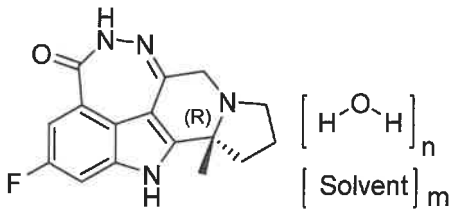
CLAIMS:

1. A compound of Formula **I**,



Formula **I**

wherein n is a number from 0.0 to 2.0; m is a number from 0.0 to 20.0; and wherein the solvate is formed by solvation of solvent selected from isopropanol, ethanol, methanol, acetone, THF, 1,4-dioxane, acetic acid, acetonitrile, water, or a combination thereof;

wherein the compound has:

a) a Crystalline Form D, which has a powder X-ray diffraction pattern comprising three or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 5.7±0.2, 6.4±0.2, 6.8±0.2, 9.3±0.2, 9.8±0.2, 10.3±0.2, 11.5±0.2, 12.4±0.2, 12.9±0.2, 13.4±0.2,13.9±0.2, 17.8±0.2, 18.3±0.2, 18.8±0.2, 18.9±0.2, 23.7±0.2, 25.0±0.2, 25.7±0.2, 25.9±0.2, and 26.7±0.2 degrees; or

b) a Crystalline Form E, which has a powder X-ray diffraction pattern comprising three or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 6.2±0.2, 8.6±0.2, 9.5±0.2, 11.0±0.2, 11.5±0.2, 12.0±0.2, 12.5±0.2, 13.4±0.2, 13.8±0.2, 14.4±0.2, 14.7±0.2, 15.1±0.2, 15.3±0.2, 16.2±0.2, 16.9±0.2, 17.9±0.2, 18.3±0.2, 19.0±0.2, 19.5±0.2, 20.1±0.2, 21.3±0.2, 22.2±0.2, 22.9±0.2, 23.3±0.2, 24.2±0.2, 24.6±0.2, 25.1±0.2, 25.7±0.2, 26.3±0.2, 27.0±0.2, 27.4±0.2, and 30.9±0.2 degrees; or

c) a Crystalline Form F, which has a powder X-ray diffraction pattern comprising three or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 5.2±0.2, 6.3±0.2, 7.7±0.2, 9.7±0.2, 10.4±0.2, 11.8±0.2, 13.7±0.2, 15.6±0.2, 17.5±0.2, 18.0±0.2, 19.5±0.2, 20.2±0.2, 21.7±0.2, 23.1±0.2, 24.7±0.2, 25.3±0.2, and 27.3±0.2 degrees; or

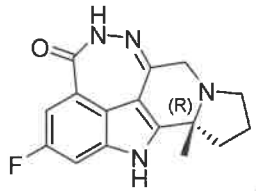
d) a Crystalline Form H, which has a powder X-ray diffraction pattern comprising four or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 9.5±0.2, 12.0±0.2, 13.5±0.2, 15.4±0.2, 17.0±0.2, 19.0±0.2, 23.0±0.2, 24.2±0.2, 27.0±0.2, 27.4±0.2, 31.0±0.2, 34.7±0.2, and 34.8±0.2 degrees; or

e) a Crystalline Form K, which has a powder X-ray diffraction pattern comprising three or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 6.4±0.2, 10.8±0.2, 12.6±0.2, 12.8±0.2, 19.2±0.2, 25.2±0.2, 25.8±0.2, 32.4±0.2, and 34.1±0.2 degrees; or

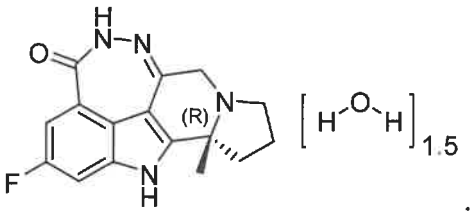
f) a Crystalline Form I, which has a powder X-ray diffraction pattern comprising four or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 9.8±0.2, 10.0±0.2, 11.1±0.2, 11.7±0.2, 12.9±0.2, 13.3±0.2, 13.9±0.2, 14.4±0.2, 17.1±0.2, 17.4±0.2, 17.6±0.2, 17.9±0.2, 18.4±0.2, 18.5±0.2, 19.4±0.2, 20.8±0.2, 21.9±0.2, 23.7±0.2, 26.4±0.2, 26.9±0.2, and 29.4±0.2 degrees; or

g) a Crystalline Form J, which has a powder X-ray diffraction pattern comprising four or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 6.4±0.2, 8.7±0.2, 9.9±0.2, 10.3±0.2, 11.7±0.2, 12.8±0.2, 13.9±0.2, 18.1±0.2, 19.3±0.2, 23.0±0.2, 23.8±0.2, and 25.8±0.2 degrees.

2. A hydrate of (R)-2-fluoro-10a-methyl-7,8,9,10,10a,11-hexahydro-5,6,7a,11-tetraazacyclohepta[def]cyclopenta[a]fluoren-4(5H)-one free base:



3. The compound of claim 2, which is a crystalline sesqui-hydrate of (R)-2-fluoro-10a-methyl-7,8,9,10,10a,11-hexahydro-5,6,7a,11-tetraazacyclohepta[def]cyclopenta[a]fluoren-4(5H)-one having the structure of Formula **III**:



Formula **III**

4. The compound of claim 3 in Crystalline Form C**, which is a single crystal as substantially illustrated in FIGs. 1, 2, 3, and/or 4.

5. The compound of claim 2,

a) having Crystalline Form A, which has a powder X-ray diffraction pattern comprising three or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 6.3±0.2, 8.5±0.2, 8.6±0.2, 9.9±0.2, 10.4±0.2, 11.0±0.2, 11.1±0.2, 12.6±0.2, 12.8±0.2, 14.7±0.2, 18.0±0.2, 18.1±0.2, 20.1±0.2, 21.4±0.2, 22.2±0.2, 24.6±0.2, 25.7±0.2, and 30.0±0.2 degrees; or

b) having Crystalline Form G, which has a powder X-ray diffraction pattern comprising three or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 6.3±0.2, 8.6±0.2, 9.6±0.2, 10.3±0.2, 11.0±0.2, 12.6±0.2, 17.5±0.2, and 25.4±0.2degrees; or

c) having Crystalline Form B, which has a powder X-ray diffraction pattern comprising three or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 6.3±0.2, 8.7±0.2, 11.1±0.2, 12.6±0.2, 14.5±0.2, 14.8±0.2, 15.2±0.2, 18.0±0.2, 23.9±0.2, 25.3±0.2, and 25.8±0.2_degrees.

6. The compound of claim 2 having Crystalline Form C, which has a powder X-ray diffraction pattern comprising three or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 5.3±0.2, 6.3±0.2, 6.5±0.2, 6.9±0.2, 8.7±0.2, 10.6±0.2, 11.1±0.2, 11.6±0.2, 12.6±0.2, 13.1±0.2, 13.7±0.2, 14.4±0.2, 14.8±0.2, 15.1±0.2, 15.9±0.2, 16.2±0.2, 17.3±0.2, 18.0±0.2, 18.7±0.2, 19.0±0.2, 19.4±0.2, 20.2±0.2, 20.6±0.2, 21.0±0.2, 2±0.2, 21.5±0.2, 22.3±0.2, 22.7±0.2, 23.4±0.2, 23.8±0.2, 24.3±0.2, 24.7±0.2, 25.3±0.2, 25.7±0.2, 26.1±0.2, 26.4±0.2, and 27.4±0.2 degrees.

7. The compound of claim 2 having Crystalline Form C*, which has a powder X-ray diffraction pattern comprising three or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 6.1±0.2, 6.3±0.2, 6.9±0.2, 8.5±0.2, 11.1±0.2, 11.6±0.2, 13.2±0.2, 14.5±0.2, 15.2±0.2, 16.3±0.2, 18.1±0.2, 20.3±0.2, 22.5±0.2, 24.8±0.2, 26.1±0.2, 26.6±0.2, and 27.7±0.2 degrees.

8. The compound of claim 6, wherein the compound has a crystalline form which is substantially Crystalline Form C.

9. The compound of claim 1, having a powder X-ray diffraction pattern substantially similar to a pattern selected from the group consisting of FIGs. 8, 9, 10, 12, 13, 14, 15, and 16.

10. A method for preparing a crystalline form of a hydrate, an anhydrate or a solvate/hydrate of (R)-2-fluoro-10a-methyl-7,8,9,10,10a,11-hexahydro-5,6,7a,11-tetraazacyclohepta[def]cyclopenta[a]fluoren-4(5H)-one comprising any one of the following procedures:

(a) dissolving free base or a hydrate of (R)-2-fluoro-10a-methyl-7,8,9,10,10a,11-hexahydro-5,6,7a,11-tetraazacyclohepta[def]cyclopenta[a]fluoren-4(5H)-one in a solvent or a solvent mixture to form a solution or a suspension; and precipitating out (R)-2-fluoro-10a-methyl-7,8,9,10,10a,11-hexahydro-5,6,7a,11-tetraazacyclohepta[def]cyclopenta[a]fluoren-4(5H)-one sesqui-hydrate in a crystalline form;

(b) dissolving or suspending (R)-2-fluoro-10a-methyl-7,8,9,10,10a,11-hexahydro-5,6,7a,11-tetraazacyclohepta[def]cyclopenta[a]fluoren-4(5H)-one hydrate in a solvent or a solvent mixture; and precipitating out (R)-2-fluoro-10a-methyl-7,8,9,10,10a,11-hexahydro-5,6,7a,11-tetraazacyclohepta[def]cyclopenta[a]fluoren-4(5H)-one hydrate in a crystalline form with an anti-solvent;

(c) storing a crystalline (R)-2-fluoro-10a-methyl-7,8,9,10,10a,11-hexahydro-5,6,7a,11-tetraazacyclohepta[def]cyclopenta[a]fluoren-4(5H)-one solvate/hydrate for an extended period to obtain a crystalline form;

(d) heating a crystalline or an amorphous (R)-2-fluoro-10a-methyl-7,8,9,10,10a,11-hexahydro-5,6,7a,11-tetraazacyclohepta[def]cyclopenta[a]fluoren-4(5H)-one to an elevated temperature, and cooling to obtain a crystalline form; and

(e) exposing a crystalline or an amorphous (R)-2-fluoro-10a-methyl-7,8,9,10,10a,11-hexahydro-5,6,7a,11-tetraazacyclohepta[def]cyclopenta[a]fluoren-4(5H)-one to a vapor of a solvent to obtain a crystalline form.

11. The method of claim 10, wherein:

(i) the procedure (a) or (b) further comprises one or more procedures independently selected from heating, filtering to remove undissolved impurities, distilling solvent, adding a counter solvent or solvent mixture, adding crystal seeds, adding precipitaion inducing agent(s), cooling, precipitating, or filtering to collect the crystalline product;

(ii) the procedure (a) or (b), wherein the solvent or the solvent mixture is selected from the group consisting of water, lower alkyl alcohols, ketones, ethers, esters, lower aliphatic carboxylic acids, lower aliphatic nitriles, optionally halogenated aromatic solvents, and combinations thereof;

(iii) the solvent is isopropanol, ethanol, methanol, acetone, THF, 1,4-dioxane, acetic acid, acetonitrile, water, or a combination thereof;

(iv) the free base is an isolated and purified free base, an isolated but unpurified free base, or a crude reaction product containing the free base;

(v) the procedure (c), wherein said extended period is at least three days, at least one week, or at least two weeks;

(vi) the procedure (d), wherein said elevated temperature is at least 40 °C, at least 60 °C, at least 80 °C, or at least 100 °C, but lower than decomposition temperature of the sesqui-maleate salt; or

(vii) the procedure (e), wherein the vapor is a vapor of acetic acid.

12. The method of claim 11,

(i) comprising the procedure (a) or (b), wherein the solvent or solvent mixture is selected from the group consisting of water, lower alkyl alcohols, ketones, ethers, esters, lower aliphatic carboxylic acids, lower aliphatic nitriles, optionally halogenated aromatic solvents, and combinations thereof; or

(ii) wherein the solvent is isopropanol, ethanol, methanol, acetone, THF, 1,4-dioxane, acetic acid, acetonitrile, water, or a combination thereof.

13. The method of claim 11, wherein:

1) said procedure (a) or (b) using isopropanol-water (v/v = 20/40) as the solvent to produce Crystalline Form C**;

2) said procedure (a) or (b) using MTBE as the solvent to produce Crystalline Form B;

3) said procedure (a) or (b) using i-PrOH/H_2O as the solvent to produce Crystalline Form C or C*;

4) said procedure (c) adding toluene into HOAc as the solvent to produce Crystalline Form D;

5) said procedure (d) letting Crystalline Form A interact with DMA vapor to produce Crystalline Form E;

6) said procedure (e) letting Crystalline Form A interact with acetic acid vapor to produce Crystalline Form F;

7) said procedure (d) subjects Crystalline Form A to a desorption and adsorption cycle in DVS (dynamic vapor sorption) to produce Crystalline Form G;

8) said procedure (d) heating Crystalline Form E to 80 °C to produce Crystalline Form H;

9) said procedure (d) heating Crystalline Form E to 150 °C to produce Crystalline Form I;

10) said procedure (d) heating Crystalline Form A to 150 °C to produce Crystalline Form J;

11) said procedure (e) letting Crystalline Form A interact with MeOH vapor to produce Crystalline Form K;

12) said procedure (d) heating Crystalline Form K to 150 °C to produce Crystalline Form L.

14. A pharmaceutical composition comprising a therapeutically effective amount of the compound

15. A process for preparing a crystalline (R)-2-fluoro-10a-methyl-7,8,9,10,10a,11-hexahydro-5,6,7a,11-tetraazacyclohepta[def]cyclopenta[a]fluoren-4(5H)-one sesqui-hydrate of claim 4 comprising mixing (R)-2-fluoro-10a-methyl-7,8,9,10,10a,11-hexahydro-5,6,7a,11-tetraazacyclohepta[def]cyclopenta[a]fluoren-4(5H)-one free base in a mixed solvent of i-PrOH and H_2O at about 80°C to provide a mixture.

16. The process of claim 15, further comprising adding crystal seeds into the mixture after cooling to room temperature, and letting the mixture stand for a certain duration.

17. The process of claim 15, wherein the mixing is performed with stirring.

18. The compound of claim 2, wherein the compound is in a crystalline form.

19. A method for preparing Crystalline Form C of claim 6 comprising:

(i) reacting (R)-2-fluoro-10a-methyl-7,8,9,10,10a,11-hexahydro-5,6,7a,11-tetraazacyclohepta[def]cyclopenta[a]fluoren-4(5H)-one free base (Compound A) with a resolving agent in an appropriate solvent in the presence of an alkaline to provide a crude Compound A; and

(ii) recrystallizing the crude Compound A from step (i) in a mixed solvent to obtain Crystalline Form C.

20. The compound of claim 2, having a powder X-ray diffraction pattern substantially similar to a pattern selected from the group consisting of FIGs. 4, 5, 6, 7A, 7B, and/or 11.