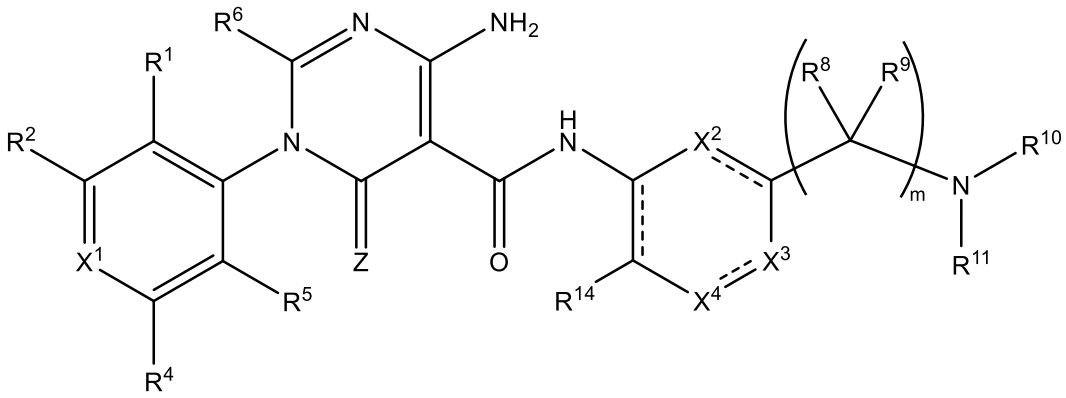
(e.g., myeloid compartment) in the tumor microenvironment. GSK3α-selective inhibitors may be useful as novel therapies for treating cancer and other diseases.

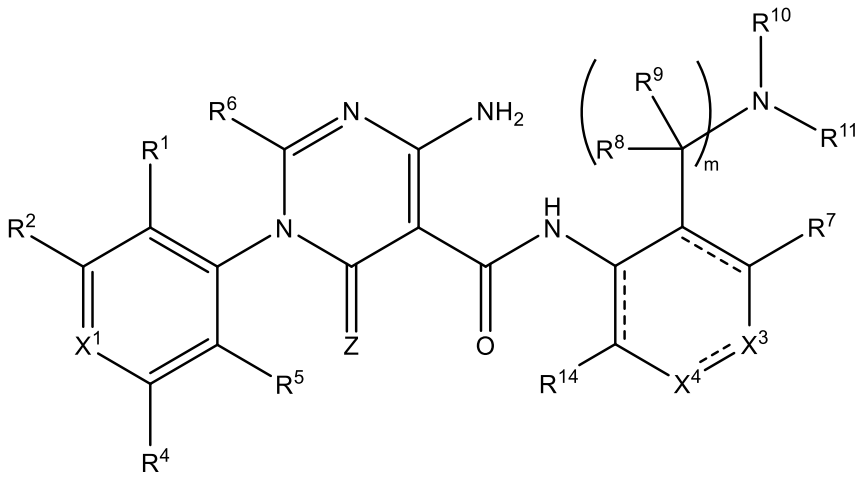
SUMMARY

Provided herein are compounds and compositions which inhibit GSK3, more specifically, GSK3α, thereby enhancing an immune response in a subject. For example, the IC_{50} values for inhibition of GSK3α provided in **Table 1** demonstrate that these compounds are potent inhibitors of GSK3α. Compounds provided herein are selective inhibitors of GSK3α. Also disclosed are methods of using the compounds and compositions described herein for treating cancer.

The present disclosure provides a compound of Formula (I') or Formula (X):



(I') or



(X),

or a pharmaceutically acceptable salt thereof, wherein:

---- is a single bond or a double bond;

membered heteroaryl, wherein the C_1-C_4alkyl, C_3-C_{10}cycloalkyl, and 4 to 12-membered aryl are each optionally substituted with 1 to 4 groups each independently selected from the group consisting of halo, OH and CN, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^d and then are optionally substituted on a ring carbon with 1 to 4 groups each independently selected from the group consisting of halo, OH and CN;

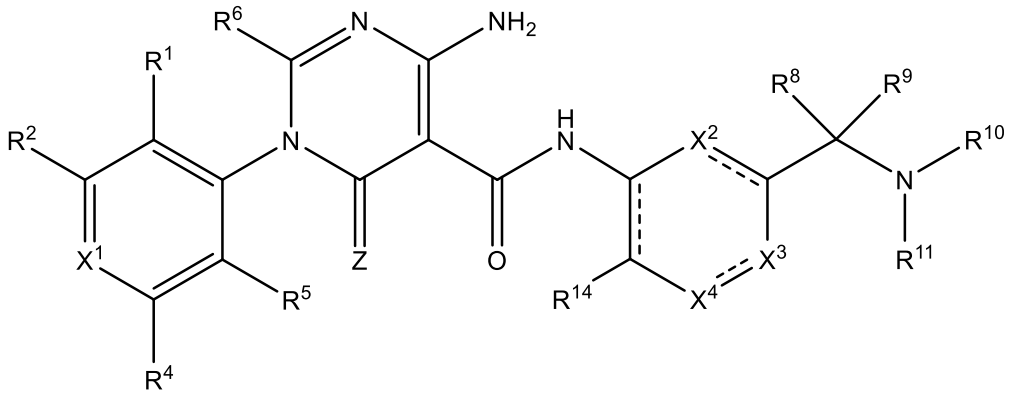
Each R^c is independently selected from the group consisting of H, D, halo, OH, CN, C_1-C_4alkyl, and C_1-C_4alkoxy, or two R^c, attached to the same atom, form a =O, wherein said C_1-C_4alkyl and C_1-C_4alkoxy are each optionally substituted with 1 to 4 groups each independently selected from the group consisting of halo, OH and CN;

Each R^d is independently selected from the group consisting of H, D, C_1-C_4alkyl, and C(O)C_1-$_4$alkyl; and

m is 1, 2, or 3, and

n is 0, 1, 2, or 3.

In one aspect, the present disclosure relates to a compound of Formula (I),



(I),

or a pharmaceutically acceptable salt thereof,

wherein

 is a single bond or a double bond;

X^1 is CR^3 or N;

X^2 is selected from the group consisting of CR^7, N, and NR^d;

X^3 is selected from the group consisting of CR^{12}, N, and NR^d;

X^4 is selected from the group consisting of CR^{13}, N, and NR^d;

Z is O or S;

R^1 is selected from the group consisting of halo, OH, CN, C_1-C_4alkyl, and C_1-C_4alkoxy, wherein the C_1-C_4alkyl and C_1-C_4alkoxy are each optionally substituted with 1 to 4 groups each independently selected from the group consisting of halo, OH and CN;

R^2 is selected from the group consisting of H, D, halo, C_1-C_4alkyl, and C_3-C_{10}cycloalkyl;

R^3 is selected from the group consisting of H, D, halo, CN, C_1-C_4alkyl, $-(C(R^a)_2)_n-OR^b$, $-(C(R^a)_2)_n-C(O)OR^b$, $-(C(R^a)_2)_n-SO_2-R^b$, $-N(R^a)_2$, C_3-C_{10}cycloalkyl, 4 to 12-membered heterocyclyl, 4 to 12-membered aryl, and 4 to 12-membered heteroaryl, wherein the C_1-C_4alkyl, C_3-C_{10}cycloalkyl, and 4 to 12-membered aryl are each optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^d and then are each optionally substituted on a ring carbon with 1 to 4 R^c;

R^4 is selected from the group consisting of H, D, halo, C_1-C_4alkyl, and C_3-C_{10}cycloalkyl;

R^5 is selected from the group consisting of halo, OH, CN, C_1-C_4alkyl, and C_1-C_4alkoxy, wherein the C_1-C_4alkyl and C_1-C_4alkoxy each optionally substituted with 1 to 4 groups each independently selected from the group consisting of halo, OH and CN;

R^6 is H or D;

R^7 is selected from the group consisting of H, D, halo, C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_{10}cycloalkyl, 4 to 12-membered heterocyclyl, 4 to 12-membered aryl, and 4 to 12-membered heteroaryl, wherein the C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_{10}cycloalkyl, and 4 to 12-membered aryl are each optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^d and then are each optionally substituted on a ring carbon with 1 to 4 R^c;

R^8 is selected from the group consisting of H, D, halo, C_1-C_4alkyl, and C_3-C_{10}cycloalkyl;

R^9 are each independently selected from the group consisting of H, D, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, $-(C(R^a)_2)_n-OR^b$, C_3-C_{10}cycloalkyl, 4 to 12-membered heterocyclyl, 4 to 12-membered aryl, and 4 to 12-membered heteroaryl, wherein the C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_3-C_{10}cycloalkyl, and 4 to 12-membered aryl

are each optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^d and then are each optionally substituted on a ring carbon with 1 to 4 R^c; or

R^7 and R^9 are taken together with the carbon atoms to which they are attached to form Ring A, wherein Ring A is C_3-C_{10}cycloalkyl or 4 to 12-membered heterocyclyl, wherein the C_3-C_{10}cycloalkyl is optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, and NR^d, and then is optionally substituted on a ring carbon by 1 to 4 R^c; or

R^8 and R^9 are taken together with the carbon atom to which they are attached to form Ring B, wherein Ring B is C_3-C_{10}cycloalkyl or 4 to 12-membered heterocyclyl, wherein the C_3-C_{10}cycloalkyl is optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, and NR^d, and then is optionally substituted on a ring carbon by 1 to 4 R^c; or

R^8 and R^9 are taken together form a =O;

R^{10} is selected from the group consisting of H, D, C_1-C_4 alkyl, -$(C(R^a)_2)_n$-OR^b, -$(C(R^a)_2)_n$-SO_2R^b, C_3-C_{10}cycloalkyl, 4 to 12-membered heterocyclyl, 4 to 12-membered aryl, and 4 to 12-membered heteroaryl, wherein the C_1-C_4alkyl, C_3-C_{10}cycloalkyl, and 4 to 12-membered aryl are each optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^d and then are each optionally substituted on a ring carbon with 1 to 4 R^c; or

R^9 and R^{10} are taken together with the carbon atom and the nitrogen atom to which they are attached, respectively, to form Ring C, wherein Ring C is a 4 to 12-membered heterocyclyl having 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, and NR^d, and then is optionally substituted on a ring carbon by 1 to 4 R^c; or

R^7 and R^9 are taken together with the carbon atoms to which they are attached to form Ring A, and R^8 and R^{10} are taken together with the carbon atom and the nitrogen atom to

which they are attached, respectively, to form Ring C, wherein Ring A and Ring C are each optionally substituted on a ring carbon by 1 to 4 R^c;

R^{11} is selected from the group consisting of H, D, C_1-C_4alkyl, C_1-C_4haloalkyl, and C_3-C_{10}cycloalkyl;

R^{12} is selected from the group consisting of H, D, halo, C_1-C_4alkyl, and C_3-C_{10}cycloalkyl; or

R^{11} and R^{12} are taken together with the nitrogen atom and the carbon atom to which they are attached, respectively, to form Ring D, wherein Ring D is selected from the group consisting of a 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^d, and then are each optionally substituted on a ring carbon by 1 to 4 R^c;

R^{13} is selected from the group consisting of H, D, halo, CN, C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_{10}cycloalkyl, 4 to 12-membered heterocyclyl, 4 to 12-membered aryl, and 4 to 12-membered heteroaryl, wherein the C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_{10}cycloalkyl, and 4 to 12-membered aryl are each optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^d and then are each optionally substituted on a ring carbon with 1 to 4 R^c;

R^{14} is selected from the group consisting of H, D, and C_1-C_4alkyl;

Each R^a is independently selected from the group consisting of H, D, halo, CN, C_1-C_4alkyl, and C_1-C_4alkoxy, wherein the C_1-C_4alkyl and C_1-C_4alkoxy each optionally substituted with 1 to 4 groups each independently selected from the group consisting of halo, OH and CN;

Each R^b is independently selected from the group consisting of H, D, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, 4 to 12-membered heterocyclyl, 4 to 12-membered aryl, and 4 to 12-membered heteroaryl, wherein the C_1-C_4alkyl, C_3-C_{10}cycloalkyl, and 4 to 12-membered aryl are each optionally substituted with 1 to 4 groups each independently selected from the group consisting of halo, OH and CN, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^d and then are optionally substituted on a ring carbon with 1 to 4 groups each independently selected from the group consisting of halo, OH and CN;

Each R^c is independently selected from the group consisting of H, D, halo, OH, CN, C_1-C_4alkyl, and C_1-C_4alkoxy, or two R^c, attached to the same atom, form a =O, wherein said C_1-C_4alkyl and C_1-C_4alkoxy are each optionally substituted with 1 to 4 groups each independently selected from the group consisting of halo, OH and CN;

Each R^d is independently selected from the group consisting of H, D, C_1-C_4alkyl, and C(O)C_1-$_4$alkyl; and

n is 0, 1, 2, or 3.

One example of the disclosure is a pharmaceutical composition comprising a pharmaceutically acceptable carrier, excipient, or diluent and a compound disclosed herein, or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising: i) the compound as described herein or a pharmaceutically acceptable salt thereof; and ii) a pharmaceutically acceptable carrier, excipient or diluent. Another example of the disclosure is a method of treating a disease or disorder responsive to inhibition of GSK3 (*e.g.*, GSK3α), comprising administering to the subject an effective amount of a compound disclosed herein or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the compound(s) or a pharmaceutically acceptable salt thereof. In some examples, the disease or disorder is a cancer.

Another example of the disclosure is the use of a compound disclosed herein or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the compound(s) or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for treating a disease or disorder responsive to inhibition of GSK3 (*e.g.*, GSK3α). In some examples, the disease or disorder is a cancer.

In another aspect, the present disclosure relates to use of the compound as described herein or a pharmaceutically acceptable salt thereof or the pharmaceutical composition as described herein in the manufacture of a medicament for treating a subject with a disease or disorder responsive to inhibition of glycogen synthase kinase 3 (GSK3) activity, wherein the disease or disorder is diabetes, cancer, viral infections or a CNS disorder, optionally, wherein the disease or disorder is cancer.

Another example of the disclosure is a compound disclosed herein or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the compound(s) or a pharmaceutically acceptable salt thereof, for use in treating a disease or disorder responsive

to inhibition of GSK3 (*e.g.*, GSK3α). In some examples, the disease or disorder is a cancer.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows tumor volume in an MC38 mouse model of colorectal cancer with treatment with anti-PD-L1 antibody, Compound 178 or a combination of anti-PD-L1 antibody and Compound 178.

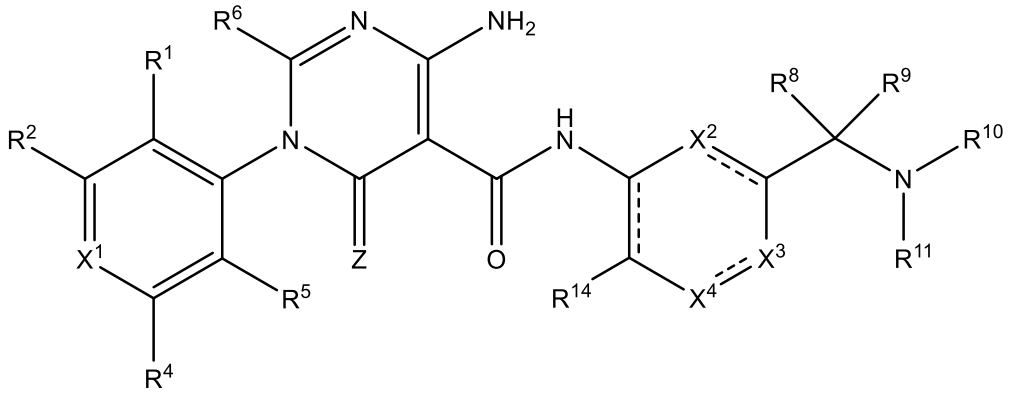
DETAILED DESCRIPTION

The disclosed compounds are GSK3α inhibitors, which can be used for treating a a disease or disorder responsive to inhibition of GSK3α. Such diseases or disorders include cancer.

Compound Embodiments

Example embodiments include:

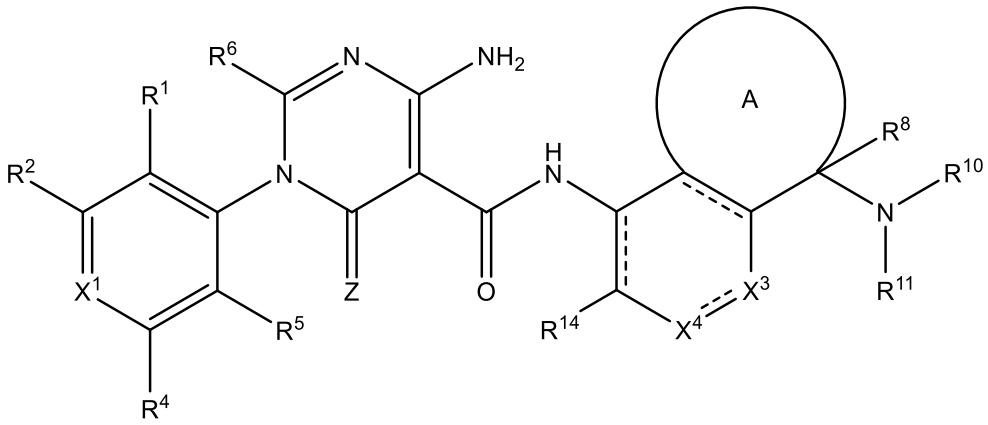
First embodiment: a compound represented by Formula (I):



(I),

or a pharmaceutically acceptable salt thereof. The variables in Formula (I) are as described above for Formula (I') in the first aspect.

Second embodiment: a compound represented by Formula (II):

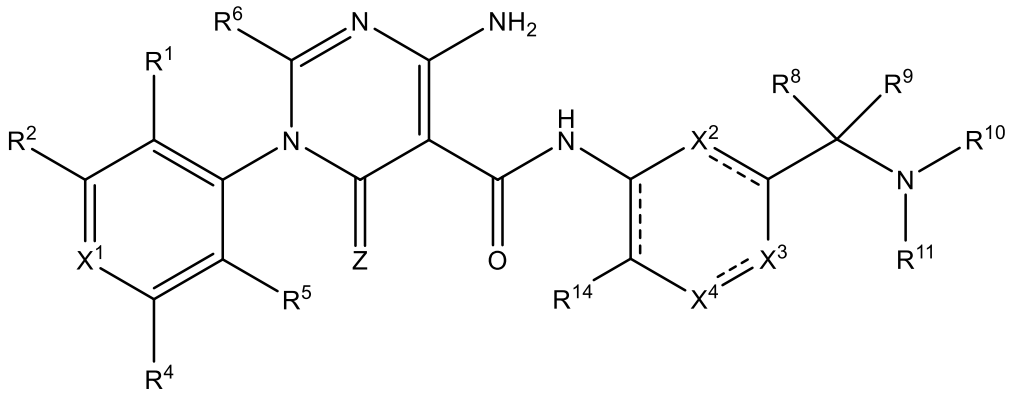


(II),

CLAIMS

What is claimed is:

1. A compound of Formula (I),



(I),

or a pharmaceutically acceptable salt thereof,

wherein

 is a single bond or a double bond;

X^1 is CR^3 or N;

X^2 is selected from the group consisting of CR^7, N, and NR^d;

X^3 is selected from the group consisting of CR^{12}, N, and NR^d;

X^4 is selected from the group consisting of CR^{13}, N, and NR^d;

Z is O or S;

R^1 is selected from the group consisting of halo, OH, CN, C_1-C_4alkyl, and C_1-C_4alkoxy, wherein the C_1-C_4alkyl and C_1-C_4alkoxy are each optionally substituted with 1 to 4 groups each independently selected from the group consisting of halo, OH and CN;

R^2 is selected from the group consisting of H, D, halo, C_1-C_4alkyl, and C_3-C_{10}cycloalkyl;

R^3 is selected from the group consisting of H, D, halo, CN, C_1-C_4alkyl, $-(C(R^a)_2)_n-OR^b$, $-(C(R^a)_2)_n-C(O)OR^b$, $-(C(R^a)_2)_n-SO_2-R^b$, $-N(R^a)_2$, C_3-C_{10}cycloalkyl, 4 to 12-membered heterocyclyl, 4 to 12-membered aryl, and 4 to 12-membered heteroaryl, wherein the C_1-C_4alkyl, C_3-C_{10}cycloalkyl, and 4 to 12-membered aryl are each optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from

the group consisting of O, S, N, and NR^d and then are each optionally substituted on a ring carbon with 1 to 4 R^c;

R^4 is selected from the group consisting of H, D, halo, C_1-C_4alkyl, and C_3-C_{10}cycloalkyl;

R^5 is selected from the group consisting of halo, OH, CN, C_1-C_4alkyl, and C_1-C_4alkoxy, wherein the C_1-C_4alkyl and C_1-C_4alkoxy each optionally substituted with 1 to 4 groups each independently selected from the group consisting of halo, OH and CN;

R^6 is H or D;

R^7 is selected from the group consisting of H, D, halo, C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_{10}cycloalkyl, 4 to 12-membered heterocyclyl, 4 to 12-membered aryl, and 4 to 12-membered heteroaryl, wherein the C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_{10}cycloalkyl, and 4 to 12-membered aryl are each optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^d and then are each optionally substituted on a ring carbon with 1 to 4 R^c;

R^8 is selected from the group consisting of H, D, halo, C_1-C_4alkyl, and C_3-C_{10}cycloalkyl;

R^9 are each independently selected from the group consisting of H, D, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, $-(C(R^a)_2)_n$-OR^b, C_3-C_{10}cycloalkyl, 4 to 12-membered heterocyclyl, 4 to 12-membered aryl, and 4 to 12-membered heteroaryl, wherein the C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_3-C_{10}cycloalkyl, and 4 to 12-membered aryl are each optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^d and then are each optionally substituted on a ring carbon with 1 to 4 R^c; or

R^7 and R^9 are taken together with the carbon atoms to which they are attached to form Ring A, wherein Ring A is C_3-C_{10}cycloalkyl or 4 to 12-membered heterocyclyl, wherein the C_3-C_{10}cycloalkyl is optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, and NR^d, and then is optionally substituted on a ring carbon by 1 to 4 R^c; or

R^8 and R^9 are taken together with the carbon atom to which they are attached to form Ring B, wherein Ring B is C_3-C_{10}cycloalkyl or 4 to 12-membered heterocyclyl, wherein the C_3-C_{10}cycloalkyl is optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, and NR^d, and then is optionally substituted on a ring carbon by 1 to 4 R^c; or

R^8 and R^9 are taken together form a =O;

R^{10} is selected from the group consisting of H, D, C_1-C_4 alkyl, $-(C(R^a)_2)_n-OR^b$, $-(C(R^a)_2)_n-SO_2R^b$, C_3-C_{10}cycloalkyl, 4 to 12-membered heterocyclyl, 4 to 12-membered aryl, and 4 to 12-membered heteroaryl, wherein the C_1-C_4alkyl, C_3-C_{10}cycloalkyl, and 4 to 12-membered aryl are each optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^d and then are each optionally substituted on a ring carbon with 1 to 4 R^c; or

R^9 and R^{10} are taken together with the carbon atom and the nitrogen atom to which they are attached, respectively, to form Ring C, wherein Ring C is a 4 to 12-membered heterocyclyl having 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, and NR^d, and then is optionally substituted on a ring carbon by 1 to 4 R^c; or

R^7 and R^9 are taken together with the carbon atoms to which they are attached to form Ring A, and R^8 and R^{10} are taken together with the carbon atom and the nitrogen atom to which they are attached, respectively, to form Ring C, wherein Ring A and Ring C are each optionally substituted on a ring carbon by 1 to 4 R^c;

R^{11} is selected from the group consisting of H, D, C_1-C_4alkyl, C_1-C_4haloalkyl, and C_3-C_{10}cycloalkyl;

R^{12} is selected from the group consisting of H, D, halo, C_1-C_4alkyl, and C_3-C_{10}cycloalkyl; or

R^{11} and R^{12} are taken together with the nitrogen atom and the carbon atom to which they are attached, respectively, to form Ring D, wherein Ring D is selected from the group consisting of a 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1

to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^d, and then are each optionally substituted on a ring carbon by 1 to 4 R^c;

R^{13} is selected from the group consisting of H, D, halo, CN, C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_{10}cycloalkyl, 4 to 12-membered heterocyclyl, 4 to 12-membered aryl, and 4 to 12-membered heteroaryl, wherein the C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_{10}cycloalkyl, and 4 to 12-membered aryl are each optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^d and then are each optionally substituted on a ring carbon with 1 to 4 R^c;

R^{14} is selected from the group consisting of H, D, and C_1-C_4alkyl;

Each R^a is independently selected from the group consisting of H, D, halo, CN, C_1-C_4alkyl, and C_1-C_4alkoxy, wherein the C_1-C_4alkyl and C_1-C_4alkoxy each optionally substituted with 1 to 4 groups each independently selected from the group consisting of halo, OH and CN;

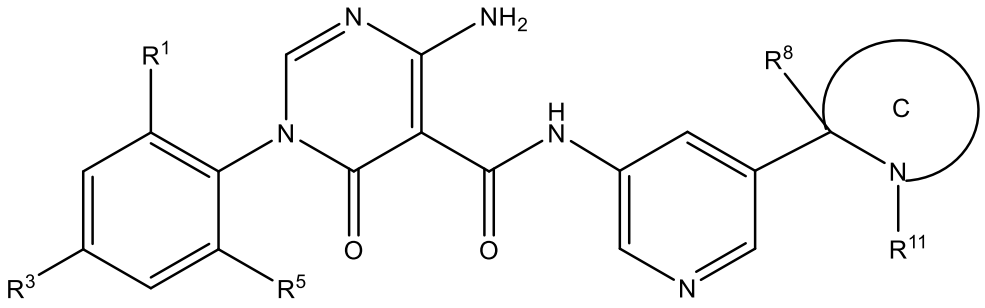
Each R^b is independently selected from the group consisting of H, D, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, 4 to 12-membered heterocyclyl, 4 to 12-membered aryl, and 4 to 12-membered heteroaryl, wherein the C_1-C_4alkyl, C_3-C_{10}cycloalkyl, and 4 to 12-membered aryl are each optionally substituted with 1 to 4 groups each independently selected from the group consisting of halo, OH and CN, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^d and then are optionally substituted on a ring carbon with 1 to 4 groups each independently selected from the group consisting of halo, OH and CN;

Each R^c is independently selected from the group consisting of H, D, halo, OH, CN, C_1-C_4alkyl, and C_1-C_4alkoxy, or two R^c, attached to the same atom, form a =O, wherein said C_1-C_4alkyl and C_1-C_4alkoxy are each optionally substituted with 1 to 4 groups each independently selected from the group consisting of halo, OH and CN;

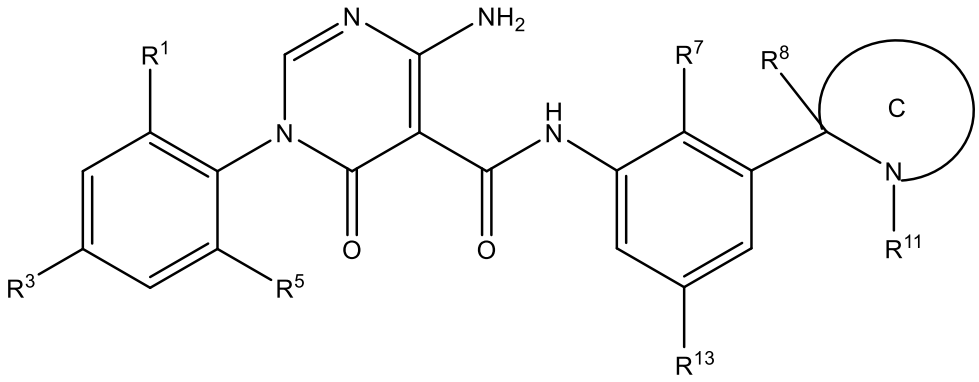
Each R^d is independently selected from the group consisting of H, D, C_1-C_4alkyl, and C(O)C_1-$_4$alkyl; and

n is 0, 1, 2, or 3.

2. The compound of claim 1, wherein the compound is of Formula (IVc) or (IVd):



(IVc); or



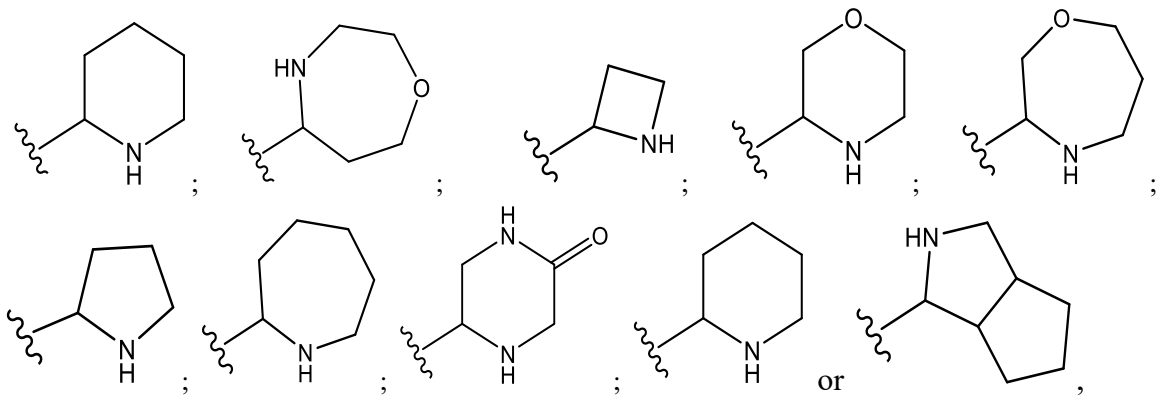
(IVd),

or a pharmaceutically acceptable salt thereof, wherein Ring C is a 4 to 10-membered heterocyclyl having 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, and NR^d, and then is optionally substituted on a ring carbon by 1 to 2 R^c.

3. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein

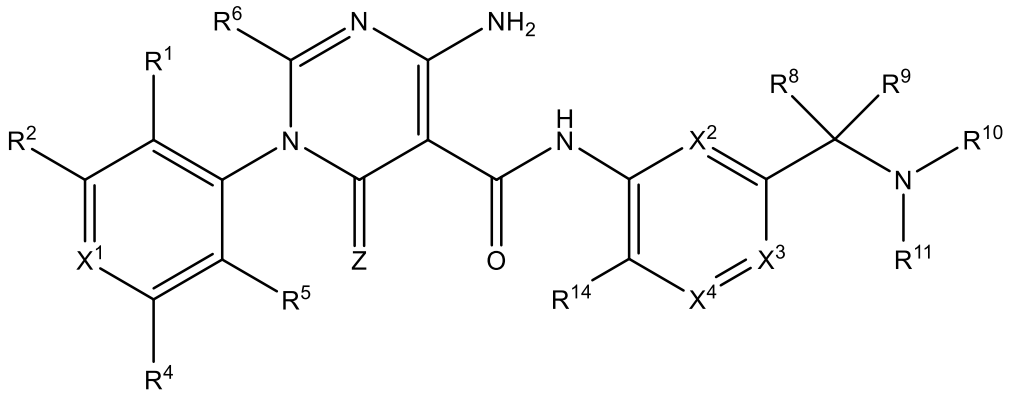
(i) Ring C is piperidine, 1,4-oxazepane, azetidine, morpholine, pyrrolidine, piperazine, piperazine-2-one, octahydrocyclopenta[c]pyrrole, or azepane, each of which is optionally substituted on a ring carbon by 1 to 2 R^c; or

(ii) Ring C is represented by



each of which is optionally substituted with 1 or 2 R^c; and each R^c is independently C_1-C_3alkyl optionally substituted with halo or OH.

4. The compound of claim 1, wherein the compound is of Formula (VI):



(VI),

or a pharmaceutically acceptable salt thereof, wherein

X^1 is CR^3 or N;

X^2 is CR^7 or N;

X^3 is CR^{12} or N;

X^4 is CR^{13} or N;

Z is O or S;

R^1 is selected from the group consisting of halo, OH, CN, C_1-C_4alkyl, C_1-C_4alkoxy, and C_1-C_4haloalkyl;

R^2 is selected from the group consisting of H, D, C_1-C_4alkyl, and C_3-C_{10}cycloalkyl;

R^3 is selected from the group consisting of H, D, halo, CN, C_1-C_4alkyl, $-(C(R^a)_2)_n$-OR^b, $-(C(R^a)_2)_n$-$C(O)OR^b$, $-(C(R^a)_2)_n$-SO_2-R^b, $-N(R^a)_2$, C_3-C_{10}cycloalkyl, 4 to 12-membered heterocyclyl, 4 to 12-membered aryl, and 4 to 12-membered heteroaryl, wherein the C_1-C_4alkyl, C_3-C_{10}cycloalkyl, and 4 to 12-membered aryl are each optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^d and then are each optionally substituted on a ring carbon with 1 to 4 R^c;

R^4 is selected from the group consisting of H, D, C_1-C_4alkyl, and C_3-C_{10}cycloalkyl;

R^5 is selected from the group consisting of halo, OH, CN, C_1-C_4alkyl, C_1-C_4alkoxy, and C_1-C_4haloalkyl;

R^6 is H or D;

R^7 is selected from the group consisting of H, D, halo, C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_{10}cycloalkyl, and 4 to 12-membered heterocyclyl, wherein the C_1-C_4alkyl, C_1-C_4alkoxy, and C_3-C_{10}cycloalkyl are each optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S and NR^d and then are each optionally substituted on a ring carbon with 1 to 4 R^c;

R^8 is selected from the group consisting of H, D, C_1-C_4alkyl, and C_3-C_{10}cycloalkyl;

R^9 are each independently selected from the group consisting of H, D, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, $-(C(R^a)_2)_n-OR^b$, C_3-C_{10}cycloalkyl, 4 to 12-membered heterocyclyl, 4 to 12-membered aryl, and 4 to 12-membered heteroaryl, wherein the C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_3-C_{10}cycloalkyl, and 4 to 12-membered aryl are each optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^d and then are each optionally substituted on a ring carbon with 1 to 4 R^c; or

R^7 and R^9 are taken together with the carbon atoms to which they are attached to form Ring A, wherein Ring A is C_3-C_{10}cycloalkyl or 4 to 12-membered heterocyclyl, wherein the C_3-C_{10}cycloalkyl is optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, and NR^d, and then is optionally substituted on a ring carbon by 1 to 4 R^c; and/or

R^8 and R^9 are taken together with the carbon atom to which they are attached to form Ring B, wherein Ring B is C_3-C_{10}cycloalkyl or 4 to 12-membered heterocyclyl, wherein the C_3-C_{10}cycloalkyl is optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, and NR^d, and then is optionally substituted on a ring carbon by 1 to 4 R^c; or

R^8 and R^9 are taken together form a =O;

R^{10} is selected from the group consisting of H, D, C_1-C_4 alkyl, -$(C(R^a)_2)_n$-OR^b, -$(C(R^a)_2)_n$-SO_2R^b, C_3-C_{10}cycloalkyl, 4 to 12-membered heterocyclyl, 4 to 12-membered aryl, and 4 to 12-membered heteroaryl, wherein the C_1-C_4alkyl, C_3-C_{10}cycloalkyl, and 4 to 12-membered aryl are each optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^d and then are each optionally substituted on a ring carbon with 1 to 4 R^c; or

R^9 and R^{10} are taken together with the carbon atom and the nitrogen atom to which they are attached, respectively, to form Ring C, wherein Ring C is a 4 to 12-membered heterocyclyl having 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, and NR^d, and then is optionally substituted on a ring carbon by 1 to 4 R^c;

R^{11} is selected from the group consisting of H, D, C_1-C_4alkyl, and C_3-C_{10}cycloalkyl;

R^{12} is selected from the group consisting of H, D, halo, C_1-C_4alkyl, and C_3-C_{10}cycloalkyl;

R^{13} is selected from the group consisting of H, D, halo, CN, C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_{10}cycloalkyl, 4 to 12-membered heterocyclyl, 4 to 12-membered aryl, and 4 to 12-membered heteroaryl, wherein the C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_{10}cycloalkyl, and 4 to 12-membered aryl are each optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^d and then are each optionally substituted on a ring carbon with 1 to 4 R^c;

R^{14} is selected from the group consisting of H, D, and C_1-C_4alkyl;

Each R^a is independently selected from the group consisting of H, D, halo, CN, C_1-C_4alkyl, and C_1-C_4alkoxy, wherein the C_1-C_4alkyl and C_1-C_4alkoxy each optionally substituted with 1 to 4 groups each independently selected from the group consisting of halo, OH and CN;

Each R^b is independently selected from the group consisting of H, D, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, 4 to 12-membered heterocyclyl, 4 to 12-membered aryl, and 4 to 12-membered heteroaryl, wherein the C_1-C_4alkyl, C_3-C_{10}cycloalkyl, and 4 to 12-membered aryl are each optionally substituted with 1 to 4 groups each independently selected from the group consisting of halo, OH and CN, wherein the 4 to 12-

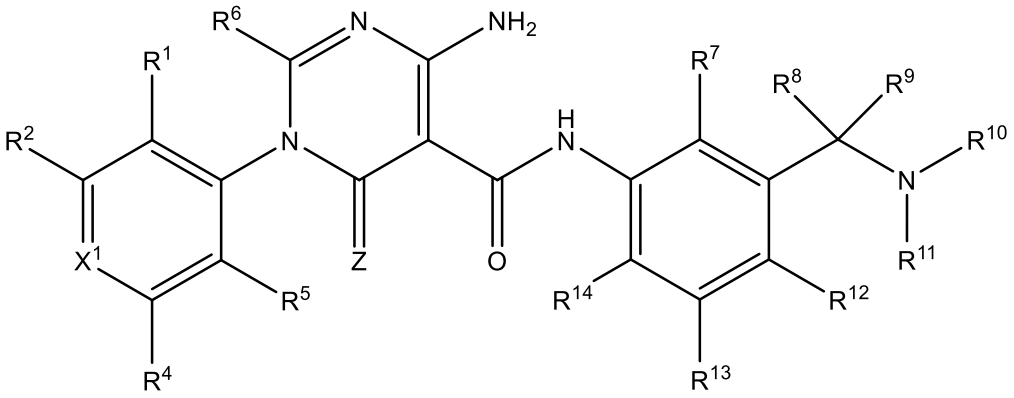
membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^d and then are optionally substituted on a ring carbon with 1 to 4 groups each independently selected from the group consisting of halo, OH and CN;

Each R^c is independently selected from the group consisting of H, D, halo, OH, CN, C_1-C_4alkyl, and C_1-C_4alkoxy, or two R^c, attached to the same atom, form a =O, wherein the C_1-C_4alkyl and C_1-C_4alkoxy are each optionally substituted with 1 to 4 groups each independently selected from the group consisting of halo, OH and CN;

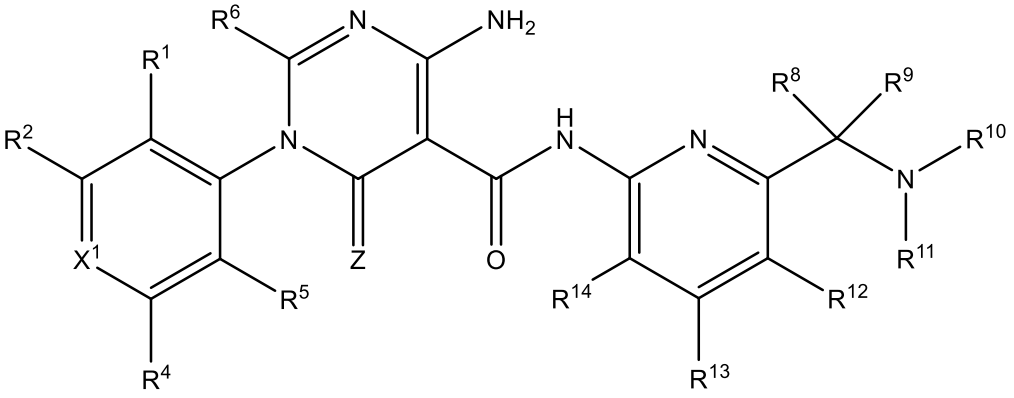
Each R^d is independently selected from the group consisting of H, D, C_1-C_4alkyl, and $C(O)C_1$-$_4$alkyl; and

n is 0, 1, 2, or 3.

5. The compound of claim 1 or 4, wherein the compound is of Formula (VIa), (VIb), (VIc), (VId), (VIe), (VIf), (VIg), or (VIh):



(VIa),



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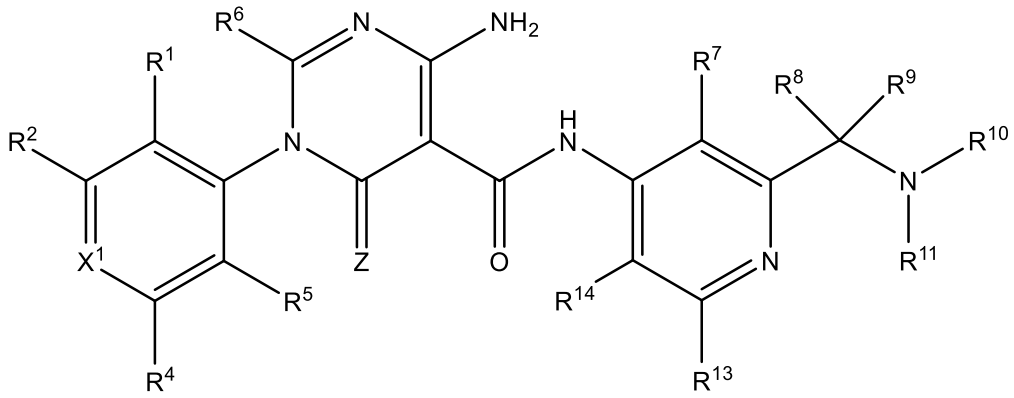

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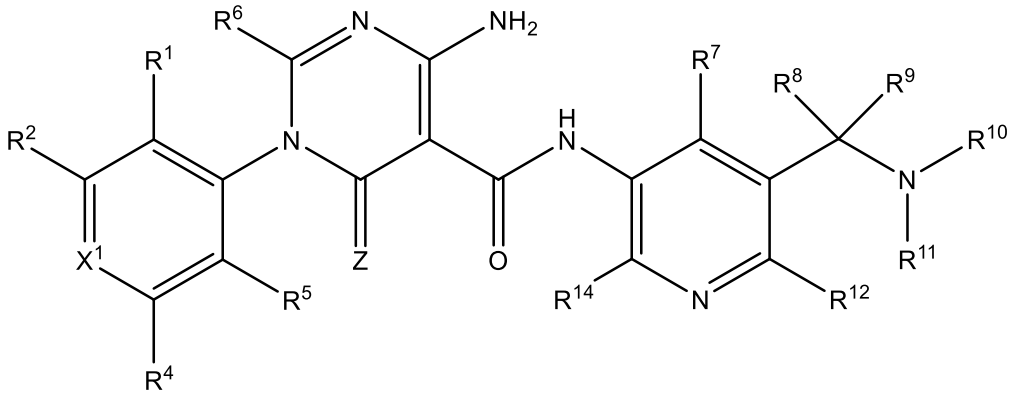
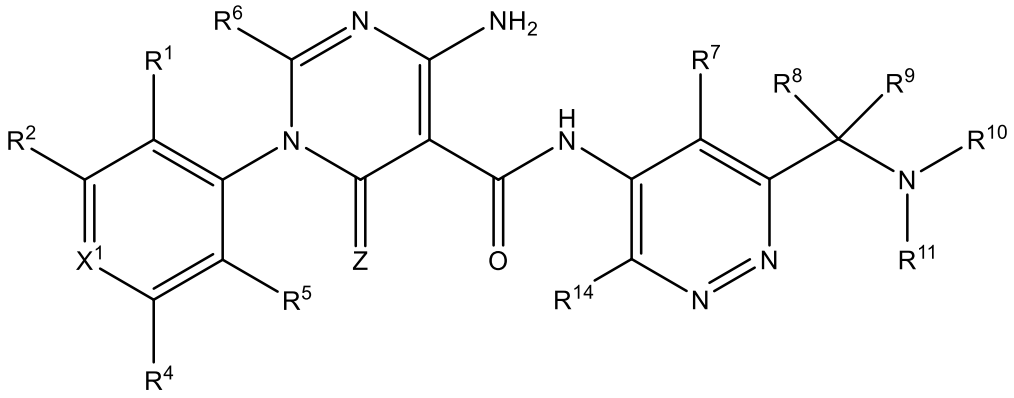
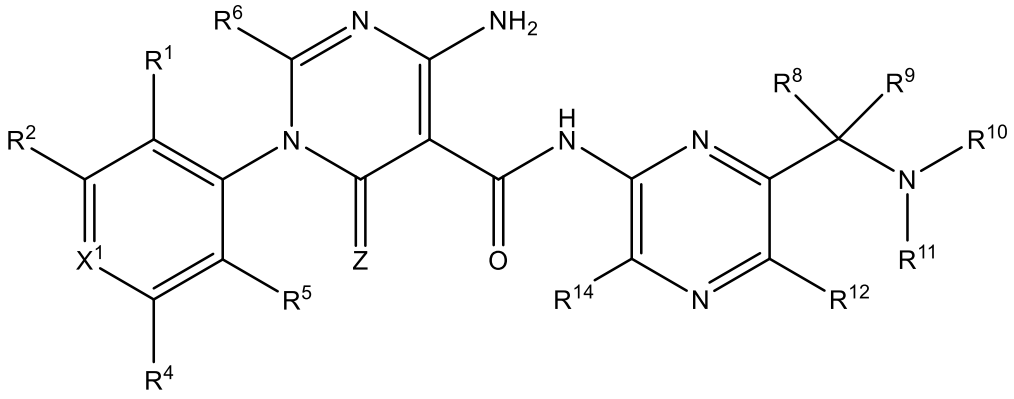


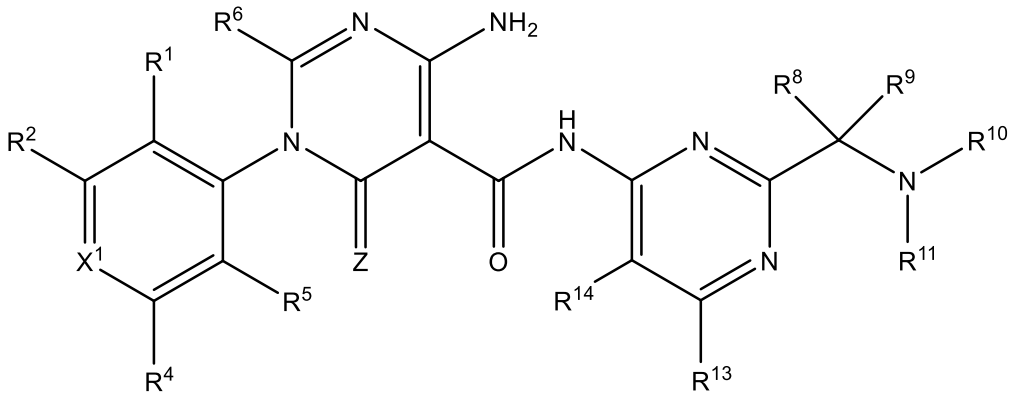
(VId),



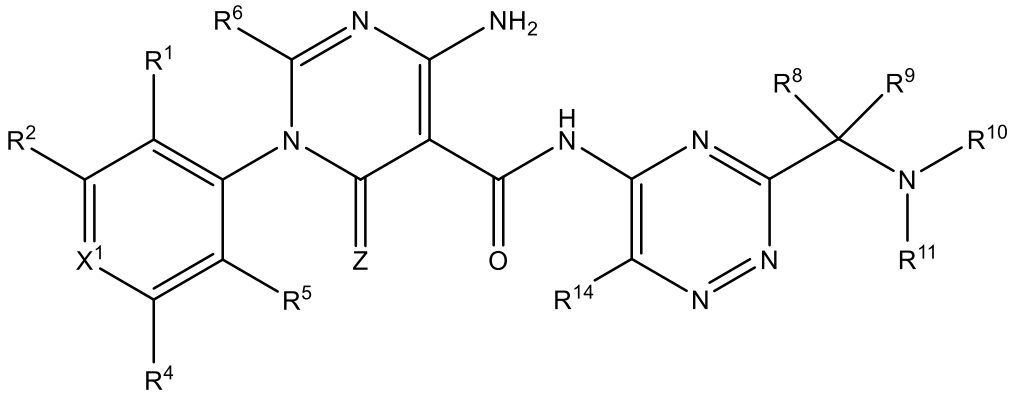
(VIe),



(VIf),



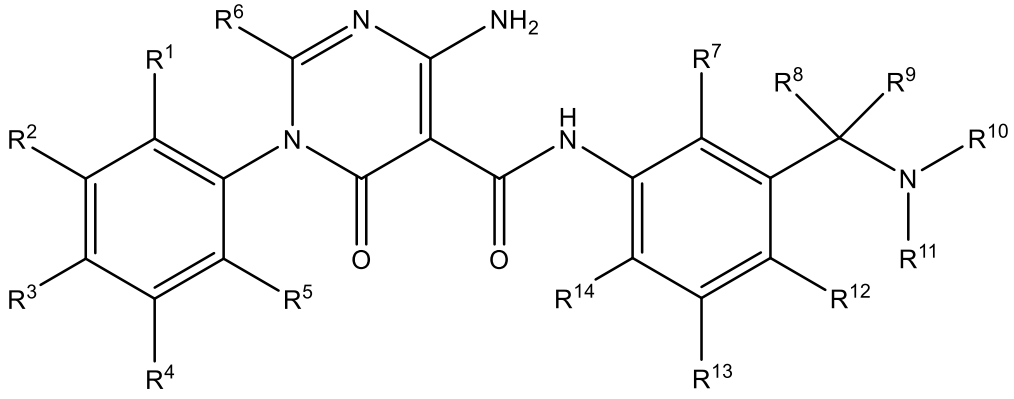
(VIg), or



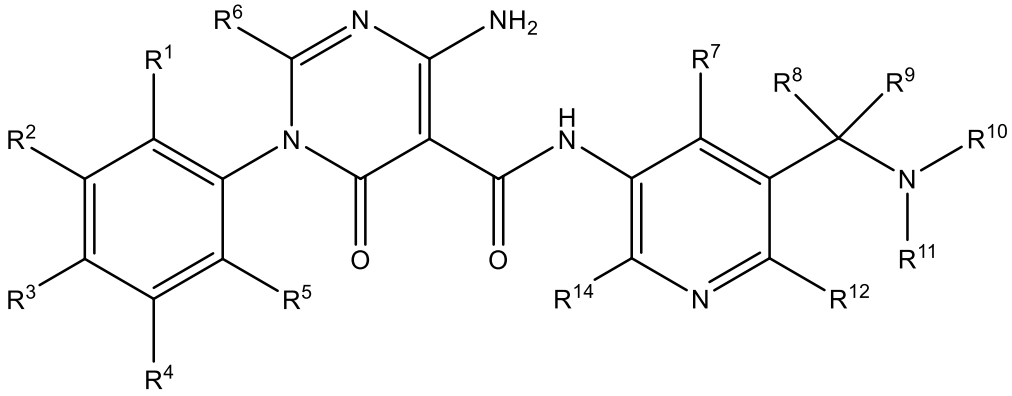
(VIh),

or a pharmaceutically acceptable salt thereof.

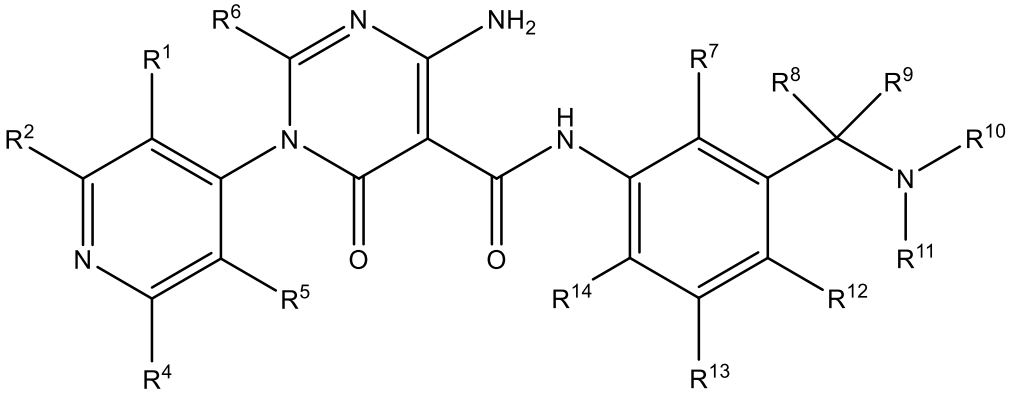
6. The compound of claim 1, wherein the compound is of Formula (VIIIe), (VIIIf), (VIIIg) or (VIIIh):



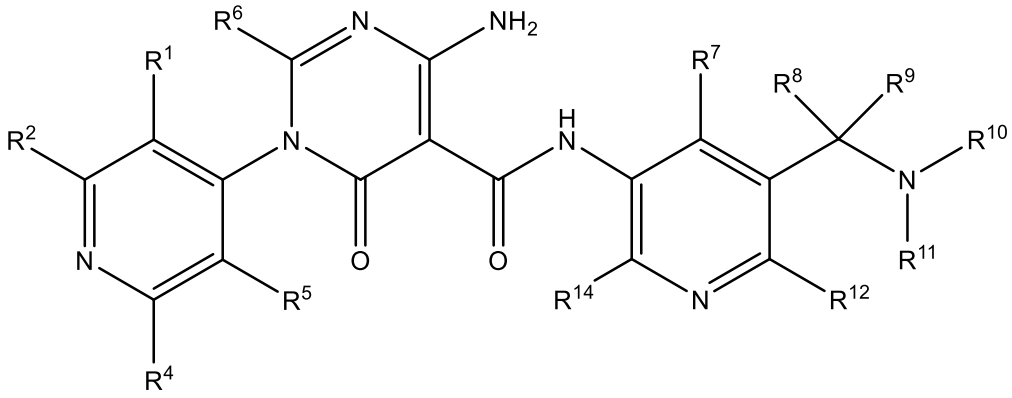
(VIIIe),



(VIIIf),



(VIIIg), or



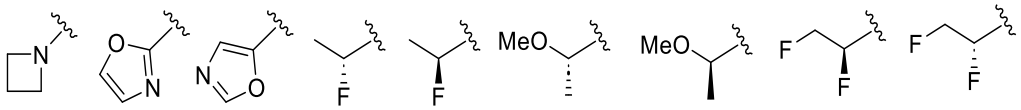
(VIIIh),

or a pharmaceutically acceptable salt thereof.

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein: (i) R^1 is halo, -OH, C_1-C_4alkyl, or C_1-C_4alkoxy; or (ii) R^1 is $–CH_3$, -Cl, -OH, or –OMe.

8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein: (i) R^3 is selected from the group consisting of H, D, halo, CN, C_1-C_4alkyl, -$(C(R^a)_2)_n$-OR^b, -$(C(R^a)_2)_n$-$C(O)OR^b$, -$(C(R^a)_2)_n$-SO_2-R^b, -$N(R^a)_2$, C_3-C_6cycloalkyl, 4 to 7-membered heterocyclyl, phenyl, and 4 to 6-membered heteroaryl, wherein the C_1-

C_4alkyl, C_3-C_6cycloalkyl, and phenyl are each optionally substituted with 1 to 4 R^c, wherein the 4 to 7-membered heterocyclyl and 4 to 6-membered heteroaryl have 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^d and then are each optionally substituted on a ring carbon with 1 to 3 R^c; (ii) R^3 is selected from the group consisting of $–CH_2CH_3$, $-CH_2OCH_3$, $-CF_3$, $-OCH_3$, H, -CN, $-CHF_2$, $-CHFCH_3$, $-CHF-CH_2F$, $-CH(CH_3)OMe$, $-OCHF_2$, Cl, $-OCH_2CH_3$, F, $-CH_3$, -O-cyclopropyl, $-O-CH_2CH_2CH_3$, $-O-CF_3$, $-N(CH_3)_2$, $-O-CH(CH_3)_2$, $-CH_2OCH_2CH_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2SO_2CH_3$, $-CF_2Me$, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_2CH_3$, $-CH_2CF_3$, and $-CH_2CO_2H$, or is represented by one of the following structures:



; or (iii) R^3 is $-CH_2CH_3$, $-CH_2OCH_3$, $-CF_3$, or $-OCH_3$.

9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein: (i) R^5 is halo, OH, C_1-C_4alkyl, C_1-C_4haloalkyl or C_1-C_4alkoxy; or (ii) R^5 is Me, Cl, -OH, $-CHF_2$ or $-OCH_3$.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein:

(i) R^9 is each independently H, D, C_1-C_4alkyl, C_2-C_4alkynyl, $-(C(R^a)_2)_n-OR^b$, or C_3-C_8cycloalkyl, wherein the C_1-C_4alkyl, C_2-C_4alkynyl, and C_3-C_8cycloalkyl are each optionally substituted with 1 to 3 R^c;

(ii) R^9 is each independently H, Me, $-CH_2OCH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_3$, $-CH_2OCH_3$, $-CH_2CHF_2$, cyclopropyl, $-CH_2C{\equiv}CH$, $-CH_2CH_2OCH_3$, or $-CHF_2$; or

(iii) R^9 is each independently H, Me, $-CH_2OCH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_3$, or $-CH_2OCH_3$.

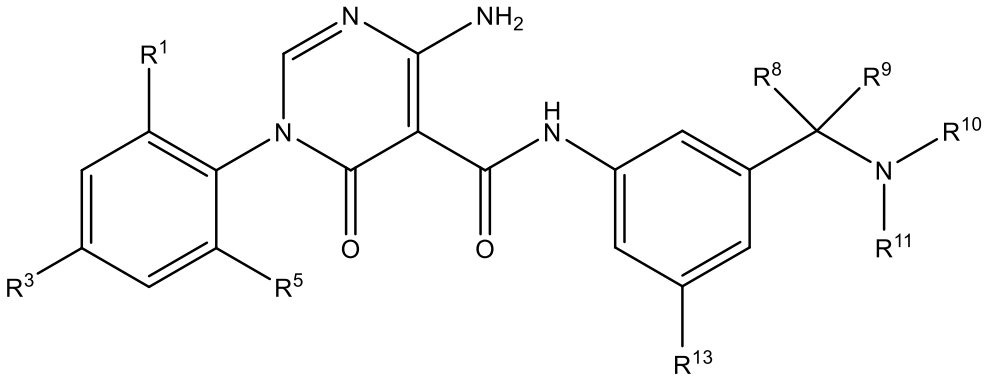
11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein:

(i) R^{10} is H, D, C_1-C_4 alkyl, $-(C(R^a)_2)_n-OR^b$, $-(C(R^a)_2)_n-SO_2R^b$, or C_3-C_8cycloalkyl, wherein the C_1-C_4 alkyl and C_3-C_8cycloalkyl are each optionally substituted with 1 to 3 R^c;

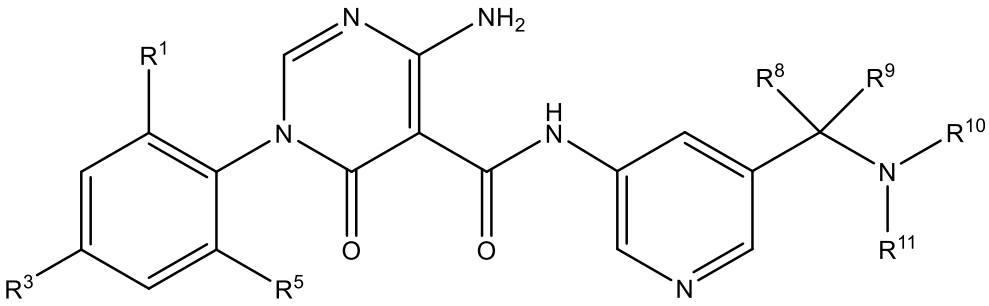
(ii) R^{10} is H, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH_2CH_2SO_2CH_3$, -CD_2CD_3, -CH_2CH_2OH, -$CH_2CH_2OCH_3$, -$CH(CH_3)_2$, or -CD_3; or

(iii) R^{10} is H, -CH_3, or -CH_2CH_3.

12. The compound of claim 1, wherein the compound is of Formula (IXa) or (IXb):



(IXa),



(IXb),

or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of halo, C_1-C_4alkyl, and C_1-C_4haloalkyl;

R^3 is selected from the group consisting of H, D, halo, CN, C_1-C_4alkyl, -$(C(R^a)_2)_n$-OR^b, -$(C(R^a)_2)_n$-$C(O)OR^b$, -$(C(R^a)_2)_n$-SO_2-R^b, -$N(R^a)_2$, C_3-C_8cycloalkyl, and 4 to 10-membered heterocyclyl, wherein the C_1-C_4alkyl and C_3-C_8cycloalkyl are each optionally substituted with 1 to 3 R^c, wherein the 4 to 10-membered heterocyclyl has 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, and NR^d and then are optionally substituted on a ring carbon with 1 to 3 R^c;

R^5 is selected from the group consisting of halo, C_1-C_4alkyl, and C_1-C_4haloalkyl;

R^8 is selected from the group consisting of H, D, and C_1-C_4alkyl;

R^9 is selected from the group consisting of H, D, C_1-C_4alkyl, -$(C(R^a)_2)_n$-OR^b, C_3-C_8cycloalkyl, and 4 to 10-membered heterocyclyl, wherein the C_1-C_4alkyl and C_3-

C_8cycloalkyl are each optionally substituted with 1 to 3 R^c, wherein the 4 to 10-membered heterocyclyl has 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, and NR^d and then are optionally substituted on a ring carbon with 1 to 3 R^c;

R^{10} is selected from the group consisting of H, D, C_1-C_4 alkyl, C_3-C_{10}cycloalkyl, and 4 to 12-membered heterocyclyl, wherein the C_1-C_4 alkyl and C_3-C_{10}cycloalkyl are each optionally substituted with 1 to 4 R^c, wherein the 4 to 12-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, and NR^d and then are optionally substituted on a ring carbon with 1 to 4 R^c; or

R^9 and R^{10} are taken together with the carbon atom and the nitrogen atom to which they are attached, respectively, to form Ring C, wherein Ring C is a 4 to 10-membered heterocyclyl having 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, and NR^d, and then is optionally substituted on a ring carbon by 1 to 3 R^c;

R^{11} is selected from the group consisting of H, D, and C_1-C_4alkyl;

R^{13} is selected from the group consisting of H, D, halo, CN, and C_1-C_4alkyl;

Each R^a is independently selected from the group consisting of H, D, and C_1-C_4alkyl;

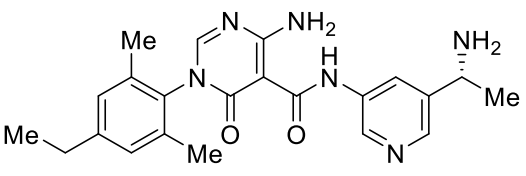
Each R^b is independently selected from the group consisting of H, D, C_1-C_4alkyl, and C_1-C_4alkoxy;

Each R^c is independently selected from the group consisting of D, halo, OH, CN, C_1-C_4alkyl, and C_1-C_4alkoxy, or two R^a, attached to the same atom, form a =O; and

Each R^d is independently selected from the group consisting of H, D, and C_1-C_4alkyl; and

n is 0, 1, or 2.

13. The compound of claim 1 selected from:



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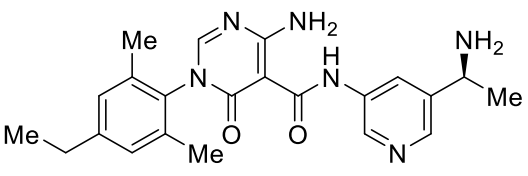

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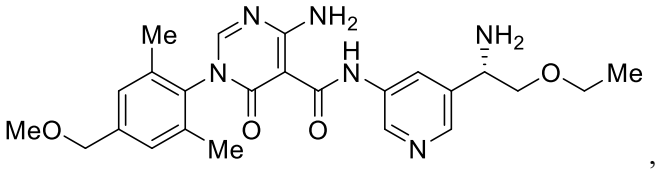
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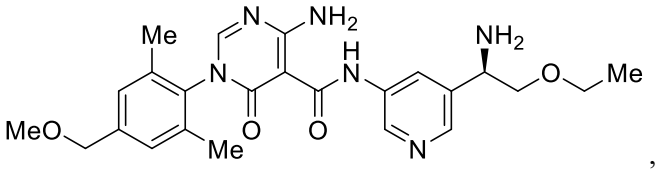
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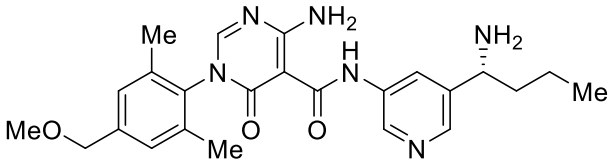
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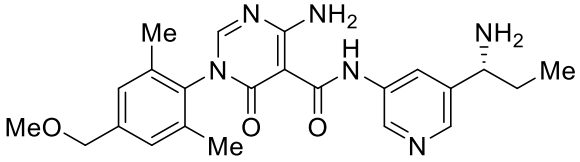
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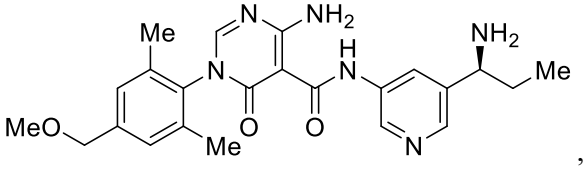
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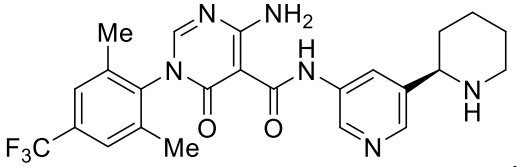
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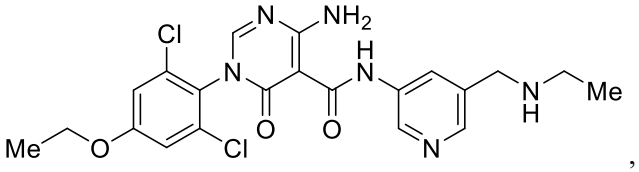
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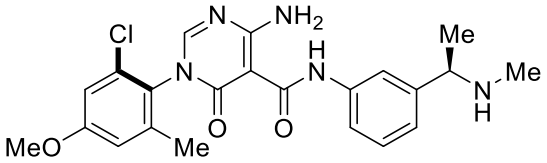
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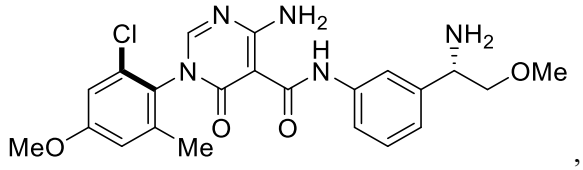
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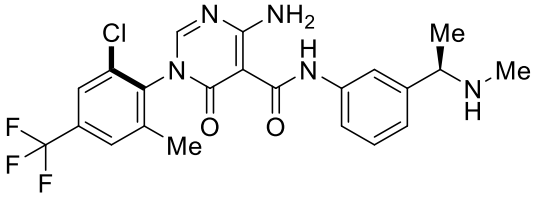
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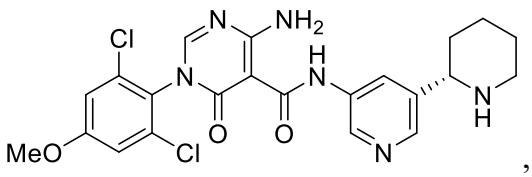
,

or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising: i) the compound of any one of claims 1-13 or a pharmaceutically acceptable salt thereof; and ii) a pharmaceutically acceptable carrier, excipient or diluent.

15. Use of the compound of any one of claims 1-13 or a pharmaceutically acceptable salt thereof or the pharmaceutical composition of claim 14 in the manufacture of a medicament for treating a subject with a disease or disorder responsive to inhibition of glycogen synthase kinase 3 (GSK3) activity, wherein the disease or disorder is diabetes, cancer, viral infections or a CNS disorder, optionally, wherein the disease or disorder is cancer.