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Development of an Efficient and Practical Route for the Multikilogram Manufacture of the SRC Kinase Inhibitor AZD0530

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Abstract:

In a previous publication (*Org. Process Res. Dev.* 2010, *14*, DOI: 10.1021/op100161y) we described the process research and development of a manufacturing route for the potent SRC kinase inhibitor AZD0530. While the route was successfully used to manufacture 4.5 kg of AZD0530 difumarate, it was still relatively long, used two Mitsunobu couplings, and was, in our opinion, undesirable for manufacture on a larger scale. Herein we describe the research and development of a shorter, more practical synthesis of AZD0530 difumarate. The new route, which required fewer steps, scaled well to produce >80 kg of AZD0530 difumarate in an overall yield of 38%.

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 a previous communication[2] we disclosed the process research and development of a manufacturing process for the synthesis of AZD0530 which was used to deliver 4.5 kg of AZD0530 Difumarate for use in toxicology and phase I clinical studies (Scheme 1). Following this successful delivery we were required to deliver a further 40 kg of AZD0530 difumarate for ongoing clinical evaluation, requiring pilot-plant rather than kilo-lab-scale manufacture. Analysis of the route we used for the kilo-lab-scale manufacture indicated that, while significant improvements had been made to the medicinal chemistry route, the resulting synthesis was still relatively long and required two Mitsunobu couplings. While it was felt that the chemistry could be developed for use on a limited pilot-plant scale, we did not feel it would be suitable for longer-term manufacture, and this directed us to investigate alternative, potentially more efficient routes to AZD0530.

Alternative Route Evaluation. Various routes were investigated for the synthesis of AZD0530, starting from a diverse range of starting materials such as 2,4,6-trifluorobenzonitrile.[3] Following a cost of goods analysis, routes from **1** were selected for further evaluation on the basis of the assumption that the cost of 5,7-diflouroquinazolinone **1** would decrease as the scale of manufacturing increased. The two principal variants of the route are shown in Scheme 2, and following initial small-scale studies these were evaluated further on multigram scale in the lab.

Routes A and B use essentially the same chemistry varying only in the order of the steps, and both were suitable for manufacturing purposes from a synthetic point of view. However, lab evaluation showed anilinoquinazoline **11** to have more favorable physical properties, more specifically ease of crystallisation and isolation, when compared to pyranyl quinazolinone **12**. Route A was therefore selected for further development. The third potential variant of the route in which aniline **4** is coupled last was also evaluated but found to be low yielding (typically <10%) in the final step.

Anilinoquinazoline 11. The first step in the selected route is the coupling of quinazolinone **1** with aniline **4** via 4-chloroquinazolinone **14** (Scheme 3). Initial screening of the reaction was carried out in toluene. While the reaction worked well, the product was found to oil out at the end of the reaction, and complete dissolution of the starting materials was never achieved. Further solvents were screened in the hope of finding a solvent that gave better solubility of difluoroquinazolinone **1** and an improved isolation of anilinoquinazoline **11**. The use of phosphoryl chloride limited the choice of solvents that could be used safely, so the reaction was screened in acetonitrile, propionitrile, toluene, chlorobenzene, and 1,1,1-trifluorotoluene. None of the solvents gave complete dissolution of **1**, but the reaction did progress satisfactorily in all cases. Chlorobenzene was selected for further investigation on the basis of reaction profile, yield, and cost.

Having selected chlorobenzene as the solvent, the mode of addition was investigated. Addition of solid **1** to a solution of diisopropylethylamine (DIPEA) and phosphorylchloride ($POCl_3$) and addition of $POCl_3$ to a slurry of **1** and DIPEA to give chloroquinazoline **14** were both investigated. Both modes of addition gave a good reaction profile and yield following the subsequent addition of aniline **4**. On the basis of results on route B (Scheme 2) the addition of $POCl_3$ to a slurry of **1**, **4**, and DIPEA in chlorobenzene was also investigated. This mode

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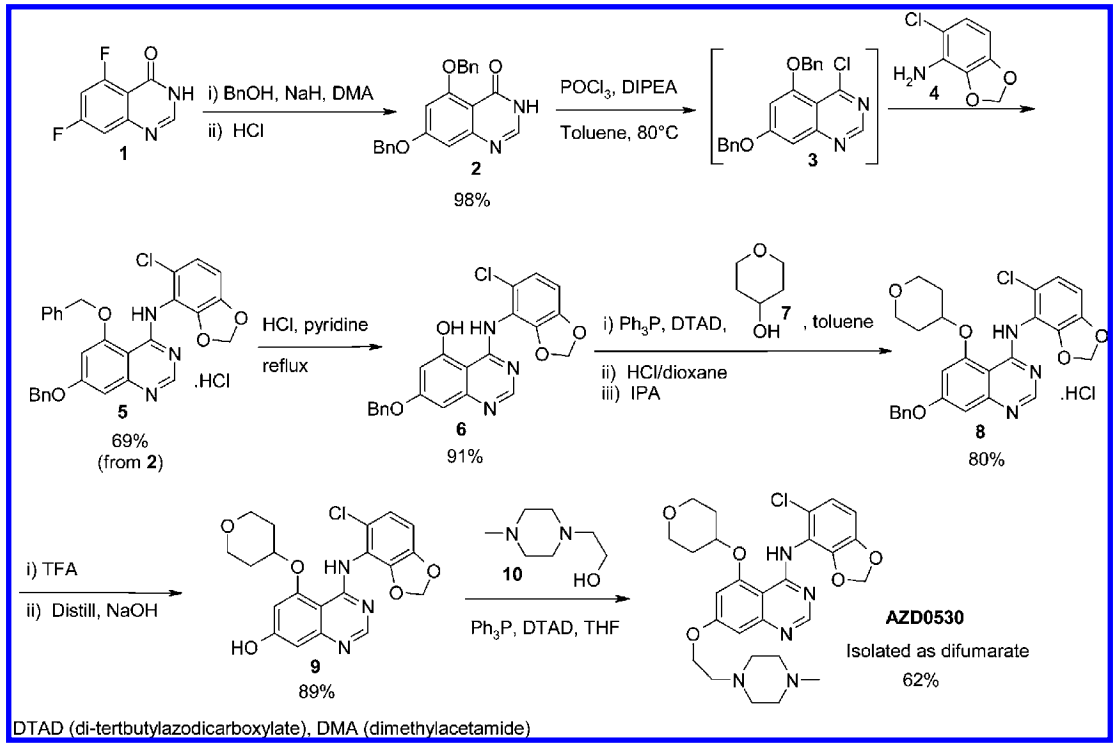
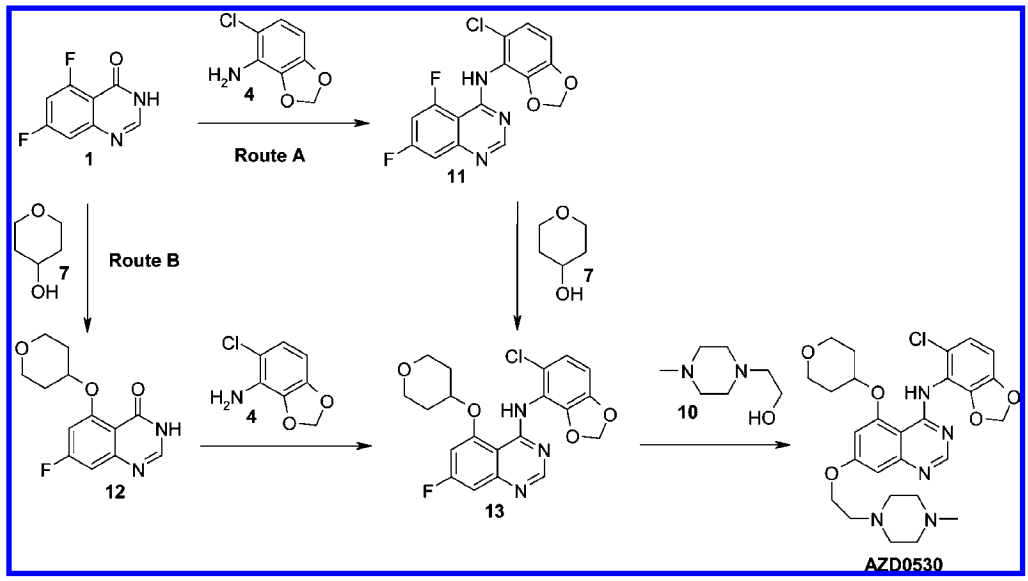
Scheme 1. **Kilo-lab synthesis of AZD0530**



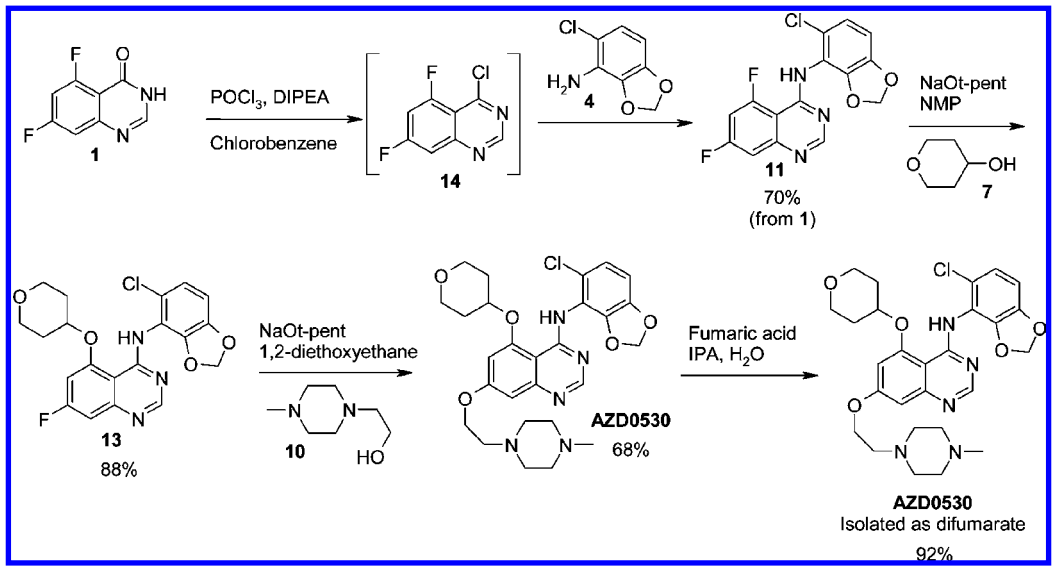
Scheme 2. **Alternative routes to AZD0530**



of addition gave a comparable reaction profile, yield, and product quality when compared with the separate preparation of **14** but resulted in a simpler process and shorter overall reaction time. Factorial experimental design was used to further optimise the addition time of $POCl_3$, equivalents of reagents, temperature, and concentration of the reaction. A more concentrated reaction was found to proceed more rapidly but resulted in poorer filtration of the product. A typical reaction involved addition of $POCl_3$ (1.5 equiv) over 20 min to a slurry of **1** (1 equiv), **4** (1.05 equiv), and DIPEA (1.2 equiv) in chlorobenzene (10 relative volumes) at 90 °C. The reaction was then held and cooled to 20 °C, and product **11** was isolated as its HCl salt.

Following this optimisation of the reaction, our process safety group examined the process using calorimetry and found significant exotherms capable of exceeding the boiling point of chlorobenzene. Examination of the data combined with lab observations and examination of a typical reaction using REACT-IR suggested that the exotherms observed were the combination of the thermodynamics of the reaction and also a significant component due to crystallisation of the hydrochloride of **11**. In order to control the exotherms, slower additions of $POCl_3$ were attempted. Addition of $POCl_3$ (1.5 equiv) over 2 h resulted in control of the exotherms, but there was a significant increase in the levels of impurities formed, and the reaction did not go to completion. Reactions could be driven to

Scheme 3. **Pilot-plant route to AZD0530**



completion by increased charges of $POCl_3$ and DIPEA. Faster additions were found to give a good reaction profile, but the exotherms could not be safely accommodated in our pilot plant. Finally, on the basis of the calorimetry results, the heating/cooling capacity of the plant vessels we intended to use, and further lab trials, a 40-min addition was stipulated. This addition time was set to give a good reaction profile while still allowing safe operation of the process. Two batches were operated in our pilot plant and behaved as predicted to give an overall yield of 66% (an additional 4% remained on the pressure filter after discharge).

Another problem with this reaction was the development of meaningful in-process tests. It was found that during the addition of $POCl_3$ to the mixture a brown solution was obtained, suggesting that **1** was soluble in the reaction mixture. As the reaction approached completion **11** was generally out of solution, however, making it difficult to monitor conversion by HPLC in a conventional manner. Ultimately, it was found that the chlorobenzene reaction solvent could be used as an internal standard to monitor disappearance of **1**, and a reasonably accurate means of monitoring conversion was obtained by standardizing the area counts of **1** against the area counts of chlorobenzene.

Pyranyl Ether 13. Initial attempts at the selective displacement of the 5-fluoro of **11** with tetrahydropyranol **7** used potassium *tert*-butoxide (KO*t*-Bu) in THF at reflux. This gave a reaction that was selective with respect to the formation of the analogous displacement of the 7-fluoro of **11** but resulted in significant levels of the undesired 5-butoxy impurity **15** (Figure 1). Indeed, using 5 equiv of KO*t*-Bu to reach reaction completion resulted in the concomitant formation of up to 20% (by HPLC area) of **15**. A variety of alternative bases were screened, including sodium and potassium hexamethyldisilazide (NaHMDS, KHMDS), LDA, LDA/TMEDA, and sodium *tert*-pentoxide (NaO*t*-Pent). The LDA reactions gave none of the desired product, and the reactions using NaHMDS or KHMDS gave the desired reaction but with a poor reaction profile by HPLC. With the use of NaO*t*-Pent the reaction was clean but relatively slow. To try and speed up the reaction, *tert*-pentanol and *N*-methylpyrrolidin-2-one (NMP) were screened, showing NMP to give the faster reaction. Using NMP at 77 °C resulted in the formation of the 5-pentoxy (**16**) and the corresponding 5-hydroxy (**17**) impurity (Figure 1), typically at levels of 2−3%. Reducing the reaction temperature to 60 °C allowed the reaction to proceed in an acceptable time (2 h) with adequate control of **16** and **17** (~0.4%).

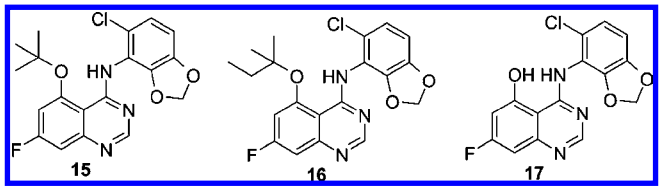


Figure 1. **Impurities in pyranyl ether 13.**

At the end of the reaction the addition of water precipitated pyranylether **13**, which was isolated by filtration. In the lab this filtration was found to be very slow, although it was interesting to note that subsequent water washes were reasonably quick. To try and improve the filtration, the addition of the reaction mass to water (reverse addition), addition of THF to the reaction, and the use of DME instead of NMP were tried. Of these only the use of DME gave a significantly improved filtration, but unfortunately the rate of reaction was slower and the profile poorer. Finally, as analysis had shown there to be minimal **13** in the liquors, a hot filtration was attempted. Interestingly, this was also found to give a significantly improved filtration, which we believe is due to the reduced viscosity of NMP at higher temperature.[4] Two batches were operated in our pilot plant and isolated at 60 °C, giving an overall yield of 88% (a small residue remained on the pressure filter after discharge).

AZD0530. The initial route screening work described above settled on the use of potassium hydroxide in diglyme at 120 °C as being suitable conditions for the reaction of pyranyl ether **13** with alcohol **10**. Further screening of conditions looked at variations in solvent (diglyme, NMP, DMSO, 1,2-diethoxyethane), base (KOH, K_3PO_4, NaH, K_2CO_3, LiO*t*-Bu, KO*t*-Bu, KHMDS, NaHMDS, CsOH, NaO*t*-Pent) and temperature. From

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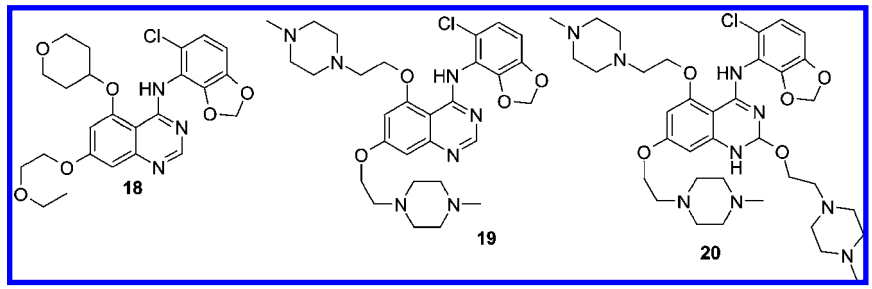

Figure 2. **Impurities in AZD0530.**

this screen it was clear that KOH and the alkoxide bases gave the best conversions with the optimum solvents being diglyme and 1,2-diethoxyethane (DEE). NaO*t*-Pent in DEE at 120 °C appeared to give the best reaction although significant formation (∼12%) of impurity **18** (Figure 2) was observed. This impurity was presumably the result of a low level of 2-ethoxyethanol in the DEE, and it was found that reducing the dilution of the reaction from 30 relative volumes of DEE to 6 relative volumes (rel vol) significantly reduced its formation as did the use of higher purity solvent.

Serendipity. Further optimization of the reaction conditions led to the use of 3 equiv of NaO*t*-Pent and 3−4 equiv of alcohol **10** at 86 °C. Although it would be expected that 2 equiv of base would be required for the reaction (due to deprotonation of both **13** and **10**), the higher stoichiometry of both base and **10** is thought to be required to drive the reaction to completion in a reasonable time. While the levels of **18** were now well controlled, impurities **19** and **20** (Figure 2) were typically observed at a combined level of ∼8% in the reaction mixture. During this work, alcohol **10** was obtained from two separate suppliers and while both samples were of good strength (>95% w/w), one sample was found to contain water (∼4% w/w, equivalent to ∼0.3 equiv). We initially considered rejecting this material as being unsuitable for use as we expected the water could lead to the analogous phenol impurity in the reaction but as KOH had previously been shown (see above) to mediate the desired reaction we decided to user trial the material. To our delight we found that the reaction proceeded well and surprisingly, combined levels of **19** and **20** were significantly reduced to 2.5%. Clearly the presence of water was having a beneficial effect on the selectivity of the reaction. Further investigation revealed the presence of 1.9−3 equiv of water to be optimal, with higher levels of water such as 4 equiv also resulting in a more selective reaction but taking longer to reach completion.

Development of a work-up and isolation was our next challenge, principally due to the need to remove the excess alcohol **10** and the poor physical properties of **AZD0530** which was known to be amorphous. During the development of the work-up we made the discovery that a crystalline trihydrate of **AZD0530** could be formed and had favorable physical properties when compared to the amorphous anhydrous material prepared previously. Following a satisfactory end of reaction check, the bulk of the DEE was removed from the reaction by distillation. The pH of the crude mixture was then adjusted to ∼7 by the addition of aqueous HCl before extracting AZD0530 into ethyl acetate (EtOAc). Separation of the aqueous layer and further water washes removed residual alcohol **10** before concentration by distillation and the addition of water induced crystallisation of the trihydrate. Two batches were operated in our pilot plant with the reaction proceeding as expected. However, a lower than expected yield of 56%, was obtained. While it was found that the first batch operated as expected and filtered well, the filtration of the second batch was extremely poor. The residue left on the pressure filter after discharge was subsequently found to be unexpectedly high for the volume of the filter, equivalent to 12% overall yield which in combination with the isolated yield brings the performance of the stage within expectations. We believe the poor filtration of the second batch and the large heel to be indicative that the trihydrate is highly compressible and that discharge of the first batch from the filter led to a highly compacted cake being left on the filter between batches which retarded the second filtration.

AZD0530 Difumarate. Finally, a difumarate salt formation process incorporating a polishing filtration was developed. This process involved addition of a solution of **AZD0530** free base in aqueous isopropanol to a solution of fumaric acid in aqueous isopropanol. This process produced material of the desired quality and was transferred to our pilot plant where we intended to manufacture three batches. Disappointingly we found that filtration and washing times were extremely long during the first batch. The process was changed such that the solution of fumaric acid was added to the solution of AZD0530 free base with the addition of seed partway through the addition. Considerable improvements were made to the filtration and drying times as a result. Using both processes, three batches of **AZD0530 difumarate** were produced in our pilot plant with an overall yield of 90%.

Conclusions

- The previous synthesis which required six synthetic steps from difluoroquinazolinone **1** has been significantly reduced to a more efficient and direct, three synthetic step process. The overall yield from **1** has been improved from 25% to 38%.
- These processes scaled well into our pilot plant, enabling us to produce >80 kg of **AZD0530 difumarate**.

- The raw material costs ($/kg AZD0530) required to produce AZD0530 using the new route was ~13% of the cost using the previous route.[2,5]
- The serendipitous discovery of the benefit of water in the final fluoride displacement had a significant impact on the development of our processes and highlights the benefit of performing experiments which might reasonably have been expected to fail.
- The discovery of a crystalline trihydrate had a significant impact on our ability to develop an isolation of **AZD0530** free base.

Experimental Section

General. Starting materials, reagent, and solvents were obtained from commercial suppliers and used without further purification. HPLC analyses were performed with an Agilent 1100 instrument. Intermediate purities were typically measured by quantitative NMR using an internal standard of known purity, typically maleic acid, benzyl benzoate, or 2,3,5,6-tetrachloronitrobenzene. Yields quoted are corrected for purity.

The processes described below are taken from the laboratory process descriptions used as the basis for plant manufacture. An indication of the scale on which these processes were operated in our pilot plant is also given for each stage.

5,7-Difluoro-*N*-(5-chloro-1,3-benzodioxol-4-yl)quinazolin-4-amine (11). Diisopropylethylamine (7.47 mL, 1.2 mol equiv) was added to a slurry of **1** (6.49 g, 99.8% w/w, 35.62 mmol) and **4** (6.72 g, 1.1 mol equiv) in chlorobenzene (64.9 mL, 10 rel vol). The resulting slurry was heated to 95 °C before adding phosphoryl chloride (4.96 mL, 1.5 mol equiv) at a constant rate over 40 min. When ~0.35 equiv had been added, a solution was obtained; when ~0.85 equiv had been added, product started to crystallise. During the addition the batch temperature was seen to rise to ~100 °C. The reaction was held at 95 °C for 10 h before cooling to 18 °C and holding for a further 30 min. The product was filtered and washed with chlorobenzene (2 × 22.8 mL, 3.5 rel vol) before drying under reduced pressure at 45 °C to constant mass to give **11** (8.90 g, 23.1 mmol, 97% w/w, 67% yield) as its hydrochloride. This process was operated in our pilot plant in two batches using an input of 39 kg of **1**. Spectroscopic analysis was in agreement with the reported data.[3]

7-Fluoro-*N*-(5-chloro-1,3-benzodioxol-4-yl)-5-(tetrahydro-2H-pyran-4-yloxy)quinazolin-4-amine (13). 11 (76.42 g, 95.4% w/w, 0.205 mol) was added portionwise to a solution of sodium *tert*-pentoxide (85.69 g, 3.80 mol equiv) in NMP (500 mL, 6.54 rel vol) over 20−30 min. This addition is highly exothermic with a 40 K temperature rise possible. The exotherm can be controlled by the rate of addition. A line wash of NMP (20 mL, 0.26 rel vol) was added before adding **7** (23.52 mL, 1.20 mol equiv) followed by a further line wash of NMP (15 mL, 0.20 rel vol). The reaction was heated to 60 °C for 2.5 h before analyzing by HPLC for completion. Water (764 mL, 10 rel vol) was added over 3 h before holding the mixture for a further 3 h at 60 °C. During the addition a sticky solid formed on the vessel walls but as the addition was continued this was converted to a free-flowing crystalline solid. The product was filtered at 60 °C, washed with water (2 × 229 mL, 3 rel vol), and dried to constant weight to give **13** (68.6 g, 0.164 mol, 95% w/w, 80% yield). This process was operated in our pilot plant in two batches using an input of 50 kg of **11**. Spectroscopic analysis was in agreement with the reported data.[3]

***N*-(5-Chloro-1,3-benzodioxol-4-yl)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-(tetrahydro-2H-pyran-4-yloxy)quinazolin-4-amine Trihydrate (AZD0530).** Alcohol **10** (13.79 g, 3.19 mol equiv) was added to a mixture of **13** (12.51 g, 30 mmol) and sodium pentoxide (9.87 g, 3.0 mol equiv) in DEE (37.5 mL, 3.0 rel vol). Water (1.34 mL, 2.48 mol equiv) was added followed by a DEE (25 mL, 2.0 rel vol) line wash before heating the reaction mixture to 86 °C and holding at this temperature for 18 h. The temperature was reduced to 50 °C before setting the vessel for distillation. Distillate (~50 mL, 4 rel vol) was removed at a pressure of ~60 mbar. A solution of hydrochloric acid (10 mL of a 36% w/w solution, 3.88 mol equiv) in water (84 mL, 6.72 rel vol) was added slowly. The addition was exothermic, and the rate of addition was controlled to prevent the reaction temperature from exceeding 60 °C. The pH was checked (expected to be between 7.0−7.6) and adjusted if necessary. Ethyl acetate (225 mL, 18 rel vol) was added and the mixture heated to 60 °C before separating the organic layer and extracting it with water (50 mL, 4 rel vol then 25 mL, 2 rel vol). The volume of the organic solution was reduced by atmospheric distillation to leave a solution (~140 mL of distillate), and the resulting solution (~100 mL, 8 rel vol) was then cooled to 65 °C before adding water (4 mL, 0.32 rel vol). The mixture was then cooled to 45 °C over 1 h and held at this temperature for 2 h during which time crystallisation occurred. The mixture was reheated to 55 °C and held at this temperature for 5 min before cooling to 18 °C over 4 h and holding for a further hour. This temperature cycling was included to aid removal of product from the vessel walls. The product was filtered and washed with water (17 mL, 1.36 rel vol) and *tert*-butylmethylether (17 mL, 1.36 rel vol) before drying to give AZD0530 trihydrate (12.5 g, 20.3 mmol, 88% w/w, 68% yield). This process was operated in our pilot plant in two batches using an input of 49 kg of **13**. Spectroscopic analysis was in agreement with the reported data.[3]

***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).** A solution of AZD0530 (27.1 g, 50 mmol) in isopropanol (210 mL, 7.75 rel vol) and water (30 mL, 1.11 rel vol) was filtered at 40 °C through Celite into a reaction vessel. A line wash of isopropanol (20 mL, 0.74 rel vol) was passed through the filter before heating the solution of AZD0530 free base to 75 °C. A solution of fumaric acid (12.77 g, 2.2 mol equiv) in isopropanol (200 mL, 7.38 rel vol) and water (20 mL, 0.74 rel vol) at 70 °C was filtered into a second vessel, and half of the resulting solution (~110 mL) was

(5) No allowances have been made for economies of scale; thus, the real reduction in costs will have been less than this. The new route produced >80 kg of AZD0530 difumarate, whereas the old route was used to produce 4.5 kg.

added to the solution of AZD0530 free base, maintaining the temperature between 70−75 °C. AZD0530 difumarate (20 mg, 0.07 wt %) was added to seed the crystallisation, and the stirred mixture was held at 75 °C for one hour after crystallisation had begun. The remainder of the solution (∼110 mL) was added over 1 h to the crystallisation vessel followed by an isopropanol (20 mL, 0.74 rel vol) line wash. The mixture was stirred at 75 °C for 14 h before cooling to 20 °C over at least 2 h. After stirring for a further 30 min the product was filtered, washed twice with a 10% solution of water in isopropanol (50 mL, 1.85 rel vol then 100 mL, 3.69 rel vol), and dried to constant mass at 45 °C under reduced pressure to give **AZD0530 difumarate** (35.8 g, 46 mmol, 98% w/w, 92% yield). This process was operated in our pilot plant in three batches using an input of 23 kg of **AZD0530**. Spectroscopic analysis was in agreement with the reported data.[3]

Acknowledgment

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