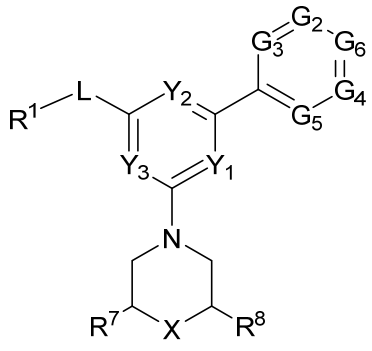
Claims

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 absent, $–S(O)_2$-, -C(O)-, -O-, $-CH_2$-, $-CF_2$-, $C(CH_3)_2$, $-C(=CH_2)$-, or $–CR^sR^t$-; wherein R^s and R^t are independently H or alkyl, or R^s and R^t are taken together with the carbon atom to which they are attached to form a cycloalkyl ring;

X is O, S, NH, $N(CO_2C_{1-4}alkyl)$, $N(SO_2C_{1-4}alkyl)$, $N(SO_2cycloalkyl)$, or CH_2;

Y_1, Y_2, and Y_3 are each independently CH or N; wherein when L is other than $–S(O)_2$-, Y_2 and Y_3 are each CH;

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 $–NR^uR^v$;

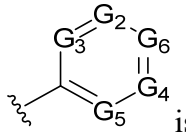
or R^{4b} is taken together with R^6 and the atoms to which they are attached to form a heteroaryl or heterocyclic ring; wherein the heteroaryl ring comprising R^{4b} and R^6 comprises no more than one N and is optionally substituted with alkyl, and the heterocyclic ring comprising R^{4b} and R^6 is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

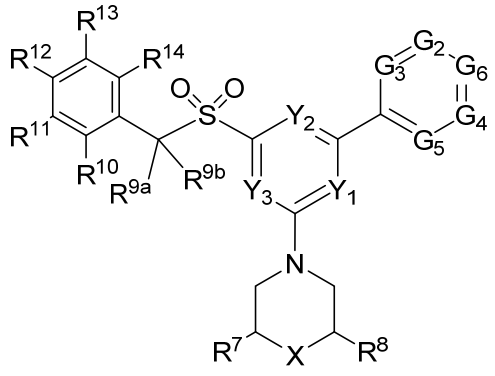
4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is $(CR^eR^f)_o$-heterocycloalkyl or $(CR^gR^h)_p$-cycloalkyl.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein L is $–S(O)_2$-.

6. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein L is -C(O)-, $-CH_2$-, $-CF_2$-, $C(CH_3)_2$, $-C(=CH_2)$-, or $–CR^sR^t$-.

7. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein L is absent.

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



(II)

wherein

X is O, S, NH, $N(CO_2C_{1-4}alkyl)$, $N(SO_2C_{1-4}alkyl)$, $N(SO_2cycloalkyl)$, 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 $–NR^uR^v$;

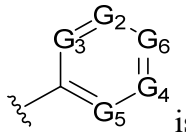
or R^{4b} is taken together with R^6 and the atoms to which they are attached to form a heteroaryl or heterocyclic ring; wherein the heteroaryl ring comprising R^{4b} and R^6 comprises no more than one N and is optionally substituted with alkyl, and the heterocyclic ring comprising R^{4b} and R^6 is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

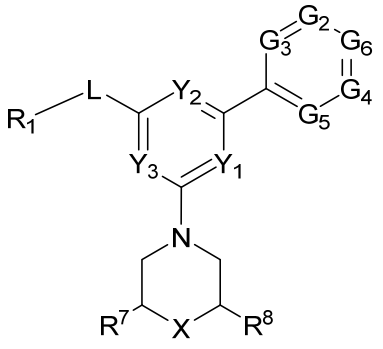
R^{bb} is hydrogen or C_{1-4}alkyl;

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.

9. 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 when L is SO_2, 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,

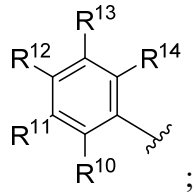
or R^a and R^b are taken together to form $=CH_2$ or =O;

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_2aryl, -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 absent, –$S(O)_2$-, -C(O)-, -O-, -CH_2-, -CF_2-, $C(CH_3)_2$, -C(=CH_2)-, or –CR^sR^t-; where R^s and R^t are independently H or alkyl, or R^s and R^t are taken together with the carbon atom to which they are attached to form a cycloalkyl ring;

X is O, S, NH, N(CO_2C_{1-4}alkyl), N(SO_2C_{1-4}alkyl), N(SO_2cyclo-alkyl), or CH_2;

Y_1, Y_2, and Y_3 are each independently CH or N; wherein when L is other than –$S(O)_2$-, Y_2 and Y_3 are each CH;

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;

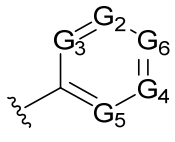
or R^{4b} is taken together with R^6 and the atoms to which they are attached to form a heteroaryl or heterocyclic ring; wherein the heteroaryl ring comprising R^{4b} and R^6 comprises no more than one N and is optionally substituted with alkyl, and the heterocylic ring comprising R^{4b} and R^6 is optionally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

R^u is H or C_{1-4}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 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.

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

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

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

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

14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein X is O.

15. The compound of any one of claims 1-13, 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_2cyclo-alkyl).

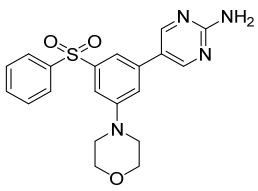
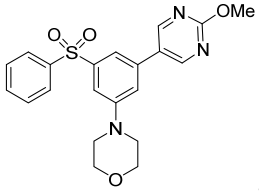
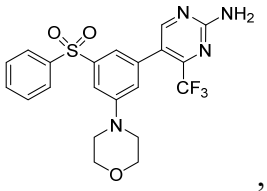
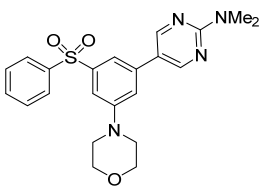
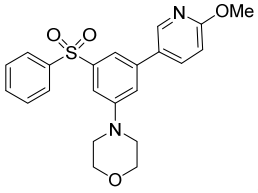
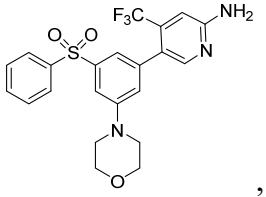
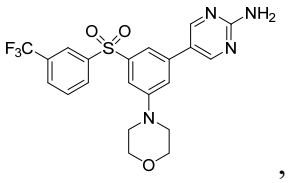
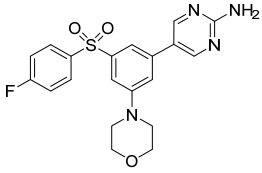
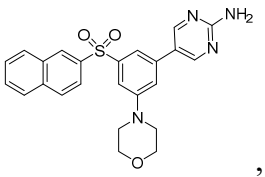
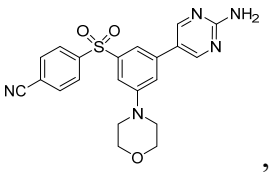
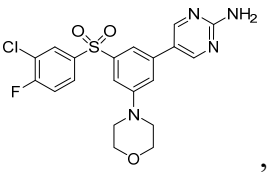
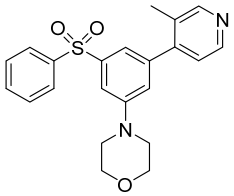
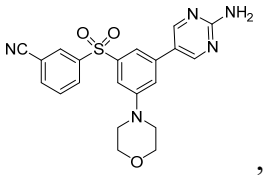
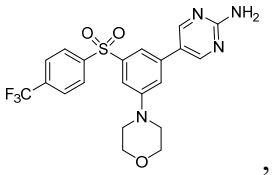
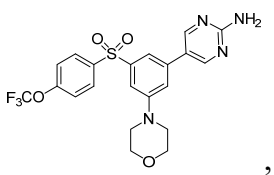
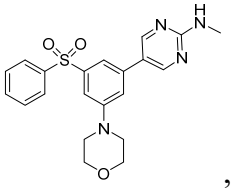
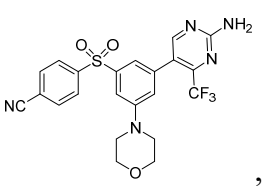
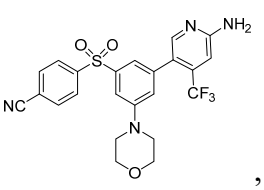
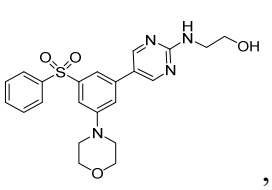
16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein G_2 and G_4 are each N, and G_6 is CR^6.

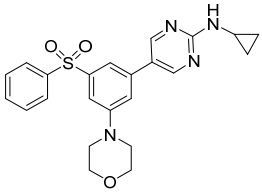
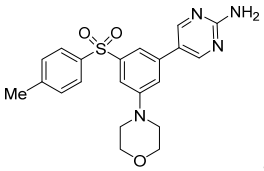
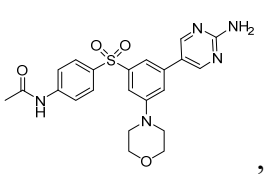
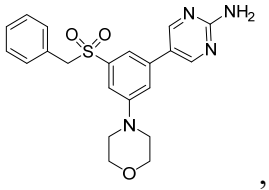
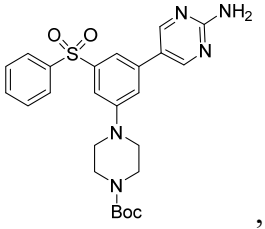
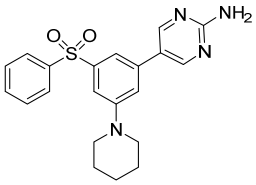
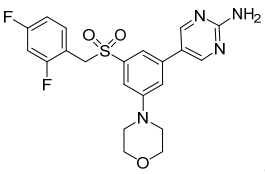
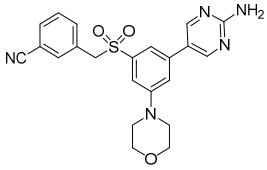
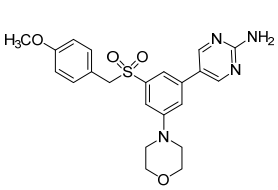
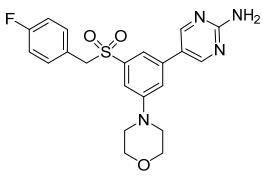
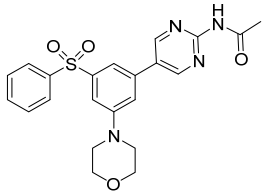
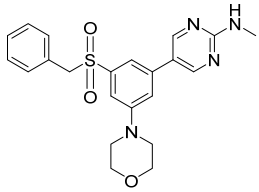
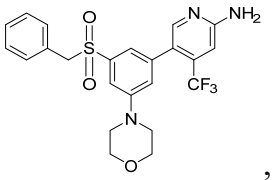
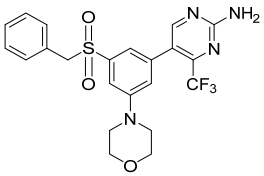
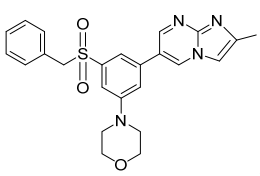
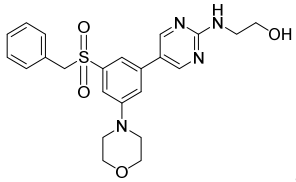
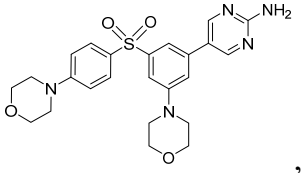
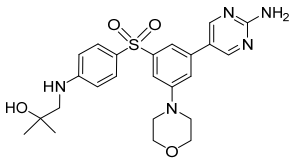
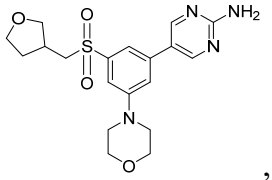
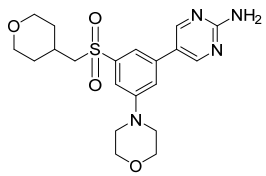
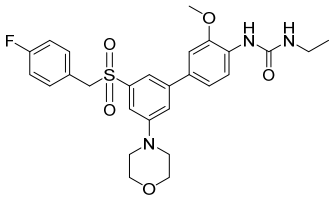
17. The compound of claim 16, or a pharmaceutically acceptable salt thereof, wherein G_3 is CR^3 and G_5 is CR^5.

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

19. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof,wherein R^6 is $–NR^uR^v$.

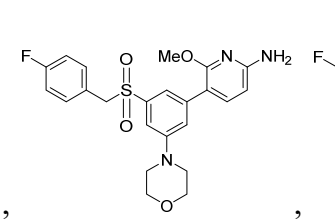
20. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein R^{4b} is taken together with R^6 and the atoms to which they are attached to form a heteroaryl or heterocyclic ring.

21. A compound that is , , , , , , , , , , , , , , , , , , .


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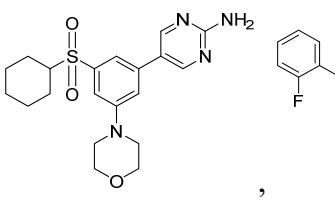
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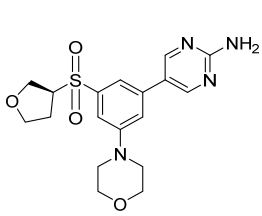
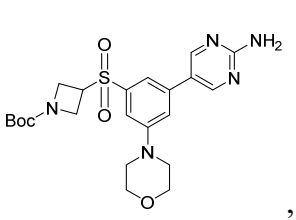
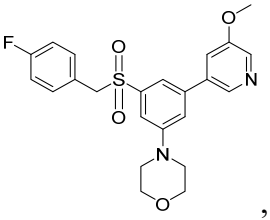
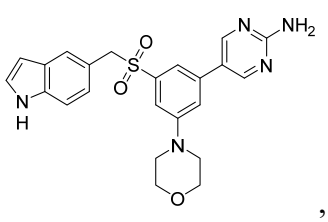
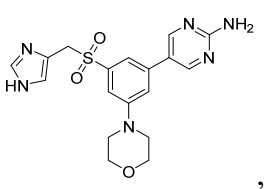
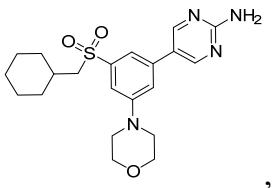
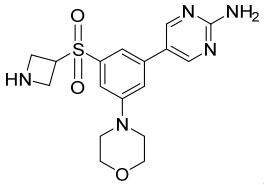
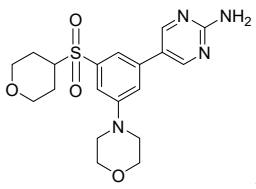
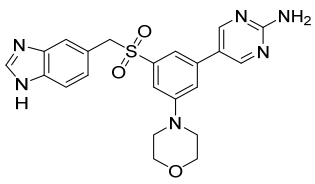
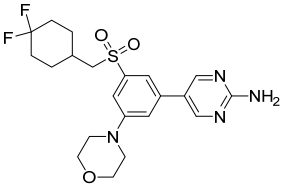
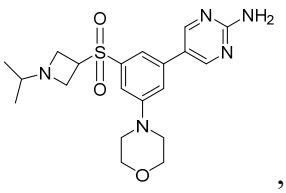
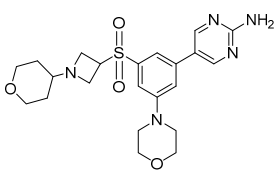
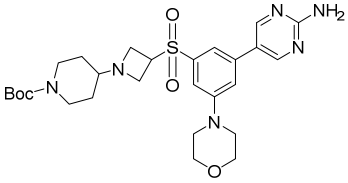
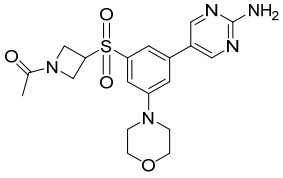
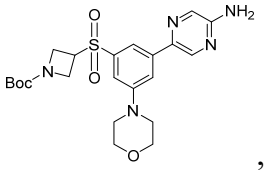
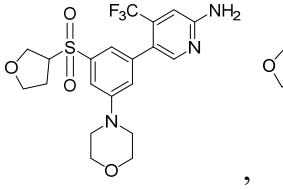
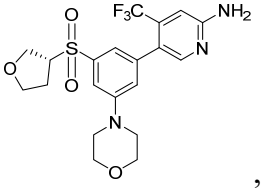
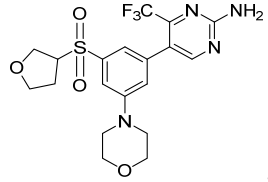
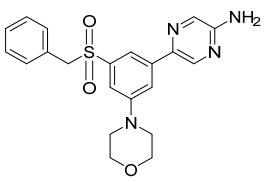
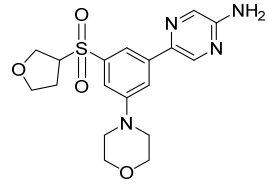
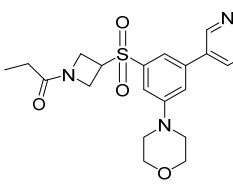
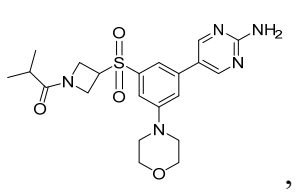
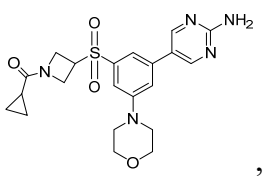
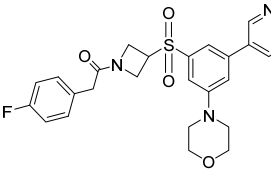
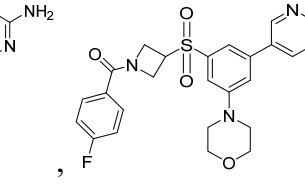
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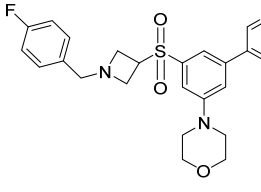
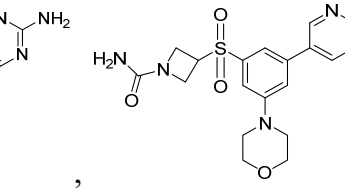
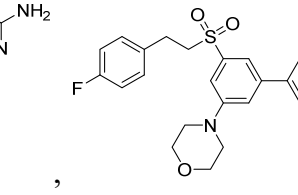
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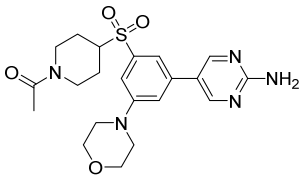
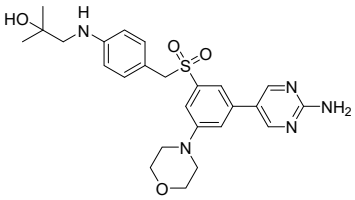
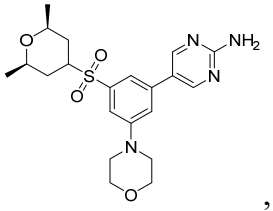
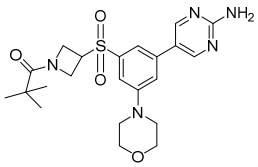
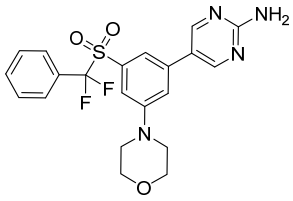
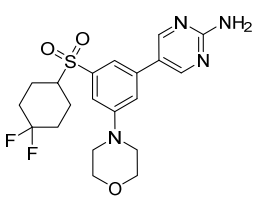
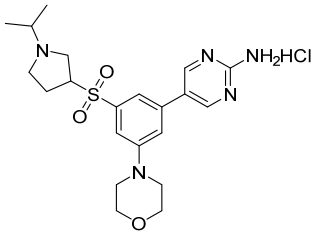
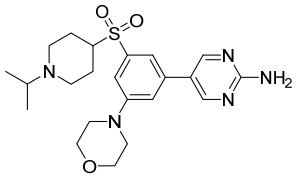
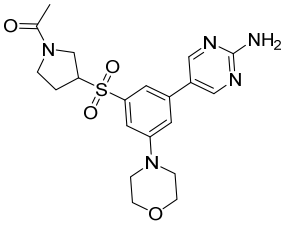
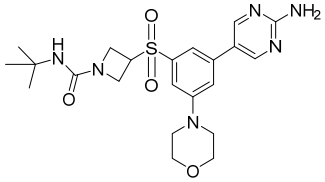
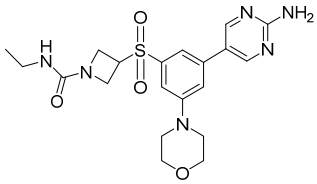
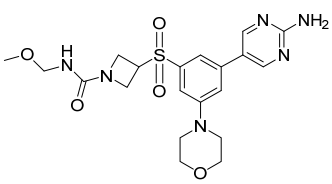
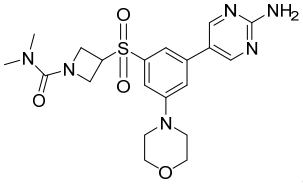
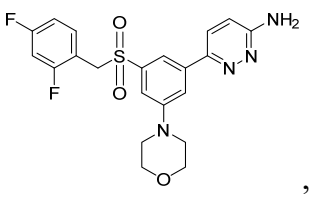

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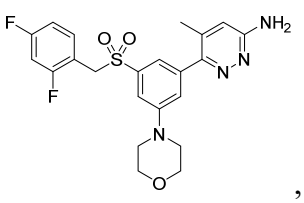
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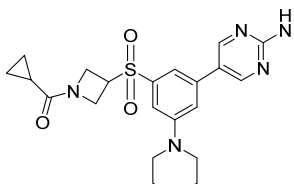
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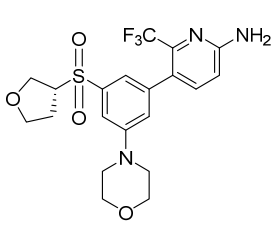
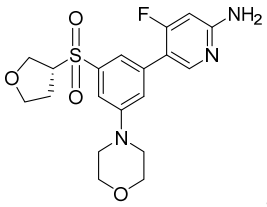
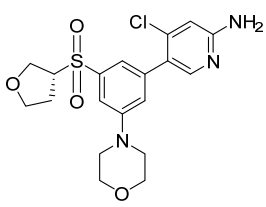
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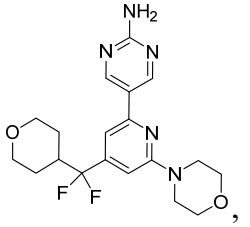
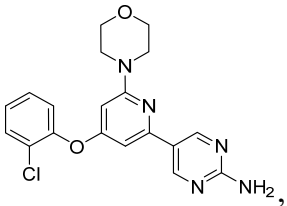
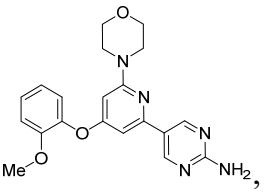
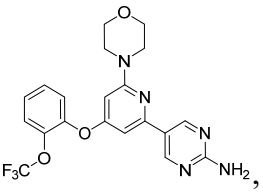
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24. A compound of any one of claims 1-21, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 22, for use in the treatment of a disease or medical condition associated with autophagy or the PI3K-AKT-MTOR pathway.

25. The compound or pharmaceutical composition for use of claim 24, 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, or aging.

26. The compound or pharmaceutical composition for use of claim 24, wherein the disease or medical condition is rosacea, acne, psoriasis, or atopic dermatitis.

27. Use of at least one compound of any one of claims 1-21, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 22, in the manufacture of a medicament for the treatment of a disease or medical condition associated with autophagy or the PI3K-AKT-MTOR pathway.

28. The use of claim 27, 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, or aging.

29. The use of claim 27, wherein the disease or medical condition is rosacea, acne, psoriasis, or atopic dermatitis.