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(71) Applicant: **OSI PHARMACEUTICALS, LLC** [US/US]; 500 Bi-County Boulevard, Suite 118, Farmingdale, NY 11735 (US).

(72) Inventors: **CASTELHANO, Arlindo L.**; Astellas US LLC, 500 Bi-County Boulevard, Suite 118, Farmingdale, NY 11735 (US). **RECHKA, Josef A.**; Astellas US LLC, 500 Bi-County Boulevard, Suite 118, Farmingdale, NY 11735 (US). **SENANAYAKE, Chandrawansha**; Astellas US LLC, 500 Bi-County Boulevard, Suite 118, Farmingdale, NY 11735 (US). **DEVANATHAN, Krishnaswamy**; Astellas US LLC, 500 Bi-County Boulevard, Suite 118, Farmingdale, NY 11735 (US). **GNANAVELU, Karunanidhi**; Astellas US LLC, 500 Bi-County Boulevard, Suite 118, Farmingdale, NY 11735 (US).

(74) Agents: **FORMAN, Frank W.** et al.; Astellas US LLC, 500 Bi-County Boulevard, Suite 118, Farmingdale, NY 11735 (US).

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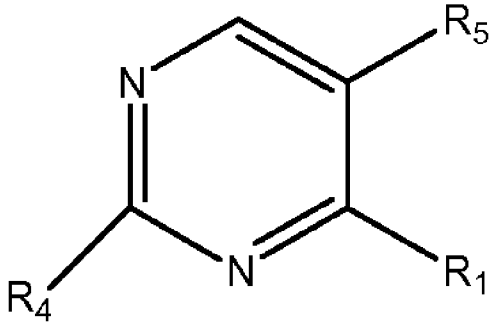

I

(57) Abstract: Disclosed are compounds of the Formula I:(I) where R_1, R_4, and R_5 are described herein, and methods of making the compounds, including regioselective functionalization.

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REGIOSELECTIVE SYNTHESIS OF SUBSTITUTED PYRIMIDINES

FIELD AND BACKGROUND

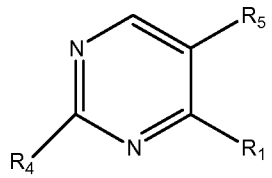
The present invention pertains at least in part to chemical compounds, substituted pyrimidines, including intermediates, and to chemical synthesis, and regioselective chemical synthesis. The compounds and syntheses can be useful, for example, in connection with the preparation of biologically active compounds.

Syntheses of diaminopyrimindes has been described in US7122670 and in publications cited therein. See also Xu et al., *J. Org. Chem.*, 57, 3839-3845 (1992).

SUMMARY

In some aspects, the present invention concerns compounds of general Formula I, as shown below, and methods of preparing the compounds, which can be useful in application such as pharmaceutical intermediates.

In some aspects, the invention includes a compound of Formula I, or a salt thereof:



I

wherein:

R_1 is R_4 or is selected from halogen, OH, or $-NR_2R_3$;

or R_1 is a leaving group such as alkyl or aryl sulfonate, or alkyl or aryl sulfinate;

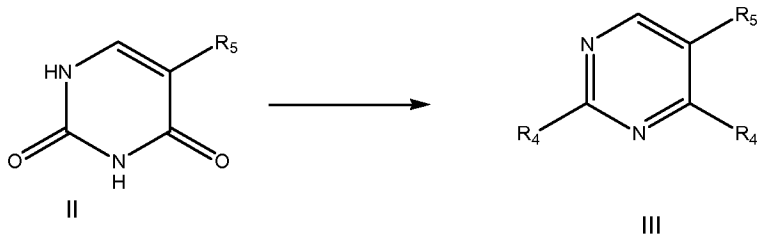
R_2 and R_3 are independently H, optionally substituted C_{1-12}aliphatic, or optionally substituted $_{4-10}$cyclic, except R_2 and R_3 are not both H;

or R_2 and R_3, together with the N to which they are attached, form an optionally substituted $_{4-10}$cyclic.

each R_4 is 1,2,3-triazol-1-yl or 1,2,4-triazol-1-yl, either of which is optionally substituted; and

R_5 is $-CF_3$, -CN, halogen, or C_{1-3}aliphatic.

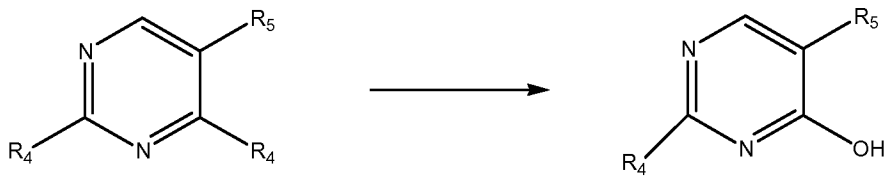
In some aspects, the invention includes a process for preparing a compound of Formula III, according to the scheme:



II III

comprising reacting Compound II with triazole in the presence of $POCl_3$.

In some aspects, the invention includes a process for preparing compounds of Formula IV according to the scheme:



III IV

comprising hydrolyzing a compound of Formula III under basic conditions. In some embodiments, the hydrolyzing is regioselective.

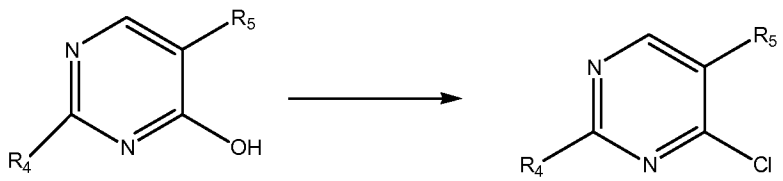
In some aspects thereof, the basic conditions are aqueous basic conditions. In some aspects thereof, the basic conditions include at least one of pyridine, DIPEA, or lutidine. In some aspects thereof, the basic conditions include pyridine.

In some aspects thereof, the process is carried out at about 90-100 °C.

In some aspects thereof, IV is isolated by evaporating the reaction mixture, slurrying the crude product in an alcohol or alcohol mixture, and separating the liquid.

In some aspects thereof, IV is obtained in a purity of about 98% or greater. In some aspects thereof, IV is obtained in an amount of about 1 kg or more per reaction. In some aspects thereof, IV is obtained from III in a yield of about 70% or more.

In some aspects, the invention includes a process for preparing a compound of Formula V according to the scheme:



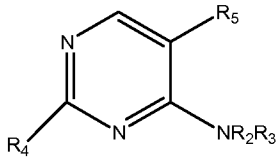
IV V

comprising chlorinating Compound IV.

In some aspects thereof, the invention includes chlorinating with $POCl_3$. In some aspects thereof, the chlorination is carried out in the presence of catalytic phosphoric acid or DMF.

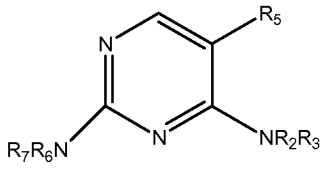
In some aspects thereof, V is obtained from IV in a purity of about 98% or greater. In some aspects thereof, V is obtained in an amount of about 1 kg or more. In some aspects thereof, V is obtained from IV in a yield of about 65% or more.

In some aspects, the invention includes a process for preparing a compound of Formula I, wherein R_1 is $-NR_2R_3$ (Formula VI), comprising reacting III or V with a compound of the formula NHR_2R_3.



VI

In some aspects, the invention includes a process of treating a compound of Formula VI with an amine NHR_6R_7, such as an aniline, to obtain a compound of Formula VII:



VII

wherein R_6 and R_7 are independently defined as in R_2 and R_3 of Formula I.

DETAILED DESCRIPTION

The compounds of the Formula I may be prepared by the methods described below, together with synthetic methods known in the art of organic chemistry, or modifications and derivatizations that are familiar to those of ordinary skill in the art. The starting materials used herein are commercially available or may be prepared by routine methods known in the art (such as those methods disclosed in standard reference books such as the COMPENDIUM OF ORGANIC SYNTHETIC METHODS, Vol. I-VI (published by Wiley-Interscience)). Preferred methods include those described below.

During any of the following synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This can be achieved by means of conventional protecting groups, such as those described in T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, 1981; T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991, and T. W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1999, which are hereby incorporated by reference.

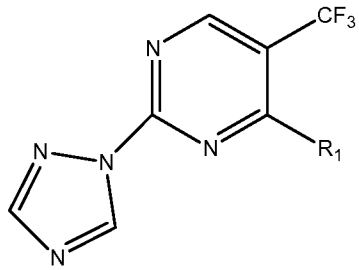
Compounds of Formula I, or their pharmaceutically acceptable salts, can be prepared according to the reaction Schemes discussed hereinbelow and the general skill in the art.

Unless otherwise indicated, the substituents in the Schemes are defined as above. Isolation and purification of the products is accomplished by standard procedures, which are known to a chemist of ordinary skill.

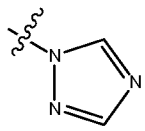
When a general or exemplary synthetic procedure is referred to, one skilled in the art can readily determine the appropriate reagents, if not indicated, extrapolating from the general or exemplary procedures. Some of the general procedures are given as examples for preparing specific compounds. One skilled in the art can readily adapt such procedures to the synthesis of other compounds. Representation of an unsubstituted position in structures shown or referred to in the general procedures is for convenience and does not preclude substitution as described elsewhere herein. For specific groups that can be present, either as R groups in the general procedures or as optional substituents not shown, refer to the descriptions in the remainder of this document, including the claims, summary and detailed description.

In some aspects, the present invention concerns compounds of general Formula I, as shown below, and methods of preparing the compounds, which can be useful in application such as pharmaceutical intermediates.

In some aspects, the invention includes a compound of Formula Ia, or a salt thereof, wherein:

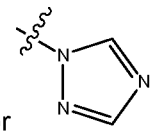


Ia

R_1 is selected from halogen, -OH,  , or $-NR_2R_3$; and

R_2 and R_3 are independently H, optionally substituted $C_{1\text{-}12}$aliphatic, or optionally substituted $_{4\text{-}10}$cyclic, except R_2 and R_3 are not both H;

or R_2 and R_3, together with the N to which they are attached, form an optionally substituted $_{4\text{-}10}$cyclic.

In some aspects, the invention includes a compound of Formula Ia, wherein R_1 is selected from halogen, -OH, or  .

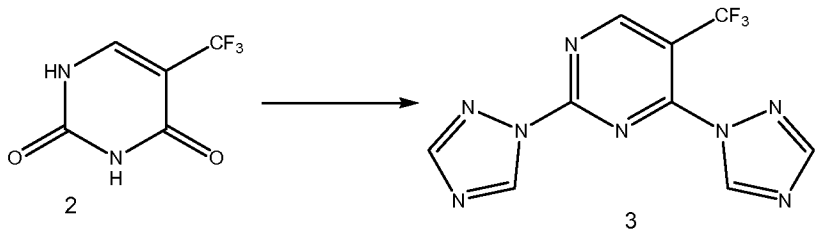
In some aspects, the invention includes a compound of Formula I, described above, wherein: R_1 and R_4 are 1,2,3-triazol-1-yl or 1,2,4-triazol-1-yl; and R_5 is $-CF_3$. In some aspects, the invention includes Compound 3.

In some aspects, the invention includes a compound of Formula I, described above, wherein: R_1 is 1,2,3-triazol-1-yl or 1,2,4-triazol-1-yl; R_4 is OH; and R_5 is $-CF_3$. In some aspects, the invention includes Compound 4.

In some aspects, the invention includes a compound of Formula I, described above, wherein: R_1 is 1,2,3-triazol-1-yl or 1,2,4-triazol-1-yl; R_4 is Cl; and R_5 is $-CF_3$. In some aspects, the invention includes Compound 5.

5-trifluoromethyluracil (Compound 2 herein) is disclosed in published literature. It can be prepared by known methods, such as disclosed in *Heidelberger et al.*, JACS, 84, 3597-98 (1962), and US7884202, example 1 thereof, which are incorporated herein by this reference. Also known are halouracils such as 5-chlorouracil.

In some aspects, the invention includes a process for preparing Compound 3 of Formula I, according to the scheme:



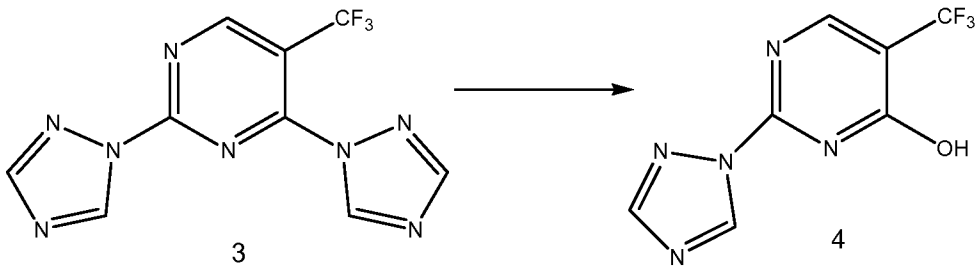
comprising reacting Compound 2 with 1,2,4-triazole in the presence of $POCl_3$.

Compound 3 (2,4-bis[1,2,4]triazol-1-yl-5-trifluoromethyl-pyrimidine) can be prepared from Compound 2 basically according to literature procedures. In some embodiments, Compound 2 is treated with phosphorous oxychloride ($POCl_3$) and 1,2,4-triazole. *See, e.g.*, Webb et al., Nucl. Acid. Res., 14, 7661-74 (1986), which is incorporated herein by this reference. The skilled artisan can vary and further optimize particular conditions as desired.

In some embodiments, about 5 or more, 10 or more, or 15 or more eq. of 1,2,4-triazole are used. In some embodiments, about 2 or more, 4 or more, or 6 or more eq. of $POCl_3$ are used. In some embodiments, a base such as Et_3N is used, which in some embodiments can be included in an amount of about 5 or more, 10 or more, or 15 or more eq.

The reaction can be carried out in a suitable solvent, which is not limited, such as CH_2Cl_2 and/or CH_3CN. In some embodiments, the reaction is carried out at about 0-5 °C. In some embodiments, the reaction is carried out at a scale of about 1 kg or more of starting Compound 2. In some embodiments, the yield of Compound 3 is about 85% or greater.

In some aspects, the invention includes a process for preparing Compound 4 (2-[1,2,4]triazol-1-yl-5-trifluoromethyl-pyrimidin-4-ol) according to the scheme:



3 4

comprising hydrolyzing Compound 3 under basic conditions.

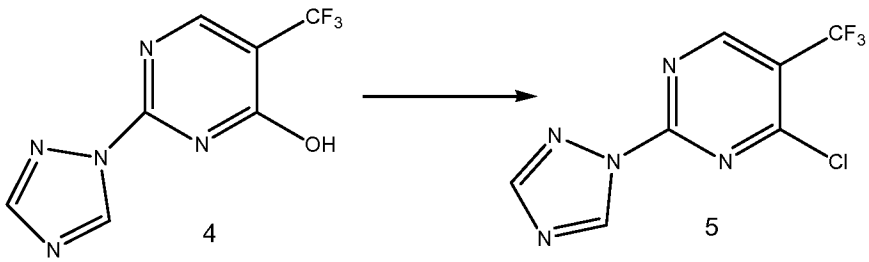
In some aspects thereof, the basic conditions are aqueous basic conditions. In some aspects thereof, the basic conditions include at least one amine based such as pyridine, DIPEA, DMAP, Et_3N, NMP, or lutidine. In some aspects thereof, the basic conditions include pyridine. In some aspects, the basic conditions include one or more of NaOH or LiOH.

In some aspects thereof, the process is carried out with heating, such as at about 40-100, 60-100, or about 90-100 °C.

In some aspects thereof, Compound 4 is isolated by evaporating the reaction mixture, slurrying the crude product in an alcohol or alcohol mixture, and separating the liquid. The separating may be by filtration.

In some aspects thereof, Compound 4 is obtained in a purity of about 90% or greater, 95 or greater, or 98% or greater. In some aspects thereof, Compound 4 is obtained in an amount of about 1 kg or more or about 5 kg or more per reaction. In some aspects thereof, Compound 4 is obtained from Compound 3 in a yield of about 60% or more, 70% or more, 80% or more, or 90% or more.

In some aspects, the invention includes a process for preparing Compound 5 (4-chloro-2-[1,2,4]triazol-1-yl-5-trifluoromethyl-pyrimidine) according to the scheme:



4 5

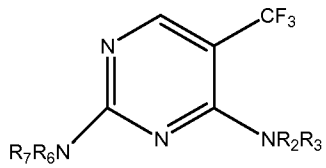
comprising chlorinating Compound 4.

In some aspects thereof, the invention includes chlorinating with $POCl_3$. In some aspects thereof, the chlorination is carried out in the presence of catalytic phosphoric acid or DMF.

In some aspects thereof, Compound 5 is obtained from Compound 4 in a purity of about 90% or more, 95% or more, 98% or more. In some aspects thereof, Compound 5 is obtained in an amount of about 1 kg or more or 5 kg or more. In some aspects thereof, Compound 5 is obtained from Compound 4 in a yield of about 65% or more, 75% or more, or 85% or more.

In some aspects, the invention includes a process for preparing a compound of Formula VI, wherein R_5 is $-CF_3$, comprising reacting Compound 3 or Compound 5 with a compound of the formula NHR_2R_3. R_2 and R_3 are not limited by the representative possibilities described above.

In some aspects, the invention includes a process of treating a compound of Formula VI, wherein R_5 is $-CF_3$, with an amine NHR_6R_7, such as an aniline, to obtain a compound of the formula:



wherein R_6 and R_7 are independently H, optionally substituted $C_{1\text{-}12}$aliphatic, or optionally substituted $_{4\text{-}10}$cyclic, except R_6 and R_7 are not both H; or R_6 and R_7, together with the N to which they are attached, form an optionally substituted $_{4\text{-}10}$cyclic.

EXPERIMENTAL

Example 1:

Description	Qty	M.W.	Mol	Eq.
Trifluoromethyl uracil (2)	250 g	180	1.38	1
1,2,4-triazole	1438 g	69.07	20.83	15
$POCl_3$(d=1.645g/ml)	450 mL	153.33	4.88	3.52
Triethylamine(d=0.726)	2900 mL	101.19	20.82	15
DCM	6250 mL	---	----	25 vol.

To a suspension of 1,2,4-triazole (Compound 2) (1.44 kg, 20.82 mol) in dichloromethane (6.25 L) was added phosphorous oxychloride (450 mL, 4.88 mol) over 30 min at 0-5 °C. After complete addition of $POCl_3$, triethylamine (2.9 L, 20.82 mol) was added at 0-5 °C slowly over a period of 3 h. After complete addition of triethylamine, the reaction mixture was stirred at 0-5 °C for 1h. After 1h, 5-trifluoromethyl uracil (250 g, 1.38 mol) was added in lots (50 g x 5) over a period of 30 min at 0-5 °C. After complete addition of 5-trifluoromethyl uracil, the reaction mixture was allowed to reach 23-25 °C and stirred for 16 h. Reaction completion was monitored by TLC (solvent system: 80 % ethyl acetate in pet ether). After completion, the reaction mixture was diluted with dichloromethane (10 L) and washed with water (6 L x 4). Aqueous layer was back extracted with dichloromethane (3 L x 2) and the combined organic extracts were dried over sodium sulfate, filtered and concentrated to get the crude product as yellow solid (400g). The crude product was slurried with 2-propanol (750 mL) for 1h, filtered, and the filtered cake was washed with 2-propanol (250 mL). The off-white obtained was dried under vacuum to get Compound 3.

Yield: 340 g (87 %); HPLC 99.6% area, R_t = 9.18 min; purity: > 98%; MS (M+1) 283 amu; ^{1}H NMR {*d6*-DMSO}: δ(ppm) 9.92 (s, 1 H), 9.91 (s, 1 H), 9.55 (s, 1 H), 8.55 (s, 1 H), 8.47 (s, 1H).

Example 2:

Description	Qty	M.W.	Mole	Eq.
Compound 3	100g	282.19	0.354	1
Pyridine	140ml	79.1	1.77	5eq
Water	500ml	--	--	5vol

A suspension of Compound 3 (100 g, 0.354 mol) in pyridine (140 ml) and water (500 ml) was heated to 95-100 °C for 10 h (reaction mixture becomes a clear solution). Reaction completion was monitored by TLC (100% ethyl acetate). After completion of reaction, the reaction mixture was evaporated to get the yellow solid (115g). The crude product was slurried with 300 mL of 30% methanol/ethanol for 6 h at 25 °C, filtered, and the solid was washed with 80 mL of 30% methanol/ethanol. The pale yellow solid thus obtained was dried under vacuum at 25 °C to get pure product Compound 4. Yield: (65 g; 78 %); HPLC 96.3% area, R_t = 8.35 min, purity: > 97%; ^{1}H NMR {*d6*-DMSO}: δ (ppm) 9.43 (s, 1 H), 8.66 (s, 1 H), 8.41 (s, 1 H); MS: (M+1) 232 amu.

Example 3:

Description	Qty	M.W.	Mol	Eq.
Compound 4	650g	231.14	2.81	1
$POCl_3$(d=1.645g/ml)	980ml	153.33	---	1.5 vol.
Phosphoric acid (85%)	27 ml	---	---	0.041vol
DIPEA(d=0.742)	490ml	129.27	2.81	1.0

To a cooled (0 °C) suspension of Compound 4 (650 g, 2.81mol) in phosphorous oxychloride (980 ml) was added phosphoric acid (27ml), followed by diisopropyl ethylamine drop wise over a period of 30min, at 0-5 °C. After complete addition of diisopropyl ethylamine, the temperature of the reaction mixture was adjusted to 25 °C and then it was heated to 100 °C for 30 min. Reaction completion was monitored by TLC (80% ethyl acetate in pet ether). TLC showed no starting material. After completion of the reaction, ethyl acetate (3L) was added and the mixture was poured in to ice cold water (2L). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 750 mL). The combined organic solutions were washed with saturated sodium bicarbonate solution (2 x 250 mL), water (2 x 500 mL) and brine

(500 mL). The aqueous layer was back extracted with ethyl acetate (2 x 250 mL).The combined organic solutions were dried over sodium sulfate and concentrated to get the crude product as a pale brown solid. The crude product (610 g) was slurried with a mixture of 610 mL of ethanol and 915 mL of pet ether for 30 min at 25 °C. The pale yellow solid was collected by filtration and was dried under vacuum at 25 °C to give Compound 5. Yield: 460g, 65 %; HPLC purity: > 98 %.

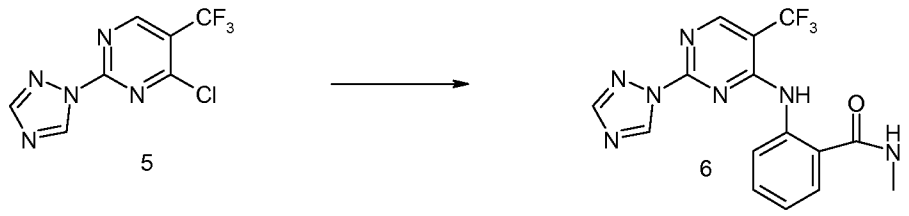
Example 4:

Reagents	Quantity	MW	Mol	Eq. / Vol.
Compound 4	500g	231.14	2.163	1eq
$POCl_3$ (d=1.645)	663g (405 mL)	153.3	4.326	2eq
Toluene	10L	--	--	20vol
DMF	50ml	--	--	0.1vol

To a suspension of Compound 4 (500 g, 2.16 mol) in toluene (10L) was added $POCl_3$ (405 mL, 663 g) slowly at 23-25 °C and then DMF (50ml) was added slowly at 23-25 °C. After complete addition, the reaction mixture was heated to 100 °C for 1h. (HPLC showed absence of starting materials). After completion of the reaction the reaction mass was allowed to warm to 15-20 °C and was then quenched with ice cold water (5L) at 15-20 °C. The toluene layer was separated, then aqueous layer was extracted with ethyl acetate (5L x 3). The combined toluene and ethyl acetate solutions were washed with sodium bicarbonate solution (5 L), and brine solution (2 L). The combined aqueous solutions were extracted with ethyl acetate (3 L) and the combined organic layers were dried over sodium sulfate then concentrated to give a pale yellow solid (432g, 94% purity). The crude material was slurried with a mixture of ethanol (250 mL) and hexane (375 mL) at 23-25 °C for 30 min. The solid was collected by filtration, washed with hexane (100 mL) and dried to give Compound 5 as a pale yellow solid.

Yield: 350g, 65%; purity: 99% by HPLC, 98.8% area, R_t = 10.04 min; ^{1}H NMR {*CDCl$_3$*}: δ (ppm) 9.30 (s, 1 H), 8.03 (s, 1 H), 8.25 (s, 1 H); MS: (M+1) 250 amu.

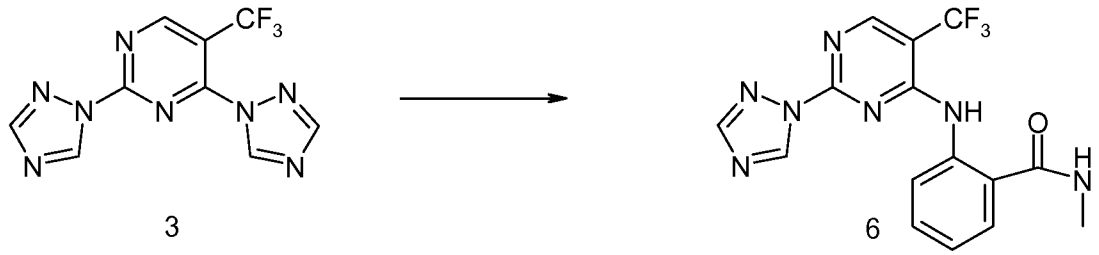
Example 5



To a sealed tube with a magnet was added 4-chloro-2-(1*H*-1,2,4-triazol-1-yl)-5-(trifluoromethyl)pyrimidine (0.050 g, 0.200 mmol), and 2-propanol (0.5 mL). To the reaction mixture 2-amino-*N*-methylbenzamide (0.030 g, 0.20 mmol) and DIPEA (0.067 mL, 0.40 mmol) were added and to the mixture was stirred in an oil bath at 90 °C. The progress of the reaction was monitored by HPLC. After reaction completion, the suspension was allowed to cool to RT and diluted with water (1 mL) and 2-propanol (1mL) and stirred. The product was collected by filtration, washed with water and 2-propanol then dried under vacuum to give 60 mg of Compound 6 (N-methyl-2-{[2-(1*H*-1,2,4-triazol-1-yl)-5-(trifluoromethyl)pyrimidin-4-yl]amino}benzamide).

Analytical: HPLC: 99.1% area, R_t = 6.66 min; ^{1}H NMR {*CDCl*$_3$}: δ(ppm) 11.68(br s, 1 H, N*H*), 9.13 (s, 1 H, Ar*H*), 8.66 (s, 1 H, Ar*H*), 8.60 (d, *J* = 7.8 Hz, 1 H, Ar*H*), 8.17 (s, 1 H), 7.62 (t, *J* = 7.1 Hz, 1 H, Ar*H*), 7.55 (d, *J* = 7.8 Hz, 1 H, Ar*H*), 7.23 (t, *J* = 7.5 Hz, 1 H, Ar*H*), 6.29 (br s, 1 H, N*H*), 3.05 (s, 3 H, CH_3).

Example 6



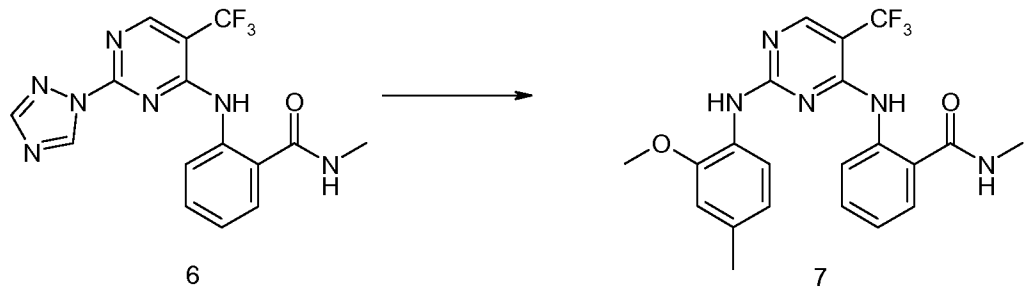
3 6

To a 3 N 500 mL RBF with a mechanical stirrer, a thermocouple and a reflux condenser with a N_2 inlet was added 2,4-di-(1*H*-1,2,4-triazol-1-yl)-5-(trifluoromethyl)pyrimidine (10.00 g, 35.44 mmol), 2-amino-*N*-methylbenzamide (7.983 g, 53.16 mmol) and THF (200 mL). The resulting suspension was cooled using a dry ice/2-propanol bath and 2 M trimethylaluminum in toluene (28.35 mL, 56.70 mmol) was added using a syringe over 10 min. while maintaining the temperature below -30 °C. After the addition was complete, the pale yellow suspension was slowly allowed to warm and was heated to 60 °C. The progress of the reaction was monitored by HPLC. After reaction completion, the suspension was allowed to cool to RT and further cooled using a water/ice bath. An aqueous solution of ammonium chloride (28% w/w, 80 mL) was added using an addition funnel at 0-5 °C over 5 min. The resulting suspension was stirred at RT and the solid was collected by filtration, rinsed with water (2 X 20 mL), toluene (20 mL) and methanol (20 mL). Solid was suspended in 2% aqueous NaOH (200 mL) and stirred at RT, then collected by filtration. After washing with water (3 X 20 mL) the damp solid was dried under vacuum ~ 40 °C to give 10.6 g of Compound 6.

Analytical: HPLC: 98.8% area, R_t = 6.66 min; ^{1}H NMR {*CDCl*$_3$}: δ(ppm) 11.68(br s, 1 H, N*H*), 9.13 (s, 1 H, Ar*H*), 8.66 (s, 1 H, Ar*H*), 8.61 (d, *J* = 8.3 Hz, 1 H, Ar*H*), 8.17 (s, 1 H), 7.62 (t,

J = 7.3 Hz, 1 H, Ar*H*), 7.54 (d, *J* = 7.8 Hz, 1 H, Ar*H*), 7.22 (t, *J* = 7.6 Hz, 1 H, Ar*H*), 6.29 (br s, 1 H, N*H*), 3.05 (s, 3 H, CH_3).

Example 7 (2-({2-[(2-Methoxy-4-methylphenyl)amino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)-*N*-methylbenzamide)



6 7

To a test tube with a magnet stirrer bar was added *N*-methyl-2-{[2-(1*H*-1, 2, 4-triazol-1-yl)-5- (trifluoromethyl) pyrimidin-4-yl] amino} benzamide (Compound 6, 0.200 g, 0.550 mmol) and 2-methoxy-4-methyl aniline (0.083 g, 0.606 mmol, 1.1 eq.). To the mixture, trimethylacetic acid (1.0 g, 9.791 mmol, 17.8 eq.) was added and the resulting suspension was stirred and heated in an oil bath set at 130 °C. The progress of the reaction was monitored by HPLC. After 29 h the reaction mixture was cooled to room temperature, quenched with 3 N NaOH (3.9 mL, 11.75 mmol, 21 eq.) and diluted with toluene. Insoluble solids were filtered off and the layers were separated. The organic phase was washed with water and brine and then concentrated under vacuum. The residue was stirred in a mixture of heptanes and dichloromethane at room temperature and the resultant solids were collected by filtration and rinsed with heptane. The damp solid was dried under high vacuum to give 118 mg of the desired product as a pale solid.

^{1}H NMR {*CDCl*$_3$}: δ(ppm) 10.75 (br s, 1 H, N*H*), 8.46 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 8.36 (s, 1 H, Ar*H*), 8.14 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 7.64 (br s, 1 H, N*H*), 7.45 – 7.49 (m, 2 H, 2X Ar*H*), 7.13 (t, *J* = 8.0 Hz, 1 H, Ar*H*), 6.72 (s, 1 H, Ar*H*), 6.68 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 6.18 (br s, 1 H, N*H*), 3.88 (s, 3 H, OCH_3), 3.02 (d, *J* = 4.0 Hz, 3 H, NCH_3), 2.34 (s, 3 H, CH_3).

^{19}F NMR {*CDCl*$_3$}: δ(ppm) 61.4.

HPLC: 97.2% area, R_t = 7.34 min

GENERAL DEFINITIONS AND ABBREVIATIONS

Except where otherwise indicated, the following general conventions and definitions apply. Unless otherwise indicated herein, language and terms are to be given their broadest reasonable interpretation as understood by the skilled artisan. Any examples given are nonlimiting.

Any section headings or subheadings herein are for the reader's convenience and/or formal compliance and are non-limiting.

Each variable definition above includes any subset thereof and the compounds of Formula I include any combination of such variables or variable subsets.

The invention includes the compounds and salts thereof, and their physical forms, preparation of the compounds.

The compounds of the invention and term “compound” in the claims include any pharmaceutically acceptable salts or solvates, and any amorphous or crystal forms, or tautomers, whether or not specifically recited in context.

A recitation of a compound herein is open to and embraces any material or composition containing the recited compound (*e.g.*, a composition containing a racemic mixture, tautomers, epimers, stereoisomers, impure mixtures, *etc.*). In that a salt, solvate, or hydrate, polymorph, or other complex of a compound includes the compound itself, a recitation of a compound embraces materials containing such forms. Isotopically labeled compounds are also encompassed except where specifically excluded. For example, hydrogen is not limited to hydrogen containing zero neutrons.

The term “substituted” and substitutions contained in formulas herein refer to the replacement of one or more hydrogen radicals in a given structure with a specified radical, or, if not specified, to the replacement with any chemically feasible radical. When more than one position in a given structure can be substituted with more than one substituent selected from specified groups, the substituents can be either the same or different at every position (independently selected) unless otherwise indicated. In some cases, two positions in a given structure can be substituted with one shared substituent. It is understood that chemically impossible or highly unstable configurations are not desired or intended, as the skilled artisan would appreciate.

In descriptions and claims where subject matter (*e.g.*, substitution at a given molecular position) is recited as being selected from a group of possibilities, the recitation is specifically intended to include any subset of the recited group. In the case of multiple variable positions or substituents, any combination of group or variable subsets is also contemplated. Unless indicated otherwise, a substituent, diradical or other group referred to herein can be bonded through any suitable position to a referenced subject molecule. For example, the term “indolyl” includes 1-indolyl, 2-indolyl, 3-indolyl, etc.

The convention for describing the carbon content of certain moieties is "(C_{a-b})" or “C_a-C_b” meaning that the moiety can contain any number of from “a” to “b” carbon atoms. C_0alkyl means a single covalent chemical bond when it is a connecting moiety, and a hydrogen when it is a terminal moiety. Similarly, "x-y" can indicate a moiety containing from x to y atoms, *e.g.*, $_{5\text{-}6}$heterocycloalkyl means a heterocycloalkyl having either five or six ring members. "C_{x-y}" may be used to define number of carbons in a group. For example, “$C_{0\text{-}12}$alkyl” means alkyl having

0-12 carbons, wherein C_0alkyl means a single covalent chemical bond when a linking group and means hydrogen when a terminal group.

Unless otherwise indicated (such as by a connecting "-"), the connections of compound name moieties are at the rightmost recited moiety. That is, the substituent name starts with a terminal moiety, continues with any bridging moieties, and ends with the connecting moiety. For example, "heteroarylthioC_{1-4}alkyl is a heteroaryl group connected through a thio sulfur to a C_{1-4} alkyl, which alkyl connects to the chemical species bearing the substituent.

The term "aliphatic" means any hydrocarbon moiety, and can contain linear, branched, and cyclic parts, and can be saturated or unsaturated.

The term "alkyl" means any saturated hydrocarbon group that is straight-chain or branched. Examples of alkyl groups include methyl, ethyl, propyl, 2-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, and the like.

The term "cyclic" means any ring system with or without heteroatoms (N, O, or $S(O)_{0-2}$), and which can be saturated or unsaturated. Ring systems can be bridged and can include fused rings. The size of ring systems may be described using terminology such as "$_{x-y}$cyclic," which means a cyclic ring system that can have from x to y ring atoms. For example, the term "$_{9-10}$carbocyclic" means a 5,6 or 6,6 fused bicyclic carbocyclic ring system which can be satd., unsatd. or aromatic. It also means a phenyl fused to one 5 or 6 membered satd. or unsatd. carbocyclic group. Nonlimiting examples of such groups include naphthyl, 1,2,3,4 tetrahydronaphthyl, indenyl, indanyl, and the like.

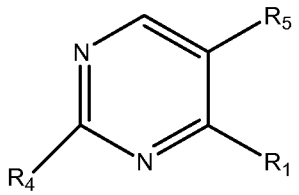
The term "halo" or "halogen" means fluoro, chloro, bromo, or iodo.

The term "leaving group"

The term "protecting group" means a suitable chemical group that can be attached to a functional group and removed at a later stage to reveal the intact functional group. Examples of suitable protecting groups for various functional groups are described in T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2d Ed., John Wiley and Sons (1991 and later editions); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed. Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995). The term "hydroxy protecting group", as used herein, unless otherwise indicated, includes Ac, CBZ, and various hydroxy protecting groups familiar to those skilled in the art including the groups referred to in Greene.

CLAIMS

1. A compound of Formula I, or a salt thereof:



I

wherein:

R_1 is R_4 or is selected from halogen, -OH, or $-NR_2R_3$;

or R_1 is a leaving group selected from an optionally substituted arylsulfonate, alkylsulfonate, alkylsulfinate, or arylsulfinate;

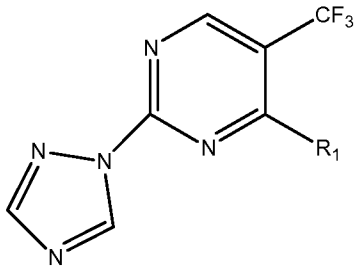
R_2 and R_3 are independently H, optionally substituted C_{1-12}aliphatic, or optionally substituted $_{4-10}$cyclic, except R_2 and R_3 are not both H;

or R_2 and R_3, together with the N to which they are attached, form an optionally substituted $_{4-10}$cyclic;

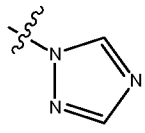
each R_4 is 1,2,3-triazol-1-yl or 1,2,4-triazol-1-yl, either of which is optionally substituted; and

R_5 is $-CF_3$, -CN, halogen, or C_{1-3}aliphatic.

2. A compound of Claim 1, or a salt thereof, having the Formula Ia:

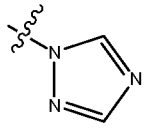


Ia

wherein R_1 is selected from halogen, OH,  , or $-NR_2R_3$; and

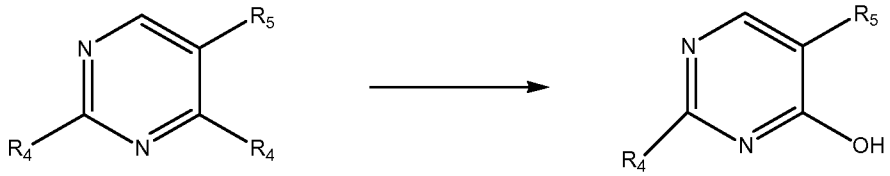
R_2 and R_3 are independently H, optionally substituted C_{1-12}aliphatic, or optionally substituted $_{4-10}$cyclic, except R_2 and R_3 are not both H; or R_2 and R_3, together with the N to which they are attached, form an optionally substituted $_{4-10}$cyclic.

3. The compound or salt of Claim 2, wherein R_1 is selected from halogen, -OH, or



.

4. A process for regioselectively preparing a compound of Formula IV, comprising hydrolyzing a compound of Formula III under basic conditions according to the scheme:

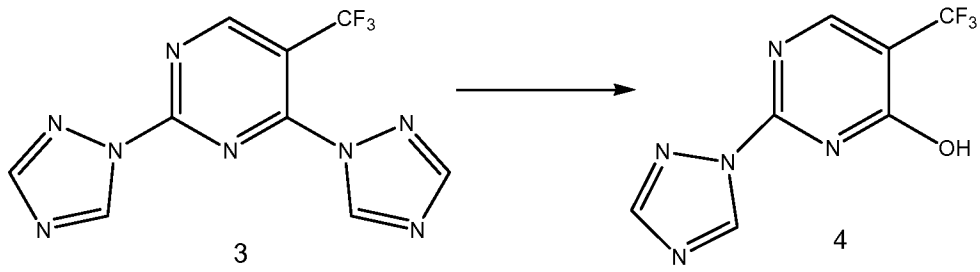


III IV

wherein:

each R_4 is 1,2,3-triazol-1-yl or 1,2,4-triazol-1-yl, either of which is optionally substituted; and R_5 is $-CF_3$, -CN, halogen, or C_{1-3}aliphatic.

5. The process of Claim 4, comprising hydrolyzing Compound 3 under basic conditions according to the scheme:



3 4

to obtain Compound 4.

6. The process of Claim 4 or 5, wherein the basic conditions are aqueous basic conditions.

7. The process of any one of Claims 4-6, wherein the basic conditions include at least one of pyridine, DIPEA, or lutidine.

8. The process of any one of Claims 4-6, wherein the basic conditions include pyridine.

9. The process of any one of Claims 4-7, wherein the hydrolysis is carried out at about 90-100 °C.

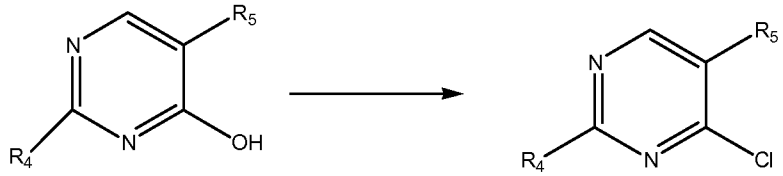
10. The process of any one of Claims 5-9, wherein Compound 4 is isolated by evaporating the reaction mixture, slurrying the crude product in an alcohol or alcohol containing mixture, and separating the liquid.

11. The process of any one of Claims 5-10, wherein Compound 4 is obtained in a purity of about 98% or greater.

12. The process of any one of Claims 5-11, wherein Compound 4 is obtained in an amount of about 1 kg or more from a single reaction mixture.

13. The process of any one of Claims 5-12, wherein Compound 4 is obtained from Compound 3 in a yield of about 70% or more.

14. A process for preparing a compound of Formula V, according to the scheme:



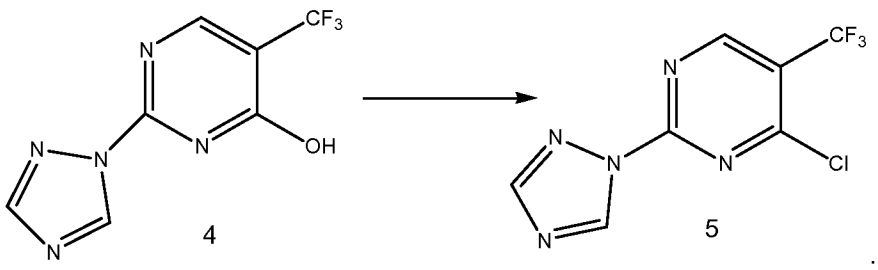
IV V

comprising chlorinating a compound according to Formula IV; wherein

R_4 is 1,2,3-triazol-1-yl or 1,2,4-triazol-1-yl, either of which is optionally substituted; and

R_5 is $-CF_3$, -CN, halogen, or C_{1-3}aliphatic.

15. The process of Claim 14, comprising chlorinating Compound 4 to obtain Compound 5 according to the scheme:



16. The process of Claim 15, comprising chlorinating with $POCl_3$.

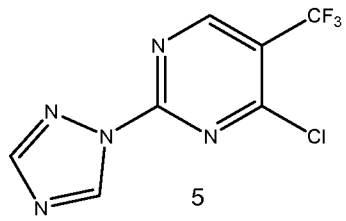
17. The process of any one of Claims 14-16, wherein the chlorination is carried out in the presence of catalytic phosphoric acid or DMF.

18. The process of any one of Claims 15-17, wherein Compound 5 is obtained from Compound 4 in a purity of about 98% or greater.

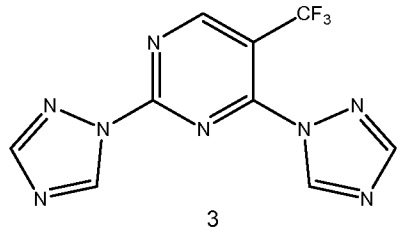
19. The process of any one of Claims 15-18, wherein Compound 5 is obtained in an amount of about 1 kg or more from a single reaction mixture.

20. The process of any one of Claims 15-19, wherein Compound 5 is obtained from Compound 4 in a yield of about 65% or more.

21. A process for preparing a compound of Claim 1, wherein R_1 is $-NR_2R_3$, comprising reacting Compound 5 or Compound 3 with a compound of the formula NHR_2R_3

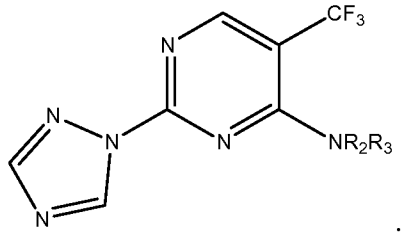


5



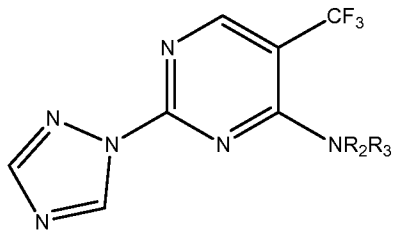
3

to obtain a compound of the formula:

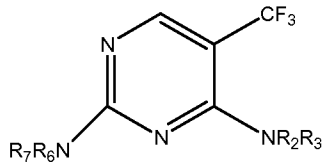


.

22. The process of Claim 21, further comprising treating the compound of the formula:

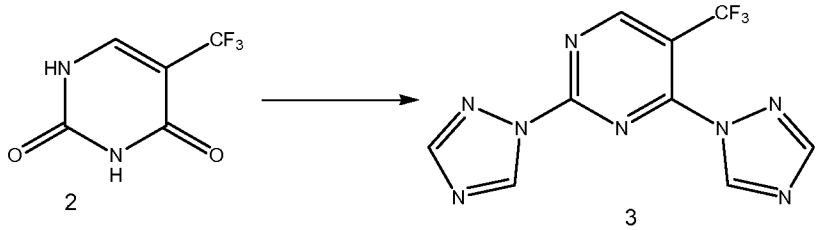


with an amine having the formula NHR_6R_7 to obtain a compound of the formula



wherein R_6 and R_7 are independently H, optionally substituted C_{1-12}aliphatic, or optionally substituted $_{4-10}$cyclic, except R_6 and R_7 are not both H; or R_6 and R_7, together with the N to which they are attached, form an optionally substituted $_{4-10}$cyclic.

23. A process for preparing Compound 3, according to the scheme:



comprising reacting Compound 2 with 1,2,4-triazole in the presence of $POCl_3$.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/015925

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/04 C07D403/14
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DYATKINA N ET AL: "Formation and Reactivity of 2,4-Ditriazolyl Pyrimidine C-Nucleoside Derived from Pseudouridine", NUCLEOSIDES, NUCLEOTIDES AND NUCLEIC ACIDS, TAYLOR & FRANCIS, PHILADELPHIA, PA, USA, vol. 19, no. 3, 1 January 2000 (2000-01-01), pages 585-591, XP009176915, ISSN: 1525-7770	1
A	page 587 - page 588; compounds 5,6,7	2,3

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 March 2014	22/07/2014

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	Härtinger, Stefan

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/015925

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	YAO ZHONG XU ET AL: "Synthesis of DNA containing modified bases by post-synthetic substitution. Synthesis of oligomers containing 4-substituted thymine: O4-alkylthymine, 5-methylcytosine, N4-dimethylamino-5-methylcytosine, and 4-thiothymine", THE JOURNAL OF ORGANIC CHEMISTRY, vol. 57, no. 14, 1 July 1992 (1992-07-01), pages 3839-3845, XP055107411, ISSN: 0022-3263, DOI: 10.1021/jo00040a024 cited in the application *Scheme II*; page 3840; compounds 1,2	1-3
X	WO 2008/116139 A2 (VERTEX PHARMA [US]; WANNAMAKER MARION [US]; SALITURO FRANCESCO [US]; P) 25 September 2008 (2008-09-25) claims; table 1; compounds 39-41,43-44,46-57	1-3
Y	US 7 122 670 B2 (KATH JOHN C [US] ET AL KATH JOHN CHARLES [US] ET AL) 17 October 2006 (2006-10-17) column 1 - column 6	1-3
Y	WO 01/64654 A1 (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; PEASE ELIZABETH JANET [G) 7 September 2001 (2001-09-07) *formulae III, IVA, IV, V, VI*; page 14 - page 16	1-3
Y	WO 03/030909 A1 (BAYER AG [US]; NAGARATHNAM DHANAPALAN [US]; WANG CHUNGUANG [US]; CHEN) 17 April 2003 (2003-04-17) *formulae II, III, IV, Ia, Ib*; page 20	1-3
Y	WO 2012/168817 A1 (PFIZER [US]; HELAL CHRISTOPHER J [US]; CHAPPIE THOMAS ALLEN [US]; HUMP) 13 December 2012 (2012-12-13) *formulae II, III*; page 29 - page 30	1-3

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/015925

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE REAXYS [Online] Reed Elsevier Properties SA; 1998, GEIES A. A.: "Synthesis of Thieno<2',3':4,5>pyrimido<2,1-c><1,2,4>Triazoles and Pyrazolyl Thieno<2,3-d><4,5-d'>Dipyrimidines", XP002721918, Database accession no. Rx-ID 5031443 the whole document -----	1-3
A,P	OLEG GOLUBEV ET AL: "Metal-Ion-Binding Analogs of Ribonucleosides: Preparation and Formation of Ternary Pd 2+ and Hg 2+ Complexes with Natural Pyrimidine Nucleosides", HELVETICA CHIMICA ACTA, vol. 96, no. 9, 18 September 2013 (2013-09-18), pages 1658-1669, XP055108619, ISSN: 0018-019X, DOI: 10.1002/hlca.201300042 page 1660; compounds 3,4,7 -----	1-3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/015925

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-3(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-3(partially)

   Compound (I) wherein R1 is R4

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2. claims: 1-3(partially)

   Compound (I) wherein R1 is a halogen leaving group

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3. claims: 1-3(partially)

   Compound (I) wherein R1 is OH

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4. claims: 1, 2(partially)

   Compound (I) wherein R1 is an NR2R3 amino group other than triazolyl

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5. claims: 4-13

   Process which converts III to IV

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6. claims: 14-20

   Process which converts IV to V

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7. claims: 21, 22

   Process which converts 5 or 3 to the -NR2R3 substituted pyrimidine

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8. claim: 23

   Process which converts 2 to 3

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/015925

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