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Process Research and Development for the Kilogram Manufacture of the SRC Kinase Inhibitor AZD0530

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Abstract:

Process research and development of a synthetic route towards a novel SRC kinase inhibitor is described. The Medicinal Chemistry route was very long and suffered from extensive use of chlorinated solvents and chromatography. A number of steps in the Medicinal Chemistry route were also unattractive for large-scale use for a variety of reasons. The route was modified to produce a shorter synthetic scheme that started from more readily available materials. By using the modified route, the title compound was manufactured on kilogram scale without recourse to chromatography and in significantly fewer steps. The scaled synthesis required two Mitsunobu couplings, which were developed and scaled successfully. An interesting hydrazine impurity was identified in the second Mitsunobu coupling; a mechanism for its formation is proposed, and a method for its control is described. The formation and control of some other interesting impurities are also described.

Introduction

AZD0530 is a potent SRC kinase inhibitor with a number of ongoing phase II clinical trials in a variety of solid tumour malignancies.[1] In order to provide material for toxicological studies and phase I clinical trials we were required to manufacture 2 kg (as free base equivalent) of the active pharmaceutical ingredient (API) in our kilo-lab facility at Macclesfield.

Our colleagues in Medicinal Chemistry had used the chemistry shown in Scheme 1 successfully to produce a 100 g campaign.[1] However, some aspects of the synthesis were of concern for further scale-up. First the sequence is very long: 17 linear steps, 7 of which are protecting group manipulations. In addition, a number of issues with specific stages were also identified.

- 3,5-Dimethoxyaniline was not found to be readily available on scale.
- Conversion of aniline **1** to isatin **2** and the deprotection of the methoxy group of **8** both required high temperatures not readily achieved in our kilo-lab at the time.
- Anthranilic acid **3** was known to be unstable (decarboxylation).
- Use of triphenylphosphine/carbon tetrachloride for the conversion of quinazolinone **9** to the corresponding 4-chloroquinazoline.
- Three Mitsunobu couplings.

Further discussions with medicinal chemists identified that an alternative route to AZD0530 via 5,7-dibenzyloxyquinazolin-4-one, **20** (Scheme 2), was possible and that the chemistry had been demonstrated on milligram scale within discovery. Advantages of this route over the chemistry shown in Scheme 1 were the following:

- Aniline **14** was more readily available.
- Milder conditions for the formation of isatin **16**.
- 3,5-Difluoroanthranilic acid **17** was significantly more stable than **3**.
- The benzyl protecting groups could be removed under milder conditions than the corresponding methoxy groups.

Clearly this offered advantages over the first-generation route to AZD0530 although a number of challenges remained for the kilogram-scale manufacture using this chemistry including the following:

- extensive use of chlorinated solvents
- extensive use of chromatography
- development of Mitsunobu couplings
- route length

Owing to the urgency with which we were required to provide material for further studies we decided that while this route still presented significant challenges it could be developed sufficiently to deliver a 2 kg campaign.

During our investigations it was determined that a difumarate salt of AZD0530 was the preferred form for isolation of the API.[2]

This paper discusses our route and process development for the successful kilogram-scale synthesis of AZD0530.

Results and Discussion

Synthesis of 5,7-Difluoroquinazolin-4-one 19. Our attention turned first towards the synthesis of 5,7-difluoroquinazolin-4-one **19** which, following some process development in our

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(1) Hennequin, L. F.; Allen, J.; Breed, J.; Curwen, J.; Fennell, M.; Green, T. P.; Lambert van der Brempt, C.; Morgentin, R.; Norman, R. A.; Olivier, A.; Otterbein, L.; Ple, P. A.; Warin, N.; Costello, G. *J. Med. Chem.* **2006**, *49*, 6465–6488.

(2) Ford, J. G.; McCabe, J. F.; O'Kearney-McMullan, A.; O'Keefe, P.; Pointon, S. M.; Powell, L. Purdie, M.; and Withnall, J. WO/2006/064217, 2006.

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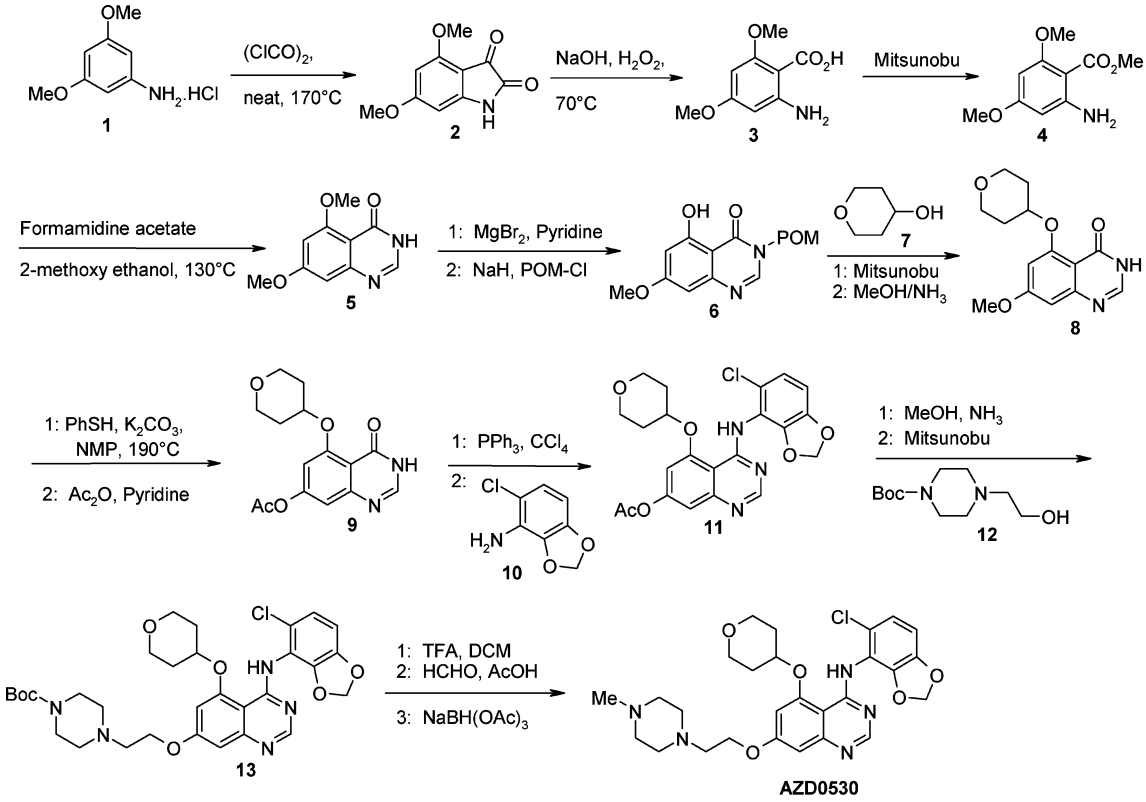
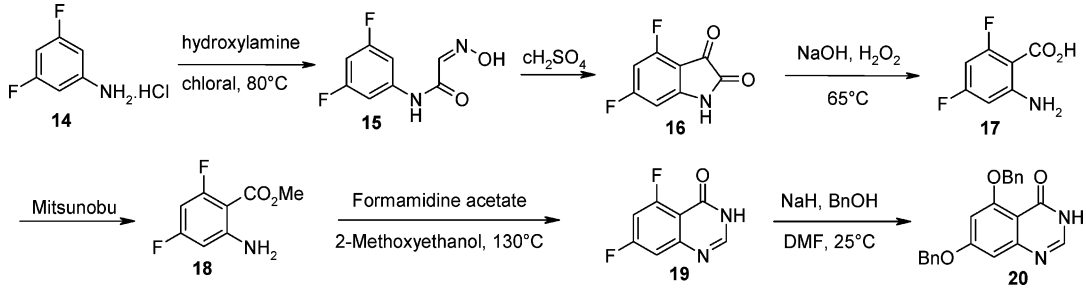
Scheme 1. **First-generation synthesis of AZD0530**



Scheme 2. **Route to 5,7-Dibenzyloxyquinazolinone**

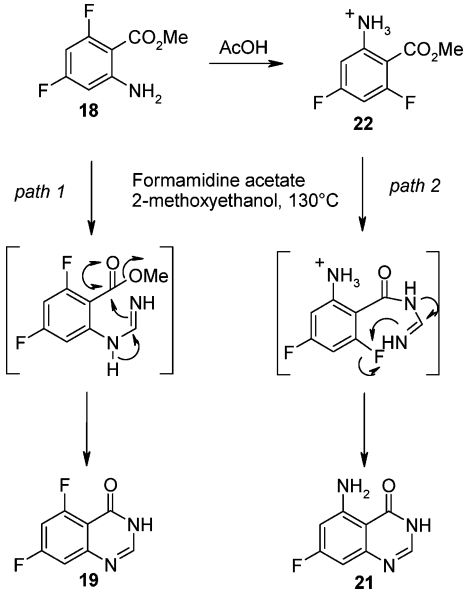


laboratories, was transferred to an outsourcing partner. The route that had been used previously within Medicinal Chemistry was essentially retained with some modifications for ease of scale-up. Oxime **15** was synthesised using a reported procedure for isatin.[3] Unfortunately, the original procedure suffered from low output and poor physical form. The reaction is performed in water, and it was found that by using the hydrochloride salt of aniline **14** and adding a small amount of toluene during the crystallisation both the output and physical form of **15** could be improved. One final note of caution with this process was the detection of ppm quantities of hydrogen cyanide in the off gases produced. Conversion of **15** to isatin **16** was also examined by using the reported procedure for isatin.[3] Following the literature procedure we found the reaction to be exothermic and difficult to control. Portionwise addition of oxime **15** to the acid allowed the exotherm to be controlled, and the reaction was performed at 60 °C to prevent accumulation of **15**. The oxidative hydrolysis of isatin **16** to anthranilic acid **17** was also based on literature precedence,[4,5] and again controlled additions were required to allow dissipation of the significant exotherms generated during the addition of both the peroxide and the hydrochloric acid. At the end of the reaction the product was extracted into methyl *tert*-butyl ether (MTBE) and then solvent swapped into 1-methylpyrrolidin-2-one (NMP) to give a solution of **17**, which was used directly in the next stage. Anthranilic acid **17** could be crystallised from a variety of solvents, but it was found that little purification was achieved, and in any case the quality prior to crystallisation was acceptable in the subsequent chemistry. Conversion of **17** to give ester **18** had been carried out previously using Mitsunobu conditions and required chromatographic purification of **18**. However, we were aware that esterification of **3** to produce **4** using dimethylsulfate had also been carried out within Medicinal Chemistry. Gratifyingly, we found that **18** could also be produced using dimethylsulfate and potassium carbonate, as with the acid, **18** was isolated as a solution (in MTBE) suitable for use in the

(3) Marvel, C. S.; Hiers, G. S. *Organic Syntheses*; Wiley & Sons: New York, 1941; Collect. Vol. I, pp 327−330.

(4) Newman, H.; Angier, R. B. *J. Org. Chem.* **1969**, *34*, 3484–3491.
(5) Reissenweber, G.; Mangold, D. *Angew. Chem.* **1980**, *92*, 882–883.

Scheme 3. **Proposed mechanism for formation of aniline impurity**

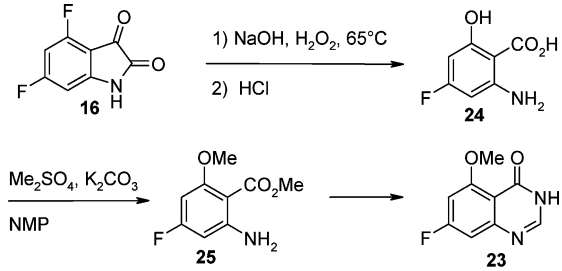


subsequent stage without the need for chromatography. Conversion of ester **18** to quinazolinone **19** using formamidine acetate had been successfully carried out in Medicinal Chemistry. However, the procedures used chlorinated solvents, and the product required chromatographic purification. Screening of alternative solvents determined that the process could be carried out in 2-methoxyethanol under Dean−Stark conditions to remove methanol and water produced by the reaction. Upon completion of the reaction, the volume was reduced by distillation and aqueous isopropanol added, allowing subsequent crystallisation of quinazolinone **19**.

Impurities in Difluoroquinazolinone 19. During our laboratory investigations, the formation of significant levels of impurity **21** were observed. It was postulated that during the 10−14 h reaction period the ammonium acetate byproduct could disproportionate and ammonia would be lost under the Dean−Stark conditions employed. This would result in a reduction in pH of the reaction mixture. Reasoning that the desired reaction occurs *via* initial reaction of the aniline moiety with formamidine (Scheme 3, path 1), a reduction in pH could result in the formation of ammonium salt **22**, shutting down the desired reaction pathway. Under acidic conditions we then reasoned that **22** could react with formamidine *via* the ester group and subsequent intramolecular S_NAr displacement of the ortho-fluorine would generate aniline **21** (Scheme 3, path 2). Investigations showed that the addition of diethylisopropylamine (DIPEA) significantly reduced the formation of impurity **21**. Finally, the addition of formamidine acetate and DIPEA in aliquots over the duration of the reaction was found to be beneficial, and this was the process operated on scale.

During production at the contract manufacturer a new impurity, methoxyquinazolinone, **23**, was observed at levels of up to 20%. It was postulated that impurity **23** could be the ultimate result of partial fluoride displacement during the formation of anthranilic acid **17**.[6] As shown in Scheme 4, the 3-hydroxy-anthranilic acid **24** could be produced under the alkaline conditions required for the oxidative hydrolysis of

Scheme 4. **Possible route for formation of methoxy impurity**



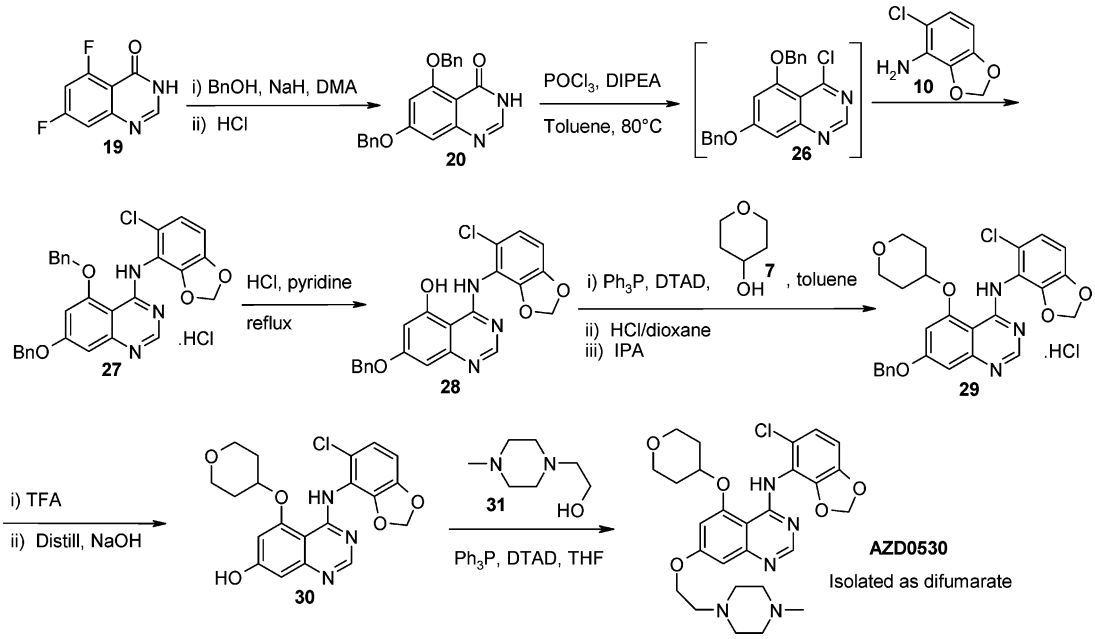
isatin **16**. This could then proceed through the subsequent stages as shown to give methoxyquinazolinone **23**. The conditions operated for the conversion of **16** to **17** used 10 equiv of sodium hydroxide (18% w/w) and ∼3 equiv of hydrogen peroxide at 60−65 °C. We reasoned that on scale prolonged heating and cooling operations may have allowed hydrolysis not seen on the lab scale. To investigate this further, isatin **16** was subjected to caustic hydrolysis at ambient temperature and at 65 °C. At ambient temperature very little fluoride displacement was observed, but by using 20% w/w sodium hydroxide at 65 °C complete decomposition of isatin **16** was observed after 2.5 h with the expected 5-hydroxy-7-fluoroisatin as the main decomposition product. Further studies then showed that the process could be operated successfully with the use of reduced charges of reagents and at lower temperature. Using 3.6 equiv of sodium hydroxide (∼5% w/w) and 1.5 equiv of hydrogen peroxide at 25 °C material was produced which ultimately gave difluoroquinazolinone **19** free from methoxyquinazolinone **23**.

Conversion of 5,7-Difluoroquinazolin-4-one 19 to AZD0530. The second-generation synthesis of AZD0530 is shown in Scheme 5 and in addition to the advantages discussed in the Introduction presents other improvements over the first-generation synthesis. Changes to the order in which the main fragments of AZD0530 are coupled together, and in particular the coupling of aniline **10** prior to manipulation of the 5,7-oxyfunctionality allows the overall synthesis to be shortened. Principally, this is done by avoiding the requirement for multiple protecting group manipulations present in the first-generation synthesis.

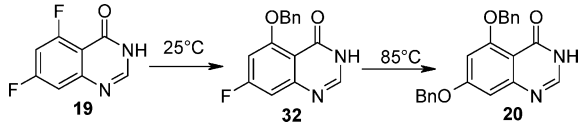
The conversion of **19** to AZD0530 commences with the double S_NAr reaction to form dibenzyloxyquinazolinone **20**. The conditions supplied from our discovery department used sodium hydride in DMF. Although a good yield could be achieved, the proposed process suffered from low volume productivity in addition to the known safety concerns of using sodium hydride in DMF.[7] A screen of different bases and solvents determined that potassium carbonate and triethylamine were not sufficiently basic to effect the reaction. Interestingly potassium *tert*-butoxide was strong enough to promote the conversion to the monobenzylquinazolinone **32**, but the final conversion to dibenzylquinazolinone **20** could not be driven to completion. Following further experiments and discussions with colleagues from our process safety group it was

(6) Cantrell, W. R.; Bauta, W. E.; Engles, T. *Tetrahedron Lett.* **2006**, *47*, I4249−4251.
(7) Pitt, M. J. *Bretherick's Handbook of Reactive Chemical Hazards*, 6th ed.; Butterworth Heinemann: Oxford, 1999.

Scheme 5. **Second-generation synthesis of AZD0530**



Scheme 6. **Conversion of difluoroquinazolinone 19 to dibenylquinazolinone 20**



determined that with appropriate controls sodium hydride in dimethylacetamide (DMA) could be used safely for the process. Benzyl alcohol (3.0 equiv) was reacted with sodium hydride (3.9 equiv) at 25 °C. Controlled addition of difluoroquinazolinone **19** then allowed the conversion to monobenzylquinazolinone **32** to occur, and the reaction was then warmed to 85 °C to effect the second displacement to give **20**. To ensure a safe process, 3 equiv of benzyl alcohol in addition to the acidic quinazolinone **19** and 3.9 equiv of sodium hydride were used such that there was no unreacted hydride remaining prior to warming the reaction to 85 °C (the excess of NaH over the alcohol is required due to deprotonation of quinazolinone **19**). The reaction was worked up by neutralising with hydrochloric acid and then cooling to crystallise the product. Pleasingly, it was found that this process and isolation allowed **20** to be manufactured in high yield, typically 90%, and with good rejection of the impurities derived from **21** and **23**. Unsurprisingly, corrosivity tests showed that glass was damaged by the reaction conditions, and as a result this stage was also outsourced to the same contractor as for **19**, owing to the availability of a suitable Hastelloy vessel.

Conversion of **20** to anilinoquinazoline **27** had been carried out in the Medicinal Chemistry laboratories using phosphorous oxychloride and DIPEA in methylene chloride (DCM). The volatiles were then removed by rotary evaporation to yield crude chloroquinazoline **26**, which was used directly in the coupling with aniline **10**. Toluene was found to be a suitable replacement for DCM, giving the best yield and product strength of the solvents examined. The stoichiometry of the reaction was then investigated followed by the order of addition. It was found to be necessary to add quinazolinone **20** to a solution of phosphorous oxychloride in anhydrous toluene in a controlled manner as uncontrolled addition or reverse addition resulted in significant formation of a pseudodimeric species (Figure 1). Unfortunately the poor solubility of quinazolinone **20** in toluene necessitated that the material was added in solid portions but this was deemed to be suitable for the required scale of manufacture. Once the conversion to chloroquinazoline **26** was complete, a solution of aniline **10** was added directly to the reaction mixture to give anilinoquinazoline **27**, which was subsequently isolated as its hydrochloride salt.

With the anilino group in place selective deprotection of **27** was required. This was readily achieved using reaction conditions that were largely unchanged from those used in Medicinal Chemistry. Hydrochloric acid was added to a solution of **27** in pyridine and the resulting mixture heated to reflux. While the reaction conditions required little modification, it was deemed necessary to modify the work-up and isolation. The Medicinal Chemistry procedure involved a lengthy extractive work-up which involved evaporations to dryness and purification of the product by chromatography. DCM was used in both the work-up and in the eluent for the chromatography. A simpler procedure involving removal of some of the pyridine by distillation, addition of aqueous sodium hydroxide to neutralise the acid, and further distillation allowed **28** to be isolated in acceptable yield and purity. The neutralisation was required to

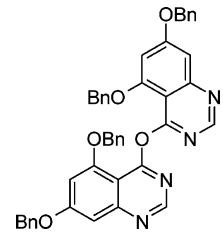


Figure 1. **Dimeric impurity formed in phosphorous oxychloride reaction.**

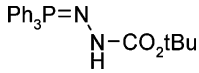


Figure 2. ***tert*-Butyl 2-(triphenylphosphoranylidene)hydrazinecarboxylate.**

prevent acidic hydrolysis of **28** back to **10** and 5-hydroxy-7-benzyloxyquinazolin-4-one during the second distillation.

The conversion of **28** to tetrahydropyranyl ether **29** had been carried out in our Medicinal Chemistry department by reaction with tetrahydropyran-4-ol **7** under Mitsunobu conditions. The conditions used performed the reaction in DCM followed by evaporation to dryness before isolating **29** as its HCl salt. Our initial investigations looked at alternative solvents, stoichiometry, and the optimal order of addition of the reagents. The reaction was found to proceed well at room temperature in a variety of solvents such as toluene, THF, ethyl acetate or at higher temperature in MTBE or acetonitrile. However, the reactions did not routinely reach completion and it was apparent that residual **28** was not readily removed during work-up and was likely to cause significant impurity problems in the subsequent steps. The incomplete reactions were traced to the water content of **28** where 1.7% w/w corresponds to ~50 mol %. As a result of this, toluene was selected as the optimal solvent as it allowed the introduction of an azeotropic drying step at the beginning of the reaction to ensure robustness. Following the reaction, hydrochloric acid in 1,4-dioxane was added and **29** isolated as its HCl salt. Product obtained in this way was found to be low strength, typically 50−60% w/w, and the purity was increased by slurrying in isopropanol (IPA). Following this IPA treatment, the strength of the product was typically >90% w/w, the main impurities being removed were triphenylphosphine oxide and what we believe on the basis of HPLC/MS analysis to be the phosphoranylidenehydrazine derivative shown in Figure 2. The upgrade in purity was found to be important for the performance of the following deprotection step with lower-strength material resulting in longer reaction times and a concomitant increase in impurity formation.

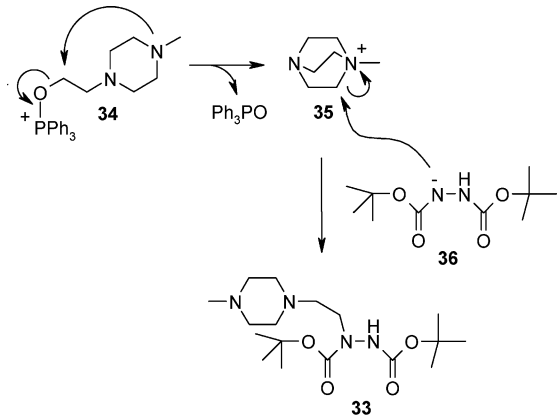
The final deprotection had been carried out in discovery by reflux in a large excess of TFA, distilling to dryness and purifying the resulting crude **30** by chromatography using DCM as the primary component of the eluent. Our investigations focused on finding and optimising scalable reaction conditions and isolating **30** without recourse to chromatography or chlorinated solvents. Isolation was made difficult by the poor solubility of phenol **30** in most organic solvents and the need to separate **30** from benzyl alcohol and benzyl trifluoracetate that were formed as byproducts of the reaction. Inefficient separation of the byproducts typically led to the precipitation of **30** with poor solid form or worse still as a viscous oil. Alternative methods for the debenzylation were investigated, and while conditions such as hydrobromic acid in glacial acetic acid were also effective, isolation of the product proved intractable. Hydrogenolysis was also investigated briefly, but slow reactions and concerns about the potential for dehalogenation of the 2-chloro-5,6-dioxoleaniline ring led us to abandon this approach.

After returning to the original TFA conditions we found that the high excesses of TFA (70 equiv) were required in order to achieve acceptable reaction times, typically 5−7 h at reflux. Following the reaction the bulk of the TFA was removed by distillation under reduced pressure, and a variety of work-up and isolation protocols were investigated. It was eventually found that **30** could be isolated in acceptable form by adding a 1:1 mixture of water and ethyl acetate and neutralising with sodium hydroxide. The addition of water and ethyl acetate resulted in a biphasic mixture as the residual TFA solubilised **30**. Neutralisation then resulted in precipitation of **30** from around pH 4.5. Under these conditions benzyltrifluoroacetate was retained in the organic layer, and the product could be filtered from the three-phase mixture as a white solid with acceptable form and purity.

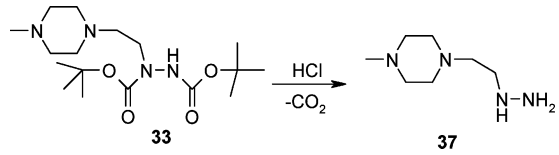
The final synthetic step required another Mitsunobu coupling which in Discovery had been carried out using BOC-protected hydroxyethylpiperazine **12**. Investigations in our laboratories showed no advantage in performing the reaction with the BOC-protected material over the *N*-methyl analogue **31**, which also offered a shorter synthesis. The conversion of **30** to AZD0530 was the last synthetic step in the preparation of our GMP material, and we were therefore concerned about controlling the levels of impurities and numerous expected byproducts such as triphenylphosphine oxide in material destined for use in the clinic. The conditions supplied used di-*tert*-butylazodicarboxylate (DTAD) for the coupling and carried out the reaction in DMF, but we were concerned that this may limit our options for work-up and isolation and also that DMF would be difficult to remove from the product. A solvent screen was carried out which showed acetonitrile and benzotrifluoride to give poorer reaction profiles than DMF. THF and DME both gave better profiles, and THF was therefore selected for further development due to its lower boiling point and higher allowable limits according to the ICH guidelines.[8] According to the literature there are two preferred procedures for addition of the reagents in Mitsunobu couplings.[9] In the conversion of **30** to AZD0530 the mode of addition made negligible impact to the profile of the reaction. We believe this is due to the limited solubility of **30** in THF, which effectively results in a slow addition of **30** to the reaction mixture. As with the conversion of **28** to **29**, the reaction was found to be sensitive to the presence of moisture with small-scale reactions stalling unless they were carried out under an inert atmosphere. With suitable control of starting material quality and exclusion of moisture the reactions were found to be robust. Following the reaction in THF the mixture was solvent swapped into ethyl acetate, and we were pleased to find that after a basic wash to remove DTAD byproducts AZD0530 could be extracted into aqueous acid which allowed a number of organic soluble byproducts, principally triphenylphosphine oxide, to be extracted out. Basification of the mixture then allowed AZD0530 to be extracted back into *n*-butyl alcohol, which was then solvent swapped into IPA. The resulting solution of ADZ0530 freebase in IPA could then be used for the preparation and controlled crystallisation of AZD0530 difumarate.

(8) *ICH Harmonised Tripartite Guideline, ICH Q3C Impurities: Guideline for Residual Solvents*, (R3); U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER): Rockville, MD, 2005.
(9) Hughes, D. L. *Org. React. (N.Y.)* **1992**, *42*, 335–395.

Scheme 7. **Proposed mechanism for formation of hydrazine impurity**



Scheme 8. **Hydrolysis and decarboxylation of hydrazine impurity**



Impurities and Byproducts Formed during the Crude Stage. During the crude stage a number of expected and unexpected impurities were formed. As discussed above the expected Mitsunobu byproducts were readily removed by extractive work-up procedures. However, early samples of AZD0530 difumarate prepared in our laboratories were found to contain a higher than expected stoichiometry of fumaric acid to AZD0530 when analysed by NMR. Instead of the expected 2:1 ratio, the stoichiometry observed ranged from 2.3:1 to 4:6:1. Further analysis of the NMRs and recollection of an impurity that had been suggested by our colleagues in Medicinal Chemistry suggested that the solution of AZD0530 free base in IPA also contained hydrazine **33**.

It is postulated that this impurity forms as shown in Scheme 7 by an intramolecular displacement of triphenylphosphine oxide from Mitsunobu intermediate **34**. The resulting ammonium salt is then susceptible to ring-opening by hydrazine **36** generated by the same displacement. An interesting observation relating to this impurity is that the analogous species was not seen when Boc-protected analogue **12** was used, presumably due to the reduced nucleophilicity of the carbamate protected nitrogen relative to the tertiary amine present in **31**. This difference between the Boc and methyl analogues also suggests that the reaction proceeds as shown *via* the [2.2.2] bicyclic intermediate rather than *via* an aziridinium intermediate as this alternative pathway would be open to both **12** and **31**.

Having identified this impurity we were then able to modify the existing work-up to remove it. One advantage of DTAD over more commonly used Mitsunobu reagents such as DEAD is the susceptibility of the *tert*-butyl ester groups in the byproducts to acidic hydrolysis.[10] Using the existing work-up it was found that, following extraction of AZD0530 into the aqueous acid, addition of further hydrochloric acid and a suitable

(10) Kiankarimi, M.; Lowe, R.; McCarthy, J. R.; Whitten, J. P. *Tetrahedron Lett.* **1999**, *40*, 4497–4500.

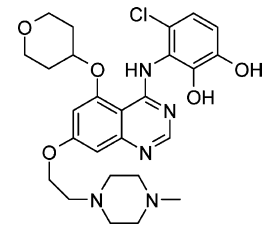


Figure 3. **Catechol impurity.**

hold resulted in hydrolysis of **33** followed by decarboxylation to give hydrazine **37**. Hydrazine **37** was significantly more water-soluble than **33** and was readily removed following the basification and extraction of AZD0530 into *n*-butyl alcohol.

By analogy with hydrazine we were concerned about the potential toxicity of **37**, the efficiency of its removal by the process, and its potential contamination of the API. Hydrazine was also a potential contaminant resulting from hydrolysis and decarboxylation of di-*tert*-butyl hydrazine-1,2-dicarboxylate, the expected Mitsunobu byproduct. Neither of these species has a conventional chromophore, so a derivatisation method was used for their measurement. The levels were found to be acceptable (<10 ppm), and interestingly, use of the derivatisation method showed that during the desired hydrolysis of **33** to **37** considerable further hydrolysis of **37** to give hydrazine and presumably **31** was also occurring.

Another impurity that was observed in samples of AZD0530 difumarate was the catechol shown in Figure 3. The analogous impurity had been observed during the conversion of **29** to**30**, but it may also have been formed during the acidic work-up of AZD0530. While the levels of the catechol were not a great concern, its presence suggests the possible contamination of the API with formaldehyde. Fortunately, we were able to show the presence of <30 ppm of formaldehyde in AZD0530.

Finally, a crystallisation of AZD0530 difumarate incorporating a polishing filtration, was carried out in aqueous isopropanol to give material of sufficient quality for clinical use.

Conclusions

- The original Medicinal Chemistry synthesis was significantly shortened from 17 synthetic steps to 11, primarily by removal of unnecessary protecting group manipulations.
- The quantity of 4.5 kg of AZD0530 difumarate was successfully manufactured using the processes described above.
- The use of chlorinated solvents was eliminated, and no chromatographic purification was required for any of the stages.
- Two Mitsunobu couplings were successfully developed and operated on multikilogram scale.

Overall the development and manufacture of AZD0530 difumarate was successful, but we were conscious that the route described above was probably not suitable for manufacture on a significantly larger scale. Alternative routes for AZD0530 have been investigated, and the development of a more efficient route will be discussed in a later publication.[12]

Experimental Section

General. Starting materials, reagents, and solvents were obtained from commercial suppliers and used without further purification. IR spectra were recorded using a Thermo Electron Avatar FT-IR instrument. Melting points were obtained with a Mettler Toledo DSC822e instrument. NMR spectra were obtained using Bruker DPX 400, DRX 500, and Avance 600 instruments; ^{1}H spectra were measured with reference to an internal standard of tetramethylsilane at 0 ppm, and ^{13}C spectra were measured with reference to the DMSO signal at 39.5 ppm. LC−MS and HRMS data were obtained using Waters Micromass ZMD4000 and Waters Micromass LCT Classic instruments, respectively. HPLC analyses were performed with an Agilent 1100 instrument.

(2*Z*)-*N*-(3,5-Difluorophenyl)-2-(hydroxyimino)acetamide (15). Sodium sulphate (29.0 kg, 204.2 mol) was dissolved in water (75 L) at 45−50 °C. Chloral (17.3 kg, 117.4 mol) was added over 1 h, maintaining the temperature between 45−50 °C. A water (13 L) line wash was applied and the reaction mixture stirred for 20 min at 45 °C. A solution of 3,5-difluoroaniline (11.0 kg, 85.9 mol), and hydrochloric acid (9.2 kg of a 36% solution, 90.8 mol) in water (43.5 L), preheated to 60 °C, was added to the reaction mixture over 20 min. (The solution of **14** must be kept above 50 °C to prevent precipitation.) A water (11 L) line wash was applied before adding toluene (19 kg). The reaction mixture was heated to 55 °C before a solution of hydroxylamine hydrochloride (19.0 kg, 273.4 mol) in water (41 L) was added to the reaction mixture over 1 h, maintaining the temperature at 55 °C. A water (11 L) line wash at 41 °C was applied and the reaction held at 55 °C for 7 h. The reaction mixture was cooled to 10 °C over 4 h and held for 1 h. The product was filtered and washed with chilled water (3 × 44 L, 5−10 °C) and dried under reduced pressure at 50 °C to give **15** (11.6 kg at 94% w/w, 54.5 mol, 63% yield). ^{1}H NMR (300 MHz, 300 K, DMSO-d_6) δ 12.32 (1H, s), 10.56 (1H, s), 7.64 (1H, s), 7.51−7.43 (2H, m), 6.95 (1H, tt, J = 9.3, 2.4); ^{13}C NMR (100 MHz, 300 K, DMSO-d_6) δ 162.3 (dd, J_{CF} = 243, 15), 160.9, 143.7, 140.9 (t, J_{CF} = 14), 102.6 (dd, J_{CF} = 21, 9), 98.9 (t, J_{CF} = 26); HRMS (ES accurate mass) calcd for $C_8H_7F_2N_2O_2$ 201.0470, found 201.0501.

4,6-Difluoro-1*H*-indole-2,3-dione (16). Sulphuric acid (28 kg of 50% w/w, 143 mol) was cooled to 5 °C before adding sulphuric acid (316.3 kg, 3225 mol), maintaining the temperature at 5 °C.[11] The solution was heated to 60 °C before adding **15** (42.81 kg, 214 mol) in 10 equal portions over 5 h, maintaining the temperature between 58−62 °C. The reaction was stirred for a further 1.5 h before cooling to 10 °C and adding to water (800 L) precooled to 5 °C followed by a water (170 L) line wash. After 2 h the mixture was filtered and the cake washed with water (3 × 210 L at 0−6 °C) before drying under reduced pressure at 45 °C to give **16** (35.35 kg at 83% w/w, 160 mol, 75% yield). Spectroscopic analysis was in agreement with the reported data.[1]

2-Amino-4,6-difluorobenzoic Acid (17). A solution of sodium hydroxide (102.1 kg, 2553 mol) in water (113 L) was added to a suspension of **16** (35.35 kg, 193 mol) in water (210 L) at ambient temperature over 1 h. A water (55 L) line wash was applied. The mixture was heated to 63 °C before adding hydrogen peroxide (67.5 L of a 30% solution in water, 595 mol) over 2.5 h, maintaining the temperature at 63−67 °C. Water (17 L) was added as a line wash and the mixture stirred for 1 h before cooling to 3 °C. Hydrochloric acid (188 L of a 36% w/w solution, 1856 mol) was added over 4 h followed by a water (18 L) line wash. Acetic acid (20 L, 349 mol) was charged over 1 h to adjust the pH to 3 (desired range 2−4), and a water (18 L) line wash was applied. The mixture was heated to 20 °C before extracting three times with MTBE (720 kg, 239 kg and 236 kg). The combined organics were washed with a solution of sodium sulphite (3.55 kg, 28.2 mol) in water (176 L) for 15 min and the organics tested for the presence of peroxide with test strips. The organics were washed twice with a solution of potassium carbonate (3.50 kg in 176 L water in two equal aliquots) and water (170 L). The organic phase was concentrated by distillation (55 °C, 636 L of distillate, ∼160 L remaining) before adding MTBE (136 kg) and redistilling (55 °C, 177 L distillate, 160 L remaining). The solution was cooled to ambient temperature and used directly in the next step. **17** (119 kg, 18.9% w/w, 130 mol, 67% yield). Spectroscopic analysis of a sample evaporated to dryness was in agreement with the reported data.[1]

2-Amino-4,6-difluorobenzoic Acid (17), Alternative Procedure. To a solution of sodium hydroxide (11.5 kg, 287 mol) in water (59 L) at ambient temperature was added **16** (4.6 kg, 26.6 mol) in aliquots over 40 min, maintaining the temperature at 25 °C. Hydrogen peroxide (4.3 L of a 30% solution in water, 38 mol) was added over 2.5 h, maintaining the temperature at 20−25 °C. Water (2 L) was added as a line wash and the mixture stirred for 4 h before adding water (23 L). Hydrochloric acid (∼10 kg of a 36% w/w solution, mol) was added over 1 h, maintaining the temperature below 15 °C to adjust the pH to 2 (caution, frothing). A water (1 L) line wash was applied. The mixture was stirred for 30 min before filtering, washing the cake with water (2 × 10 L), and drying under reduced pressure (50−60 °C) to give **17** (3.5 kg, 92% w/w, 18.6 mol, 70% yield). Spectroscopic analysis of a sample evaporated to dryness was in agreement with the reported data.[1]

Methyl 2-Amino-4,6-difluorobenzoate (18). To a solution of **17** in MTBE (119 kg of a 18.9% w/w solution, 130 mol) was added NMP (119 kg). The mixture was distilled under reduced pressure to remove the MTBE (40 °C, 135 L distillate, 113 L remaining). The resulting solution was added to a mixture of potassium carbonate (44.64 kg, 323 mol) in NMP (42 kg) at 3 °C over 1 h. (*Caution gas evolution*!) Dimethyl sulphate (18.2 kg, 144 mol) was added to the mixture at 2 °C over 1 h before stirring further for an hour. Analysis showed that the reaction was not complete, so additional potassium carbonate (2.25 kg, 16 mol) and dimethyl sulphate (0.9 kg, 7 mol) were charged, and the resulting mixture was stirred further for 35 min. The mixture was warmed to ambient temperature before adding

(11) The use of concentrated sulphuric acid in lab experiments frequently resulted in ejection of the reaction mixture from the vessel, presumably due to the heat generated by the interaction of sulphuric acid with the water released by the reaction. By using sulphuric acid which already contained a small amount of water, this could be prevented.

(12) Ford, J. G.; O'Kearney-McMullan, A.; Pointon, S. M.; Powell, L.; Siedlecki, P. S.; Purdie, M.; Withnall, J.; O'Keefe, P.; Wood, F., *Org. Process. Res. Dev.*, **2010**, *14*, DOI: 10.1021/op100163m.

water (478 L) and extracting with MTBE (2 × 115 L). The organic extracts were washed with water (2 × 154 L) before adding MTBE (117 kg) and concentrating the resulting solution by distillation (55 °C, 79 L remaining) to give a solution of **18** (60.4 kg of a 26.3% w/w solution, 85 mol, 65% yield), which was used directly in the next step. Spectroscopic analysis of a sample evaporated to dryness was in agreement with the reported data.[1]

5,7-Difluoroquinazolin-4(3*H*)-one (19). A mixture of **18** (60.4 kg of a 26.3% w/w solution, 85 mol) and 2-methoxyethanol (153 kg) was distilled under reduced pressure (35 °C, 80 L of distillate, 159 L remaining). The distillation was continued at atmospheric pressure until a batch temperature of 122−124 °C was achieved, periodically adding 2-methoxyethanol to maintain a batch volume of 159 L. The mixture was cooled to 100 °C before adding DIPEA (37 kg, 286 mol) and formamidine acetate (29 kg, 279 mol). The resulting mixture was heated to reflux (124 °C) for 17 h. The reaction mixture was cooled to 23 °C before distilling under reduced pressure (50−60 °C, ∼64 L remaining). The mixture was adjusted to 50 °C before adding water (205 L) and IPA (16.5 kg). The resulting mixture was heated to 96 °C and held for 10 min. The resulting solution was cooled to ambient temperature over 4 h and held at ambient temperature for 1.5 h before filtering and washing with a mixture of water (71 L) and IPA (4.5 kg) in two equal aliquots. The cake was dried to constant weight under reduced pressure (50 °C) to give **19** (10.6 kg at 76.5% w/w, 44.5 mol, 52% yield).

19 obtained in this way was further purified by slurrying in MTBE (4 relative volumes), filtering, and drying, prior to the next step.

5,7-Difluoroquinazolin-4(3*H*)-one (19) Alternative Procedure. A slurry of **18** (2.65 kg, 14 mol in toluene 1 L) was mixed with 2-methoxyethanol (25.6 kg) before adding formamidine acetate (1.5 kg, 14 mol) and DIPEA (1.84 kg, 14 mol) and heating to reflux (123 °C). Further formamidine acetate (3.32 kg, 32 mol) and DIPEA (4.20 kg, 32 mol) were added in four equal portions at 2 h intervals at 40 °C, reheating to reflux between additions. After 10 h the reaction mixture was cooled and distilled under reduced pressure (60−70 °C, ∼24 kg distillate). Water (34 kg) and IPA (3.5 kg were added to the mixture at 50 °C before heating to 95 °C. The resulting solution was cooled to ambient temperature over at least 4 h before filtering and washing with a mixture of water (11.5 kg) and IPA (1 kg) and then with water (6 kg). The cake was dried under reduced pressure (50 °C) to give **19** (2.4 kg, 95% w/w, 12.5 mol, 89% yield). Spectroscopic analysis was in agreement with the reported data.[1]

5,7-Bis(benzyloxy)quinazolin-4(3*H*)-one (20). Benzyl alcohol (21.1 kg, 183 mol) was added to a slurry of sodium hydride (10.32 kg, 60% w/w, 258 mol) in DMA (110 kg) over 1 h, maintaining a batch temperature of 17−22 °C. The resulting mixture was cooled to 11 °C before adding **19** (11.86 kg, 83% w/w, 54 mol) in 10 aliquots over 1 h, maintaining the temperature between 11−20 °C. The mixture was stirred for 7 h at 20 °C before warming to 80−90 °C for 9 h. Water (130 L) was added over 75 min followed by a solution of hydrochloric acid (38 kg of 37% w/w, 386 mol) in water (150 L) over 45 min. The resulting slurry was cooled to 25 °C and filtered; the wet cake was slurried in water (120 L) for 1 h and then filtered. The wet cake was slurried in methanol (210 kg) for 1 h then filtered, washed with heptane (2 × 23 kg); and dried under reduced pressure (45 °C) to give **20** (19.8 kg, 95.5% w/w, 53 mol, 98% yield). Spectroscopic analysis was in agreement with the reported data.[1]

5,7-Bis(benzyloxy)-*N*-(5-chloro-1,3-benzodioxol-4-yl)quinazolin-4-amine Hydrochloride (27). Anhydrous toluene (63.5 L), phosphorous oxychloride (1.437 L, 15.42 mol) and DIPEA (3.195 L, 18.34 mol) were charged to a 100 L vessel. The mixture was heated to 80 °C before adding **20** (4.500 kg at 95% w/w, 11.96 mol) in ten equal portions over 1 h. The mixture was stirred for a further 3 h before cooling to ambient temperature and holding overnight. The reaction mixture was reheated to 80 °C before adding a solution of **10** (2.364 kg at 92% w/w, 12.68 mol) in anhydrous toluene (8.5 L) over 30 min. A toluene (500 mL) line wash was applied. The reaction was stirred at 80 °C for 4 h before cooling to ambient temperature and holding overnight. Isopropanol (10 L) was added to the reaction vessel, and the contents were stirred for 30 min before isolating the product by filtration. The product was washed with IPA (2 × 10 L then 1 × 20 L) before drying to constant weight under reduced pressure at 50 °C to give **27** (4.994 kg at 91% w/w, 8.29 mol, 69% yield). ^{1}H NMR (300 MHz, 300 K, DMSO-d_6) δ 10.40 (1H, br s), 8.66 (1H, s), 7.61−7.55 (2H, m), 7.52−7.45 (2H, m), 7.45−7.29 (6H, m), 7.10 (1H, d, J = 8.7), 6.97 (3H, m), 6.14 (2H, s), 5.63 (2H, s), 5.27 (2H, s); ^{13}C NMR (100 MHz, 300 K, DMSO-d_6) δ 164.3, 159.1, 157.0, 151.9, 147.3, 144.8, 144.6, 135.5, 135.4, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 123.6, 121.5, 117.9, 108.2, 102.7, 101.3, 99.6, 95.8, 70.5, 70.3; HRMS (ES, accurate mass) calcd for $C_{29}H_{23}ClN_3O_4$ 512.1372, found 512.1385.

7-(Benzyloxy)-4-[(5-chloro-1,3-benzodioxol-4-yl)amino]-quinazolin-5-ol (28). To a stirred solution of **27** (8.915 kg at 89% w/w, 14.47 mol) in pyridine (34.5 L) at 65 °C in a 100 L vessel was added concentrated hydrochloric acid (3.424 L, 41.70 mol) over 25 min. A water (100 mL) line wash was applied. The resulting mixture was refluxed at 105 °C for 6 h before cooling to ambient temperature overnight. Pyridine was removed by distillation (55 °C, 150−180 mbar, 18 L collected) before cooling to 70 °C. A sodium hydroxide solution (34 L of a solution prepared by mixing 2.14 L of 47% w/w NaOH with 40 L of water) was added to adjust the pH to 6.1 before adding further water (8 L). Further pyridine was removed by distillation (47 °C, 150 mbar, 17 L collected) before stopping the distillation and adding water (17 L). The mixture was cooled to ambient temperature and held for 30 min before isolating the product by filtration. A water (5.3 L) wash was applied *via* the vessel to the cake before drying to constant weight under reduced pressure at 50 °C to give **28** (6.126 kg at 91.9% w/w, 13.36 mol, 92% yield).

Further Purification of 7-(Benzyloxy)-4-[(5-chloro-1,3-benzodioxol-4-yl)amino]quinazolin-5-ol (28). A slurry of **28** (12.509 kg at 92% w/w, 27.29 mol) in methanol (20 L) and water (30 L) was stirred in a 100 L vessel for 2 h at ambient temperature. The mixture was filtered, and the water (12.5 L) vessel and cake were washed before drying to constant

weight under reduced pressure at 50 °C to give **28** (12.223 kg at 93% w/w, 26.95 mol 99% yield). ^{1}H NMR (300 MHz, 300 K, DMSO-d_6) δ 10.81 (1H, br s), 8.71 (1H, s), 7.51−7.46 (2H, m), 7.45−7.34 (3H, m), 7.08 (1H, d, J = 8.4), 7.00 (1H, d, J = 8.4), 6.83 (1H, d, J = 2.3), 6.82 (1H, d, J = 2.3), 6.12 (2H, s), 5.27 (2H, s), (Phenolic shift nor observed); ^{13}C NMR (100 MHz, 300 K, DMSO-d_6) δ 165.3, 160.3, 158.8, 151.3, 147.4, 144.8, 141.2, 135.7, 128.7, 128.4, 128.0, 123.7, 121.6, 117.7, 108.4, 102.9, 102.2, 98.4, 93.1, 70.3; HRMS (ES, accurate mass) calcd for $C_{22}H_{17}ClN_3O_4$ 422.0902, found 422.0906.

7-(Benzyloxy)-*N*-(5-chloro-1,3-benzodioxol-4-yl)-5-(tetrahydro-2*H*-pyran-4-yloxy)quinazolin-4-amine (29). 29 (7.999 kg at 93% w/w, 17.63 mol) was refluxed under Dean−Stark conditions in toluene (32.6 L) for 2 h in a 100 L vessel. A solution of **7** (2.537 L, 2.717 kg, 26.60 mol), DTAD (8.441 kg, 36.66 mol), and triphenylphosphine (9.612 kg, 36.65 mol) in toluene (25.6 L) was added over 1 h 55 min, maintaining the temperature below 27 °C. The reaction mixture was stirred at ambient temperature for 1 h 15 min. The reaction was not complete, so further **7** (125 mL, 1.31 mol) was added and the mixture stirred overnight. Hydrochloric acid (4.806 kg of a 4.0 M solution in 1,4-dioxane, 20.19 mol) was added over 40 min, maintaining the temperature between 20−26 °C before stirring for a further 1.5 h. The mixture was filtered and the cake washed with ethyl acetate (50 L) and pulled dry on the filter. The cake was slurried in IPA (49.75 L) at 76 °C and then cooled to ambient temperature over 1.5 h. The slurry was filtered and the cake washed with IPA (12.5 L) before drying to constant weight under reduced pressure at 50 °C to give **29** (7.929 kg at 96% w/w, 14.03 mol, 80% yield). Spectroscopic analysis was in agreement with the reported data.[13]

4-[(5-Chloro-1,3-benzodioxol-4-yl)amino]-5-(tetrahydro-2*H*-pyran-4-yloxy)quinazolin-7-ol (30). 29 (3.700 kg at 96% w/w, 6.55 mol) was heated to reflux (71 °C) in TFA (33 L) in a 100 L vessel for 7 h before cooling to ambient temperature overnight. TFA was removed by distillation (37 °C, 180 mbar, 27 L distillate collected) before releasing the vacuum and adding ethyl acetate (33 L) and water (33 L) and cooling to 15 °C. Sodium hydroxide (2.7 L of a 47% w/w solution in water, 31.72 mol) was added to adjust the pH to 5.9 and the mixture stirred overnight. During this time the pH had fallen to 5.1, so further sodium hydroxide (30 mL of a 47% w/w solution in water, 0.35 mol) was added to give a pH of 5.6. The mixture was filtered and the cake washed with water (4.2 L) and ethyl acetate (2 × 4.2 L) before drying to constant weight under reduced pressure at 60 °C to give **30** (2.679 kg at 91% w/w, 5.86 mol, 89% yield). Spectroscopic analysis was in agreement with the reported data.[1,13]

***N*-(5-Chloro-1,3-benzodioxol-4-yl)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-(tetrahydro-2*H*-pyran-4-yloxy)quinazolin-4-amine Difumarate (AZD0530 Difumarate).** To a slurry of **30** (2.139 kg at 92% w/w, 4.73 mol) and DTAD (2.771 kg, 12.03 mol) in THF (31 L) at ambient temperature in a 100 L vessel was added a solution of triphenylphosphine (3.057 kg, 11.66 mol) in THF (8 L) over 15 min. A THF (2 L) line wash was applied, and the mixture was stirred for 10 min. The reaction mixture was cooled to 15 °C, and a filtered (to remove undissolved particulates) solution of **31** (1.050 L, 1.049 kg, 7.27 mol) in THF (3 L) was added to the reaction mixture over 12 min, keeping the reaction below 20 °C. A THF (1 L) line wash was applied. The reaction was stirred for 50 min at ambient temperature after which time the reaction was not complete. A filtered solution of **31** (348.5 mL, 348.2 g, 2.41 mol) in THF (1 L) was added and the reaction stirred for a further 1.5 h. The reaction mixture was concentrated on a rotary evaporator (40 °C, 100 mbar) before adding ethyl acetate (4 L) and reconcentrating. The resulting oil was dissolved in ethyl acetate (30 L) and washed with potassium carbonate (20 L of a 0.2 M solution in water). The organic phase was extracted twice with hydrochloric acid (20 L then 4 L of a 0.5 M solution in water), and the combined acid phases were washed with ethyl acetate (10 L). Hydrochloric acid (12 L of a 37% w/w solution in water) was added to the mixture over 15 min, maintaining the temperature at 19−20 °C and the resulting mixture stirred at ambient temperature for 2 h. Sodium hydroxide (3 L of a 47% w/w solution in water) was added over 35 min, keeping the temperature below 30 °C. *n*-Butyl alcohol (20 L) was added followed by sodium hydroxide (3 L of a 47% w/w solution in water) followed by a water (1 L) line wash to adjust the pH of the mixture to 13. The mixture was separated and the lower aqueous phase extracted with *n*-butyl alcohol (10 L). The combined butyl alcohol phases were concentrated (first in the vessel and then on a rotary evaporator, 60 °C bath temperature, <100 mbar), and the resulting oil was dissolved in IPA (4 L) and reconcentrated. The oil was dissolved again in IPA (6 L) and filtered through Celite, and the vessel and Celite were washed with IPA (6 L). The combined solution was added to a solution of fumaric acid (1.228 kg, mol, mol equiv) in IPA (30 L) at 75 °C. An IPA (3 L) line wash was applied, and the resulting solution was allowed to cool. Crystallisation commenced at 73 °C, and the mixture was held at this temperature for 30 min before cooling to ambient temperature overnight. The mixture was filtered and the cake washed with IPA (7 L as a slurry wash and 7 L as a displacement wash) before drying to constant weight under reduced pressure at 50 °C to give **AZD0530 difumarate** (3.546 kg at 89% w/w, 4.08 mol, 86% yield).

Final Purification of *N*-(5-Chloro-1,3-benzodioxol-4-yl)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-(tetrahydro-2H-pyran-4-yloxy)quinazolin-4-amine Difumarate (AZD0530 Difumarate). AZD0530 difumarate (4.234 kg at 89% w/w, 4.87 mol) was refluxed in a mixture of IPA (10.L) and water (10.L, Fresenius). A solution was not obtained, so further IPA (450 mL) and water (450 mL, Fresenius) were added, and the mixture was refluxed. The resulting solution was cooled to 68 °C and screened over 3.5 min through a 20 μm in-line filter into a vessel preheated to 65 °C. IPA(20.4 L) at 65 °C was added via the first vessel and in-line filter, and the resulting solution was stirred at 65 °C for 2 h. Crystallisation was evident after 20 min. The mixture was allowed to self-cool to ambient temperature overnight before filtering and washing the cake with a mixture (prescreened through a 20 μm membrane) of water (640 mL) and IPA (5.76 L). The cake was washed with IPA (6.4 L, prescreened) and MTBE (6.4 L, prescreened) and dried to

(13) Hennequin, L.; Francois A.; Ple, P. WO/2001/094341, 2001.

constant weight under reduced pressure at 50 °C to give **AZD0530 difumarate** (2.865 kg, at 95.2% w/w, 3.52 mol, 72% yield). Spectroscopic analysis was in agreement with the reported data.[2]

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