

PROCESS FOR THE PREPARATION OF N-[(1S,2E)-1-CYCLOPROPYL-3-(METHANESULFONYL)PROP-2-EN-1-YL]-2-(1,1-DIFLUOROETHYL)-4-PHENOXYPYRIMIDINE-5-CARBOXAMIDE

Field of the Invention

The present invention relates to intermediates and processes useful for *N*-[(1S,2E)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide and salts thereof. The present invention further relates to *N*-[(1S,2E)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide and salts thereof when prepared by such processes and to associated pharmaceutical compositions and uses for the treatment and prevention of medical disorders and diseases, most especially by WRN inhibition.

Background of the Invention

N-[(1S,2E)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide is a WRN helicase inhibitor. There is a need to provide improved processes for preparing *N*-[(1S,2E)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide and salts thereof. In particular, there is a need to provide efficient processes that are suitable for large scale synthesis and which, for example, avoid multiple, complex and partially low yielding chemical steps and overall atom inefficient synthesis. For example, in the present invention, new steps involving flow chemistry manufacturing are better adapted for product scale-up to larger quantities of products sensitive to temperature (e.g. hot spots in batch mode) and prone to racemization and unstable intermediates.

Detailed Description of the Invention

Definitions

The term “pharmaceutically acceptable salt” refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of formula I and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Acid-addition salts include for example those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as p-toluenesulfonic acid, salicylic acid, methanesulfonic acid,

oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethyl ammonium hydroxide. The chemical modification of a pharmaceutical compound into a salt is a technique well known to pharmaceutical chemists in order to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. It is for example described in Bastin R.J., et al., Organic Process Research & Development 2000, 4, 427-435; or in Ansel, H., et al., In: Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th ed. (1995), pp. 196 and 5 1456-1457.

Abbreviations

Boc: tert-Butoxycarbonyl

KF: Karl Fischer

NMM: N-Methylmorpholine

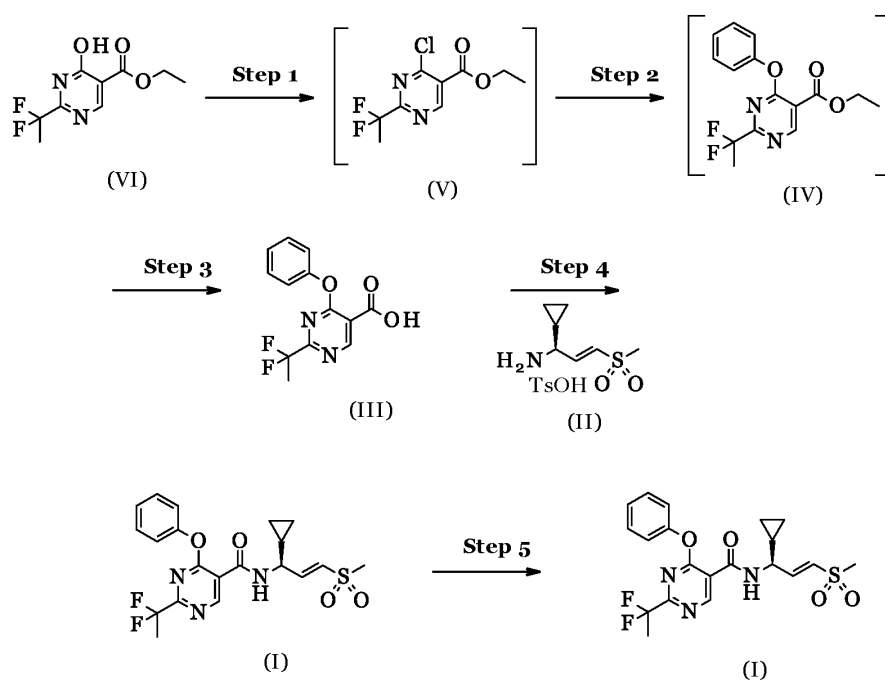
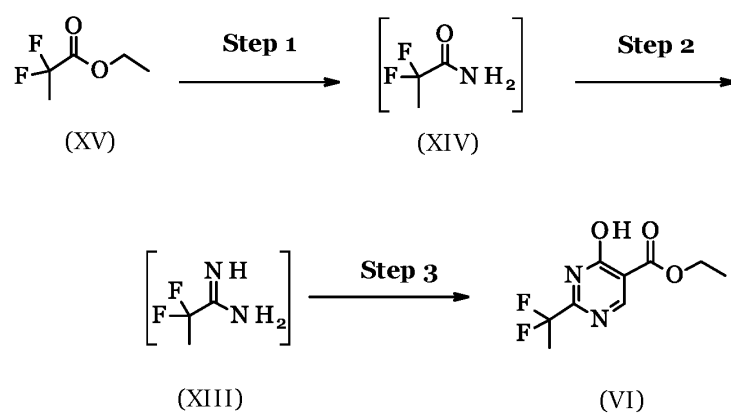
T3P: Propanephosphonic acid anhydride

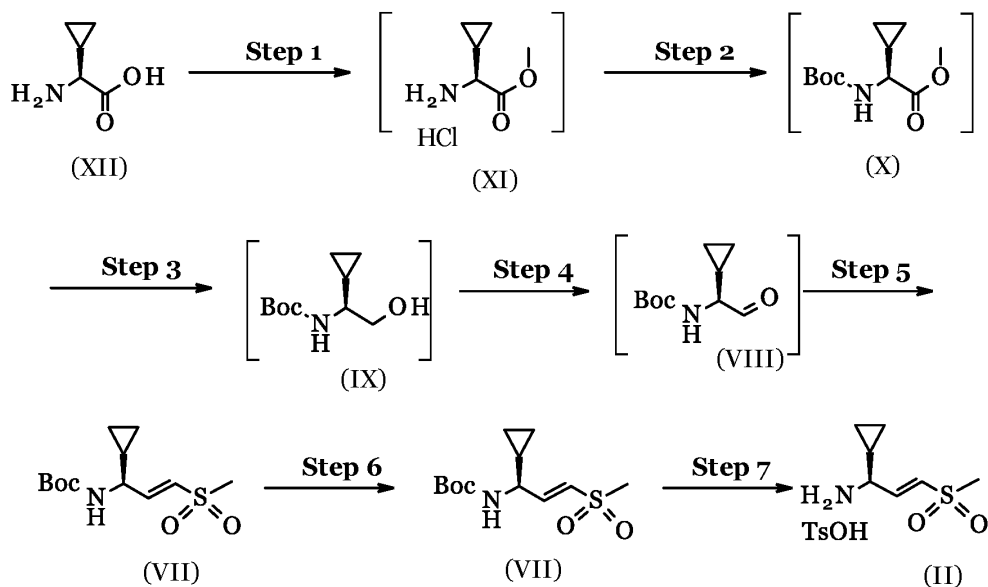
TsOH: p-Toluenesulfonic acid

Brief Description of the Drawings

Figure 1 illustrates the equipment train for the flow reactions utilized in Scheme 3.

The present invention provides the process for preparing the compound (I) as outlined in the **Scheme 1**, the compound (VI) as outlined in **Scheme 2**, and the compound (II) as outlined in the **Scheme 3**.

Scheme 1**Scheme 2**

Scheme 3

The synthesis of compound (I) comprises one or more of the following steps:

- (a) The formation of compound (I) via the reaction of compound (III) with compound (II);
- (b) The formation of compound (III), via the reaction of compound (VI) to compound (III);
- (c) The formation of compound (VI) via the reaction of compound (XV) to compound (XIV), the reaction of compound (XIV) to compound (XIII), and the reaction of compound (XIII) to compound (VI);
- (d) The formation of compound (II) via the reaction of compound (XII) to compound (VII) through the intermediates (XI), (X), (IX) and (VIII), and the reaction of compound (VII) to compound (II).

In the synthesis of compound (I), the process starting from the alcohol (IX) to give (VII) via intermediate (VIII) in step 4 above can be performed as a flow process.

A detailed description of the synthesis of compound (I) in the present invention of process steps is as following:

The formation of compound (I) is performed by reacting compound (III) with compound (II) in ethyl acetate in the presence of T3P (Propanephosphonic acid anhydride) and triethylamine.

Alternatively, the formation of compound (I) is performed by reacting compound (III) with compound (II) in ethyl acetate in the presence of pivaloyl chloride and N-Methylmorpholine.

The recrystallization of compound (I) is performed using isopropanol or ethyl acetate and n-heptane.

The recrystallization of compound (I) using ethyl acetate and n-heptane is performed by suspending compound (I) in ethyl acetate, heating and filtering the solution, then heating and adding n-heptane to the mixture. Cooling and seeding the mixture with compound (I) suspended in ethyl acetate and n-heptane allows isolation by filtration at 5°C to form white to off white crystals when recrystallized.

The formation of compound (III) is performed by

- first reacting compound (VI) with oxalyl chloride in the presence of toluene, acetonitrile and a catalytic amount of dimethylformamide till complete conversion to (V)
- then reacting the resulting organic solution with phenol in the presence of potassium carbonate to (IV) and finally forming the product (III) by saponification with sodium hydroxide followed by concentrating the solution and then treating with aqueous HCl or sulphuric acid, leading to the precipitation of the desired product

More specifically, the formation of compound (III) is performed by

- first reacting compound (VI) with oxalyl chloride in the presence of toluene, acetonitrile and a catalytic amount of dimethylformamide till complete conversion to (V), and quenching with aqueous solution of potassium dihydrogen phosphate, extracted with toluene, washed with water, and finally performing a solvent swap to acetonitrile

- then reacting the resulting organic solution with phenol in the presence of potassium carbonate to (IV)
- and finally forming the product (III) by saponification with sodium hydroxide followed by concentrating the solution and then treating with aqueous HCl, leading to the precipitation of the desired product

Alternatively, the formation of compound (III) is performed by

- first combining compound (VI) with N,N-dimethylformamide in toluene
- adding oxalyl chloride and heating the reaction mixture, followed by aqueous work-up and azeotrope distillation with toluene
- Adding a solution of phenol in toluene to the reactor, heating the reaction mixture and adding 1-Methylimidazol in toluene, followed by aqueous work-up
- Adding water and an aqueous solution of sodium hydroxide, heating and concentrating the reaction mixture
- Then cooling the reaction mixture and adding an aqueous solution of sulphuric acid to achieve a $\text{pH} \leq 1.5$, and then finally filtering to receive a wet cake that can be dried under vacuum to yield compound (III).

The formation of compound (VI) is performed by reacting compound (XV) to compound (XIV) by charging a reaction vessel with n-heptane and ammonia gas. The resulting product (XIV) is then charged with dichloromethane and trimethyloxonium tetrafluoroborate to yield product (XIII) in the presence of ammonia gas, which is then further reacted with (XIII) to compound (VI) in dichloromethane into a reaction vessel charged with acetonitrile, potassium carbonate and diethyl ethoxymethylenemalonate. After filtration, the solvent is switched from acetonitrile to ethyl acetate through coevaporation with ethyl acetate. Water is added and the aqueous phase is extracted with ethyl acetate and methyl-tert-butyl ether. After pH adjustment with aq. HCl the product is extracted with Ethyl acetate. The combined organic layer is washed with brine, concentrated and crystallized from methyl-tert-butyl ether, the resulting suspension filtered to yield product (VI).

The formation of compound (II) is performed by reacting compound (IX) to (VIII) in dichloromethane with dimethyl sulfoxide and diisopropylethylamine, and oxalyl chloride in a flow reaction using a plug-flow reactor or a cascade of continuous stirred tanks. (VIII) in dichloromethane is reacted with diethyl(methylsulfonyl)methyl)

phosphate in presence of potassium tert-butoxide to form a resulting product (VII), which is reacted to product (II) in a reaction tank charged with acetonitrile and p-toluene sulfonic acid.

The formation of compound (IX) is performed by first reacting compound (XII) to compound (X) by charging a reaction vessel with compound (XII) in methanol and thionyl chloride and adding di-tert-butyl dicarbonate in tetrahydrofuran, followed by reacting compound (X) to compound (IX) using a solution of lithium aluminium hydride or lithium borohydride in tetrahydrofuran.

In the formation of compound (VIII) the reaction steps comprising reacting compound (XII) to compound (X), and then compound (X) to compound (VIII) through compound (IX) are telescoped.

The coupling reaction step of forming compound (II) from compound (VIII) was found to be advantageous due to resulting in a high yield and improved selectivity.

Embodiment 1: A process for the preparation of compound (I), or an acceptable salt thereof, comprising the reaction of compound (III) with compound (II).

Embodiment 2: The process of Embodiment 1, wherein the process is carried out in the presence of a coupling agent.

Embodiment 3: The process of Embodiment 2, wherein the coupling agent is propanephosphonic acid anhydride.

Embodiment 4: The process of any of Embodiment 1 to 3, wherein the reaction step is carried out in the presence of a base.

Embodiment 5: The process of Embodiment 4, wherein the base is triethylamine.

Embodiment 6: The process of Embodiments 1-5, wherein compound (I) is purified by recrystallization, performed using a solvent system comprising isopropanol or ethyl acetate and n-heptane.

Embodiment 7: The process of Embodiments 1, wherein pivaloyl chloride is used as a coupling agent and N-methylmorpholine is used as a base to form a mixed anhydride intermediate prior to the coupling reaction.

The process of Embodiment 7 helps assure a very high quality production of compound (I) by allowing very high control over impurity formation.

The formation of compound (I) has a high yielding amide coupling step that delivers the product in high quality.

Embodiment 8: The process of Embodiments 1-7, wherein the process includes the preparation of compound (III).

Embodiment 9: The process of Embodiments 1-8, wherein compound (III) is prepared by reacting compound (VI) with phenol in the presence of potassium carbonate.

In embodiment 9 the solvent may be acetonitrile.

Embodiment 10: The process of Embodiments 1-9, wherein compound (III) is isolated by adjusting the pH of the reaction mixture to 1-1.5 with hydrochloric acid, followed by cooling and filtration.

The process to form compound (III) is fully telescoped and ultimately leads to deliver compound (I) with high quality.

Embodiment 11: The process of Embodiment 1-10, wherein compound (II) is prepared by

- a) Protecting a cyclopropylamine with a tert-butoxycarbonyl group
- b) Reducing the ester moiety of the protected cyclopropylamine to form an alcohol
- c) Oxidizing the alcohol to form an aldehyde
- d) Reacting the aldehyde with a vinyl methylsulfonyl compound to yield the compound of formula (II).

Embodiment 12: The process of Embodiments 1-11, wherein the synthesis of compound (II) involves the intermediate formation of compound (VIII).

Embodiment 13: The process of Embodiment 12, wherein compound (VIII) is formed by the reaction of compound (IX) with oxalyl chloride in the presence of dimethyl sulfoxide and diisopropylethylamine.

Embodiment 14: The process of Embodiment 12 or 13, wherein the compound (VIII) is obtained from compound (IX) using a flow chemistry process. Starting from a chiral amino acid, the whole process is telescoped.

Embodiment 15: The process of Embodiment 13, wherein compound (IX) is obtained by the reduction of compound (X) with lithium aluminium hydride or lithium borohydride. Preferred reducing agent is lithium borohydride.

Embodiment 16: The process of Embodiment 15, wherein compound (X) is synthesized from compound (XII) using thionyl chloride to obtain compound (XI), followed by using di-tert-butyl dicarbonate to obtain compound (X).

Embodiment 17: The process of Embodiments 1-13, wherein synthesis of compound (II) involves the reaction of compound (VIII) to compound (VII) with diethyl(methylsulfonyl)methylphosphonate in the presence of potassium carbonate.

Embodiment 18: The process of Embodiment 17, wherein the reaction to form compound (VII) includes subsequent extractions with water, hydrogen peroxide solution, sodium sulfite solution and sodium chloride solution.

The process to convert compound (VIII) to compound (VII) in a selective HWE (Horner–Wadsworth–Emmons) coupling leads exclusively to the desired trans isomer, and after further recrystallization and boc-deprotection/precipitation to compound (II) in high enantiopurity.

Embodiment 19: The process of Embodiments 1-18, wherein compound (II) is formed by the deprotection of compound (VII) using p-toluene sulfonic acid in acetonitrile.

Embodiment 20: The process of Embodiment 19, wherein compound (II) is isolated by heating the reaction mixture to 50°C-60°C, following by cooling, stirring and filtration to obtain a white solid.

Embodiment 21: The process of Embodiment 10, wherein compound (VI) is prepared from compound (XIII) and diethyl ethoxymethylenemalonate in the presence of acetonitrile and potassium carbonate.

Embodiment 22: The process of Embodiment 21, wherein the reaction to form compound (VI) includes heating the reaction mixture to 65-75°C.

Embodiment 23: The process of Embodiments 21-22, wherein compound (VI) is purified by solvent exchange with ethyl acetate and subsequent aqueous extractions.

Embodiment 24: The process of Embodiment 9 wherein compound (VI) is prepared by

- a) Reacting 2,2-difluoropropanoic acid ethyl ester (XV) with ammonia to form an amide (XIV)
- b) Converting the amide to an amidine (XIII)
- c) Reacting the amidine with diethyl ethoxymethylenealonate to yield the compound (VI).

Embodiment 25: The process of Embodiments 22-24 wherein the compound of formula (VI) is purified by a process comprising the steps of

- a) Solvent exchange from acetonitrile to ethyl acetate, and concentrating the reaction mixture under vacuum
- b) Extracting with ethyl acetate and methyl-tert-butyl ether
- c) Adjusting the pH with hydrochloric acid
- d) Separating the organic layer and washing with brine
- e) Concentrating the organic layer and recrystallizing to yield the compound (VI).

The reaction to form compound (VI) and the hydroxypyrimidine ring is fully telescoped and efficient.

Embodiment 26: The process of Embodiments 21, wherein compound (XIII) is obtained by reacting compound (XIV) with trimethyloxonium tetrafluoroborate followed by treatment with ammonia gas.

Embodiment 27: The process of Embodiment 26, wherein Compound (XIV) is prepared by reacting compound (XV) with ammonia gas in n-heptane.

The compounds used in and provided by the present invention can be used both, in their free base form and their acid addition salt form. For the purposes of this invention, a “salt” of a compound of the invention includes an acid addition salt. Acid addition salts are preferably pharmaceutically acceptable, non-toxic addition salts with suitable acids, including but not limited to inorganic acids such as hydrohalogenic acids (for example, hydrofluoric, hydrochloric, hydrobromic or hydroiodic acid) or other inorganic acids (for example, nitric, perchloric, sulfuric or phosphoric acid); or organic acids such as organic carboxylic acids (for example, propionic, butyric, glycolic, lactic, mandelic, citric, acetic, benzoic, salicylic, succinic, malic or hydroxysuccinic, tartaric, fumaric, maleic, hydroxymaleic, mucic or galactaric, gluconic, pantothenic or pamoic acid), organic sulfonic acids (for example, methanesulfonic, trifluoromethanesulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, benzenesulfonic, toluene-p-sulfonic, naphthalene-2-sulfonic or camphorsulfonic acid) or amino acids (for example, ornithinic, glutamic or aspartic acid). The acid addition salt may be a mono-, di-, tri- or multi-acid addition salt. A preferred salt is a hydrohalogenic, sulfuric, phosphoric or organic acid addition salt. A preferred salt is a hydrochloric acid addition salt.

Where a compound of the invention includes a quaternary ammonium group, typically the compound is used in its salt form. The counter ion to the quaternary ammonium group may be any pharmaceutically acceptable, non-toxic counter ion. Examples of suitable counter ions include the conjugate bases of the protic acids discussed above in relation to acid addition salts.

The compounds used in and provided by the present invention can also be used both, in their free acid form and their salt form. For the purposes of this invention, a “salt” of a compound of the present invention includes one formed between a protic acid functionality (such as a carboxylic acid group or a urea group) of a compound of the present invention and a suitable cation. Suitable cations include, but are not limited to lithium, sodium, potassium, magnesium, calcium and ammonium. The salt may be a

mono-, di-, tri- or multi-salt. Preferably the salt is a mono- or di-lithium, sodium, potassium, magnesium, calcium or ammonium salt. More preferably the salt is a mono- or di-sodium salt or a mono- or di-potassium salt.

Preferably, any salt is a pharmaceutically acceptable non-toxic salt. However, in addition to pharmaceutically acceptable salts, other salts are included in the present invention, since they have potential to serve as intermediates in the purification or preparation of other, for example, pharmaceutically acceptable salts, or are useful for identification, characterisation or purification of the free acid or base.

The compounds and/or salts used in and provided by the present invention may be anhydrous or in the form of a hydrate (e.g. a hemihydrate, monohydrate, dihydrate or trihydrate) or other solvate. Such other solvates may be formed with common organic solvents, including but not limited to, alcoholic solvents e.g. methanol, ethanol or isopropanol.

The compounds, salts and solvates used in and provided by the present invention may contain any stable isotope including, but not limited to ^{12}C , ^{13}C , ^1H , ^2H (D), ^{14}N , ^{15}N , ^{16}O , ^{17}O , ^{18}O , ^{19}F and ^{127}I , and any radioisotope including, but not limited to ^{11}C , ^{14}C , ^3H (T), ^{13}N , ^{15}O , ^{18}F , ^{123}I , ^{124}I , ^{125}I and ^{131}I .

Unless stated otherwise, the compounds, salts and solvates used in and provided by the present invention may be in any polymorphic or amorphous form.

Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Aulton's Pharmaceutics - The Design and Manufacture of Medicines", M. E. Aulton and K. M. G. Taylor, Churchill Livingstone Elsevier, 4th Ed., 2013. Pharmaceutically acceptable excipients including adjuvants, diluents or carriers that may be used in the pharmaceutical compositions of the invention, are those conventionally employed in the field of pharmaceutical formulation.

An additional aspect of the present invention provides compound (I) or the salt thereof, as obtained from the processes described above, for use in medicine, and/or for use in the treatment or prevention of a disease, disorder or condition.

An additional aspect of the present invention provides a pharmaceutical composition comprising compound (I) or the salt thereof, as from the processes described above, for use in medicine, and/or for use in the treatment or prevention of a disease, disorder or condition.

In a further aspect of the present invention, the disease is cancer. In a preferred embodiment the cancer is selected from the group consisting of colon cancer, colorectal cancer, gastric cancer, endometrium cancer, ovarian cancer, hepatobiliary tract cancer, urinary tract cancer, brain cancer, skin cancer, and MSI-H cancer.

Brief description of the drawings

Figure 1 illustrates the equipment train for the flow reactions utilized in Scheme 3.

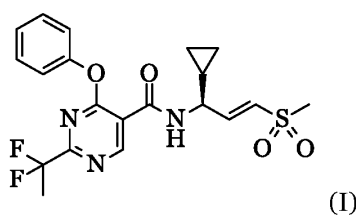
Examples

All solvents, reagents and compounds were purchased and used without further purification unless stated otherwise.

Synthesis Examples

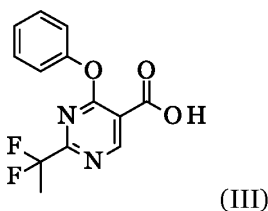
Example 1

***N*-[*(1S,2E)*-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy-pyrimidine-5-carboxamide**



N-[*(1S,2E)*-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy-pyrimidine-5-carboxamide was prepared according to the reaction sequence illustrated in Scheme 1.

Scheme 1, Steps 1-3: 2-(1,1-difluoroethyl)-4-phenoxy-pyrimidine-5-carboxylic acid

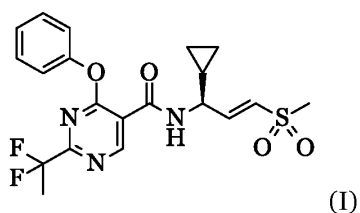


Ethyl 2-(1,1-difluoroethyl)-4-hydroxy-pyrimidine-5-carboxylate (VI) (56.4 kg, 243 mol, 1.00 eq.), toluene (167 L) and acetonitrile (59 kg) were combined in a reaction vessel 1. N,N-dimethylformamide (530 g, 7.28 mol, 0.03 eq.) in acetonitrile (1.0 kg) was added, the flask rinsed with acetonitrile (3.0 kg). The reaction mixture was heated to 30 °C and oxalyl chloride (34.5 kg, 97.4 mol) added over 45 minutes. The dosing equipment was rinsed with acetonitrile (24.0 kg). The reaction mixture was stirred at 30 °C until complete conversion, then cooled to 15 °C and a 12 % aqueous solution of potassium dihydrogen phosphate (243 kg) over 45 minutes and water (65 kg) was added over 30 minutes. Toluene (210 L) was added and the aqueous layer separated. Water (280 kg) was added to the organic layer and the aqueous layer was separated. The organic layer was concentrated below 50 °C and a solvent exchange was performed with acetonitrile to a volume of 225 L.

In a second reaction vessel 2, potassium carbonate 325 mesh (44.3 kg, 321 mol, 1.32 eq.) and acetonitrile (86 kg) were combined, and Phenol (24.2 kg, 257 mol, 1.06 eq.) in acetonitrile (43 kg) was added at 15 – 30 °C, the addition vessel rinsed with acetonitrile (31 kg).

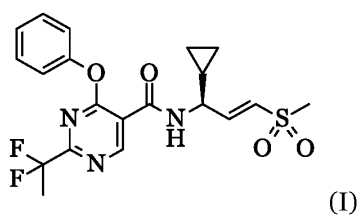
The content of the reaction vessel 1 was added onto the content of the reaction vessel 2 at 30 °C within 20 minutes, the vessel 1 rinsed with acetonitrile (110 kg). The reaction mixture was stirred at 30 °C until complete conversion, then an aqueous solution of sodium hydroxide 5.5 % (391 kg) was added within 10 minutes and water (60 kg) was added over 90 minutes. The reaction mixture was concentrated below 50 °C to a volume of 440 L. Water (120 kg) was added, the mixture cooled to 15 °C and a 8 % aqueous solution of hydrochloric acid (~430 kg) added within 120 minutes to achieve pH = 1 – 1.5. The suspension was stirred at 15 °C and then filtered, the wet cake rinsed with water (total 420 kg). The product was dried under vacuum at 55 °C to yield 2-(1,1-difluoroethyl)-4-phenoxy-pyrimidine-5-carboxylic acid (III) (61.1 kg) as a white solid.

Scheme 1, Step 4: N-[(1S,2E)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy-pyrimidine-5-carboxamide



2-(1,1-difluoroethyl)-4-phenoxy-pyrimidine-5-carboxylic acid (III) (30.2 kg) and rac-(E,1S)-1-cyclopropyl-3-methylsulfonyl-prop-2-en-1-amine, para-toluenesulfonic acid salt (II) (37.4 kg) and ethyl acetate (250 L) were combined in a reaction vessel. Triethylamine (35.1 kg) was added to the mixture at 25 °C within 10 minutes and the addition vessel rinsed with ethyl acetate (48 L). Propanephosphonic acid anhydride (T3P) 50 % in ethyl acetate (90.5 kg) was added to the mixture at 25 °C within 30 minutes and the addition vessel rinsed with ethyl acetate (48 L). The reaction mixture was stirred at 25 °C until complete conversion, then water (300 kg) was added over 10 minutes and the aqueous layer separated. A 6 % aqueous solution of sodium hydroxide (10 kg) was added to the organic layer added to achieve pH = 8.0 – 9.0 and the aqueous layer was separated. Water (250 kg) was added to the organic layer and the aqueous layer separated. A 10 % aqueous solution of citric acid (24.4 kg) was added to the organic layer and the aqueous layer was separated. Water (250 kg) was added to the organic layer and the aqueous layer separated. The organic layer was concentrated below 50 °C under vacuum and a solvent exchange was performed with isopropanol to a volume of 225 L. The suspension was heated to 65 °C till a clear solution was obtained, the solution cooled to 53 °C, seeded, the suspension cooled to 45 °C within 4 hours, then cooled down to 20 °C within 4 hours and stirred at 20 °C. The suspension was filtered, the wet cake rinsed with isopropanol (total 126 kg). The product was dried under vacuum at 50 °C to yield N-[(1S,2E)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy-pyrimidine-5-carboxamide (I) (38.2 kg) as a white solid.

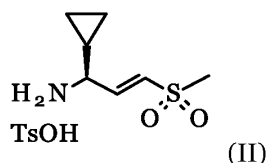
Scheme 1, Step 5: N-[(1S,2E)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy-pyrimidine-5-carboxamide, recrystallized



N-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide (37.9 kg) and ethyl acetate (266 L) were combined in a reaction vessel 1. The mixture was stirred till complete dissolution and filtered to a second reaction vessel 2, the vessel 1 was rinsed with ethyl acetate (67 L). The solution was concentrated below 50 °C under vacuum and a solvent exchange was performed with isopropanol to a volume of approx. 225 L. Isopropanol (446 kg) was added to the suspension and the mixture was heated to 65 °C till a clear solution was obtained, the solution cooled to 53 °C, seeded, the suspension cooled to 45 °C within 4 hours, then cooled down to 20 °C within 4 hours and stirred at 20 °C. The suspension was filtered, the wet cake rinsed with isopropanol (total 104 kg). The product was dried under vacuum at 50 °C to yield N-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide (I), recrystallized (32.7 kg) as a white solid.

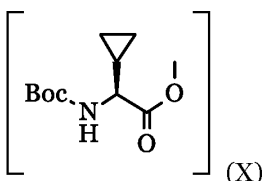
Example 2:

(*E*,1*S*)-1-cyclopropyl-3-methylsulfonyl-prop-2-en-1-amine;4-methylbenzenesulfonic acid



(*E*,1*S*)-1-cyclopropyl-3-methylsulfonyl-prop-2-en-1-amine;4-methylbenzenesulfonic acid was prepared according to the reaction sequence illustrated in Reaction Scheme 3.

Scheme 3. Steps 1 and 2: methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-2-cyclopropyl-acetate



A reaction vessel was charged with methanol (216 kg) and 2-cyclopropyl-L-glycine (XII) (109.1 kg, 948 mol, 1.00 eq.) at room temperature. The reactor was rinsed with additional methanol (216 kg). The inner temperature was adjusted to -10 to 5 °C. Then thionyl chloride (141.2 kg, 1187 mol, 1.25 eq) was charged into the reactor while keeping the inner temperature at -5 to 5 °C. After the addition the inner temperature was

raised to 15 to 25 °C and the reaction mixture was stirred for 15 hours at 15 to 25 °C. After completion of the reaction the mixture was concentrated at a temperature below 30°C under vacuum. Then the inner temperature was adjusted to 15 to 25 °C before water (236 kg), triethylamine (99.8 kg, 986 mol, 1.04 eq.), sodium hydrogencarbonate (124 kg, 1476 mol, 1.5 eq.) followed by water (470 kg) was added to the mixture, while maintaining the inner temperature at 15 to 25 °C. Then the inner temperature was lowered to -5 to 5 °C.

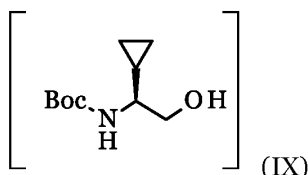
To a second tank tetrahydrofuran (106 kg) and di-tert-butyl dicarbonate (203.2 kg, 912 mol, 0.97 eq.) was added and mixed.

The di-tert-butyl dicarbonate solution in tetrahydrofuran was dosed slowly for 6 hours into the reactor while maintaining the inner temperature at -5 to 5°C. After the addition the inner temperature was adjusted 15 to 25 °C and the mixture was stirred for 15 hours. The reaction mixture was concentrated under vacuum to 975 to 1195 L at a temperature below 40°C.

Then tetrahydrofuran (300 kg) was added into the reactor and the mixture was stirred for 1 hour, while the temperature was maintained at 15 to 25 °C. The obtained mixture was filtered, the filter was rinsed with tetrahydrofuran (89 kg) and the clear solution was transferred back into the reactor. The filter and piping were rinsed additionally with tetrahydrofuran (50 kg). Afterwards the aqueous layer was separated.

The organic layer was extracted with aqueous 25% sodium chloride solution (244 kg). After phase separation the organics were concentrated under vacuum at a temperature below 40°C to a volume of 216 to 432 L. Then tetrahydrofuran (200 kg) was added into the reactor and the mixture was concentrated under vacuum at a temperature below 40°C to a volume of 216 to 432 L. The addition and concentration procedure was repeated twice before the inner temperature in the reactor was adjusted to 15 to 25 °C to yield 470 kg of methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-2-cyclopropyl-acetate (X) as a solution in tetrahydrofuran (assay 42.5 (w/w%)).

Scheme 3. Step 3: *tert*-butyl *N*-[(1*S*)-1-cyclopropyl-2-hydroxy-ethyl]carbamate

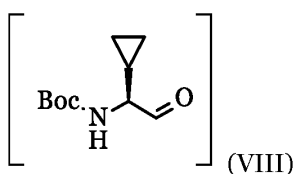


In a 3000 L glass line reactor tetrahydrofuran (894 kg) was added. The inner temperature was adjusted to -10 to 0 °C, followed by the addition of a 2.5 M solution of Lithium aluminum hydride in tetrahydrofuran (423.4 kg, 217 mol, 1.30 eq.), while

maintaining the inner temperature at -10 to 0 °C. After the addition, the line was rinsed with tetrahydrofuran (34 kg) and the reaction mixture was stirred for 2.5 hours at -10 to 0 °C. The solution of methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-2-cyclopropyl-acetate (X) in tetrahydrofuran (199.1 kg, 868 mol, 1.00 eq) was slowly added to the reactor for 11 hour while maintaining the inner temperature at -10 to 0°C. After the addition, the feeding pipe was rinsed with tetrahydrofuran (190 kg) and the mixture was stirred for 10 hours at 15 to 25 °C.

After completion of the reaction the inner temperature was adjusted to 10 to 20 °C and the mixture was quenched with Na₂SO₄•10 H₂O (503 kg, 1561 mol, 1.80 eq) at 10 to 20 °C for 21 hour. The resulting slurry was filtered through a centrifuge and the filter cake has been washed with 5 portions tetrahydrofuran (in total 529 kg). The washed filter cake was transferred into the reactor. Then tetrahydrofuran (896 kg) was added into the reactor at inner temperature of 10 to 20°C. The slurry was stirred at 15 to 25 °C for 3 hours. The slurry was filtered again via centrifuge and the filter cake was washed with 5 portions Tetrahydrofuran (in total 529 kg). The filtrates were combined in a reactor and concentrated under vacuum at a temperature below 40°C to appr. 200 kg. The concentrated product was diluted with dichloromethane (538 kg) and the mixture was concentrated under vacuum at inner temperature below 40°C. This process of dilution with dichloromethane and concentration under vacuum was repeated additional two times. The concentrated product in the reactor was diluted with dichloromethane (528 kg) to yield 721.4 kg of *tert*-butyl *N*-[(1*S*)-1-cyclopropyl-2-hydroxy-ethyl]carbamate (IX) as a solution in dichloromethane (assay 24.1 (w/w%)).

Scheme 3. Step 4: *tert*-butyl *N*-[(1*S*)-1-cyclopropyl-2-oxo-ethyl]carbamate



Preparation of starting material solution:

In a reactor with the solution of *tert*-butyl *N*-[(1*S*)-1-cyclopropyl-2-hydroxy-ethyl]carbamate (IX) (86 kg, 427 mol, 1.00 eq., in 275 kg dichloromethane) was added dichloromethane (304 kg) followed by the addition of dimethyl sulfoxide (102 kg, 1306 mol, 3.00 eq.). The mixture was stirred for 0.5 h at 20 to 30 °C inner temperature

until a clear solution was observed. The solution was filtered into a storage tank under nitrogen.

Preparation of diisopropylethylamine solution

After the reactor was emptied, dichloromethane (574 kg) was charged, followed by the charging of diisopropylethylamine (222 kg, 1718 mol, 4.00 eq.). This mixture was stirred for 0.5 hours at 20 to 30 °C inner temperature until a clear solution was observed. The amine base solution in dichloromethane was transferred under filtration into storage tank under nitrogen.

Preparation of citric acid solution

The empty reactor was charged with citric acid monohydrate (188.6 kg, 898 mol, 2.00 eq), followed by the addition of water (738 kg). The mixture was stirred for 0.5 h at 20 to 30 °C inner temperature until a clear solution was observed. The aqueous citric acid solution was filtered into a storage tank under nitrogen.

Preparation of oxalyl chloride solution

A reactor was charged with dichloromethane (620 kg), followed by the addition of oxalyl chloride (84 kg, 662 mol, 1.55 eq). The mixture was stirred for 0.5 hours at 20 to 30 °C inner temperature until a clear solution was observed. The oxalyl chloride solution was filtered into a storage tank under nitrogen.

Flow reaction

The equipment train was installed according Figure 1 using flow reactors in series.

Abbreviations: FLR: Flow reactor; TCU: Temperature control unit;

Adjust Temperature control unit (TCU1) to -30 ± 20 °C.

Adjust Temperature control unit (TCU2) to -5 ± 5 °C.

Adjust temperature of FLR1, FLR2 to -10 ± 10 °C.

Adjust temperature of FLR3, FLR4, FLR5 to -5 ± 5 °C.

Set ranges and conditions for the flow reactions as follow:

Pump 1 (starting material (IX) solution): 356 mL/min (1.0 eq.)

Pump 2 (oxalylchloride solution): 304 mL/min (1.2 to 1.4 eq.)

Pump 3 (diisopropylamine solution): 387 mL/min (3.0 to 4.0 eq.)

Pump 4 (citric acid solution): 263 mL/min

Start Pump 1, Pump 2, Pump 3, Pump 4 and Pump 5;

Continuously transfer the starting material (IX) solution into FLR1 by Pump 1.

Continuously transfer the oxalylchloride solution solution into FLR1 by Pump 2.

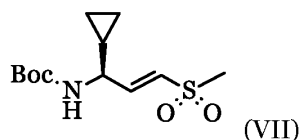
Continuously transfer the diisopropylamine solution into FLR3 by Pump 3.

Continuously transfer the citric acid solution into FLR5 by Pump 4.
Continuously transfer the reaction mixture from FLR1 into FLR2.
Continuously transfer the reaction mixture from FLR2 into FLR3.
Continuously transfer the reaction mixture from FLR3 into FLR4
Continuously transfer the reaction mixture from FLR5 into the collection vessel by Pump 5.

Work up (Batch operation)

The obtained product solution in dichloromethane was transferred to a reactor. The pH of the aqueous layer was adjusted with 20% aqueous citric acid solution at inner temperature -5 to 5°C to pH 3.0 to 4.0, followed by phase separation and removal of the aqueous layer. Water (443 kg) was charged to the reactor and the pH adjusted with a 7% aqueous sodium hydrogen carbonate solution (70 kg) at 0 to 10 °C. After stirring, phases were separated and the aqueous layer was removed. Water (615 kg) was charged to the reactor, followed by the addition of a 25% aqueous sodium chloride solution (258 kg) at 0 to 10°C. After stirring, the phases were separated and the aqueous layer was removed. The product solution was concentrated under vacuum at inner temperature below 20°C. The reactor and piping was rinsed with dichloromethane (87 kg) and 520 kg of *tert*-butyl *N*-[(1*S*)-1-cyclopropyl-2-oxo-ethyl]carbamate (VIII) as a solution in dichloromethane was obtained (assay 13.4%)

Scheme 3. Steps 5 & 6: *tert*-butyl *N*-[(*E*,1*S*)-1-cyclopropyl-3-methylsulfonyl-allyl]carbamate



To a stainless steel tank charged with dichloromethane (110 kg), Diethyl-(methylsulfonyl)methyl phosphonate (54.9 kg, 238 mol, 1.00 eq.) was added at 20 to 30°C inner temperature under stirring, followed by rinsing the tank and piping with dichloromethane (72 kg). The mixture was stirred at 20 to 30°C (inner temperature) for 1 hour. The solution was filtered into a reactor and the filter and piping was rinsed with dichloromethane (42 kg). Potassium carbonate (70.7 kg, 512 mol, 2.15 eq) was added to the solution at 20 to 30 °C inner temperature, followed by rinsing with dichloromethane (44 kg). To this mixture the solution of *tert*-butyl *N*-[(1*S*)-1-cyclopropyl-2-oxo-ethyl]carbamate (VIII) in dichloromethane (70.2 kg, 352 mol, 1.48 eq.) was added at 20 to 30°C. The reaction mixture was stirred for 7.5 hours, while maintaining the inner temperature at 20 to 30°C.

The inner temperature was adjusted to 10 to 20 °C and the organic solution was extracted with water (274 kg), followed by extraction with 3% aqueous hydrogen peroxide solution (276 kg) at 10 to 20 °C. Afterwards the organic layer was extracted with aqueous sodium sulfite solution (43.9 kg sodium sulfite in 248 kg water), followed by extraction with 15% aqueous sodium chloride solution (188 kg).

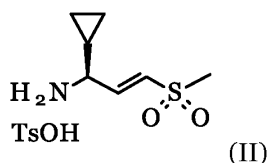
The organic layers of two batches (2 x 54.9 kg = 109.8 kg, 476 mol) were combined for further work-up and isolation in a reactor. The obtained solution of product in dichloromethane was concentrated to dryness and diluted with iso-propanol (308 kg). The mixture was concentrated and diluted with iso-propanol (308 kg) two times in repetition.

To this mixture iso-propanol (44 kg) was added. The inner temperature was increased to 45 to 55°C and the mixture was stirred for 1 hour at this temperature. Then the temperature of the solution was adjusted to 25 to 35°C and seed crystals (1 kg) were added. The mixture was stirred for 1 hour at 25 to 35°C, before n-heptane (300 kg) was dosed into the reactor over 5 hours. The temperature was lowered to -5 to 5°C over 6 hours and the slurry was stirred for 6 hours at -5 to 5°C. The slurry was filtered and washed with a mixture of iso-propanol and n-heptane (1:8, 165 kg).

The wet filter cake was charged back into the reactor filled with tetrahydrofuran (62 kg). The reactor and piping was rinsed with tetrahydrofuran (44 kg). The mixture was stirred at 15 to 25°C for 1 hour and n-heptane (52 kg) was charged over 1 hour. Seed crystals (1 kg) were charged to the reactor, followed by dosing of n-heptane (52 kg) over 5 hours. The obtained slurry was filtered and washed with a mixture of tetrahydrofuran and n-heptane (1:4, 161 kg).

The wet solid was dried under vacuum at a temperature below 45°C for not less than 24 hours to yield 76.75 kg of *tert*-butyl *N*-[(*E*,1*S*)-1-cyclopropyl-3-methylsulfonyl-allyl]carbamate (VII).

Scheme 3. Step 7: (*E*,1*S*)-1-cyclopropyl-3-methylsulfonyl-prop-2-en-1-amine;4-methylbenzenesulfonic acid



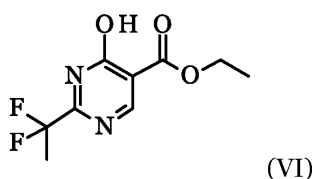
To a stainless steel tank charged with acetonitrile (160 kg), *tert*-butyl *N*-[(*E*,1*S*)-1-cyclopropyl-3-methylsulfonyl-allyl]carbamate (VII) (66.9 kg, 243 mol, 1.00eq.) was

added at 20 to 30°C inner temperature under stirring, followed by rinsing the tank and piping with acetonitrile (27 kg). The mixture was stirred at 20 to 30°C for 2 hours. The solution was filtered into a reactor, the filter and piping was rinsed with acetonitrile (28 kg) and the inner temperature was adjusted to 20 to 30°C. P-toluene sulfonic acid (pTSA x H₂O, 56.4 kg, 297 mol, 1.2 eq) was added to the solution at 20 – 30 °C inner temperature over a period of 3 hours, followed by addition of seed crystals (2.67 kg). The charging pipe was rinsed with acetonitrile (55.5 kg) into the reactor. The reaction mixture was heated to 50-60°C (inner temperature) and stirred for 16 hours, while maintaining the temperature at 50 to 60 °C. After the reaction, the mixture was cooled to 15 to 25 °C (inner temperature) and stirred for 3.5 hours at this temperature. The obtained slurry was filtered and washed with acetonitrile (260kg).

The wet solid was dried under vacuum at a product temperature of 40 to 45°C for 20 hours to yield 68.1 kg (*E,1S*)-1-cyclopropyl-3-methylsulfonyl-prop-2-en-1-amine;4-methylbenzenesulfonic acid (II) as a white solid.

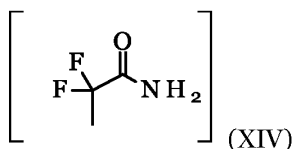
Example 3:

Ethyl 2-(1,1-difluoroethyl)-4-hydroxy-pyrimidine-5-carboxylate



Ethyl 2-(1,1-difluoroethyl)-4-hydroxy-pyrimidine-5-carboxylate was prepared according to the reaction sequence illustrated in Reaction Scheme 2.

Scheme 2, Step 1: 2,2-difluoropropanamide

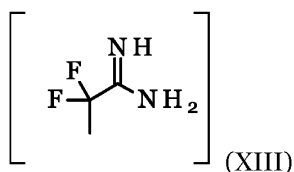


A reaction vessel was charged with n-heptane (280 kg) and 2,2-difluoropropionic acid ethyl ester (XV) (77.2 kg, 559 mol, 1.00 eq.) at room temperature. The pipe was rinsed with n-heptane (16 kg) into the reactor. The inner temperature was adjusted to -5 to 5 °C. Ammonia gas (17.0 kg, 998 mol, 1.75 eq.) was charged to the reactor over 14 hours while keeping the inner temperature at -5 to 5°C. After the addition the reaction mixture was stirred for 16 hours at -5 to 5 °C, while the product began to precipitate from the reaction mixture. The temperature was adjusted to 15 to 25°C (inner temperature)

and the mixture was stirred for 1 hour at this temperature. After completion of the reaction, the mixture was concentrated at a temperature below 28°C under vacuum to 3 to 4 volumes.

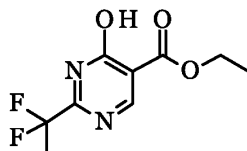
Then the inner temperature was adjusted to -15 to -5 °C and the mixture was cooled over 5 hours. The slurry was stirred for additional 8 hours at this temperature, before being filtered over a stainless steel centrifuge. The filtered product cake was washed with two portions of n-heptane (total amount 37 kg), before the product was transferred into single cone dryer. The product was dried at 30 to 40 °C (jacket temperature) for a total of 13 hours under nitrogen purging. After completion of drying 57.4 kg 2,2-difluoropropanamide (XIV) were obtained.

Scheme 2, Step 2: 2,2-Difluoropropanamidine



A reactor was charged with dichloromethane (188 kg) and 2,2-difluoropropionic amide (XIV) (27.0 kg, 248 mol, 1.00 eq.) at room temperature. The pipe was rinsed with dichloromethane (10 kg) into the reactor. The inner temperature was set to 15 to 25 °C. Trimethyloxonium tetrafluoroborate (36.8 kg, 248 mol, 1.00 eq.) was charged to the reactor and the pipe was rinsed with dichloromethane (46 kg) into the reactor. After the addition the reaction mixture was stirred for 18 hours at 15 to 25 °C. The temperature was adjusted to -45 to -35°C (inner temperature) and ammonia gas (11.8 kg, 693 mol, 2.8 eq.) was charged into the reactor over 8h at internal temperature of -45 to -35°C. After addition the mixture was stirred for 1 hour at this temperature and the inner temperature was then increased to 15 to 25°C. The reaction mixture was stirred for further 16 hours at 15 to 25°C inner temperature.

After completion of the reaction, the mixture was filtrated through a centrifuge to separate the product solution from the solids. The wet cake was washed with dichloromethane (40 kg) and the organic solution was transferred back into the reactor. The product solution was concentrated under vacuum at a temperature below 20°C to 1 to 2 volumes. Dichloromethane (34 kg) was charged into the reactor and the product solution was concentrated again under vacuum at a temperature below 20°C to 1 to 2 volumes. The transfer pipe was rinsed with dichloromethane (6 kg) into the reactor and 64.4 kg of 2,2-difluoropropanamidine (XIII) in dichloromethane was obtained.

Scheme 2, Step 3: Ethyl 2-(1,1-difluoroethyl)-4-hydroxy-pyrimidine-5-carboxylate

(VI)

A reactor was charged with acetonitrile (216.0 kg) and potassium carbonate (55.0 kg, 398 mol, 1.6 eq) at room temperature. The pipe was rinsed with acetonitrile (8 kg) into the reactor. The inner temperature was set to 65 to 75 °C. Diethyl ethoxymethylenemalonate (53.8 kg, 249 mol, 1.00 eq.) was charged to the reactor and the pipe was rinsed with acetonitrile (10 kg) into the reactor. Then the solution of 2,2-difluoropropanamidine (XIII) (64.4 kg solution, 27 kg starting material, 249 mol, 1.0 eq.) in dichloromethane was added into the reactor at inner temperature 65 to 75 °C. The charging pipe was rinsed with acetonitrile (14 kg) into the reactor. After the addition the reaction mixture was stirred for 16 hours at 65 to 75 °C (inner temperature).

The temperature was adjusted to 50 to 60°C (inner temperature) and the reaction mixture was filtered. The filter was washed with acetonitrile (41.0 kg). The acetonitrile solution was transferred back into the reactor and the pipe was rinsed with acetonitrile (50 kg). The product solution was concentrated at an inner temperature below 40°C under vacuum to 2.5 to 3.5 volumes. Then ethyl acetate (65 kg) was charged into the reactor. The product solution was concentrated at an inner temperature below 40°C under vacuum to 2.5 to 3.5 volumes. Ethyl acetate (65 kg), water (287 kg) and methyl-tert-butyl ether (150 kg) were charged into the reactor. The product solution was concentrated at an inner temperature below 40°C under vacuum to 2.5 to 3.5 volumes. Ethyl acetate (65 kg) was charged into the reactor.

The mixture was stirred for 1 hour at inner temperature 15 to 25°C and the organic layer was separated and removed. Ethyl acetate (40 kg) and methyl-tert-butyl ether (79 kg) were added to the aqueous layer in the reactor. The mixture was stirred for 1 hour at inner temperature 15 to 25°C and the organic layer was separated and removed. Ethyl acetate (248 kg) was added to the aqueous layer in the reactor and the pH was adjusted to 2.5 through addition of 35% aq. HCl solution (22.4 kg) at inner temperature 15 to 25 °C. The mixture was stirred for 1 hour at inner temperature 15 to 25°C and the organic layer was separated and stored in plastic drums. The aqueous layer was extracted two times with ethyl acetate (50 kg each). After removal of the aqueous phase from the reactor, the separated organic layers were combined in the reactor. The combined organic layers were extracted with 25% brine solution (59 kg). The separated organic

layer was concentrated at inner temperature below 40°C under vacuum to 1 – 2 volumes and methyl-tert-butyl ether (40 kg) was charged into the reactor. The solution was concentrated at inner temperature below 40°C under vacuum to 1 to 2 volumes and methyl-tert-butyl ether (40 kg) was charged into the reactor. The solution was concentrated a third time at inner temperature below 40°C under vacuum to 1 – 2 volumes and methyl-tert-butyl ether (38 kg) was charged into the reactor. The temperature was adjusted to 10 to 20 °C.

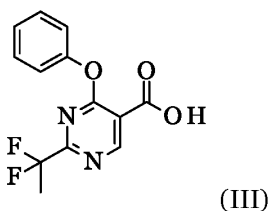
The mixture was further concentrated at inner temperature below 40°C under vacuum to 1 to 2 volumes and the temperature was adjusted to 10 to 20 °C. The slurry was stirred at this temperature for 1 hour, filtered and the filter cake was washed with methyl-tert-butyl ether (26 kg).

The obtained filter cake was combined with a second batch for further purification. The wet crude product cake was charged, together with a second batch into the reactor. Methyl-tert-butyl ether (80 kg) was added into the reactor. The inner temperature was adjusted to 10 to 20 °C and the slurry was stirred for 16 hours at this temperature. The slurry was filtered and washed with methyl-tert-butyl ether (59 kg) in two portions.

The product was dried in a single cone dryer to yield 57.2 kg of Ethyl 2-(1,1-difluoroethyl)-4-hydroxy-pyrimidine-5-carboxylate (VI) after sieving.

Example 4

2-(1,1-difluoroethyl)-4-phenoxy-pyrimidine-5-carboxylic acid



Alternatively to Scheme 1 Steps 1-3, the preparation of 2-(1,1-difluoroethyl)-4-phenoxy-pyrimidine-5-carboxylic acid (III) can be performed as described below:

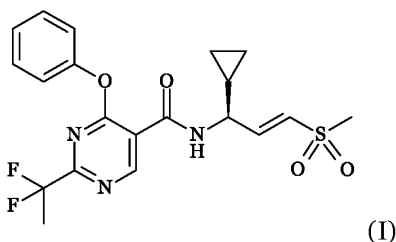
Ethyl 2-(1,1-difluoroethyl)-4-hydroxy-pyrimidine-5-carboxylate (VI) (107 kg, 461 mol, 1.00 eq.) and toluene (314 kg) were combined in a reaction vessel 1. N,N-dimethylformamide (1.01 kg, 13.8 mol, 0.03 eq.) was added, the flask rinsed with

toluene (1.0 kg). The reaction mixture was heated to 30 °C and oxalyl chloride (65.5 kg, 516 mol) added over 135 minutes. The dosing equipment was rinsed with toluene (5 kg). The reaction mixture was stirred at 30 °C until complete conversion, then cooled to 20 °C and water (375 kg) was added over 100 minutes. The aqueous layer was separated. Water (375 kg) was added to the organic layer and the aqueous layer was separated. Toluene (231 kg) was added to the organic layer and the mixture was concentrated below 50 °C to a volume of 400 L.

To the mixture in reactor a 34 % solution of Phenol in toluene (135 kg, 488 mol, 1.06 eq.) was added at 20 – 50 °C, the addition vessel rinsed with toluene (255 kg). The reaction mixture was heated to 50 °C and a 31 % solution of 1-Methylimidazol in toluene (134.6 kg, 507 mol, 1.10 eq.) was added, the addition vessel rinsed with toluene (23 kg). The reaction mixture was stirred at 50 °C until complete conversion, then cooled to 20 °C and an aqueous solution of citric acid 22 % (402.5 kg) was added. The aqueous layer was separated. Water (266 kg) was added to the organic layer and the aqueous layer was separated. Water (266 kg) was added to the organic layer and the aqueous layer was separated. The reaction mixture was concentrated below 50 °C to a volume of 250 L. A solvent exchange was performed with acetonitrile (1074 L) and acetonitrile was then added (800 L) to reach a volume of 1060 L. Water (744 kg) and aqueous sodium hydroxide 28% (72.4 kg) were added at 30°C, the pipe was rinsed with water (5 kg), the mixture stirred and then concentrated below 50 °C to a volume of 850 L. The mixture was cooled to 15 °C, water (851 kg) was added and a 30 % aqueous solution of sulfuric acid (~151 kg) was added to achieve pH ≤ 1.5, the pipe was rinsed with water (5 kg). The suspension was stirred at 15 °C and then filtered, the wet cake rinsed with water (total 803 kg). The product was dried under vacuum at 50 °C to yield 2-(1,1-difluoroethyl)-4-phenoxy-pyrimidine-5-carboxylic acid (III) (111 kg) as a white solid.

Example 5

***N*-[*(1S,2E)*-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy-pyrimidine-5-carboxamide**

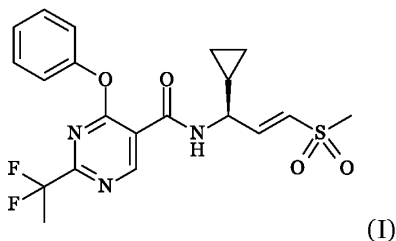


Alternatively to Scheme 1 Step 4, the preparation of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy-pyrimidine-5-carboxamide (I) from the reaction of 2-(1,1-difluoroethyl)-4-phenoxy-pyrimidine-5-carboxylic acid (III) with (E,1*S*)-1-cyclopropyl-3-methylsulfonyl-prop-2-en-1-amine;4-methylbenzenesulfonic acid (II) can be performed as described below:

In a 200 ml reactor, 5.00 g (17.8 mmol) of acid (III) were suspended at room temperature in 40 ml of ethyl acetate. 2.15 g (17.8 mmol) of pivaloyl chloride were added. The vessel was rinsed with 2.5 mL ethyl acetate. The mixture was cooled to 0-5°C and 1.80 g (17.8 mmol) of NMM (N-Methylmorpholine) were added over 15 minutes. The vessel and the pipe were rinsed with 2.5 mL ethyl acetate. The resulting white suspension was stirred for 3 hours at 0-5°C.

In a 100 ml reactor, 6.20 g (17.8 mmol) of Tosylate ((E,1*S*)-1-cyclopropyl-3-methylsulfonyl-prop-2-en-1-amine;4-methylbenzenesulfonic acid) (III) were suspended in 30 ml of ethyl acetate at room temperature. The Tosylate ((E,1*S*)-1-cyclopropyl-3-methylsulfonyl-prop-2-en-1-amine;4-methylbenzenesulfonic acid) suspension was transferred to the mixed anhydride suspension and the reactor and transfer line were rinsed with 2x10 mL of ethyl acetate. 3.61 g (35.7 mmol) of NMM were added over 20 minutes. The reaction mixture was stirred for 3 hours at approx. 0-5°C. The reaction mixture was quenched with water. The lower aqueous layer was separated. Water was added to the organic layer and the pH was adjusted between pH 7-8 with a sodium hydroxide (5.6%) solution. The lower aqueous layer was separated. The org. layer was washed with water. The pH was adjusted with a 4% citric acid solution to pH 2-3 after separating the layers the organic layer was washed with water.

The organic layer was concentrated to approx. 50 mL under reduced pressure at 50°C. When the residual volume was reached, 80 g ethyl acetate were added. The organic layer was concentrated again to approx. 50 mL under reduced pressure at 50°C. After reaching the level 50 mL of n-heptane were first added to the solution and the crystallization was initiated at 60°C using seed crystals. The crystal growing was kept for 30 minutes before proceeding slow dosage of 80 g of n-heptane and a cooling ramp to 20°C within 4-6 hours. The product was isolated by filtration at 20°C and washed with 2x 20 g ethyl acetate/n-heptane (1:4 V/V). The crystals were dried for 28 hours at 50°C in a vacuum drying oven, whereby the amide 3 (6.62 g, 15.7 mmol, 85% yield) was obtained as white crystals. HPLC purity: 99.8% (254 nm).

Example 6***N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide**

Alternatively to Scheme 1 Step 5, the preparation of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide (I), recrystallized can be performed as described below:

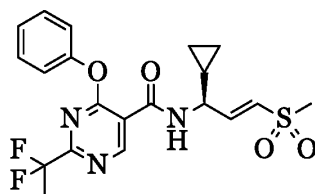
In a 500 ml reactor, 52.0 g (118.9 mmol) of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide were suspended at room temperature in 210 g of ethyl acetate. The mixture was heated to 40 °C and the clear solution filtered through a 0.45 µm filter into a 500 ml reactor. Reactor and pipe were rinsed with 42.0 g ethyl acetate (40°C) and filtered into the receiving reactor. The resulting mixture was stirred and heated to 73 °C. 195.0 g *n*-heptane were added within 20 minutes, maintaining 73 °C.

The clear solution was cooled to 65 °C and seeded with a mixture of 78.0 mg jet milled (I) suspended in mixture 0,35 g ethyl acetate and 3,15 g *n*-heptane. After aging for 15 minutes the suspension was cooled to 5 °C (0-10 °C) in 5 hours. Subsequently 210 g *n*-heptane were added within 100 minutes and additional 210 g *n*-heptane were added within 45 minutes. After addition the suspension is aged for min. 6 hours.

The product was isolated by filtration at 5 °C and washed with a mixture of 52.0 g ethyl acetate and 104.0 *n*-heptane (1:2 w/w). The crystals were dried at 50 °C under vacuum until weight constant. (I), recrystallized was obtained as white to off white crystals (50.3 g, 96.6% yield). HPLC purity: 99.8% (254 nm).

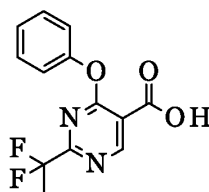
Claims

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



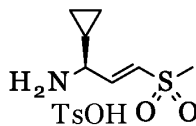
(I)

or an acceptable salt thereof, comprising the reaction of compound (III)



(III)

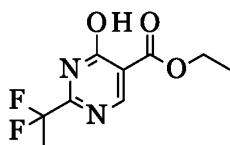
with compound (II)



(II)

2. The process of claim 1, wherein the process is carried out in the presence of a coupling agent.
3. The process of claim 2, wherein the coupling agent is propanephosphonic acid anhydride.
4. The process of any of claims 1 to 3, wherein the reaction step is carried out in the presence of a base.
5. The process of claim 4, wherein the base is triethylamine.

6. The process of claims 1 to 5, wherein compound (I) is purified by recrystallization, performed using a solvent system comprising isopropanol or ethyl acetate and n-heptane.
7. The process of claim 4, wherein pivaloyl chloride is the coupling agent and N-methylmorpholine is the base.
8. The process of claims 1-7, wherein the process includes the preparation of compound (III).
9. The process of claims 1-8, wherein compound (III) is prepared by reacting compound (VI)

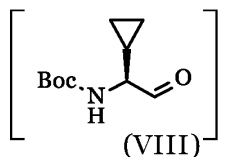


(VI)

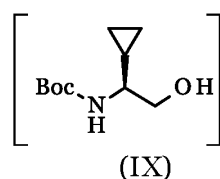
with phenol in the presence of potassium carbonate.

10. The process of claims 1-9, wherein compound (III) is isolated by adjusting the pH of the reaction mixture to 1-1.5 with hydrochloric acid, followed by cooling and filtration.
11. The process of claims 1-10, wherein compound (II) is prepared by
- Protecting a cyclopropylamine with a tert-butoxycarbonyl group
 - Reducing the ester moiety of the protected cyclopropylamine to form an alcohol
 - Oxidizing the alcohol to form an aldehyde
 - Reacting the aldehyde with a vinyl methylsulfonyl compound to yield the compound of formula (II).

12. The process of claims 1-11, wherein the synthesis of compound (II) involves the intermediate formation of compound (VIII)



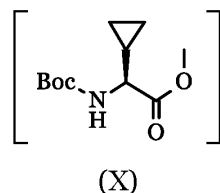
13. The process of claim 12, wherein compound (VIII) is formed by the reaction of compound (IX)



with oxalyl chloride in the presence of dimethyl sulfoxide and diisopropylethylamine.

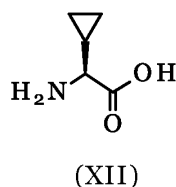
14. The process of claim 12 or claim 13, wherein the compound (VIII) is obtained from compound (IX) using a flow chemistry process.

15. The process of claim 13, wherein compound (IX) is obtained by the reduction of compound (X)



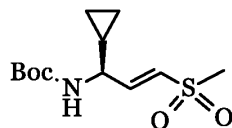
with lithium aluminium hydride or lithium borohydride.

16. The process of claim 15, wherein compound (X) is synthesized from compound (XII)



using thionyl chloride and di-tert-butyl dicarbonate.

17. The process of claims 1-13, wherein synthesis of compound (II) involves the reaction of compound (VIII) to compound (VII)



(VII)

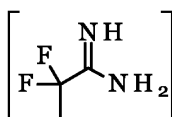
with diethyl(methylsulfonyl)methyl)phosphonate in the presence of potassium carbonate.

18. The process of claim 17, wherein the reaction to form compound (VII) includes subsequent extractions with water, hydrogen peroxide solution, sodium sulfite solution and sodium chloride solution.

19. The process of claim 1-18, wherein compound (II) is formed by the deprotection of compound (VII) using p-toluene sulfonic acid in acetonitrile.

20. The process of claim 19, wherein compound (II) is isolated by heating the reaction mixture to 50°C-60°C, following by cooling, stirring and filtration to obtain a white solid.

21. The process of claim 10, wherein compound (VI) is prepared from compound (XIII)



(XIII)

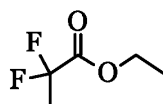
and diethyl ethoxymethylenemalonate in the presence of acetonitrile and potassium carbonate.

22. The process of claim 21, wherein the reaction to form compound (VI) includes heating the reaction mixture to 65-75°C.

23. The process of claims 21-22, wherein compound (VI) is purified by solvent exchange with ethyl acetate and subsequent aqueous extractions.

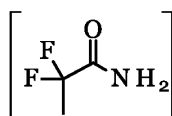
24. The process of claim 9 wherein compound (VI) is prepared by

- a) Reacting 2,2-difluoropropanionic acid ethyl ester (XV)



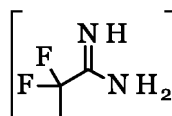
(XV)

with ammonia to form an amide (XIV)



(XIV) ;

- b) Converting the amide to an amidine (XIII)



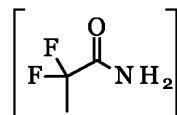
(XIII) ;

- c) Reacting the amidine with diethyl ethoxymethylenesulfonate to yield the compound (VI).

25. The process of claims 22-24 wherein the compound of formula (VI) is purified by a process comprising the steps of

- Solvent exchange from acetonitrile to ethyl acetate, and concentrating the reaction mixture under vacuum
- Extracting with ethyl acetate and methyl-tert-butyl ether
- Adjusting the pH with hydrochloric acid
- Separating the organic layer and washing with brine
- Concentrating the organic layer and recrystallizing to yield the compound (VI).

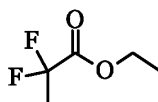
26. The process of claim 21, wherein compound (XIII) is obtained by reacting compound (XIV)



(XIV)

with trimethyloxonium tetrafluoroborate followed by treatment with ammonia gas.

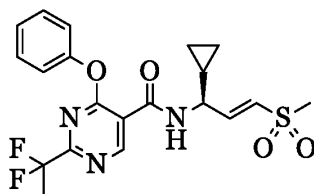
27. The process of claim 26, wherein Compound (XIV) is prepared by reacting compound (XV)



(XV)

with ammonia gas in n-heptane.

28. Compound (I),



(I)

or a salt thereof, prepared by or preparable by a process according to any one of claims 1 to 27.

29. Compound (I) or a salt thereof of claim 28, prepared by a process according to any one of claims 1 to 27.

30. A pharmaceutical composition comprising Compound (I) or a salt thereof of either claim 28 or claim 29, and a pharmaceutically acceptable excipient.