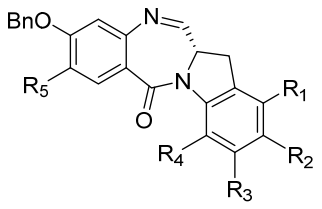
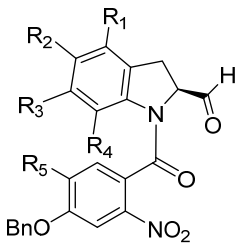
CLAIMS

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



(I),

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



(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, $-(CH_2CH_2X)_n-R^c$, 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 -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;

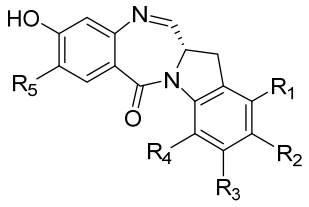
R' and R'' are each independently selected from -H, -OH, -OR, -NHR, $-NR_2$, -COR, an optionally substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, a polyethylene glycol unit $-(CH_2CH_2X)_n-R^c$, and an optionally substituted 3- to

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.

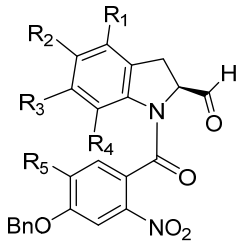
2. A method of preparing a compound of formula (III):



(III),

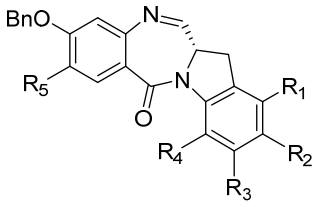
or a salt thereof, comprising the steps of:

a) reacting the compound of formula (II):



(II)

with Fe in the presence of NH_4Cl to form a compound of formula (I):



(I); and

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.

3. The method of claim 1 or 2, wherein the reaction of claim 1 or the reaction of step (a) of claim 2 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 of claim 1 or the reaction of step (a) of claim 2 is carried out in a mixture of THF, methanol and water.

5. The method of any one of claims 1-4, wherein the reaction of claim 1 or the reaction of step (a) of claim 2 is carried out at a temperature between 40 °C and 90 °C, between 50 °C and 80 °C, or between 60 °C and 70 °C, or the reaction is carried out at 65 °C.

6. The method of any one of claims 1-5, wherein the compound of formula (I) in the reaction of claim 1 is purified by one or more precipitations, re-crystallizations or a combination thereof, or the compound of formula (I) is purified by one or more precipitations, re-crystallizations or a combination thereof before the reaction of step (b) of claim 2 is carried out.

7. The method of any one of claims 2-6, wherein the palladium catalyst in step (b) of claim 2 is a Pd/Alox catalyst or a Pd/C catalyst.

8. The method of claim 7, wherein the palladium catalyst in step (b) of claim 2 is 5 wt% Pd/Alox.

9. The method of claim 7 or 8, wherein (i) 0.05 to 0.2 equivalent of Pd is used for every 1 equivalent of the compound of formula (I), (ii) 0.075 to 0.15 equivalent of Pd is used for 1 equivalent of the compound of formula (I), or (iii) 0.09 or 0.1 equivalent of Pd is used for 1 equivalent of the compound of formula (I).

10. The method of any one of claims 2-9, wherein the hydrogenation reagent in step (b) of claim 2 is 1,4-cyclohexadiene.

11. The method of claim 10, wherein (i) 1.0 to 5.0 equivalent of 1,4-cyclohexadiene is used for every 1 equivalent of the compound of formula (I), (ii) 1.1 to 2.0 equivalent of 1,4-cyclohexadiene is used for every 1 equivalent of the compound of formula (I), (iii) 1.3 to 1.8 equivalent of 1,4-cyclohexadiene is used for every 1 equivalent of the compound of formula (I), or (iv) 1.5 to 1.7 equivalent of 1,4-cyclohexadiene is used for every 1 equivalent of the compound of formula (I).

12. The method of any of claims 2-6, wherein the reaction of step (b) of claim 2 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).

13. The method of any one of claims 2-12, wherein the reaction of step (b) of claim 2 is carried out in a solvent or a solvent mixture, optionally, 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.

14. The method of claim 13, wherein the reaction of step (b) of claim 2 is carried out in a mixture of DMSO and ethanol.

15. The method of any one of claims 2-14, wherein the reaction of step (b) of claim 2 is carried out at a temperature between 30 °C and 90 °C, between 40 °C and 70 °C, between 40 °C and 60 °C, or between 45 °C and 55 °C, or the reaction is carried at 50 °C.

16. The method of any one of claims 1-15, wherein R_1, R_2, R_3, and R_4 are each independently selected from the group consisting of -H, (C_1-C_3)alkyl, halogen, -OH, (C_1-C_3)alkoxy, and cyano, and R_5 is a (C_1-C_3)alkoxy; optionally, wherein R_1, R_2, R_3, and R_4 are all H and R_5 is –OMe.