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Practical Synthesis of 5-Fluoro-2-(piperidin-4-yloxy)pyrimidin-4-amine, a Key Intermediate in the Preparation of Potent Deoxycytidine Kinase Inhibitors

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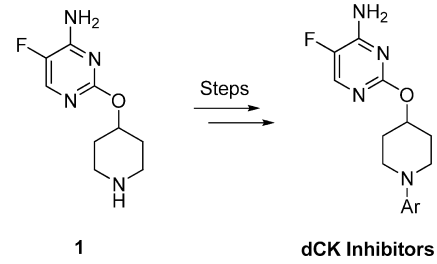
Abstract:

A practical synthesis of 5-fluoro-2-(piperidin-4-yloxy)pyrimidin-4-amine, a key intermediate in the preparation of a new class of potent deoxycytidine kinase (dCK) inhibitors, is described. The commercially available 2,4-dichloro-5-fluoropyrimidine (12) is converted in four telescoped steps to *tert*-butyl 4-(4-amino-5-fluoropyrimidin-2-yloxy)piperidine-1-carboxylate (6a) which upon deprotection gives 5-fluoro-2-(piperidin-4-yloxy)pyrimidin-4-amine dihydrochloride (1a) in about 68% overall yield. This process proved to be an economical alternative to a Mitsunobu-based synthesis.

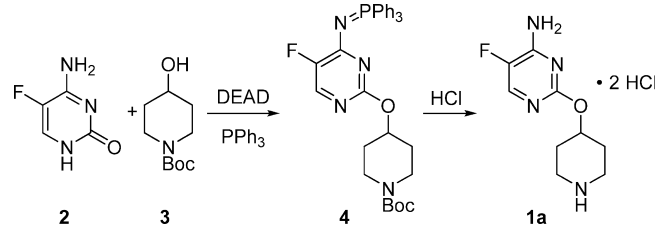
Introduction

Deoxycytidine kinase (dCK) is an enzyme that catalyzes phosphorylation of pyrimidine and purine deoxynucleosides, one of the initial biochemical steps in the deoxynucleoside salvage pathway that supplies precursors for DNA synthesis.[1] Human dCK is known to be involved in the activation of several chemotherapeutically important nucleoside analogues.[2] Through phenotypical analysis of knockout (KO) mice, Lexicon identified dCK as a potential drug target in multiple therapeutic areas within cancer, immunological disorders, and infectious diseases.[3] Internal medicinal chemistry research led to a class of *O*-linked pyrimidin-4-amine-based compounds as potent inhibitors of dCK.[4] We report herein a scalable synthesis of a key intermediate for the preparation of this class of compounds, 5-fluoro-2-(piperidin-4-yloxy)pyrimidin-4-amine (**1**, Scheme 1).

Scheme 1. **Preparation of dCK inhibitors from 1**



Scheme 2. **Medicinal chemistry synthesis of 1a**



Results and Discussion

The medicinal chemistry group used a synthesis based on the Mitsunobu reaction[5] of commercially available 5-fluorocytosine (**2**)[6] and *N*-Boc-4-piperidinol (**3**) (Scheme 2).[4] The resulting iminophosphorane[7] **4** is then treated with HCl to give the 5-fluoro-2-(piperidin-4-yloxy)pyrimidin-4-amine dihydrochloride (**1a**) in about 60% yield. While this synthesis worked well on small scale and provided rapid access to gram quantities of **1** for early investigations of structure activity relationships (SAR), it gave inconsistent yields on scale-up. As a process, it also suffers several major shortcomings in addition to the usual issues associated with Mitsunobu reactions. Up to 2 equiv of **2** are required to fully convert the piperidinol **3** at a reasonable reaction rate. The low solubility of **2** as well as that of **4** necessitates a very large volume of reaction solvent (100 mL THF/g of **3**). Additionally, the unreacted **2** remaining in the reaction mixture poses significant purification challenges. As a result, the iminophosphorane **4** had to be purified by chromatography to remove large amounts of **2** and side products prior to deprotection in order to produce **1a** of acceptable purity. Although a vendor was able to use this chemistry to produce 500 g of **1a** in about 40% overall yield to support lead

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(1) (a) Arner, E. S. J.; Eriksson, S. *Pharmacol. Ther.* **1995**, *67*, 155–186, and references cited therein. (b) Chottiner, E. G.; Shewach, D. S.; Datta, N. S.; Ashcraft, E.; Gribbin, D.; Ginsburg, D.; Fox, I. H.; Mitchell, B. S. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 1531–1535.

(2) (a) Van Rompay, A. R.; Johansson, M.; Karlsson, A. *Pharmacol. Ther.* **2003**, *100*, 119–139. (b) Sabini, E.; Ort, S.; Monnerjahn, C.; Konrad, M.; Lavie, A. *Nat. Struct. Mol. Biol.* **2003**, *10*, 513–519. (c) Sabini, E.; Hazra, S.; Konrad, M.; Burley, S. K.; Lavie, A. *Nucleic Acids Res.* **2007**, *35*, 186–92. (d) Lee, H.; Hanes, J.; Johnson, K. A. *Biochemistry* **2003**, *42*, 14711–14719.

(3) Some deoxycytidine kinase inhibitors have been reported. For examples, see: (a) Krenitsky, T. A.; Tuttle, J. V.; Koszalka, G. W.; Chen, I. S.; Beacham, L. M., III.; Rideout, J. L.; Elion, G. B. *J. Biol. Chem.* **1976**, *251*, 4055–4061. (b) Ward, A. D.; Baker, B. R. *J. Med. Chem.* **1977**, *20*, 88–92.

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(5) For a review of the Mitsunobu reaction, see: Hughes, D. L. *Org. React.* **1992**, *42*, 335–656.

(6) (a) 5-Fluorocytosine is an antifungal with the generic drug name of flucytosine. For a recent review on this prodrug, see: (b) Vermes, A.; Guchelaar, H.-J.; Dankert, J. *J. Antimicrob. Chemother.* **2000**, *46*, 171–179.

(7) For recent reviews on iminophosphorane, see: (a) Wamhoff, H.; Richardt, G.; Stoelben, S. *Adv. Heterocl. Chem.* **1995**, *64*, 159–249. (b) Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, *1197*, 218.

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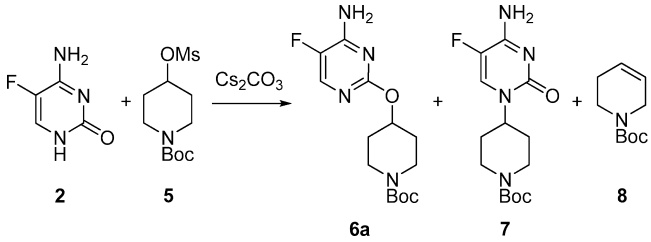
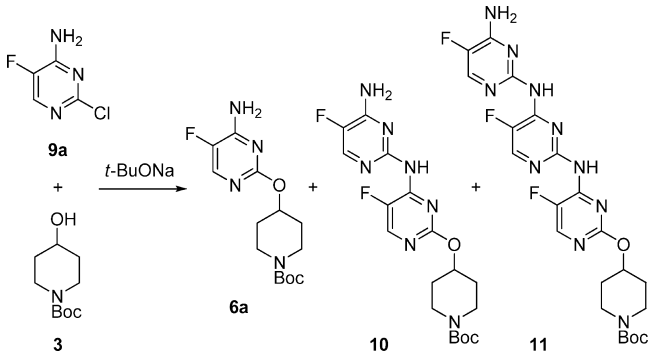
Scheme 3. **Alkylation of 5-fluorocytosine (2)**



Scheme 4. **Alkoxylation of aminochloropyrimidine 9a**



optimization work, a significant amount of experimental effort resulted in little improvement of this process. Clearly, a different approach was needed to support a potentially very aggressive development timeline for the eventual drug candidate.

Initial process development effort on using a different alkylating agent, such as the mesylate **5**, was not fruitful (Scheme 3). Contrary to the milder Mitsunobu conditions (room temperature), reaction of **5** required prolonged heating at higher temperature (80 °C) and resulted in a mixture of the *O*- and *N*-substituted products (**6a** and **7**, respectively)[3b,8] in addition to a significant amount of the elimination product **8**. Even under conditions that favor *O*-alkylation (cesium carbonate as the base and DMSO as the solvent) mesylate **5** reacted with 5-fluorocytosine (**2**) to give about 35% yield of **6a**, 14% yield of **7**, and 32% yield of **8** after column chromatography.[9] A number of other leaving groups were screened under various conditions without significant yield improvement.[10]

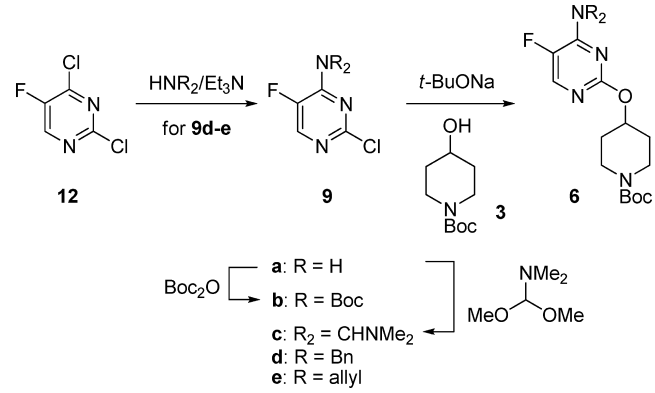
To eliminate the selectivity problem associated with the alkylation approach, an alternative bond connection based on alkoxylation of commercially available 2-chloro-5-fluoropyrimidin-4-amine (**9a**) was investigated (Scheme 4). However, in addition to the desired product **6a**, this reaction produces a significant amount of amination side products **10** and **11**,[11] which were difficult to remove without chromatography. Under conditions that discourage these side reactions (2 equiv of **3**, sodium *tert*-butoxide, diglyme, 120 °C), a mixture of **6a**, **10**, and **11** were produced in about 83/15/2 ratio by HPLC area.

(8) Brown, D. J. *The Pyrimidines*; Wiley: New York, 1962. Supplements: 1970, 1985, and 1994.

(9) (a) It should be noted that isolation of the *N*- and *O*-alkylation products **6a** and **7** enabled structural confirmation of the original Mitsunobu product by NMR techniques. (b) For automated structure verification by NMR, see: Keyes, P.; Hernandez, G.; Cianchetta, G.; Robinson, J.; Lefebvre, B. *Magn. Reson. Chem.* **2009**, *47*, 38–52.

(10) Leaving groups screened: tosylate, 4-chlorobenzenesulfonate, 4-nitrobenzenesulfonate, 2-napthalenesulfonate, triflate, and iodide; bases screened: sodium hydride, lithium *tert*-butoxide, potassium carbonate, and DBU; polar solvents screened: 1,4-dioxane, DMF, NMP, and HMPA.

Scheme 5. **Alkoxylation of protected aminochloropyrimidines 9**

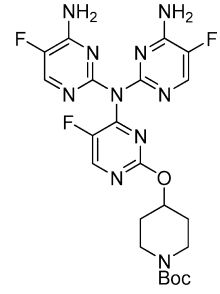


The desired alkoxylation product **6a** was isolated in about 58% yield after column chromatography.[12] Various other conditions were screened without significant improvement.[13]

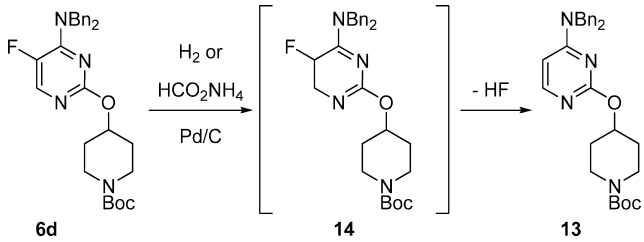
We reasoned that the reactivity of **9a** is likely attenuated by partial deprotonation of the amino group under the strongly basic reaction conditions. Indeed, the aqueous pK_a of 2-chloropyrimidin-4-amine, the des-fluoro analogue of **9a**, was reported to be 16.4,[14] which is comparable to that of *tert*-butanol.[15] Moreover, both the deprotonated starting material **9a** and deprotonated product **6a** can compete with the alkoxide of **3** in reactions with **9a**, leading to the amination side products **10** and **11**.[16] Therefore, protection of both hydrogens on the amino group of **9a** should not only prevent the amination side reactions but also improve its reactivity as an electrophile.

A number of protected chloropyrimidines (**9b**−**e**) were evaluated (Scheme 5). Among these, **9b** and **9c**, both prepared from **9a**, underwent deprotection under the reaction conditions even at a lower temperature (50 °C), giving similar alkoxylation results as reaction of **9a**. The dibenzyl-protected chloropyrimidine **9d**, a crystalline compound readily available from reaction of the inexpensive 2,4-dichloro-5-fluoropyrimidine (**12**) with dibenzylamine,[17] reacted with **3** in the presence of sodium *tert*-butoxide at 50 °C to give the crystalline product **6d** in high yield (90%). However, complete debenzylation of **6d** under various conditions was not successful. For example, under hydrogenation or transfer hydrogenation conditions, **6d** was converted cleanly to the des-fluoro compound **13**, probably through the ring-hydrogenated intermediate **14** followed by dehydrofluorination (Scheme 6). It is surprising to note that the

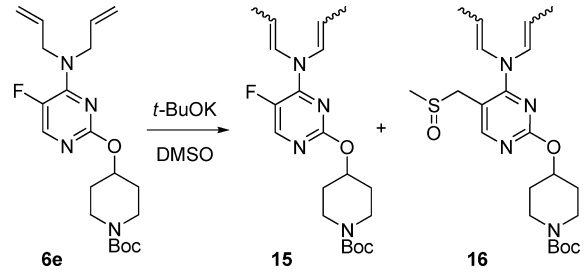
(11) Structure of **11** was based on LC−MS analysis and stereochemical considerations. The isomeric structure shown below cannot be completely ruled out.



Scheme 6. **Hydrogenation of 6d**



Scheme 7. **Isomerization of the allyl groups in 6e**



benzyl groups survived these conditions. Alternative deprotection conditions were attempted without success.[18]

Gratifyingly, double-protection with the allyl group gave satisfactory results. The alkoxylation product **6e** was prepared by means similar to that for **6d**.[17] Although rhodium- or palladium-catalyzed deallylation is well-known,[19] limited screening experiments using transition-metal-catalyzed deallylation did not give any promising leads. However, isomerization under standard base-catalyzed conditions (potassium *tert*-butoxide in DMSO, room temperature) gave a mixture of bis-enamine geometric isomers **15** (Scheme 7). Interestingly, a significant amount of DMSO-substituted side product **16** (up to 30% by HPLC area) was observed under these conditions. Upon a limited screen of reaction conditions, it was discovered that formation of side product **16** was readily controlled by using lithium *tert*-butoxide as the base. These reaction conditions gave an intensely dark color which was not removed by charcoal treatment and resulted in difficult workup and isolation of **6a**. We speculated that the dark substances may be due to further reactions of the allylic anions, and therefore adding a proton source in the reaction medium could help control the color. Although the isomerization using lithium *tert*-butoxide in *tert*-butanol was slow, it proceeded at a reasonable rate in a mixture of DMSO and *tert*-butanol, resulting in adequate control of the color. The optimum solvent ratio was determined to be 1:1 DMSO/*tert*-butanol.

Among the intermediates, **6a** is a solid, while **9e**, **6e**, and **15** are oils, and thus isolation is not convenient. Although **15** can be directly converted to **1** under strongly acidic conditions, isolation and purification of **1** proved difficult due to the presence of oily impurities and byproduct. We decided to telescope the steps from the amination through the hydrolysis (see Experimental Section) and effect purification on **6a**. Hydrolysis of **15** was carried out at pH 2.0−3.0 without affecting the Boc group.[19] The propionaldehyde side product was removed by extraction with aqueous sodium bisulfite, and residual color was further reduced with a charcoal treatment. Compound **6a** was isolated in about 75% overall yield by crystallization from ethyl acetate/*n*-heptane. The purity of **6a** was typically greater than 98%.

Due to the very high water solubility of **1**, Boc-deprotection and isolation of **1a** were carried out under anhydrous conditions. Screening experiments led to isopropyl alcohol as the optimum solvent for the reaction and isolation. Upon treatment of **6a** with excess anhydrous HCl in isopropyl alcohol, the product **1a** was isolated as a white to pale-yellow solid in about 90% yield directly from the reaction mixture by a simple filtration.

This process was successfully demonstrated at 100 g scale (Scheme 8). The overall yield of **1a** was 68%, and the purity was greater than 99% compared to 40% yield and similar purity for the Mitsunobu process practiced at the aforementioned contract manufacturer. In fact, the same contract manufacturer gave a quotation for 10 kg of **1a** using this process that was more than 50% lower than that using the Mitsunobu process.

In summary, we have developed a practical and economical synthesis for 5-fluoro-2-(piperidin-4-yloxy)pyrimidin-4-amine hydrochloride (**1a**) from inexpensive 2,4-dichloro-5-fluoropyrimidine (**12**). This synthesis avoids numerous process issues arising from practicing the alternative chemistry based on the Mitsunobu reaction.

Experimental Section

HPLC Conditions. Method 1: Column: Sunfire C18, 5 μm, 4.6 mm × 50 mm. Column temperature: 40 °C. Flow: 3 mL/min. Wavelength: 220 nm. Solvent A: 0.1% trifluoroacetic acid

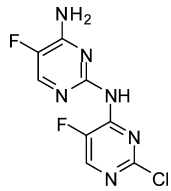
(12) Due to the higher solubility of **9a**, the volume efficiency of this alkoxylation reaction was much better than the Mitsunobu reaction. Additionally, purification of **6a** from this reaction mixture was simpler than that from the Mitsunobu reaction. As a result, the medicinal chemistry group utilized this approach to prepare larger quantities of **1a** (see ref 4).

(13) Bases screened: DBU, cesium carbonate, lithium *tert*-butoxide, potassium *tert*-butoxide, sodium hydride, methyl magnesium bromide, diethylzinc, and methyllithium; solvents screened: dioxane, DMF, DMSO, triglyme; and temperatures screened: 80, 100, and 120 °C.

(14) Harris, M. G.; Stewart, R. *Can. J. Chem.* **1977**, *55*, 3800–3806.

(15) (a) Smith, M. B.; March, J.; Eds. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th ed.; Wiley: New York, 2001; p 331. (b) Reeve, W.; Erikson, C. M.; Aluotto, P. F. *Can. J. Chem.* **1979**, *57*, 2747–2754.

(16) The self-condensation product of **9a** shown below was detected by LC−MS during the reaction.

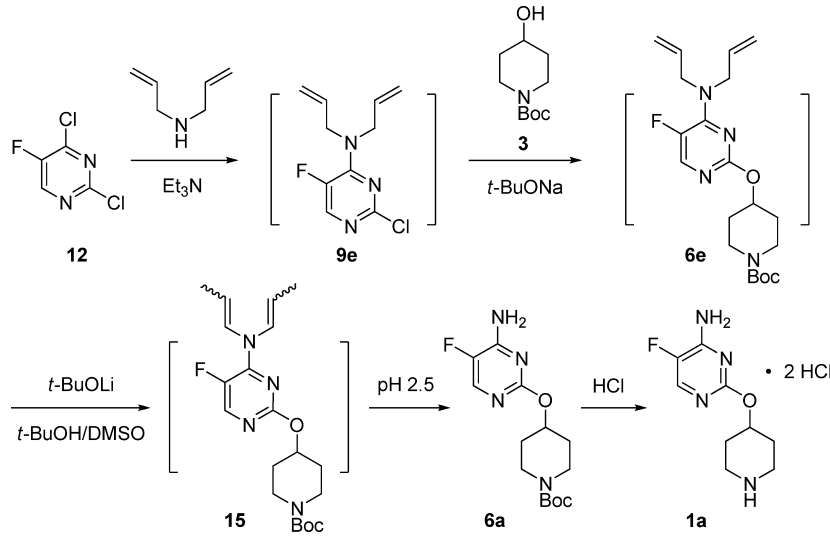


(17) Only product from amination of the 4-chloro position was observed. Durr, G. J. *J. Med. Chem.* **1965**, *8*, 253–255. See also ref 8.

(18) (a) Boc-deprotection was observed without debenzylation under strongly acidic conditions such as hydrobromic acid and methanesulfonic acid. Product **1** was found to be unstable in the presence of excess triflic acid. No debenzylation was observed under oxidative conditions such as DDQ and cerium ammonium nitrate (CAN). (b) Similarly difficult debenzylation was reported previously for a 4-dibenzylaminopyrimidine, see: Boger, D. L.; Honda, T.; Dang, Q. *J. Am. Chem. Soc.* **1994**, *116*, 5619–5630.

(19) Greene, T. W., Wuts, P. G. M., Eds. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.

Scheme 8. **Final synthesis of 1a**



in water. Solvent B: acetonitrile. Linear gradient: 10% B to 90% B in 5 min. Method 2 (for analysis of final product **1a** only): Column: Luna C18(2), 5 μm, 4.6 mm × 250 mm. Flow: 0.7 mL/min. Wavelength: 220 nm. Solvent A: 10 mM ammonium acetate in water. Solvent B: acetonitrile. Linear gradient: 10% B to 90% B in 8 min and hold for 2 min.

Retention times: **1a**, 0.25−0.32 min (method 1), 6.66 min (method 2); **6a**, 1.61 min; **6e**, 2.85 min; **9e**, 3.44 min; **12**, 2.16 min; **15**, 3.97 and 4.06 min.

***tert*-Butyl 4-(4-amino-5-fluoropyrimidin-2-yloxy)piperidine-1-carboxylate (6a).** To a solution of 2,4-dichloro-5-fluoropyrimidine (**12**, 100.0 g, 0.60 mol) in THF (1000 mL) was added diallylamine (64.00 g, 81.1 mL, 1.1 equiv) followed by triethylamine (166.7 mL, 1.20 mol) over 15 min, and the resulting mixture was stirred at room temperature for 2 h (HPLC showed >99% conversion). The mixture was filtered, and the solids were washed with THF (100 mL × 2). The pale-yellow filtrate was washed with a mixture of brine (150 mL) and 10% aqueous citric acid (250 mL). The organic layer was concentrated under vacuum at a temperature below 40 °C to about 200 mL (additional THF was added during the distillation to ensure a KF of the concentrate of below 0.4%) and diluted with 200 mL of THF. Residual solid was removed by filtration and washed with THF (100 mL). The crude amination product **9e** (98.7% purity by HPLC area) in the combined filtrates were used directly in the next chemical step. An analytically pure sample of **9e** was obtained by column chromatography and characterized. MS: $MH^+ = 228.0$; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, $J = 6.0$ Hz, 1H), 5.85 (m, 2H), 5.22 (m, 4H), 4.18 (dd, $J =$ 5.6 Hz, 1.0 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 154.4, 152.9 (d, $J =$ 6.6 Hz), 145.7 (d, $J = 257$ Hz), 144.0 (d, $J = 26.3$ Hz), 132.7, 118.2, 51.3, 51.2.

To a THF solution (500 mL) of sodium *tert*-butoxide (86.50 g, 0.90 mol) and Boc-piperidinol **3** (126.8 g, 0.63 mol) was added the above THF solution of **9e** over 15 min. This mixture was stirred at 40 °C for 2 h (HPLC showed >98% conversion). Without cooling, water (500 mL) and brine (300 mL) were added. The layers were spli,t and the organic layer was washed with brine (500 mL). The organic layer was then concentrated under vacuum at a temperature below 40 °C to about 200 mL (additional THF was added during the distillation to ensure dryness of the concentrate) and diluted with 400 mL THF. Residual solids were removed by filtration and washed with THF (100 mL). The combined filtrates were concentrated and diluted with DMSO (400 mL) to give a solution of compound **6e** (96.3% purity by HPLC area) which is used directly in the next step. An analytically pure sample of **6e** was obtained by column chromatography and characterized. MS: $MH^+ = 393.1$; ^{1}H NMR ($CDCl_3$) δ 7.85 (d, $J = 14.0$ Hz, 1H), 5.87 (m, 2H), 5.20 (m, 4H), 4.98 (m, 1H), 4.16 (d, $J = 5.3$ Hz, 4H), 3.80 (m, 2H), 3.24 (m, 2H), 1.90 (m, 2H), 1.78 (m, 2H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 159.8, 155.2, 152.8 (d, $J = 6.6$ Hz), 144.1 (d, $J = 27.8$ Hz), 143.0 (d, $J = 257$ Hz), 133.5, 117.5, 79.8, 72.7, 51.2, 51.1, 31.7, 28.8.

To a solution of lithium *tert*-butoxide (71.92 g, 0.90 mol) in a mixture of *tert*-butanol (400 mL) and DMSO (400 mL), was added the above compound **6e** in DMSO. This mixture was heated to 60 °C and stirred for 1 h (HPLC showed complete isomerization of both allyl protecting groups) to give compound **15** (mixture of two isomers in about 40/60 ratio by HPLC). The reaction mixture was cooled to 50 °C, and 6 N HCl was added slowly until the pH of the mixture reached about 2.5 (about 174 mL 6 N HCl). This mixture was stirred at 50 °C for 12 h (HPLC shows complete deprotection of diallyl with the Boc protecting group intact). It was cooled to room temperature and diluted with ethyl acetate (1000 mL) and then carefully neutralized with a mixture of saturated aqueous sodium bicarbonate (500 mL) and brine (300 mL). The organic layer was washed with 30% sodium bisulfite (300 mL) and then with water (300 mL × 2). The organic layer was then heated with charcoal (Darco G-60, 20 g) and Celite (Celpure P100, 20 g) at 40 °C for 1 h. This mixture was filtered through a Celite pad (Celpure P100), and the filtrate was concentrated under vacuum at a temperature below 40 °C to afford a yellow slurry. The slurry was diluted with ethyl acetate (500 mL), and the mixture was heated at about 80 °C until all solids were dissolved. The solution was concentrated atmospherically to 300 mL, and heptane was added slowly until the mixture

started to turn cloudy (about 500 mL). This mixture was then cooled gradually to 0 °C and stirred for 1 h at 0 °C. The solids were collected by filtration, washed at 0 °C with 1:3 ethyl acetate/heptane (100 mL × 2), and dried under vacuum at 50 °C to give **6a** as a yellow solid (138.0 g, 74% yield, 98.6% purity by HPLC area). Mp by DSC (differential scanning calorimetry): 166 °C (peak temperature). HRMS: Calcd for $C_{14}H_{22}FN_4O_3$ (MH^+): 313.1676. Found: 313.1662. ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 2.4 Hz, 1H), 5.18 (s, 2H), 5.04 (m, 1H), 3.78 (m, 2H), 3.30 (m, 2H), 1.95 (m, 2H), 1.78 (m, 2H), 1.47 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 160.0, 155.2, 155.1 (d, J = 13 Hz), 142.7 (d, J = 247 Hz), 141.1 (d, J = 20 Hz), 80.0, 72.4, 40.9 (br s), 31.0, 28.8.

5-Fluoro-2-(piperidin-4-yloxy)pyrimidin-4-amine Dihydrochloride (1a). To a solution of **6a** (138.0 g, 0.44 mol) in isopropyl alcohol (552 mL) was added slowly at 60 °C a solution of HCl in isopropyl alcohol which was preprepared by slow addition of acetyl chloride (126 mL, 1.77 mol) to isopropyl alcohol (276 mL) at 0 °C. The mixture was heated at 60 °C for 1 h (HPLC shows complete deprotection), cooled to 0 °C, and stirred for 1 h at 0 °C. The solid was filtered, washed with isopropyl alcohol (138 mL), and dried under vacuum at 50 °C to constant weight to afford **1a** as a pale-yellow solid (116.0 g, 92% yield, 99.2% purity by HPLC area). Mp by DSC: 224−246 °C dec. Anal. Calcd for $C_9H_{15}Cl_2FN_4O$: C, 37.91; H, 5.30; N, 19.65; Cl, 24.87. Found: C, 37.65; H, 5.47; N, 19.21; Cl, 24.67. HRMS: calcd for $C_9H_{14}FN_4O$ (MH^+): 213.1152. Found: 213.1145. ^{1}H NMR (D_2O) δ 7.90 (d, J = 2.4 Hz, 1H), 5.30 (m, 1H), 3.30 (m, 2H), 3.20 (m, 2H), 2.10 (m, 4H). ^{13}C NMR (D_2O) δ 158.8 (d, J = 15 Hz), 154.7, 140.2 (d, J = 249 Hz), 128.4 (d, J = 31 Hz), 72.6, 40.7, 26.6.

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