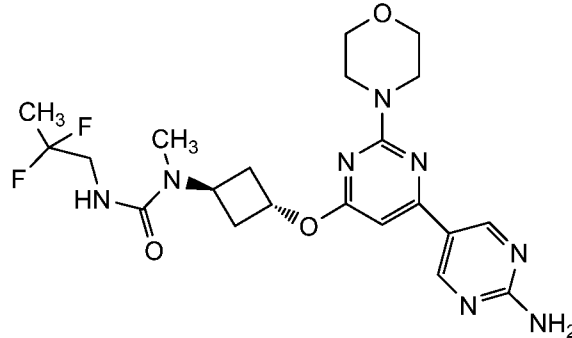
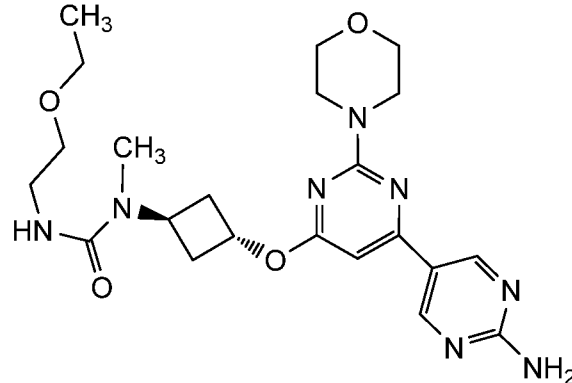
Example Number	Structure and Chemical Name	Observed MW	RT (min)	Method
208	 1-(<i>trans</i>-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-3-(2-methoxyethyl)-1-methylurea	459	2.206	PF-AB01
209	 1-(<i>trans</i>-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-1-methyl-3-propylurea	443	2.383	PF-AB01

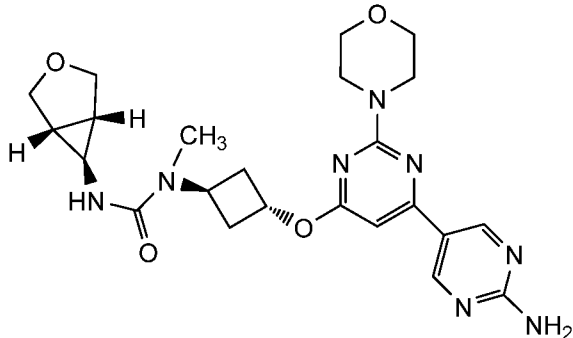
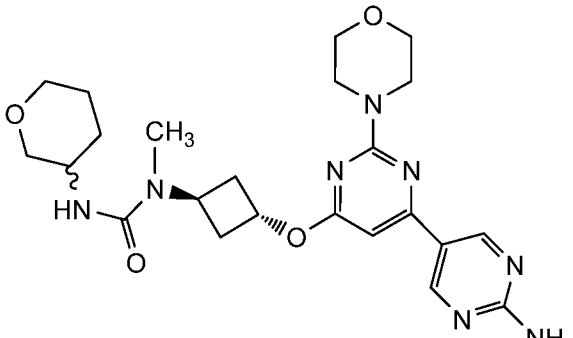
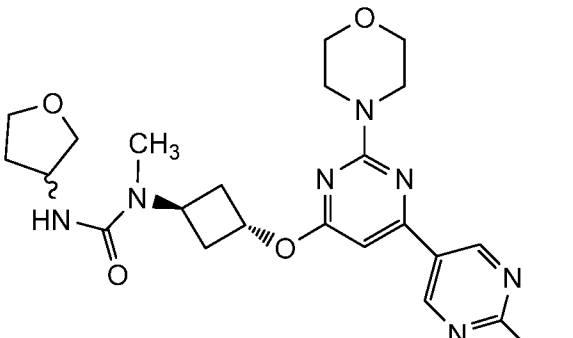
Example Number	Structure and Chemical Name	Observed MW	RT (min)	Method
210	 (1S,4S)-N-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-N-methyl-6-oxo-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide	496	1.777	PF-CD05
211	 N-(<i>trans</i>-3-([2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy)cyclobutyl)-4,4-difluoro-N-methylpiperidine-1-carboxamide	505	2.644	PF-AB01

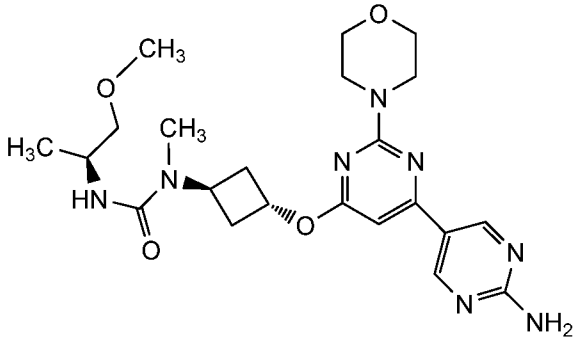
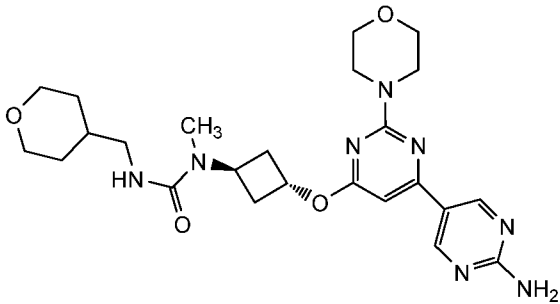
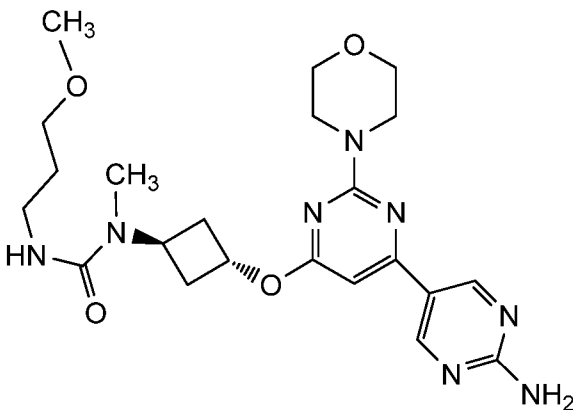
Example Number	Structure and Chemical Name	Observed MW	RT (min)	Method
212	 <i>N</i>-(<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-<i>N</i>,4-dimethylpiperazine-1-carboxamide	484	1.973	PF-AB01
213	 1-(<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-[(3,3-difluorocyclobutyl)methyl]-1-methylurea	505	2.541	PF-AB01

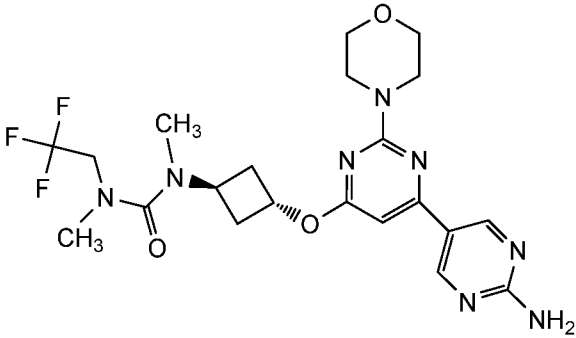
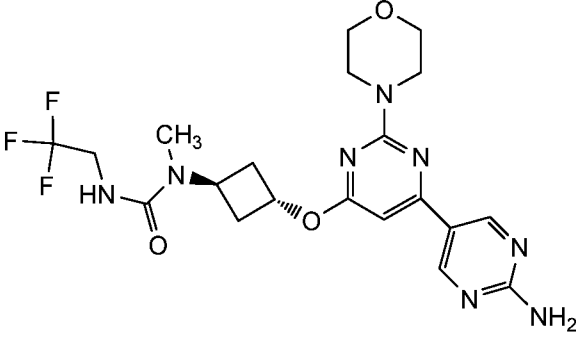
Example Number	Structure and Chemical Name	Observed MW	RT (min)	Method
214	 1-(<i>trans</i>-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-1-methyl-3-[(2<i>S</i>)-tetrahydrofuran-2-ylmethyl]urea	485	2.286	PF-AB01
215	 1-(<i>trans</i>-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-1-methyl-3-(pyridin-2-ylmethyl)urea	492	1.993	PF-AB01
216	 1-(<i>trans</i>-3-[[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy]cyclobutyl)-3-[(2<i>R</i>)-1-methoxypropan-2-yl]-1-methylurea	473	2.31	PF-AB01

Example Number	Structure and Chemical Name	Observed MW	RT (min)	Method
217	 1-(<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-bicyclo[1.1.1]pent-1-yl-1-methylurea	467	2.506	PF-AB01
218	 1-(<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1-methyl-3-[2-(pyrrolidin-1-yl)ethyl]urea	498	2.015	PF-AB01
219	 1-(<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1-methyl-3-[(2<i>R</i>)-tetrahydrofuran-2-ylmethyl]urea	485	2.287	PF-AB01

Example Number	Structure and Chemical Name	Observed MW	RT (min)	Method
220	 1-(<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-(cyclopropylmethyl)-1-methylurea	455	2.424	PF-AB01
221	 1-(<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-(2,2-difluoropropyl)-1-methylurea	479	2.398	PF-AB01
222	 1-(<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-(2-ethoxyethyl)-1-methylurea	473	2.31	PF-AB01

Example Number	Structure and Chemical Name	Observed MW	RT (min)	Method
223	 1-(<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1-methyl-3-[(1<i>R</i>,5<i>S</i>,6<i>r</i>)-3-oxabicyclo[3.1.0]hex-6-yl]urea	483	2.216	PF-AB01
224	 1-(<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1-methyl-3-(tetrahydro-2<i>H</i>-pyran-3-yl)urea	485	2.295	PF-AB01
225	 1-(<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1-methyl-3-(tetrahydrofuran-3-yl)urea	471	2.194	PF-AB01

Example Number	Structure and Chemical Name	Observed MW	RT (min)	Method
226	 1-(<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-[(2<i>S</i>)-1-methoxypropan-2-yl]-1-methylurea	473	2.31	PF-AB01
227	 1-(<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1-methyl-3-(tetrahydro-2<i>H</i>-pyran-4-ylmethyl)urea	499	2.558	PF-AB01
228	 1-(<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-3-(3-methoxypropyl)-1-methylurea	473	2.284	PF-AB01

Example Number	Structure and Chemical Name	Observed MW	RT (min)	Method
229	 1-(<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1,3-dimethyl-3-(2,2,2-trifluoroethyl)urea	497	2.659	PF-AB01
230	 1-(<i>trans</i>-3-{[2'-amino-2-(morpholin-4-yl)-4,5'-bipyrimidin-6-yl]oxy}cyclobutyl)-1-methyl-3-(2,2,2-trifluoroethyl)urea	483	2.427	PF-AB01

Enzyme Production for Biochemical Assays:

1) PI3K α complex (full length p110 α and p85 α)("PI3KA FL")

Genes encoding for full length p110 α and p85 α subunits of PI3K α complex were subcloned from existing constructs into pFASTBAC Dual vector (Life Technologies, Carlsbad, CA) using standard cloning procedures. Gene encoding p110 α subunit was subcloned into polyhedrine promoter while gene encoding p85 α subunit was subcloned into p10 promoter. Additionally, sequence encoding for histidine tag and Tobacco Etch Virus ("TEV") cleavage site preceded p110 α ORF (Open Reading Frame). Recombinant baculovirus was generated using Bac-to-Bac protocol (Life Technologies, Carlsbad, CA) and large scale expression was conducted in Sf21 (Life Technologies, Carlsbad, CA) cells at a multiplicity of infection ("MOI") = 1 for 72 hours. Cells were lysed in 50 mM Tris pH 8.0, 250 mM NaCl, 5% glycerol, 0.25 mM TCEP, and 20 mM imidazole. The PI3K α

complex was purified from clarified supernatant using Immobilized Metallo Affinity Chromatography ("IMAC"). The protein was eluted from the column using 50 mM Tris pH 8.0, 200 mM NaCl, 5% glycerol, 0.25 mM TCEP, and 200 mM imidazole, and further desalted into 50 mM Tris pH 8.0, 20 mM NaCl, and 0.25 mM TCEP prior to loading on
5 MonoQ sepharose (GE Healthcare, Piscataway, NJ). PI3K α complex was eluted from MonoQ sepharose over 20 column volumes using 0-30% gradient of buffer B (50 mM Tris pH 8.0, 1 M NaCl, and 0.25 mM TCEP). The peak fractions were pulled together and loaded on Superdex 200 26/60 SEC column equilibrated in 50 mM Tris pH 8.0, 200 mM NaCl, and 0.5 mM TCEP. Following SEC, chromatography peak fractions were
10 pulled and concentrated to 1.87 mg/mL. Purity and integrity of the complex was confirmed using LCMS, analytical SEC and SDS-PAGE (sodium dodecyl sulfate polyacrylamide gel electrophoresis) analysis.

2) p110 α -iSH2 p85 α complex (full length p110 α and p85 α iSH2)("PI3KA Act")

Genes encoding for full length p110 α and p85 α nSH-iSH2=niSH2 (p85 α
15 aminoacids 322-600) subunits of PI3K α complex were subcloned from existing constructs into pFASTBAC Dual vector (Life Technologies, Carlsbad, CA) using standard cloning procedures. Gene encoding p110 α subunit was subcloned into polyhedrine promoter while gene encoding p85 α niSH2 domains was subcloned into p10 promoter. Additionally, Human Rhinovirus 3C Protease ("HRV 3C") site was
20 introduced between nSH2 and iSH2, replacing aminoacids 431-438 of p85a with LEVLFQGP HRV 3C recognition sequence, using standard QuickChange mutagenesis protocol (Agilent Technologies, CA). Recombinant baculovirus was generated using Bac-to-Bac protocol (Life Technologies, Carlsbad, CA). Large scale expression was conducted in Sf21 (Life Technologies, Carlsbad, CA) cells at a multiplicity of infection
25 ("MOI") = 1 for 48 hours. Cells were lysed in 50 mM Tris pH 8.0, 250 mM NaCl, 5% glycerol, 0.25 mM TCEP, and 20 mM imidazole. The p110 α -niSH2 p85 α complex was purified from clarified supernatant using Immobilized Metallo Affinity Chromatography ("IMAC"). The protein was eluted from the column using 50 mM Tris pH 8.0, 200 mM NaCl, 0.25 mM TCEP, and 200 mM imidazole. Following elution p110a-niSH2 p85 α
30 complex was dialyzed against 4 liters of 50 mM Tris pH 8.0, 200 mM NaCl, 0.25 mM TCEP, and 40 mM imidazole in the presence of PreScission Protease (1:70 molar ratio of Protease to Protein) and TEV protease (1:40 molar ratio protease to protein) for 16

hours at 4 °C. The protein was further purified using reverse IMAC to remove cleaved histidine tag and contaminants captured during initial IMAC purification. The mixture of p110 α -iSH2 p85 α complex and cleaved nSH2 was recovered in reverse IMAC 40 mM imidazole flow through and 60 mM imidazole wash fractions. Those fractions were
5 pulled together and loaded on Superdex 200 26/60 SEC column equilibrated in 25 mM Tris, pH 8.0, 100mM NaCl, 2% glycerol, and 2 mM TCEP. Following SEC, chromatography peak fractions containing p110 α -iSH2 p85 α complex were pulled and concentrated to 4.3 mg/mL. Purity and integrity of the complex was confirmed using LCMS, analytical SEC and SDS-PAGE (sodium dodecyl sulfate polyacrylamide gel
10 electrophoresis) analysis.

Biochemical Assays

The biochemical assays of kinase activity of full-length PI3K α (full-length p110 α /p85 α) or truncated PI3K α (p110 α /iSH2 p85 α) were conducted using a
15 fluorescence polarization format similar to the procedure of Yuan J., *et al.*, (2011) "PF-04691502, a Potent and Selective Oral Inhibitor of PI3K and mTOR Kinases with Antitumor Activity", *Mol Cancer Ther.* **10**, 2189-2199. The enzymatic reactions were conducted in 50 μ L volumes in 96-well plates. The reactions contained human recombinant PI3K α (2 nM full-length p110 α /p85 α or 0.5 nM p110 α /iSH2 p85) and 30 μ M
20 phosphatidylinositol 4,5-bisphosphate ("PIP2") (Cayman Chemical Company, Ann Arbor, MI) and were sonicated for 1 minute prior to adding PI3K α enzyme (PI3KA_Act or PI3KA_FL), DMSO or test compound (12-point 3-fold serial dilution, 3 μ M top dose, 2 % DMSO final concentration), 5 mM MgCl₂, 50 mM HEPES pH 7.4, 150 mM NaCl, 1 mM DTT, and 0.05% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate
25 ("CHAPS"). The reactions were initiated by the addition of ATP (41 μ M, ~Km-level, for full-length p110 α /p85 or 1 mM ATP for p110 α /iSH2 p85), following a 15-min preincubation. The reactions were incubated for 30 min at room temperature, stopped with EDTA pH 8 (10 mM final concentration). In a detection plate, 15 μ L of detector/probe mixture, containing 480 nM GST-Grp1PH domain protein (University of
30 Dundee, Dundee, UK) and 12 nM carboxytetramethylrhodamine ("TAMRA")-tagged fluorescent phosphatidylinositol (3,4,5)-triphosphate ("PIP3") (Echelon Biosciences, Inc., Salt Lake City, UT) in assay buffer, was mixed with 15 μ L of kinase reaction mixture.

The plate was shaken for 30 minutes and fluorescence polarization values were measured on an LJL Analyst HT plate reader (Molecular Devices, Sunnyvale, CA). The inhibitors were shown to be ATP-competitive from kinetic and crystallographic studies. The inhibition constants (K_i) were calculated by fitting fluorescence polarization values, corresponding to initial reaction rates, to the Morrison equation (Morrison, J. F. (1969) Kinetics of the reversible inhibition of enzyme catalysed reactions by tight-binding inhibitors. *Biochim. Biophys. Acta* **185**, 269–286) for tight-binding competitive inhibitors using non-linear regression method (GraphPad Prism, GraphPad Software, San Diego, CA).

The results of the biological assays for the compounds tested are listed in Table 4.

Table 4

Example Number	PI3KA_Act K _i (nM)	PI3KA_FL K _i (nM)
1	N/A	0.419
2	N/A	0.418
3	0.512	0.318
4	N/A	0.621
5	N/A	≤0.229
6	N/A	≤0.229
7	N/A	0.776
8	N/A	0.769
9	N/A	7.661
10	N/A	9.990
11	N/A	≤0.229
12	N/A	18.897
13	N/A	2.615
14	N/A	≤0.229
15	N/A	99.841
16	N/A	4.227
17	N/A	≤0.229
18	N/A	56.941
19	N/A	1.533
20	N/A	116.872

Example Number	PI3KA_Act Ki (nM)	PI3KA_FL Ki (nM)
21	N/A	1.322
22	N/A	2.212
23	N/A	1.604
24	N/A	≤0.229
25	N/A	16.388
26	N/A	21.307
27	N/A	14.936
28	N/A	1.486
29	N/A	1.286
30	N/A	2.779
31	N/A	5.481
32	N/A	≤0.229
33	N/A	0.452
34	N/A	≤0.229
35	N/A	2.145
36	N/A	≤0.229
37	N/A	≤0.229
38	N/A	0.578
39	N/A	≤0.229
40	N/A	≤0.229
41	N/A	≤0.229
42	N/A	17.959
43	N/A	1.165
44	N/A	0.568
45	N/A	0.302
46	N/A	0.664
47	N/A	0.618
48	N/A	1.582
49	N/A	0.618
50	N/A	0.890
51	N/A	0.494
52	N/A	5.724
53	N/A	0.921
54	N/A	<0.324

Example Number	PI3KA_Act Ki (nM)	PI3KA_FL Ki (nM)
55	N/A	<0.302
56	N/A	≤0.228
57	N/A	≤0.228
58	N/A	3.686
59	N/A	≤0.228
60	N/A	≤0.228
61	N/A	0.607
62	N/A	18.200
63	N/A	≤0.228
64	N/A	0.984
65	N/A	≤0.228
66	N/A	2.680
67	N/A	0.602
68	N/A	1.385
69	N/A	2.030
70	N/A	≤0.228
71	N/A	≤0.228
72	N/A	0.402
73	N/A	3.174
74	N/A	0.881
75	N/A	≤0.228
76	N/A	0.641
77	N/A	1.408
78	N/A	29.997
79	0.165	≤0.229
80	N/A	0.985
81	N/A	91.534
82	N/A	≤0.229
83	N/A	6.578
84	0.323	≤0.229
85	0.232	≤0.229
86	0.156	≤0.229
87	0.254	≤0.229
88	N/A	≤0.229

Example Number	PI3KA_Act Ki (nM)	PI3KA_FL Ki (nM)
89	N/A	2.637
90	N/A	1.784
91	N/A	0.577
92	N/A	2.041
93	N/A	2.497
94	N/A	0.456
95	N/A	≤0.229
96	N/A	1.118
97	N/A	≤0.229
98	N/A	0.510
99	N/A	1.074
100	N/A	0.419
101	0.146	≤0.229
102	0.521	≤0.229
103	N/A	3.774
104	N/A	0.348
105	N/A	0.306
106	N/A	≤0.229
107	N/A	≤0.229
108	0.371	0.316
109	0.387	0.491
110	2.441	5.399
111	0.202	≤0.229
112	0.205	≤0.229
113	0.394	≤0.229
114	N/A	0.721
115	0.198	0.288
116	0.099	0.235
117	N/A	0.569
118	0.103	0.292
119	2.127	3.608
120	0.104	≤0.229
121	0.229	≤0.229
122	0.276	≤0.229

Example Number	PI3KA_Act Ki (nM)	PI3KA_FL Ki (nM)
123	0.178	≤0.229
124	0.179	≤0.229
125	0.107	≤0.229
126	0.093	≤0.229
127	0.113	0.241
128	0.269	≤0.229
129	0.393	0.400
130	0.114	≤0.229
131	0.202	≤0.229
132	0.187	≤0.229
133	N/A	1.420
134	0.222	≤0.229
135	N/A	0.771
136	0.161	≤0.229
137	0.141	≤0.229
138	0.053	≤0.229
139	0.109	≤0.229
140	0.363	≤0.229
141	0.048	≤0.229
142	0.161	≤0.229
143	0.142	≤0.229
144	0.039	≤0.229
145	0.118	≤0.229
146	0.141	≤0.229
147	0.096	N/A
148	0.153	N/A
149	0.165	N/A
150	0.020	N/A
151	0.098	N/A
152	0.448	N/A
153	0.220	N/A
154	0.176	N/A
155	0.485	N/A
156	0.120	N/A

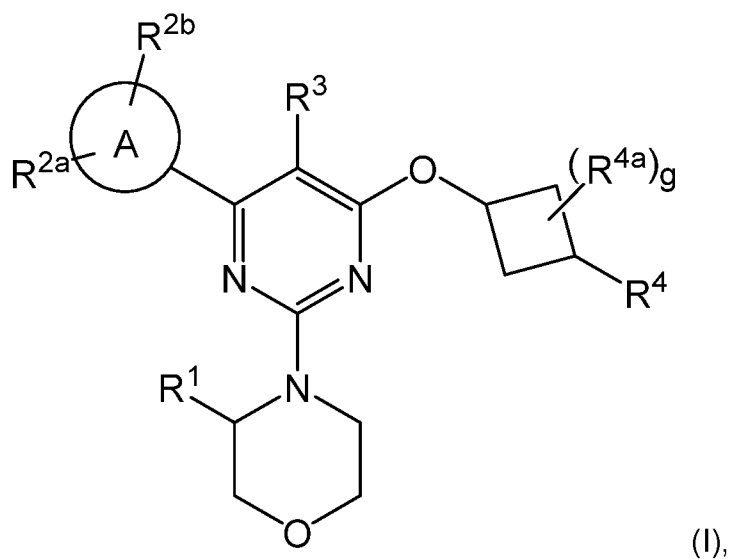
Example Number	PI3KA_Act Ki (nM)	PI3KA_FL Ki (nM)
157	0.232	N/A
158	0.414	N/A
159	0.083	N/A
160	0.325	N/A
161	0.420	N/A
162	0.463	N/A
163	0.172	N/A
164	0.227	N/A
165	0.297	N/A
166	0.191	N/A
167	1.398	N/A
168	0.219	N/A
169	0.041	N/A
170	0.111	N/A
171	0.032	N/A
172	0.278	N/A
173	0.134	N/A
174	0.168	N/A
175	0.254	N/A
176	0.078	N/A
177	0.021	N/A
178	0.595	N/A
179	0.388	N/A
180	0.460	N/A
181	0.073	N/A
182	0.367	N/A
183	0.308	N/A
184	0.203	N/A
185	0.050	N/A
186	0.760	N/A
187	N/A	7.023
188	N/A	2.003
189	N/A	≤0.229
190	N/A	≤0.229

Example Number	PI3KA_Act Ki (nM)	PI3KA_FL Ki (nM)
191	N/A	1.337
192	N/A	1.868
193	N/A	≤ 0.229
194	N/A	0.705
195	N/A	0.400
196	N/A	1.072
197	N/A	1.046
198	N/A	0.511
199	N/A	≤ 0.229
200	N/A	1.217
201	N/A	1.454
202	N/A	< 0.229
203	N/A	0.885
204	N/A	≤ 0.229
205	N/A	1.715
206	N/A	1.172
207	N/A	0.689
208	N/A	0.530
209	N/A	≤ 0.229
210	N/A	≤ 0.229
211	N/A	≤ 0.229
212	N/A	≤ 0.229
213	N/A	≤ 0.229
214	N/A	≤ 0.229
215	N/A	≤ 0.229
216	N/A	0.475
217	N/A	0.339
218	N/A	≤ 0.229
219	N/A	≤ 0.229
220	N/A	≤ 0.229
221	N/A	0.365
222	N/A	≤ 0.229
223	N/A	13.206
224	N/A	1.112

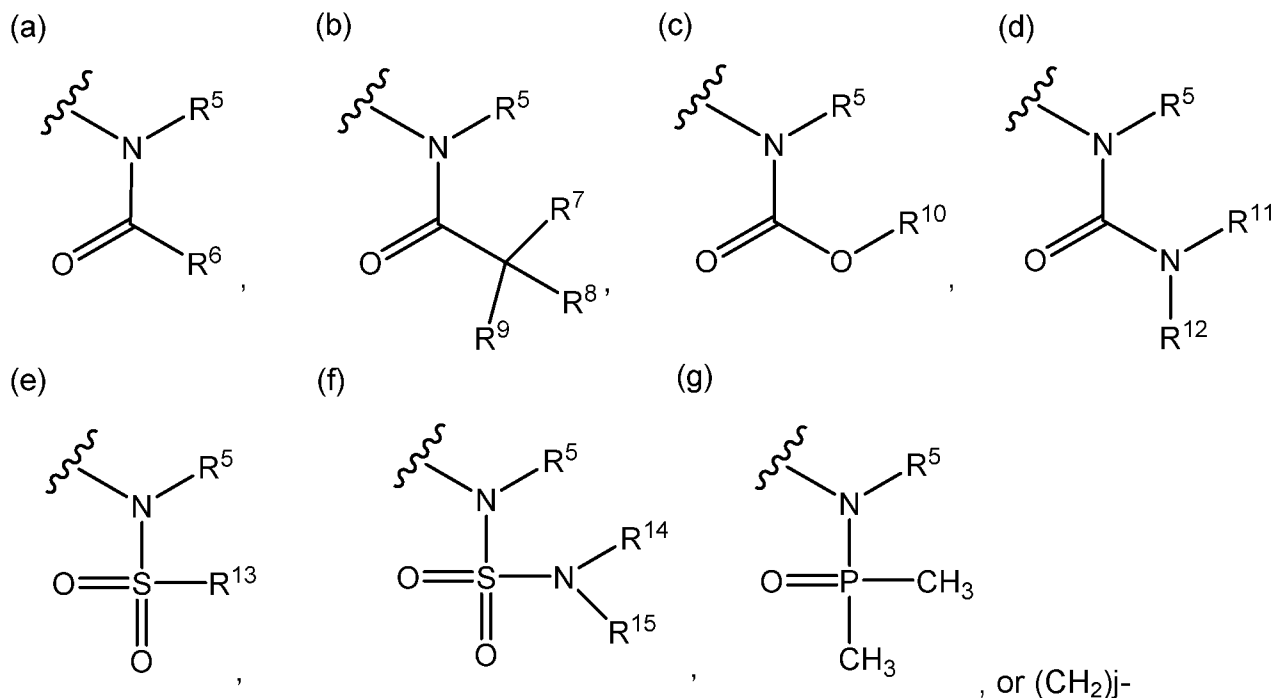
Example Number	PI3KA_Act Ki (nM)	PI3KA_FL Ki (nM)
225	N/A	0.463
226	N/A	0.523
227	N/A	≤ 0.229
228	N/A	0.344
229	N/A	1.479
230	N/A	0.364

What is claimed is:

1. A compound of formula (I)



- 5 or a pharmaceutically acceptable salt thereof,
wherein
- R¹ is hydrogen or methyl;
ring A is 6 membered heteroaryl;
R^{2a} and R^{2b} are each independently hydrogen, halogen, -CN, C₁-C₄ alkyl, -CHF₂,
10 -CF₃, hydroxy, methoxy, -NH₂, or C₃-C₄ cycloalkyl;
R³ is hydrogen, halogen, -CN, C₁-C₃ alkyl, -CF₃, or methoxy;
R⁴ is



N(R¹⁶)(R¹⁷);

each R^{4a} is independently fluorine, -CN, methyl, hydroxy, or methoxy;

5 R⁵ is hydrogen, C₁-C₃ alkyl, or C₃-C₄ cycloalkyl;

R⁶ is hydrogen, phenyl, or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl is optionally substituted by methyl, -(CH₂)₂OH, or -(CH₂)₂CN;

R⁷ is hydrogen, -CN, C₁-C₄ alkyl, -CF₃, -N(R¹⁸)(R¹⁹), -SO₂(C₁-C₃ alkyl), C₃-C₆ cycloalkyl, 4-6 membered heterocycloalkyl, -(CH₂)_m-(phenyl), or -(CH₂)_n-(5-10 membered heteroaryl), wherein the C₁-C₄ alkyl is optionally substituted by hydroxy, further wherein the C₃-C₆ cycloalkyl and the 4-6 membered heterocycloalkyl are each independently optionally substituted by one or two R²⁰ groups, even further wherein the -(CH₂)_m-(phenyl) and the -(CH₂)_n-(5-10 membered heteroaryl) are each independently optionally substituted by one or two substituents selected from the group consisting of

15 halogen, -CN, methyl, -CF₃, C₁-C₃ alkoxy, -NH₂, and cyclopropyl;

R⁸ is hydrogen, methyl, hydroxy, methoxy, or NH₂,

provided that R⁸ cannot be hydroxy, methoxy or NH₂, when R⁷ is -N(R¹⁸)(R¹⁹);

R⁹ is hydrogen or C₁-C₆ alkyl,

provided that R⁷ may form a 5-6 membered heterocycloalkyl ring with R⁵, R⁷ may form a C₃-C₆ cycloalkyl ring or a 4-8 membered heterocycloalkyl ring with R⁹, or R⁸ may form a C₃-C₆ cycloalkyl ring with R⁹, wherein the 5-6 membered heterocycloalkyl ring,

20

the C₃-C₆ cycloalkyl ring, and the 4-8 membered heterocycloalkyl ring formed are each independently optionally substituted by one or two R²⁰ groups;

R¹⁰ and R¹¹ are each independently C₁-C₄ alkyl, -(CH₂)_x-(C₃-C₅ cycloalkyl), -(CH₂)_y-(4-6 membered heterocycloalkyl), or -(CH₂)_z-(5-6 membered heteroaryl),

5 wherein the C₁-C₄ alkyl is optionally substituted by one or two substituents selected from the group consisting of fluorine, -CN, -CF₃, C₁-C₃ alkoxy, and -N(R¹⁸)(R¹⁹), further wherein the -(CH₂)_x-(C₃-C₅ cycloalkyl) is optionally substituted by one or two fluorine atoms, even further wherein the -(CH₂)_y-(4-6 membered heterocycloalkyl) and the -(CH₂)_z-(5-6 membered heteroaryl) are each independently optionally substituted by one
10 or two substituents selected from the group consisting of fluorine, -CN, methyl, hydroxy, methoxy, and -N(R¹⁸)(R¹⁹),

provided that R¹⁰ or R¹¹ may form a 4-7 membered heterocycloalkyl ring with R⁵, wherein the 4-7 membered heterocycloalkyl ring formed is optionally substituted by one or two R²⁰ groups;

15 R¹² is hydrogen or C₁-C₄ alkyl,

provided that R¹¹ and R¹² may form a 4-8 membered heterocycloalkyl ring, wherein the 4-8 membered heterocycloalkyl ring formed is optionally substituted by one or two R²¹ groups, further wherein a carbon atom of the 4-8 membered heterocycloalkyl ring formed is optionally replaced by a nitrogen atom or an oxygen atom;

20 R¹³ is C₁-C₄ alkyl or C₃-C₆ cycloalkyl,

provided that R¹³ may form a 5-6 membered heterocycloalkyl ring with R⁵, wherein the 5-6 membered heterocycloalkyl ring formed is optionally substituted by one or two R²⁰ groups;

R¹⁴ and R¹⁵ are each independently hydrogen, C₁-C₃ alkyl, or C₃-C₄ cycloalkyl,

25 provided that R¹⁴ may form a 5-6 membered heterocycloalkyl ring with R⁵ or R¹⁴ and R¹⁵ may form a 4-8 membered heterocycloalkyl ring, wherein the 5-6 membered heterocycloalkyl ring formed is optionally substituted by one or two R²⁰ groups, further wherein the 4-8 membered heterocycloalkyl ring formed is optionally substituted by one or two R²¹ groups, even further wherein a carbon atom of the 4-8 membered
30 heterocycloalkyl ring formed is optionally replaced by a nitrogen atom or an oxygen atom;

R¹⁶ and R¹⁷ are each independently hydrogen or C₁-C₃ alkyl,

provided that R^{16} and R^{17} may form a 4-6 membered heterocycloalkyl ring, wherein the 4-6 membered heterocycloalkyl ring formed is optionally substituted by one or two R^{20} groups, further wherein one carbon of the 4-6 membered heterocycloalkyl ring formed may be optionally replaced with an oxygen atom;

5 each R^{18} and R^{19} is independently hydrogen or methyl,
provided that R^{18} and R^{19} may form a 4-8 membered heterocycloalkyl ring, wherein the 4-8 membered heterocycloalkyl ring formed is optionally substituted by one or two substituents selected from the group consisting of =O, fluorine, -CN, methyl, -CF₃, hydroxy, methoxy, and -N(R^{22})(R^{23}), further wherein a carbon atom of the 4-8
10 membered heterocycloalkyl ring formed is optionally replaced by a nitrogen atom or an oxygen atom;

each R^{20} is independently fluorine, -CN, methyl, -CF₃, hydroxy, and methoxy;

each R^{21} is independently =O, fluorine, -CN, methyl, -CF₃, hydroxy, methoxy, and -N(R^{18})(R^{19});

15 each R^{22} and R^{23} is independently hydrogen or methyl,
provided that R^{22} and R^{23} may form a 4-8 membered heterocycloalkyl ring, wherein the 4-8 membered heterocycloalkyl ring formed is optionally substituted by one or two substituents selected from the group consisting of =O, fluorine, -CN, methyl, -CF₃, hydroxy, methoxy, -NH₂, -NHCH₃ and -N(CH₃)₂, further wherein a carbon atom of
20 the 4-8 membered heterocycloalkyl ring formed is optionally replaced by a nitrogen atom or an oxygen atom;

g is 0, 1, 2, 3, or 4;

j is 0, 1, or 2;

m is 0, 1, or 2;

25 n is 0 or 1;

x is 0 or 1;

y is 0, 1, or 2; and

z is 0 or 1.

- 30 2. The compound or salt of claim 1, wherein R^1 is hydrogen.
3. The compound or salt of claim 1, wherein R^1 is methyl.
4. The compound or salt of any of claims 1-3, wherein ring A is pyridine.
5. The compound or salt of any of claims 1-3, wherein ring A is pyrimidine.
6. The compound or salt of any of claims 1-5, wherein R^{2a} is -NH₂.

7. The compound or salt of any of claims 1-6, wherein R^3 is hydrogen.

8. The compound or salt of any of claims 1-7, wherein g is 0.

9. The compound or salt of any of claims 1-7, wherein g is 1.

10. The compound or salt of any of claims 1-9, wherein R^5 is hydrogen or C_1 -

5 C_3 alkyl.

11. The compound or salt of any of claims 1-10, wherein R^7 is hydrogen, $-CN$, C_1 - C_4 alkyl, $-CF_3$, $-NH_2$, or $-SO_2CH_3$.

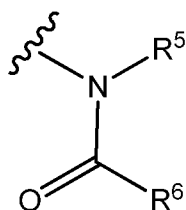
12. The compound or salt of any of claims 1-10, wherein R^8 is hydrogen, methyl, hydroxy, or methoxy.

10 13. The compound or salt of any of claims 1-10, wherein R^7 and R^9 form a C_3 - C_6 cycloalkyl ring optionally substituted by one or two fluorine groups.

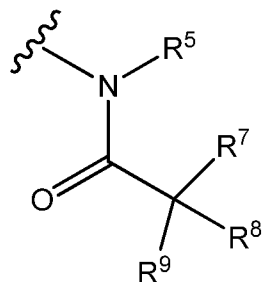
14. The compound or salt of any of claims 1-10, wherein R^{10} is C_1 - C_4 alkyl.

15. The compound or salt of any of claims 1-14, wherein R^4 is

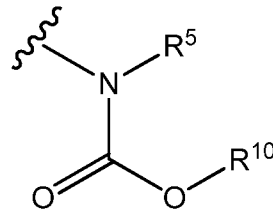
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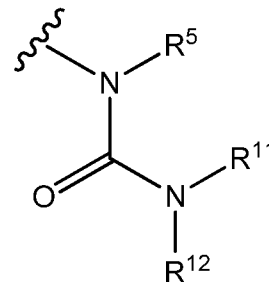
(b)



(c)



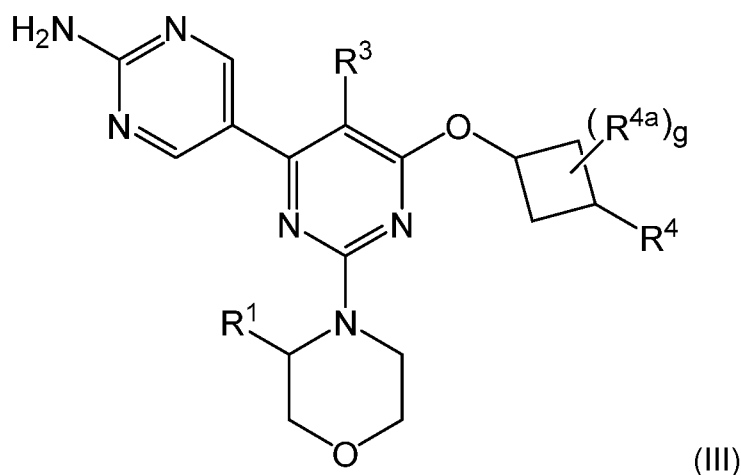
(d)



, or

15

16. A compound formula (III)



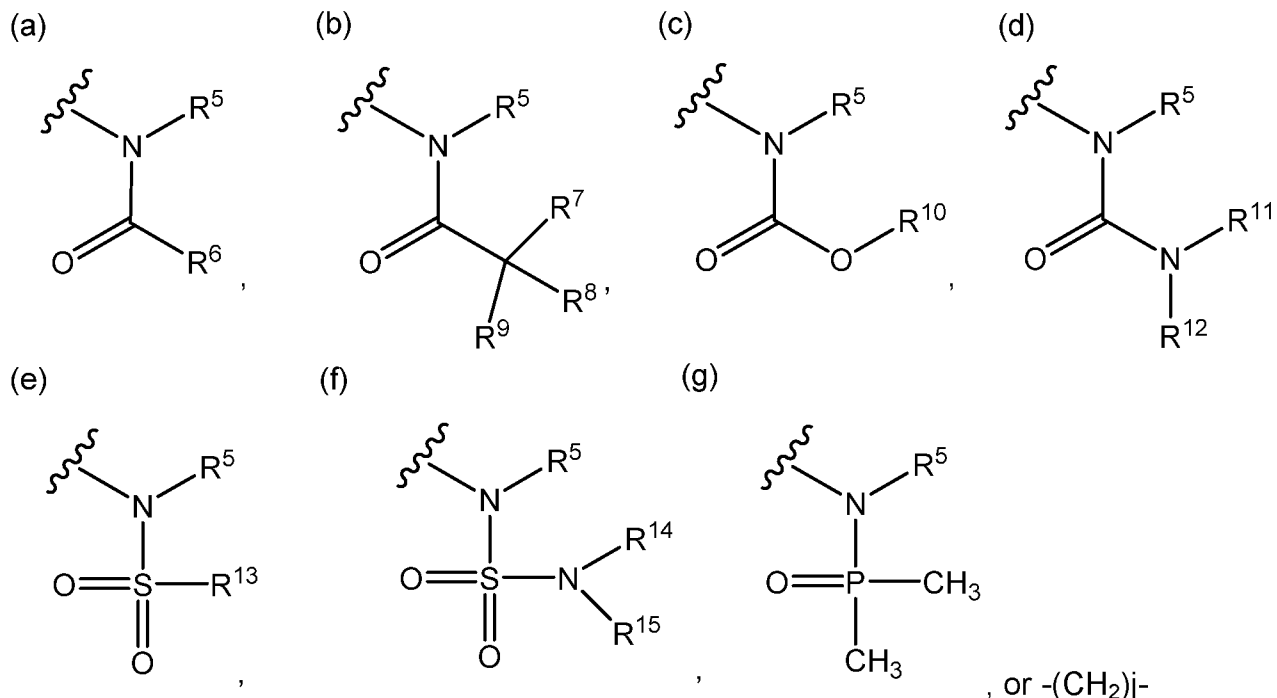
or a pharmaceutically acceptable salt thereof,

wherein

R^1 is hydrogen or methyl;

R^3 is hydrogen, halogen, -CN, C_1 - C_3 alkyl, -CF₃, or methoxy;

R^4 is



5 $N(R^{16})(R^{17})$;

each R^{4a} is independently fluorine, -CN, methyl, hydroxy, or methoxy;

R^5 is hydrogen, C_1 - C_3 alkyl, or C_3 - C_4 cycloalkyl;

R^6 is hydrogen, phenyl, or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl is optionally substituted by methyl, -(CH₂)₂OH, or -(CH₂)₂CN;

10 R^7 is hydrogen, -CN, C_1 - C_4 alkyl, -CF₃, -N(R^{18})(R^{19}), -SO₂(C_1 - C_3 alkyl), C_3 - C_6 cycloalkyl, 4-6 membered heterocycloalkyl, -(CH₂)_m-(phenyl), or -(CH₂)_n-(5-10 membered heteroaryl), wherein the C_1 - C_4 alkyl is optionally substituted by hydroxy, further wherein the C_3 - C_6 cycloalkyl and the 4-6 membered heterocycloalkyl are each independently optionally substituted by one or two R^{20} groups, even further wherein the

15 -(CH₂)_m-(phenyl) and the -(CH₂)_n-(5-10 membered heteroaryl) are each independently optionally substituted by one or two substituents selected from the group consisting of halogen, -CN, methyl, -CF₃, C_1 - C_3 alkoxy, -NH₂, and cyclopropyl;

R^8 is hydrogen, methyl, hydroxy, or methoxy,

provided that R^8 cannot be hydroxy or methoxy, when R^7 is -N(R^{18})(R^{19});

20 R^9 is hydrogen or C_1 - C_6 alkyl,

provided that R^7 may form a 5-6 membered heterocycloalkyl ring with R^5 , R^7 may form a C_3 - C_6 cycloalkyl ring or a 4-8 membered heterocycloalkyl ring with R^9 , or R^8 may

form a C₃-C₆ cycloalkyl ring with R⁹, wherein the 5-6 membered heterocycloalkyl ring, the C₃-C₆ cycloalkyl ring, and the 4-8 membered heterocycloalkyl ring formed are each independently optionally substituted by one or two R²⁰ groups;

R¹⁰ and R¹¹ are each independently C₁-C₄ alkyl, -(CH₂)_x-(C₃-C₅ cycloalkyl), -
5 (CH₂)_y-(4-6 membered heterocycloalkyl), or -(CH₂)_z-(5-6 membered heteroaryl),
wherein the C₁-C₄ alkyl is optionally substituted by one or two substituents selected
from the group consisting of fluorine, -CN, -CF₃, C₁-C₃ alkoxy, and -N(R¹⁸)(R¹⁹), further
wherein the -(CH₂)_x-(C₃-C₅ cycloalkyl) is optionally substituted by one or two fluorine
atoms, even further wherein the -(CH₂)_y-(4-6 membered heterocycloalkyl) and the -
10 (CH₂)_z-(5-6 membered heteroaryl) are each independently optionally substituted by one
or two substituents selected from the group consisting of fluorine, -CN, methyl, hydroxy,
methoxy, and -N(R¹⁸)(R¹⁹),

provided that R¹⁰ or R¹¹ may form a 4-7 membered heterocycloalkyl ring with R⁵,
wherein the 4-7 membered heterocycloalkyl ring formed is optionally substituted by one
15 or two R²⁰ groups;

R¹² is hydrogen or C₁-C₄ alkyl,

provided that R¹¹ and R¹² may form a 4-8 membered heterocycloalkyl ring,
wherein the 4-8 membered heterocycloalkyl ring formed is optionally substituted by one
or two R²¹ groups, further wherein a carbon atom of the 4-8 membered heterocycloalkyl
20 ring formed is optionally replaced by a nitrogen atom or an oxygen atom;

R¹³ is C₁-C₄ alkyl or C₃-C₆ cycloalkyl,

provided that R¹³ may form a 5-6 membered heterocycloalkyl ring with R⁵,
wherein the 5-6 membered heterocycloalkyl ring formed is optionally substituted by one
or two R²⁰ groups;

25 R¹⁴ and R¹⁵ are each independently hydrogen, C₁-C₃ alkyl, or C₃-C₄ cycloalkyl,
provided that R¹⁴ may form a 5-6 membered heterocycloalkyl ring with R⁵ or R¹⁴
and R¹⁵ may form a 4-8 membered heterocycloalkyl ring, wherein the 5-6 membered
heterocycloalkyl ring formed is optionally substituted by one or two R²⁰ groups, further
wherein the 4-8 membered heterocycloalkyl ring formed is optionally substituted by one
30 or two R²¹ groups, even further wherein a carbon atom of the 4-8 membered
heterocycloalkyl ring formed is optionally replaced by a nitrogen atom or an oxygen
atom;

R¹⁶ and R¹⁷ are each independently hydrogen or C₁-C₃ alkyl,

provided that R^{16} and R^{17} may form a 4-6 membered heterocycloalkyl ring, wherein the 4-6 membered heterocycloalkyl ring formed is optionally substituted by one or two R^{20} groups, further wherein one carbon of the 4-6 membered heterocycloalkyl ring formed may be optionally replaced with an oxygen atom;

5 each R^{18} and R^{19} is independently hydrogen or methyl, provided that R^{18} and R^{19} may form a 4-8 membered heterocycloalkyl ring, wherein the 4-8 membered heterocycloalkyl ring formed is optionally substituted by one or two substituents selected from the group consisting of =O, fluorine, -CN, methyl, -CF₃, hydroxy, methoxy, and -N(R^{22})(R^{23}), further wherein a carbon atom of the 4-8
10 membered heterocycloalkyl ring formed is optionally replaced by a nitrogen atom or an oxygen atom;

each R^{20} is independently fluorine, -CN, methyl, -CF₃, hydroxy, and methoxy;

each R^{21} is independently =O, fluorine, -CN, methyl, -CF₃, hydroxy, methoxy, and -N(R^{18})(R^{19});

15 each R^{22} and R^{23} is independently hydrogen or methyl, provided that R^{22} and R^{23} may form a 4-8 membered heterocycloalkyl ring, wherein the 4-8 membered heterocycloalkyl ring formed is optionally substituted by one or two substituents selected from the group consisting of =O, fluorine, -CN, methyl, -CF₃, hydroxy, methoxy, -NH₂, -NHCH₃ and -N(CH₃)₂, further wherein a carbon atom of
20 the 4-8 membered heterocycloalkyl ring formed is optionally replaced by a nitrogen atom or an oxygen atom;

g is 0, 1, 2, 3, or 4;

j is 0, 1, or 2;

m is 0, 1, or 2;

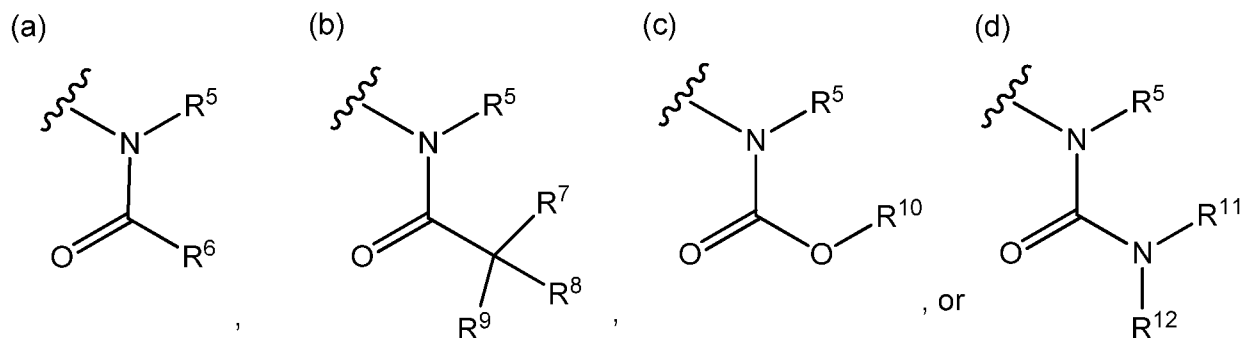
25 n is 0 or 1;

x is 0 or 1;

y is 0, 1, or 2; and

z is 0 or 1.

17. The compound or salt of any of claims 16, wherein R^4 is



18. A pharmaceutical composition comprising a compound of any of the preceding claims, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

5 19. A combination of a compound of any of claims 1-17, or a pharmaceutically acceptable salt thereof, with an anti-tumor agent or with radiation therapy, for the treatment of cancer.

10 20. A method of treating abnormal cell growth in a mammal comprising administering to the mammal an amount of a compound of any of claims 1-17, or a pharmaceutically acceptable salt thereof, that is effective in treating abnormal cell growth.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/054632

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/04 C07D403/04 C07D403/14 A61K31/5377 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/084786 A1 (NOVARTIS AG [CH]; BURGER MATTHEW [US]; NI ZHI-JIE [US]; PECCHI SABINA) 26 July 2007 (2007-07-26) claims 1-4, 19, 40-47; compound 27 -----	1-20
X	EP 2 604 601 A1 (ASTELLAS PHARMA INC [JP]) 19 June 2013 (2013-06-19) claims 1-14; examples A255, A350 -----	1-20
X	WO 2009/066084 A1 (HOFFMANN LA ROCHE [CH]; GENENTECH INC [US]; CHUCKOWREE IRINA [GB]; FOL) 28 May 2009 (2009-05-28) claims 1-25; example 11 -----	1-20



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

21 September 2015

Date of mailing of the international search report

30/09/2015

Name and mailing address of the ISA/

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Authorized officer

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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Information on patent family members

International application No

PCT/IB2015/054632

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WO 2009066084	A1	28-05-2009	NONE