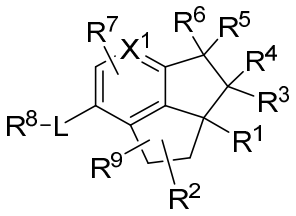
What is Claimed:

1 A compound of Formula (I):



(I)

wherein:

X^1 is CH ~~or N~~;

R^1 is hydroxy~~,~~ or ~~halo,~~ amino~~, OP(O)(OH)$_2$, OCH$_2$OP(O)(OH)$_2$, OCOR^{10}, OCOOR^{11}, OCONR^{12}R^{13}, OCHR^{14}OCOR^{15} or OCHR^{14}OCOOR^{15a} where R^{10}, R^{11}, and R^{15} and R^{15a} are independently alkyl or alkyl substituted with amino, carboxy or hydroxy, R^{12} and R^{13} are independently hydrogen, alkyl, or alkyl substituted with amino, carboxy or hydroxy or R^{12} and R^{13} together with the nitrogen atom to which they are attached form optionally substituted heterocyclyl, and each R^{14} is hydrogen, alkyl, or haloalkyl~~;

R^2 is hydrogen ~~, deuterium,~~ or alkyl~~, haloalkyl, alkenyl, or alkynyl~~;

R^3 and R^4 are independently hydrogen or~~,~~ ~~deuterium, alkyl, cycloalkyl,~~ halo~~;, haloalkyl, hydroxyalkyl, or alkoxyalkyl; or~~

~~R^3 and R^4 together with the carbon to which they are attached form oxo, 3 to 6 membered cycloalkylene, or 4 to 6 membered optionally substituted heterocyclylene;~~

R^5 is hydrogen ~~, deuterium, alkyl,~~ or halo~~, haloalkyl, hydroxy, or alkoxy~~;

R^6 is hydrogen~~, deuterium, alkyl, cycloalkyl,~~ or halo; or

~~R^5 and R^6 together with the carbon to which they are attached form oxo, alkyldienyl, 3 to 6 membered cycloalkylene, or 4 to 6 membered optionally substituted heterocyclylene; provided R^5 and R^6 and R^3 and R^4 together with the carbon to which they are attached do not form oxo, cycloalkylene or optionally substituted 4 to 6 membered heterocyclylene simultaneously;~~

R^7 is hydrogen~~, deuterium, alkyl, alkoxy, cyano, halo, haloalkyl, or haloalkoxy;~~

L is O ~~a bond, S, SO, SO$_2$, O, CO, or NR^{16} where R^{16} is hydrogen or alkyl~~;

R^8 is ~~alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, cycloalkyl, cycloalkenyl, bicyclic cycloalkyl, oxocycloalkenyl, cycloalkylalkyl,~~ aryl or~~, aralkyl, heterocyclyl, spirocycloalkyl, spiroheterocyclyl, heterocyclylalkyl,~~ heteroaryl ~~, or heteroaralkyl~~ wherein the aryl and ~~or~~ heteroaryl ~~, each by itself or as part of aralkyl or heteroaralkyl, or heterocyclyl by itself or as part of heterocyclylalkyl is~~are substituted with R^a, R^b, and R^c independently selected from

hydrogen, alkyl, haloalkyl, haloalkyloxy, alkoxy, hydroxy, halo, cyano, hydroxyalkyl, alkoxyalkyl, aminoalkyl, ~~alkenyl, alkynyl, alkylidenyl,~~ optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocyclyl

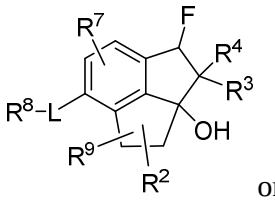
R^9 is hydrogen, alkyl, ~~cycloalkyl,~~ hydroxy, or ~~alkoxy, cyano,~~ halo~~, haloalkyl, haloalkoxy, alkylsulfoxide, alkylsulfonyl, or heteroaryl wherein the heteroaryl is optionally substituted with R^d, R^e, and R^f independently selected from hydrogen, alkyl, haloalkyl, haloalkoxy, alkoxy, hydroxy, halo, and cyano~~; or

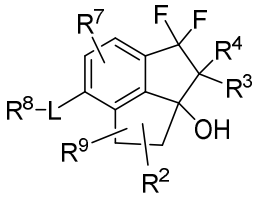
when R^9 and R^2 are attached to the same carbon atom, they can combine to form oxo, alkyldienyl, or 3 to 6 membered cycloalkylene~~, or 4 to 6 membered heterocyclylene~~; or

a pharmaceutically acceptable salt thereof.

~~2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein X^1 is CR^7.~~

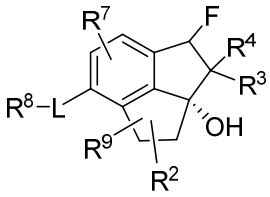
~~3~~2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the structure of formula (IIa) or (IIb):

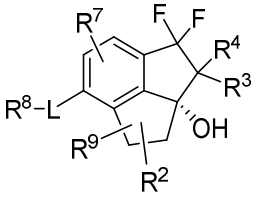


or


(IIa) (IIb).

~~4~~3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the structure of formula (IIa') or (IIb'):



or


(IIa') (IIb').

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

~~6~~5. The compound of any one of claims 1 to ~~4~~3, or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are fluoro.

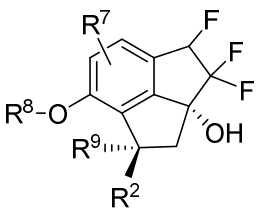
~~7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein L is O.~~

~~8~~6. The compound of any one of claims 1 to ~~7~~5, or a pharmaceutically acceptable salt, thereof, wherein R^8 is phenyl substituted with R^a, R^b, and R^c independently selected from

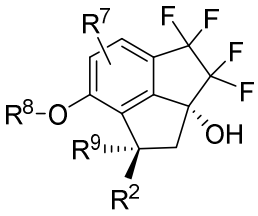
hydrogen, alkyl, haloalkyl, haloalkyloxy, alkoxy, hydroxy, halo, cyano, hydroxyalkyl, alkoxyalkyl, aminoalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocyclyl.

~~9~~7. The compound of any claims 1 to ~~8~~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.

~~10~~8. The compound of any one of claims ~~4 to 9~~3 to 7, or a pharmaceutically acceptable salt thereof having the structure of formula (VIIIa) or (VIIIb):



or



(VIIIa) (VIIIb).

~~11~~9. The compound of claim ~~10~~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.

~~12~~10. ~~The compound of claim 1,~~ 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;

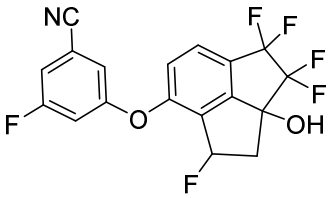
(R)-3-fluoro-5-((3,3,4,4-tetrafluoro-2a-hydroxy-1-oxo-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile; and

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.

~~13~~11. The compound of claim 10, selected from:

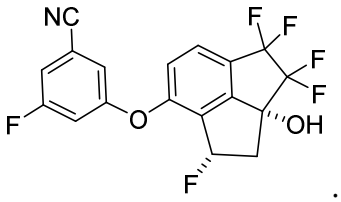
3-fluoro-5-((1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile according to the structure:



and a pharmaceutically acceptable salt thereof.

~~14~~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:



~~15~~13. A crystalline Form A polymorph of the compound of claim ~~14~~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.

~~16~~14. The crystalline Form A polymorph of claim ~~15~~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.

~~17~~15. The crystalline Form A polymorph of claim ~~15~~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.

~~18~~16. The crystalline Form A polymorph of claim ~~15~~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.

~~19. A crystalline Form A polymorph of the compound of claim 14, having an X-ray powder diffraction pattern comprising peaks at angular positions substantially as shown in Fig. 1.~~

~~20~~17. A pharmaceutical composition comprising a compound of any one of claims 1 to ~~13~~11, or a pharmaceutically acceptable salt thereof, or the compound of claim ~~14~~12, or comprising the crystalline Form A polymorph of any one of claims ~~15 to 19~~13 to 16; and a pharmaceutically acceptable excipient.

~~21~~18. Use of a compound of any one of claims 1 to ~~13~~11, or a pharmaceutically acceptable salt thereof, or the compound of claim ~~14~~12, or a crystalline Form A polymorph of any one of claims ~~15 to 19~~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.

~~22~~19. The use of claim ~~21~~18, wherein the disease is cancer and the compound of claim 1 to ~~13~~11 or a pharmaceutically acceptable salt thereof, or the compound of claim ~~14~~12, or the crystalline Form A polymorph of any one of claims ~~15~~13 to ~~19~~16, ~~can be~~ is optionally to be administered in combination with at least one other anticancer agent.

~~23~~20. The use of claim ~~21 or 22~~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.

~~24~~21. The use of claim ~~23~~20, wherein the cancer is clear cell renal cell carcinoma or hepatocellular carcinoma.

~~25~~22. The use of any one of claims ~~22-24~~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.