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Syntheses of a Triad of Flt3 Kinase Inhibitors: From Bench to Pilot Plant†

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Abstract:

We have designed and developed an alternative synthesis for the manufacturing of a triad of Flt3 kinase inhibitors (AST487, ATH686, and AUZ454) to support clinical assessments of patients with Flt3-dependent tumor diseases. The new synthesis is convergent, environmentally friendly, practical, and safe and requires no chromatographic purification.

Introduction

FMS-like-tyrosine kinase-3 (Flt3) mutations are the most common molecular abnormalities found in acute myeloid leukemia (AML).[1] Targeting of this tyrosine kinase by inhibition is the focus of both preclinical and clinical research in AML.[2] AST487 (**1**), ATH686 (**2**), and AUZ454 (**3**) (Figure 1) were identified as novel and potent Flt3 inhibitors at Novartis.[3,4] It is not uncommon for drug discovery organizations to identify several molecules meeting the requirements of a drug candidate nomination for a specific therapeutic target. As such, a few compounds might be progressed through the preclinical and early clinical stage to gain additional information to select the best candidate for further development. This was the case for the Flt3 kinase program at Novartis. Herein, we disclose a strategy that we used for the manufacturing of a triad of Flt3 inhibitors, to be evaluated for the treatment of AML.

Results and Discussion

Research Synthesis. The original synthetic strategies employed by our colleagues in Discovery Chemistry for the preparation of **1**, **2**, and **3** (Scheme 1) are not suitable for large-scale manufacturing since they are not safe, chemical selective, nor environmentally friendly. Some of these drawbacks are discussed as follows.

For the preparation of AST487 (Scheme 1), free radical chemistry and carbon tetrachloride were employed for the preparation of a substituted benzyl bromide **6**. These conditions were not environmentally optimal. To synthesize isocyanate **11**, hazardous phosgene was used. In the final drug substance formation step, reaction of the pyrimidine ring of **12** with methylamine had poor regioselectivity and resulted in the formation of 83% of **1** and 17% of byproduct **13**, which had been removed by chromatography. For manufacturing purposes, chromatographic purification is not a desired process as it is more expensive, more labor-intensive, and time-consuming.

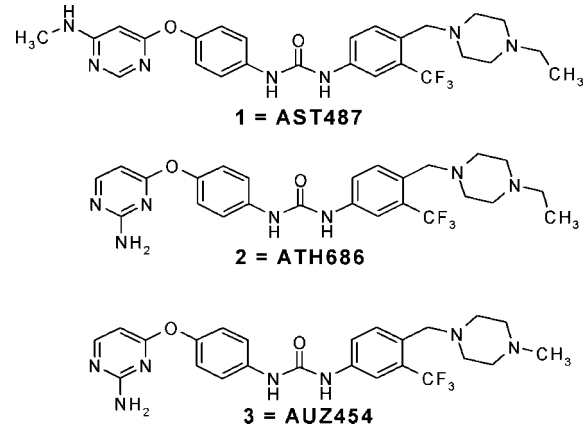

Figure 1

After evaluating the last three steps of the original synthesis for ATH686 (Scheme 2), we identified several drawbacks. Ether **15** was prepared in 25% yield by treating pyrimidine **14** with aqueous ammonia solution. Under these conditions, byproduct chlorohydroxypyrimidine **16** was formed as the major product. The final urea formation leading to **2** was assembled by condensing aniline **9**, a common intermediate for AST487 (Scheme 1), with **17** in the presence of triphosgene, affording the desired product in 38% yield. From a cost and process throughput point of view, this three-step sequence is not an ideal route for large-scale synthesis since its overall yield was as low as 10%.

Since AUZ454 (**3**) is an unsymmetrical urea, whose left-handed fragment is identical to that of **2** and the right-handed fragment is an analogue of **1**, our Research colleagues utilized the same strategy (Scheme 3) as described in the last two sections. Consequently, manufacturing of **3** will face the same aforementioned synthetic hurdles mentioned for **6**, **17**, and urea formation.

Synthesis Plan. To facilitate the process scale-up, we decided to develop an alternative synthetic strategy that can be applied to all three Flt3 kinase inhibitors **1**, **2**, and **3**. We set the goal of our new synthesis to meet the following criteria: (1) convergent, (2) through same intermediates (providing

† This paper is dedicated to Professor E. J. Corey on the occasion of his 80th birthday.

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(1) Pratz, K.; Levis, M. *Leuk. Lymphoma* **2008**, *49*, 852–863.

(2) (a) Tickenbrock, L.; Müller-Tidow, C.; Berdel, W.; Serve, H. *Expert Opin. Emerging Drugs* **2006**, *11*, 153–165. (b) Levis, M.; Small, D. *Expert Opin. Invest. Drugs* **2003**, *12*, 1951–1962.

(3) (a) Floersheimer, A.; Furet, P.; Manley, P. W.; Bold, G.; Boss, E.; Guagnano, V.; Vaupel, A. PCT Int. Appl., 2003. (b) WO 03/099771 A2, 2003:950982; *Chem. Abstr.* **2003**, *140*:16736.

(4) (a) Bold, G.; Caravatti, G.; Floersheimer, A.; Guagnano, V.; Imbach, P.; Masuya, K.; Roesel, J; Vaupel, A.; Garcia-Echeverria, C. PCT Int. Appl., 2005; (b) WO 2005/051366 A2, 2005:493496; *Chem. Abstr.* **2005**, *143*:43694.

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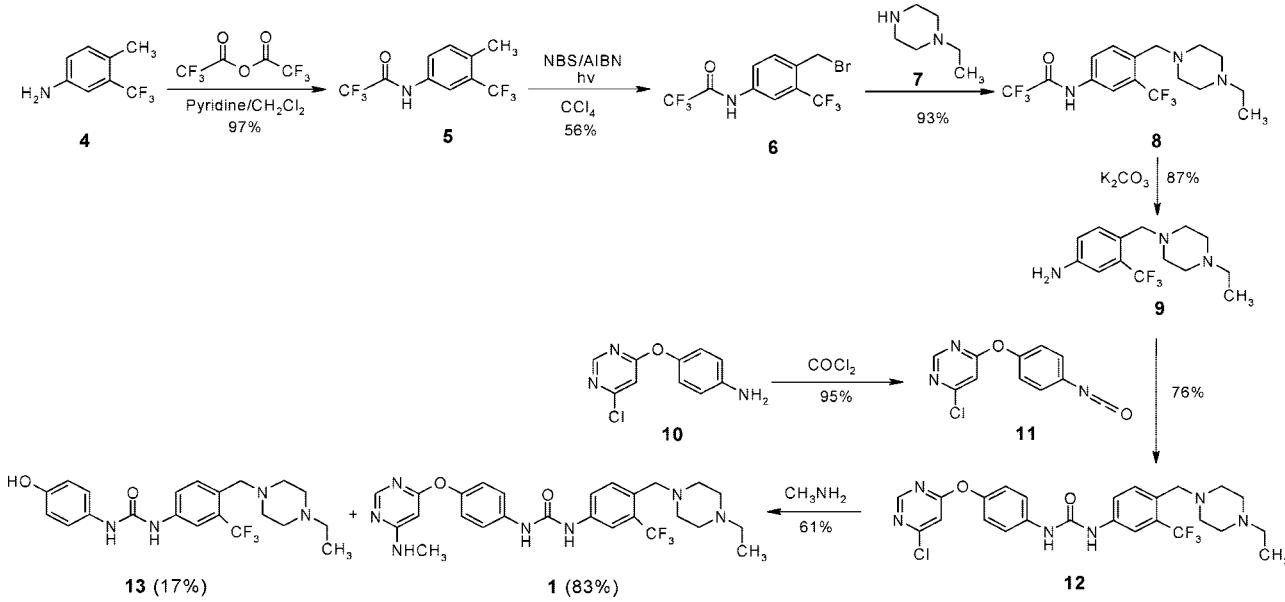
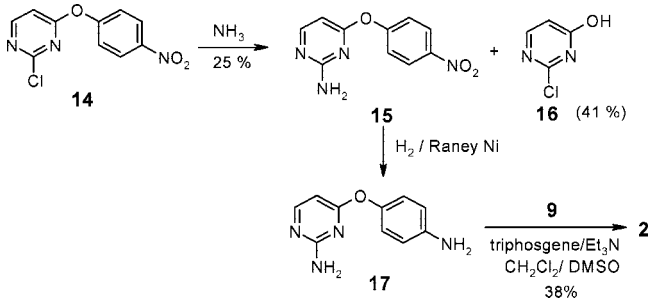
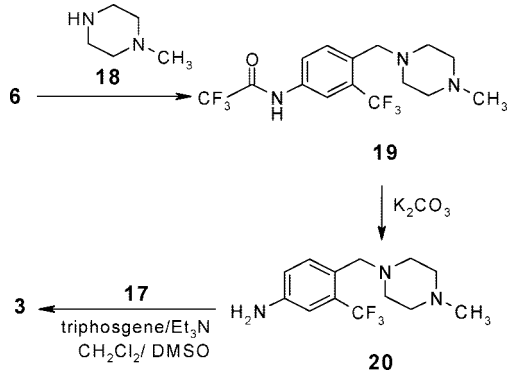
Scheme 1



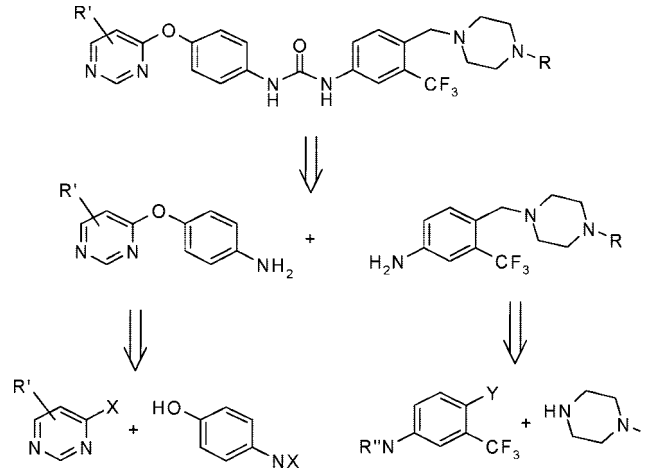
Scheme 2



Scheme 3



Scheme 4

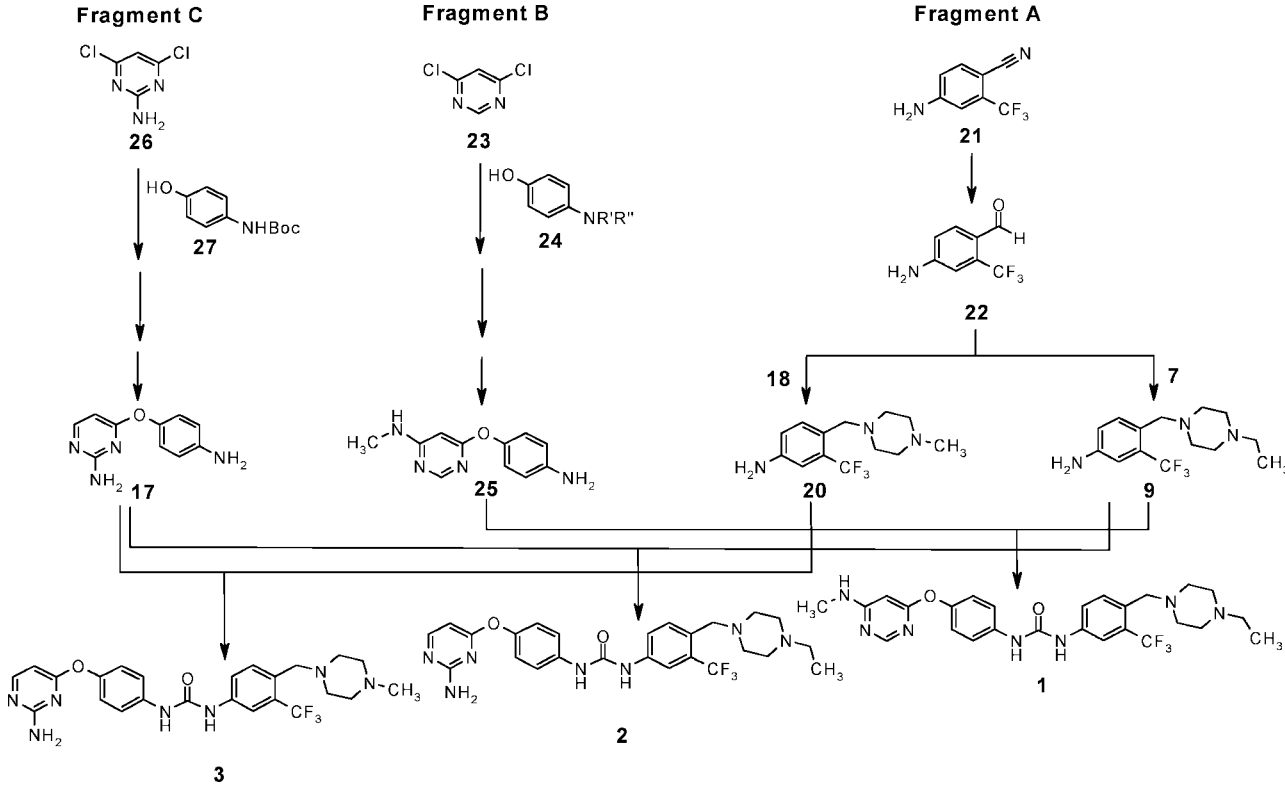


synergy that can reduce cost and resources), (3) commercial availability of starting materials, and (4) green and safe. On the basis of retrosynthetic analysis (Scheme 4), we proposed an alternative synthetic strategy to meet these criteria. After a literature search and assessment of starting materials costs, we decided to investigate the new synthesis starting with **21**, **23**, and **26**, as described in Scheme 5, for the preparation of **1**, **2**, and **3**.

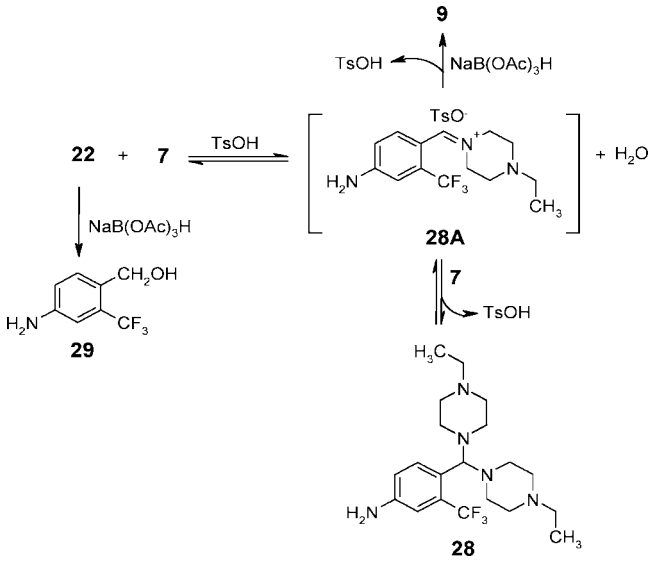
Fragment A Synthesis. Benzonitrile **21**, commercially available in bulk quantities, was chosen as the starting material for the fragment A synthesis that would lead to both intermediates **9** and **20**. Reduction of **21** with DIBAL cleanly afforded aldehyde **22** in 98% yield with 96% purity. We found that **22**, containing both amino and aldehyde functional groups, can transform itself into oligomers upon standing at room temperature. Fortunately, this did not become an issue, since all oligomers can easily be converted back to monomer **22** by a simple aqueous HCl solution treatment immediately before its being used for the next step. Original attempts to carry out the reductive amination reaction[5] involving aldehyde **22**, piperazine **7** (5 equiv), $NaB(OAc)_3H$ (2 equiv), and a catalytic amount (10 mol %) of pyridinium-*p*-toluenesulfonate furnished the desired aniline **9** in only 50% conversion with starting material remaining. An equilibrium presumably existed between aldehyde **22** and iminium salt **28A** involving water molecules generated *in situ* (Scheme 6). To facilitate conversion to imine, we decided to preform **28A** under dehydrating conditions that would minimize the aldehyde concentration prior to the addition of the reducing agent. Removing water from the system should shift the equilibrium toward **28A** and subsequently increase the yield of **9**. This was accomplished by azeotropic distillation of

(5) For recent reviews on acyloxyborohydride reductive aminations of aldehydes and ketones, see: (a) Abdel-Magid, A. F.; Mehrman, S. J. *Org. Process Res. Dev.* **2006**, *10*, 971–1031. (b) Gribble, G. W. *Org. Process Res. Dev.* **2006**, *10*, 1062–1075.

Scheme 5

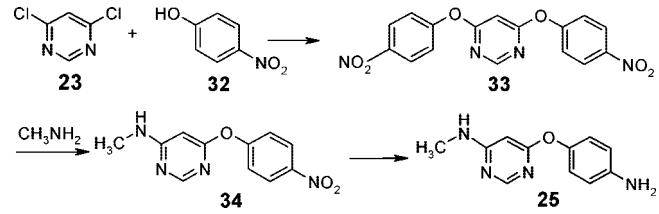


Scheme 6



ethyl acetate from the system at 76−78 °C under atmospheric pressure until its content was determined to be less than 0.3% by Karl-Fisher titration. Sodium triacetoxyborohydride was then added, affording aniline **9** in excellent yield (81%) along with small amount of **29** (5%). A plausible mechanism for the reductive amination under the above conditions is proposed in Scheme 6, which is supported by the isolation and characterization of intermediate **28**. Condensation of aldehyde **22** with piperazine **7** affords **28A** and water. This is a reversible transformation. Trapping of imine **28A** with piperazine (which is present in excess) leads to the formation of **28** and regeneration of toluenesulfonic acid, which will catalyze the formation of more **28A** and **28**. Elimination of one piperazine from **28** regenerates **28A**, which is reduced with sodium triacetoxyborohydride to **9**. Similarly, aniline **20**, the methyl analogue of **9**, was prepared in 88% yield from aldehyde **22** and piperazine **18**, employing the same approach.

Scheme 7



Fragment B Synthesis. As mentioned in the research synthesis of AST487 (Scheme 1), reaction of **12** with methylamine resulted in the formation of a major byproduct **13**. From a synthesis design point of view, if a competitive pathway is inevitable for a particular transformation, one should consider carrying out this step at an earlier stage so that advanced intermediates are not wasted. On the basis of this principle, we decided to investigate a novel approach to install the methylamine group earlier as shown in Scheme 7. Substitution of 4,6-dichloropyrimidine **23**, commercially available in bulk quantity, with the *p*-nitrophenol sodium salt in the presence of a catalytic amount of potassium iodide afforded bis-alkylated pyrimidine **33** in 92% yield. Treating **33** with methylamine cleanly furnished **34** in 96% yield. Monoaddition of methylamine was possible because of the deactivating nature of the aniline upon the first addition. Catalytic hydrogenation of **34** using 10% palladium-on-charcoal in THF generated **25** in quantitative yield according to HPLC analysis. To remove residual palladium from the product, **25** was crystallized from 2-propanol to furnish pure **25** in 64% yield with palladium content at 2 ppm. This

Scheme 8

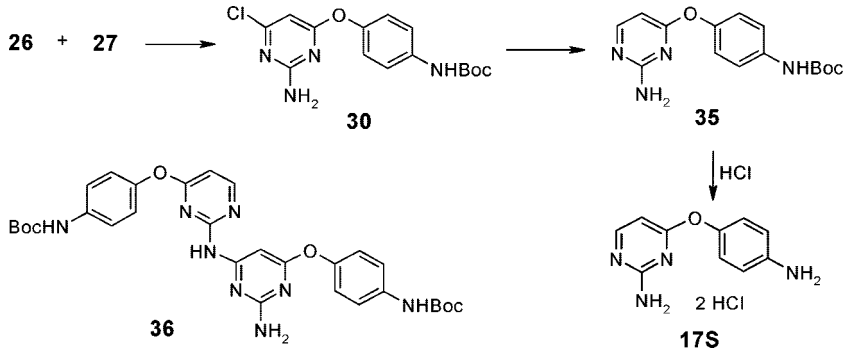


Table 1. **Catalytic dechlorination with 10% palladium-on-carbon**

entry	base	reductant	% **35**[a]	% **36**[a]	% unknown[a]
1	NMM	HCOOH	96	2	1.5
2	*i*-Pr_2NEt	HCOOH	86	0.3	2.8
3	NMM	Et_3SiH	91	0.4	1.9
4	none	HCOONa	88	0.5	4.5
5	$KHCO_3$	HCOOH	96	0	3

[a] Product distribution was determined by HPLC (UV absorption, area normalization) analysis of the reaction mixture.

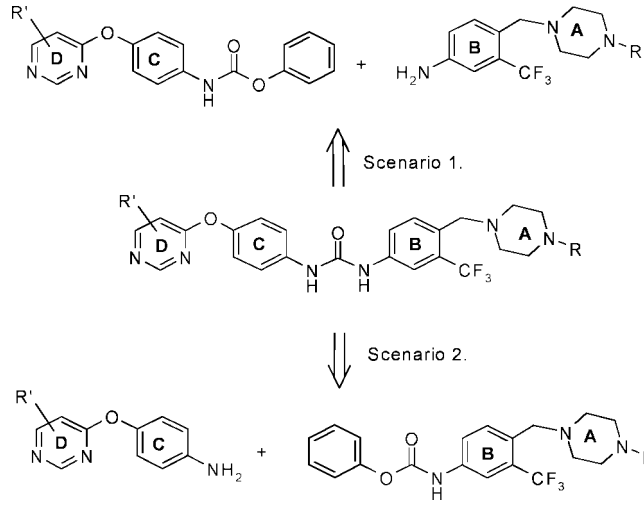
alternative side-chain synthesis furnished **25** (HPLC purity 99%) in an overall yield of 57% over three steps.

Fragment C Synthesis. We decided to explore fragment C synthesis starting with 2-amino-4,6-dichloropyrimidine (**26**) and 4-Boc-aminophenol (**27**) (Scheme 8) because of their commercial availability. Reaction of **26** with **27** in the presence of K_2CO_3 and KI at 120 °C afforded ether **30** in 85% yield. Catalytic chlorine hydrogenolysis of **30** with 10% palladium-on-carbon, formic acid, and *N*-methyl morpholine furnished the desired **35** in 96% yield as well as two byproducts (one identified as **36**, the other unknown) in 2% and 1.5% (HPLC area %), respectively (Table 1, entry 1). Efforts to separate dimer **36** from product **35** by crystallization were unsuccessful. As a result, optimization of the dechlorination step to avoid **36** formation were pursued (Table 1, entries 2−5). The best result was obtained when potassium bicarbonate and formic acid were employed (entry 5), which generated no dimer **36**. To remove residual palladium metal from the product, the reaction mixture after dechlorination was treated with activated charcoal (PICA 1400) affording **35** as a white fluffy solid in 81% yield. Deprotection of **35** with a hydrochloric acid (6 N in IPA, Aldrich) in EtOAc afforded aniline dihydrochloride salt **17S** (HPLC purity 99%) as a white solid in 99% yield.

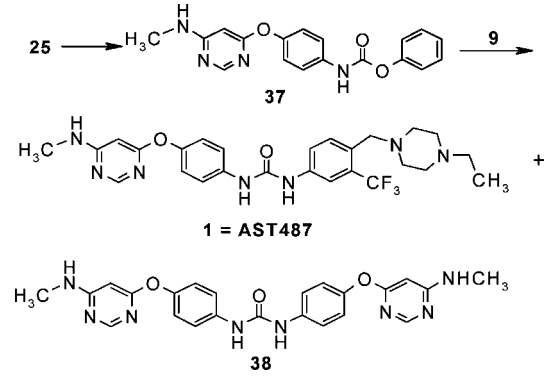
End-Game Synthesis Leading to Unsymmetrical Urea. Synthesis of unsymmetrical ureas from amines or anilines via carbamates have been well documented.[6] Impressed by the reported efficiency and simplicity, we decided to employ phenyl carbamate[6a] for the synthesis of all three Flt3 kinase inhibitors (diaryl urea derivatives) as shown

(6) For reported synthesis of unsymmetrical urea derivatives via carbamates, see:(a) Thavonekham, B. *Synthesis* **1997**, 1189. (b) Vauthey, I.; Valot, F.; Gozzi, C.; Fache, F.; Lemaire, M. *Tetrahedron Lett.* **2000**, *41*, 6347. (c) Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1994**, *35*, 4055. (d) Gastaldi, S.; Weinreb, S. M.; Stien, D. *J. Org. Chem.* **2000**, *65*, 3239. (e) Chong, P. Y.; Janicki, S. Z.; Petillo, P. A. *J. Org. Chem.* **1998**, *63*, 8515.

Scheme 9



Scheme 10



in Scheme 9. Being unable to predict which of the two scenarios would be the preferred "nucleophile−electrophile pair", we decided to evaluate the efficiency of both, beginning with the Scenario 1 approach.

Scenario 1, AB-Ring As Nucleophile and CD-Ring As Electrophile. Intermediate **25** was converted into phenyl carbamate **37** in 77% yield with phenyl chloroformate in THF at −5 °C in the presence of triethylamine (Scheme 10). Condensation of **37** with aniline **9** in various solvents afforded the desired urea **1** in 71−96% yield (Table 2, entries 1−3). Under elevated temperature conditions (100−140 °C), the symmetrical urea **38** was observed from 4−29% as assayed by HPLC. This byproduct was difficult to separate from **1** by recrystallization. The same condensation at lower temperature promoted by potassium *tert*-butoxide in THF did not eliminate

Table 2. **Condensation of carbamate 37 with aniline 9**

entry	base	solvent	temp °C	% **1**	% **38**
1	none	NMP	100	71	29
2	none	diglyme	140	93	7
3	none	DMSO	100	96	4
4	*t*-BuOK	THF	−20	94	6

[a] Product distribution was determined by HPLC (UV absorption, area normalization) analysis of the reaction mixture.

the formation of **38** (Table 2, entry 4). We then probed the Scenario 2 approach to find out if symmetrical urea formation could be avoided.

Scenario 2, AB-Ring As Electrophile and CD-Ring As Nucleophile. Synthesis of carbamate **39** from aniline **9** was not straightforward (Scheme 11). Employing the same conditions for the synthesis of carbamate **37**, phenyl chloroformate/Et_3N/THF/−5 °C, we obtained no carbamate **39** from aniline **9**. Treatment of **9** with phenyl chloroformate in THF at 65 °C *in the absence of triethylamine*, the desired carbamate was obtained as a hydrochloride salt **39S** in excellent yield (95% by HPLC) along with 5% of byproduct **41**, which was easily removed during isolation of **39S** by filtration. Performing the same reaction at lower temperature (such as −20 °C) in the absence of triethylamine, we observed more carbamate **41** (about 50%) formation. A plausible mechanism is proposed in Scheme 11 to explain these outcomes. Since a piperazine nitrogen is more nucleophilic than the aniline nitrogen atom, phenyl chloroformate presumably reacted with a piperazine nitrogen atom, generating an active carbamate salt **40**. At higher temperature, such as 65 °C, the thermodynamic pathway involving the bimolecular reaction of **40** and **9** is the dominant one furnishing carbamate **39S** as the major product. On the other hand, a lower temperature (−5 °C) favored the kinetic pathway involving unimolecular elimination of **40** and the formation of **41** and **43**.

The final assembly of ABCD-ring from AB- and CD-rings employing the Scenario 2 approach turned out to be the most rewarding step for our alternative synthetic strategy. Condensation of carbamate **39S** with aniline **25** in DMSO at 60 °C in the presence of *N*,*N*′-diisopropyl ethylamine (DIEA) furnished AST487 (**1**) in quantitative yield with 99% HPLC purity. Similarly, treating carbamate **44** (Figure 2) with aniline dihydrochloride salt **17S** under the same conditions, AUZ454 (**3**) was obtained in quantitative yield (HPLC 98% purity). For the preparation of ATH686 (**2**), phenyl carbamate **39S** was condensed with aniline **25** (Scheme 5) affording **2** in 98% yield with 98% HPLC purity.

Pilot-Plant Manufacturing of AST487. On the basis of preclinical results using active pharmaceutical ingredients **1**, **2**, and **3** synthesized by the alternative synthetic strategy described in previous sections, the Novartis Flt3 project team selected AST487 for further clinical assessments. To support these studies, multikilogram quantities of GMP-grade drug substance **1** was manufactured in our pilot plant. The synthetic route and corresponding yields for each individual step are shown in Scheme 12. To obtain high-quality drug substance (>99% purity) for clinical trials, pharmaceutical active ingredient **1** was further recrystallized from ethanol in 85% yield. As the yields differed little (±9%) between the laboratory and plant for the individual steps, the robustness of the new synthesis and process is demonstrated.

Conclusions

Our results have demonstrated an efficient, scalable, and robust synthesis of unsymmetrical diaryl urea derivatives, employing phenyl carbamates and the corresponding anilines. This new synthesis was convergent (4 + 3 steps), practical, safe, environmentally friendly, and required no chromatographic purification. The overall yield for the synthesis of **1**, **2**, and **3** from **21** was determined to be highly consistent at 58, 57, and 58%, respectively.

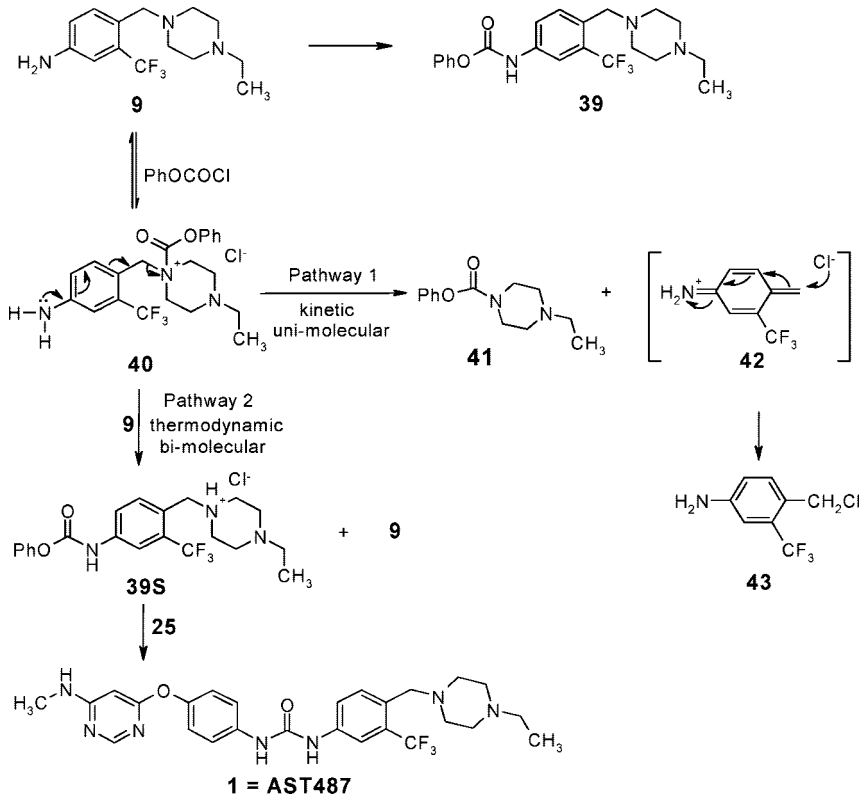
Experimental Section

General. Proton magnetic resonance spectra were recorded on an FT-NMR spectrometer Bruker ARX300, Bruker ARX400, or Bruker ARX500. HREIMS analysis was performed on a Waters Micromass LCT. Reverse phase HPLC analyses were performed on a Waters Alliance HPLC system with a Waters 996 PDA detector (area normalization, Max Plot: 210 to 400 nm). All elemental analyses were performed by Robertson Microlit Laboratories (Madison, NJ).

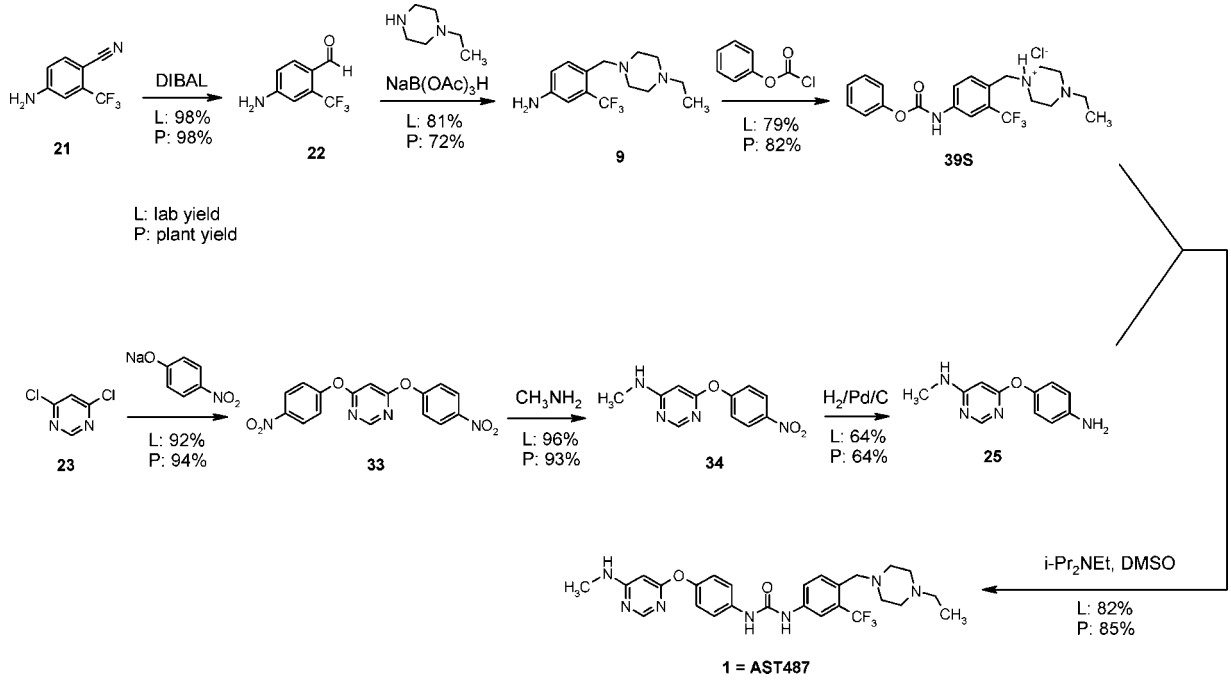
4-Amino-2-trifluoromethylbenzaldehyde (22). Under a nitrogen atmosphere at 23 °C, compound **21** (3.0 kg, 16.1 mol) and dry THF (9.0 L) were charged into a 30-L reactor equipped with a pitched-blade impeller, thermocouple, reflux condenser, liquid addition inlet, and nitrogen inlet−outlet. A solution of diisobutylaluminum hydride (26.7 L, 1.5 M in toluene) was added at 23−30 °C over 75 min [CAUTION: hydrogen gas evolution]. Upon complete addition, the resulting solution was stirred for an additional 5 min, assayed by HPLC (<1 area % **21**), and transferred to a 100-L reactor containing a mixture of methanol (4.5 L) and an aqueous saturated Rochelle salt solution (3 M, 39 L) at 23−45 °C over 1 h [CAUTION: hydrogen gas evolution]. After the quench was complete, the mixture was stirred at 45−50 °C for 10 min. *tert*-Butyl methyl ether (18 L) was added and stirred for 10 min. Layers were separated, and the organic layer was concentrated under vacuum (30−60 Torr) until a residual volume of 5 L was obtained. The solution, containing 3.0 kg of compound **22** and 1.5 kg of toluene, was used directly in the next step (96% HPLC purity, 98.4% yield). An analytical sample of **22** was isolated: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.92 (1 H, s), 7.86 (1H, d, J = 8.9 Hz), 7.02 (1H, s), 6.87 (3H, m); HREIMS m/z 188.0263 (calcd m/z 188.0323 for M − H). HPLC for **21** (t_R = 3.1 min); **22** (t_R = 3.3 min): Phenomenex Ultracarb ODS-30 5 μm C-18 250 mm × 4.6 mm, flow rate = 1.0 mL/min, 25 °C, isocratic, 75:25 A:B; A = acetonitrile; B = water.

4-(4-Ethyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenylamine (9). Portions of the toluene solution from the previous step (3.0 kg, containing 2.0 kg of **22**, 10.5 mol, and 1.0 kg of toluene), ethyl acetate (15 L), and aqueous 1 N HCl solution (10 L) were charged a 50-L reactor. The mixture was stirred rapidly at 20−25 °C for 5 min. A solution of aqueous 1 N NaOH (8 L) was charged to the mixture over 5 min and stirred for an additional 5 min. The organic layer was separated, washed with 10% (w/w) aqueous NaCl solution (10 L), and charged to a 100-L reactor equipped with a pitched-blade

Scheme 11



Scheme 12



impeller, thermocouple, reflux condenser, liquid addition inlet, and nitrogen inlet−outlet. 1-Ethylpiperazine (6 kg, 52.6 mol), pyridinium-*p*-toluenesulfonate (264 g, 1.1 mol) and ethyl acetate (5 L) were charged. The mixture was heated to reflux (76−78 °C), and ethyl acetate was distilled off under atmosphere pressure. After each 5 L portion of distillate had been collected, fresh ethyl acetate (5 L) was charged to the reaction mixture. This distillation−addition operation was repeated until a total of 45 L of ethyl acetate was collected. A sample was removed and analyzed by Karl-Fisher titration for water content and

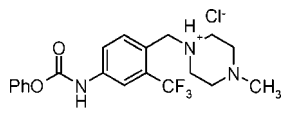


Figure 2

found to contain <0.3%. The mixture was cooled to 50 °C, and sodium triacetoxyborohydride (4.8 kg, 22.6 mol) was charged in portions at 50−60 °C over 1 h. The reaction mixture was cooled to 10−15 °C and quenched with water (15 L) over 1 h while maintaining the batch temperature below 20 °C. The organic layer was separated, washed with water (2 × 15 L), and concentrated at an internal temperature of 75−83 °C until a residual volume of 11 L was obtained. The resulting solution, containing 2.7 kg of compound **9** and 7.5 kg of ethyl acetate, was used as is for the next step (HPLC purity 89%, adjusted yield 81%). An analytical sample of **9** was isolated as a solid: mp 100−106 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.29 (1H, d, J = 8.2 Hz), 6.87 (1H, d, J = 2.2 Hz), 6.76 (1H, d, J = 8.2 Hz), 5.42 (2H, s), 3.39 (2H, s), 2.30 (10H, m), 0.97 (3H, t, J = 5 Hz); ^{13}C NMR δ 147.7, 131.7, 127.7, 125.8, 122.8, 116.8, 110.3, 57.6, 52.7, 52.4, 51.6, 11.9; HREIMS m/z 288.1643 (calcd m/z 288.1688 for M + H$^+$). Anal. Calcd for $C_{14}H_{20}F_3N_3$: C, 58.59; H, 7.02; N, 14.64; F, 19.86. Found: C, 58.59; H, 7.20; N, 14.63; F, 19.66. An analytical sample of **28** was isolated: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.23 (d, J = 10.0, 1 H), 6.87 (s, 1H), 6.78 (d, J = 10.0 Hz, 1H), 5.51 (s, 2H), 3.97 (s, 1H), 2.68 (t, J = 5.0 Hz, 2H), 2.26 (m, 18H), 0.94 (t, J = 5.0 Hz, 6H). Anal. Calcd for $C_{20}H_{32}F_3N_5$: C, 60.13; H, 8.07; N, 17.53. Found: C, 60.13; H, 8.83; N, 17.41. HPLC for **22** (t_R = 9.2 min); **9** (t_R = 4.3 min): Alltech Inertsil ODS-2 5 μm C-18 150 mm × 4.6 mm, flow rate = 1.0 mL/min, 40 °C, gradient elution from 10:90 A:B to 65:35 A:B over 15 min; A = acetonitrile; B = 0.05 M NaH_2PO_4 (pH 2.5).

[4-(4-Ethyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]carbamic Acid Phenyl Ester Hydrochloride (39S). Phenyl chloroformate (1.8 kg, 11.5 mol) and dry THF (42 L) were charged to a 100-L reactor equipped with a pitched-blade impeller, thermocouple, reflux condenser, liquid addition inlet, and nitrogen inlet−outlet and then heated to reflux (64−65 °C). The solution containing 2.7 kg (8.5 mol) of compound **9** and 7.5 kg of ethyl acetate from the previous step was diluted with THF (33 L) in a 50-L reactor and charged via a Teflon diaphragm pump over 45 min to the phenyl chloroformate solution in the 100-L reactor, while maintaining the batch temperature at 63−65 °C. After the addition, the resulting suspension was cooled to 20−23 °C over 45 min. Product was collected by filtration using a Nutsche filter fitted with a polypropylene pad, rinsed with THF (4 L), and dried at 40−45 °C under vacuum (10−20 mmHg) for 12 h to obtain **39S** as a solid (3.3 kg, contains 9% THF, 98.2% HPLC purity, 79.2% corrected yield): mp 224−228 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.84 (bs, 1H), 10.4 (s, 1H), 8.07 (s, 2H), 7.86 (d, J = 8.2 Hz, 1H), 7.43 (t, J = 7.9 Hz, 2H), 7.24 (m, 3H), 4.14 (bs, 2H) 3.75−3.00 (m, 10H), 1.26 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.6, 151.8, 150.9, 150.3, 129.4, 129.3, 125.6, 125.4, 124.9, 122.7, 121.8, 115.5, 55.5, 50.6, 49.6, 48.5, 8.62.

4,6-Bis-(4-nitrophenoxy)pyrimidine (33). 4,6-Dichloropyrimidine (**23**) (45 g, 0.3 mol), 4-nitrophenol sodium salt (136 g, 0.66 mol), potassium iodide (5 g, 0.03 mol), and 1-methyl-2-pyrrolidinone (360 mL) were charged to a 2-L flask, equipped with a mechanical stirrer, thermocouple, heating/cooling capacity, addition funnel, and nitrogen inlet/outlet. The mixture was heated to 100 °C over 1 h and stirred for an additional 1 h. Water (720 mL) was added over 30 min, while maintaining the batch temperature at 70 °C. The mixture was cooled to 23 °C over 30 min and stirred for an additional 1 h. Product was isolated by filtration, rinsed with water (400 mL), and dried at 50 °C under vacuum (5 mmHg) for 16 h to furnish **23** (98 g, 92% yield) as a solid: mp 177−179 °C; HPLC assay 99%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.50 (s, 1H), 8.33 (d, J = 9.2 Hz, 4H), 7.52 (d, J = 9.2 Hz, 4H), 7.01 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.6, 158.3, 157.7, 145.1, 126.0, 122.9, 94.9. HPLC for **23** (t_R = 8.2 min); **33** (t_R = 13.3 min): Alltech Inertsil ODS-2 5 μm C-18 150 mm × 4.6 mm, flow rate = 1.0 mL/min, 40 °C, gradient elution from 10:90 A:B to 65:35 A:B over 15 min; A = acetonitrile; B = 0.05 M NaH_2PO_4 (pH 2.5).

Methyl-[6-(4-nitrophenoxy)pyrimidin-4-yl]amine (34). Compound **33** (96 g, 0.27 mol), tetrahydrofuran (330 mL), and methylamine (105 g, 40 wt % in water, 1.35 mol) were charged to a 2-L flask equipped with a mechanical stirrer, thermocouple, heating/cooling capacity, addition funnel, and a nitrogen inlet/outlet. The mixture was heated to 30 °C and stirred for an additional 16 h. A solution of sodium hydroxide (11.0 g) and water (1 L) was charged over 30 min while maintaining the batch temperature below 25 °C. The mixture was cooled to 0 °C and stirred for an additional 1 h. Product was collected by filtration, rinsed with water (800 mL), and dried at 50 °C under vacuum (5 mmHg) for 16 h to obtain **34** (64 g, 96% yield) as an off-white solid: mp 164−166 °C; HPLC purity 99%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.26 (d, J = 7.0 Hz, 2H), 8.17 (s, b, 1H), 7.50 (d, J = 4.7 Hz, 1H), 7.38 (d, J = 7.1 Hz, 2H), 6.02 (s, 1H), 2.80 (s, b, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.7, 158.9, 158.5, 144.2, 126.7, 125.8, 122.1, 120.1, 27.8. HPLC for **33** (t_R = 13.3 min); **34** (t_R = 8.8 min): Alltech Inertsil ODS-2 5 μm C-18 150 mm × 4.6 mm, flow rate = 1.0 mL/min, 40 °C, gradient elution from 10:90 A:B to 65:35 A:B over 15 min; A = acetonitrile; B = 0.05 M NaH_2PO_4 (pH 2.5).

[6-(4-Aminophenoxy)pyrimidin-4-yl]methylamine (25). A 1-L RC1 reactor equipped with a mechanical stirrer, thermocouple, and gas inlet−outlet was pressurized with nitrogen gas to 60 psi and then depressurized to 0 psi. The pressurization−depressurization sequence with nitrogen gas was repeated for four times. To the reactor, 10% palladium on charcoal (2.0 g, 50% wet, Degussa lot no. 20038056), compound **34** (51 g, 0.2 mol), and THF (360 mL) were charged under nitrogen purge. The mixture was heated to 45 °C, pressurized with hydrogen gas to 60 psi, and then depressurized to 0 psi. The pressurization−depressurization sequence with hydrogen gas was repeated for four times. After the final depressurization, the reactor pressure was set to 60 psi with hydrogen and stirred at 550 rpm for 5 h The reaction was considered complete when no more hydrogen gas had been taken up. The reactor was depressurized, and the mixture was cooled to 25 °C under nitrogen purge. The palladium catalyst was removed by filtration through Celite (40 g) and rinsed with THF (260 mL) under a nitrogen blanket. The organic solution was concentrated at 45 °C under vacuum (150 mmHg) until a final volume of 150−200 mL was reached. 2-Propanol (300 mL) was added, and the organic solution was concentrated at 55 °C under vacuum (110 mmHg) until a final volume of 150−200 mL was reached. 2-Propanol (120 mL)

was added, and the heterogeneous mixture was heated to 80 °C to obtain a solution. The mixture was cooled to 65 °C, seeded, cooled to 55 °C over 20 min, and stirred for an additional 1 h. The mixture was cooled to 0 °C over 2 h and stirred for an additional 8 h. Product was collected by filtration, rinsed with 2-propanol (130 mL), and dried under vacuum (15 mbar) at 50 °C for 16 h to obtain **25** (29 g, 64% yield) as a solid: mp 150−152 °C; HPLC purity 99%;^{1}H NMR (300 MHz, DMSO-d_6) δ 8.10 (s, 1H), 7.17 (d, J = 4.7 Hz, 1H), 6.79 (d, J = 8.8 Hz, 2H), 6.60 (d, J = 8.8 Hz, 2H), 5.60 (s, 1H), 5.04 (s, 2H), 2.72 (s, b, 3H). HPLC for **34** (t_R = 9.3 min); **25** (t_R = 6.0 min): Analtech ODS-2 5 μm C-18 150 mm × 4.6 mm, flow rate = 1.0 mL/min, 40 °C, gradient elution from 10:90 A:B to 65:35 A:B over 15 min; A = acetonitrile; B = water.

1-[4-(4-Ethylpiperazin-1-ylmethyl)-3-trifluoromethylphenyl]-3-[4-(6-methylaminopyrimidin-4-yloxy)phenyl]urea (1 = AST487). Piperazine hydrochloride **39S** (900 g, contains 9% THF, 1.84 mol corrected), aniline **25** (400 g, 1.85 mol), DMSO (2 L), and diisopropylethylamine (260 g, 2.0 mol) were charged to a 5-L flask, equipped with a mechanical stirrer, thermocouple, heating/cooling capacity, addition funnel, and nitrogen inlet/outlet. The mixture was heated to 60 °C, stirred for an additional 2 h, and then cooled to 50 °C. An aqueous solution of potassium hydroxide (143 g) in water (260 mL) was charged to the mixture while maintaining the batch temperature between 50−57 °C. The resulting brown solution was transferred to warm (50 °C) EtOAc (10 L) in a 22-L flask equipped with a mechanical stirrer, thermocouple, heating/cooling capacity, addition funnel, and nitrogen inlet/outlet. Water (4 L) was charged to the mixture and stirred at 50 °C for 10 min. The organic layer was separated, washed with aqueous 20% (w/w) NaCl solution (5 L) at 50 °C, and concentrated under vacuum until a residual volume of 4.2 L was obtained. The resulting tan slurry was cooled to 25 °C. *n*-Heptane (4.2 L) was added over 40 min and stirred for an additional 30 min. Product was isolated by filtration, rinsed with *n*-heptane (2 L), and dried at 25 °C under vacuum (5 mmHg) for 16 h to obtain **1** (965 g, 100% yield, HPLC assay 99%) as a solid. For further purification of drug substance, **1** was dissolved in ethanol (9.6 L, 200 proof) at 50 °C and filtered through a filter paper into a 22-L flask equipped with a mechanical stirrer, thermocouple, heating/cooling capacity, addition funnel, and a nitrogen inlet/outlet. The solution was heated to reflux (78 °C), and water (9 L) was charged over 1 h while maintaining the batch temperature between 73−78 °C. The mixture was seeded, cooled to 60 °C over 30 min, and stirred for an additional 45 min. The resulting slurry was cooled to 25 °C over 2 h. Product was collected by filtration, rinsed with a mixture of ethanol/water (3 L, 1:1 ratio), and dried at 50 °C under vacuum (5 mmHg) for 16 h to obtain purified **1** (835 g, 86%) as a solid: mp 133−135 °C; HPLC assay >99%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.78 (s, 1H), 8.13 (bs, 1H), 7.97 (s,1H), 7.63 (d, J = 8.5 Hz, 1 H), 7.58 (d, J = 8.5 Hz, 1 H,), 7.50 (d, J = 9.1 Hz, 1H), 7.27 (d, J = 4.8 Hz, 1H), 7.07 (dd, J = 9.1, 3.2 Hz, 1H) 5.74 (s, 1H), 3.53 (s, 2H), 2.77 (bs, 3H), 2.51−2.29 (m, 10H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.2, 165.1, 157.8, 152.6, 147.5, 138.8, 136.4, 131.3, 130.0, 127.4, 125.4, 123.3, 121.8, 121.5, 119.7, 115.0, 57.4, 52.8, 52.4, 51.5, 27.4, 11.9. Anal. Calcd for $C_{26}H_{30}F_3N_7O_2H_2O$: C, 57.09; H, 5.90; N, 17.92; F, 10.40. Found: C, 56.82; H, 5.90; N, 17.81; F, 9.87. HPLC for **39S** (t_R = 8.6 min); **1** (t_R = 7.0 min): Alltech Inertsil ODS-2 5 μm C-18 150 mm × 4.6 mm, flow rate = 1.0 mL/min, 40 °C, gradient elution from 10:90 A:B to 65:35 A:B over 15 min; A = acetonitrile; B = 0.05 M NaH_2PO_4 (pH 2.5).

[4-(2-Amino-6-chloro-pyrimidin-4-yloxy)phenyl]-carbamic Acid *tert*-Butyl Ester (30). 2-Amino-4,6-dichloropyrimidine **26** (2.6 kg, 15.8 mol), 4-Boc-aminophenol **27** (3 kg, 14.3 mol), potassium carbonate (2.2 kg, 15.8 mol), potassium iodide (238 g, 1.43 mol), and DMF (16 L) were charged into a 100-L reactor equipped with a pitched-blade impeller, thermocouple, reflux condenser, liquid addition inlet, and nitrogen inlet−outlet. The mixture was heated to 100 °C over 30 min, stirred for an additional 10 min, and then heated to 120 °C and stir for an additional 2.5 h. The mixture was cooled to 70 °C and water (32 L) was added over 45 min while maintaining the batch temperature at 70 °C. The mixture was cooled to 25 °C over 40 min and stirred for an additional 1 h. The solids were collected by filtration, rinsed with water (12 L), and dried at 60 °C under vacuum for 16 h to obtain crude **30** as a brown solid (4.4 kg). Crude **30** was dissolved in ethanol (44 L) at 80 °C. Water (44 L) was added to the batch over 1 h while keeping the temperature higher than 70 °C. The mixture was cooled to 25 °C and stirred for an additional 1 h. Product was isolated by filtration, rinsed with water (10 L), and dried at 60 °C under vacuum for 16 h to obtain ether **30** (4.1 kg, 85%) as a solid: HPLC purity 99%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.43 (s, 1H), 7.47 (d, J = 8.8 Hz, 2H), 7.14 (s, b, 2H), 7.08 (d, J = 8.8 Hz, 2H), 6.16 (s, 1H), 1.47 (s, 9H).

[4-(2-Amino-pyrimidin-4-yloxy)phenyl]carbamic Acid *tert*-Butyl Ester (35). Ether **30** (2.0 kg, 5.9 mol), potassium bicarbonate (709 g, 7.1 mol), 10% palladium-on-charcoal (198 g, 50% wet), ethanol (19.8 L, 95%), and formic acid (95%, 367 g, 7.7 mol) were charged into a 30-L reactor equipped with a pitched-blade impeller, thermocouple, reflux condenser, liquid addition inlet, and nitrogen inlet−outlet. The mixture was heated to 55 °C over 70 min. A solution of formic acid (95%, 85 g) in ethanol (500 mL) was charged and stirred at 55 °C for an additional 1 h. The mixture was cooled to 35 °C. Any solid was removed by filtration and rinsed with ethanol (4.5 L). To the combined filtrate, an aqueous solution of potassium bicarbonate (236 g) in water (990 mL) was added. Ethanol was removed by distillation at 25 °C under vacuum until a total volume of 23 L was collected. EtOAc (20 L) and water (10 L) were charged to the residue, and the mixture was heated to 32 °C. The organic layer was separated, washed with aqueous saturated NaCl solution (2 × 7.5 L), diluted with EtOAc (15 L), and concentrated at atmosphere pressure until a total of 15 L of solvent was collected. Charcoal (PICA1400, 150 g) and EtOAc (15 L) were added to the solution, heated to 65 °C, and stirred for an additional 30 min. Charcoal was removed by filtration through a Celite pad (450 g). The filtrate was concentrated under vacuum until the final volume of 20 L was reached. The resulting slurry was heated to 78 °C to obtain a clear solution. *n*-Heptane (15 L) was charged to the mixture while maintaining the temperature higher than 75 °C. The mixture was cooled to 0 °C over 1 h and stirred for an additional

1 h. Product was collected by filtration, rinsed with *n*-heptane (5 L), and dried at 40 °C under vacuum for 16 h to obtain **35** (1.5 kg, 81% yield) as a solid: HPLC purity >99%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.38 (s, 1H), 8.07 (d, J = 5.6 Hz, 1H), 7.46 (d, J = 8.9 Hz, 2H), 7.04 (d, J = 9.0 Hz, 2H), 6.60 (s, 2H), 6.04 (d, J = 5.6 Hz, 1H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.8, 163.6, 159.9, 152.9, 146.9, 136.6, 121.9, 119.4, 95.7, 79.0, 28.1.

4-(4-Amino-phenoxy)pyrimidin-2-ylamine Dihydrochloride Salt (17S). To a 12-L flask equipped with a mechanical stirrer, thermocouple, addition funnel, nitrogen inlet/outlet, and a gas bubbler connected to 2 N NaOH solution were charged compound **35** (700 g, 2.32 mol) and EtOAc (2.8 L). The mixture was stirred at 25 °C for 15 min to obtain a homogeneous paste. A solution of 6 N HCl in IPA (3 L) was charged all at once and stirred for an additional 24 h. EtOAc (1.4 L) was added to the slurry and stirred for an additional 30 min. Product was collected by filtration, rinsed with EtOAc (1.4 L), and dried at 25 °C under vacuum for 16 h to obtain **17S** (dihydrochloride salt) (647 g, 100% yield) as a solid: mp 237−238 °C; HPLC purity 99%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (s, b, 4H), 8.96 (s, b, 1H), 8.71 (s, b, 1H), 8.39 (d, J = 7.0 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 6.72 (d, J = 7.0 Hz, 1H). Anal. Calcd for $C_{10}H_{12}C_{l1}N_4O$: C, 43.65; H, 4.40; N, 20.23; Cl, 25.77. Found: C, 44.00; H, 4.26; N, 20.14; Cl, 25.95. HPLC for **35** (t_R = 3.57 min); **17S** (t_R = 2.28 min): Phenomenex Ultracarb ODS-30 5 μm C-18 250 mm × 4.6 mm, flow rate = 1.0 mL/min, 20 °C, isocratic, 75:25 A:B; A = acetonitrile; B = water.

1-[4-(2-Amino-pyrimidin-4-yloxy)phenyl]-3-[4-(4-ethyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]urea (2 = ATH686). Piperazine hydrochloride **39S** (745 g, contains 9% THF, 1.5 mol corrected), aniline **27** (488 g, dihydrochloride salt, 1.8 mol), DMSO (2 L), and diisopropylethylamine (693 g, 5.4 mol) were charged to a 5-L flask, equipped with a mechanical stirrer, thermocouple, heating/cooling capacity, addition funnel, and nitrogen inlet/outlet. The mixture was heated to 65 °C, stirred for an additional 2 h, and then cooled to 50 °C. An aqueous solution of potassium hydroxide (375 g) in water (750 mL) was charged to the mixture while maintaining the batch temperature between 48−50 °C. More water (7 L) was charged to the resulting solution at 50−55 °C over 45 min. The resulting slurry was cooled to 25 °C. Product was collected by filtration, rinsed with water (2 L), and dried at 50 °C under vacuum (5 mmHg) for 16 h to obtain **2** (769 g, 98% yield, HPLC assay 98%) as a solid. For a higher purity of drug substance, **2** was dissolved in ethanol (5 L, 200 proof) at 50−55 °C and filtered through a filter paper into a 22-L flask, equipped with a mechanical stirrer, thermocouple, heating/cooling capacity, addition funnel, and nitrogen inlet/outlet. The solution was heated to reflux (78 °C, and water (2.5 L) was charged over 45 min while maintaining the temperature between 78−81 °C. The mixture was seeded, cooled first to 70 °C over 1 h and then to 25 °C over 2 h. Solid was collected by filtration, rinsed with a mixture of ethanol/water (2 L, 2:1 ratio), and dried at 50 °C under vacuum (5 mmHg) for 16 h to obtain purified **2** (634 g, 82%) as a solid: mp 169−173 °C; HPLC assay >99%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.78 (s, 1H), 8.09 (d, J = 5.3 Hz, 1H), 7.97 (s, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 6.59 (s, 1H), 6.07 (d, J = 5.7 Hz, 1H), 3.53 (s, 2H), 2.51 - 2.29 (m, 10H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.8, 163.7, 159.9, 152.6, 147.1, 138.8, 136.5, 131.3, 130.0, 127.6, 125.5, 122.0, 121.6, 119.8, 115.0, 95.8, 57.4, 52.8, 52.4, 51.6, 12.0. Anal. Calcd for $C_{25}H_{28}F_3N_7O_2H_2O$: C, 56.28; H, 5.67; N, 18.38; F, 10.68. Found: C, 56.16; H, 5.60; N, 18.36; F, 10.58. HPLC for **39S** (t_R = 8.57 min); **2** (t_R = 5.98 min): Alltech Inertsil ODS-2 5 μm C-18 150 mm × 4.6 mm, flow rate = 1.0 mL/min, 40 °C, gradient elution from 10:90 A:B to 65:35 A:B over 15 min; A = acetonitrile; B = 0.05 M NaH_2PO_4 (pH 2.5).

1-[4-(2-Amino-pyrimidine-4-yloxy)phenyl]-3-[4-(4-methyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]urea (3 = AUZ454). Aniline dihydrochloride **17S** (488 g, 1.8 mol), piperazine hydrochloride **44** (725 g, 1.7 mol), DMSO (2.4 L), and diisopropylethylamine (725 g, 5.6 mol) were charged to a 5-L flask equipped with a mechanical stirrer, thermocouple, heating/cooling capacity, an addition funnel, and a nitrogen inlet/outlet. The mixture was heated to 60−65 °C, stirred for an additional 2 h, and cooled to 50 °C. An aqueous solution of potassium hydroxide (375 g) in water (750 mL) was added to the mixture while maintaining the temperature between 50−57 °C. The solution was transferred to a 22-L flask equipped with a mechanical stirrer, thermocouple, heating/cooling capacity, addition funnel, and nitrogen inlet/outlet. Water (1 L) was added at 50−55 °C followed by seeds. More water (6.5 L) was charged at 50−55 °C over 1 h. The resulting slurry was cooled to 25 °C over 1 h. Product was collected by filtration, rinsed with water (2 L), and dried at 50 °C under vacuum (5 mmHg) for 16 h to obtain **3** (827 g, 100% yield, HPLC assay 98%) as a solid. To improve the purity of drug substance, **3** was dissolved in ethanol (8.2 L, 200 proof) at 50 °C. The resulting brown solution was filtered through a filter paper into a 22-L flask equipped with a mechanical stirrer, thermocouple, heating/cooling capacity, an addition funnel, and a nitrogen inlet/outlet. The solution was heated to reflux (78 °C) and water (8.2 L) was charged over 45 min while maintaining the temperature between 71−75 °C. The mixture was first cooled to 60 °C over 1 h to obtain a slurry and then cooled again to 25 °C over 2 h. Product was collected by filtration, rinsed with a mixture of ethanol/water (2 L, 1:1 ratio), and dried at 50 °C under vacuum (5 mmHg) for 16 h to obtain purified **3** (750 g, 91% yield) as a solid: mp 144−147 °C; HPLC purity >99%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.78 (s, 1H), 8.09 (d, J = 5.7 Hz, 1H), 7.97 (s, 1H), 7.62 (d, J = 8.9 Hz, 1H), 7.58 (d, J = 8.9 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 6.60 (s, 1H), 6.07 (d, J = 5.6 Hz, 1H), 3.53 (s, 2H), 2.51−2.30 (m, 8H), 2.15 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.8, 163.6, 159.9, 152.6, 147.1, 138.8, 136.5, 131.3, 130.0, 127.4, 125.5, 122.0, 121.6, 119.8, 115.0, 95.8, 57.4, 54.7, 52.6, 45.7. Anal. Calcd for $C_{24}H_{26}F_3N_7O_21.5H_2O$: C, 54.99; H, 5.53; N, 18.53. Found: C, 54.28; H, 5.28; N, 18.42. HPLC for **44** (t_R = 8.31 min); **3** (t_R = 5.80 min): Alltech Inertsil ODS-2 5 μm C-18 150 mm × 4.6 mm, flow rate = 1.0 mL/min, 40 °C, gradient elution from 10:90 A:B to 65:35 A:B over 15 min; A = acetonitrile; B = 0.05 M NaH_2PO_4 (pH 2.5).

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