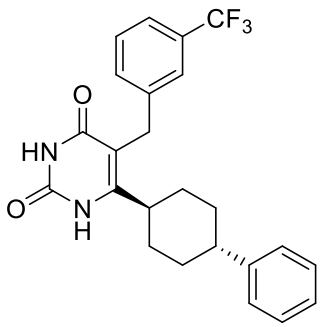
WHAT IS CLAIMED IS:

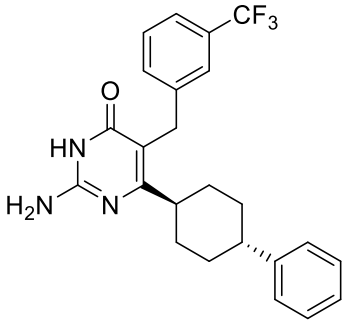
1. A method of preparing a compound of Formula I:



(I)

the method comprising:

(a) forming a first reaction mixture comprising an oxidizing agent and a compound of Formula II, or a hydrate thereof:



(II)

under conditions suitable to prepare the compound of Formula I.

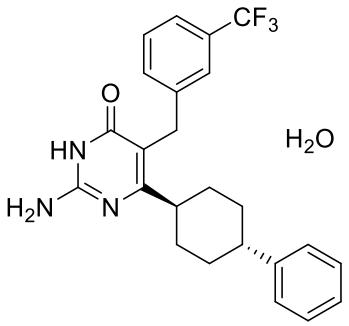
2. The method of claim 1, wherein the oxidizing agent comprises at least one of sodium nitrite ($NaNO_2$), potassium nitrite (KNO_2), tetrabutylammonium nitrite [$(n\text{-}C_4H_9)_4N^+ NO_2^-$], nitrosylsulfuric acid, [$HOSO_2\text{-}O\text{-}N{=}O$], methyl nitrite ($CH_3O\text{-}N{=}O$), ethyl nitrite ($CH_3CH_2O\text{-}N{=}O$), n-propylnitrite ($CH_3CH_2CH_2O\text{-}N{=}O$), isopropyl nitrite [$(CH_3)_2CHO\text{-}N{=}O$], n-butyl nitrite [$CH_3(CH_2)_3O\text{-}N{=}O$], isobutyl nitrite [$(CH_3)_2CH(CH_2)_2O\text{-}N{=}O$], isopentyl nitrite [$(CH_3)_2CH(CH_2)_2O\text{-}N{=}O$], or phenyl nitrite ($C_6H_5O\text{-}N{=}O$).

3. The method of claim 1 or 2, wherein the first reaction mixture further comprises a first acid comprising hydrochloric acid, sulfuric acid, formic acid, acetic acid, propanoic acid, butyric acid, hexanoic acid, octanoic acid, trifluoroacetic acid, tetrafluoroboric acid (HBF_4), or mixtures thereof.

4. The method of any one of claims 1 to 3, wherein the first reaction mixture further comprises a first solvent comprising N,N-dimethylformamide (DMF), N,N-

dimethylacetamide (DMAc), isopropanol, 2-methyltetrahydrofuran (2-MeTHF), tetrahydrofuran, water, or mixtures thereof.

5. The method of any one of claims 1 to 4, wherein the compound of Formula II is the monohydrate form:



.

6. The method of any one of claims 1 to 5, wherein the first reaction mixture comprises acetic acid, sodium nitrite and the monohydrate form of the compound of Formula II.

7. The method of any one of claims 1 to 6, further comprising:

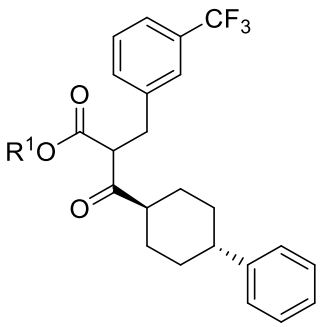
(a1) dissolving the compound of Formula I in a solvent mixture comprising methanol in an amount of about 15% (v/v) and dichloromethane in an amount of about 85% (v/v);

(a2) heating the solvent mixture to remove dichloromethane and adding methanol to the solvent mixture to replace the removed dichloromethane, thereby preparing a methanol solvent mixture; and

(a3) cooling the methanol solvent mixture, thereby forming crystalline Formula I.

8. The method of any one of claims 1 to 7, wherein the compound of Formula II, or the hydrate thereof, is prepared by the method comprising:

(b) forming a second reaction mixture comprising guanidine and salts thereof, and a compound of Formula III:

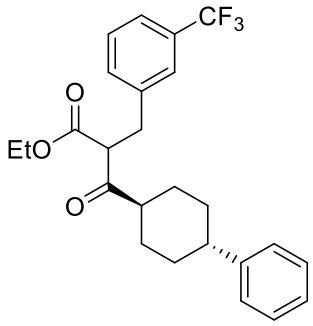


(III)

under conditions suitable to prepare the compound of Formula II, or the hydrate thereof,

wherein R^1 is C_{1-6} alkyl.

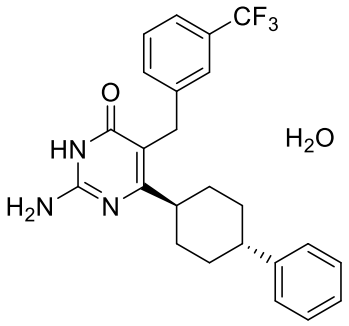
9. The method of claim 8, wherein the compound of Formula III is the compound of Formula IIIa:



(IIIa) .

10. The method of claim 8 or 9, wherein the second reaction mixture further comprises a second solvent comprising ethanol, isopropanol, methyl acetate, ethyl acetate, isopropyl acetate, N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAc), 2-methyltetrahydrofuran (2-MeTHF), tetrahydrofuran (THF), water, or mixtures thereof.

11. The method of any one of claims 8 to 10, wherein the second reaction mixture comprises ethyl acetate, guanidine free base, and the compound of Formula IIIa, under conditions suitable to prepare the monohydrate form of the compound of Formula II:



.

12. The method of any one of claims 8 to 11, wherein prior to step (b), the method further comprises:

(b1) forming a third reaction mixture comprising guanidine salt and a base to prepare the guanidine free base.

13. The method of claim 12, wherein the third reaction mixture further comprises a third solvent comprising methanol, ethanol, n-propanol, iso-propanol, water, or mixtures thereof.

14. The method of claim 13, wherein the third reaction mixture further comprises a water scavenger.

15. The method of any one of claims 12 to 14, wherein prior to step (b), the method further comprises:

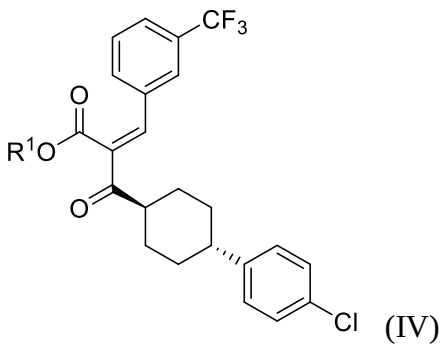
(b1) forming the third reaction comprising ethanol, guanidine hydrochloride salt and sodium ethoxide to prepare the guanidine free base.

16. The method of any one of claims 12 to 15, wherein following step (b), the method further comprises:

(b2) adding water to the second reaction thereby crystallizing the compound of Formula II, or the hydrate thereof.

17. The method of any one of claims 8 to 16, wherein the compound of Formula III is prepared by:

(c) forming a fourth reaction mixture comprising a reducing agent and a compound of Formula IV:



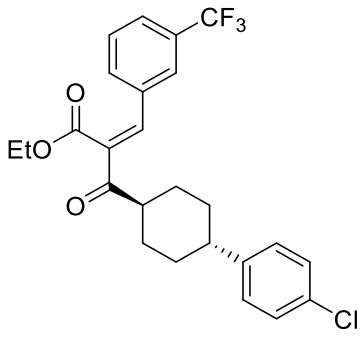
(IV)

under conditions suitable to prepare the compound of Formula III.

18. The method of claim 17, wherein the reducing agent is the hydrogenation catalyst comprising palladium on carbon (Pd-C), palladium on silicon dioxide, palladium on calcium carbonate, platinum on carbon, palladium hydroxide, platinum hydroxide, palladium(II) chloride, Raney Nickel, rhodium on alumina, rhodium(III) chloride trihydrate/Aliquat 336 (N-methyl N-trioctylammonium chloride), $Ru(BINAP)]_2*NEt_3$, or nickel boride (Ni_2B).

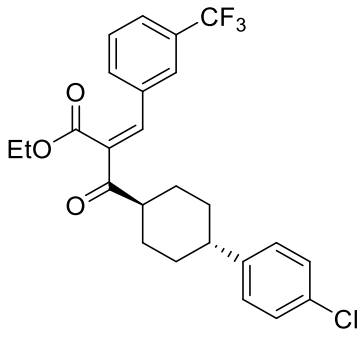
19. The method of claim 17 or 18, wherein the fourth reaction mixture comprises a fourth solvent comprising methanol, ethanol, n-propanol, iso-propanol, n-butanol, ethyl acetate, isopropyl acetate, n-butyl acetate, formic acid, acetic acid, trifluoroacetic acid, water, or mixtures thereof.

20. The method of any one of claims 17 to 19, wherein the compound of Formula IV is the compound of Formula IVa:



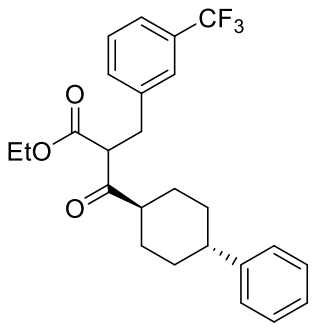
(IVa) .

21. The method of any one of claims 17 to 20, wherein the fourth reaction mixture comprises ethanol, 5% Pd-C, hydrogen, sodium acetate, and the compound of Formula IV is the compound of Formula IVa:



(IVa) ,

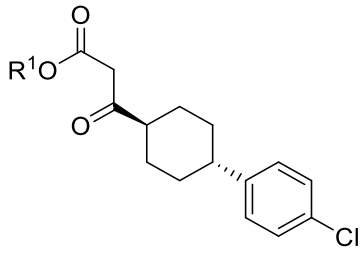
thereby preparing the compound of Formula IIIa:



(IIIa) .

22. The method of any one of claims 17 to 21, wherein the compound of Formula IV is prepared by:

(d) forming a fifth reaction mixture comprising a first amine base, a second acid, 3-trifluoromethylbenzaldehyde, and a compound of Formula V:

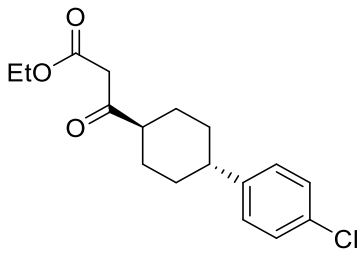


(V)

under conditions suitable to prepare the compound of Formula IV.

23. The method of claim 22, wherein the first amine base comprises triethylamine, N,N-diisopropyl ethylamine (DIPEA), N,N-dimethyl isopropylamine (DIMPA), piperidine, 1-ethylpiperidine, N-methylmorpholine, N-methylpyrrolidine, N,N-dimethylamine, piperazine, N-methylpiperazine, tris(Hydroxymethyl)methylamine [$(HOCH_2)_3CNH_2$], benzylamine, pyridine, N,N-dimethylaniline, N,N-diethylaniline, 2,6-lutidine, 2,4,6-collidine, 4-dimethyl aminopyridine (DMAP), quinuclidine, 4-pyrrolidinopyridine, 1,4-diazabicyclo[2.2.2]octane (DABCO), or mixtures thereof.

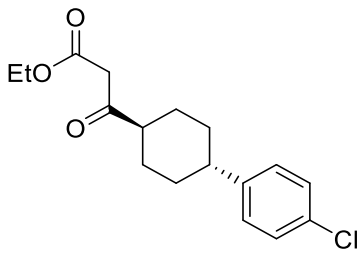
24. The method of claim 22 or 23, wherein the compound of Formula V is the compound of Formula Va:



(Va) .

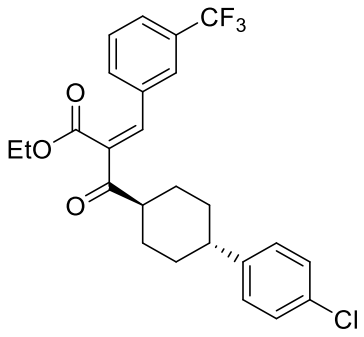
25. The method of any one of claims 22 to 24, wherein the fifth reaction mixture further comprises a fifth solvent comprising methanol, ethanol, n-propanol, iso-propanol, acetonitrile, dichloromethane, diethyl ether, 2-methyltetrahydrofuran (2-MeTHF), cyclopropylmethyl ether (CPME), tetrahydrofuran, 2,2,2-trifluoroethanol, toluene, xylene, mesitylene, or mixtures thereof.

26. The method of any one of claims 22 to 25, wherein the fifth reaction mixture comprises ethanol, piperidine, acetic acid, 3-trifluoromethylbenzaldehyde, and the compound of Formula V is the compound of Formula Va:



(Va) ,

thereby preparing the compound of Formula IVa:



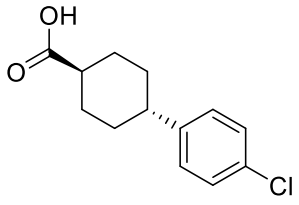
(IVa) .

27. The method of any one of claims 22 to 26, further comprising:

(d1) adding to the fifth reaction mixture a crystalline seed of the compound of Formula IV to prepare the crystalline form of the compound of Formula IV.

28. The method of any one of claims 22 to 27, wherein the compound of Formula V is prepared by:

(e1) forming a seventh reaction mixture comprising isopropylidene malonate, a carboxyl coupling agent, a second amine base, and a compound of Formula VI:



(VI)

under conditions suitable to prepare an intermediate mixture; and

(e2) heating a sixth reaction mixture comprising the intermediate mixture, thereby preparing the compound of Formula V.

29. The method of claim 28, wherein the carboxyl activating agent is dicyclohexylcarbodiimide (DCC), N,N’-diisopropylcarbodiimide (DIC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl (EDAC), bis[[4-(2,2-dimethyl-1,3-dioxolyl)]methyl]carbodiimide (BDDC), *N*-cyclohexyl-*N′*-(2-morpholinoethyl)carbodiimide methyl-*p*-toluenesulfonate, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide methiodide, thionyl chloride, oxalyl chloride, 2-ethoxy-1-ethoxycarbonyl-1,2-

dihydroquinoline (EEDQ), carbonyl diimidazole, bis(1,2,4-triazolyl)methanone, n-propanephosphonic acid anhydride, ethylmethylphosphonic anhydride (EMPA), cyanuric chloride, 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorphonium chloride (DMTMM), guanidinium salt, uronium salt, hexafluorophosphate benzotriazole tetramethyl uronium (HBTU), hexafluorophosphate azabenzotriazole tetramethyl uronium (HATU), 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate (TBTU), O-(2-Oxo-1(2H)pyridyl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate (TPTU), or N-[[[(1-Cyano-2-ethoxy-2-oxoethylidene)amino]oxy](dimethylamino)methylene]-N-methyl-methanaminium tetrafluoroborate (TOTU).

30. The method of claim 28 or 29, wherein the second amine base comprises triethylamine, N,N-diisopropyl ethylamine (DIPEA), N,N-dimethyl isopropylamine (DIMPA), 1-ethylpiperidine, N-methylmorpholine, N-methylpyrrolidine, pyridine, N,N-dimethylaniline, N,N-diethylaniline, 2,6-lutidine, 2,4,6-collidine, 4-dimethyl aminopyridine (DMAP), quinuclidine, 4-pyrrolidinopyridine, 1,4-diazabicyclo[2.2.2]octane (DABCO), or mixtures thereof.

31. The method of any one of claims 28 to 30, wherein the seventh reaction mixture further comprises a seventh solvent comprising acetonitrile, tetrahydrofuran, 2-methyltetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide, dichloromethane, chloroform, toluene, or mixtures thereof.

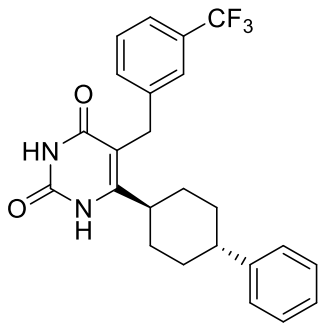
32. The method of any one of claims 28 to 31, wherein the seventh reaction mixture comprises dichloromethane, isopropylidene malonate, EDAC, dimethylaminopyridine (DMAP), and the compound of Formula VI.

33. The method of any one of claims 28 to 32, wherein the sixth reaction mixture further comprises a sixth solvent comprising methanol, ethanol, n-propanol, iso-propanol, n-butanol, t-butanol, pentanol, hexanol, or mixture thereof.

34. The method of any one of claims 28 to 33, further comprising the step of

(e3) adding heptane to the sixth reaction mixture to crystallize the compound of Formula V.

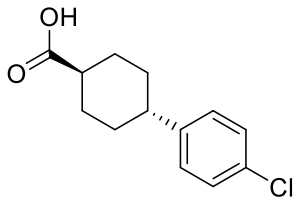
35. A method of preparing a compound of Formula I:



(I) ,

the method comprising:

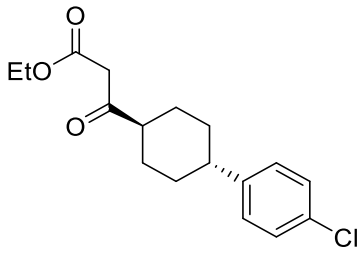
(e1) forming a seventh reaction mixture comprising dichloromethane, isopropylidene malonate, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl (EDAC), dimethylaminopyridine (DMAP), and a compound of Formula VI:



(VI)

under conditions suitable to prepare an intermediate mixture;

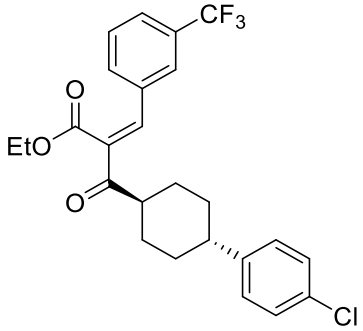
(e2) heating a sixth reaction mixture comprising the intermediate mixture and ethanol, thereby preparing a compound of Formula Va:



(Va) ;

(e3) adding heptane to the sixth reaction mixture to crystallize the compound of Formula Va;

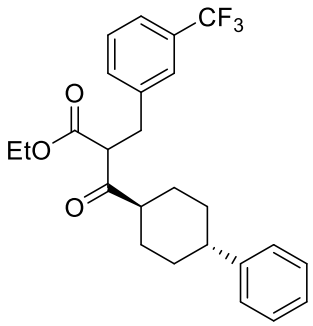
(d) forming a fifth reaction mixture comprising ethanol, piperidine, acetic acid, 3-trifluoromethylbenzaldehyde, and the compound of Formula Va, under conditions suitable to prepare a compound of Formula IVa:



(IVa) ;

(d1) adding to the fifth reaction mixture a crystalline seed of the compound of Formula IVa to prepare a crystalline form of the compound of Formula IVa;

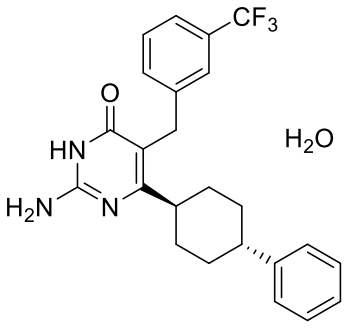
(c) forming a fourth reaction mixture comprising ethanol, 5% Pd-C, hydrogen, sodium acetate, and the compound of Formula IVa, under conditions suitable to prepare a compound of Formula IIIa:



(IIIa) ;

(b1) forming a third reaction mixture comprising ethanol, guanidine hydrochloride salt and sodium ethoxide to prepare a guanidine free base;

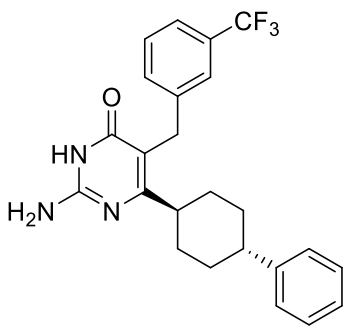
(b) forming a second reaction mixture comprising ethyl acetate, the guanidine free base, and the compound of Formula IIIa, under conditions suitable to prepare a monohydrate form of a compound of Formula II:



; and

(a) forming a first reaction mixture comprising acetic acid, sodium nitrite and the monohydrate form of the compound of Formula II, under conditions suitable to prepare the compound of Formula I.

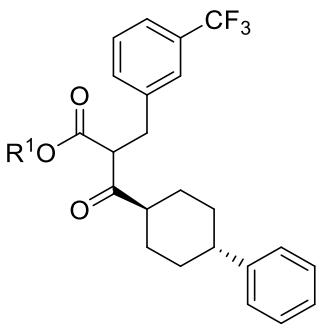
36. A method of preparing a compound of Formula II, or a hydrate thereof:



(II) ,

the method comprising:

(b) forming a second reaction mixture comprising guanidine and salts thereof, and a compound of Formula III:

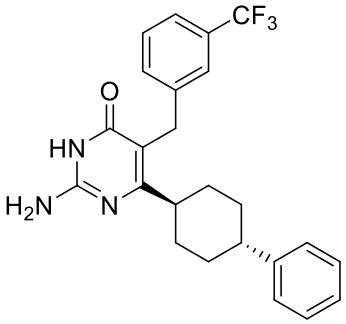


(III)

under conditions suitable to prepare the compound of Formula II, or the hydrate thereof,

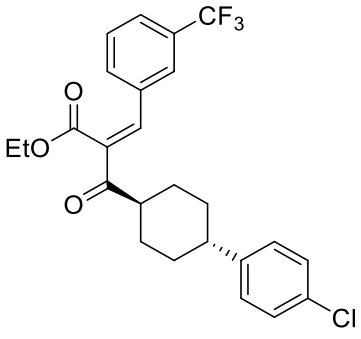
wherein R^1 is C_{1-6} alkyl.

37. A compound of Formula II, or a hydrate thereof:



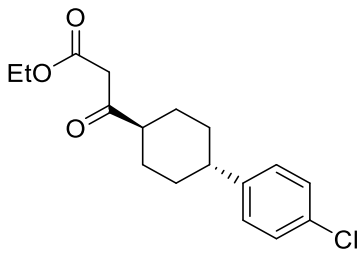
(II) .

38. A compound of Formula IVa:



(IVa) .

39. A compound of Formula Va:



(Va) .