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Development of a Practical Process for the Synthesis of PDE4 Inhibitors

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Development of a Practical Process for the Synthesis of PDE4 Inhibitors

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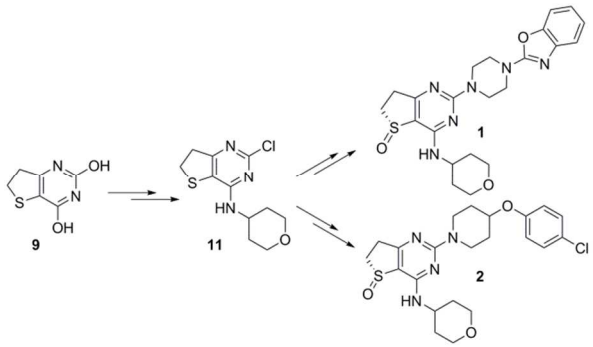


Abstract: A practical, safe and efficient process for the synthesis of PDE4 (phosphodiesterase type 4) inhibitors represented by **1** and **2** was developed and demonstrated on a multikilogram scale. Key aspects of the process include the regioselective synthesis of dihydrothieno[3,2-*d*]pyrimidine-2,4-diol **9** and the asymmetric sulfur oxidation of intermediate **11**.

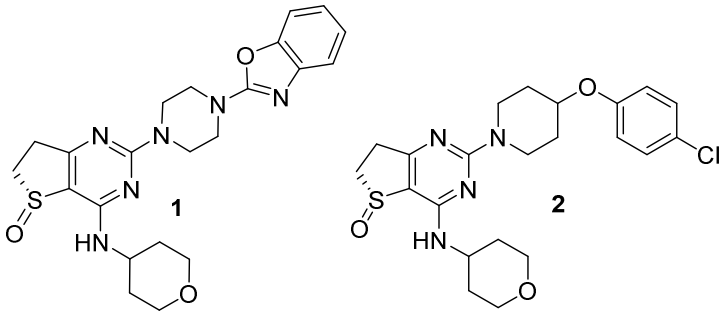
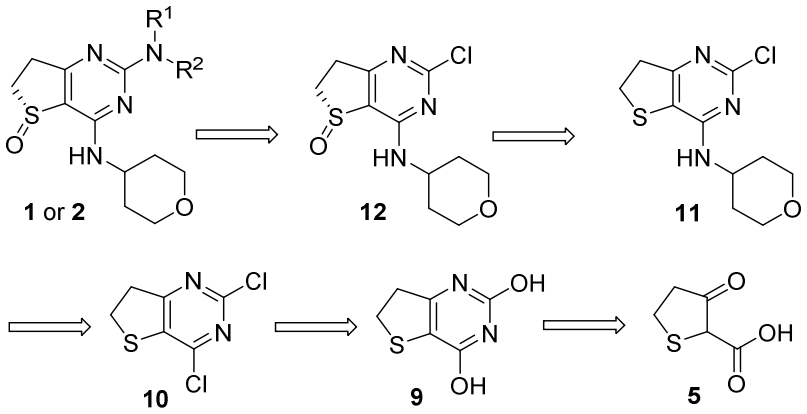


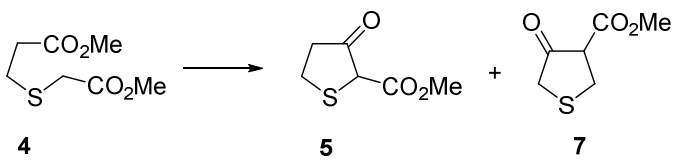
Figure 1. PDE4 Inhibitors **1** and **2**

The use of PDE4 (phosphodiesterase type 4) inhibitors for the treatment of COPD (Chronic Obstructive Pulmonary Disease) by reducing inflammation and improving lung function is well documented.[1,2,3] Given the potential therapeutic benefit offered by these compounds, a number of PDE4-selective inhibitors containing a dihydrothieno[3,2-*d*]pyrimidine core were identified as pre-clinical candidates in our Discovery laboratories.[4a] The continued profiling and evaluation of these compounds as potential therapeutic agents inevitably necessitated the synthesis of increasingly larger quantities in a safe, cost-effective and practical manner which could not be accommodated using the initial synthetic route.[4a-c] Herein we describe the development of a practical and scalable approach to these compounds.



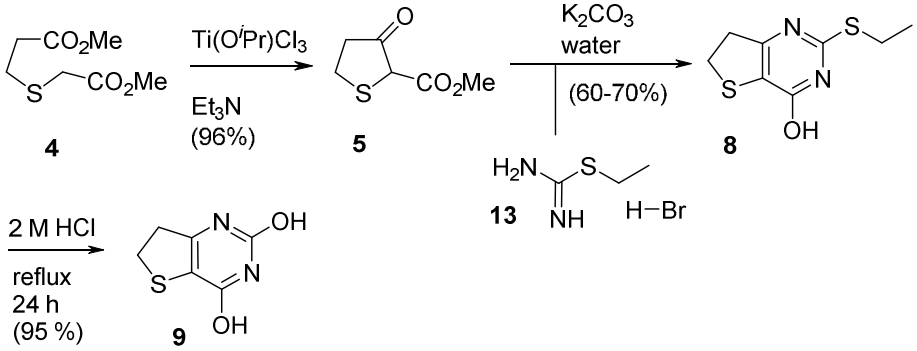
Scheme 1. Retrosynthetic analysis for **1** and **2**

The general approach to PDE4 inhibitors **1** and **2** is shown in Scheme 1 and the first challenge for the development of an efficient synthesis process was the preparation of intermediate **5**. The existing process for the synthesis of **5** from **4** (See Eq. 1) had to be significantly modified to obtain a reliable, high yielding and regioselective process. Intermediate **4** was obtained from methyl thioglycolate (**3**) and methyl acrylate according to a modified literature procedure.[5] Initially, **5** was obtained from **4** under strongly basic conditions (sodium hydride, DME) at low temperature (-40 °C) resulting in the desired product along with varying amounts of the undesired regioisomer **7.** However, the undesired regioisomer (**7**) could only be removed by silica gel chromatography or high vacuum distillation (Eq 1) making this approach undesirable for multi-kilo scale synthesis.[6] To solve the above limitations, we evaluated a number of reported literature procedures for the synthesis of similar compounds.



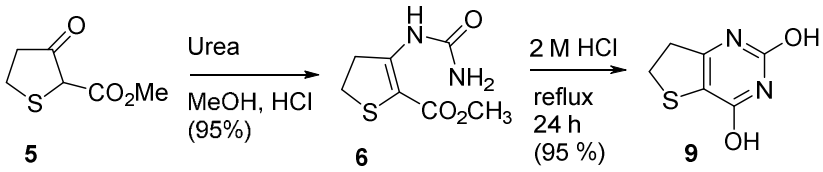
(1)

The selective synthesis of compounds like **5** from half-thiol diesters by controlled Dieckmann type condensations under basic conditions (NaH, NaOMe, etc.) had been reported[7] as well as from α-diazoketones via rhodium catalyzed insertion.[8] These results suffered the drawbacks of releasing an equivalent of ethanethiol[7] or utilizing undesirable diazo compounds,[8] both of which are potential issues for large scale synthesis. However, as we also observed, the use of ordinary diesters like **4** for the base promoted Dieckmann condensation is reported to occur without selectivity to afford a mixture of difficult to separate regioisomers.[6,9] Similarly, the $TiCl_4$-mediated[10] regioselective formation of **5** from **4** in the presence of Et_3N gave numerous impurities arising from chlorination and dehydrohalogenation as reported by Deshmukh and coworkers. In addition, the workup procedure resulted in the formation of vast quantities of solids that had to be laboriously removed. Hence, given the limitations of the $TiCl_4$ procedure, alternative Lewis acids ($TiCl_3(O^iPr)$, $TiCl_2(O^iPr)_2$, $TiCl(O^iPr)_3$, $Ti(O^iPr_4)$, etc.), amine bases and work-up conditions were evaluated resulting in a robust and practical procedure that utilized $TiCl_3(O^iPr)$ and triethylamine to give **5** as a single regioisomer from **4** in 96% yield.



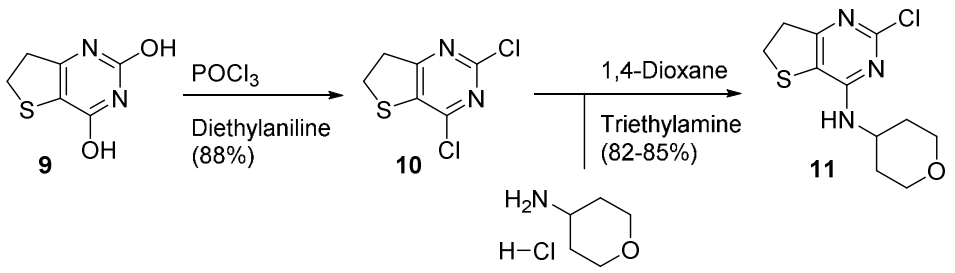
Scheme 2. Early synthesis of pyrimidine-2,4-diol **9**

The synthesis of pyrimidine-2,4-diol **9** from **5** was originally carried out through 2-ethylthio-pyrimidin-4-ol **8** following the Medicinal Chemistry route shown in Scheme 2.[4a,11] One key issue with this approach was the synthesis and hydrolysis of **8**; preparation of this intermediate required two equivalents of the relatively expensive ethylisothiourea hydrobromide **13** as a raw material and the yield was a modest 60-70%. In addition, there was significant decomposition of **5** under the basic reaction conditions that resulted in the formation foul-smelling byproducts. Furthermore, the hydrolysis of **8** for the subsequent synthesis of **9** resulted in the release of ethanethiol that also caused a strong unpleasant stench which proved difficult to contain and neutralize.



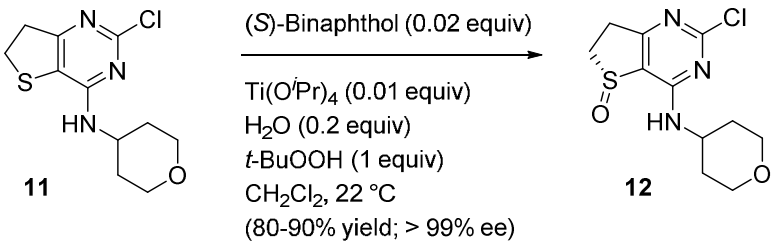
(2)

To overcome the issues stated above, a new streamlined and cost-effective process for the synthesis of **9**, in which inexpensive urea was used in place of the much more costly ethyl-isothiourea hydrobromide (**13**) was developed.[12] This new process completely eliminated the strong stench associated with both the synthesis of **8** and the liberation of ethanethiol upon its hydrolysis. In addition, the overall cost of the drug substance was significantly reduced and the new process (Eq. 2) provided a stable, easy-to-purify, solid intermediate (**6**), eliminating the complications associated with the transport or storage of crude and non-crystalline **5**.



(3)

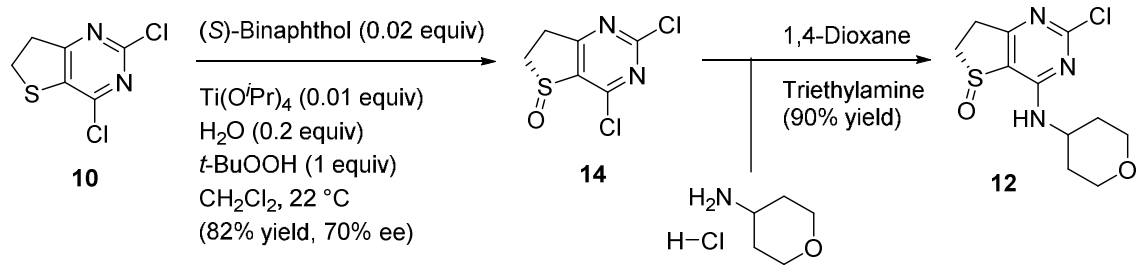
The process for the synthesis of **10** from **9** was also streamlined from the existing procedure[4a,b] by reducing the amount of $POCl_3$ from 10 to 2.0 equiv. and by increasing the reaction temperature from 85 to 105-110 °C to afford **10** in 88% yield.[13] These changes facilitated the work-up, increased the throughput and improved the inherent safety of the process both by having less reagent to quench and giving more control over a notable exotherm present during the reaction[14] The synthesis of **11** was then accomplished by carrying out an S_NAr displacement of the chlorine at C4 of **10** (Eq. 3) with 4-aminotetrahydropyran. This transformation was not completely regioselective and approximately 15% of the product resulting from displacement of the chlorine at C2 was observed. Investigation of alternative bases (diisopropylethylamine, DABCO, *N*-methylpyrrolidine, etc.) and solvents (DMSO, acetonitrile, isopropanol, water as a co-solvent, etc.) failed to improve the regioselectivity, however, the undesired regioisomer was significantly more soluble than **11** and was completely removed from the product during the isolation by filtration. As a result, **11** was obtained in approximately 82-85% isolated yield as a single regioisomer.



(4)

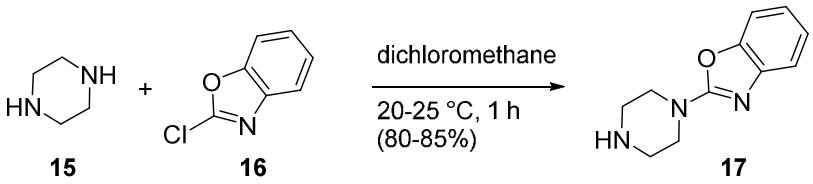
The synthesis of **12** (Eq. 4) was accomplished by a modified version of the previous Discovery procedure[4b] which in turn was based on a general procedure for the asymmetric oxidation of sulfides reported by Uemura and coworkers.[15] Key improvements over earlier protocols include an increase in concentration/throughput, a reduction of the catalyst loading, replacement of the solvent from chloroform or carbon tetrachloride to dichloromethane and streamlining of the isolation procedure. In the current protocol the product is isolated as a crystalline solid by filtration following a solvent switch from dichloromethane to isopropanol upon completion of the reaction. The above modifications resulted in a streamlined, practical and scalable procedure that provided **12** in good yield (80-90%) and excellent enantioselectivity (>99%).

In an attempt to improve the regioselectivity of the S_NAr addition, an alternative approach to **12** in which the asymmetric oxidation was carried out on **10** first, followed by the S_NAr reaction on the resulting product **14** was also investigated. Although the yield for both transformations (Eq. 5) was comparable to the previous approach to **12** (Eq. 3 and 4), and the selectivity of the S_NAr reaction improved modestly (91:8 vs. 85:15 diastereomeric ratio), intermediate **14** was obtained with a low 70% ee and this approach was abandoned**.**



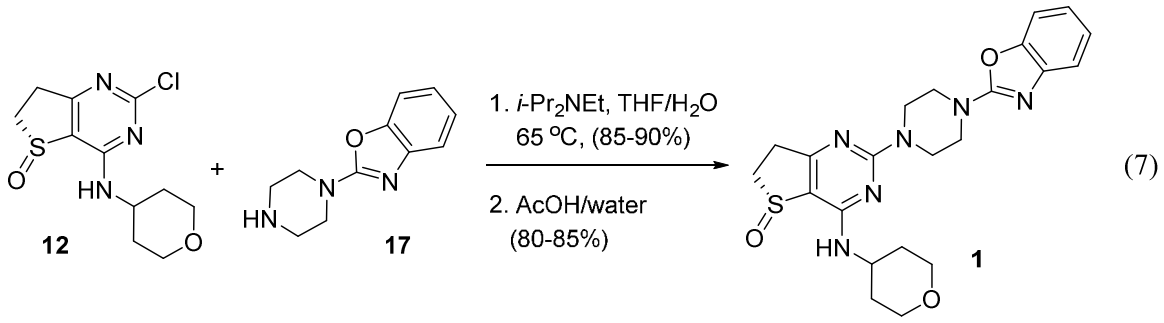
(5)

Once a robust and scalable approach to **12** was identified, we focused our attention on the synthesis of **1** via the addition of the 2-(piperazin-1-yl)benzo[d]oxazole building block (**17**) to **12**. Accordingly, the synthesis of **17** was carried out from piperazine **15** and commercially available 2-chloro-benzoxazole **16** using a modification of the procedure reported by Sato and coworkers[16] with optimized reaction conditions (Eq. 6).[17] To complete the synthesis of **1**, a suitable procedure was identified and implemented to couple **11** to **17** under basic conditions affording the desired product in 85-90% yield (Eq. 7).



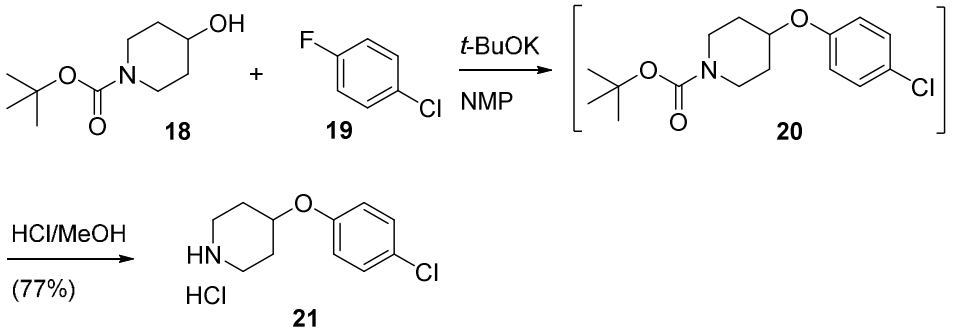
15 **16** **17** (6)

The development of a final crystallization process for **1** was carried out next. Identification of a crystallization process to obtain a proper crystal form is extremely important and oftentimes very challenging during the development phase of an API (Active Pharmaceutical Ingredient). Accordingly, extensive solvent screening studies were carried out for **1** until a solvent system consisting of acetic acid and water was found to reproducibly and exclusively provide a suitable and stable polymorph. The acetic acid/water crystallization process was then successfully implemented on multi-kilogram scale to provide the desired polymorph of **1** in 80-85% yield.

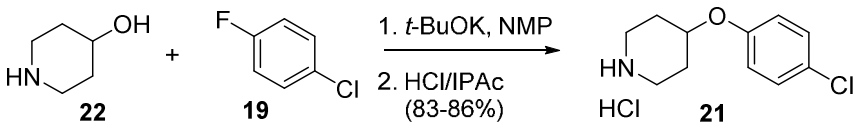


(7)

As in the case of **1**, once a process for the synthesis of **12** became available we turned our attention to the synthesis of the 4-(4-chlorophenoxy)piperidine moiety (**21**) to complete the synthesis of **2**. Initially, **21** was prepared in a two-step modified literature procedure consisting of an S_NAr coupling of **18** and **19** followed by BOC-deprotection[18] to give **21** in 75-77% yield (Eq. 8). Later, a more streamlined atom-economic and inexpensive O-selective S_NAr procedure was developed (Eq. 9) with unprotected piperidin-4-ol (**22**) that gave **21** in 83-86% yield.

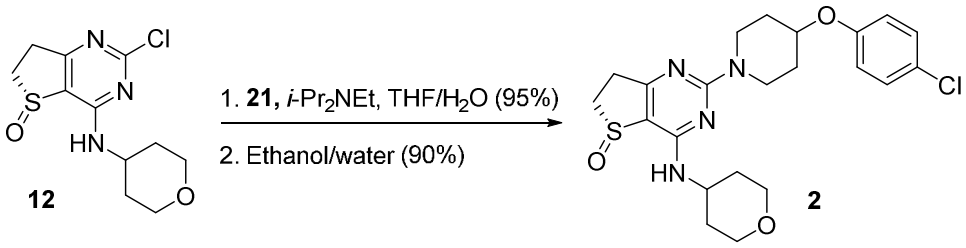


(8)



(9)

The synthesis of **2** was then completed by the S_NAr coupling of **12** and **21** under mild basic conditions followed by crystallization of the crude API from ethanol/water to give the product in 83-86% yield (Eq. 10).



(10)

In conclusion, a practical, safe and efficient process for the synthesis of PDE4 inhibitors **1** and **2** was developed and demonstrated on a multikilogram scale that allowed for the efficient preparation of the desired APIs to support clinical development activities. Key aspects of the process are the regioselective synthesis of dihydrothieno[3,2-*d*]pyrimidine-2,4-diol **9** and the asymmetric sulfur oxidation of intermediate **11**. In addition, the unanticipated efficient synthesis of **21** from unprotected **22** resulted in a more streamlined and cost effective process for **2**.

Experimental section:

Unless otherwise specified, all reactions were carried out in oven-dried glassware under an atmosphere of nitrogen. NMR spectra were recorded on a 400 MHz NMR spectrometer. Chemical Shifts are reported in ppm relative to tetramethylsilane; coupling constants (*J*) are reported in hertz, referred to as apparent peak multiplicities, and may not necessarily reflect true coupling constants. High resolution mass spectral data was acquired using a LC/MSD TOF (time-of-flight) mass spectrometer in an electrospray positive ionization mode via flow injection. The commercially available starting materials were used as received without further purification and all solvents were dried by standard methods prior to use.

Methyl 3-((2-methoxy-2-oxoethyl)thio)propanoate (4): Methyl thioglycolate (11.0 kg, 95% $^{w}/_{w}$, 98.4 mol) and piperidine (167 g, 1.96 mol) were charged under nitrogen into a jacketed reactor with mechanical stirring. Methyl acrylate (9.42 kg, 111 mol) was then slowly charged over 30 min keeping the internal temperature at approximately 45 °C. The resulting mixture was stirred at 45 °C for 1 h, piperidine (674 g, 7.92 mol) was charged and the mixture was then stirred for an additional 30 min. The mixture was cooled to 15 °C and MTBE (9.4 L) followed by 5% aqueous HCl (9.43 kg, 12.9 mol) were charged keeping the internal temperature at approximately 15 °C. The organic layer (bottom layer) was collected, washed with water (9.4 kg) and filtered. The organic portion was charged back into the reactor and concentrated by distillation at 55 °C to the minimum stirrable volume. Dichloromethane (9.4 L) was then charged and the resulting mixture was again concentrated to the minimum stirrable volume by distillation at 40-45 °C to give 27.2 kg of a 70% solution of **5** in

dichloromethane (18.9 kg, 99.8% yield) that was used in the subsequent step without additional purification. The spectral data of **4** is consistent with literature values.[5,9]

Methyl 3-oxotetrahydrothiophene-2-carboxylate (5): Dichloromethane (51.0 L) followed by $TiCl_4$ (10.84 kg, 57.15 mol) were charged under nitrogen into a jacketed reactor equipped with temperature probe, mechanical stirrer and dropping funnel. The solution was cooled to -10 °C and isopropanol (3.36 kg, 55.9 mol) was charged. The mixture was stirred for 30 min and dimethyl 3-thiaadipate **4** (13.63 kg of a 70.0% solution in dichloromethane, 49.6 mol) was charged over 1 hour keeping the internal temperature at or below -10 °C. The resulting mixture was stirred for 30 min and triethylamine (17.42 kg, 172.2 mol) was charged over 1.5 h. The resulting mixture was stirred at or below -10 °C for 1.5 and 3N HCl (48.1 kg, 144.3 mol) was slowly charged starting at -10 ºC and keeping the internal temperature below 10 °C. The batch was then stirred vigorously at 30 °C for a minimum of 1 hour. The mixture was allowed to settle, the organic portion was collected and the aqueous layer was extracted with dichloromethane twice (24 L per extraction). The combined organic layer was washed with water twice (24 L per wash) and concentrated under reduced pressure by distillation to give 7.45 kg (95.8 % weight by assay; 44.6 mol) of **5** in 89.8% yield. The spectral data of **5** is consistent with literature values.[6,9]

3-Ureido-4,5-dihydro-thiophene-2-carboxylic acid methyl ester (6): Urea (2.09 kg, 34.8 mol) was charged into a dry, jacketed reactor equipped with a stirrer, N_2 line and thermocouple thermometer. 3-oxo-tetrahydro-thiophene-2-carboxylic acid methyl ester **5** (3.0 kg) was charged followed by methanol (4.5 L). Conc. HCl (290 mL, 3.48 mol) was charged at 20-25 °C and the mixture stirred at reflux for

4-6 hours. The reaction mixture was cooled to 0 °C and the resulting solid was collected by filtration. The cake was washed with water twice (2 L water per wash) and dried in a vacuum oven at 50 °C to afford compound **6** as a white solid in 95% yield, ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.10 (dd, 2 H, J = 8.5, 8.5 Hz), 3.50 (dd, 2 H, J = 8.5, 8.5 Hz), 3.73 (s, 3 H), 6.50-7.20 (bs, 2 H), 9.47 (s, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 28.7, 37.8, 52.4, 100.0, 151.6, 154.7, 165.7; LCMS (EI) for $C_7H_{11}N_2O_3S$, (M+H)+ calcd. 203.0, measd. 203.0.

6,7-Dihydro-thieno[3,2-*d*]pyrimidine-2,4-diol (9): 3-Ureido-4,5-dihydro-thiophene-2-carboxylic acid methyl ester **(6)** (2.0 kg, 9.47 mol) was added to a solution of water (6.0 L) and NaOH (379 g, 9.47 mol) at ambient temperature. The above mixture was stirred at 85 ºC for 3 hours. After cooling to 0 °C, conc. HCl (861 mL, 10.4 mol) was added slowly until the pH of the solution was 0-1. The mixture was cooled to 0 ºC, stirred for 5-10 min and the resulting solid was collected by filtration. The cake was washed thoroughly with water twice (1 L per rinse), air-dried for 2-3 hours (suction) and then dried further in a vacuum oven at 50 °C for 12-16 hours to afford 1.67 kg (92.0% $^{w}/_{w}$, 95.0% yield) of compound **9** as a white solid. ^{1}H NMR (500 MHz, (DMSO-d_6) δ 3.11 (dd, 2 H, J = 8.5, 8.5 Hz), 3.31 (dd, 2 H, J = 8.5, 8.5 Hz), 11.14 (s, 1 H), 11.38 (s, 1 H); ^{13}C NMR (125 MHz, (DMSO-d_6) δ 29.3, 35.4, 108.5, 150.5, 152.4, 160.4; LCMS (EI) for $C_6H_7N_2O_2S$, $(M+H)^+$ calcd. 171.0, measd. 171.0.

2,4-dichloro-thieno[3,2-d]pyrimidine (10): Solid 6,7-dihydro-thieno[3,2-*d*]pyrimidine-2,4-diol (**9**) (800 g, 4.66 mol) was charged into to an inert and dry jacketed reactor (reactor 1) equipped with a temperature probe, mechanical stirrer and a dropping funnel. 1.5 L (9.31 mol) of diethylaniline were

charged over 30 min to 1 h keeping the temperature at or below 25 °C. The internal temperature was brought up to 105-110 °C and 0.68 equiv. (868 ml, 34% of the total) of phosphorus oxychloride was added into the reactor (reactor 1) over 5-10 min. When the inside temperature began to decrease, the internal temperature was maintained at 110 °C and addition of the remaining $POCl_3$ (1.32 equiv. or 66% of the total) was resumed over a period of 30-40 min. The internal temperature was adjusted to 105-110 °C and the mixture was stirred for 18-24 h or until complete (HPLC analysis). The mixture was cooled to 45 °C and THF (400 mL) was charged at 45 °C. The above crude mixture was placed into a secondary dry reactor (reactor 2). 4.8 L of water were charged into reactor 1 and cooled to 5 °C. The crude reaction mixture (in reactor 2) was then slowly charged into reactor 1 containing water keeping the temperature at 5-10 °C. The mixture was stirred at 5 °C for 30 min to 1 h and the resulting solid was collected by filtration. The cake was rinsed with water twice (1.6 L per rinse) and the cake was air dried in the funnel for 6-8 h to afford 964 g (92% $^{w}/_{w}$; 88% yield) of crude Compound **10**. Dichloromethane (4.6 L) was charged into a 10 L reactor. Crude Compound **10** and activated carbon (46.2 g) were charged into the reactor and the mixture was heated to 40 °C for 20 min. The resulting solution was collected by filtration through a filter media to remove charcoal. The cake was rinsed with dichloromethane twice (175 ml per rinse). The solution was concentrated under reduced pressure to a minimum stirrable volume and the remaining dichloromethane was chased by distillation with a minimum amount of petroleum ether. Additional petroleum ether (1.3 L) was charged into the reactor and the mixture was cooled to 10 °C then stirred for 1 h. The resulting solid was collected by filtration and the cake was rinsed with petroleum ether twice (150 ml per rinse). The cake was air dried in the funnel (suction) until it appeared dry. The resulting solid Compound **10** was transferred to a suitable tared container and dried in an oven at 50 °C for 6 h to get the final product: ^{1}H NMR (400 MHz,

DMSO-d_6) δ 3.45-3.56 (m, 4H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 29.3, 36.5, 134.8, 151.0, 154.1, 175.9.

2-chloro-*N*-(tetrahydro-2H-pyran-4-yl)-6,7-dihydrothieno[3,2-d]pyrimidin-4-amine (11): 2,4-Dichloro-thieno[3,2-d]pyrimidine (**10**) (2.62 kg, 12.4 mol), 4-aminotetrahydropyran hydrochloride (1.87 kg, 13.6 mol)**,** acetonitrile (13.1 L) and triethylamine (3.76 L, 37.2 mol) were sequentially charged at ambient temperature into an inert and dry reactor equipped with a temperature probe, mechanical stirrer, reflux condenser and dropping funnel. The resulting mixture was heated to 70 °C (reflux) for approximately 20 h. Water (13.1 L) was charged, the mixture was cooled to 5 °C and then stirred for approximately 1 h. The resulting solid was collected by filtration and the cake was rinsed twice with a 1:1 solution of acetonitrile/water (2.6 L per rinse) followed by a rinse with acetonitrile (1.3 L). The cake was dried under vacuum in the filter funnel for approximately 2 h and then dried further in a vacuum oven for 6 h at 50 °C to afford 2.89 kg of product (96.6% $^{w}/_{w}$, 82.9% yield) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (dq, J = 4.8, 11.6 Hz, 2H), 2.02 (br d, J = 11.6 Hz), 3.26 (t, J = 8.4 Hz, 2H), 3.42 (t, J = 8.4 Hz, 2H), 3.55 (br t, 11.6 Hz), 4.00 (br d, J = 11.6 Hz, 2H), 4.26 (br, 1H), 4.38 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.7, 33.2, 36.7, 47.2, 66.7, 114.0, 156.6, 156.9, 167.9.

(*R*)-2-chloro-4-((tetrahydro-2*H*-pyran-4-yl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (12): (*S*)-(-)-Binaphthol (28.7 g, 98.2 mmol), followed by **11** (2.76 kg, 9.82 mol) were charged to clean, inert and dry reactor equipped with temperature probe, mechanical stirrer and a dropping funnel

at ambient temperature (20-25 °C). Next, dichloromethane (15.5 L), titanium (IV) isopropoxide (14.4 g, 49.12 mmol) and purified water (17.69 g, 982.4 mmol) were sequentially charged at ambient temperature (20-25 °C) and the mixture was then stirred at 20-25 °C for 1 h. The jacket temperature was then adjusted to 10 °C and *tert*-butyl hydroperoxide solution (70 % aqueous, 1.39 kg, 1.1 equiv.) was charged slowly while the jacket temperature was adjusted to control the exotherm so as not to exceed 40 °C or reflux too vigorously. The mixture was then stirred for 2 h while allowing it to cool to ambient temperature (approx. 20 °C). Heptane (10.2 L) was charged at or below 25 °C and the mixture was stirred for 1 h at 20-25 °C. The resulting solid was collected by filtration and cake was rinsed twice with isopropyl acetate (5.1 L per rinse). The cake was then air-dried under vacuum (suction) in the filter funnel for at least 16 h. A 5 % $^{w}/_{w}$ sodium sulfite solution (248 g, 1.96 mmol) was charged to the filtrate and stirred for a minimum of 1 h at approximately 20 °C and stirred until the peroxide test was negative. The material in the filter was then dried in a vacuum oven for a minimum of 12 h at 20°C to give 2.83 kg (89.8 % $^{w}/_{w}$, 90 % yield) of product as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (dq, J = 4.8, 11.6 Hz, 1H), 1.63 (dq, J = 4.8, 11.6 Hz, 1H), 1.79 (br d, J = 11.6 Hz, 1H), 1.92 (obs m, 1H), 3.21 (m, 2H), 3.51 (m, 2H), 3.96 (br t, J = 11.6 Hz, 2H), 4.32 (m, 1H), 6.4 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.1, 32.4, 33.0, 47.6, 50.0, 66.7, 116.7, 159.2, 164.1, 173.9.

2-(Piperazin-1-yl)benzo[*d*]oxazole (17): Piperazine (561 g, 6.45 mol) and dichloromethane (5.0 L) were charged into an inert and dry jacketed reactor equipped with a temperature probe and mechanical stirrer. 2-Chlorobenzoxazole (500 g, 3.22 mol) was then charged over a period of 1 h keeping the internal temperature at or below 25 °C. The mixture was stirred for 16 h at ambient temperature and

the resulting sold (piperazine hydrochloride) was removed by filtration. The filter cake was rinsed with dichloromethane twice (0.5 L per rinse) and the filtrate was charged back into the reactor. The solution in the reactor was cooled to 0 °C and water (3.0 L) followed by conc. HCl (0.3 L, 3.60 mol) was slowly added keeping the temperature at or below 30 °C. The resulting aqueous mixture was washed with dichloromethane twice (1.9 L per rinse) and cooled once again to 0-10 °C. 50% NaOH aqueous solution (0.20 L, 7.58 mol) was charged to bring the pH of the solution to 11-12 and the resulting solution was then extracted with dichloromethane twice (1.9 L per rinse). The aqueous layer was discarded, the organic placed back in the reactor and heptane (1.9 L) was charged. The solution was concentrated by vacuum distillation to the minimum stirrable volume at 40 °C or below and then additional heptane (1.9 L) was charged. The resulting solid was collected by filtration and dried in a vacuum oven overnight at 50 °C to give 549 g (99.4% $^{w}/_{w}$, 88.3% yield) of product as a white solid. The spectral data of **17** is consistent with literature values.[16]

4-(4-Chlorophenoxy)piperidine hydrochloride (21): Potassium *t*-butoxide (1.37 kg, 95% $^{w}/_{w}$, 11.6 mol), 4-hydroxypiperidine (600 g, 5.81 mol) and *N*-methylpyrrolidinone (3.0 L) were charged into an inert and dry jacketed reactor equipped with a temperature probe, mechanical stirrer and dropping funnel keeping the internal temperature at or below 35 °C. The temperature was increased to 65 °C and the mixture as stirred for 0.5 h. 1-Chloro-4-fluorobenzene (774 g, 5.81 mol) was charged over a period of 1 h maintaining the temperature at 65-75 °C and then the mixture was stirred at 65 °C for 3 h. The mixture was cooled to ambient temperature and MTBE (6.0 L) followed by water (6.0 L) were charged. The mixture was stirred for 3-5 min and then allowed to settle. The organic layer was collected and the aqueous layer was extracted with MTBE (3.0 L). The combined organic portion was

washed with water (3.0 L) and concentrated by vacuum distillation at 38-39 °C to the minimum stirrable volume. Isopropyl acetate (6.0 L) was charged and a freshly prepared solution of HCl in isopropyl acetate (3.4 L of a 2.6 M solution) was slowly added keeping the internal temperature at 15-25 °C. The mixture was stirred at ambient temperature for 1 h and the resulting solid was collected by filtration. The cake was rinsed with isopropyl acetate twice (3.0 L per rinse), air-dried in the filter funnel for 6 h and then dried in a vacuum oven for 6 h at 50 °C to afford 1.24 kg (95.6% $^{w}/_{w}$, 83.2% yield) of product as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.86 (m, 2 H), 2.11 (m, 2H), 3.04 (m, 2H), 3.19 (m, 2H), 4.66 (m, 1H), 7.04 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 9.0 Hz, 2H), 9.31 (br, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.9, 40.3, 69.5, 117.6, 124.7, 129.4, 155.4.

(*R*)-2-(4-(benzo[d]oxazol-2-yl)piperazin-1-yl)-4-((tetrahydro-2*H*-pyran-4-yl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (1): (*R*)-2-chloro-4-((tetrahydro-2*H*-pyran-4-yl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (**12**, 750 g, 88.0% $^{w}/_{w}$, 2.29 mol), 2-(piperazin-1-yl)benzo[*d*]oxazole (**17**, 516 g, 94.8% $^{w}/_{w}$, 2.41 mol), tetrahydrofuran (6.00 L) and water (1.50 L) were sequentially charged at ambient temperature into an inert jacketed reactor equipped with a temperature probe, mechanical stirrer and dropping funnel. The mixture was stirred for 30 min, diisopropylethylamine (444 mL, 2.52 mol) was charged, the mixture was then heated to 65 °C (mild reflux) and stirred for 4 h. The temperature was brought down to 0 °C, the mixture was stirred for 2 h and the resulting solid was collected by filtration. The reactor and cake were rinsed sequentially with a 1:1 mixture of tetrahydrofuran/water (1.50 L) and tetrahydrofuran (0.75 L) and then air-dried in the filter funnel for 2 h. The resulting solid was then dried in a vacuum oven at 50 °C for 12 h to afford 1.02 kg (95.0% $^{w}/_{w}$, 93.0% yield) of crude product as a white solid. The resulting crude material was charged back into a reactor followed by a premixed 1 : 0.05 solution of acetic acid (2.40 L) and water

(120 mL). The mixture was heated at 35 °C and water (396 mL) was added followed by seed crystals (55.0 g). Additional water (4.50 L) was then charged at a constant rate over a period of 4 h at 35 °C and after completing the water addition the mixture was stirred for an additional 2 h. The resulting solid was collected by filtration and the cake was rinsed with water three times (4.07 L per rinse) and once with acetone (4.07 L). The resulting solid was air-dried in the funnel for 1 h and then in a drying oven at 80 °C for 12 h to afford 0.93 kg (99.7% $^{w}/_{w}$, 96.0 % yield for the crystallization) of product as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (m, 2H), 1.97 (m, 2H), 3.02-3.09 (m, 2H), 3.35-3.43 (m, 1H), 3.47-3.54 (m, 2H), 3.57-3.66 (m, 1H), 3.76 (t, *J* = 5.2Hz, 4H), 4.01 (m, 4H), 4.16-4.24 (m, 1H), 5.73 (d, *J* = 7.2 Hz, 1H), 7.05 (t, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.0, 33.1, 33.3, 43.9, 45.8, 47.7, 50.4, 67.1, 108.9, 109.2, 116.9, 121.3, 124.5, 143.3, 149.2, 159.5, 162.4, 163.5. LCMS (EI) for $C_{22}H_{27}N_6O_3S$, $(M+H)^+$ calcd. 455.19, measd. 455.32.

(*R*)-2-(4-(4-chlorophenoxy)piperidin-1-yl)-4-((tetrahydro-2*H*-pyran-4-yl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (2): Amine hydrochloride **21** (8.5 kg, 99.9% $^{w}/_{w}$, 34.3 mol), sulfoxide **12** (10.3 kg, 91.3% $^{w}/_{w}$, 32.7 mol), tetrahydrofuran (67.0 L) and water (16.9 L) were charged to a mixing tank, heated to 55 °C and passed through a pad of decolorizing charcoal (4.7 kg) into an inert jacketed reactor equipped with a temperature probe, mechanical stirrer and dropping funnel. The charcoal pad was then rinsed with a mixture of tetrahydrofuran (15 L) and water (3.8 L) and the rinse was transferred to the reactor. *N*,*N*-Diisopropylethylamine (14.2, 81.7 mol) was added keeping the internal temperature at or below 68 °C. The mixture was then stirred at 68 °C for 3 h and water (132 L) was charged over a period of 1 h keeping the internal temperature at 68 °C. The mixture was then cooled to 20-25 °C linearly over a period of 1 h and stirred for an additional 1 h at this temperature.

The resulting solid was collected by filtration and then dried in a vacuum oven at 48-50 °C for 6 h to afford 13.1 kg (99.1 $^{w}/_{w}$, 86.6 % yield) of crude product as a white solid. The crude material, followed by a premixed solution made of ethanol (194 L) and water (17.0 L) were charged into an inert jacketed reactor equipped with a temperature probe, mechanical stirrer and addition funnel. The mixture was heated to 60 °C and seed crystals (131 g) were charged. The mixture was stirred at 60 °C and then cooled linearly to 0 °C over a period of 5 h. The resulting solid was collected by filtration and the cake was then rinsed with acetone (26.0 L) and dried in a vacuum oven at 60 °C for 12 h to afford 10.6 kg (99.1% $^{w}/_{w}$, 80.1% yield from crude material). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (dq, *J* = 4.2, 11.8 Hz, 1H), 1.62 (dq, *J* = 4.2, 11.8 Hz, 1H), 1.74-1.89 (m, 3H), 1.90-2.02 (m, 3H), 2.96-3.07 (m, 2H), 3.29 (dt, *J* = 13.6, 8.4 Hz, 1H), 3.44 (ddd, *J* = 19.2, 11.2, 2.0 Hz, 2H), 3.62 (dt, *J* = 17.2, 7.8 Hz, 1H), 3.76 (m, 2H), 3.96 (dd, *J* = 15.6, 12.8 Hz, *J* = 2H), 4.09-3.99 (m, 3H), 4.51 (m, 1H), 6.21 (br d, *J* = 6.0 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.4, 32.5, 32.7, 41.0, 47.2, 49.6, 66.9, 66.9, 72.9, 107.8, 117.5, 125.9, 129.5, 155.8, 158.9, 163.0, 174.6.

SUPPORTING INFORMATION

^{1}H and ^{13}C NMR spectra of compounds **1**, **2**, **6**, **9**, **10**, **11**, **12**, **21** and ^{1}H NMR spectra for **17**.

REFERENCES

1. V. Boswell-Smith, D. Spina *Int. J. Chron. Obstruct. Pulmon. Dis.*, **2007**, *2*, 121-129

2. D. Spina, *Br. J. Pharmacol*, **2008**, *155*, 308-315

3. S. B. Christensen, A. Guider, C. J. Forster, J. G. Gleason, P. E. Bender, J. M. Karpinski, W. E. DeWolf Jr., M. S. Barnette, D. C. Underwood, D. E. Griswold, L. B. Cieslinkski, M. Burman, S. Bochnowicz, R. R. Osborn, C. D. Manning, M. Grouos, L. M. Hillegas, J. O. Bartus, M. D. Ryan, D. S. Eggleston, R. C. Haltiwanger and T. J. Torphy, *J. Med. Chem.* **1998**, *41*, 821-835

4. a) P. Pouzet, C. Hoenke, D. Martyres, P. Nickolaus, B. Jung and H. Hamman, Patent number WO 2006111549 A1, **2006**. b) P. Pouzet, C. Hoenke, P. Nickolaus, R. Goeggel, T. Fox, D. Fiegen, K. Klinder, Patent number WO 2009053268 A1, **2009**. c) P. Pouzet, R. Anderskewitz, H. Dollinger, D. Fiegen, T. Fox, R. Goeggel, C. Hoenke, D. Martyres, P. Nickolaus, K. Klinder, Patent number WO 2009050242 AS.

5. J. Sicar, S. K. C. Kumar, T. H. James, W. Ying, WO 2006/102191 A1, **2006**

6. H.-J. Liu, K. N. Teng, *Can. J. Chem.* **1982**, *60*, 437

7. Y. Yamada, I. Toshihide, M. Kimura, K. Hosaka, *Tetrahedron Lett.* **1981**, *22*, 1353

8. M. P. Moyer, P. L. Feldman, H. Rapoport, *J. Org. Chem.* **1985**, *50*, 5223.

9. P. Dowd, S.-C. Choi, *Tetrahedron*, **1991**, *47*, 4847

10. M. N. Deshmukh, K. K. Gangakhedar, U. S. Kumar, *Synth. Commun.,* **1996***, 26*, 1657.

11. G. Ohnacker, E. Woitun, Patent number US 3,318,881, **1967**

12. R. Frutos, T. Tampone, J. A. Mulder, D. Krishnamurthy, C. H. Senanayake, Patent number WO 2009/140127 A2, **2009**

13. P. Pouzet, P. Nickolaus, U. Werthmann, R. Frutos, B.-S. Yang, S. Kim, J. A. Mulder, N. Patel, C. H. Senanayake, T. G. Tampone, X. Wei, Patent number W0 2013026797 A1, **2013**

14. At 85 °C unreacted $POCl_3$ accumulated in the mixture shortly after its addition and then reacted vigorously with a sharp increase in the reaction temperature. At a higher temperature $POCl_3$ reacted as it was being added and the reaction could be carried under a controlled fashion.

15. N. Komatsu, M. Hashizume, T. Sugita, S. Uemura, *J. Org. Chem.* **1993**, *58*, 4529

16. Y. Sato, M Yamada, S. Yoshida, T. Soneda, M. Ishikawa, T. Nizato, K. Suzuki and F. Konno, *J. Med. Chem.* **1998**, *41*, 3015

17. A brief screening of common solvents and amine bases was carried out

18. I. Borza, J. Nagy, S. Kolok, C. Horbath, S. Farkas, Patent number WO 2006/10967 A1, **2006**.