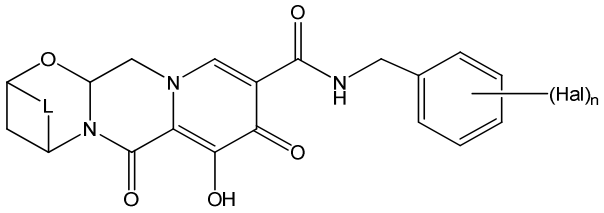
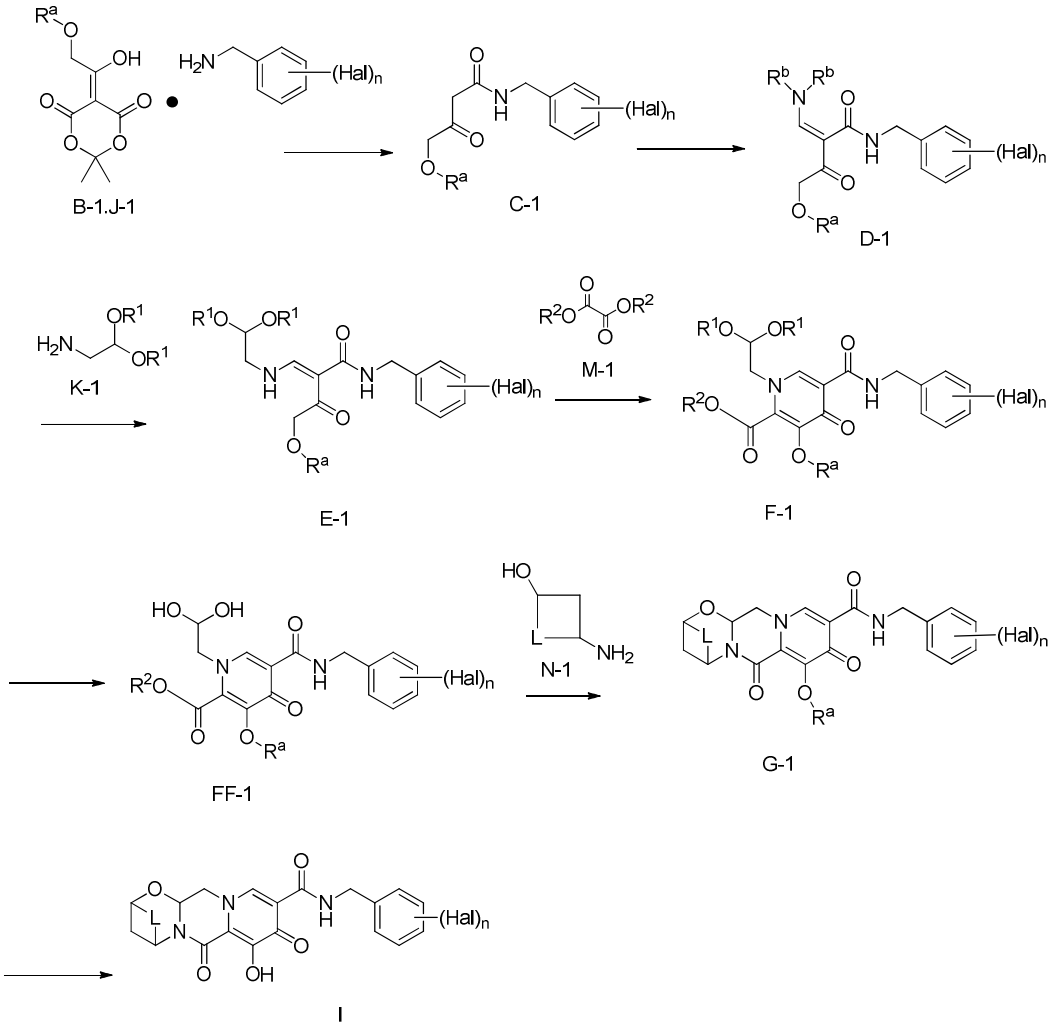
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A process to prepare a compound of Formula I:



I

according to the following General Scheme VI



wherein the process comprises the following steps:

reacting B-1.J-1 in the presence of an acid to yield C-1;

reacting C-1 with an alkylated formamide acetal to yield D-1;

reacting D-1 with K-1 to yield E-1;

reacting E-1 with M-1 in the presence of a base to yield F-1;

reacting F-1 with at least one acid to yield FF-1;

reacting FF-1 with N-1, or salts or co-crystals thereof, in the presence of an additive to yield G-1;

reacting G-1 under conditions suitable to yield a compound of Formula I;

wherein

Hal is halogen, which may be the same or different,

n is 1, 2, or 3,

L is $-C(R^c)_2-$, $-C(R^c)_2C(R^c)_2-$, $-C(R^c)_2C(R^c)_2C(R^c)_2-$, or $-C(R^c)_2C(R^c)_2C(R^c)_2C(R^c)_2-$,

each R^c is, independently, hydrogen, halo, hydroxyl or C_1-C_4alkyl,

each R^a, R^1, and R^2 is, independently, (C_1-C_4)alkyl, (C_6-C_{10})aryl, or (C_6-C_{10})aryl (C_1-C_4)alkyl;

each R^b is independently (C_1-C_4)alkyl.

2. The process of claim 1 wherein B-1.J-1 is reacted in an acid selected from the group consisting of an inorganic acid, an organic acid, a halogenated organic acid, a Lewis acid and mixtures thereof.

3. The process of claim 2 wherein the acid is selected from the group consisting of hydrochloric acid, hydrobromic acid, hydroiodic acid, trifluoromethanesulfonic acid, formic acid, trifluoroacetic acid, trichloroacetic acid, perfluoropropionic acid, dichloroacetic acid, chloroacetic acid, acetic acid, para-toluenesulfonic acid, methane sulfonic acid, zinc chloride, magnesium bromide, magnesium triflate, copper triflate, scandium triflate, and a mixture thereof.

4. The process of claim 2 or 3 wherein the acid is trifluoroacetic acid.

5. The process of any one of claims 1 to 4 wherein the alkylated formamide acetal is selected from the group consisting of *N*,*N*-dimethylformamide dimethyl acetal, *N*,*N*-dimethylformamide diethyl acetal, *N*,*N*-dimethylformamide diisopropyl acetal, *N*,*N*-diethylformamide dimethyl acetal, and *N*,*N*-diisopropylformamide dimethyl acetal.

6. The process of any one of claims 1 to 5 wherein the alkylated formamide 7

7. The process of any one of claims 1 to 6 wherein C-1 is reacted with an alkylated formamide acetal in the presence of an acid selected from the group consisting of trifluoroacetic acid, formic acid, acetic acid, sulfuric acid trifluoroacetic acid, trichloroacetic acid, and perfluoropropionic acid.

8. The process of claim 7, wherein the acid is trifluoroacetic acid.

9. The process of any one of claims 1 to 83 wherein K-1 is selected from the group consisting of aminoacetaldehyde diethylacetal, aminoacetaldehyde dipropylacetal, aminoacetaldehyde dimethylacetal, and aminoacetaldehyde dibutalacetal.

10. The process of any one of claims 1 to 9 wherein K-1 is aminoacetaldehyde dimethylacetal.

11. The process of any one of claims 1 to 1065 wherein M-1 is selected from the group consisting of dimethyl oxalate, diethyl oxalate, dipropyl oxalate, and dibutyl oxalate.

12. The process of any one of claims 14 to 11 wherein M-1 is dimethyl oxalate.

13. The process of any one of claims 1 to 12 wherein E-1 is reacted with M-1 in the presence of a base selected from the group consisting of a metal hydride, an alkoxide, an inorganic carbonate, a bis(triaklylsilyl)amide base, and a mixture thereof.

14. The process of claim 13 wherein the base is selected from the group consisting of sodium hydride, potassium hydride, lithium hydride, sodium methoxide, sodium *tert*-butoxide, sodium ethoxide, potassium *tert*-butoxide, potassium ethoxide, sodium *tert*-pentoxide, lithium *tert*-butoxide, lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, and a mixture thereof.

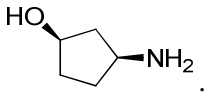
15. The process of claim 13 or 14, wherein the base is sodium methoxide.

16. The process of any one of claims 1 to 15 wherein F-1 is reacted with at least one acid selected from the group consisting of an organic acid, an inorganic acid, an organic carboxylic acids, and mixtures thereof.

17. The process of claim 16 wherein the at least one acid is selected from the group consisting of methanesulfonic acid, acetic acid, trifluoromethanesulfonic acid, trifluoroacetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, formic acid, butyric acid, propionic acid, benzoic acid, p-toluenesulfonic acid, camphorsulfonic acid, and mixtures thereof.

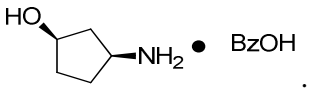
18. The process of claim 16 or 17, wherein the at least one acid is *p*-toluenesulfonic acid.

19. The process of any one of claims 1 to 18 wherein L is $–CH_2-CH_2-$.

20. The process of any one of claims 1 to 19 wherein N-1 is 

.

21. The process of any one of claims 1 to 20 wherein N-1 is in the form of a salt or co-crystal.

22. The process of claim 21 wherein N-1 is 

.

23. The process of any one of claims 1 to 22 wherein N-1 is in solution.

24. The process of any one of claims 1 to 23 wherein the additive is selected from the group consisting of a carboxylate salt, an inorganic carbonate, a metal hydride, an alkoxide, a water scavenger and a mixture thereof.

25. The process of any one of claims 1 to claim 24 wherein the additive is selected from the group consisting of lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, lithium hydride, sodium methoxide, sodium *tert*-butoxide, sodium ethoxide, potassium *tert*-butoxide, potassium ethoxide, sodium *tert*-pentoxide, lithium *tert*-butoxide, sodium propionate, potassium propionate, molecular sieves, trimethyl orthoacetate, potassium acetate, sodium acetate, lithium acetate and trimethyl orthoformate.

26. The process of any one of claims 1 to 25 wherein the additive is potassium acetate.

27. The process of any one of claims 1 to 26, wherein G-1 is reacted with at least one reagent selected from the group consisting of metal salts, Lewis acids, sodium ethanethiolate, sodium hexamethyldisiloxane, trifluoroacetic acid, and combinations thereof.

28. The process of claim 27, wherein the at least one reagent is selected from the group consisting of magnesium bromide, lithium chloride, lithium bromide, lithium iodide, aluminum trichloride, aluminum tribromide, chlorotrimethylsilane, iodotrimethylsilane, boron trichloride, boron tribromide, sodium ethanethiolate, sodium hexamethyldisiloxane, palladium, boron trifluoride diethyl etherate, and trifluoroacetic acid.

29. The process of claim 27 or 28, wherein the at least one reagent is magnesium bromide.

30. The process of any one of claims 1 to 29 wherein each R^a, R^b, R^1, and R^2 is, independently C_1-C_4alkyl.

31. The process of any one of claims 1 to 30 wherein:

R^2 is $–CH_3$; and/or

R^1 is $–CH_3$; and/or

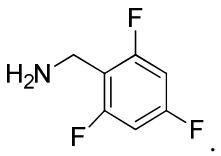
is $–CH_3$; and/or

R^b is $–CH_3$.

32. The process of any one of claims 1 to 31 wherein each Hal is independently –F or -Cl.

33. The process of any one of claims 1 to 32 wherein Hal is F.

34. The process of any one of claims 1 to 33 wherein n is 3.

35. The process of any one of claims 1 to 34 wherein J-1 is 

.