Development of a Scaleable Synthesis of NDT 9533750, a Key Intermediate to a Series of Novel Subtype Preferring GABA_A Partial Agonists

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Abstract:

A scaleable route to 6-chloro-4-[2-(3-fluoropyridin-2-yl)-imidazol-1-ylmethyl]-5-propyl-pyrimidine (NDT 9533750), a key intermediate to a series of novel subtype preferring GABA_A partial agonists, is described in which various scaleup issues were addressed to provide an efficient and robust route for the preparation of kilogram quantities of the compound.

Introduction

GABA (γ-aminobutyric acid) is the major inhibitory neurotransmitter in the mammalian central nervous system, binding to three different receptor types, GABA_A, GABA_B, and GABA_C. In addition to binding GABA, each receptor possesses a number of allosteric sites that bind a variety of ligands, leading to a modulation of the action of GABA. The Bz (benzodiazepine) binding site is found in GABA_A receptors containing β and $\gamma 2$ subunits in conjuction with an $\alpha 1$, $\alpha 2$, $\alpha 3$, or $\alpha 5$ (but not $\alpha 4$ or $\alpha 6$) subunit. Bz site full agonists which nonselectively interact at $\alpha 1$-, $\alpha 2$-, $\alpha 3$-, and $\alpha 5$-containing subtypes enhance the inhibitory effects of GABA and display sedative hypnotic, anaesthetic, muscle-relaxant, anticonvulsant, and anxiolytic activities, but they are also associated with side effects such as amnesia, tolerance, dependence, and alcohol potentiation.[1,2]

In an effort to discover and develop novel subtype preferring GABA_A partial agonists for the treatment of sleep disorders with less side effects, an efficient large-scale synthesis of a key intermediate 6-chloro-4-[2-(3-fluoropyridin-2-yl)-imidazol-1-ylmethyl]-5-propyl-pyrimidine (NDT 9533750) (Scheme 1) was required.[3] NDT 9533750 was constructed from the two key intermediates 5-propyl-6-halomethyl-4-chloropyrimidine (**1**) and 3-fluoro-2-(1*H*-imidazol-2-yl)-pyridine (**2**). The preparation of these two key intermediates and their coupling posed several synthetic challenges for a large-scale synthesis. This paper describes how these challenges were overcome to provide a robust and efficient large-scale synthesis of NDT 9533750.

Scheme 1
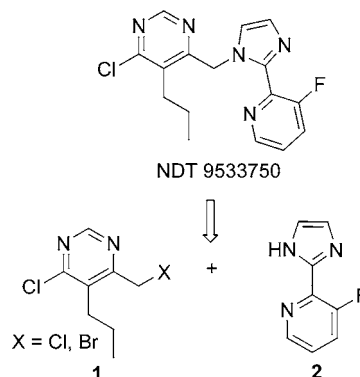
Scheme 2
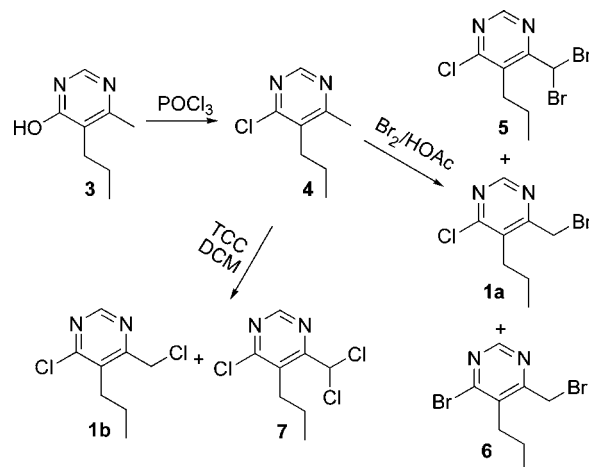
Results and Discussion

Preparation of 5-Propyl-6-halomethyl-4-chloropyrimidine (1). The initial small scale synthesis of NDT 9533750 involved 5-propyl-6-bromomethyl-4-chloropyrimidine (**1a**) (Scheme 2) which was prepared from 5-propyl-6-methyl-4-hydroxypyrimidine (**3**) in *ca.* 40% yield by chlorination and subsequent regioselective bromination of the intermediate 5-propyl-6-methyl-4-chloropyrimidine (**4**) with 1 equiv of bromine in HOAc at 85 °C. While conversion of 4-hydroxy-pyrimidine **3** to 4-chloropyrimidine **4** with POCl₃ was a straightforward procedure, reaction of **4** with bromine in HOAc was not amenable to scaleup. Careful chromatographic purification was required to separate **1a** from three major impurities: dibromomethylpyrimidine **5** (~10%), chloride to bromide exchanged byproduct **6** (~40%), and starting material **4** (~10%). Attempts to drive the reaction to

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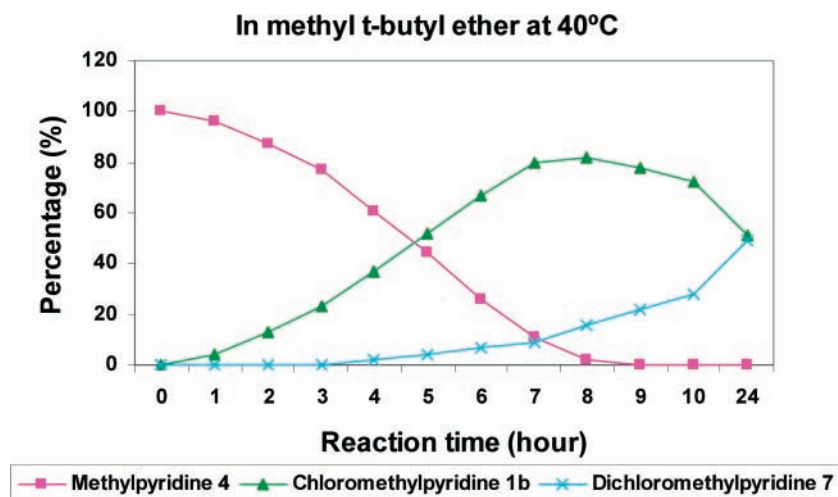
Figure 1. Composition of the reaction mixture of methylpyrimidine **4** with TCC (1.5 mol equiv) in MTBE at 40 °C as a function of time based on LC−MS.

completion by using an excess amount of bromine or higher temperatures led to the predominant formation of dibromomethylpyrimidine **5**.

To avoid the halogen−halogen exchange side reaction, optimization work was focused on the preparation of the corresponding chloride, 5-propyl-6-chloromethyl-4-chloropyrimidine (**1b**). The inexpensive chlorinating agent trichloroisocyanuric acid (TCC), a component of some industrial deoderants and household cleaning products under the trade name Chloreal,[4] was reported to chlorinate *N*-heterocyclic compounds such as 2-methylpyridine, 2-methylquinoline, and 2-methylquinoxaline to the corresponding chloromethyl derivatives in good yields.[5] In our system, initial exploration indicated that TCC was clearly superior to other chlorination reagents such as Cl$_2$, 1,3-dichloro-5,5-dimethylhydantoin, and NCS in terms of reactivity and selectivity. Thus, TCC was chosen as the chlorination reagent for further investigation.

We found that 1.5 mol equiv of TCC (4.5 equiv of chlorine) were required for good conversion of methylpyrimidine **4** to chloromethylpyrimidine **1b**. It seemed that only the first chlorine of TCC was consumed and the resulting dichloroisocyanuric acid was not as reactive as TCC. At the early stages of the reaction only chloromethylpyrimidine **1b** was formed. However, overchlorination to dichloromethylpyrimidine **7** started before methylpyrimidine **4** was completely consumed as indicated by the initial evaluation in methyl *tert*-butyl ether (MTBE) at 40 °C (Figure 1). Thus, efforts were focused on finding optimal reaction conditions to enhance the yield and purity of **1b**.

An array of parallel reactions between methylpyrimidine **4** and TCC (with a molar ratio of 1 to 1.5) was undertaken to evaluate various solvents, temperatures, and reaction times. Reactions were monitored by HPLC (Table 1). The best results were observed with dichloromethane (DCM) as the solvent (Table 1, entries 8−10) providing the highest ratio of monochloride **1b**/dichloride **7** (∼ 96:2) and highest yield

Table 1. Solvent, temperature, and time screening reactions of methylpyrimidine **4** with TCC

entry	solvent	temperature	time	**1b**	**7**	**4**
1	heptane	60 °C	10 h	30%	0%	70%
2	heptane	80 °C	18 h	90%	7%	3%
3	heptane	reflux	5 h	90%	10%	0%
4	*t*-BuOMe	40 °C	8 h	82%	16%	2%
5	*t*-BuOMe	60 °C	5 h	70%	30%	0%
6	AcOH	60 °C	5 h	60%	40%	0%
7	toluene	60 °C	10 h	88%	10%	0%
8	CHCl$_3$	60 °C	10 h	90%	10%	0%
9	DCM	rt	6 d	96%	2%	2%
10	DCM	30 °C	24 h	96%	2%	2%
11	DCM	reflux	15 h	96%	2%	2%

(∼ 96%). The reaction time course of methylpyrimidine **4** with TCC in DCM at 30 °C was illustrated in Figure 2.

Our kiloscale reaction was carried out in DCM at 30 °C for 24 h. The reaction was stopped by cooling to 5 °C and subsequent filtration to remove excess TCC and the resultant dichloroisocyanuric acid.[6] The filtrate was washed with aqueous sodium bisulfite solution to remove residual chlorinating agents. Chloromethylpyrimidine **1b** was obtained upon removal of solvent in high yield (>96%) and purity (96−98%).

Preparation of 3-Fluoro-2-(1*H*-imidazol-2-yl)-pyridine (2). The original discovery research preparation of **2** (Scheme 3) involved regioselective C-2 lithiation[7] and formylation of 3-fluoropyridine **8** to generate pyridyl-2-carboxaldehyde **9**, which was condensed with glyoxal and ammonium hydroxide to afford **2** in *ca.* 28% overall yield. The need for low temperatures (−76 °C to −50 °C) and column chromatography to purify the aldehyde **9** in the first step presented challenges for large-scale operations. A more robust and practical method to 3-fluoro-2-(1*H*-imidazol-2-yl)-pyridine (**2**) was needed.

Since we could access bulk quantities of 3-fluoropyridine-2-carbonitrile (**10**) from commercial sources, we turned our

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(5) Jeromin, G. E.; Orth, W.; Rapp, B.; Weiss, W. *Chem. Ber.* **1987**, *120*, 649−651.

(6) TCC dust is extremely destructive to eyes, skin, and lungs. Operations should be carried out in a fume hood. Filtered residual chlorinating agent was destroyed with aq. bisulphate solution.
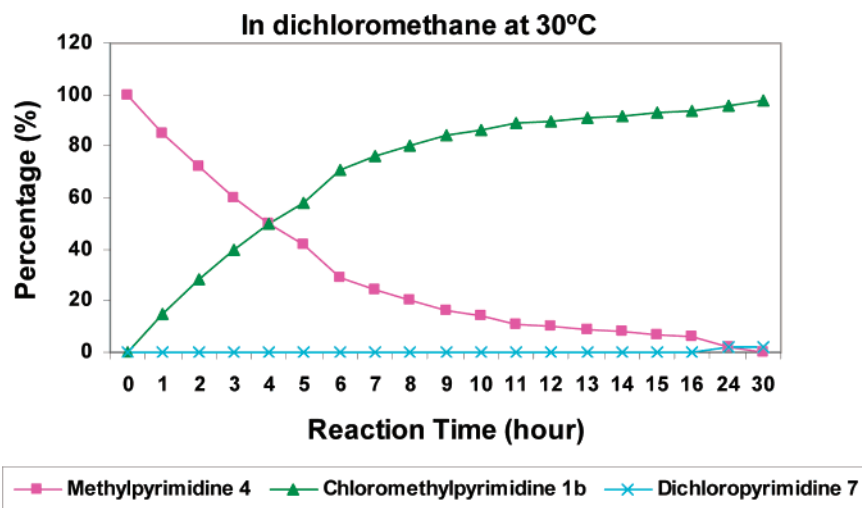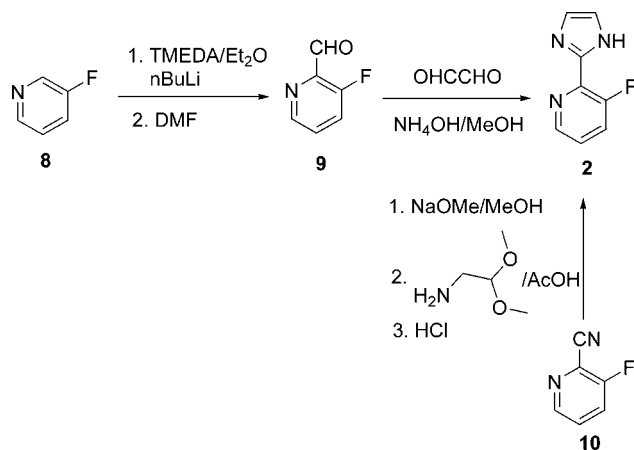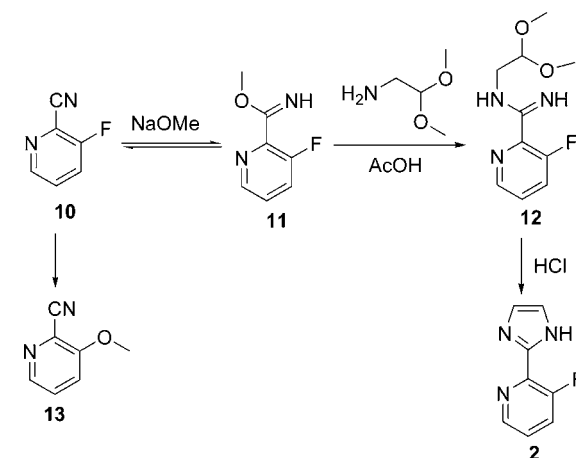(7) Marsaia, F.; Gueguiner, G. *Tetrahedron* **1983**, *39*, 2009.

Figure 2. Composition of the reaction mixture of methylpyrimidine 4 with TCC (1.5 mol equiv) in DCM at 30 °C as a function of time based on LC−MS.

Scheme 3

Scheme 4

attention to the classic imidazole formation method reported by Lawson[8] from imidates and α-amino acetals. It is worth noting that conversion of nitriles directly to imidines with a promoting agent such as AlCl₃,[9] ZnCl₂,[9] aluminium amides,[10] lanthanide(III) triflates,[11] or Cu(I)[12] has been reported in the literature. More recently, Frutos et al. have reported an expedient imidazole synthesis by the direct CuCl-mediated reaction of nitriles with α-amino acetals followed by cyclization, avoiding the formation of imidates.[13] However, attempts to utilize these methods in our system were fruitless: nucleophlic displacement of fluorine competed significantly with the nucleophilic addition to the nitrile when **10** was treated with 2,2-dimethoxyethylamine under these conditions.

Nitriles were reported to be converted to imidates by either gaseous HCl in alcoholic solvents[8] or alcoholic alkoxide.[14]

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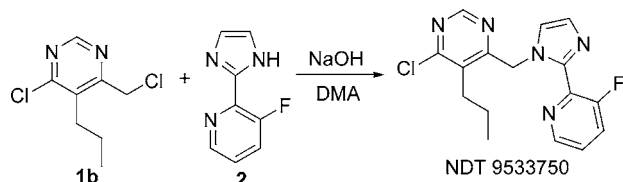(14) Clews, J.; Morgan, N. G.; Ramsden, C. A. *Synthesis* **2001**, *10*, 1546.

Our attempts to convert 3-fluoropyridine-2-carbonitrile (**10**) to the corresponding imidate with gaseous HCl in methanol failed due to lack of reactivity, possibly as a result of the basicity of the pyridine nucleus.

The most commonly used alkoxide in the literature for imidate formation is sodium methoxide. Treatment of **10** with 1 equiv of methanolic sodium methoxide at ambient temperature followed by refluxing with 2,2-dimethoxyethylamine and acetic acid gave imidine **12**, which, upon acidification with 5 M HCl and heating, was converted to imidazole **2** (Scheme 4). This three-step one-pot procedure afforded 3-fluoro-2-(1*H*-imidazol-2-yl)-pyridine (**2**) in 40% overall yield along with *ca.* 30% of 3-methoxypyridine-2-carbonitrile (**13**) as byproduct, formed by methoxide displacement of fluorine.

In order to minimize the formation of **13** and improve the yield of imidazole **2**, various metallic methoxides (sodium methoxide, lithium methoxide, and magnesium methoxide) and different reaction temperatures were evaluated. Two optimal conditions were obtained: magnesium methoxide at ambient temperature and sodium methoxide at −20 °C. Both conditions provided the highest ratio of imidazole **2** to 3-methoxypyridine-2-carbonitrile (**13**) (70:15). Due to a supply issue with obtaining a large quantity of magnesium

Scheme 5

methoxide at the time, the kilogram scale reaction was conducted with sodium methoxide.

3-Fluoropyridine-2-carbonitrile (**10**) was dissolved in methanol and treated with 1 equiv of sodium methoxide at −20 °C, resulting in the formation of imidate **11** and 3-methoxypyridine-2-carbonitrile (**13**) (Scheme 4). Fortunately, only the fluorine of the nitrile **10** was prone to replacement, but not the fluorine of the imidate **11**. Furthermore, **13** did not react further with methoxide to form its corresponding imidate under the reaction conditions. After 4 h at −20 °C equilibrium was reached consisting of a mixture of imidate **11** (70%), methoxypyridine **13** (15%), and starting material **10** (15%). Thus, it was important to wait a full 4 h before adding 2,2-dimethoxyethylamine and acetic acid. Upon heating this mixture at 60 °C for 30 min the intermediate imidine **12** was formed.

Imidazole ring closure was realized by acidification with 5 M HCl followed by heating. Besides reducing the overall yield of product, formation of **13** created a secondary problem, by liberating fluoride. When HCl was added, corrosive HF formed and severely etched the glass reaction vessel. This problem was resolved by adding CaCl$_2$ (10 mol % based on **10**), a commonly used reagent for fluoride removal,[15,16] to sequester free fluoride before acidification with HCl.

After the cyclization was complete, methanol was removed by distillation. After cooling, 30% NaOH was added until pH > 12 was achieved. Adjusting the pH to greater than 12 was critical to dissolving all the inorganics, especially CaF$_2$. This step allowed a clean phase separation in the subsequent organic solvent extraction. The product 3-fluoro-2-(1H-imidazol-2-yl)-pyridine (**2**) is not very soluble in many organic solvents and has significant aqueous solubility. Consequently, many solvents were screened, and it was found that n-butanol extraction gave very good separation from aqueous solution and afforded the best recovery. A single recrystallization of the crude **2** from acetonitrile gave the product as a yellow solid in 52% yield over the three-step, one-pot reaction, with >99% purity.

Preparation of 6-Chloro-4-[2-(3-fluoropyridin-2-yl)-imidazol-1-ylmethyl]-5-propyl-pyrimidine (NDT 9533750). Final Coupling Reaction. The final nucleophilic displacement reaction between 3-fluoro-2-(1H-imidazol-2-yl)-pyridine (**2**) and chloromethylpyrimidine **1b** (Scheme 5) was carried out in N,N-dimethylacetamide (DMA). Sodium hydroxide was chosen as the base due to the much shorter reaction time required for complete conversion compared to potassium carbonate (30 min vs 24 h) although both bases provided similar yields. It was observed that **1b** was sensitive

to aqueous basic conditions and decomposed slowly itself. Thus, a set of experiments were carried out to determine the optimal ratio of chloromethylpyrimidine **1b** to imidazole **2**. The best yield was obtained when 1.2 equiv of **1b** were used. Water was added to precipitate the product, which was isolated in quantitative yield. Crude NDT 9533750 was recrystallized from i-PrOAc and TBME and isolated as a white solid in 86% yield (>99% purity).

Conclusions

This paper describes the preparation of 6-chloro-4-[2-(3-fluoropyridin-2-yl)-imidazol-1-ylmethyl]-5-propyl-pyrimidine (NDT 9533750), a key intermediate to a series of novel subtype preferring GABA$_A$ partial agonists, in a robust and efficient manner suitable for kilogram scale. The original medicinal chemistry synthesis was modified to eliminate column chromatography and low-temperature reactions. Productivity and yields were greatly improved. This, together with the optimization of reaction conditions allowed NDT 9533750 to be prepared in an overall yield of ca. 75% from hydroxypyrimidine **3**.

Experimental Section

All reagents and solvents were commercially available. ^{1}H and ^{13}C NMR spectra were recorded with a Varian-300 (300 MHz) spectrometer using tetramethylsilane as an internal standard. LC−MS analysis was performed using a Micromass Time-of Flight LCT, equipped with a Waters 600 pump, Waters 996 photodiode array detector, Gilson 215 autosampler, and Gilson 841 microinjector. Elemental analyses were carried out by Robertson Microlit Laboratories, Inc.

5-Propyl-4-chloro-6-methyl-pyrimidine (4). 5-Propyl-6-methyl-4-hydroxypyrimidine[17] (**3**, 1000 g, 5.58 mol) and toluene (5.5 L) were charged to a nitrogen-purged reactor and heated to 100 °C with mechanical stirring. POCl$_3$ (899 g, 5.86 mol) was added at an internal temperature of 100 °C within 30 min. The reaction mixture was stirred at 100 °C for 4 h. The solution was cooled to 10 °C. Water (1.5 L) was added to the solution over a period of 30 min. The mixture was treated with 30% of NaOH (2.5 L) over a period of 75 min while maintaining the temperature below 50 °C. The pH of the solution was around 10. The layers were separated, and the aqueous layer was extracted with toluene (2 L). The combined extracts were washed with water (1 L). The organic layer was filtered over a Buchner funnel, which was charged with silica gel (500 g). The silica plug was washed with toluene (2 L). The combined organic solution was concentrated under reduced pressure to dryness to afford **4** as a light yellow oil (834 g, 87.5%). ^{1}H NMR (CDCl$_3$): δ 1.04 (3H, t, J = 7.5 Hz), 1.60 (2H, m), 2.57 (3H, s), 2.73 (2H, t, J = 7.5 Hz), 8.68 (1H, s). ^{13}C NMR (CDCl$_3$): δ 14.23, 21.49, 22.42, 31.08, 132.42, 155.39, 160.81, 167.22. Mass (e/z): 171.14 (M + 1). Anal. Calcd for C$_8$H$_{11}$ClN$_2$: C, 56.31; H, 6.50; N, 16.42. Found: C, 56.57; H, 6.51; N, 16.48.

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(17) 5-Propyl-6-methyl-4-hydroxypyrimidine (**3**) was purchased from Fontarome Chemical. The material contained *ca.* 17% inorganic salt which had no influence on the outcome of the chlorination reaction.

5-Propyl-6-chloromethyl-4-chloropyrimidine (1b). To a mixture of 5-propyl-4-chloro-6-methyl-pyrimidine (**4**, 987 g, 5.784 mol) and DCM (5.9 L) was added TCC (2016 g, 8.67 mol) in portions over a period of 30 min. The reaction mixture was heated at 30 °C for 23 h. The reaction mixture was cooled to 5 °C and filtered. The solid cake was washed with DCM (1.5 L). Saturated Na₂SO₃ (aq.) solution was added until the pH reached ∼8 and the mixture was then stirred for 1 h. The solution was filtered through Celite, and the layers were separated. The organic layer was washed with water (1.5 L) and concentrated to dryness to afford product **1b** (1189 g, 96−98% purity with 4-chloro-6-dichloromethyl-5-propylpyrimidine as the major impurity), which was used for the next step reaction without further purification. ¹H NMR (CDCl₃): δ 1.00 (3H, t, $J = 7.5$ Hz), 1.61 (2H, m), 2.75 (2H, t, $J = 7.5$ Hz), 4.57 (2H, s), 8.74 (1H, s). ¹³C NMR (CDCl₃): δ 14.47, 22.47, 30.81, 43.48, 133.41, 156.18, 162.57, 163.99.

3-Fluoro-2-(1*H*-imidazol-2-yl)-pyridine (2). 2-Cyano-3-fluoropyridine (**9**, 1000 g, 8.196 mol) was charged into a three-neck flask under nitrogen at room temperature, followed by the addition of MeOH (5.0 L). The solution was cooled to *ca.* −20 °C. A solution of NaOMe (25%, 1772 g, 8.196 mol) in MeOH was added *via* an additional funnel within 30 min, while maintaining the internal temperature at *ca.* −20 °C. The mixture was stirred at −20 °C for an additional 4 h.

Aminoacetaldehyde dimethylacetal (775 g, 7.376 mol) was added to the suspension at −20 °C within 5 min, followed by the addition of acetic acid (978 g, 16.3 mol) over a period of 5 min. The resulting mixture was heated at 65 °C for 30 min and was then cooled to room temperature and stirred overnight.

CaCl₂ (90 g, 0. 818 mol) was added to the solution, followed by the addition of 5 N HCl (6 L). The suspension was heated at 65 °C for 4 h. MeOH (∼4 L) was removed at reduced pressure. The residue was cooled to room temperature. Water (4 L) was added, followed by the addition of 30% NaOH solution to pH *ca.* 12 upon cooling with an ice−water bath.

To the suspension was added *n*-BuOH (5 L). The layers were separated. The aqueous layer was extracted with *n*-BuOH (2 L). The organic layers were combined and concentrated to dryness at reduced pressure. To the residue was added MeCN (2.5 L). The suspension was heated to 80 °C and filtered while hot. The filtrate was cooled to 0 °C to allow crystallization. The product was collected by filtration,

washed with *t*-BuOMe (1 L × 2), and dried under vacuum. The product (**2**, 696 g) was obtained as a yellow solid (52%). ¹H NMR (CDCl₃): δ 7.21−7.26 (3H, m), 7.51 (1H, td, $J = 8.4, 1.2$ Hz), 8.33 (1H, dt, $J = 4.5, 1.5$ Hz), 11.00 (1H, br). ¹³C NMR (CDCl₃): δ 124.30 (d, $J = 4.6$ Hz), 125.15 (d, $J = 19.8$ Hz), 137.12 (d, $J = 9.9$ Hz), 143.16 (d, $J = 9.9$ Hz), 144,90, 144.95, 155.30, 157.95. Mass (*e/z*): 164.17 (M + 1). Anal. Calcd for C₈H₆FN₃: C, 58.89; H, 3.71; N, 25.76. Found: C, 58.82; H, 3.66; N, 25.80.

4-Chloro-6-[2-(3-fluoropyridin-2-yl)-imidazol-1-yl-methyl]-5-propyl-pyrimidine (NDT 9533750). 3-Fluoro-2-(1*H*-imidazol-2-yl)-pyridine (**2**, 742 g, 4.548 mol) was charged in a flask under nitrogen, followed by the addition of DMA (2.8 L) and 3 N NaOH solution (1.744 L, 5.23 mol). Upon cooling to 10−15 °C, 5-propyl-6-chloromethyl-4-chloropyrimidine (**1b**, 1120 g, 5.458 mol) was added streamwise to the mixture in *ca.* 30 min to give a brownish slurry, which was stirred at room temperature for an additional 30 min. Ice water (2.5 kg) was added, and the resulting mixture was stirred for another 30 min and filtered. The collected solid was rinsed with water (300 mL × 3) and dried in a hood overnight to give the crude product (NDT 9533750, 1.6 kg containing ∼6% water) in 99% yield, >95.9% HPLC purity.

Recrystallization. Crude NDT 9533750 (2.35 kg, containing ∼6% water, from 2 lots) was mixed with *i*-PrOAc (4.0 L) and *t*-BuOMe (4.0 L) under nitrogen. The mixture was slowly heated to a gentle reflux. After stirring at the same temperature (about 55−58 °C) for 1 h, the mixture was cooled to 30 °C and filtered. The collected solid was rinsed with *i*-PrOAc (150 mL × 3) and dried in air overnight to give NDT 9533750 (1.89 kg) as a white solid in 86% yield (>99% purity). ¹H NMR (CDCl₃): δ 0.99 (3H, t, $J = 7.5$ Hz), 1.56 (2H, m), 2.75 (2H, t, $J = 7.5$ Hz), 5.86 (2H, s), 7.11 (1H, d, $J = 1.2$ Hz), 7.21−7.26 (1H, m), 7.31 (1H, d, $J = 1.2$ Hz), 7.52 (1H, td, $J = 8.4, 1.2$ Hz), 8.23 (1H, dt, $J = 4.5, 1.5$ Hz), 8.64 (1H, s). ¹³C NMR (CDCl₃): δ 14.43, 21.79, 30.28, 50.29, 123.96, 124.37 (d, $J = 4.6$ Hz), 125.11 (d, $J = 19.8$ Hz), 129.44, 131.72, 138.72 (d, $J = 9.2$ Hz), 140.95 (d, $J = 8.4$ Hz), 143.94 (d, $J = 5.3$ Hz), 156.12, 157.66 (d, $J = 267.8$ Hz), 161.65, 164.37. Mass (*e/z*): 332.07 (M + 1). Anal. Calcd for C₁₆H₁₅ClFN₅: C, 57.92; H, 4.56; N, 21.11. Found: C, 57.81; H, 4.64; N, 21.27.