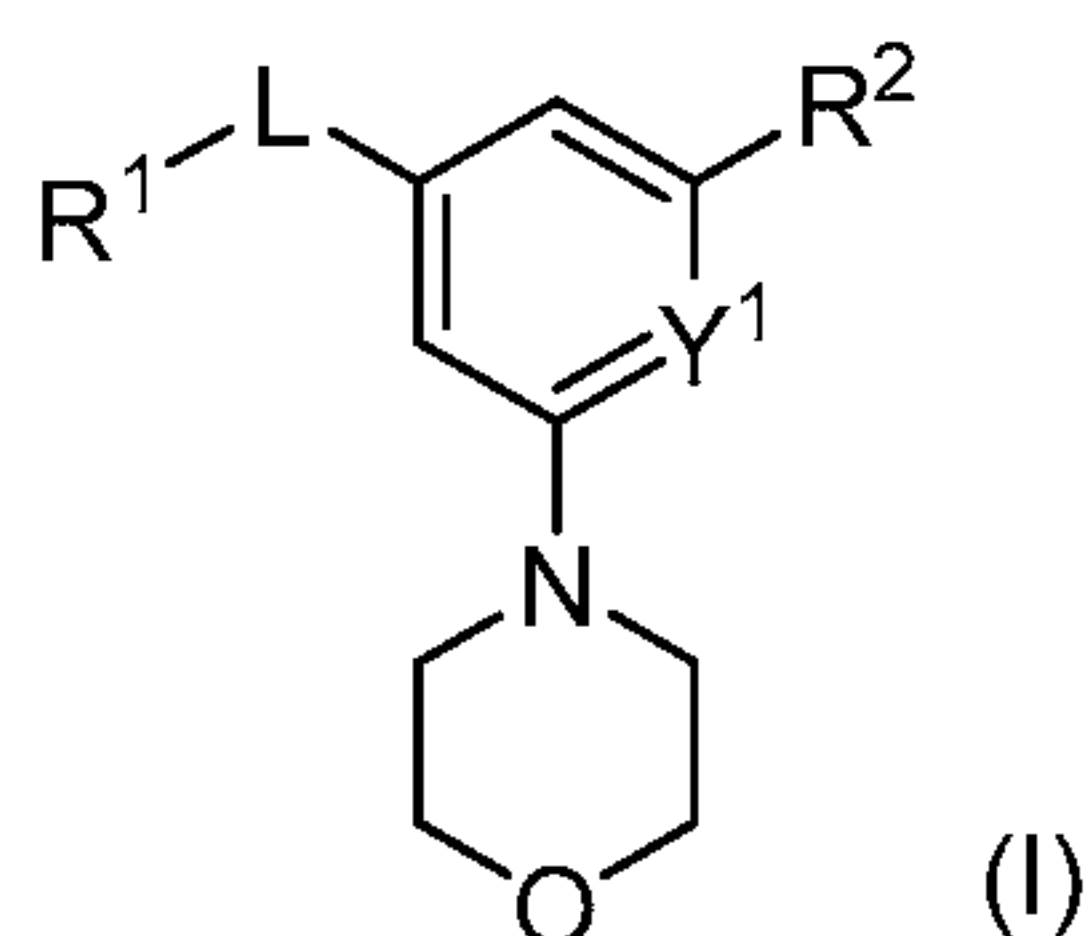


Claims

1. A compound of Formula I:



wherein

R^1 is C_6 - C_{14} aryl, 5- to 10-membered heteroaryl, C_3 - C_6 cycloalkyl, or 4- to 10-membered heterocycloalkyl, wherein the C_6 - C_{14} aryl, 5- to 10-membered heteroaryl, C_3 - C_6 cycloalkyl, or 4- to 10-membered heterocycloalkyl of R^1 are each unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -CN, -NO₂, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl, -OR^a, -SR^a, -S(O)₂R^a, -NR^bR^c, -C(O)R^a, -OC(O)R^a, -C(O)OR^a, -C(O)NR^bR^c, -OC(O)NR^bR^c, -NR^aC(O)R^b, -NR^aC(O)OR^b, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_3 - C_6 cycloalkenyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 4- to 10-membered heterocycloalkyl;

L is -S(O)₂-, -O-, -C(O)- or -CH₂-;

Y¹ is CH or N;

R^2 is a 5-membered heteroaryl or a 5-membered heterocycloalkyl, wherein the 5-membered heteroaryl and 5-membered heterocycloalkyl of R^2 are each unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -CN, -NO₂, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl, -OR^d, -SR^d, -S(O)₂R^d, -NR^eR^f, -C(O)R^d, -OC(O)R^d, -C(O)OR^d, -C(O)NR^eR^f, -OC(O)NR^eR^f, -NR^dC(O)R^e, -NR^dC(O)OR^e, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_3 - C_6 cycloalkenyl,

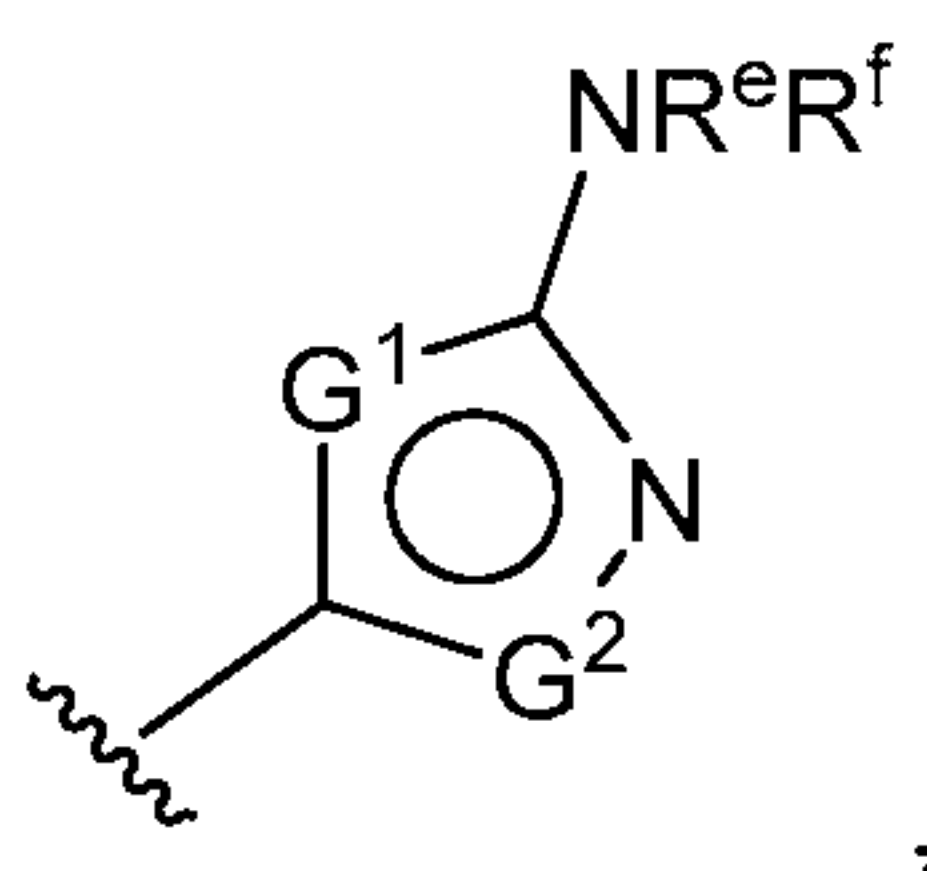
substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 4- to 10-membered heterocycloalkyl; and

R^a, R^b, R^c, R^d, R^e, and R^f are each independently H or C₁₋₄ alkyl;

wherein when L is -S(O)₂- and Y¹ is N, R¹ is not 4,4-difluoro-piperidin-1-yl; or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is C₆-C₁₄ aryl or 4- to 10-membered heterocycloalkyl.
3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is phenyl.
4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is 5- or 6-membered heterocycloalkyl.
5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl.
6. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein R¹ is tetrahydrofuran-3-yl.
7. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein R¹ is tetrahydropyran-4-yl.
8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein L is -S(O)₂-.
9. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein L is -O-.

10. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein L is $-\text{C}(\text{O})-$.
11. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein L is $-\text{CH}_2-$.
12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein Y^1 is CH.
13. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein Y^1 is N.
14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein R^2 is a 5-membered heteroaryl ring.
15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein R^2 is a 5-membered heteroaryl ring substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl and NR^eR^f , wherein R^e and R^f are independently H or C_{1-4} alkyl.
16. The compound of any one of claims 1-15, wherein R^2 is thiazolyl or thiadiazolyl substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl and NR^eR^f , wherein R^e and R^f are independently H or C_{1-4} alkyl.
17. The compound of any one of claims 1-16, wherein R^2 is thiazolyl or thiadiazolyl substituted with one or more substituents selected from the group consisting of methyl, CF_3 and NH_2 .
18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein R^2 is:



wherein

G^1 is S or N;

G^2 is CR^3 , S, or N;

R^3 is H, C_{1-6} alkyl or C_{1-6} haloalkyl; and

R^e and R^f are independently H or C_{1-4} alkyl.

19. The compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein G^1 is S and G^2 is CR^3 .

20. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein R^3 is H.

21. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein R^3 is C_{1-6} alkyl.

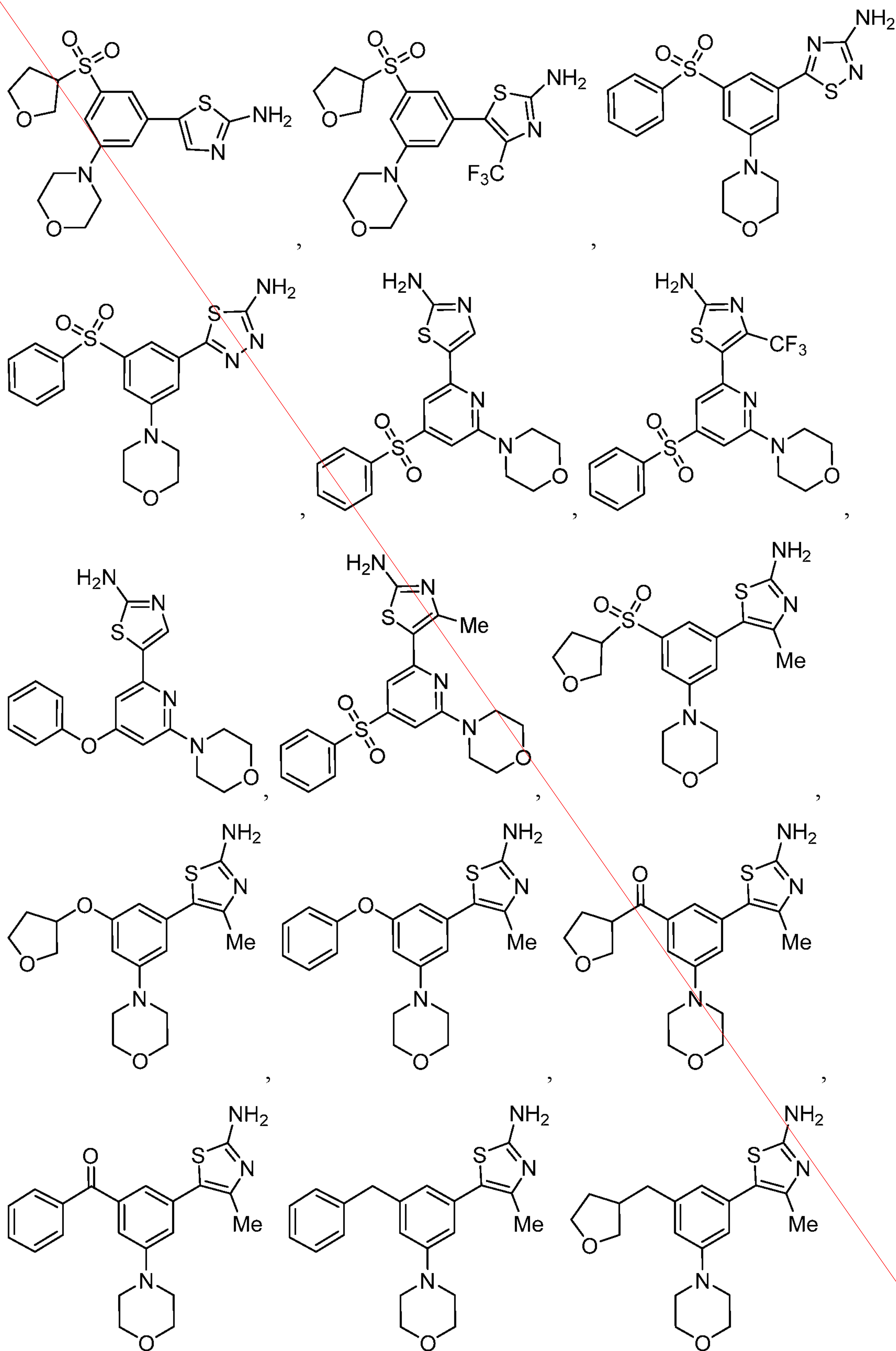
22. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein R^3 is C_{1-6} haloalkyl.

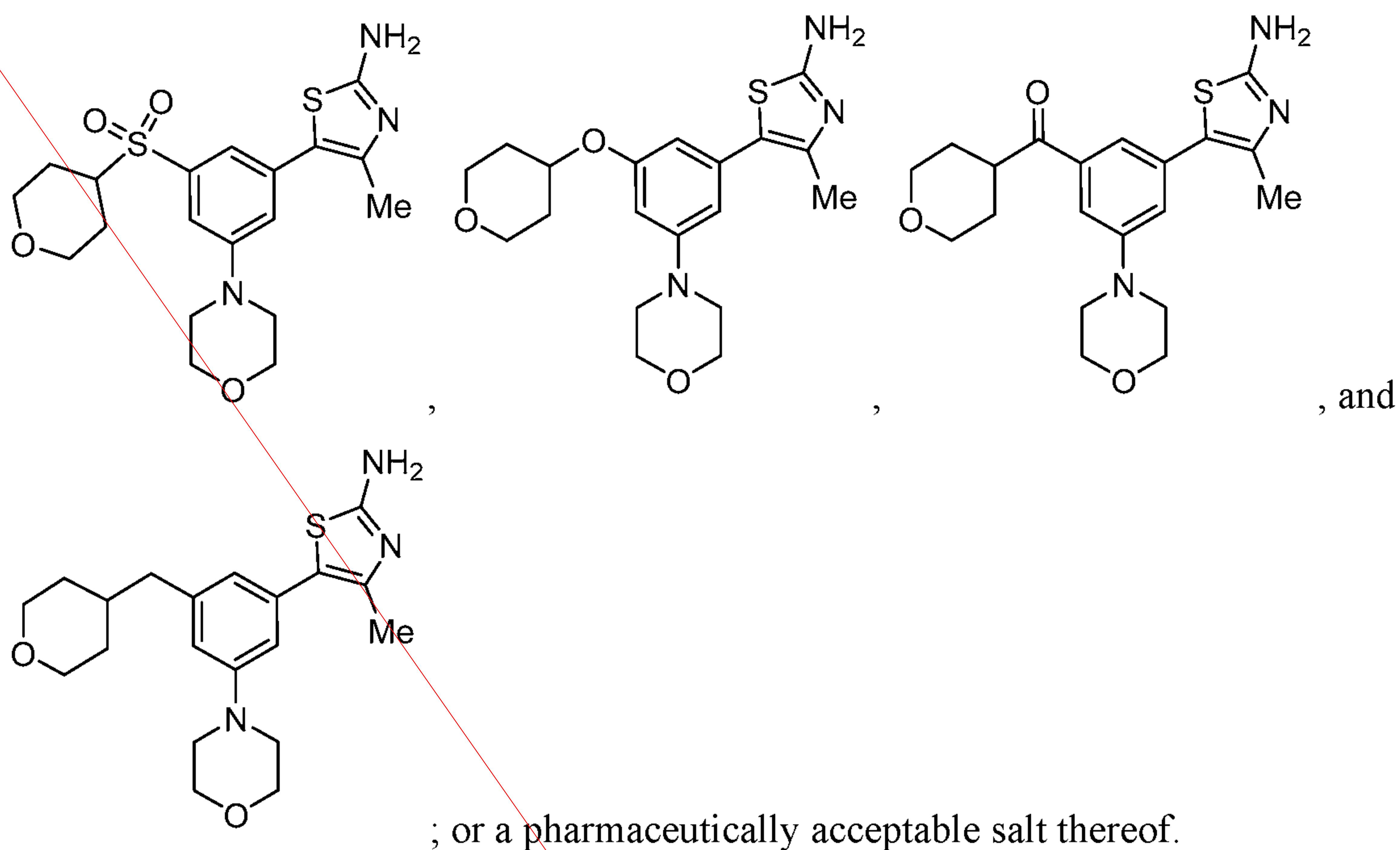
23. The compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein G^1 is N and G^2 is S.

24. The compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein G^1 is S and G^2 is N.

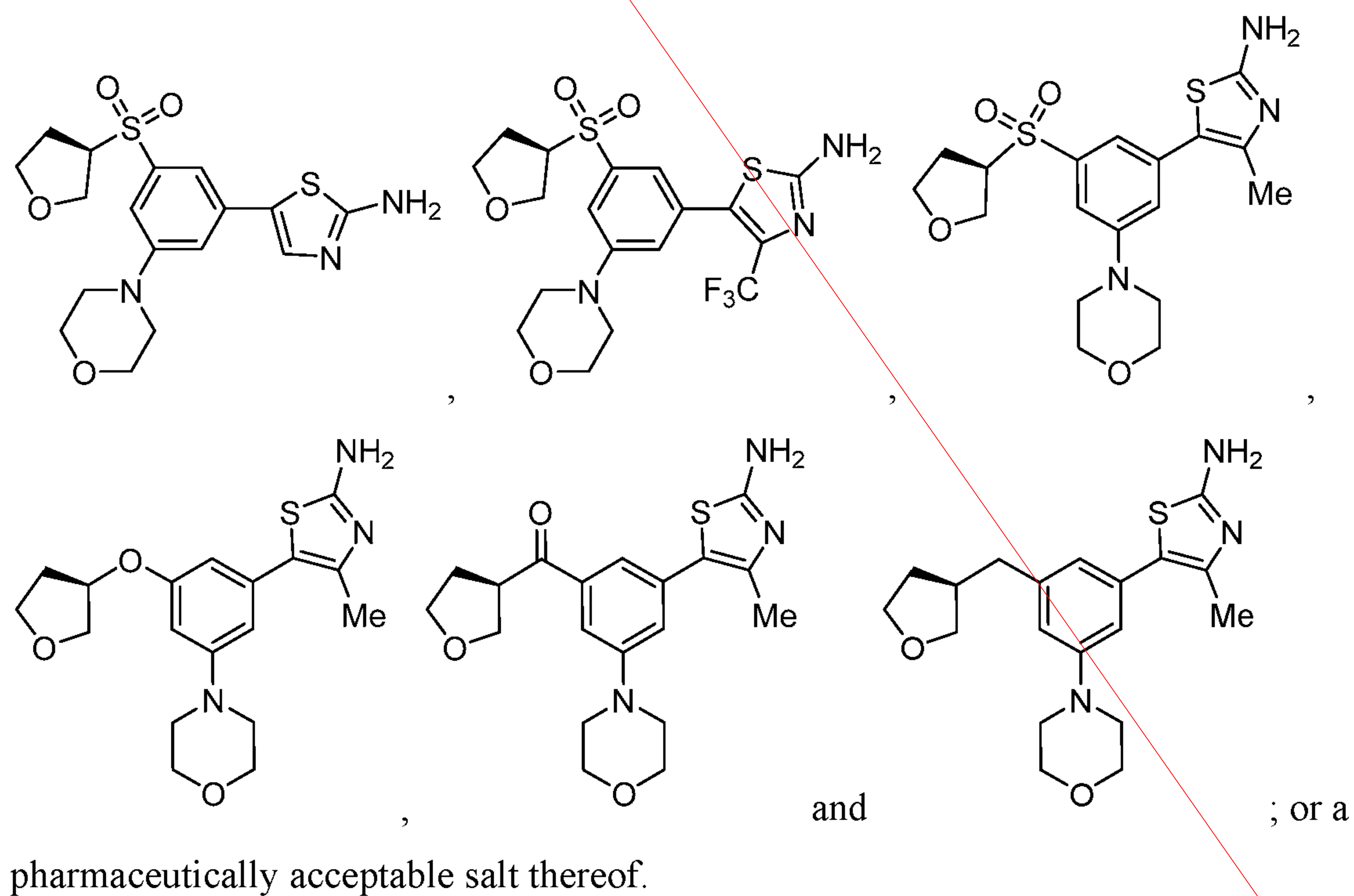
25. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, wherein R^e and R^f are both H.

26. A compound selected from the group consisting of:

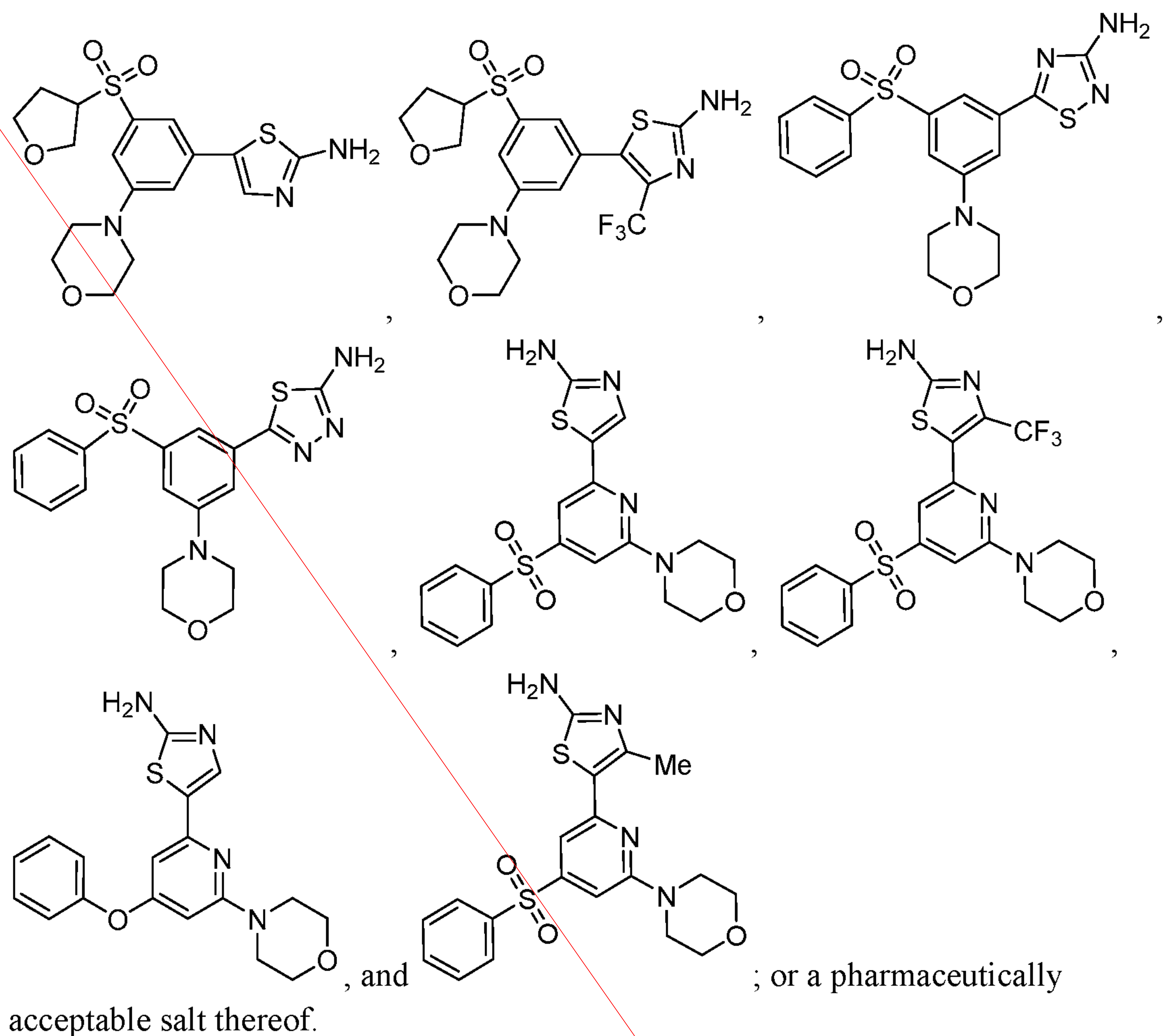




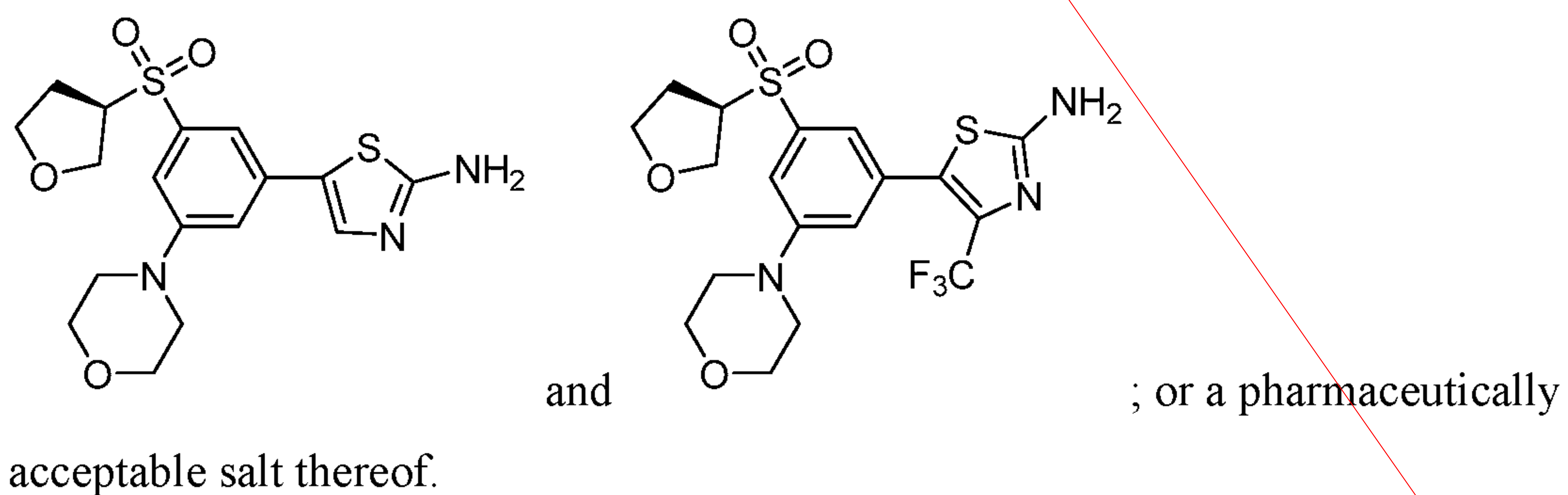
27. The compound of claim 26, wherein the compound is selected from the group consisting of:



28. A compound selected from the group consisting of:



29. The compound of claim 28, wherein the compound is selected from the group consisting of:



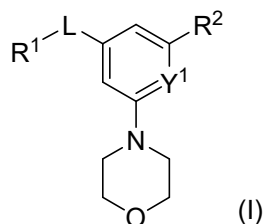
30. A pharmaceutical composition comprising (a) at least one compound of any one of claims 1-29, or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable excipient.

31. A method of treating a disease or medical condition associated with regulation of the Vps34/ PI3K III signaling pathway, comprising administering to a subject in need of such treatment an effective amount of at least one compound of any one of claims 1-29, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 30.
32. The method of claim 31, wherein the disease or medical condition is diabetes, polycystic ovarian syndrome, diabetes-associated cardiovascular disease, cancer, neuro-inflammation or ischemic stroke.
33. The method of claim 32, wherein the disease or medical condition is cancer, and the cancer is glioblastoma, renal cell carcinoma, or melanoma.
34. A compound of any one of claims 1-29, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 30, for use in the treatment of a disease or medical condition associated with regulation of the Vps34/ PI3K III signaling pathway.
35. The compound or pharmaceutical composition of claim 34, wherein the disease or medical condition is diabetes, polycystic ovarian syndrome, diabetes-associated cardiovascular disease, cancer, neuro-inflammation or ischemic stroke.
36. The compound or pharmaceutical composition of claim 35, wherein the disease or medical condition is cancer, and the cancer is glioblastoma, renal cell carcinoma, or melanoma.
37. Use of at least one compound of any one of claims 1-29, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 30, in the manufacture of a medicament for the treatment of a disease or medical condition associated with regulation of the Vps34/ PI3K III signaling pathway.
38. The use of claim 37, wherein the disease or medical condition is diabetes, polycystic ovarian syndrome, diabetes-associated cardiovascular disease, cancer, neuro-inflammation or ischemic stroke.

39. The use of claim 38, wherein the disease or medical condition is cancer, and the cancer is glioblastoma, renal cell carcinoma, or melanoma.
40. A method of interfering with the Vps34/ PI3K III signaling pathway in a cell, or modulating, preventing, slowing, reversing, or inhibiting of the Vps34/ PI3K III signaling pathway in a cell, comprising contacting the cell with an effective amount of at least one compound according to any one of claims 1-29, or a salt thereof, and/or with at least one pharmaceutical composition according to claim 30, wherein the contacting is *in vitro*, *ex vivo*, or *in vivo*.

CLAIMS

1. A compound of Formula I:



wherein

R^1 is C_6 - C_{14} aryl, 5- to 10-membered heteroaryl, C_3 - C_6 cycloalkyl, or 4- to 10-membered heterocycloalkyl, wherein the C_6 - C_{14} aryl, 5- to 10-membered heteroaryl, C_3 - C_6 cycloalkyl, or 4- to 10-membered heterocycloalkyl of R^1 are each unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -CN, -NO₂, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl, -OR^a, -SR^a, -S(O)₂R^a, -NR^bR^c, -C(O)R^a, -OC(O)R^a, -C(O)OR^a, -C(O)NR^bR^c, -OC(O)NR^bR^c, -NR^aC(O)R^b, -NR^aC(O)OR^b, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_3 - C_6 cycloalkenyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 4- to 10-membered heterocycloalkyl;

L is -S(O)₂-, -O-, -C(O)- or -CH₂-;

Y¹ is CH or N;

R^2 is a 5-membered heteroaryl or a 5-membered heterocycloalkyl, wherein the 5-membered heteroaryl and 5-membered heterocycloalkyl of R^2 are each unsubstituted or substituted with one or more substituents selected from the group consisting of halogen, -CN, -NO₂, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl, -OR^d, -SR^d, -S(O)₂R^d, -NR^eR^f, -C(O)R^d, -OC(O)R^d, -C(O)OR^d, -C(O)NR^eR^f, -OC(O)NR^eR^f, -NR^dC(O)R^e, -NR^dC(O)OR^e, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_3 - C_6 cycloalkenyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted

5- to 10-membered heteroaryl, and substituted or unsubstituted 4- to 10-membered heterocycloalkyl; and

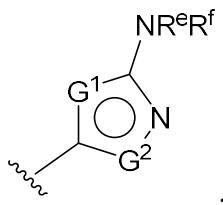
R^a , R^b , R^c , R^d , R^e , and R^f are each independently H or C_{1-4} alkyl;

wherein when L is $-S(O)_2-$ and Y^1 is N, R^1 is not 4,4-difluoro-piperidin-1-yl;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_6 - C_{14} aryl or 4- to 10-membered heterocycloalkyl.
3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is phenyl.
4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is 5- or 6-membered heterocycloalkyl.
5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl.
6. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein R^1 is tetrahydrofuran-3-yl.
7. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein R^1 is tetrahydropyran-4-yl.
8. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L is $-S(O)_2-$.
9. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L is $-O-$.
10. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L is $-C(O)-$.

11. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L is –CH₂–.
12. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Y¹ is CH.
13. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Y¹ is N.
14. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R² is a 5-membered heteroaryl ring.
15. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R² is a 5-membered heteroaryl ring substituted with one or more substituents selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl and NR^eR^f, wherein R^e and R^f are independently H or C₁₋₄ alkyl.
16. The compound of claim 1, wherein R² is thiazolyl or thiadiazolyl substituted with one or more substituents selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl and NR^eR^f, wherein R^e and R^f are independently H or C₁₋₄ alkyl.
17. The compound of claim 1, wherein R² is thiazolyl or thiadiazolyl substituted with one or more substituents selected from the group consisting of methyl, CF₃ and NH₂.
18. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R² is:



wherein

G^1 is S or N;

G^2 is CR^3 , S, or N;

R^3 is H, C_{1-6} alkyl or C_{1-6} haloalkyl; and

R^e and R^f are independently H or C_{1-4} alkyl.

19. The compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein G^1 is S and G^2 is CR^3 .

20. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein R^3 is H.

21. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein R^3 is C_{1-6} alkyl.

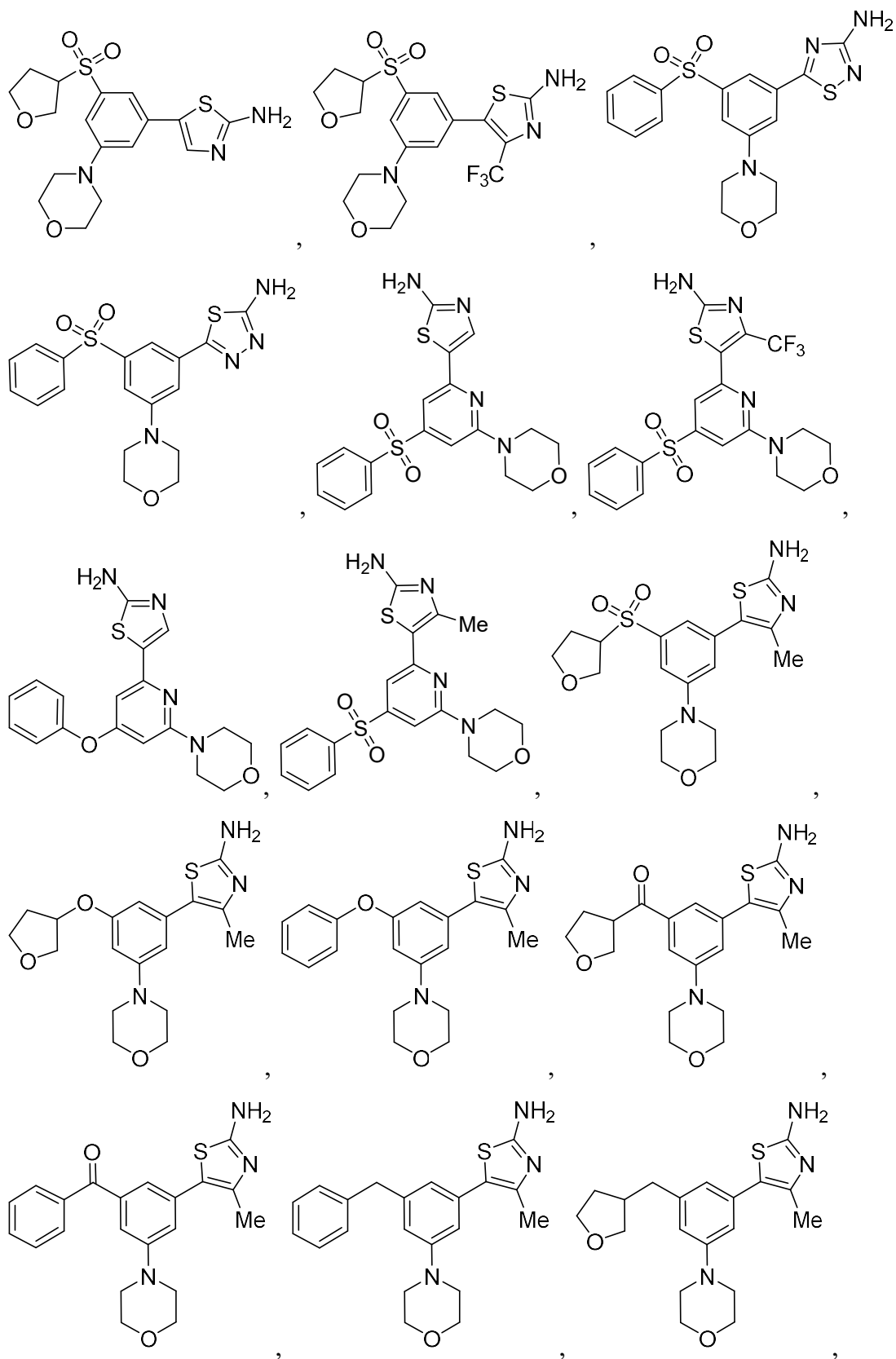
22. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein R^3 is C_{1-6} haloalkyl.

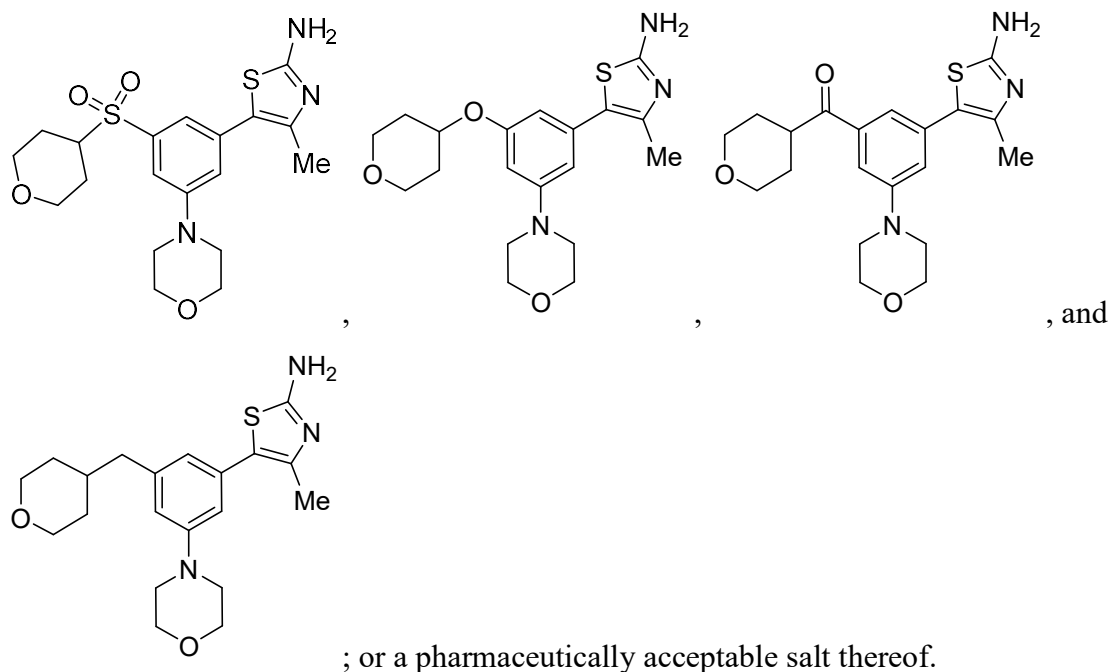
23. The compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein G^1 is N and G^2 is S.

24. The compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein G^1 is S and G^2 is N.

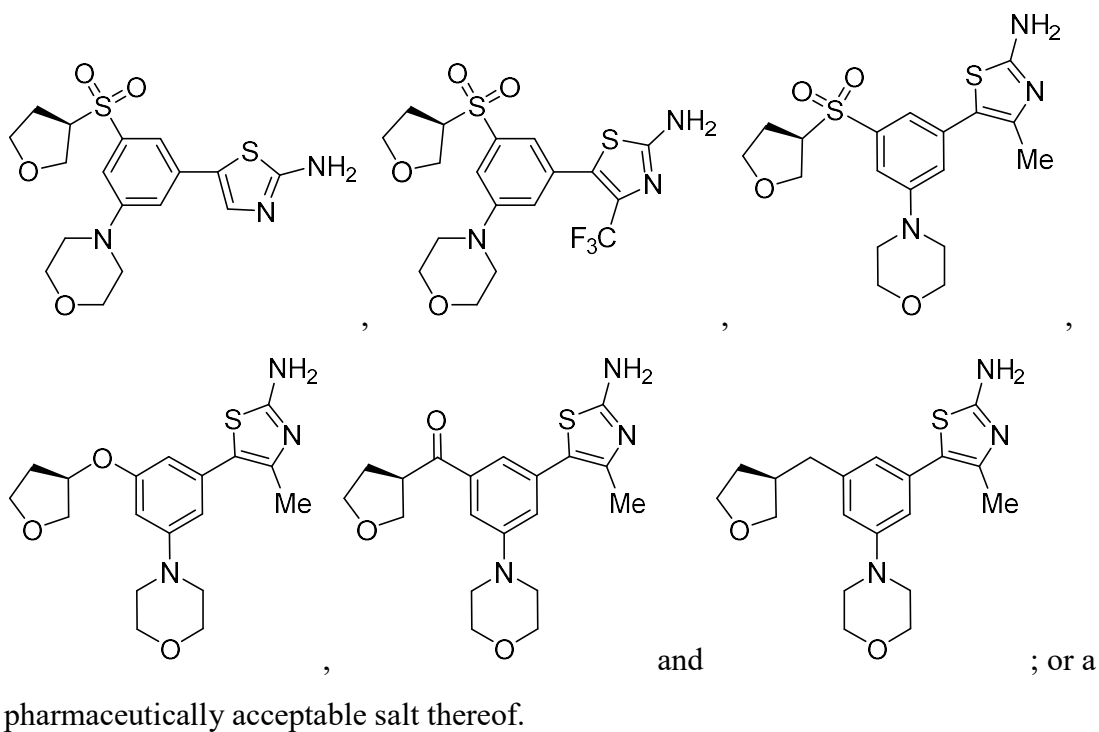
25. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^e and R^f are both H.

26. A compound selected from the group consisting of:

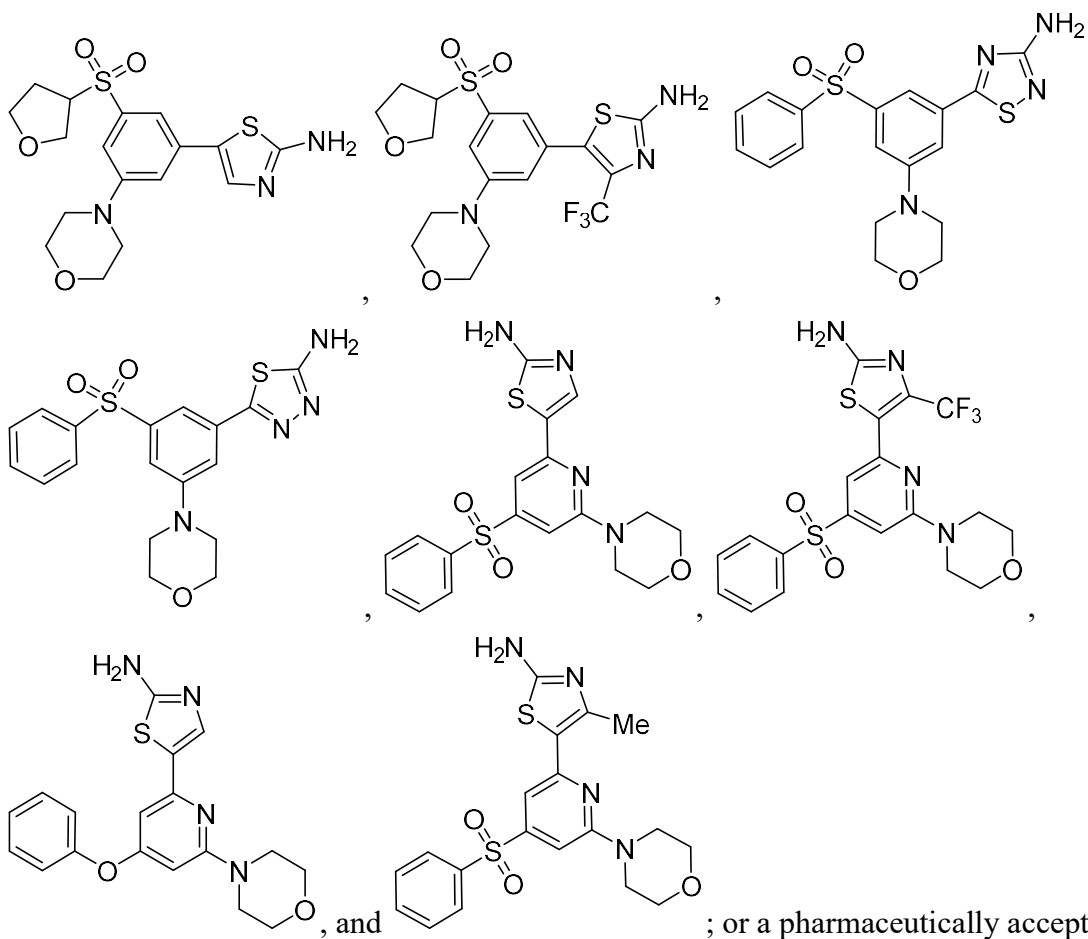




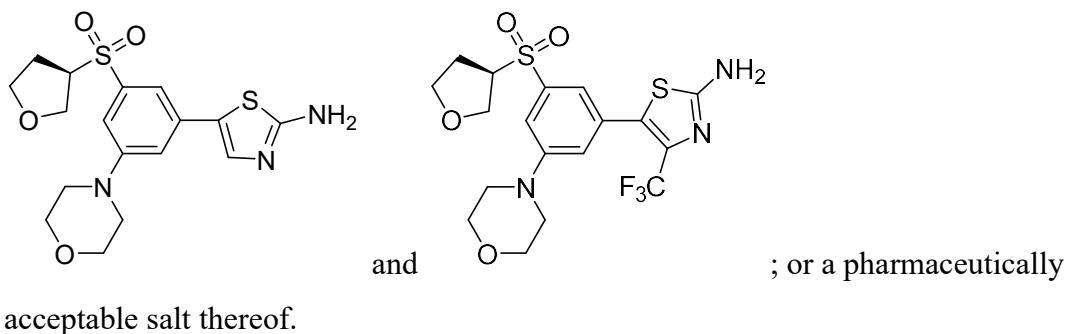
27. The compound of claim 26, wherein the compound is selected from the group consisting of:



28. A compound selected from the group consisting of:



29. The compound of claim 28, wherein the compound is selected from the group consisting of:



30. A pharmaceutical composition comprising (a) at least one compound of claim 1, or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable excipient.

31. Use of the compound of any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 30 in the manufacture of a medicament for the treatment of a disease or medical condition associated with regulation of the Vps34/ PI3K III signaling pathway in a subject in need of such treatment, wherein an effective amount of at least one of the compound, or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition is to be administered to the subject.
32. The use of claim 31, wherein the disease or medical condition is diabetes, polycystic ovarian syndrome, diabetes-associated cardiovascular disease, cancer, neuro-inflammation or ischemic stroke.
33. The use of claim 32, wherein the disease or medical condition is cancer, and the cancer is glioblastoma, renal cell carcinoma, or melanoma.
34. A method of interfering with the Vps34/ PI3K III signaling pathway in a cell, or modulating, preventing, slowing, reversing, or inhibiting of the Vps34/ PI3K III signaling pathway in a cell, comprising contacting the cell with an effective amount of at least one compound according to claim 1, or a pharmaceutically acceptable salt thereof wherein the contacting is *in vitro*, or *ex vivo*.
35. The compound of any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 30 for use as a medicament.