# BICYCLIC COMPOUNDS

## CROSS-REFERENCE

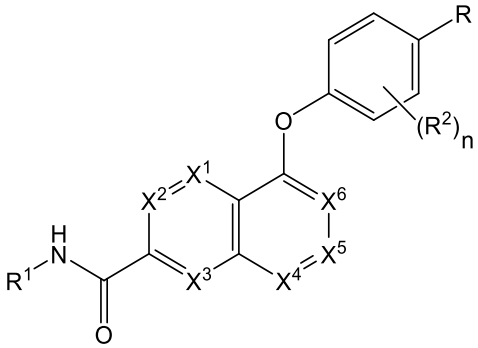
**[0001]** This application claims benefit of U.S. Provisional Patent Application No. 62/834,671 filed on April 16, 2019, which incorporated herein by reference in its entirety.

## BACKGROUND OF THE DISCLOSURE

**[0002]** YAP and 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 transcriptional enhancer associate domain (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. Described herein are inhibitors associated with one or more members of the Hippo pathway network, such as inhibitors of YAP/TAZ or inhibitors that modulate the interaction between YAP/TAZ and TEAD.

## SUMMARY

**[0002a]** In an aspect of the present disclosure, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I)

wherein,

$X^1$, $X^4$, and $X^5$, is independently $CR^X$; $X^6$ is $CR^X$;

each $X^2$ and $X^3$ is independently $CR^Y$;

each $R^X$ is independently hydrogen, halogen, nitro, $-OR^3$, $-SR^3$, -CN, $-C(=O)R^3$, $-C(=O)N(R^3)_2$, $-C(=O)OR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-N(R^3)_2$, $-NR^3S(=O)_2R^3$, $-NR^3C(=O)R^3$, $-NR^3C(=O)OR^3$, substituted or unsubstituted $C_1$-$C_6$ alkyl, substituted or unsubstituted $C_1$-$C_6$fluoroalkyl, substituted or unsubstituted $C_2$-$C_4$alkenyl, substituted or unsubstituted $C_2$-$C_4$alkynyl, substituted or unsubstituted $C_1$-$C_6$heteroalkyl, substituted or

unsubstituted $C_3$-$C_{10}$cycloalkyl, substituted or unsubstituted $C_2$-$C_{10}$heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each $R^Y$ is independently hydrogen, halogen, nitro, -CN, $-C(=O)R^3$, $-C(=O)N(R^3)_2$, $-C(=O)OR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-N(R^3)_2$, $-NR^3S(=O)_2R^3$, $-NR^3C(=O)R^3$, $-NR^3C(=O)OR^3$, substituted or unsubstituted $C_1$-$C_6$ alkyl, substituted or unsubstituted $C_1$-$C_6$fluoroalkyl, substituted or unsubstituted $C_2$-$C_4$alkenyl, substituted or unsubstituted $C_2$-$C_4$alkynyl, substituted or unsubstituted $C_1$-$C_6$heteroalkyl, substituted or unsubstituted $C_3$-$C_{10}$cycloalkyl, substituted or unsubstituted $C_2$-$C_{10}$heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R is halogen, nitro, -CN, $-OR^3$, $-SR^3$, $-C(=O)R^3$, $-C(=O)N(R^3)_2$, $-C(=O)OR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-N(R^3)_2$, $-NR^3S(=O)_2R^3$, $-NR^3C(=O)R^3$, $-NR^3C(=O)OR^3$, or substituted or unsubstituted $C_1$-$C_6$fluoroalkyl;

$R^1$ is

(a) $C_1$-$C_6$alkyl substituted with $–OR^3$; and $R^3$ is hydrogen, substituted or unsubstituted $C_1$-$C_6$alkyl, substituted or unsubstituted $C_1$-$C_6$fluoroalkyl, or substituted or unsubstituted $C_3$-$C_{10}$cycloalkyl;

(b) $C_1$-$C_6$alkyl substituted with 6-membered heteroaryl ring selected from substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyridazinyl, and substituted or unsubstituted triazinyl; or

(c) $C_1$-$C_6$alkyl substituted with 1, 2, or 3 substituents each independently selected from -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, and pyridinyl;

each $R^2$ is independently halogen, nitro, $-N_3$, -CN, $-OR^3$, $-SR^3$, $-S(=O)_2R^3$, $-N(R^3)_2$, $-C(=O)OR^3$, substituted or unsubstituted $C_1$-$C_6$alkyl, substituted or unsubstituted $C_1$-$C_6$fluoroalkyl, substituted or unsubstituted $C_1$-$C_6$heteroalkyl, substituted or unsubstituted $C_3$-$C_{10}$cycloalkyl, substituted or unsubstituted $C_2$-$C_{10}$heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each $R^3$ is independently hydrogen, substituted or unsubstituted $C_1$-$C_6$alkyl, substituted or unsubstituted $C_1$-$C_6$fluoroalkyl, substituted or unsubstituted $C_1$-$C_6$heteroalkyl, substituted or unsubstituted $C_3$-$C_{10}$cycloalkyl, substituted or unsubstituted $C_2$-$C_{10}$heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or if two $R^3$ are on the same nitrogen atom, then two $R^3$ are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted $C_3$-$C_7$ heterocycloalkyl; and

n is 0, 1, 2, 3, or 4.

**[0002b]** In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt or solvate disclosed herein, and a pharmaceutically acceptable excipient.

**[0002c]** In a further aspect of the present disclosure, there is provided a use of the compound or pharmaceutically acceptable salt or solvate disclosed herein, in the manufacture of a medicament for treating cancer in a subject in need thereof.

**[0002d]** In another aspect of the present disclosure, there is provided a use of the compound or pharmaceutically acceptable salt or solvate disclosed herein, in the manufacture of a medicament for treating polycystic kidney disease or liver fibrosis in a subject in need thereof.

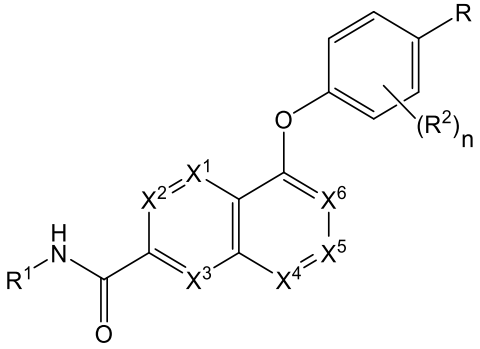
**[0003]** Provided herein are bicyclic compounds and pharmaceutical compositions comprising said compounds. In some examples, the subject compounds are useful for the treatment of cancer.

**[0004]** In one example, the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof

## CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I)

wherein,

$X^1$, $X^4$, and $X^5$, is independently $CR^X$; $X^6$ is $CR^X$;

each $X^2$ and $X^3$ is independently $CR^Y$;

each $R^X$ is independently hydrogen, halogen, nitro, $-OR^3$, $-SR^3$, -CN, $-C(=O)R^3$, $-C(=O)N(R^3)_2$, $-C(=O)OR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-N(R^3)_2$, $-NR^3S(=O)_2R^3$, $-NR^3C(=O)R^3$, $-NR^3C(=O)OR^3$, substituted or unsubstituted $C_1$-$C_6$ alkyl, substituted or unsubstituted $C_1$-$C_6$fluoroalkyl, substituted or unsubstituted $C_2$-$C_4$alkenyl, substituted or unsubstituted $C_2$-$C_4$alkynyl, substituted or unsubstituted $C_1$-$C_6$heteroalkyl, substituted or unsubstituted $C_3$-$C_{10}$cycloalkyl, substituted or unsubstituted $C_2$-$C_{10}$heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each $R^Y$ is independently hydrogen, halogen, nitro, -CN, $-C(=O)R^3$, $-C(=O)N(R^3)_2$, $-C(=O)OR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-N(R^3)_2$, $-NR^3S(=O)_2R^3$, $-NR^3C(=O)R^3$, $-NR^3C(=O)OR^3$, substituted or unsubstituted $C_1$-$C_6$ alkyl, substituted or unsubstituted $C_1$-$C_6$fluoroalkyl, substituted or unsubstituted $C_2$-$C_4$alkenyl, substituted or unsubstituted $C_2$-$C_4$alkynyl, substituted or unsubstituted $C_1$-$C_6$heteroalkyl, substituted or unsubstituted $C_3$-$C_{10}$cycloalkyl, substituted or unsubstituted $C_2$-$C_{10}$heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R is halogen, nitro, -CN, $-OR^3$, $-SR^3$, $-C(=O)R^3$, $-C(=O)N(R^3)_2$, $-C(=O)OR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-N(R^3)_2$, $-NR^3S(=O)_2R^3$, $-NR^3C(=O)R^3$, $-NR^3C(=O)OR^3$, or substituted or unsubstituted $C_1$-$C_6$fluoroalkyl;

$R^1$ is

(a) $C_1$-$C_6$alkyl substituted with –$OR^3$; and $R^3$ is hydrogen, substituted or unsubstituted $C_1$-$C_6$alkyl, substituted or unsubstituted $C_1$-$C_6$fluoroalkyl, or substituted or unsubstituted $C_3$-$C_{10}$cycloalkyl;

(b) $C_1$-$C_6$alkyl substituted with 6-membered heteroaryl ring selected from substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyridazinyl, and substituted or unsubstituted triazinyl; or

(c) $C_1$-$C_6$alkyl substituted with 1, 2, or 3 substituents each independently selected from -OH, -$OCH_3$, -$NH_2$, -$NHCH_3$, -$N(CH_3)_2$, and pyridinyl;

each $R^2$ is independently halogen, nitro, -$N_3$, -CN, -$OR^3$, -$SR^3$, -$S(=O)_2R^3$, -$N(R^3)_2$, -$C(=O)OR^3$, substituted or unsubstituted $C_1$-$C_6$alkyl, substituted or unsubstituted $C_1$-$C_6$fluoroalkyl, substituted or unsubstituted $C_1$-$C_6$heteroalkyl, substituted or unsubstituted $C_3$-$C_{10}$cycloalkyl, substituted or unsubstituted $C_2$-$C_{10}$heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each $R^3$ is independently hydrogen, substituted or unsubstituted $C_1$-$C_6$alkyl, substituted or unsubstituted $C_1$-$C_6$fluoroalkyl, substituted or unsubstituted $C_1$-$C_6$heteroalkyl, substituted or unsubstituted $C_3$-$C_{10}$cycloalkyl, substituted or unsubstituted $C_2$-$C_{10}$heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or if two $R^3$ are on the same nitrogen atom, then two $R^3$ are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted $C_3$-$C_7$ heterocycloalkyl; and

n is 0, 1, 2, 3, or 4.

2. The compound or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein:

each $R^X$ is independently hydrogen, halogen, -$OR^3$, -$SR^3$, -$S(=O)R^3$, -$S(=O)_2R^3$, -$N(R^3)_2$, -$NR^3S(=O)_2R^3$, -$NR^3C(=O)R^3$, substituted or unsubstituted $C_1$-$C_6$alkyl, substituted or unsubstituted $C_1$-$C_6$fluoroalkyl, or substituted or unsubstituted $C_2$-$C_4$alkynyl; and

each $R^3$ is independently hydrogen, substituted or unsubstituted $C_1$-$C_6$alkyl, substituted or unsubstituted $C_1$-$C_6$fluoroalkyl, or substituted or unsubstituted $C_3$-$C_{10}$cycloalkyl; or if two $R^3$ are on the same nitrogen atom, then two $R^3$ are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted $C_3$-$C_7$ heterocycloalkyl.

3. The compound or pharmaceutically acceptable salt or solvate thereof of claim 1 or claim 2, wherein:

each $R^X$ is independently hydrogen, F, Cl, Br, $-CH_3$, -OH, $-OCH_3$, or $-OCF_3$.

4. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-3, wherein:

each $R^X$ is hydrogen.

5. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-4, wherein:

each $R^Y$ is independently hydrogen, halogen, $-S(=O)R^3$, $-S(=O)_2R^3$, $-N(R^3)_2$, $-NR^3S(=O)_2R^3$, $-NR^3C(=O)R^3$, substituted or unsubstituted $C_1$-$C_6$alkyl, substituted or unsubstituted $C_1$-$C_6$fluoroalkyl, or substituted or unsubstituted $C_2$-$C_4$alkynyl; and

each $R^3$ is independently hydrogen, substituted or unsubstituted $C_1$-$C_6$alkyl, substituted or unsubstituted $C_1$-$C_6$fluoroalkyl, or substituted or unsubstituted $C_3$-$C_{10}$cycloalkyl; or if two $R^3$ are on the same nitrogen atom, then two $R^3$ are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted $C_3$-$C_7$ heterocycloalkyl.

6. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-4, wherein:

each $R^Y$ is independently hydrogen, F, Cl, or $-CH_3$.

7. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-4, wherein:

each $R^Y$ is hydrogen.

8. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-7, wherein:

$R^1$ is $C_1$-$C_6$alkyl substituted with $–OR^3$; and $R^3$ is hydrogen, substituted or unsubstituted $C_1$-$C_6$alkyl, substituted or unsubstituted $C_1$-$C_6$fluoroalkyl, or substituted or unsubstituted $C_3$-$C_{10}$cycloalkyl.

9. The compound or pharmaceutically acceptable salt or solvate thereof of claim 8, wherein:

$R^1$ is $C_1$-$C_6$alkyl substituted with –OH.

10. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-7, wherein:

$R^1$ is $C_1$-$C_6$alkyl substituted with 6-membered heteroaryl ring selected from substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyridazinyl, and substituted or unsubstituted triazinyl.

11. The compound or pharmaceutically acceptable salt or solvate thereof of claim 10, wherein:

$R^1$ is $C_1$-$C_6$alkyl substituted with pyridinyl.

12. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-7, wherein:

$R^1$ is $C_1$-$C_6$alkyl substituted with 1, 2, or 3 substituents each independently selected from -OH, -$OCH_3$, -$NH_2$, -$NHCH_3$, -$N(CH_3)_2$, and pyridinyl.

13. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-12, wherein:

R is halogen, nitro, -CN, -$OR^3$, -$C(=O)R^3$, -$C(=O)N(R^3)_2$, -$C(=O)OR^3$, -$S(=O)R^3$, -$S(=O)_2R^3$, -$NR^3S(=O)_2R^3$, -$NR^3C(=O)R^3$, -$NR^3C(=O)OR^3$, or substituted or unsubstituted $C_1$-$C_6$fluoroalkyl; and

each $R^3$ is independently hydrogen, substituted or unsubstituted $C_1$-$C_6$alkyl, substituted or unsubstituted $C_1$-$C_6$fluoroalkyl, substituted or unsubstituted $C_1$-$C_6$heteroalkyl, substituted or unsubstituted $C_3$-$C_{10}$cycloalkyl, or substituted or unsubstituted $C_2$-$C_{10}$heterocycloalkyl; or if two $R^3$ are on the same nitrogen atom, then two $R^3$ are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted $C_3$-$C_7$ heterocycloalkyl.

14. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-12, wherein:

R is F, Cl, -CN, -$OCF_3$, -$CHF_2$, or -$CF_3$.

15. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-12, wherein:

R is F, Cl, or -$CF_3$.

16. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-12, wherein:

R is -$CF_3$.

17. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-16, wherein:

each $R^2$ is independently F, Cl, -$OCF_3$, or -$CF_3$.

18. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-16, wherein:

each $R^2$ is independently F or Cl.

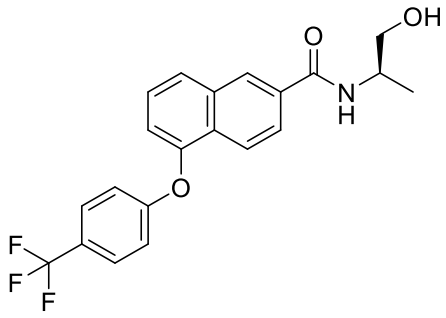
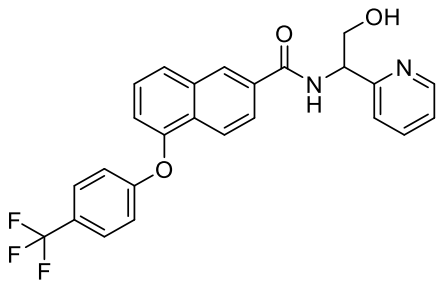
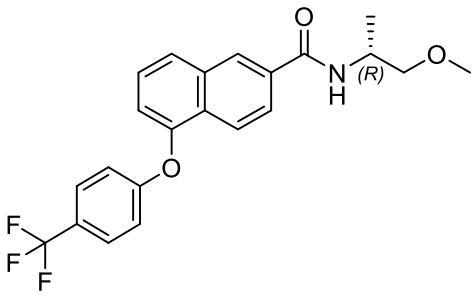
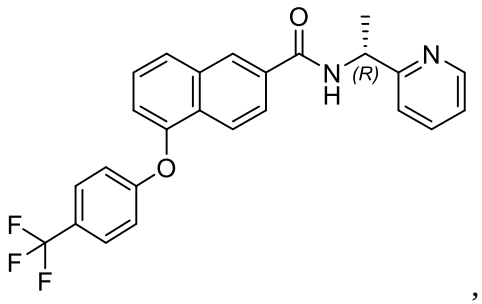
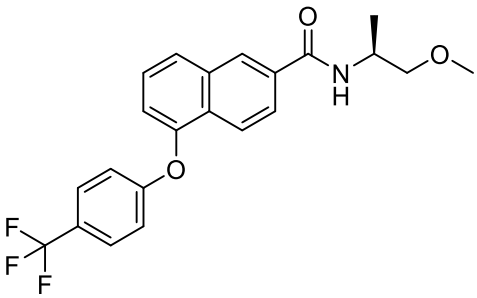
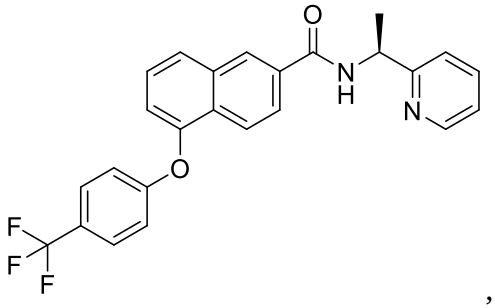
19. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-18, wherein: n is 0.

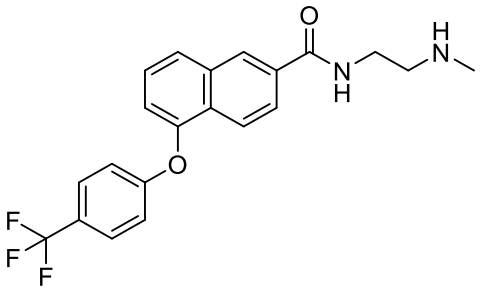
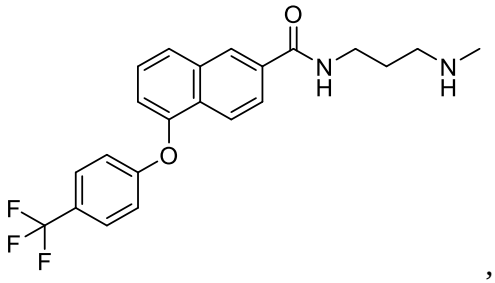
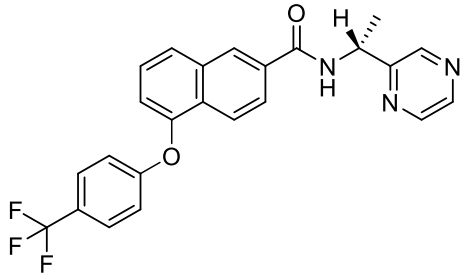
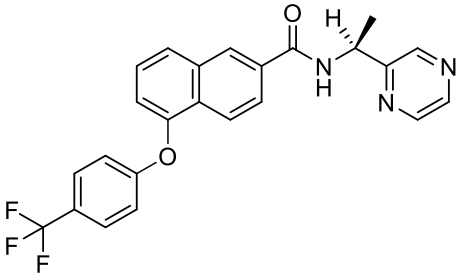
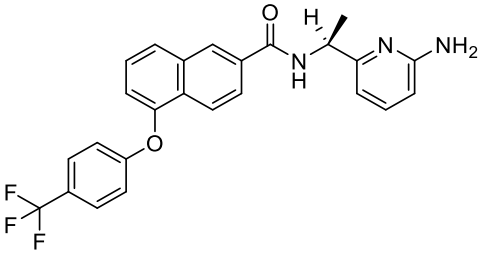
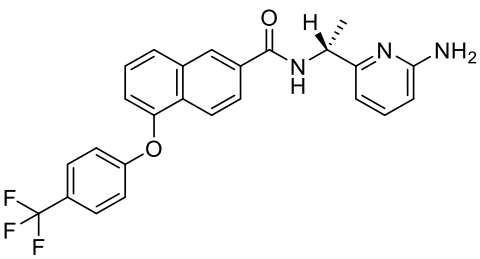
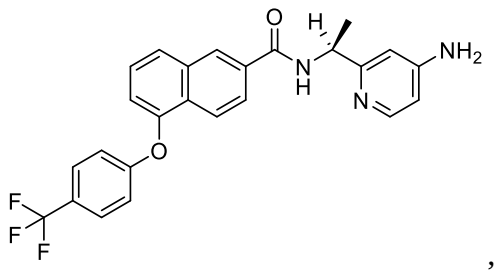
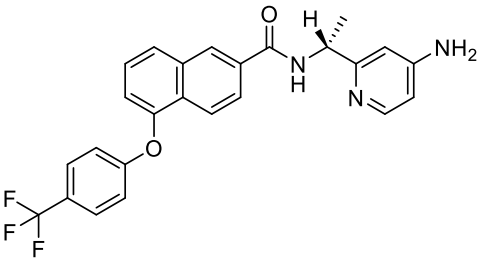
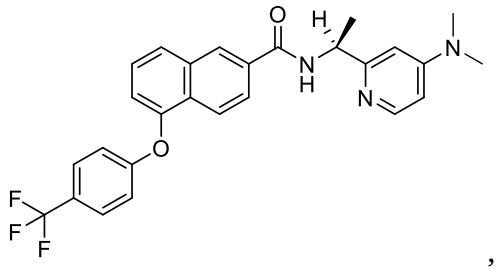
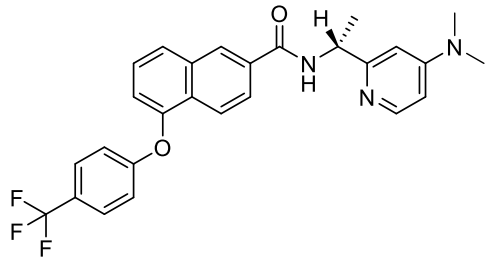
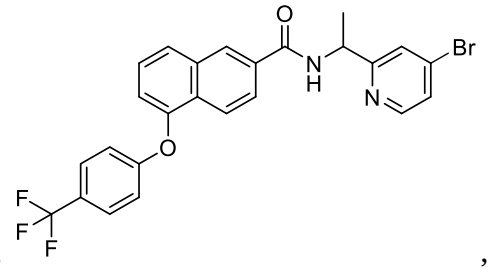
20. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-18, wherein: n is 1 or 2.

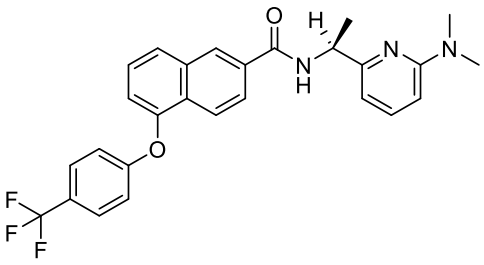
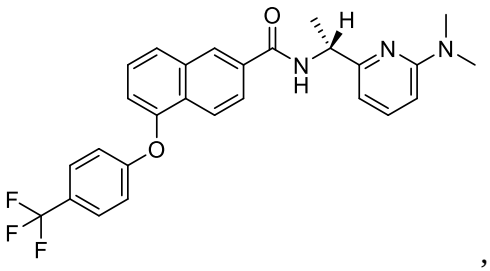
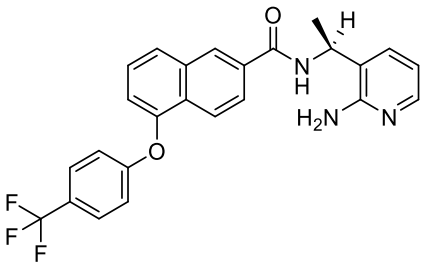
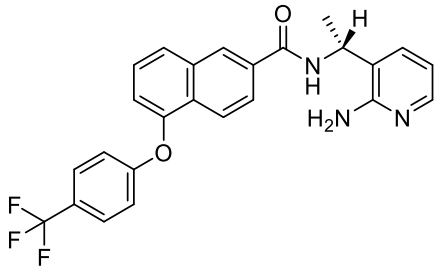
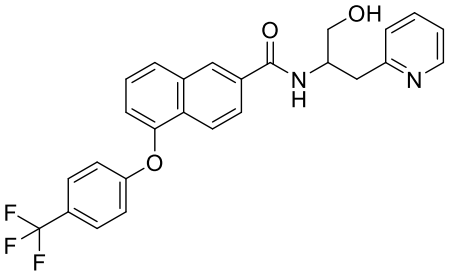
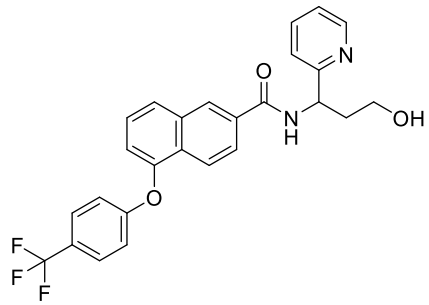
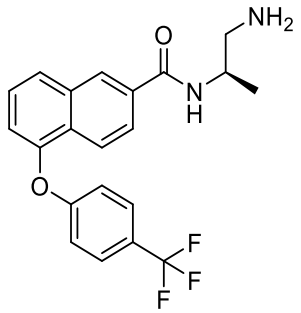
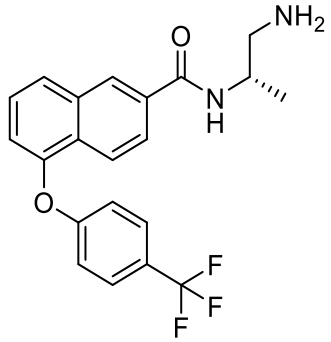
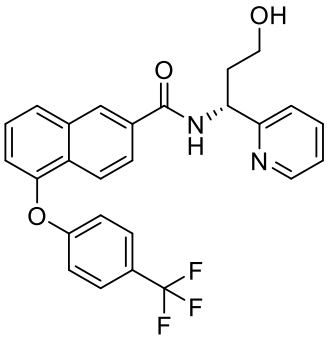
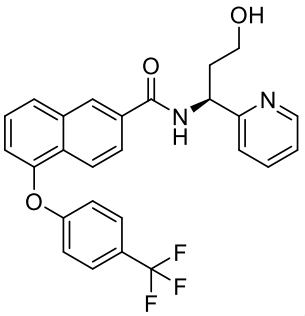
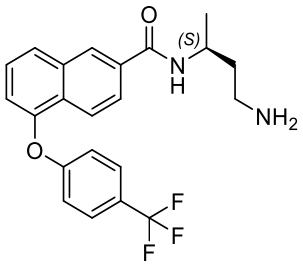
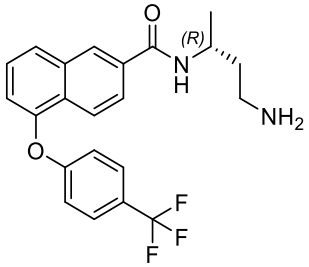
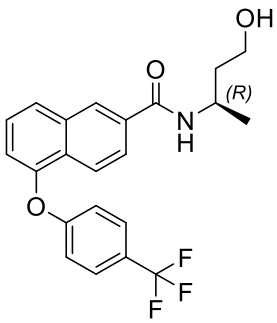
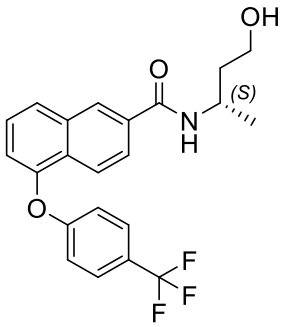
21. The compound or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein:
each $R^X$ is independently hydrogen, F, Cl, Br, $-CH_3$, -OH, $-OCH_3$, or $-OCF_3$;
each $R^Y$ is hydrogen.

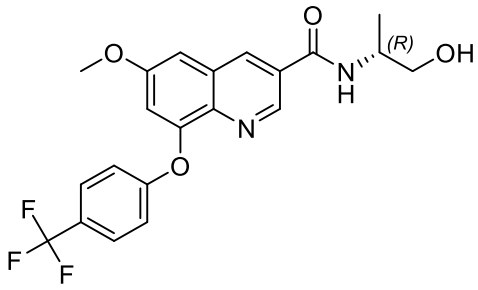
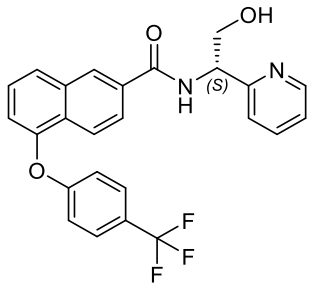
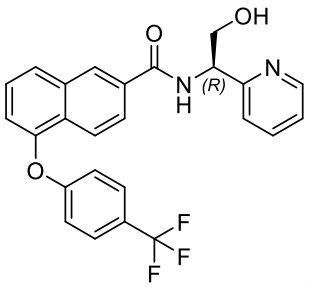
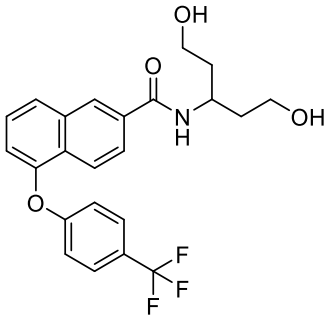
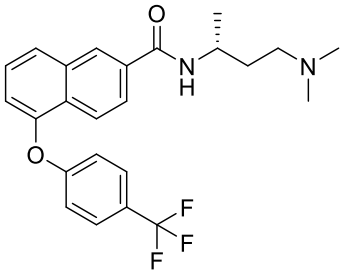
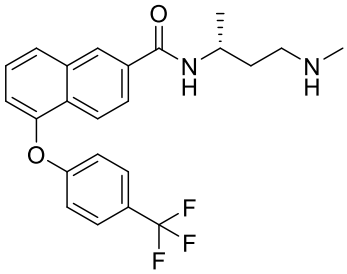
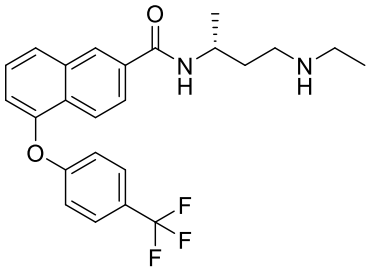
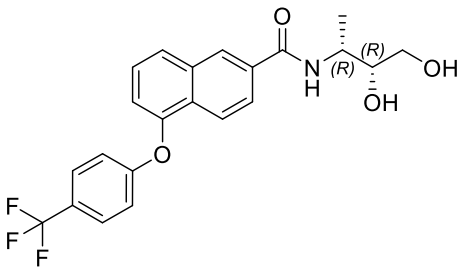
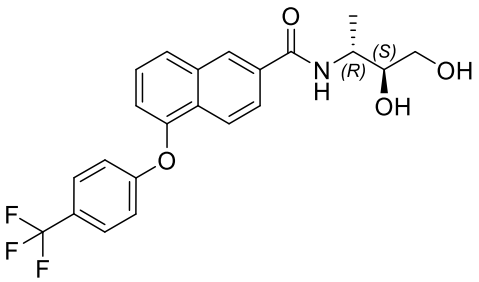
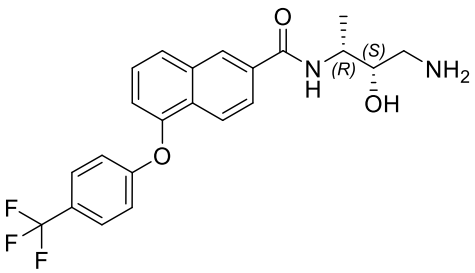
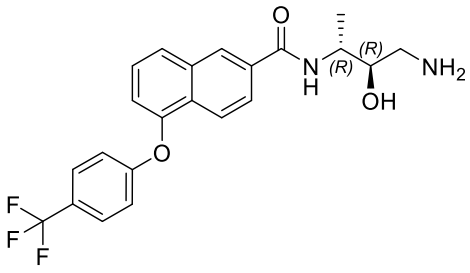
22. The compound or pharmaceutically acceptable salt or solvate thereof of claim 21, wherein:
$R^1$ is $C_1$-$C_6$alkyl substituted with $–OR^3$; and $R^3$ is hydrogen or unsubstituted $C_1$-$C_6$alkyl;
R is $-CF_3$; and
n is 0.

23. The compound or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein the compound is selected from the group consisting of:

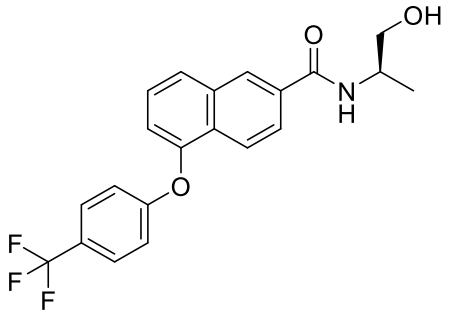
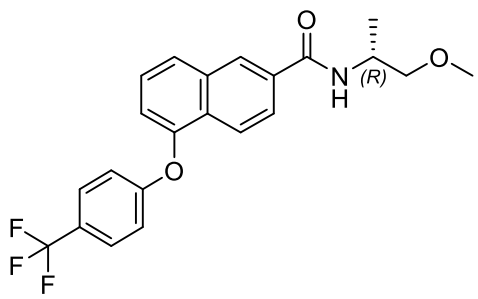
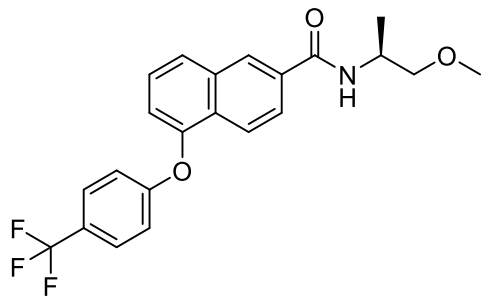
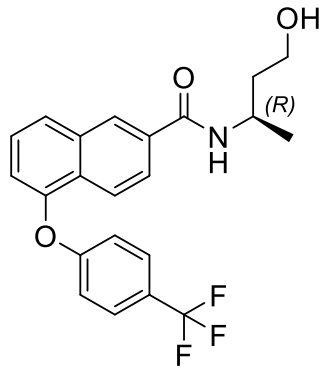
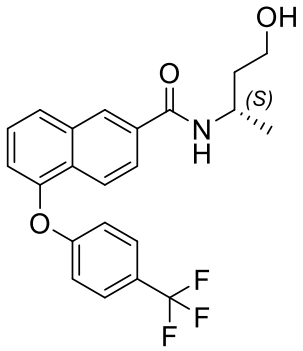
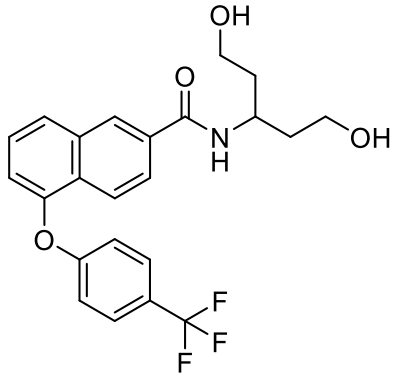
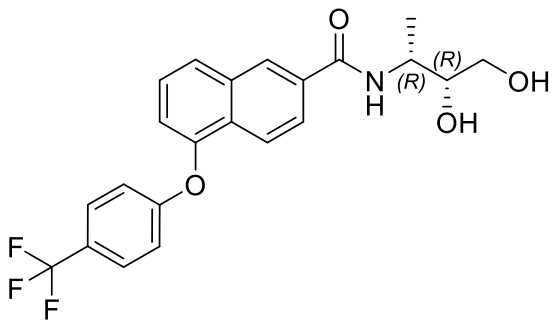
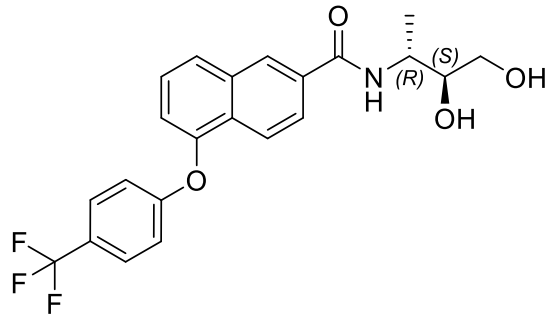

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

, and

.

24. The compound or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein the compound is selected from the group consisting of:


,

,

,

,

,

,

, and

.

25. A pharmaceutical composition comprising the compound or pharmaceutically acceptable salt or solvate of any one of claims 1-24, and a pharmaceutically acceptable excipient.

26. Use of the compound or pharmaceutically acceptable salt or solvate of any one of claims 1-24, in the manufacture of a medicament for treating cancer in a subject in need thereof.

27. The use of claim 26, wherein the cancer is selected from mesothelioma, hepatocellular carcinoma, meningioma, malignant peripheral nerve sheath tumor, Schwannoma, lung cancer, bladder carcinoma, cutaneous neurofibromas, prostate cancer, pancreatic cancer,

glioblastoma, endometrial adenosquamous carcinoma, anaplastic thyroid carcinoma, gastric adenocarcinoma, esophageal adenocarcinoma, ovarian cancer, ovarian serous adenocarcinoma, melanoma, and breast cancer.

28. Use of the compound or pharmaceutically acceptable salt or solvate of any one of claims 1-24, in the manufacture of a medicament for treating polycystic kidney disease or liver fibrosis in a subject in need thereof.