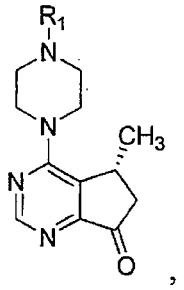
Claims

We claim:

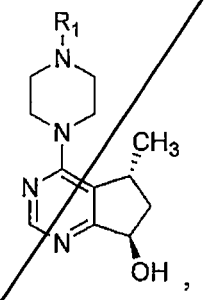
1. A process comprising contacting a compound of formula II or a salt thereof:



II

wherein:

R^1 is hydrogen or an amino protecting group; with a ketoreductase enzyme to form a compound of formula III:



III

or a salt thereof.

2. The process of claim 1, wherein said ketoreductase is selected from KRED-101, KRED-112, KRED-113, KRED-114, KRED-115, KRED- 121, KRED-123, KRED-124, KRED-130, KRED-132, KRED-133, KRED-135, KRED-142, KRED-145, KRED-153, Codexis- 134, Codexis-150, Codexis-168, Codexis-112, Codexis- 102, Codexis-151, Codexis-123, Codexis-103, Codexis-119, Codexis-128, Codexis-136, Codexis-174, Codexis-105, Codexis-129, Codexis-137, Codexis-161, Codexis-176, Codexis-154, Codexis-106, Codexis-131, Codexis-155, Codexis-148, Codexis-165, Codexis-129, Codexis-108, Codexis-116, Codexis-125, Codexis-149, Codexis-111, DAICEL-E073, DAICEL-E087, BCC 111, C-LEcta-ADH-44s, DAICEL-E005, DAICEL-E077, C-LEcta-ADH-24s, BCC 103; C-LEcta-ADH-14s, C-LEcta-ADH-16s, DAICEL-E007, DAICEL-E008, DAICEL-E080, DAICEL-E082, DAICEL-E052, BCC 101, C-LEcta-ADH-48s, BCC 109, EVO-1.1.211, DAICEL-E072, ADH-1, ADH-2, ADH-3, ADH-A, ADH-B, ADH-III and C-LEcta-ADH-50s.

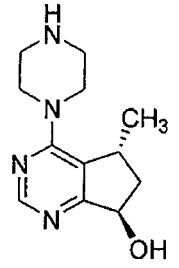
3. The process of claims 1-2, wherein said ketoreductase is KRED-101.

4. The process of claims 1-3, wherein said contacting step further comprises contacting a compound of formula II or a salt thereof with cofactor.

5. The process of claim 4, wherein said cofactor comprises one of NADP, NADH, NADPH or GDH.

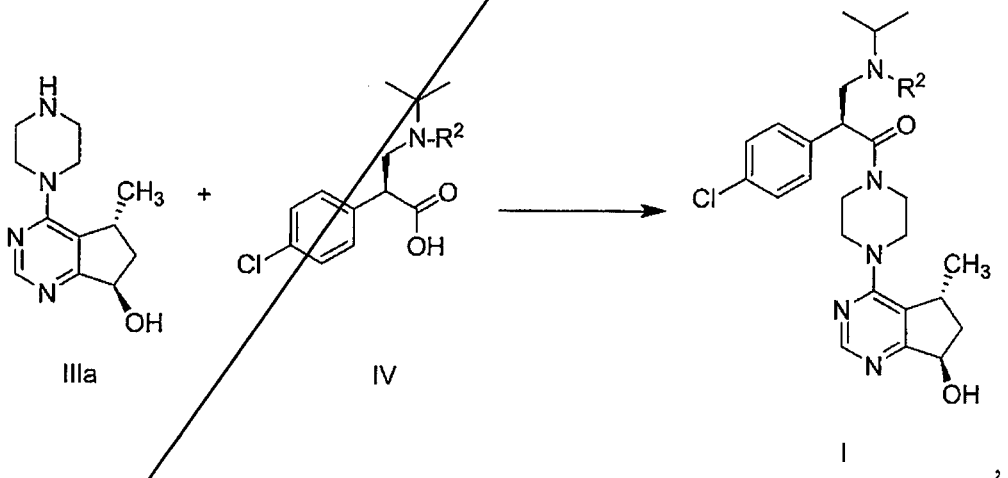
6. The process of claims 4-5, wherein said cofactor comprises NADP and GDH.

7. The process of claims 1-6, further comprising reacting a compound of formula III or salt thereof wherein R^1 is a protecting group with acid to form a compound of formula IIIa:



IIIa or salt thereof.

8. The process of claim 7, further comprising reacting a compound of formula IIIa or salt thereof with a compound of formula IV or salt thereof under conditions that form a compound of formula I or salt thereof,



IIIa IV I

wherein R^2 in formulae IV and I is independently hydrogen or amino protecting group, and said conditions comprise propanephosphonic anhydride.

9. The process of claim 8, further comprising reacting a compound of formula I or salt thereof, wherein R^2 is amino protecting group, with acid to form a dihydrochloride salt of a compound of formula I, wherein R^2 is hydrogen.

10. The process of claim 9, further comprising contacting the dihydrochloride salt of compound of formula I with base to form a monohydrochloride salt of a compound of formula I, wherein R^2 is hydrogen.

11. The process of claim 10, wherein said base is a polymeric resin comprising a functionalized styrene divinylbenzene copolymer.

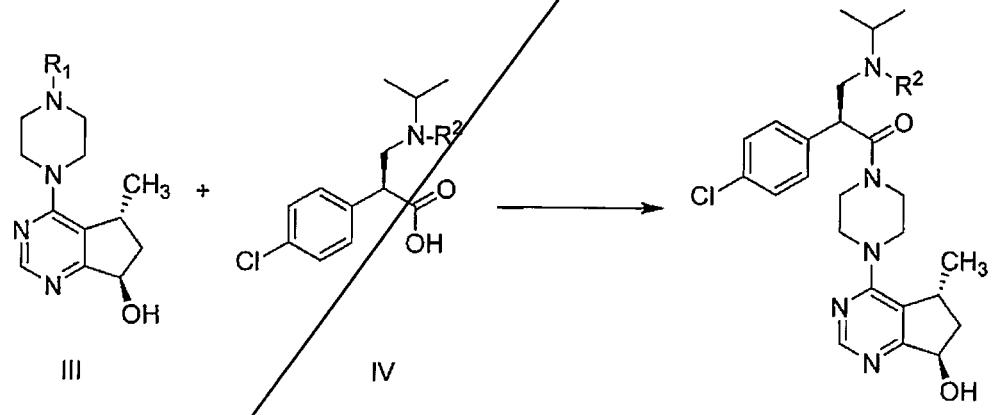
12. (*S*)-2-(4-chlorophenyl)-1-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one benzene sulfonic acid salt.

13. The salt of claim 12, wherein the salt is crystalline.

14. (*S*)-2-(4-chlorophenyl)-1-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one *p*-toluene sulfonic acid salt.

15. The salt of claim 14, wherein the *p*-toluene sulfonic acid salt is crystalline.

16. The process of claims 1-6, further comprising reacting a compound of formula III or salt thereof, wherein R_1 is hydrogen, with a compound of formula IV or salt thereof under conditions that form a compound of formula I or salt thereof,



wherein R^2 in formula IV and I is independently hydrogen or amino protecting group, and said conditions comprise propanephosphonic anhydride.

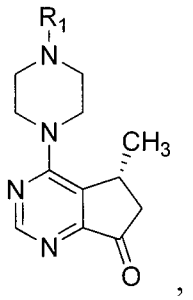
17. The process of claim 16, further comprising reacting a compound of formula I or salt thereof, wherein R^2 is amino protecting group, with acid to form a dihydrochloride salt of a compound of formula I, wherein R^2 is hydrogen.

18. The process of claim 17, further comprising contacting the dihydrochloride salt of compound of formula I with base to form a monohydrochloride salt of a compound of formula I, wherein R^2 is hydrogen.

19. The process of claim 18, wherein said base is a polymeric resin comprising a functionalized styrene divinylbenzene

CLAIMS

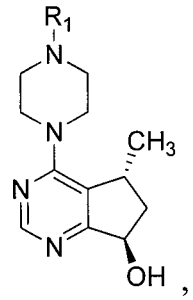
1. A process comprising contacting a compound of formula II or a salt thereof:



II

wherein:

R^1 is hydrogen or an amino protecting group; with a ketoreductase enzyme or an alcohol dehydrogenase enzyme to form a compound of formula III:



III

or a salt thereof.

2. The process of claim 1, wherein said ketoreductase or alcohol dehydrogenase enzyme is selected from KRED-101, KRED-112, KRED-113, KRED-114, KRED-115, KRED- 121, KRED-123, KRED-124, KRED-130, KRED-132, KRED-133, KRED-135, KRED-142, KRED-145, KRED-153, Codexis- 134, Codexis-150, Codexis-168, Codexis-112, Codexis- 102, Codexis-151, Codexis-123, Codexis-103, Codexis-119, Codexis-128, Codexis-136, Codexis-174, Codexis-105, Codexis-129, Codexis-137, Codexis-161, Codexis-176, Codexis-154, Codexis-106, Codexis-131, Codexis-155, Codexis-148, Codexis-165, Codexis-129, Codexis-108, Codexis-116, Codexis-125, Codexis-149, Codexis-111, DAICEL-E073, DAICEL-E087, BCC 111, C-LEcta-ADH-44s, DAICEL-E005, DAICEL-E077, C-LEcta-ADH-24s, BCC 103, C-LEcta-ADH-14s, C-LEcta-ADH-16s, DAICEL-E007, DAICEL-E008, DAICEL-E080, DAICEL-E082, DAICEL-E052, BCC 101, C-LEcta-ADH-48s, BCC 109, EVO-1.1.211, DAICEL-E072, ADH-1, ADH-2, ADH-3, ADH-A, ADH-B, ADH-III and C-LEcta-ADH-50s.

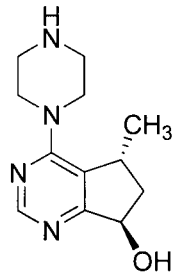
3. The process of claims 1-2, wherein said ketoreductase is KRED-101.

4. The process of claims 1-3, wherein said contacting step further comprises contacting a compound of formula II or a salt thereof with a cofactor.

5. The process of claim 4, wherein said cofactor comprises one of NADP, NADH, NADPH or GDH.

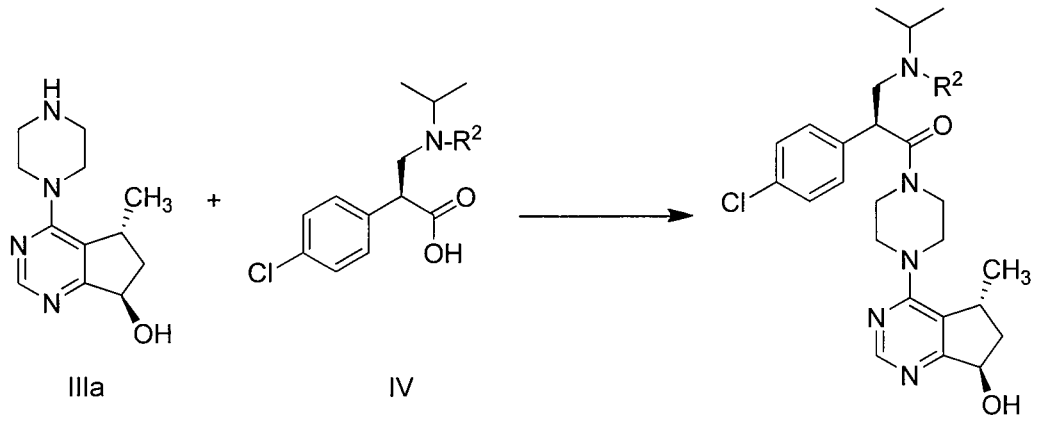
6. The process of claims 4-5, wherein said cofactor comprises NADP and GDH.

7. The process of claims 1-6, further comprising reacting a compound of formula III or salt thereof wherein R^1 is an amino protecting group with acid to form a compound of formula IIIa:



IIIa or salt thereof.

8. The process of claim 7, further comprising reacting a compound of formula IIIa or salt thereof with a compound of formula IV or salt thereof under conditions that form a compound of formula I or salt thereof,



IIIa IV I ,

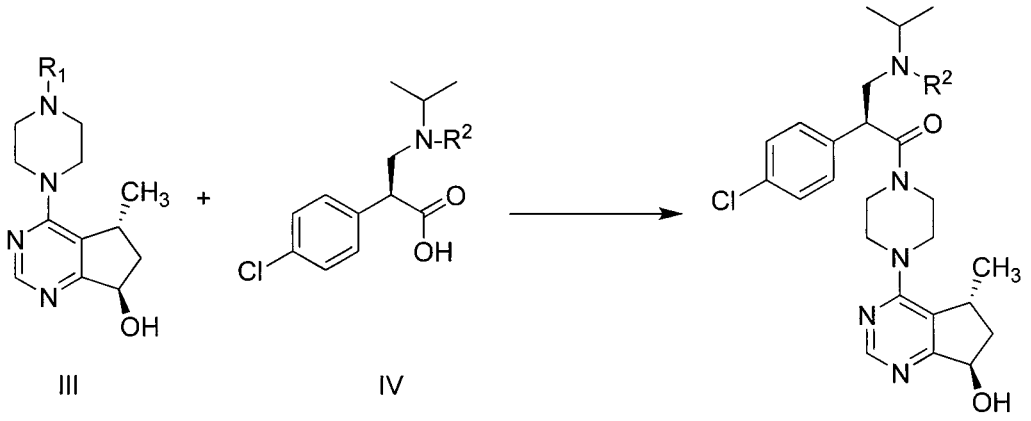
wherein R^2 in formulae IV and I is independently hydrogen or amino protecting group, and said conditions comprise propanephosphonic anhydride.

9. The process of claim 8, further comprising reacting a compound of formula I or salt thereof, wherein R^2 is amino protecting group, with acid to form a dihydrochloride salt of a compound of formula I, wherein R^2 is hydrogen.

10. The process of claim 9, further comprising contacting the dihydrochloride salt of compound of formula I with base to form a monohydrochloride salt of a compound of formula I, wherein R^2 is hydrogen.

11. The process of claim 10, wherein said base is a polymeric resin comprising a functionalized styrene divinylbenzene copolymer.

12. The process of claims 1-6, further comprising reacting a compound of formula III or salt thereof, wherein R_1 is hydrogen, with a compound of formula IV or salt thereof under conditions that form a compound of formula I or salt thereof,



III IV I

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wherein R^2 in formula IV and I is independently hydrogen or amino protecting group, and said conditions comprise propanephosphonic anhydride.

13. The process of claim 12, further comprising reacting a compound of formula I or salt thereof, wherein R^2 is amino protecting group, with acid to form a dihydrochloride salt of a compound of formula I, wherein R^2 is hydrogen.

14. The process of claim 13, further comprising contacting the dihydrochloride salt of compound of formula I with base to form a monohydrochloride salt of a compound of formula I, wherein R^2 is hydrogen.

15. The process of claim 14, wherein said base is a polymeric resin comprising a functionalized styrene divinylbenzene.

16. The process of claim 1 comprising contacting a compound of formula II or a salt thereof with a ketoreductase enzyme.