(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 July 2020 (23.07.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/148352 A1

(51) **International Patent Classification:**
*C07D 471/04* (2006.01)

(21) **International Application Number:**
PCT/EP2020/050951

(22) **International Filing Date:**
16 January 2020 (16.01.2020)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
PCT/CN2019/072102
17 January 2019 (17.01.2019) CN

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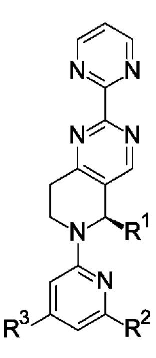
(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17:**
— *of inventorship (Rule 4.17(iv))*

**Published:**
— *with international search report (Art. 21(3))*

# (54) Title: A PROCESS FOR THE PREPARATION OF TETRAHYDROPYRIDOPYRIMIDINES

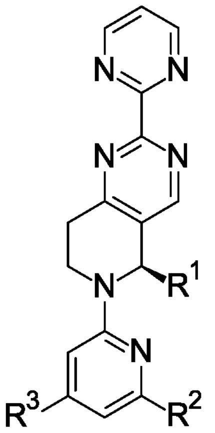


(I)

(57) **Abstract:** The present invention relates to a process for synthesizing a compound of formula (I), or a pharmaceutically acceptable salt 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.

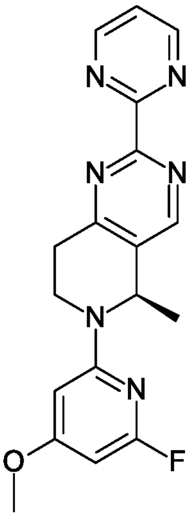
# A process for the preparation of tetrahydropyridopyrimidines

The present invention relates to a process for the preparation of compounds of formula (I),


(I),

wherein $R^1$ is $C_{1\text{-}6}$alkyl; $R^2$ is $C_{1\text{-}6}$alkyl or halogen; $R^3$ is $C_{1\text{-}6}$alkyl or $C_{1\text{-}6}$alkoxy.

Particularly, the present invention relates to a process for the preparation of (5R)-6-(6-fluoro-4-methoxy-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine,


,

or a pharmaceutically acceptable salt.

## BACKGROUND OF THE INVENTION

The previous synthetic approach of compounds of formula (I) was disclosed in patent WO2016/177655, however, it is not suitable for commercial manufacturing due to the following issues:

(a) The overall yield for making the compound (I) is very low (only ~1.5%) and has scalability concerns as indicated in the patent due to several steps with low reaction yield and regioselective synthesis concerns.

(b) The column purifications are needed for the critical intermediates, which are 8-(6-fluoro-4-methoxy-2-pyridyl)-1,4-dioxa-8-azaspiro[4.5]decane, 1-(6-fluoro-4-methoxy-2-pyridyl)piperidin-4-one and 6-(6-fluoro-4-methoxy-2-pyridyl)-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine.

(c) All intermediates are regio-isomers, therefore extensive HPLC purification for these intermediates are required to make the sale-up synthesis becoming very challenge.

(d) Scalability and cost concern for the production because of the oxidation reaction used expensive $RuCl_3/NaIO_4$ in a huge volume of solvent, which leads to low efficiency overall.

Based on the issues above, one object of this invention therefore is to find an alternative efficient synthetic approach which can be applied on a technical scale and/or result in obtaining the product in a higher yield and/or desired purity. Addressing all these issues (a) to (d) mentioned above is also one of the objects for this invention.

## DETAILED DESCRIPTION OF THE INVENTION

## DEFINITIONS

As used herein, the term "$C_{1-6}$alkyl" alone or in combination signifies a saturated, linear- or branched chain alkyl group containing 1 to 6, particularly 1 to 4 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl and the like. Particular "$C_{1-6}$alkyl" group is methyl.

The term "$C_{1-6}$alkoxy" alone or in combination signifies a group $C_{1-6}$alkyl-O-, wherein the "$C_{1-6}$alkyl" is as defined above; for example methoxy, ethoxy, propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, 2-butoxy, *tert*-butoxy, pentoxy, hexyloxy and the like. Particular “$C_{1-6}$alkoxy” group is methoxy.

The term “halogen” and “halo” are used interchangeably herein and denote fluoro, chloro, bromo, or iodo.

The compounds according to the present invention may exist in the form of their pharmaceutically acceptable salts. 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. Particular are the sodium salts of the compounds of formula (I).

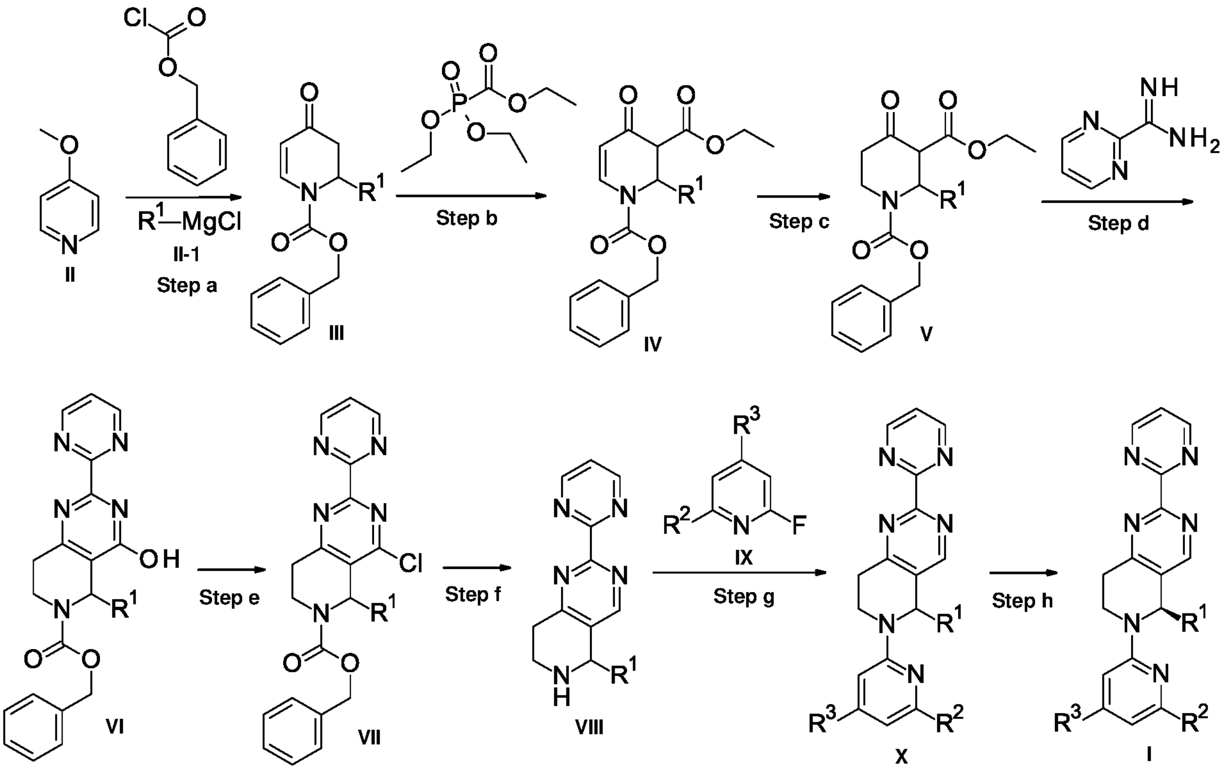
## ABBREVIATIONS

| | |
|---|---|
| ACN | Acetonitrile |
| eq | Equivalent |
| DCM | Dichloromethane |
| DIPEA | N,N-Diisopropylethylamine |
| MeOH | Methanol |
| EtOH | Ethanol |
| IPA | Isopropanol |
| IPAc | Isopropyl acetate |
| MTBE | Methyl tert-butyl ether |
| $Et_2O$ | Diethyl ether |

| | |
|---|---|
| TEA | Triethylamine |
| AcOH | Acetic acid |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| NMM | N-methylmorpholine |
| t-BuONa | Sodium *tert*-butoxide |
| LDA | Lithium diisopropylamide |
| LiHMDS | Lithium bis(trimethylsilyl)amide |
| NaHMDS | Sodium bis(trimethylsilyl)amide |
| $NaBH_4$ | Sodium borohydride |
| TFA | Trifluoroacetic acid |
| THF | Tetrahydrofuran |
| MeTHF | 2-Methyl Tetrahydrofuran |
| DMF | N,N-Dimethylformamide |
| DMAc | N,N-Dimethylacetamide |
| DMSO | Dimethyl sulfoxide |
| NMP | 1-Methyl-2-pyrrolidinone |
| V | volume |
| wt% | weight percent |

The present invention provides a process for preparing the compounds of formula (I) as outlined in the **scheme 1**.

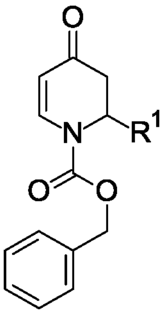
**Scheme 1**



wherein $R^1$ is $C_{1-6}$alkyl; $R^2$ is $C_{1-6}$alkyl or halogen; $R^3$ is $C_{1-6}$alkyl or $C_{1-6}$alkoxy.

The synthesis comprises one or more of the following steps:

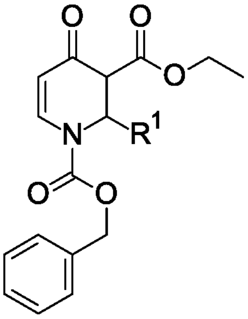
step a) the formation of the dihydropyridine (III),



(III),

wherein $R^1$ is $C_{1-6}$alkyl;

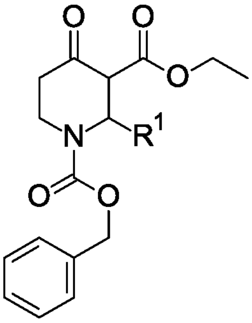
step b) the formation of the compound of formula (IV) via the alkylation reaction of the dihydropyridine (III) and ethyl diethoxyphosphorylformate,



(IV),

wherein $R^1$ is $C_{1-6}$alkyl;

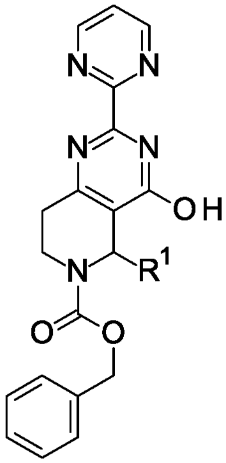
step c) the formation of the piperidine (V) via the reduction reaction of the compound of formula (IV),



(V),

wherein $R^1$ is $C_{1-6}$alkyl;

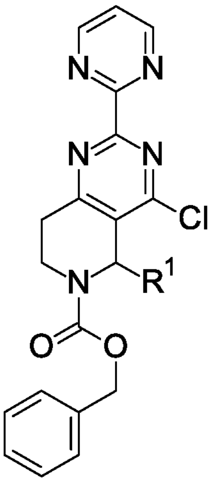
step d) the formation of the compound of formula (VI) via the cyclization reaction of the piperidine (V) and pyrimidine-2-carboxamidine,



(VI),

wherein $R^1$ is $C_{1-6}$alkyl;

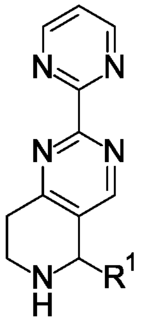
step e) the formation of the compound of formula (VII) via chloration of the compound of formula (VI),



(VII),

wherein $R^1$ is $C_{1\text{-}6}$alkyl;

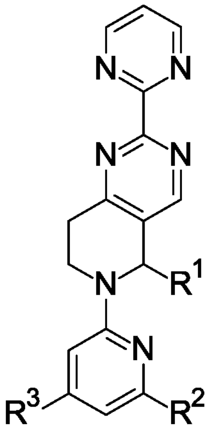
step f) the formation of the compound of formula (VIII) via selective hydrogenation of the compound of formula (VII),



(VIII),

wherein $R^1$ is $C_{1\text{-}6}$alkyl;

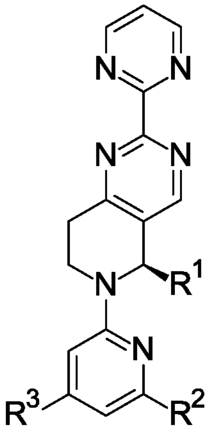
step g) the formation of the compound of formula (X) by N-alkylation of the compound of formula (VIII) with the compound of formula (IX),



(X),

wherein $R^1$ is $C_{1-6}$alkyl; $R^2$ is $C_{1-6}$alkyl or halogen; $R^3$ is $C_{1-6}$alkyl or $C_{1-6}$alkoxy;

step h) SFC separation of the compound of formula (X) to afford the compound of formula (I),



(I),

wherein $R^1$ is $C_{1-6}$alkyl; $R^2$ is $C_{1-6}$alkyl or halogen; $R^3$ is $C_{1-6}$alkyl or $C_{1-6}$alkoxy.

In another embodiment of this invention, wherein $R^1$ is methyl; $R^2$ is F or methyl; and $R^3$ is methyl or methoxy.

In another embodiment of this invention, wherein $R^1$ is methyl; $R^2$ is F; and $R^3$ is methoxy.

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

Step a) Alkylation reaction to form the dihydropyridine (III).

The formation of the dihydropyridine (III) is performed in the presence of a suitable metal reagent and a suitable organic solvent. The conversion as a rule is performed under a cooling condition.

The suitable metal reagent is selected from methyl, ethyl and isopropyl Grignard reagent. Particularly the metal reagent is methyl Grignard reagent.

The suitable organic solvent is selected from MTBE, THF, $Et_2O$ and Me-THF. Particularly the organic solvent is THF.

The temperature of the alkylation reaction as a rule is performed at -30°C - 0°C. Particularly temperature of the reaction is performed at -10°C - 0°C.

Step b) C-alkylation reaction to form the compound of formula (IV).

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

The suitable base is selected from t-BuONa, LDA, LiHMDS and NaHMDS. Particularly the base is LiHMDS.

The suitable organic solvent is selected from MTBE, THF, $Et_2O$ and MeTHF. Particularly the organic solvent is THF.

The temperature of the C-alkylation reaction as a rule is performed at 0°C- 25°C. Particularly temperature of the reaction is performed at 0°C - 5°C.

Step c) Reduction reaction to form the piperidine (V).

The formation of the piperidine (V) is performed in the presence of a suitable reductive reagent and a suitable organic solvent. The conversion as a rule is performed under a heating condition.

The suitable reductive reagent is selected from Fe powder, Zn powder and $NaBH_4$. Particularly the reagent is Zn powder.

The suitable organic solvent is selected from MeOH, EtOH, AcOH and formic acid. Particularly the organic solvent is AcOH.

The temperature of the reductive reaction as a rule is performed at 55°C - 80°C. Particularly temperature of the reductive reaction is performed at 65°C - 70°C.

Step d) Condensation reaction to form the compound of formula (VI).

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

The suitable base is selected from DIPEA, $Cs_2CO_3$, $K_2CO_3$ and $K_3PO_4$. Particularly the base is $K_2CO_3$.

The suitable organic solvent is selected from isopropyl alcohol, methanol, trifluoroethanol and ethanol. Particularly the organic solvent is trifluoroethanol.

The temperature of the condensation reaction as a rule is performed at 60°C- 80°C. Particularly temperature of the reaction is performed at 65°C - 70°C.

Step e) Chloration reaction to form the compound of formula (VII).

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

The suitable base is selected from TEA, DIPEA and tripropylamine. Particularly the base is tripropylamine.

The suitable organic solvent is selected from DCM, MTBE, toluene and 1,2-dimethoxyethane. Particularly the organic solvent is toluene.

The temperature of the chloration reaction as a rule is performed at 50°C - 80°C. Particularly temperature of the reaction is performed at 55°C - 60°C.

Step f) Hydrogenation reaction to form the compound of formula (VIII).

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

The suitable base is selected from DIPEA, tripropylamine, $NH_3.H_2O$ and TEA. Particularly the base is $NH_3.H_2O$.

The suitable organic solvent is selected from IPAc, isopropyl alcohol, ethanol and methanol. Particularly the organic solvent is ethanol.

The temperature of the formylation reaction as a rule is performed at 20°C - 40°C, Particularly temperature of the reaction is performed at 25°C - 30°C.

Step g) N-alkylation reaction to form the compound of formula (X).

The formation of compound of formula (X) is 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 DIPEA, TEA, tripropylamine, 2,2,6,6-tetramethylpiperidine, N,N-dicyclohexylmethylamine, DBU, NMM, triethanolamine, pyridine, potassium tert-butylate, magnesium tert-butylate, $K_3PO_4$, $K_2CO_3$, $Cs_2CO_3$, CsF and CaO. Particularly the base is $K_3PO_4$ or CsF. Most particularly the base is CsF.

The suitable organic solvent is selected from IPA, trifluoroethanol, 4-Methyl-2-pentanol, 1,2-propandiol, ACN, DMF, DMAc, DMSO, sulfolane, NMP, pyridine and 1-butyl-3-methylimidazolium tetrafluoroborate. Particularly the organic solvent is NMP or 1-butyl-3-methylimidazolium tetrafluoroborate. Most particularly the organic solvent is 1-butyl-3-methylimidazolium tetrafluoroborate.

The temperature of the substitution reaction as a rule is performed at the temperature between 90 °C and 120 °C. Particularly temperature of the reaction is performed at temperature between 90 °C and 100 °C.

Step h) SFC separation of the compound of formula (X) to afford the compound of formula (I).

The compound of formula (I) is separated out in the presence of a chiral column and a suitable organic solvent. The conversion as a rule is performed under a heating condition.

The suitable chiral column is selected from Chiralcel OD and CHIRALPAK AD-3, Particularly the chiral column is Chiralcel OD, 300×50mm I.D., 10um.

The suitable solvent is selected from MeOH, EtOH, 95% EtOH and isopropyl alcohol. Particularly the solvent is methanol.

The temperature of the intermolecular reaction as a rule is performed at 30°C - 45°C. Particularly temperature of the reaction is performed at 35°C - 40°C.

## EXAMPLES

The invention is illustrated further by the following examples. They should not, however, be construed as limiting the scope of the invention.

## GENERAL EXPERIMENTAL CONDITIONS

LC-MS high resolution spectra were recorded with an Agilent LC-system consisting of Agilent 1290 high pressure gradient system, a CTC PAL auto sampler and an Agilent 6520

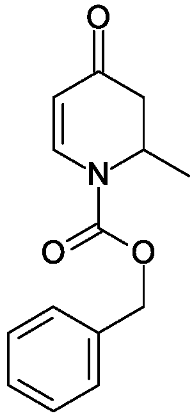
QTOF. The separation was achieved on a Zorbax Eclipse Plus C18 1,7 µm 2.1x50mm column at 55°C; A=0.02% formic acid in Water; B= acetonitrile with 0.01% formic acid at a flow rate of 0.8 mL/min. gradient: 0 minute 5%B, 0.3 minute 5%B, 4.5 minutes 99 %B, 5 minutes 99%B. The injection volume was 2 µL. Ionization was performed in Agilents Multimode source. The mass spectrometer was run in “2 GHz extended dynamic range” mode, resulting in a resolution of about 10 000 at m/z=922. Mass accuracy was ensured by internal drift correction. Mass spectra (MS): generally only ions which indicated the parent mass were reported, and unless otherwise stated the mass ion quoted was the positive mass ion (M+H)+.

NMR Spectra were obtained on a Bruker 400MHz Avance III spectrometer equipped with a 5mm TCI cryoprobe.

All reactions involving air-sensitive reagents were performed under a nitrogen atmosphere. Reagents were used as received from commercial suppliers without further purification unless otherwise noted.

## Example 1

**benzyl 2-methyl-4-oxo-2,3-dihydropyridine-1-carboxylate**



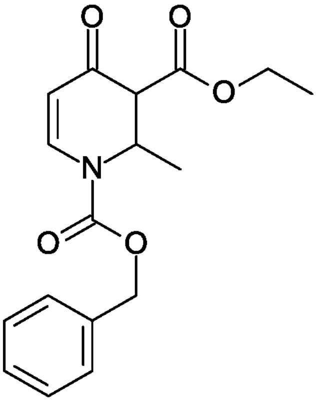
Preparation of benzyl 2-methyl-4-oxo-2,3-dihydropyridine-1-carboxylate

To a 5 L jacket reactor was charged with 4-methoxypyridine (170 g, 1.56 mol) and THF (2.55 L) at room temperature under $N_2$ atmosphere. The mixture was cooled to -5 ~ -10°C using Huber chiller. To the stirred mixture was charged with benzyl carbonochloridate (279 g, 1.64 mol) at -5 ~ -10°C in 10 ~ 15minutes, the white solid appeared once addition. The mixture was agitated using a magnetic stirrer at -5~-10°C for another 10 minutes. To the mixture was charged with methylmagnesium chloride (134 g, 1.79 mol, 3M solution in THF) dropwise at -5 ~ -10°C in 1 hour, the white solid dissolved slowly. The mixture was stirred at -5~-10°C for another 1 hour.

Then to the mixture was charged with 4N aqueous HCl (680 mL) and the mixture was stirred at room temperature for 10 minutes. To the mixture was charged with MTBE (1.02 L) and the mixture was stirred at room temperature for another 10 minutes. Two layers separated, the organic layer was washed with water (1 L) and sat. NaCl (1 L) sequentially. The organic layer was filtered through a $Na_2SO_4$ pad, and concentrated under reduced pressure to give Example 1 (345 g, purity: 94.98 %, yield: 90 %) as a colorless oil, which was directly used for the preparation of Example 2. MS m/e = 246.3 [M+H]+. $^1$H NMR (400 MHz, ) $\delta$ = 7.67 (d, $J$ = 7.9 Hz, 1H), 7.34 (d, $J$ = 7.4 Hz, 1H), 7.34 (d, $J$ = 7.4 Hz, 1H), 7.33 (t, $J$ = 7.4 Hz, 1H), 7.33 (t, $J$ = 7.4 Hz, 1H), 7.29 (t, $J$ = 7.4 Hz, 1H), 5.29 (d, $J$ = 7.9 Hz, 1H), 5.21 (s, 2H), 4.70 (qt, $J$ = 6.2, 6.8 Hz, 1H), 2.71 (dd, $J$ = 6.8, 16.6 Hz, 1H), 2.36 (dd, $J$ = 6.8, 16.6 Hz, 1H), 1.19 (d, $J$ = 6.2 Hz, 3H).

## Example 2

## O1-benzyl O3-ethyl 2-methyl-4-oxo-2,3-dihydropyridine-1,3-dicarboxylate



Preparation of O1-benzyl O3-ethyl 2-methyl-4-oxo-2,3-dihydropyridine-1,3-dicarboxylate Method A)

To a 5 L jacket reactor was charged with benzyl 2-methyl-4-oxo-2,3-dihydropyridine-1-carboxylate (350 g, 1.43 mol, Example 1) and THF (1.05 L, super dry, stabilized with BHT) at room temperature. The mixture was cooled to 0~5°C using Huber Chiller. To the mixture was charged with LiHMDS (478 g, 2.85 mol, 1M in THF) at 0~5°C. The addition was maintained for 15 minutes, and the reaction temperature was changed from 3°C to 9°C. The mixture was agitated using a magnetic stirrer at 0~5°C for 60 minutes. Then to the mixture was charged with ethyl (diethoxyphosphoryl)formate (318 g, 1.51 mol) at 0~5°C. The addition was maintained for 5minutes, and the reaction temperature was then changed from 3°C to 12°C. The mixture was stirred at 0~5°C for another 1 hour. Then to the mixture was charged with sat. $NH_4Cl$ (50 mL) at 0~5°C. After stirring at room temperature for 10 minutes, the mixture was extracted with IPAc

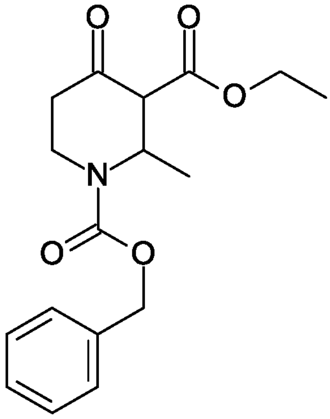
(160 mL). The organic layer was washed with water (150 mL) and sat. NaCl (1.5 L). The organic layer was filtered through a $Na_2SO_4$ pad, and concentrated under reduced pressure to give Example 2 (410 g, purity: 90 %, yield: 87 %) as a light yellow oil, which was directly used for the preparation of Example 3. MS m/e = 318.3 [M+H]+. $^1$H NMR (400 MHz, ) δ = 7.77 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 7.4 Hz, 1H), 7.34 (d, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 5.59 (d, *J* = 8.4 Hz, 1H), 5.23 (s, 2H), 4.85 (qd, *J* = 6.2, 8.1 Hz, 1H), 4.13 (dq, *J* = -11.4, 7.1 Hz, 1H), 4.13 (dq, *J* = -11.4, 7.1 Hz, 1H), 3.58 (d, *J* = 8.1 Hz, 1H), 1.42 (d, *J* = 6.2 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H)

Method B)

The title compound was prepared in analogy to Method A) of Example **2,** replacing ethyl (diethoxyphosphoryl)formate with ethyl chlorocarbonate (yield 31%, purity 56%). MS m/e = 318.3 $[M+H]^+$.

## Example 3

## O1-benzyl O3-ethyl 2-methyl-4-oxo-piperidine-1,3-dicarboxylate

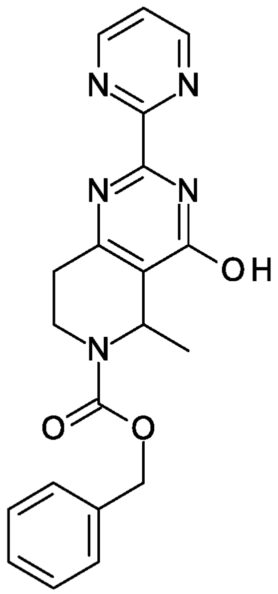


Preparation of O1-benzyl O3-ethyl 2-methyl-4-oxo-piperidine-1,3-dicarboxylate

To a 5 L jacket reactor was charged with O1-benzyl O3-ethyl 2-methyl-4-oxo-2,3-dihydropyridine-1,3-dicarboxylate (260 g, 819 mmol, Example 2), Acetic acid (2.08 L) and Znic powder (161 g, 2.46 mol) at room temperature. The mixture was agitated using a magnetic stirrer at 65~70°C for 3hours. The mixture was cooled to room temperature and filtered through a pad of celite to remove Zn. The mixture was concentrated under reduced pressure to remove acetic acid. To the mixture was charged with IPAc (150 mL) and sat. $Na_2CO_3$ (100 mL). The organic layer was washed with sat. $Na_2CO_3$ (80 mL*2), then sat. NaCl (100 mL*2), dried over $Na_2SO_4$, concentrated under reduced pressure to give the desired product as a brown oil. The organic layer was filtered through a $Na_2SO_4$ pad, and concentrated under reduced pressure to give Example 3 (229 g, purity: 86.3 %, yield: 88 %) as a light brown oil, which was directly used for the preparation of Example 4. MS m/e = 320.4 [M+H]+.-_$^1$H NMR (400 MHz, ) δ = 7.32 (d, *J* = 7.4 Hz, 1H), 7.32 (d, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 7.4 Hz, 1H), 5.11 (s, 2H), 4.77 (qd, *J* = 6.2, 8.1 Hz, 1H), 4.14 (dq, *J* = -11.4, 7.1 Hz, 1H), 4.14 (dq, *J* = -11.4, 7.1 Hz, 1H), 3.57 (ddd, *J* = 4.5, 7.5, 13.5 Hz, 1H), 3.53 (ddd, *J* = 3.5, 4.5, 13.5 Hz, 1H), 3.48 (d, *J* = 8.1 Hz, 1H), 2.58 (ddd, *J* = 3.5, 4.5, 16.0 Hz, 1H), 2.58 (ddd, *J* = 4.5, 7.5, 16.0 Hz, 1H), 1.31 (d, *J* = 6.2 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).

## Example 4

### benzyl 4-hydroxy-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylate



Preparation of benzyl 4-hydroxy-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylate

Method A)

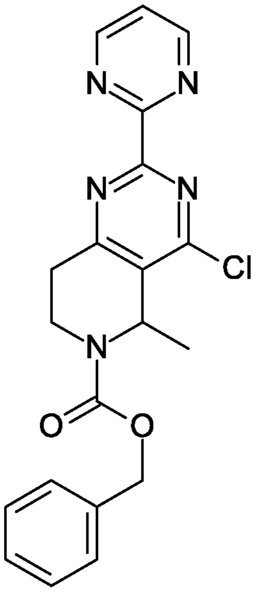
To a 5 L jacket reactor was charged with 1-benzyl 3-ethyl 2-methyl-4-oxopiperidine-1,3-dicarboxylate (340 g, 1.06 mol, Example 3), pyrimidine-2-carboximidamide hydrochloride (169 g, 1.06 mol), Trifluoroethanol (3.4 L) and $K_2CO_3$ anhydrous (367 g, 2.66 mol) at room temperature. The mixture was agitated using a magnetic stirrer at 65~70°C for 17 hours. To the mixture was charged with water (20 mL) and IPAc (30 mL) at room temperature. The aqueous layer was re-extracted with EA (30 mL). Then the organic layer was washed with sat. NaCl (50 mL). The organic layer was filtered through a $Na_2SO_4$ pad, and concentrated under reduced pressure to give Example 4 (341 g, purity: 95 %, yield: 85 %) as a light yellow solid, which was directly used for the preparation of Example 5. MS m/e = 378.4 [M+H]+. $^1$H NMR (400 MHz, ) $\delta$ = 8.95 (d, $J$ = 4.9 Hz, 2H), 7.41 (t, $J$ = 4.9 Hz, 1H), 7.31 (t, $J$ = 7.4 Hz, 1H), 7.31 (t, $J$ = 7.4 Hz, 1H), 7.31 (t, $J$ = 7.4 Hz, 1H), 7.30 (d, $J$ = 7.4 Hz, 1H), 7.30 (d, $J$ = 7.4 Hz, 1H), 5.85 (q, $J$ = 6.8 Hz, 1H), 5.13 (d, $J$ = 12.9 Hz, 1H), 5.13 (d, $J$ = 12.9 Hz, 1H), 4.11 (td, $J$ = 6.1, 13.3 Hz, 1H), 4.04 (td, $J$ = 6.1, 13.3 Hz, 1H), 3.19 (td, $J$ = 6.1, 15.0 Hz, 1H), 3.12 (td, $J$ = 6.1, 15.0 Hz, 1H), 1.68 (d, $J$ = 6.8 Hz, 3H).

Method B)

The title compound was prepared in analogy to Method A) of Example **4,** replacing trifluoroethanol with Ethanol (yield: 38%, purity: 72%). MS m/e = 378.4 $[M+H]^+$.

## Example 5

### benzyl 4-chloro-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylate

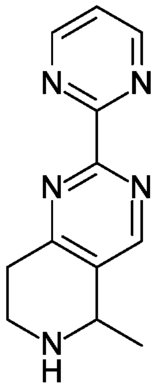


Preparation of benzyl 4-chloro-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylate

To a 100 mL flask was charged with benzyl 4-hydroxy-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylate (10.5 g, 27.8 mmol, Example 4), Toluene (105 mL), tripropylamine (9.97 g, 69.6 mmol), $NH_4Cl$ (1.49 g, 27.8 mmol) and $POCl_3$ (10.7 g, 69.6 mmol) at room temperature. The mixture was stirred at 55~60°C for 3 hours. The mixture was cooled to room temperature. To the mixture was charged with water (30 mL) to quench the reaction. EA (80 mL) was also added to the reaction mixture. After stirring at room temperature for 5 minutes, two layers separated. The aqueous layer was adjusted to pH 7~8 by adding 2N NaOH (15 mL), then extracted with EA (50 mL). The organic layer was combined, and washed with 10% NaCl (50 mL) and sat. NaCl (80 mL). The organic layer was filtered through a $Na_2SO_4$ pad, and concentrated under reduced pressure to give Example 5 (9.3 g, purity: 90 %, yield: 83 %) as a light brown solid, which was directly used for the preparation of Example 6. MS m/e = 396.8 [M+H]+.-_$^1$H NMR (400 MHz, ) δ = 9.00 (d, *J* = 4.9 Hz, 2H), 7.41 (t, *J* = 4.9 Hz, 1H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 7.4 Hz, 1H), 5.87 (q, *J* = 6.8 Hz, 1H), 5.13 (d, *J* = 12.9 Hz, 1H), 5.13 (d, *J* = 12.9 Hz, 1H), 4.17 (td, *J* = 6.1, 13.3 Hz, 1H), 4.10 (td, *J* = 6.1, 13.3 Hz, 1H), 3.28 (td, *J* = 6.1, 15.0 Hz, 1H), 3.21 (td, *J* = 6.1, 15.0 Hz, 1H), 1.72 (d, *J* = 6.8 Hz, 3H).

## Example 6

## 5-methyl-2-pyrimidin-2-yl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine



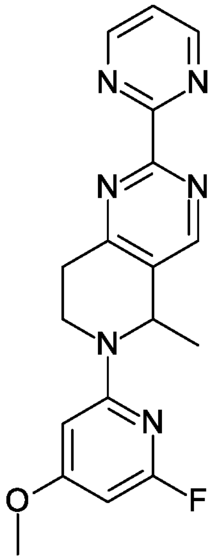
Preparation of 5-methyl-2-pyrimidin-2-yl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine

To a 25 mL flask was charged with benzyl 4-chloro-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylate (3.2g, 8.08 mmol, Example 5), EtOH (32 mL), water (8 mL), $NH_3.H_2O$ (8 mL) and Palladium 10% on carbon (wetted with ca. 55% water) (300 mg, 2.82 mmol) at room temperature. The mixture was stirred at room temperature under $H_2$ for 20 hours. The mixture was filtered through celite, washed with EtOH (20 mL*2). The filtration was concentrated under reduced pressure to give the desired product, and the solid was then re-slurried in IPAc (25 mL) to give Example 6 (1.8 g, purity: 95 %, yield: 95 %) as a yellow solid, which was directly used for the preparation of Example 7. MS m/e = 228.3 [M+H]+. $^1$H NMR (400 MHz, ) δ = 9.00 (d, *J* = 4.9 Hz, 2H), 8.86 (s, 1H), 7.41 (t, *J* = 4.9 Hz, 1H), 4.41 (dq, *J*

= 2.6, 6.7 Hz, 1H), 3.61 (dtd, *J* = 2.8, 6.2, 12.5 Hz, 1H), 3.33 (dtd, *J* = 3.7, 6.2, 12.5 Hz, 1H), 3.24 (dt, *J* = -15.3, 6.2 Hz, 1H), 3.17 (dt, *J* = -15.3, 6.2 Hz, 1H), 1.40 (d, *J* = 6.7 Hz, 3H).

## Example 7

## 6-(6-fluoro-4-methoxy-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine

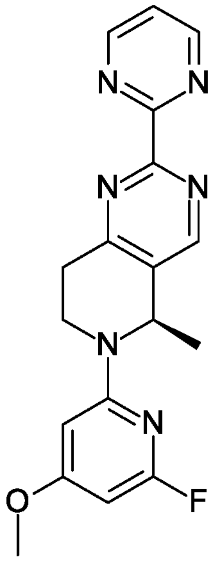


Preparation of 6-(6-fluoro-4-methoxy-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine

To A 5 L reactor was charged with 5-methyl-2-pyrimidin-2-yl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (500 g, 1.30mol, Example 6), CsF (1.36 kg, 8.95mol) and 1-butyl-3-methylimidazolium tetrafluoroborate (1.68 L, 3.3V) under $N_2$. To the mixture, 2,6-difluoro-4-methoxy-pyridine (486 g, 3.35 mol) was added. The reaction mixture was stirred at 90 °C for 48 hours. Then the mixture was cooled in an ice/water bath, and to the mixture was charged with water (18 L). The mixture was extracted with EtOAc (18 L) for twice. The combined organic layer was washed with brine (30 L) and concentrated under reduced pressure to give the crude product. The crude product was purified through silical gel column to give Example 7 (345 g, purity: 94.98 %, yield: 70 %) as a colorless oil, which was directly used for the preparation of Example 8. MS m/e = 353.1 [M+H]+. $^1$H NMR (400 MHz, ) δ = 9.00 (d, *J* = 4.9 Hz, 2H), 8.81 (s, 1H), 7.41 (t, *J* = 4.9 Hz, 1H), 6.09 (s, 1H), 5.83 (d, *J* = 10.8 Hz, 1H), 4.83 (q, *J* = 6.6 Hz, 1H), 4.16 (td, *J* = 6.2, 13.1 Hz, 1H), 4.09 (td, *J* = 6.2, 13.1 Hz, 1H), 3.90 (s, 3H), 3.19 (dt, *J* = -15.3, 6.2 Hz, 1H), 3.19 (dt, *J* = -15.3, 6.2 Hz, 1H), 1.64 (d, *J* = 6.6 Hz, 3H).

## Example 8

### (5R)-6-(6-fluoro-4-methoxy-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine



Preparation of (5R)-6-(6-fluoro-4-methoxy-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine

The 6-(6-fluoro-4-methoxy-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (450g, 0.85 mol, Example 7, light yellow solid) was diluted to a solution in methanol (2.09 Kg, 25wt%). This solution was separated by chiral SFC, and the condition was as following, Column: Chiralcel OD, 300×50mm I.D., 10um; Mobile phase: A for $CO_2$ and B for methanol; Gradient: B 40%; Flow rate: 200mL /min; Back pressure: 100bar; Column temperature: 38 °C; Wavelength: 220nm; Cycle time: ~10min. The crude product (205 g) was dissolved in methanol (610 mL) again. To the solution was charged with activated charcoal (Darco@60, 25 g) and the mixture was stirred at 50 °C for 1 hour, then filtrated through diatomite Pad. Methanol was removed under reduced pressure and further removed by azeotroping with IPAc. The solid was collected by filtration and the cake was washed with IPAc. The wet cake was dried at 40°C in vacuum with nitrogen fleet for 20 hours to give the desired product. The white solid was used directly, giving 184.8 g of (5R)-6-(6-fluoro-4-methoxy-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine. The purity was 98.8 %, the yield was 40.7 %. MS m/e = 353.1 [M+H]+. $^1$H NMR (400 MHz, ) $\delta$ = 9.00 (d, $J$ = 4.9 Hz, 2H), 8.81 (s, 1H), 7.41 (t, $J$ = 4.9 Hz, 1H), 6.09 (s, 1H), 5.83 (d, $J$ = 10.8 Hz, 1H), 4.83 (q, $J$ = 6.8 Hz, 1H), 4.21 (dt, $J$ = -12.5, 5.7 Hz, 1H), 4.05 (dt, $J$ = -12.5, 5.7 Hz, 1H), 3.90 (s, 3H), 3.23 (dt, $J$ = -15.3, 5.7 Hz, 1H), 3.17 (dt, $J$ = -15.3, 5.7 Hz, 1H), 1.64 (d, $J$ = 6.8 Hz, 3H).

## Example 9 Comparative study

The advantages from this process in this invention, compared to the one disclosed in WO2016/177655, are showed in the following aspects:

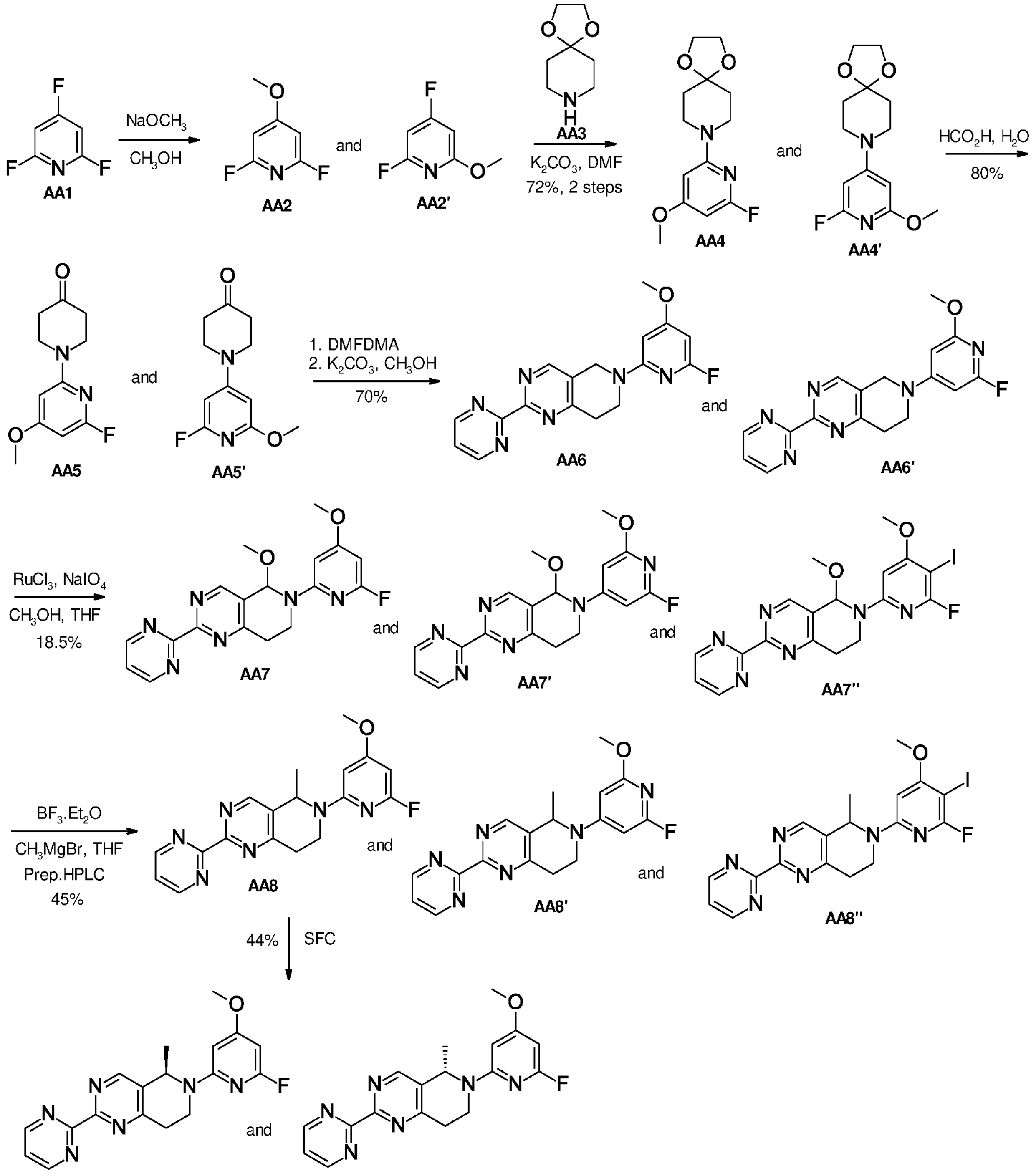
(a) The overall production yield of (5R)-6-(6-fluoro-4-methoxy-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine was increased from 1.5% to 13% with total 8 steps synthesis.

The individual step yields of Example 1 to Example 8 were shown in Table 1. The overall yield in the longest linear sequence was 13.1%.

Table 1 Yield of Each Step from Example 1 to Example 8

| *The overall yield for the new process is calculated as follows:* | *Yield achieved* |
|---|---|
| Example 1 | 90% |
| Example 2 | 87% |
| Example 3 | 88% |
| Example 4 | 85% |
| Example 5 | 83% |
| Example 6 | 95% |
| Example 7 | 70% |
| Example 8 | 41% |

According to the synthetic procedure disclosed in WO2016/177655, the overall yield was 1.5% with the details below:



(b) The regioselctivity issue was solved through the sequence of double bond’s occupation, thus the overall synthesis efficiency and yield were significantly improved.

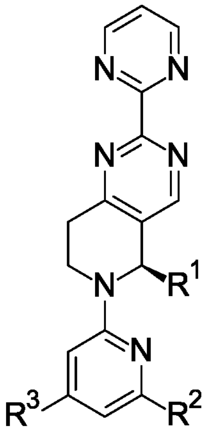
(c) The number of column purification was reduced from 3 to 1.

(d) The synthesis of Example 6 is achieved through selective hydrogenation, and the production yield is increased to 95%.

(e) A greener and more efficient synthesis procedure was innovatively developed with Ionic Liquids and CsF condition for step g in this invention. The ionic liquid,1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM][$BF_4$]), is an excellent media as a green solvent for the N-Arylation reaction and CsF was identified as an only effective base for this high yield reaction after extensive base screening. The advantages for this developed new reaction condition include removed non-green organic solvent, DMSO or DMF, with much higher yield, lower reaction temperature, less byproducts and easier work-up of purification so to significantly improve reaction scalability for the manufacture process of the API supply.

## Claims

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



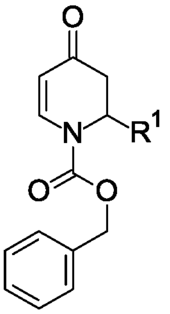
(I),

wherein $R^1$ is $C_{1\text{-}6}$alkyl; $R^2$ is $C_{1\text{-}6}$alkyl or halogen; $R^3$ is $C_{1\text{-}6}$alkyl or $C_{1\text{-}6}$alkoxy;

or a pharmaceutically acceptable salt;

comprising one or more of the following steps:

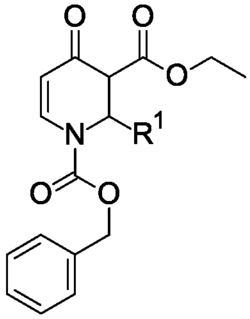
step a) the formation of the dihydropyridine (III),



(III),

wherein $R^1$ is $C_{1\text{-}6}$alkyl;

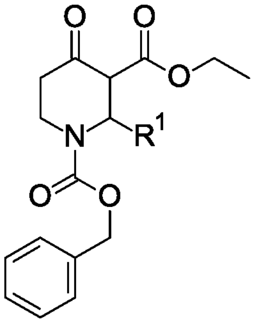
step b) the formation of the dihydropyridine (IV) via the alkylation reaction of the dihydropyridine (III) and ethyl diethoxyphosphorylformate,



(IV),

wherein $R^1$ is $C_{1-6}$alkyl;

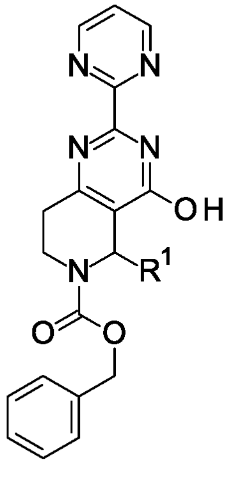
step c) the formation of the piperidine (V) via the reduction reaction of the compound of formula (IV),



(V),

wherein $R^1$ is $C_{1-6}$alkyl;

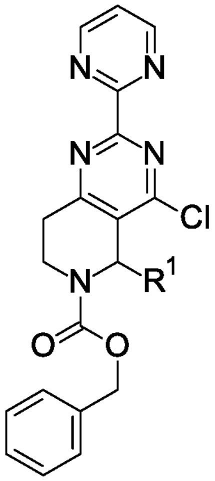
step d) the formation of the compound of formula (VI) via the cyclization reaction of the piperidine (V) and pyrimidine-2-carboxamidine,



(VI),

wherein $R^1$ is $C_{1-6}$alkyl;

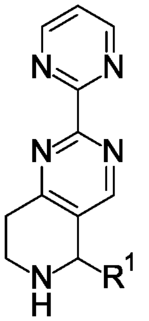
step e) the formation of the compound of formula (VII) via chloration of the compound of formula (VI),



(VII),

wherein $R^1$ is $C_{1-6}$alkyl;

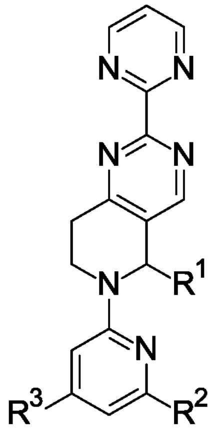
step f) the formation of the compound of formula (VIII) via selective hydrogenation of the compound of formula (VII),



(VIII),

wherein $R^1$ is $C_{1-6}$alkyl;

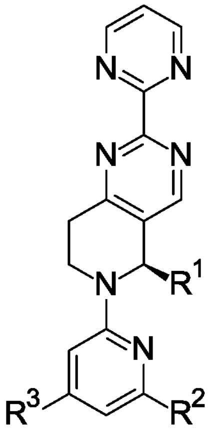
step g) the formation of the compound of formula (X) by N-alkylation of the compound of formula (VIII) with the compound of formula (IX),



(X),

wherein $R^1$ is $C_{1-6}$alkyl; $R^2$ is $C_{1-6}$alkyl or halogen; $R^3$ is $C_{1-6}$alkyl or $C_{1-6}$alkoxy;

step h) SFC separation of the compound of formula (X) to afford the compound of formula (I),



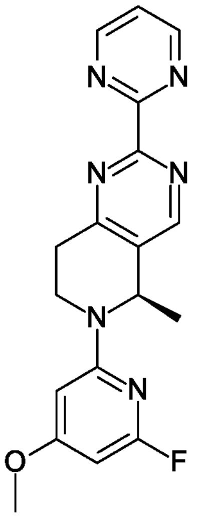
(I),

wherein $R^1$ is $C_{1-6}$alkyl; $R^2$ is $C_{1-6}$alkyl or halogen; $R^3$ is $C_{1-6}$alkyl or $C_{1-6}$alkoxy.

2. A process according to claim 1, wherein $R^1$ is $C_{1-6}$alkyl; $R^2$ is halogen; $R^3$ is $C_{1-6}$alkoxy; or a pharmaceutically acceptable salt thereof.

3. A process according to claim 2, wherein $R^1$ is methyl; $R^2$ is F; $R^3$ is methoxy; or a pharmaceutically acceptable salt thereof.

4. A process according to any one of claims 1 to 3 for the synthesis of



, or a pharmaceutically acceptable salt thereof.

5. A process according to any one of claims 1 to 4, characterized in that the formation of the dihydropyridine (III) in step a) is performed in the presence of a metal reagent in an organic solvent; wherein the metal reagent is selected from methyl, ethyl and isopropyl Grignard reagent, particularly the metal reagent is methyl Grignard reagent; and wherein the organic solvent is selected from MTBE, THF, $Et_2O$ and Me-THF, particularly the organic solvent is THF.

6. A process according to any one of claims 1 to 5, characterized in that the formation of the compound of formula (IV) in step b) is performed in the presence of a base in an organic solvent; wherein the base is selected from selected from t-BuONa, LDA, LiHMDS and NaHMDS, particularly the base is LiHMDS; and wherein the organic solvent is selected from MTBE, THF, $Et_2O$ and MeTHF, particularly the organic solvent is THF.

7. A process according to any one of claims 1 to 6, characterized in that the formation of the piperidine (V) in step c) is performed in the presence of a reductive reagent in an organic solvent; wherein the reductive reagent is selected from Fe powder, Zn powder and $NaBH_4$, particularly the reductive reagent is Zn powder; and wherein the organic solvent is selected from MeOH, EtOH, AcOH and formic acid, particularly the organic solvent is AcOH.

8. A process according to any one of claims 1 to 7, characterized in that the formation of the compound of formula (VI) in step d) is performed in the presence of a base in an organic solvent; wherein the base is selected from DIPEA, $Cs_2CO_3$, $K_2CO_3$ and $K_3PO_4$, particularly the base is $K_2CO_3$; and wherein the organic solvent is selected from isopropyl alcohol, methanol, trifluoroethanol and ethanol, particularly the organic solvent is trifluoroethanol.

9. A process according to any one of claims 1 to 8, characterized in that the formation of the compound of formula (VII) in step e) is performed in the presence of a base in an organic solvent; wherein the base is selected from TEA, DIPEA and tripropylamine, particularly the base is tripropylamine; and wherein the organic solvent is selected from DCM, MTBE, toluene and 1,2-dimethoxyethane, particularly the organic solvent is toluene.

10. A process according to any one of claims 1 to 9, characterized in that the formation of the compound of formula (VIII) in step f) is performed in the presence of a base in an organic solvent; wherein the base is selected from DIPEA, tripropylamine, $NH_3.H_2O$ and TEA, particularly the base is $NH_3.H_2O$; and wherein the organic solvent is selected from IPAc, isopropyl alcohol, ethanol and methanol, particularly the organic solvent is ethanol.

11. A process according to any one of claims 1 to 10, characterized in that the formation of the compound of formula (X) in step g) is performed in the presence of a base in an organic solvent; wherein the base is selected from DIPEA, TEA, tripropylamine, 2,2,6,6-Tetramethylpiperidine, N,N-dicyclohexylmethylamine, DBU, NMM, triethanolamine, pyridine, potassium tert-butylate, magnesium tert-butylate, $K_3PO_4$, $K_2CO_3$, $Cs_2CO_3$, CsF and CaO, particularly the base is $K_3PO_4$ or CsF; and wherein the organic solvent is selected from IPA, trifluoroethanol, 4-Methyl-2-pentanol, 1,2 –propandiol, ACN, DMF, DMAc, DMSO, sulfolane, NMP, pyridine and 1-butyl-3-methylimidazolium tetrafluoroborate, particularly the organic solvent is NMP or 1-butyl-3-methylimidazolium tetrafluoroborate.

12. A process according to claim 11, wherein the base is CsF.

13. A process according to claim 11 or 12, wherein the organic solvent is 1-butyl-3-methylimidazolium tetrafluoroborate.

14. A process according to any one of claims 1 to 13, characterized in that the compound of formula (I) in step h) is separated out by a chiral column; wherein the chiral column is selected from Chiralcel OD and CHIRALPAK AD-3, particularly the chiral column is Chiralcel OD.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/050951

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04
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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | WO 2018/001952 A1 (F HOFFMANN-LA ROCHE AG [CH]; HOFFMANN-LA ROCHE INC [US]) 4 January 2018 (2018-01-04)<br>Scheme 1;<br>page 35 - page 36; claims 1-31; examples 1-2<br>----- | 1-14 |
| Y | WO 2016/177655 A1 (F HOFFMANN-LA ROCHE AG [CH]; HOFFMANN-LA ROCHE INC [US]) 10 November 2016 (2016-11-10)<br>cited in the application<br>Schemes 1-4; examples;<br>claims 1-24; examples 1,127,142,188<br>----- | 1-14 |

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

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| Date of the actual completion of the international search<br>20 April 2020 | Date of mailing of the international search report<br>30/04/2020 |
| Name and mailing address of the ISA/<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Authorized officer<br>Rufet, Jacques |

1

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2020/050951

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
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| | | EP 3478680 A1 | 08-05-2019 |
| | | JP 2019519585 A | 11-07-2019 |
| | | US 2019241559 A1 | 08-08-2019 |
| | | WO 2018001952 A1 | 04-01-2018 |
| WO 2016177655 A1 | 10-11-2016 | CN 107624113 A | 23-01-2018 |
| | | EP 3292120 A1 | 14-03-2018 |
| | | JP 6462155 B2 | 30-01-2019 |
| | | JP 2018514575 A | 07-06-2018 |
| | | TW 201704233 A | 01-02-2017 |
| | | US 2016326167 A1 | 10-11-2016 |
| | | WO 2016177655 A1 | 10-11-2016 |