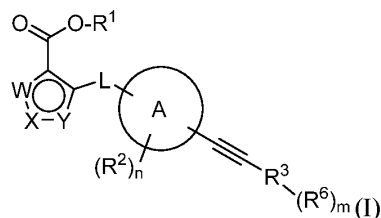


CLAIMS

What is claimed is:

1. A compound of structural Formula I



or a salt, polymorph, or tautomer thereof, wherein:

W is chosen from N, NH, S, O, and CCH₃;

X is chosen from NH, S, O, and CH;

Y is N or NH;

R¹ is chosen from hydrogen, C₁–C₆ alkyl, C₁–C₆ haloalkyl, and C₁–C₆ cycloalkyl;

L is chosen from O, S, CH₂, NH, NR⁴, S(O), SO₂, and CR⁴=CR⁵;

A is chosen from monocyclic or bicyclic aryl, and monocyclic or bicyclic heteroaryl;

each R² is independently chosen from C₆–C₁₀ aryl, 5-10-membered heteroaryl, C₁–C₆ alkoxy, C₁–C₆ alkyl, C₃–C₆ alkyl, C₁–C₆ alkylsulfonyl, C₁–C₆ alkylthio, C₁–C₆ haloalkoxy, C₁–C₆ haloalkyl, cyano, and halogen;

n is 0, 1, or 2;

R³ is chosen from 3-10-membered heterocycloalkyl, 5-10-membered heteroaryl, C₆–C₁₀ aryl, C₁–C₆ alkyl, C₁–C₆ sulfonyl, C₃–C₆ cycloalkyl, 3-10-membered heterocycloalkylalkyl, 5-10-membered heteroarylalkyl, C₆–C₁₀ arylalkyl, and C₃–C₆ cycloalkylalkyl;

R⁴ and R⁵ are each independently chosen from hydrogen and C₁–C₆ alkyl, or R⁴ and R⁵, together with the atoms to which they are attached, form a cycloalkenyl; and

each R⁶ is independently chosen from 4-6-membered heterocycloalkyl, 5-10-membered heteroaryl, amino, C₁–C₆ alkoxy, C₁–C₆ alkyl, C₁–C₆ alkylsulfonyl, C₁–C₆ haloalkyl, C₃–C₆ cycloalkyl, C₃–C₆ cycloalkylalkyl, carboxyl, cyano, halogen, hydroxyl, methyl-, 4-6-membered heterocycloalkyl, and phenyl; and

m is 0, 1, 2, or 3.

2. The compound of claim 1, wherein:

W is N, X is N, and Y is NH;

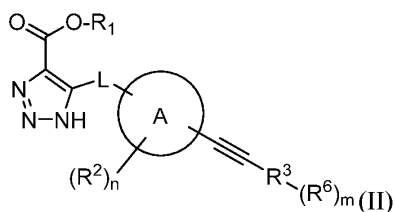
W is CCH₃, X is NH, and Y is N;

W is CCH₃, X is O and Y is N;

W is N, X is O, and Y is N; or

W is N, X is CH and Y is NH.

3. The compound of claim 2, wherein W is N, X is N, and Y is NH.
4. The compound of any one of claims 1 to 3, wherein each R² is independently chosen from 5-10-membered heteroaryl, C₁-C₆ alkoxy, C₁-C₆ alkyl, C₁-C₆ alkylsulfonyl, C₁-C₆ alkylthio, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, C₆-C₁₀ aryl, cyano, and halogen;
5. The compound of any one of claims 1 to 4, wherein R³ is chosen from 3-10-membered heterocycloalkyl, 5-10-membered heteroaryl, C₁-C₆ alkyl, C₁-C₆ sulfonyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkylalkyl, C₆-C₁₀ aryl, and C₆-C₁₀ arylalkyl.
6. A compound of claim 1, having structural Formula II



or a salt, polymorph, or tautomer thereof, wherein:

R¹ is chosen from hydrogen, C₁-C₆ alkyl, and C₁-C₆ cycloalkyl;

L is chosen from O, S, CH₂, NH, NR⁴, S(O), SO₂, and CR⁴=CR⁵;

A is chosen from monocyclic or bicyclic aryl, and monocyclic or bicyclic heteroaryl;

each R² is independently chosen from 5-10-membered heteroaryl, C₁-C₆ alkoxy, C₁-C₆ alkyl, C₁-C₆ alkylsulfonyl, C₁-C₆ alkylthio, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, C₆-C₁₀ aryl, cyano, and halogen;

n is 0, 1, or 2;

R³ is chosen from 3-10-membered heterocycloalkyl, 5-10-membered heteroaryl, C₁-C₆ alkyl, C₁-C₆ sulfonyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkylalkyl, C₆-C₁₀ aryl, and C₆-C₁₀ arylalkyl;

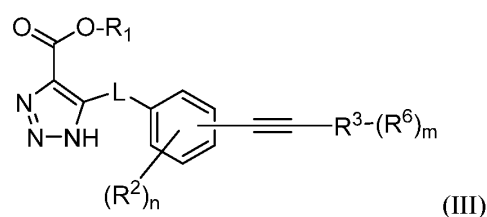
R⁴ and R⁵ are each independently chosen from hydrogen and C₁-C₆ alkyl, or R⁴ and R⁵, together with the atoms to which they are attached, form a cycloalkenyl; and

each R⁶ is independently chosen from 4-6-membered heterocycloalkyl, 5-10-membered heteroaryl, amino, C₁-C₆ alkoxy, C₁-C₆ alkyl, C₁-C₆ alkylsulfonyl, C₁-C₆ haloalkyl,

C₃–C₆ cycloalkyl, C₃–C₆ cycloalkylalkyl, carboxyl, cyano, halogen, hydroxyl, methyl-4-6-membered heterocycloalkyl, and phenyl; and

m is 0, 1, 2, or 3.

7. The compound of any one of claims 1 to 6, wherein A is chosen from indazolyl, indolyl, naphthalenyl, oxazolyl, oxodihydropyridinyl, phenyl, pyridazinyl, pyridinyl, and thiazolyl.
8. The compound of any one of claims 1 to 6, wherein A is monocyclic aryl.
9. The compound of claim 8, wherein A is phenyl.
10. A compound of claim 6, having structural Formula III,



or a salt, polymorph, or tautomer thereof, wherein:

R¹ is chosen from hydrogen, C₁–C₆ alkyl, and C₁–C₆ cycloalkyl;

L is chosen from O, S, CH₂, NH, NR⁴, S(O), SO₂, and CR⁴=CR⁵;

each R² is independently chosen from 5-10-membered heteroaryl, C₁–C₆ alkoxy, C₁–C₆ alkyl, C₁–C₆ alkylsulfonyl, C₁–C₆ alkylthio, C₁–C₆ haloalkoxy, C₁–C₆ haloalkyl, C₆–C₁₀ aryl, cyano, and halogen;

n is 0, 1, or 2;

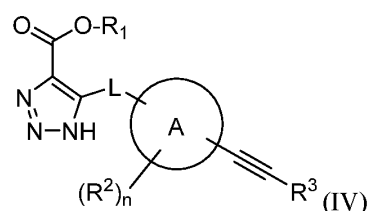
R³ is chosen from 3-10-membered heterocycloalkyl, 5-10-membered heteroaryl, C₁–C₆ alkyl, C₁–C₆ sulfonyl, C₃–C₆ cycloalkyl, C₃–C₆ cycloalkylalkyl, C₆–C₁₀ aryl, and C₆–C₁₀ arylalkyl;

R⁴ and R⁵ are each independently chosen from hydrogen and C₁–C₆ alkyl, or R⁴ and R⁵, together with the atoms to which they are attached, form a cycloalkenyl; and

each R⁶ is independently chosen from 4-6-membered heterocycloalkyl, 5-10-membered heteroaryl, amino, C₁–C₆ alkoxy, C₁–C₆ alkyl, C₁–C₆ alkylsulfonyl, C₁–C₆ haloalkyl, C₃–C₆ cycloalkyl, C₃–C₆ cycloalkylalkyl, carboxyl, cyano, halogen, hydroxyl, methyl-4-6-membered heterocycloalkyl, and phenyl; and

m is 0, 1, 2, or 3.

11. The compound of any one of claims 1 to 10, wherein R^3 is chosen from methyl, propyl, cyclopropyl, cyclobutyl, cyclopentyl, tetrahydrofuranyl, cyclohexyl, tetrahydropyranyl, piperidinyl, dihydropyranyl, indazolyl, benzodioxolyl, phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, benzoxazolyl, oxodihydropyridinyl, thiazolyl, tetrazolyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, benzyl, dioxaspirodecanyl, oxocyclohexyl, and bicyclo[1.1.1]pentyl, any of which is optionally substituted with 1, 2, or 3 R^6 groups.
12. The compound of any one of claims 1 to 10, wherein R^3 is chosen from C_1 – C_6 alkyl, C_3 – C_6 cycloalkyl, and C_3 – C_6 cycloalkylalkyl, any of which is optionally substituted with 1, 2, or 3 R^6 groups.
13. The compound of any one of claims 1 to 10, wherein R^3 is chosen from propyl and cyclopropylmethyl.
14. The compound of any one of claims 1 to 13, wherein R^6 is chosen from methyl, hydroxyl, amino, dimethylamino, propyl, cyclopropylmethyl, indazolyl, benzodioxolyl, cyclopropyl, tetrahydrofuranyl, cyclohexyl, tetrahydropyranyl, piperidinyl, methylpiperidinyl, phenyl, fluoro, chloro, methylsulfonyl, cyano, trifluoromethyl, methoxy, carboxyl, and fluoromethyl.
15. The compound of claim 14, wherein R^6 is chosen from chloro, methyl, cyano, fluoro, methylsulfonyl, methoxy, carboxyl, trifluoromethyl.
16. The compound of any one of claims 1 to 15, wherein m is 0.
17. A compound of claim 4, having structural Formula IV,



or a salt, polymorph, or tautomer thereof, wherein:

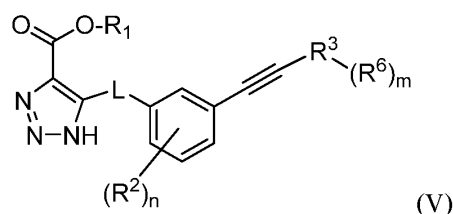
R^1 is chosen from hydrogen, C_1 – C_6 alkyl, and C_1 – C_6 cycloalkyl;

L is chosen from O, S, CH_2 , NH, NR^4 , $S(O)$, SO_2 , and $CR^4=CR^5$;

A is chosen from monocyclic or bicyclic aryl, and monocyclic or bicyclic heteroaryl;

each R^2 is independently chosen from 5-10-membered heteroaryl, C_1 – C_6 alkoxy, C_1 – C_6 alkyl, C_1 – C_6 alkylsulfonyl, C_1 – C_6 alkylthio, C_1 – C_6 haloalkoxy, C_1 – C_6 haloalkyl, C_6 –

- C₁₀ aryl, cyano, and halogen;
 n is 0, 1, or 2;
 R³ is chosen from C₁–C₆ alkyl, C₃–C₆ cycloalkyl, and C₃–C₆ cycloalkylalkyl; and
 R⁴ and R⁵ are each independently chosen from hydrogen and C₁–C₆ alkyl, or R⁴ and R⁵, together with the atoms to which they are attached, form a cycloalkenyl.
18. The compound of any one of claims 1 to 17, wherein L is chosen from O, S, CH₂, and NH.
19. The compound of claim 18, wherein L is O or S.
20. The compound of any one of claims 15 to 19, wherein A is chosen from indazolyl, indolyl, naphthalenyl, oxazolyl, oxodihydropyridinyl, phenyl, pyridazinyl, pyridinyl, and thiazolyl.
21. The compound of claim 20, wherein A is monocyclic aryl.
22. The compound of claim 21, wherein A is phenyl.
23. The compound of any one of claims 1 to 22, wherein each R² is independently chosen from fluoro, chloro, methyl, methoxy, trifluoromethyl, methylthio, methylsulfonyl, trifluoromethoxy, trifluoroethoxy, phenyl, and pyrazolyl.
24. The compound of claim 23, wherein each R² is independently chosen from fluoro, chloro, methyl, trifluoromethyl, methylsulfonyl, and methoxy.
25. The compound of any one of claims 1 to 24, wherein n is 0.
26. The compound of any one of claims 17 to 25, wherein R³ is chosen from isobutyl and cyclopropylmethyl.
27. A compound of claim 10, having structural Formula V,



or a salt, polymorph, or tautomer thereof, wherein:

R¹ is chosen from hydrogen, C₁–C₆ alkyl, and C₁–C₆ cycloalkyl;

L is chosen from O and S;

each R² is independently chosen from 5-10-membered heteroaryl, C₁–C₆ alkoxy, C₁–C₆ alkyl, C₁–C₆ alkylsulfonyl, C₁–C₆ alkylthio, C₁–C₆ haloalkoxy, C₁–C₆ haloalkyl, C₆–

C₁₀ aryl, cyano, and halogen;

n is 0, 1, or 2;

R³ is chosen from C₂–C₆ alkyl, C₃–C₆ cycloalkyl, and C₃–C₆ cycloalkylalkyl;

and

each R⁶ is C₁–C₆ alkoxy, C₁–C₆ alkyl, C₁–C₆ haloalkyl, C₃–C₆ cycloalkyl, cyano, halogen, and hydroxyl; and

m is 0, 1, 2, or 3.

28. The compound of claim 27, wherein R¹ is hydrogen.

29. The compound of claim 27 or 28, wherein n is 0.

30. The compound of any one of claims 27–29, wherein n is 0 or 1; and R⁶, if present, is halogen.

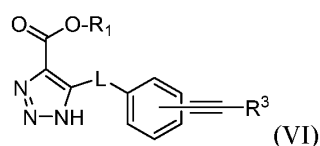
31. The compound of any one of claims 27–30, wherein R³ is chosen from C₂–C₆ alkyl, C₃–C₆ cycloalkyl, and C₃–C₆ cycloalkylmethyl.

32. The compound of any of claims 27–31, wherein R³ is chosen from ethyl, propyl, isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, and bicyclo[1.1.1]pentylmethyl.

33. The compound of any of claims 27–31, wherein R³ is chosen from ethyl, propyl, isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, and cyclohexylmethyl.

34. The compound of any one of claims 26 to 33, wherein R³ is chosen from isobutyl and cyclopropylmethyl.

35. A compound of claim 17, having structural Formula VI,



or a salt, polymorph, or tautomer thereof, wherein:

R¹ is chosen from hydrogen, C₁–C₆ alkyl, and C₁–C₆ cycloalkyl;

L is chosen from O, S, CH₂, and NH; and

R³ is chosen from C₂–C₆ alkyl, C₃–C₆ cycloalkyl, and C₃–C₆ cycloalkylalkyl.

36. The compound of any one of claims 1 to 35, wherein R¹ is chosen from methyl, ethyl,

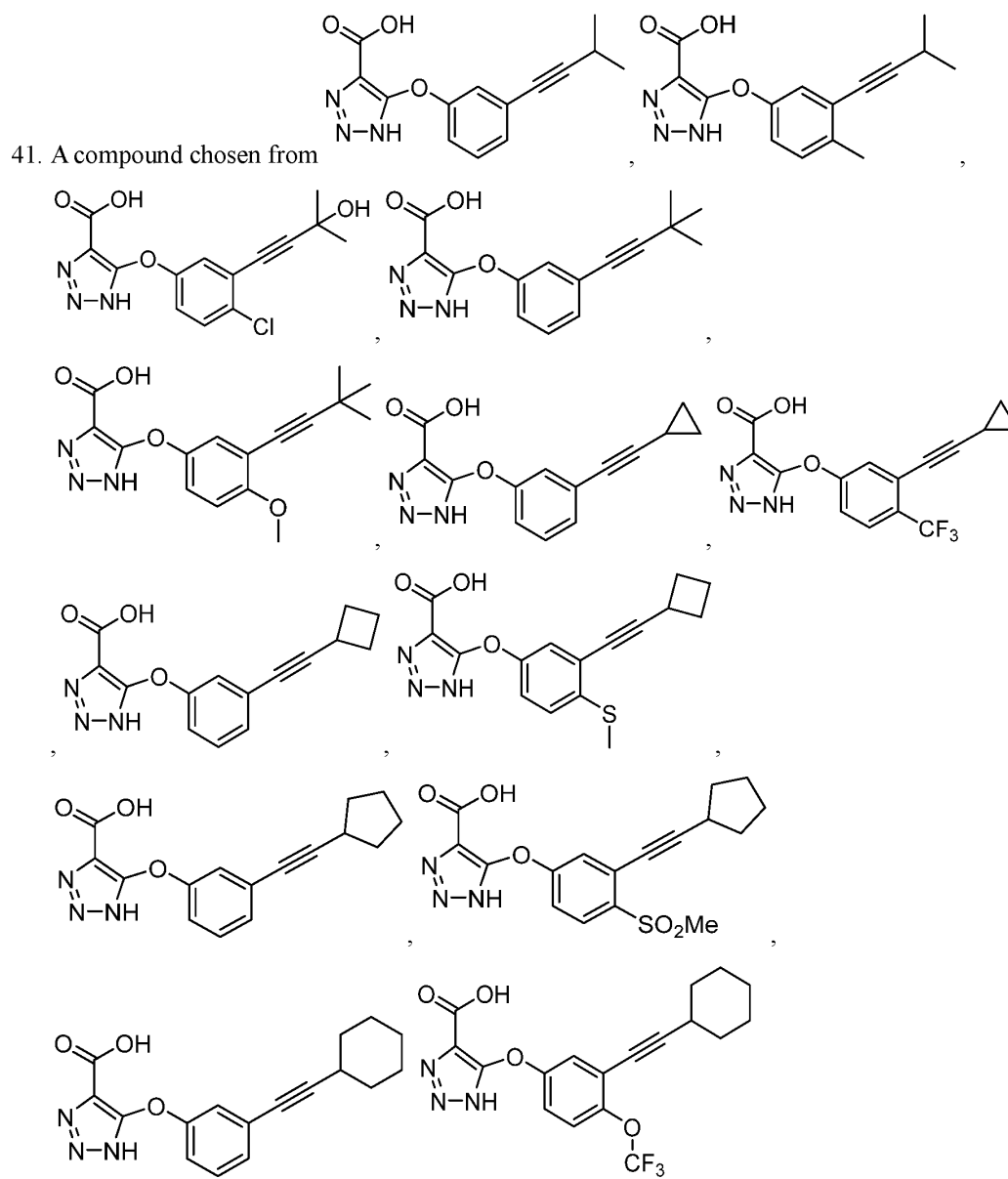
isopropyl, t-butyl, and hydrogen.

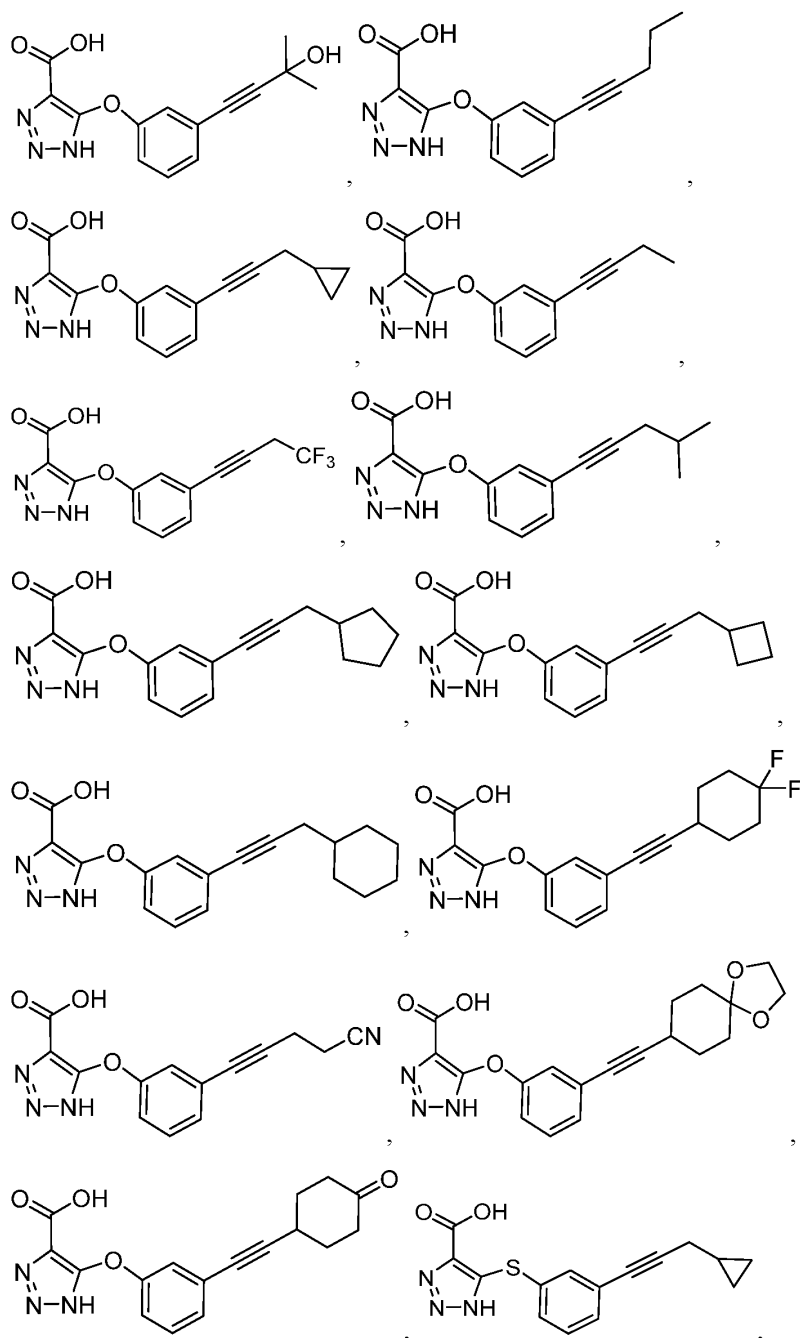
37. The compound of claim 36, wherein R^1 is hydrogen.

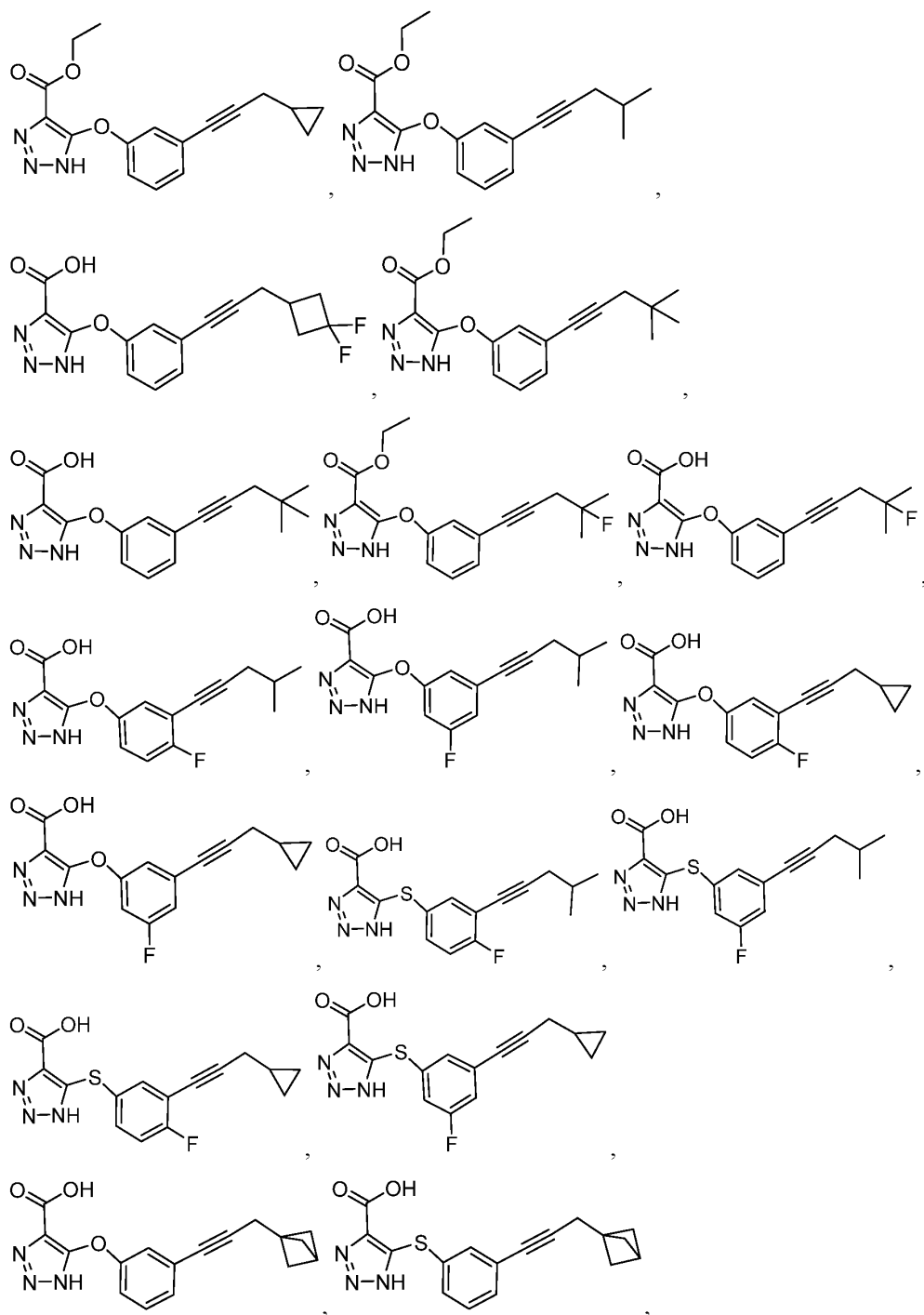
38. The compound of claim 35, wherein L is O or S.

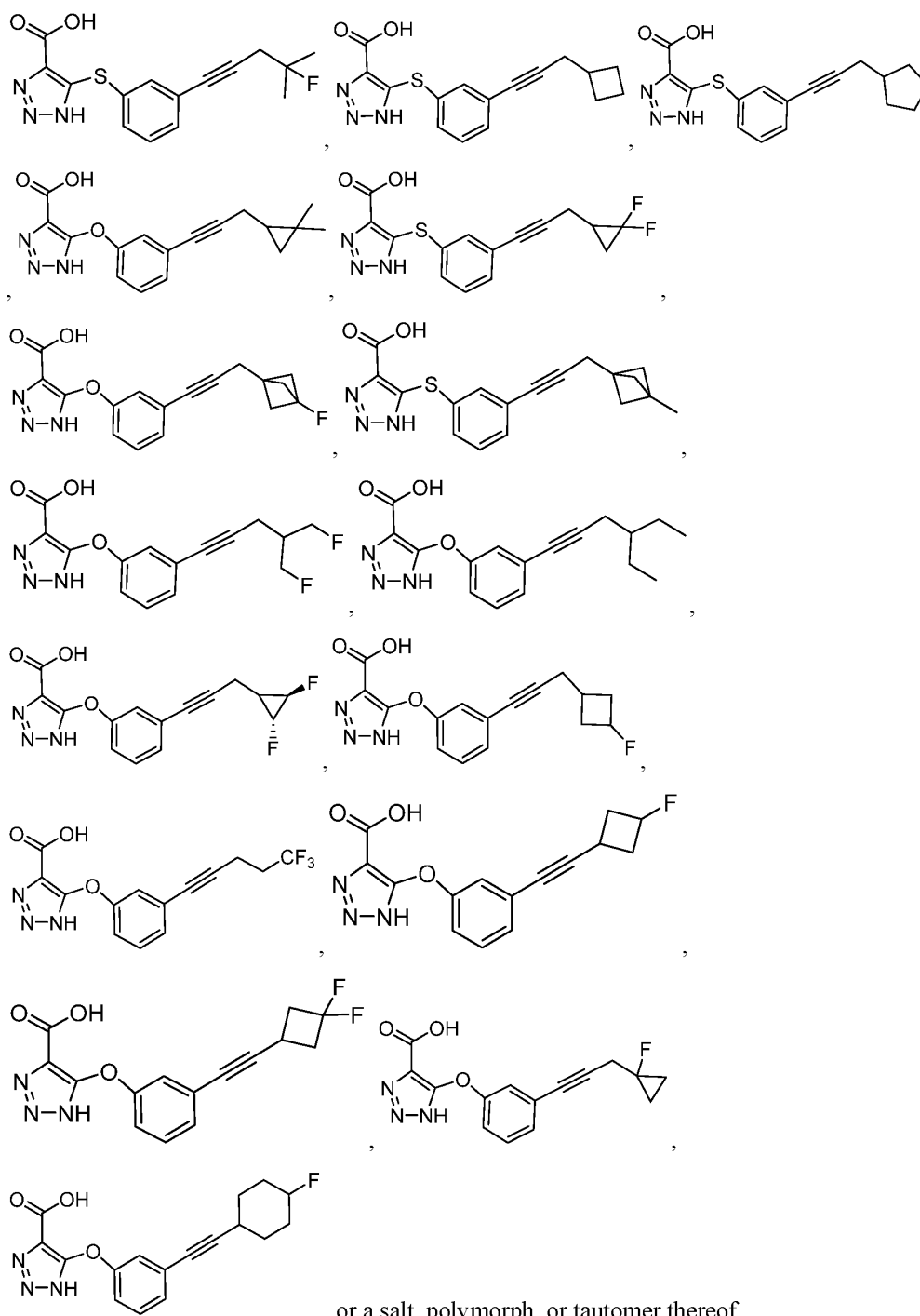
39. The compound of claim 35, wherein R^3 is chosen from isobutyl and cyclopropylmethyl.

40. A compound chosen from Examples 3–414 or a salt, polymorph, or tautomer thereof.









, or a salt, polymorph, or tautomer thereof.

42. A compound of any of claims 1-41, or a salt, polymorph, or tautomer thereof, for use as a

medicament.

43. A compound of any of claims 1–41, or a salt, polymorph, or tautomer thereof, for use in manufacturing a medicament for preventing or treating an oxalate-related disease.
44. A pharmaceutical composition comprising a compound of any of claims 1–41, or a salt, polymorph, or tautomer thereof together with a pharmaceutically acceptable carrier.
45. The pharmaceutical composition of any of claims 1–41, formulated for oral administration.
46. The pharmaceutical composition of any of claims 1–41, additionally comprising another therapeutic agent.
47. A method of inhibiting glycolate oxidase (GOX) activity in a biological sample comprising contacting the biological sample with a pharmaceutical composition as recited in any of claims 44–46, or a compound of any of claims 1–41, or a salt, polymorph, or tautomer thereof.
48. A method of treating an oxalate-related disease in a subject in need thereof, comprising the step of administering to the subject a pharmaceutical composition as recited in any of claims 44–46, or a compound of any of claims 1–41 or a salt, polymorph, or tautomer thereof.
49. The method of claim 48, wherein the subject is human.
50. The method of claim 49, wherein the oxalate-related disease is hyperoxaluria.
51. The method of claim 50, wherein the oxalate-related disease is primary hyperoxaluria.
52. The method of claim 50, wherein the oxalate-related disease is enteric hyperoxaluria.
53. The method of claim 48, wherein the oxalate-related disease is calcium oxalate kidney stones.
54. The method of claim 48, wherein the oxalate-related disease is idiopathic calcium oxalate stone former (ICSF).
55. The method of claim 48, wherein the oxalate-related disease is calcium oxalate kidney stones after bariatric surgery.
56. The method of claim 48, wherein the oxalate-related disease is urolithiasis or nephrolithiasis for gastrointestinal diseases such as Crohn's disease and ulcerative colitis.
57. A method of treating an oxalate-related disease in a subject in need thereof, comprising the sequential or co-administration of a pharmaceutical composition as recited in any of claims 44–46, or a compound of any of claims 1–41 and a second therapeutic agent.

58. A pharmaceutical composition as recited in any of claims 44–46, or a compound of any of claims 1–41 or a salt, polymorph, or tautomer thereof, for use in human therapy.
59. A pharmaceutical composition as recited in any of claims 44–46, or a compound of any of claims 1–41 or a salt, polymorph, or tautomer thereof, for use in treating an oxalate-related disease.
60. Use of a compound of any of claims 1–41 or a salt, polymorph, or tautomer thereof, for manufacturing a medicament to treat an oxalate-related disease.