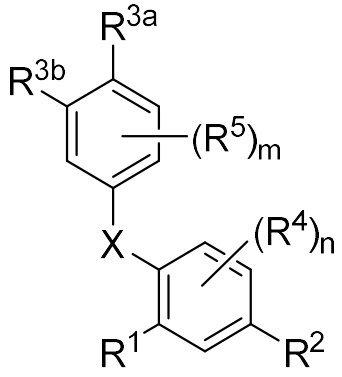
CLAIMS

What is claimed is:

1. A compound having the chemical formula (I'):



(I'), or a pharmaceutically acceptable salt thereof, wherein:

X is NR^a or S;

R^1 is a 5-10 membered heteroaryl having one, two, three, or four heteroatoms each independently selected from the group consisting of N, O, and S; wherein the 5-10 membered heteroaryl is optionally substituted;

R^2 is 3-10 membered heterocyclyl or -(C_1-C_4alkylene)-(3-10 membered heterocyclyl), wherein the 3-10 membered heterocyclyl contains at least 2 carbon atoms and one, two, three or, four heteroatoms and is optionally substituted, wherein the heteroatoms are nitrogen, and wherein the C_1-C_4alkylene is optionally substituted;

one of R^{3a} and R^{3b} is selected from the group consisting of halogen, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), C_{3-10} cycloalkyl, phenyl, naphthyl, and 5-10 membered heteroaryl, wherein the C_{3-10} cycloalkyl, phenyl, naphthyl, and 5-10 membered heteroaryl are optionally substituted; and the other one of R^{3a} and R^{3b} is selected from the group consisting of hydrogen, halogen, and -C_1-C_6 alkyl;

each R^4 is independently selected from halogen and -C_1-C_6 alkyl;

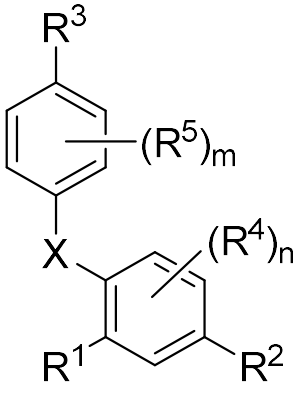
each R^5 is independently selected from halogen and -C_1-C_6 alkyl;

m is selected from the group consisting of 0, 1, 2, and 3;

n is selected from the group consisting of 0, 1, 2, and 3; and

R^a is selected from hydrogen and -C_1-C_6 alkyl.

2. A compound having the chemical formula (I-1):



(I-1), or a pharmaceutically acceptable salt thereof, wherein:

X is NR^a or S;

R^1 is a 5-10 membered heteroaryl having one, two, three, or four heteroatoms each independently selected from the group consisting of N, O, and S; wherein the 5-10 membered heteroaryl is optionally substituted;

R^2 is 3-10 membered heterocyclyl or -(C_1-C_4alkylene)-(3-10 membered heterocyclyl); wherein the 3-10 membered heterocyclyl has one, two, three, or four heteroatoms each independently selected from the group consisting of N, O, and S, and is optionally substituted, wherein the C_1-C_4alkylene is optionally substituted;

R^3 is selected from the group consisting of halogen, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), C_{3-10} cycloalkyl, phenyl, naphthyl, and 5-10 membered heteroaryl, wherein the C_{3-10} cycloalkyl, phenyl, naphthyl, and 5-10 membered heteroaryl are optionally substituted;

each R^4 is independently selected from halogen and -C_1-C_6 alkyl;

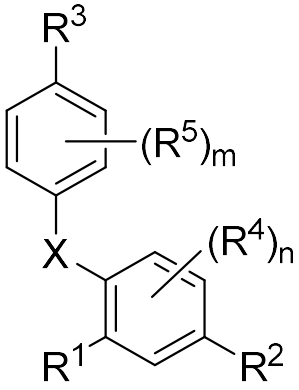
each R^5 is independently selected from halogen and -C_1-C_6 alkyl;

m is selected from the group consisting of 0, 1, 2, 3, and 4;

n is selected from the group consisting of 0, 1, 2, and 3; and

R^a is selected from hydrogen and -C_1-C_6 alkyl.

3. The compound of claim 1 or 2, wherein the compound has the chemical formula (I-1'):



(I-1'), or a pharmaceutically acceptable salt thereof, wherein:

X is NR^a or S;

R^1 is a 5-10 membered heteroaryl having one, two, three, or four heteroatoms each independently selected from the group consisting of N, O, and S; wherein the 5-10 membered heteroaryl is optionally substituted;

R^2 is 3-10 membered heterocyclyl or -(C_1-C_4alkylene)-(3-10 membered heterocyclyl); wherein the 3-10 membered heterocyclyl contains at least 2 carbon atoms and one, two, three, or four heteroatoms and is optionally substituted, wherein the heteroatoms are nitrogen, and wherein the C_1-C_4alkylene is optionally substituted;

R^3 is selected from the group consisting of halogen, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), C_{3-10} cycloalkyl, phenyl, naphthyl, and 5-10 membered heteroaryl, wherein the C_{3-10} cycloalkyl, phenyl, naphthyl, and 5-10 membered heteroaryl are optionally substituted;

each R^4 is independently selected from halogen and -C_1-C_6 alkyl;

each R^5 is independently selected from halogen and -C_1-C_6 alkyl;

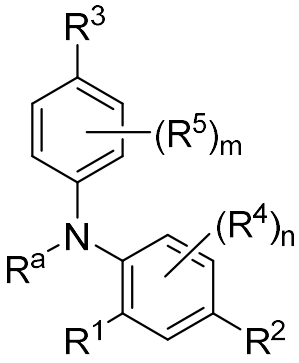
m is selected from the group consisting of 0, 1, 2, 3, and 4;

n is selected from the group consisting of 0, 1, 2, and 3; and

R^a is selected from hydrogen and -C_1-C_6 alkyl.

4. The compound of any one of claims 1-3, wherein X is NR^a.

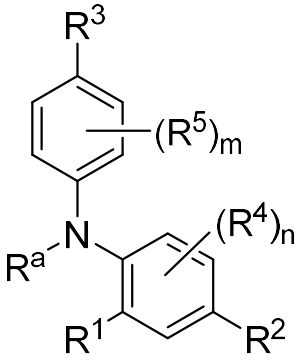
5. The compound of claim 2, wherein the compound is a compound of formula (Ia):

 (Ia), or a pharmaceutically acceptable salt thereof, wherein:

R^3 is -C_1-C_6 alkyl or -C_1-C_6 haloalkyl; and

the rest of the variables are as defined in claim 2.

6. The compound of claim 1 or 3, wherein the compound is a compound of formula (Ia'):

 (Ia'), or a pharmaceutically acceptable salt thereof, wherein:

R^3 is -C_1-C_6 alkyl or -C_1-C_6 haloalkyl; and

the rest of the variables are as defined in claim 1.

7. The compound of any one of claims 1-6, wherein R^1 is 5-6 membered heteroaryl that is optionally substituted.

8. The compound of any one of claims 1-7, wherein R^1 is 5-6 membered heteroaryl that is optionally substituted with 1, 2, 3, or 4 substituents each independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), and -N(R^b)$_2$, wherein each R^b is independently selected from hydrogen and C_1-C_6 alkyl.

9. The compound of any one of claims 1-8, wherein R^1 is 5-6 membered heteroaryl that is optionally substituted with 1, 2, 3, or 4 substituents each independently selected from halogen and -C_1-C_6 alkyl.

10. The compound of any one of claims 1-9, wherein R^1 is 5-6 membered heteroaryl selected

from the group consisting of oxadiazole, imidazole, pyrazole, oxazole, triazole, tetrazole, pyridine, pyrazine, and pyridazine, wherein the 5-6 membered heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents each independently selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), and -N(R^b)$_2$, wherein each R^b is independently selected from hydrogen and C_1-C_6 alkyl.

11. The compound of any one of claims 1-10, wherein R^1 is 5-6 membered heteroaryl selected from the group consisting of oxadiazole, imidazole, pyrazole, oxazole, triazole, tetrazole, pyridine, pyrazine, and pyridazine, wherein the 5-6 membered heteroaryl is optionally substituted with C_1-C_6 alkyl.

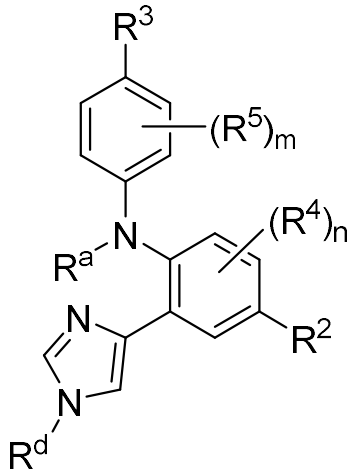
12. The compound of any one of claims 1-11, wherein R^1 is imidazole optionally substituted with methyl.

13. The compound of any one of claims 1-11, wherein R^1 is oxazole.

14. The compound of any one of claims 1-11, wherein R^1 is tetrazole optionally substituted with methyl.

15. The compound of any one of claims 1-11, wherein R^1 is oxadiazole, e.g., 1,3,4-oxadiazole, optionally substituted with methyl.

16. The compound of claim 2 or 5, wherein the compound is a compound of formula (Ib):



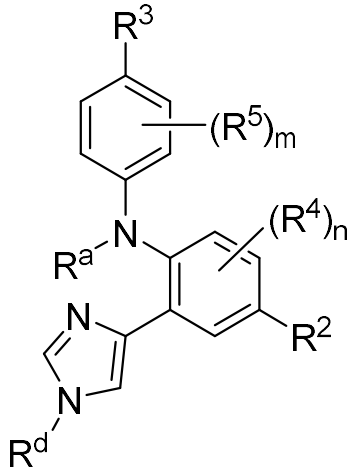
(Ib), or a pharmaceutically acceptable salt thereof, wherein:

R^d is selected from hydrogen and -C_1-C_6 alkyl; and

the rest of the variables are as defined in claim 5.

17. The compound of any one of claims 1, 3, or 6, wherein the compound is a compound of

formula (Ib'):

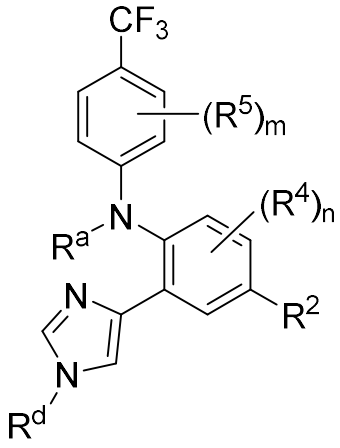


(Ib'), or a pharmaceutically acceptable salt thereof, wherein:

R^d is selected from hydrogen and -C_1-C_6 alkyl; and

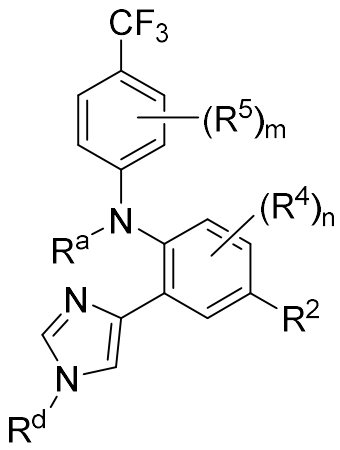
the rest of the variables are as defined in claim 6.

18. The compound of claim 16, wherein the compound is a compound of formula (Ic):



(Ic), or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in claim 16.

19. The compound of claim 17, wherein the compound is a compound of formula (Ic'):



(Ic'), or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in claim 17.

20. The compound of any one of claims 1-19, wherein R^2 is 3-7 membered monocyclic heterocyclyl or -(C_1-C_4alkylene)-(3-7 membered monocyclic heterocyclyl), wherein the 3-7 membered monocyclic heterocyclyl contains at least 2 carbon atoms and one, two, three, or four heteroatoms, wherein the heteroatoms are nitrogen and wherein the 3-7 membered monocyclic heterocyclyl is optionally substituted, and wherein the C_1-C_4alkylene is optionally substituted (e.g., optionally substituted with C_{1-6}alkyl, C_{1-6}haloalkyl, or two geminal hydrogens on a carbon of the C_{1-4}alkylene can be taken together with the carbon atom to which they are attached to form a 3-7 membered cycloalkyl ring).

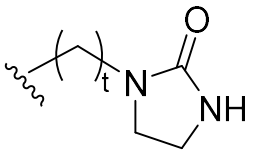
21. The compound of any one of claims 1-20, wherein R^2 is 3-7 membered monocyclic heterocyclyl or -(C_1-C_4alkylene)-(3-7 membered monocyclic heterocyclyl), wherein the 3-7 membered monocyclic heterocyclyl contains at least 2 carbon atoms and one, two, three, or four heteroatoms, wherein the heteroatoms are nitrogen and wherein the 3-7 membered monocyclic heterocyclyl is optionally substituted with 1, 2, 3, or 4 substituents each independently selected from the group consisting of C_1-C_6 alkyl, oxo, hydroxyl, halogen, C_1-C_6 haloalkyl, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -N(R^b)$_2$, -C(O)OR^g, -C(O)N(R^f)$_2$, -S(O)$_2$N(R^f)$_2$, -OC(O)N(R^f)$_2$, -NR^fC(O)N(R^f)$_2$, and -S(O)$_r$-R^f, wherein each of R^b, R^g, and R^f is independently selected from hydrogen and C_1-C_6 alkyl, wherein each r is 1 or 2, and wherein each R^f is independently selected from C_{1-6}alkyl and phenyl.

22. The compound of any one of claims 1-21, wherein R^2 is 3-7 membered monocyclic heterocyclyl, wherein the 3-7 membered monocyclic heterocyclyl contains at least 2 carbon atoms and one, two, three, or four heteroatoms, wherein the heteroatoms are nitrogen and wherein the 3-7 membered monocyclic heterocyclyl is optionally substituted with 1, 2, 3, or 4 substituents each independently selected from the group consisting of halogen, -C_1-C_6 alkyl, oxo, and hydroxyl.

23. The compound of any one of claims 1-21, wherein R^2 is 5-membered heterocyclyl having one or two heteroatoms, wherein the heteroatoms are nitrogen atoms, and wherein the 5-membered heterocyclyl is optionally substituted with 1, 2, or 3 substituents each independently selected from C_1-C_6 alkyl, oxo, and hydroxyl.

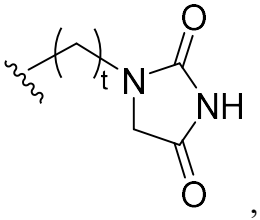
24. The compound of any one of claims 1-21, wherein R^2 is -(C_1-C_4alkylene)-(5-membered heterocyclyl having one or two heteroatoms), wherein the heteroatoms are nitrogen atoms, and wherein the 5-membered heterocyclyl is optionally substituted with 1, 2, or 3 substituents each independently selected from C_1-C_6 alkyl oxo, and hydroxyl.

25. The compound of any one of claims 1-21, wherein R^2 is:



, wherein t is selected from the group consisting of 0, 1, 2, and 3.

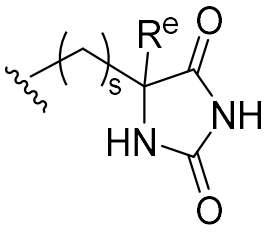
26. The compound of any one of claims 1-21, wherein R^2 is:



, wherein t is selected from the group consisting of 0, 1, 2, and 3.

27. The compound of claim 25 or 26, wherein t is 1.

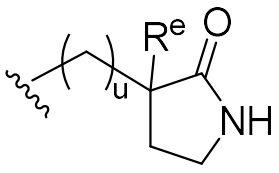
28. The compound of any one of claims 1-21, wherein R^2 is:



, wherein s is selected from the group consisting of 0, 1, 2, and 3, and R^e is selected from hydrogen and C_1-C_6 alkyl.

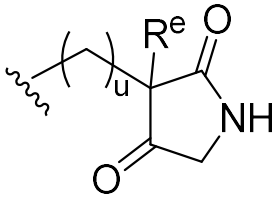
29. The compound of claim 28, wherein s is 0 and R^e is methyl.

30. The compound of any one of claim 1-21, wherein R^2 is:



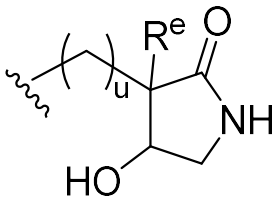
, wherein u is selected from the group consisting of 0, 1, 2, and 3, and R^e is selected from hydrogen and C_1-C_6 alkyl.

31. The compound of any one of claims 1-21, wherein R^2 is:



, wherein u is selected from the group consisting of 0, 1, 2, and 3, and R^e is selected from hydrogen and C_1-C_6 alkyl.

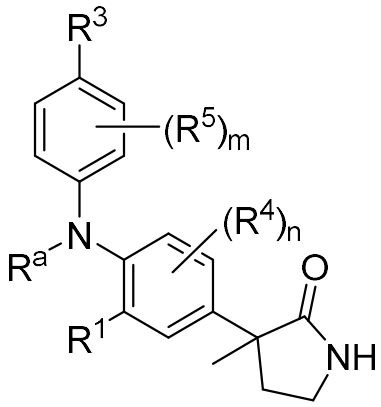
32. The compound of any one of claims 1-21, wherein R^2 is:



, wherein u is selected from the group consisting of 0, 1, 2, and 3, and R^e is selected from hydrogen and C_1-C_6 alkyl.

33. The compound of any one of claims 30-32, wherein u is 0 and R^e is methyl.

34. The compound of any one of claims 1-23 and 30, wherein the compound is a compound of formula (Id):

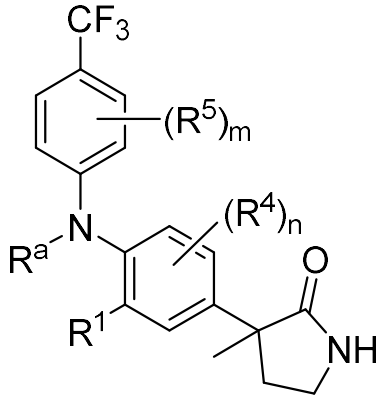


(Id), or a pharmaceutically acceptable salt thereof,

wherein R^3 is -C_1-C_6 alkyl or -C_1-C_6 haloalkyl; and

the rest of the variables are as defined in claim 5.

35. The compound of claim 34, wherein the compound is a compound of formula (Ie):



(Ie), or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in claim 34.

36. The compound of any one of claims 1-9 and 20-35, wherein R^1 contains at least one ring carbon atom and contains only carbon and nitrogen atoms.

37. The compound of any one of claims 1-36, wherein R^3 is C_1-C_6 alkyl or -C_1-C_6 haloalkyl.

38. The compound of any one of claims 1-37, wherein R^3 is halogen.

39. The compound of any one of claims 1-38, wherein R^3 is trifluoromethyl.

40. The compound of any one of claims 1-39, wherein m and n are both 0.

41. The compound of any one of claims 1-40, wherein R^a is hydrogen.

42. The compound of any one of claims 1-41, wherein the compound is selected from Table 1 or a pharmaceutically acceptable salt thereof.

43. A pharmaceutical composition, comprising: (a) a compound or a pharmaceutically acceptable salt thereof of any one of claims 1-42; and (b) a pharmaceutically acceptable excipient.

44. Use of a compound or pharmaceutically acceptable salt of any one of claims 1-42, or a pharmaceutical composition of claim 43 in the manufacture of a medicament for treating a disease or condition mediated by hyperactivation of a TEAD isoform selected from TEAD1 and TEAD4 in a subject in need thereof.

45. The use of claim 44, wherein the disease or condition is a cancer characterized by hyperactivation of a TEAD isoform selected from TEAD1 and TEAD4.

46. The use of claim 45, wherein the cancer is selected from the group consisting of: a breast cancer, a lung cancer, a gastric cancer, a colorectal cancer, a pancreatic cancer including pancreatic adenocarcinoma, a mesothelioma including malignant mesothelioma, a hepatocellular cancer, a prostate cancer, a head and neck cancer, a renal cell carcinoma, and a medulloblastoma.

47. The use of claim 46, wherein the pancreatic cancer is pancreatic adenocarcinoma.

48. The use of claim 46, wherein the mesothelioma is malignant mesothelioma.

49. The use of 45 or 46, wherein the cancer is selected from the group consisting of: a hepatocellular cancer, a breast cancer, a pancreatic adenocarcinoma, and a mesothelioma.

50. The use of any one of claims 45, 46, and 49, wherein the cancer is mesothelioma.

51. The use of any one of claims 45-50, wherein the cancer is a metastatic cancer.

52. The use of claim 51, wherein the cancer is a metastatic breast cancer.

53. The use of claim 51, wherein the cancer is a metastatic lung cancer.

54. The use of claim 51, wherein the cancer is a metastatic gastric cancer.

55. The use of claim 51, wherein the cancer is a metastatic colorectal cancer.

56. The use of claim 51, wherein the cancer is a metastatic prostate cancer.

57. The use of claim 51, wherein the cancer is a metastatic head and neck cancer.

58. The use of claim 51, wherein the cancer is a metastatic renal cell carcinoma.

59. The use of claim 51, wherein the cancer is a metastatic mesothelioma.

60. The use of claim 51, wherein the cancer is a metastatic pancreatic cancer.

61. The use of claim 51, wherein the cancer is a metastatic hepatocellular cancer.

62. The use of any one of claims 44-61, wherein the compound or pharmaceutically acceptable salt of any one of claims 1-42, or the pharmaceutical composition of claim 43, is to be administered in combination with one or more other therapeutic agents.

63. A compound or pharmaceutically acceptable salt of any one of claims 1-42, or the

pharmaceutical composition of claim 43, for use in treating a disease or condition mediated by hyperactivation of a TEAD isoform selected from TEAD1 and TEAD4 in a subject in need thereof.

64. The compound or pharmaceutically acceptable salt or pharmaceutical composition for use of claim 63, wherein the disease or condition is a cancer characterized by hyperactivation of a TEAD isoform selected from TEAD1 and TEAD4.

65. The compound or pharmaceutically acceptable salt or pharmaceutical composition for use of claim 64, wherein the cancer is selected from the group consisting of: a breast cancer, a lung cancer, a gastric cancer, a colorectal cancer, a pancreatic cancer including pancreatic adenocarcinoma, a mesothelioma including malignant mesothelioma, a hepatocellular cancer, a prostate cancer, a head and neck cancer, a renal cell carcinoma, and a medulloblastoma.