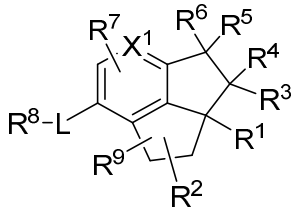
What is Claimed:

1 A compound of Formula (I):



(I)

wherein:

X^1 is CH;

R^1 is hydroxy or amino;

R^2 is hydrogen or alkyl;

R^3 and R^4 are independently hydrogen or halo;

R^5 is hydrogen or halo;

R^6 is hydrogen or halo; or

R^7 is hydrogen;

L is O;

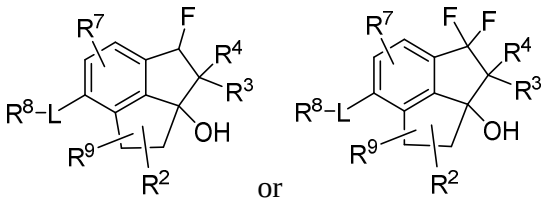
R^8 is aryl or heteroaryl wherein the aryl and heteroaryl are substituted with R^a, R^b, and R^c independently selected from hydrogen, alkyl, haloalkyl, haloalkyloxy, alkoxy, hydroxy, halo, cyano, hydroxyalkyl, alkoxyalkyl, aminoalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocyclyl

R^9 is hydrogen, alkyl, hydroxy, or halo; or

when R^9 and R^2 are attached to the same carbon atom, they can combine to form oxo, alkyldienyl, or 3 to 6 membered cycloalkylene; or

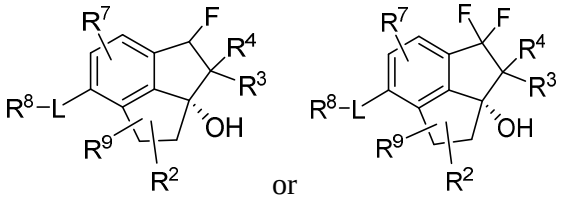
a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the structure of formula (IIa) or (IIb):



(IIa) or (IIb).

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the structure of formula (IIa') or (IIb'):



(IIa') (IIb').

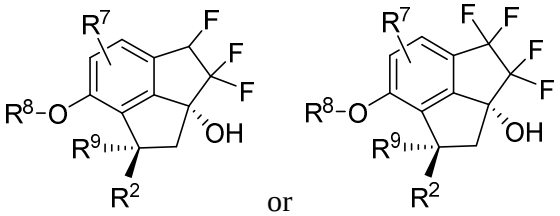
4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein R^3 is fluoro.

5. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are fluoro.

6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt, thereof, wherein R^8 is phenyl substituted with R^a, R^b, and R^c independently selected from hydrogen, alkyl, haloalkyl, haloalkyloxy, alkoxy, hydroxy, halo, cyano, hydroxyalkyl, alkoxyalkyl, aminoalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocyclyl.

7. The compound of any claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R^8 is 3-chloro-5-fluorophenyl, 3,5-difluorophenyl, 3-fluoro-5-methoxyphenyl, 3-cyano-5-fluorophenyl, 3-chloro-5-cyanophenyl, 3-cyano-5-methylphenyl, 3-chloro-4-fluorophenyl, 3-chloro-5-fluorophenyl, 3-fluoro-5-methylphenyl, 3-cyanophenyl, 3-trifluoromethylphenyl, 3,4-dichlorophenyl, 3-chloro-2-methylphenyl, 3,5-dichlorophenyl, 3,5-dimethylphenyl, 2-chloro-6-methylphenyl, 2,6-difluorophenyl, 3,4,5-trifluorophenyl, 3,4-difluorophenyl, 4-fluoro-3-methylphenyl, 3-cyano-4-fluorophenyl, or 3-cyano-5-difluoromethylphenyl.

8. The compound of any one of claims 3 to 7, or a pharmaceutically acceptable salt thereof having the structure of formula (VIIIa) or (VIIIb):



(VIIIa) (VIIIb).

9. The compound of claim 8, or a pharmaceutically acceptable salt thereof having a structure of formula (VIIIb) wherein R^2 is hydrogen and R^9 is hydrogen, fluoro, or methyl.

10. A compound selected from:

3-fluoro-5-((3,3,4,4-tetrafluoro-2a-hydroxy-1-methylene-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile;

3-fluoro-5-((3,3,4,4-tetrafluoro-2a-hydroxy-1-oxo-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile;

3-fluoro-5-((3,3,4,4-tetrafluoro-1,2a-dihydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile;

3-fluoro-5-((1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile;

3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile;

3-fluoro-5-(((1R,2aS)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile;

3-fluoro-5-(((1R,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile;

1,3,3,4,4-pentafluoro-7-((5-fluoropyridin-3-yl)oxy)-1,2,3,4-tetrahydro-2aH-cyclopenta[cd]inden-2a-ol;

3-fluoro-5-((3,3,4,4-tetrafluoro-2a-hydroxy-2,2a,3,4-tetrahydrospiro[cyclopenta[cd]-indene-1,1'-cyclopropan]-7-yl)oxy)benzonitrile;

3-fluoro-5-((3,3,4,4-tetrafluoro-2a-hydroxy-1-methyl-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile;

3-fluoro-5-((3,3,4,4-tetrafluoro-1,2a-dihydroxy-1-methyl-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile;

3-fluoro-5-((1,3,3,4,4-pentafluoro-2a-hydroxy-1-methyl-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile;

3-fluoro-5-((3,3,4,4-tetrafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile;

3-((2a-amino-1,3,3,4,4-pentafluoro-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)-5-fluorobenzonitrile;

(R)-3-fluoro-5-((3,3,4,4-tetrafluoro-2a-hydroxy-1-methylene-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile;

(S)-3-fluoro-5-((3,3,4,4-tetrafluoro-2a-hydroxy-1-methylene-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile;

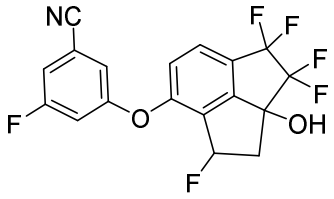
(R)-3-fluoro-5-((3,3,4,4-tetrafluoro-2a-hydroxy-1-oxo-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile; and

3-fluoro-5-(((1R,2aR)-3,3,4,4-tetrafluoro-1,2a-dihydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd] inden-7-yl)oxy)benzonitrile; or

a pharmaceutically acceptable salt thereof.

11. The compound of claim 10, selected from:

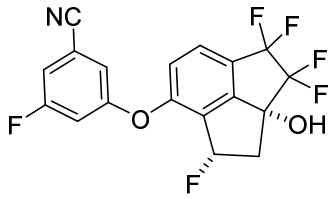
3-fluoro-5-((1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile according to the structure:



and a pharmaceutically acceptable salt thereof.

12. A compound:

3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)-benzonitrile according to the structure:



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13. A crystalline Form A polymorph of the compound of claim 12, having an X-ray powder diffraction pattern comprising peaks at angular positions 15.8 and 18.6, wherein the angular positions may vary by + 0.2° 2θ as measured by X-ray powder diffraction using an X-ray wavelength of 1.5418 Å.

14. The crystalline Form A polymorph of claim 13, wherein the Form A polymorph X-ray powder diffraction pattern comprises peaks at angular positions 15.8, 18.6, and 20.1, wherein the angular positions may vary by + 0.2° 2θ.

15. The crystalline Form A polymorph of claim 13, wherein the Form A polymorph X-ray powder diffraction pattern comprises peaks at angular positions 12.9, 15.8, 18.6, and 20.1, wherein the angular positions may vary by + 0.2° 2θ.

16. The crystalline Form A polymorph of claim 13, wherein the Form A polymorph X-ray powder diffraction pattern comprises peaks at angular positions 11.4, 12.9, 15.8, 18.6, and 20.1, wherein the angular positions may vary by + 0.2° θ.

17. A pharmaceutical composition comprising a compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, or the compound of claim 12, or comprising the

crystalline Form A polymorph of any one of claims 13 to 16; and a pharmaceutically acceptable excipient.

18. Use of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, or the compound of claim 12, or a crystalline Form A polymorph of any one of claims 13 to 16, in the preparation of a medicament for the treatment of cancer, inflammatory disease, liver disease, iron overload, or pulmonary disease in a patient.

19. The use of claim 18, wherein the disease is cancer and the compound of claim 1 to 11 or a pharmaceutically acceptable salt thereof, or the compound of claim 12, or the crystalline Form A polymorph of any one of claims 13 to 16, is optionally to be administered in combination with at least one other anticancer agent.

20. The use of claim 18 or 19, wherein the disease is cancer selected from renal cancer, glioblastoma, neuroblastoma, paraganglioma, pheochromocytoma, pancreatic neuroendocrine tumors, liver cancer, colorectal cancer, somatostatinomas, hemangioblastomas, gastrointestinal stromal tumors, pituitary tumors, leiomyomas, leiomyosarcomas, polycythaemia, retinal cancers, von Hippel-Lindau disease, astrocytoma, lung cancer, non-small cell lung cancer, melanoma, breast cancer, cervical cancer, head and neck cancer, ovarian cancer, prostate cancer, esophageal squamous cell carcinoma, and uterine leiomyomatosis.

21. The use of claim 20, wherein the cancer is clear cell renal cell carcinoma or hepatocellular carcinoma.

22. The use of any one of claims 19-21, wherein the at least one other anticancer agent is selected from the group consisting of sunitinib, sorafenib, regorafinib, lenvatinib, vandetanib, cabozantinib, axitinib, aflibercept, bevacizumab, pazopanib, rapamycin (sirolimus), temsirolimus, everolimus, XL388, XL765, AZD2013, PF04691502, PKI-587, BEZ235, GDC0349, MPDL3280A (atezolizumab), MEDI4736 (durvalumab), abemaciclib, palbociclib, and ribociclib.