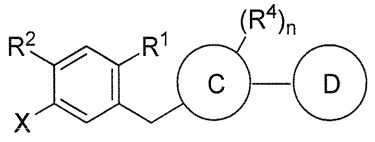
various environmental conditions, stability of the active substance during production of the pharmaceutical formulation and the stability of the active substance in the final medicament compositions. In order to provide the necessary stability, the pharmaceutically active substance used in the medicament should be as pure as possible, leading to its stability in long-term storage under various environmental conditions.

**[0004]** The compounds prepared according to the present invention have been prepared previously according to the methods described in WO2001/027128, US2004/0230045, US2005/0124555, US2006/0122126, US2007/0238866, US2007/0275907, US2008/0242596, US2008/0132563, US2008/0318874, WO2008/034859, US2009/0030006, US2009/0030198, US2009/0118201, US2009/0156516, US2010/0056618, US2010/0063141 and WO2010/147430. Other compounds prepared by the methods of the present invention that have been prepared previously by different methods can be found in WO2005/003196.

## BRIEF SUMMARY OF THE INVENTION

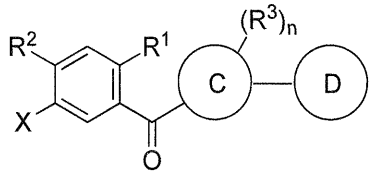
[0004a] In one aspect, there is provided a method for preparing the compound of Formula I:



(I) ,

the method comprising:

forming a reaction mixture comprising a compound of Formula II:



(II) ,

a silane reducing agent,

a catalyst selected from the group consisting of $B(C_6F_5)_3$, $BF_3$ THF, $BF_3$ $Bu_2O$, $BF_3$ MeCN, $BF_3AcOH$, $BF_3H_3PO_4$, and $BF_3$, and

a solvent, under conditions suitable to prepare the compound of Formula I,

wherein

X is bromo or iodo,

$R^1$ is selected from the group consisting of halogen and $C_1$-$C_3$ alkyl selected from the group consisting of hydrogen and $C_{1-3}$ alkyl,

each $R^3$ is selected from the group consisting of $C_1$-$C_3$ alkoxy, $C_1$-$C_3$ hydroxyalkoxy, $C_3$-$C_6$ cycloalkoxy, $C_3$-$C_6$ heterocycloalkoxy, ($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkoxy, ($C_1$-$C_3$ haloalkoxy)$C_1$-$C_3$ alkoxy, ($C_2$-$C_4$ alkenyloxy)$C_1$-$C_3$ alkoxy, ($C_2$-$C_4$ alkynyloxy)$C_1$-$C_3$ alkoxy, ($C_3$-$C_6$ cycloalkoxy)$C_1$-$C_3$ alkoxy, ($C_3$-$C_6$ heterocycloalkoxy)$C_1$-$C_3$ alkoxy, ($C_3$-$C_6$ cycloalkyl)$C_1$-$C_3$ alkoxy, ($C_3$-$C_6$ cycloalkyl)$C_2$-$C_4$ alkenyloxy and ($C_3$-$C_6$ cycloalkyl)$C_2$-$C_4$ alkynyloxy;

each $R^4$ is $-OR^{4a}$,

wherein $R^{4a}$ is selected from the group consisting of hydrogen and a silyl group;

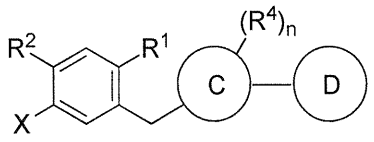
ring C is selected from the group consisting of an aryl and a heteroaryl,

ring D is absent or selected from the group consisting of an aryl and a heteroaryl,

subscript n is an integer from 1 to 4,

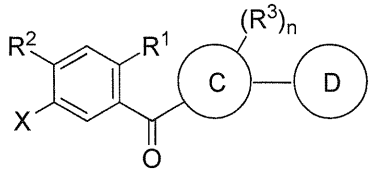
wherein the alkyl, alkoxy, cycloalkyl, alkenyloxy, alkynyloxy, cycloalkoxy, hydroxyalkoxy, and heterocycloalkoxy groups or portions thereof may optionally be partially or completely fluorinated.

**[0005]** Also disclosed is a method for preparing the compound Formula I:




(I) .

The method includes forming a reaction mixture including a compound of Formula II:

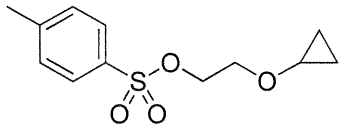



(II) .

The reaction mixture also includes a silane reducing agent, a catalyst, and a solvent. The reaction mixture is under conditions suitable to prepare the compound of Formula I.

**[0006]** Radical X can be bromo or iodo. Radical $R^1$ can be hydrogen, halogen, $C_1$-$C_3$ alkyl, $C_2$-$C_4$ alkene, $C_2$-$C_4$ alkyne, $C_3$-$C_6$ cycloalkyl, or –CN. Each $R^2$ and $R^3$ can independently be hydrogen, halo, hydroxy, $C_1$-$C_3$ alkyl, $C_2$-$C_4$ alkenyl, $C_1$-$C_3$ alkoxy, $C_1$-$C_3$ alkyl-hydroxy, $C_3$-$C_6$ cycloalkyl, ($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkyl, ($C_1$-$C_3$ haloalkoxy)$C_1$-$C_3$ alkyl,

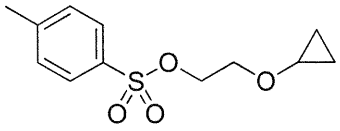
**[0009]** In some examples, the present disclosure provides a crystalline form of the compound having the structure:



.

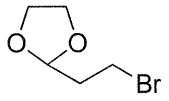
**[0010]** In some examples, the present disclosure provides a crystalline form of a compound of the present invention which is isotopically labeled.

**[0011]** In some examples, the present disclosure provides a method of preparing a compound of Formula III:



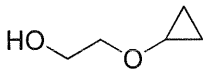
(III) ,

wherein the method includes a step (a) of forming a first reaction mixture including Mg and a compound having the structure:



,

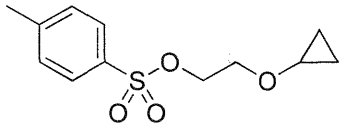
in tetrahydrofuran solvent, under conditions suitable to form an intermediate compound having the structure:



.

The method also includes a step (b) of contacting the first reaction mixture with water and 2-methyl-tetrahydrofuran such that the intermediate of step (a) is substantially dissolved in the 2-methyl-tetrahydrofuran. The method also includes a step (c) of forming a second reaction mixture with 4-methylbenzene-1-sulfonyl chloride (Tosyl-Cl) and the 2-methyl-tetrahydrofuran of step (b) containing the intermediate of step (a), under conditions suitable to form the compound of Formula III.

**[0012]** In some examples, the present disclosure provides a method for preparing a crystalline form of a compound having the structure:



,

wherein the method includes a step (a) of mixing 2-cyclopropoxyethyl-4-methylbenzenesulfonate and a first solvent that is a polar protic solvent to form a solution, and a step (b) of adding a second solvent to the solution to provide a mixture, under conditions suitable to form the crystalline form of the compound.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0013]** Figure 1 provides a scheme for the preparation of 2-(4-(2-cyclopropoxyethoxy)benzyl)-1-chloro-4-iodobenzene.

**[0014]** Figure 2 provides the X-ray powder diffraction (XRPD) spectra of crystalline 2-cyclopropoxyethyl 4-methylbenzenesulfonate prepared from ethanol/water.

**[0015]** Figure 3 shows an expanded version of the XRPD spectra in Figure 2

**[0016]** Figure 4 provides a Table of XRPD data for the XRPD spectra in Figure 2 and Figure 3.

**[0017]** Figure 5 provides the X-ray powder diffraction (XRPD) spectra of crystalline 2-cyclopropoxyethyl 4-methylbenzenesulfonate prepared from methanol/heptane.

**[0018]** Figure 6 provides a Table of XRPD data for the XRPD spectra in Figure 5.

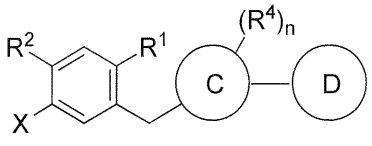
**[0019]** Figure 7 provides the Raman spectra of crystalline 2-cyclopropoxyethyl 4-methylbenzenesulfonate prepared from methanol/heptane.

**[0020]** Figure 8 provides a Raman peak list for the Raman spectra in Figure 7.

**[0021]** Figure 9 provides a Differential Scanning Calorimetry (DSC) chart of crystalline 2-cyclopropoxyethyl 4-methylbenzenesulfonate prepared from methanol/heptane. The peak at -0.09°C is due to melting ice used to cool the sample.

WHAT IS CLAIMED IS:

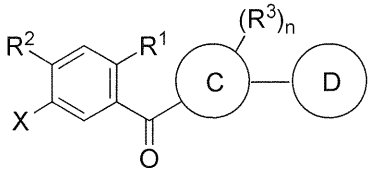
1. A method for preparing the compound of Formula I:




(I) ,

the method comprising:

forming a reaction mixture comprising a compound of Formula II:




(II) ,

a silane reducing agent,

a catalyst selected from the group consisting of $B(C_6F_5)_3$, $BF_3$ THF, $BF_3$ $Bu_2O$, $BF_3$ MeCN, $BF_3AcOH$, $BF_3H_3PO_4$, and $BF_3$, and

a solvent, under conditions suitable to prepare the compound of Formula I,

wherein

X is bromo or iodo,

$R^1$ is selected from the group consisting of halogen and $C_1$-$C_3$ alkyl selected from the group consisting of hydrogen and $C_{1-3}$ alkyl,

each $R^3$ is selected from the group consisting of $C_1$-$C_3$ alkoxy, $C_1$-$C_3$ hydroxyalkoxy, $C_3$-$C_6$ cycloalkoxy, $C_3$-$C_6$ heterocycloalkoxy, ($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkoxy, ($C_1$-$C_3$ haloalkoxy)$C_1$-$C_3$ alkoxy, ($C_2$-$C_4$ alkenyloxy)$C_1$-$C_3$ alkoxy, ($C_2$-$C_4$ alkynyloxy)$C_1$-$C_3$ alkoxy, ($C_3$-$C_6$ cycloalkoxy)$C_1$-$C_3$ alkoxy, ($C_3$-$C_6$ heterocycloalkoxy)$C_1$-$C_3$ alkoxy, ($C_3$-$C_6$ cycloalkyl)$C_1$-$C_3$ alkoxy, ($C_3$-$C_6$ cycloalkyl)$C_2$-$C_4$ alkenyloxy and ($C_3$-$C_6$ cycloalkyl)$C_2$-$C_4$ alkynyloxy;

each $R^4$ is $-OR^{4a}$,

wherein $R^{4a}$ is selected from the group consisting of hydrogen and a silyl group;

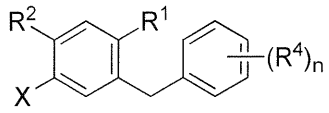
ring C is selected from the group consisting of an aryl and a heteroaryl,

ring D is absent or selected from the group consisting of an aryl and a heteroaryl,

subscript n is an integer from 1 to 4,

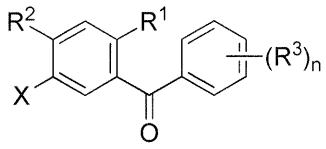
wherein the alkyl, alkoxy, cycloalkyl, alkenyloxy, alkynyloxy, cycloalkoxy, hydroxyalkoxy, and heterocycloalkoxy groups or portions thereof may optionally be partially or completely fluorinated.

2. The method of claim 1, wherein the compound of Formula I has the structure of Formula Ia:



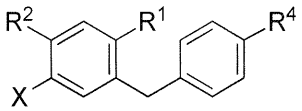
(Ia)

and the compound of Formula II has the structure of Formula IIa:

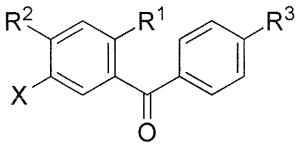


(IIa) .

3. The method of claims 1 or 2, wherein the compound of Formula Ia has the structure:



and the compound of Formula IIa has the structure:



.

4. The method of any one of claims 1 to 3, wherein $R^1$ is halogen.

5. The method of any one of claims 1 to 4, wherein $R^3$ is selected from the group consisting of $C_1$-$C_3$ alkoxy, and $C_3$-$C_6$ cycloalkoxy.

6. The method of any one of claims 1 to 5, wherein

$R^1$ is chloro;

$R^2$ is H;

$R^3$ is $C_1$-$C_3$ alkoxy; and

$R^4$ is $-OR^{4a}$.

7. The method of any one of claims 1 to 6, wherein $R^3$ is methoxy.

8. The method of any one of claims 1 to 7, wherein the silane reducing agent is selected from the group consisting of tetramethyldisiloxane (TMDS), pentamethyldisiloxane (PMDS), polymethylhydrosiloxane (PMHS), and $Et_3SiH$.

9. The method of any one of claims 1 to 8, wherein the silane reducing agent is tetramethyldisiloxane (TMDS).

10. The method of any one of claims 1 to 9, wherein the silane reducing agent is present in an amount of from about 1.0 to about 5.0 eq. (mol/mol) to the compound of Formula II.

11. The method of any one of claims 1 to 10, wherein the silane reducing agent is present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula II.

12. The method of any one of claims 1 to 11, wherein the catalyst is $B(C_6F_5)_3$.

13. The method of any one of claims 1 to 12, wherein the catalyst is present in an amount of less than about 0.1 eq. (mol/mol) to the compound of Formula II.

14. The method of any one of claims 1 to 13, wherein the catalyst is present in an amount of less than about 0.01 eq. (mol/mol) to the compound of Formula II.

15. The method of any one of claims 1 to 14, wherein the solvent comprises at least one member selected from the group consisting of pentanes, hexanes, heptanes, cyclopentanes, cyclohexanes, benzene, toluene, xylene, trifluoromethylbenzene and chlorobenzene, or combinations thereof.

16. The method of any one of claims 1 to 15, wherein the solvent comprises toluene.

17. The method of any one of claims 1 to 16, wherein the reaction mixture is at a temperature of from about -25 °C to about 50 °C.

18. The method of any one of claims 1 to 17, wherein the reaction mixture is at a temperature of from about -10 °C to about 25 °C.

19. The method of any one of claims 1 to 18, wherein the reaction mixture is at a temperature of from about 0 °C to about 20 °C.

20. The method of any one of claims 1 to 19, wherein the compound of Formula I is prepared in at least 75% yield.

21. The method of any one of claims 1 to 20, wherein the compound of Formula I is prepared in at least 90% yield.

22. The method of any one of claims 1 to 21, wherein the compound of Formula I is prepared in at least 95% yield.

23. The method of any one of claims 1 to 22, wherein the compound of Formula I is prepared in at least 95% purity.

24. The method of any one of claims 1 to 23, wherein the compound of Formula I is prepared in at least 98% purity.

25. The method of any one of claims 1 to 24, wherein $R^{4a}$ is the silyl group, and wherein the method further comprises:

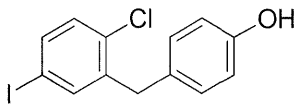
adding an acid to the reaction mixture, under conditions sufficient to prepare the compound of Formula I wherein $R^4$ is –OH.

26. The method of claim 25, wherein the acid is selected from the group consisting of hydrochloric acid, sulfuric acid, phosphoric acid, and nitric acid.

27. The method of claim 26, wherein the acid is hydrochloric acid.

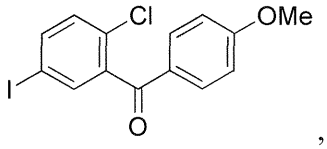
28. The method of any one of claims 25 to 27, further comprising heating the reaction mixture, thereby preparing the compound of Formula I wherein $R^4$ is –OH.

29. The method of claim 1, wherein the compound of Formula I has the structure:




the method comprising:

forming the reaction mixture comprising the compound of Formula II having the structure:




,

tetramethyldisiloxane (TMDS), a catalytic amount of $B(C_6F_5)_3$, and toluene; and adding hydrochloric acid to the reaction mixture, under conditions suitable to prepare the compound of Formula I.