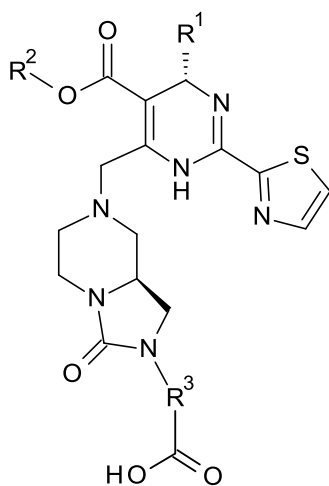


5 (f) 3-[(8aS)-3-oxo-1,5,6,7,8,8a-hexahydroimidazo[1,5-a]pyrazin-2-yl]-2,2-dimethylpropanoic acid (TFA salt, containing massive inorganic salt) is a sticky semi-solid, causing poor conversion and more impurities in final step, which leads to HPLC purification for the final API.

Based on the issues above, one object of the embodiments disclosed herein therefore is to find an alternative efficient synthetic approach which can be applied on a technical scale and/or
10 result in obtaining the product in a higher yield and/or desired purity. Addressing any of the issues (a) to (f) mentioned above is also one of the objects of the embodiments disclosed herein.

SUMMARY

One aspect of the present disclosure relates to a process for the preparation of a compound of the formula (I),



15 (I),

wherein

R¹ is phenyl, which is unsubstituted or substituted with one, two or three substituents independently selected from halogen and C₁₋₆alkyl;

R² is C₁₋₆alkyl;

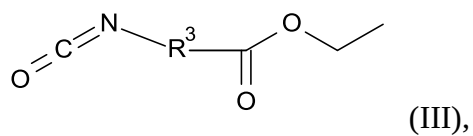
20 R³ is -C_xH_{2x}-;

x is 1, 2, 3, 4, 5, 6 or 7;

or pharmaceutically acceptable salt or diastereomer thereof;

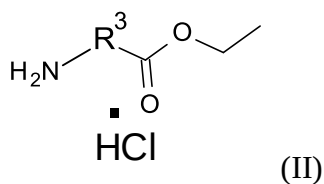
5 consisting of the following steps:

step a) the formation of the isocyanate (III),



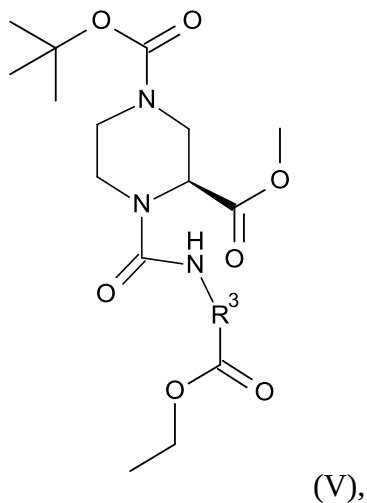
wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7,

by reacting the compound of formula (II)



with triphosgene;

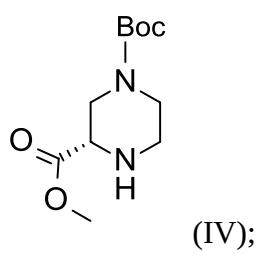
step b) the formation of urea (V)



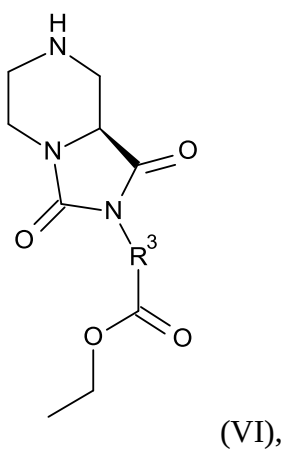
wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7.

via the addition reaction of isocyanate (III) and compound (IV)

5

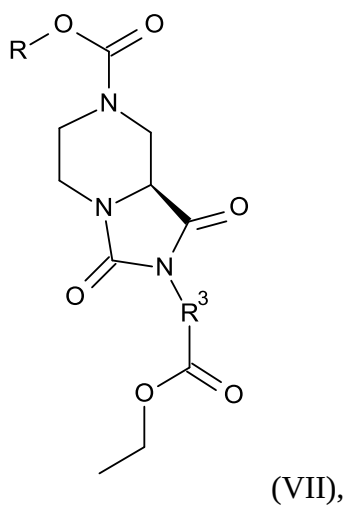


step c) the formation of the compound of formula (VI) via the cyclization reaction of urea (V),



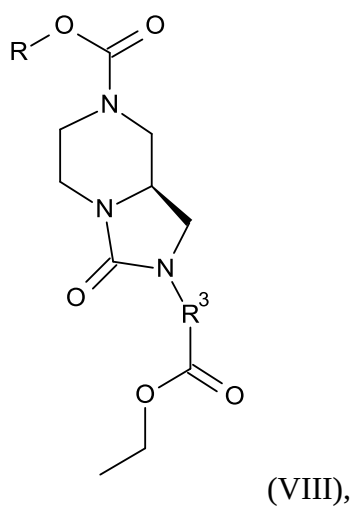
5 wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7;

step d) the formation of the compound of formula (VII) by protection of the compound of formula (VI),



wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7; R is C_{1-6} alkyl;

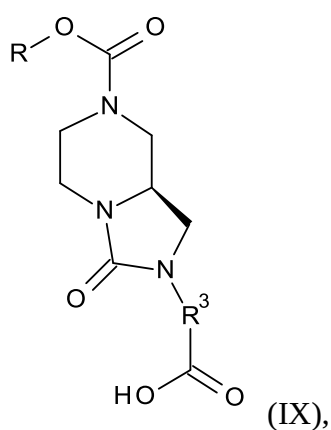
10 step e) the formation of the compound of formula (VIII) via selective reduction of the compound of formula (VII),



wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7; R is C_{1-6} alkyl;

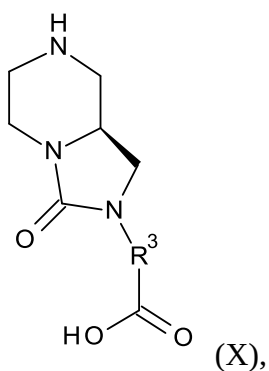
15 step f) the formation of the compound of formula (IX) via hydrolysis of the compound of formula (VIII),

5



wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7; R is C_{1-6} alkyl;

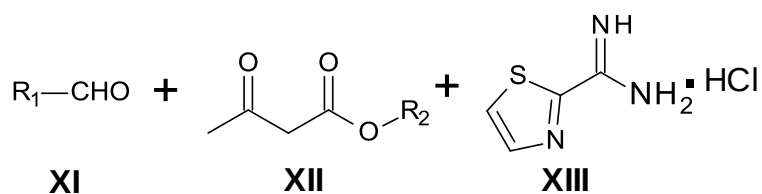
step g) the formation of compound of formula (X) by de-protection of the compound of formula (IX),



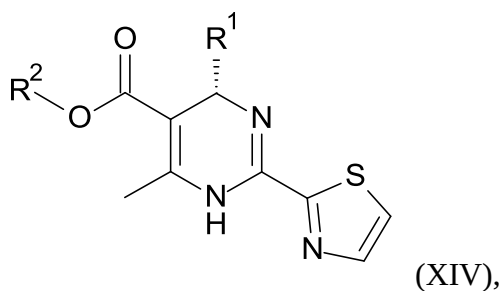
10

wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7;

step h) the formation of compound of formula (XIV) via Biginelli-like reaction, , by reacting compounds of formulae (XI), (XII) and (XIII)

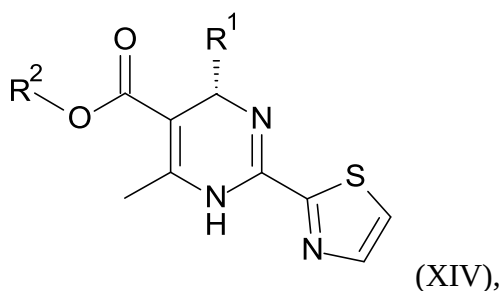


, to obtain the compound of formula (XIV)



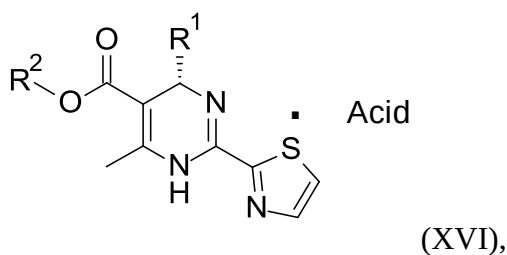
wherein R^1 is phenyl, which is unsubstituted or substituted with one, two or three substituents independently selected from halogen and C_{1-6} alkyl; R^2 is C_{1-6} alkyl;

step i) the formation of the compound of formula (XVI) by reacting the compound of formula (XIV)



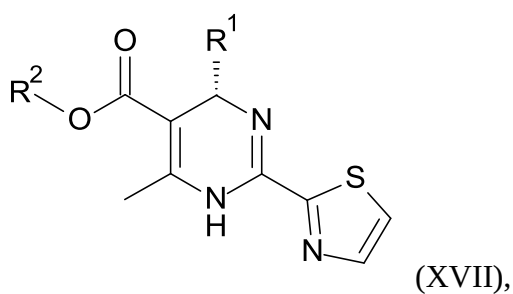
with an organic acid (XV),

and recrystallization of the enantiomeric salt of compound of formula (XVI) or solvate,



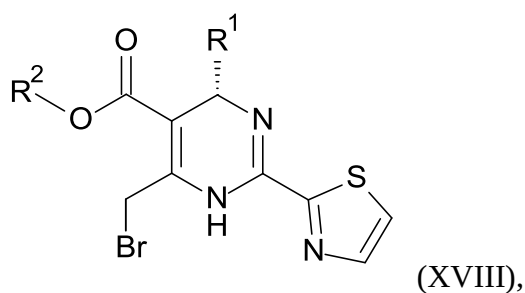
15 wherein R^1 is phenyl, which is unsubstituted or substituted with one, two or three substituents independently selected from halogen and C_{1-6} alkyl; R^2 is C_{1-6} alkyl; acid is D-(+)-DTTA, L-DTTA, L-Tartaric acid, D-DBTA, (+)-CSA, (S)-(+)-1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate or (R)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate;

step j) the recovery of enantiomeric compound of formula (XVII) from its enantiomeric salt of formula (XVI) or solvate,



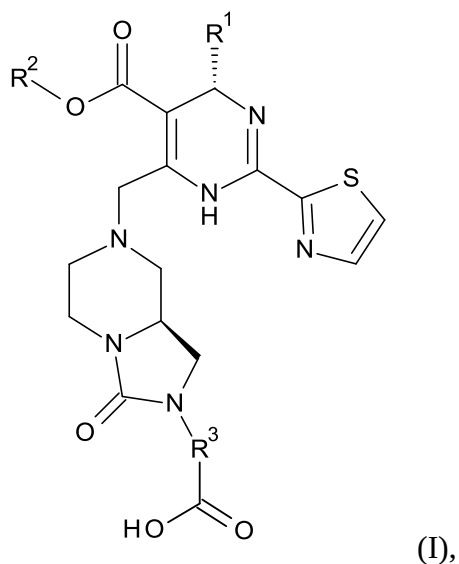
wherein R^1 is phenyl, which is unsubstituted or substituted with one, two or three substituents independently selected from halogen and C_{1-6} alkyl; R^2 is C_{1-6} alkyl;

step k) the formation of compound of formula (XVIII) via the bromination reaction of compound of formula (XVII),



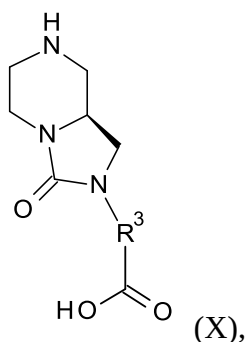
wherein R^1 is phenyl, which is unsubstituted or substituted with one, two or three substituents independently selected from halogen and C_{1-6} alkyl; R^2 is C_{1-6} alkyl;

step l) the formation of compound of formula (I) via the substitution reaction of compound of formula (XVIII) with compound of formula (X) ,



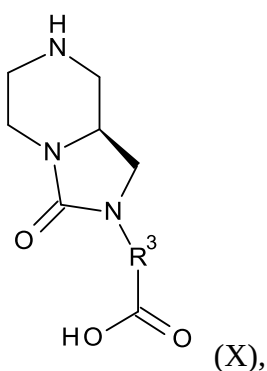
5 wherein R^1 is phenyl, which is unsubstituted or substituted with one, two or three substituents independently selected from halogen and C_{1-6} alkyl; R^2 is C_{1-6} alkyl; R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7.

The present disclosure also relates to a novel process for the preparation of a compound of the formula (X):



wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another aspect of the present disclosure relates to a process for the preparation of a compound of the formula (X),



wherein

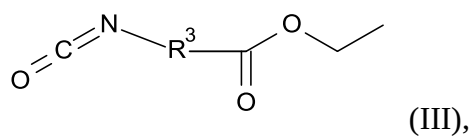
R^3 is $-C_xH_{2x}-$;

x is 1, 2, 3, 4, 5, 6 or 7;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof;

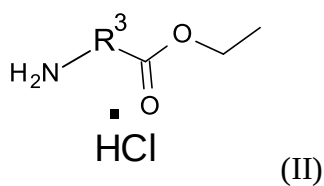
20 comprising one or more of the following steps:

5 step a) the formation of the isocyanate (III),



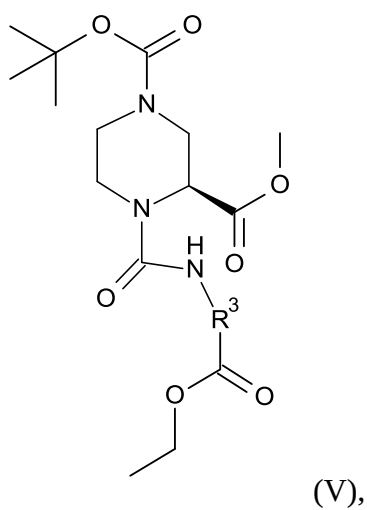
wherein R³ is -C_xH_{2x}-; x is 1, 2, 3, 4, 5, 6 or 7,

by reacting the compound of formula (II)



10 with triphosgene;

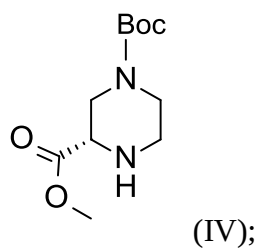
step b) the formation of urea (V)



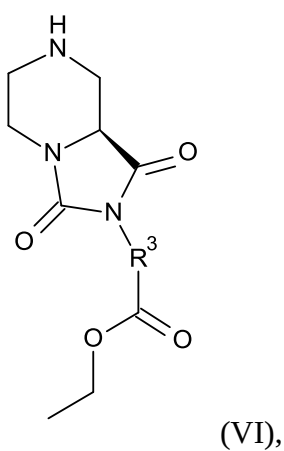
wherein R³ is -C_xH_{2x}-; x is 1, 2, 3, 4, 5, 6 or 7

via the addition reaction of isocyanate (III) and compound (IV),

5

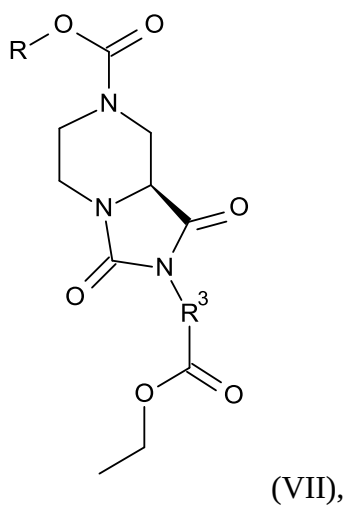


step c) the formation of the compound of formula (VI) via the cyclization reaction of urea (V),



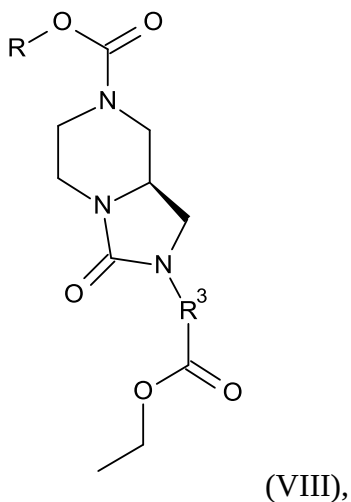
wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7;

10 step d) the formation of the compound of formula (VII) by protection of the compound of formula (VI),



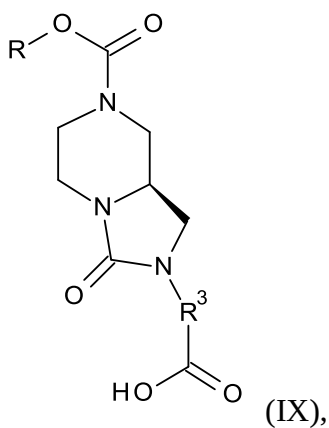
wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7; R is C_{1-6} alkyl;

- 5 step e) the formation of the compound of formula (VIII) via selective reduction of the compound of formula (VII),



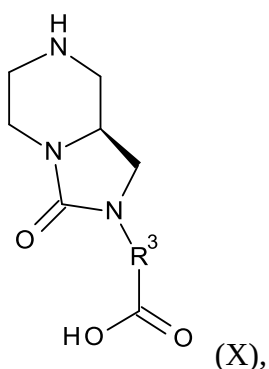
wherein R^3 is $-\text{C}_x\text{H}_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7; R is C_{1-6} alkyl;

- 10 step f) the formation of the compound of formula (IX) via hydrolysis of the compound of formula (VIII),



wherein R^3 is $-\text{C}_x\text{H}_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7; R is C_{1-6} alkyl;

- step g) the formation of compound of formula (X) by de-protection of the compound of formula (IX),



wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7.

Compound of the formula (X) is a key intermediate in the synthesis and manufacture of pharmaceutically active compound of formula (I) as described herein.

10 DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

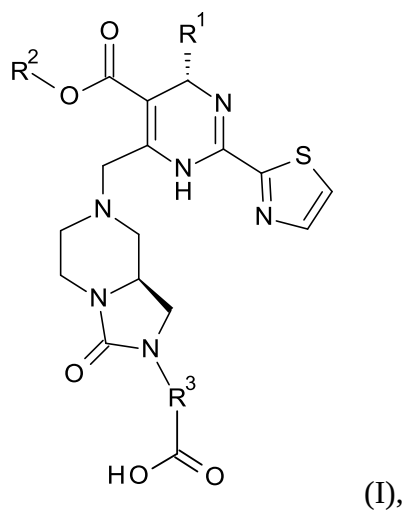
As used herein, the term “ C_{1-6} alkyl” signifies a saturated, linear- or branched chain alkyl group containing 1 to 6, particularly 1 to 5 carbon atoms, for example methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *tert*-butyl and the like. Particular “ C_{1-6} alkyl” group is methyl or ethyl.

15 The term “halogen” signifies fluorine, chlorine, bromine or iodine, particularly fluorine or chlorine.

5

Claims

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



wherein

10 R¹ is phenyl, which is unsubstituted or substituted with one, two or three substituents independently selected from halogen and C₁₋₆alkyl;

R² is C₁₋₆alkyl;

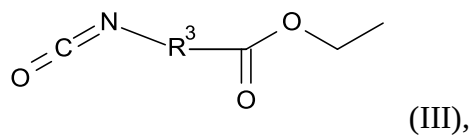
R³ is -C_xH_{2x}-;

x is 1, 2, 3, 4, 5, 6 or 7;

or pharmaceutically acceptable salt or diastereomer thereof;

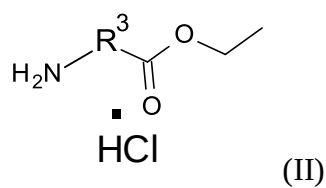
15 consisting of the following steps:

step a) the formation of the isocyanate (III),



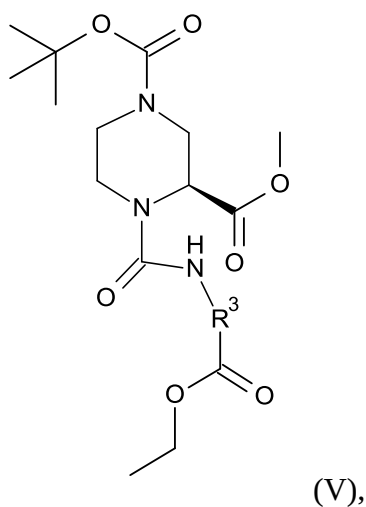
wherein R³ is -C_xH_{2x}-; x is 1, 2, 3, 4, 5, 6 or 7,

5 by reacting the compound of formula (II)



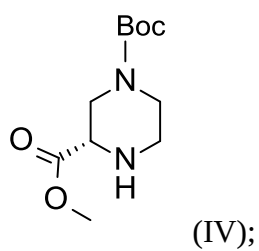
with triphosgene;

step b) the formation of urea (V)

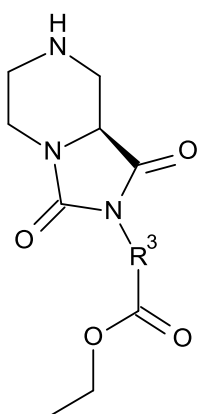


10 wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7,

via the addition reaction of isocyanate (III) and compound (IV)



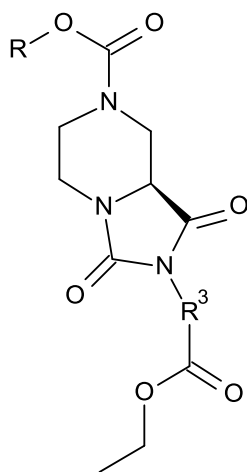
step c) the formation of the compound of formula (VI) via the cyclization reaction of urea (V),



5 (VI),

wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7;

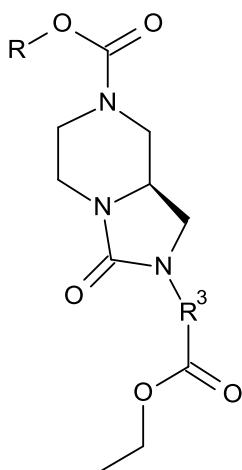
step d) the formation of the compound of formula (VII) by protection of the compound of formula (VI),



(VII),

10 wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7; R is C_{1-6} alkyl;

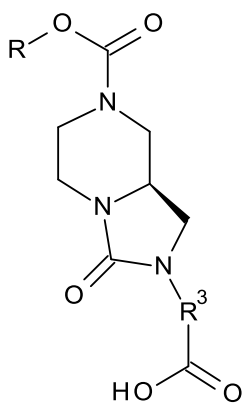
step e) the formation of the compound of formula (VIII) via selective reduction of the compound of formula (VII),



(VIII),

wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7; R is C_{1-6} alkyl;

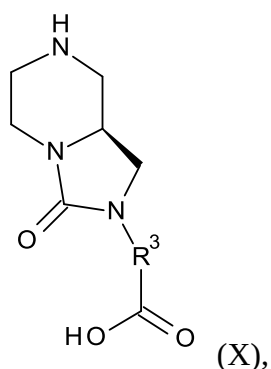
step f) the formation of the compound of formula (IX) via hydrolysis of the compound of formula (VIII),



(IX),

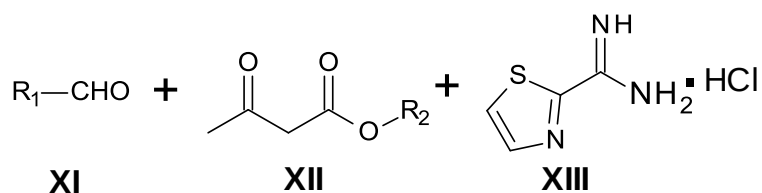
wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7; R is C_{1-6} alkyl;

step g) the formation of compound of formula (X) by de-protection of the compound of formula (IX),



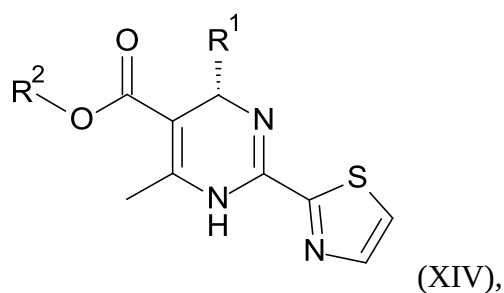
wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7;

step h) the formation of compound of formula (XIV) via Biginelli-like reaction, by reacting compounds of formulae (XI), (XII) and (XIII)



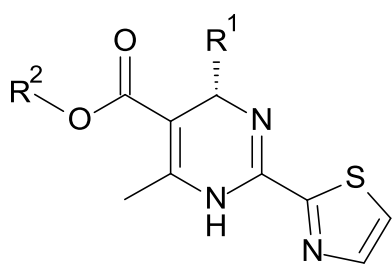
, to obtain the compound of

formula (XIV)



wherein R^1 is phenyl, which is unsubstituted or substituted with one, two or three substituents independently selected from halogen and C_{1-6} alkyl; R^2 is C_{1-6} alkyl;

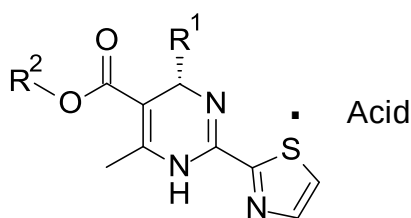
step i) the formation of the compound of formula (XVI) by reacting the compound of formula (XIV)



5 (XIV),

with an organic acid (XV),

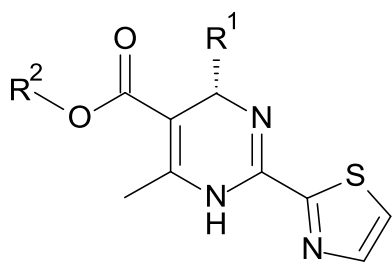
and recrystallization of the enantiomeric salt of compound of formula (XVI) or solvate,



(XVI),

10 wherein R¹ is phenyl, which is unsubstituted or substituted with one, two or three substituents independently selected from halogen and C₁₋₆alkyl; R² is C₁₋₆alkyl; acid is D-(+)-DTTA, L-DTTA, L-Tartaric acid, D-DBTA, (+)-CSA, (S)-(+)-1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate or (R)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate;

step j) the recovery of enantiomeric compound of formula (XVII) from its enantiomeric salt of formula (XVI) or solvate,

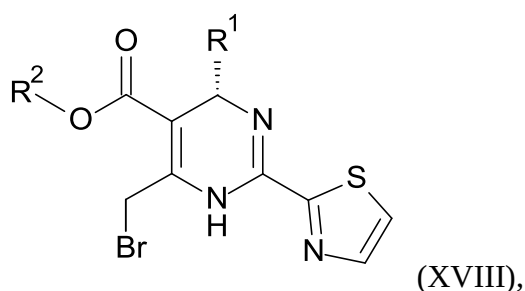


15 (XVII),

wherein R¹ is phenyl, which is unsubstituted or substituted with one, two or three substituents independently selected from halogen and C₁₋₆alkyl; R² is C₁₋₆alkyl;

step k) the formation of compound of formula (XVIII) via the bromination reaction of compound of formula (XVII),

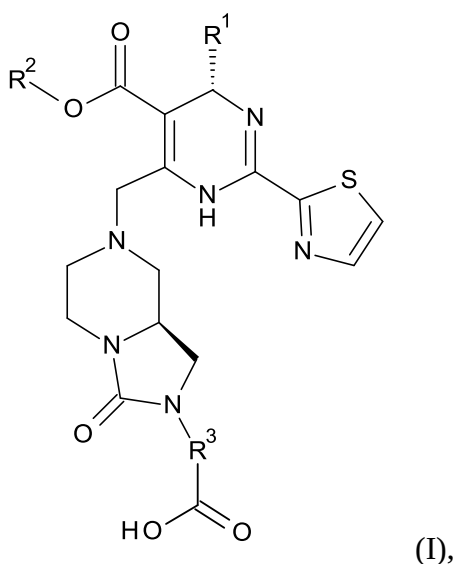
5



wherein R^1 is phenyl, which is unsubstituted or substituted with one, two or three substituents independently selected from halogen and C_{1-6} alkyl; R^2 is C_{1-6} alkyl;

step 1) the formation of compound of formula (I) via the substitution reaction of compound of formula (XVIII) with compound of formula (X) ,

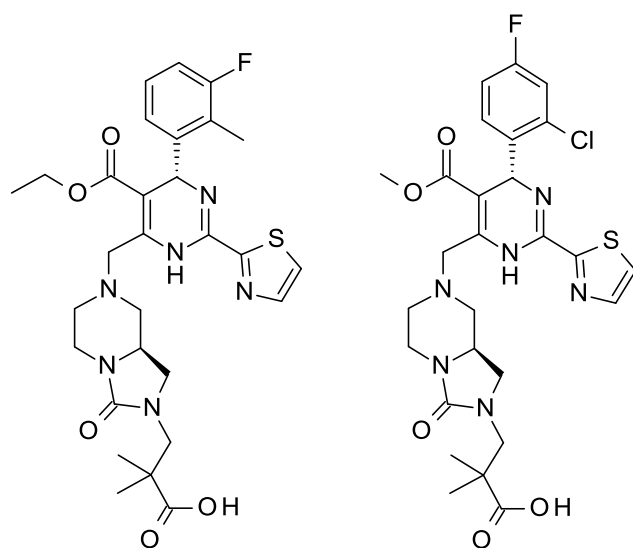
10



wherein R^1 is phenyl, which is unsubstituted or substituted with one, two or three substituents independently selected from halogen and C_{1-6} alkyl; R^2 is C_{1-6} alkyl; R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7.

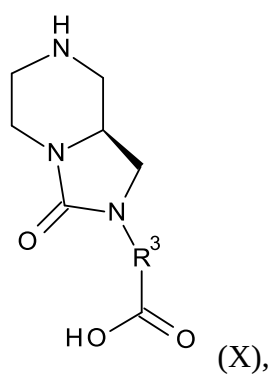
2. A process according to claim 1, wherein R^1 is chlorofluorophenyl or methylchlorophenyl; R^2 is methyl or ethyl; R^3 is $-CH_2-C(CH_3)_2-$; or pharmaceutically acceptable salt or diastereomer thereof.

3. A process according to claim 1 or 2 for the synthesis of



5 or ; or pharmaceutically acceptable salt or diastereomer thereof.

4. Process for the preparation of a compound of the formula (X),



wherein

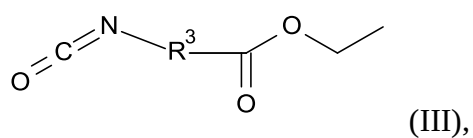
10 R^3 is $-C_xH_{2x-}$;

x is 1, 2, 3, 4, 5, 6 or 7;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof;

comprising one or more of the following steps:

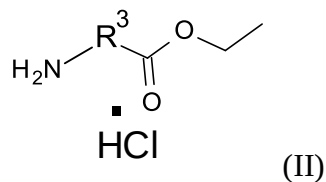
step a) the formation of the isocyanate (III),



15

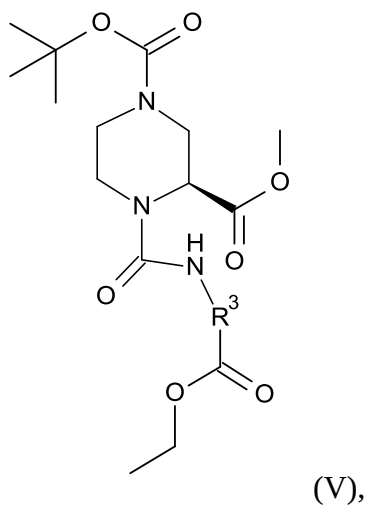
5 wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7,

by reacting the compound of formula (II)



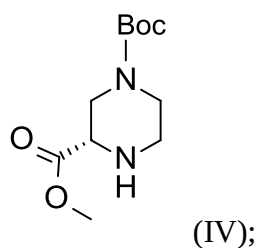
with triphosgene;

step b) the formation of urea (V)

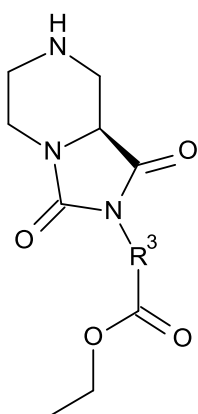


wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7

via the addition reaction of isocyanate (III) and compound (IV),



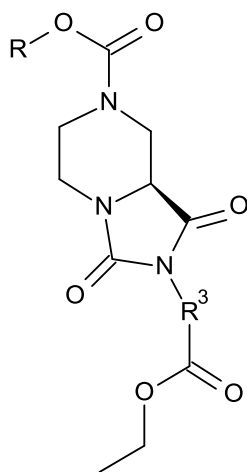
15 step c) the formation of the compound of formula (VI) via the cyclization reaction of urea (V),



5 (VI),

wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7;

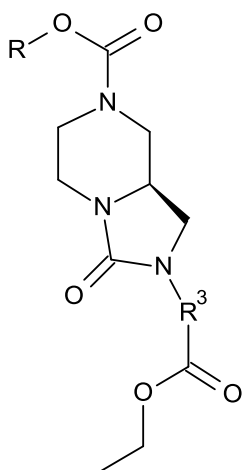
step d) the formation of the compound of formula (VII) by protection of the compound of formula (VI),



(VII),

10 wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7; R is C_{1-6} alkyl;

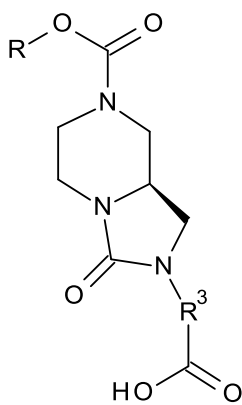
step e) the formation of the compound of formula (VIII) via selective reduction of the compound of formula (VII),



(VIII),

wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7; R is C_{1-6} alkyl;

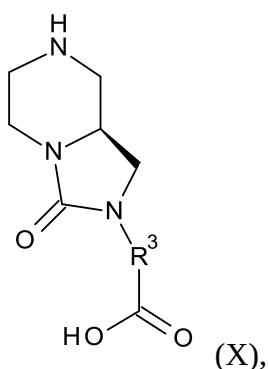
step f) the formation of the compound of formula (IX) via hydrolysis of the compound of formula (VIII),



(IX),

wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7; R is C_{1-6} alkyl;

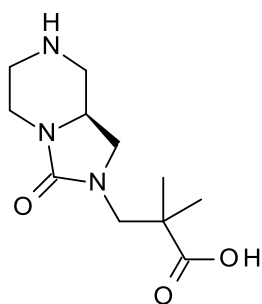
step g) the formation of compound of formula (X) by de-protection of the compound of formula (IX),



wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7.

5. A process according to claim 4, wherein R^3 is $-\text{CH}_2-\text{C}(\text{CH}_3)_2-$; or pharmaceutically acceptable salt or diastereomer thereof.

6. A process according to claim 4 or 5 for the synthesis of



; or pharmaceutically acceptable salt or diastereomer thereof.

7. A process according to any one of claims 1 to 6, characterized in that the formation of the isocyanate (III) in step a) is performed in the presence of a base in a solvent with phosgene reagent, wherein the solvent is selected from 2-MeTHF, THF, IPAc, EA, toluene and DCM, particularly the solvent is DCM.

8. A process according to claim 7, wherein the base is selected from Na_2CO_3 , NaHCO_3 , K_2CO_3 , Na_3PO_4 and K_3PO_4 , particularly the base is aqueous Na_2CO_3 at concentration of 5-25 wt% or aqueous K_2CO_3 at concentration of 5-30 wt%, more particularly the base is aqueous Na_2CO_3 at concentration of 10-15 wt%.

9. A process according to claim 7 or 8, wherein the phosgene reagent is selected from phosgene, diphosgene and triphosgene, particularly the phosgene reagent is triphosgene; wherein the amount of triphosgene is 0.34-1.0 eq. of compound of formula (II), particularly 0.34-0.45 eq.

- 5 10. A process according to any one of claims 1 to 9, characterized in that the formation of the compound of formula (VI) in step c) is performed in the presence of an acid in an organic solvent, wherein the solvent is selected from 2-MeTHF, IPAc, EA, toluene, DCM, methanol and ethanol, particularly the solvent is ethanol.
11. A process according to claim 10, wherein the acid is selected from boron trifluoride etherate, phosphoric acid, sulphuric acid, HBr and HCl, particularly the acid is HCl, more particularly the acid is concentrated HCl.
12. A process according to any one of claims 1 to 11, characterized in that the formation of the compound of formula (VII) in step d) is performed in the presence of a base with a protecting reagent in a solvent, wherein the protecting reagent is selected from the chloroformates and anhydrides, particularly the protecting reagent is benzyl chloroformate or Boc anhydride, more particularly the protecting reagent is Boc anhydride.
13. A process according to claim 12, wherein the solvent is selected from 2-MeTHF, THF, IPAc, EtOAc and DCM; particularly the solvent is THF or 2-MeTHF.
14. A process according to claim 12 or 13, wherein the base is selected from TEA, DIPEA, Na₂CO₃, NaHCO₃, K₂CO₃, Na₃PO₄ and K₃PO₄; particularly the base is Na₂CO₃ or NaHCO₃; more particularly the base is aqueous Na₂CO₃ or aqueous NaHCO₃.
15. A process according to any one of claims 1 to 14, characterized in that the formation of the compound of formula (VIII) in step e) is performed in the presence of a catalytic Lewis acid and a reductive reagent, wherein the catalytic Lewis acid is selected from InCl₃, YCl₃, ZnCl₂, Zn(OAc)₂ and BF₃·Et₂O; particularly the Lewis acid is BF₃·Et₂O, wherein the amount of BF₃·Et₂O is 0.05-1.1eq. of the compound of formula (VII), particularly 0.2 eq.
16. A process according to claim 15, wherein the reductive reagent is selected from lithium aluminum hydride, sodium dihydro-bis-(2-methoxyethoxy)aluminate, borane dimethylsulfide, phenylsilane and borane tetrahydrofuran complex; particularly the reductive reagent is borane tetrahydrofuran complex, wherein the amount of borane tetrahydrofuran complex is 1.6-5.0 eq. of the compound of formula (VII), particularly 1.6-2.0 eq.
17. A process according to any one of claims 1 to 16, characterized in that the compound of formula (IX) in step f) is isolated through a work-up procedure, wherein the work-up procedure

- 5 comprises extraction with an organic solvent to remove the impurities, wherein the organic solvent is selected from THF, EA, IPAc, MTBE and toluene, particularly the organic solvent is IPAc.
18. A process according to any one of claims 1 to 17, characterized in that the formation of the compound of formula (X) in step g) is performed in the presence of an acid in a solvent, wherein
10 the acid is selected from TFA, phosphoric acid, MSA, sulphuric acid, HBr and HCl, particularly the acid is HCl.
19. A process according to claim 18, wherein the solvent is selected from DCM, dioxane, EtOAc, IPAc, IPA, acetone, MIBK and mixed solvent of MIBK and acetone; particularly the solvent is MIBK.
- 15 20. A process according to claim 18 or 19, characterized in that the compound of formula (X) in step g) is isolated as through recrystallization in a solvent, wherein the solvent is selected from acetonitrile, IPAc, MIBK, ethanol, acetone, mixed solvent of acetone and methanol, and mixed solvent of acetone and MIBK, particularly the solvent is acetone.
21. A process according to any one of claims 1 to 3 and 7 to 20, characterized in that the
20 enantiomeric salt of compound of formula (XVI) or solvate in step i) is recrystallized in a solvent, wherein the solvent is selected from ethanol, MIBK, IPAc, toluene and MTBE, particularly the solvent is ethanol.
22. A process according to any one of claims 1 to 3 and 7 to 21, characterized in that the formation of the compound of formula (I) in step l) is performed in the presence of a base,
25 wherein the base is selected from TMP, DIPEA, TEA, tripropylamine, N,N-dicyclohexylmethylamine, DBU, NMM, 2,6-lutidine, 1-methylimidazole, 1,2-dimethylimidazole, tetra methylpiperidine-4-ol, Na₂CO₃, K₂CO₃, NaHCO₃ and tris(2-hydroxyethyl)amine; particularly the base is TMP or tris(2-hydroxyethyl)amine; and more particularly the base is tris(2-hydroxyethyl)amine.
- 30 23. A process according to claim 22, characterized in that the compound of formula (I) is purified in step l) through an acid-base work-up, wherein the acid used in the acid-base work-up is selected from HCl, HBr, H₂SO₄, H₃PO₄, MSA, toluene sulfonic acid and camphor sulfonic acid; particularly the acid is H₃PO₄, wherein the concentration of aqueous H₃PO₄ is selected from 15

5 wt% to 60 wt%, particularly the concentration of aqueous H_3PO_4 is from 35wt% to 40 wt%; the amount of H_3PO_4 is 5-25 eq. of compound of formula (XVII), particularly 10-15 eq.

24. A process according to any one of claim 22 or 23, characterized in that the compound of formula (I) is recrystallized in step I) in an organic solvent, wherein the organic solvent is selected from IPA, ethanol, EtOAc, IPAc, butyl acetate, toluene, MIBK, mixed solvent of acetone and water, mixed solvent of IPA and water, and mixed solvent of ethanol and water; particularly the solvent is mixed solvent of ethanol and water.

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