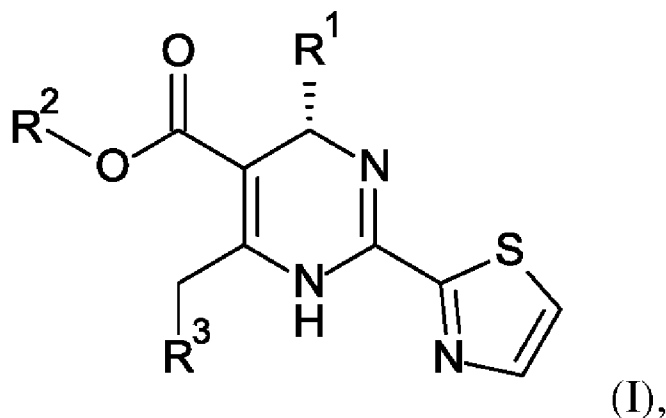




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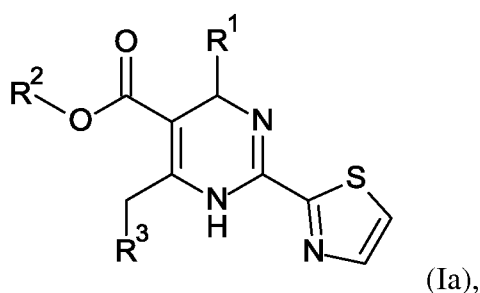
(54) **Title:** PROCESS FOR THE PREPARATION OF 4-PHENYL-5-ALKOXYCARBONYL-2-THIAZOL-2-YL-1,4-DI-HYDROPYRIMIDINE ANALOGUES



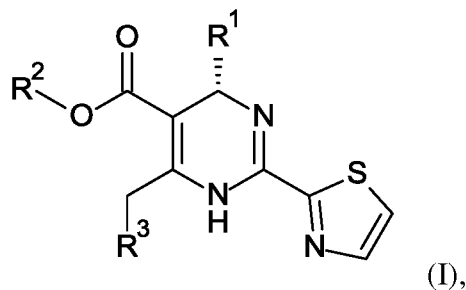
(57) **Abstract:** The present invention relates to a process for synthesizing a compound of formula (I), (I), wherein R¹ is phenyl, which is unsubstituted, or once, twice or three times substituted by halogen; R² is C₁₋₆alkyl; R³ is heterocyclyl; and diastereomer, pharmaceutically acceptable salts thereof, 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.

Process for the preparation of 4-phenyl-5-alkoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidine analogues

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



in particular a compound of formula (I),



wherein R¹ is phenyl, which is unsubstituted, or once, twice or three times substituted by
 10 halogen; R² is C₁₋₆alkyl; R³ is heterocyclyl; or diastereomer, pharmaceutically acceptable salts 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

5 The patent WO2014029193 disclosed synthetic approaches to obtain compounds of formula (I) or (Ia). However, the synthetic approach disclosed in patent WO2014029193 needs to be improved in terms of overall low yield, racemic synthesis and column purification.

 One object of this invention is to develop an effective and scalable synthetic process to synthesize compounds of formula (I) or (Ia). Another object is to simplify purification of the
10 compound of formula (I) or (Ia) by either formation of MSA salt or acid/base extraction. A further object of this invention is to provide synthetic approach which can be applied on technical scale and allows obtaining the product in good yield, desired purity and stable form.

DETAILED DESCRIPTION OF THE INVENTION

15 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.

 The term “halogen” signifies fluorine, chlorine, bromine or iodine, particularly fluorine or
20 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
25 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,
30 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

5 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.

The term “heterocycle” or “heterocyclyl” refers to a saturated or partly unsaturated
10 monocyclic or bicyclic ring containing from 3 to 10 ring atoms which can comprise one, two or three atoms selected from nitrogen, oxygen and/or sulfur. Bicyclic means consisting of two cycles having two ring atoms in common, i.e. the bridge separating the two rings is either a single bond or a chain of one or two or more ring atoms. Examples of monocyclic heterocyclyl rings containing in particular from 3 to 7 ring atoms include aziridinyl, azetidiny, oxetanyl,
15 piperidinyl, piperazinyl, azepinyl, diazepanyl, pyrrolidinyl, pyrazolidinyl, imidazoliny, imidazolidinyl, pyridinyl, pyridazinyl, pyrimidinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, thiadiazolidinyl, dihydrofuryl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,1-dioxo-hexahydro-1,6-thiopyranyl and thiomorpholinyl. Examples of bicyclic heterocyclyl rings containing in particular from 5 to 12 ring atoms include 3-oxa-9-
20 azabicyclo[3.3.1]nonan-9-yl and 6,6-difluoro-8-azabicyclo[3.2.1]octan-8-yl. Monocyclic and bicyclic heterocyclyl rings can be further substituted by C₁₋₆alkyl, cyano, carboxy, carboxy C₁₋₆alkyl, for example carboxymorpholinyl, 7-(carboxymethyl)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl, 3-(carboxymethyl)-6,6-difluoro-8-azabicyclo[3.2.1]octan-8-yl.

The term “heterocyclylamine” refers to an amine with nitrogen atom on the heterocyclyl
25 ring, wherein heterocyclyl is defined above.

ABBREVIATION

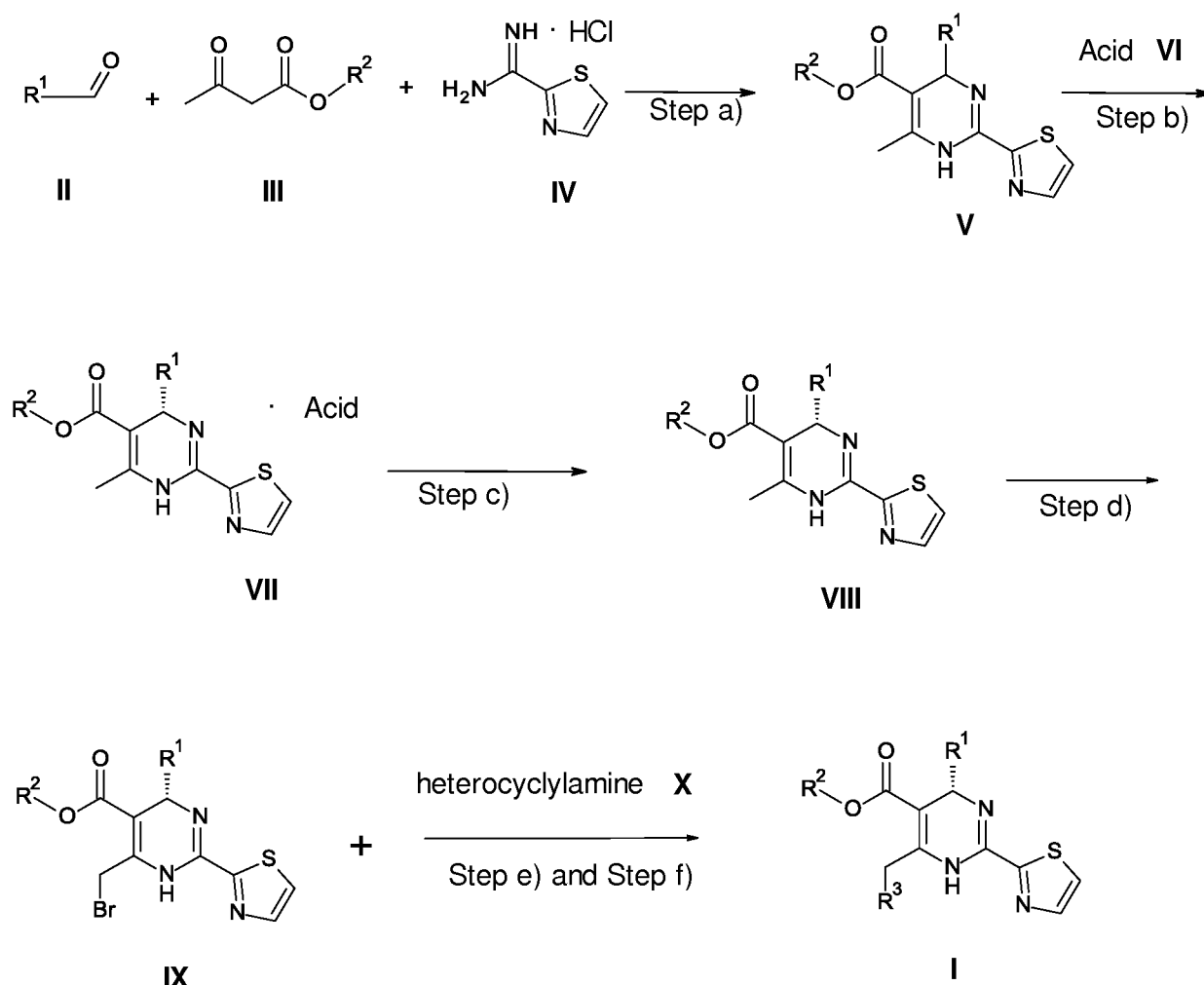
	ACN	Acetonitrile
	eq	Equivalent
30	CSA	Camphorsulfonic acid
	DTTA	Di-p-toluoyl-tartaric acid
	DBTA	Dibenzoyl-tartaric acid

5	DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
	DCM	Dichloromethane
	DIPEA	N,N-Diisopropylethylamine
	GABA	γ -aminobutyric acid
	IPA	Isopropanol
10	IPAc	Isopropyl acetate
	MEK	2-Butanone
	MIBK	Methyl isobutyl ketone
	MSA	Methanesulfonic acid
	MTBE	Methyl tert-butyl ether
15	NBS	N-Bromosuccinimide
	NMM	N-methylmorpholine
	TEA	Triethylamine
	TFA	Trifluoroacetic acid
	THF	Tetrahydrofuran
20	TMP	2,2,6,6-Tetramethylpiperidine
	V	volume
	V65	2,2'-Azobis-(2,4-dimethylvaleronitrile)
	wt%	weight percentage

The present invention provides a process for preparing the compounds of formula (I) as
25 outlined in the **scheme 1** exemplified for the compound with R¹ is phenyl, which is unsubstituted,
or once, twice or three times substituted by halogen; R² is C₁₋₆alkyl; R³ is heterocyclyl.

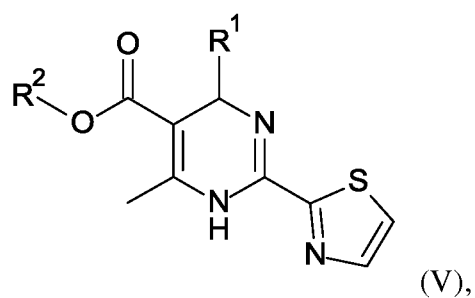
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5 Scheme 1



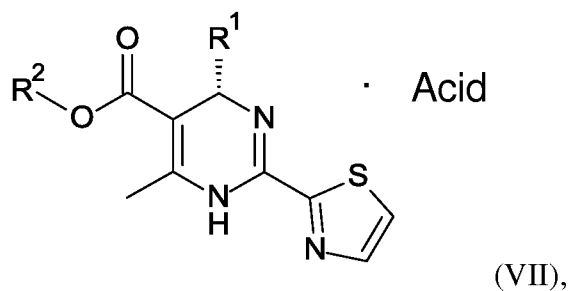
The whole synthesis comprises the following steps:

Step a) Beignelli reaction to form the compound of formula (V),



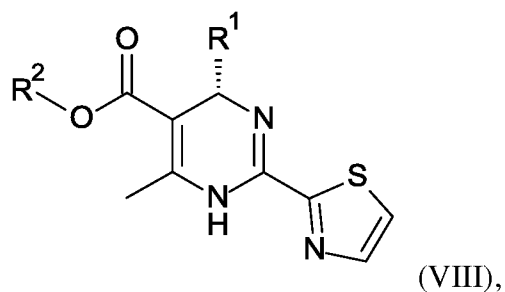
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- 5 Step b) The formation and recrystallization of the enantiomeric salt of formula (VII), or solvate,



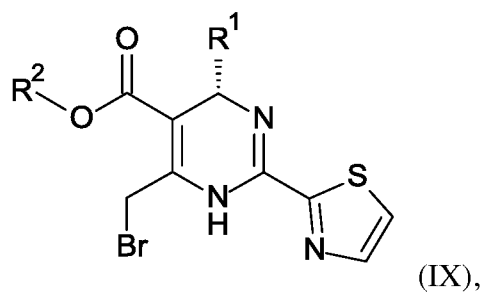
wherein R^1 and R^2 are defined as above;

- 10 Step c) The recovery of enantiomeric compound of formula (VIII) from its enantiomeric salt of formula (VII) or solvate,



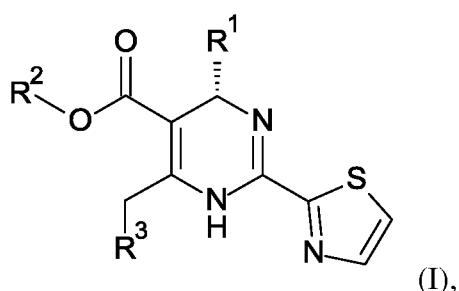
wherein R^1 and R^2 are defined as above;

- Step d) The bromination of compound of formula (VIII) to form a compound of formula (IX),



wherein R^1 and R^2 are defined as above;

- Step e) The substitution of the compound of formula (IX) to form a compound of formula (I),



wherein R^1 , R^2 and R^3 are defined as above;

Step f) The purification and recrystallization of compound of formula (I).

Another embodiment of this invention is that compound of formula (Ia) can also be synthesized in analogy to Scheme 1 without chiral separation step.

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

Step a) Biginelli reaction to form the compound of formula (V).

The formation of compound of formula (V) is usually performed in the presence of a suitable catalyst and a suitable base in a suitable organic solvent. The conversion as a rule is performed under a heating condition.

15 The suitable catalyst is selected from TEA, a mixture of TEA and AcOH, Pyridine, a mixture of Pyridine and AcOH, Glycine, β -Alanine, GABA, DBU, a mixture of DBU and AcOH, a mixture of AcOH and piperidine, particularly the catalyst is a mixture of AcOH and piperidine.

The suitable base is selected from TEA, DIPEA, DBU, particularly the base is TEA.

20 The suitable organic solvent is selected from MeOH, EtOH, IPA, tBuOH and toluene, particularly the organic solvent is IPA.

The Biginelli reaction as a rule is performed at 0°C - 80°C , particularly at 75°C - 80°C .

Step b) The formation and recrystallization of the enantiomeric salt of formula (VII), or solvate.

25 The formation of the enantiomeric salt of formula (VII) or solvate is usually performed in the presence of a suitable organic acid (VI) in a suitable organic solvent. The conversion as a rule is performed under a heating condition.

5 The suitable organic acid used in salt formation is selected from 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, particularly the organic acid is (R)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate or (S)-(+)-1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate.

10 The suitable organic solvent used in salt formation is selected from tetrahydrofuran, MTBE, isopropyl ether, methoxycyclopentane, MeOH, EtOH, IPA, IPAc, EtOAc, MEK, DCM, heptane, acetone, ACN, toluene, water, MIBK, trifluoroethanol, cyclohexane, DCM, xylene, fluorobenzene, chlorobenzene and a mixture thereof, particularly the organic solvent is MIBK, IPAc or a mixture of ACN and MTBE.

15 The suitable amount of organic acid (VI) is 0.5 eq - 1.0 eq, particularly the amount is 0.8 eq.

The salt formation as a rule is performed at 0°C - 80°C, particularly at 60°C - 75°C.

Recrystallization of the crude enantiomeric salt of formula (VIII) or solvate is achieved by selective crystallization in a suitable solvent. The other enantiomeric salt as a rule remains in the mother liquor.

20 The suitable solvent used in recrystallization is selected from MIBK, IPAc, diisopropylether, toluene and tert-butylmethylether, particularly the organic solvent is MIBK, IPAc or a mixture of ACN and MTBE.

Step c) The recovery of enantiomeric compound of formula (VIII) from its enantiomeric salt of formula (VII) or solvate.

25 The recovery of enantiomeric compound of formula (VIII) can be achieved by reacting desired enantiomeric salt of formula (VII) or solvate with a suitable amount of base in a suitable organic solvent, followed by a suitable work up procedure to remove water residual.

The suitable base is selected from TEA, DIPEA, methyldicyclohexylamine, NMM, NaOH, Na₂CO₃, NaHCO₃ and a mixture thereof, particularly the base is NaOH.

30 The reaction is usually performed in an organic solvent which is selected from DCM, methyltetrahydrofuran, tert-butylmethylether and fluorobenzene, particularly the organic solvent is DCM.

5 The suitable base amount is selected from 1.0 eq - 1.5 eq, particularly the base amount is 1.1 eq.

 The suitable work up to remove the water residual was selected by dried through Mg_2SO_4 , Na_2SO_4 , and azeotropy, particular the work up is azeotropy.

10 Step d) The bromination of compound of formula (VIII) to form a compound of formula (IX).

 The bromination of compound of formula (VIII) to form a compound of formula (IX) is usually performed in the presence of a suitable reagent in a suitable organic solvent and suitable additive. The conversion as a rule is performed under a heating condition.

15 The suitable bromination reagents is selected from liquid bromine, NBS, pyridine tribromide, 1,3-dibromo-5,5-dimethylhydantion, particularly the bromination reagent is NBS.

 The reaction is usually performed in an organic solvent which is selected from carbon tetrachloride, benzene, fluorobenzene, chlorobenzene, cyclohexane and DCM, particularly the organic solvent is DCM.

 The bromination as a rule is performed at 0°C - 80°C , particularly at 35°C - 40°C .

20 The suitable additive is selected from NH_4Cl , NH_4Br , NH_4OAc , V_{65} , AuCl_3 , FeCl_3 , AlCl_3 , PBr_3 , KBr , ZnBr , MSA , TFA , H_2SO_4 and AcOH , particularly the additive is PBr_3 .

 Step e) The substitution of the compound of formula (IX) to form a compound of formula (I).

25 The substitution of the compound of formula (IX) to form a compound of formula (I) is usually performed in the presence of a suitable base in a suitable organic solvent. The conversion as a rule is performed under a heating condition.

 The suitable base is selected from NaOH , KOH , NaOtBu , NaH , NEt_3 , DIPEA , DBU and TMP particularly the base is TMP .

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

5 The coupling reaction as a rule is performed at 0°C - 40°C, particularly 35°C - 40°C.

Step f) The purification and recrystallization of compound of formula (I).

10 The purification of compound of formula (I) is performed with a suitable acid in a suitable solvent to form a salt or through an acid-base work-up; and recrystallization of compound of formula (I) is performed with suitable seeding amount in the suitable pH range or a direct recrystallization in a suitable organic solvent.

15 The suitable acid used in the purification of compound of formula (I) for salt formation is selected from HCl, HBr, H₂SO₄, H₃PO₄, MSA, toluene sulfonic acid and camphor sulfonic acid, particularly the acid is MSA. The acid used in the purification of compound of formula (I) for acid-base work-up is selected from HCl, HBr, H₂SO₄, H₃PO₄, MSA, toluene sulfonic acid and camphor sulfonic acid, particularly the acid is H₃PO₄. The base used in the purification of compound of formula (I) for acid-base work-up is selected from NaOH, KOH, K₂CO₃ and Na₂CO₃, particularly the base is NaOH.

 The suitable organic solvent for purification is selected from THF, IPAc, MTBE, fluorobenzene, benzene and DCM, particularly the organic solvent is DCM.

20 The suitable solvent for recrystallization of compound of formula (I) was selected from acetone, ACN, MeOH, EtOH and IPA, particularly the solvent is acetone.

 The suitable seeding amount is selected from 1wt% - 100 wt%, particularly the seeding amount is 1wt%.

 The suitable pH range is from 0 to 10, particularly the pH is 7.

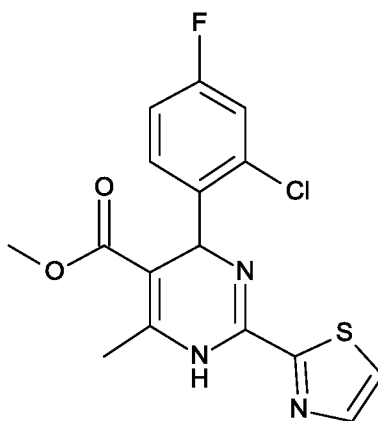
25 The suitable recrystallization time is from 2 hours to 4 days, particularly the recrystallization time is 3 days.

 The suitable organic solvent used in direct recrystallization is selected from acetone, ACN, MeOH, EtOH, IPA and a co-solvent of IPA and heptane, particularly the suitable organic solvent is co-solvent of IPA and heptane.

5 EXAMPLES

Example 1

Preparation of 4-(2-chloro-4-fluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester:



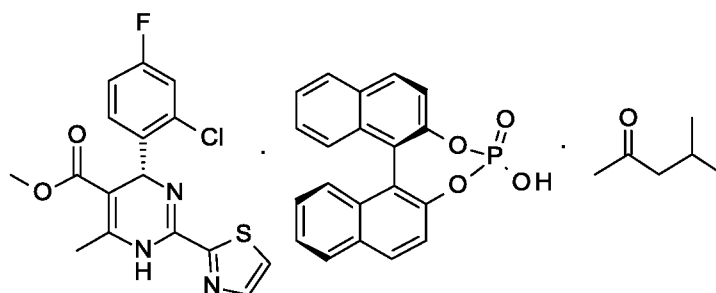
10 To a 1000 L glass-lined reactor was charged 2-chloro-4-fluoro-benzaldehyde (30.8 kg, 194 mol) and isopropanol (188.0 kg). To the solution was then added methyl acetoacetate (22.7 kg, 195 mol) followed by piperidine (1.74 kg, 20.4 mol) and acetic acid (1.32 kg, 22.0 mol). The mixture was then heated to 43 °C - 47 °C and stirred under this temperature for 5 hours. To the reaction mixture was then added thiazole-2-carboxamide hydrochloride salt (19.8 kg, 121.0mol)
15 and triethyl amine (20.0 kg, 198.0 mol). The reaction mixture was heated to 80 °C - 85 °C and stirred for 7 hours.

After reaction completion, the reaction mixture was cooled to 20 °C - 25 °C. To the mixture was then added water (52.0 kg). The resulting suspension was stirred at 20 °C - 25 °C for 2 hours. The suspension was centrifuged and the collected solid was washed with isopropanol/water (42
20 kg; 10v/3v). The wet solid was dried in vacuum oven to afford 35.05 kg of 4-(2-chloro-4-fluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester (Example 1). The purity was 95.8%, the yield was 79.2 %, and MS m/e = 366.2 [M+H]⁺.

Example 2

Preparation of (R)-4-(2-chloro-4-fluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-
25 **dihydropyrimidine-5-carboxylic acid methyl ester mono (R)-(-)-1,1'-Binaphthyl-2,2'-diyl**
hydrogenphosphate salt mono MIBK solvate

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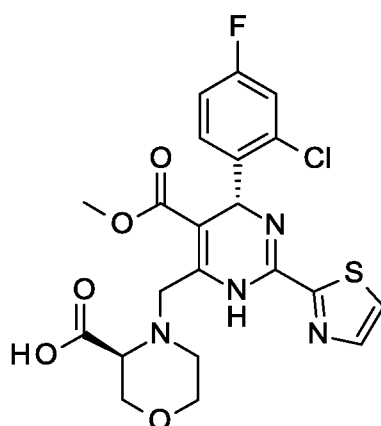
To a 1000 L flask was charged with 4-(2-chloro-4-fluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester (Example 1, 23.8 kg, 65.06 mol), MIBK (660 L) and purified water (6.6 L) at room temperature. The mixture was stirred at room temperature for another 20 minutes until all yellow solid was dissolved. (R)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate (18.1 kg, 52.05 mol) was added in one portion at room temperature. The reaction mixture was heated to 75 °C and the agitation was maintained for 14 hours. The mixture was slowly cooled to 40 °C in 6 hours, then the reaction mixture was stirred at 40 °C for another 2 hours. Reaction mixture was filtrated, and the collected solid was rinsed with MIBK (50 L) for 3 times. The resulting solid was dried under vacuum at 55 °C for 24 hours until the weight was constant to give 21.75 kg product as light yellow solid. The chiral purity was 99.45%, the yield was 87%, the mol ratio of Acid: (R)-4-(2-chloro-4-fluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester: MIBK was 1:1:1, and the MS m/e = 366.2 [M+H]⁺.

20

Example 3

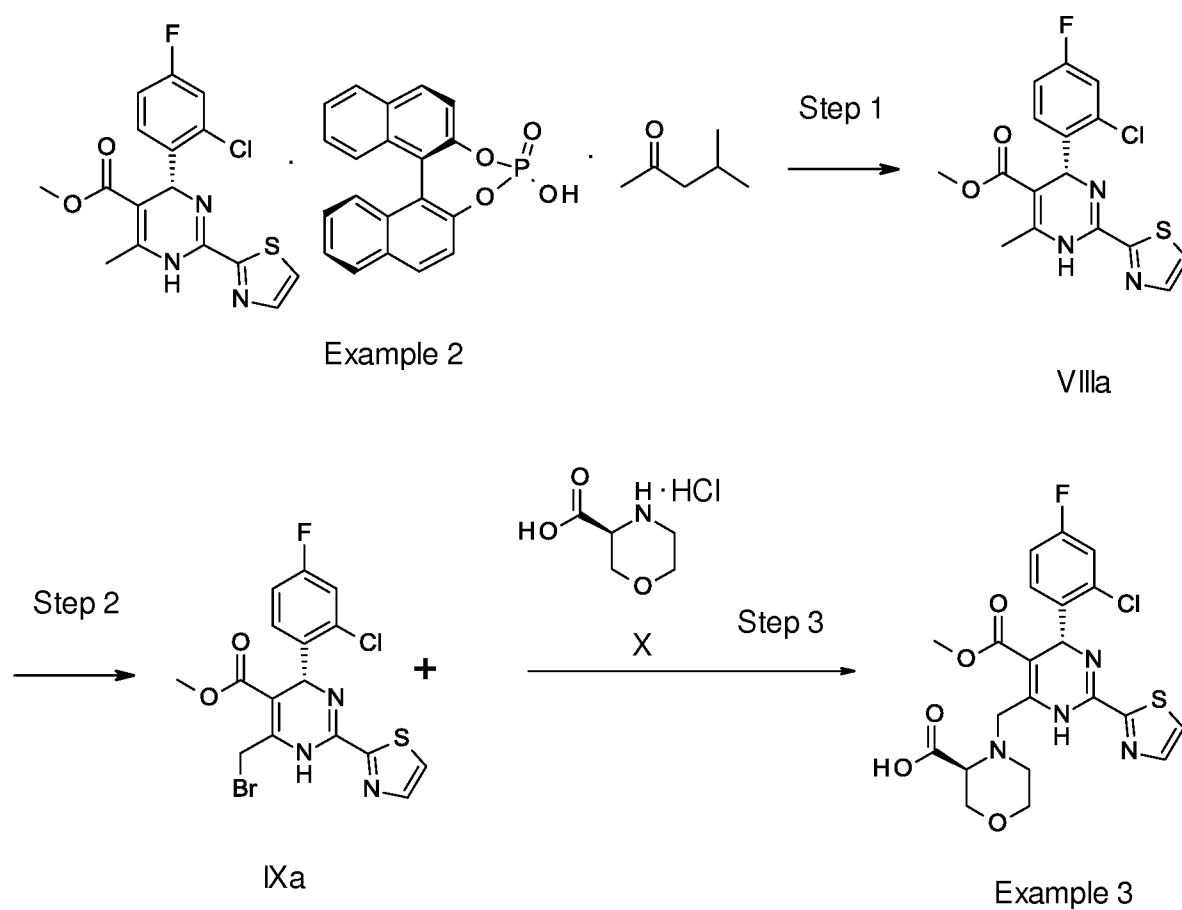
Preparation of (3S)-4-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]morpholine-3-carboxylic acid

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5

The title compound was prepared according to following scheme:



Step 1) preparation of (4R)-4-(2-chloro-4-fluorophenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester (compound VIIIa)

10

5 To a 50 L flask was charged with (R)-4-(2-chloro-4-fluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester mono (R)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate salt mono MIBK solvate (Example 2, 2.50 kg, 3.07 mol) and dichloromethane (25.0 L). The mixture was stirred at room temperature for another 20 minutes until all yellow solid dissolved. Aqueous NaOH solution (20 wt%, 1.1 eq., 0.68 kg, 3.38 mol)
10 was added to the previous solution in one portion at room temperature. The reaction mixture was stirred for 2 hours, then filtrated, and the collected solid was rinsed with dichloromethane (5.0 L) twice. The collected organic solution was concentrated till dryness *in vacuo*. To the left residue was added DCM (7.5 L), the resulting solution was concentrated till dryness *in vacuo* and this process was repeated one more time. The resulting yellow oil (compound **VIIIa**) was used in the
15 next step without further purification.

Step 2) preparation of (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester (compound **IXa**)

(4R)-4-(2-chloro-4-fluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester (compound **VIIIa**, 1.0 eq, 1.12 kg, 3.07 mol) from last step was
20 dissolved in DCM (12.5 L). The previous solution was then heated to 33 °C - 38 °C. Then NBS (0.63 kg, 3.53 mol) was added to previous solution portionwise with careful monitoring the starting material conversion using HPLC. After reaction completion, NaHCO₃ aqueous solution (3.5 wt%, 5.80 kg) was added to the reaction mixture to quench the reaction. Phase separation and resulting organic solution was used in next step without further purification.

25 Step 3) preparation of (3S)-4-[[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]morpholine-3-carboxylic acid (Example 3)

The 50 L flask was charged with crude (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester (compound **IXa**) from last step) in dichloromethane solution, (3S)-morpholine-3-carboxylic acid hydrochloride
30 salt (1.02 eq, 0.53 kg, 3.14 mol) and 2,2,6,6-tetramethylpiperidine (2.87 eq, 1.24 kg, 8.80 mol) at 25 °C - 28 °C. The resulting solution was stirred at 25 °C - 28 °C for 16 hours.

After reaction completion, water (10.0 L) was added to reaction mixture to quench the reaction. The reaction mixture was adjusted to pH = 2.5 using H₃PO₄. After phase separation, the organic phase was washed with acid solution (using H₃PO₄ to adjust pH = 2.5) twice to remove

-15-

5 all the TMP. The organic solution was concentrated to dryness *in vacuo* and the residue was re-dissolved in MIBK (10.0 L). To the solution was then added MSA (0.78 eq, 0.23 kg, 2.39 mol) slowly in 2 hours. After the addition of MSA, the solution was heated to 40 °C - 45 °C and stirred for 2 hours. The resulting suspension was cooled to 23 °C - 25 °C. The reaction mixture was filtered and the collected solid was rinsed with MIBK (1.0 L). The resulting solid was dried in
10 vacuum oven at 45 °C for 16 hours to afford the MSA salt of Example 3 (1.45 kg).

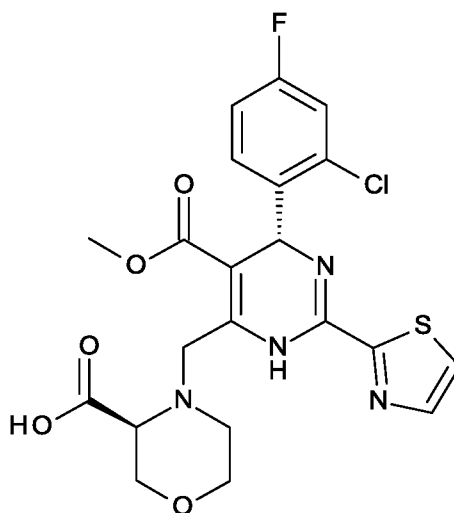
To a 20 L flask was charged with MSA salt of Example 3 (1.45 kg, 2.45 mol), EtOAc (15.0 L) and NaHCO₃ aqueous solution (10 wt%, 1.33 kg) at room temperature. After phase separation, the organic phase was washed with water (3.0 L). The organic solution was concentrated to dryness *in vacuo* and the residue was re-dissolved in acetone (1.10 L).

15 The resulting acetone solution was slowly added into water (12.0 L) in 12 hours at 20 °C - 25 °C. The resulting suspension was stirred for an additional 72 hours at 20 °C - 25 °C. Reaction mixture was filtered and the collected solid was rinsed with water (5.0 L) for 2 times. The resulting solid was dried under vacuum at 55 °C for 72 hours until the weight was constant to give 1.01 kg product as light yellow solid. The purity was 99.5%, the yield was 66.6% for 3 steps,
20 and the MS m/e = 495.1 [M+H]⁺.

Example 4

Alternative method for preparation of (3S)-4-[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl)methyl]morpholine-3-carboxylic acid
25

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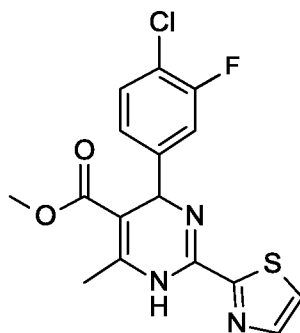
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The compound **IXa** in DCM solution was prepared in analogy to Example 3 step 1) and 2). To the previous solution was then added (3S)-morpholine-3-carboxylic acid hydrochloride salt (compound **X**, 1.03 eq, 1.06 kg, 6.32 mol), and 2,2,6,6-tetramethylpiperidine (2.84 eq, 2.46 kg, 17.42 mol). The resulting solution was stirred at 25 °C - 28 °C for 16 hours.

10 After reaction completion, aqueous NaHCO₃ (3.5 wt%, 15.0 L) solution was added to quench the reaction. The reaction mixture was adjusted to pH = 2.5 using H₃PO₄. After phase separation, the organic phase was washed with acid solution (using H₃PO₄ to adjust pH = 2.5) twice to remove all the TMP. Water (15.0 L) was added and the aqueous phase of the mixture was adjust to pH = 0.26 - 0.3 with H₃PO₄ (85 wt%). The solution was stirred for another
15 30 mins. After phase separation, the aqueous layer was washed with DCM (15.0 L) twice. Then the aqueous layer was adjusted to pH=2.5 with aqueous NaOH solution (40 wt%). The resulting solution was extracted with EtOAc (20.0 L). After phase separation, the organic phase was washed with water (3.0 L) and filtered through polish filter. The organic solution was concentrated till dryness *in vacuo*. The left residue was re-dissolved in acetone (4.0 L).

20 The resulting acetone solution was slowly added into water (30.00 L) in 1 hour at 20 °C - 25 °C. The resulting suspension was stirred for another 72 hours at 20 °C -25 °C. Then the previous suspension was filtered and the collected solid was rinsed with water (5.0 L) twice. The resulting solid was dried in vacuum oven at 55 °C for 72 hours until the weight was constant to give 2.29 kg product as a light yellow solid. The purity was 99.5%, the yield was 75.5%, and the
25 MS m/e =495.1 [M+H]⁺.

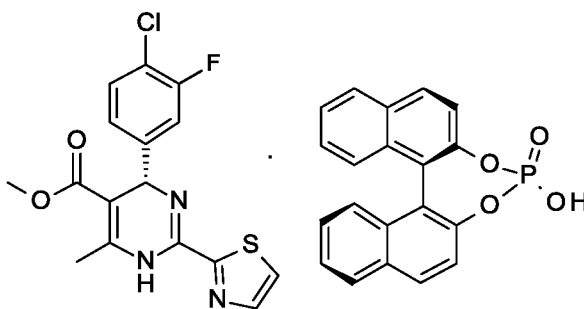
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Example 5**Preparation of 4-(4-chloro-3-fluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester**

The title compound was prepared in analogy to Example 1 by using 4-chloro-3-fluoro-benzaldehyde (94.80g, 0.60mol) instead of 2-chloro-4-fluoro-benzaldehyde. 113.00 g product was obtained as light yellow solid. The purity was 81.0%, the yield was 51.6%, and MS $m/e = 366.3 [M+H]^+$.

Example 6

Preparation of (S)-4-(4-chloro-3-fluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester mono (R)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate salt



The title compound was prepared in analogy to Example 2 by using 4-(4-chloro-3-fluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester (Example

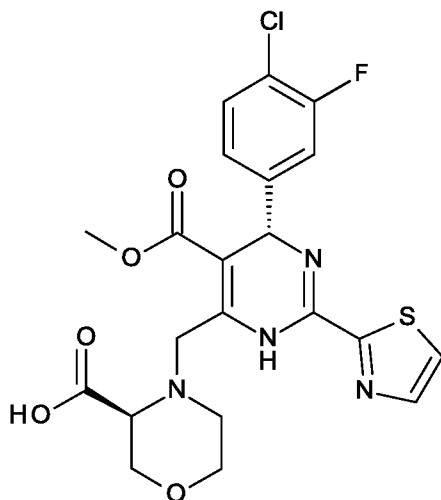
-18-

- 5 **5**, 182 g, 0.50 mol) and (R)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate (140 g, 0.40 mol) instead of methyl 4-(2-chloro-4-fluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate (Example 1) and (R)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate. 110 g product was obtained as light yellow solid. The chiral purity was 99.3%, the yield was 72.0%, and MS $m/e = 366.3$ $[M+H]^+$.

10

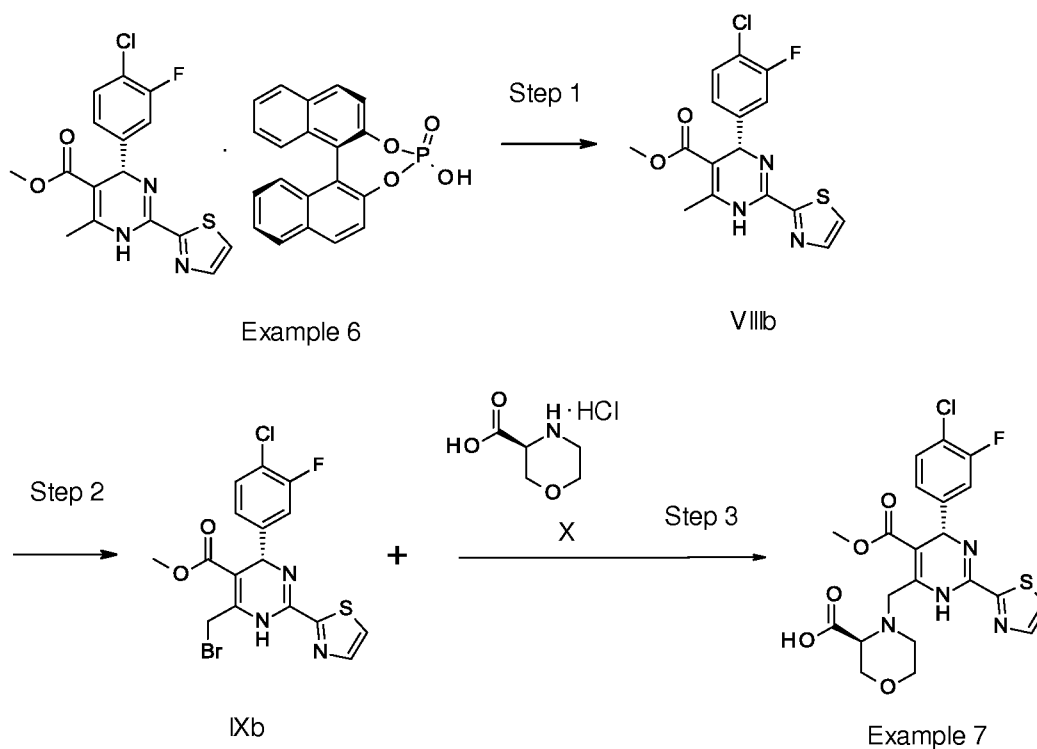
Example 7

Preparation of (3S)-4-[[[(4S)-4-(4-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]morpholine-3-carboxylic acid



- 15 The title compound was prepared according to following scheme:

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Step 1) preparation of (4S)-4-(4-chloro-3-fluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester (compound VIIIb)

Compound **VIIIb** was prepared in analogy to step 1) of Example 3 by using (S)-4-(4-chloro-3-fluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester mono (R)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate salt (Example 6, 100 g, 0.14 mol) instead of (R)-4-(2-chloro-4-fluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester mono (R)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate salt mono MIBK solvate (Example 2). The resulting yellow solid (compound **VIIIb**) was used in next step without further purification.

Step 2) preparation of (4S)-6-(bromomethyl)-4-(4-chloro-3-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester mono methane sulfonic acid salt (compound IXb)

To a 5 L flask was charged with the (4S)-4-(4-chloro-3-fluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester (compound **VIIIb**, 127 g, 0.35 mol) and DCM (3.0 L). The solution was heated to 35 °C -38 °C and to the solution was added PBr₃ (4.71 g, 17.4 mmol). Then NBS (71.13 g, 0.40 mol) was added to the reaction mixture portionwise with careful monitoring the starting material conversion using HPLC. After reaction

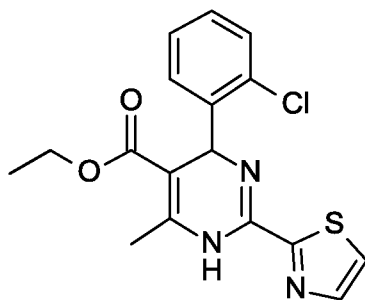
5 completion, NaHCO_3 (3.5 wt%, 700 g) was added to quench the reaction. After phase separation, the organic phase was dried with Na_2SO_4 . The DCM was removed under vacuum. IPAc (500 mL) was added to the residue followed by addition of MSA (1.0 eq; 33.36 g, 0.35 mol). The resulting solution was heated to 55 °C - 58 °C and the agitation was maintained for 2 hours. The suspension was then cooled to 25 °C - 28 °C and stirred for 2 hours. Reaction mixture was
 10 filtered and the collected solid was rinsed with IPAc (100 mL) twice. The resulted solid was dried in vacuum oven at 55 °C for 72 hours to afford 114.00 g product as a white solid. The purity was 91.4%, the yield was 55.1%, and the MS $m/e = 444.0$ $[\text{M}+\text{H}]^+$.

Step 3) preparation of (3S)-4-[[[(4S)-4-(4-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl]-1,4-dihydropyrimidin-6-yl]methyl]morpholine-3-carboxylic acid (Example 7)

15 The compound of Example 7 was prepared in analogy to step 3) of Example 3 by using (4S)-6-(bromomethyl)-4-(4-chloro-3-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester mono methane sulfonic acid salt (compound **IXb**, 114g, 0.21mol) instead of (4R)-6-(bromomethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester (compound **IXa**). 105 g product was obtained
 20 as a light yellow solid. The chiral purity was 99.88%, purity was 99.1%, the yield was 97.9%, and MS $m/e = 494.3$ $[\text{M}+\text{H}]^+$

Example 8

Preparation of 4-(2-chlorophenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid ethyl ester



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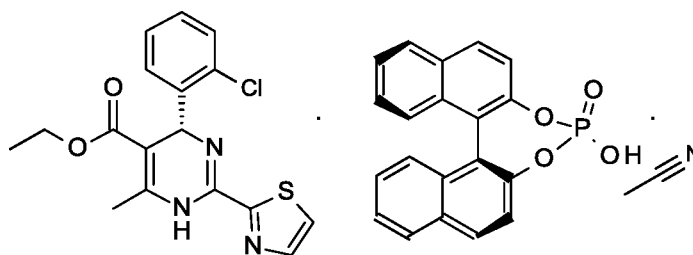
The title compound was prepared in analogy to Example 1 by using 2-chlorobenzaldehyde (140 g, 1.00 mol) and ethyl 3-oxobutanoate (130 g, 1.00 mol) instead of 2-chloro-4-fluoro-

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- 5 benzaldehyde and methyl 3-oxobutanoate. 224 g product was obtained as a light yellow solid. The purity was 99.0%, the yield was 62.2% and MS $m/e = 362.3$ $[M+H]^+$.

Example 9

Preparation of (R)-4-(2-chlorophenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid ethyl ester mono (S)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate salt
 10 **mono ACN solvate**



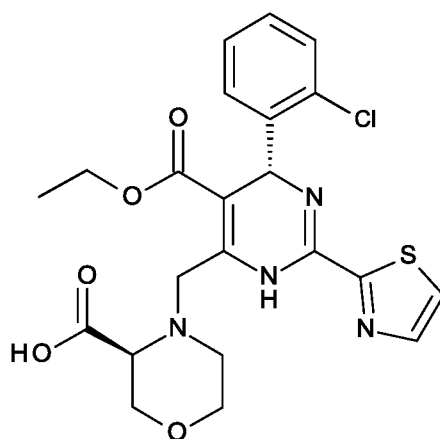
- To a 2 L flask was charged with 4-(2-chlorophenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid ethyl ester (Example 8, 120 g, 0.33 mol), ACN (0.60 L), MTBE (0.60 L) and purified water (120 mL) at room temperature. (S)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate (115 g, 0.33 mol) was added to the previous reaction mixture in one portion at room temperature. The reaction mixture was heated to 75 °C and agitation was maintained for 16 hours. After that, the reaction mixture was slowly cooled to room temperature, and stirred at room temperature for another 2 hours. Then the reaction mixture was filtered, and the collected solid was rinsed with ACN/MTBE (0.40 L, v/v 1:1) for 2 times. The collected solid
 15 was dried in vacuum oven at 55°C for 24 hours to give 85 g product as a light yellow solid. The chiral purity was 99.3%, the yield was 72.0%, the mol ratio of Acid: (R)-4-(2-chlorophenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid ethyl ester : ACN was 1:1:1, and MS $m/e = 362.3$ $[M+H]^+$.
 20

25

Example 10

Preparation of (3S)-4-[(4S)-4-(4-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]morpholine-3-carboxylic acid

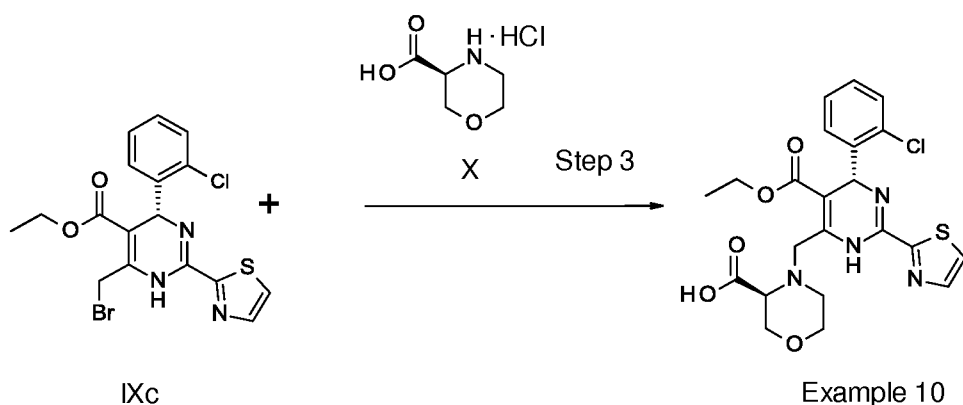
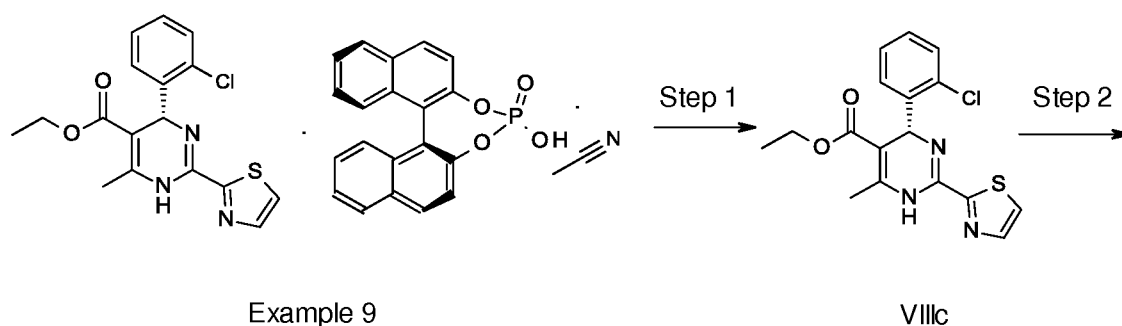
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Example 10

The title compound was prepared according to following scheme:



10 Step 1) preparation of (R)-4-(2-chlorophenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid ethyl ester (compound VIIIc)

The compound **VIIIc** was prepared in analogy to step 1) of Example 3 by using (R)-4-(2-chlorophenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid ethyl ester mono (S)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate salt mono ACN solvate (Example 9) instead

5 of (R)-4-(2-chloro-4-fluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester mono (R)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate salt mono MIBK solvate (Example 2). The chiral purity was 99.2%, the yield was 98.0%, and MS $m/e = 362.3 [M+H]^+$.

10 Step 2) preparation of (R)-4-(2-chlorophenyl)-6-bromomethyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid ethyl ester (compound IXc)

The compound **IXc** was prepared in analogy to step 2) of Example 3 by using (R)-4-(2-chlorophenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid ethyl ester (compound **VIIIc**) instead of (4R)-4-(2-chloro-4-fluoro-phenyl)-6-methyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester (compound **VIIIa**). The purity was 81.0%, the
15 yield was 79.3%, and MS $m/e = 440.0 [M+H]^+$.

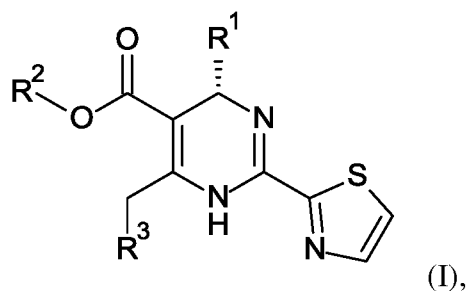
Step 3) preparation of (3S)-4-[[[(4R)-4-(2-chlorophenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]morpholine-3-carboxylic acid (Example 10)

To the 100 mL flask was charged with (R)-4-(2-chlorophenyl)-6-bromomethyl-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylic acid ethyl ester (compound **IXc**, 8.14g, 18.50 mmol) in
20 DCM solution, (3S)-morpholine-3-carboxylic acid hydrochloride salt (compound **X**, 1.50 eq., 4.64 g, 27.70 mmol) and 2,2,6,6-tetramethylpiperidine (5.10 eq, 13.03 g, 94.16 mmol). The reaction mixture was stirred at 25 °C - 28 °C for 16 hours. After reaction completion, the reaction mixture was adjusted to pH = 2.5 using H₃PO₄. After phase separation, the organic phase was washed with acid water (using H₃PO₄ to adjust to pH = 2.5) twice to remove all the TMP and
25 concentrated till dryness *in vacuo*. The residue was dissolved in EtOAc (30 mL) at 25 °C -28 °C. To the previous solution was then slowly added n-heptane (50 mL) while maintain at 25 °C -28 °C. The resulted suspension was stirred for another 0.5 hour at 25 °C -28 °C. After vacuum filtration, the collected solid was dried in vacuum oven at 55 °C for 16 hours until the weight was constant to give 7.40 g product (Example 10) as a yellow solid. The purity was 99.0%, the yield
30 was 80.7%, and MS $m/e = 491.3 [M+H]^+$.

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Claims

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



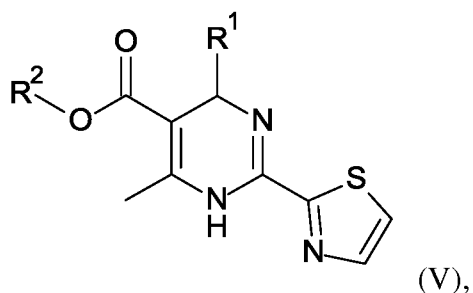
wherein R¹ is phenyl, which is unsubstituted, or once, twice or three times substituted by halogen; R² is C₁₋₆alkyl; R³ is heterocyclyl;

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and pharmaceutically acceptable addition salts thereof;

comprising the following steps:

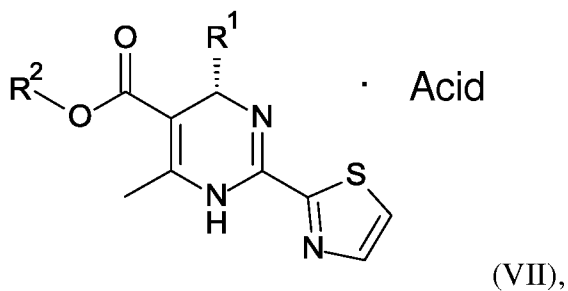
Step a) Beginelli reaction to form the compound of formula (V),



wherein R¹ and R² are defined as above;

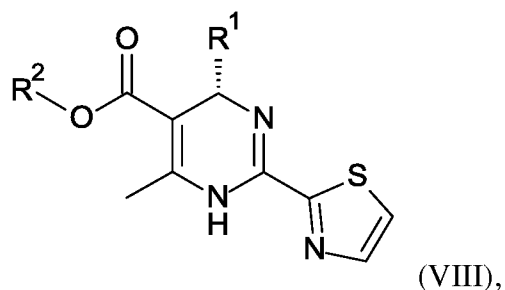
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Step b) The formation and recrystallization of the enantiomeric salt of formula (VII), or solvate,



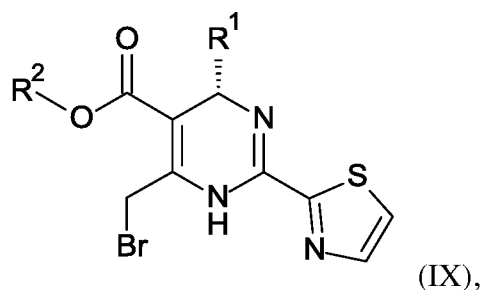
5 wherein R^1 and R^2 are defined as above;

Step c) The recovery of enantiomeric compound of formula (VIII) from its enantiomeric salt of formula (VII) or solvate,



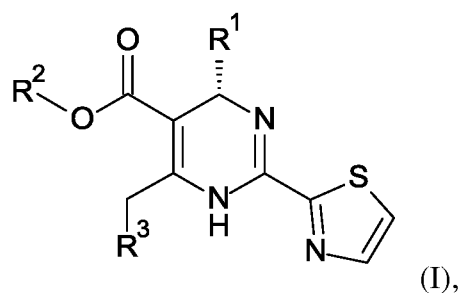
wherein R^1 and R^2 are defined as above;

10 Step d) The bromination of compound of formula (VIII) to form a compound of formula (IX),



wherein R^1 and R^2 are defined as above;

15 Step e) The substitution of the compound of formula (IX) to form a compound of formula (I),



wherein R^1 , R^2 and R^3 are defined as above;

- 5 Step f) The purification and recrystallization of compound of formula (I).
2. A process according to claim 1, wherein R^1 is chlorofluorophenyl or chlorophenyl; R^2 is methyl or ethyl; R^3 is carboxymorpholinyl.
3. A process according to claim 1 or 2, wherein the bromination of compound of formula (VIII) in step d) is performed in the presence of a reagent in an organic solvent and additive, wherein
10 the additive is selected from NH_4Cl , NH_4Br , NH_4OAc , V_{65} , $AuCl_3$, $FeCl_3$, $AlCl_3$, PBr_3 , KBr , $ZnBr$, MSA , TFA , H_2SO_4 and $AcOH$, particularly the additive is PBr_3 .
4. A process according to any one of claims 1 to 3, wherein the product of bromination of compound of formula (VIII) in step d) is followed by a salt formation between the product and MSA .
- 15 5. A process according to any one of claims 1 to 4, wherein the substitution of the compound of formula (IX) in step e) is performed in the presence of a base in an organic solvent, wherein the base is selected from $NaOH$, KOH , $NaOtBu$, NaH , TEA , $DIPEA$, DBU and TMP , particularly the base is TMP .
6. A process according to any one of claims 1 to 5, wherein the purification of compound of
20 formula (I) in step f) is performed with an acid in a solvent to form a salt or through an acid-base work-up; wherein the acid used in the purification of compound of formula (I) for salt formation is selected from HCl , HBr , H_2SO_4 , H_3PO_4 , MSA , toluene sulfonic acid and camphor sulfonic acid, particularly the acid is MSA .
7. A process according to any one of claims 1 to 6, wherein the acid used in the purification of
25 compound of formula (I) for acid-base work-up in step f) 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 base used in the purification of compound of formula (I) for acid-base work-up in step f) is selected from $NaOH$, KOH , K_2CO_3 and Na_2CO_3 , particularly the base is $NaOH$.
8. A process according to claim 6 or 7, wherein and recrystallization of compound of formula (I)
30 in step f) is performed with seeding amount in the pH range or a direct recrystallization in a suitable organic solvent; wherein the suitable seeding amount is selected from 1 wt%- 100 wt%, particularly the seeding amount is 1 wt%.

5 9. A process according to claim 8, wherein the suitable pH range is from 0 to 10, particularly the pH is 7.

10. A process according to claim 8 or 9, wherein the suitable recrystallization time is from 2 hours to 4 days, particularly the recrystallization time is 3 days.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2015/080750

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D417/14
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014/037480 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) 13 March 2014 (2014-03-13) page 94; compound 2 -----	1-10
A	WO 2014/184328 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) 20 November 2014 (2014-11-20) page 86; compound Ia -----	1-10



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

27 January 2016

Date of mailing of the international search report

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Authorized officer

Jeanjean, Fabien

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2015/080750

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