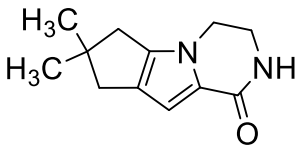
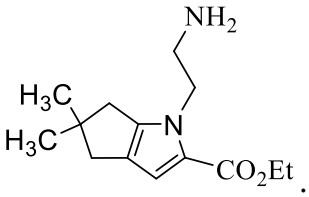
[0003] The US 2013/0116235 publication further discloses a useful five-step process for the preparation of tricyclic lactam compounds used as intermediates in the preparation of 2-{3'-hydroxymethyl-1-methyl-5-[5-((S)-2-methyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopen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



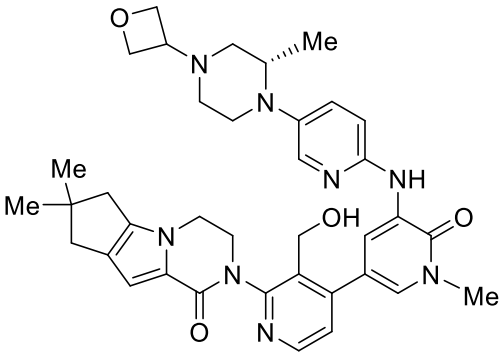
.

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.

SUMMARY

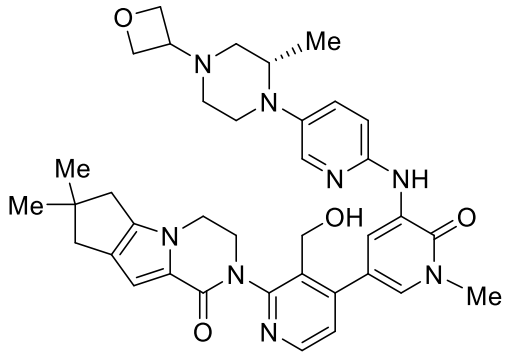
[0005] The disclosure is directed to a method of preparing compound 200, stereoisomers thereof, geometric isomers thereof, tautomers thereof, and salts thereof:



200

.

[0010a] In one aspect, the present disclosure provides a method of preparing compound 200, or salt thereof,



200

,

the method comprising:

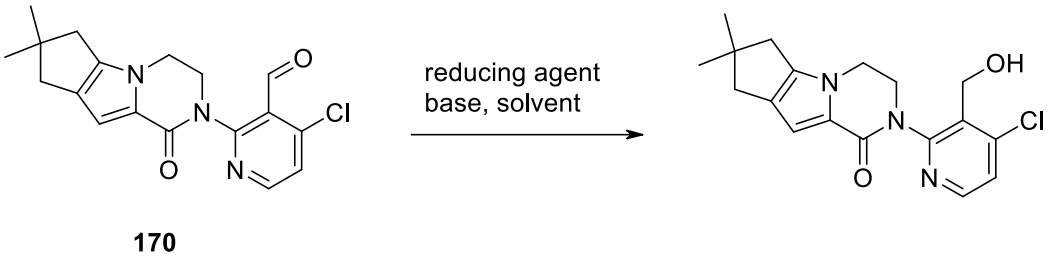
(i) (1) forming a first reaction mixture comprising compound 170, a reducing agent, a base and a solvent, to reduce the aldehyde moiety of compound 170 to form compound 171, and

(2) isolating compound 171 from the first product mixture,

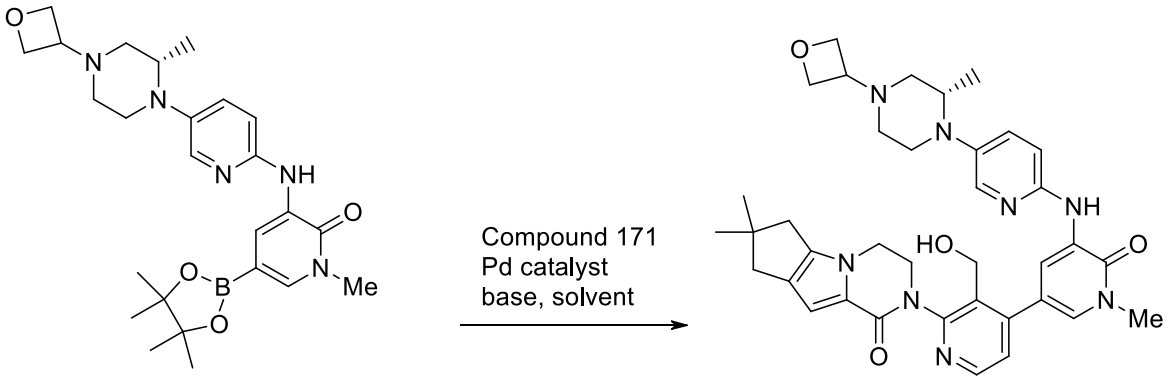
(ii) (1) forming a second reaction mixture comprising compound 171, compound 182, a palladium catalyst, a solvent system comprising water, and a base, to form compound 200, and

(2) isolating compound 200, or salt thereof, from the second product mixture,

according to the following scheme:

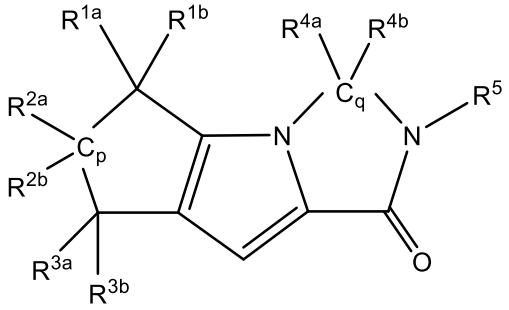


170 **171**



182 **200**

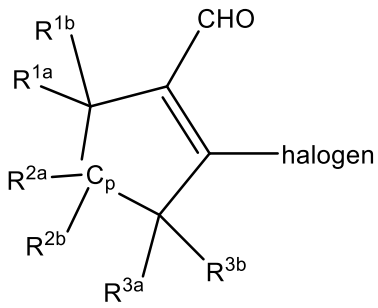
[0011] The disclosure is directed to a method for preparing a tricyclic lactam of formula 400, stereoisomers thereof, geometric isomers thereof, tautomers thereof, and salts thereof:



400

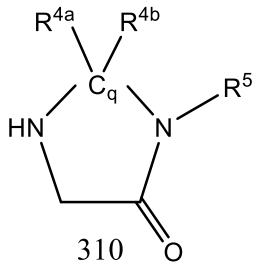
.

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



300

and



310

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[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 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.

BRIEF DESCRIPTION OF THE DRAWINGS

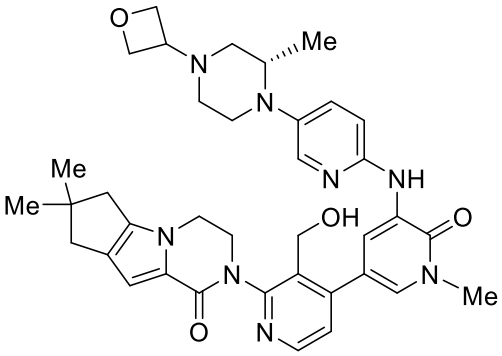
[0014] Figure 1 shows a method for the preparation of compounds 170, 182, 190 and 200.

[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.

WHAT IS CLAIMED IS:

1. A method of preparing compound 200, or salt thereof,



200

,

the method comprising:

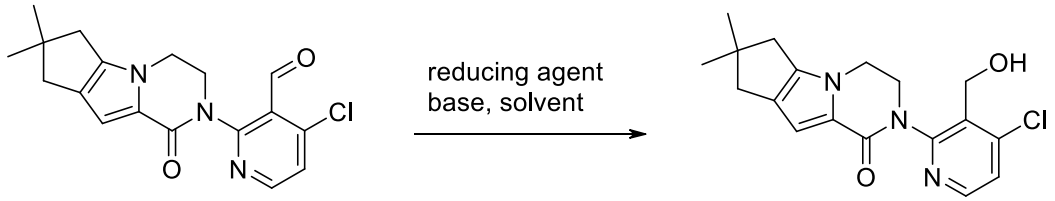
(i) (1) forming a first reaction mixture comprising compound 170, a reducing agent, a base and a solvent, to reduce the aldehyde moiety of compound 170 to form compound 171, and

(2) isolating compound 171 from the first product mixture,

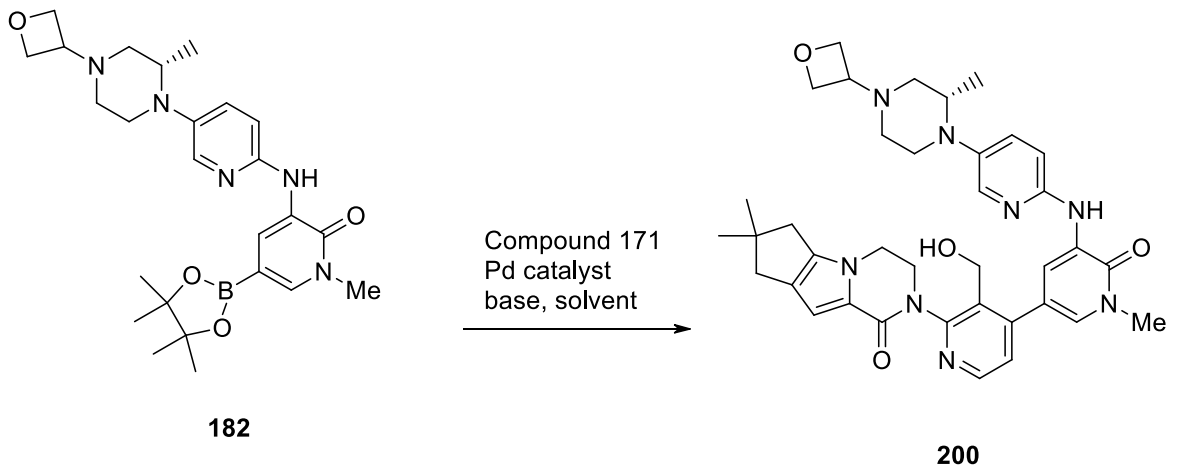
(ii) (1) forming a second reaction mixture comprising compound 171, compound 182, a palladium catalyst, a solvent system comprising water, and a base, to form compound 200, and

(2) isolating compound 200, or salt thereof, from the second product mixture,

according to the following scheme:



170 **171**



182

200

2. The method of claim 1, wherein the reducing agent in step (i) is $NaBH_4$.

3. The method of claim 1 or 2, wherein the base in step (i) is K_2HPO_4.

4. The method of any of claims 1 to 3, wherein the solvent in step (i) is THF.

5. The method of any of claims 1 to 4, wherein the Pd catalyst in step (ii) is $Pd(PCy_3)_2$.

6. The method of any of claims 1 to 5, wherein the base in step (ii) is K_3PO_4, Et_3N or di-isopropylethylamine.

7. The method of any of claims 1 to 6, wherein the equivalent ratio of the Pd catalyst to compound 171 is less than 0.05:1.

8. The method of any of claims 1 to 7, wherein the ratio of compound 182 to compound 171 is greater than 1:1.

9. The method of any of claims 1 to 8, wherein: the reducing agent in step (i) is $NaBH_4$; the base in step (i) is K_2HPO_4; and the solvent in step (i) is THF.

10. The method of any of claims 1 to 9, wherein: the base in step (ii) is K_3PO_4, Et_3N or di-isopropylethylamine; the equivalent ratio of the Pd catalyst to compound 171 is less than 0.05:1; and the ratio of compound 182 to compound 171 is greater than 1:1.

11. The method of any of claims 1 to 10, wherein:

the reducing agent in step (i) is $NaBH_4$;

the base in step (i) is K_2HPO_4;

the solvent in step (i) is THF;

the Pd catalyst in step (ii) is $Pd(PCy_3)_2$;

the base in step (ii) is K_3PO_4, Et_3N or di-isopropylethylamine;

the equivalent ratio of the Pd catalyst to compound 171 is less than 0.05:1; and

the ratio of compound 182 to compound 171 is greater than 1:1.