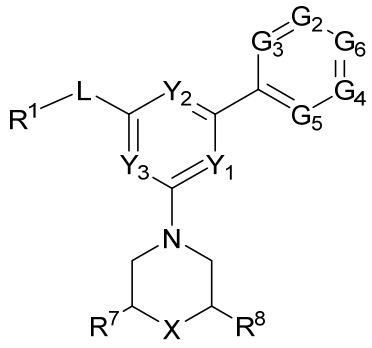
## Claims

1. A compound of Formula (I):



(I)

wherein

$R^1$ is $-(CR^aR^b)_m$-aryl, -CH=CH-aryl, $-(CR^cR^d)_n$-heteroaryl, $-(CR^eR^f)_o$-heterocycloalkyl, or $-(CR^gR^h)_p$-cycloalkyl;

m, n, o, and p are each independently 0, 1, or 2;

$R^a$, $R^b$, $R^c$, $R^d$, $R^e$, $R^f$, $R^g$, and $R^h$ are each independently H, halo, or $C_{1-4}$alkyl,

or $R^a$ and $R^b$ are taken together with the carbon to which they are attached to form a cycloalkyl ring,

or $R^a$ and $R^b$ are taken together to form $=CH_2$ or =O;

each aryl, heteroaryl, heterocycloalkyl, or cycloalkyl present in $R^1$ is unsubstituted or substituted with one or two $R^x$ substituents;

wherein each $R^x$ substituent is independently halo, $C_{1-4}$alkyl, cycloalkyl, $-C_{1-2}$-haloalkyl, -OH, $-OC_{1-4}$alkyl, $-O-C_{1-2}$-haloalkyl, cyano, $-C(O)C_{1-4}$alkyl, $-C(O)NR^iR^j$, $-SO_2C_{1-4}$alkyl, $-SO_2NR^kR^l$, $-NR^qR^r$, -C(O)-cycloalkyl, -C(O)-aryl (optionally substituted with methyl or halo), $-CO_2C_{1-4}$alkyl, $-CO_2$aryl, $-C(O)CH_2$-aryl (optionally substituted with methyl or halo), $-CH_2$-aryl (optionally substituted with methyl or halo), or monocyclic heterocycloalkyl (optionally substituted with methyl, $-C(O)C_{1-4}$alkyl, or $-CO_2C_{1-4}$alkyl);

wherein $R^i$, $R^j$, $R^k$, and $R^l$ are each independently H, $C_{1-4}$alkyl, $-C_{1-4}$alkyl-OH, or $-C_{1-4}$alkyl-O-$C_{1-4}$alkyl,

wherein $R^q$ and $R^r$ are each independently H, $C_{1-4}$alkyl, $-C_{1-4}$alkyl-OH, $-C_{1-4}$alkyl-O-$C_{1-4}$alkyl, $-C(O)C_{1-4}$alkyl, $-CO_2C_{1-4}$alkyl, or $-SO_2C_{1-4}$alkyl;

L is $-S(O)_2$-;

X is O, S, NH, $N(CO_2C_{1-4}$alkyl), $N(SO_2C_{1-4}$alkyl), $N(SO_2$cycloalkyl), or $CH_2$;

$Y_1$, $Y_2$, and $Y_3$ are each independently CH or N;

$G_2$ is N or $CR^2$;

$G_3$ is N or $CR^3$;

$G_4$ is N, $NR^{4b}$, or $CR^{4a}$;

$G_5$ is N or $CR^5$; and

$G_6$ is N or $CR^6$;

wherein $R^2$, $R^3$, $R^{4a}$, $R^5$, and $R^6$ are each independently hydrogen, halogen, -OH, -alkyl, -Oalkyl, -haloalkyl, -O-haloalkyl, or $-NR^uR^v$;

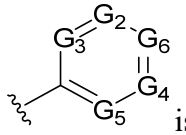
or $R^{4b}$ is taken together with $R^6$ and the atoms to which they are attached to form a heteroaryl or heterocyclic ring; wherein the heteroaryl ring comprising $R^{4b}$ and $R^6$ comprises no more than one N and is optionally substituted with alkyl, and the heterocyclic ring comprising $R^{4b}$ and $R^6$ is optionally substituted with oxo,

$R^u$ is H or $C_{1-4}$alkyl;

$R^v$ is H, $C_{1-4}$alkyl, monocyclic cycloalkyl, $-C(O)C_{1-4}$alkyl, or $-C(O)NR^wR^y$;

wherein each alkyl present in $R^v$ is unsubstituted or substituted with -OH, $-NH_2$, $-NH(C_{1-4}alkyl)$, or $-N(C_{1-4}alkyl)_2$,

$R^w$ and $R^y$ are each independently H or $C_{1-4}$alkyl;

wherein  is not unsubstituted phenyl; and

$R^7$ and $R^8$ are each independently hydrogen or $C_{1-4}$alkyl,

or $R^7$ and $R^8$ are taken together to form $-CH_2CH_2-$;

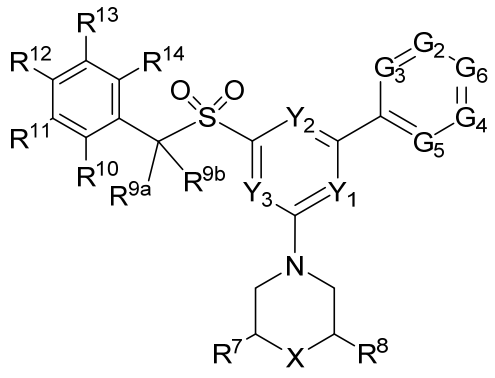
or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein $R^1$ is $-(CR^aR^b)_m$-aryl.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein $R^1$ is $(CR^cR^d)_n$-heteroaryl.

4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein $R^1$ is $(CR^eR^f)_o$-heterocycloalkyl or $(CR^gR^h)_p$-cycloalkyl.

5. The compound of claim 1, wherein the compound is of Formula (II):



(II)

wherein

X is O, S, NH, N($CO_2C_{1-4}$alkyl), N($SO_2C_{1-4}$alkyl), N($SO_2$cycloalkyl), or $CH_2$;

$Y_1$, $Y_2$, and $Y_3$ are each independently CH or N;

$G_2$ is N or $CR^2$;

$G_3$ is N or $CR^3$;

$G_4$ is N, $NR^{4b}$, or $CR^{4a}$;

$G_5$ is N or $CR^5$; and

$G_6$ is N or $CR^6$;

wherein $R^2$, $R^3$, $R^{4a}$, $R^5$, and $R^6$ are each independently hydrogen, halogen, -OH, -alkyl, -Oalkyl, -haloalkyl, -O-haloalkyl, or $-NR^uR^v$;

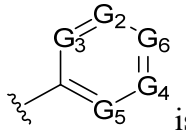
or $R^{4b}$ is taken together with $R^6$ and the atoms to which they are attached to form a heteroaryl or heterocyclic ring; wherein the heteroaryl ring comprising $R^{4b}$ and $R^6$ comprises no more than one N and is optionally substituted with alkyl, and the heterocyclic ring comprising $R^{4b}$ and $R^6$ is optionally substituted with oxo,

$R^u$ is H or $C_{1-4}$alkyl;

$R^v$ is H, $C_{1-4}$alkyl, monocyclic cycloalkyl, $-C(O)C_{1-4}$alkyl, or $-C(O)NR^wR^y$;

wherein each alkyl present in $R^v$ is unsubstituted or substituted with -OH, $-NH_2$, -NH($C_{1-4}$alkyl), or -N($C_{1-4}$alkyl)$_2$, and

$R^w$ and $R^y$ are each independently H or $C_{1-4}$alkyl;

wherein  is not unsubstituted phenyl;

$R^7$ and $R^8$ are each independently hydrogen or $C_{1-4}$alkyl,

or $R^7$ and $R^8$ are taken together to form -$CH_2CH_2$-;

$R^{9a}$ and $R^{9b}$ are each independently hydrogen or halogen;

$R^{10}$, $R^{11}$, $R^{12}$, $R^{13}$, and $R^{14}$ are each independently hydrogen, halogen, -OH, -CN, -alkyl, -Oalkyl, -haloalkyl, heterocycloalkyl, -O-haloalkyl, -$SO_2C_{1-4}$alkyl, or -$NR^{aa}R^{bb}$;

$R^{aa}$ is hydrogen, $C_{1-4}$alkyl, or -$C_{1-4}$alkyl-OH;

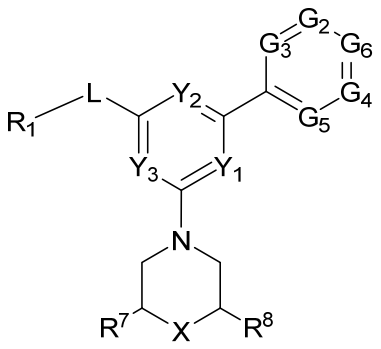
$R^{bb}$ is hydrogen or $C_{1-4}$alkyl;

or $R^{9a}$ is taken together with $R^{10}$ and the interposed atoms to form a heteroaryl or heterocyclic ring;

or $R^{11}$ is taken together with $R^{12}$ and the atoms to which they are attached to form a heteroaryl or heterocyclic ring;

or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1, wherein the compound is of Formula (III)




(III)

wherein

$R^1$ is -$(CR^aR^b)_m$-aryl, -CH=CH-aryl, $(CR^cR^d)_n$-heteroaryl, $(CR^eR^f)_o$- heterocycloalkyl, or $(CR^gR^h)_p$-cycloalkyl, wherein the heteroaryl and the heterocycloalkyl present in $R^1$ are each monocyclic;

m is 0 or 2;

n, o, and p are each independently 0, 1, or 2;

$R^a$, $R^b$, $R^c$, $R^d$, $R^e$, $R^f$, $R^g$, and $R^h$ are each independently H, halo, or $C_{1-4}$alkyl,

or $R^a$ and $R^b$ are taken together with the carbon to which they are attached to form a cycloalkyl ring,

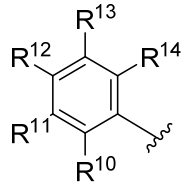
or $R^a$ and $R^b$ are taken together to form =$CH_2$ or =O;

each aryl, heteroaryl, heterocycloalkyl, or cycloalkyl present in $R^1$ is unsubstituted or substituted with one or two $R^x$ substituents;

wherein each $R^x$ substituent is independently halo, $C_{1-4}$alkyl, cycloalkyl, -$C_{1-2}$-haloalkyl, -OH, -$OC_{1-4}$alkyl, -O-$C_{1-2}$-haloalkyl, cyano, -$C(O)C_{1-4}$alkyl, -$C(O)NR^iR^j$, -$SO_2C_{1-4}$alkyl, -$SO_2NR^kR^l$, -$NR^qR^r$, -C(O)-cycloalkyl, -C(O)-aryl (optionally substituted with methyl or halo), -$CO_2C_{1-4}$alkyl, -$CO_2$aryl, -$C(O)CH_2$-aryl (optionally substituted with methyl or halo), -$CH_2$-aryl (optionally substituted with methyl or halo), or monocyclic heterocycloalkyl (optionally substituted with methyl, -$C(O)C_{1-4}$alkyl, or -$CO_2C_{1-4}$alkyl);

wherein $R^i$, $R^j$, $R^k$, and $R^l$ are each independently H, $C_{1-4}$alkyl, -$C_{1-4}$alkyl-OH, or -$C_{1-4}$alkyl-O-$C_{1-4}$alkyl,

wherein $R^q$ and $R^r$ are each independently H, $C_{1-4}$alkyl, -$C_{1-4}$alkyl-OH, -$C_{1-4}$alkyl-O-$C_{1-4}$alkyl, -$C(O)C_{1-4}$alkyl, -$CO_2C_{1-4}$alkyl, or -$SO_2C_{1-4}$alkyl;

or $R^1$ is 

;

wherein

$R^{10}$, $R^{11}$, $R^{12}$, $R^{13}$, and $R^{14}$ are each independently hydrogen, halogen, -OH, -CN, -alkyl, -Oalkyl, -haloalkyl, heterocycloalkyl, -O-haloalkyl, -$SO_2C_{1-4}$alkyl, or -$NR^{aa}R^{bb}$;

$R^{aa}$ is hydrogen, $C_{1-4}$alkyl, or -$C_{1-4}$alkyl-OH;

$R^{bb}$ is hydrogen or $C_{1-4}$alkyl;

or $R^{10}$ is taken together with $R^{11}$ and the atoms to which they are attached to form a heteroaryl or heterocyclic ring;

or $R^{11}$ is taken together with $R^{12}$ and the atoms to which they are attached to form a heteroaryl or heterocyclic ring;

L is -$S(O)_2$-;

X is O, S, NH, N($CO_2C_{1-4}$alkyl), N($SO_2C_{1-4}$alkyl), N($SO_2$cyclo-alkyl), or $CH_2$;

$Y_1$, $Y_2$, and $Y_3$ are each independently CH or N;

$G_2$ is N or $CR^2$;

$G_3$ is N or $CR^3$;

$G_4$ is N, $NR^{4b}$, or $CR^{4a}$;

$G_5$ is N or $CR^5$; and

$G_6$ is N or $CR^6$;

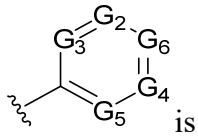
wherein $R^2$, $R^3$, $R^{4a}$, $R^5$, and $R^6$ are each independently hydrogen, halogen, -OH, -alkyl, -Oalkyl, -haloalkyl, -O-haloalkyl, or $-NR^uR^v$;

or $R^{4b}$ is taken together with $R^6$ and the atoms to which they are attached to form a heteroaryl or heterocyclic ring; wherein the heteroaryl ring comprising $R^{4b}$ and $R^6$ comprises no more than one N and is optionally substituted with alkyl, and the heterocylic ring comprising $R^{4b}$ and $R^6$ is optionally substituted with oxo,

$R^u$ is H or $C_{1\text{-}4}$alkyl;

$R^v$ is H, $C_{1\text{-}4}$alkyl, monocyclic cycloalkyl, $-C(O)C_{1\text{-}4}$alkyl, or $-C(O)NR^wR^y$; wherein each alkyl present in $R^v$ is unsubstituted or substituted with -OH, $-NH_2$, $-NH(C_{1\text{-}4}$alkyl), or $-N(C_{1\text{-}4}$alkyl$)_2$,

$R^w$ and $R^y$ are independently H or $C_{1\text{-}4}$alkyl;

wherein  is not unsubstituted phenyl; and

$R^7$ and $R^8$ are each independently hydrogen or $C_{1\text{-}4}$alkyl,

or $R^7$ and $R^8$ are taken together to form $-CH_2CH_2-$;

or a pharmaceutically acceptable salt thereof.

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein $Y_1$, $Y_2$, and $Y_3$ are each CH.

8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein $Y_1$ is N and $Y_2$ and $Y_3$ are each CH.

9. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein $Y_2$ is N and $Y_1$ and $Y_3$ are each CH.

10. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein $Y_3$ is N and $Y_1$ and $Y_2$ are each CH.

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

12. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein X is NH, N($CO_2C_{1-4}$alkyl), N($SO_2C_{1-4}$alkyl), or N($SO_2$cyclo-alkyl).

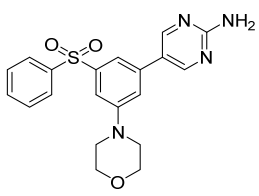
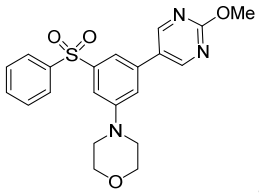
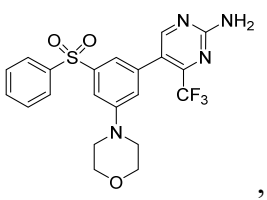
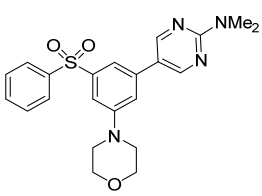
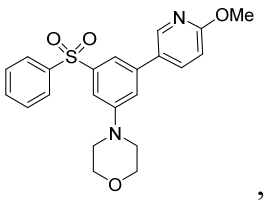
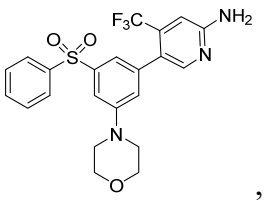
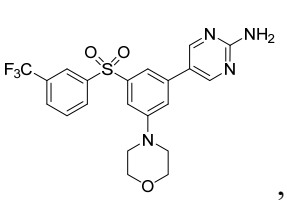
13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein $G_2$ and $G_4$ are each N, and $G_6$ is $CR^6$.

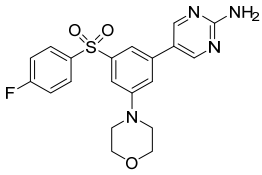
14. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein $G_3$ is $CR^3$ and $G_5$ is $CR^5$.

15. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein one of $G_2$ and $G_4$ is N.

16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof,wherein $R^6$ is -$NR^uR^v$.

17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein $R^{4b}$ is taken together with $R^6$ and the atoms to which they are attached to form a heteroaryl or heterocyclic ring.

18. A compound that is , , , , , , ,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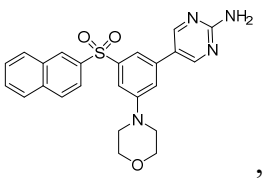
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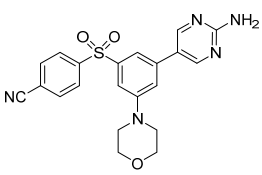
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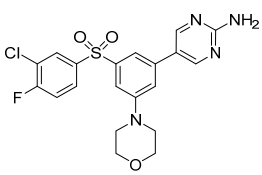
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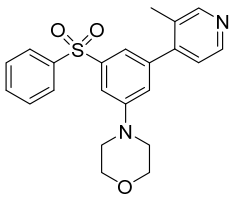
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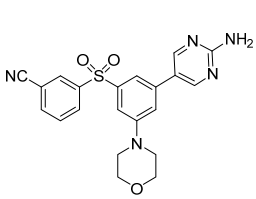
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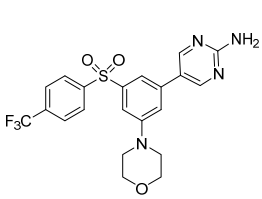
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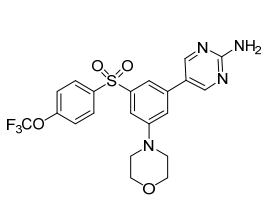
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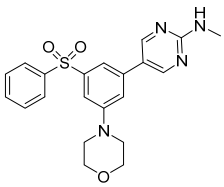
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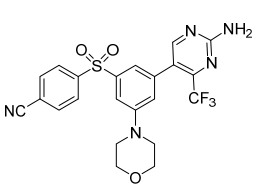
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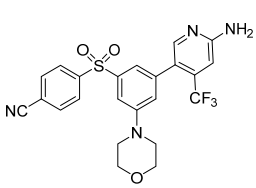
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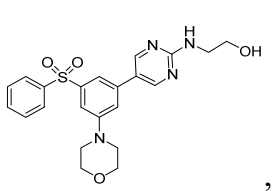
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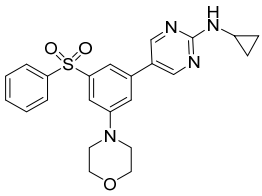
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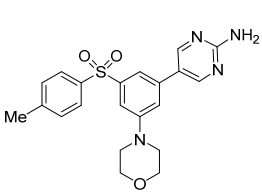
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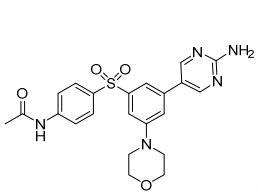
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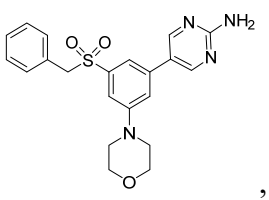
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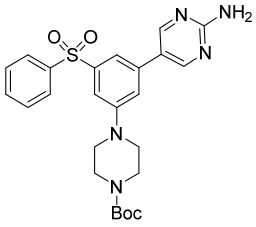
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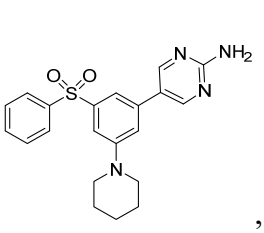
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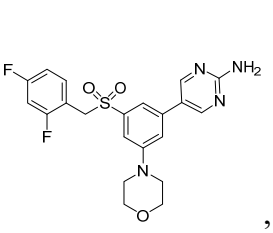
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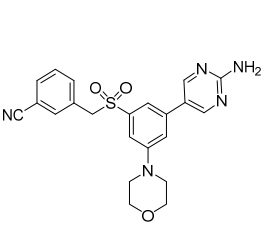
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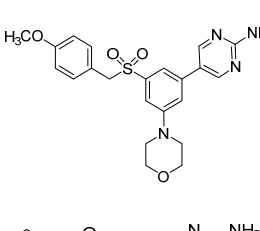
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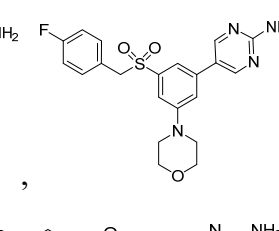
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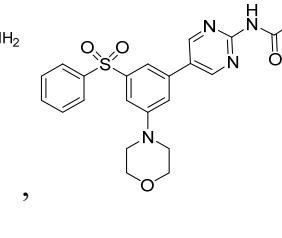
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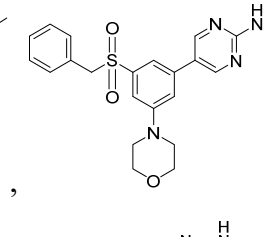
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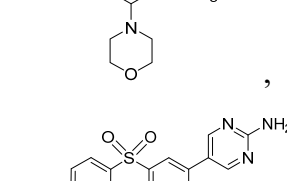
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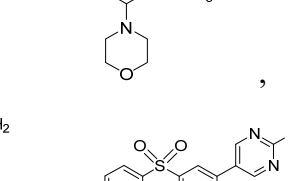
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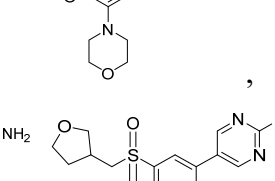
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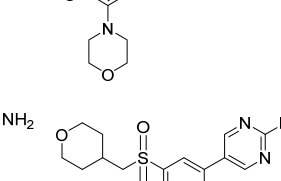
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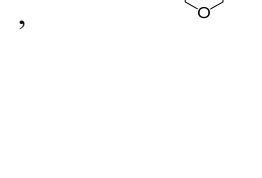
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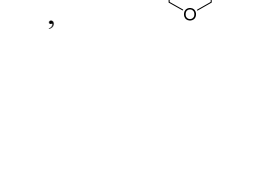
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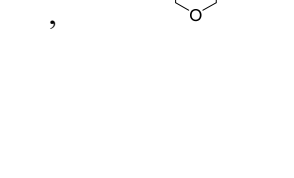
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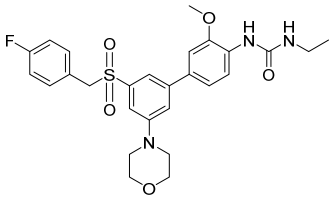
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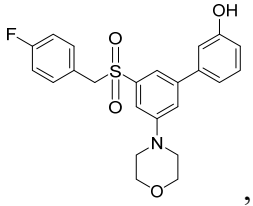
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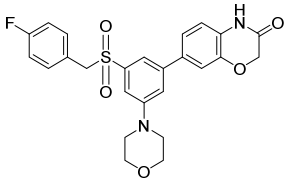
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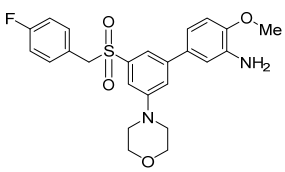
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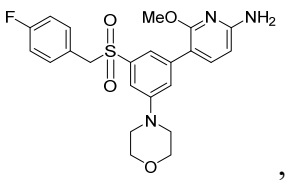
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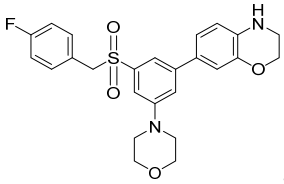
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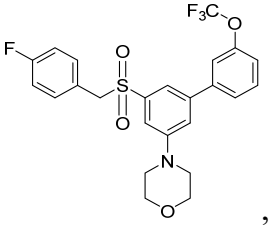
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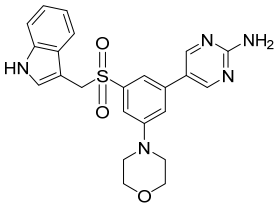
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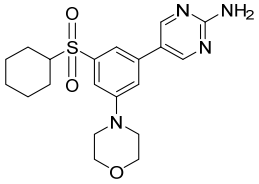
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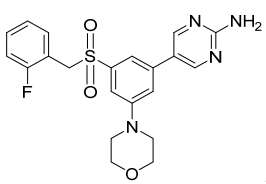
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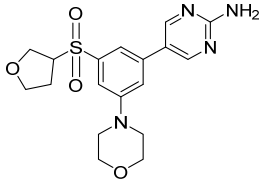
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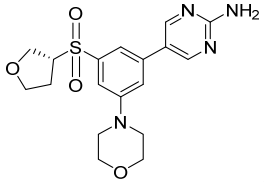
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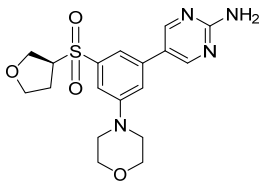
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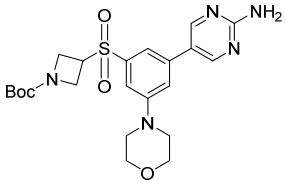
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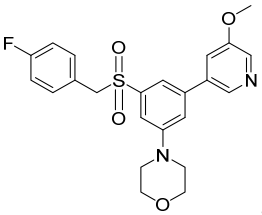
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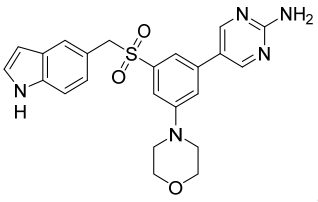
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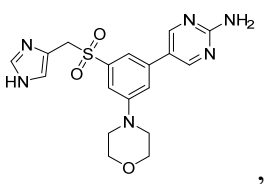
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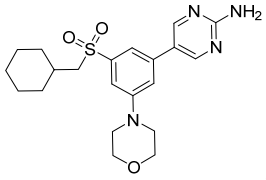
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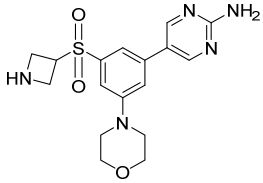
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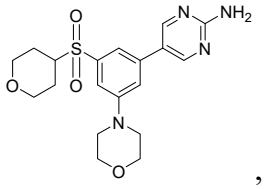
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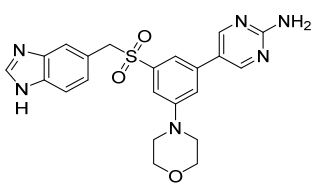
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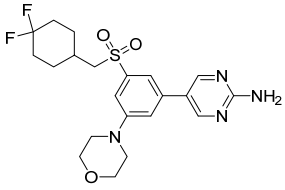
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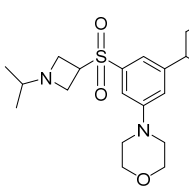
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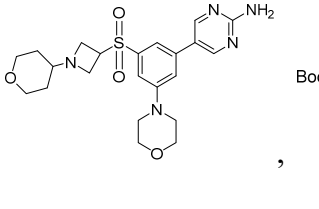
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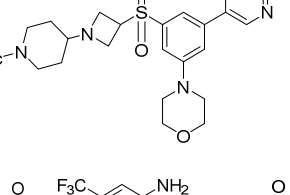
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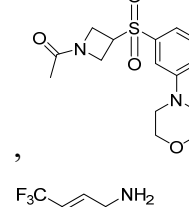
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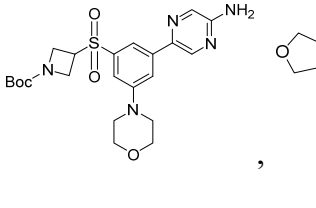
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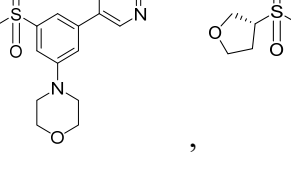
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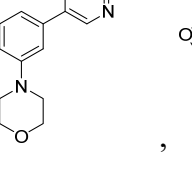
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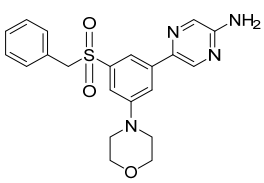
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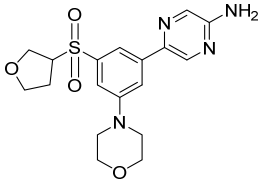
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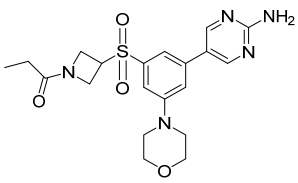
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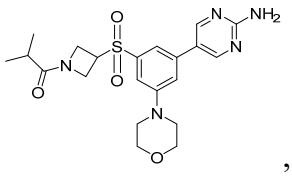
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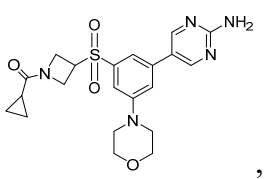
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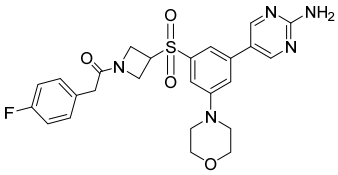
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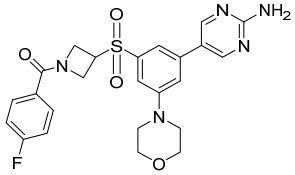
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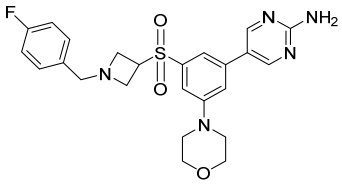
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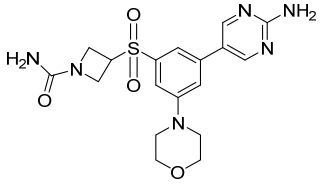
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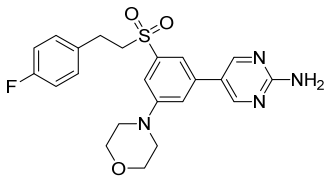
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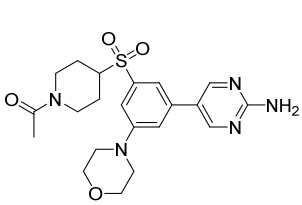
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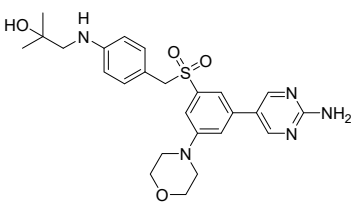
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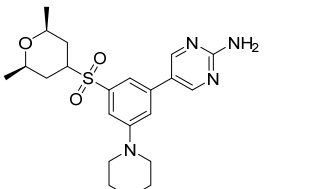
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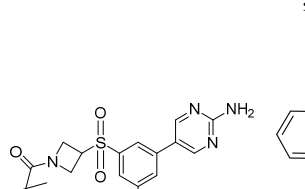
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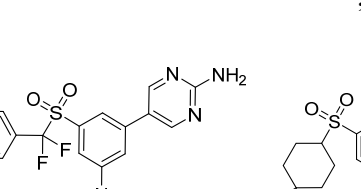
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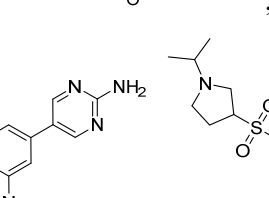
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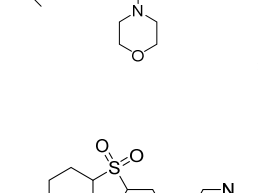
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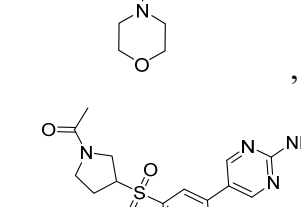
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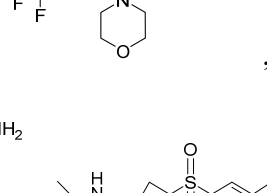
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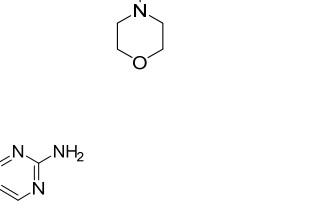
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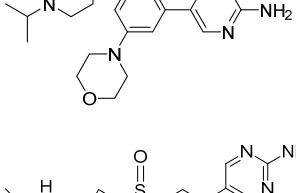
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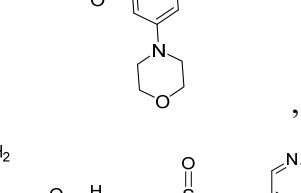
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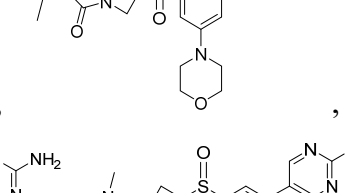
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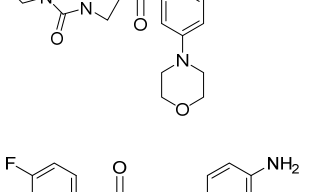
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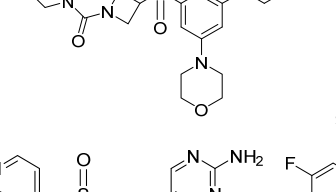
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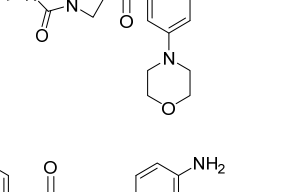
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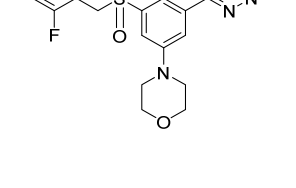
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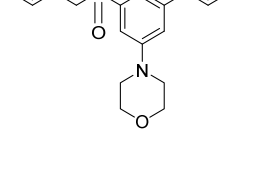
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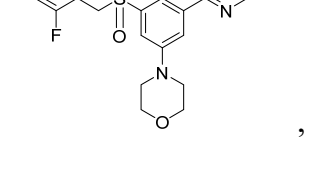
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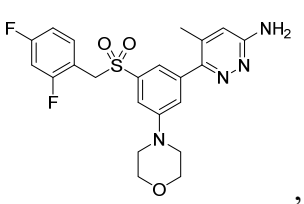
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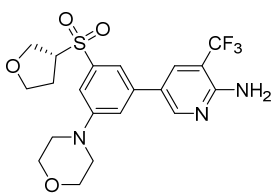
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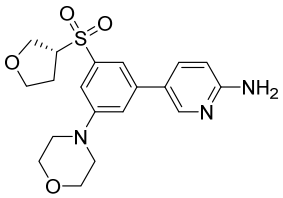
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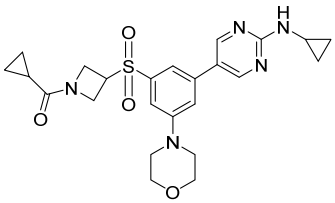
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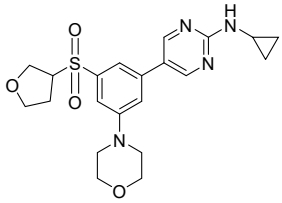
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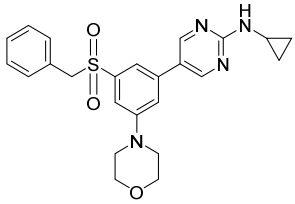
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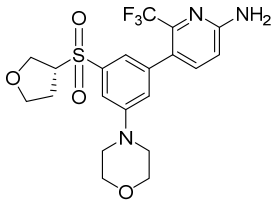
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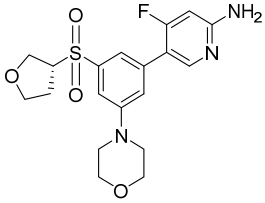
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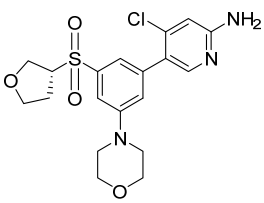
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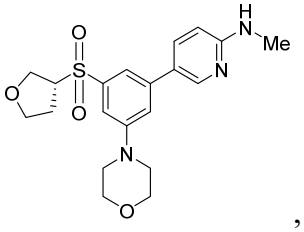
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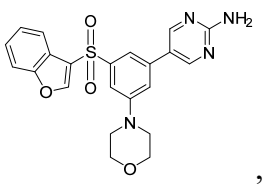
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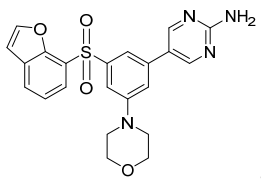
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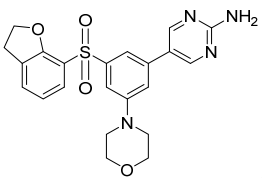
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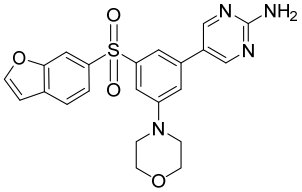
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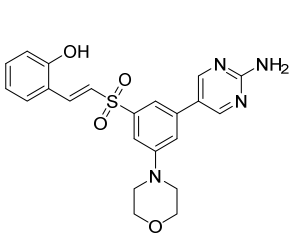
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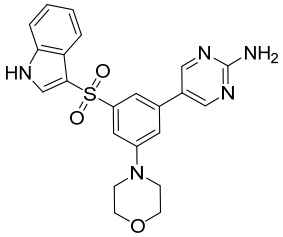
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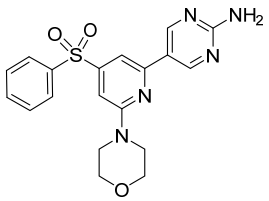
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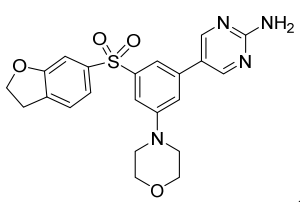
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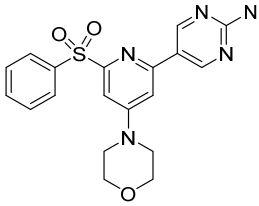
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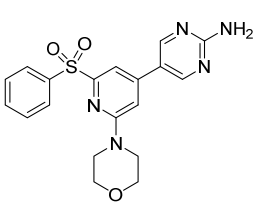
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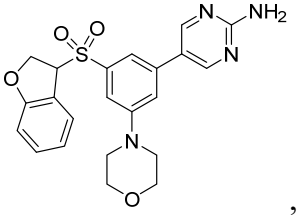
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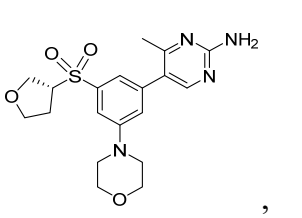
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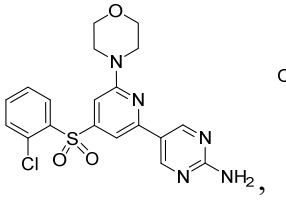
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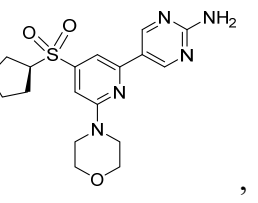
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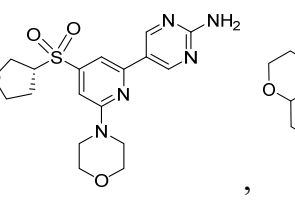
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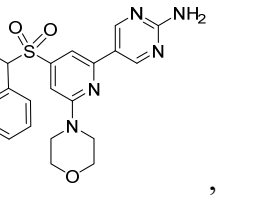
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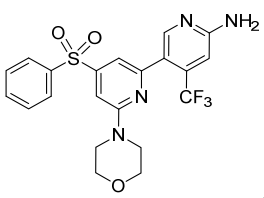
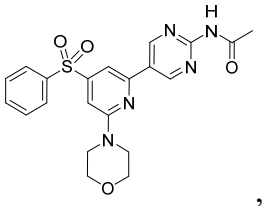
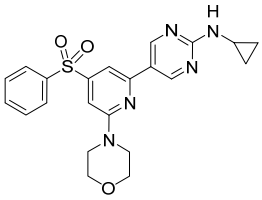
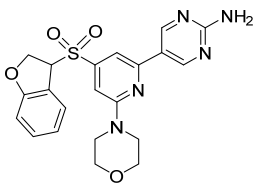
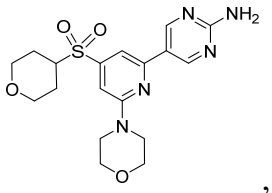
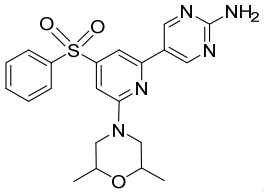
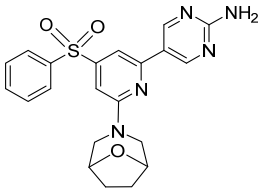
, , , , , , , or , or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising (a) at least one compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable excipient.

20. A compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 19, for use as a medicament.

21. A compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 19, for use in the treatment of a disease or medical condition associated with autophagy or the PI3K-AKT-MTOR pathway, wherein the disease or medical condition is Alzheimer's Disease, Parkinson's Disease, fronto-temporal dementia, dementia with Lewy Bodies, PD dementia, multiple system atrophy, Huntington's disease, Amyotrophic lateral sclerosis, cancer, infection, Crohn's disease, heart disease, Paget's disease, Charcot-Marie-Tooth Disease, macular degeneration, cardiomyopathy, aging, rosacea, acne, psoriasis, or atopic dermatitis.

22. Use of at least one compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 19, in the manufacture of a medicament for the treatment of a disease or medical condition associated with autophagy or the PI3K-AKT-MTOR pathway, wherein the disease or medical condition is Alzheimer's Disease, Parkinson's Disease, fronto-temporal dementia, dementia with Lewy Bodies, PD dementia, multiple system atrophy, Huntington's disease, Amyotrophic lateral sclerosis, cancer, infection, Crohn's disease, heart disease, Paget's disease, Charcot-Marie-Tooth

Disease, macular degeneration, cardiomyopathy, aging, rosacea, acne, psoriasis, or atopic dermatitis.