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Process Development and Scale-Up of AZD7545, a PDK Inhibitor

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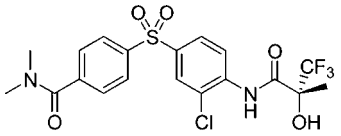
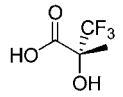
ABSTRACT: A brief comparison of the early manufacturing routes to AZD7545 is given. Process development of the preferred long-term manufacturing route is reported in detail, and changes from the initial kilogram-scale route are discussed. Scale-up experience from the pilot-plant manufacture is included in the discussion of each stage. Noteworthy aspects throughout the development of AZD7545 concerned chemical hazards, mechanisms, analysis, and impurities, upon which this case study will focus.

INTRODUCTION

AZD7545 (**1**) is a pyruvate dehydrogenase kinase (PDK) inhibitor[1] designed to provide an oral treatment for type II diabetes[2] and was the first of a number of compounds to enter development from AstraZeneca's PDK project.[3] Consideration of the structure of AZD7545 reveals that it can be assembled in numerous ways. To aid in the route selection process, we applied a Kepner-Tregoe decision analysis (KTDA) tool as described in an earlier article,[4] from which the preferred manufacturing route was identified, as discussed in a companion article.[5] This article concludes the series by presenting the scale-up issues involved with the manufacturing processes that were developed and as experienced on the pilot plant. It will focus on those aspects of the development and manufacture most likely to be of interest to readers of this journal, namely issues of chemical hazards, mechanism, analysis, and impurities. Additional important points to note regarding AZD7545 are its low activity (~300 mg/day dosing) and the high cost of chiral acid (**2**),[5] which immediately presented a cost of goods issue for the project. This provided a strong incentive to introduce the chiral acid unit late in the synthesis.



AZD7545 (1)



Chiral Acid (2)

COMPARISON OF THE MANUFACTURING ROUTES

Our Discovery colleagues had produced 270 g of bulk drug **1** (purified by chromatography) prepared by a convergent route[1,5] from **3** and **4** to give **5** which contained much of the structure of AZD7545 (Scheme 1). This introduced the expensive chiral acid **2** before the key bond formation in the moderately yielding Ullmann reaction. This was a major disadvantage although it did facilitate easy introduction of analogues into the left-hand portion of **1** (as drawn).

A contractor was chosen to supply the next delivery of 1−5 kg which was soon increased to 10−12 kg when the low potency of AZD7545 became apparent. This used a significantly modified route that emerged from early collaboration between AstraZeneca and the contractor and in which chiral acid **2** was added at the penultimate stage (Scheme 2). The functionalities on both aromatic rings required for the key Ullmann coupling step were transposed in **7a−d** and **10** (compared to **3** and **4** in Scheme 1), which also avoided the relatively expensive starting materials of **3** and 2-chloro-4-iodoaniline required in the original route. The dimethylamide unit was conveniently incorporated into the proposed benzamide portion (**7a−d**) early in this synthesis, rather than after structure **5**. Although this route was more convergent than the original one, repeat manufactures were required to support ongoing toxicity studies.

Due to manufacturing problems, which effectively indicated that this route was not reliably scalable, concurrent development of the proposed long-term manufacturing began at AstraZeneca. The next deliveries were to be of 23 and 35 kg, respectively, and the early stages were to be manufactured jointly, with half of the material accelerated to the later stages to meet clinical trial deadlines. Table 1 summarises this information, from which it will be seen that there was considerable overlap in the delivery schedule. The result was several small deliveries at short intervals with little or no time between them to incorporate improvements. On the other hand, it did increase the learning that was possible on each stage for both routes (campaigns 2 and 3) such that the chemistry for each stage was thought to be well-understood.

The data for choosing the new route over the old one has been presented before,[5] but a brief review may be helpful. Although the campaign 2 route was more convergent, a major advantage of the linear campaign 3 route was that it avoided the difficult Ullmann reaction (Scheme 2). This still had a moderate yield with a difficult and dilute workup procedure, albeit somewhat improved over the equivalent Discovery chemistry stage (cf. Scheme 1). However, the contractor had to introduce

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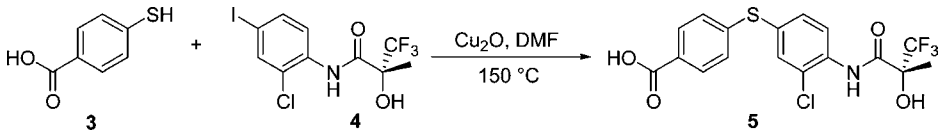
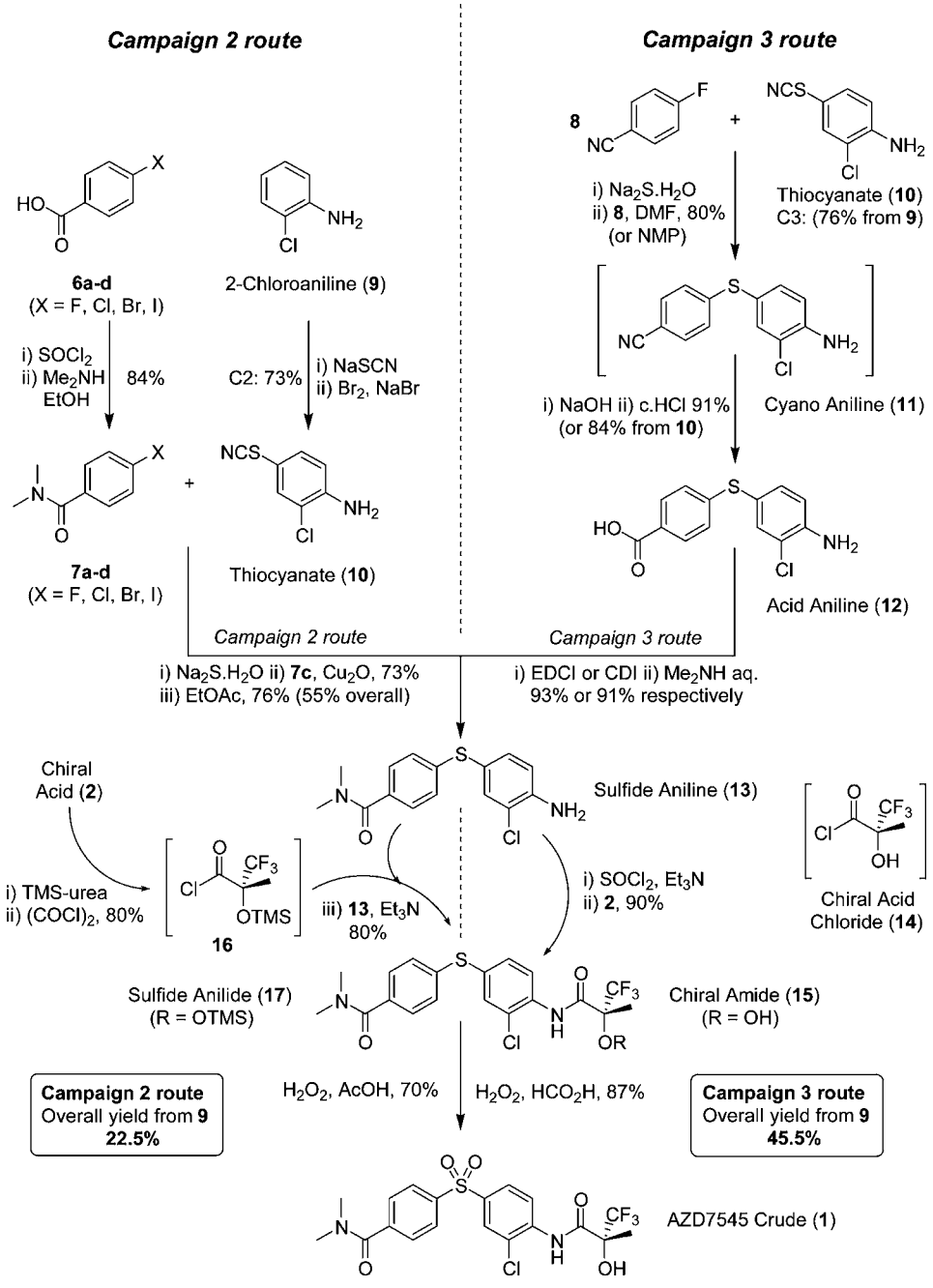
Scheme 1



Scheme 2. Comparison of the manufacturing routes



a recrystallization to purify the sulfide aniline **13** and to remove copper residues which were simply not present in the campaign 3 route. There was also considerable doubt that the Ullmann reaction would be scalable at campaign 3 scale.

Despite the linear nature of the new route, much of the chemistry was expected to be simple and robust, including the hydrolysis of the nitrile from **11** to **12**. Formation of thiocyanate **10** from 2-chloroaniline (**9**) used the same reaction (but not process) as the campaign 2 route. Sulfide aniline **13** was the key common intermediate from which the subsequent steps would be identical, although in fact chiral acid **2** was added as its unprotected acid chloride (**14**), rather than as the TMS-protected acid chloride (**16**), which avoided another difficult step.

The remainder of this article will discuss the development and scale-up of the campaign 3 processes, although learning

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Table 1. Summary of planned and actual manufacturing campaigns[a]

campaign	planned delivery (kg)	actual delivery[a] (kg)	planned delivery date	actual delivery date	location	plant
1	n/a	0.25	n/a	Aug. 2000	AZ (Discovery)	kilo lab
2a	10−12	4.5	May 2001	Sept. 2001	CRO	pilot plant
2b	12	4.5	Apr. 2002	Jul. 2002	CRO	pilot plant
2b′	1.5	2.3	Mar. 2002	Apr. 2002	AZ (PR&D)	kilo lab
3a	23	n/a[b]	June 2002	n/a[b]	AZ (PR&D)	pilot plant
3b (plan)	35	n/a	Dec. 2002	n/a	AZ (PR&D)	pilot plant
4 (plan)	55	n/a	Nov. 2002	n/a	not decided	n/a
5 (plan)	250	n/a	mid 2003	n/a	not decided	n/a

[a]n/a = not applicable; [b]Halted in April 2002 after first batch of sulfide aniline.

from the analogous campaign 2 stages will be included where relevant. To aid the reader, the development of each stage is presented as a smooth and continuous process, rather than in the order in which some developments actually occurred, which would be less easy to follow. On a final point, note that in AstraZeneca terminology, the unrecrystallised bulk drug is termed "Crude" and the recrystallized but unformulated bulk drug is termed "Pure". The chemical structures for both are identical in this case (**1**), since there was no salt formation. There was a crystallization step to further purify crude **1** to pure **1**, but this will not be discussed here.

CAMPAIGN 3 ROUTE DISCUSSION

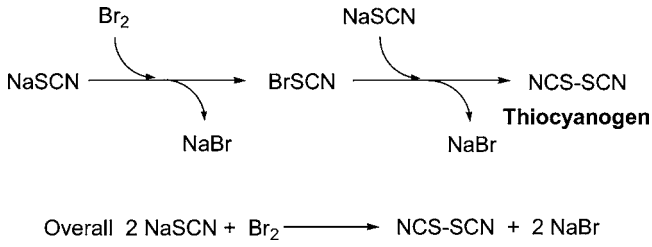
Thiocyanate Stage (10). The chemistry for the thiocyanate stage was based on the use of thiocyanogen (SCN-NCS) from an older ICI/Zeneca project (ZD5522).[6] In that procedure, a full equivalent of thiocyanogen had been prepared in acetonitrile solution before being added to its reaction partner. This had required cooling and careful control on plant scale[7] due to the instability of thiocyanogen as noted in Bretherick (polymerises explosively above its melting point of −2 °C).[8] The AZD7545 process as developed for the campaign 2 route[5] generated the thiocyanogen in situ in the presence of **9** which could react immediately. The workup used solid $NaHCO_3$ to quench the excess acidic residues, generating much gas, and involved a solvent exchange from methanol into toluene. A final peculiarity of the process involved the addition of NaBr to the reaction for which there was little obvious reason.

Before discussing the chemical hazard issues of this process further, which were adequately controlled for both ZD5522 and AZD7545 campaign 2 manufacture, some discussion of the mechanism is necessary, since this will explain some of the previous points. The reaction mechanism requires 2 equiv of NaSCN for the formation of thiocyanogen (NCS-SCN) which is generated by reaction with bromine, as shown in Scheme 3. Two full equivalents of NaBr are produced as the byproduct.

It is thiocyanogen, which can behave as a pseudohalide, which then achieves a standard electrophilic aromatic substitution reaction directly with electron-rich aniline **9**.[9] One full equivalent of NaSCN is generated as the byproduct (cf. Scheme 2). Care must be taken not to acidify the reaction liquors, since acidic hydrolysis of thiocyanogen can produce HCN (the ZD5522 procedure required base treatment in any case for the ongoing reaction).[6,7]

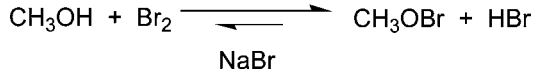
The campaign 2 process avoided the potential chemical hazard issue of generating stoichiometric thiocyanogen by instead forming it in situ so that it could react with **9** immediately. However, conducting the reaction in methanol

Scheme 3. Mechanism of thiocyanogen formation



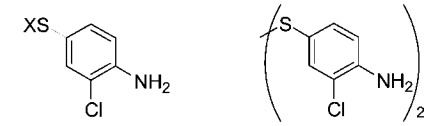
presented another problem due to the interaction of bromine with methanol which can produce methyl hypobromite (Scheme 4), a member of the generally unstable class of alkyl

Scheme 4



hypohalite compounds.[8] NaBr had been used in both the ZD5522 process and the contractor's campaign 2 process, presumably with the aim of increasing $[Br^-]$ to help deter the forward reaction. Comparison of the chemical hazard assessments on processes with and without added NaBr revealed that its presence raised the self-heating onset temperature by 18 K from 11 to 29 °C, but that the size of the eventual exotherm was nearly doubled. Overall, this suggested that NaBr was helpful in delaying a thermal event, but that the consequences would be worse if it was allowed to develop.

Work at AstraZeneca for campaign 3 manufacture started with the campaign 2 process. A drown-out with aqueous $NaHCO_3$ precipitated the product **10** in good quality, which avoided the solvent exchange into toluene and subsequent distillation to a low volume. Using NaOH instead did avoid CO_2 evolution but tended to produce a lot of the disulfide **19**, which had been a problem in the campaign 2 process. A reverse drown-out into aqueous bicarbonate was found to work even better for the physical form of the product and had the advantage of keeping the main reaction vessel dry for the next batch.



Thiol (X = H) (**18a**)
Thiolate (X = Na) (**18b**)

Disulfide (**19**)

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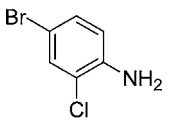
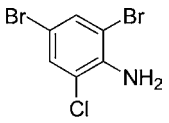
Addition of the bromine/methanol solution over 1.5 h was not only better for controlling the heat of reaction but also gave lower levels of the mono- and dibrominated impurities **20** and **21**; a dump charge of bromine (on small scale) resulted in a notably higher level of **20**. Both impurities are presumably formed by direct electrophilic aromatic substitution reaction. It was decided to use a precise 1.00 equivalent charge of bromine to minimize formation of these impurities, especially as they were crystalline solids, whereas residual **9** was a liquid and more easily washed out of the product cake. An alternative approach would have been to preform the thiocyanogen separately as in the ZD5522 process, which probably would have further reduced the direct bromination of **9**. Since the levels of brominated impurities **20** and **21** were not high, this idea was not investigated to avoid stoichiometric thiocyanogen.



Bromide (**20**)



Dibromide (**21**)

However, the chemical hazard assessment showed that the bromine/methanol solution still presented a significant risk on plant scale; there was an adiabatic temperature rise of 36 K on addition of bromine to methanol, and a further 45 K rise on adding this solution to the NaSCN solution. The bromine could have been added neat to the methanolic solution of NaSCN and **9**, and this was a safer recommendation, but the slow addition required would have been difficult to implement on plant scale due to the small charge size of undiluted bromine. Even on laboratory scale, slow addition of bromine proved difficult to achieve, and any uneven addition resulted in an uneven temperature profile and raised levels of the brominated impurities **20** and **21**.

The ZD5522 process had used acetonitrile as the reaction solvent.[6] When this was tried instead of methanol (keeping all other factors identical), conversion and quality were very good, but the product failed to precipitate on addition of the aqueous $NaHCO_3$ solution due to a phase separation with acetonitrile. The obvious solution was to dilute the bromine with acetonitrile (thus avoiding the hazardous interaction with methanol whilst providing a useful charge volume) and add this to a methanolic solution of NaSCN and **9**, thus keeping methanol as the bulk reaction solvent. With this modification both the reaction and the drown-out worked well with only a few percent drop in yield and no loss in quality. The chemical hazard assessment confirmed that the acetonitrile/bromine mixture was stable at room temperature once formed (adiabatic temperature rise of only 4 K, presumably due to mixing, with no self-heating up to 125 °C in a sealed tube test over 6 h). There was also no accumulation of bromine in the main methanolic reaction mixture, so the chemical hazards were now well controlled. Yields of 80−85% with assay of 90−95% were reliably obtained.

Although we had designed a chemically safe process using bromine, accommodating it on the plant now proved problematic due to an incompatibility with several materials of construction (MoC). A coupon test showed that the bromine/methanol solution could significantly corrode Hastelloy, tantalum, and tantalum/tungsten components (~20% loss of mass over 1 week). The tantalum condensors could be blanked off since they were not needed, but the tungsten temperature probe and bottom-runoff valve would need replacing. Engineering modifications were not easy to put in place, especially at a relatively late date before manufacture. As an alternative, the reaction was tried using NBS to generate the thiocyanogen, which appeared to work well in principle.[10] Even so, the effect on the quality of the product **10** was not fully assessed, and it was felt to be too late to make such a major change to the process, which would have required its own hazard assessment and development of the workup and isolation stages. However, it did establish the principle of using NBS as an alternative to bromine, which would certainly have been reviewed in a following campaign.

The MoC issues were resolved when a glass-lined mild steel (GLMS) reactor module became available sooner than expected (in place of the planned Hastelloy reactor), and the tantalum temperature probes were found to be sufficiently resistant to bromine on the basis of previous use. Other Hastelloy components in the plant module were replaced or bypassed.

As a final minor improvement, the product was also isolated after cooling to 5 °C, which gave a small increase in the yield with no loss in quality. Analysis of aqueous reaction residues indicated that thiocyanate **10** gradually decomposed to the thiol/thiolate (**18a**/**b**), from which the disulfide **19** then formed. Although this had been earlier thought to be a problem in the campaign 2a/b manufactures, the knowledge that the disulfide **19** could react in the cyano aniline (**11**) stage to give the required acid aniline (**12**) meant that a more generous specification level could be set with regard to this "impurity". It also meant that a long hold point was potentially available if required during plant processing. Finally, the assay of the product could be somewhat low in some batches (80−90%) due to their high inorganic content. Although the following two stages coped well with high levels of inorganic salts, slurry washes were implemented in place of displacement washes, and the wash sizes increased, which improved product assay without loss of yield.

The results for the campaign 2a batches prepared at the contractor using the original method, their repeat campaign 2b manufacture, and the results for the campaign 3a manufacture are shown in Table 2. Campaign 3a batches had improved assay and yield but had marginally reduced quality due almost entirely to raised levels of the dibromide impurity **21** in each batch (~2−3%). This may have been due to uneven mixing on larger scale since for mechanical reasons a smooth addition proved difficult to achieve. Even so, this clearly shows that the

Table 2. Summary of AZD7545 thiocyanate (10) manufacturing campaigns

	campaign 2a	campaign 2b	campaign 3a
no. of batches	11	6	4
input of **9** (kg)	1.34	6.7	38−41
batch size (L)	17	87	500−530
assay range (%)	79−91	88−94	92−96
quality range (%)	n/a[a]	95−97	94−95
yield range (%)	58−83	63−83	78−81
overall yield (%)	75	74	80
total delivery (kg)	15.9	36.1	183
location	CRO	CRO	AZ (PR&D)

[a]n/a = not available.

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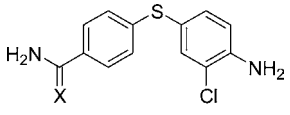
improved campaign 3 process could be safely scaled up to 500 L with no loss in yield or quality.

Cyano Aniline Stage (11). Although we planned to generate the intermediate thiol/thiolate **18a/b** in situ from thiocyanate **10** for the formation of cyano aniline **11**, to simplify the process, the first attempt used isolated thiol **18a** with 4-fluorobenzonitrile (**8**) in NMP with K_2CO_3. This gave a conversion of 92% after only 1.5 h at 80 °C and established the principle of the benzonitrile route (campaign 3) as a viable alternative to the benzamide route (campaign 2). Significantly, it showed that the key coupling reaction could be achieved by a simple uncatalysed S_NAr reaction when using a more electron-deficient aromatic acceptor species (i.e., **8** instead of **7a–d**). This avoided the high-temperature copper-catalysed Ullmann reaction with its moderate yield, inefficient isolation procedure, and copper waste stream. This also avoided the need to test for and remove copper in the final bulk drug. After initial development, the S_NAr reaction was found not to require K_2CO_3, but two significant and variable impurities were identified as the primary amide **22** and the thioamide **23**. The 4-chlorobenzonitrile analogue of **8**, which was cheaper and had a higher mp, was also tried and worked in principle but gave rise to higher levels of the amide **22** and an unknown impurity, so this approach was not investigated further.



Amide (**22**) (X = O)
Thioamide (**23**) (X = S)

Having established the principle of reaction, however, development for scale-up proved somewhat troublesome. A solvent screen gave no product in the cases of acetonitrile, ethyl acetate, methanol, or toluene, with the disulfide **19** being the major product in the case of acetonitrile and ethyl acetate; NMP proved to be the best solvent, with DMA and DMF also good candidates. However, cyano aniline **11** was difficult to isolate from NMP, did not have good physical form, and was of low and variable assay despite being apparently pure by ^{1}H NMR spectroscopy. It was suspected that residual inorganic compounds were present in the NMP solvent, since the mass balance could not be corrected accounting for the known masses of the amide, thioamide, and residual **10** which were present.

Throughout this work the thioamide **23** level also varied considerably, being generally higher when more Na_2S was used in the thiocyanate hydrolysis and for longer reaction times. When the product was isolated by extraction into ethyl acetate instead of drowning out with water from NMP, the inorganic content (ash assay) was low. A long reaction time (>18 h) had been used, and **22** and **23** accounted for 30% of the product mass in this case. With a short reaction time and extraction into toluene, product of 87% assay in an 83% yield was obtained with only 2–3% **22** and **23**. Whilst this worked well in the lab, the workup with toluene extraction had some other problems, tending to oil out and give poor recovery. It was also a poor fit with possible telescoping with the following aqueous hydrolysis stage. Changing to DMA or DMF from NMP and using an aqueous drown-out reliably gave a solid in the case of DMF but not with DMA.

At the same time, the assay and quality of the Na_2S was also investigated. The nonahydrate ($Na_2S{\cdot}9H_2O$) is in fact 33% Na_2S by weight, whereas the technical grade is ~60% Na_2S by weight. It was found that the source of the Na_2S did not matter, but the quantity of water did, with the nonahydrate performing poorly or not at all, depending on the stoichiometry. Using $Na_2S{\cdot}9H_2O$ at 2.0 equiv put 12% water into the reaction mixture (v/v with DMF), compared to only 4% when using the technical grade (water from other sources such as the thiocyanate and DMF was insignificant). To confirm this, technical grade Na_2S (>60%) was used and water added up to the 12% level, whereupon the reaction failed. Other preparations at intermediate water content levels showed a general decline in formation of **11**, **22**, and **23** as the water content increased, with a significant drop above ~9%, as shown in Figure 1. Azeotropically drying the intermediate thiolate **18b**

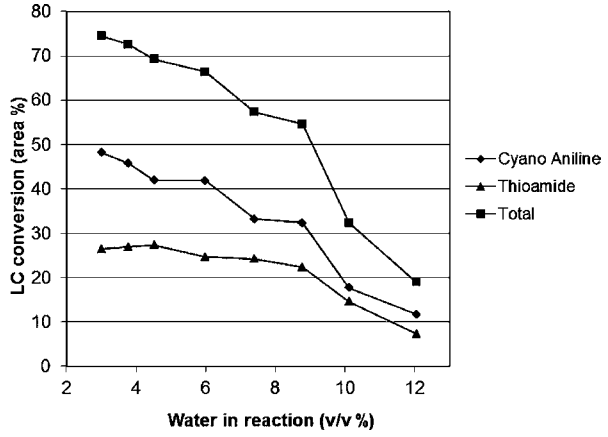


Figure 1. Formation of cyano aniline (**11**) and thioamide (**23**) against water content of reaction.

before addition to the benzonitrile solution increased the yield by a few percent but was judged not to be worth the additional operational complexity at pilot scale.

The process now gave a solid by direct aqueous drown-out from DMF with better physical form, good assay (87%), and acceptable yield (72%) with less thioamide (6%). However, both impurities **22** and **23** could, in practice, be hydrolysed in the next stage to give the desired acid aniline **12**; as a result, the yield was nominally higher. Disulfide **19** was also tried instead of thiocyanate **10** with 4-fluorobenzonitrile (**8**) and found to give a good conversion to cyano aniline **11**; thus, formation of disulfide in the thiocyanate cleavage of **10** to **18a/b** was no longer a chemical concern. A factorial experimental design (FED) of eight experiments was run, covering four factors (Na_2S equivalents, temperature, concentration, and reaction time) plus four additional centre points (12 experiments in total). As a result, minor adjustments were made by increasing the reaction temperature to 60 °C, which also enabled better solution of Na_2S in DMF, and increasing the charge of Na_2S to 1.8 equiv. This led to higher levels of thioamide, as did longer reaction times. However, the centre points gave reproducible results and proved that the process was already effectively optimized. A final modification was to use a reverse drown-out, which improved the form of the isolated solid **11** still further.

There were no major chemical hazard concerns with any part of the process. The adiabatic temperature rise on addition of **10** to the DMF/NaSCN solution was 38 K, and there was a further

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30 K rise on addition of **8** to the thiolate solution. However, both of these exothermic additions were well controlled by slow additions, and there were no other concerns.

Lastly, there was agreement from the analytical department to include the amide **22** and thioamide **23** levels in the specification for cyano aniline (based on aniline base assay) with thiol **18a** and disulfide **19** set at <0.5% each. This meant the expected yield based on the sum of **11**, **22**, and **23** was now in the range 84−94%. Ironically, just as the process was fully optimized and a robust isolation procedure finally developed, the telescoped reaction with the acid aniline stage became viable. However, the understanding gained on this stage was not wasted. The acid aniline stage is treated briefly below before discussing the telescoped process for the joint stages.

Acid Aniline Stage (12). It was quickly established that cyano aniline **11** could be hydrolysed to acid aniline **12** with either strong acid or base, either from isolated **11** or from crude reaction liquors. In both cases, HPLC analysis confirmed that the amide and thioamide impurities converted to acid aniline (**12**), which simplified the analysis and proved that both "impurities" could contribute to the overall yield of this hydrolysis stage.

Initially, acidic conditions were preferred by the pilot plant to avoid concerns regarding the use of strong, hot alkaline mixtures. Concentrated HCl at 100 °C looked promising and gave good conversion and yield of the product as its HCl salt, but the form was poor and difficult to isolate, possibly due to hygroscopicity. Neutralisation and extraction into an organic solvent at various pHs to obtain the neutral acid aniline avoided these issues but gave disappointing yields for an apparently trivial reaction (60−65%) with moderate assay (80−85%).

Hydrolysis of **11** by concentrated H_2SO_4 gave a new product initially thought to be an electrophilic ring sulfonation product but, in fact, was later identified as amide **22**. However, concentrations of aqueous H_2SO_4 at 5, 10, and 15 M all gave good conversions to the sulfate salt of **12** in good form. Direct use of the sulfate salt in the following stage (sulfide aniline, **13**) failed completely, however, even with the addition of extra base to neutralize the acidic counterion in the coupling step. In addition, both HCl- and H_2SO_4-mediated hydrolyses suffered from incomplete reaction conversions and gave products with low assays. Parallel lab work showed that hot alkaline processes appeared to hydrolyse **11** both faster and more cleanly, leaving less residual amide **22**.

Fortunately, the Hastelloy reactor planned for the thiocyanate stage became available in the pilot plant at this time, and so work switched to developing the alkaline process in earnest. Ethanolic NaOH worked well, as expected, giving full conversion after 4 h with impurities at the same level as those from the acidic processes, but methanol was used instead because the form of the isolated solid was improved. Other bases were also tried (LiOH and KOH) but offered no advantage over the standard NaOH. The neutralization process at the end of reaction was not straightforward, but yields of 80−85% could be obtained, corrected for a moderate assay of 80%. Overall, the base-mediated process was faster than the acid-mediated ones, giving full conversion in less time with equivalent quality and in better form as the neutral species of **12** rather than as the salts. There were no chemical hazard issues of concern, and the process was ready to be scaled up as a stand-alone process when the decision to telescope it with the preceding cyano aniline stage was made.

Cyano Aniline/Acid Aniline Telescope (11/12). Given the initial difficulty experienced in designing a suitable isolation procedure for cyano aniline **11** in good form, its low assay, and the fact that the two major impurities (**22** and **23**) were partial hydrolysis intermediates on the way to acid aniline **12**, it had been desirable from an early stage to try and telescope these two reactions together. Once problems with the cyano aniline stage were understood and the Hastelloy reactor became available, the telescoped reaction could be investigated.

As a starting point, a standard cyano aniline preparation was drowned-out with water and extracted with toluene, to which 48% aqueous NaOH in ethanol was added. The reaction mixture was heated to 80 °C for 6 h, which converted all of intermediate **11** into desired acid aniline **12**. This batch was then split, and one-half isolated as the sodium salt, the other neutralized to pH 6 and isolated as the neutral species **12**. The assays of both products were low (67 and 76%, respectively), and the overall yield of 51% was lower than the individual steps. However, it did establish the principle of the telescoped process. Further scrutiny showed that toluene extraction resulted in high losses and poor form; changing to MTBE was much better and allowed a solvent exchange into higher-boiling ethanol for the hydrolysis step. Acidification with concentrated HCl gave on isolation a product of improved physical form with 93% assay in 74% overall yield from thiocyanate **10**. However, a strongly sulfurous-smelling grey scum was noted from the reaction which was difficult to clean out and would be a problem on plant scale.

Various solvents were screened to see if a single solvent could be used for both processes, and whilst several worked well in the cyano aniline stage, only MIBK worked in the hydrolysis step. Due to the imminent start of plant manufacture, this result could only be noted for future study. NMP was retried for the cyano aniline stage and found to give less grey scum and bad odor, and also less thioamide **23**. DMF had been the preferred solvent for the single reaction and gave a better form of **11**, but now that extraction was replacing isolation, the need for a good drown-out solvent was not required. Although **11** could crystallise from MTBE on storage, it remained stable in solution when ethanol was added, so could be stored for several weeks.

The charge of Na_2S was reduced to 1.5 equiv which also gave less grey scum. When using less pure batches of thiocyanate **10**, the grey scum was again higher, suggesting that it was related to impurities in **10** more than the charge of Na_2S. A large lab-scale preparation (5-L scale) using plant-derived **10** worked well with the solvent exchange from MTBE to ethanol after the extraction procedure and gave expected yield and quality. Typical laboratory batches now had only two major impurities, residual amide **22** and dibromide **21** carried over from the thiocyanate stage, both at ∼1% each and lost in the following sulfide aniline stage. In this state, the process was expected to give ∼75−80% yield of product with ∼90−95% assay. There were no additional chemical hazard concerns beyond those of the individual stages. The change from DMF back to NMP meant that exothermic activity was slightly more noticeable due to the lower Cp of NMP, but less of an issue due to its much higher bp (202 °C).

Manufacture proceeded with five batches as planned in fully telescoped manner on 25-kg (225 L) scale. However, the first two batches were found to have unusually high amide **22** content as measured by LC at the cyano aniline stage (19−35%). In theory, this should not have been a problem since the amide **22** would be hydrolyzed to acid aniline **12** in the second

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step, but in practice it was found that much of **22** was lost to the aqueous phase in the intermediate extractions, resulting in low isolated yields of **12** (49−64%). An extended extraction procedure was introduced to aid partition of **22** into the MTBE phase, but this gave only marginal improvement. A laboratory user trial with plant-supplied NMP and Na_2S indicated that this combination resulted in the high level of **22**. For the last two batches, the reaction temperature was reduced to 45 °C for the cyano aniline stage and the reaction time lengthened to 4 h which resulted in only 2−3% amide before the extraction and an 86% yield of cyano aniline.

In total, 135 kg of acid aniline **12** were produced in five batches in an average yield of 71%. Notably, however, the isolated yield for the last two batches was 87% compared to 54−66% for the first three in which high levels of amide **22** had resulted in high losses. Irrespective of the yield, all batches were of excellent quality by ^{1}H NMR assay (98−100%) and purity by HPLC (97−99%), demonstrating a robust purification procedure.

Overall, the telescoped process was a worthwhile improvement over the individual stages, and compensated in some measure for the linear nature of this route by avoiding one isolation step, often the lengthiest part of processing. The telescope gave a higher yield with similar quality, reduced plant time, and operations and avoided form and analytical issues at the cyano aniline stage. The solvent exchange distillation worked well, and cleaning was not an issue in NMP. The only remaining issue to be resolved was the poor performance of the initial plant batches, which had been attributed to the source and quality of the plant NMP and Na_2S, but further investigations were not needed.

Sulfide Aniline Stage (13). As with the preceding two stages, this one also had no counterpart in the campaign 2 route, and looked simple on paper. Both reagents used in campaign 2 route (oxalyl chloride or thionyl chloride) were tried to activate **12** as its acid chloride to couple with dimethylamine, but neither conditions would work. This did not appear to be due to polymerization of the bifunctional acid aniline **12**.

Changing to a standard peptide coupling reagent such as EDCI gave the desired reaction. When the level of hydroxybenzotriazole (HOBt) was low, however (10 mol %), the reaction was incomplete, and an impurity formed, assumed to be one of the *N*-acyl ureas.[12] At stoichiometric levels, the reaction conversion was complete, but 20% w/w HOBt contaminated the product which was not easily removed by recrystallization. Attempts to use the sulfate salt of **12** directly in the reaction, with additional dimethylamine or Et_3N to neutralize the acidic counterion, did not work, even with a preneutralisation step. However, the neutralized salt of **12** could be extracted and taken directly into the EDCI reaction successfully. The sodium salt of **12** also coupled directly with aqueous dimethylamine mediated by EDCI after some study.

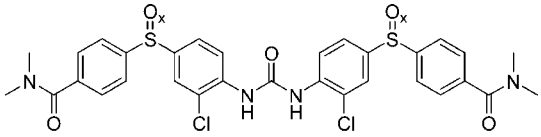
Aqueous dimethylamine was next used instead of ethanolic dimethylamine, as had been used in the campaign 2 bromobenzamide stage (**6** to **7**) which had given rise to an ethyl ester impurity. Aqueous dimethylamine avoided this problem and gave a faster reaction and higher yield, but the addition became more exothermic and required a longer addition time. A modest increase in the charge of EDCI to 1.2 equiv achieved complete conversion after 2 h at 20 °C, and after further addition of water, a 95% yield of product with 95% assay could be obtained directly in fair form. The reaction mixture was heterogeneous, but this did not appear to be a concern. Residual HOBt could be washed out with a citrate wash. The process was prepared for plant manufacture with EDCI, but at a late stage, there was a desire to find an alternative coupling reagent, given the relatively high cost of EDCI (a noncontributory reagent).

Oxalyl and thionyl chlorides were briefly reinvestigated now that higher-quality acid aniline **12** was available, but they still did not work. Otherwise, only CDI was investigated, and this looked promising from the first reaction in acetonitrile at 50 °C. The CDI (1.05 equiv) was added as a solid in one portion which had no exothermicity but did evolve some CO_2. Aqueous dimethylamine was then added which reacted instantaneously (adiabatic temperature change of 10 K). The product was isolated after an aqueous drown-out (also moderately exothermic) and cooling to 0 °C, which gave good yield (>90%), quality (>95%), and physical form. To avoid the minor inconvenience of solid charging, CDI was dissolved in acetonitrile at 50 °C and added to a slurry of **12** at 50 °C, whereupon it reacted instantly. This also allowed the heat of reaction to be controlled better. This simple process was prepared for manufacture.

However, it was noted that CDI was prone to lose activity on reaction with moisture, which meant the stoichiometry could not be too tight. Furthermore, the CDI had to be assayed by ^{1}H NMR spectroscopy to determine its strength prior to charging on the plant. A troublesome impurity had been observed, especially when the CDI charge was higher, which was difficult to remove in the following stages. We planned to scale the batch size to whole units of the supplier's pack size of CDI to minimize the possibility of exposure to water. CDI could crystallise from acetonitrile at the planned concentration but stayed in solution in warm acetonitrile for a long period (24 h) which led to a successful reaction. Although the reaction was heterogeneous at the start, it appeared to perform well, and there were no special issues with chemical hazards, both exothermic additions being well within plant capability and CO_2 generation being addition-rate controlled.

An FED indicated that the charge of CDI should be increased from 1.1 to 1.2 equiv, and that of dimethylamine from 1.5 to 1.75 equiv. The acetonitrile volume for dissolving the CDI was increased to 6 relative volumes, and this ensured the CDI stayed in solution even at room temperature. A reverse drown-out had also been investigated, but the normal drown-out was found to be better. Lastly, just before the pilot-plant manufacture, a 5 L laboratory preparation provided a final confirmation that the process was ready.

Only one batch was performed on plant scale (30 kg, 330 L) before the project was put on hold. Filtration, washing, and drying times were much slower than expected during isolation on the pressure filter i.e. days instead of hours. Pilot-plant vessel agitation was subsequently thought to be significantly better (using several methods) than on laboratory scale, and analysis of the solid indicated that some particle attrition had occurred. In addition, the very poor form of the damp paste damaged the agitator drive in the pressure filter during the prolonged drying regime. The batch had to be discharged as a 12% water-wet paste (~34 kg), and the assay was low at 86%. It also had two impurities at 3.6 and 1.2%, which were identified by LCMS as di- and tri-adducts respectively, the diadduct being tentatively identified as structure **24a**. These impurities had been noted in the process before, but well below 1%.



Di-adduct sulfide (**24a**) (x = 0)
Di-adduct sulfoxide (**24b**) (x = 1)
Di-adduct sulfone (**24c**) (x = 2)

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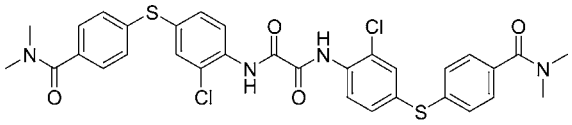
The proposed cause of their formation was from an overcharge of CDI, which was traced back to an error in the method used to determine its assay. This figure had been used in the FED which had set the level of CDI required for plant scale, but had effectively led to an overcharge. A laboratory experiment with a significant overcharge (1.5 equiv compared to planned 1.2) gave a 98% yield of product but containing 15% of **24a** and ~1% of the triadduct.

Investigations to rescue the first batch by treating a portion with a large excess of aqueous dimethylamine removed or destroyed both impurities but also gave another significant impurity. The solvent combination used by the contractor in campaign 2 to remove copper residues from their sulfide aniline also proved of no help in removing **24a**. Postponing the problem and taking a sample through to the final stages did not reduce these impurities sufficiently in the final crystallization. Furthermore, LCMS analysis in the penultimate oxidation process indicated they had transmuted into the analogous sulfoxide (**24b**) and sulfone (**24c**) diadducts.

The project was canceled before a decision on the following batch(es) was required. Clearly the charge of CDI could be set correctly once the problems with the assay were understood. The value of the FED study was that the results could be readjusted by taking account of the known error, and no experimental repetition was required. In the short term, batch 1 could be quarantined whilst a suitable crystallization solvent was identified, since the split campaigns 3a and 3b meant that the full campaign delivery did not have to be made at the first pass.

Chiral Amide Stage (15). Throughout the previous campaigns, there had been a desire to add the unprotected chiral acid unit (**2**) via its acid chloride (**14**) instead of through the TMS-protected derivative (**16**). The double TMS-protection with bis-TMS urea had proven capricious at Discovery chemistry scale, and the intermediate TMS-protected acid chloride (**16**) was volatile and difficult to isolate without high losses. Furthermore, the TMS-protected sulfide aniline product (**17**) was also difficult to isolate and had to be protected from moisture and heat; a sample held for 5 days in dichloromethane, for example, lost most of the TMS group over this period, although the subsequent oxidation worked well and easily removed the remainder of the TMS group. This would not be acceptable as a long-term manufacturing method and in any case would require the solution assay of **16** to be determined for reaction with sulfide aniline. Furthermore, no single analytical method could monitor the reaction. HPLC could not analyze the non-UV-active derivatives (**14** and **16**), and GC could not monitor the heavier components. Use of the unprotected chiral acid **2** would therefore avoid many of these analytical, chemistry, and storage issues and remove one step from the reaction sequence.

Direct coupling of chiral acid **2** with sulfide aniline **13** using EDCI under standard conditions gave no reaction. Oxalyl chloride appeared to work well, but any slight excess reacted with **13** to generate an oxalate-bridged diadduct (**25**) which could not be removed and which tracked through in subsequent stages. This had also been identified as a troublesome impurity in the campaign 2a/b manufactures when forming **17** from **15** and **16**, and was the reason both manufactures had performed poorly. The formation of **25** could be prevented by the use of only one equivalent of oxalyl chloride, but under these conditions the acid chloride formation (**14**) was slow to reach completion.

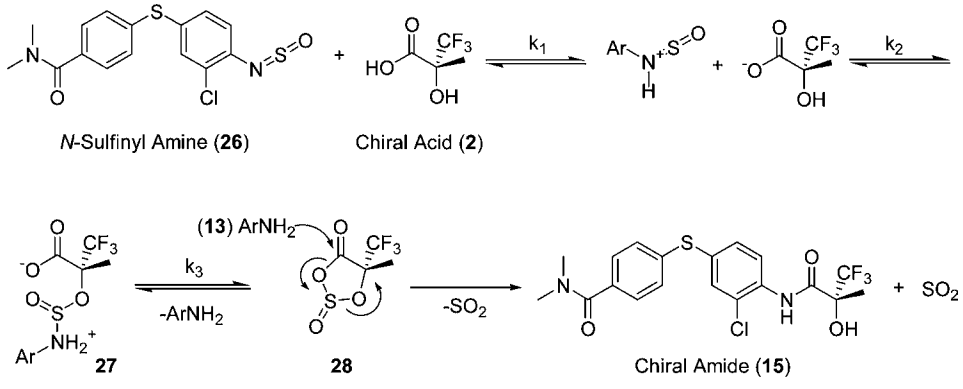


Oxalate-bridged di-adduct (**25**)

Use of standard thionyl chloride coupling conditions in acetonitrile with triethylamine gave a 66% yield of **15** after an aqueous drown-out on the first attempt. This proved the viability of using the unprotected chiral acid **2** but the conversion was incomplete. Use of more thionyl chloride or triethylamine, a higher temperature or a longer reaction time, and purging with nitrogen beforehand all gave no improvement.

An alternative approach to the formation of α-hydroxy amides had been used on another Zeneca project (ZD6169)[11] taking advantage of neighbouring group participation of the α-hydroxyl group. In such cases, a weakly nucleophilic amine (aniline) can be activated using thionyl chloride to give the *N*-sulfinyl amine (**26**)[12] which is then reacted directly with an α-hydroxyacid (**2**) to give the desired α-hydroxy amide (i.e., chiral amide **15**). The proposed mechanism is based on the report of Shim and Kim (Scheme 5).[13] They proposed intermolecular protonation by the carboxylate group and then an intramolecular attack by the α-hydroxyl group which, after further protonation and regeneration of the amine (**13**), effectively activates the cyclic intermediate (**28**) as a mixed anhydride to attack by the free amine (**13**). They also proposed reversible steps for all but the last, and claimed that addition of either stronger acids or bases hindered the reaction by suppressing

Scheme 5. Mechanism of α-hydroxy amide formation



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the forward reaction to zwitterionic intermediate **27**. This last point is contested by Chidambaram et al. who nevertheless used this approach very successfully in nonracemic systems.[14] Our experience was that the reaction proceeded well in the presence of residual thionyl chloride used in excess for the *N*-sulfinyl amine formation.

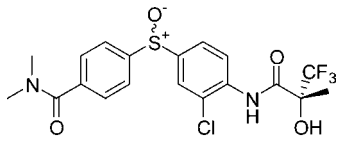
Following the ZD6169 project, we adopted the "all-in" approach without isolation of the *N*-sulfinyl amine (**26**) to form the chiral amide **15**. To determine whether the reaction proceeded by *N*-sulfinyl amine **26** or the more obvious acid chloride **14**, both chiral acid **2** and sulfide aniline **13** were prereacted with thionyl chloride for 1 h under the standard reaction conditions before their reaction partners (**13** or **2**, respectively) were added to each mixture. The acid chloride-mediated process via **14** proceeded with a fast initial reaction which faded away to an incomplete reaction. The *N*-sulfinyl amine-mediated process via **26** progressed steadily to completion over 18−24 h. It is proposed that the irreversible loss of SO_2 from the cyclic reaction intermediate **27** helps to drive the reaction completion.[12] Since sulfide aniline **13** cannot be reformed from intermediate **26**, it continues to react with the chiral acid **2** until it is all consumed. Attempts to confirm the structure of the (in our case) nonisolated *N*-sulfinyl amine **26** using IR techniques were inconclusive, and the project was canceled before a more thorough investigation of this intriguing mechanism could take place.

Initial process development indicated a slight excess of thionyl chloride (1.15 equiv) over triethylamine (1.05 equiv) was better for the reaction, which could be conducted in acetonitrile. After formation of the *N*-sulfinyl amine intermediate over 2 h at 40 °C, an excess (1.15 equiv) of chiral acid **2** was added and the reaction stirred at 20 °C overnight. The workup proved troublesome, in that the product **15** tended to oil out. Normal and reverse drown-outs into water, brine and bicarbonate solutions were all tried with mixed success; a warm drown-out into a brine/bicarbonate solution was the preferred option and gave the best physical form. Despite these problems, reliable yields of 85−90% of product with 96−99% assay could be obtained reproducibly.

A use-test of the damp sulfide aniline **13** from the first plant batch failed as expected due to the high water content (12%). When the sample of **13** was dried azeotropically, reaction conversion was almost complete at 98% and an oven-dried sample gave complete conversion. However, in both cases the physical form of the product chiral amide **15** was notably poorer than when prepared from laboratory samples of **13**, and the level of diadduct **24** was not reduced. This simply confirmed that sulfide aniline batches would need to be dry before further reaction and with a low level of di- and triadducts.

There were no major chemical hazard concerns with the process. The addition of thionyl chloride was exothermic and SO_2 was evolved when adding the chiral acid, but both parameters were addition-rate controlled and well managed by slow additions. There were some remaining minor concerns with compatibility of thionyl chloride and MoC, and physical form and isolation issues, but in all other respects, the chiral amide stage was essentially ready for plant manufacture when the project was halted. The batch size would have been on 25 kg (350 L).

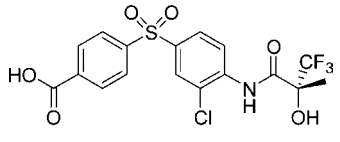
Crude Stage (1). The oxidation process of chiral amide to give "crude" bulk drug **1** was inherited from the campaign 2 process, itself adopted from the Discovery chemistry process. This had started with 16 equiv of H_2O_2 in neat glacial acetic acid at 90 °C, which might have been acceptable on small scale, but would cause issues on the plant. The contractor wisely reduced this to 2.0 equiv of H_2O_2 heated at 60 or 80 °C, which gave complete conversion at an acceptable rate. The intermediate sulfoxides **29** were confirmed as intermediates by LCMS (as co-eluting diastereomers). On 40-g scale however, there was an exothermic temperature rise to 102 °C from 80 °C and significant gassing, assumed to be from decomposition of H_2O_2.



Sulfoxides (**29**)

A series of tube-scale experiments were performed to investigate various parameters in both formic and acetic acids. The reaction was found to be generally faster in formic acid than acetic acid, not much affected by concentration, and not requiring more than 3.0 equiv to go to completion. Slow addition of H_2O_2 also worked well and showed that the risk of accumulation could be avoided. Laboratory-scale preparations were performed in acetic acid at 80 °C and in formic acid at 60 °C (which was quicker and safer), and the results were passed to the contractor for their campaign 2 studies.

Further studies within AstraZeneca in formic acid showed that the first equivalent of H_2O_2 gave complete conversion to the sulfoxides **29** after 30 min; addition of a further equivalent then gave the sulfone (i.e., crude **1**) after 50 min, suggesting a long reaction time was not needed. In practice, a small excess of H_2O_2 was used, which could be quenched with sodium metabisulfite solution. A new impurity was detected and identified as the benzoic acid derivative (**30**). Although the product sometimes crystallised on cooling and could be isolated and washed with water in ∼90% crude yield, generally the workup proved problematic because the product oiled out or had poor form. Eventually, an 80% yield of product with 96% assay could be isolated, which retained 1.0% of the sulfoxides **29** and 0.7% of the benzoic acid **30**.



Benzoic acid (**30**)

Attempting an extraction procedure instead of direct isolation was also problematic. The solubility of **1** in low polarity solvents such as dichloromethane or toluene was low, resulting in high volumes; more polar solvents were miscible with the formic acid, and intermediate ones tended to extract some formic acid, which resulted in higher levels of **30** if concentration was attempted without neutralization of the acidic residues. Attempts to distill off the formic acid before using any of these extraction procedures had the same effect. Eventually, MIBK was identified as a suitable midpolarity solvent, from which most of the extracted formic acid could be removed by an aqueous back-wash, followed by neutralisation of the remainder with $KHCO_3$. Addition of a hydrocarbon solvent

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such as octane helped to crystallise the product **1** in good form and up to 90% yield with >98% purity. The benzoic acid **30** was largely removed under these conditions, and the sulfoxides **29** were not detected in any case now that the H_2O_2 charge had been increased to 2.3 equiv, which was important because these were not readily removed in the recrystallization stage.

Although the process now worked well, the pilot plant had some residual concerns about chemical hazards. The formic acid/H_2O_2 process was preferred due to giving the cleanest reaction profile, especially when there were issues with removing impurities in the final recrystallization process, but the chemical hazards group were concerned that formic acid/H_2O_2 mixtures were known to be potentially explosive, albeit at high concentrations.[8] The reagent controlled addition of dilute H_2O_2 avoided these conditions, but even so, the chemical hazard assessment indicated an adiabatic temperature rise of 57 K. Therefore it was agreed to investigate the use of base-mediated H_2O_2 in acetonitrile[15] which had been developed for plant scale on Sibenadet hydrochloride.[16] Using the standard 3.6 equiv of H_2O_2 for this process with K_2CO_3 at 45 °C in acetonitrile gave an initial reaction with 63% yield of product with 98% assay. The equivalent chemical hazard assessment on the same scale indicated an adiabatic temperature rise of only 28 K. The sulfoxides **29** were present at slightly higher levels, but not significantly so. However, as with the formic acid-mediated process, product **1** oiled out; some improvements were hastily made in subsequent preparations.

Both processes were then subjected to a Kepner–Tregoe decision making process to compare them,[17] which confirmed that there was little to choose between the two processes when taking all factors into account. However, the Sibenadet-derived process was judged to be marginally safer on scale (although neither process was judged to be unsafe) and since this was the preference of the plant personnel, this process was scheduled for manufacture.

Use-tests of plant-derived sulfide aniline **13** were conducted for both processes to determine if they could cope with the high diadduct **24a** impurity levels. In both cases, the diadduct was reduced to <0.05%, but a new impurity was detected at 1.5%, unsurprisingly determined by LCMS as the fully oxidized diadduct sulfone **24c**; the intermediate diadduct sulfoxides **24b** were present at 0.2–0.3% in the final (pure) stage which was acceptable. Neither process was trouble-free when performed on the plant-derived materials, and simply confirmed that the following processes could not cope with the diadduct **24a** at 3.6%; the problems with the sulfide aniline stage would therefore have to be resolved at the that stage. Pilot-plant manufacture of AZD7545 was halted in April 2002 after the first batch of **13** had been prepared, and development of AZD7545 was terminated in July 2002 with no further work conducted.

CONCLUSIONS

The decision to choose the linear benzonitrile route (campaign 3) over the convergent benzamide route (campaign 2) was readily justified by their respective overall yields of 45.5% and 22.5% for the longest linear sequence from thiocyanate **9**. The benzonitrile route may appear to have benefitted from more development, but the benzamide route was effectively as good as could be achieved after two or three iterations on each stage, and further scale-up was thought to be impractical. Furthermore, these figures do not account for the fact that all the steps in the linear route are counted, whereas two steps in the convergent route are not. Indeed, the step-count of actual isolations was only five for the linear route and seven for the convergent route, which no doubt contributed to this result, in addition to the improved yields.

The benzonitrile route was felt to be a viable long-term manufacturing route and a significant improvement over the more convergent benzamide route for many other reasons. The improved thiocyanate (**10**) process was inherently safer and worked better than before. Use of benzonitrile **8** allowed for a facile S_NAr reaction, and avoided the problematic Ullmann reaction between **7c** and **10**. The more linear nature of the route was mitigated by the simple chemistry of the cyano aniline/acid aniline telescope which proved reliable after initial modification giving excellent quality product (**12**). The root cause of the problem with the first batch of sulfide aniline (**13**) was well understood and should have been controlled by adjusting the CDI charge. The chiral amide (**15**) stage was improved over the analogous sulfide anilide (**17**) stage by an understanding of the *N*-sulfinyl amine mediated reaction with an α-hydroxy acid, which avoided unnecessary protection of the chiral acid **2** and the resulting losses. The remaining two processes for the pilot-plant manufacture were also well developed and had good scale-up precedent (chiral amide type process on ZD6169 and crude-stage oxidation in campaign 2 and/or Sibenadet), and two options were available for the final stage oxidation. Hazard issues for all stages were well understood and controlled.

We are confident the benzonitrile route would have become the long-term manufacturing route, probably with acid aniline **12** or sulfide aniline **13** as registered starting material, along with chiral acid **2**.[18]

EXPERIMENTAL SECTION

General Procedures. Reaction mixtures and products were analysed by reverse phase HPLC on Hewlett-Packard 1050 or 1100 instruments according to the following conditions: column, Genesis C18 100 mm × 4.6 mm i.d., particle size 3 μm; eluent A, 99.9% purified water with 0.1% v/v trifluoroacetic acid; eluent B, 90% acetonitrile and 9.9% purified water with 0.1% v/v trifluoroacetic acid; flow rate 0.60 mL/min.; wavelength 215 nm; temperature 40 °C; injection volume 5 μL; at t = 0 min, 20% eluent B; at t = 15 min, 85% eluent B; at t = 16 min, 85% eluent B; 4 min post time. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 400 spectrometer at 400 and 100.6 MHz, respectively, with chemical shifts given in ppm relative to TMS at δ = 0. Electrospray (ES^+) mass spectra were determined on a Micromass LCT with time-of-flight. Analytical TLC was carried out on commercially prepared plates coated with 0.25 mm of self-indicating Merck Kieselgel 60 F_{254} and visualised by UV light at 254 nm. Preparative scale silica gel flash chromatography was carried out by standard procedures using Merck Kieselgel 60 (230–400 mesh). Product purity was determined in most cases by both ^{1}H NMR assay against an internal standard of either maleic acid or tetrachloronitrobenzene, and by HPLC area % standardized against a sample of the product of known concentration.

In the preparations that follow, the largest scale plant processes have been given for those stages manufactured at campaign 3. For stages which did not reach manufacture, or where laboratory scale alternatives have been discussed, details are supplied for the finalized laboratory processes on which the campaign 3 plant processes would have been scaled.

Plant-Scale Preparation of AZD7545 Thiocyanate (10). [**Safety note #1:** unlike the initial process for this stage

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reported previously,[5] this procedure has been safely scaled up to 530 L (41 kg based on **9**). Even so, there are still chemical hazards of note, including a significant interaction between bromine and alcohols as noted in Bretherick.[8] Although this procedure largely mitigates against this issue, it remains important that all chemical hazards are fully considered, *especially if any changes are made to this process.* See the discussion in the text for a full presentation of the potential concerns. **Safety note #2:** late in the project, AZD7545 thiocyanate was identified as a *potential* skin-sensitizing agent, which seemed to be supported by experience during manufacture. This was not further investigated before the project was canceled but should be borne in mind if conducting future preparations].

Sodium thiocyanate (49.1 kg, 607 mol, 2.0 equiv) and methanol (270 L) were charged to a suitably serviced reaction vessel, A, and cooled to 2 °C. 2-Chloroaniline (**9**) (38.7 kg, 303 mol) was added with stirring at 100 rpm over 10 min (**caution:** moderate exothermic addition). The addition vessel was washed with methanol (116 L) and added into vessel A. Acetonitrile (97 L) was added to a second vessel, B, and cooled to 2 °C. Bromine (48.5 kg 303 mol, 1.0 equiv) was added slowly from a bomb to vessel B with stirring at 100 rpm over 30 min, maintaining a temperature of 0−5 °C (**caution:** moderate exothermic addition). The line was washed with acetonitrile (20 L) and added into vessel B. Both reaction mixtures were recooled to 2 °C, and the bromine/acetonitrile solution from vessel B was added slowly into the aniline/methanol solution over 2.5 h with stirring at 100 rpm, maintaining the temperature at 3 °C (**caution:** exothermic addition). Vessel B was washed with acetonitrile (20 L) and added into vessel A. The reaction mixture was stirred at 2 °C for 15−19 h. Sodium bicarbonate (53.5 kg, 637 mol, 2.1 equiv) and water (830 L) were added to a third vessel C with stirring at 10 rpm and cooled to 10 °C. The reaction mixture from vessel A was added into vessel C with stirring at a rate sufficient to maintain the temperature below 20 °C and commensurate with the gas disengagement capacity of vessel C (30 min on this scale) (**caution:** a vigorous effervescence of CO_2 and an exothermic addition is observed). The product crystallises as a white or pale-yellow precipitate during this addition. Vessel A was washed with methanol (40 L) and added into vessel C. The reaction mixture was cooled to 0−5 °C for 30 min before isolation by filtration. (The reaction mixture can be left for 18 h at 0−5 °C before being isolated but slow decomposition of product **10** is observed with some loss of product quality). The reaction mixture was transferred to a filter-dryer in several portions using positive N_2 pressure to deliquor the product cake. The product was slurry-washed twice with water (155 L each) on the filter-dryer, deliquored fully and dried using positive N_2 pressure at 40 °C to yield the title compound as an off-white to pale yellow solid (46.7 kg @ 96% assay; overall yield 80%). HPLC (t_R 9.3 min, quality 94.6%); ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.57 (1H, d, J = 2.3 Hz), 7.35 (1H, dd, J = 8.5, 2.3 Hz), 6.86 (1H, d, J = 8.5 Hz), 6.04 (2H, s); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 147.25, 133.81, 133.17, 117.29, 116.12, 112.68, 106.54; MS (ES$^+$) 185/187 (M + H, 30%, 3:1), 226/228 (M + MeCNH$^+$, 45%, 3:1), 283/285 (100%, 3:1). **Data for AZD7545 Disulfide (19):** HPLC (t_R 14.9 min); ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.21 (2H, d, J = 2.0 Hz), 7.09 (2H, dd, J = 8.4, 2.0 Hz), 6.76 (2H, d, J = 8.4 Hz), 5.81 (4H, bs); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 145.98, 133.22, 132.61, 121.53, 116.71, 115.54; MS (ES$^+$) 317/319/321 (M + H$^+$, 100%, 9:6:1).

Laboratory-Scale Preparation of AZD7545 Cyano Aniline (11) (single process). Sodium sulfide (technical grade reagent, 19.3 g @ 60%, 11.6 g @ 100%, 148 mmol, 1.80 equiv) and DMF (61 mL) were charged to a suitably serviced reaction vessel A, and the mixture was stirred and heated to 60 °C. Some sodium sulfide remained out of solution as a yellow solid; the liquid phase of the mixture became dark green/blue. AZD7545 thiocyanate (**10**) (15.2 g @ 100%, 82.2 mmol, 1.00 equiv) and DMF (53 mL) were charged to a second vessel, B, and stirred to form a dark-yellow solution. (If the thiocyanate contains a high level of inorganic impurities, then some material remains out of solution at this point. These fines can be removed by passing through a line filter in the following transfer, but this is not necessary for standard quality thiocyanate.) This solution was added to vessel A over 10 min (**caution:** exothermic addition). The colour of the batch changed from green/blue to orange. Vessel B was rinsed with a line-wash of DMF (4.0 mL) and added into vessel A. The reaction mixture was stirred at 60 °C for 30 min (but up to 4 h is also acceptable and a longer hold period is unlikely to be detrimental). 4-Fluorobenzonitrile (**8**) (10.5 g, 86.4 mmol, 1.05 equiv) and DMF (15 mL) were charged to a third vessel, C, and stirred to form a colourless solution. This solution was added to vessel A over 10 min (**caution:** exothermic addition; an exotherm of 4 K is observed on this scale). Vessel C was rinsed with a line-wash of DMF (4.0 mL) and added into vessel A. The batch was stirred at 60 °C for 3 h, during which time the batch turned paler in colour and a yellow solid formed. Water (380 mL) was added to a fourth vessel D and heated to 60 °C. The reaction mixture was added to vessel D over 15 min, during which time the batch became cloudy (**caution:** moderate exothermic addition). Vessel A was rinsed with a line-wash of DMF (8.0 mL) and added into vessel D. The batch was cooled evenly to 20 °C at a rate of 0.5 K/min and then stirred at 20 °C for at least 1 h. A yellow solid precipitated during the cooling period and hold time. The solid was isolated by vacuum filtration, slurry-washed twice with water (76 mL each), and dried in a vacuum oven at 50 °C to yield the title compound as a yellow solid (19.4 g @ 87.1% assay, not including related impurities **22** and **23**; absolute yield of **11** 79% yield corrected for assay). HPLC (t_R 12.8 min, assay 87.1%); ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.69 (2H, d, J = 8.7 Hz), 7.43 (1H, d, J = 2.1 Hz), 7.23 (1H, dd, J = 8.5, 2.1 Hz), 7.13 (2H, d, J = 8.7 Hz), 6.91 (1H, d, J = 8.5 Hz), 5.96 (2H, s); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 147.2, 146.7, 136.0, 135.5, 132.6 (2C), 125.4 (2C), 118.8, 117.4, 116.3, 113.1, and 107.0; MS (ES$^+$) 280/282 (M + H$^+$). **Safety note:** the reaction liquors and aqueous washes will contain NaCN and may also contain Na_2S. Both will present a serious toxic hazard if the liquors become acidified. Na_2S also has a strong smell. In the laboratory, the aqueous waste was treated with bleach before being sent for disposal; on plant scale, more substantial waste disposal measures will be required.

Data on Related Impurities Amide 22 and Thioamide 23. Samples of AZD7545 cyano aniline may also contain significant quantities of two impurities, the amide and thioamide, both of which are hydrolysed in the following process to yield the desired AZD7545 acid aniline. **Data for AZD7545 Amide (22):** HPLC (t_R 8.8 min); ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.89 (1H, br s), 7.76 (2H, d, J = 8.4 Hz), 7.39 (1H, d, J = 2.0 Hz), 7.30 (1H, br s), 7.21 (1H, dd, J = 8.4, 2.0 Hz), 7.07 (2H, d, J = 8.0 Hz), 6.88 (1H, d, J = 8.4 Hz), 5.86 (2H, br s);

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^{13}C NMR (100.6 MHz, d_6-DMSO) δ 167.27, 146.19, 143.33, 135.52, 135.07, 131.07, 128.19 (2C), 125.26 (2C), 117.24, 116.15 and 115.07; MS (ES^+) 279/281 ($M + H^+$). **Data for AZD7545 Thioamide (23):** HPLC (t_R 11.4 min); ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.77 (1H, br s), 9.40 (1H, br s), 7.81 (2H, d, J = 8.4 Hz), 7.39 (1H, d, J = 2.0 Hz), 7.21 (1H, dd, J = 8.4, 2.0 Hz), 7.03 (2H, d, J = 8.4 Hz), 6.88 (1H, d, J = 8.8 Hz), 5.87 (2H, s); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 198.88, 146.22, 143.60, 136.09, 135.50, 135.05, 128.04, 124.88, 117.26, 116.16, and 114.97.

Laboratory Scale Preparation of AZD7545 Acid Aniline (12) (single process). AZD7545 cyano aniline (**11**) (5.0 g @ assumed 100% assay, 19.2 mmol) was dissolved in absolute ethanol (50 mL) with stirring at 25 °C to form a yellow solution. Sodium hydroxide liquor (2.6 mL @ 47% w/w, 45.1 mmol, 2.35 equiv) was added, followed by water (5.0 mL). The stirred reaction mixture was heated to reflux at 80 °C for 22 h. (**NB:** It is important to achieve reflux to remove gaseous byproduct.) The reaction mixture was cooled to 50 °C and water (5.0 mL) added. Concentrated hydrochloric acid (4.3 mL @ 32% w/w, 45.1 mmol) was added and the product crystallized from solution (**caution:** moderate exothermic addition). The reaction mixture was cooled to 0 °C and the solid product isolated by vacuum filtration. The reactor vessel was rinsed with water (12 mL) and the rinse wash passed through the product cake by displacement. The water wash (12 mL) was repeated and the damp solid dried in a vacuum oven at 50 °C to yield the title compound as a pale yellow solid (5.3 g @ 92.3% assay; overall yield 91%). HPLC (t_R 9.8 min); ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.81 (1H, br s), 7.79 (2H, d, J = 8.8 Hz), 7.38 (1H, d, J = 1.6 Hz), 7.20 (1H, dd, J = 8.4, 1.6 Hz), 7.06 (2H, d, J = 8.4 Hz), 6.87 (1H, d, J = 8.0 Hz), 5.87 (2H, br s); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 168.87, 146.40, 145.82, 137.78, 135.32, 129.95 (2C), 127.30, 125.05 (2C), 117.30, 116.22, and 114.30; MS (ES^+) 280/282 ($M + H^+$).

Plant Scale Preparation of AZD7545 Acid Aniline (12) (telescoped process from AZD7545 Thiocyanate 10). Sodium sulfide (technical grade reagent, 15.8 kg @ 100%, 203 mol, 1.50 equiv) and NMP (100 L) were charged to a suitably serviced reaction vessel, A, and the mixture was stirred and heated to 45 °C. Some sodium sulfide remained out of solution as a yellow solid; the liquid phase of the mixture became dark coloured. AZD7545 thiocyanate (**10**) (25.0 kg @ 100% 135 mol, 1.0 equiv) and NMP (87 L) were charged to a second vessel, B, and stirred to form a dark-yellow solution with a small quantity of fines. This solution was added to vessel A through an in-line filter over 10 min (**caution:** exothermic addition). Vessel B was rinsed with a line-wash of NMP (6 L) and added into vessel A. The reaction mixture was stirred at 45 °C for 60 min (but up to 4 h is also acceptable, and a longer hold period is unlikely to be detrimental), during which time the colour became orange. 4-Fluorobenzonitrile (**8**) (18.1 kg, 149 mol, 1.1 equiv) and NMP (25 L) were charged to a third vessel, C, and stirred to form a colourless solution. This solution was added to vessel A over 10 min (**caution:** an exothermic addition is observed). Vessel C was rinsed with a line-wash of NMP (6 L) and added into vessel A. The reaction mixture was stirred at 60 °C for 4 h before being transferred to a fourth vessel, D. During this time it became paler in colour, and a yellow solid formed. Vessel A was rinsed with water (600 L) which was charged into vessel D, and the resulting mixture cooled to 20 °C for 60 min. The mixture can be held at both temperatures for longer periods without detriment to quality if required. Vessel A was then rinsed with MTBE (250 L) which was also charged into vessel D. The reaction mixture was stirred vigorously for 10 min, and the resulting layers were allowed to separate. The lower aqueous layer was removed and the upper MTBE layer containing the intermediate crude cyano aniline washed twice more with water (150 L each) before being transferred back to vessel A. Vessel D was rinsed with absolute ethanol (150 L) and added to the yellow MTBE solution in vessel A. A second wash of absolute ethanol (150 L) was rinsed through vessel D and added into vessel A. The reaction mixture was distilled until a head temperature of 75−80 °C was achieved to remove the MTBE solvent. The mass of cyano aniline (**11**) extract retained was 175 kg with ∼275 L distillate collected. The reaction mixture was cooled back to 50 °C, and sodium hydroxide liquor (33.7 kg @ 32% w/w, 270 mol, 2.0 equiv) was added, followed by a line-wash of water (25 L). The stirred reaction mixture was heated to 80 °C, held for 18−22 h, and then cooled to 50 °C. (**NB:** It is important to achieve reflux to remove gaseous byproduct.) Concentrated hydrochloric acid (37.0 kg @ 36% w/w, 365 mol, 2.7 equiv) was added over 5 min with good agitation (**caution:** moderate exothermic addition), followed by a line-wash of water (25 L). During this addition, the product crystallized from solution. The reaction mixture was cooled to 0 °C at 0.5 K/min and transferred to an oyster filter for isolation. The product cake was washed by displacement twice with water (60 L each) in the oyster filter, deliquored fully, and dried at 50 °C to yield the title compound as a pale-brown solid (33.4 kg @ 99% assay; overall yield 88%). HPLC quality 98.8%. Other data for AZD7545 acid aniline are as noted above.

Alternative Laboratory-Scale (EDCI) Preparation of AZD7545 Sulfide Aniline (13). AZD7545 acid aniline (**12**) (8.0 g, 28.6 mmol), hydroxybenzotriazole (4.1 g, 30.0 mmol, 1.05 equiv) and acetonitrile (50 mL) were charged to a suitably serviced reaction vessel A and stirred at 20 °C to form a slurry. EDCI.HCl (6.7 g, 34.3 mmol, 1.20 equiv) was dissolved in acetonitrile/water (1:1, 19 mL total) in a second vessel, B, to give a clear solution which was added to vessel A over 10 min at 20 °C. Vessel B was rinsed with a line-wash of acetonitrile (1.0 mL) and added into vessel A. The reaction mixture was stirred at 20 °C for 1.5 h, during which time a cream-coloured precipitate formed. Aqueous dimethylamine solution (40% w/v, 9.7 mL, 76.4 mmol, 2.7 equiv) was added over 1 h (**caution:** moderate exothermic addition) followed by a line-wash of acetonitrile (1.0 mL) and the reaction mixture stirred for 15 min. Water (50 mL) was then added over 50 min (**caution:** moderate exothermic addition) and stirred for a further 1 h, during which time the product crystallised. The reaction mixture was cooled to 2 °C and stirred at this temperature for 2 h. (Additional water may be added at this point if crystallization is incomplete.) The product was isolated by vacuum filtration, the slurry washed twice with water (40 mL each) and dried in a vacuum oven at 50 °C to yield the title compound as an off-white solid (7.9 g @ 96.7% assay; overall yield 93%). HPLC (t_R 10.5 min); ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.39 (1H, d, J = 1.8 Hz), 7.31 (2H, d, J = 8.4 Hz), 7.22 (1H, dd, J = 8.4, 1.8 Hz), 7.06 (2H, d, J = 8.4 Hz), 6.87 (1H, d, J = 8.4 Hz), 5.85 (2H, s), 2.93 (3H, br s), 2.90 (3H, br s); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 169.54, 146.17, 141.01, 135.58, 135.12, 131.18, 127.91 (2C), 125.45 (2C), 117.23, 116.15, 115.23, 38.80 and 34.77; MS (ES^+) 308/310 ($M + H^+$).

Plant-Scale (CDI) Preparation of AZD7545 Sulfide Aniline (13). AZD7545 acid aniline (**12**) (30.0 kg, 107.3 mol)

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and acetonitrile (300 L) were charged to a suitably serviced reaction vessel A and heated to 50 °C to form a mobile slurry. CDI (21.3 kg @ *assumed* 100% assay, 131.3 mol, 1.22 equiv.) and acetonitrile (150 L) were charged to a second vessel, B, and heated to 50 °C to to form a clear solution. (**NB:** The assay of CDI was incorrect; see the main discussion for explanation.) The CDI solution was added to vessel A over 30 min at 50 °C (**caution:** gas evolution), during which time a yellow solution formed. Vessel B was rinsed with a line-wash of acetonitrile (60 L) and added to vessel A. The reaction mixture was stirred at 50 °C for 75 min and then cooled to 25 °C. Aqueous dimethylamine solution (14.6 kg @ 40% w/v, 129.5 mol, 1.20 equiv) was added smoothly over 15 min (**caution:** exothermic addition). The line was washed with water (15 L) and added into vessel A. The yellow colour disappeared, and a white precipitate formed. The reaction mixture was stirred at 25 °C for 30 min, then cooled to −2 °C. Water (480 L) was added over 30 min (**caution:** moderate exothermic addition) and the reaction mixture stirred for a further 30 min at 5 °C. The reaction mixture was transferred to a filter-dryer in several portions using positive N_2 pressure to deliquor the product cake (this took 3 days on plant scale). The product was washed by displacement twice with water (160 L each) on the filter-dryer (this took 8−15 h on plant scale), deliquored fully, and dried using positive N_2 pressure at 70 °C to yield the title compound as an off-white solid (34.4 kg @ 86% assay; overall yield 89%). HPLC quality 94.4%. Other data for AZD7545 sulfide aniline as noted above, allowing for lower quality in this case.

Laboratory-Scale Preparation of AZD7545 Chiral Amide (15). AZD7545 sulphide aniline (**13**) (20.0 g, 65.2 mmol) and acetonitrile (100 mL) were charged to a suitably serviced reaction vessel A and stirred at 20 °C to give a mobile slurry. Triethylamine (6.9 g, 9.6 mL, 68.4 mmol, 1.05 equiv) was added directly to the vessel over 1 min, followed by a line-wash of acetonitrile (40 mL). Thionyl chloride (9.0 g, 5.5 mL, 75.0 mmol, 1.15 equiv) was added over 1 h (on this scale by syringe pump) keeping the temperature below 22 °C (**caution:** exothermic addition), followed by a line-wash of acetonitrile (40 mL). A dark solution resulted which was stirred at 20 °C for 2 h (and not longer than 4 h). AZD7545 chiral acid (**2**) (11.9 g, 75.0 mmol, 1.15 equiv) was dissolved in acetonitrile (40 mL) in a second vessel, B. This solution was added to vessel A over 1 h (to minimize gassing, the addition is not exothermic), followed by a vessel rinse and line-wash of acetonitrile (40 mL). The resulting dark reaction mixture was stirred at 20 °C for ∼16 h (but up to 40 h has no detrimental effect). Sodium chloride (57.6 g) and water (250 mL) were charged to a third vessel, C, and heated to 50 °C to form a clear solution. The reaction mixture from vessel A was added into the solution in vessel C smoothly over 30 min to form two clear phases. Vessel A was rinsed with acetonitrile (20 mL) which was washed into vessel C, and the reaction mixture was stirred at 50 °C for 30 min. The mixture was allowed to separate and the lower aqueous phase removed. Fresh saturated brine solution (120 mL) was added, followed by aqueous sodium carbonate solution (1.0 M, typically ∼50 mL), added carefully over 30 min until the pH was in the range 6.5−7.5. The mixture was allowed to separate and the lower aqueous phase removed. The temperature was adjusted to 42 °C and water (100 mL) added over 1 h with stirring. The reaction mixture was stirred at 42 °C for 30 min, during which time the product started to crystallise. Further water (100 mL) was added over 1 h and the mixture stirred at 42 °C for an additional 30 min before cooling to 20 °C over 1 h. The reaction mixture may be stirred overnight at this temperature for convenience; a minimum of 8 h is recommended for full product crystallization; longer periods will not affect yields but may result in crystal attrition. The product was isolated by filtration, washed by displacement with water (100 mL), and dried in a vacuum oven at 60 °C to yield the title compound as an off-white solid (26.8 g @ 98.2% assay; overall yield 90%). HPLC (t_R 12.1 min, quality 99%); ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.77 (1H, s), 8.04 (1H, dd, J = 8.8, 3.0 Hz), 7.89 (1H, s), 7.61 (1H, d, J = 2.2 Hz), 7.43 (1H, dd, J = 8.8, 2.2 Hz), 7.40 (2H, d, J = 8.4 Hz), 7.32 (2H, d, J = 8.4 Hz), 2.96 (3H, s), 2.90 (3H, s), 1.61 (3H, s); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 169.31, 167.10, 136.53, 135.15, 133.61, 132.26, 131.69, 130.84, 129.22 (2C), 128.23 (2C), 125.78, 123.92, 74.80 (q, J = 27.6 Hz); MS (ES^+) 447/449 ($M + H^+$); (ES^-) 446/448 ($M - H^-$).

Laboratory-Scale Preparation of Crude AZD7545 (1) (draft formic acid process finalized for pilot-plant manufacture). AZD7545 chiral amide (**15**) (5.0 g, 10.6 mmol) was dissolved in formic acid (25 mL) in a suitably serviced reaction vessel and heated to 60 °C with stirring. Hydrogen peroxide (12% w/w solution, 7.2 mL, 24.5 mmol, 2.3 equiv) was added over 2 h (on this scale by syringe pump), maintaining the temperature at or below 60 °C (**caution:** exothermic addition). The reaction mixture was stirred at 60 °C for a further 1 h, then cooled to 40 °C. Sodium metabisulfite (0.90 g, 4.6 mmol, 0.43 equiv) as a solution in water (2.0 mL) was added smoothly over 3 min and the mixture stirred for 10 min before confirming residual peroxide residues had been quenched. MIBK (40 mL) was added over 3 min, maintaining the temperature at 40 °C, followed by water (50 mL), also added over 5 min, maintaining the temperature at 40 °C. The reaction mixture was stirred vigorously for 10 min, and then the phases were allowed to separate, and the lower aqueous 3was phase removed. Fresh water (50 mL) was added over 10 min, maintaining the temperature at 40 °C (so as not to precipitate the product prematurely). The reaction mixture was stirred vigorously for 10 min, and then the phases were allowed to separate, and the lower aqueous phase was removed. Fresh water (10 mL) was added over 5 min, maintaining the temperature at 40 °C. Potassium carbonate (15.0 g, 14.9 mmol) as a solution in water (60 mL) was added carefully with good agitation (**caution:** gas evolution) to achieve pH 7. The phases were allowed to separate, and the lower aqueous phase was removed. Fresh water (30 mL) was added over 5 min, maintaining the temperature at 40 °C (so as not to precipitate the product prematurely). The reaction mixture was stirred vigorously for 10 min, then the phases were allowed to separate, and the lower aqueous phase was removed. The MIBK phase was heated to 45 °C and octane (40 mL) added smoothly over 60 min. The reaction mixture was then cooled to 20 °C and stirred overnight at this temperature, during which time the product crystallised. The product was isolated by filtration, washed by displacement with octane (10 mL) and then with petroleum ether (10 mL), and dried in a vacuum oven at 50−60 °C to yield the title compound as a white solid (4.4 g @ 100% assay; overall yield 87%). HPLC (t_R 9.8 min); ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.94 (1H, s), 8.36 (1H, d, J = 8.7 Hz), 8.21 (1H, d, J = 2.1 Hz), 8.07 (2H, d, J = 8.2 Hz), 8.03 (1H, dd, J = 8.7, 2.1 Hz), 7.65 (2H, d, J = 8.2 Hz), 3.00 (3H, s), 2.84 (3H, s), 1.62 (3H, s); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 168.3, 167.4, 141.7, 141.1, 138.3, 137.3, 128.6, 128.1 (2C), 127.7 (3C), 125.1, 124.3 (q, J = 286.2 Hz), 122.6, 74.9

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(q, J = 27.6 Hz), 38.7, 34.6, and 19.4. MS (ES^+) 479/481 ($M + H^+$, 45%, 3:1), 520/522 ($M + MeCNH^+$, 100%, 3:1); (ES^-) 477/479 ($M - H^-$, 100%, 3:1).

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Notes

The authors declare no competing financial interest.

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