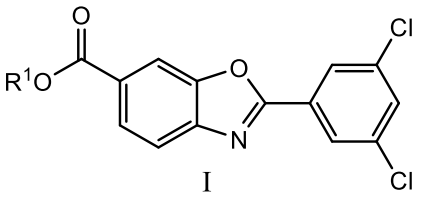
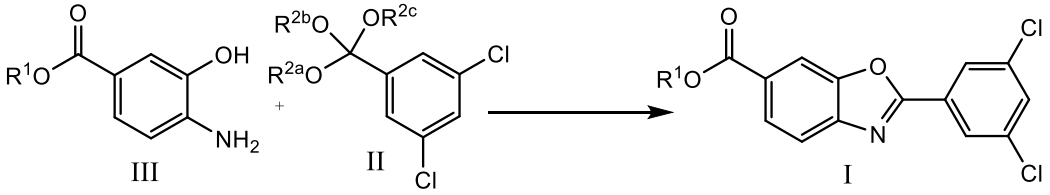
CLAIMS

1. A process for preparing a 6-Carboxy-2-(3,5-dichlorophenyl)benzoxazole compound of Formula I



I

the process comprising reacting a 4-Amino-3-hydroxybenzoic acid compound of Formula III with a 3,5-Dichlorophenyl ortho ester compound of Formula II in the presence of an acid catalyst or a base catalyst to provide the compound of Formula I



III II I

wherein R^1 is hydrogen or a carboxy protecting group; and R^{2a}, R^{2b} and R^{2c} are each independently C_1-C_6alkyl or any two of R^{2a}, R^{2b} and R^{2c} taken together are a C_1-C_6alkanediyl or R^{2a}, R^{2b} and R^{2c} taken together are a C_3-C_{10}alkanetriyl.

2. The process of claim 1 wherein the reaction of the compound of Formula III with the compound of Formula II to provide the compound of Formula I is carried out in a solvent.

3. The process of claim 2 wherein the solvent is selected from the group consisting of methanol, ethanol, isopropanol, n-butanol, acetone, methyl ethyl ketone, tetrahydrofuran, 1,4-dioxane, t-butyl methyl ether, anisole, ethyl acetate, chloroform, chlorobenzene, heptane, cyclohexane, toluene, acetonitrile and 1,2-dimethoxyethane.

4. The process of claim 3 wherein the solvent is selected from the group consisting of methanol, isopropanol, acetonitrile, ethyl acetate, 1,2-dimethoxyethane, tetrahydrofuran, t-butyl methyl ether and 1,4-dioxane.

5. The process of any one of claims 1 to 4 wherein the reaction of the compound of Formula III with the compound of Formula II to provide the compound of Formula I is carried out in the presence of an acid catalyst.

6. The process of claim 5 wherein the acid catalyst is selected from the group consisting of trifluoroacetic acid, acetic acid, hydrochloric acid and methanesulfonic acid.

7. The process of any one of claims 1 to 4 wherein the reaction of the compound of Formula III with the compound of Formula II to provide the compound of Formula I is carried out in the presence of a base catalyst.

8. The process of claim 7 wherein the base catalyst is triethylamine.

9. The process of any one of claims 1 to 8 wherein the reaction of the compound of Formula III with the compound of Formula II to provide the compound of Formula I is carried out at a temperature of room temperature to 100 °C.

10. The process of claim 9 wherein the temperature is room temperature to 65 °C.

11. The process of any one of claims 1 to 10 wherein the reaction of the compound of Formula III with the compound of Formula II to provide the compound of Formula I is carried out for a period of 0.25 hours to 40 hours.

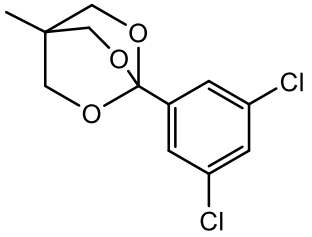
12. The process of any one of claims 1 to 11 wherein R^1 is hydrogen.

13. The process of any one of claims 1 to 12 wherein R^{2a}, R^{2b} and R^{2c} are each independently C_1-C_6alkyl.

14. The process of claim 13 wherein R^{2a}, R^{2b} and R^{2c} are each methyl.

15. The process of any one of claims 1 to 12 wherein R^{2a}, R^{2b} and R^{2c} taken together are a C_3-C_{10}alkanetriyl.

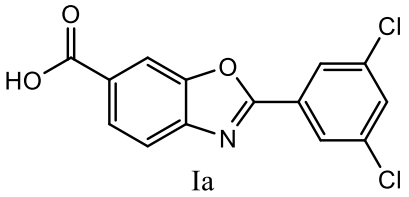
16. The process of claim 15 wherein the compound of Formula II is



17. The process of any one of claims 1 to 16 further comprising the step of isolating the compound of Formula I.

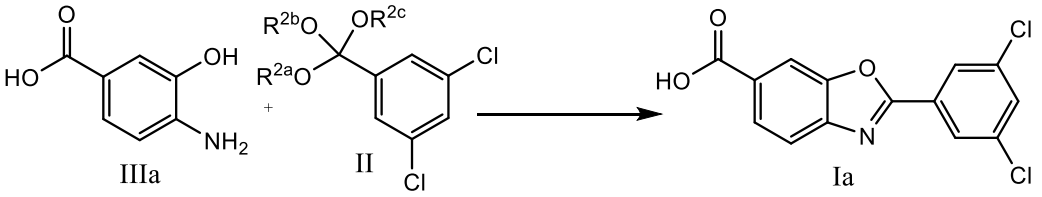
18. The process of claim 17 wherein the compound of Formula I is isolated by filtration.

19. A process for preparing 6-Carboxy-2-(3,5-dichlorophenyl)benzoxazole of Formula Ia



Ia

the process comprising reacting 4-Amino-3-hydroxybenzoic acid of Formula IIIa with a 3,5-Dichlorophenyl ortho ester compound of Formula II in the presence of an acid catalyst or a base catalyst to provide 6-Carboxy-2-(3,5-dichlorophenyl)benzoxazole of Formula Ia



wherein R^{2a}, R^{2b} and R^{2c} are each independently C_1-C_6alkyl or any two of R^{2a}, R^{2b} and R^{2c} taken together are a C_1-C_6alkanediyl or R^{2a}, R^{2b} and R^{2c} taken together are a C_3-C_{10}alkanetriyl.

20. The process of claim 19 wherein the reaction of the compound of Formula IIIa with the compound of Formula II to provide the compound of Formula Ia is carried out in a solvent.

21. The process of claim 20 wherein the solvent is selected from the group consisting of methanol, ethanol, isopropanol, n-butanol, acetone, methyl ethyl ketone,

tetrahydrofuran, 1,4-dioxane, t-butyl methyl ether, anisole, ethyl acetate, chloroform, chlorobenzene, heptane, cyclohexane, toluene, acetonitrile and 1,2-dimethoxyethane.

22. The process of claim 21 wherein the solvent is selected from the group consisting of methanol, isopropanol, acetonitrile, ethyl acetate, 1,2-dimethoxyethane, tetrahydrofuran, t-butyl methyl ether and 1,4-dioxane.

23. The process of any one of claims 19 to 22 wherein the reaction of the compound of Formula IIIa with the compound of Formula II to provide the compound of Formula Ia is carried out in the presence of an acid catalyst.

24. The process of claim 23 wherein the acid catalyst is selected from the group consisting of trifluoroacetic acid, acetic acid, hydrochloric acid and methanesulfonic acid.

25. The process of claim 24 wherein the acid catalyst is trifluoroacetic acid.

26. The process of any one of claims 19 to 22 wherein the reaction of the compound of Formula IIIa with the compound of Formula II to provide the compound of Formula Ia is carried out in the presence of a base catalyst.

27. The process of claim 26 wherein the base catalyst is triethylamine.

28. The process of any one of claims 19 to 27 wherein the reaction of the compound of Formula III with the compound of Formula II to provide the compound of Formula I is carried out at a temperature of room temperature to 100 °C.

29. The process of claim 28 wherein the temperature is room temperature to 65 °C.

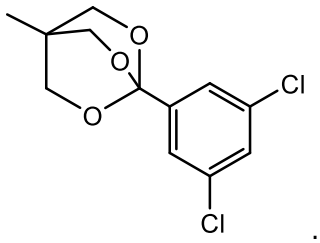
30. The process of any one of claims 19 to 29 wherein the reaction of the compound of Formula III with the compound of Formula II to provide the compound of Formula I is carried out for a period of 0.25 hours to 40 hours.

31. The process of any one of claims 19 to 30 wherein R^{2a}, R^{2b} and R^{2c} are each independently C_1-C_6alkyl.

32. The process of claim 31 wherein R^{2a}, R^{2b} and R^{2c} are each methyl.

33. The process of any one of claims 19 to 30 wherein R^{2a}, R^{2b} and R^{2c} taken together are a C_3-C_{10}alkanetriyl.

34. The process of claim 33 wherein the compound of Formula II is



.

35. The process of any one of claims 19 to 34 further comprising the step of isolating the compound of Formula Ia.

36. The process of claim 35 wherein the compound of Formula Ia is isolated by filtration.

37. The process of any one of claims 19 to 36 further comprising the step of reacting the 6-Carboxy-2-(3,5-dichlorophenyl)benzoxazole of Formula Ia with a pharmaceutically acceptable base to provide a pharmaceutically acceptable salt of 6-Carboxy-2-(3,5-dichlorophenyl)benzoxazole.

38. The process of claim 37 wherein the 6-Carboxy-2-(3,5-dichlorophenyl) benzoxazole is reacted with meglumine in an appropriate solvent to provide 6-Carboxy-2-(3,5-dichlorophenyl)benzoxazole meglumine salt.

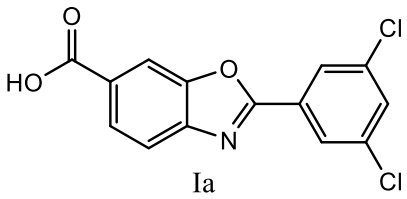
39. The process of claim 38 wherein 6-Carboxy-2-(3,5-dichlorophenyl) benzoxazole is reacted at room temperature with meglumine in a solvent selected from methyl isobutyl ketone, MTBE and EtOAc and the resulting solid is isolated and dried to provide the Form E polymorph of 6-Carboxy-2-(3,5-dichlorophenyl)benzoxazole meglumine salt.

40. The process of claim 38 wherein the 6-Carboxy-2-(3,5-dichlorophenyl) benzoxazole is reacted with meglumine in a mixture of IPA and water and the resulting solid is isolated and

dried to provide the Form M polymorph of 6-Carboxy-2-(3,5-dichlorophenyl)benzoxazole meglumine salt.

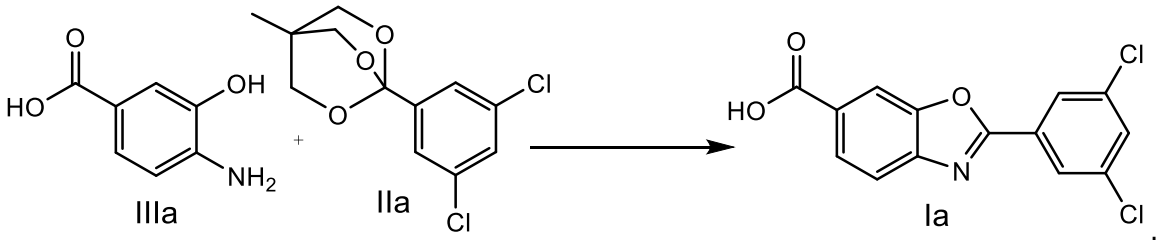
41. The process of claim 35 further comprising the step of stirring the compound of Formula Ia in a mixture of water and IPA then isolating and drying the resulting solid to provide the Form 1 polymorph of 6-Carboxy-2-(3,5-dichlorophenyl)benzoxazole.

42. A process for preparing 6-Carboxy-2-(3,5-dichlorophenyl)benzoxazole of Formula Ia



Ia

the process comprising reacting one molar equivalent of 4-Amino-3-hydroxybenzoic acid of Formula IIIa with one molar equivalent of the 3,5-Dichlorophenyl ortho ester compound of Formula IIa in a solvent to provide 6-Carboxy-2-(3,5-dichlorophenyl)benzoxazole of Formula Ia



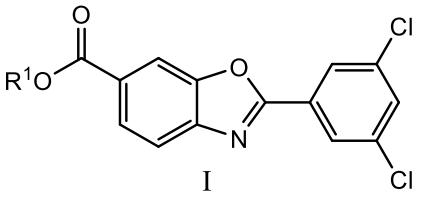
43. The process of claim 42 wherein the solvent is selected from the group consisting of methanol, ethanol, isopropanol, n-butanol, acetone, methyl ethyl ketone, tetrahydrofuran, 1,4-dioxane, t-butyl methyl ether, anisole, ethyl acetate, chloroform, chlorobenzene, heptane, cyclohexane, toluene, acetonitrile and 1,2-dimethoxyethane.

44. The process of claim 43 wherein the solvent is selected from the group consisting of methanol, isopropanol, acetonitrile, ethyl acetate, 1,2-dimethoxyethane, tetrahydrofuran, t-butyl methyl ether and 1,4-dioxane.

45. The process of claim 44 wherein the process is carried out using an acid catalyst selected from the group consisting of trifluoroacetic acid, acetic acid, hydrochloric acid and methanesulfonic acid.

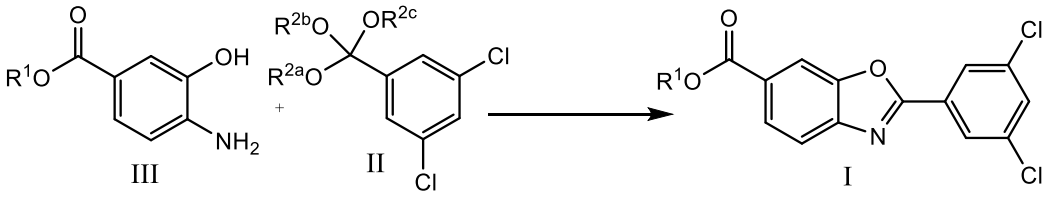
46. The process of claim 44 wherein the acid catalyst is trifluoroacetic acid and the solvent is isopropanol.

47. A process for preparing a 6-Carboxy-2-(3,5-dichlorophenyl)benzoxazole compound of Formula I



I

the process comprising reacting a 4-Amino-3-hydroxybenzoic acid compound of Formula III with a 3,5-Dichlorophenyl ortho ester compound of Formula II to provide the compound of Formula I



III II I

wherein R^1 is hydrogen or a carboxy protecting group; and R^{2a}, R^{2b} and R^{2c} are each independently C_1-C_6alkyl or any two of R^{2a}, R^{2b} and R^{2c} taken together are a C_1-C_8alkanediyl or R^{2a}, R^{2b} and R^{2c} taken together are a C_3-C_{12}alkanetriyl, wherein the C_1-C_8alkanediyl and C_3-C_{12}alkanetriyl are each optionally substituted with a phenyl which is optionally substituted with one to two groups independently selected from halo, C_1-C_3alkyl and C_1-C_3alkoxy.

48. The process of claim 47 wherein the compound of formula III is 4-Amino-3-hydroxybenzoic acid and the compound of formula II is selected from the group consisting of
1,3-Dichloro-5-(trimethoxymethyl)benzene;
1-(3,5-Dichlorophenyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane;
1-(3,5-Dichlorophenyl)-4-ethyl-2,6,7-trioxabicyclo[2.2.2]octane;
1-(3,5-Dichlorophenyl)-4-phenyl-2,6,7-trioxabicyclo[2.2.2]octane;
2-(3,5-Dichlorophenyl)-2-methoxy-1,3-dioxolane;

1-(3,5-Dichlorophenyl)-2,7,8-trioxabicyclo[3.2.1]octane;

3-(3,5-Dichlorophenyl)-2,4,10-trioxaadamantane;

1-(3,5-dichlorophenyl)-4-isopropyl-2,6,7-trioxabicyclo[2.2.2]octane; and

4-(*tert*-butyl)-1-(3,5-dichlorophenyl)-2,6,7-trioxabicyclo[2.2.2]octane.

49. The process of claim 48 wherein the reaction of the compound of Formula II with Formula III is carried out in IPA as solvent in the presence of MSA as acid catalyst.

50. A compound selected from the group consisting of

1-(3,5-Dichlorophenyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane;
1-(3,5-Dichlorophenyl)-4-ethyl-2,6,7-trioxabicyclo[2.2.2]octane;
1-(3,5-Dichlorophenyl)-4-phenyl-2,6,7-trioxabicyclo[2.2.2]octane;
2-(3,5-Dichlorophenyl)-2-methoxy-1,3-dioxolane;

1-(3,5-Dichlorophenyl)-2,7,8-trioxabicyclo[3.2.1]octane;

3-(3,5-Dichlorophenyl)-2,4,10-trioxaadamantane;

1-(3,5-dichlorophenyl)-4-isopropyl-2,6,7-trioxabicyclo[2.2.2]octane; and

4-(*tert*-butyl)-1-(3,5-dichlorophenyl)-2,6,7-trioxabicyclo[2.2.2]octane.

51. The compound of claim 50 which is 1-(3,5-Dichlorophenyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane.

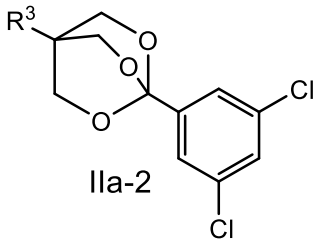
52. The compound of claim 51 which is which is a crystalline form of 1-(3,5-Dichlorophenyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane characterized by PXRD peaks at 21.2, 19.7 and 14.4 degrees 2-theta, each ±0.2 degrees 2-theta.

53. The compound of claim 52 which is characterized by PXRD peaks at 21.2, 19.7, 14.4 and 23.7 degrees 2-theta, each ±0.2 degrees 2-theta.

54. The compound of claim 53 which is characterized by PXRD peaks at 21.2, 19.7, 14.4, 23.7 and 24.2 degrees 2-theta, each ±0.2 degrees 2-theta.

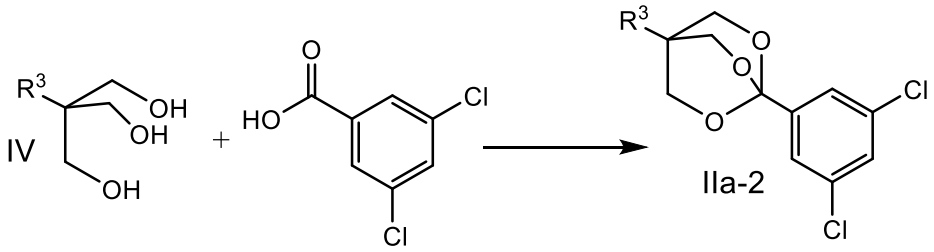
55. The compound of claim 54 which is characterized by PXRD peaks at 21.2, 19.7, 14.4, 23.7, 24.2 and 30.6 degrees 2-theta, each ±0.2 degrees 2-theta.

56. A process of preparing a compound of formula IIa-2



IIa-2

wherein R^3 is selected from the group consisting of isopropyl, tert-butyl and neo-pentyl comprising reacting a compound of formula IV with 3,5-dichlorobenzoic acid



IIa-2

in a solvent in the presence of an acid catalyst.

57. The process of claim 56 wherein R^3 is isopropyl or tert-butyl.

58. The process of claim 57 wherein the solvent is toluene and the acid catalyst is methanesulfonic acid.