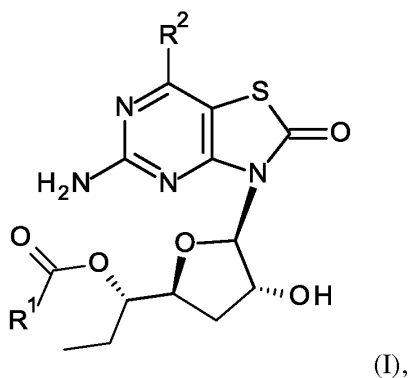


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Claims

1. Process for the preparation of a compound of the formula (I),



wherein

10

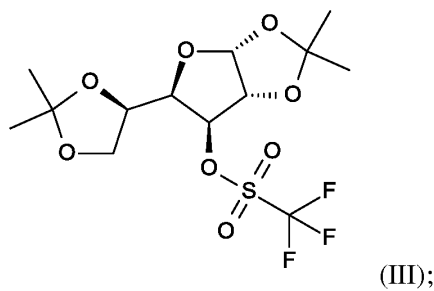
R^1 is H or C_{1-6} alkyl;

R^2 is H or hydroxy;

or pharmaceutically acceptable enantiomer or diastereomer thereof;

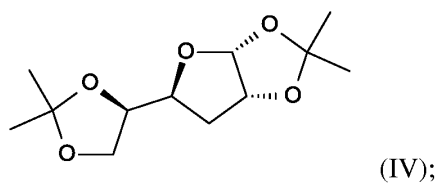
comprising one or more of the following steps:

step a) the formation of compound (III),



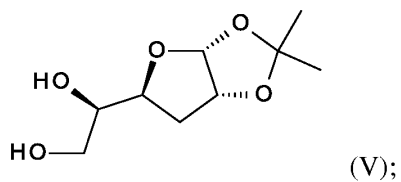
15

step b) the formation of compound (IV),

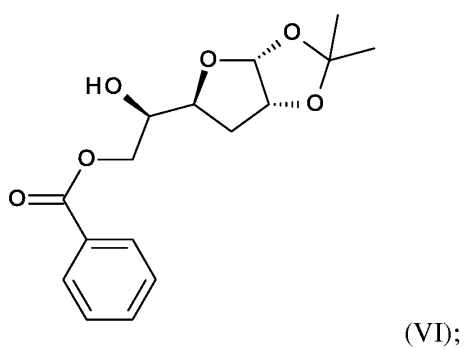


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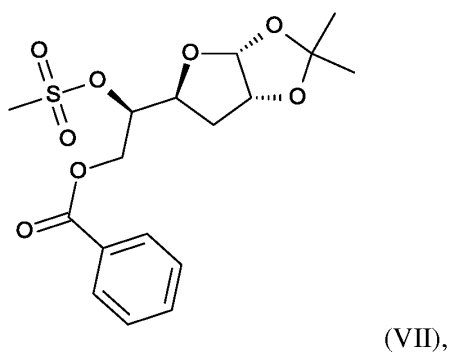
5 step c) the formation of the compound (V),



step d) the formation of compound (VI),

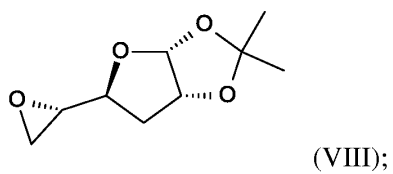


step e) the formation of compound (VII),



10

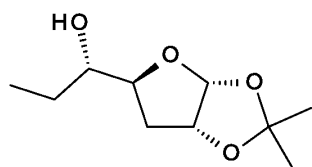
step f) the formation of compound (VIII),



step g) the formation of compound (IX),

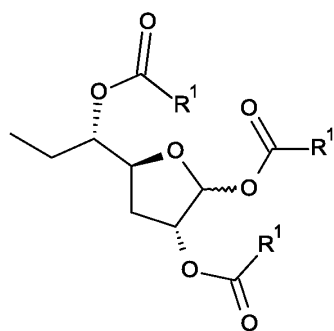
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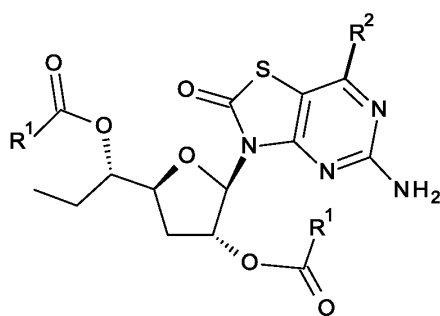
(IX);

step h) the formation of compound of formula (X),



(X);

step i) the formation of compound of formula (XII),



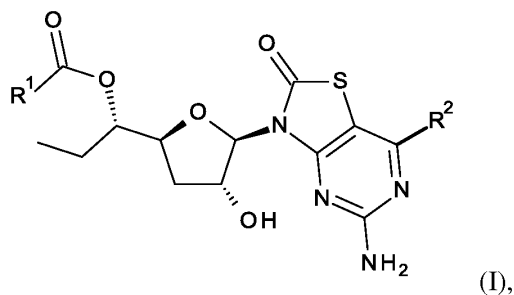
(XII);

10

wherein R^1 is H or C_{1-6} alkyl; R^2 is H or hydroxy;

step j) the formation of compound of formula (I) via the hydrolysis of compound of formula (I),

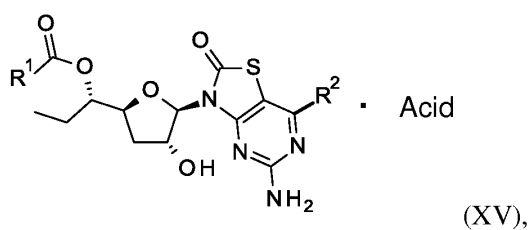
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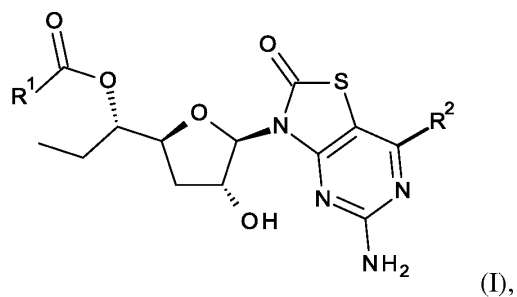
wherein R^1 is H or C_{1-6} alkyl; R^2 is H or hydroxy;

step k) the formation of compound of formula (XV),



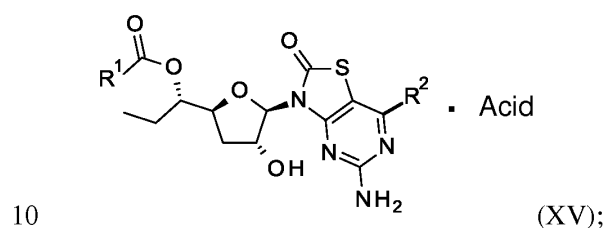
wherein R^1 is H or C_{1-6} alkyl; R^2 is H or hydroxy; the acid is selected from D-glutamic acid,
 10 L-mandelic acid, 1-hydroxy-2-naphthoic acid, citric acid, 4-aminosalicylic acid, L-tartaric acid,
 hippuric acid, malonic acid, glutaric acid, oxalic acid, fumaric acid, succinic acid, 4-
 aminobenzoic acid, 2,5-dihydroxybenzoic acid, L-malic acid, salicylic acid, maleic acid,
 (1S,3R)-(-)-camphoric acid, pamoic acid, mucic acid, palmitic acid, oleic acid and lactobionic
 acid;

15 step l) the formation of compound of formula (I) via dissociation from compound of
 formula (XV),



wherein R^1 is H or C_{1-6} alkyl; R^2 is H or hydroxy.

- 5 2. A process according to claim 1 consisting of step a) to step l).
3. A process according to claim 1 or 2, wherein R^1 is methyl; or pharmaceutically acceptable enantiomer or diastereomer thereof.
4. A process according to any one of claims 1 to 3 for the synthesis of compound of formula (XV),



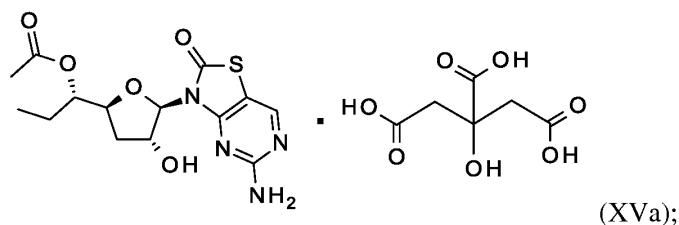
wherein

- acid is selected from D-glutamic acid, L-mandelic acid, 1-hydroxy-2-naphthoic acid, citric acid, 4-aminosalicylic acid, L-tartaric acid, hippuric acid, malonic acid, glutaric acid, oxalic acid, fumaric acid, succinic acid, 4-aminobenzoic acid, 2,5-dihydroxybenzoic acid, L-malic acid, salicylic acid, maleic acid, (1S,3R)-(-)-camphoric acid, pamoic acid, mucic acid, palmitic acid, oleic acid and lactobionic acid; particularly the acid is selected from 1-hydroxy-2-naphthoic acid, citric acid, 4-aminosalicylic acid, L-tartaric acid, 2,5-dihydroxybenzoic acid; more particularly the acid is citric acid;
- 15

R^1 is H or C_{1-6} alkyl;

- 20 R^2 is H or hydroxy;
or pharmaceutically acceptable enantiomer or diastereomer thereof.

5. A process according to claim 4 for the synthesis of compound (XVa),



or pharmaceutically acceptable enantiomer or diastereomer thereof.

- 5 6. A process according to any one of claims 1 to 5, characterized in that the formation of the compound (VI) in step d) is performed in the presence of a base with an acylating reagent and a catalyst, wherein the catalyst is selected from DMAP, MgCl_2 and Bu_2SnO ; particularly the catalyst is Bu_2SnO .
7. A process according to claim 6, wherein the amount of catalyst is 0.001-0.2 eq., particularly
10 0.05 eq.
8. A process according to any one of claims 1 to 7, characterized in that the formation of the compound of formula (X) in step h) is performed in the presence of an acylating reagent with an acid in a solvent; wherein the solvent is selected from DCM, CHCl_3 , 2-MeTHF, toluene, IPAc and EtOAc; particularly the solvent is EtOAc.
- 15 9. A process according to any one of claims 1 to 8, characterized in that the formation of the compound of formula (XV) in step k) is performed in the presence of an acid in an organic solvent; wherein the acid is selected from D-glutamic acid, L-mandelic acid, 1-hydroxy-2-naphthoic acid, citric acid, 4-aminosalicylic acid, L-tartaric acid, hippuric acid, malonic acid, glutaric acid, oxalic acid, fumaric acid, succinic acid, 4-aminobenzoic acid, 2,5-
20 dihydroxybenzoic acid, L-malic acid, salicylic acid, maleic acid, (1S,3R)-(-)-camphoric acid, pamoic acid, mucic acid, palmitic acid, oleic acid and lactobionic acid; particularly the acid is selected from 1-hydroxy-2-naphthoic acid, citric acid, 4-aminosalicylic acid, L-tartaric acid, 2,5-dihydroxybenzoic acid; more particularly the acid is citric acid.
10. A process according to claim 9, wherein the solvent is selected from MeOH, EtOH, n-
25 propanol, IPA, MeCN, acetone, THF, toluene; particularly the solvent is MeCN.
11. A process according to claim 10, wherein the solvent is added with an additive, wherein the additive is water.
12. A process according to claim 11, wherein the volume ratio of additive to solvent ($V_{\text{water}}/V_{\text{solvent}}$) is 0.005-0.015, particularly 0.005.
- 30 13. A process according to claim 12, wherein the volume ratio of water to MeCN ($V_{\text{water}}/V_{\text{MeCN}}$) is 0.005-0.015, particularly 0.005.
14. A process according to any one of claims 1 to 13, characterized in that the formation of compound of formula (I) via dissociation from compound of formula (XV) in step l) is performed

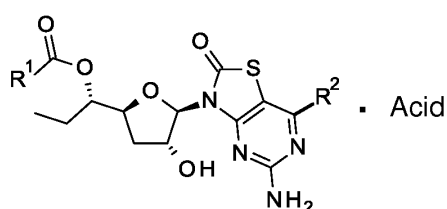
5 in the presence of a base in a solvent, followed by a recrystallization procedure; wherein the solvent used in recrystallization procedure is a mixture of water and an organic solvent, wherein the organic solvent is selected from MeOH, EtOH and n-propanol, particularly the organic solvent is EtOH.

15. A process according to claim 14, wherein the weight percentage of organic solvent in water
10 (wt.%) is 0-30wt.%, particularly 7.8 wt.%.

16. A process according to any one of claims 1 to 13, characterized in that the formation of compound of formula (I) via dissociation from compound of formula (XV) in step 1) is performed in the presence of a base in a solvent, followed by a recrystallization procedure; wherein the solvent used in recrystallization procedure is a mixture of an polar organic solvent and a non-
15 polar organic solvent; wherein the polar organic solvent is selected from MeOH, EtOH, n-propanol and n-butanol; the non-polar organic solvent is selected from n-heptane and n-hexane; particularly, the solvent used in recrystallization procedure is a mixture of n-propanol and n-heptane.

17. A process according to claim 16, characterized in that the weight percentage of polar solvent
20 in the solvent mixture is 0-80 wt.%, particularly 60-75 wt.%, more particularly 60 wt.%.

18. A compound of formula (XV),



(XV); wherein

the acid is selected from D-glutamic acid, L-mandelic acid, 1-hydroxy-2-naphthoic acid, citric
acid, 4-aminosalicylic acid, L-tartaric acid, hippuric acid, malonic acid, glutaric acid,
25 oxalic acid, fumaric acid, succinic acid, 4-aminobenzoic acid, 2,5-dihydroxybenzoic acid,
L-malic acid, salicylic acid, maleic acid, (1S,3R)-(-)-camphoric acid, pamoic acid, mucic
acid, palmitic acid, oleic acid and lactobionic acid; particularly the acid is selected from
1-hydroxy-2-naphthoic acid, citric acid, 4-aminosalicylic acid, L-tartaric acid, 2,5-
dihydroxybenzoic acid; more particularly the acid is citric acid;

- 5 R^1 is H or C_{1-6} alkyl;
 R^2 is H or hydroxy;
 or pharmaceutically acceptable enantiomer or diastereomer thereof.

19. [(1S)-1-[(2S,4R,5R)-5-(5-amino-2-oxo-thiazolo[4,5-d]pyrimidin-3-yl)-4-hydroxy-
tetrahydrofuran-2-yl]propyl] acetate citric acid; or pharmaceutically acceptable enantiomer or
10 diastereomer thereof.