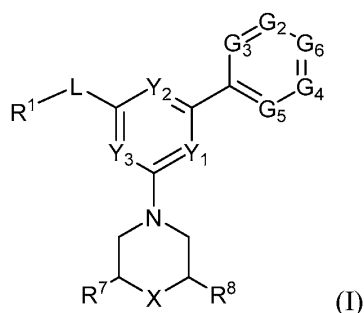


Claims

1. A compound of Formula (I):



wherein

R¹ 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 C₁₋₄alkyl,

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 R¹ is unsubstituted or substituted with one or two R^x substituents;

wherein each R^x substituent is independently halo, C₁₋₄alkyl, 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 Rⁱ, R^j, R^k, and R^l are each independently H, C₁₋₄alkyl, $-C_{1-4}$ alkyl-OH, or $-C_{1-4}$ alkyl-O-C₁₋₄alkyl,

wherein R^q and R^r are each independently H, C₁₋₄alkyl, $-C_{1-4}$ alkyl-OH, $-C_{1-4}$ alkyl-O-C₁₋₄alkyl, $-C(O)C_{1-4}$ alkyl, $-CO_2C_{1-4}$ alkyl, or $-SO_2C_{1-4}$ alkyl;

L is absent, $-\text{S}(\text{O})_2-$, $-\text{C}(\text{O})-$, $-\text{O}-$, $-\text{CH}_2-$, $-\text{CF}_2-$, $\text{C}(\text{CH}_3)_2$, $-\text{C}(=\text{CH}_2)-$, or $-\text{CR}^s\text{R}^t-$; 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, $\text{N}(\text{CO}_2\text{C}_{1-4}\text{alkyl})$, $\text{N}(\text{SO}_2\text{C}_{1-4}\text{alkyl})$, $\text{N}(\text{SO}_2\text{cycloalkyl})$, or CH_2 ;

Y_1 , Y_2 , and Y_3 are each independently CH or N; wherein when L is other than $-\text{S}(\text{O})_2-$, 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, $-\text{OH}$, $-\text{alkyl}$, $-\text{Oalkyl}$, $-\text{haloalkyl}$, $-\text{O-haloalkyl}$, or $-\text{NR}^u\text{R}^v$;

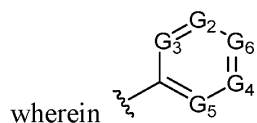
or R^{4b} is taken together with R^6 and the atoms to which they are attached to form a heteroaryl or heterocyclic ring; wherein the heteroaryl ring comprising R^{4b} and R^6 comprises no more than one N and is optionally substituted with alkyl, and the heterocyclic ring comprising R^{4b} and R^6 is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

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

R^v is H, $\text{C}_{1-4}\text{alkyl}$, monocyclic cycloalkyl, $-\text{C}(\text{O})\text{C}_{1-4}\text{alkyl}$, or $-\text{C}(\text{O})\text{NR}^w\text{R}^v$;

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

R^w and R^v are each independently H or $\text{C}_{1-4}\text{alkyl}$;



wherein Z is not unsubstituted phenyl; and

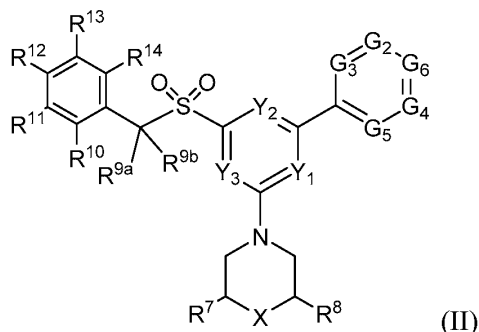
R^7 and R^8 are each independently hydrogen or $\text{C}_{1-4}\text{alkyl}$,

or R^7 and R^8 are taken together to form $-\text{CH}_2\text{CH}_2-$;

or a pharmaceutically acceptable salt thereof.

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

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)



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 R², R³, R^{4a}, R⁵, and R⁶ are each independently hydrogen, halogen, -OH, -alkyl, -Oalkyl, -haloalkyl, -O-haloalkyl, or -NR^uR^v;

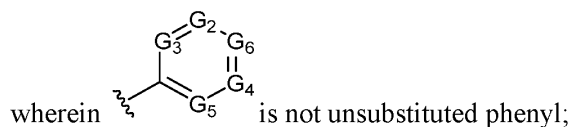
or R^{4b} is taken together with R⁶ and the atoms to which they are attached to form a heteroaryl or heterocyclic ring; wherein the heteroaryl ring comprising R^{4b} and R⁶ comprises no more than one N and is optionally substituted with alkyl, and the heterocyclic ring comprising R^{4b} and R⁶ is optionally substituted with oxo,

R^u is H or C₁₋₄alkyl;

R^v is H, C₁₋₄alkyl, monocyclic cycloalkyl, -C(O)C₁₋₄alkyl, or -C(O)NR^wR^y;

wherein each alkyl present in R^v is unsubstituted or substituted with -OH, -NH₂, -NH(C₁₋₄alkyl), or -N(C₁₋₄alkyl)₂, and

R^w and R^y are each independently H or C₁₋₄alkyl;



R⁷ and R⁸ are each independently hydrogen or C₁₋₄alkyl,

or R⁷ and R⁸ are taken together to form -CH₂CH₂-;

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

R¹⁰, R¹¹, R¹², R¹³, and R¹⁴ are each independently hydrogen, halogen, -OH, -CN, -alkyl, -Oalkyl, -haloalkyl, heterocycloalkyl, -O-haloalkyl, -SO₂C₁₋₄alkyl, or -NR^{aa}R^{bb};

R^{aa} is hydrogen, C₁₋₄alkyl, or -C₁₋₄alkyl-OH;

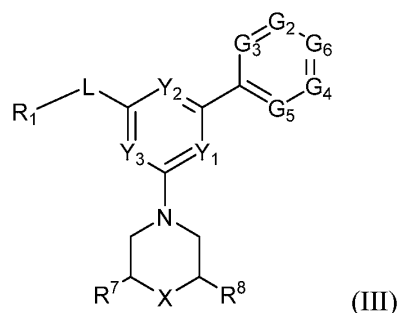
R^{bb} is hydrogen or C₁₋₄alkyl;

or R^{9a} is taken together with R¹⁰ and the interposed atoms to form a heteroaryl or heterocyclic ring;

or R¹¹ is taken together with R¹² 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)



wherein

R^1 is $-(CR^aR^b)_m$ -aryl, $-\text{CH}=\text{CH}$ -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,

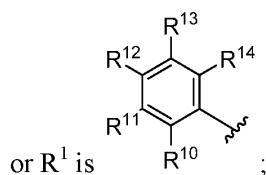
or R^a and R^b are taken together to form $=\text{CH}_2$ or $=\text{O}$;

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, $-\text{C}_{1-2}$ -haloalkyl, $-\text{OH}$, $-\text{OC}_{1-4}$ alkyl, $-\text{O}-\text{C}_{1-2}$ -haloalkyl, cyano, $-\text{C}(\text{O})\text{C}_{1-4}$ alkyl, $-\text{C}(\text{O})\text{NR}^i\text{R}^j$, $-\text{SO}_2\text{C}_{1-4}$ alkyl, $-\text{SO}_2\text{NR}^k\text{R}^l$, $-\text{NR}^q\text{R}^r$, $-\text{C}(\text{O})$ -cycloalkyl, $-\text{C}(\text{O})$ -aryl (optionally substituted with methyl or halo), $-\text{CO}_2\text{C}_{1-4}$ alkyl, $-\text{CO}_2$ aryl, $-\text{C}(\text{O})\text{CH}_2$ -aryl (optionally substituted with methyl or halo), $-\text{CH}_2$ -aryl (optionally substituted with methyl or halo), or monocyclic heterocycloalkyl (optionally substituted with methyl, $-\text{C}(\text{O})\text{C}_{1-4}$ alkyl, or $-\text{CO}_2\text{C}_{1-4}$ alkyl);

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

wherein R^q and R^r are each independently H, C_{1-4} alkyl, $-\text{C}_{1-4}$ alkyl-OH, $-\text{C}_{1-4}$ alkyl-O- C_{1-4} alkyl, $-\text{C}(\text{O})\text{C}_{1-4}$ alkyl, $-\text{CO}_2\text{C}_{1-4}$ alkyl, or $-\text{SO}_2\text{C}_{1-4}$ alkyl;



wherein

R¹⁰, R¹¹, R¹², R¹³, and R¹⁴ are each independently hydrogen, halogen, -OH, -CN, -alkyl, -Oalkyl, -haloalkyl, heterocycloalkyl, -O-haloalkyl, -SO₂C₁₋₄alkyl, or -NR^{aa}R^{bb};

R^{aa} is hydrogen, C₁₋₄alkyl, or -C₁₋₄alkyl-OH;

R^{bb} is hydrogen or C₁₋₄alkyl;

or R¹⁰ is taken together with R¹¹ and the atoms to which they are attached to form a heteroaryl or heterocyclic ring;

or R¹¹ is taken together with R¹² and the atoms to which they are attached to form a heteroaryl or heterocyclic ring;

L is absent, -S(O)₂-, -C(O)-, -O-, -CH₂-, -CF₂-, C(CH₃)₂-, -C(=CH₂)-, 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(CO₂C₁₋₄alkyl), N(SO₂C₁₋₄alkyl), N(SO₂cyclo-alkyl), or CH₂;

Y₁, Y₂, and Y₃ are each independently CH or N; wherein when L is other than -S(O)₂-, Y₂ and Y₃ are each CH;

G₂ is N or CR²;

G₃ is N or CR³;

G₄ is N, NR^{4b}, or CR^{4a};

G₅ is N or CR⁵; and

G₆ is N or CR⁶;

wherein R², R³, R^{4a}, R⁵, and R⁶ are each independently hydrogen, halogen, -OH, -alkyl, -Oalkyl, -haloalkyl, -O-haloalkyl, or -NR^uR^v;

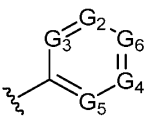
or R^{4b} is taken together with R⁶ and the atoms to which they are attached to form a heteroaryl or heterocyclic ring; wherein the heteroaryl ring comprising R^{4b} and R⁶ comprises no more than one N and is optionally substituted with alkyl, and the heterocyclic ring comprising R^{4b} and R⁶ is optionally substituted with oxo,

R^u is H or C₁₋₄alkyl;

R^v is H, C₁₋₄alkyl, monocyclic cycloalkyl, -C(O)C₁₋₄alkyl, or -C(O)NR^wR^v;

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 of Table 1, or a pharmaceutically acceptable salt thereof.
22. A pharmaceutical composition comprising (a) at least one compound of any one of claims 1-21, or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable excipient.
23. A method of treating a disease or medical condition associated with autophagy or the PI3K-AKT-MTOR pathway, comprising administering to a subject in need of such treatment an effective amount 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.
24. The method of claim 23, 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.
25. The method of claim 23, wherein the disease or medical condition is rosacea, acne, psoriasis, or atopic dermatitis.

26. 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.

27. The compound or pharmaceutical composition of claim 26, 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.

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

29. 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.

30. The use of claim 29, 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.

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