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Development of an Efficient, Scalable Route for the Preparation of a Novel Insulin-Like Growth Factor-1 Receptor Modulator

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Supporting Information

ABSTRACT: A chromatography-free and efficient synthesis of insulin-like growth factor-1 receptor (IGF-1R) modulator is reported. Herein we describe an improved synthesis for the target compound, which features facile introduction of a novel pyrrolidinyl-pyrimidyl isoxazole **8**, via in situ sulfone displacement by fluorine. The overall process consists of six chemical steps and five isolations, with introduction of the expensive triheterocyclic unit **8** towards the end of the synthesis.

INTRODUCTION

The insulin-like growth factor (IGF) axis consists of ligands, receptors, binding proteins and proteases. The two ligands, IGF-I and IGF-II, are mitogenic peptides that signal through interaction with the type 1 IGF-1R, a heterotetrameric cell surface receptor. Binding of either ligand stimulates activation of a tyrosine kinase domain in the intracellular region of the β-chain and results in phosphorylation of several tyrosine residues resulting in the recruitment and activation of various signaling molecules. The intracellular domain has been shown to transmit signals for mitogenesis, survival, transformation and differentiation in cells. The structure and function of the IGF-1R has been reviewed by Adams et al.[1] Since increased IGF signaling is implicated in the growth and survival of tumor cells and blocking IGF-1R function can reverse this, inhibition of the IGF-1R tyrosine kinase domain is a promising approach for evaluation in the treatment of cancer.

Research activity at AstraZeneca resulted in the discovery of penta-heterocyclic compound **1**, a modulator of the insulin-like growth factor-1 receptor (Figure 1). In order to evaluate pharmacological and safety properties of **1**, we required an efficient and chromatography-free synthesis. In this report we describe our efforts in arriving at a regioselective and scalable synthesis of **1**.

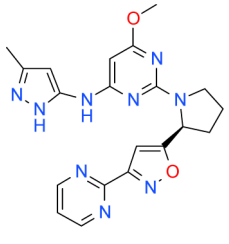

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Figure 1. Penta-heterocyclic compound.

DISCOVERY SYNTHESIS

The medicinal chemistry approach[2] for the synthesis of **1** involves the preparation of two key intermediates, **8** and **11**, and then coupling them to attain the intermediate **12** (Scheme 1). Methoxylation of **12** in the subsequent step provides the target compound **1**.

The triheterocyclic unit **8** was synthesized in five steps from commercially available diethoxy acetonitrile **2** (Scheme 1). The major drawback of this synthesis was poor regioselectivity during the formation of intermediate **7**. Isoxazole **7** and its regioisomer **7a** were formed in a ratio of 6:4 which required chromatographic purification to obtain pure **7**. The key bicyclic intermediate **11** was prepared by the reaction of amino pyrazole **10a** with commercially available trichloropyrimidine **9** which resulted in a 7:3 mixture of the desired **11** and undesired regioisomer **11a** (Scheme 1). Chromatography was employed at this point to separate the pure isomer **11** with 65% isolated yield.

Coupling of intermediate **8** and **11** provided **12** in pure form after chromatography, which on subsequent reaction with sodium methoxide under microwave conditions furnished racemic compound **13** after chromatographic purification. Chiral chromatography was employed at this point to obtain desired enantiomer **1**. The synthesis of **1** was achieved in *eight* chemical steps and *five* chromatographic purifications with an overall yield of *5%* starting from diethoxy acetonitrile **2**.

One further approach utilized by our medicinal chemistry colleagues for the synthesis of **1** is depicted in Scheme 2.

Starting from barbituric acid **14**, the intermediate **16** was synthesized in two steps. Reaction of **16** with aminopyrazole **10a** under Buchwald conditions furnished a mixture of the desired **17** (minor isomer) and undesired regioisomer **17a** (Scheme 2). Pure compound **17** was isolated after chromatographic purification. Zinc acetate-mediated coupling of

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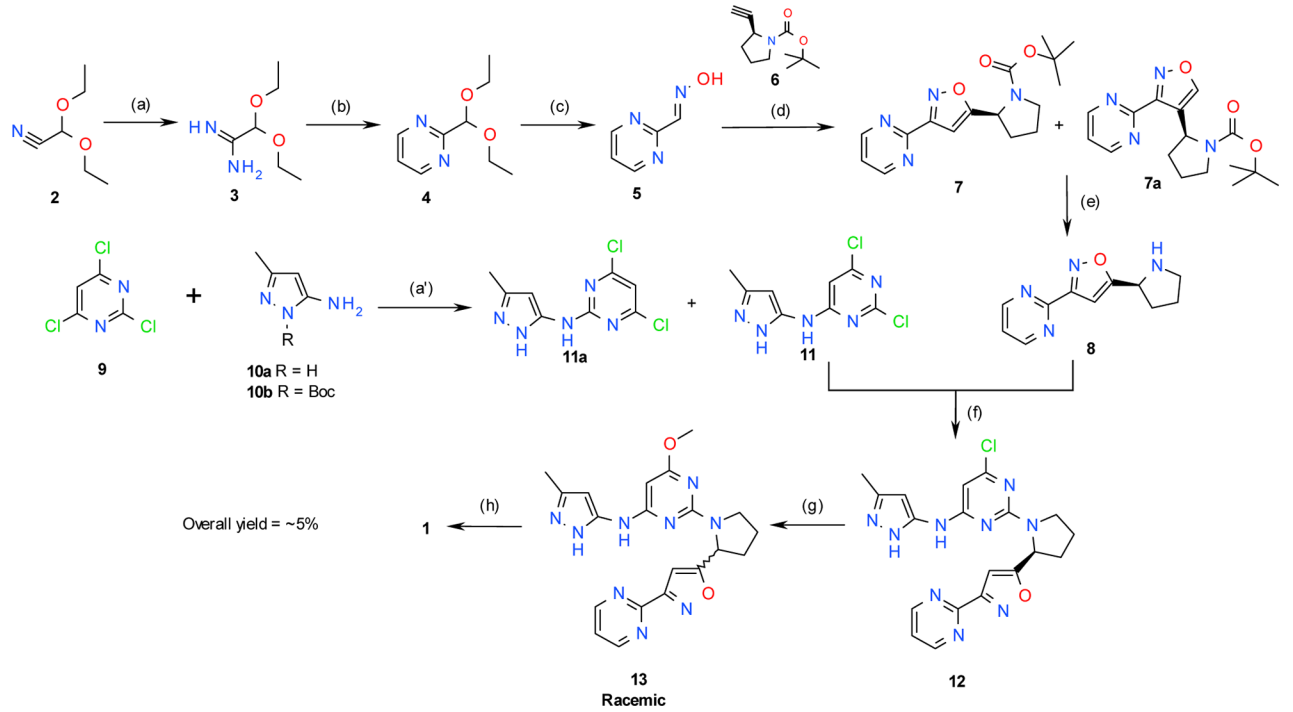
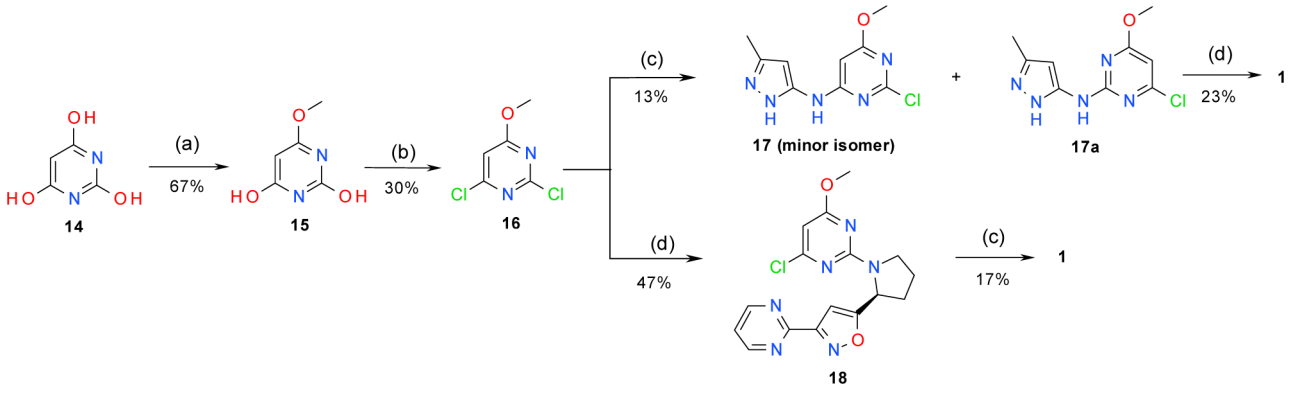
Scheme 1. Medicinal chemistry synthesis[a]



[a]Reagents and conditions: (a) i) MeOH/H+, ii) NH_3; (b) 3-dimethylamino-propenal, NaOMe, EtOH; (c) $NH_2OH{\cdot}HCl$; (d) i) NaOCl, ii) chromatography; (e) i) TFA, ii) chromatography; (f) i) $Zn(OAc)_2$, ii) chromatography; (g) i) NaOMe, EtOH, microwave, ii) chromatography; (h) chiral chromatography; (a′) i) Na_2CO_3, EtOH, ii) chromatography.

Scheme 2. Alternate medicinal chemistry approach[a]



[a]Reagents and conditions: (a) BF_3·etherate, MeOH, reflux, 3 h; (b) $POCl_3$, reflux, 4 h; (c) **10a**, $Pd_2(dba)_2$, xanthene, Cs_2CO_3, dioxane, 80−82 °C, 18 h, ii) chromatography; (d) i) **8**, $Zn(OAc)_2$, 2-propanol, reflux, 17 h, ii) chromatography.

triheterocyclic unit **8** with **17** afforded **1** in 23% yield after chromatography.

In another variant, **16** was coupled first with triheterocyclic unit **8** in the presence of zinc acetate (Scheme 2). Chromatography was employed at this point to isolate pure intermediate **18**. In the final stage, aminopyrazole **10a** was coupled with **18** using Buchwald methodology. Pure compound **1** was isolated with 17% yield after chromatography.

With the objective of supplying the material for preclinical evaluation, we assessed the medicinal chemistry approaches (Schemes 1, 2) for scalability. Both the approaches were considered unattractive due to low convergence, poor regioselectivity, low-yielding stages, and multiple chromatographic purifications. Another drawback was that the expensive tricycle **8** was introduced at an early stage of the synthesis. This prompted us to consider some alternative approaches.

RESULTS AND DISCUSSIONS

Modified Medicinal Chemistry Route. Our approach (Scheme 3) to the 2,4-dichloro-6-methoxypyrimidine **16**, utilized the commercially available trichloropyrimidine **9** as starting material. Initial attempts for the synthesis of **16** using sodium methoxide, resulted in the formation of the 4-chloro-2,6-dimethoxypyrimidine impurity at high levels. Later we examined tetrabutylammonium hydroxide (TBAH)-mediated methoxylation of **9** in DMSO.[3] A stoichiometric quantity of methanol was used for this reaction, resulting in a 7:3 mixture of the desired isomer **16** and the undesired regioisomer **16a**.

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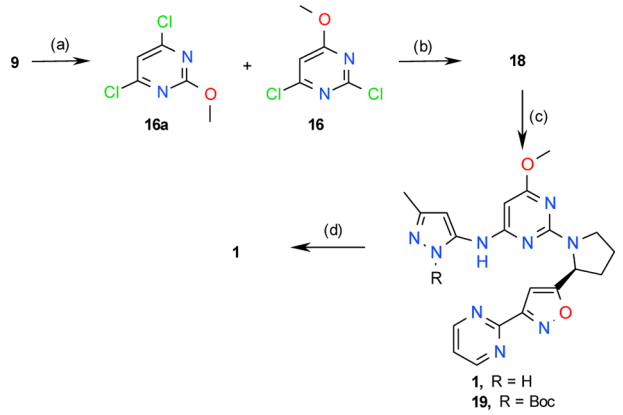
Scheme 3. Modified medicinal chemistry approach[a]

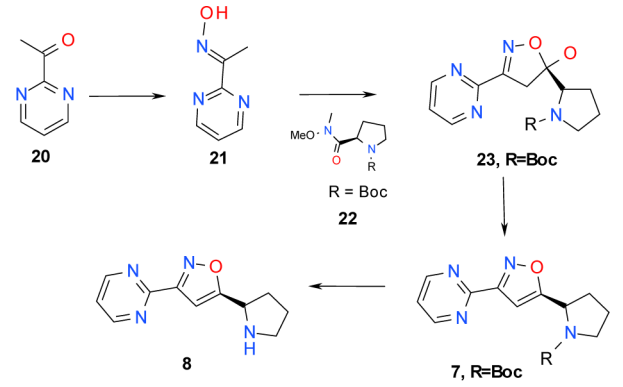


[a]Reagents and conditions: (a) 20% w/w TBAH in methanol, DMSO, 55%; (b) **8**, DIPEA, NMP, 55%; (c) **10a** or **10b**, Buchwald screening, 120 °C, 20–24 h, 43% (conversion by HPLC area %); (d) chromatography.

Recrystallization of this mixture from isopropyl alcohol afforded pure **16** in 55% yield.

The tricyclic fragment **8** was then reacted with **16** in NMP resulting in a 56% yield of the desired product **18** after crystallization from isopropyl alcohol. For the investigation of this approach we utilized key intermediate **8** synthesized as shown in Scheme 4.

Scheme 4. Alternative approach for the synthesis of intermediate 8



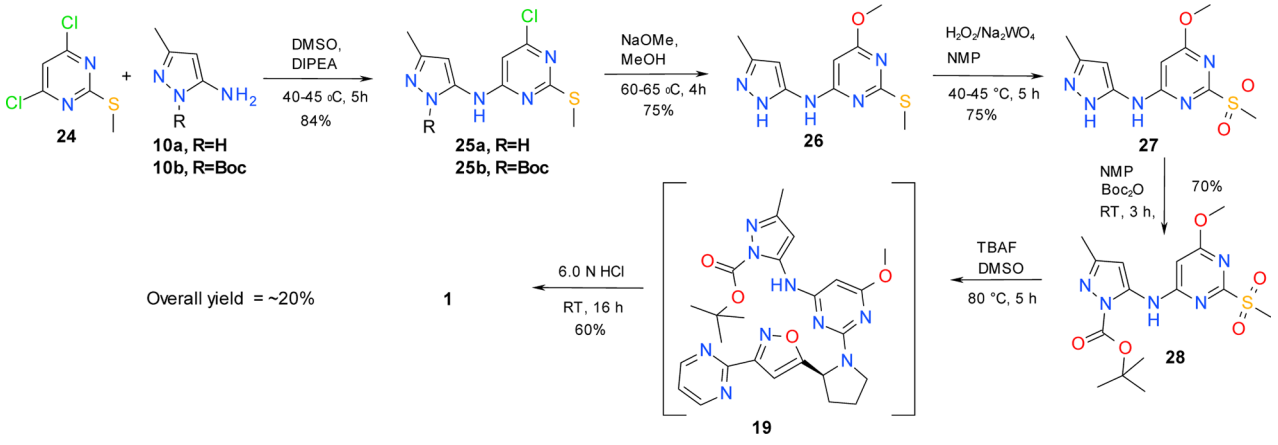
The coupling of aminopyrazole **10a** and BOC protected aminopyrazole **10b** with intermediate **18** was attempted using Buchwald methodology. A quick screen of conditions (Pd source, solvent, ligand, and temperature) revealed that the reaction is not promising as maximum conversion of 43% (see Supporting Information [SI], Table 1, entry 22) was achieved with a significant amount of starting material left unreacted. Reactions were maintained at 120 °C for 20 to 24 h. Incomplete conversion of **18** was attributed to the more nucleophilic endocyclic nitrogens relative to the exocyclic 5-amino group in **10a** or **10b** that inhibits the catalyst activity. Hence, we decided to terminate further investigations on this approach.

Improved Synthesis of Triheterocyclic Unit (8). The original medicinal chemistry synthesis was unsuitable for supplying multikilogram quantities of triheterocyclic unit **8** (Scheme 1) due to poor regioselectivity and low-yielding stages. Therefore, a better route was sought. A novel and efficient process for the synthesis of functionalized Boc-pyrolidine isoxazoles such as **7** was demonstrated by our colleagues at AstraZeneca (Scheme 4).[2] Reaction of hydroxylamine hydrochloride with acetyl pyrimidine **20** furnished oxime **21**, which was subsequently treated with the proline-derived Weinreb amide **22** in the presence of *n*-butyllithium and diisopropylamine to obtain hydroxyisoxazole **23**.[4,5] Dehydration of hydroxyisoxazole **23** with thionyl chloride in dichloromethane, afforded Boc-isoxazole **7** that, on deprotection, furnished the triheterocyclic unit **8** in good yields and high enantiomeric purity.

Final Choice of Route. In the new synthetic strategy we wanted to introduce the expensive triheterocyclic unit **8** towards the end of the synthesis. With an appropriately functionalized, commercially available pyrimidine[9] such as **24**, nucleophilic substitutions can be achieved at the 4 and 6 positions in the beginning of the synthesis (Scheme 5). Subsequent oxidation of the sulfide function to sulfone was envisaged to facilitate nucleophilic displacement at the 2-position of pyrimidine with the triheterocyclic unit **8**, towards the end of the synthesis.

In the first step, Boc-aminopyrazole **10b** was coupled with the substituted pyrimidine **24** in DMSO medium, resulting in the formation of intermediate **25b** in high yield. It was found that the Boc group of intermediate **25b** was very labile under the subsequent methoxylation conditions. Hence, we decided

Scheme 5. Final route for the synthesis of 1



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to couple aminopyrazole **10a** with **24** which resulted in the formation of intermediate **25a** in high yield.

A screen of various solvents, temperatures, molar ratios of sodium methoxide, etc. was followed to maximise the conversion of **25a** to **26**. The use of sodium methoxide in methanol at reflux temperature was identified as the best condition (see SI, Table 2, entry 6) for this transformation. The crude intermediate **26** (contaminated with **29**) was taken into the oxidation[6] without purification. Complete conversion of **26** to **27** was achieved using the combination of hydrogen peroxide−sodium tungstate in NMP within 4 h. At this point we were able to purify sulfone **27** from dimethoxy impurity **29** by employing a hot methanol slurry to get pure **27** with 75% isolated yield. A solution of **27** in NMP was then treated with potassium carbonate followed by di-*tert*-butyldicarbonate (Boc_2O) to afford a 9:1 mixture of desired mono-Boc **28** and di-Boc protected compound **30** (Figure 2) in high yield. This mixture was taken for downstream processing without purification.

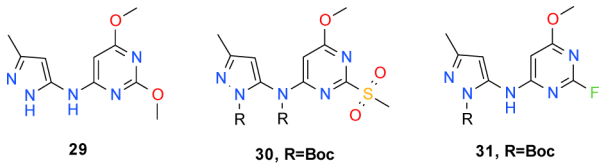

Figure 2. Impurities observed during synthesis of **1**.

Intermediates **27** and **28** were assessed for crucial sulfone group displacement with the triheterocyclic unit **8**. A screen of conditions (temperature, base, and solvent) was conducted to ascertain the best conversion. Initial screening (see SI, Table 3) revealed that the sulfone displacement reaction is sluggish and the best conversion achieved was about 10% with DMSO and potassium carbonate even with an excess of the triheterocyclic unit **8**. Prolonged heating at an elevated temperature led to a complex mixture.

To our surprise, we were able to achieve facile displacement of the sulphone group in the intermediate **28** with less bulky amines[7] such as benzylamine and morpholine. At this point we reasoned that steric hindrance could be the major factor that slows down the sulphone displacement reaction. A thought on sulfone group displacement by fluoride, which could reduce the steric hindrance for the triheterocyclic unit **8** substitution, prompted us to use tetrabutylammonium fluoride (TBAF) during the reaction. Reaction of **28** with a stoichiometric amount of TBAF in DMSO furnished the fluoro intermediate **31** (Figure 2) in 85% isolated yield. The reaction of **31** with triheterocyclic unit **8** resulted in the much higher conversions to the final compound **1** via fluoride displacement.[8] In a subsequent experiment, the desired transformation was accomplished without isolating the fluoro intermediate **31**. Eventually, addition of stoichiometric amount of TBAF to the reaction mixture containing **28** and triheterocyclic unit **8** in DMSO dramatically improved the reaction profile with the best conversion observed (>90%) to **19** (see SI, Table 3, entry 6).

Deprotection of the Boc group in compound **19** was accomplished utilizing 6.0 N HCl solution at 20−25 °C. In a further iteration, the isolation of intermediate **19** was avoided, which allowed us to telescope the process from **28** to obtain the target molecule **1** in 60% yield. Thus, starting from **24**, the final compound **1** was obtained in an overall yield of 20% and high optical purity.

CONCLUSION

A practical, highly regioselective synthesis of an insulin-like growth factor-1 receptor (IGF-1R) inhibitor was developed. In the new approach, metal-mediated coupling reactions were replaced by simple displacement reactions, and the expensive tricyclic unit **8** was introduced towards the end of the synthesis with just one equivalent being used.[10] The project was discontinued before a scale-up campaign in our kilo lab could be carried out.

EXPERIMENTAL SECTION

General. ^{1}H NMR spectra were obtained at 300 MHz, ^{13}C NMR spectra were obtained at 100 MHz at 25 °C in DMSO-d_6 or $CDCl_3$, and coupling constants are quoted in hertz. HPLC monitoring of most reactions was carried out with the use of commercially available reverse-phase columns (Zorbax XDB-C18 150 mm × 4.6 mm, 5 μ), eluted with ammonium acetate (aq) and acetonitrile. LC−MS spectra were run using the same HPLC system described above connected to an Agilent 1100 series LC-MSD, using APCI + ES ion source. Chiral analysis for enantiomers of compound **1** was carried out with commercially available chiral column (Chiralpak AS-H 250 mm × 4.6 mm, 5 μ), eluted with *n*-hexane, ethanol, and diethylamine. Melting points were determined by closed cell DSC.

Procedures. *6-Chloro-N-(3-methyl-1H-pyrazol-5-yl)-2-(methylsulfanyl)pyrimidine-4-amine (**25a**).* To a solution of 4,6-dichloro-2-(methylsulfanyl)pyrimidine **24** (25.0 g, 0.128 mol) in DMSO (150 mL) was charged aminopyrazole **10a** (18.68 g, 0.192 mol) and *N*,*N*-diisopropylethylamine (24.85 g, 0.192 mol) at 20−25 °C. The progress of the reaction was monitored by HPLC. After completion of the reaction, the reaction mass temperature was raised to 40−45 °C and maintained for 5 h. The reaction vessel contents were cooled to 20−25 °C and diluted with water (1 L). The mixture was stirred for 30 min, and the resulting solid was collected by filtration and dried under vacuum to afford product **25a** as white solid. **Yield**: 27.6 g (84.2%); **^{1}H NMR assay**: 98% (w/w) using DMSO-d_6 as a solvent and maleic acid as an internal standard. **^{1}H NMR**: (300 MHz, DMSO-d_6) δ 12.15 (s, 1H), 10.13 (s, 1H), 7.01 (s, 1H), 6.17 (s, 1H), 2.49 (s, 3H), 2.21 (s, 3H); **LC−MS**: *m*/*z* 257 (M^+ + 1); **Melting point**: 153−155 °C.

*6-Methoxy-N-(3-methyl-1H-pyrazol-5-yl)-2-(methylsulfanyl)pyrimidin-4-amine (**26**).* To a suspension of **25a** (27.0 g, 0.106 mol) in methanol (270 mL), was charged sodium methoxide (20.04 g, 0.371 mol) at 20−25 °C. The reaction mass temperature was then raised to 60−65 °C and the mixture stirred for 22 h. After completion of the reaction, the contents were cooled to 20−25 °C and diluted with water (270 mL). The mixture was stirred for 60 min, and the resulting solid was collected by filtration and dried under vacuum to afford product **26** as a white solid. **Yield**: 19.90 g (75%). **^{1}H NMR**: (300 MHz, DMSO-d_6) δ 11.91 (s, 1H), 9.52 (s, 1H), 6.39 (s, 1H), 5.96 (s, 1H), 3.84 (s, 3H), 2.49 (s, 3H), δ 2.19 (s, 3H); **LC−MS**: *m*/*z* 252 (M^+ + 1); **Melting point**: 187−190 °C.

*6-Methoxy-N-(3-methyl-1H-pyrazol-5-yl)-2-(methanyl sulfonyl)pyrimidin-4-amine (**27**).* To a solution of **26** (20 g, 0.079 mol) in NMP (200 mL) was charged $Na_2WO_4{\cdot}2H_2O$

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(2.34 g, 0.1 mol) at 20−25 °C. The reaction mass temperature was then raised to 40−45 °C and H_2O_2 (23.20 g, 35% (w/w), 0.238 mol) was added dropwise over a period of 30 min. The reaction was held for 4.0 h at 40−45 °C. After completion of the reaction (by HPLC), the reaction was cooled to 20−25 °C, and water (300 mL) was charged over a period of 15 min. Excess of H_2O_2 was destroyed by charging a solution of $Na_2S_2O_5$ (5% w/w aqueous) until a peroxide test-strip showed no peroxide. The reaction mixture was stirred for a further hour, and the resulting solid was collected by filtration and dried under vacuum at 50 °C for 10 h to afford pure **27** as an off-white solid. **Yield**: 16.90 g (75%); **^{1}H NMR assay**: 98% (w/w) using DMSO-d_6 as a solvent and maleic acid as an internal standard. **^{1}H NMR**: (300 MHz, DMSO-d_6) δ 12.10 (s, 1H), 10.26 (s, 1H), 7.01 (s, 1H), 5.98 (s, 1H), 3.39 (s, 3H), 3.31 (s, 3H), 2.19 (s, 3H); **LC−MS**: m/z 284 (M^+ + 1); **Melting point**: 188−190 °C.

*tert-Butyl-5-{[6-methoxy-2-(methylsulfonyl)pyrimidin-4-yl]amino}-3-methyl-1H-pyrazole-1-carboxylate (**28**).* To a solution of **27** (15.0 g, 0.053 mol) in NMP (150.0 mL) was charged potassium carbonate (10.26 g, 0.074 mol) at 20−25 °C followed by Boc_2O (13.88 g, 0.064 mol) dropwise over a period of 5.0 min, and the reaction contents were stirred for 3 h. After completion of the reaction (by HPLC), the inorganic salts were separated, and the reaction solution was diluted with water (200 mL). The resulting solid was collected by filtration and dried under vacuum to afford product **28** as an off-white solid. **Yield**: 14.21 g (70%). **^{1}H NMR**: (300 MHz, DMSO-d_6) δ 10.78 (s, 1H), 7.15 (s, 1H), 6.39 (s, 1H), 3.96 (s, 3H), 3.35 (s, 3H), 2.47 (s, 3H), 1.58 (s, 9H); **LC−MS**: m/z 384 (M^+ + 1); **Melting point**: 152−155 °C.

*6-Methoxy-N-(3-methyl-1H-pyrazol-5-yl)-2-[(2S)-2-(3-pyrimidin-2-ylisoxazol-5-yl)-pyrrolidin-1-yl]pyrimidin-4-amine (**1**).* To a solution of **28** (5.0 g, 0.013 mol) in DMSO (25.0 mL), was charged TBAF hydrate (6.80 g, 0.026 mol) and triheterocyclic unit **8** (3.10 g, 0.014 mol) at 20−25 °C. The reaction temperature was raised to 75−80 °C and stirred for 5 h. After completion of the reaction (by HPLC), the reaction contents were cooled down to 20−25 °C; HCl solution (6 N aqueous, 45 mL) was added, and the mixture was stirred at 25 °C for 14−16 h. Then the pH of the solution was adjusted to 7.0−7.5 using NaOH (5.0 N) solution. After stirring at 20 °C for an hour, the precipitated solid was filtered, washed with water (20 mL), and dried under vacuum at 60 °C for 22 h to afford 3.90 g of crude **1**. The crude material was suspended in acetone (10 mL) and stirred for 1 h. The resulting crystals were filtered, washed with cold (0 °C) acetone (5 mL), and dried under vacuum at 60 °C for 12 h to afford pure **1** as an off-white solid. **Yield**: 3.28 g (60%); **HPLC purity**: 98%, ee: 97%. **^{1}H NMR**: (300 MHz, DMSO-d_6) δ 11.83 (s, 1H), 8.94 (d, 2H), 7.59 (t, 1H), 6.76 (s, 1H), 6.21 (s, 1H), 6.11 (s, 1H) 5.81 (s, 1H), 5.42 (m, 1H), 3.64 (m, 5H), 2.36 (m, 2H), 2.09 (m, 5H); **LC−MS**: m/z 420 (M^+ + 1); **Melting point**: 147−148 °C.

*tert-Butyl-5-[(2-fluoro-6-methoxy-pyrimidin-4-yl)amino]-3-methyl-pyrazole-1-carboxylate (**31**).* To a solution of **28** (500 mg, 1.30 mmol) in DMSO (3.0 mL) was charged TBAF hydrate (510 mg, 1.96 mmol). The reaction mass temperature was then raised to 75−80 °C and stirred for 6 h. After completion of the reaction (by HPLC), the vessel contents were cooled to 20−25 °C and diluted with water (20 mL). The mixture was stirred for 10 min, and the resulting solid was collected by filtration and dried under vacuum to afford product **31** as a pale-yellow solid. **Yield**: 360 mg (85.3%). **^{1}H NMR**: (300 MHz, $CDCl_3$) δ 6.43 (s, 1H), 6.28 (s, 1H), 4.74 (br, 1H), 3.86 (s, 3H), 2.44 (s, 3H), 1.55 (s, 9H); **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 172.52, 172.36, 172.44, 162.03, 161.31, 161.22, 161.14, 160.97, 159.91, 148.6, 147.5, 143.6, 101.6, 85.89, 83.93, 53.4, 26.9, 13.7; **^{19}F NMR**: (300 MHz, $CDCl_3$) δ −45.19 ppm; **LC−MS**: m/z 324 (M^+ + 1).

■ ASSOCIATED CONTENT

Supporting Information

Tables of results. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

Boc, *tert*-butoxy carbonyl; Boc_2O, di-*tert*-butyl dicarbonate

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(9) Trifluoropyrimidine was also considered during the route scouting exercise. However, it was expensive and not commercially available.

(10) All approaches considered for the synthesis compound **1**, employ the tricyclic fragment **8** at some point. Although the improvement in the synthesis of **8** is a major factor, it still remains the most expensive fragment, and any process or route would look to utilise this material as efficiently as possible. Our work introduces the fragment cleanly at the final bond-forming step, without any heavy metal catalysis (one could imagine that removal of metals from such a potentially complex structure such as the API would be difficult), consuming only one equivalent. From the process efficiency calculations we estimated the quantity of tricyclic fragment **8** required for making 1.0 kg of final compound **1** is around 11.0 kg for the earlier approaches, while it is only 2.2 kg for the new approach.

■ NOTE ADDED AFTER ASAP PUBLICATION

This paper was published on the Web July 25, 2012, with errors in Schemes 1, 3, and 5 and errors in reference 10 and in the Supporting Information. The corrected version was reposted on August 3, 2012.