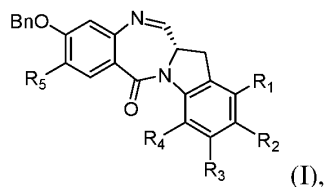
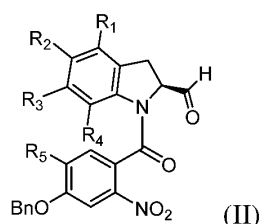


CLAIMS

1. A method of preparing a compound of formula (I):



or a salt thereof, comprising reacting the compound of formula (II):



or a salt thereof, with Fe in the presence of NH_4Cl , wherein:

R_1 , R_2 , R_3 , and R_4 are each independently selected from -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, - $(\text{XCH}_2\text{CH}_2)_n\text{-R}^c$, halogen, - $\text{NH}(\text{C}=\text{NH})\text{NH}_2$, -OR, - $\text{NR}'\text{R}''$, -NCO, - $\text{NR}'\text{COR}''$, -SR, -SOR', - $\text{SO}_2\text{R}'$, - SO_3H , - OSO_3H , - $\text{SO}_2\text{NR}'\text{R}''$, cyano, azido, -COR', -OCOR', and -OCONR'R'';

X is selected from O, NH and S;

R_5 is -H, -R, -OR, -SR, - $\text{NR}'\text{R}''$, or halogen;

R, for each occurrence, is independently selected from -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(\text{CH}_2\text{CH}_2\text{X})_n\text{-R}^c$, an optionally substituted aryl having 6 to 18 carbon atoms, an optionally substituted 5- to 18-membered heteroaryl ring containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an optionally substituted 3- to 18-membered heterocyclic ring containing 1 to 6 heteroatoms independently selected from O, S, N and P;

R' and R'' are each independently selected from -H, -OH, -OR, -NHR, - NR_2 , -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(\text{CH}_2\text{CH}_2\text{X})_n\text{-R}^c$, and an optionally substituted 3- to 18-membered heterocyclic ring having 1 to 6 heteroatoms independently selected from O, S, N and P;

R^c is -H or a substituted or unsubstituted linear or branched alkyl having 1 to 4 carbon atoms; and

n is an integer from 1 to 24.

2. The method of claim 1, wherein the reaction is carried out in a solvent selected from tetrahydrofuran (THF), 2-methyltetrahydrofuran (MeTHF), N-methyl-2-pyrrolidone (NMP), methanol, ethanol, isopropanol, dichloromethane, dichloroethane, acetonitrile, dimethylformamide (DMF), dimethylacetamide (DMA), cyclopentyl methyl ether (CPME), ethyl acetate, water, and a combination thereof.

3. The method of claim 2, wherein the reaction is carried out in a mixture of water and one or more organic solvents.

4. The method of any one of claims 1-3, wherein the reaction is carried out in a mixture of THF, methanol and water.

5. The method of any one of claims 1-4, wherein the reaction is carried out at a temperature between 40 °C and 90 °C.

6. The method of claim 5, wherein the reaction is carried out at a temperature between 50 °C and 80 °C.

7. The method of claim 6, wherein the reaction is carried out at a temperature between 60 °C and 70 °C.

8. The method of claim 7, wherein the reaction is carried out at 65 °C.

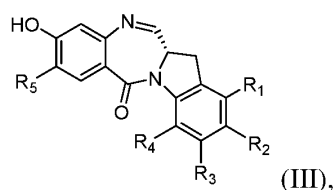
9. The method of any one of claims 1-8, wherein the reaction is carried out for 1 hour to 1 week.

10. The method of claim 9, wherein the reaction is carried out for 24 hours to 72 hours.

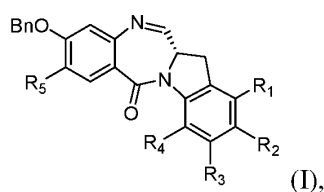
11. The method of claim 9, wherein the reaction is carried out for 48 hours.

12. The method of any one of claims 1-11, wherein the reaction is carried out under an inert atmosphere.

13. The method of claim 12, wherein the reaction is carried out under N₂ atmosphere.
14. The method of any one of claims 1-13, wherein the compound of formula (I) is purified by one or more precipitations, re-crystallizations or a combination thereof.
15. The method of claim 14, wherein the compound of formula (I) is re-crystallized or precipitated in a mixture of dichloromethane and ethanol.
16. The method of claim 15, wherein the volume ratio of dichloromethane and ethanol is 1:1.
17. The method of any one of claims 14-16, wherein the compound of formula (I) is further purified by re-crystallization or precipitation.
18. The method of claim 17, wherein the compound of formula (I) is re-crystallized or precipitated in a mixture of toluene and acetonitrile.
19. The method of claim 18, wherein the compound of formula (I) is re-crystallized by dissolving the compound in toluene at an elevated temperature and addition of acetonitrile.
20. The method of claim 19, wherein the compound of formula (I) is re-crystallized by dissolving the compound in toluene at 80 °C, followed by filtration and addition of acetonitrile.
21. A method of preparing a compound of formula (III):



or a salt thereof, comprising reacting the compound of formula (I):



or a salt thereof, with a hydrogenation reagent in the presence of a palladium catalyst, wherein:

R_1 , R_2 , R_3 , and R_4 are each independently selected from the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, $-(CH_2CH_2X)_n-R^c$, halogen, $-NH(C=NH)NH_2$, -OR, $-NR'R''$, -NCO, $-NR'COR''$, -SR, -SOR', $-SO_2R'$, $-SO_3H$, $-OSO_3H$, $-SO_2NR'R''$, cyano, azido, $-COR'$, $-OCOR'$, and $-OCONR'R''$;

X is selected from O, NH and S;

R_5 is -H, -R, -OR, -SR, $-NR'R''$, or halogen;

R, for each occurrence, is independently selected from the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(CH_2CH_2X)_n-R^c$, an optionally substituted aryl having 6 to 18 carbon atoms, an optionally substituted 5- to 18-membered heteroaryl ring containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an optionally substituted 3- to 18-membered heterocyclic ring containing 1 to 6 heteroatoms independently selected from O, S, N and P;

R' and R'' are each independently selected from -H, -OH, -OR, -NHR, $-NR_2$, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(CH_2CH_2X)_n-R^c$, and an optionally substituted 3- to 18-membered heterocyclic ring having 1 to 6 heteroatoms independently selected from O, S, N and P;

R^c is -H or a substituted or unsubstituted linear or branched alkyl having 1 to 4 carbon atoms; and

n is an integer from 1 to 24.

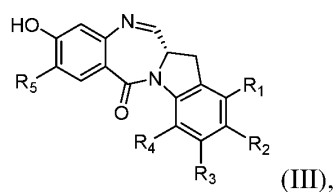
22. The method of claim 21, wherein the palladium catalyst is a Pd/Alox catalyst.

23. The method of claim 22, wherein the palladium catalyst is 5 wt% Pd/Alox.

24. The method of claim 21, wherein the palladium catalyst is a Pd/C catalyst.

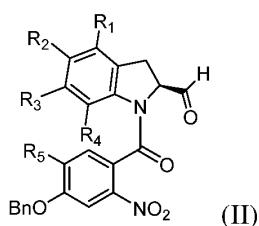
25. The method of any one of claims 21-24, wherein 0.05 to 0.5 equivalent of Pd is used for every 1 equivalent of the compound of formula (I).
26. The method of claim 25, wherein 0.075 to 0.15 equivalent of Pd is used for every 1 equivalent of the compound of formula (I).
27. The method of claim 25, wherein 0.09 or 0.1 equivalent of Pd is used for every 1 equivalent of compound of formula (I).
28. The method of any one of claims 21-27, wherein the hydrogenation reagent is 1,4-cyclohexadiene.
29. The method of claim 28, wherein 1.0 to 5.0 equivalent of 1,4-cyclohexadiene is used for every 1 equivalent of the compound of formula (I).
30. The method of claim 28, wherein 1.1 to 2.0 equivalent of 1,4-cyclohexadiene is used for every 1 equivalent of the compound of formula (I).
31. The method of claim 28, wherein 1.3 to 1.8 equivalent of 1,4-cyclohexadiene is used for every 1 equivalent of the compound of formula (I).
32. The method of claim 28, wherein 1.5 to 1.7 equivalent of 1,4-cyclohexadiene is used for every 1 equivalent of the compound of formula (I).
33. The method of claim 21, wherein the method comprises reacting the compound of formula (1) with 1,4-cyclohexadiene in the presence of 5 wt.% Pd/Alox, and wherein 1.5 to 1.7 equivalent of 1,4-cyclohexadiene and 0.075 to 0.15 equivalent of Pd are used for every 1 equivalent of the compound of formula (I).
34. The method of any one of claims 21-33, wherein the reaction is carried out in a solvent or a mixture of solvents.
35. The method of claim 34, wherein the solvent is selected from dimethylsulfoxide (DMSO), tetrahydrofuran (THF), 2-methyltetrahydrofuran (MeTHF), N-methyl-2-pyrrolidone (NMP), methanol, ethanol, isopropanol, dichloromethane, dichloroethane, acetonitrile, dimethylformamide (DMF), dimethylacetamide (DMA), cyclopentyl methyl ether (CPME), ethyl acetate, water, and a combination thereof.

36. The method of claim 35, wherein the reaction is carried out in a mixture of DMSO and ethanol.
37. The method of any one of claims 21-36, wherein the reaction is carried out at a temperature between 30 °C and 90 °C.
38. The method of claim 37, wherein the reaction is carried out at a temperature between 40 °C and 70 °C.
39. The method of claim 37, wherein the reaction is carried out at a temperature between 40 °C and 60 °C.
40. The method of claim 37, wherein the reaction is carried out at a temperature between 45 °C and 55 °C.
41. The method of claim 37, wherein the reaction is carried out at 50 °C.
42. A method of preparing a compound of formula (III):

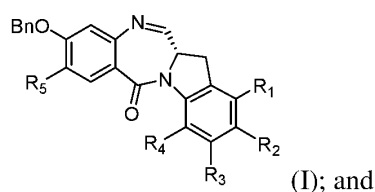


or a salt thereof, comprising the steps of:

- a) reacting the compound of formula (II):



with Fe in the presence of NH₄Cl to form a compound of formula (I):



b) reacting the compound of formula (I) with a hydrogenation reagent in the presence of a palladium catalyst to form the compound of formula (III), wherein:

R_1 , R_2 , R_3 , and R_4 are each independently selected from the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, $-(CH_2CH_2X)_n-R^c$, halogen, $-NH(C=NH)NH_2$, -OR, $-NR'R''$, -NCO, $-NR'COR''$, -SR, -SOR', $-SO_2R'$, $-SO_3H$, $-OSO_3H$, $-SO_2NR'R''$, cyano, azido, -COR', -OCOR', and $-OCONR'R''$;

X is selected from O, NH and S;

R_5 is -H, -R, -OR, -SR, $-NR'R''$, or halogen;

R, for each occurrence, is independently selected from the group consisting of -H, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(CH_2CH_2X)_n-R^c$, an optionally substituted aryl having 6 to 18 carbon atoms, an optionally substituted 5- to 18-membered heteroaryl ring containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an optionally substituted 3- to 18-membered heterocyclic ring containing 1 to 6 heteroatoms independently selected from O, S, N and P;

R' and R'' are each independently selected from -H, -OH, -OR, -NHR, $-NR_2$, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(CH_2CH_2X)_n-R^c$, and an optionally substituted 3- to 18-membered heterocyclic ring having 1 to 6 heteroatoms independently selected from O, S, N and P;

R^c is -H or a substituted or unsubstituted linear or branched alkyl having 1 to 4 carbon atoms; and

n is an integer from 1 to 24.

43. The method of claim 42, wherein the solvent is selected from tetrahydrofuran (THF), 2-methyltetrahydrofuran (MeTHF), N-methyl-2-pyrrolidone (NMP), methanol, ethanol, isopropanol, dichloromethane, dichloroethane, acetonitrile, dimethylformamide (DMF), dimethylacetamide, cyclopentyl methyl ether (CPME), ethyl acetate, water, and a combination thereof.

44. The method of claim 43, wherein the reaction of step (a) is carried out in a mixture of water and one or more organic solvents.

45. The method of any one of claims 42-44, wherein the reaction of step (a) is carried out in a mixture of THF, methanol and water.

46. The method of any one of claims 42-45, wherein the reaction of step (a) is carried out at a temperature between 40 °C and 90 °C.

47. The method of claim 46, wherein the reaction of step (a) is carried out at a temperature between 50 °C and 80 °C.

48. The method of claim 47, wherein the reaction of step (a) is carried out at a temperature between 60 °C and 70 °C.

49. The method of claim 48, wherein the reaction of step (a) is carried out at 65 °C.

50. The method of any one of claims 42-49, wherein the reaction of step (a) is carried out for 1 hour to 1 week.

51. The method of claim 50, wherein the reaction of step (a) is carried out for 24 hours to 72 hours.

52. The method of claim 51, wherein the reaction of step (a) is carried out for 48 hours.

53. The method of any one of claims 42-52, wherein the reaction of step (a) is carried out under an inert atmosphere.

54. The method of claim 53, wherein the reaction of step (a) is carried out under N₂ atmosphere.

55. The method of any one of claims 42-54, wherein the compound of formula (I) is purified by one or more precipitations, re-crystallizations or a combination thereof before the reaction of step (b) is carried out.

56. The method of claim 55, wherein the compound of formula (I) is re-crystallized or precipitated in a mixture of dichloromethane and ethanol.
57. The method of claim 56, wherein the volume ratio of dichloromethane and ethanol is 1:1.
58. The method of any one of claims 55-57, wherein the compound of formula (I) is further purified by re-crystallization or precipitation.
59. The method of claim 58, wherein the compound of formula (I) is re-crystallized or precipitated in a mixture of toluene and acetonitrile.
60. The method of claim 59, wherein the compound of formula (I) is re-crystallized by dissolving the compound in toluene at an elevated temperature and addition of acetonitrile.
61. The method of claim 59, wherein the compound of formula (I) is re-crystallized by dissolving the compound in toluene at 80 °C followed by filtration and addition of acetonitrile.
62. The method of any one of claims 42-61, wherein the palladium catalyst in step (b) is a Pd/Alox catalyst.
63. The method of claim 62, wherein the palladium catalyst in step (b) is 5 wt% Pd/Alox.
64. The method of any one of claims 42-61, wherein the palladium catalyst is a Pd/C catalyst.
65. The method of any one of claims 62-64, wherein 0.05 to 0.2 equivalent of Pd is used for every 1 equivalent of the compound of formula (I).
66. The method of claim 65, wherein 0.075 to 0.15 equivalent of Pd is used for 1 equivalent of the compound of formula (I).
67. The method of claim 65, wherein 0.09 or 0.1 equivalent of Pd is used for 1 equivalent of the compound of formula (I).

68. The method of any one of claims 42-67, wherein the hydrogenation reagent in step (b) is 1,4-cyclohexadiene.

69. The method of claim 68, wherein 1.0 to 5.0 equivalent of 1,4-cyclohexadiene is used for every 1 equivalent of the compound of formula (I).

70. The method of claim 69, wherein 1.1 to 2.0 equivalent of 1,4-cyclohexadiene is used for every 1 equivalent of the compound of formula (I).

71. The method of claim 69, wherein 1.3 to 1.8 equivalent of 1,4-cyclohexadiene is used for every 1 equivalent of the compound of formula (I).

72. The method of claim 69, wherein 1.5 to 1.7 equivalent of 1,4-cyclohexadiene is used for every 1 equivalent of the compound of formula (I).

73. The method of any of claims 42-61, wherein the reaction of step (b) comprises reacting the compound of formula (I) with 1,4-cyclohexadiene in the presence of 5 wt.% Pd/Alox, and wherein 1.5 to 1.7 equivalent of 1,4-cyclohexadiene and 0.075 to 0.15 equivalent of Pd are used for every 1 equivalent of the compound of formula (I).

74. The method of any one of claims 42-73, wherein the reaction of step (b) is carried out in a solvent or a solvent mixture.

75. The method of claim 74, wherein the solvent is selected from tetrahydrofuran (THF), 2-methyltetrahydrofuran (MeTHF), N-methyl-2-pyrrolidone (NMP), methanol, ethanol, isopropanol, dichloromethane, dichloroethane, acetonitrile, dimethylformamide (DMF), dimethylacetamide, cyclopentyl methyl ether (CPME), ethyl acetate, water, and a combination thereof.

76. The method of claim 74, wherein the reaction is carried out in a mixture of DMSO and ethanol.

77. The method of any one of claims 42-76, wherein the reaction of step (b) is carried out at a temperature between 30 °C and 90 °C.

78. The method of claim 77, wherein the reaction is carried out at a temperature between 40 °C and 70 °C.

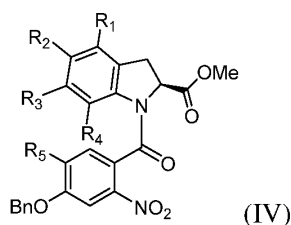
79. The method of claim 77, wherein the reaction is carried out at a temperature between 40 °C and 60 °C.

80. The method of claim 77, wherein the reaction is carried out at a temperature between 45 °C and 55 °C.

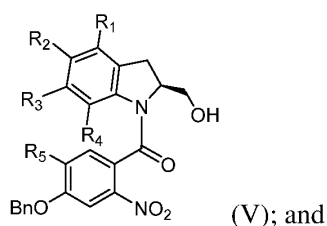
81. The method of claim 77, wherein the reaction is carried out at 50 °C.

82. The method of any one of claims 1-20 and 42-81, wherein the compound of formula (II) is prepared by a method comprising the following steps:

a) reducing the compound of formula (IV):



with a reducing agent to form the compound of formula (V):



b) oxidizing the compound of formula (V) with an oxidizing agent to form the compound of formula (II).

83. The method of claim 82, wherein the reducing agent is a hydride reducing agent.

84. The method of claim 82, wherein the reducing agent is sodium borohydride, sodium triacetoxy borohydride, sodium cyanoborohydride, lithium aluminum hydride, hydrogen gas, ammonium formate, borane, 9-borabicyclo[3.3.1]nonane (9-BBN), diisobutylaluminum hydride (DIBAL), lithium borohydride (LiBH₄), potassium borohydride (KBH₄), or sodium bis(2-methoxyethoxy)aluminumhydride (Red-Al).

85. The method of claim 82, wherein the reducing agent is sodium borohydride.

86. The method of any one of claims 82-85, wherein the oxidizing agent is Dess–Martin periodinane (DMP), 2-iodoxybenzoic acid, Collins reagent ($\text{CrO}_3 \cdot \text{Py}_2$), pyridinium dichromate (PDC), pyridinium chlorochromate (PCC), tetrapropylammonium perruthenate (TPAP)/*N*-methymorpholine *N*-oxide (NMO), (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO)/NaClO, DMSO/oxalyl chloride, DMSO/carbodiimide or DMSO/ $\text{SO}_3 \cdot \text{Py}$.

87. The method of claim 86, wherein the oxidizing agent is DMP.

88. The method of any one of claims 1-87, wherein R_1 , R_2 , R_3 , and R_4 are each independently selected from the group consisting of -H, $(\text{C}_1\text{-C}_3)\text{alkyl}$, halogen, -OH, $(\text{C}_1\text{-C}_3)\text{alkoxy}$, and cyano.

89. The method of claim 88, wherein R_1 , R_2 , R_3 , and R_4 are all H.

90. The method of any one of claims 1-89, wherein R_5 is a $(\text{C}_1\text{-C}_3)\text{alkoxy}$.

91. The method of claim 90, wherein R_5 is -OMe.

92. The method of any one of claims 1-87, wherein R_1 , R_2 , R_3 , and R_4 are all H; and R_5 is -OMe.