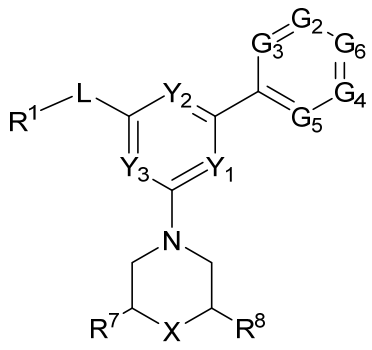
Claims

1. A compound of Formula (I):



(I)

wherein

R^1 is -(CR^{a}R^b)$_m$-aryl, -CH=CH-aryl, -(CR^{c}R^d)$_n$-heteroaryl, -(CR^{e}R^f)$_o$-heterocycloalkyl, or -(CR^{g}R^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^{i}R^j, -SO_2C_{1-4}alkyl, -SO_2NR^{k}R^l, -NR^{q}R^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;

L is ~~absent, -~~S(O)$_2$-~~, -C(O)-, -O-, -CH$_2$-, -CF$_2$-, C(CH$_3$)$_2$, -C(=CH$_2$)-, or -CR^{s}R^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$_2$C$_{1-4}$alkyl), N(SO$_2$C$_{1-4}$alkyl), N(SO$_2$cycloalkyl), 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^{u}R^v;

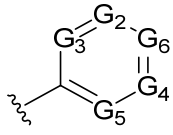
or R^{4b} is taken together with R^6 and the atoms to which they are attached to form a heteroaryl or heterocyclic ring; wherein the heteroaryl ring comprising R^{4b} and R^6 comprises no more than one N and is optionally substituted with alkyl, and the heterocyclic ring comprising R^{4b} and R^6 is 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^{w}R^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$_2$CH$_2$-;

or a pharmaceutically acceptable salt thereof.

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

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

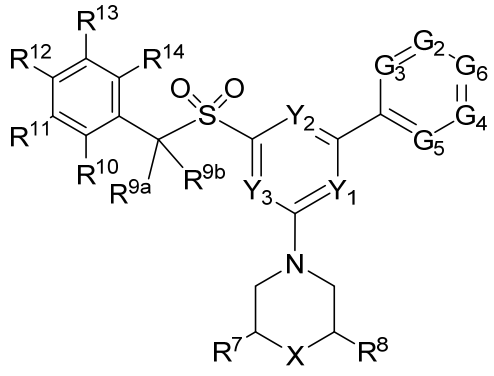
4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is $(CR^eR^f)_o$-heterocycloalkyl or $(CR^gR^h)_p$-cycloalkyl.

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



(II)

wherein

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

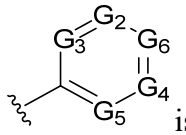
or R^{4b} is taken together with R^6 and the atoms to which they are attached to form a heteroaryl or heterocyclic ring; wherein the heteroaryl ring comprising R^{4b} and R^6 comprises no more than one N and is optionally substituted with alkyl, and the heterocyclic ring comprising R^{4b} and R^6 is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

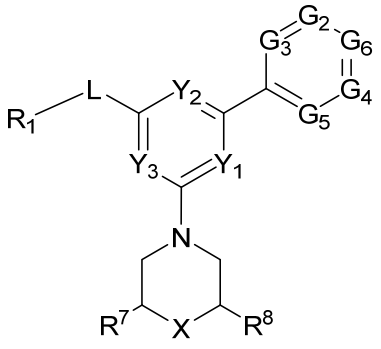
R^{bb} is hydrogen or C_{1-4}alkyl;

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~~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 ~~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,

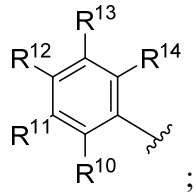
or R^a and R^b are taken together to form $=CH_2$ or =O;

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;

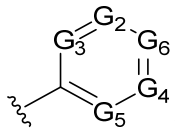
or R^{4b} is taken together with R^6 and the atoms to which they are attached to form a heteroaryl or heterocyclic ring; wherein the heteroaryl ring comprising R^{4b} and R^6 comprises no more than one N and is optionally substituted with alkyl, and the heterocyclic ring comprising R^{4b} and R^6 is 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 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~~7. The compound of any one of claims ~~1-9~~1-6, or a pharmaceutically acceptable salt thereof, wherein Y_1, Y_2, and Y_3 are each CH.

~~11~~8. The compound of any one of claims ~~1-10~~1-7, or a pharmaceutically acceptable salt thereof, wherein Y_1 is N and Y_2 and Y_3 are each CH.

~~12~~9. The compound of any one of claims ~~1-10~~1-7, or a pharmaceutically acceptable salt thereof, wherein Y_2 is N and Y_1 and Y_3 are each CH.

~~13~~10. The compound of any one of claims ~~1-10~~1-7, or a pharmaceutically acceptable salt thereof, wherein Y_3 is N and Y_1 and Y_2 are each CH.

~~14~~11. The compound of any one of claims ~~1-13~~1-10, or a pharmaceutically acceptable salt thereof, wherein X is O.

~~15~~12. The compound of any one of claims ~~1-13~~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_2cyclo-alkyl).

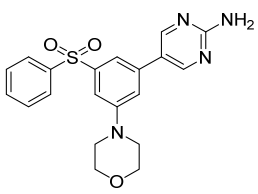
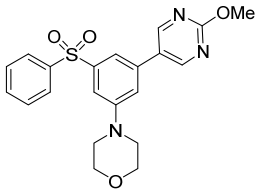
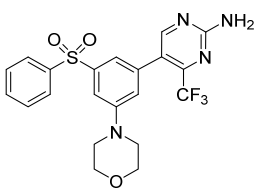
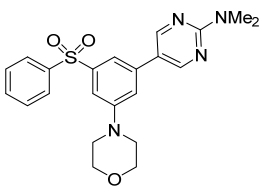
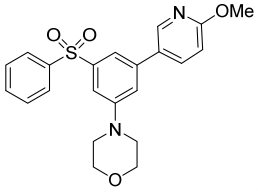
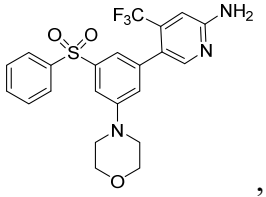
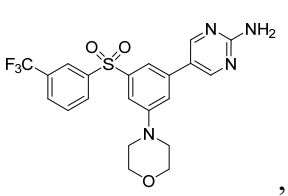
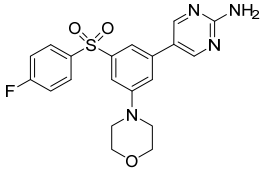
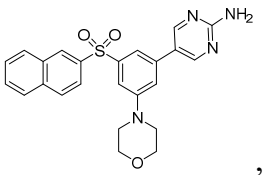
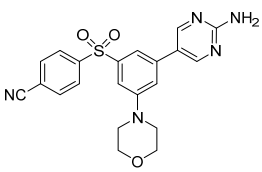
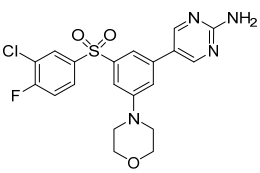
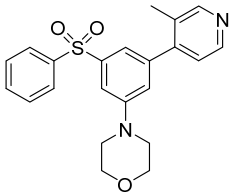
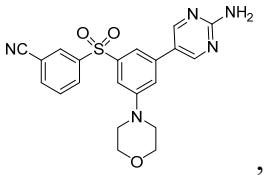
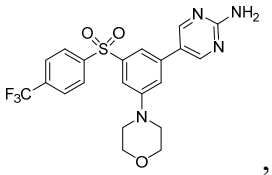
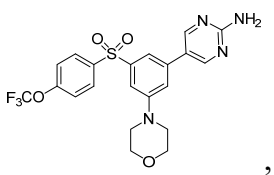
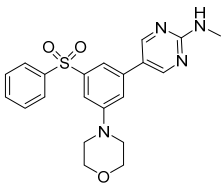
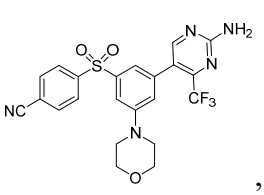
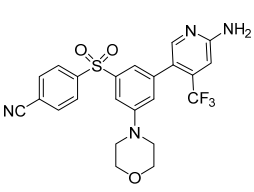
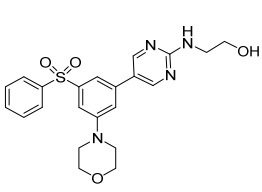
~~16~~13. The compound of any one of claims ~~1-15~~1-12, or a pharmaceutically acceptable salt thereof, wherein G_2 and G_4 are each N, and G_6 is CR^6.

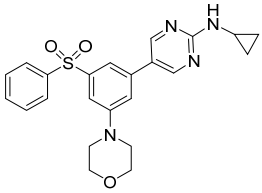
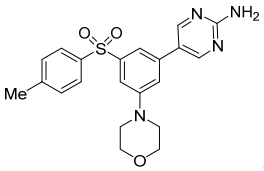
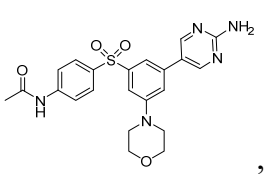
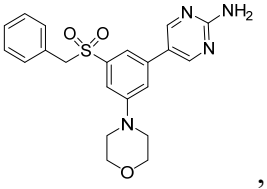
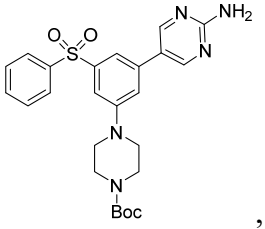
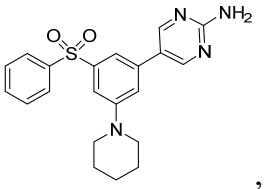
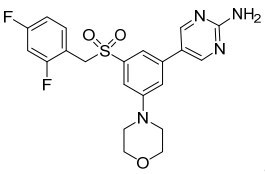
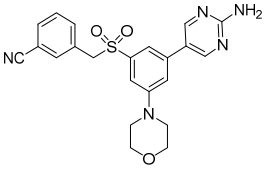
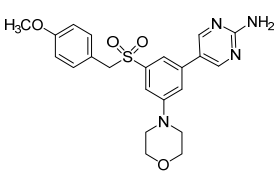
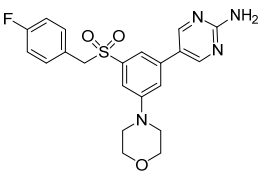
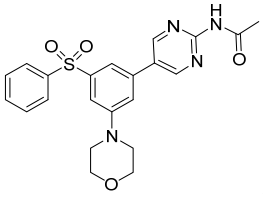
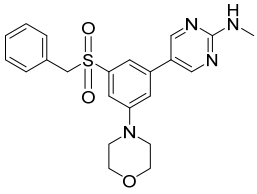
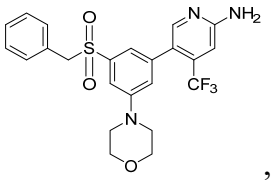
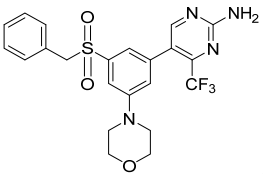
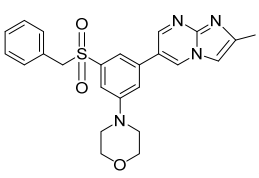
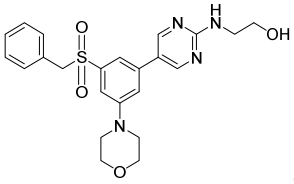
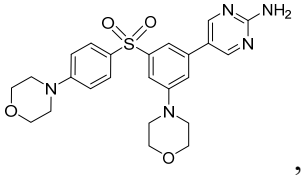
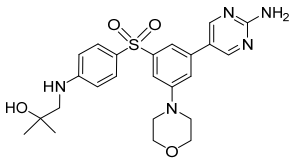
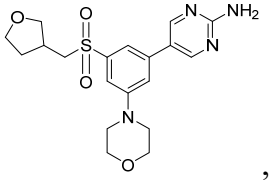
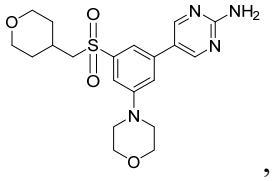
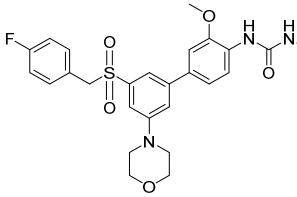
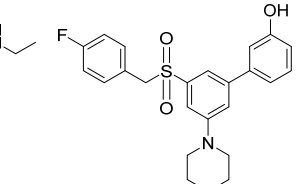
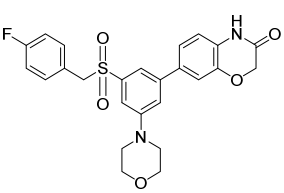
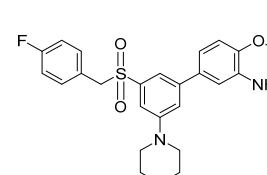
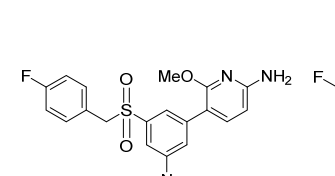
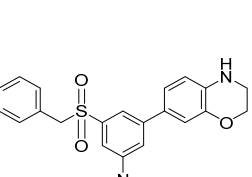
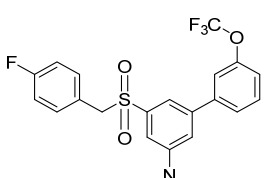
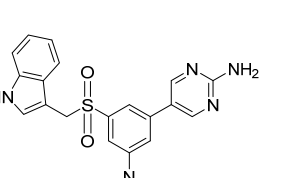
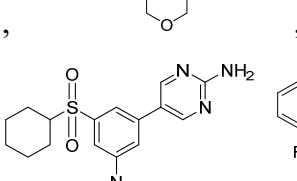
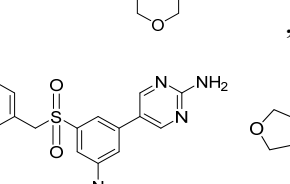
~~17~~14. The compound of claim ~~16~~13, or a pharmaceutically acceptable salt thereof, wherein G_3 is CR^3 and G_5 is CR^5.

~~18~~15. The compound of any one of claims ~~1-15~~1-12, or a pharmaceutically acceptable salt thereof, wherein one of G_2 and G_4 is N.

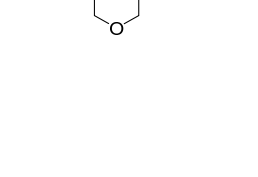
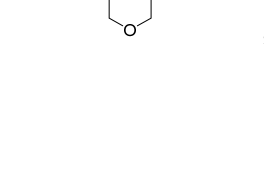
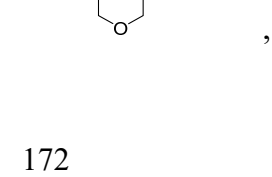
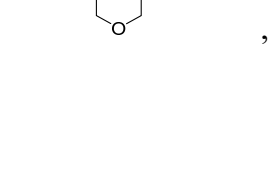
~~19~~16. The compound of any one of claims ~~1-18~~1-15, or a pharmaceutically acceptable salt thereof,wherein R^6 is ~~--~~NR^uR^v.

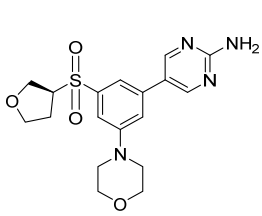
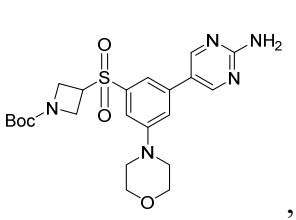
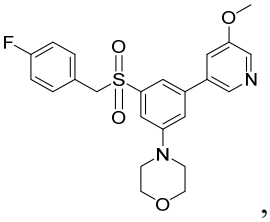
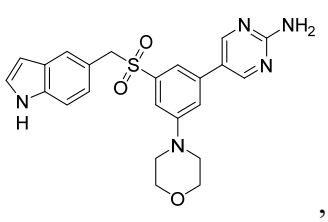
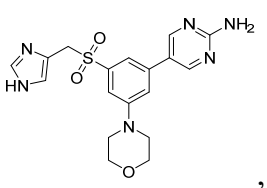
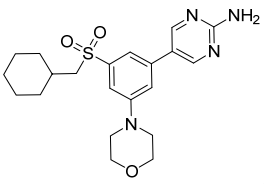
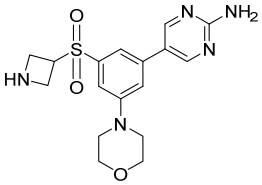
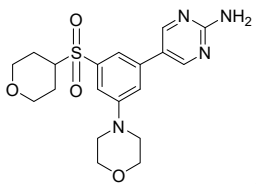
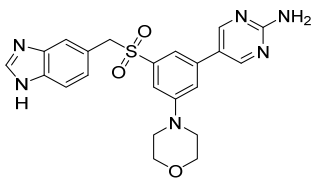
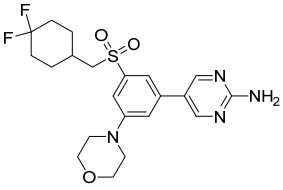
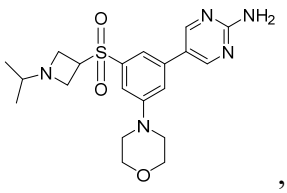
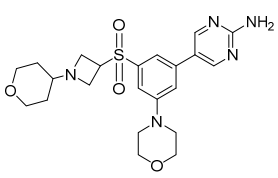
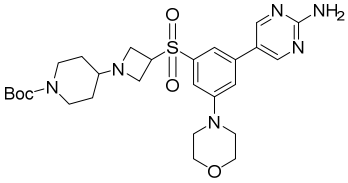
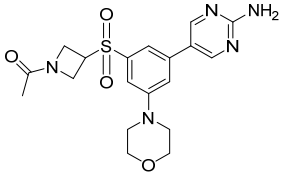
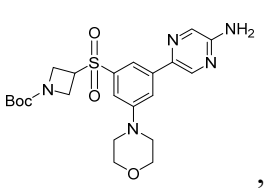
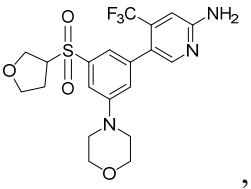
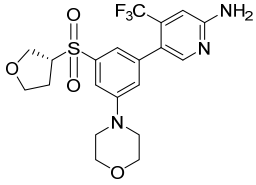
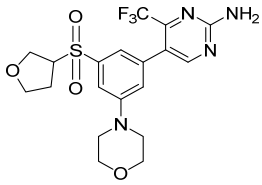
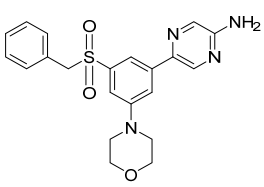
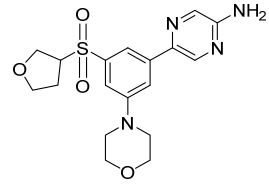
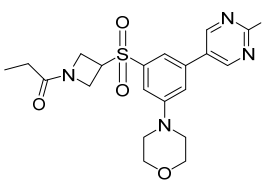
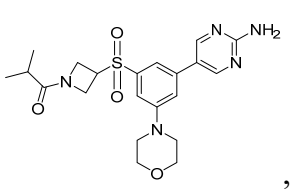
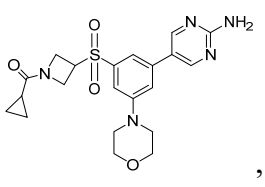
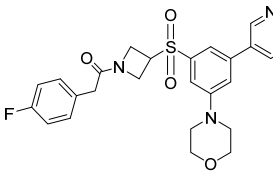
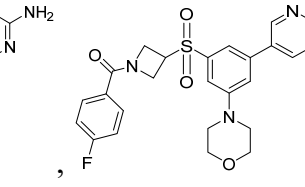
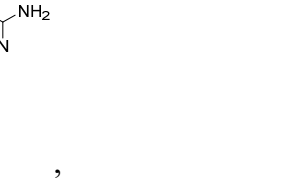
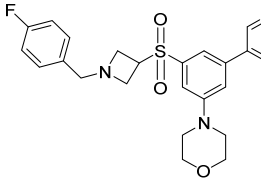
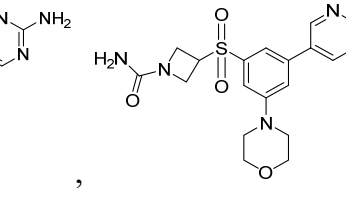
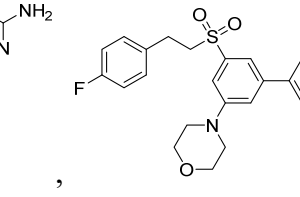
~~20~~17. The compound of any one of claims ~~1-19~~1-16, or a pharmaceutically acceptable salt thereof, wherein R^{4b} is taken together with R^6 and the atoms to which they are attached to form a heteroaryl or heterocyclic ring.

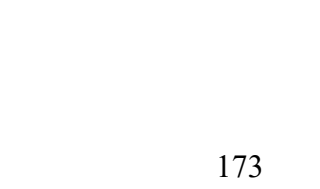
~~21~~18. A compound that is , , , , , , , , , , , , , , , , , , .


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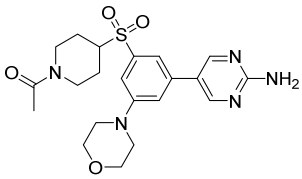
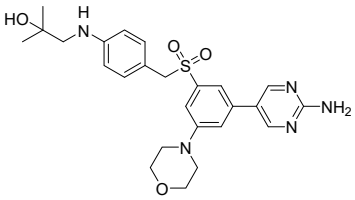
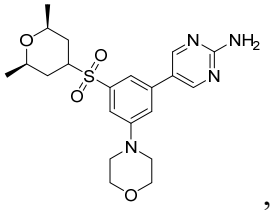
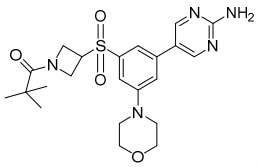
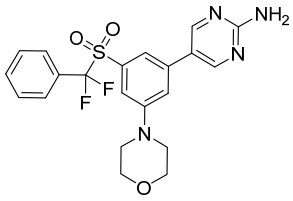
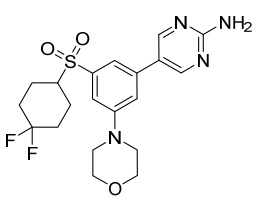
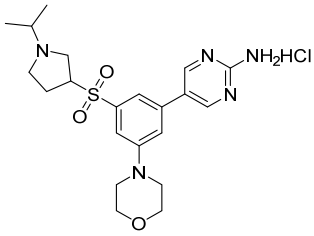
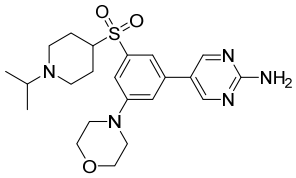
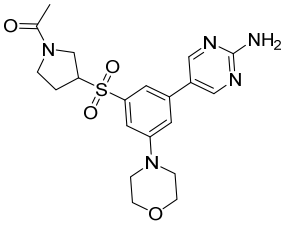
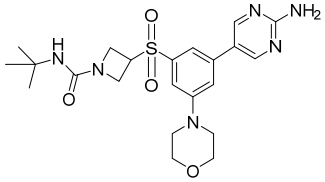
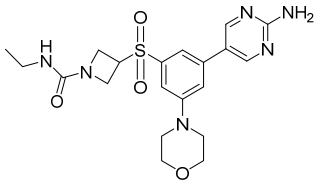
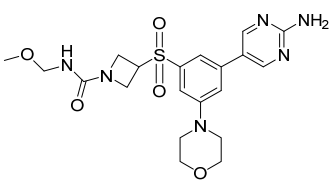
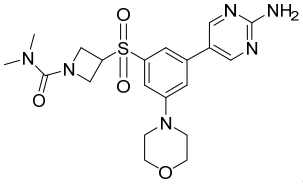
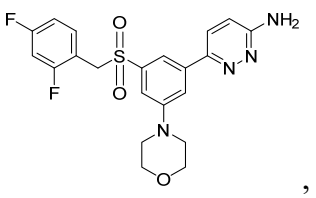
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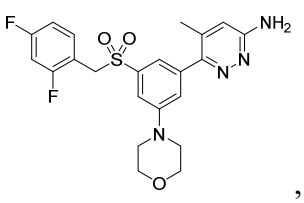

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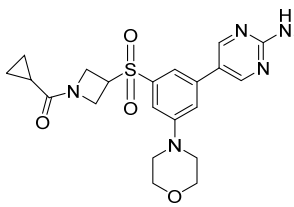
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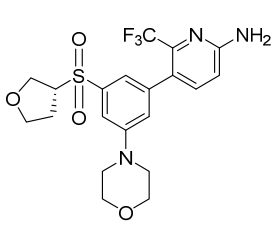
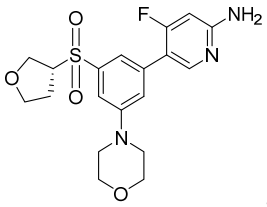
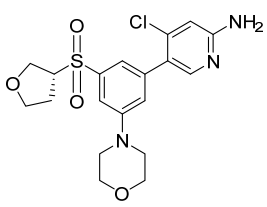
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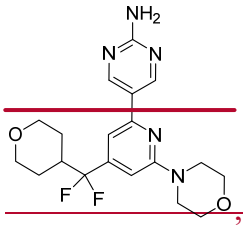
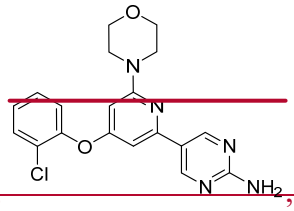
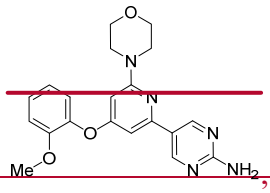
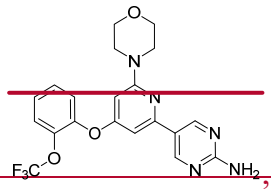
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or medical condition associated with autophagy or the PI3K-AKT-MTOR pathway, wherein the disease or medical condition is Alzheimer's Disease, Parkinson's Disease, fronto-temporal dementia, dementia with Lewy Bodies, PD dementia, multiple system atrophy, 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.

~~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~~22. Use of at least one compound of any one of claims ~~1-21~~1-18, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim ~~22~~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.

~~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.~~