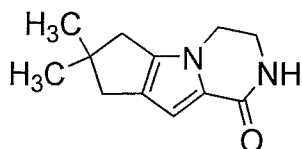
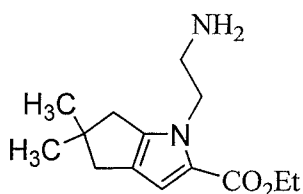


[0003] The US 2013/0116235 publication further discloses a useful five-step process for the preparation of tricyclic lactam compounds used as intermediates in the preparation of 2-{3'-hydroxymethyl-1-methyl-5-[5-((S)-2-methyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one and having the structure:



In the final step, the above-reference tricyclic lactam compound is generated by ring closure from the following compound:

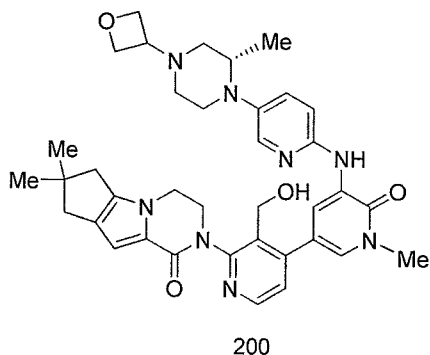


The multistep process requires two chromatographic purification steps and the overall yield based on the starting material was low.

[0004] A need therefore exists for improved method for preparing 2-{3'-hydroxymethyl-1-methyl-5-[5-((S)-2-methyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one and intermediate compounds therefore.

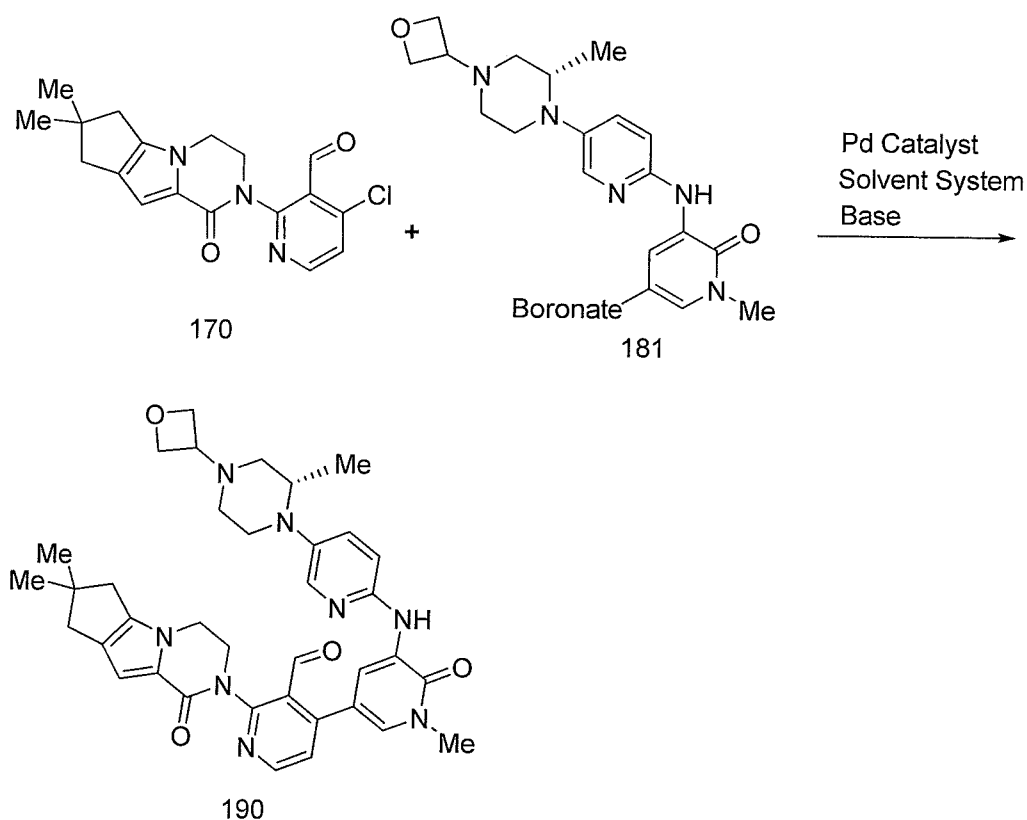
BRIEF DESCRIPTION

[0005] The disclosure is directed to a method of preparing compound 200, stereoisomers thereof, geometric isomers thereof, tautomers thereof, and salts thereof:



[0006] The method comprises forming a first reaction mixture comprising compound 170, compound 181, a palladium catalyst, a solvent system comprising water, and a base, wherein the ratio of solvent volume to compound 170 weight in the reaction mixture is less than 20:1 liters per kg, the equivalent ratio of compound 181 to compound 170 is greater than 1:1, and the equivalent ratio of the palladium catalyst to compound 170 is from about 0.005:1 to about 0.05:1.

[0007] The method further comprises reacting the first reaction mixture to form a first reaction product mixture comprising compound 190 according to the following scheme:

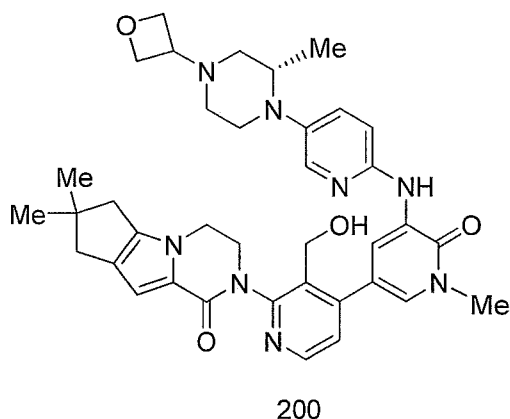


[0008] Compound 190 is isolated from the first reaction mixture.

[0009] A second reaction mixture is formed comprising compound 190, a reducing agent, a base and a solvent. The second reaction mixture is reacted to reduce the aldehyde moiety of compound 190 and form a second reaction product mixture comprising compound 200. Compound 200 is isolated from the reaction product mixture.

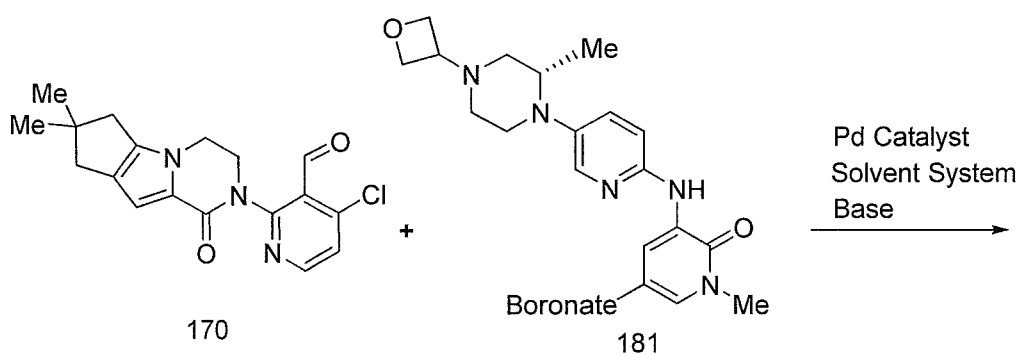
[0010] The yield of compound 190 is at least 50% based on compound 170, and the yield of compound 200 is at least 50% based on compound 190.

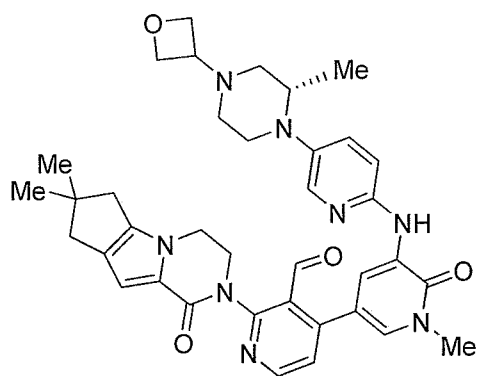
[0010a] One aspect of the disclosure is directed to a method of preparing compound 200, stereoisomers thereof, geometric isomers thereof, tautomers thereof, and salts thereof,



the method comprising:

- (i) (1) forming a first reaction mixture comprising compound 170, compound 181, a palladium catalyst, a solvent system comprising water, and a base, wherein the ratio of solvent volume to compound 170 weight in the reaction mixture is less than 20:1 liters per kg, the equivalent ratio of compound 181 to compound 170 is greater than 1:1, and the equivalent ratio of the palladium catalyst to compound 170 is from about 0.005:1 to about 0.05:1,
- (2) reacting the first reaction mixture to form a first reaction product mixture comprising compound 190 according to the following scheme:





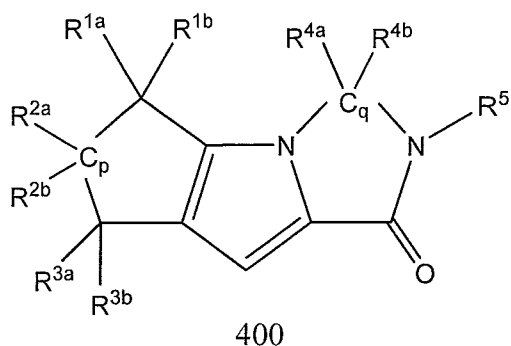
190

, and

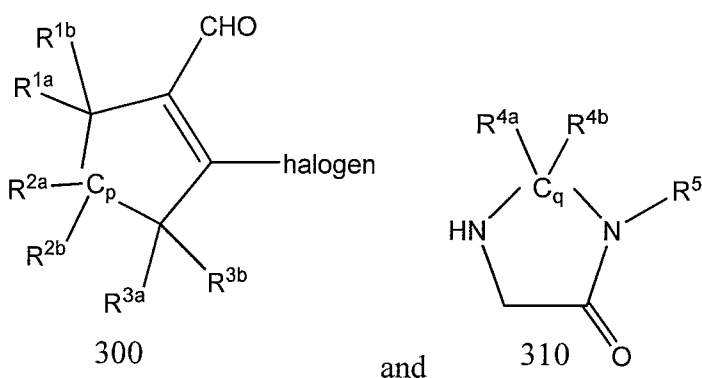
- (3) isolating compound 190 from the first reaction product mixture; and
- (ii) (1) forming a second reaction mixture comprising compound 190, a reducing agent, a base and a solvent, (2) reacting the second reaction mixture to reduce the aldehyde moiety of compound 190 and form a second reaction product mixture comprising compound 200, and (3) isolating compound 200 from the second reaction product mixture,

wherein the yield of compound 190 is at least 50% based on compound 170, and the yield of compound 200 is at least 50% based on compound 190.

[0011] The disclosure is also directed to a method for preparing a tricyclic lactam of formula 400, stereoisomers thereof, geometric isomers thereof, tautomers thereof, and salts thereof:

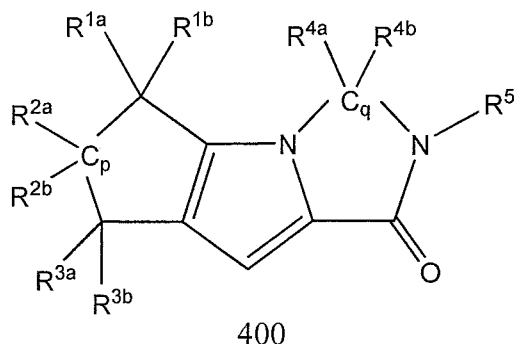


[0012] The method comprises forming a reaction mixture comprising an organic solvent, an organic base, and the compounds of formulas 300 and 310:

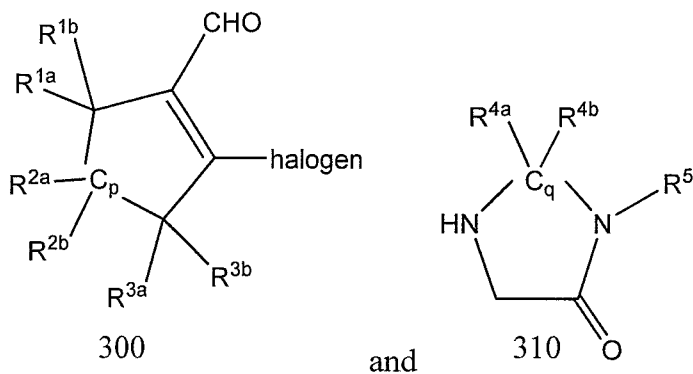


[0013] The reaction mixture is reacted to form a reaction product mixture comprising the tricyclic lactam of formula 400. R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a} and R^{4b} are independently selected from H, and C₁₋₆ alkyl. R⁵ is selected from H, C₁₋₆ alkyl, cycloalkyl, aryl, substituted aryl, benzyl, substituted benzyl, heteroaryl, substituted heteroaryl. p is 1, 2, 3 or 4; and q is 1, 2, 3 or 4.

[0013a] Another aspect of the disclosure is directed to a method for preparing a tricyclic lactam of formula 400, stereoisomers thereof, geometric isomers thereof, tautomers thereof, and salts thereof,



the method comprising forming a reaction mixture comprising an organic solvent, an organic base, and formulas 300 and 310



and reacting the reaction mixture to form a reaction product mixture comprising the tricyclic lactam of formula 400,

wherein:

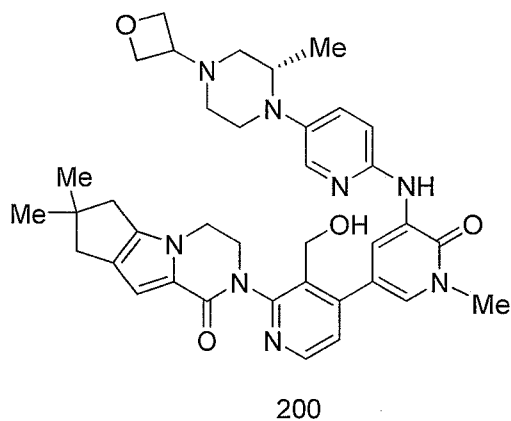
R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{3a} , R^{3b} , R^{4a} and R^{4b} are independently selected from H, and C_{1-6} alkyl;

R^5 is selected from H, C_{1-6} alkyl, cycloalkyl, aryl, substituted aryl, benzyl, substituted benzyl, heteroaryl, substituted heteroaryl;

p is 1, 2, 3 or 4; and

q is 1, 2, 3 or 4.

[0013b] Another aspect of the disclosure is directed to a method of preparing compound 200, stereoisomers thereof, geometric isomers thereof, tautomers thereof, and salts thereof,

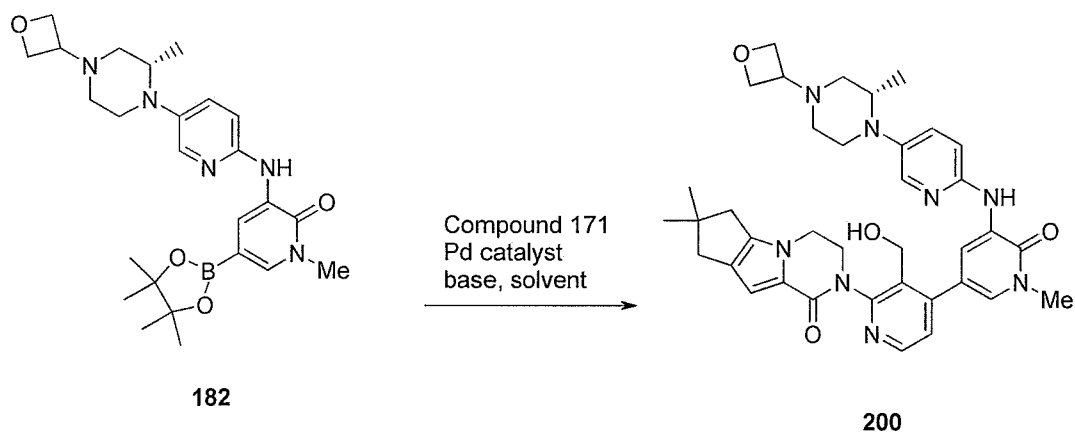


the method comprising:

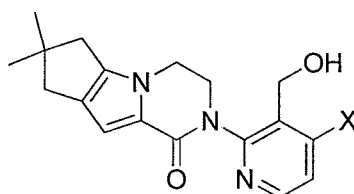
- (i) (1) forming a first reaction mixture comprising compound 170, a reducing agent, a base and a solvent, to reduce the aldehyde moiety of compound 170 to form compound 171, and
 - (2) isolating compound 171 from the first product mixture,
- (ii) (1) forming a second reaction mixture comprising compound 171, compound 182, a palladium catalyst, a solvent system comprising water, and a base, to form compound 200, and
 - (2) isolating compound 200 from the second product mixture,

according to the following scheme:





[0013c] Another aspect of the disclosure is directed to a compound having the structure:



wherein X is selected from the group consisting of Cl, Br, and I.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Figure 1 shows a method for the preparation of compounds 170, 182, 190 and 200.

[0015] Figure 2 shows a method for the preparation of compounds 170 and 182, and another method for the preparation of compounds 190 and 200.

[0016] Figure 3 shows a method for the preparation of compounds 70, 90, 40, 154, 153, 140, 141 and 180.