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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 May 2022 (27.05.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/106547 A1

(51) International Patent Classification:
C07D 487/04 (2006.01)

(21) International Application Number:
PCT/EP2021/082158

(22) International Filing Date:
18 November 2021 (18.11.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/115,655 19 November 2020 (19.11.2020) US

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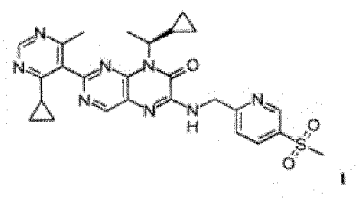
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, 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,

(54) Title: PROCESS FOR SYNTHESISING A ROR GAMMA INHIBITOR



(57) Abstract: The application describes a process for synthesising the compound of formula 1, which is a ROR gamma inhibitor, for use in medicine. The process is distinguished in that reagents and solvents are used which improve process safety and environmental compatibility, provide higher yields, improve the quality of the intermediate and end products, make it possible to carry out the process on an industrial scale and improve efficiency, for example by omitting operations such as distillation, using shorter reaction times, or eliminating chromatography for purification.

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[Continued on next page]

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:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

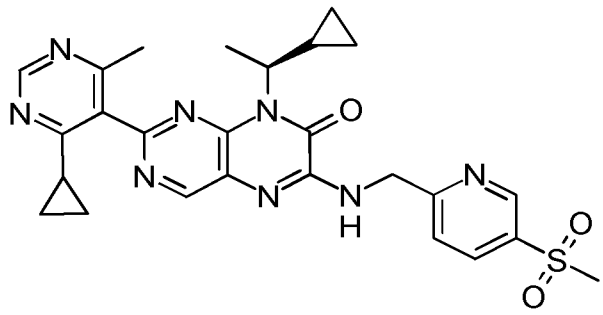
Published:

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

PROCESS FOR SYNTHESISING A ROR GAMMA INHIBITOR

BACKGROUND OF THE INVENTION

The present invention describes a process for synthesising the compound of formula **1**



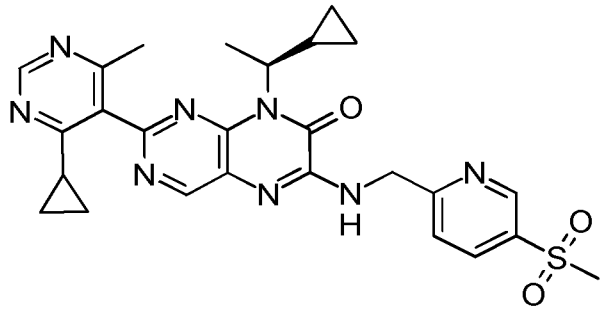
1

The process disclosed below for synthesising the compound of formula **1** is distinguished in that reagents and solvents are used which improve process safety and environmental compatibility (e.g. no chlorinated solvents), provide higher yields, improve the quality of the intermediate and end products, make it possible to carry out the process on an industrial scale, and improve efficiency, for example by omitting operations such as distillation, using shorter reaction times, or eliminating chromatography for purification.

The compound of formula **1** is known from WO 2015 160654.

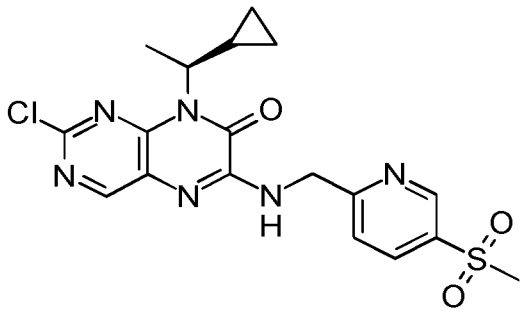
DETAILED DESCRIPTION OF THE INVENTION

What is claimed is a process for synthesising the compound of formula **1**



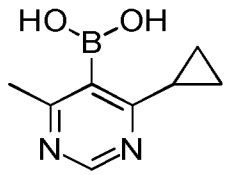
1

characterized in that a compound of formula **2**



2

is reacted with a compound of formula **3**



3

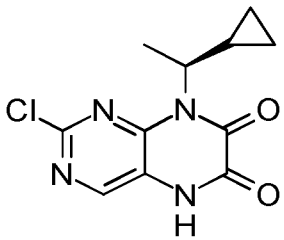
- Initially compounds **2** (1.0 eq.) and **3** (1.0-2.0 eq., preferably 1.4-1.2 eq., more preferably 1.3 eq.) are provided.
- The two compounds are reacted in the presence of a palladium catalyst, preferably crotyl(amphos)palladium(II) chloride or bis(amphos)palladium(II) chloride, more preferably bis(amphos)palladium(II) chloride (0.1 to 0.001 eq., preferably 0.003-0.001 eq., more preferably 0.002 eq.).
- An alcohol, preferably an alcohol selected from the group consisting of n-butanol, isopropanol, n-propanol, and ethanol, more preferably n-propanol, is used as a suitable solvent.
- The reactor contents are heated, preferably to 80-100°C, more preferably to 90-95°C, and then, within 1-3 hours, preferably 90-145 minutes, more preferably 120 minutes, a base is added, preferably sodium carbonate, dipotassium hydrogen phosphate, or potassium fluoride, more preferably potassium fluoride (2.0-4.0 eq., preferably 2.3-3.0 eq.,

more preferably 2.7 eq.), preferably as a 12-18% aqueous solution, more preferably as a 14-16% aqueous solution.

- The mixture is then stirred for 1-3 hours, preferably 75-130 minutes, more preferably 85-110 minutes, preferably at a constant temperature, more preferably at reflux temperature.
- Then acetylcysteine (0.05-1.0 eq., preferably 0.1-0.3 eq., more preferably 0.2 eq.), more preferably dissolved in water, is added and the mixture is stirred for 40-80 minutes at 60-80°C, preferably 65-75°C, more preferably 70°C.
- The water phase is then separated off, the org. phase is then preferably filtered, more preferably using an activated carbon filter module.
- The organic phase is then adjusted to a pH of 2-3, preferably 2.4-2.8, more preferably 2.6, with phosphoric acid and stirred for 50-205 minutes, preferably 50-120 minutes, more preferably 60 minutes, at 70-90°C, preferably 75-85°C, more preferably 80°C.
- Then water is added at 45-95°C, preferably 50-70°C, more preferably 60°C, and, if necessary, the mixture is seeded. The crystal suspension is cooled and the product **1** is isolated.
- The product can then be recrystallized from ethanol/water to obtain a higher purity.

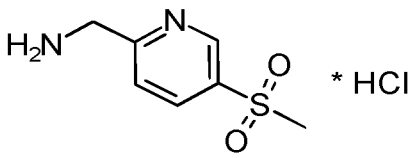
Alternatively, compound 1 can be synthesised by initially introducing all the reagents and starting materials together, heating them together while stirring, and working up as described above after the reaction has ended.

The compound of formula **2** can be obtained by reacting a compound of formula **4**



4

with a compound of formula **5**

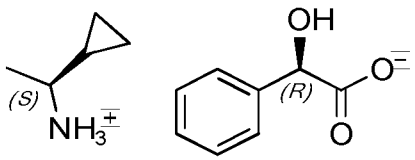


5

- Compound **4** (1.0 eq.), together with N,N-dimethylformamide (0.05-0.5 eq., preferably 0.15-0.35 eq., more preferably 0.25 eq.), is suspended in an organic solvent, preferably an aprotic organic solvent selected from the group consisting of diethyl ether, methyl tert-butyl ether, and THF, more preferably THF, and the temperature is brought to 10-40°C, preferably 15-35°C, more preferably 20-30°C.
- Oxalyl chloride (1.0-4.0 eq., preferably 1.2-2.5 eq., more preferably 1.8 eq.) is then metered in and the mixture is stirred.
- The contents of the system are cooled to -10-20°C, preferably -5-10°C, more preferably 0-10°C, and water and then sodium hydroxide solution are added; the internal temperature should be less than or equal to 15°C.
- Then the phases are separated from this apparatus (apparatus 1).

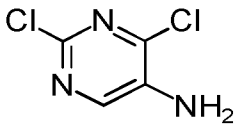
- Then, in a further apparatus, compound **5** (0.8-2.0 eq., preferably 0.8-1.5 eq., more preferably 1.0 eq.) or its free base or another salt of compound **5**, is mixed with the organic phase from apparatus 1 and heated to 10-40°C preferably 15-35°C, more preferably 20-30°C.
- Then N,N-diisopropylethylamine (1.5-4.0 eq., preferably 1.7-3.0 eq., more preferably 2.1 eq.) is metered in at 20-30°C and stirred for 100-360 minutes, preferably 100-180 minutes, more preferably 120 minutes.
- Then the contents of the apparatus are heated to reflux and stirred at reflux for 2-6 hours, preferably 2-4 hours, more preferably 3 hours.
- Then the mixture is stirred for 20-360 minutes, preferably 20-60 minutes, more preferably 30 minutes, at 25°C and the product is isolated.

The compound of formula **4** can be obtained by reacting a compound of formula **6**



6

with a compound of formula **7**

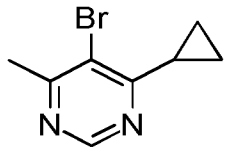


7

- (S)-1-cyclopropylethylamine-(R)-2-hydroxy-2-phenyl acetate
- (**6**, 1.0 eq.) or its free base or another salt of compound **6** and 2,4-dichloro-5-aminopyrimidine **7** (0.8-2.0 eq., preferably 1-1.5 eq., more preferably 1.05 eq.) are initially provided together with a base, preferably N,N-diisopropylethylamine, and then N-methylpyrrolidinone (NMP) is added at room temperature.
- The reactor contents are then heated to 115-145°C, preferably 120-140°C, more preferably 125-130°C, and stirred for at least 450-630 minutes, preferably 500-600 minutes, more preferably 540 minutes.
- Then the reactor contents are cooled to room temperature and an alcohol, preferably ethanol, and a reagent from the group of dimethyl oxalate or diethyl oxalate (0.8-3.0 eq., preferably 1.3 eq.) is added, and a reagent from the group of sodium ethoxide or sodium methylate (3.0-5.0 eq., preferably 3.4 eq.) is added in a temperature-oriented manner at 15-40°C, preferably 15-30°C.
- A vacuum is then applied so that the solvent can largely be distilled off at an internal temperature of about 40-75°C.
- Then the mixture is stirred while adding water, 3-7 eq. preferably 4-6, more preferably 5-5.5 eq., an aqueous acid selected from the group consisting of hydrochloric acid, hydrogen bromide, phosphoric acid, sulfuric acid, or nitric acid, preferably

hydrochloric acid, and again water, and the suspension is cooled. The suspension is centrifuged to isolate the product **4**.

The compound of formula **3** can be obtained in two ways. A compound of formula **8**



8

is reacted as described in variant A or variant B.

Variant A:

- The compound **8** (1.0 eq.) is provided in an organic solvent, preferably an organic solvent selected from the group consisting of diethyl ether, methyl tert-butyl ether, 2-methyl-THF, and THF, more preferably 2-methyl-THF, and azeotropically dewatered. The goal is to have the lowest possible water content of less than 400 ppm, preferably less than 200 ppm.
- At room temperature, 1.0 to 2.5 eq., preferably 1.4-2 eq., more preferably 1.6 eq. triisopropyl borate, is added and the resulting starting material solution (with a mass percentage of 3.5-4.5 mass%) is reacted with 1.2-1.8 eq., preferably 1.4-1.7 eq., more preferably 1.6 eq., n-butyllithium, (2.5 mol/L in hexane, toluene, or heptane, preferably hexane), initially at -60 to -40°C, preferably -50°C, and later is reacted continuously adiabatically in the tubular reactor.
- The product solution continuously obtained at the outlet of the reactor is quenched in 3-4 eq. preferably 3.0-3.5 eq., more preferably 3.3 eq., hydrochloric acid, more preferably ~22% hydrochloric acid, with cooling, more preferably at 0-10°C. At the end of the reaction, water is again added to the mixture and the mixture is stirred. The phases are then separated.
- For crystallization, the product from the lower phase is adjusted with 15-45% NaOH, more preferably 22.5% NaOH, to pH 2.5 to 6.5, preferably in two steps to

pH 3-4 and then pH 6-7, more preferably in a plurality of steps to pH 2.5, then pH 3.2, and finally pH 6.0-6.5.

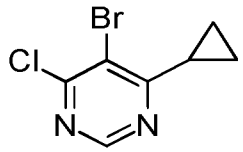
- The solid is isolated, optionally washed with water and MTBE, and dried at 10-40°C, preferably 20-35°C, more preferably 30°C.

Variant B:

- Compound **8** (1.0 eq.), a diborone, more preferably bis(neopentylglycolato)diborone (1.0-2.0 eq., preferably 1.0-1.5 eq., more preferably 1.05 eq.) and potassium acetate (2.0-5.0 eq., preferably 2.5-3.5 eq., more preferably 3.0 eq.) are suspended in an aromatic solvent selected from the group consisting of 1,2-xylene, 1,3-xylene, 1,4-xylene, toluene, preferably toluene, more preferably 7 parts by volume toluene, and degassed with nitrogen.
- Then 0.2-0.6 mol%, preferably 0.3-0.5 mol%, more preferably 0.4 mol%, of a palladium catalyst, preferably a palladium catalyst suitable for Suzuki-Miyaura couplings, more preferably $Pd(PPh_3)_2Cl_2$ is added and the mixture is heated for 1-3 hours, preferably 60-120 minutes, more preferably 90-120 minutes, to 90-110°C, preferably 100-110°C, more preferably 105°C.
- The jacket is then cooled to 80-90°C and 3-5 mol%, preferably 3.5-4.5 mol%, more preferably 4 mol%, of N-acetylcysteine, is added, then 1.5-3 parts by volume, preferably 2.0-2.5 parts by volume, more preferably 2.2 parts by volume, of water is added and the mixture is stirred.
- It is preferred to add a filter aid to the mixture, more preferably 2-20% by weight (based on compound **8**) of kieselguhr, and then to filter. The aqueous phase is separated off and the organic phase is extracted twice with water and twice with hydrochloric acid, preferably with concentrated hydrochloric acid, more preferably with 37% hydrochloric acid.
- The combined hydrochloric acid water phases are initially adjusted to pH 3-4, preferably pH 3.2-3.7, more preferably pH 3.5, with 4-5 parts by volume of water and sodium hydroxide solution at room temperature.
- Then further sodium hydroxide solution is used to adjust to pH 5-8, preferably pH 5.5-7.0, more preferably 6.0.

- The resulting solid is isolated using a centrifuge, optionally washed with water and MTBE, and dried at 10-40°C, preferably 25-35°C, more preferably 30°C.

The compound of formula **8** can be obtained by reacting a compound of formula **9**



9

- 2.0 to 6.0 eq., preferably 3.0-5.0 eq., more preferably 4.0 eq. of a base, preferably potassium carbonate, and 1.0 eq. of compound **9** are provided and suspended in an organic solvent, preferably one from the group N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, sulfolane, tetrahydrofuran, or methyltetrahydrofuran, more preferably N,N-dimethylformamide, heated to 60-120°C, preferably 75-105°C, more preferably 80-100°C.
- Then 0.9-2.0 eq., preferably 1.2-1.5 eq., more preferably 1.3 eq., dimethyl malonate is added over 45-360 minutes, preferably 60-90 minutes, more preferably 60 minutes.
- The reactor contents are heated to 80-120°C, preferably 85-115°C, more preferably 90-110°C, and stirred for 45-120 minutes, preferably 50-90 minutes, more preferably 60 minutes. Then an alcohol, preferably ethanol, methanol, or isopropanol, more preferably 1-2 parts by volume of isopropanol and then water, preferably 4-8 parts by volume of water, is added. The reactor contents are heated to reflux and stirred for 200-420 minutes, preferably 250-400 minutes, more preferably 330 minutes.
- Then a phase separation is carried out at 20-90°C, preferably at 75-85°C.
- Alternatively, compound 8 can also be isolated without phase separation.
- For crystallization, the mixture is cooled, more preferably to room temperature, a further 3-5 parts by volume of water are added, and then the mixture is cooled to -

10-20°C, preferably -5-15°C, more preferably 0-10°C, and stirred. The resulting solid is isolated using a filter dryer or a centrifuge, optionally washed with water and dried at 20-40°C, preferably 25-35°C, more preferably 30°C.

- Alternatively, the compound of formula 3.2 can be isolated as hydrobromide salt by adding HBr or as *p*-tosylate salt by adding *p*-toluenesulfonic acid.

TERMS AND DEFINITIONS

If a range has been defined, this range includes the limits. For example, for a temperature range of 10-20°C, this means that this range includes 10°C, 20°C, and all temperatures inbetween. Optimal reaction conditions and times can vary, depending on the structure of the reaction, external and internal pressure, at temperature, etc., wherein the person skilled in the art can recognize when small variations are necessary.

An organic solvent is selected by way of example from the group consisting of 2-methyl-THF, THF, diethyl ether, methyl tert-butyl ether, and dibutyl ether.

An aprotic organic solvent is selected by way of example from the group consisting of 2-methyl-THF, THF, diethyl ether, methyl tert-butyl ether, and dibutyl ether.

An alcohol is selected by way of example from the group consisting of methanol, ethanol, propanol, butanol, cyclohexanol; ethanol, iso-propanol, and n-propanol are preferred

An aromatic solvent is selected by way of example from the group consisting of benzene, toluene, 1,2-xylene, 1,3-xylene, 1,4-xylene; toluene is preferred.

Room temperature or RT is 15-25°C, more preferably 20°C.

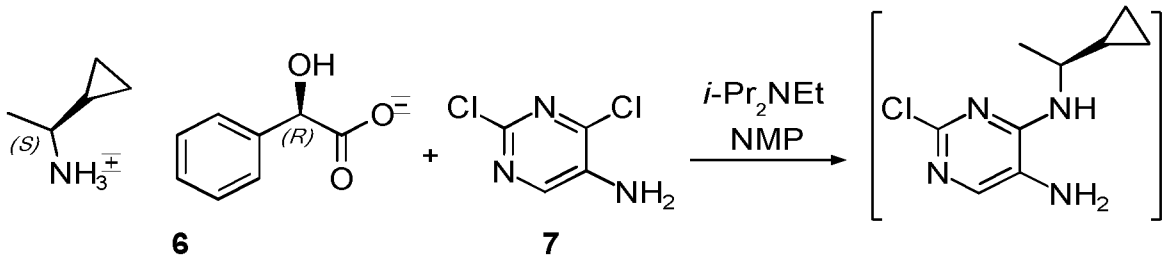
ACN	= Acetonitrile
eq.	= Equivalent, indicates the molar ratio of the input materials
GC	= Gas chromatography, used as an in-process control for the reaction
DIPEA	= N,N-diisopropylethylamine

HPLC	=	High performance liquid chromatography, used as an in-process control for the reaction
MTBE	=	Methyl tert-butyl ether
NMP	=	N-methylpyrrolidinone
MP	=	Melting point
THF	=	Tetrahydrofuran
TV	=	Loss on drying, used as in-process control for the drying process
KF	=	Karl Fischer titration, used as an in-process control for the drying process
v. or vol.	=	Parts by volume (e.g. of solvent) in L per kg of starting material.

The starting materials and reagents shown in the experimental are either available commercially, synthesised by methods known to the person skilled in the art, or synthesised as disclosed in WO 2015 160654.

EXPERIMENTAL

STAGE 1



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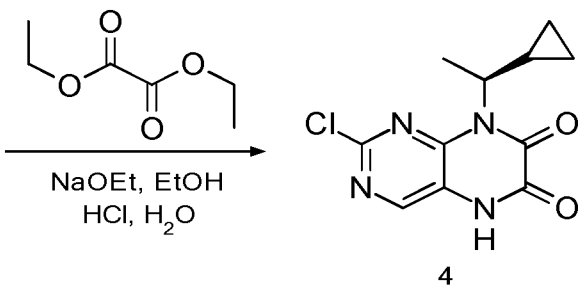


4

(S)-1-cyclopropylethylamine-(R)-2-hydroxy-2-phenyl acetate **(6,** 181 kg, 763 mol, 1.0 eq.) and 2,4-dichloro-5-aminopyrimidine **(7,** 131 kg, 801 mol, 1.05 eq.), with N,N-diisopropylethylamine (296 kg, 2288 mol, 3.0 eq.), are provided in an inertized reactor 1. NMP (503 kg, 488 L, 2.7 vol) is added at room temperature via the metering vessel. The contents of the reactor are heated to 130°C and stirred at this temperature for at least 9 hours.

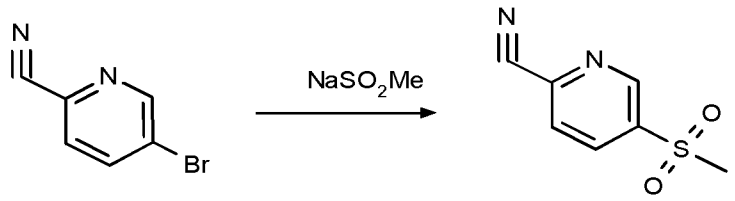
After the stirring period, the reactor contents are cooled to RT and the reaction solution is transferred with ethanol (113 kg, 143 L, 0.79 vol.) to a second inertized reactor and heated to 20°C. Then diethyl oxalate (145 kg, 992 mol, 1.3 eq.) is added to the reaction solution. Then sodium ethoxide (21% solution in ethanol, 816 kg, 2671 mol, 3.5 eq.) is added at 20°C over a period of time in temperature-oriented manner such that the temperature does not rise above 30°C (addition is exothermic at the beginning). The metering vessel is rinsed with ethanol (10 kg). The reaction mixture is stirred for 30 minutes at 20°C and then quenched with water (253 kg). The contents of the system are brought to a temperature of 60°C and 6.5 parts by volume of solvent (1176 L) are distilled off under a slight vacuum.

Following the distillation, the mixture is heated to 70°C and water (507 kg, 2.8 vol.) is added at this temperature and the mixture is stirred for 15 minutes. Thereafter, hydrochloric acid (36% aqueous solution, 414 kg, 5.35 eq.) is metered in at 70°C via the metering vessel. Then water (634 kg, 3.5 vol.) is again added and the suspension is cooled to 20°C over a period of 40 minutes. The mixture is stirred for a further 30 minutes, then the product is isolated. The crystals are centrifuged and the cake is washed first with a mixture of ethanol/water (121 kg/154 kg) and then with ethanol (200 kg). It is dried at 70°C until the termination criterion of $\leq$ 0.5% TV is reached.

152 kg (74.5%) of compound **4** is obtained (MP 263°C).

STAGE 2

Preliminary stage - Compound 11

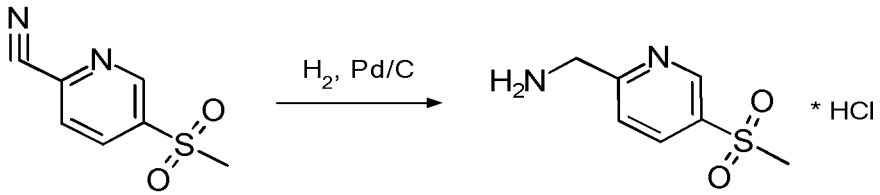


10 11

5-bromo-pyridine-2-carbonitrile **10** (200 kg, 1092 mol, 1.0 eq.), with sodium ethyl sulfinate (140 kg, 1608 mol, 1.5 eq.) and NMP (1030 kg, 1000 L, 5.0 vol.), is provided in an inertized reactor. The resulting mixture is heated to 120°C for 6 h; after the reaction is complete, the suspension is cooled to 20°C and water (1520 kg, 7.6 vol.) is added such that the internal temperature does not rise above 40°C. The crystals are centrifuged and the cake is washed with water (1000 kg). The moist product is dried at 65°C in vacuo.

175 kg (88.0%) of 5-methanesulfonyl-pyridine-2-carbonitrile **11** is isolated (MP: 138°C).

Preliminary stage - Compound 5



11 5

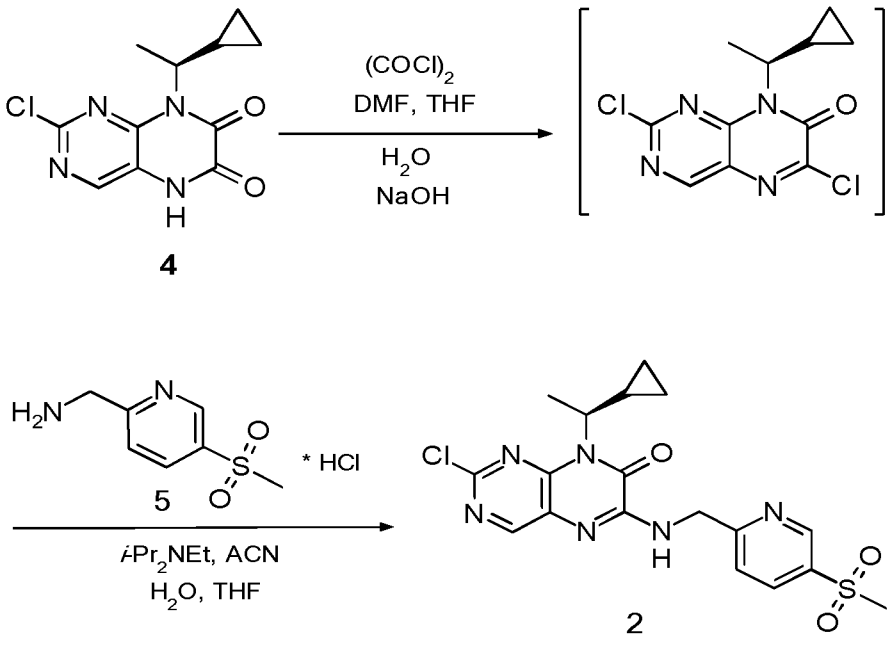
Compound **11** (110 kg, 604 mol, 1.0 eq.), with 5% Pd/C (7.8 kg), acetic acid (1155 kg, 1100 L, 10.0 vol.) and ethanol (353 kg, 445 L, 4.0 vol.), is provided in an inertized reactor 1. After a renewed inertization, the hydrogen gassing is started and regulated such that the internal temperature does not rise above 30°C and a maximum overpressure of 4 bar occurs until no more hydrogen uptake is observed.

The mixture is then heated to 25°C, the hydrogen is displaced by protective gas, and the catalyst is filtered off, the reaction mixture being transferred to a further inertized reactor 2.

The contents of the apparatus are heated to 60°C, after which hydrochloric acid (36% aqueous solution, 65 kg, 740 mol, 1.3 eq.) and ethyl acetate (393 kg, 436 L, 4.0 vol.) are added. After the addition has been completed, the resulting crystal suspension is stirred for 10 minutes and then cooled to 20°C over a period of 120 minutes. To isolate the product, the product suspension is cooled to 10°C and centrifuged. The cake is washed with a mixture of MTBE (163 kg) and ethanol (174 kg). The moist product is dried at 50°C in vacuo.

101 kg (89.9%) of compound **5** is isolated (MP: 269°C).

Synthesis of compound 2



Compound **4** (145 kg, 544 mol, 1.0 eq.), with N,N-dimethylformamide (10 kg, 136 mol, 0.25 eq.) and THF (1032 kg, 1161 L, 8.0 vol.), is provided in an inertized reactor 1 at 25°C. Oxalyl chloride (124 kg, 979 mol, 1.8 eq.) is metered into the suspension at an internal temperature of 25°C over a period of 120 minutes via a metering pump, and the mixture is stirred for a further 60 minutes at this temperature.

The contents of the system are then cooled to 5°C. For quenching, a mixture of water in THF (259 kg THF, 15 kg water, 833 mol, 1.5 eq.) is now added to the system contents

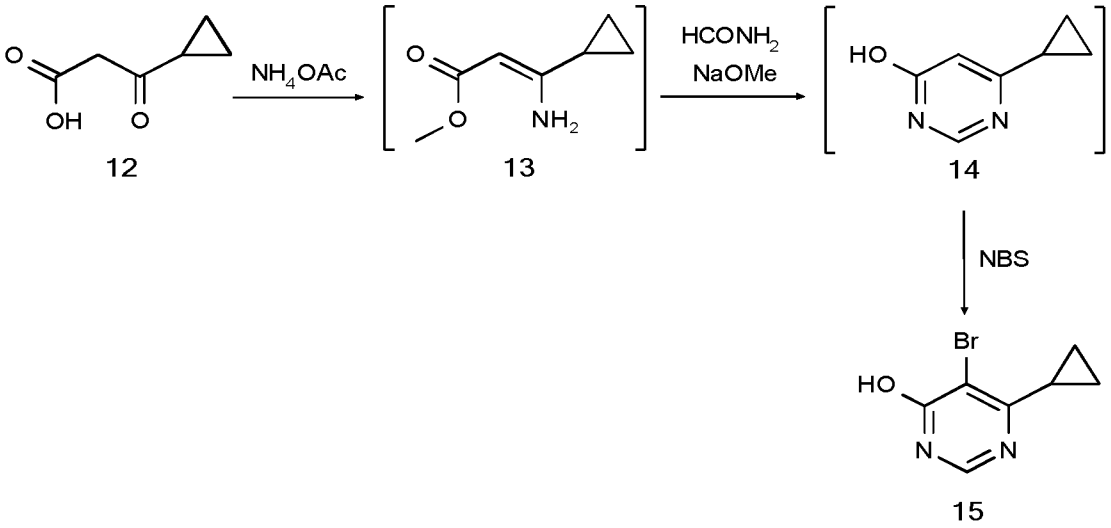
such that the internal temperature does not rise above 15°C. After the quenching, water (653 kg, 4.5 vol.) and sodium hydroxide solution (50% aqueous solution; 78 kg) are again metered into the system contents at 15°C. The lower aqueous phase is then separated off at 15°C and discarded.

Compound **5** (121 kg, 543 mol, 1.0 eq.) is placed in the inertized apparatus 2, and the organic phase from apparatus 1 is added. Apparatus 1 is rinsed with acetonitrile (639 kg, 813 L, 5.6 vol.) (rinsing solution is added to the mixture in apparatus 2). The system contents (suspension) in apparatus 2 are heated to 25°C and N,N-diisopropylethylamine (148 kg, 1142 mol, 2.1 eq.) are metered in at this temperature via the metering vessel over 90 minutes. The mixture is then stirred at 25°C for a further 2 hours.

For aging (Ostwald ripening) of the product crystals, the contents of the apparatus are heated to reflux (approx. 68°C) and stirred at reflux for 3 hours. The mixture is then cooled to 20°C, water (435 kg, 3.0 vol.) is added, and the mixture is stirred at 20°C for a further 30 minutes. The product is now isolated. The crystals are centrifuged and the cake is washed, first with a mixture of THF/water (258 kg/580 kg) and then with water (580 kg). The moist product is dried in vacuo at 70°C until the termination criterion of TV $\leq$ 1.5% is reached.

203 kg (85.9%) is isolated from compound **2** (MP: 245°C).

STAGE 2.01 - BROMINE CHLORINE STEP 1



12 13 14 15

Compound **12** (250 kg, 1759 mol, 1.0 eq.), with ammonium acetate (542 kg, 7035 mol, 4.0 eq.) and methanol (990 kg, 1250 L, 5.0 vol.), are provided at RT in an inertized reactor 1. The suspension is stirred for 5 h at room temperature and the reaction is checked (termination criterion: **12** ≤ 10 area% measured by GC; if the criterion is not met, stirring is continued for 1 h and the measurement is repeated). The mixture is heated to 50°C and concentrated to a volume of 875 L under reduced pressure. Then n-butanol (506 kg, 625 L, 2.5 vol.) is added and the mixture is heated to 70°C and again concentrated to a volume of 875 L under reduced pressure, a suspension being formed. Once the reaction is complete (termination criterion: **12** ≤ 3 area% measured by GC; if the criterion is not reached, n-butanol [506 kg, 625 L, 2.5 vol.] is added again and concentrated to 875 L), toluene (1084 kg, 1250 L, 5.0 vol.) is added and the mixture is concentrated to 1250 L at 70°C under reduced pressure (suspension becomes thicker). Toluene (2168 kg, 2500 L, 10.0 vol.) is added again, the mixture is cooled to 20°C and filtered until clear. The filter cake is washed with toluene (1084 kg, 1250 L, 5.0 vol.) (filter cake is then discarded) and the combined filtrates are heated to 70°C and concentrated to 625 L under reduced pressure. The water value is now checked (termination criterion: KF ≤ 0.2%; if the criterion is not met, toluene [1084 kg, 1250 L, 5.0 vol.] is added, concentrated to 625 L, and the measurement is repeated) and then the mixture is cooled to 20°C.

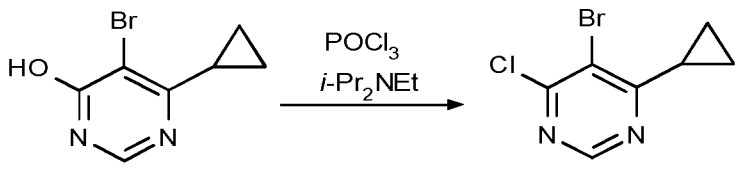
In a second reactor, formamide (190 kg, 4422 mol, 2.4 eq.), N-butanol (446 kg, 550 L, 2.2 vol.) and sodium methoxide (25% solution in methanol, 760 kg, 3518 mol, 2.0 eq.) are added to the reaction mixture at 20°C and heated to reflux. Over a period of 5 hours, at reflux low-boiling constituents are removed by distillation (during the distillation, the

boiling point of the mixture rises from approx. 86°C to approx. 107°C) until a volume of 750 L is reached. Once the reaction is complete (termination criterion: **13** ≤ 2 area% measured by HPLC; if this criterion is not met, stirring is continued for 1 h at reflux and the measurement is repeated), the mixture is cooled to 20°C and THF (2223 kg, 2500 L, 10.0 vol.) and hydrochloric acid (36% aqueous solution, 347 kg, 3518 mol, 2.0 eq.) are added, a suspension forming. Filtration until clear is performed, and the filter cake is washed with THF (445 kg, 500 L, 2.0 vol.) (the filter cake is then discarded). The combined filtrates are heated to 50°C and concentrated to 1250 L under reduced pressure, a thin suspension forming. Then cooling to 20°C is performed.

In a separate reactor, N-bromosuccinimide (344 kg, 1935 mol) is dissolved in acetonitrile (2200 kg, 2800 L, 11.2 vol.). The resulting solution is now added to the reaction mixture so that the internal temperature does not rise above 35°C. Once the reaction is complete, stirring is continued for 1 h at 20°C and the conversion is checked (termination criterion: **14** ≤ 2 area% measured by HPLC; if this criterion is not met, stirring is continued for 1 h and the measurement is repeated). The mixture is then heated to 40°C and concentrated to 1250 L under reduced pressure. After cooling to 20°C, water (1250 kg, 5.0 vol.) is added, the product crystallizing out. The product is centrifuged and the cake is washed with water (500 kg) and MTBE (370 kg). It is dried at 40°C in vacuo until the termination criterion of KF ≤ 0.5% water is reached.

233 kg (61.6%) of compound **15** is isolated.

STAGE 2.02 - BROMINE CHLORINE STEP 2



15 9

Compound **15** (190 kg, 884 mol, 1.0 eq.) is suspended in acetonitrile (747 kg, 950 L, 5.0 vol.) in an inertized reactor 1 and the mixture is stirred at 20°C for 1 hour. The water value is then checked (termination criterion: KF ≤ 0.2%; if the criterion is not met, 597 kg

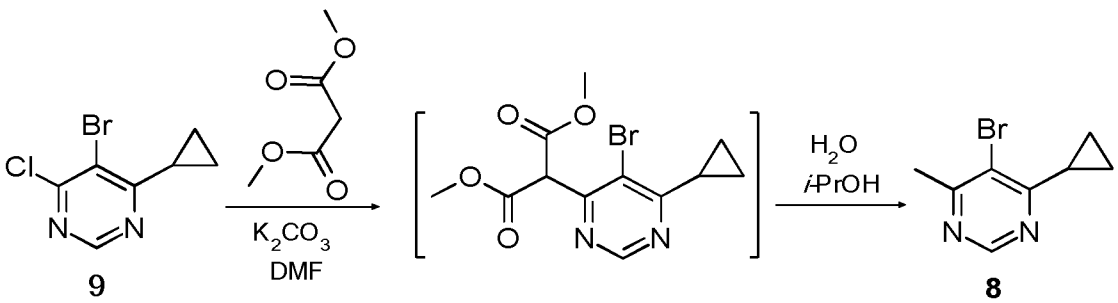
acetonitrile is added, the mixture is heated to 50°C and concentrated to a volume of 1235 L, and the measurement is repeated). When the water value is reached, DIPEA (114 kg, 884 mol, 1.0 eq.) is added and the mixture is heated to 65°C. $POCl_3$ (203 kg, 1324 mol, 1.5 eq.) is then added over a period of time such that the internal temperature does not rise above 82°C and the mixture is stirred at 70°C for a further hour. Once the reaction is complete (termination criterion: **15** ≤ 1.0%; if the criterion is not met, stirring is continued for an hour at 70°C and then the measurement is repeated), the mixture is cooled to 10°C over a period of 3 hours. Then water (1330 kg, 7.0 vol.) is added over a period of time such that the internal temperature does not rise above 25°C. The suspension is stirred for a further 1 h at 15°C, then the product is isolated. The cake is washed first with water (1330 kg), then with a mixture of water (142.5 kg) and acetonitrile (111 kg), and then is dried at 50°C in vacuo until the termination criterion of KF ≤ 0.3% water is reached.

184 kg (90.1%) of compound **9** is isolated (MP: 95°C).

For recrystallization, **9** (183 kg, 784 mol, 1.0 eq.) is suspended in isopropanol (549 kg, 698 L, 3.8 vol.) and heated to 65°C, a clear solution forming. The mixture is cooled to 60°C and seeded (approx. 1.8 kg of seed crystals). The mixture is then cooled to 0°C over a period of 3 hours and stirred for a further hour at this temperature. The product is then isolated. After centrifugation, the cake is washed with 0°C cold isopropanol (183 kg) and then dried in vacuo at 50°C until the termination criterion of TV ≤ 0.5% (and KF ≤ 0.3% water) is reached.

168 kg (91.4%) of compound **9** is isolated (MP: 95°C).

STAGE 2.1



Potassium carbonate (355 kg, 2570 mol, 4.0 eq.), compound **9** (150 kg, 642 mol, 1.0 eq.) and DMF (570 kg, 603 L, 4.0 vol.) are provided in an inertized reactor. The suspension is heated to 90°C and dimethyl malonate (110 kg, 835 mol, 1.3 eq.) is added at this temperature over a period of 60 minutes (addition is exothermic). The contents of the reactor are heated to 100°C and stirred for 60 minutes at this temperature. Following the stirring period, isopropanol (187 kg, 238 L, 1.6 vol.; addition directly into the reaction mixture, so that no boiling is observed even at 100°C) and then water (975 kg, 6.5 vol.) are added. The reactor contents are heated to reflux and allowed to react for 5.5 hours under reflux.

The reaction mixture is then cooled to 80°C and the lower aqueous phase is separated off and discarded. For crystallization, the organic phase is cooled to 20°C over a period of 60 minutes. Water (600 kg, 4.0 vol.) is added to the resulting crystal suspension and the mixture is then cooled to 5°C and stirred for a further 60 minutes. The product is then isolated. The crystals are spun and the cake is washed with water (600 kg). Drying is conducted at 30°C in vacuo until the termination criterion of KF $\leq$ 1% water is reached.

118 kg (86.2%) of compound **8** is isolated (MP: 63°C).

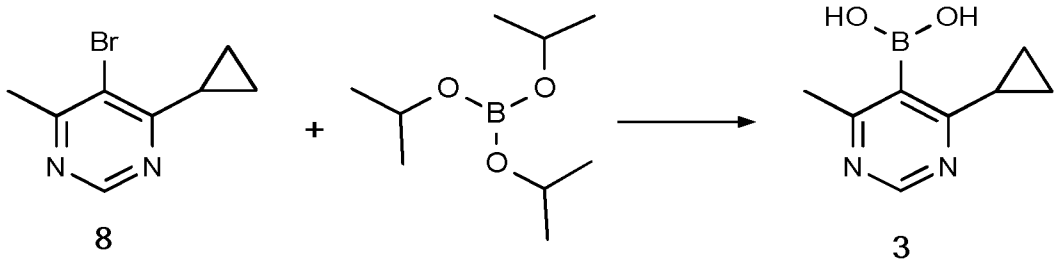
Instructions for precipitating compound **8** as hydrobromide salt: The conversion of compound **9** (12.5 g, 0.54 mol, 1.0 eq.) to compound **8** is carried out according to the method described above. Once the reaction is complete, the reaction mixture is cooled to 80°C and the phases are separated, the aqueous lower phase being discarded. Toluene (50 mL) and water (50 mL) are added to the organic phase while stirring and the mixture is then cooled to 60°C. The phases are separated and the aqueous phase is extracted a second time with toluene (50 mL) at 60°C. The combined organic extracts are heated to reflux and concentrated by distillation to a residue volume of 90 mL. The mixture is then cooled to 40°C and HBr solution in glacial acetic acid (45% solution, 9.7 mL, 0.54 mol, 1.0 eq.) is added, the product crystallizing out. The product is suctioned off through a suction filter, washed with toluene (10 mL), and dried at 50°C to constant weight.

10.75 g (68.3%) of **8** is isolated as the hydrobromide salt (MP: 202°C).

Instructions for precipitating compound **8** as tosylate salt: The conversion of compound **9** (30.35 g, 0.13 mol, 1.0 eq.) to compound **8** is carried out according to the method described above. Once the reaction is complete, the reaction mixture is cooled to 80°C and the phases are separated, the aqueous lower phase being discarded. Toluene (184 mL) and water (99 mL) are added to the organic phase while stirring and the mixture is cooled to 25°C. The phases are then separated and the organic phase is extracted 2 more times with water (49 mL each time), whereupon the aqueous extracts are discarded. The organic solution is heated to 45°C and concentrated to a residue of 120 mL. Methyl-THF and then 2.5 mL p-TsOH solution (10% solution in Me-THF, produced from p-TsOH monohydrate) is then added to the distillation residue at 45°C and seeded (approx. 300 mg seed crystals). A further 22.5 mL p-TsOH solution (10% solution in Me-THF, produced from p-TsOH monohydrate) is now added and the resulting product suspension is cooled to 5°C. The product is suctioned off through a suction filter, washed with cold methyl-THF (0-10°C, 150 mL), and dried at 50°C to constant weight.

36.5 g (73.0%) of **8** is isolated as tosylate salt (MP: 125°C).

STAGE 2.2A



Compound **8** (23 kg; 107.9 mmol; 1.0 eq.) is provided in an inertized stirring apparatus 1, dissolved in methyl THF (530 kg, 23 vol.) at room temperature, and dehydrated azeotropically, depending on water content, until a water content of ≤ 200 ppm (measured by Karl Fischer titration; if necessary, methyl-THF is added and further distillation is conducted) is reached; the amount of methyl THF distilled off is added after the termination criterion has been reached. Triisopropyl borate (32.5 kg; 172.8 mmol; 1.6 eq.)

is added at room temperature to the resulting starting material solution. The resulting starting material solution has a mass fraction of 3.5-4.5 mass% of **8**, the exact content of which is determined by means of HPLC in order to enable an exact molar flow ratio. This defined mixture serves as the first starting material solution **A** to be delivered. The second starting material solution **B** is n-butyllithium (2.5 mol/l in n-hexane), which is metered in in 1.4 to 1.6 eq. as a controlled molar flow. The mass flow ratio is ~10-13: 1 **A**:**B.**

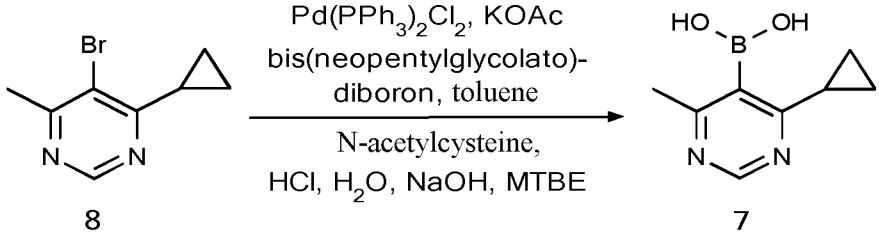
Both starting material streams are precooled to -50°C and reacted in a temperature-controlled, mixed coaxial heat exchanger reactor having a mixed structure in the inlet mixing region (micromixer or static mixer, e.g. CSE-X). For this first reaction step, the goal is a dwell time of 5 to 10 s.

For the second partial reaction, the mixture is conducted at -30°C to -10°C, with a dwell time of 40-50 s, through a further temperature-controlled or adiabatic, mixed coaxial heat exchanger reactor having a mixed structure in the inlet mixing region.

The product solution continuously occurring at the outlet of the reactor is quenched in ~22% hydrochloric acid (57 kg; 355.6 moles, 3.3 eq.) at 5°C. At the end of the quench, water (165 kg; 7.2 vol.) is again added to the mixture and the mixture is stirred. The phases are then separated at 5°C. The product in the lower phase is separated off in a further reactor and is adjusted there to pH 3.2 with 22.5% NaOH (pH 2.5 beginning of crystallization) and stirred again. The pH is then adjusted to 6.2 with 22.5% NaOH to complete the crystallization. The mixture is stirred at 5°C and the solid is isolated using a centrifuge. The cake is washed in two portions with water (66 kg, 2.0 vol.) and in two portions with MTBE (49 kg, 66 L, 2.0 vol.). The moist product is dried in vacuo at 30°C until the termination criterion of TV $\leq$ 1% water is reached.

74% of the compound **3** is isolated (decomposition: 135°C).

STAGE 2.2B



Compound **8** (200 kg, 939 mol, 1.0 eq.), bis(neopentylglycolato)diboron (224 kg, 991 mol, 1.06 eq.), and potassium acetate (276 kg, 2816 mol, 3.0 eq.) are suspended in toluene (1211 kg, 1397 L, 7.0 vol.) in an inertized reactor 1 and degassed with nitrogen for at least 15 minutes. Then bis(triphenylphosphine) palladium(II)dichloride (2.7 kg, 3.85 mol, 0.4 mol%) is added and the mixture is heated to 105°C for 90 min. Once the reaction is complete (termination criterion: **8** $\leq$ 2 area% measured using HPLC; if the criterion is not met, stirring is continued for 30 minutes and the measurement is repeated; if necessary, a suitable amount of bis(neopentylglycolato)diboron can be added in order to achieve further reaction), the mixture is cooled to 90°C, N-acetylcysteine (6.2 kg, 3.80 mol, 4 mol%) is added, and the mixture is stirred for 30 min at 90°C. Now water (440 kg, 2.2 vol.) is added, and the mixture is cooled to 75°C and stirred for 30 minutes at this temperature.

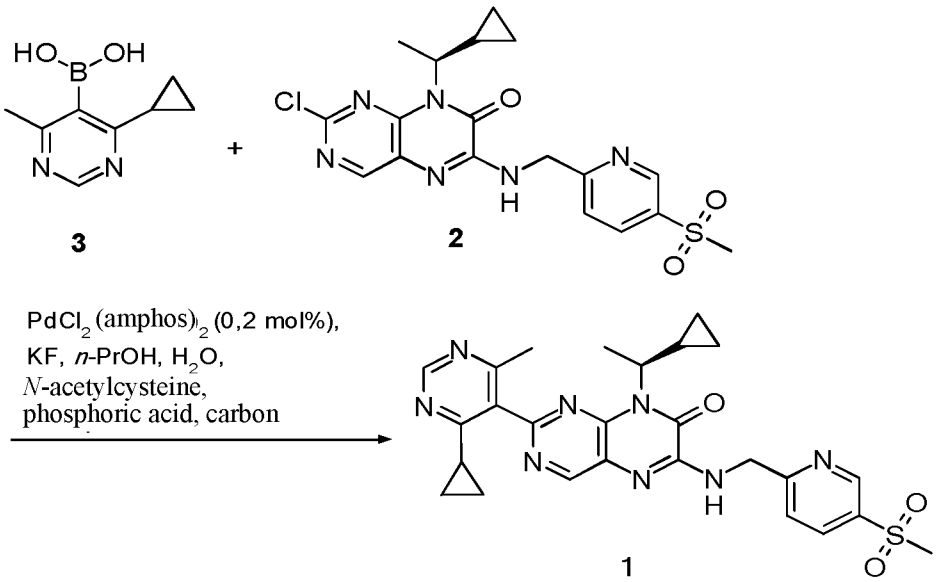
Kieselguhr (10 kg, 5% by weight) is added to the mixture, then the mixture is filtered and rinsed with toluene (173 kg, 200 L, 1.0 vol.). Finally, the lower aqueous phase is separated off (is discarded). Water (589 kg, 2.9 vol.) and hydrochloric acid (36% aqueous solution, 93 kg, 919 mol, 1.0 eq.) are added to the organic phase and the mixture is stirred vigorously at 45°C for 30 minutes. The aqueous, product-carrying lower phase is separated off in a second reactor. This procedure is repeated for a second extraction of the organic phase with the same amounts of water and hydrochloric acid, then the organic phase is discarded.

The combined hydrochloric acid water phases are stirred for 30 minutes at 20°C in vacuo in order to remove volatile organic residues and then water (882 kg, 4.4 vol.) is added. Then sodium hydroxide solution (25% aqueous solution) is added at 20°C until pH 3.0 is reached (approx. 201 kg). The mixture is stirred for 60 minutes at room temperature (suspension forms) and then further sodium hydroxide solution (25% aqueous solution) is added until the pH is adjusted to 6.5 (approx. 125 kg) and the mixture is stirred again for

60 minutes. It is then cooled to 5°C, stirred for a further 30 minutes, and finally the product is isolated. After centrifuging, the cake is washed with water (1174 kg) and with t-butyl methyl ether (870 kg). It is dried in vacuo at 30°C until the termination criterion of TV ≤ 1% water is reached.

123 kg (84.1%) of compound **3** is obtained (decomposition: 135°C).

STAGE 3.1



Compound **2** (135 kg, 310 mol, 1 eq.), bis(amphos) palladium(II)chloride (0.49 kg, 0.69 mol, 0.2 mol%), compound **3** (72 kg, 404 mol, 1.3 eq.), and n-propanol (585 kg, 729 L, 5.4 vol.) are provided in an inertized reactor and degassed. The reactor contents are heated to reflux (approx. 93°C) and then potassium fluoride (15% aqueous solution, 318 kg, 822 mol, 2.7 eq.) is added to the reactor contents at 93°C within 2 h. The mixture is then stirred at reflux for a further 110 min.

Once the reaction is complete (termination criterion: **2** ≤ 0.2 area% measured by HPLC; if the criterion is not met, stirring is continued for 60 minutes and the measurement is repeated; if necessary, a suitable amount of bis(amphos) palladium(II)chloride or compound **3** or both can be added), the reaction is quenched at 75°C by adding a solution of acetylcysteine (10.2 kg, 62.5 mol, 0.2 eq.) in water (135 kg, 1.0 vol.) and the mixture is

stirred at 70°C for a further 1 h. Then the aqueous lower phase is separated off (is discarded) and the org. phase is filtered through an activated carbon filter module. The filter is washed with a mixture of n-propanol (42 kg, 52 L, 0.4 vol.) and water (52 kg, 0.4 vol.), heated to 70°C.

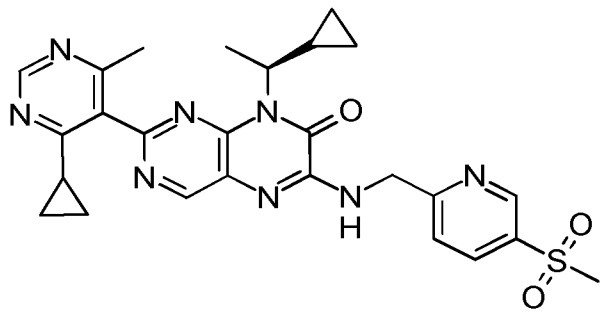
The filtrate is then adjusted with phosphoric acid (50% aqueous solution, approx. 39 kg) to pH 2.6 at 80°C and stirred at 80°C for 1 h. Then water (1035 kg, 7.7 vol.) is added such that the temperature does not fall below 60°C and seeding occurs at 60°C. The crystal suspension is cooled to 20°C within at least 90 minutes and water (405 kg, 3 vol.) is added again within at least 30 minutes. After 8 hours of stirring at 20°C, the product is isolated. After centrifugation, the cake is washed with water (581 kg). The crude compound **1** is dried at a jacket temperature of 50°C until the termination criterion of TV $\leq$ 2.0% is reached. 137 kg (83.0%) of the crude compound **1** is isolated.

For recrystallization, the crude compound **1** (110 kg, 207 mol, 1.0 eq.), with ethanol (543 kg, 688 L, 6.3 vol.) and water (172 kg, 1.6 vol.), is provided in an inertized reactor and heated to 75°C until a solution forms. Filtration until clear takes place and the filter is rinsed with a mixture of ethanol (86.7 kg, 110 L, 1.0 vol.) and water (55 kg, 0.5 vol.), heated to 75°C. The combined filtrate is cooled to 60°C and seeded (approx. 1.1 kg seed crystals, ground). The mixture is then stirred for 15 min at 60°C. Water (859 kg, 7.8 vol.) is now added at 60°C over at least 30 minutes and the suspension is cooled to 20°C within at least 90 minutes. After stirring at 20°C for at least 2 hours, the product is isolated. The cake is washed with water (293 kg). The product is dried at 50°C until the termination criterion of TV $\leq$ 0.4% is reached.

103 kg (93.6%) of compound **1** is isolated (MP: 188°C).

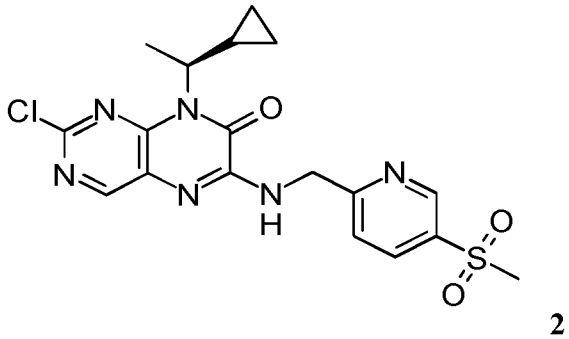
CLAIMS

1. Method for synthesising the compound of formula **1**,



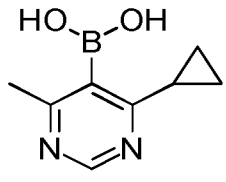
1

characterized in that 1 eq. of a compound of formula **2**



2

is reacted with a compound of formula **3**



3

in the presence of 0.1 to 0.001 eq. of a palladium catalyst.

2. Method according to claim 1, wherein the palladium catalyst is

crotyl(amphos)palladium(II) chloride or bis(amphos)palladium(II) chloride.

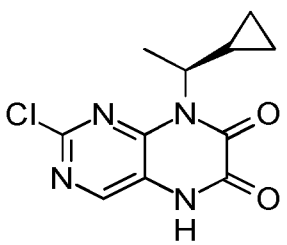
3. Method according to claim 1, wherein the palladium catalyst is bis(amphos)palladium(II) chloride.

4. Method according to any of claims 1 to 3, wherein for said method, in an alcohol selected from the group consisting of methanol, erhanol, propanol, butanol, cyclohexanol, 2.0-4.0 eq. potassium fluoride is added at 80-100°C within 1-3 hours, then the mixture is stirred for 1-3 hours and then 0.05-1.0 eq. acetylcysteine is added and the mixture is stirred at 60-80°C for a further 40-80 minutes.

5. Method according to claim 4, wherein the potassium fluoride is added as a 14-16% aqueous solution.

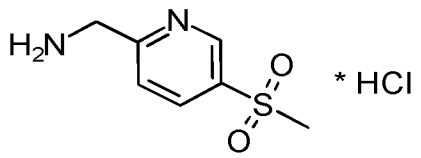
6. Method according to any of claims 1 to 3, wherein after the reaction has ended, the organic phase is filtered, adjusted to a pH of 2-3 with phosphoric acid, and stirred for 50-205 minutes at 70-90°C until water is added at 45-95°C to crystallize the product.

7. Method according to any of claims 1 to 6, wherein the compound of formula **2** is obtained in that a compound of formula **4**



4

is reacted with a compound of formula **5**

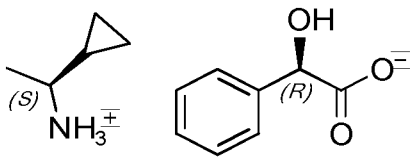


5.

8. Method according to claim 7, wherein the compound of formula **4** is first suspended with 0.05 to 0.5 eq. N,N-dimethylformamide in an aprotic organic solvent at 10-40°C and 1.0-4.0 eq. oxalyl chloride is added and then the organic phase of the mixture is added to 0.8-2.0 eq. of compound **5** and 1.5-4.0 eq. N,N-diisopropylethylamine is added.

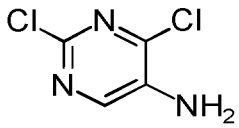
9. Method according to claim 8, wherein the product is recrystallized after the synthesis and, in order to age the product crystals, the contents of the apparatus are heated to reflux and stirred for 2-4 hours.

10. Method according to any of claims 1 to 9, wherein the compound of formula **4** is obtained by reacting a compound of formula **6**



6

with a compound of formula **7**

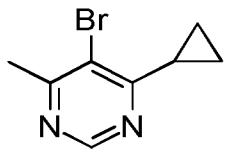


7.

11. Method according to claim 10, wherein compound **6** and 0.8-2.0 eq. of compound **7**, N,N-diisopropylethylamine, and N-methylpyrrolidinone (NMP) are heated to 115-145°C and then cooled to room temperature with ethanol, 0.8-3.0 eq. diethyl oxalate, and 3.0-5.0 eq. sodium ethylate are added.

12. Method according to claim 11, wherein after the reaction has taken place, the solvent is distilled off and then 3-7 eq. hydrochloric acid and then water are added and the resulting suspension is cooled to room temperature.

13. Method according to any of claims 1 to 12, wherein the compound of formula **3** is obtained by adding to a compound of formula **8**



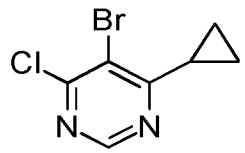
8

in an organic solvent 1.0 to 2.5 eq. triisopropyl borate and 1.2-1.8 eq. n-butyllithium (2.5 mol/L in hexane) and reacting continuously, initially at -60°C, later adiabatically in the tubular reactor.

14. Method according to any of claims 1 to 12, wherein the compound of formula **3** is obtained by suspending a compound of formula **8** in an aromatic solvent selected from the group consisting of benzene, toluene, 1,2-xylene, 1,3-xylene, 1,4-xylene, with 1.0-2.0 eq. of a diboron and 2.0-5.0 eq. potassium acetate, and then 0.5-06 mol% of a palladium catalyst is added.

15. Method according to claim 14, wherein the diboron is bis(neopentylglycolato)diboron and the palladium catalyst is $Pd(PPh_3)_2Cl_2$.

16. Method according to any of claims 1 to 15, wherein the compound of formula **8** is obtained by suspending a compound of formula **9**



9

and 2.0 to 6.0 eq. potassium carbonate in N,N-dimethylformamide and, after heating with 0.9-2.0 eq. dimethyl malonate to 80-120°C and subsequent addition of 4-8 vol. water and 1-2 vol. isopropanol and stirring at 80-120°C, the phases are separated and the product is caused to crystallize by cooling the organic phase.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/082158

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04
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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/160654 A1 (BOEHRINGER INGELHEIM INT [DE]; BAKONYI JOHANNA [US] ET AL.) 22 October 2015 (2015-10-22) cited in the application Synthesis of compound 136; page 154 Synthesis of Example 9; Synthesis of Example 11; Synthesis of Example 17; Synthesis of Example 65; Synthesis of Example 133; Page 102, NNN in combination with Method 1, pages 85-86 Method 29; page 145 - page 146 -----	1-16

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

☒ See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
16 December 2021	05/01/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sarakinos, Georgios

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2021/082158

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