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Development of a Robust Scale-Up Synthetic Route for BPR1K871: A Clinical Candidate for the Treatment of Acute Myeloid Leukemia and Solid Tumors

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ABSTRACT: Herein, a robust and scalable procedure for the synthesis of multikinase inhibitor BPR1K871 (**1**, a quinazoline compound bearing a substituted thiazoline side chain), which is a clinical candidate for the treatment of acute myeloid leukemia and solid tumors, is reported. The previously reported medicinal chemistry synthetic route A with seven steps had encountered several issues during scale-up syntheses such as low yields (7.7% overall yield), the formation of inseparable impurities, particularly in the chlorination step, use of hazardous reagents (NaH/DMF), and laborious column chromatography steps for the purification of the products. A step-by-step approach to overcome the above issues was planned and implemented through two similar routes (B1 and B2) on a gram scale and finally through route B3 on a kilogram scale to synthesize **1**. The final optimized synthetic route B3 does not require column chromatography purification steps. It is one step shorter than the original route A and avoided hazardous reagents for the alkylation reaction in step 2. Furthermore, the highlights of the new route B3 include liquid−liquid continuous extraction of compound **13** in step 2, the use of $POCl_3$ instead of $SOCl_2$ to minimize the formation of impurities in the chlorination step 3, and telescoped synthesis of key Boc-protected amino intermediate **15** from **13**, in high purity. Using the scale-up route B3, the final product **1** (3.09 kg, yield of 16.5% over six steps with an HPLC purity of 97.8%) was obtained in a single batch for preclinical testing and facilitated clinical testing of **1**, which is underway.

KEYWORDS: *acute myeloid leukemia (AML), BPR1K871, scale-up synthesis, quinazoline, clinical candidate, telescoped synthesis*

1. INTRODUCTION

Acute myeloid leukemia (AML) is a life-threatening hematological malignancy in children and adolescents. More than a quarter of a million people get diagnosed annually worldwide with AML. Despite significant progress over the last three decades in the treatment of AML, more than half of young adult patients and about 90% of older adults still die due to its severity.[1] Therefore, a more effective and less toxic new generation of AML therapeutics is required urgently.[2]

In this respect, targeting altered signaling molecules in cancer is a time-tested strategy, resulting in the development of several anti-cancer drugs. Kinase inhibitors are a class of targeted anti-cancer drugs that block the overexpressed and/or mutant kinase functions. Kinases act as a molecular switch, turning "on" or "off" the signaling in several cellular pathways.[3] Of the 518 kinases reported in the human genome,[4] US FDA (U.S.A. Food and Drug Administration) approved 62 inhibitors that target around 20 kinases.[5] Additionally, many kinase inhibitors are registered in clinical trials and are at different drug development phases.[6] Analysis of the reported kinase inhibitors has shown that the quinazoline core is a privileged scaffold for inhibiting adenosine triphosphate (ATP)-dependent kinases. Moreover, among the 62 clinically approved kinase inhibitors, 7 contained the quinazoline scaffold.[5,7]

In recent years, several research groups focused on the development of small molecules targeting the Aurora kinases and found a common approach for the discovery of new molecularly targeted cancer therapeutics for the treatment of solid tumors, hematological malignancies, and AML.[8] Barasertib (AZD1152), a quinazoline developed by AstraZeneca,[9] CCT241736, an imidazopyridine established by UK Cancer Therapeutics Unit,[10] indolinone derivative from Chern *et al.*[11] and pyrrolopyrimidine,[12] and furanopyrimidine[13] derivatives developed from our research group are a few agents that are reported for the treatment of AML and have both Aurora and FLT3 kinase inhibition.

The FMS-like tyrosine kinase-3 (FLT3) is a class-III tyrosine kinase receptor family and plays a key role in the survival, proliferation, and differentiation of hematopoietic cells.[14] Meanwhile, Aurora kinases A, B, and C are the members of the serine/threonine kinase family, which are essential in the cell mitosis process.[15] BPR1K871 (**1**, Figure 1) is a quinazoline derivative that was identified as a potent dual

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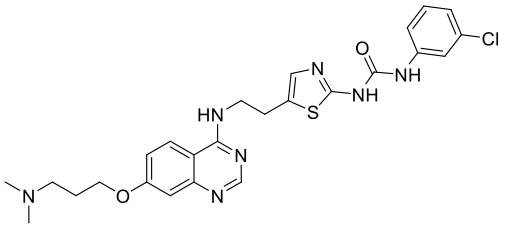


Figure 1. Structure of multikinase inhibitor BPR1K871 (**1**).

inhibitor of Aurora and FLT3 kinases (AURKA IC_{50} = 22 nM, AURKB IC_{50} = 13 nM, FLT3 IC_{50} = 19 nM); it has a single-digit nanomolar level cellular activities in AML cell lines (MOLM-13 and MV4-11, EC_{50} ~5 nM).[7] The kinase profile of **1** using the KINOMEScan technology revealed that 77 therapeutically important kinases out of 395 nonmutant kinases were inhibited (65% at 1000 nM). *In vitro* and *in vivo* studies have proven **1** as a potent multikinase inhibitor and a US FDA approved investigational new drug (IND) for Phase I testing.

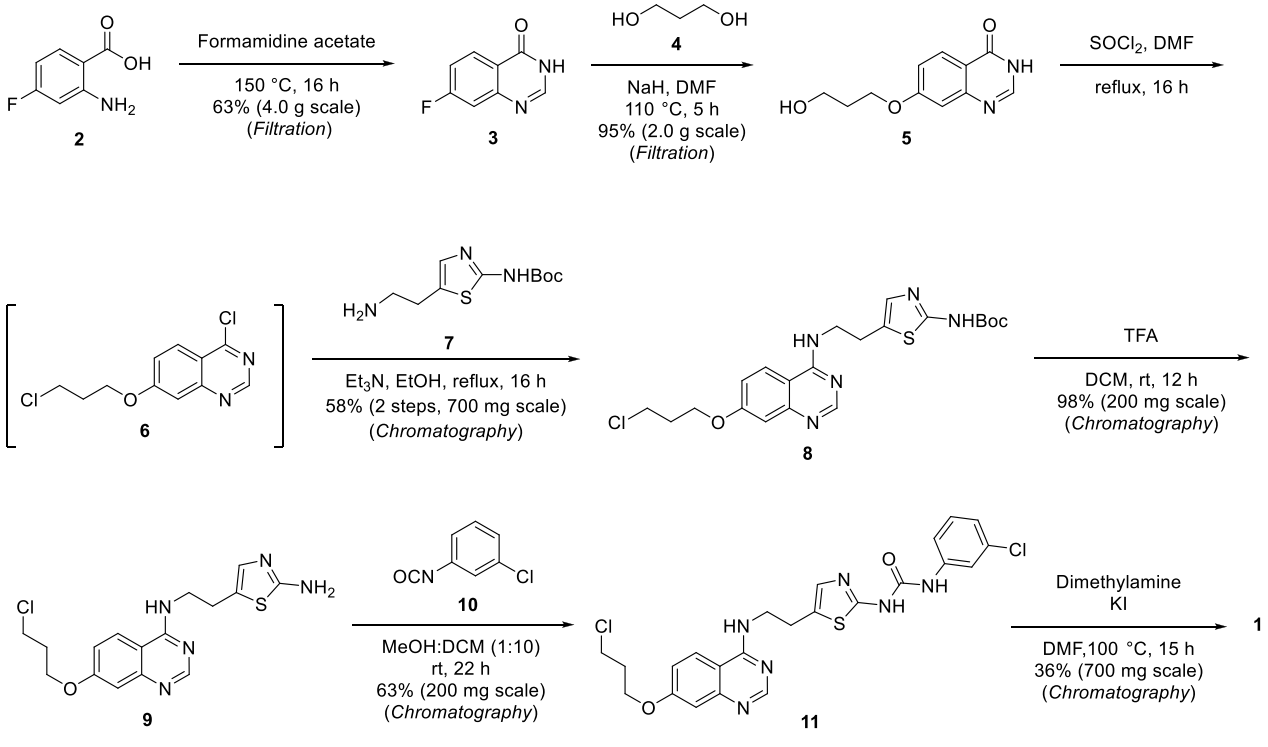
As candidate **1** is advanced to clinical development, large-scale manufacturing of this compound in the multikilogram scale requires a practical and robust synthetic method. Such a multikilogram synthesis of active pharmaceutical ingredients (API) is critical for the program progression. Herein, we describe the synthetic process development activities through routes A, B1, B2, and B3 resulting in a practical and scale-up procedure that can operate on a 3 kg scale for the non-GMP production of **1**.

1.1. Medicinal Chemistry Synthesis of 1.[7] The initial medicinal chemistry synthetic strategy for compound **1** is shown in Scheme 1.[7] The synthesis of compound **1** commenced with the condensation of 2-amino 4-fluorobenzoic acid (**2**) with formamidine acetate to afford intermediate **3**.[16] Subsequently, the S_NAr reaction of **3** with 1,3-propanediol (**4**) in the presence of NaH base gave **5**. The quinazolinone **5** was treated with thionyl chloride at reflux to furnish the dichloride **6**.[9a] Subsequently, compound **6** underwent an S_NAr reaction with *tert*-butyl (5-(2-aminoethyl)thiazol-2-yl)carbamate (**7**)[17] (synthesized from our lab in 17.0% yield over six steps), in the presence of triethylamine base to furnish compound **8**. In turn, this was reacted with trifluoroacetic acid at 26 °C, followed by the base treatment provided the free amine **9** in excellent yield after column purification. For the formation of the urea functional group, amine intermediate **9** was reacted with 3-chlorophenyl isocyanate (**10**) to yield **11** in a 63% yield. The last stage of the synthesis installed the dimethylamino group through the S_N2 reaction of chloro compound **11** with dimethylamine in the presence of KI to afford **1** with a 36% yield.

Synthetic route A (Scheme 1)[7] is already reported and was developed to produce the milligram scale of compound **1** during the *in vitro* and *in vivo* assessment of kinase inhibitory/anti-cancer activity. Synthetic route A consisted of seven steps from commercially available 2-amino-4-fluorobenzoic acid (**2**) and resulted in an overall yield of 7.7% on a milligram scale. However, scale-up to gram-scale synthesis resulted in a decrease in yield.

Medicinal chemistry synthetic routes aim to explore the structure−activity relationship (SAR) in a series of compounds under investigation. For such SAR exploration, there is a requirement for synthesizing diverse analogues. Hence, it was advantageous to introduce the chemical diversity as later as possible in the synthetic route to obtain the desired analogues. Hence, during the medicinal chemistry optimization of **1**, two important chemical diversity points, the urea functional group and dimethylamino groups, were introduced at the 6th and 7th

Scheme 1. Synthetic Route A for 1



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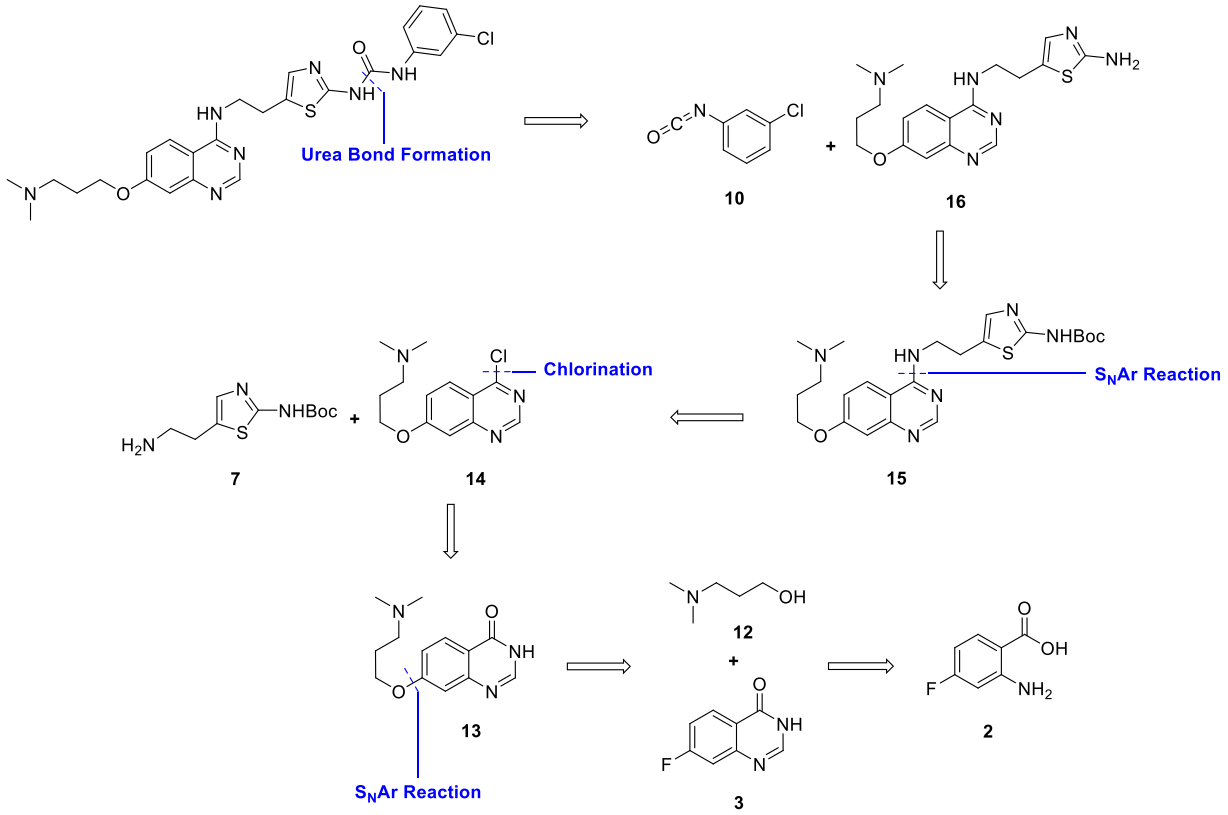
Scheme 2. Retrosynthetic Analysis of 1



step of the seven-step synthetic route A, respectively. This route was advantageous for optimization in the medicinal chemistry program but was not suitable for the multigram scale-up synthesis of **1** that is essential for preclinical investigations.

Several drawbacks were identified during the scale-up synthesis of **1** using route A including, (i) variable yields during the chlorination and S_NAr step to form the intermediate **8** and the final dimethyl amination step. Moreover, a low yield in the final step leads to the increased use of the key thiazole intermediate **7**, which was synthesized in six steps. Hence the overall cost of synthesis also increased, (ii) the use of unsafe reagent NaH/DMF in step 2 for the formation of **5**,[18] and (iii) the requirement for several column chromatography purifications steps. Moreover, several unknown side products were formed in the final dimethylamino substitution reaction during the scale-up of **1**, resulting in a decreased yield and necessitated an increased effort during the purification with column chromatography.

The above disadvantages motivated us to seek an alternative, safe, and efficient route to provide multikilograms of **1** in a high yield with easy to purify steps. As the final installation of the dimethylamino group in **1** was a major source of the problem, installing this functionality at an early stage was envisaged. For this purpose, a retro-synthetic analysis of **1** was carried out for planning an alternative synthetic route.

1.2. Retrosynthetic Analysis of 1. The retro-synthetic analysis of target molecule **1** is shown in Scheme 2. Accordingly, the method of assembling the target molecule **1** would be via a urea linkage between the subunit **16** and 3-chlorophenyl isocyanate (**10**). Meanwhile, the amine **16** could be obtained by the removal of Boc from protected amine **15**. Compound **15** could be constructed using a similar strategy to route A, from compound **13** by a chlorination step followed by the S_NAr reaction of the resulting compound **14** with thiazole intermediate **7**. While the intermediate **13** could be assembled via S_NAr reaction between 7-fluoroquinazolin-4(3*H*)-one (**3**) and 3-(dimethylamino)propan-1-ol (**12**). Compound **3** could be made from commercially available 2-amino-4-fluorobenzoic acid (**2**), as in route A.

2. RESULTS AND DISCUSSION

2.1. Milligram-Scale Synthesis of 1 Using Route B1. Initially, the intermediate **14** was planned to be synthesized from the dichloride compound **6** (Scheme 1). However, the 4-chloro group on the pyrimidine ring is more reactive than the chloro group on the alkyl chain. Hence, the dimethylamino group could not be installed before the thiazole side chain on the dichloride intermediate **6**. Further, attempts were made to synthesize the monochloride intermediate or install another leaving group triflate (OTf) on the alkyl chain terminal but could not get satisfying results. Hence, as shown in Scheme 3 (synthetic route B1), the 3-(dimethylamino)propan-1-ol (**12**) group was directly installed using an S_NAr-type reaction on the quinazolinone ring in the presence of the base KOH.[19] This avoided using sodium hydride to install the side-chain group at the 7-position of the quinazoline ring. Moreover, this provided a good yield of the intermediate **13** and avoided using a laborious column chromatography procedure for the purification. Additionally, the dimethylamino intermediate **13** could be synthesized in one-pot two-step synthesis from commercially available 2-amino-4-fluorobenzoic acid (**2**) with an 83% yield.[16,19]

Subsequently, the intermediate **13** underwent chlorination by treatment with 20.0 equiv of thionyl chloride to provide the

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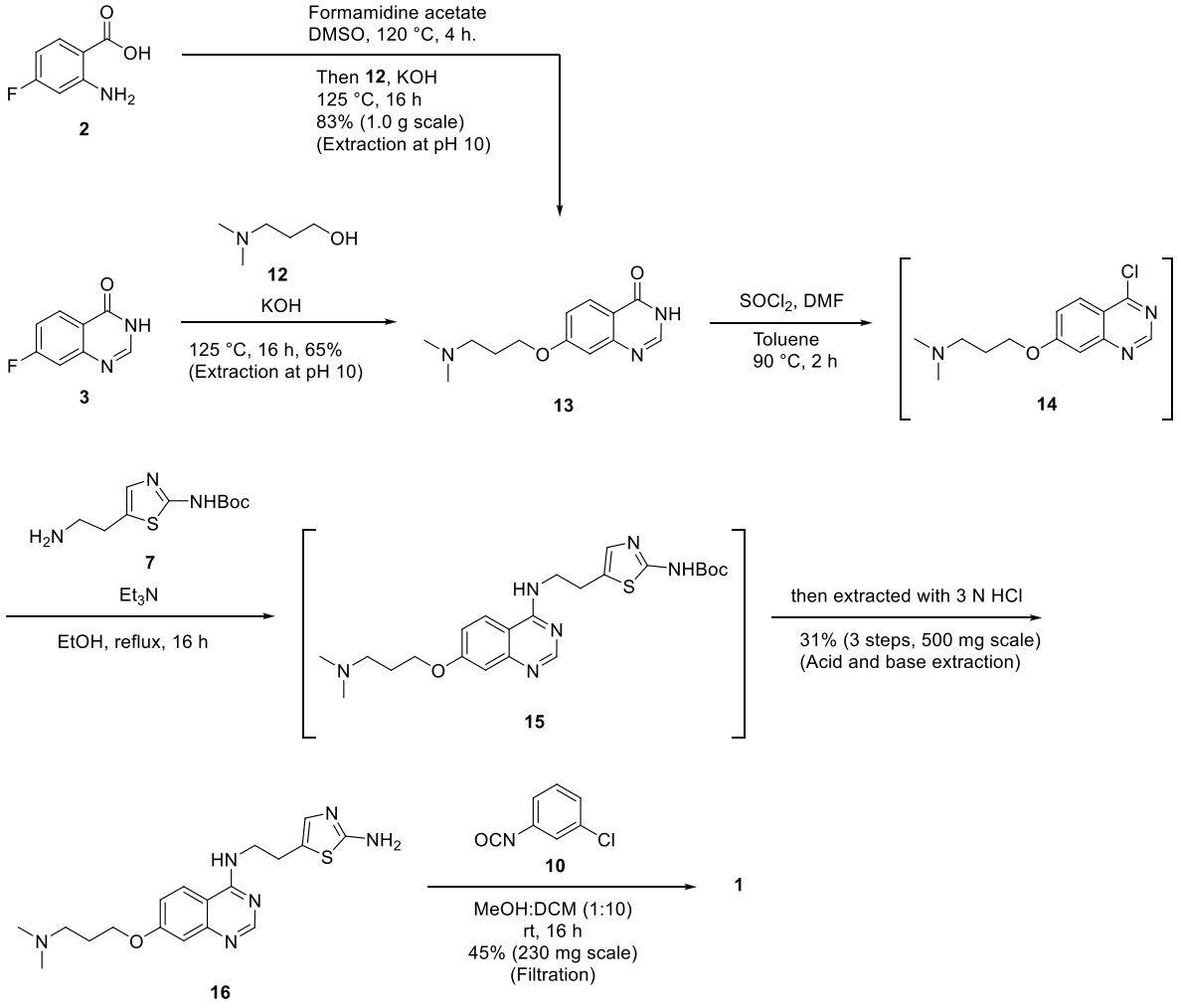
Scheme 3. Synthetic Route B1 for 1



4-chloro quinazoline intermediate **14**.[9] As this compound was unstable, it was directly reacted with the thiazole intermediate **7**, which was followed by acidic extraction for the deprotection of the Boc group to furnish the final amino intermediate **16** in 31% yield over three steps. Finally, the amine **16** was reacted with 3-chlorophenyl isocyanate (**10**) to give **1** in a moderate yield of 45%. Overall, route B1 was much more straightforward than route A with six-step synthesis from the commercially available starting material, with an overall yield of 11.6%. This synthetic route's major advantage is the easy purification steps, requiring only extraction and filtration without column chromatography. However, for kilogram-scale manufacturing to supply **1** for preclinical and clinical studies, several changes are still required to ensure a robust synthetic procedure.

2.2. Gram-Scale Synthesis of 1 Using Route B2. Although route B1 proved to be more efficient for synthesizing **1**, this methodology could still not be applied for a multigram scale-up synthesis due to two main problems. The first one is the variable yields in the one-pot synthesis of dimethylamino pyrimidinone intermediate **13**, which was affected by the unknown impurity present in the starting material 2-amino-4-fluorobenzoic acid (**2**) due to degradation. This problem could be overcome by recrystallization in EtOH before reaction, which caused lower yield and a concomitant increase in the cost. However, the original two-step procedure for the synthesis of **13**, instead of the one-pot synthesis, overcame the influence of starting material purity. The second and the most important problem is the chlorination reaction, which needed 20−30 equiv of thionyl chloride to complete the monochloro intermediate **14** formation. During the scale-up synthesis, more impurities were formed after quenching the reaction, perhaps due to inefficient heat transfer while quenching with saturated $NaHCO_3$ solution. This dramatically affected both the yield and subsequent purification process. To overcome this issue, an alternative chlorination reagent was sought. Phosphoryl trichloride was found to be a suitable alternative reagent for pyrimidinone chlorination,[20] as it was also widely used, similar to that of thionyl chloride. The use of this regent decreased the amounts (equivalent) of reagent required to complete chlorination. It decreased the number of impurities formed, thus simplified the purification process. The chloro intermediate **14**, without purification, was reacted with the key thiazole intermediate **7**, and the resultant product **15** isolated in 52% yield over two steps in multigram scales. Next, the removal of the Boc protection was carried out with trifluoroacetic acid. The amine **16** was isolated as trifluoroacetic acid salt by recrystallization from a mixture of methanol diethyl ether. As the trifluoroacetate salt increased the solubility of **16** in DCM, the final urea formation reaction proceeded in DCM assisted by the base triethylamine resulting in an improved yield of 73% for the formation of final product **1**. Overall, the synthetic route B2 (Scheme 4) incorporating

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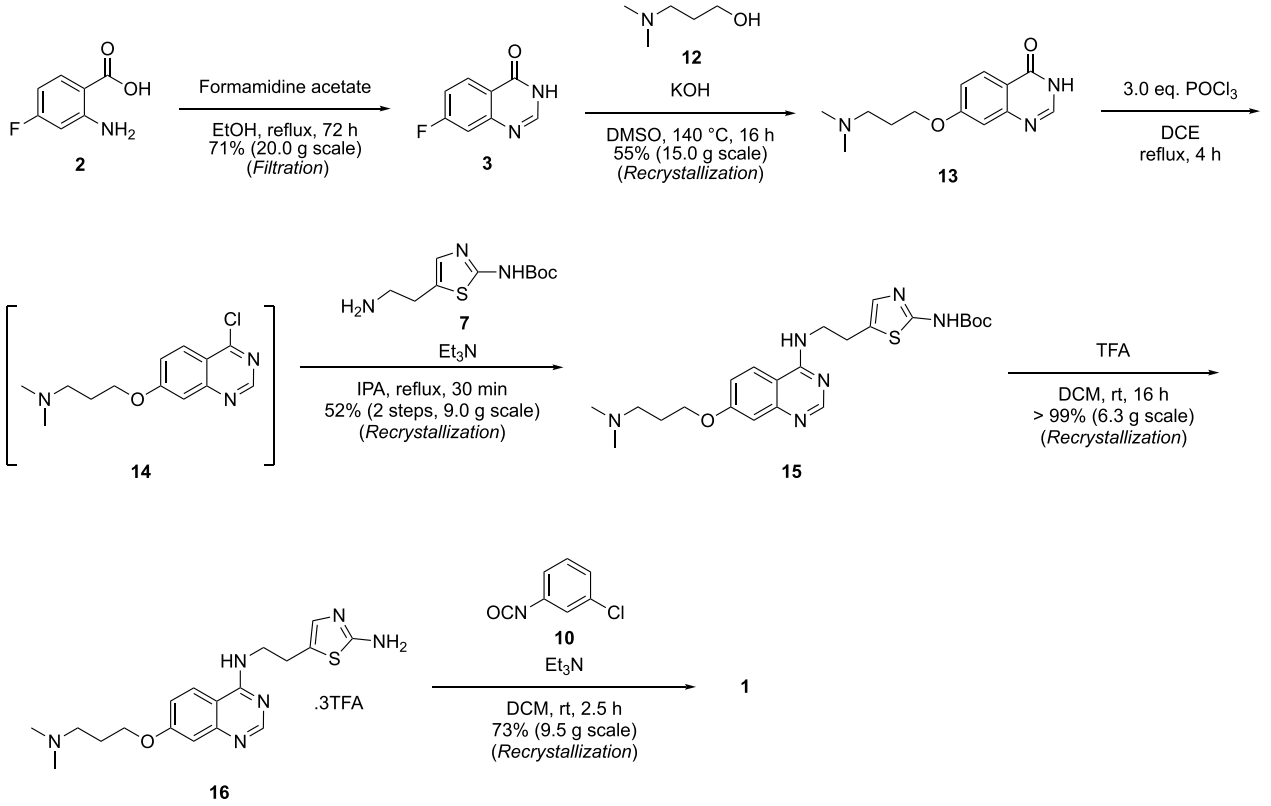
Scheme 4. Synthetic Route B2 for 1

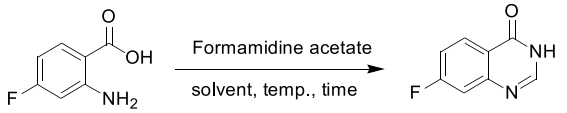


the modified conditions for reactions with different reagents/solvents has resulted in an improved overall yield of 14.7% for the synthesis of **1** on multigram scales.

2.3. Kilogram-Scale Synthesis of 1 Using Route B3. As a brief finding, the modified synthetic route B2 (Scheme 4) is more advantages than synthetic route B1 (Scheme 3) due to the replacement of $SOCl_2$ with $POCl_3$ for the chlorination step, which required lower equivalents of reagents and at the same time suppressed the number of impurities formed. The isolation of **16** as a TFA salt facilitated the final urea bond formation reaction in DCM, as **16** TFA salt was highly soluble in DCM. Due to these, the overall yield for **1** using the route B2 was 14.7%, which is a significant 2-fold improvement compared to 7.7% for **1** using the original route A. Further, route B2 has improved safety due to the avoidance of dangerous NaH/DMF[18] used in route A, which may have potential safety issues during the scale-up. Since the route B2 was advantageous in several ways, we intended to use the same for the large-scale (kilogram level) synthesis of **1**. However, it was intended to optimize further the reaction conditions and reagents used in each step to improve the yield. This led to the preparation of large quantities of compound **1** to enable preclinical testing.

2.4. Optimization of Quinazolinone Intermediate 3 Synthesis. The first step in the process development campaign is similar to the medicinal chemistry synthesis of the quinazolinone **3** from the starting material **2** by condensation with formamidine acetate. The following three conditions were studied to optimize this reaction for a 10.0 g scale of starting material **2** (Table 1). Condensation of **2** with formamidine acetate in solvent-free condition (neat) or the presence of DMSO solvent gave a low yield due to incomplete conversion of the starting material and formation of several

Table 1. Optimization of Quinazolinone 3 Synthesis[a]



entry	solvent	time (h)	temp (°C)	**3** yield (%)[b]
1	neat	12	120	63
2	DMSO	4	120	83
3	EtOH	40	reflux	93

[a]Reaction performed with benzoic acid **2** (1.0 equiv) and formamidine acetate (2.0 equiv). [b]Isolated yields of product **3** and purity determined by HPLC analysis (C18 HPLC column, 0.1% TFA in ACN/0.1% TFA in H_2O).

unknown impurities. The formation of impurities precluded increasing the reaction time to drive it to completion. However, the reaction of **2** with 2.0 equiv of formamidine acetate in EtOH under reflux condition was found to be excellent with an enhanced (> 90%) yield of product **3**.[17] In this reaction system, the resulting product **3** was not soluble in EtOH at room temperature, facilitating the easy isolation of a pure product by simple filtration.

To execute the optimized reaction conditions on a bulk scale (10.0 kg), the reaction was performed in ethanol under reflux for 48 h. The completion of the reaction was monitored by HPLC analysis, which indicated the presence of 4.3% unreacted starting material (R_f = 10.15 min). The unreacted starting material **2** could be removed successfully in the workup process. Once the reaction is completed, the batch temperature was gradually decreased to about 10−15 °C and stirred for 4 h. The precipitated product was centrifuged to get

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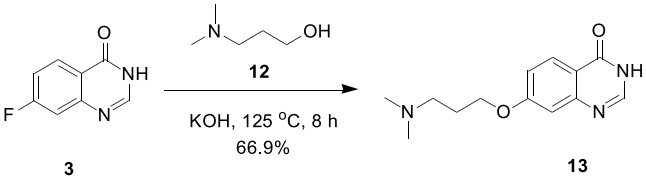
the cake, rinsed with cold EtOH, and dried under vacuum at 55 °C for 24 h to afford **3** (8.70 kg, 89.4% yield) with an HPLC purity of >99%.

2.5. Formation of Intermediate 13. Next, for the synthesis of **13**, we set out to optimize the reaction condition for kilogram-scale synthesis (Table 2). S_NAr reaction of 3-(dimethylamino) propan-1-ol (**12**) and compound **3** in a DMSO solvent using KOH as the base at 125 °C smoothly produced **13** in 83% yield on a small scale (10.0 g). Even though the current protocol had avoided the dangerous NaH originally used in the medicinal chemistry synthesis of **1**,[18] KOH/DMSO is still hazardous for large-scale manufacturing.[21] Hence, other conditions were tested to replace the DMSO solvent. Thus, the reaction could be progressed in neat 3-(dimethylamino)propan-1-ol (**12**) using KOH as the base, the reaction was quenched with water, and then the product **13** isolated by ethyl acetate extraction in good yields (88% isolated yield) in a 10.0 g scale reaction.[19]

Table 2. Synthesis of Intermediate 13[a]



				13[b]	
entry	batch size (3, g)	solvent	temp (°C)	yield (%)	purity (%)
1	10.0	DMSO	140	55	98.5
2	10.0	DMSO	125	83	98.1
3	20.0	neat	120	73	98.4
4	560.0	neat	120	79	99.1

[a]Reaction performed with quinazolinone **3** (1.0 equiv), amino alcohol **12** (4.5 equiv), KOH (4.0 equiv), and reaction time 16 h. [b]Isolated yields of product **13** and purity determined by HPLC analysis (C18 HPLC column, 0.1% TFA in ACN/0.1% TFA in H_2O).

This reaction proceeds smoothly, but the isolation of the desired product **13** on a large scale via the traditional batch extraction method is inefficient due to the product's poor solubility. This would particularly be a major problem in kilogram-scale synthesis, as the amount of solvent required for extraction would be enormous. Therefore, a special apparatus (Figure 2) was used for the continuous extraction of the aqueous phase for a longer time (3 days) using ethyl acetate or CH_2Cl_2 under different pH levels using a test batch of 20.0 g reaction. While continuous extraction with EtOAc under pH ∼9−10 (pH adjusted by adding 6 N HCl) gave compound **13** along with one major impurity **17** (LCMS: 163.0 [M + 1] and 185.0 [M + Na]), possibly from the ether bond cleavage of **13**, whereas continuous extraction with CH_2Cl_2 under the pH ∼9−10 gave **13** along with another impurity **18** (LCMS: 296.1 [M + 1]; quaternary ammonium salt, Figure 2) possibly from the addition of **13** and CH_2Cl_2.

In contrast, continuous extraction with EtOAc without adjustment of pH by adding 6 N HCl to the reaction mixture (pH >10) successfully provides the desired product **13** with relatively good yield and purity (after slurry purification disposal). Based on the optimized extraction conditions with EtOAc, the isolated yield of **13** for a medium-scale reaction of 560.0 g was 79%. However, when this procedure was demonstrated on a kilogram scale (9.22 kg), the desired compound **13** provided a moderate yield (66.9%) with a 98.5% HPLC purity. The lower yield during kilogram-scale synthesis might be due to incomplete continuous extraction even after reflux for 3 days. Also, 2.7% product **13** was found in 42 kg of the filtrate using a mixture of EtOH/EtOAc for washing. Therefore, some process development works are still needed to improve the yield and potential manufacture.

2.6. Telescoped Synthesis of Boc-Protected Amino-Thiazole Intermediate 15. As a next step, we set out to optimize the telescoped reaction sequence involving the chlorination of **13**, followed by the S_NAr reaction to produce the intermediate **15** in kilogram scales. The chlorination reaction of **13** with $POCl_3$/DCE was not suitable for manufacturing on a kilogram scale due to the DCE solvent's high toxicity. Hence, we investigated the chlorination reactions with two different solvents and reaction conditions for the efficient production of **14** (Table 3). Completion of the reaction was monitored using HPLC, both by monitoring the disappearance of the reactant **13** and the formation of the product **14**. The purity of the product was influenced both by the reaction solvent and reaction's batch size. The chlorination reaction of **13** in toluene affords **14** with a large number of impurities. In contrast, the reaction in acetonitrile was promising with a higher purity of the product during a multigram-scale synthesis of **14** (entry 5 in Table 2, HPLC purity: 96.7%).[20] The conversion rate of the reaction was influenced by the increased batch size, temperature, and time. The crude product **14** was directly used in the next step (S_NAr reaction) after workup, as it was not stable on isolation. Moreover, it was found that the presence of **7** helps the intermediate **14** to maintain stability. Therefore, compound **7** was added during the reaction workup process for **14**, and then the reaction mixture was concentrated. The solvent was exchanged with dichloromethane to perform the second step of the telescoped synthesis.

For the large-scale synthesis quenching and workup of the reaction mixture to get the crude product **14** with high purity required careful handling, as the chlorinated product **14** at pH ≤ 3 or ≥ 10 hydrolyzed to the starting material **13**.[22] Therefore, upon completion of the chlorination reaction, the batch temperature was decreased to 26 °C; this resulted in the solidification of the reaction mixture, which was difficult to handle. Moreover, when the reaction was diluted with DCM at the batch temperature of 26 °C, the brown sticky precipitate was suspended in the reaction mixture. It was difficult to transfer into another reactor for workup. As the reaction's quenching process was exothermic in nature, the crude reaction temperature was decreased to −5 °C and neutralized with a 10% K_2CO_3 aqueous solution to raise the pH to 3. The resulting clear solution was further neutralized with a 10% K_2CO_3 aqueous solution by maintaining the same temperature until pH 9. For the workup process, the quenched solution was transferred to another reactor, warmed to ∼15 °C, agitated for 20 min, and settled to split layers and extracted with DCM to isolate the product. Unfortunately, during this workup process, it was found that over 50% of **14** hydrolyzed back to the starting material **13**.

The hydrolysis of **14** increased in the reaction with side product HCl autocatalyzing the reaction. Therefore, in the next attempt, we successfully applied the quenching and workup process by adopting the method developed by Pesti *et al.*[22] Cold aqueous K_2HPO_4 would be an advantageous quench

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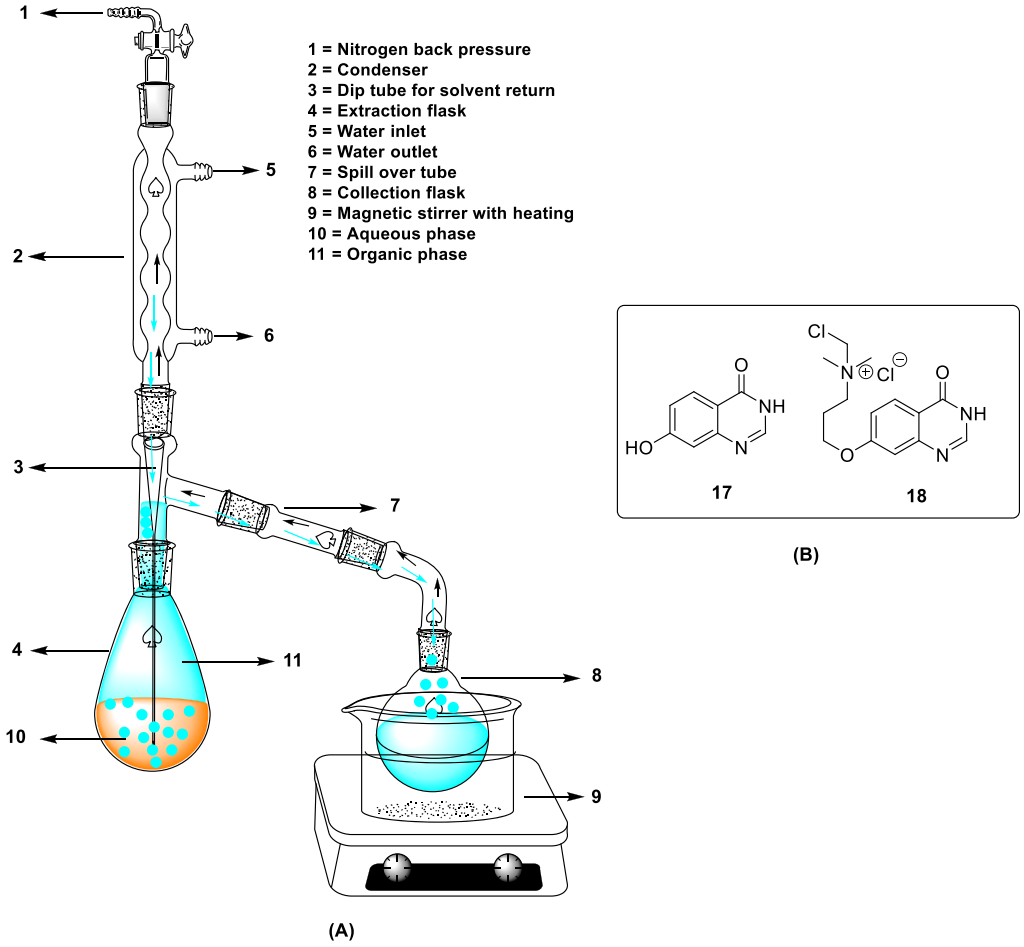
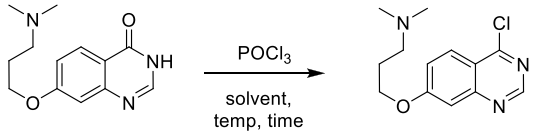


Figure 2. Continuous liquid−liquid extraction. (A) Liquid−liquid continuous extractor for solvents less dense than water (for example. EtOAc/H_2O). The flow of the organic (EtOAc) gas phase is shown using black-color arrows, and the movement of the liquid phase is shown using blue-color arrows. The organic liquid phase extracts the product from the aqueous layer present in flask 4 and gets collected in a separate flask 8 and (B) structure of impurities (17 and 18) formed during the extraction process.

Table 3. Chlorination of 13 with $POCl_3$ under Different Conditions[a]



13 14

entry	batch size (**13**, g)	temp (°C)	solvent	time (h)	HPLC (%)[b] **14**	HPLC (%)[b] impurities
1	0.70	70	toluene	2.0	77.4	19.2
2	5.00	65	CH_3CN	2.0	93.9	2.7
3	20.00	65	CH_3CN	1.5	94.1	3.0
4	108.00	70	CH_3CN	1.5	90.2	5.4
5	164.00	80	CH_3CN	8.0	96.7	2.1

[a]Reaction performed with quinazolinone **13** (1.0 equiv), $POCl_3$ (2.0 equiv). [b]Purity determined by HPLC analysis (C18 HPLC column, 0.1% TFA in ACN/0.1% TFA in H_2O).

solution; as in the case of an accidental overcharge, it would not result in an overly caustic quench mixture. Moreover, using a base with more strength to neutralize acid, i.e., K_2CO_3, that required less water to dissolve per base equivalent, was not advantageous in the initial neutralization of $POCl_3$. Therefore, in the next attempt, the batch temperature was carefully decreased to 30−35 °C (this prevented solidification of the reaction mixture), and then the reaction mixture was diluted with CH_2Cl_2. Next, the reaction mixture was quenched by the slow addition of 12.5% K_2HPO_4 aqueous solution to reach a pH of 4 to 5 by maintaining the reaction temperature at −5 to +5 °C. The reaction mixture was further neutralized with a 50% K_2CO_3 aqueous solution to reach a pH of 9 to 10 by maintaining the reaction mixture at low temperatures. Subsequently, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 and concentrated under vacuum to a minimum amount of solvent; this was centrifuged to get crude **14**. The unstable intermediate **14** is efficiently accessible under careful workup conditions with a purity of 96.7% in kilogram scales. The optimized chlorination process was scaled up effectively for **14**, with a batch size of 1.45 kg of the starting material.

We tested different types of bases and solvent conditions for the next telescoped S_NAr displacement reaction of **14** with **7** (commercially available) (Table 4). Use of Et_3N, or K_2CO_3 in EtOH, *i*-PrOH, DMF, DMAC, or CH_3CN solvents, resulted in a high level of impurities (7.4−16.5%) with a mass of 688.4 (M + 1) at 11.7 min (HPLC analysis) (Table 4). The impurity with M + 1 of 688.4 is likely to be a pseudo-dimeric impurity formed by S_NAr reaction between the dimethylamino nitrogen

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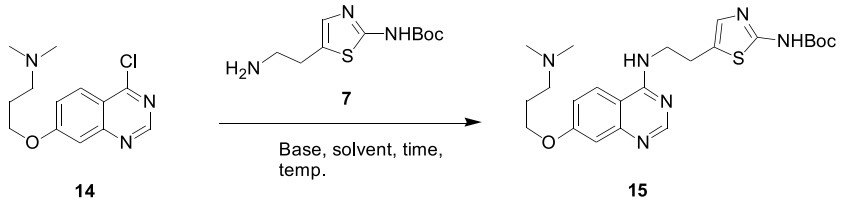
Table 4. Optimization of S_NAr Reaction of 14 under Different Reaction Conditions[a]



entry	14 (purity)	base[b]	solvent	temp (°C)	time (h)	HPLC (%) 15	HPLC (%) impurities[c]
1	0.60 g (95.4%)	Et_3N	*i*-PrOH	80	2.5	83.0	8.9
2	0.60 g (95.4%)	Et_3N	EtOH	80	2.5	83.3	8.0
3	5.00 g (86.3%)	K_2CO_3	DMF	70	2.0	72.4	9.7
4	3.30 g (91.3%)	K_2CO_3	DMAC	70	2.5	75.1	12.2
5	3.34 g (92.0%)	DIPEA	*i*-PrOH	80	3.0	79.1	11.3
6	0.50 g (93.2%)	DIPEA	EtOH	80	2.0	68.3	16.5
7	1.20 g (89.8%)	DIPEA	CH_3CN	65	7.0	96.4	3.5
8	517.30 g (91.0%)	DIPEA	CH_3CN	65	9.0	95.0	3.3

[a]Reaction performed with chloroimidate **14** (1.0 equiv), amine **7** (1.0 equiv). [b]Base (1.0 equiv). [c]Purity determined by HPLC analysis (C18 HPLC column, 0.1% TFA in ACN/0.1% TFA in H_2O). Moreover, the different bases generated the same types of impurities and are provided in %.

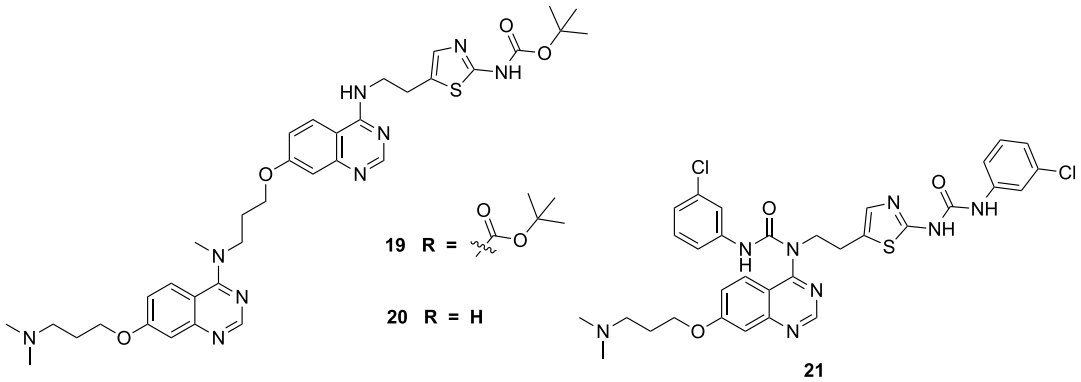
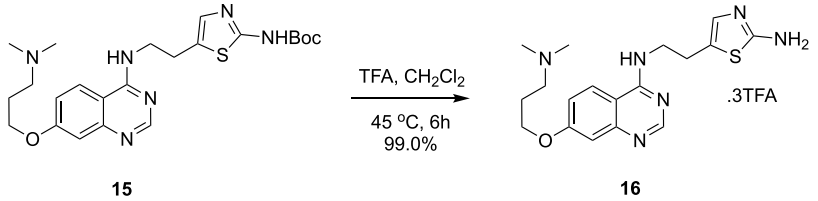


Figure 3. Structure of impurities of **19**, **20**, and **21**.

Scheme 5. Synthesis of Amino-thiazole 16



of product **15** and starting material **14**, followed by demethylation. The possible structure of impurity (**19**) is shown in Figure 3. The formation of such pseudo-dimeric compounds is reported earlier.[23] However, the use of diisopropylethylamine (DIPEA) in acetonitrile gave promising results for this reaction. Therefore, we attempted bulk-scale synthesis using **14** (entry 8, 517.3 g, purity: 91.0% HPLC) under the same condition, which produced **15** (95.0% purity), with a low level of impurity (3.3%).[24] This indicates that the formation of impurity **19** is suppressed to a minimum level.

Even though the above reaction condition minimized the amount of impurity **19** formed, there was a need to remove the ~3% level of impurity present in the final product. For this, the crude compound **15** was washed with several solvents such as EtOAc, MeOH, EtOH, *i*-PrOH, CH_3CN, CH_2Cl_2, and acetone, which could not remove the impurity to a satisfactory limit. In contrast, the use of a mixture of EtOAc/MeOH (10:1.5) solvent to wash the product removed the impurity successfully (due to differential solubility of impurity and the product **15**), and only a minimum level (0.8−0.9%) was detected in the final product **15**.

2.7. Synthesis of Intermediate 16. We used the same reaction method in route B2 to synthesize penultimate compound **16** (Scheme 5) for kilogram-scale synthesis. To obtain high purity on a bulk scale, compound **15** was reacted with TFA in dichloromethane at around 40−45 °C to remove the Boc protective group to get **16** as TFA salt.[12] During the process development, it was found that the impurity **19** (688.4 [M + 1]) from the previous step remained, which gave a corresponding de-Boc impurity **20** (Figure 3) at 5.8 min (588.3 [M + 1], HPLC analysis) after the reaction. Further, it was found that the purity of **16** depends only on the quality of

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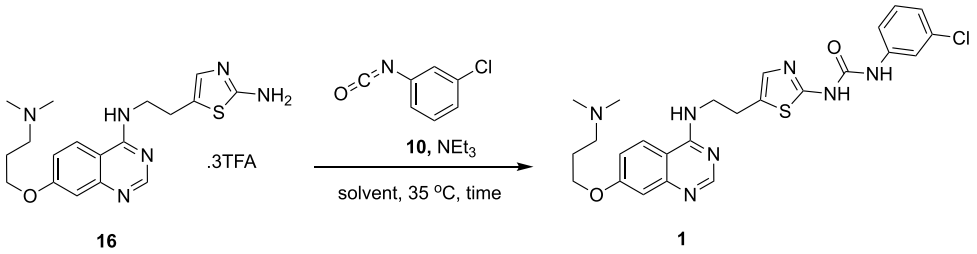
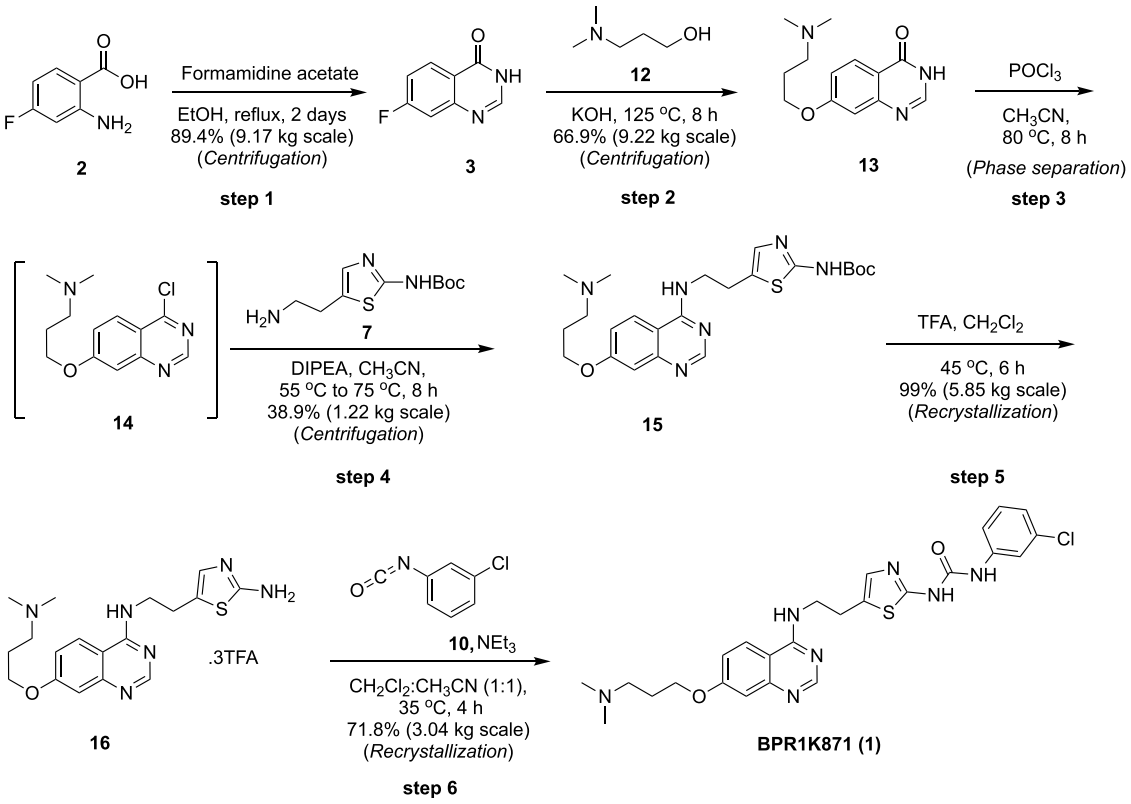
Table 5. Solvent Screening for Urea Bond Formation to Get 1[a]



				1	
entry	16 (purity)	solvent	time (h)	yield (%)[b]	purity (%)[c]
1	10.0 g (95.0%)	CH_2Cl_2	12	65.2	89.4
2	10.0 g (98.1%)	CH_2Cl_2/MeOH	12	66.0	96.5
3	16.6 g (98.1%)	CH_2Cl_2/CH_3CN	5	69.3	96.9
4	130.0 g (98.2%)	CH_2Cl_2/CH_3CN	5	92.9	97.7

[a]Reaction performed with amine **16** (1.0 equiv), isocyanate **9** (1.5 equiv), and Et_3N (3.0 equiv). [b]Isolated yields of product **1**. [c]Purity determined by HPLC analysis (C18 HPLC column, 0.1% TFA in ACN/0.1% TFA in H_2O).

Scheme 6. Kilogram-Scale Synthesis of 1 (Route B3)



starting material **15** and does not change with minor variations in the reaction conditions. Hence, the pure product's isolation from the reaction mixture required a robust recrystallization procedure, for which MTBE (methyl *tert*-butyl ether) and MeOH solvent mixture was used.

Consequently, using the above reaction and workup method, intermediate **16** was obtained in an excellent yield (99%) and HPLC purity (98.2%) on a single large-scale batch of 5.5 kg without the need for column purification. As it was found that **16** absorbed moisture easily over a short time (4.6% to 9.0% over 24 h, as determined by Karl Fischer titration), it was stored under anhydrous condition (desiccant) until consumed in the next step.

2.8. Synthesis of BPR1K871 (1). The final compound **1** was synthesized using the same coupling reaction used in route B2, where the reaction between intermediate **16** and 3-chlorophenyl isocyanate (**10**) was carried out in DCM using Et_3N as a base (Scheme 4).[12,24] At first, the reaction on a large scale using DCM as a solvent alone resulted in the incomplete reaction due to the formation of a sticky suspension. Hence, unreacted starting material **16** was still present even after prolonged reaction time. Hence, we sought an alternative solvent system to carry out the reaction (Table 5). The use of the CH_2Cl_2/MeOH solvent system to conduct the reaction showed that the coupling reaction did not occur efficiently. Moreover, the use of an additional quantity of **10** to drive the

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reaction to completion resulted in the formation of an impurity **21** (679.0 [M + 1]) at 14.2 min in HPLC (Figure 3) due to diurea formation. Finally, the reaction in CH_2Cl_2/CH_3CN (1:1) solvent mixture went on to completion with a good yield of the final product **1**, which was isolated by recrystallization from a mixture of CH_3CN and MeOH (1:1). The CH_2Cl_2/CH_3CN (1:1) solvent system avoided sticky gel formation during the reaction process. Moreover, it was found that the starting material's moisture content needs to be kept at a minimum so that **16** could be consumed completely during the reaction to get the final product in high purity. This procedure was used on a kilogram scale to get 3.09 kg of **1** (71.8% yield) with 97.8% HPLC purity.

2.9. Final Scale-Up Synthetic Route. The optimized process manufacturing was run on a multikilogram scale in a kilo lab facility using a six-step reaction sequence (Scheme 6). All the steps provided the product as solid and were centrifugation either from the reaction mixture directly or recrystallized from solvents to get the product in high purity. In the first step, the quinazolinone **3** was formed from the commercially available material **2**. Once the reaction was completed, simple centrifugation provided the product in high purity. While in the second step, the isolation of **13** from the reaction mixture required continuous liquid−liquid extraction due to poor solubility of **13** in EtOAc. Product **14** from step 3 was telescoped directly to step 4 due to instability of the chloro product **14**. A well-controlled quenching process with a 12.5% K_2HSO_4 aqueous solution and saturated K_2CO_3 aqueous solution ensured the preparation of **14** in high purity. Recrystallization from MTBE and MeOH solvents provided **16** in excellent purity (98.2%) in step 5, ready for the final reaction. Finally, urea formation in a mixture of the CH_2Cl_2/CH_3CN (1:1) solvent system produced 3.09 kg of final product **1** in a single batch.

3. CONCLUSIONS

In summary, we established a robust and scalable process for the synthesis of multitargeted kinase inhibitor BPR1K871 (**1**) as a clinical candidate. During the scale-up synthesis, we overcame several inherent difficulties associated with the initial medicinal chemistry synthetic method (route A). Particularly, the terminal dimethyl amino functional groups in the earlier step in the synthesis enabled easy purification of the products. The isolation of less soluble intermediate **13** was successfully carried out by continuous liquid−liquid extraction. During the scale-up process, the formation of various impurities **17**−**21** was minimized using optimized reaction conditions and careful processing steps, which helped to avoid column chromatography purification steps. The scale-up synthetic method (route B3) was one step shorter than the initial route A (seven steps; 7.7% yield) and provided **1** with an improved yield of 16.5%. Product **1** was prepared in a single batch of 3.09 kg (97.8% HPLC purity) for preclinical testing. Improved yield, avoidance of several column chromatography purification steps, the use of safe reagents, and the minimum amounts of reagents/solvents resulted in the synthesis of **1** cost-effectively. The developed methodology could be employed for the synthesis of **1** to support the clinical development.

4. EXPERIMENTAL SECTION

4.1. General Procedure. All the starting materials, reagents, and solvents were obtained from commercial suppliers and used without further purification. The process campaign reactions are performed in a glass or glass-lined jacketed reactor flushed with dry nitrogen. The compounds were characterized by ^{1}H-NMR and ^{13}C-NMR spectra using Varian Mercury 400 MHz spectrometers. ^{1}H-NMR chemical shifts are reported as δ values in part per million (ppm) and relative to the deuterated solvents' residual resonance. In-process control analysis coducting by HPLC for intermediates using method 1 and the final product was conducted using HPLC method 1 and 2. HPLC method 1: Agilent 1100 DAD system, Agilent Zorbax Eclipse Plus C18 column, 150 × 4.6 mm, 3.5 μM, 1.0 mL/min, at 30 °C, DAD detector, UV detection at 220, 240, 254, 260 nm, injection volume 5 μL and Mobile phase A (0.1% TFA in H_2O), and mobile phase B (0.1%TFA in ACN). The gradient elution program at 0 min was mobile phase A 95 and 5% mobile phase B, at 14 min was mobile phase A 40 and 60% mobile phase B, 18−22 min was mobile phase A 10 and 90% mobile phase B with an acquisition time of 22 min. Method 2: Agilent 1200 DAD system, Agilent Zorbax SB-CN column, 150 × 4.6 mm, 3.5 μm, 1.0 mL/min, at 30 °C, DAD detector, UV detection at 254, nm, injection volume 5 μL and mobile phase A (10 mM KH_2PO_4 in water (adjusted pH = 2.5 by H_3PO_4)), and mobile phase B (ACN/THF = 95/5). The gradient elution program at 0 min was mobile phase A 95 and 5% mobile phase B and at 22 min 10% mobile phase A and 90% mobile phase B with an acquisition time of 22 min. High-resolution mass spectra (HRMS) were recorded using a VARIAN 901-MS.

4.2. Synthetic Route A. The experimental details and compound characterization (NMR and HRMS) for the synthesis of BPR1K871, according to route A, were previously reported.[7]

4.3. Synthetic Route B1. *4.3.1. 7-(3-(Dimethylamino)-propoxy)quinazolin-4(3H)-one (**13**).* To a stirred solution of 2-amino-4-fluorobenzoic acid (**2**) (1.00 g, 6.45 mmol) in DMSO (2 mL) was added formamidine acetate (1.07 g, 10.31 mmol) at room temperature, and the resulting mixture was heated to 120 °C for 4 h. Further, 3-dimethylamino-1-propanol (7.98 g, 77.35 mmol) was added to the reaction mixture and stirred at the same temperature for 1 h. To the resulting mixture at 120 °C, KOH (4.34 g, 77.35 mmol) was added as one portion, and stirring was continued at 125 °C for 16 h. The mixture was cooled to room temperature and diluted with H_2O (200 mL), and the solution pH value adjusted to 10 with an 18% HCl solution before being extracted with CH_2Cl_2 (6 × 200 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford compound **13** (1.32 g, 83%) as a yellow solid.

*4.3.2. 3-((4-Chloroquinazolin-7-yl)oxy)-N,N-dimethylpropan-1-amine (**14**).* To a stirred solution of **13** (0.50 g, 2.02 mmol) and DMF (0.5 mL) in toluene (5 mL) was heated to 90 °C and then added $SOCl_2$ (2.93 mL, 40.44 mmol). The resulting solution was stirred at the same temperature for 2 h. The reaction was cooled to room temperature, removed the excess reagent under reduced pressure, and diluted with CH_2Cl_2 (40 mL) and sat. $NaHCO_3$ aqueous solution (40 mL). The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford crude product **14** (0.52 g) as a brown solid. This compound was used immediately for the next step without further purification.

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*4.3.3. 5-(2-((7-(3-(Dimethylamino)propoxy)quinazolin-4-yl)amino)ethyl)thiazol-2-amine (**16**).* To a stirred solution of the above compound **14** and *tert*-butyl (5-(2-aminoethyl)-thiazol-2-yl)carbamate (**7**) (0.49 g, 2.02 mmol) in EtOH (10 mL) added triethylamine (0.61 g, 6.07 mmol) at room temperature. The resulting mixture was heated to 85 °C for 16 h. The reaction was cooled to room temperature, the solvent evaporated under reduced pressure, and the residue was diluted with CH_2Cl_2 (100 mL) and H_2O (100 mL). The organic layer was separated, and then 3 N HCl (100 mL) was added and extracted. The organic layer was discarded. The aqueous layer containing the compound was separated and further diluted with a mixture of H_2O (100 mL) and CH_2Cl_2 (100 mL), and the pH value adjusted to 12 with 2 N NaOH. The organic phase was separated. The aqueous phase extract with CH_2Cl_2 (2 × 100 mL); the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford **16** (0.23 g, 31.1%, over three steps).

*4.3.4. 1-(3-Chlorophenyl)-3-(5-(2-((7-(3-(dimethylamino)-propoxy)quinazolin-4-yl)amino)ethyl)thiazol-2-yl)urea (**1**).* A solution of compound **16** (0.23 g, 0.62 mmol) and 3-chlorophenyl isocyanate (1.91 g, 12.46 mmol) in MeOH (0.7 mL) and CH_2Cl_2 (7 mL) was stirred at room temperature for 16 h. Once the reaction is over, the solvent was removed under reduced pressure; acetone (20 mL) was added to the residue and stirred at room temperature for 16 h. The resulting solid was collected to afford compound **1** (0.15 g, 45%) as a white solid.

4.4. Synthetic Route B2. *4.4.1. 7-Fluoroquinazolin-4(3H)-one (**3**).* A stirred solution of 2-amino-4-fluorobenzoic acid (**2**) (20.00 g, 0.13 mol) in EtOH (200 mL) was heated to reflux for 1 h. The resulting mixture at room temperature was filtered, and formamidine acetate (13.32 g, 0.13 mol) was added to the collected filtrate and heated to reflux for 3 days. The reaction mixture was cooled to room temperature, and the formed solid product was filtered and washed with EtOH (30 mL) to afford compound **3** (15.00 g, 71%) as a brown solid.

*4.4.2. 7-(3-(Dimethylamino)propoxy)quinazolin-4(3H)-one (**13**).* To a stirred solution of compound **3** (15.00 g, 0.09 mol), 3-(dimethylamino)propan-1-ol (42.42 g, 0.41 mmol) in DMSO (30 mL) at room temperature, was added KOH (20.02 g, 0.37 mol). The resulting solution was stirred at 140 °C for 16 h. Then, the reaction was cooled down to room temperature and diluted with H_2O (150 mL) and EtOAc (100 mL). The solution pH was adjusted to 10 with a 6 N HCl and then filtered to remove insoluble particles. The resulting filtrate was continuously extracted with EtOAc (200 mL) for about 16 h using a continuous liquid−liquid extractor (shown in Figure 2). The collected organic phase was cooled to room temperature, concentrated to about 50 mL, and stirred at room temperature for 4 h to precipitate the compound. The precipitate was filtered and dried to afford compound **13** (12.53 g, 55%) as a white solid.

*4.4.3. 3-((4-Chloroquinazolin-7-yl)oxy)-N,N-dimethylpropan-1-amine (**14**).* To a stirred solution of **13** (9.00 g, 36.39 mmol) in 1,2-dichloroethane (18 mL) was added $POCl_3$ (9.18 mL, 98.26 mmol) under a nitrogen atmosphere at room temperature. The resulting solution was heated to the reflux temperature of the solvent for 4 h. The reaction was quenched with ice water (200 mL), and then the pH was adjusted to 9 with sat. Na_2CO_3 solution. The reaction mixture was extracted with CH_2Cl_2 (2 × 300 mL), and to the combined organic phases were added acid clay (9.0 g) and $MgSO_4$ (9.0 g), followed by being stirred for 15 min. The mixture was filtered, and the collected filtrate concentrated under reduced pressure to afford the product **14** (8.24 g, 85%) as a red liquid.

*4.4.4. tert-Butyl(5-(2-((7-(3-(dimethylamino)propoxy)-quinazolin-4-yl)amino)ethyl)thiazol-2-yl) Carbamate (**15**).* To a solution of the above compound **14** (8.24 g, 31.00 mmol) and Et_3N (4.32 mL, 31.00 mmol) at room temperature were added *i*-PrOH (16 mL) and *tert*-butyl (5-(2-aminoethyl)-thiazol-2-yl)carbamate (**7**) (9.05 g, 37.20 mmol). The resulting solution was heated to reflux under a N_2 atmosphere for 30 min. Next, the solvent was removed under reduced pressure and diluted with CH_2Cl_2 (50 mL) and H_2O (50 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL); the combined organic phases were washed with sat. $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was dissolved in a mixture of EtOH (8 mL) and diethyl ether (80 mL) by heating to boiling, filtered, and then cooled to room temperature. This solution was stirred overnight to precipitate the product, which was collected by filtration to afford **15** (8.95 g, 52%) as a white solid.

*4.4.5. 5-(2-((7-(3-(Dimethylamino)propoxy)quinazolin-4-yl)amino)ethyl)thiazol-2-amine (**16**).* To a solution of **15** (6.30 g, 13.33 mmol) in CH_2Cl_2 (102 mL) at room temperature was added TFA (21.42 mL, 0.27 mol). The resulting mixture was stirred at the same temperature for 16 h. The solvent was removed under reduced pressure, added MeOH (6 mL) and diethyl ether (24 mL), and stirred for 2 h. The precipitate formed was filtered to get **16** (9.30 g, ∼99%) as a white solid.

*4.4.6. 1-(3-Chlorophenyl)-3-(5-(2-((7-(3-(dimethylamino)-propoxy)quinazolin-4-yl)amino)ethyl)thiazol-2-yl)urea (**1**).* To a solution of compound **16** (9.5 g, 13.29 mmol) in dry CH_2Cl_2 (190 mL) under an N_2 atmosphere at room temperature was added Et_3N (3.70 mL, 26.58 mmol). The resulting solution was stirred for 30 min and then added slowly 1-chloro-3-isocyanatobenzene (**10**) (3.24 mL, 26.59 mmol) for about 80 min at room temperature and stirred for an additional 30 min. The precipitated product from the reaction mixture was collected by filtration. The crude product was dissolved in EtOAc (40 mL) and added Et_3N (3.7 mL) dropwise at 0 °C; then H_2O (40 mL)was added to the solution at that same temperature and stirred for 2 h. The product precipitated out and was filtered to obtain **1** (5.12 g, 73%) as a white solid with HPLC purity of 99.1%.

4.5. Synthetic Route B3. *4.5.1. 7-Fluoroquinazolin-4(3H)-one (**3**).* A 200.0 L glass-lined jacketed reactor was charged with ethanol (70.0 kg) and 2-amino-4-fluorobenzoic acid (**2**) (9.70 Kg, 62.52 mol, 1.0 equiv). The resulting mixture was stirred at room temperature and then added formamidine acetate (13.13 kg, 125.04 mol, 2.0 equiv) in one portion at the same temperature. The reaction mixture was warmed to reflux and stirred for 2 days. When the HPLC analysis indicated <4% of the starting material **2** remained, the batch temperature was gradually decreased to 10−15 °C and stirred for 4 h at that temperature. While maintaining the internal temperature of 10−15 °C, the compound was precipitated, the mixture was centrifuged, and the cake was rinsed with ethanol (8.0 Kg). The wet cake was dried in an oven under vacuum at 55 °C for 24 h to afford compound **3** (9.17 kg, 89.4%) as an off-white solid with an HPLC purity of 99.8%. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.35 (brs, 1H), 8.16 (dd, J = 8.8, 6.4 Hz, 1H),

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8.13 (s, 1H), 7.45 (dd, J = 10.4, 2.8 Hz, 1H), 7.39 (ddd, J = 8.4, 8.8, 2.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6), δ 166.8−164.3 (d, J = 249.3 Hz), 160.0, 150.9 (d, J = 13.0 Hz), 146.8, 128.9 (d, J = 10.7 Hz), 119.6, 115.2 (d, J = 23.7 Hz), 112.3 (d, J = 21.4 Hz). HRMS (ESI) calcd for $C_8H_5FN_2NaO$ [M + Na]: 187.0283; found 187.0283.

*4.5.2. 7-(3-(Dimethylamino)propoxy)quinazolin-4(3H)-one (**13**).* A 200.0 L glass-lined jacketed reactor was charged with 3-(dimethylamino)propan-1-ol (**12**) (31.62 kg, 306.59 mol, 5.5 equiv) and powdered KOH (12.51 kg, 222.98 mol, 4.0 equiv). The resulting mixture was warmed to 120 °C and stirred for 1 h. Then, quinazolinone **3** (9.15 kg, 55.75 mol, 1.0 equiv) was added to the reactor at that temperature. The reaction mixture was stirred at the same temperature for 8 h; HPLC analysis indicated only 0.3% of **3** remained (Rt = 6.9 min). The reaction mixture was cooled down to 15 °C, and H_2O (100.0 L) was added to the reactor dropwise over a 1 h period while maintaining the internal temperature at 20−25 °C. The resulting mixture was continuously extracted with EtOAc (650.0 kg) for 3 days using a liquid−liquid continuous extractor, as shown in Figure 2. Finally, the aqueous phase was extracted twice with a mixture of EtOAc (150.0 kg × 2) and EtOH (10.0 kg × 2); the combined organic phase was concentrated under vacuum at 50 °C until the volume was about 55.0 L. The mixture was treated with EtOH (5.0 kg) and heated to 45 °C for 1 h. The solution temperature was decreased to 15 °C and held for about 2 h to afford the product's precipitation. The mixture was centrifuged, collected the solid, and the cake rinsed with a mixture of EtOAc (4.9 kg) and EtOH (0.46 kg), which gave 11.20 kg wet cake. The wet cake was dried in an oven under vacuum at 45 °C for 18 h to give the desired product **13** (9.22 kg, 66.9%) as a white solid, with an HPLC purity of 98.5%.^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.07 (brs, 1H), 8.04 (s, 1H), 8.00 (d, J = 9.6 Hz, 1H), 7.08 (t, J = 7.6 Hz, 2H), 4.13 (t, J = 6.4 Hz, 2H), 2.37 (t, J = 6.8 Hz, 2H), 2.15 (s, 6H), 1.91−1.84 (m, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6), δ 163.2, 160.2, 150.9, 145.9, 127.4, 116.3, 115.9, 108.8, 66.3, 55.5, 45.1, 26.6. HRMS (ESI) calcd for $C_{13}H_{18}N_3O_2$ [M + H]: 248.1399; found 248.1395.

*4.5.3. 3-((4-Chloroquinazolin-7-yl)oxy)-N,N-dimethylpropan-1-amine (**14**).* A 50.0 L glass-lined jacketed reactor was charged with CH_3CN (7.8 kg) and **13** (1.64 kg, 6.63 mol, 1.0 equiv) and stirred at room temperature. Further, $POCl_3$ (2.03 kg, 13.26 mol, 2.0 equiv) was added into the reaction mixture over 10 min while maintaining the batch temperature below 30 °C. The temperature was increased to ∼80 °C over 45 min (the reaction mixture cleared at 56 °C) and held for 8 h. The completion of the reaction was established by HPLC analysis, which indicated that the unreacted starting material was around 1%. The reaction was cooled to ∼35 °C over 1 h, charged with CH_2Cl_2 (46.0 kg), and then transferred into a dropping tank. The mixture in the dropping tank was transferred into a 12.5% K_2HPO_4 aqueous quench solution (97.4 kg) in a 200.0 L reactor over a 20 min period while maintaining the temperature −5 to +5 °C to reach the target pH 4−5. Then, 50% K_2CO_3 aqueous solution (14.8 kg) was charged into the reactor over 20 min at 5−15 °C until pH 9−10. The mixture was stirred for 20 min at about 15 °C and settled to split layers. The organic layer was separated, and the aqueous layer was washed with CH_2Cl_2 (46.0 kg) again. The combined organic phase was washed with 5% brine (33.0 kg) and dried over Na_2SO_4 (6.6 kg) for 2 h. The mixture was filtered and rinsed with CH_2Cl_2 (13.0 kg), the filtrate was sampled for HPLC purity and found to be 96.7%. Due to the instability of chloro compound **14**, the above filtrate was directly used for the next step.

*4.5.4. tert-Butyl(5-(2-((7-(3-(dimethylamino)propoxy)-quinazolin-4-yl)amino)ethyl)thiazol-2-yl) Carbamate (**15**).* The amine **7** (1.45 kg, 5.97 mol, 0.9 equiv) was directly charged into the filtrate **14**, which was obtained in the earlier step. The reaction mixture was then concentrated under vacuum at 20 °C to about 2.5 L volume and was charged with CH_3CN (8.2 kg) and then concentrated to about 4.1 L volume. The mixture was transferred to a 50.0 L reactor, and CH_3CN (6.6 kg) and DIPEA (0.856 kg, 6.63 mol, 1.0 equiv) were charged into the reactor. The mixture was heated to 55 °C and held for 2 h; then the batch temperature raised to 65 °C over 30 min and held for 2 h with stirring. An additional amount of amine **7** (0.161 kg, 0.663 mol, 0.1) was charged into the reactor at that temperature. The reaction temperature was raised to 75 °C and stirred for 4 h. The reaction mixture was sampled by HPLC, which detected 3.5% unreacted starting material **14**. Then, MeOH (0.62 L) was added into the reactor while the temperature was maintained at about 65 °C and held for 1 h. The mixture was cooled to 20 °C over 2 h. The mixture was stirred for about 5 h and then centrifuged to get the crude cake and washed with a mixture of CH_3CN (7.0 kg) and MeOH (0.40 kg) to get 4.56 kg **15** as a wet-cake with 89.5% HPLC purity. A solution of EtOAc (6.32 kg) and MeOH (1.26 kg) and the wet cake 4.56 kg in a 50 L reactor was heated to 85 °C for 12 h. Then, the reaction temperature cooled to 20 °C over 2.5 h and held for 3 h. The mixture was centrifuged, and the cake was rinsed with EtOAc (4.0 kg) to afford a 1.30 kg product. The wet cake was dried in an oven under vacuum at 50 °C for 10 h to get the product **15** (1.22 kg, 38.9% yield over two steps) as a light brown solid with 96.8% HPLC purity. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.16 (brs, 2H), 8.41 (s, 1H), 8.24 (t, J = 5.2 Hz, 1H), 8.10 (d, J = 9.2 Hz, 1H), 7.11 (dd, J = 9.2, 2.4 Hz, 2H), 7.07 (dd, J = 8.4, 2.4 Hz, 2H), 4.12 (t, J = 6.4 Hz, 2H), 3.70 (q, J = 12.8, 6.8 Hz, 2H), 3.06 (t, J = 6.8 Hz, 2H), 2.38 (t, J = 7.2 Hz, 2H), 2.15 (s, 6H), 1.92−1.85 (m, 2H), 1.44 (s, 9H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 161.7, 158.9, 158.3, 155.5, 152.7, 151.3, 134.9, 128.3, 124.2, 116.9, 109.1, 107.4, 80.8, 66.1, 55.5, 45.1, 41.7, 27.8, 26.6, 25.7. HRMS (ESI) calcd for $C_{23}H_{32}N_6NaO_3S$ [M + Na]: 495.2154; found 495.2679.

*4.5.5. 5-(2-((7-(3-(Dimethylamino)propoxy)quinazolin-4-yl)amino)ethyl)thiazol-2-amine (**16**).* A 100.0 L jacketed reactor was flushed with nitrogen and charged with Boc-amine **15** (4.00 kg, 8.46 mol, 1.0 equiv) and CH_2Cl_2 (42.2 kg). Trifluoroacetic acid (15.20 kg, 132.88 mol, 15.7 equiv) was dropwise added into the reactor over a period of 1 h, while the reaction temperature was maintained <30 °C. The resultant mixture was heated to 45 °C and stirred at that temperature for about 6 h. When the HPLC analysis indicated that <1% of **15** remained, then, the reaction was concentrated to about 10.0 L volume. Subsequently, MeOH (3.2 kg) and MTBE (12.0 kg) were charged into the reactor and stirred at room temperature for about 6 h. The mixture was filtered, and the solid obtained was washed with MTBE (12.0 kg). The wet cake was dried in a vacuum oven at 50 °C for about 2 days to yield 5.85 kg (∼99%) of **16** as a white solid with 98.2% HPLC purity. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.98 (brs, 1H), 9.83 (brs, 1H), 8.86 (s, 1H), 8.69 (s, 1H), 8.38 (d, J = 9.6 Hz, 1H), 7.40 (dd, J = 9.2, 2.4 Hz, 1H), 7.25 (d, J = 2.4 Hz, 1H), 7.04 (s, 1H), 4.24 (t, J = 6.0 Hz, 2H), 3.86 (q, J = 12.4, 6.4 Hz, 2H), 3.25 (brs,

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2H), 3.03 (t, J = 6.4 Hz, 2H), 2.83 (s, 6H), 2.22−2.15 (m, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6), δ 169.6, 163.6, 160.1, 158.9 (q, J = 64.9, 32.8 Hz, C═O, trifluoroacetic acid), 151.4, 140.2, 125.7 (d, J = 98.4 Hz), 121.4 (CF_3, trifluoroacetic acid), 118.4 (d, J = 31.3 Hz), 115.3, 106.9, 101.2, 65.9, 53.9, 42.2, 41.8, 25.5, 23.6. HRMS (ESI) calcd for $C_{18}H_{25}N_6OS$ [M + H]: 373.1810; found 373.1807.

*4.5.6. 1-(3-Chlorophenyl)-3-(5-(2-((7-(3-(dimethylamino)-propoxy)quinazolin-4-yl)amino)ethyl)thiazol-2-yl)urea (**1**).* A 200.0 L jacketed reactor flushed with nitrogen was charged with **16** (5.57 kg, 8.05 mol, 1.0 equiv), CH_2Cl_2 (61.0 kg), and dry CH_3CN (36.8 kg) while stirring at 32 °C. Then, Et_3N (2.80 kg, 27.60 mol, 3.43 equiv) was added at that temperature over 15 min and stirred for 10 min. Next, 3-chlorophenyl isocyanate (2.06 kg, 13.44 mol, 1.67 equiv) was added at that temperature over 5 min, and the mixture was stirred for about 4 h while the temperature was maintained at about 35 °C; HPLC analysis determined that <0.07% of the starting material **16** remained unreacted. The reaction was cooled to 25 °C, held for 1 h, and then centrifuged to obtain the product as a cake, which was recrystallized with a CH_3CN (46.0 kg) and MeOH (36.8 kg) solvent mixture. The wet cake was dried in an oven under vacuum at 50 °C for over 12 h to afford the final product **1** (3.04 kg, 71.8%) as a white solid with purity of 97.8% (HPLC methods 1 and 2) and 97.2% assay purity with a single maximum impurity of ∼0.6−0.7%. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.64 (brs, 1H), 9.20 (brs, 1H), 8.41 (s, 1H), 8.25 (t, J = 5.6 Hz, 1H), 8.11 (d, J = 9.2 Hz, 1H), 7.70 (s, 1H), 7.33−7.28 (m, 2H), 7.11 (dd, J = 9.2, 3.2 Hz, 2H), 7.05 (m, 2H), 4.12 (t, J = 6.4 Hz, 2H), 3.72 (q, J = 12.8, 6.8 Hz, 2H), 3.07 (t, J = 7.2 Hz, 2H), 2.38 (t, J = 7.2 Hz, 2H), 2.15 (s, 6H), 1.92−1.85 (m, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 161.7, 159.2, 158.9, 155.6, 152.5, 151.3, 140.5, 133.2, 132.7, 130.4, 127.3, 124.2, 122.0, 117.8, 116.9, 109.1, 107.4, 66.0, 55.5, 45.1, 41.6, 26.6, 25.8. HRMS (ESI) calcd for $C_{25}H_{28}ClN_7NaO_2S$ [M + Na]: 548.1611; found 548.1598.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00515.

^{1}H and ^{13}C NMR spectra and HPLC characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

AML, acute myeloid leukemia; FDA, food and drug administration; FLT3, FMS-like receptor kinase tyrosine inhibitor; AURKA, Aurora Kinase A; AURKB, Aurora kinase B; MOLM-13, human leukemia cell lines; MV4-11, human leukemia cell lines; IND, investigational new drug; API, active pharmaceutical ingredient; GMP, good manufacturing practice; S_NAr, nucleophilic aromatic substitution; ATP, adenosine triphosphate; DCM, dichloromethane; ACN, acetonitrile; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; HPLC, high-performance liquid chromatography; LCMS, liquid chromatography-mass spectrometry; DCE, 1,2-dichloroethane; DMAC, dimethylacetamide; DIPEA, diisopropylethylamine; TFA, trifluoroacetic acid; MTBE, methyl *tert*-butyl ether; HRMS, high-resolution mass spectrometry; ESI, electrospray ionization

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