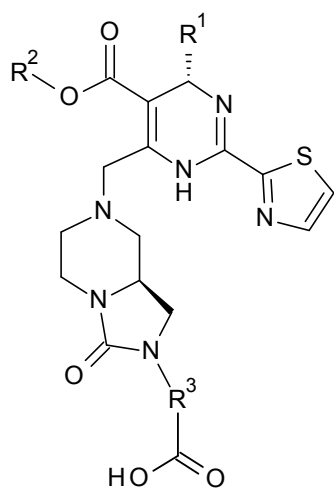


5 (f) 3-[(8aS)-3-oxo-1,5,6,7,8,8a-hexahydroimidazo[1,5-a]pyrazin-2-yl]-2,2-dimethylpropanoic acid (TFA salt, containing massive inorganic salt) is a sticky semi-solid, causing poor conversion and more impurities in final step, which leads to HPLC purification for the final API.

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;

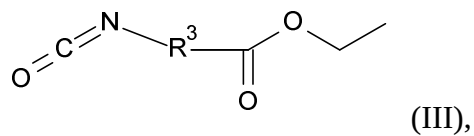
20 R³ is -C_xH_{2x}-;

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

or pharmaceutically acceptable salt or diastereomer thereof;

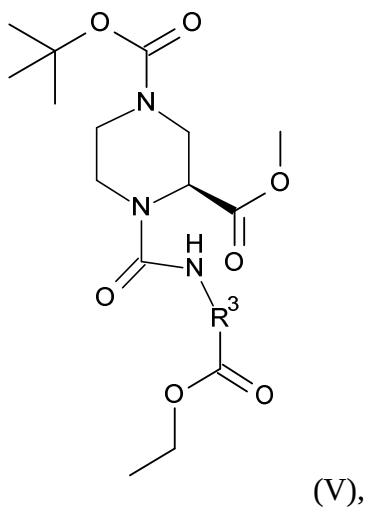
5 comprising one or more of the following steps:

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



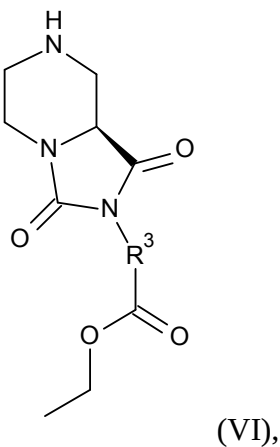
wherein R^3 is $-C_xH_{2x-}$; x is 1, 2, 3, 4, 5, 6 or 7;

10 step b) the formation of urea (V) via the addition reaction of isocyanate (III) and compound (IV),



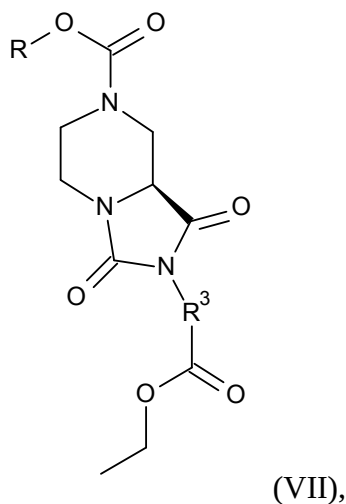
wherein R^3 is $-C_xH_{2x-}$; x is 1, 2, 3, 4, 5, 6 or 7;

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



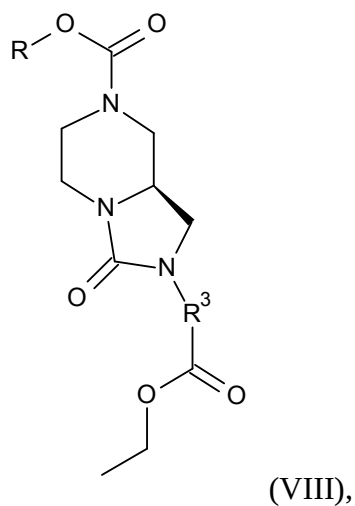
5 wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7;

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



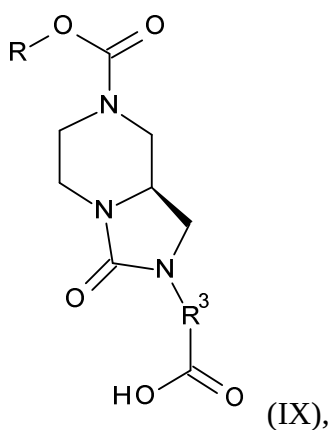
wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7; R is C_{1-6} alkyl;

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;

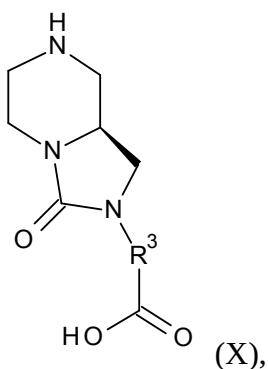
15 step f) the formation of the compound of formula (IX) via hydrolysis of the compound of formula (VIII),



5

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

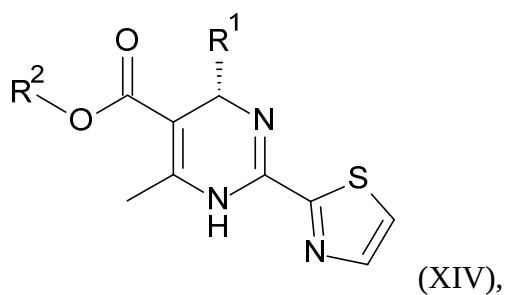
step g) the formation of compound of formula (X) by de-protection of the compound of formula (IX),



10

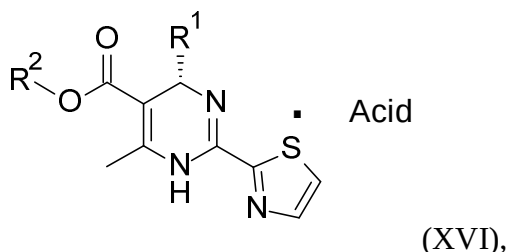
wherein R^3 is $-C_xH_{2x-}$; x is 1, 2, 3, 4, 5, 6 or 7;

step h) the formation of compound of formula (XIV) via Biginelli-like reaction,



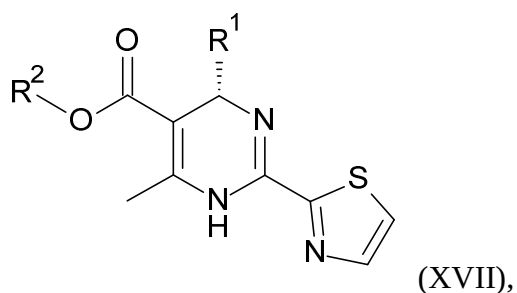
wherein R^1 is phenyl, which is unsubstituted or substituted with one, two or three substituents independently selected from halogen and C_{1-6} alkyl; R^2 is C_{1-6} alkyl;

- 5 step i) the formation and recrystallization of the enantiomeric salt of compound of formula (XVI) or solvate,



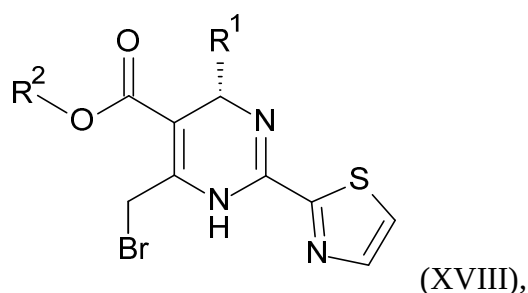
- wherein R^1 is phenyl, which is unsubstituted or substituted with one, two or three substituents independently selected from halogen and C_{1-6} alkyl; R^2 is C_{1-6} alkyl; acid is D-(+)-DTTA, L-DTTA, L-Tartaric acid, D-DBTA, (+)-CSA, (S)-(+)-1,1'-Binaphthyl-2,2'-diyl
- 10 hydrogen phosphate or (R)-(-)-1,1'-Binaphthyl-2,2'-diyl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

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



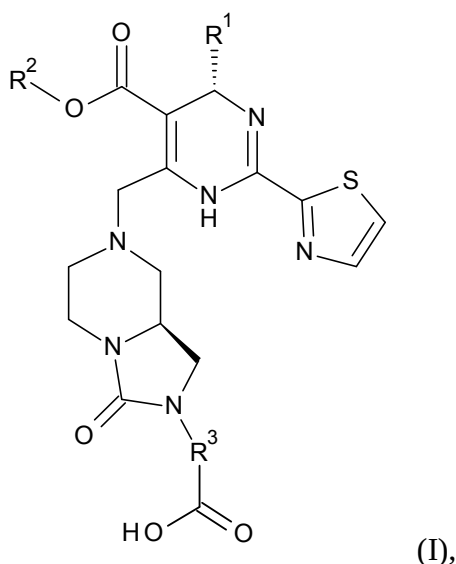
- 15 wherein R^1 is phenyl, which is unsubstituted or substituted with one, two or three substituents independently selected from halogen and C_{1-6} alkyl; R^2 is C_{1-6} alkyl;

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



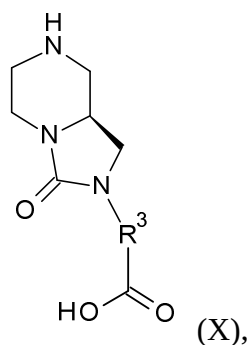
5 wherein R^1 is phenyl, which is unsubstituted or substituted with one, two or three substituents independently selected from halogen and C_{1-6} alkyl; R^2 is C_{1-6} alkyl;

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



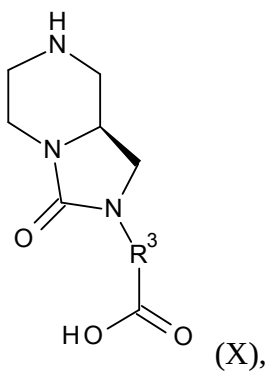
10 wherein R^1 is phenyl, which is unsubstituted or substituted with one, two or three substituents independently selected from halogen and C_{1-6} alkyl; R^2 is C_{1-6} alkyl; R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7.

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



15 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.

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



wherein

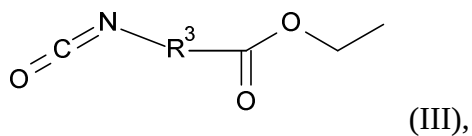
R^3 is $-C_xH_{2x}-$;

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

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof;

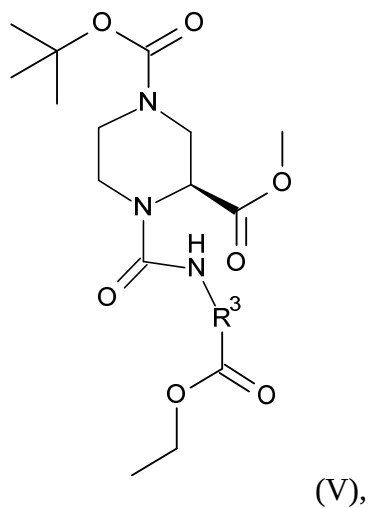
comprising one or more of the following steps:

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



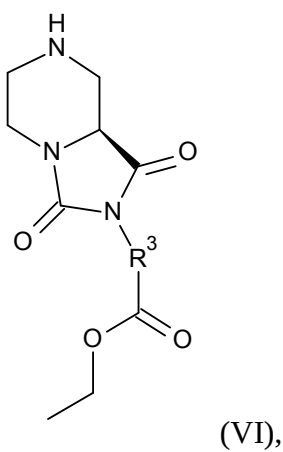
- 15 wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7;

5 step b) the formation of urea (V) via the addition reaction of isocyanate (III) and compound (IV),



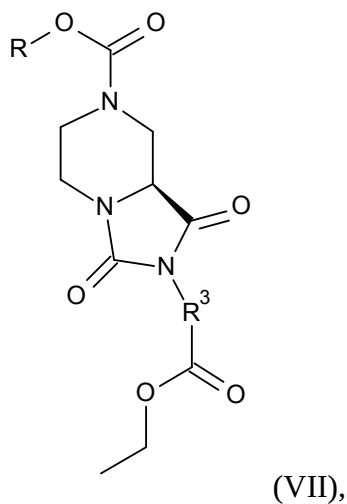
wherein R³ is -C_xH_{2x}-; x is 1, 2, 3, 4, 5, 6 or 7;

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



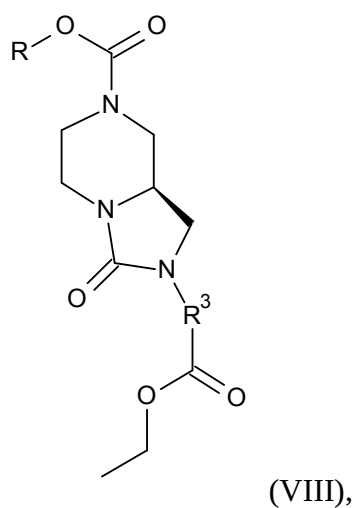
wherein R³ is -C_xH_{2x}-; x is 1, 2, 3, 4, 5, 6 or 7;

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



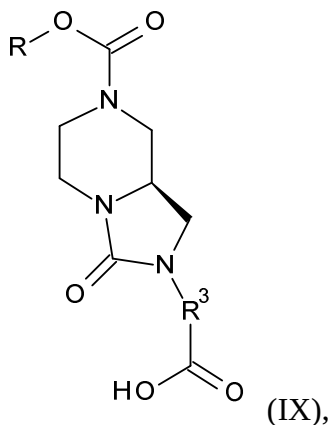
wherein R^3 is $\text{-C}_x\text{H}_{2x-}$; x is 1, 2, 3, 4, 5, 6 or 7; R is C_{1-6} alkyl;

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



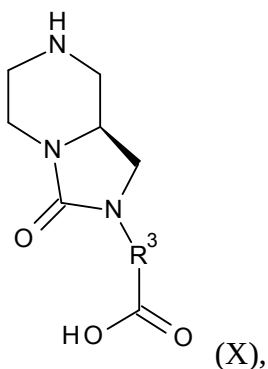
wherein R^3 is $\text{-C}_x\text{H}_{2x-}$; x is 1, 2, 3, 4, 5, 6 or 7; R is C_{1-6} alkyl;

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



wherein R³ is -C_xH_{2x}-; x is 1, 2, 3, 4, 5, 6 or 7; R is C₁₋₆alkyl;

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



wherein R³ 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.

5 DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

As used herein, the term “C₁₋₆alkyl” 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 “C₁₋₆alkyl” group is methyl or ethyl.

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