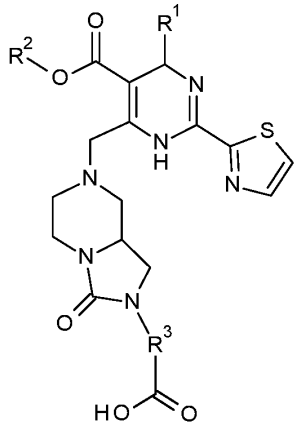
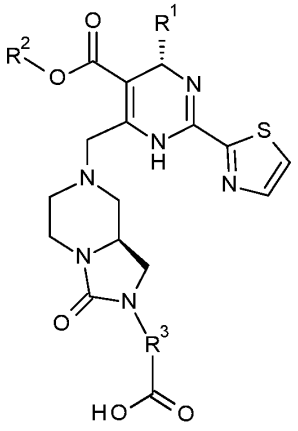
Alternative process for the preparation of 4-phenyl-5-alkoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1H-imidazo[1,5-a]pyrazin-2-yl]-carboxylic acid

The present invention relates to an alternative process for the preparation of a compound of formula (Ia),



(Ia),

particularly a compound of formula (I),



(I),

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;

or pharmaceutically acceptable salt or diastereomer thereof, which is useful for prophylaxis and treatment of a viral disease in a patient relating to hepatitis B infection or a disease caused by hepatitis B infection.

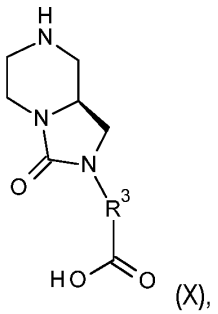
BACKGROUND OF THE INVENTION

An approach for synthesizing compounds of formula (I) was disclosed in patent WO 2015/132276. However, the synthetic approach is not suitable for a commercial process due to a number reasons which among others include (i) an overall low yield, (ii) expensive starting materials, (iii) cumbersome stereochemical separation and purification of chiral intermediates and the final product, and (iv) lack of robustness of the Swern oxidation step.

A more efficient synthetic approach which could also be applied on a technical scale and which allows for higher product yield and stereochemical purity was disclosed in WO 2017/140750.

The present invention now discloses a further modified synthetic approach for preparing a compound of formula (Ia) and in particular a compound of formula (I) suitable on an industrial scale which has a further reduced number of steps of the overall process, substantially reduces waste generation and is therefore more favorably in terms of overall costs compared to the processes previously described.

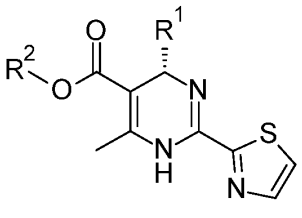
A first aspect of the present invention relates to a novel process for the preparation of a compound of the formula (X):



(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.

A second aspect of the present invention relates to a novel process for the preparation of a compound of formula (XVIII)

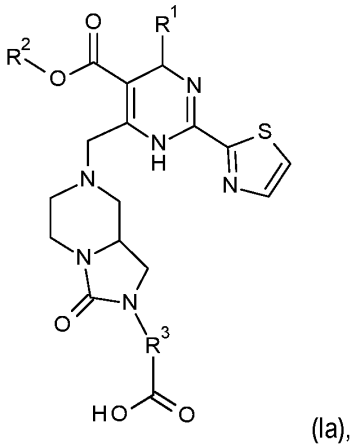


(XVIII),

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; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

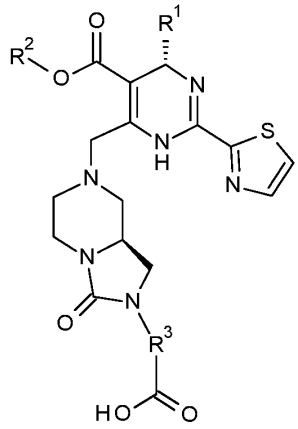
Compound of the formulae (X) and (XIX) are key intermediates in the synthesis and manufacture of pharmaceutically active compound of formula (I) as described herein.

A third aspect of the present invention relates to a novel process for the preparation of a compound of formula a compound of formula (Ia),



(Ia),

and in particular a compound of formula (I),



(I),

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;

or pharmaceutically acceptable salt or diastereomer thereof.

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. Particularly, "C_{1-6}alkyl" group is methyl or ethyl.

The term "halogen" signifies fluorine, chlorine, bromine or iodine, particularly fluorine or chlorine.

The term "diastereomer" denotes a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another.

The term "pharmaceutically acceptable salt" refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of formula I and are

formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Acid-addition salts include for example those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as *p*-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethyl ammonium hydroxide. The chemical modification of a pharmaceutical compound into a salt is a technique well known to pharmaceutical chemists in order to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. It is for example described in Bastin R.J., *et al.*, Organic Process Research & Development 2000, 4, 427-435; or in Ansel, H., *et al.*, In: Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th ed. (1995), pp. 196 and 1456-1457.

ABBREVIATION

ACN	Acetonitrile
API	active pharmaceutical ingredient
Boc	tert-Butoxycarbonyl
(R)-BNP acid	(R)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate
CPME	Cyclopentyl methyl ether
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIPEA	N,N-Diisopropylethylamine
eq	Equivalent
GABA	γ-aminobutyric acid
IPA	Isopropanol
IPAc	Isopropyl acetate
EtOAc or EA	ethyl acetate

MEK	2-Butanone
2-MeTHF	2-Methyltetrahydrofuran
MIBK	Methyl isobutyl ketone
MSA	Methanesulfonic acid
MTBE	Methyl tert-butyl ether
NBS	N-bromosuccinimide
NMM	N-methylmorpholine
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	tetrahydrofuran
TMP	2,2,6,6-Tetramethylpiperidine
v/v	Volume ratio
V65	2,2'-Azobis-(2,4-dimethylvaleronitrile)
wt%	Weight percentage

The present invention provides a process for preparing the compounds of formula (X) as outlined in the **Scheme 1** and compounds of formulae (XVIII) and (I) as outlined in the **Scheme 2**.

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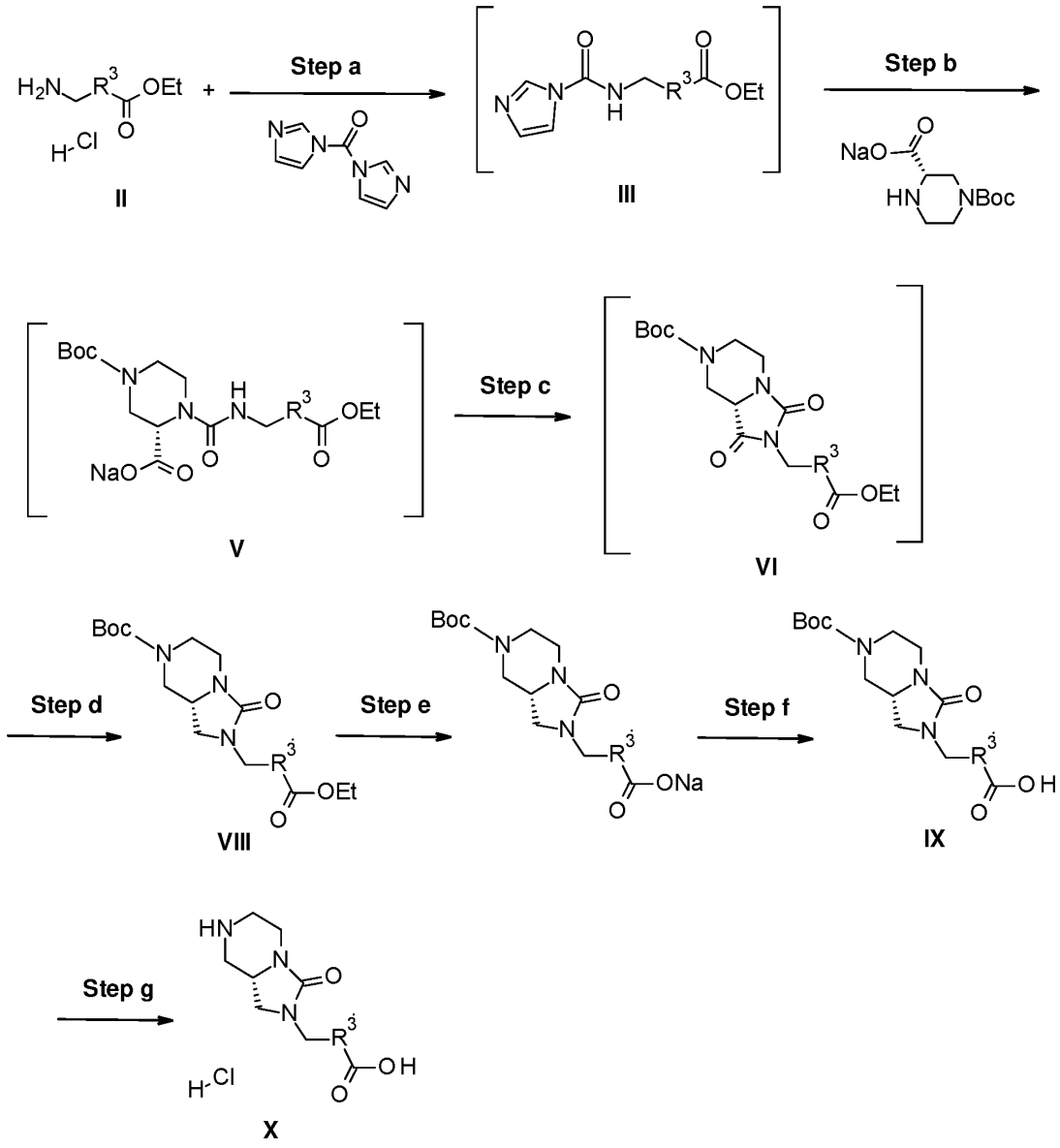
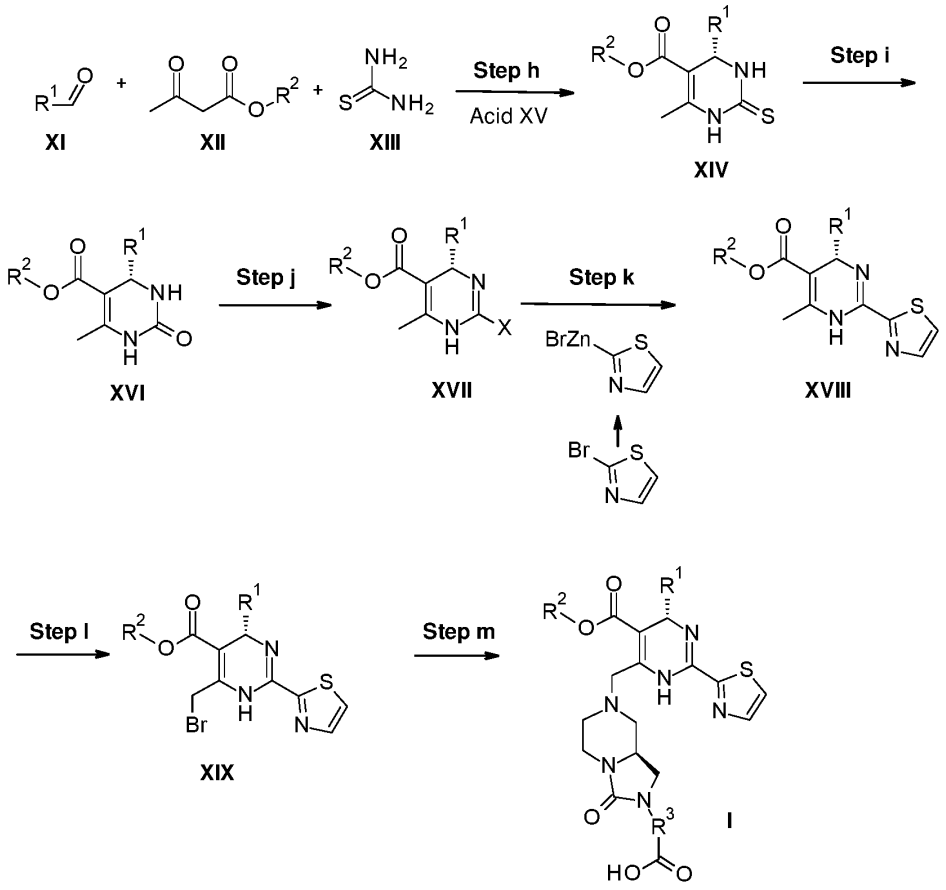
Scheme 1


Step a
Step b
Step c
Step d
Step e
Step f
Step g
II
III
V
VI
VIII
IX
X

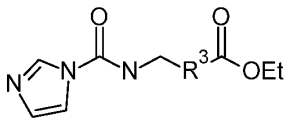
Scheme 2



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; Acid (XV) is (R)-3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate, (S)-3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate, (R)-(–)-3,3'-Bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate, (R)-(–)-VAPOL hydrogenphosphate, (+)-CSA, or (S)-(+)-1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate, (R)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate. Preferably, the acid of formula (XV) which functions as catalyst in step h) is (R)-(–)-3,3'-Bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate.

The synthesis comprises one or more of the following steps:

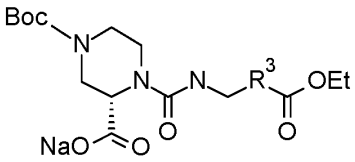
step a) the formation of compound (III),



(III),

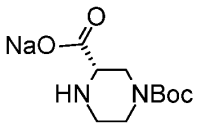
wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7;

step b) the formation of urea (V)



(V)

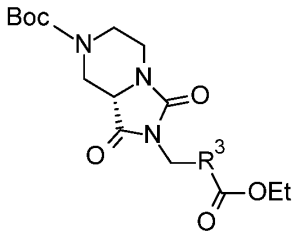
via the addition reaction of compound (III) and compound (IV)



(IV),

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

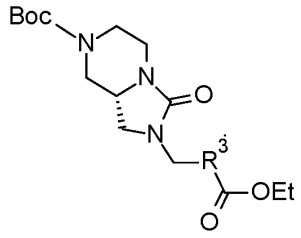
step c) the formation of the hydantoin of formula (VI) via the cyclization reaction of urea (V),



(VI),

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

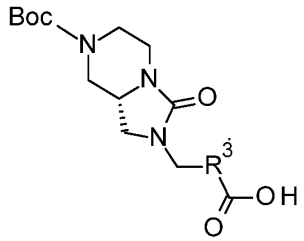
step d) the formation of the urea of formula (VIII) via selective reduction of the compound of formula (VI),



(VIII),

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

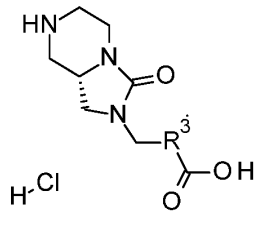
steps e) and f) the formation of the compound of formula (IX) via hydrolysis of the compound of formula (VIII),



(IX),

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

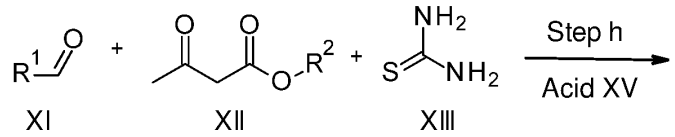
step g) the formation of compound of formula (X) by de-protection of the compound of formula (IX),



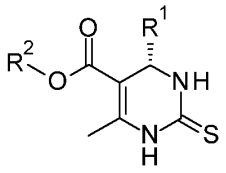
(X),

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 the reaction of compounds (XI), (XII) and (XIII) in the presence of acid (XV),



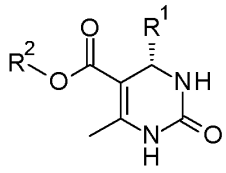
XI XII XIII



(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;

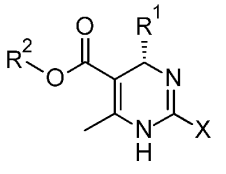
step i) the formation of compound of formula (XVI),



(XVI),

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;

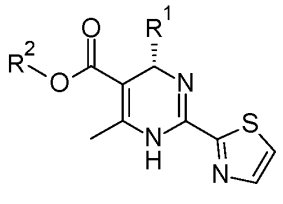
step j) the formation of compound of formula (XVII),



(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; X is halogen, preferably chlorine;

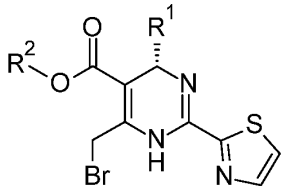
step k) the formation of compound of formula (XVIII),



(XVIII),

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;

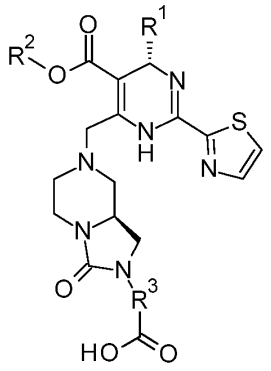
step l) the formation of compound of formula (XIX) via the bromination reaction of compound of formula (XVIII),



(XIX),

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 m) the formation of compound of formula (I) via the substitution reaction of compound of formula (XIX) with compound of formula (X),



(I),

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.

A detailed description of present invention of process steps is as following:

Step a) the formation of compound (III).

Compound (III) is formed in the presence of a suitable base in a suitable solvent from compound (II) and a suitable reagent, preferably 1,1'-carbonyldiimidazole (CDI). The conversion as a rule is performed under a cooling condition.

The suitable solvent is selected from 2-MeTHF, THF, IPAc, EA, DCM, DMF, toluene and anisole, particularly the suitable solvent is anisole.

The suitable base is selected from Na_2CO_3, NaOtPent, K_2CO_3, Na_3PO_4, K_3PO_4 and triethylamine (TEA). Preferably, the suitable base is TEA. The rate of the reaction is controlled at a temperature between -20 °C and 40 °C, particularly between 0°C and 5 °C.

The suitable reagent is selected from CDI, phosgene, diphosgene, disuccinimidyl carbonate, and triphosgene, preferably the reagent is CDI. The amount of CDI is from 1.0 to 2.0 eq. of compound of formula (II), particularly 1.1 to 1.5 eq.

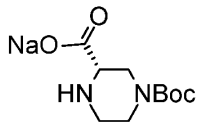
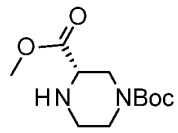
WO 2017/140750 discloses an alternative synthetic path for making compound X which uses a phosgene reagent in the formation of an isocyanate intermediate. The phosgene reagent is selected from phosgene, diphosgene and triphosgene. It is well known in the art that all those phosgene reagents are highly toxic. The synthetic process according to the present invention avoids any phosgene reagent and instead uses for instance CDI in step a).

Step b) the formation of urea (V) via the addition reaction of compounds (III) and (IV).

The urea (V) is synthesized in a suitable organic solvent. The conversion as a rule is performed under a mild heating condition.

The condensation reaction is conducted in a suitable organic solvent, which is selected from 2-MeTHF, THF, IPAc, EA, DMF, anisole, toluene and DCM. Particularly the solvent is anisole

The reaction is performed at temperature between 0 °C and 80 °C, particularly between 0 °C and 60 °C, more particularly between 30 °C and 50 °C.

In the present synthesis,  is used in step b) instead of  as in the previously described synthesis (WO 2017/140750). The sodium compound is substantially cheaper than the methoxy compound used in the previously described synthesis. Because of the presence of the free NH, it is more cumbersome to make the ester from the free acid (requires several steps). Thus, the sodium salt is substantially lot cheaper.

Step c) the formation of the hydantoin of formula (VI) via the cyclization reaction of urea (V).

The compound of formula (VI) is synthesized via the cyclization of urea (V) in the presence of a suitable acid in a suitable organic solvent. The conversion as a rule is performed under a cooling condition.

The suitable solvent is selected from 2-MeTHF, IPAc, EA, toluene, DCM, anisole, and DMF. Preferably the solvent is anisole

The suitable acidic dehydrating agent is selected from boron trifluoride etherate, phosphoric acid, sulphuric acid, chlorosulphonic acid, trifluoroacetic acid, HBr, HCl, $AlCl_3$, $TiCl_4$, $SnCl_4$, $ZrCl_4$, TMSOTf, pivaloyl chloride, isobutyl chloroformate and oxalyl chloride. Preferably, the acidic dehydrating agent is oxalyl chloride. The reaction is performed at temperatures between -20 °C and 20 °C, particularly between -5°C and 5 °C.

Step d) the formation of the urea of formula (VIII) via selective reduction of the compound of formula (VI).

The compound of formula (VIII) is synthesized in the presence of a suitable catalytic Lewis acid and a suitable reducing agent in a suitable solvent. The conversion is performed under a cooling condition.

The suitable solvent is selected from THF, 2-MeTHF and cyclopentyl methyl ether, particularly the solvent is THF or 2-MeTHF or anisole.

The suitable reducing agent is selected from lithium aluminum hydride, sodium dihydro-bis-(2-methoxyethoxy)aluminate, borane dimethylsulfide, phenylsilane, borane, borane dimethylsulphide complex and borane tetrahydrofuran complex, particularly the reductive reagent is borane tetrahydrofuran complex. The amount of borane tetrahydrofuran complex is 1.6-5.0 eq. of the compound of formula (VI), particularly 1.6-2.0 eq.

The catalytic Lewis acid is selected from $InCl_3$, YCl_3, $ZnCl_2$, $Zn(OAc)_2$, TMSCl, $TiCl_4$, $ZrCl_4$, $AlCl_3$, BF_3·THF, and BF_3·Et_2O, particularly the Lewis acid is BF_3·Et_2O. The amount of BF_3·Et_2O is 0.05-1.1eq. of the compound of formula (VI), particularly 0.2 eq.

The reaction is performed at a reaction temperature between -40 and 40 °C, particularly between 10 °C and 15 °C.

Usually 4-5 eq. of borane tetrahydrofuran complex can give 100 % conversion but suffer from poor selectivity of reduction over other carbonyl groups. With catalytic amounts of BF_3· Et_2O, not only the selectivity is improved but also the amount of borane tetrahydrofuran complex is decreased from 4-5 eq. to 1.6-2.0 eq.

Steps e) and f) the formation of the compound of formula (IX) via hydrolysis of the compound of formula (VIII).

The compound of formula (IX) is synthesized in the presence of a suitable base in a suitable solvent followed by a work-up procedure.

The suitable solvent is selected from THF, MeTHF, TBME, toluene, anisole, isopropanol, methanol and ethanol and their mixtures with water. Particularly the solvent is a mixture of water andanisole.

The suitable base for hydrolysis is selected from LiOH, LiOOH, NaOTMS, KOTMS, KOtBu, NaOH and KOH. Particularly the base is aq. NaOH.

The reaction is performed at temperature between 0 °C and 70 °C, particularly between 40 °C and 60 °C.

The compound of formula (IX) is isolated through a work-up procedure comprising of phase separation, acidification and isolation of the resulting free acid.

In one embodiment of the present invention, steps a) to f) will be carried out in a single reaction vessel as a so-called one-pot synthesis. This circumvents several purification procedures of the intermediates formed in relation to steps a) to f) and thereby minimizing chemical waste, saving time and simplifying other aspects of the chemical process like reducing energy consumption and use of equipment.

Step g) the formation of compound of formula (X) by deprotection of the compound of formula (IX).

Compound of formula (X) is synthesized in the presence of a suitable acid in a suitable solvent.

The suitable solvent is selected from DCM, toluene, dioxane, EtOAc, IPAc, IPA, 1-propanol, acetone, MIBK and mixed solvent of MIBK and acetone. Particularly the solvent is MIBK.

The suitable acid is selected from TFA, phosphoric acid, MSA, sulphuric acid, HBr and HCl. Particularly the acid is TFA or HCl, and more particularly the acid is HCl.

The addition rate of the acid is controlled while the reaction temperature is maintained between 0 °C and 60 °C, particularly between 20 °C and 30 °C while the gas release can be controlled.

The amount of acid is 3-10 eq. of the compound of formula (IX), particularly 3-4 eq.

After an appropriate amount of time, usually 0.5-2 hours, the reaction is completed with monitoring by HPLC. The compound of formula (X) is isolated as a solid from the reaction mixture. The compound of formula (X) precipitates in the reaction mixture and is separated by filtration followed by one or more washing steps using the solvent in which the reaction had been carried out.

One aspect of the present invention relates to a synthetic process for making the compound of formula (X) comprising at least one of the steps a) to g).

Step h) the formation of compound of formula (XIV) via the reaction of compounds (XI), (XII) and (XIII) in the presence of acid (XV).

Compound of formula (XIV) is synthesized in the presence of a suitable catalyst in a suitable solvent. The conversion as a rule is performed under Dean-Stark water removal conditions (reduced pressure).

The suitable solvent is selected from methanol, ethanol, IPA, tert-BuOH, 2,2,2-trifluroethanol, benzene, xylene, anisole, chlorobenzene and toluene, particularly the solvent is toluene.

The suitable organic acid catalyst used in the enantioselective Biginelli reaction is selected from (S)-(+)-3,3'-Bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl hydrogen-phosphate, (R)-(-)-3,3'-Bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl hydrogen-phosphate, D-(+)-DTTA, L-DTTA, L-Tartaric acid, D-DBTA, (+)-CSA, (S)-(+)-1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate and (R)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate, (R)-3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate, (S)-3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate, (R)-(–)-VAPOL hydrogenphosphate particularly the organic acid is (R)-(-)-3,3'-Bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl hydrogen-phosphate.

WO 2017/140750 discloses an alternative synthetic path for making compound (XIX) wherein in the formation and recrystallization of the enantiomeric salt of the compound of formula (XVI) preferably either (S)-(+)-1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate or (R)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate is used. In one embodiment of the present invention, either (S)-(+)-3,3'-Bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl hydrogen-phosphate or (R)-(-)-3,3'-Bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl hydrogen-phosphate, preferably (R)-(-)-3,3'-Bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl hydrogen-phosphate is used in the step h) wherein the compound of formula (XIV) is formed enantiospecifically. In contrast to the teaching of WO 2017/140750 wherein equimolar amounts of either (S)-(+)-3,3'-Bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl hydrogen-phosphate or (R)-(-)-3,3'-Bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl hydrogen-phosphate are necessary, the amount of the corresponding 1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate needed in the process step h) according to the present invention is just 0.01 equimolar. Therefore, a substantial reduction of process waste and costs over the processes previously described in the art is possible with the synthetic path according to the present invention.

Step i) the formation of compound of formula (XVI).

Compound of formula (XVI) is synthesized in the presence of a suitable catalyst at a suitable pH using a suitable reagent in a suitable solvent.

The suitable solvent is selected from mixtures of water with two of either methanol, ethanol, 2,2,2-trifluroethanol, toluene, ACN, DMF, EtOAc or dimethyl carbonate, particularly the solvent is a mixture of water, ethanol and ACN.

The suitable reagent used in the reaction is selected from sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, formic acid, acetic acid, particularly the catalyst is sodium hydrogencarbonate.

The suitable pH for this reaction is between 5 and 12, particularly the pH is between 7 and 10.

The suitable reagent used in the reaction is selected from mCPBA, tBuOOH, urea hydrogen peroxide complex, dibenzoyl peroxide, oxone, and an aqueous solution of hydrogen peroxide, particularly the reagent is an aqueous solution of hydrogen peroxide.

Step j) the formation of compound of formula (XVII).

Compound of formula (XVII) is synthesized using a suitable reagent in a suitable solvent.

The suitable solvent is selected from toluene, xylenes, chlorobenzene, heptane, ACN, dichloromethane, particularly the solvent is toluene.

The suitable reagent is selected from oxalyl chloride, PCl_5, $POCl_3$, $SOCl_2$, and MsCl, particularly the reagent is $POCl_3$.

Step k) the formation of compound of formula (XVIII).

Compound of formula (XVIII) is synthesized using a suitable catalyst and a suitable reagent in a suitable solvent and isolated as a suitable salt, preferably as the HBr salt.

The suitable catalyst is selected from complexes of either Xantphos or dppf with Palladium(II)-salts, particularly the catalyst is $XantphosPdCl_2$.

The suitable reagent is selected from bromo(thiazol-2-yl)magnesium, thiazol-2-ylboronic acid and bromo(thiazol-2-yl)zinc, particularly the reagent is bromo(thiazol-2-yl)zinc.

The suitable solvent is selected from toluene, xylenes, chlorobenzene, THF, 2-Methyltetrahydrofurane, ACN, dichloromethane, particularly the solvent is toluene.

Step l) the formation of compound of formula (XIX) via the bromination reaction of compound of formula (XVIII).

Compound of formula (XVIII) is synthesized in the presence of a suitable bromination reagent with or without a suitable additive in a suitable organic solvent. The conversion as a rule is performed under a heating condition.

The suitable bromination reagent is selected from NBS, bromine, pyridine tribromide and 1,3-dibromo-5,5-dimethylhydantion, particularly the bromination reagent is NBS. The bromination reaction is performed at the temperature between 0 °C and 80 °C, particularly between 35 °C and 40 °C.

The reaction is usually performed in an organic solvent selected from carbon tetrachloride, 1,2-Dichloroethane, ACN, acetic acid, fluorobenzene, chlorobenzene and DCM, particularly the organic solvent is DCM.

Another aspect of the present invention relates to a synthetic process for making the compound of formula (XIX) comprising at least one of the steps h) to l).

WO 2017/140750 discloses an alternative synthetic path for making compound (XIX). However, the synthetic process according to the present invention is estimated to provide for (i) >50% waste reduction, (ii) >20% lower costs and (iii) a substantially shortened process of ≥3 steps shorter over the process disclosed in WO 2017/140750.

Step m) the formation of compound of formula (I) via the substitution reaction of compound of formula (XIX) with compound of formula (X).

Compound of formula (I) is synthesized in the presence of a suitable base in a suitable organic solvent.

The suitable 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, Na_2CO_3, K_2CO_3, $NaHCO_3$ and tris(2-hydroxylethyl)amine; particularly the base is TMP or tris(2-hydroxylethyl)amine; and more particularly the base is tris(2-hydroxylethyl)amine.

The suitable pKa and nucleophilicity of the base are directly related to the yield and impurities formation in this step. Both TMP and tris(2-hydroxylethyl)amine could result in good yield with high

selectivity, but hydrazine related impurities might be introduced to the final API when using TMP as the base.

The suitable organic solvent is selected from THF, IPAc EtOAc, MTBE, fluorobenzene, chlorobenzene and DCM, particularly the organic solvent is DCM.

The substitution reaction as a rule is performed at the temperature between 0 °C and 40 °C, particularly at temperature between 10 °C and 25 °C.

An efficient purification procedure through an acid-base work-up and recrystallization is needed to ensure the purity of API.

The purification procedure of compound of formula (I) includes: 1) acid-base work-up with a suitable acid and a suitable base in a suitable solvent; and 2) recrystallization which is performed with or without suitable seeding in a suitable organic solvent.

The acid used in the acid-base work-up for purification of compound of formula (I) is selected from HCl, HBr, H_2SO_4, H_3PO_4, MSA, toluene sulfonic acid and camphor sulfonic acid, particularly the acid is H_3PO_4. The concentration of aqueous H_3PO_4 is selected from 15 wt% to 60 wt%; particularly the concentration of aqueous H_3PO_4 is from 35 wt% to 40 wt%. The amount of H_3PO_4 is essential and carefully designed to get the maximum recovery of API and minimum impurities.

The base used in the acid-base work-up for purification of compound of formula (I) is selected from NaOH, KOH, K_2CO_3 and Na_2CO_3, particularly the base is NaOH.

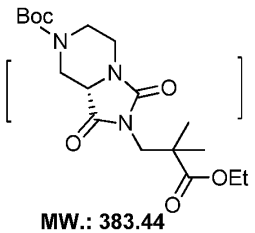
The suitable organic solvent used for extracting impurities in the acid-base work-up for purification of compound of formula (I) is selected from MTBE, EA, IPAc, butyl acetate, toluene and DCM; particularly, the organic solvent is EA or DCM; and more particularly the solvent is DCM.

The suitable solvent for recrystallization of compound of formula (I) 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. Seeding amount is 0.1-5 wt% of compound of formula (I), particularly the seeding amount is 1wt%.

EXAMPLES

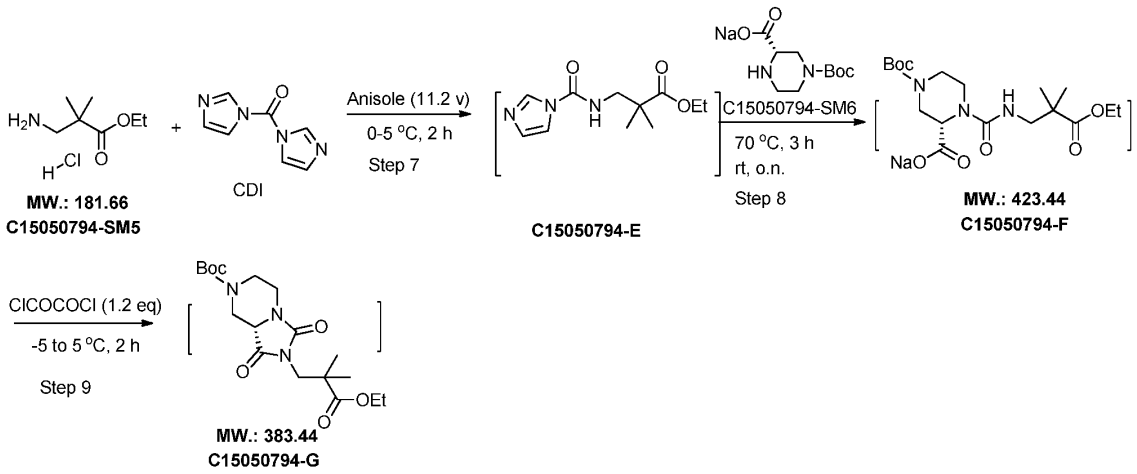
Example 1

Preparation of C15050794-G (Example 1):



MW.: 383.44
C15050794-G

The title compound was prepared according to following scheme:



Production of C15050794-G was carried out in two batches. For C15050794-G17601, 1243.4 kg of C15050794-G anisole solution was obtained from 118.35 kg of C15050794-SM6 and 90.0 kg C15050794-SM5 with 92.8% purity, 12.6% assay, 96.6% e.e. in 87% yield. For C15050794-G17602, 1214.6 kg anisole solution of C15050794-G was obtained from 117.35 kg of C15050794-SM6 and 88.9 kg C15050794-SM5 with 93.3% purity, 12.2% assay, 97.5% e.e. in 83% yield. The details are summarized in table below.

Raw materials for preparation of C15050794-G17601

Batch No.	Material	MW	Quantity (kg)	Rel Wt/Vol (1X=118 kg)	Spec	Eq.
C13022716-K17401	C15050794-SM6 (S)-4-(tert-butoxycarbonyl) Piperazine-2-carboxylate	252.24	118	1.00	Purity≥98.0% e.e.≥98.0%	1.00
17081873	C15050794-SM5 Ethyl-3-amino-2,2-di-methylpropanoat ehydrochloride	181.66	90.0	0.76	Assay≥78%	1.06
17032708	CDI	N/A	93.3	0.79	Assay≥98%	N/A
15070656	Oxalyl chloride	N/A	109	0.92	Purity≥98.0%	N/A
16031116	Methoxybenzene (anisole)	N/A	962	8.2	Purity≥99%	N/A
17051771	Et_3N	N/A	48.2	0.4	Purity≥99.0% KF≤0.2%	N/A
17081716/17012242	$KHCO_3$	N/A	249.15	2.1	Assay≥99.0%	N/A
170721/170803/170912	25% NaCl aq.	N/A	2002	2002	N/A	N/A
N/A	THF	N/A	893.26	7.57	Purity≥99.8% KF≤0.05%	N/A
170915/PW-21074 170912/PW-21073	Process water	N/A	3182	26.97	pH 6.5-8.5	N/A

Raw materials for preparation of C15050794-G17602

Batch No.	Material	MW	Quantity (kg)	Rel Wt/Vol (1X=118 kg)	Spec	Eq.
17082963/17082965/17082964	C15050794-SM6 (S)-4-(tert-butoxycarbonyl)Piperazine-2-carboxylate	252.24	117	0.99	Purity≥98.0% e.e.≥98.0%	1.00
17081873	C15050794-SM5 Ethyl-3-amino-2,2-di-methylpropanoat ehydrochloride	181.66	88.9	0.75	Assay≥78%	1.06

Batch No.	Material	MW	Quantity (kg)	Rel Wt/Vol (1X=118 kg)	Spec	Eq.
17032708	CDI	N/A	92.3	0.78	Assay≥98%	N/A
16062306/16072761	Oxalyl chloride	N/A	102	0.86	Purity≥98.0%	N/A
16032125/16031116	Methoxybenzene (anisole)	N/A	946	8.02	Purity≥99%	N/A
17051771	Et_3N	N/A	47	0.40	Purity≥99.0% KF≤0.2%	N/A
C15050794-G17601	12% $KHCO_3$	N/A	1296	10.98	Assay≥99.0 %	N/A
170721/170919	25% NaCl aq.	N/A	1404	11.90	N/A	N/A
N/A	THF	N/A	689	5.84	Purity≥99.8% KF≤0.05%	N/A
170920/21074	Process water	N/A	804	6.81	pH 6.5-8.5	N/A

Plant result for preparation of C15050794-G

Batch No.	Starting Material (corrected by assay)	Product	Purity (HPLC Area)	Purity (w/w assay)	e.e.	Yield
C15050794-G17601	118.35 kg	1243.4 kg	92.8%	12.6%	96.6%	87%
C15050794-G17602	117.35 kg	1214.6 kg	93.3%	12.2%	97.5%	83%

Equipment for preparation of C15050794-G17601~G17602

Equip. Name	MBR Code	Process Requirement	Equip. Code
Reactor	R1	GL/3000L	R210303
	R2	GL/3000L	R210103
Pump	P1	SS	P630040
Peristaltic pump	P2	SS	P636005
Pump	P3	SS	P634004

Equip. Name	MBR Code	Process Requirement	Equip. Code
Tank	T1	HDPE	T12074
	T2	HDPE	T12046
	T3	HDPE	T12102
	T4	HDPE	T12101
	T5	HDPE	T12103
	T6	HDPE	T12105
	T7	HDPE	T12040
	T8	HDPE	T21063

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Detailed Process Description of C15050794-G

Operation	G17601 (1X=118)	G17602 (1X=118)
1. Charge process water (15.0-22.0X) into R210103	2360 kg	N/A
2. Adjust R210103 to 25-35°C	27.2 °C	N/A
3. Charge $KHCO_3$ (2.0-3.0X) into R210103	240 kg	N/A
4. Stir R210303 at 25-35°C for NLT 0.5 h	40 min	N/A
5. Load the material into tank		N/A
6. Charge THF into R210303	323 L	323 L
7. Heat R210303 to 60-70°C, distillate for 15-30 min	64.2 °C	61.2°C
8. Reflux R210303 for 15-30 min	30 min	30 min
9. Adjust R210103 to 20-30°C	28.8 °C	26.1°C
10. Load the material into drums		
11. Adjust R210303 to 100-110°C	104.9 °C	105.0°C
12. Dry R210303 for 1-2 h at 100-110°C	1 h	2 h
13. Adjust R210303 to 20-40°C	34.7 °C	35.4°C
14. Charge CDI (0.67-0.80X) into R210303	93.3 kg	92.3 kg
15. Charge anisole (6.8-9.0X) into R210303	840 kg	837kg
16. Adjust R210303 to -5-5°C	-2.3 °C	-1.2°C

Operation	G17601 (1X=118)	G17602 (1X=118)
17. Charge C15050794-SM5 (0.67-0.77X) into R210303	90 kg	88.9 kg
18. Charge anisole into R210303	50 kg	41 kg
19. Stir R210303 at -5-5°C for 1-3 h	2 h	2 h
20. Charge TEA (0.36-0.42X) into R210303	48.2 kg	47 kg
21. Stir R210303 at -5-5°C for 10-20 h	20 h	20 h
22. Charge C15050794-SM6 (0.99-1.01X) into R210303	118 kg	117 kg
23. Charge anisole into R210303	50 kg	48kg
24. Adjust R210303 to 35-45°C and stir for 5-15 h	7 h 35 min	8 h
25. IPC: Purity of F (Spec.: FIO), SM6/F≤1.0%	F%=65.4%, SM6/F=0.1%	F%=65.8%, SM6/F=0.2%
26. Adjust R210303 to -5-5°C	-2.7°C	0.7°C
27. Charge oxalyl chloride (0.76-1.05X) into R210303	109 kg	102 kg
28. Charge anisole into R210303	22 kg	20 kg
29. Stir R210303 for 1-3 h	1 h	1 h
30. IPC: Purity of G (Spec.: FIO), F/G≤1.5%	G%=76.5%, F/G=0.5%	G%=74.3%, F/G=0.8%
31. Charge 12% $KHCO_3$ (8-12X) of step 5 into R210303 at -5-10°C	1300 kg	1296 kg
32. Adjust R210303 to 15-25°C and stir for 30-60 min	1 h	1 h
33. Stand for 30-60 min	1 h	1 h
34. Transfer the aqueous layer into tank		
35. IPC: residual of G in aqueous layer (Spec.: FIO)	0.2%	0.01%
36. Charge 25% NaCl (4-5X) into R210303	590 kg	580 kg
37. Charge process water (6-7X) into R210303	822 kg	804 kg
38. Adjust R210303 to 15-25°C and stir for 30-60 min	1 h	1 h

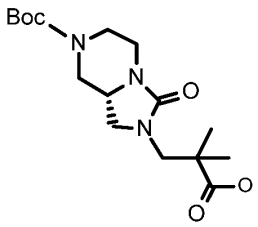
Operation	G17601 (1X=118)	G17602 (1X=118)
39. Stand for 30-60 min	1 h	1 h
40. Transfer the aqueous layer into tank		
41. Charge 25% NaCl (10-12X) into R210303	1412 kg	1404 kg
42. Adjust R210303 to 15-25°C and stir for 30-60 min	1 h	1 h
43. Stand for 30-60 min	1 h	1 h
44. Transfer the aqueous layer into tank		
45. IPC: residual of G in aqueous layer (Spec.: FIO)	N.D.	0.01%
46. Charge THF into R210303	472 L	452 L
47. Concentrate R210303 mixture to 1062-1534 L at ≤45°C	27.5°C	25.5°C
48. Adjust R210303 to 20-30°C	27.3°C	25.4°C
49. IPC: KF≤0.10%	0.03%	0.03%
50. Adjust R210303 to 10-30°C	23.6°C	25.7°C
51. Load the material into drum (C15050794-G anisole solution)	Total weight: 1243.4 kg	Total weight: 1214.6 kg
52. IPC: G% (Spec.: FIO), assay of G% (Spec.: FIO), e.e.% of G (Spec.: FIO)	G%=92.8%, assay of G%=12.6%, e.e.% of G=96.6%	G%=93.3%, assay of G%=12.2%, e.e.% of G=97.5%

C15050794-G (Example 1):

MS calcd C18 H29 N3 O6 [M+Na]+: 406.2, Found: 406.4, 1H NMR (300 MHz, CDCl3) δ ppm 4.50 (br s, 1H), 4.23 - 4.01 (m, 4H), 3.96 (dd, J = 4.7, 11.2 Hz, 1H), 3.66 (s, 2H), 3.01 (dt, J = 3.8, 12.8 Hz, 1H), 2.81 - 2.59 (m, 2H), 1.55 - 1.42 (m, 9H), 1.37 - 1.23 (m, 6H), 1.21 (s, 6H)

Example 2

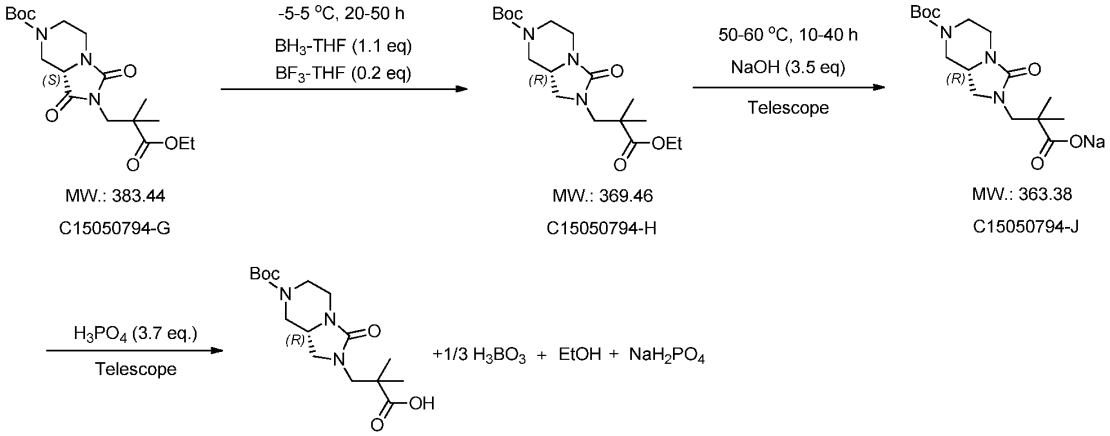
Preparation of C15050794-K (Example 2):



MW.: 341.40

C15050794-K

The title compound was prepared according to following scheme:



Production of C15050794-K was carried out in two batches. For C15050794-K17601, 56.75 kg (purity: 100.0%, assay: 100.0%, e.e. %: 99.2%) and 36.70 kg (purity: 100.0%, assay: 99.5%, e.e. %: 99.1%) of C15050794-K was obtained from 1239.0 kg of C15050794-G anisole solution (assay: 12.60%) in 67% yield. For C15050794-K17602, 54.45 kg (purity: 100.0%, assay: 98.6%, e.e. %: 99.4%) and 50.05 kg (purity: 100.0%, assay: 99.6%, e.e. %: 99.4%) of C15050794-K was obtained from 1214.6 kg of C15050794-G anisole solution (assay: 12.20%) in 78% yield. The details are summarized in table below.

Raw materials for preparation of C15050794-K17601

Batch No.	Material	MW	Quantity (kg)	Rel Wt/Vol (1X=156.0 kg)	Spec	Eq.
C15050794-G17601	C15050794-G	383.44	156.1	1.00	Assay=12.60%	1.00
17091163	BF_3-THF	139.91	13	0.08	Assay≥45%	0.23
17092868	BF_3-THF (1M)	85.94	463	2.97	Conc.=0.95M~1.10M	1.3
PC00637-125-K	C15050794-K Seed	341.4	0.25	0.00	N/A	N/A
17071961	Na_2CO_3	N/A	45	0.29	Assay=98%~101%	N/A
171003/171027B	25% NaCl solution	N/A	1350	8.65	N/A	N/A
16071562	NaOH	N/A	65.7	0.42	Assay≥98%	N/A
171031	MTBE	N/A	402	2.58	Purity≥98.0% KF≤0.1%	N/A
171031	MeOH	N/A	400	2.56	Purity≥99.5% KF≤0.10%	N/A
17091862	H_3PO_4	N/A	200.1	1.28	Assay≥85.0%	N/A
171028/PW-21074, 171029/ PW -21073, 171030/ PW -21079, 171101/ PW -21079, 171102/ PW -21079, 171104/ PW -21074, 171105/ PW -21074	Process water	N/A	4740	30.38	pH=6.5-8.5	N/A
171027/171029	THF	N/A	324	2.08	N/A	N/A

Raw materials for preparation of C15050794-K17602

Batch No.	Material	MW	Quantity (kg)	Rel Wt/Vol (1X=148.0 kg)	Spec	Eq.
C15050794-G17602	C15050794-G	383.44	148.2	1.00	Assay=12.20%	1.00

Batch No.	Material	MW	Quantity (kg)	Rel Wt/Vol (1X=148.0 kg)	Spec	Eq.
17091163	BF_3-THF	139.91	12.5	0.08	Assay≥45%	0.23
17092868	BF_3-THF (1M)	85.94	460.2	3.11	Conc.=0.95M~1.10M	1.3
PC00637-125-K	C15050794-K Seed	341.4	0.31	0.00	N/A	N/A
17071961/17091467	Na_2CO_3	N/A	45	0.30	Assay=98%~101%	N/A
171027B/171027A	25% NaCl solution	N/A	1356	9.16	N/A	N/A
16071562	NaOH	N/A	65	0.44	Assay≥98%	N/A
171104	MTBE	N/A	402	2.72	Purity≥98.0% KF≤0.1%	N/A
171104/171107	MeOH	N/A	542	3.66	Purity≥99.5% KF≤0.10%	N/A
17091862/17061610	H_3PO_4	N/A	204.9	1.38	Assay≥85.0%	N/A
171031/ PW -21074, 171101/ PW -21074, 171103/ PW -21079, 171104/ PW -21079, 171105/ PW -21077, 171106/ PW -21039, 171107/ PW -21039	Process water	N/A	5410	36.55	pH=6.5-8.5	N/A
171027/171029	THF	N/A	234	1.58	N/A	N/A

Plant result for preparation of C15050794-K

Batch No.	Starting Material (corrected by assay)	Product	Purity (HPLC Area)	Purity (w/w assay)	e.e	Yield
C15050794-K17601	156.11 kg	56.75 kg	100.0%	100.0%	99.2%	67%
		36.70 kg	100.0%	99.5%	99.1%	
C15050794-K17602	148.18 kg	54.45 kg	100.0%	98.6%	99.4%	78%
		50.05 kg	100.0%	99.6%	99.4%	

Equipment for preparation of C15050794-K17601~K17602

Equip. Name	MBR Code	Process Requirement	Equip. Code
Reactor	R1	GL/3000L	R210302
	R2	GL/5000L	R210304
	R3	SS316L/3000L	R210403
Tank	T1	HDPE	T631121
	T2	HDPE	T631134
	T3	HDPE	T631158
	T4	SS	T630013
	T5	SS	T630018
	T6	HDPE	T631159
	T7	HDPE	T631166
	V1	GL	V2104C
	V2	GL	V2104B
	V3	GL	V2103A
Pump	P1	PP	P634008
	P2	PP	P634005
	P3	SS	P630056
Bag filter	Fb1	SS	Fb630002
Centrifuge	M1	TI/HL	M210302
	M2	TI/HL	M210101
Mother liquor tank	MV1	GL	MV210302
	MV2	GL	MV210101
Dryer	D1	SS, Tray	D211001
	D2	SS, Tray	D211005

Detailed Process Description of C15050794-K

Operation	K17601 (1X=156.0 kg)	K17602 (1X=148.0 kg)
53. Charge C15050794-G (1.00X±0.01X) anisole solution into R210302	156.1 kg	148.2 kg

Operation	K17601 (1X=156.0 kg)	K17602 (1X=148.0 kg)
54. Charge THF (5-15 kg) into R210302	10 kg	8 kg
55. Adjust R210302 to -10-5°C	-5.1°C	-4.8°C
56. Charge BH_3-THF (1M) (0.3-2.0X) into R210302	88.0 kg	87.2 kg
57. Charge THF (5-15 kg) into R210302	12 kg	14 kg
58. Charge BH_3-THF (0.065-0.106X) into R210302	13.0 kg	12.5 kg
59. Charge THF (5-15 kg) into R210302	8 kg	6 kg
60. Charge BH_3-THF (1M) (1.5-3.5X) into R210302	375 kg	373 kg
61. Charge THF (5-15 kg) into R210302	6 kg	8 kg
62. Adjust R210302 to -5-5°C	-1.6°C	-1.4°C
63. Stir R210302 for 20-50 h	30 h	28 h
64. IPC: G/H% (Spec.≤3%), purity of H% (Spec.: FIO)	G/H%=1%, H%=81.4%	G/H%=1%, H%=82.7%
65. Adjust R210302 to -10-0°C	-0.2°C	-4.6°C
66. Charge Na_2CO_3 (0.16-0.48X) into R210304	45.0 kg	45.0 kg
67. Charge process water (9-13X) into R210304	1754 kg	1796 kg
68. Adjust R210302 to 25-35°C, stir NLT 0.5 h	30.8°C	26.8°C
69. Adjust R210302 to 0-20°C	8.1°C	8.1°C
70. Charge C15050794-H solution into R210304 in portions		
71. Charge THF (20-50 kg) into R210302	46 kg	30 kg
72. Charge the THF solution above into R210304		
73. Stir R210304 for 0.5-1.0 h	40 min	45 min
74. Adjust R210304 to 20-30°C, stir for 0.5-1.0 h and stand for 1-5 h	21.6°C	23.5°C
75. Transfer R210304 aqueous layer into T631121 and T631134		

Operation	K17601 (1X=156.0 kg)	K17602 (1X=148.0 kg)
76. IPC: Residual of H in aqueous layer (%,w/w) (Spec.: FIO)	Residual of H in aqueous layer (%,w/w)=0.02%	Residual of H in aqueous layer (%,w/w)=0.02%
77. Charge 25% NaCl solution (2.4-4.7X) into R210304	450 kg	454 kg
78. Charge process water (2.4-4.7X) into R210304	450 kg	436 kg
79. Adjust R210304 to 20-30°C, stir for 0.5-1.5 h and stand for 2-4 h	24.8°C	24.5°C
80. Transfer R210304 aqueous layer into V2103A and T631158, label material tag		
81. Charge 25% NaCl solution (4.7-8.2X) into R210304	900 kg	902 kg
82. Adjust R210304 to 20-30°C, stir for 0.5-1.5 h and stand for 1-3 h	24.2°C	24.0°C
83. Transfer R210304 aqueous layer into V2103A and T631158, label material tag		
84. IPC: KF≤3.0%	KF =1.1%	KF =1.0%
85. IPC: Purity of H% (Spec.: FIO), assay of H (%,w/w) (Spec.: FIO)	Purity of H%=85.8%, assay of H (%,w/w)=7.9%	Purity of H%=86.0%, assay of H (%,w/w)=8.0%
86. Transfer R210304 organic layer into T630013 and t630018 and label material tag		
87. IPC: Residual of H in aqueous layer (%,w/w): FIO	Residual of H in aqueous layer (%,w/w)=0.003%	Residual of H in aqueous layer (%,w/w)=0.001%
88. Load the material in V2103A into iron drums and label material tag		
89. Transfer tank organic layer into R210403		
90. Charge THF (5-30 kg) into R210403	30 kg	30 kg
91. Charge process water (0.0-0.3X) into R210403	14 kg	20 kg
92. Charge THF (0-4X) into R210403	166 kg	168 kg

Operation	K17601 (1X=156.0 kg)	K17602 (1X=148.0 kg)
93. Charge NaOH (0.35-0.59X) in portions into R210403	65.7 kg	65.0 kg
94. Adjust R210403 to 50-60°C and stir for 10-40 h	33 h	34.5 h
95. Adjust R210403 to 30-40°C	39.8°C	38.6°C
96. IPC: Residual of H (%, w/w) (Spec.≤0.15%)	Residual of H (%,w/w) =0.001%	Residual of H (%,w/w) =0.001%
97. Adjust R210403 to 20-30°C	26.1°C	27.1°C
98. Charge process water into R210403	1202 kg	1106 kg
99. Stir R210403 for 0.5-1.5 h	1.5 h	1.0 h
100. Stand R210403 for 1-3 h	3 h	3 h
101. Transfer R210403 aqueous layer into T631159 and T631166, label material tag		
102. Transfer R210403 organic layer into V2104C and V2104B, label material tag		
103. Transfer T631159 and T631166 aqueous layer into R210403		
104. Charge process water (1.2-4.7X) into T631159 and T631166	590 kg	682 kg
105. Transfer aqueous layer in T631159 / T631166 into R210403		
106. Charge MTBE (1.8-4.1X) into R210403	402 kg	402 kg
107. Adjust R210403 to 20-30°C, stir for 0.5-1.5 h	23.6°C	23.8°C
108. Stand R210403 for 1-3 h	2 h	2 h
109. Transfer R210403 aqueous layer into T631159 and T631166		
110. Transfer R210403 organic layer into V2104C and V2104B		
111. IPC: Purity of K% in aqueous layer (Spec.:	Purity of K% in aqueous	Purity of K% in aqueous

Operation	K17601 (1X=156.0 kg)	K17602 (1X=148.0 kg)
FIO)	layer=99.1%	layer=99.7%
112. IPC: Residual of K(%,w/w) in organic layer (Spec.: FIO)	Residual of K (%,w/w) in organic layer =5.3%	Residual of K (%,w/w) in organic layer =N.D.
113. Load the material in V2104C/V2104B into iron drums and label material tag		
114. Charge THF (15-50 kg) into R210403	46 kg	MeOH: 150 kg
115. Load the material in R210403 into iron drums and label material tag		
116. Transfer T631159 and T631166 aqueous layer into R210302		
117. Charge MeOH (0.0-3.5X) into R2103202	400 kg	392 kg
118. Adjust R210302 to 20-40°C	25.9°C	26.2°C
119. Charge H_3PO_4 (0.77-1.28X) into R210302	160 kg	160 kg
120. Charge C15050794-K seed (0.0001-0.0100X) into R210302	0.250 kg	0.310 kg
121. Adjust R210302 to 30-40°C and stir for 1-2 h	31.1°C	32.3°C
122. Charge H_3PO_4 (0.19-0.32X) into R210302	40.1 kg	44.9 kg
123. Adjust R210302 to 15-25°C and stir for 1-3 h	24.9°C	24.7°C
124. IPC: Residual of K (%, w/w) in the filtrate supernatant (Spec.≤0.25%)	Residual of K (%,w/w) =0.18%	Residual of K (%,w/w) =0.16%
125. Spread centrifuge bag in M210302		
126. Transfer R210302 material in portions into M210302 for centrifuge. During the centrifuging, maintain the reactor temperature at 15-25°C and agitation		
127. Charge process water (0.19-1.5X) to rinse the wet cake	34 kg	178 kg
128. Still centrifuge and blow, R210302 for at		

Operation	K17601 (1X=156.0 kg)	K17602 (1X=148.0 kg)
least 10 min		
129. Load solid according to instruction of step 147		
130. Charge process water (0.5-1.5X) to rinse the wet cake	140 kg	180 kg
131. Still centrifuge and blow, R210302 for at least 10 min		
132. Load solid according to instruction of step 147		
133. Charge process water (0.5-1.5X) to rinse the wet cake	140 kg	180 kg
134. Still centrifuge and blow, R210302 for at least 10 min		
135. Load solid according to instruction of step 147		
136. Charge process water (0.5-1.5X) to rinse the wet cake	164 kg	832 kg
137. Still centrifuge and blow, R210302 for at least 10 min		
138. Load solid according to instruction of step 147		
139. Charge process water (0.5-1.5X) to rinse the wet cake	162 kg	N/A
140. Still centrifuge and blow, R210302 for at least 10 min		N/A
141. Load solid according to instruction of step 147		N/A
142. Charge process water (0.5-1.5X) to rinse the wet cake	230 kg	N/A
143. Still centrifuge and blow, R210302 for at		N/A

Operation	K17601 (1X=156.0 kg)	K17602 (1X=148.0 kg)
least 10 min		
144. Load solid according to instruction of step 147		N/A
145. Spread centrifuge bag in M210101		N/A
146. Transfer R210302 material in portions into M210101 for centrifuging. During the centrifuging, maintain the reactor temperature at 15-25°C and agitation		N/A
147. Load solid into fiber drum lined with PE bags and label material tag	Total weight: 153.35 kg	Total weight: 172.65 kg
148. IPC: Purity of the wet cake% (Spec.≥98.0%) e.e. % of the wet cake (Spec.≥95.0%)	Purity of the wet cake (%) =100.0% e.e.% of the wet cake=99.1%	Purity of the wet cake (%) =100.0% e.e.% of the wet cake=99.2%
149. IPC: Residua of K (%, w/w) (Spec.: FIO)	Residua; of K (%, w/w)=0.2%	Residua; of K (%, w/w)=0.2%
150. IPC: Residua of K (%, w/w) in organic layer (Spec.: FIO)	Residua; of K (%, w/w)=N.D.	N/A
151. Dry the wet cake for two batches. For the first batch: put C15050794-K wet cake into drying bag, then put the bag into D211001, adjust jacket temperature to 50-60°C	53.64°C	57.73°C
152. Dry D211001 under reduces pressure at 50-60°C for 10-20 h	19 h	20 h
153. Dry D211001 under reduces pressure at 60-70°C for 10-20 h	22 h	20 h
154. IPC: KF≤1.0%	KF=4.3%	KF=0.1%
155. Dry D211001 under reduces pressure at 50-70°C for 10-20 h	22 h	N/A

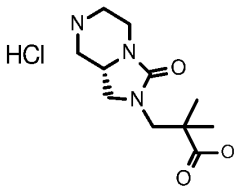
Operation	K17601 (1X=156.0 kg)	K17602 (1X=148.0 kg)
156. IPC: KF≤1.0%	KF=0.2%	N/A
157. Adjust D211001 to 20-30°C	29.51°C	25.83°C
158. Hold D211001 for 20-40 min	22 min	34 min
159. IPC: Purity of K% (Spec.≥98.0%), assay of K (%, w/w) (Spec.: FIO), e.e. % of K (Spec.≥95.0%)	Purity of K% =100.0%, assay of K (%, w/w) =100.0%, e.e.% of K =99.2%	Purity of K% =100.0%, assay of K (%, w/w) =98.6%, e.e.% of K =99.4%
160. Calculate the net wet	Total weight: 56.75 kg	Total weight: 54.45 kg
161. The second batch: put C15050794-K wet cake into drying bag, then put the bag into D211001, adjust jacket temperature to 50-60°C	55.33°C	56.65°C
162. Dry D211001 under reduces pressure at 50-60°C for 10-20 h	20 h	20 h
163. Dry D211001 under reduced pressure at 60-70°C for 10-20 h	20 h	20 h
164. IPC: KF≤1.0%	KF=0.3%	KF=0.2%
165. Adjust R211001 to 20-30°C	27.28°C	26.09°C
166. Hold D211001 for 20-40 min	25 min	37 min
167. IPC: Purity of K% (Spec.≥98.0%), assay of K (%, w/w) (Spec.: FIO), e.e. % of K (Spec.≥95.0%)	Purity of K% =100.0%, assay of K (%, w/w) =99.5%, e.e.% of K =99.1%	Purity of K% =100.0%, assay of K (%, w/w) =99.6%, e.e.% of K =99.4%
168. Calculate the net wet	Total weight: 36.70 kg	Total weight: 50.05 kg

C15050794-K (Example 2):

HRMS calcd C16 H27 N3 O5 [M+H]+: 341.1951, Found: 341.1976, 1H NMR (600 MHz, CHLOROFORM-d) δ ppm 3.90 - 4.36 (m, 2 H), 3.70 - 3.84 (m, 1 H), 3.53 - 3.63 (m, 1 H), 3.46 - 3.52 (m, 1 H), 3.29- 3.43 (m, 2 H), 3.02 (dd,J=9.1, 4.7 Hz, 1 H), 2.36 - 2.92 (m, 3 H), 1.40 - 1.50 (m, 9 H), 1.15 - 1.30 (m, 6 H)

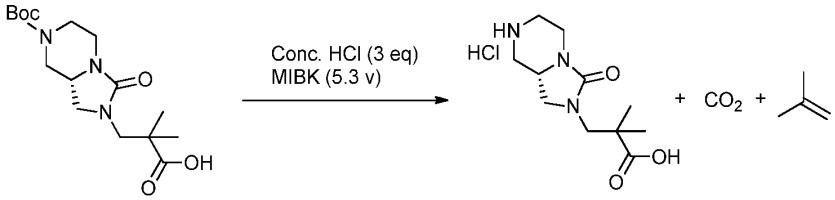
Example 3

Preparation of C15050794-SM2 (Example 3):



MW.: 277.75
C15050794-SM2

The title compound was prepared according to following scheme:



MW.: 341.40
C15050794-K

MW.: 277.75
C15050794-SM2

Production of C15050794-SM2 was carried out in one batch. For C15050794-SM2 17601, 157.25 kg of C15050794-SM2 was obtained from 197.20 kg of C15050794-K with 99.9% purity, 92.1% assay, 99.3% e.e. in 90% yield. The details are summarized in table below.

Raw materials for preparation of C15050794-SM2 17601

Batch No.	Material	MW	Quantity (kg)	Rel Wt/Vol (1X=196 kg)	Spec	Eq.
C15050794-K17601A/C15050794-K17601B/C15050794-K17602A/C15050794-K17602B	C15050794-K	341.4	197	1.01	Assay=100.0% Assay=99.5% Assay=98.6% Assay=99.6%	1.0
PC00665-100-SM2	C15050794-SM2 Seed	277.75	0.15	0.00	Assay≥78%	N/A
17093067	35% HCl	N/A	171	0.87	Assay=32%~39%	N/A
171127	Acetone	N/A	528	2.69	Purity≥99.5% KF≤0.3%	N/A
17091969	MIBK	N/A	951	4.85	Purity≥99.0% KF≤0.1%	N/A

Plant result for preparation of C15050794-SM2 17601

Batch No.	Starting Material (corrected by assay)	Product	Purity (HPLC Area)	Purity (w/w assay)	e.e.	Yield
C15050794-SM2 17601	197.20 kg	157.25 kg	99.9%	92.1%	99.3%	90%

Equipment for preparation of C15050794-SM2 17601

Equip. Name	MBR Code	Process Requirement	Equip. Code
Reactor	R1	GL/3000L	R210101
Pump	P1	PP/SS	P630058
	P2	PP	P634007
Centrifuge	M1	TI/HL	M210102
Mother liquor tank	MV1	GL	MV210102
Dray	D1	GL/SS, Double cone or SS, Single cone	D120206

Detailed Process Description of C15050794-SM2 17601

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Operation	SM2 17601 (1X=196)
169. Charge MIBK (4-5X) into R210101	901 kg
170. Charge C15050794-K (0.99-1.01X) into R210101	6.00 kg
171. Charge MIBK (20-50 kg) into R210101	50 kg
172. Adjust R210101 to 20-30°C	22.9°C
173. Charge 35% HCl (0.80-0.92X) into R210101	171.0 kg
174. Stir R210101 for 8-16 h	16 h
175. IPC: Residual of K (%, w/w) (Spec.≤0.15%)	Residual of K (%,w/w)=0.01%
176. Adjust R210101 to 15-20°C	19.5°C
177. Concentrate R210101 mixture at ≤60°C to 392-784 L	
178. Adjust R210101 to 20-40°C	31.9°C
179. Charge acetone (4.0-5.0X) into R210101	971 L
180. Concentrate R210101 mixture at ≤60°C to 588-980 L	
181. Adjust R210101 to 45-55°C	45.8°C
182. Charge acetone (4.0-5.0X) into R210101	971 L
183. Charge C15050794-SM2 (0.0001-0.0010X) crystal seed into R210101	0.150 kg
184. Charge acetone (20-50 kg) into R210101	36 kg
185. Adjust R210101 to 50-60°C	54.4°C
186. Stir R210101 for 0.5-1 h	1 h
187. Adjust R210101 to 20-40°C	35.3°C
188. IPC: Residual of SM2 (%, w/w) (Spec.≤0.7%), KF≤3.5%	Residual of SM2 (%,w/w)=0.2% , KF=2.9%
189. Adjust R210101 to 18-22°C for over 3 h	20.6°C
190. Stir R210101 for 1-3 h	3 h
191. Spread centrifuge bag in M210102	
192. Transfer R210101 material in portions into M210102 for centrifuging. During the centrifuging, maintain the reactor temperature at 18-22°C and agitation	
193. Charge acetone (1.3-5.0X) to rinse the wet cake	70 kg

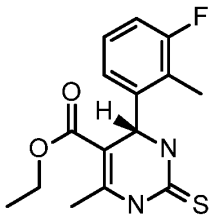
Operation	SM2 17601 (1X=196)
194. Load solid according to instruction of step 205	
195. Charge acetone (1.3-5.0X) to rinse the wet cake	74 kg
196. Load solid according to instruction of step 205	
197. Charge acetone (1.3-5.0X) to rinse the wet cake	78 kg
198. Load solid according to instruction of step 205	
199. Charge acetone (1.3-5.0X) to rinse the wet cake	68 kg
200. Load solid according to instruction of step 205	
201. Charge acetone (1.3-5.0X) to rinse the wet cake	70 kg
202. Load solid according to instruction of step 205	
203. Charge acetone (1.3-5.0X) to rinse the wet cake	132 kg
204. Load solid according to instruction of step 205	
205. Load solid into fiber drum lined with double PE bags and label material tag	Total weight: 167.60 kg
206. IPC: Purity of the wet cake% (Spec.≥98.0%)	Purity of the wet cake%=99.8%
207. IPC: Residual of SM2 (%, w/w) (Spec.: FIO)	Residual of SM2 (%, w/w)=0.1%
208. Put the wet cake into D 120206	
209. Adjust D120206 to 30-40°C	40°C
210. Dry D120206 under reduced pressure at 30-40°C for 3-5 h	4 h
211. Adjust D120206 to 40-50°C	43.3°C
212. Dry D120206 under reduced pressure at 40-50°C for 7-15 h	12 h
213. IPC: KF≤7%	KF=4%
214. Adjust D120206 to 20-30°C	29.7°C
215. Hold D120206 for 1 h	
216. IPC: Assay of SM2 (%, w/w) (Spec.: FIO), purity of SM2% (Spec.≥98.0%), e.e. of SM2% (Spec. ≥95.0%)	Assay of SM2 (%, w/w)=92.1%, purity of SM2%=99.9%, e.e. of SM2% =99.3%
217. Calculate the net wet	Total weight: 157.25 kg

C15050794-SM2 (Example 3):

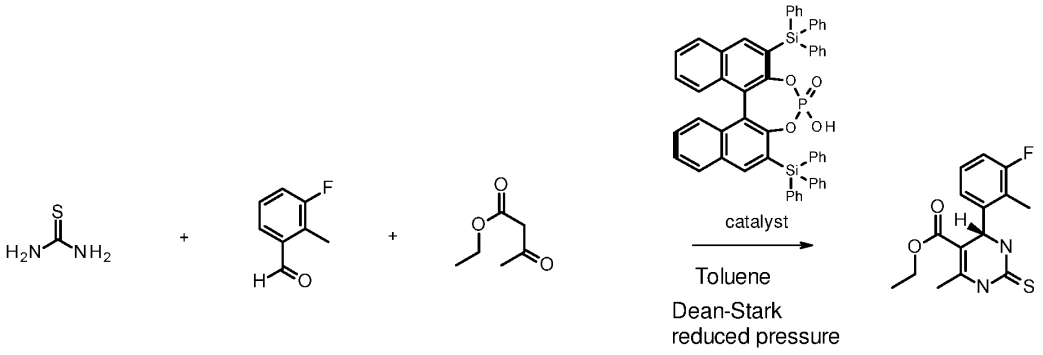
1H NMR (600 MHz, DMSO-d6) δ ppm 12.10 - 12.59 (m, 1 H), 9.32 - 9.78 (m, 2 H), 3.85 - 3.95 (m, 1 H), 3.75 - 3.76 (m, 1 H), 3.68 - 3.76 (m, 1 H), 3.41 - 3.47 (m, 1 H), 3.23 - 3.27 (m, 1 H), 3.15 - 3.18 (m, 1 H), 3.13 - 3.30 (m, 2 H), 3.13 - 3.17 (m, 1 H), 3.00 - 3.06 (m, 1 H), 2.69 - 2.79 (m, 1 H), 2.66 - 2.75 (m, 1 H), 1.08 (d, J=7.8 Hz, 6 H); HRMS calcd C11 H19 N3 O3 [M+H]+: 241.1426, Found: 241.1429

Example 4

Preparation of ethyl 4-(3-fluoro-2-methyl-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (Example 4):



The title compound was prepared according to following scheme:

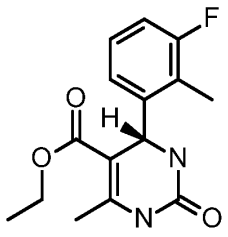


In a reactor configured for Dean-Stark water removal, a suspension was prepared from thiourea (12.73 g, 167.2 mmol, 1.05 equiv.), 3-fluoro-2-methyl-benzaldehyde (22.0 g, 159.3 mmol, 1.00 equiv.), and ethyl acetoacetate (24.87 g, 191.1 mmol, 1.20 equiv.), (*R*)-(–)-3,3'-Bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl hydrogen-phosphate (1.38 g, 1.59 mmol, 0.01 equiv.) and toluene (76.1 g). This mixture was stirred at 80 °C jacket temperature under reduced pressure in order to achieve gentle reflux and Dean-Stark removal of the water generated during the reaction over 15-18 h. Upon reaction completion, the suspension was cooled to 15 °C and stirred for at least 2 h. The crystals were filtered, washed with pre-cooled toluene (26 g) and dried under reduced pressure at 50 °C. The isolated yield was 40.6 g (82%) with 95% enantiopurity. 1H

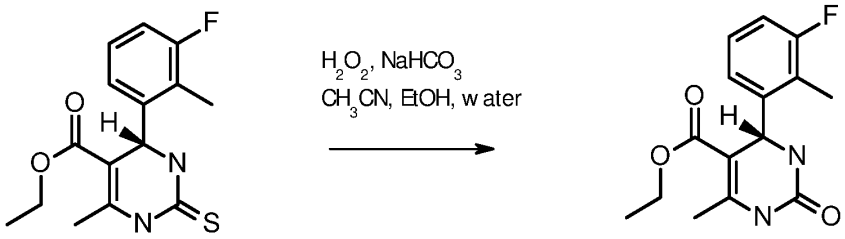
NMR (600 MHz, DMSO-d6) δ ppm 10.30 (m, 1 H), 9.56 (br d, J=0.8 Hz, 1 H), 7.23 (m, 1 H), 7.07 (m, 1 H), 7.02 (dd, J=8.1, 0.9 Hz, 1H), 5.43 (d, J=3.2 Hz, 1 H), 3.92 (q, J=7.1 Hz, 2 H), 2.33 (d, J=1.6 Hz, 3 H), 2.32 (d, J=0.5 Hz, 3 H), 1.00 (t, J=7.1 Hz, 3 H) HRMS calcd C15 H17 N2 O2 S [M+H]+: 308.0995, Found: 308.1002

Example 5

Preparation of ethyl (4S)-4-(3-fluoro-2-methyl-phenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyrimidine-5-carboxylate (Example 5):



The title compound was prepared according to following scheme:

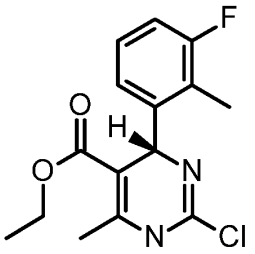


Ethyl (4S)-4-(3-fluoro-2-methyl-phenyl)-6-methyl-2-thioxo-3,4-dihydro-1H-pyrimidine-5-carboxylate (30 g, 97.3 mmol, 1.0 equiv.), suspended in acetonitrile (59.9 g), ethanol (58.95 g), sodium bicarbonate (32.79 g, 389.1 mmol, 4 equiv.) and water (390 g) was stirred at room temperature for 30 minutes. The suspension was cooled to 5-10 °C and the hydrogen peroxide (3 wt% solution in water, 75.64 g, 778 mmol, 8 equiv.) was added over 4 h. Minimal effervescence was observed with this rate of addition. The resulting suspension was stirred for 15-18 h at 5-10 °C. Upon reaction completion, water (150 g) was added and the suspension was warmed to 25 °C and stirred for another 5 h. The crystals were filtered, washed with two portions of 9:1 v/v water/acetonitrile (total 120 mL) and dried under reduced pressure at 50 °C. The isolated yield was 25.8 g (90.8%), with assay approx. 92%. Chiral purity observed in the starting material was preserved.

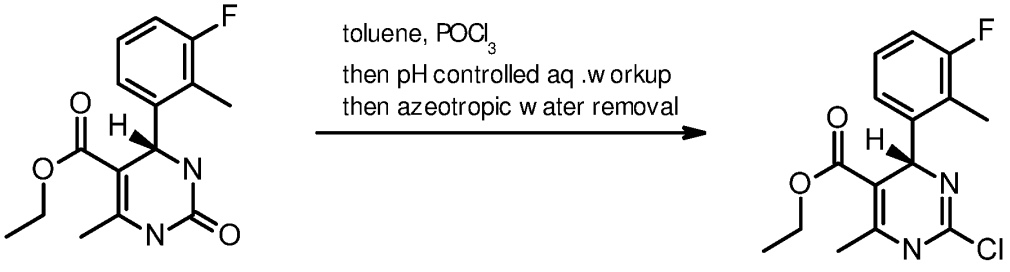
To recrystallize this material, the crude solid (25.8 g) was dissolved in MeTHF (500 mL), polish filtered, and then partially concentrated under reduced pressure (jacket temperature 30 °C) to approx. 300 mL. n-Heptane (600 mL) was added over 30 minutes and the resulting white suspension was cooled to 10-15 °C (internal temperature), filtered and dried. The overall yield was 21.4 g (75.3%), with assay approx. 100%. Chiral purity was unchanged. 1H NMR (600 MHz, DMSO-d6) δ ppm 9.20 (d, J=1.3 Hz, 1 H), 7.66 (t, J=2.3 Hz, 1 H), 7.20 (m, 1 H), 6.98 - 7.06 (m, 2 H), 5.42 (d, J=2.6Hz, 1 H), 3.89 (m, 2 H), 2.30 (d, J=1.7 Hz, 3 H), 2.29 (d, J=0.6 Hz, 3 H), 0.99 (t, J=7.1 Hz, 3 H); HRMS calcd C15 H17 N2 O3 [M+H]+: 239.1296, Found: 293.1301

Example 6

Preparation of ethyl (4S)-2-chloro-4-(3-fluoro-2-methyl-phenyl)-6-methyl-1,4-dihydropyrimidine-5-carboxylate (Example 6):



The title compound was prepared according to following scheme:

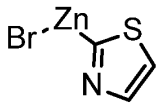


Ethyl (4S)-4-(3-fluoro-2-methyl-phenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyrimidine-5-carboxylate (20 g, 68.4 mmol, 1.0 equiv., assay min 92%) was suspended in toluene (43.2 g) and phosphoryl chloride (34.47 g, 205.3 mmol, 3.0 eqiv.). Additional toluene (8.7 g) was used to rinse the addition funnel. The white suspension was heated to 100 °C (internal temperature) and a yellow solution was obtained after approx.

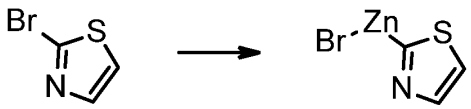
15 minutes, eventually becoming a red solution. The reaction was stirred for 24 h and then diluted with toluene (51.9 g) and cooled to 0 °C. This solution was dosed over 60 min into second vessel containing vigorously stirring mixture of toluene (51.9 g) and K_2HPO_4 (5% w/w aqueous solution, 60.0 g) at 0 °C. The quench vessel was maintained below 15 °C (internal temperature) and the pH maintained in the range 7.0-8.5 by variable rate co-dosing of KOH (48% w/w aqueous solution, 230.3 g). The addition rate of the KOH solution was continued beyond the reaction mixture dosing to maintain the pH range (end pH was approx. 7.8). The resulting biphasic mixture was warmed to 23 °C (jacket temperature) and stirred for 1 h. The lower aqueous layer was removed and the organic layer washed twice with K_2HPO_4 (5% w/w aqueous solution, 200 g total). The organic solution was polish filtered and the filter rinsed with toluene (17.3 g). The toluene solution was distilled under reduced pressure while maintaining 25 °C (jacket temperature), with replacement with fresh toluene until water-free, and to achieve a final volume of 200 mL. This 0.34 M solution of ethyl (4S)-2-chloro-4-(3-fluoro-2-methyl-phenyl)-6-methyl-1,4-dihydropyrimidine-5-carboxylate in toluene was used directly (uncorrected for assay). 1H NMR (600 MHz, DMSO-d6) δ ppm 9.81 - 10.33 (m, 1 H), 7.16 - 7.28 (m, 1 H), 7.05 (t,J=9.0 Hz, 1 H), 7.00 (d,J=7.7 Hz, 1 H), 5.74 (s, 1 H), 3.91 (d,J=7.1 Hz, 2 H), 2.24 - 2.38 (m, 6 H), 0.98 (t,J=7.1 Hz, 3 H); HRMS calcd C15 H16 Cl F N2 O2 [M+H]+: 310.0898, Found: 310.0884

Example 7

Preparation of bromo(thiazol-2-yl)zinc solution in THF (Example 7):



The title compound was prepared according to following scheme:

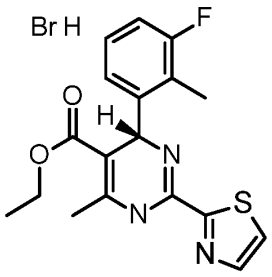


Under inert atmosphere, a reactor containing THF (200 mL) was charged with zinc (21.9 g, 335 mmol, 1,1 equiv.) and the addition port rinsed with additional THF (50 mL). With vigorous stirring at 23 °C (internal

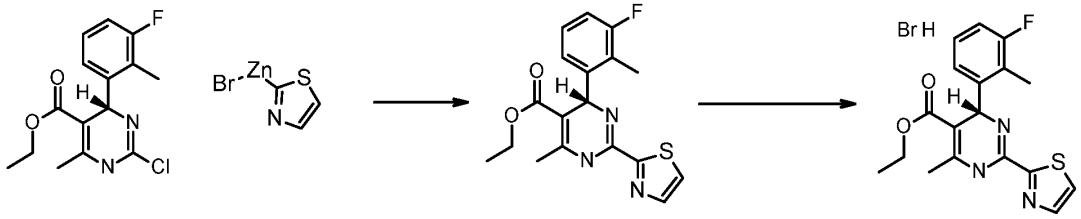
temperature), TMSCl (1.7 g, 15.2 mmol, 0.05 equiv.) was added slowly over approximiately 25 minutes, and the addition line rinsed with THF (10 mL). Vigorous stirring was continued for 30 minutes and then 2-bromothiazole (50 g, 304.8 mmol, 1.0 equiv.) was added over 2 h, and the addition line rinsed with THF (10 mL). Stirring was continued and the reaction was monitored by GC analysis for complete consumption of the 2-bromothiazole starting material. If necessary, the reaction was heated to reflux in order to complete conversion. The solution of bromo(thiazol-2-yl)zinc in THF can be filtered at ambient temperature under inert atmosphere to remove residual zinc, or used directly without filtration. The volume was adjusted by additon of THF to achieve a final volume of 305 mL, giving a 1M stock solution that is stable at room temperature when stored under inert atmosphere.

Example 8

Preparation of ethyl (4S)-4-(3-fluoro-2-methyl-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate hydrobromide (Example 8):



The title compound was prepared according to following scheme:

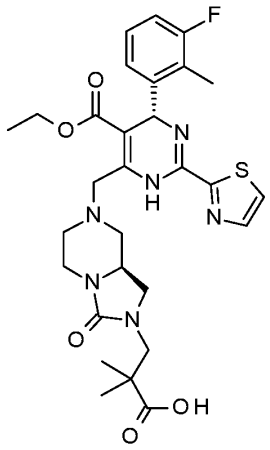


A reactor under inert atmosphere was charged with a solution of ethyl (4S)-2-chloro-4-(3-fluoro-2-methyl-phenyl)-6-methyl-1,4-dihydropyrimidine-5-carboxylate (21.26 g, 68.41 mmol, 1.0 equiv.) in toluene (0.36 M solution, 200 mL total volume), and then a portion bromo(thiazol-2-yl)zinc 1M solution in THF (6.8 mL, 0.1 equiv.), and then the catalyst dichloro[9,9-dimethyl-4,5-

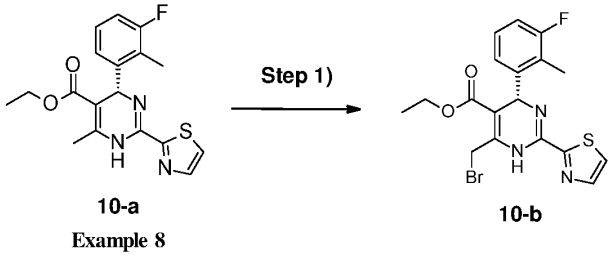
bis(diphenylphosphino)xanthene]palladium(II) (1.03 g, 1.4 mmol, 0.02 equiv.) was added as a solid, rinsing the addition port port with THF (8.9 g). The obtained red solution was heated to 70 °C (internal temperature). The remainder of bromo(thiazol-2-yl)zinc 1M solution in THF (130 mL, 1.9 equiv.) was added via infusion pump over 2 h, and the addition line rinsed with THF (8.9 g). The reaction was stirred for an addtion 1 h, at which time the reaction was typically complete. The reaction promptly worked up by cooled to 23 °C (jacket temperature) and then washed with aqueous citric acid solution (13.14 g citric acid dissolved in 100 g water), followed two washes with water (200 mL total). The organic solution was partially concentrated under reduced pressure to a volume of 60 mL and then acetonitrile (157.2 g) was added and the reaction mixture once again concentrated to 60 mL. Acetonitrile (125.8 g) was added the resulting mixture was polish filtered. The filtered acetonitrile solution was warmed to 65 °C and then aqueous HBr (11.53 g of 48% w/w solution in water, 68.4 mmol, 1.0 equiv.) was added. Water was removed by distillation under reduced pressure (75-85°C jacket temperature), with solvent replacement with acetonitrile. The reaction was concentrated to a minimal volume (approx. 40 mL) and then toluene (100 mL) added over 20 minutes (jacket temperature 85 °C). The resulting slurry was stirred for 1 h then cooled to 0 °C over 3 h, stirred for 1 h and the off-white to brown solid was isolated by filtration. The solid was washed with three portions of 5:1 toluene:acetonitrile (40 mL total volume), then dried at 50 °C under reduced pressure to provide 18.78 g (67.7 % yield over two steps) of the title compound. (note: yield corrected for 92% assay of Ethyl (4S)-4-(3-fluoro-2-methyl-phenyl)-6-methyl-2-thioxo-3,4-dihydro-1H-pyrimidine-5-carboxylate starting material). 1H NMR (600 MHz, DMSO-d6) δ ppm 10.18 - 12.25 (m, 1 H), 8.23 (m, 1 H), 8.18 (m, 1 H), 7.23 - 7.29 (m, 1 H), 7.18 - 7.22 (m, 1 H),7.08 - 7.15 (m, 1 H), 5.91 (m, 1 H), 3.85 - 4.05 (m, 2 H), 2.49 (m, 3 H), 2.43 (d, J=1.7 Hz, 3 H), 1.04 (t, J=7.1 Hz, 3 H); HRMS calcd C18 H18 F N3 O2 S [M+H]+: 360.1177, Found: 360.1181

Example 9

Preparation of 3-[(8aS)-7-[[(4S)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1H-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid (Example 9):



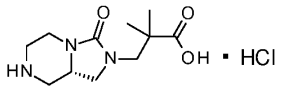
The title compound was prepared according to following scheme:



10-a

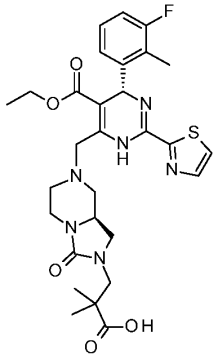
Example 8

10-b



Example 3

Step 2)



Example 9

Step 1) preparation of ethyl (4S)-6-(bromomethyl)-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (compound 10-b):

A 10 L flask equipped with mechanical stirrer, thermometer and nitrogen bubbler was charged with a solution of ethyl (4S)-4-(3-fluoro-2-methyl-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (706 mmol, **compound 10-a**) in DCM (4.0 L) from step 1). To the reaction mixture, heated to 32 °C-37 °C, NBS (125.6 g, 706 mmol) was added in portions while maintaining the temperature at 35 °C-40 °C. After 0.5 hour, additional batch of NBS (12.6 g, 70.6 mmol) was added to reaction mixture which was carefully monitored by HPLC until the conversion >95 %. The resulting solution of **compound 10-b** was cooled to 10-20 °C and used directly for the next step. MS m/e = 436.1/438.0 $[M+H]^+$.

Step 2) preparation of 3-[(8aS)-7-[[(4S)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1H-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid (Example 9):

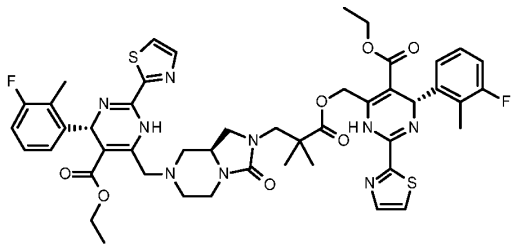
A 10 L flask equipped with mechanical stirrer, thermometer and nitrogen bubbler was charged a solution of ethyl (4S)-6-(bromomethyl)-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate in DCM from the last step. To the reaction mixture, cooled to 10-20 °C, was added 3-[(8aS)-3-oxo-1,5,6,7,8,8a-hexahydroimidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid hydrochloride (193 g, 635 mmol, purity: 91.6 wt%, **Example 3**) and followed by addition of triethanolamine (329 g, 2.33 mol) in DCM (350 mL) in portions below 25 °C. The reaction mixture was stirred at 20 °C-30 °C for 16 hours. Then to the resulting reaction mixture was added water (1.25 L) and aqueous layer was adjusted to pH =3-4 using H_3PO_4 (85 wt%). After phase separation, the organic phase was washed with acidic water (1.25 L, H_3PO_4 solution with pH=2-3). After phase separation, the organic phase was extracted with aqueous H_3PO_4 solution (35 wt%, 1980 g) once and aqueous H_3PO_4 solution (35 wt%, 990 g) once. The combined aqueous layer was extracted with DCM (500 mL). To the aqueous layer, cooled to 0 °C-10 °C, was added DCM (2.0 L). Then the aqueous layer was adjusted to pH=3-4 with aqueous NaOH solution (50 wt%, 770 g). After phase separation, the organic phase was washed with water (1.5 L) and filtered through celite (25 g) and then concentrated to about 500 mL *in vacuo*. The residue was diluted with ethanol (500 mL) and concentrated to about 500 mL *in vacuo* and this process was repeated one more time. Then the residue was diluted again with ethanol (1700 mL) and heated to 70-80 °C till all solid was dissolved. Water (2.20 L) was added to previous solution via an addition funnel while maintaining inner temperature between 60 °C and 78 °C. Then the reaction mixture was cooled to 55 °C over 2 hours and maintained at 50 °C-55 °C for 1 hour, then cooled to 25 °C over 3 hours and stirred at 25 °C for another hour. The solid was collected by filtration and washed with ethanol/water (v/v=1/1, 250 g). The wet cake was dried in a vacuum oven (45 °C-

55 °C /Ca. 0.1Mpa with a nitrogen bleed) for 35 hours to afford the product **Example 9** (260.0 g , purity: 99.1 %, chiral purity: 99.8 %, yield: 61.5 %) as a light-yellow solid. ^{1}H NMR (400 MHz, DMSO-d^6) δ 12.35 (s, 1H), 9.60 (s, 1H), 8.01 (d, *J*=3.2 Hz, 2H), 7.93 (d, *J*=3.2 Hz, 2H), 7.15-7.19 (m, 1H), 7.01-7.05 (m, 2H), 5.89 (s, 1H),3.87-4.00 (m, 4H), 3.62-3.73(m, 2H), 3.33-3.39 (m, 1H), 3.27 (d, *J*=14.0Hz, 1H), 3.16 (d, *J*=14.0Hz, 1H), 2.93-3.00 (m, 2H), 2.77-2.82 (m, 2H), 2.45 (t, *J*=1.6 Hz, 3H), 2.15 (d, *J*=11.2 Hz, 1H), 2.02 (d, *J*=11.2Hz, 1H), 1.03-1.08 (m, 9H); MS m/e = 599.6 $[M+H]^+$.

Example 10

The H_3PO_4 concentration and equivalent screening in the acid-base work-up of step I)

The amount of H_3PO_4 in the acid-base work-up of step I) is essential and carefully designed to get the maximum recovery of API and minimum impurities. The concentration and equivalent of H_3PO_4 in step 2) of **Example 9** were screened according to **Table 1**. The major impurity was **Impurity 2** shown below.



Impurity 2

After the initial H_3PO_4 solution wash (pH=3-4 and pH=2-3), the purity in organic layer was Product/Impurity 2($Rt_{(impurity)}$ = 19.4min) = 71.9/1.38 (peak area%), the selected examples of further extractions with various H_3PO_4 concentration and equivalent were tested and shown in **Table 1**.

Table 1. H_3PO_4 concentration and equivalent screening

Concentration and equivalent of H_3PO_4	Aqueous layer purity (peak area %) Product/Impurity 2	Organic layer purity (peak area %) Product/Impurity 2
30 wt% H_3PO_4 20 eq.	95.2/0.0	14.0/4.6
35 wt% H_3PO_4 10 eq.	92.6/0.0	10.8/4.7

Concentration and equivalent of H_3PO_4	Aqueous layer purity (peak area %) Product/Impurity 2	Organic layer purity (peak area %) Product/Impurity 2
35 wt% H_3PO_4 15 eq.	93.7/0.1	5.4/5.0
35 wt% H_3PO_4 20 eq.	93.9/0.1	4.0/5.0
40 wt% H_3PO_4 20 eq.	92.3/0.5	3.9/3.9
45 wt% H_3PO_4 20 eq.	90.7/1.3	4.9/1.3

5

The above study was tested with following HPLC parameters shown in **Table 2**.

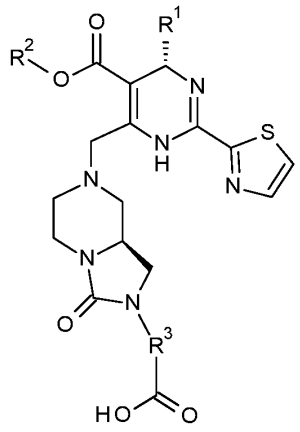
Table 2. HPLC parameters

Instrument	Agilent 1260 HPLC system with DAD detector
Column	Waters Xbridge C8 (4.6×150 mm×3.5 µm)
Oven temperature	30 ºC
Mobile phase	A: 0.12% TFA in water B: 0.12% TFA in ACN
Gradient program	Time (min) A% B% 0.00 80 20 15.00 50 50 20.00 10 90 25.00 10 90 25.01 80 20 30.00 80 20
Flow rate	1.0 mL/min
Detector	UV 299 nm
Nominal concentration	0.5 mg/mL
Diluent	ACN : water = 1 : 1
Injection volume	10 µL
Run time	30 min

According to the results shown in Table 1, the amount of H_3PO_4 in the acid-base work-up of step m) is directly related to the recovery of API and amount of impurities. Therefore, the particular concentration of H_3PO_4 was 35 wt% to 40 wt% and 10-15 equivalent of compound of formula (XVIII).

CLAIMS

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



(I),

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;

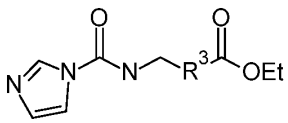
R^3 is $-C_xH_{2x}-$;

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

or pharmaceutically acceptable salt or diastereomer thereof;

comprising one or more of the following steps:

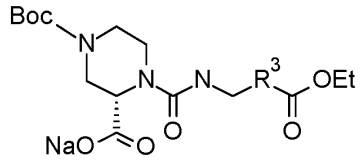
step a) the formation of compound (III),



(III),

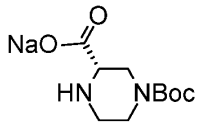
wherein R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7;

step b) the formation of urea (V)



(V)

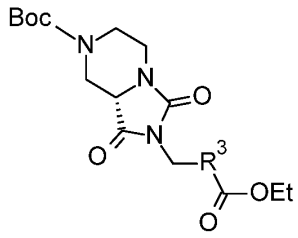
via the addition reaction of compound (III) and compound (IV)



(IV),

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

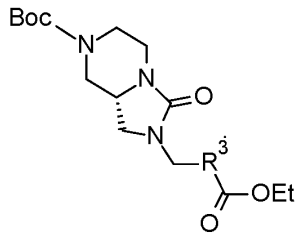
step c) the formation of the hydantoin of formula (VI) via the cyclization reaction of urea (V),



(VI),

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

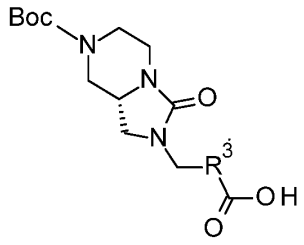
step d) the formation of the urea of formula (VIII) via selective reduction of the compound of formula (VI),



(VIII),

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

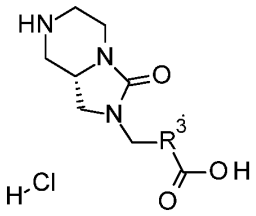
steps e) and f) the formation of the compound of formula (IX) via hydrolysis of the compound of formula (VIII),



(IX),

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

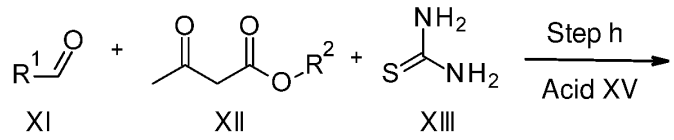
step g) the formation of compound of formula (X) by de-protection of the compound of formula (IX),



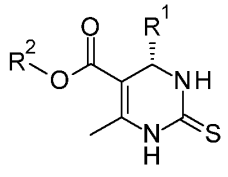
(X),

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 the reaction of compounds (XI), (XII) and (XIII) in the presence of acid (XV),



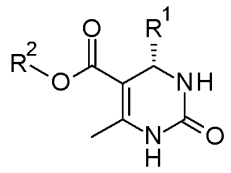
XI XII XIII



(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;

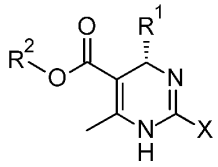
step i) the formation of compound of formula (XVI),



(XVI),

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;

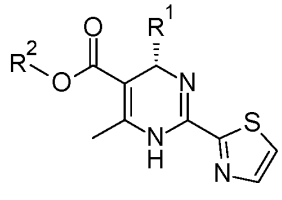
step j) the formation of compound of formula (XVII),



(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; X is halogen, preferably chlorine;

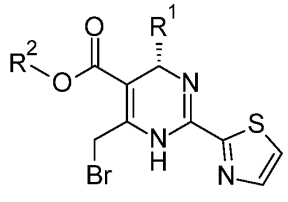
step k) the formation of compound of formula (XVIII),



(XVIII),

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;

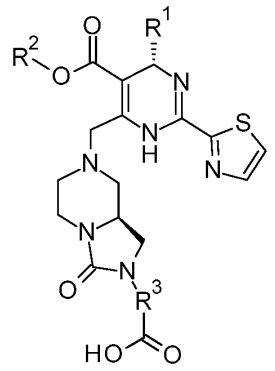
step l) the formation of compound of formula (XIX) via the bromination reaction of compound of formula (XVIII),



(XIX),

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 m) the formation of compound of formula (I) via the substitution reaction of compound of formula (XIX) with compound of formula (X),

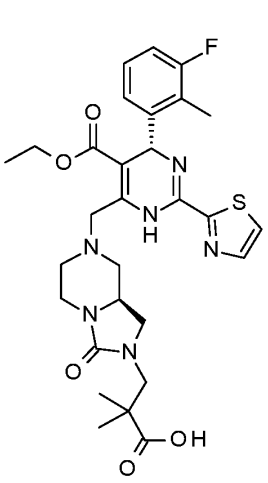


(I),

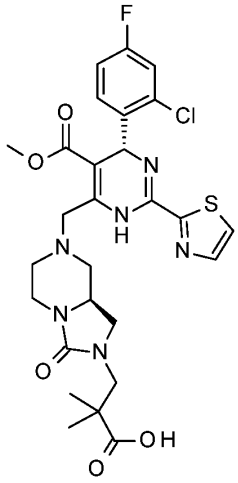
wherein R^1 is phenyl, which is unsubstituted or substituted with one, two or three substituents independently selected from halogen and C_{1-6}alkyl; R^2 is C_{1-6}alkyl; R^3 is $-C_xH_{2x}-$; x is 1, 2, 3, 4, 5, 6 or 7.

2. A process according to claim 1, wherein R^1 is chlorofluorophenyl, methylchlorophenyl or fluoromethylphenyl; R^2 is methyl or ethyl; R^3 is dimethylethyl; or pharmaceutically acceptable salt or diastereomer thereof.

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



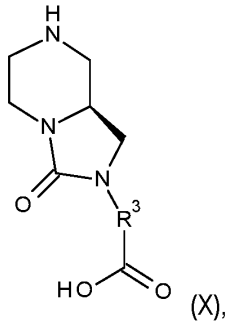
or



;

or pharmaceutically acceptable salt or diastereomer thereof.

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


(X),

wherein

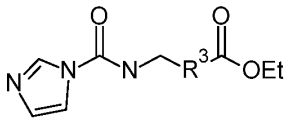
R^3 is $-C_xH_{2x}-$;

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

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof;

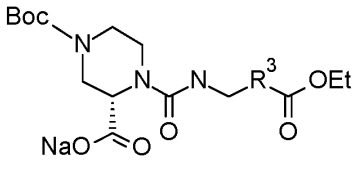
comprising one or more of the following steps:

step a) the formation of compound (III),

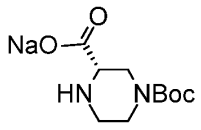

(III),

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

step b) the formation of urea (V)


(V)

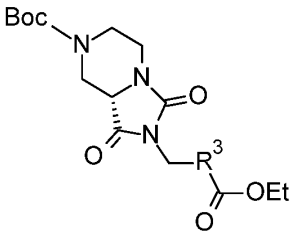
via the addition reaction of compound (III) and compound (IV)



(IV),

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

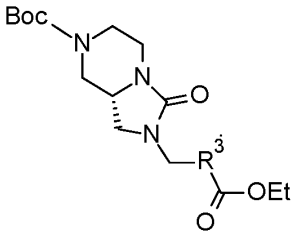
step c) the formation of the hydantoin of formula (VI) via the cyclization reaction of urea (V),



(VI),

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

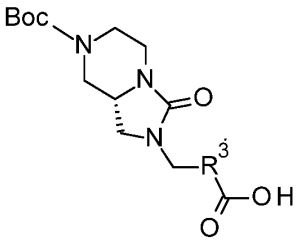
step d) the formation of the urea of formula (VIII) via selective reduction of the compound of formula (VI),



(VIII),

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

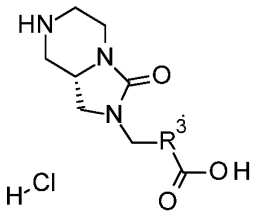
steps e) and f) the formation of the compound of formula (IX) via hydrolysis of the compound of formula (VIII),



(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),



(X),

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 dimethylethyl.

6. A process according to claim 4, wherein compound (X) is in the form of a pharmaceutically acceptable salt or diastereomer thereof.

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

8. A process according to claim 7, wherein the base is selected from Na_2CO_3, NaOtPent, $NaHCO_3$, K_2CO_3, Na_3PO_4, K_3PO_4 and triethylamine (TEA).

9. A process according to claim 7 or 8, wherein the reagent is selected from CDI, phosgene, diphosgene, disuccinimidyl carbonate, and triphosgene.

10. A process according to any one of claims 1 to 9, characterized in that the formation of the hydantoin 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, anisole, and DMF.

11. A process according to claim 10, wherein the acid is selected from boron trifluoride etherate, phosphoric acid, sulphuric acid, chlorosulphonic acid, trifluoroacetic acid, HBr, HCl, $AlCl_3$, $TiCl_4$, $SnCl_4$, $ZrCl_4$, TMSOTf, pivaloyl chloride, isobutyl chloroformate and oxalyl chloride.

12. A process according to any one of claims 1 to 11, characterized in that the formation of the urea of formula (VIII) in step d) is performed in the presence of a catalytic Lewis acid and a reducing agent, wherein the catalytic Lewis acid is selected $InCl_3$, YCl_3, $ZnCl_2$, $Zn(OAc)_2$, TMSCl, $TiCl_4$, $ZrCl_4$, $AlCl_3$, BF_3·THF, and BF_3·Et_2O.

13. A process according to claim 12, wherein the reducing agent is selected from lithium aluminum hydride, sodium dihydro-bis-(2-methoxyethoxy)aluminate, borane dimethylsulfide, phenylsilane, borane, borane dimethylsulphide complex and borane tetrahydrofurane complex.

14. A process according to any one of claims 1 to 13, characterized in that the compound of formula (IX) is synthesized in the presence of a solvent is selected from THF, MeTHF, TBME, toluene, anisole, isopropanol, methanol and ethanol and their mixtures with water.

15. A process according to any one of claims 1 to 14, characterized in that the formation of the compound of formula (X) in step g) is performed in the presence of HCl in a solvent.

16. A process according to claim 15, wherein the solvent is selected from DCM, toluene, dioxane, EtOAc, IPAc, IPA, 1-propanol, acetone, MIBK and mixed solvent of MIBK and acetone.

17. A process according to any one of claims 1 to 16, characterized in that the acid of formula (XV) in step h) is selected from the group consisting of (R)-3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate, (S)-3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate, (R)-(–)-3,3'-Bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate, (R)-(–)-VAPOL hydrogenphosphate, (+)-CSA, and (S)-(+)-1,1’-Binaphthyl-2,2’-diyl hydrogen phosphate, (R)-(-)-1,1’-Binaphthyl-2,2’-diyl hydrogen phosphate.

18. A process according to claim 17, characterized in that the acid of formula (XV) in step h) is (R)-(–)-3,3'-Bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate.