# COMBINATION OF A 3-(IMIDAZOL-4-YL)-4-(AMINO)-BENZENESULFONAMIDE TEAD INHIBITOR WITH AN EGFR INHIBITOR AND/OR MEK INHIBITOR FOR USE IN THE TREATMENT OF LUNG CANCER

## TECHNICAL FIELD OF THE INVENTION

**[0001]** The present invention relates to TEAD inhibitors, compositions thereof, and use of a TEAD inhibitor in combination with an EGFR inhibitor and/or a MEK inhibitor for treatment of cancer.

## CROSS-REFERENCE TO RELATED APPLICATIONS

**[0002]** This application claims the benefit of and priority to under 35 U.S.C. § 119(e) of United States Provisional Patent Application serial number 63/141,105, filed January 25, 2021; the contents of which are hereby incorporated by reference in their entirety.

## BACKGROUND OF THE INVENTION

**[0003]** Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) are transcriptional co-activators of the Hippo pathway network and regulate cell proliferation, migration, and apoptosis. Inhibition of the Hippo pathway promotes YAP/TAZ translocation to the nucleus, wherein YAP/TAZ interact with TEAD transcription factors and coactivate the expression of target genes and promote cell proliferation. Hyperactivation of YAP and TAZ and/or mutations in one or more members of the Hippo pathway network have been implicated in numerous cancers.

## SUMMARY

**[0003a]** In an aspect of the present disclosure, there is provided a use of a TEAD inhibitor and an EGFR inhibitor in the manufacture of a medicament for treating cancer in a patient in need thereof.

**[0003b]** In another aspect of the present disclosure, there is provided a use of a TEAD inhibitor and a MEK inhibitor in the manufacture of a medicament for treating cancer in a patient in need thereof.

**[0004]** It has been found that the combination of a TEAD inhibitor and an EGFR inhibitor has synergistic effects in treating cancer. Accordingly, in one example, the present disclosure provides a method for treating cancer in a patient comprising administering to the patient a therapeutically effective amount of a TEAD inhibitor and an EGFR inhibitor.

**[0005]** It has been also found that the combination of a TEAD inhibitor and a MEK inhibitor has synergistic effects in treating cancer. Accordingly, in one example, the present disclosure provides a method for treating cancer in a patient comprising administering to the patient a therapeutically effective amount of a TEAD inhibitor and a MEK inhibitor.

**[0006]** It has also been found that the combination of a TEAD inhibitor and an EGFR inhibitor has additional synergistic effects in treating cancer when used in further combination with an MEK inhibitor. Accordingly, in one example, the present disclosure provides a method for treating cancer in a patient comprising administering to the patient a therapeutically effective amount of a TEAD inhibitor, an EGFR inhibitor, and an MEK inhibitor.

**[0007]** In some examples, a TEAD inhibitor is selected from those as described herein. In some examples, an EGFR inhibitor is selected from those as described herein. In some examples, an MEK inhibitor is selected from those as described herein. In some examples, a cancer is selected from those as described herein.

## BRIEF DESCRIPTION OF FIGURES

**[0008]** **FIG. 1** demonstrates the apoptosis induction effects of a TEAD inhibitor **T-A-32**, an EGFR inhibitor Osimertinib, an MEK inhibitor Trametinib, and combinations thereof in HCC4006 and HCC827 cells.

**[0009]** **FIG. 2** demonstrates the effects of a TEAD inhibitor **T-A-32**, an EGFR inhibitor Osimertinib, an MEK inhibitor Trametinib, and combinations thereof on H1975 Tumor Growth in nude nu/nu mice.

**[0010]** **FIG. 3** demonstrates the effects of a TEAD inhibitor **T-A-32**, a MEK inhibitor Trametinib, and a combination thereof on tumor growth and volume in an HCT-116 tumor model, which is a KRAS G13D mutant tumor.

**[0011]** **FIG. 4** demonstrates the effects of a TEAD inhibitor **T-A-32**, a MEK inhibitor Trametinib, and a combination thereof on tumor growth and volume in an A549 tumor model, which is a KRAS G12S mutant tumor.

**[0012]** **FIG. 5** demonstrates the effects of a TEAD inhibitor **T-A-32**, a MEK inhibitor Trametinib, and a combination thereof on tumor growth and volume in a LoVo tumor model, which is a KRAS G12D mutant tumor.

## DETAILED DESCRIPTION OF THE INVENTION

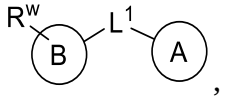
### *1. General Description of Certain Embodiments of the Invention*

**[0013]** As described herein, a combination of a TEAD inhibitor and an EGFR inhibitor demonstrated unexpected synergistic effects in treating cancer. For example, a combination of a

## CLAIMS

1. Use of a TEAD inhibitor and an EGFR inhibitor in the manufacture of a medicament for treating cancer in a patient in need thereof.

2. The use of claim 1, wherein the TEAD inhibitor is a compound of **Formula A**:



,

or a pharmaceutically acceptable salt thereof, wherein

$L^1$ is $C_{1-6}$ bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -CH(OR)-, -CH(SR)-, –CH(N(R)$_2$)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, -$SO_2$-, -$SO_2$N(R)-, -(R)N$SO_2$-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-;

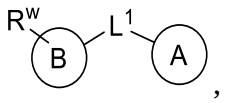
Ring A is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-10 membered bicyclic aromatic ring, or a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-10 membered bicyclic aromatic ring, a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

$R^w$ is an optionally substituted 4-, 5-, or 6- membered ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each R is independently -H or optionally substituted -$C_{1-6}$ aliphatic. .

3. The use of claim 1, wherein the TEAD inhibitor is a compound of **Formula B**:



,

or a pharmaceutically acceptable salt thereof, wherein

$L^1$ is a covalent bond, or a $C_{1-6}$ bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -CH(OR)-, -CH(SR)-, –CH(N(R)$_2$)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, -SO$_2$-, -SO$_2$N(R)-, -(R)NSO$_2$-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-;

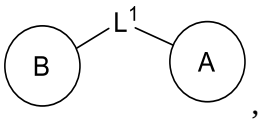
Ring A is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-10 membered bicyclic aromatic ring, or a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-10 membered bicyclic aromatic ring, a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

$R^w$ is a warhead group; wherein when $R^w$ is a saturated or partially unsaturated monocyclic carbocyclic or heterocyclic ring, it optionally forms a spiro bicyclic ring with Ring B; and

each R is independently -H or optionally substituted -$C_{1-6}$ aliphatic.

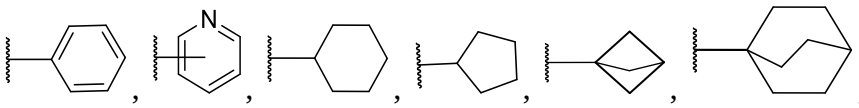
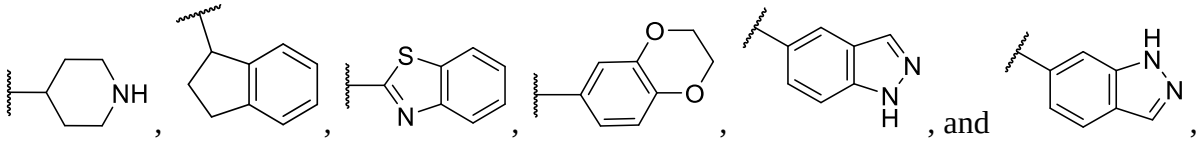
4. The use of claim 1, wherein the TEAD inhibitor is a compound of **Formula C**:

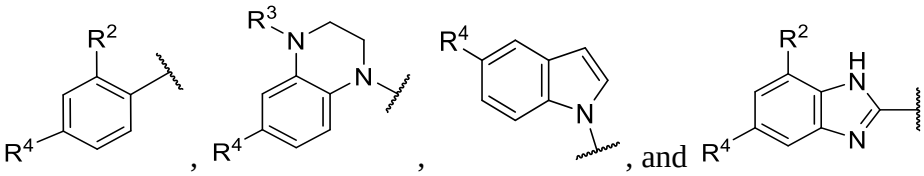


,

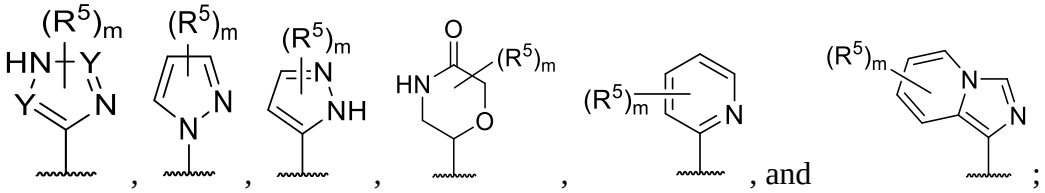
or a pharmaceutically acceptable salt thereof, wherein

$L^1$ is a covalent bound, or a $C_{1-6}$ bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -N(R)-, -O-, or -C(O)-;

Ring A is selected from  ,  , and , each of which is optionally substituted;

Ring B is selected from  , and ;

each $R^2$ is independently selected from -OR, $-C(O)NR_2$, optionally substituted $-C_{1-6}$ aliphatic,

 , and ;

each Y is independently N or $CR^5$;

$R^3$ is H, -C(O)R, or optionally substituted $-C_{1-6}$ aliphatic;

each $R^4$ is independently $-S(O)_2NR_2$, $-S(O)_2R$, $-C(O)NR_2$, -C(O)R, or optionally substituted $-C_{1-6}$ aliphatic;

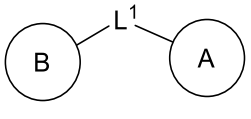
each $R^5$ is independently R, -CN, -C(O)R, $-C(O)NR_2$, or optionally substituted 5-6 membered heteroaryl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each m is independently 0, 1, or 2; and

each R is independently H, optionally substituted $-C_{1-6}$ aliphatic, optionally substituted 3-8 membered saturated or partially unsaturated monocyclic carbocyclyl, or optionally

substituted 3-8 membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

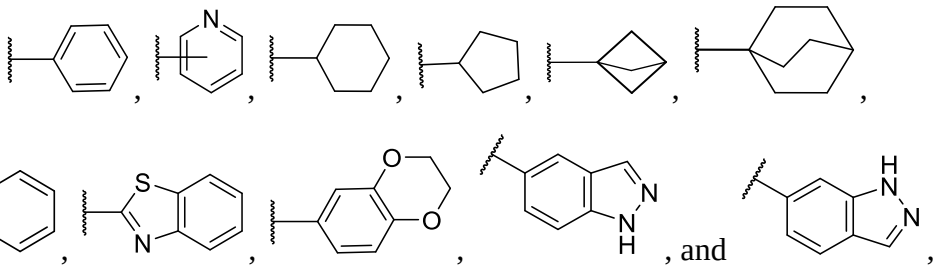
5. The use of claim 1, wherein the TEAD inhibitor is a compound of **Formula D**:

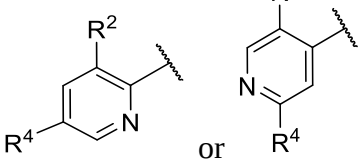


,

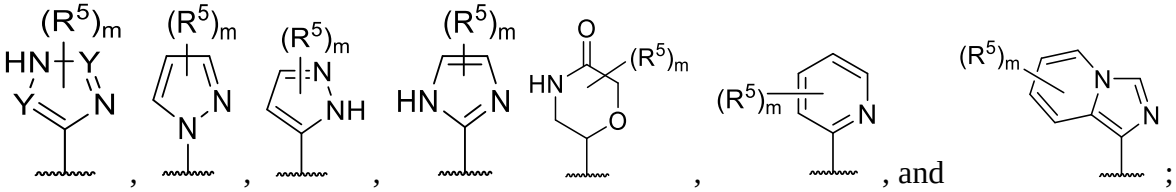
or a pharmaceutically acceptable salt thereof, wherein

$L^1$ is a covalent bound, or a $C_{1-6}$ bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -N(R)-, -O-, or -C(O)-;

Ring A is selected from  , each of which is optionally substituted;

Ring B is  or ;

each $R^2$ is independently selected from -OR, -C(O)$NR_2$, optionally substituted -$C_{1-6}$ aliphatic,

 , and ;

each Y is independently N or $CR^5$;

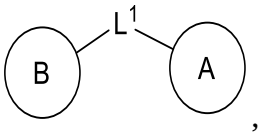
each $R^4$ is independently -$S(O)_2NR_2$, -$S(O)_2R$, -C(O)$NR_2$, -C(O)R, or optionally substituted -$C_{1-6}$ aliphatic;

each $R^5$ is independently R, -CN, -C(O)R, -C(O)$NR_2$, or optionally substituted 5-6 membered heteroaryl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each m is independently 0, 1, or 2; and

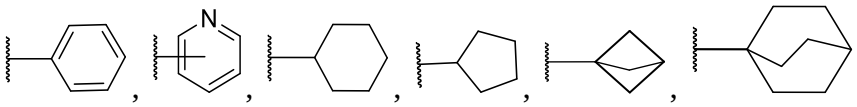
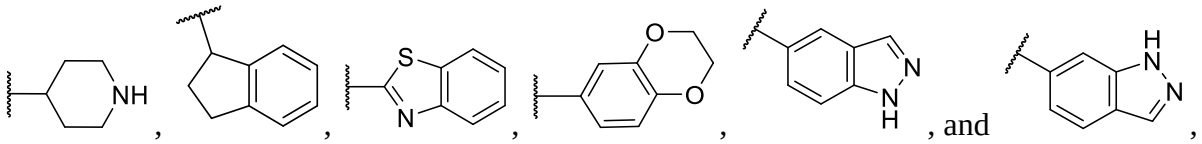
each R is independently H, optionally substituted -$C_{1-6}$ aliphatic, optionally substituted 3-8 membered saturated or partially unsaturated monocyclic carbocyclyl, or optionally substituted 3-8 membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

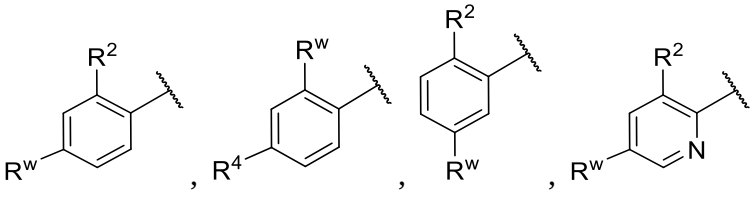
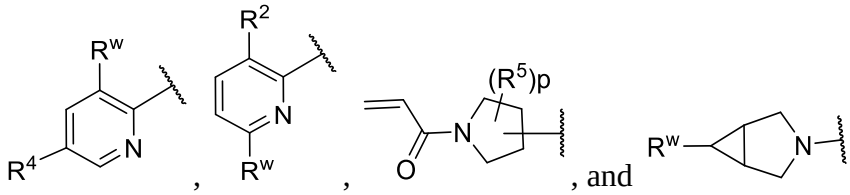
6. The use of claim 1, wherein the TEAD inhibitor is a compound of **Formula E**:

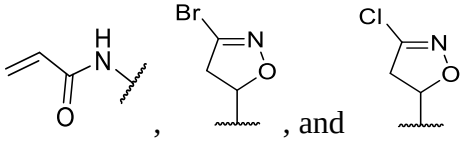



or a pharmaceutically acceptable salt thereof, wherein

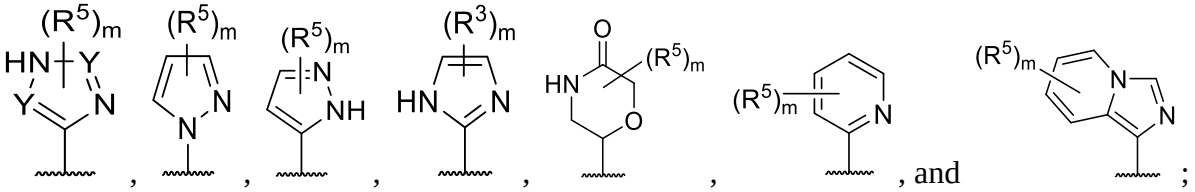
$L^1$ is a covalent bound, or a $C_{1-6}$ bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -N(R)-, -O-, or -C(O)-;

Ring A is selected from  ,  , and , each of which is optionally substituted;

Ring B is selected from  ,  , and ;

each $R^w$ is independently selected from  .

each $R^2$ is independently selected from -OR, -C(O)$NR_2$, optionally substituted -$C_{1-6}$ aliphatic,




, and ;

each Y is independently N or $CR^5$;

each $R^3$ is independently H or optionally substituted -$C_{1-6}$ aliphatic;

each $R^4$ is independently -$S(O)_2NR_2$, -$S(O)_2R$, -C(O)$NR_2$, -C(O)R, or optionally substituted -$C_{1-6}$ aliphatic;

each $R^5$ is independently R, -CN, -C(O)R, -C(O)$NR_2$, or optionally substituted 5-6 membered heteroaryl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each m is independently 0, 1, or 2;

p is 0, 1, or 2, and

each R is independently H, optionally substituted -$C_{1-6}$ aliphatic, optionally substituted 3-8 membered saturated or partially unsaturated monocyclic carbocyclyl, or optionally substituted 3-8 membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

7. The use of any one of claims 1-6, wherein the EGFR inhibitor is selected from cetuximab, necitumumab, panitumumab, zalutumumab, nimotuzumab, and matuzumab.

8. The use of any one of claims 1-6, wherein the EGFR inhibitor is selected from osimertinib, gefitinib, erlotinib, lapatinib, neratinib, vandetanib, afatinib, brigatinib, dacomitinib, and icotinib.

9. The use of any one of claims 1-8, wherein the TEAD inhibitor and the EGFR inhibitor are to be administered to the patient, and wherein an MEK inhibitor is to be further administered.

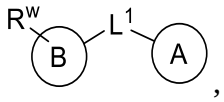
10. The use of claim 9, wherein the MEK inhibitor is selected from refametinib, selumetinib, trametinib, and cobimetinib.

11. The use of any one of claims 1-10, wherein the cancer is an EGFR mutant resistant cancer.

12. The use of claim 11, wherein the cancer is an EGFR mutant resistant lung cancer, or an EGFR mutant resistant NSCLC.

13. Use of a TEAD inhibitor and a MEK inhibitor in the manufacture of a medicament for treating cancer in a patient in need thereof.

14. The use of claim 13, wherein the TEAD inhibitor is a compound of **Formula A**:



,

or a pharmaceutically acceptable salt thereof, wherein

$L^1$ is $C_{1-6}$ bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -CH(OR)-, -CH(SR)-, –CH(N(R)$_2$)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, -SO$_2$-, -SO$_2$N(R)-, -(R)NSO$_2$-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-;

Ring A is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-10 membered bicyclic aromatic ring, or a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

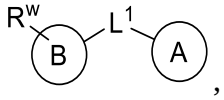
Ring B is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-

10 membered bicyclic aromatic ring, a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

$R^w$ is an optionally substituted 4-, 5-, or 6- membered ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each R is independently -H or optionally substituted -$C_{1-6}$ aliphatic. .

15. The use of claim 13, wherein the TEAD inhibitor is a compound of **Formula B**:



,

or a pharmaceutically acceptable salt thereof, wherein

$L^1$ is a covalent bond, or a $C_{1-6}$ bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -CH(OR)-, -CH(SR)-, –CH($N(R)_2$)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, -$SO_2$-, -$SO_2$N(R)-, -(R)N$SO_2$-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-;

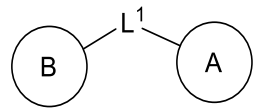
Ring A is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-10 membered bicyclic aromatic ring, or a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is an optionally substituted ring selected from phenyl, a 4-, 5-, or 6-membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-, 5-, or 6- membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 8-10 membered bicyclic aromatic ring, a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

$R^w$ is a warhead group; wherein when $R^w$ is a saturated or partially unsaturated monocyclic carbocyclic or heterocyclic ring, it optionally forms a spiro bicyclic ring with Ring B; and

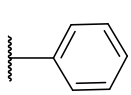
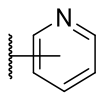
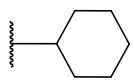
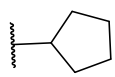
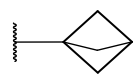
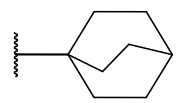
each R is independently -H or optionally substituted -$C_{1-6}$ aliphatic.

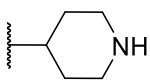
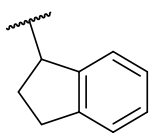
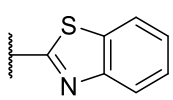
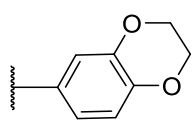
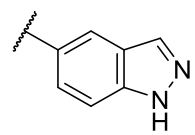
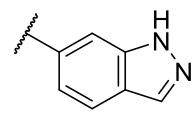
16. The use of claim 13, wherein the TEAD inhibitor is a compound of **Formula C**:


,

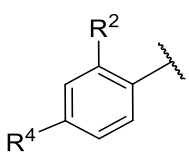
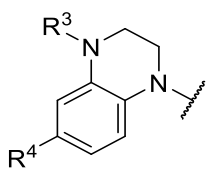
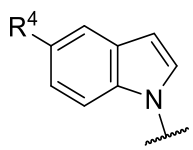
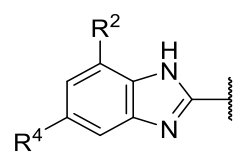
or a pharmaceutically acceptable salt thereof, wherein

$L^1$ is a covalent bound, or a $C_{1-6}$ bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -N(R)-, -O-, or -C(O)-;

Ring A is selected from  ,  ,  ,  ,  ,  ,

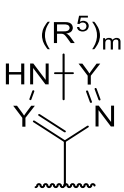
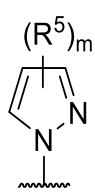
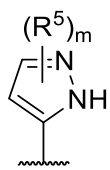
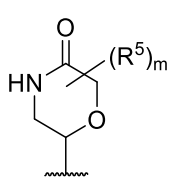
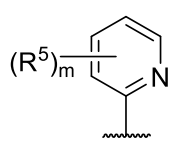
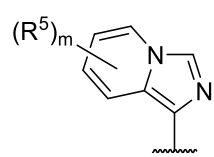
 ,  ,  ,  ,  , and  ,

each of which is optionally substituted;

Ring B is selected from  ,  ,  , and 

;

each $R^2$ is independently selected from -OR, -C(O)$NR_2$, optionally substituted -$C_{1-6}$ aliphatic,

 ,  ,  ,  ,  , and  ;

each Y is independently N or $CR^5$;

$R^3$ is H, -C(O)R, or optionally substituted -$C_{1-6}$ aliphatic;

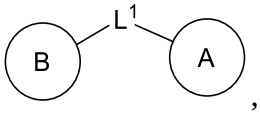
each $R^4$ is independently -$S(O)_2NR_2$, -$S(O)_2R$, -C(O)$NR_2$, -C(O)R, or optionally substituted -$C_{1-6}$ aliphatic;

each $R^5$ is independently R, -CN, -C(O)R, -C(O)$NR_2$, or optionally substituted 5-6 membered heteroaryl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each m is independently 0, 1, or 2; and

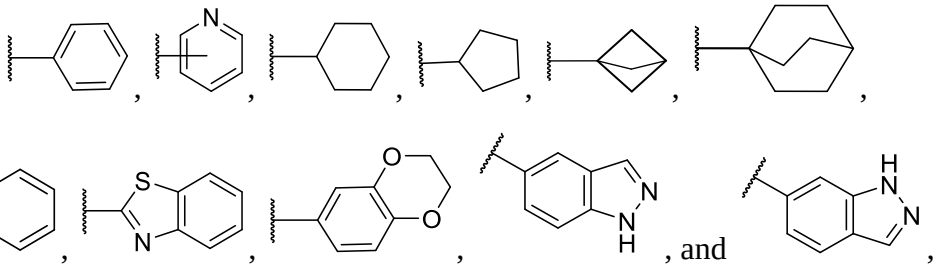
each R is independently H, optionally substituted -$C_{1-6}$ aliphatic, optionally substituted 3-8 membered saturated or partially unsaturated monocyclic carbocyclyl, or optionally substituted 3-8 membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

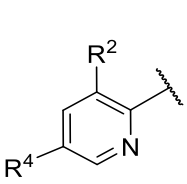
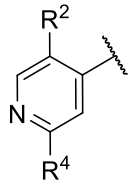
17. The use of claim 13, wherein the TEAD inhibitor is a compound of **Formula D**:



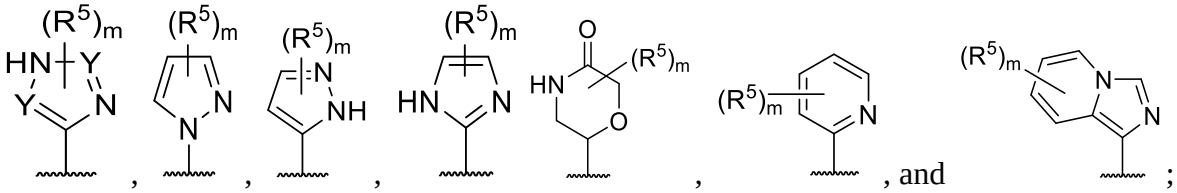

or a pharmaceutically acceptable salt thereof, wherein

$L^1$ is a covalent bound, or a $C_{1-6}$ bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -N(R)-, -O-, or -C(O)-;

Ring A is selected from  , and , each of which is optionally substituted;

Ring B is  or  ;

each $R^2$ is independently selected from -OR, -C(O)$NR_2$, optionally substituted -$C_{1-6}$ aliphatic,

 , and ;

each Y is independently N or $CR^5$;

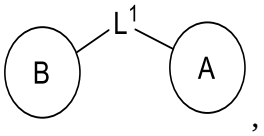
each $R^4$ is independently $-S(O)_2NR_2$, $-S(O)_2R$, $-C(O)NR_2$, $-C(O)R$, or optionally substituted $-C_{1-6}$ aliphatic;

each $R^5$ is independently R, -CN, $-C(O)R$, $-C(O)NR_2$, or optionally substituted 5-6 membered heteroaryl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each m is independently 0, 1, or 2; and

each R is independently H, optionally substituted $-C_{1-6}$ aliphatic, optionally substituted 3-8 membered saturated or partially unsaturated monocyclic carbocyclyl, or optionally substituted 3-8 membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

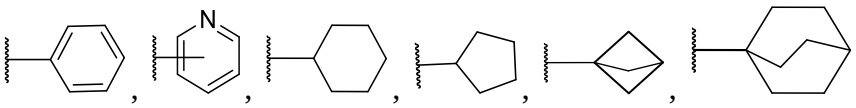
18. The use of claim 13, wherein the TEAD inhibitor is a compound of **Formula E**:

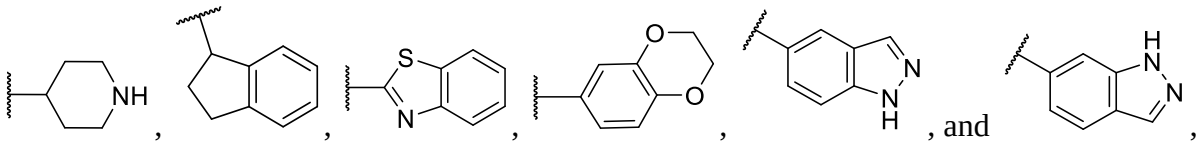


,

or a pharmaceutically acceptable salt thereof, wherein

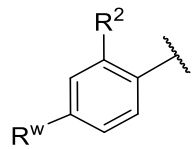
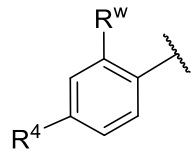
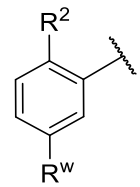
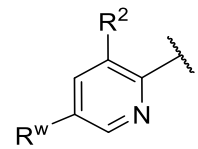
$L^1$ is a covalent bound, or a $C_{1-6}$ bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -N(R)-, -O-, or -C(O)-;

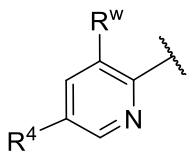
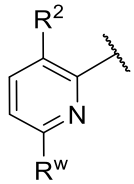
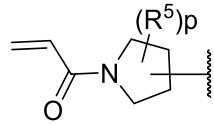
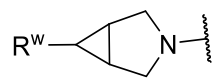
Ring A is selected from 

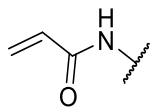
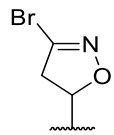
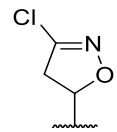
, 

, and 
,

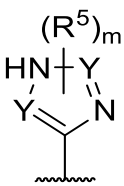
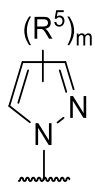
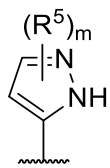
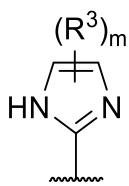
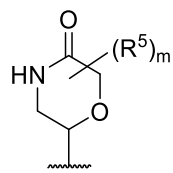
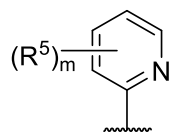
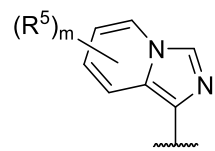
each of which is optionally substituted;

Ring B is selected from  ,  ,  ,  ,

 ,  ,  , and  ;

each $R^w$ is independently selected from  ,  , and  ;

each $R^2$ is independently selected from -OR, $-C(O)NR_2$, optionally substituted $-C_{1-6}$ aliphatic,

 ,  ,  ,  ,  ,  , and  ;

each Y is independently N or $CR^5$;

each $R^3$ is independently H or optionally substituted $-C_{1-6}$ aliphatic;

each $R^4$ is independently $-S(O)_2NR_2$, $-S(O)_2R$, $-C(O)NR_2$, -C(O)R, or optionally substituted $-C_{1-6}$ aliphatic;

each $R^5$ is independently R, -CN, -C(O)R, $-C(O)NR_2$, or optionally substituted 5-6 membered heteroaryl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each m is independently 0, 1, or 2;

p is 0, 1, or 2, and

each R is independently H, optionally substituted $-C_{1-6}$ aliphatic, optionally substituted 3-8 membered saturated or partially unsaturated monocyclic carbocyclyl, or optionally substituted 3-8 membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

19. The use of any one of claims 13-18, wherein the MEK inhibitor is selected from refametinib, selumetinib, trametinib, cobimetinib, binimetinib, mirdametinib, and pimasertib.

20. The use of any one of claims 13-19, wherein the cancer is a KRAS mutant cancer.

21. The use of claim 20, wherein the KRAS mutant cancer harbors one or more KRAS mutations selected from a KRAS G12C, a KRAS G12D mutation, a KRAS G12V mutation, and a KRAS G13 mutation.