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The Development of a Dimroth Rearrangement Route to AZD8931

William R. F. Goundry,[‡,†] Kay Boardman,[φ] Oliver Cunningham,[φ] Matthew Evans,[φ] Martin F. Jones,[φ,‡] Kirsty Millard,[φ] Raquel Rozada-Sanchez,[φ] Yvonne Sawyer,[‡] Paul Siedlecki,[φ] Brian Whitlock[φ]*

[‡] The Department of Pharmaceutical Sciences, AstraZeneca, Silk Road Business Park, Macclesfield, Cheshire, United Kingdom, SK10 2NA.

[φ]The Department of Pharmaceutical Technology and Development, AstraZeneca, Silk Road Business Park, Macclesfield, Cheshire, United Kingdom, SK10 2NA

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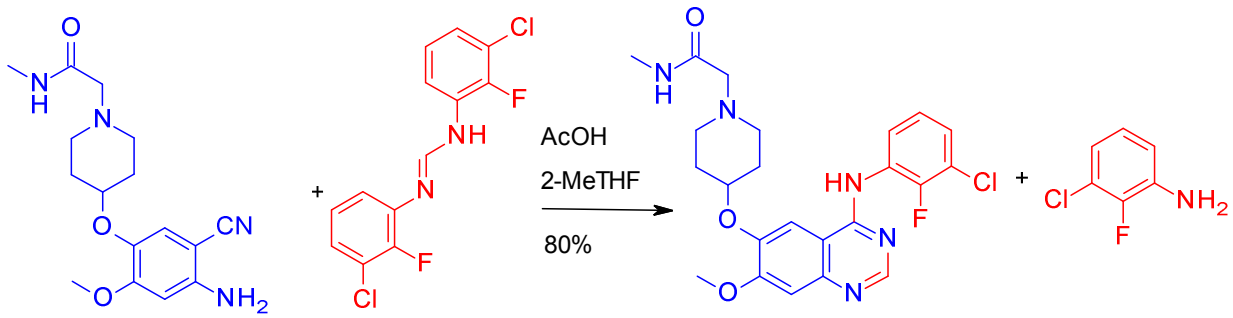


Overall yield for the route 41%, on a 30 kg scale

KEYWORDS

AZD8931, Quinazoline; Dimroth Rearrangement; Hydrogenation.

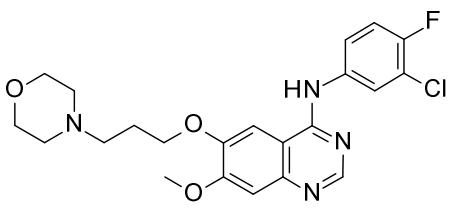
ABSTRACT

Recently the aminoquinazoline motif has been highly prevalent in anti-cancer pharmaceutical compounds. Synthetic methods are required to make this structure on a multi-kilo scale and in high purity. The initial route to aminoquinazoline AZD8931 suffered from the formation of late stage impurities. To avoid these impurities, a new high yielding Dimroth rearrangement approach to the aminoquinazoline core of AZD8931 was developed. Assessment of route options on a gram scale demonstrated that the Dimroth rearrangement is a viable approach. The processes were then evolved for large-scale production with learning from a kilo campaign and two plant scale manufactures. Identification of key process impurities offers an insight into the mechanisms of the Dimroth rearrangement as well as the hydrogenation of a key intermediate. The final processes were operated on a 30 kg scale delivering the target AZD8931 in 41% overall yield.

INTRODUCTION

Deregulation of the HER receptor family, comprising four related receptor tyrosine kinases (EGFR, HER2, HER3, and HER4), promotes proliferation, invasion, and tumor cell survival.[1-3] Such deregulation has been observed in many human cancers, including lung, head and neck, and breast.[4-5] Numerous small molecules have been investigated for inhibition of tyrosine kinases with the aminoquinazoline motif coming to the fore as a privileged scaffold. Three of the clinically available treatments, gefitinib (**1**),[6] lapatinib (**2**),[7] and erlotinib (**3**)[8] contain this arrangement as well as the candidate drug dacomitinib (**4**) (Figure 1).[9]

Figure 1. Structure of gefitinib (**1**), lapatinib (**2**), erlotinib (**3**), dacomitinib (**4**) and AZD8931 (**5**).



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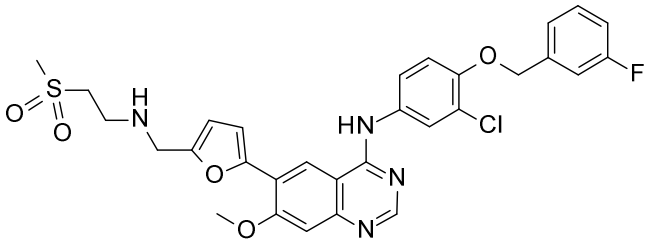

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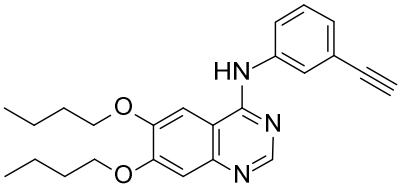

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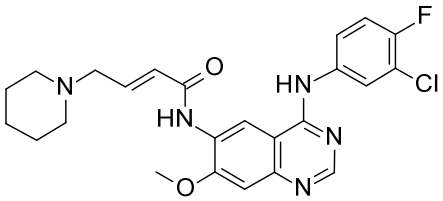

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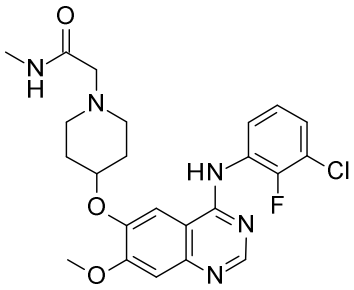


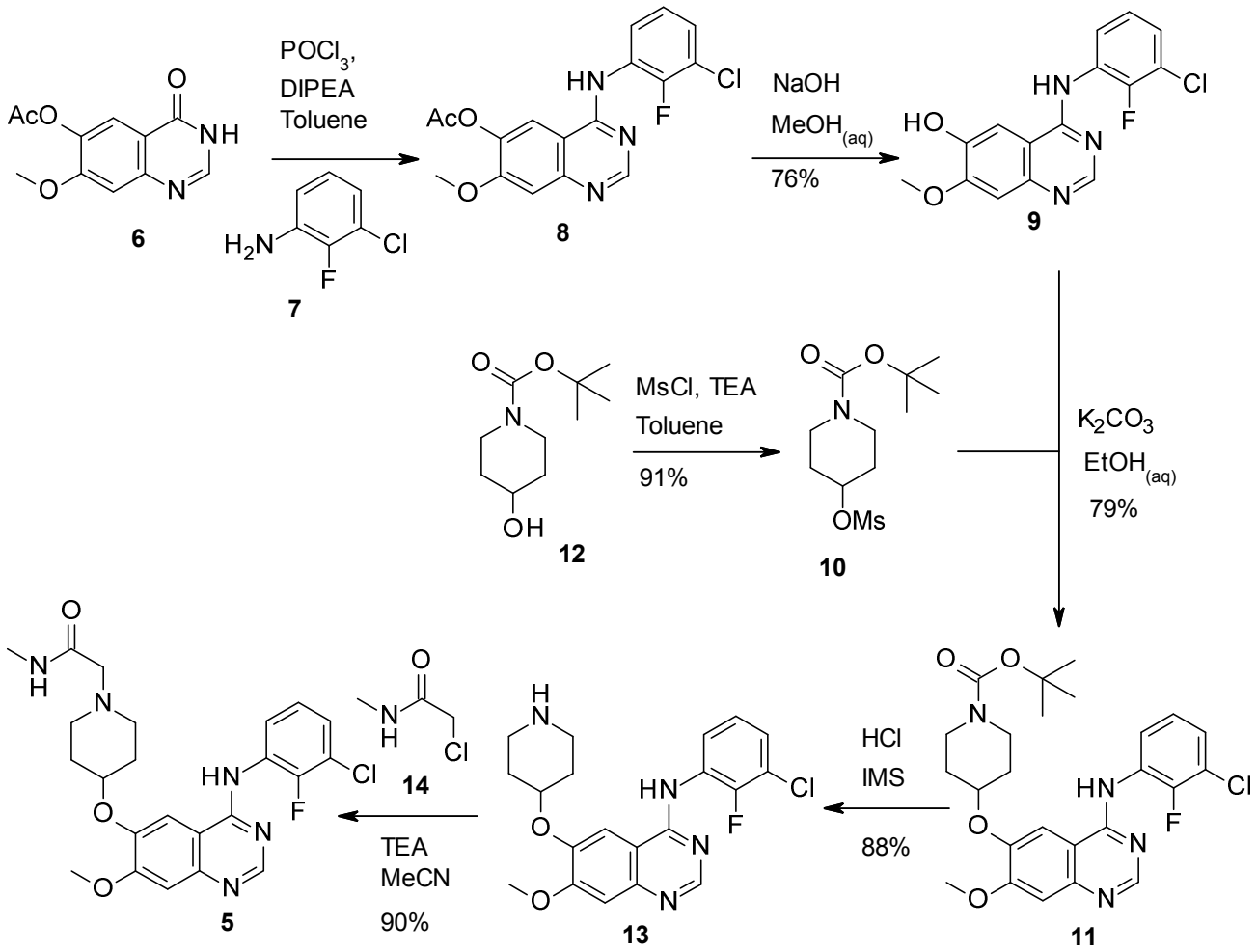
5

AstraZeneca has further explored the aminoquinazoline scaffold and identified AZD8931 (**5**) as a novel oral anti-proliferative agent for the treatment of tumors; its mode of action being reversible tyrosine kinase inhibition (Erb b2/EGFR) (Figure 1).[10] The synthetic medicinal chemistry work used to discover AZD8931 branched out from the quinazoline **6**, previously used by AstraZeneca for the manufacture of gefitinib (**1**) (Scheme 1). Using this material was an attractive option for the discovery team as it was easy to vary the functionality at the 4 and 6 positions, to explore a structure activity relationship.

FIRST GENERATION ROUTE

Early kilogram scale campaigns to deliver material for toxicological studies used the medicinal chemistry route (Scheme 1). Chlorination of quinazoline **6** then reaction with 3-chloro-2-fluoroaniline (3-CFA) (**7**) gave aminoquinazoline **8**. Deprotection of the acetate group revealed phenol **9**, which was reacted with mesylate **10** to deliver quinazoline **11**. Mesylate **10** was prepared from the commercially available Boc protected alcohol **12**.[11] Removal of the Boc group under standard acidic conditions revealed the secondary amine **13**, which was alkylated with 2-chloro-*N*-methyl-acetamide (**14**) affording the target **5**. The final difumarate salt form of **5** was then crystallized from a mixture of ethyl acetate and isopropanol, the details of which lie beyond the scope of this paper and will be discussed in a future communication.

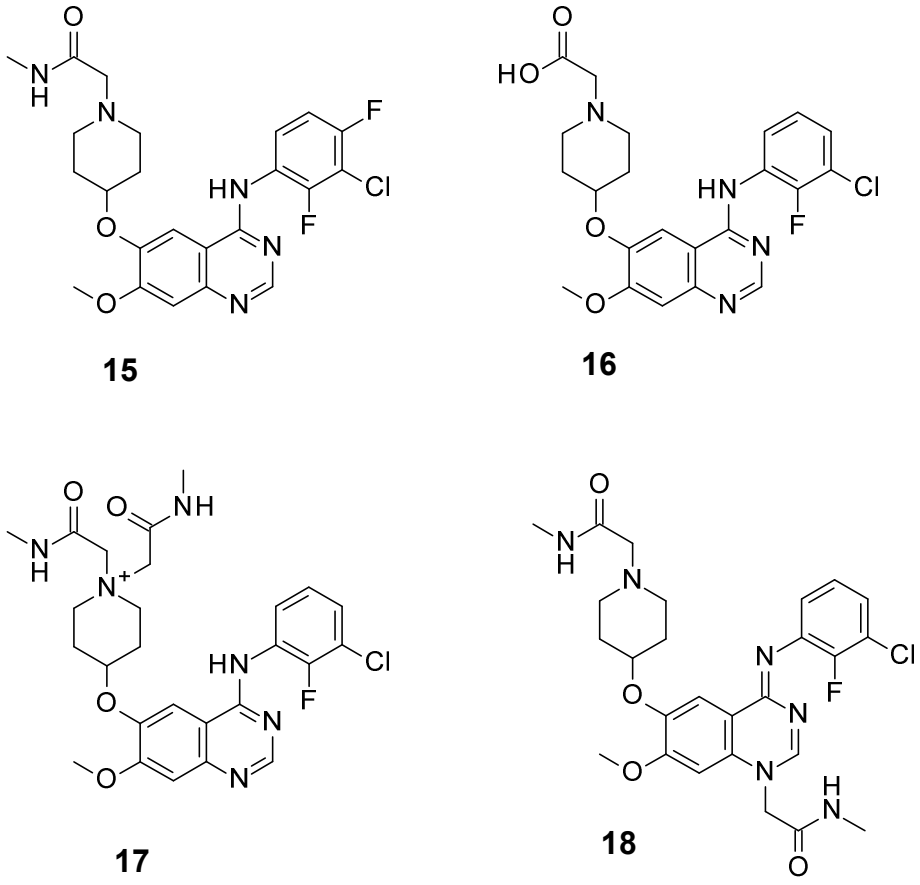
Scheme 1. The 1st generation route to AZD8931



Following tactical deliveries of 6–8 kg, the route was scaled up to deliver 220 kg of AZD8931 at which time the deficiencies of this route became apparent. The starting materials **7** and **14** contained low levels of the impurities 3-chloro-2,4-difluoroaniline and chloroacetic acid respectively, both of which were incorporated into the final structure giving impurities **15** and **16** (Figure 2). Impurities **17** and **18**, resulted from the over-alkylation of AZD8931 in the final bond-forming step. Attempts to avoid over alkylation by undercharging **14** (0.95 eq) failed, as over 10% of **13** remained at the end of reaction, and not all of this could be removed during the

work-up and isolation. Although removal of the impurities **15–18** from the free base **5** required repeated crystallisations, the final difumarate salt formation proved sufficiently effective in delivering material of the required quality. As part of our general development strategy, **5** was subjected to a thorough route evaluation to see if the problems inherent with the route could be avoided.

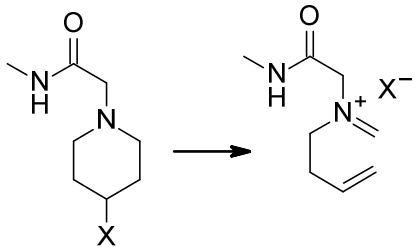
Figure 2. The main impurities from the first generation route: AZD8931 difluoro (**15**); AZD8931 acid (**16**); over-alkylation products **17** and **18**.



NEW ROUTE INVESTIGATION

Several routes were considered to avoid the late introduction of the methylamide side chain and the associated over-alkylation. Avoiding the use of the Boc protecting group on mesylate **10** by directly using the tertiary amines of general structure **19**, failed due to the instability of the piperidine ring, postulated to be due to decomposition via elimination (Scheme 2). Equally, changing the order of the steps in the original route, for example introducing the piperidine and acetamide side chain prior to the aniline, was also unsuccessful.

Scheme 2. Proposed decomposition of piperidines of general structure **19** by elimination; X=Cl, Br, I or OMs

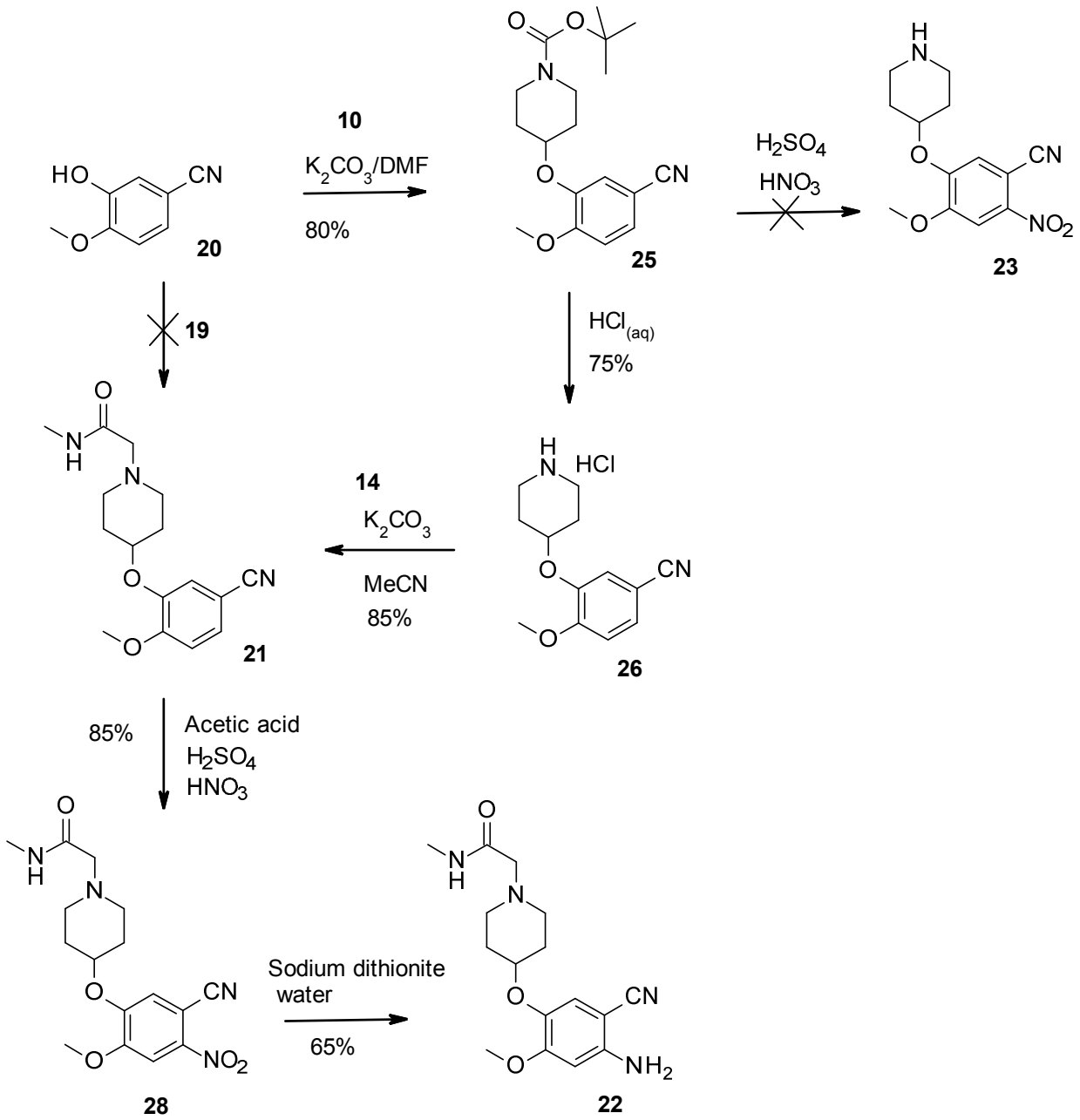


19

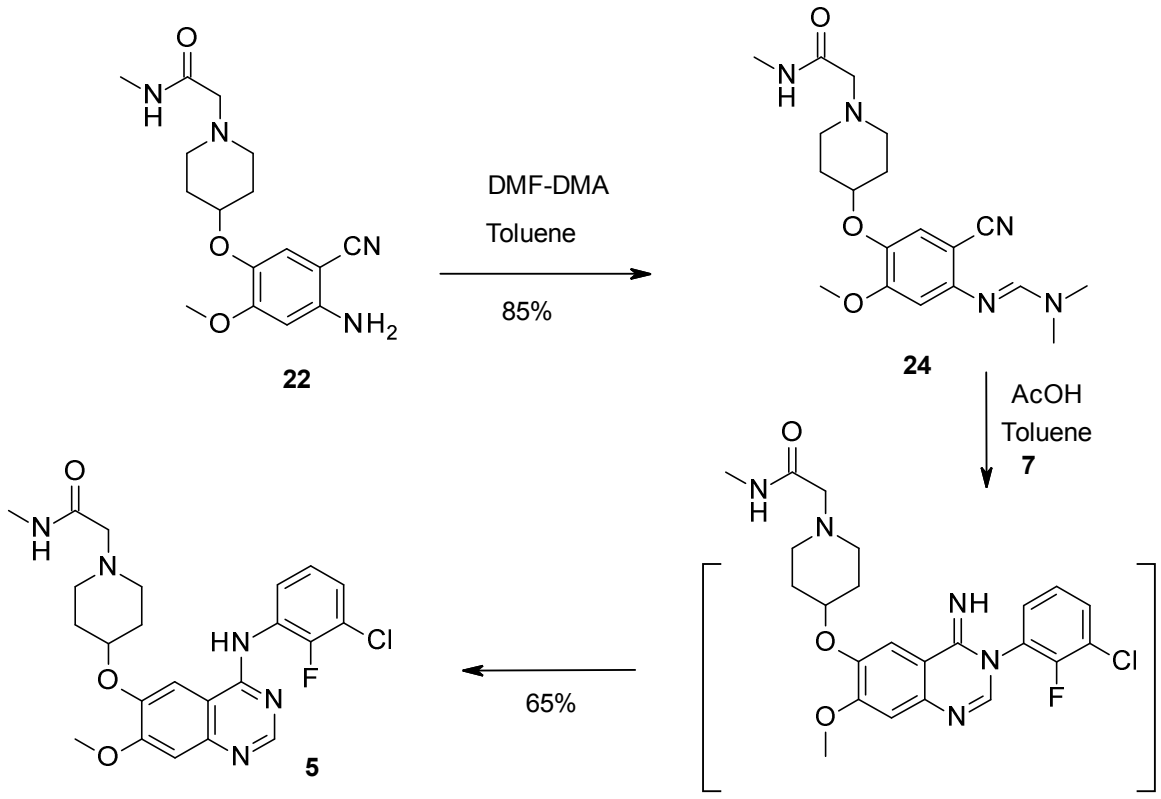
Building on existing company knowledge from the gefitinib project[11] and external learning from the literature,[9, 12-15] a Dimroth Rearrangement approach was investigated and proven on gram scale. Starting from the commercially available benzonitrile **20**, the phenol was alkylated with the previously prepared mesylate **10** (Scheme 3). Deprotection of the nitrogen followed by alkylation with chloroacetamide **14** gave acetamide **21**. Nitration, followed by dithionite reduction gave aniline **22**, the substrate for the Dimroth rearrangement. Potential short cuts in the synthesis to the key aniline (nitration with concomitant Boc deprotection to give **23** or avoidance of the Boc group by using **19**) were not fruitful. Reaction of aniline **22** with *N,N*-

dimethylformamide dimethyl acetal (DMF-DMA) formed amidine **24**, which upon heating with **7** in the presence of acetic acid underwent the Dimroth rearrangement to give AZD8931 (**5**) in 65% yield (Scheme 4). Having demonstrated this route was viable, attention turned to improving the 15% overall yield, whilst delivering a kilogram scale manufacture to provide material for toxicological studies and formulation work.

Scheme 3. Approaches to the Dimroth precursor **22**.



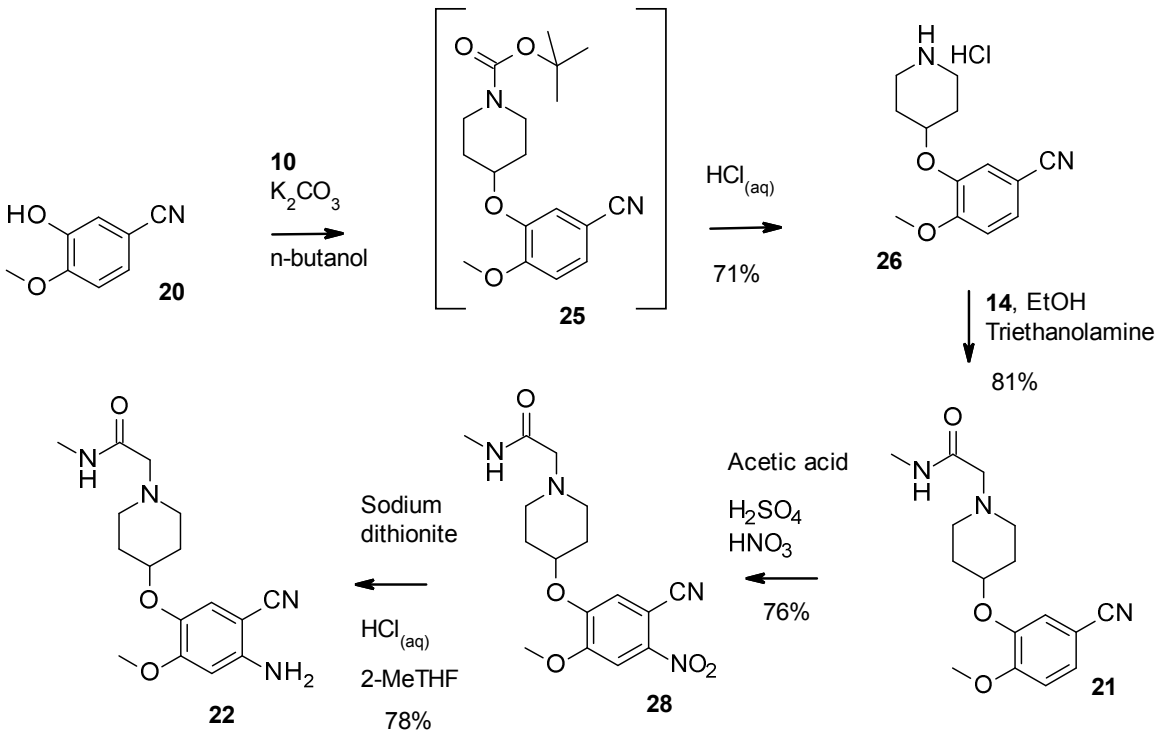
Scheme 4. Initial Dimroth rearrangement route.



FIRST KILO DIMROTH MANUFACTURE

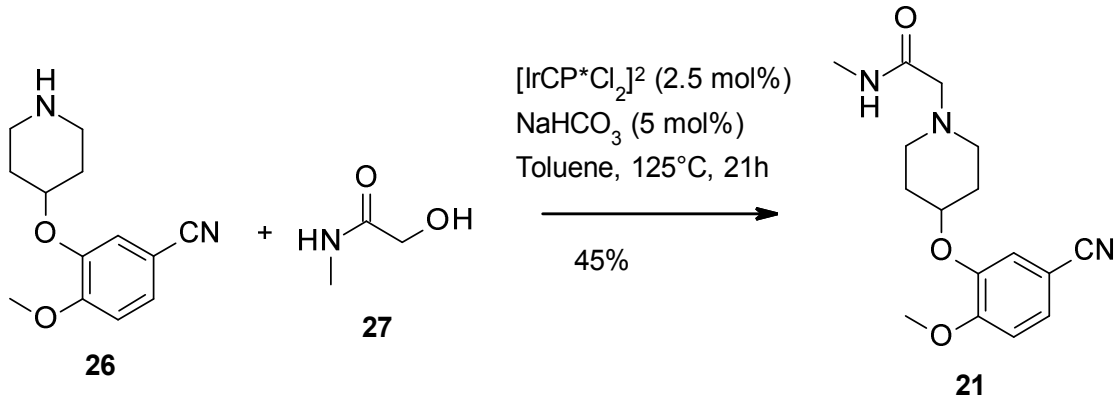
For operational efficiency, the etherification and Boc deprotection from phenol **20** to piperidine **26** were developed as a telescope process. Phenol **20** was reacted with mesylate **10** in n-butanol, which allowed a water wash to remove impurities (Scheme 5). The volume was reduced by distillation and reaction with aqueous HCl resulted in deprotection of **25** and crystallization of nitrile (**26**) as the HCl salt in 71% yield and >99% purity. Three batches were manufactured, one at 20 L scale (0.69 kg) and two at 100 L scale (3.4 kg). During the etherification step, the reaction was an extremely thick slurry, implying the chemistry could not be performed at a larger scale.

Scheme 5. First Kilogram manufacture, conditions to the Dimroth precursor **22**.



As part of our wider strategy to investigate replacing alkylating agents with the borrowing hydrogen approach (hydrogen auto-transfer), we attempted the reaction of piperidine **26** with glycolic amide **27** (Scheme 6).[16] After chromatography to remove several byproducts, a 45% yield of **21** was achieved. Although this was a promising demonstration of the borrowing hydrogen approach, due to the impurities generated it was not advanced further.

Scheme 6. Reaction of **26** and **27** under borrowing hydrogen conditions.



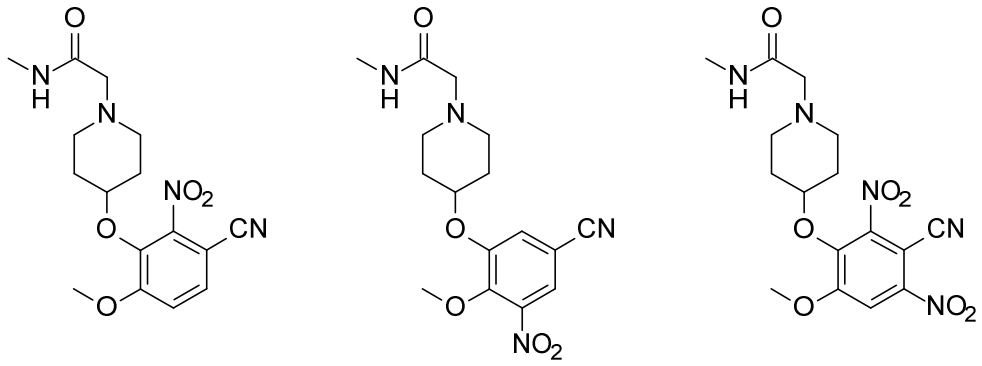
Development of the alkylation began with a combined base and solvent screen, covering a broad range of conditions. Investigation of six preliminary hits identified reaction conditions using triethanolamine as base in 4.0 rel vol (relative volumes, liters of solvent relative to kg of substrate) of ethanol. Following reaction completion, addition of water as an anti-solvent directly crystallised **21** from the solution. Two batches, one 20 L scale (1.4 kg) and one 100 L scale (5.8 kg) were manufactured. The chemistry scaled up as expected; complete dissolution occurred prior to crystallisation, which afforded a more controlled crystallisation. This stage proved robust to impurities, for example, when 2-chloro-*N*-methyl-acetamide (**14**), containing 0.4% w/w chloroacetic acid was used, none of the related acid impurity was present in the isolated product.

Safe nitration conditions using concentrated sulfuric and nitric acid were developed, leading to a high yield of **28**, with <0.1% of nitro regioisomers and dinitro compounds observed. Control of the regioisomeric nitration impurities was key, since they could carru through the synthesis to give regioisomers of AZD8931 (Figure 3). The workup developed involved quenching the strongly acidic nitration mixture with aqueous ammonia, extraction into propionitrile, and

subsequent crystallisation. The level of the nitro-regioisomers was <0.1% wt/wt in isolated **28** and these impurities and their derivatives were subsequently fully purged before the final API.

Several issues occurred during the four batch manufacture - one 20 L scale (0.4 kg) and three 100 L scale (1.9 kg). For the reaction, the vessel had a low fill volume (minimum process volume 5 rel vol) in order to accommodate the dilute work up (maximum process volume 37 rel vol). In the 100 L vessel, the agitator splashed the reaction mixture up onto the walls; as the jacket was at 5°C, the acetic acid crystallised onto the sides of the vessel, resulting in the reaction mixture becoming more concentrated. In the final crystallisation, the product oiled and plated the walls of the vessel, resulting in a problematic discharge and filtration process.

Figure 3. Regioisomeric impurities observed in the nitration reaction.



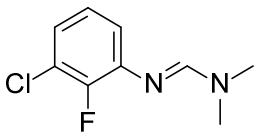
29 **30** **31**

For this delivery, the reduction of the nitro group to the aniline was achieved by sodium dithionite. To avoid reaction hazards associated with an all at once addition of solid sodium dithionite, an aqueous solution of sodium dithionite was added over 90 minutes to a slurry of

Nitro **28** in 2-methyltetrahydrofuran (2-MeTHF). After initial reduction, aqueous HCl was added over 1.5 h to facilitate the conversion of intermediate nitroso to aniline **22**. The mixture was then quenched with ammonia, the product extracted into 2-MeTHF and isolated by crystallisation. Both of the batches manufactured, 20 L (0.7 kg) and 100L (2.7 kg) suffered from crystallisation on the vessel walls, with yields of 69% and 78% respectively.

The initial route work had focused on showing the Dimroth rearrangement was viable, building the amidine functionality directly off aniline **22**. To make the route more convergent we investigated forming the required amidine on aniline **7**; two amidines were successfully synthesized, formamidine **32** and aniline dimer **33** (Figure 4). Both when reacted with aniline **22** afforded quinazoline **5** in good yield although **33** gave fewer impurities. Compound **33** can be isolated as a white crystalline solid but in contrast, formamidine **32** was a viscous oil at room temperature. Attention focused on using the amidine with both the cleaner reaction profile and the benefit of the crystalline intermediate.

Figure 4. Coupling partners **32** and **33** for the Dimroth reaction; intermediate **34**.



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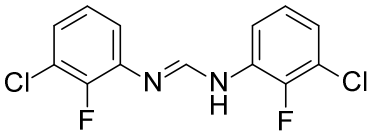

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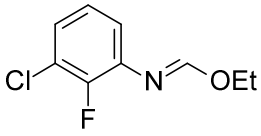
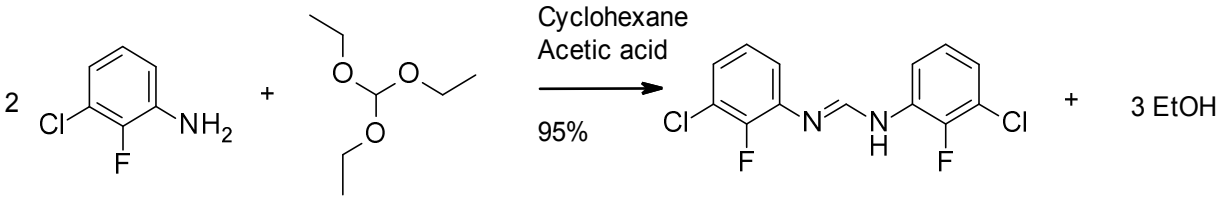


34

Investigating the formation of **33**, initial reactions of **7** in 2-MeTHF with ethyl orthoformate stalled at the ethyl imidoformate intermediate **34**, requiring distillation to remove ethanol and drive the equilibrium to product (Figure 4.). A solvent screen was performed to select a solvent with a good separation from ethanol in the distillation. In cyclohexane the reaction unexpectedly progressed without requiring distillation. Development of the process gave a simple all-in reaction from which the product crystallises as the reaction progresses (Scheme 7). Manufacture of both 20 L scale (2.5 kg) batches proceeded in excellent yield (95%) and purity (99% w/w).

Scheme 7. The synthesis of 3-CFA dimer **33**.



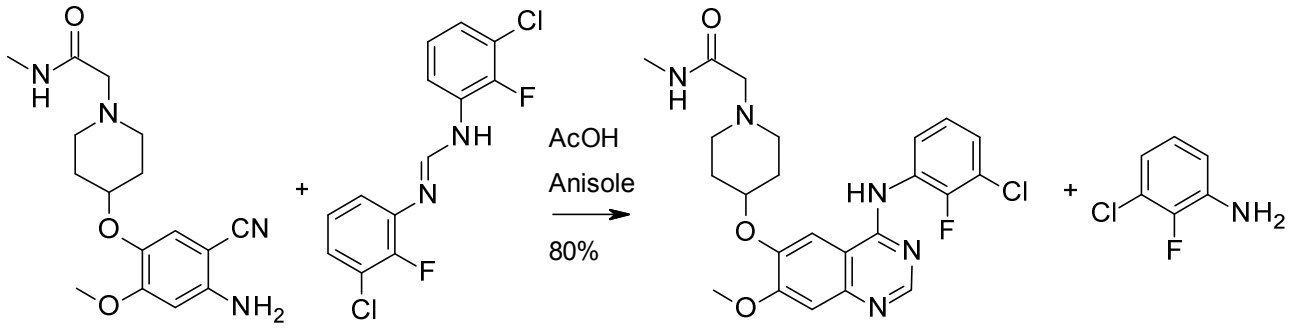
Selecting between the linear Dimroth approach *via* intermediate **24** and the convergent route utilizing amidine **33** was a finely balanced decision. The linear route offered an extra isolation point and both step yields were ~90%, however at least 2 equiv. of aniline **7** were required to achieve good purity. The convergent route using amidine **33**, which gave the slightly cleaner reaction profile in the Dimroth reaction, was chosen for scale up.

For the Dimroth rearrangement, a sequential acid and solvent screen gave reaction conditions of anisole with acetic acid as co-solvent (Scheme 8). Development by design of experiment

ensured conditions for manufacture that gave a good spread of representative impurities for the toxicological batch.

For the work-up, following the addition of ethanol, and neutralisation with aqueous base, **5** could be isolated by a seeded cooling crystallisation. Early development reactions were quenched with sodium hydroxide, but low levels of sodium acetate contaminated the crystallised product. For the manufacture, the quench was switched to ammonium hydroxide, since the resulting ammonium acetate was predicted to stay in solution. Two 20 L scale (1.1 kg) batches were manufactured in 80% yield, with only the second batch displaying a high level of acetate (Scheme 8). At scale, the product form was poor, leading to extended filtration times and retention of filter liquors. Discharge from the filter for kilo lab tray drying was difficult as the solid was damp and sticky. However, the Dimroth route was successfully delivered in the kilo lab with an overall yield of ~30%.

Scheme 8. Kilo manufacture Dimroth rearrangement conditions.



22 **33** **5** **7**

PLANT MANUFACTURES

Significant improvements were still required before delivering the material on pilot plant scale. The key points for attention were: operational issues with thick reaction mixtures; the reactions crystallising on vessel surfaces; a lengthy work-up for the nitration; improving the yield of the nitro reduction.

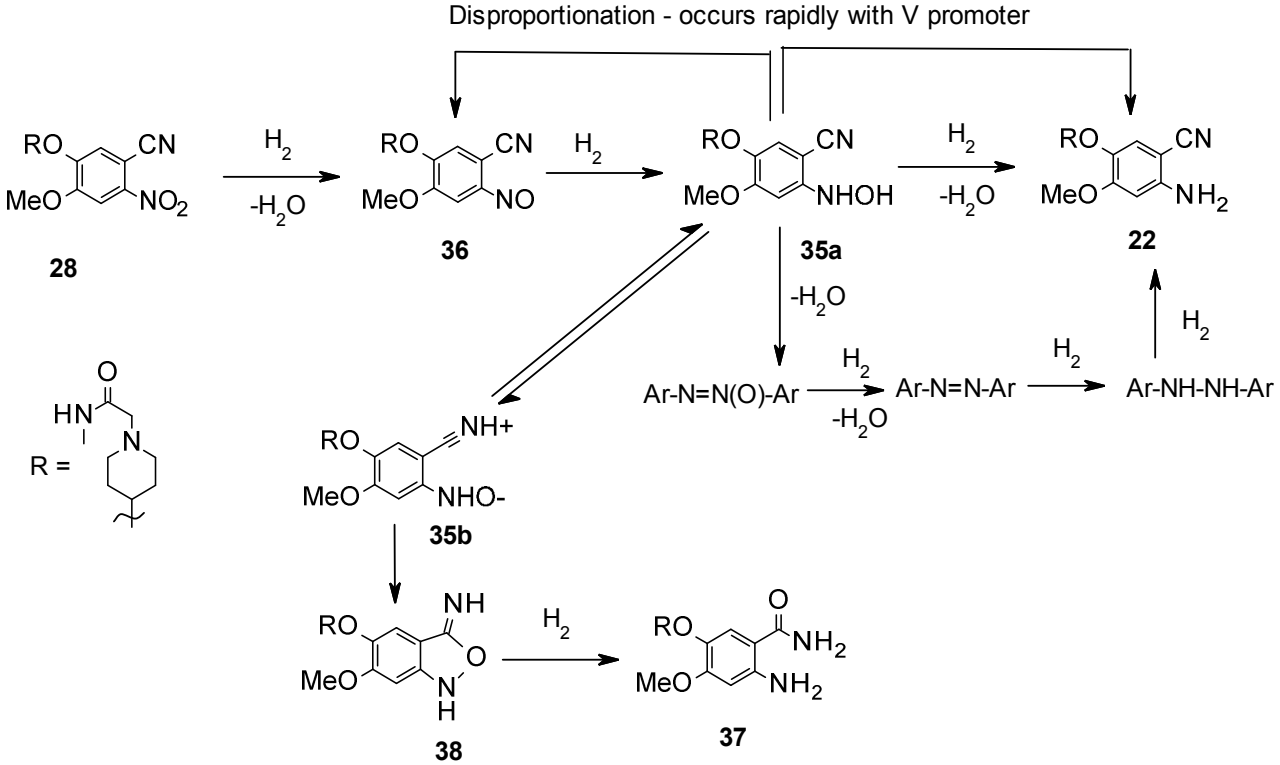
Diluting the thick reaction mixture during the etherification of **20** did not solve the problem, as it was coupled with incomplete conversion and longer reaction times. Instead, the problem was addressed by changing the solvent system to a mixture of water, PEG(400) and methylisobutylketone (MIBK). This solvent mixture gave a mobile reaction mixture, with faster reaction times and complete conversion of the starting material **20**. An aqueous separation followed by solvent swap into IPA then allowed the BOC deprotection of **25** and isolation of the hydrochloride **26**. The process was performed on a 20 kg batch scale with 89% yield. The alkylation to give **21** was unchanged from the kilo lab and scaled effectively as expected.

Development work focused on the remaining steps. A narrow window of operability was identified for the nitration reaction. Above 1.2 eq of nitric acid resulted in a thermally unstable nitration mixture, but below 1.0 eq gave an unacceptably slow conversion. Two design of experiments established that 1.05 eq of nitric acid, with 8.0 eq of sulfuric acid, and 3 rel vol of acetic acid at 45°C, gave complete reaction in 3 h. Upon completion, the reaction was diluted with pyridine, dissolved at an elevated temperature, seeded and then cooled to 0˚C to give

crystalline **28**. These improved conditions gave less than 0.05% (area/area by HPLC) of both nitro regioisomers (**29** and **30**), with a product purity of 99.4% in 67% isolated yield.

With the goal of simplifying the process and reducing the disparity between minimum and maximum reactor volumes, a hydrogenation process replaced the dithionite reduction. A mixed catalyst system of 1% platinum with 2% vanadium was used. It is postulated that vanadium causes the rapid disproportionation of the intermediate hydroxylamine **35a** to nitroso **36** and product **22**;[17] this reduces the potential formation of amide impurity **37** by rearrangement (Scheme 9). Amide impurity formation is conjectured to occur through ring closure of tautomer **35b** followed by reduction of the resulting benzoxazolimine **38**.

Scheme 9. Postulated mechanism of nitro reduction with mixed platinum and vanadium catalysis showing formation of amide **37**. There are two potential pathways for **35a** to give **22**.



The reaction was trialed on a 1.5 L scale with 5% of the amide impurity **37** produced. When transferred to a 30 kg scale on plant, the level of **37** increased to ~8%. This was attributed to reduced gas-liquid mass transfer, increasing the reaction time and affording the intermediate **35b** more time to form the impurity. It was postulated that the problem was exacerbated by increasing the agitation speed in the vessel. Under the reaction conditions, the nitro starting material is poorly soluble and the reaction is a viscous slurry; as the reaction progresses, the starting material gradually dissolves. During the manufacture, dissolution of nitro **28** had been even slower than expected at the planned agitation speed of 225 rpm, and so the speed was increased to the maximum of 300 rpm. It was thought this may have resulted in a temporary spike in the concentration of **35a** and hence a period of hydrogen starvation. A second batch with the agitation constant at 300rpm gave 5% of the impurity **37**.

Prior to the next plant manufacture, the reduction of the nitro group was reinvestigated from first principles. In the lab, reducing the hydrogen pressure from 3.5 bar to 0.5 bar only resulted in an increase in impurity **37** from 1.5% to 2.0%; increased impurity formation was not just down to poor hydrogen uptake. Experiments using different particle sizes of **28** inferred that faster dissolution of the starting material resulted in increased levels of the amide impurity **37**. Modelling of the process using computational fluid dynamics,[18] confirmed by experimentation, found that reducing the vessel fill level to maximize hydrogen uptake minimized the side reactions. The subsequent plant manufacture, produced 61 kg of **22** in 77% yield, with the amide impurity **37** <1.5%.

For plant manufacture, the formation of 3-CFA dimer **33** was intensified, reducing the solvent to 5.0 rel vol. Two 40 kg batches were successfully manufactured in 92% yield with purity >97%. For the following plant campaign, a single 85 kg batch was manufactured. Recirculation of the mother liquors ensured full transfer of the dense product crystals from the reactor to the filter, pushing up the yield to 95%.

The solvent for the Dimroth rearrangement was switched from anisole to 2-MeTHF; this gave an equivalent reaction profile but faster, cleaner separations from the aqueous layer during work-up. Following a sodium hydroxide quench of the acetic acid and discard of the aqueous phase, crystallisation of **5** was attempted directly from 2-MeTHF. When the level of residual water was >4% the product form was poor and a hydrate was suspected (this may have been the cause of product stickiness in the previous campaign). Drying the solution by distillation to a water level of <1% improved the form, but the material crystallised in low purity. A small amount of IPA was added to increase the solubility of impurities and serendipitously an IPA solvate (sub-stoichiometric solvate ~0.93 eq IPA), crystallised in high yield and purity. Optimization of the crystallisation around these conditions used a partial solvent swap into IPA to dry the reaction. The losses to liquors were highly dependent on achieving a low water level at the end of the distillation (Table 1). Aniline **7** was fully rejected by these crystallisation conditions.

Table 1. Crystallisations of **5** from 10 rel vol of 85% IPA 15% 2-MeTHF demonstrating the effect of water content.

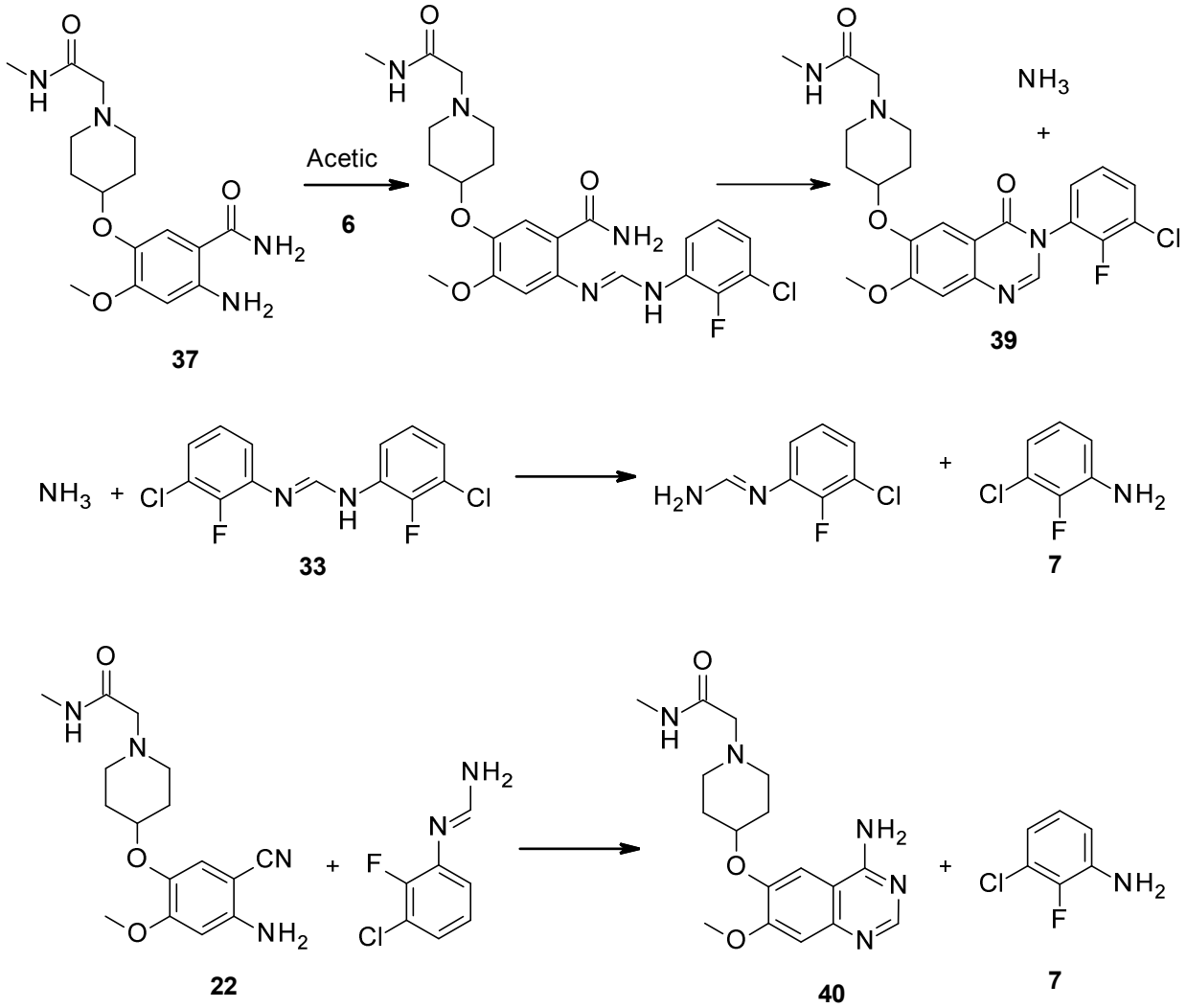
Added water (Rel Vol)	Purity of **7** (HPLC %)	Solvate formed	Losses to Liquors (%)‡

0.1	98.9	IPA	2.3
0.3	99.1	IPA	4.3
0.5	99.0	IPA	6.1
2	98.9	None	5.5

‡ Losses to Liquors, the amount of product remaining in the filtrate

For the 30 kg sized plant batches, the process performed worse than expected with a yield of 74.6%, down from the expected 83%. The increased level of amide impurity **37** in the campaign was linked to an increase in two impurities, the hydrolysed intermediate **39** and aminoquinazoline **40**, which may have accounted for the reduction in yield. Probing the formation of **39** and **40** through stressing reactions and adding ammonium chloride (a potential contaminant from the nitration work-up) showed a correlation with the level of **37**. It is proposed the formation of these impurities results from amide **37** reacting with amidine **33** to give quinazolinone **39**, releasing ammonia in the process. Ammonia can then react with additional amidine **33** and subsequently with nitrile **22** to give amino quinazoline **40** (Scheme 10).

Scheme 10. The proposed mechanism of formation for hydrolysed intermediate **39** and aminoquinazoline **40**.



Reworking of the batches by recrystallizing from 10 rel vol of IPA, reduced the levels of the impurities **39** and **40** to an acceptable level; yield for the rework was 93%. Overall, for the first plant manufacture the yield was 30% including the rework of the crude material.

The Dimroth process remained unchanged for a second plant manufacture. For the first 40 kg batch, the seed crystals dissolved at 75 ˚C, although the batch subsequently self-seeded. For the second 40 kg batch, seeding at the lower temperature of 70˚C, allowed the seed to persist and the batch to crystallise in a more controlled manner. Now with cleaner input material, due to the

improved hydrogenation conditions (**37** reduced from 5% to 1.5%), the crystallisation losses were lower, with a higher average yield of 86.5%. All impurities were rejected to an acceptable level with no need for a rework and the main goal of avoiding impurities **15-18** was achieved by switching to the Dimroth route. For the second plant manufacture, the overall yield was an improved 41%.

CONCLUSIONS

A scalable approach to the novel active agent AZD8931 has been successfully developed and operated on a multi-kilo scale. The yield of the route was comparable to that of the original approach. The original problematic impurities were both avoided and purged, whilst new impurities encountered were successfully controlled. The mechanisms of the nitro reduction and Dimroth rearrangement reactions were explored highlighting impurity formation pathways.

EXPERIMENTAL METHODS

General. All reactions were carried out in dry reaction vessels under an atmosphere of dry nitrogen unless otherwise specified. All reagents and solvents were used as received without further purification unless otherwise specified. *tert*-butyl-4-methanesulfonyloxypiperidine-1-carboxylate (**10**) was prepared as per the literature.[11]

Synthesis of 4-methoxy-3-(4-piperidyloxy)benzonitrile hydrochloride (26). 3-hydroxy-4-methoxy-benzonitrile (**20**) (20.0 kg, 134 mol, 1.00 eq), PEG400 (10.7 kg) and MIBK (32.1 kg) were charged to a 500 L glass-lined reactor which had been purged with nitrogen. After addition, the mixture was heated to 60~80˚C. A solution of potassium carbonate (22.2 kg, 161 mol, 1.20

eq) dissolved in purified water (20.1 kg) was added dropwise into the mixture at a rate of 40~60 kg/h while keeping the temperature at 60~90˚C. Then the mixture was heated to 95~100˚C. *tert*-butyl-4-methanesulfonyloxypiperidine-1-carboxylate (**10**) (56.2 kg, 281 mol, 2.10 eq) and MIBK (96.0 kg) were mixed in another 500 L glass-lined reactor which had been purged with nitrogen, and then heated to 50~70˚C to a clear solution. The solution of *tert*-butyl-4-methanesulfonyloxypiperidine-1-carboxylate (**10**) was added into the main reaction mixture at a rate of 60~90 kg/h, keeping the reaction temperature at 95~100˚C. After addition, the mixture was refluxed at 97~103˚C for reaction. The reaction was considered complete when conversion of 3-hydroxy-4-methoxy-benzonitrile (**20**) was ≥98%. After reaction completion, the mixture was cooled to 85~90˚C. Purified water (80.0 kg) was added into the mixture at a rate of 50~100 kg/h whilst maintaining the temperature at 65~90 ˚C. The mixture was stirred for 0.5h and held for 0.5h at 60~66˚C before separation. The organic phase was washed with purified water (60.0 kg) at 60~66˚C. It was then stirred for 0.5 h, held for 0.5 h and then the aqueous phase was separated off. After washing, the pH of aqueous phase was ≤10. The organic phase was cooled to ≤50˚C, and then concentrated at ≤50˚C under reduced pressure (P≤-0.08 MPa) until 70~80 L remained and the residual water of mixture was ≤0.15% by KF. The residue was diluted with isopropanol (173.5 kg) and then heated to 75~85˚C. Maintaining the temperature at 75~85˚C, HCl (21% in IPA, 36.8 kg) was added into the mixture at a rate of 30~40 kg/h. Then 4-methoxy-3-(4-piperidyloxy)benzonitrile hydrochloride **26** seed (0.1 kg, 0.43 mol, 0.003 eq) was added and stirred at 75~85˚C for 0.5h. HCl (22.4% in IPA, 18.2 kg) was added into the mixture at a rate of 30~40 kg/h whilst maintaining the temperature at 75~85˚C. The mixture was stirred at 75~85˚C until the conversion of *tert*-butyl 4-(5-cyano-2-methoxy-phenoxy)piperidine-1-carboxylate (**25**) was ≥98%. Then the mixture was cooled to -3-3˚C at a rate of 5~10˚C /h and

then stirred at 0~5˚C for at least 3h. The mixture was filtered and washed twice with IPA (47.0 kg, 48.0 kg) which was pre-cooled to 0~5˚C. Each time it was soaked for at least 15 min and then filtered. The cake was dried at 35~40˚C until the content of IPA was ≤1%, to give 4-methoxy-3-(4-piperidyloxy)benzonitrile hydrochloride (**26**) as a white powder (31.9 kg, 137 mol, 88.5% yield); 1H NMR (400 MHz, DMSO-d6) δ ppm 1.87 (m, 2 H), 2.11 (ddd, *J*=10.2, 6.7, 3.3 Hz, 2 H), 3.04 (ddd, J=12.7, 9.0, 3.4 Hz, 2 H), 3.22 (m, 2 H), 3.86 (s, 3 H), 4.66 (m, 1 H), 7.17 (d, J=8.5 Hz, 1 H), 7.47 (dd, J=8.4, 1.9 Hz, 1 H), 7.58 (d, J=1.9 Hz, 1 H), 9.28 (br. s, 2 H); m/Z ES+ 232.8 $[MH]^+$; HRMS found $[MH]^+$ = 233.1286, $C_{13}H_{16}N_2O_2$ requires $[MH]^+$ = 233.1212; Assay (QNMR) 95.2 wt %/wt.

Synthesis of 2-[4-(5-cyano-2-methoxy-phenoxy)-1-piperidyl]-N-methyl-acetamide (21). Anhydrous ethanol (50.5 kg) was charged into a 500 L glass-lined reactor which had been purged with nitrogen, followed by the addition of 4-methoxy-3-(4-piperidyloxy)benzonitrile hydrochloride (**26**) (31.9 kg, 137 mol, 1.00 eq), triethanolamine (64.2 kg, 430 mol, 3.14 eq) and anhydrous ethanol (25.0 kg). Then a solution 2-chloro-N-methylacetamide (**14**) (17.6 kg, 163 mol, 1.19 eq) in anhydrous ethanol (25.0 kg) was slowly added into the mixture. After addition, the mixture was heated to 80~81˚C and held at this temperature for 12 h. The reaction was considered complete when the tert-butyl 4-(5-cyano-2-methoxy-phenoxy)piperidine-1-carboxylate (**26**) conversion was ≥96%. After reaction completion, the mixture was cooled to 70~73 ˚C. Purified water (257.4 kg) was added into the mixture while maintaining the temperature at 65~73 ˚C; the mixture was then cooled to 58~60 ˚C. 2-[4-(5-cyano-2-methoxy-phenoxy)-1-piperidyl]-N-methyl-acetamide (**21**) seed (0.1 kg, 9.33 mol, 0.07 eq) was added and

stirred at 58~60 ˚C for at least 0.5 h. The mixture was cooled to 49~51 ˚C at a rate of ≤20 ˚C /h and stirred for further 30~60 min, heated to 59~61 ˚C and stirred for further 30~60 min; this temperature cycle was repeated four times. Then the mixture was cooled to 0~3˚C with a rate of ≤20˚C /h and stirred for further 1~2 h. The mixture was filtered on a nutsche filter. The 500 L glass-lined reactor was rinsed with mixed solvent of purified water (48.0 kg) and anhydrous ethanol (37.5 kg). The wash liquor was transferred to soak the filter cake for at least 15 min and filtered. The filter cake was soaked with purified water (96.0 kg) for at least 15 min and then filtered. The filter cake was dried at 40~45˚C until KF≤1.5% and gave 2-[4-(5-cyano-2-methoxy-phenoxy)-1-piperidyl]-N-methyl-acetamide (**21**) as white solid (29.2 kg, 96.2 mol, 81.1% yield); 1H NMR (400 MHz, DMSO-d6) δ ppm 1.70 (m, 2 H), 1.93 (m, 2 H), 2.32 (br t, *J*=9.3 Hz, 2 H), 2.64 (m, 5 H), 2.92 (s, 2 H), 3.84 (s, 3 H), 4.43 (m, 1 H), 7.13 (d, *J*=8.4 Hz, 1 H), 7.41 (dd, *J*=8.4, 1.9 Hz, 1 H), 7.48 (d, *J*=1.9 Hz, 1 H), 7.71 (m, 1 H); m/Z ES+ 304.1 $[MH]^+$; HRMS found $[MH]^+$ = 304.1660, $C_{16}H_{21}N_3O_3$ requires $[MH]^+$ = 304.1583; Assay (QNMR) 99.0 wt %/wt.

Synthesis of 2-[4-(5-cyano-2-methoxy-4-nitro-phenoxy)-1-piperidyl]-N-methyl-acetamide (28).

Acetic acid (85.0 kg) was charged to a 500 L nitrogen inerted glass-lined reactor, the stirrer was started, and 2-[4-(5-cyano-2-methoxy-phenoxy)-1-piperidyl]-N-methyl-acetamide (**21**) (29.2 kg, 96.2 mol, 1.00 eq) was added. After addition, the mixture was cooled to 10±1˚C, then concentrated sulfuric acid (77.1 kg) was added into the mixture while maintaining the temperature ≤35˚C. Then 60.3% concentrated nitric acid (10.7 kg) was added via a carboy into

the mixture at 25~35˚C. The pipe and the carboy were washed with acetic acid (7.6 kg) and then the wash liquor was transferred into the 500 L glass-lined reactor. The mixture was heated to 45˚C at a rate of ≤5˚C/h. The mixture was held at 42~48˚C for 4 h and the reaction was considered complete when conversion of 2-[4-(5-cyano-2-methoxy-phenoxy)-1-piperidyl]-N-methyl-acetamide (**21**) was ≥99%. After reaction completion, the mixture was cooled to 10~20˚C. Then the reaction mixture was quenched with mixture of purified water (118.0 kg) and ice (116.9 kg) in a nitrogen inerted 3000 L glass-lined reactor; the temperature was maintained ≤35˚C during the quench. After quenching, ammonia (22.3% 59.1 kg) was added dropwise into the mixture while maintaining the temperature at ≤25˚C. Then pyridine (258.0 kg) was added slowly into the mixture while maintaining the temperature at ≤35˚C. The mixture was warmed to 80~83˚C and stirred for 30 min until the solid dissolved completely, then held at 78~83˚C before separation. The organic phase was cooled to 72~73˚C, seeded with 2-[4-(5-cyano-2-methoxy-4-nitro-phenoxy)-1-piperidyl]-N-methyl-acetamide (**28**) (90.0g, 0.26 mol, 0.003 eq) and stirred at 72~73˚C for 1 h. The mixture was cooled to 0~5˚C, and purified water (146.2 kg) was added dropwise into the mixture. The mixture was stirred for 1 h at 0-5˚C, then the mixture was filtered. The reactor was washed with mixed solvent of purified water (58.4 kg) and anhydrous ethanol (41.0 kg). The wash liquor was transferred to wash the filter cake by soaking for at least 15 min. The reactor was washed again with mixed solvent of purified water (58.5 kg) and anhydrous ethanol (41.0 kg). The wash liquor was transferred to wash the filter cake by soaking for at least 15 min. The filter cake was dried at ≤60˚C until KF was ≤2% giving 2-[4-(5-cyano-2-methoxy-4-nitro-phenoxy)-1-piperidyl]-N-methyl-acetamide (**28**) as a light yellow solid (22.5 kg, 64.6 mol, 67.1% yield); 1H NMR (400 MHz, DMSO-d6, TFA) δ ppm 2.10 (br s, 1 H), 2.18 (br s, 1 H), 2.30 (m, 1H), 2.70 (d, *J*=4.5 Hz, 3 H), 3.21 (br s, 2 H), 3.40 (br s, 1 H), 3.58 (br d,

J=9.8 Hz, 1 H), 3.99 (m, 5 H), 4.84 (br s, 1 H), 7.89 (m, 2 H), 8.51 (br s, 1 H), 9.95 (br s, 1 H); m/Z ES+ 349.0 $[MH]^+$; HRMS found $[MH]^+$ = 349.1508, $C_{16}H_{20}N_4O_5$ requires $[MH]^+$ = 349.1234; Assay (QNMR) 99.4 wt %/wt.

Synthesis of 2-[4-(4-amino-5-cyano-2-methoxy-phenoxy)-1-piperidyl]-N-methyl-acetamide (22).

2-[4-(5-cyano-2-methoxy-4-nitro-phenoxy)-1-piperidyl]-N-methyl-acetamide (**28**) (29.0 kg, 83.2 mol, 1.00 eq), catalyst (1% Pt/2% V on carbon, 1.46 kg) and acetonitrile (456 kg) were charged to the reactor. The reactor was purged three times with nitrogen then heated to 40˚C with stirring. The agitator was stopped and the reactor purged to 2 barg with hydrogen three times. The reactor was then pressurized to 3 barg with hydrogen and stirring was restarted. The reaction mixture was held at 40˚C until hydrogen uptake leveled off (approximately 6 h on this scale). The reactor was purged to 2 barg nitrogen three times. The catalyst was removed by filtration, and the filter cake washed with acetonitrile (91.2 kg). The volume of the reaction mixture was reduced by distillation to approximately 6 rel vol. The reaction temperature was adjusted to 55˚C and seeded with 2-[4-(4-amino-5-cyano-2-methoxy-phenoxy)-1-piperidyl]-N-methyl-acetamide (**22**) seed (0.03 kg, 0.10 mol, 0.001 eq). The contents of the vessel was held at 55˚C for 1 h, cooled to 0˚C over 9 h and then held for a further 4 h. The crystalline product was isolated on a pressure filter, washed with acetonitrile (45.4 kg) and dried to a constant weight to give 2-[4-(4-amino-5-cyano-2-methoxy-phenoxy)-1-piperidyl]-N-methyl-acetamide (**22**) (61.8 kg, 77.7% yield); 1H NMR (400 MHz, DMSO-d6) δ ppm 1.63 (m, 2 H) 1.84 (br dd, *J*=9.4, 3.4 Hz, 2 H), 2.22 (br t, *J*=9.3 Hz, 2 H), 2.63 (m, 5 H), 2.87 (s, 2 H), 3.73 (s, 3 H), 4.01 (dt, J=8.3, 4.3 Hz, 1 H), 5.67 (s, 2 H), 6.40 (s, 1 H), 6.95 (s, 1 H), 7.67 (m, 1 H); m/Z ES+ 319.0 $[MH]^+$; HRMS found $[MH]^+$ = 319.1758, $C_{16}H_{22}N_4O_3$ requires $[MH]^+$ = 319.1692; Assay (QNMR) 98.7 wt %/wt.

Synthesis of N,N'-bis(3-chloro-2-fluoro-phenyl)formamidine (33).

Cyclohexane (137 kg, 5 rel vol), 3-chloro-2-fluoroaniline **7** (98.1 kg, 673 mol, 2.27 eq) were charged to an inert glass lined vessel and stirring was started. Triethyl orthoformate (44.0 kg, 297 mol, 1.00 eq), acetic acid (1.78 kg, 0.10 eq) and *N*,*N*'-bis(3-chloro-2-fluoro-phenyl)formamidine (**33**) seed (0.089 kg, 0.0001mol) were charged to the reactor. The reactor contents were heated to 48°C and held for 6 h. The contents of the reactor was cooled to 20˚C over 12 h. The crystalline product was collected by filtration, deliquored and displacement washed twice with cyclohexane (51.5 kg, 0.75 rel vol). The material was dried to a constant weight to give *N*,*N*'-bis(3-chloro-2-fluoro-phenyl)formamidine (**33**) as a white solid (83.0 kg, 96.2% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21 (m, 6 H), 8.14 (br s, 1 H), 9.99 (s, 1H); m/Z ES+ 301.0 $[MH]^+$; HRMS found $[MH]^+$ = 301.0107 requires $[MH]^+$ = 301.0033; Assay (QNMR) 96.5 wt %/wt.

Synthesis of 2-[4-[4-(3-chloro-2-fluoro-anilino)-7-methoxy-quinazolin-6-yl]oxy-1-piperidyl]-N-methyl-acetamide (5).

2-[4-(4-amino-5-cyano-2-methoxy-phenoxy)-1-piperidyl]-N-methyl-acetamide (**22**) (27.0 kg, 84.8 mol, 1.00 eq), N,N'-bis(3-chloro-2-fluoro-phenyl)formamidine (**33**) (31.9 kg, 105.9mol,

1.25 eq) and 2-methyltetrahydrofuran (69.7 kg, 3.2 rel vol) were charged to an inert glass lined reactor. Stirring was started and the reactor contents were heated to 79˚C. Acetic acid (22.7 kg, 0.8 rel vol) was charged to the reaction over 0.5 h; this was followed by a 2-methyltetrahydrofuran (4.64 kg, 0.20 rel vol) line wash. The contents of the vessel were heated to 90˚C and held for 8 h. 2-Methyltetrahydrofuran (163 kg, 7.0 rel vol) and water (33.4 kg, 1.25 rel vol) were charged to the reactor. The reactor contents were adjusted to 65˚C and held for 1 h. In a separate vessel 50% w/w sodium hydroxide (32.5 kg, 4.5 mol eq) and water (40.5 kg 1.5 rel vol) were charged. The sodium hydroxide solution was transferred into the reactor over 0.5 h. Water (6.75 kg, 0.25 rel vol) was used to wash the line clean into the reactor. The contents of the reactor were adjusted to 70˚C. Stirring in the reaction was stopped and the layers were allowed to separate. The lower aqueous phase was discarded and the organic phase was washed twice with water (81.0 kg, 3.0 rel vol) at 70˚C. The reaction mixture was distilled with a jacket temperature of 110˚C and a batch temperature of 75˚C. When 5 rel vol of solvent had been removed, isopropanol (106 kg, 5.0 rel vol) was charged to then reactor and the distillation continued. When a further 5 rel vol of distillate has been collected, the distillation was stopped and isopropanol (106 kg, 5.0 rel vol) was charged. The contents of the reactor were adjusted to 75˚C and AZD8931 Crude IPA solvate (**5**) (Seed, 0.226 kg, 0.0005 mol, 0.01 eq) was charged. The batch was held at 75˚C for 1 h then cooled to 10˚C over 7 h. The crystalline product was collected by filtration, and displacement washed twice with isopropanol (42.4 kg, 2.0 rel vol). The product was dried to constant weight at 40˚C under vacuum to give 2-[4-[4-(3-chloro-2-fluoro-anilino)-7-methoxy-quinazolin-6-yl]oxy-1-piperidyl]-N-methyl-acetamide IPA solvate (**5**) as a white solid (38.1 kg, 84.2% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.81 (m, 2 H), 2.06 (m, 2 H), 2.39 (m, 2 H), 2.63 (d, J=4.7 Hz, 3 H), 2.75 (m, 2 H), 2.95 (s, 2 H), 3.94 (s, 3 H),

4.57 (Dt, *J*=8.1, 4.2 Hz, 1 H), 7.22 (s, 1 H), 7.29 (t, *J*=8.0 Hz, 1 H), 7.51 (m, 2 H), 7.74 (br d, *J*=4.6 Hz, 1 H), 7.83 (s, 1 H), 8.37 (s, 1 H), 9.58 (br.s, 1 H); m/Z ES+ 474.2 $[MH]^+$; HRMS found $[MH]^+$ = 474.1706, $C_{23}H_{25}ClFN_5O_3$ requires $[MH]^+$ = 474.1630; Assay (QNMR) 97.5 wt %/wt.

ASSOCIATED CONTENT

Supporting Information.

NMR spectra of the synthesized materials. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*(W.R.F.G.) Tel: +44 (0)1625-519149. Email: william.goundry@astrazeneca.com

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

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ABBREVIATIONS

3-CFA, 3-chloro-2-fluoroaniline; BOC, *tert*-Butyloxycarbonyl; DIPEA, N,N-Diisopropylethylamine; DMF-DMA, *N,N*-diemthylformamide dimethyl acetal; EGFR, epidermal growth factor receptor; eq, equivalents; HER, human epidermal growth factor receptor; IMS, industrial methylated spirits; IPA, *iso*-propanol; MIBK, methylisobutylketone; PEG, polyethyleneglcol; rel vol, relative volumes; rpm, revolutions per minute; TEA, triethylamine

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