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Multi-kilo scale preparation of AZD4635 *via* C-H borylation and bromination: The corrosion of tantalum by a bromine/methanol mixture

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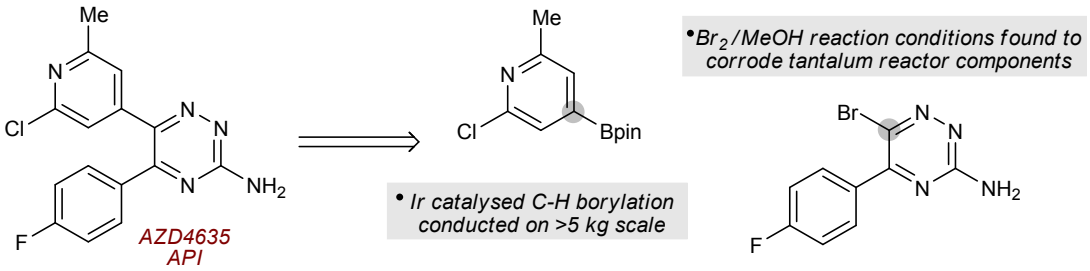
TOC GRAPHIC

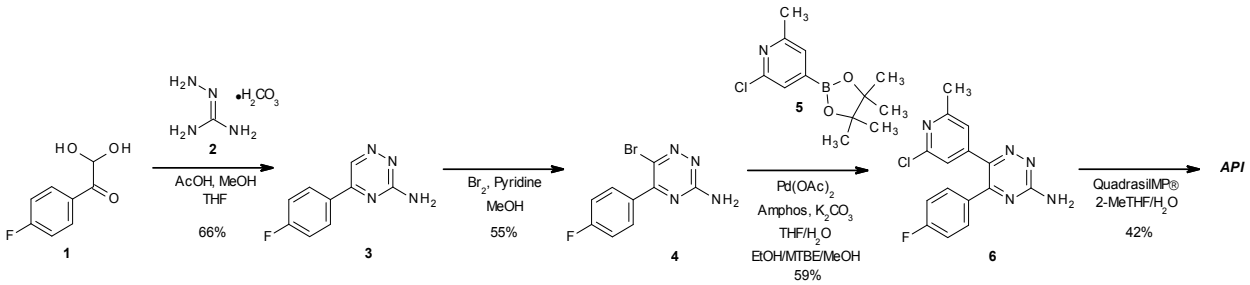

Me
N
Cl
N
N
N
NH2
F
AZD4635
API
Me
N
Cl
Bpin
• Ir catalysed C-H borylation conducted on >5 kg scale
•Br2/MeOH reaction conditions found to corrode tantalum reactor components
Br
N
N
N
NH2
F

ABSTRACT: An efficient route to AZD4635 has been developed utilizing Suzuki-Miyaura reaction of boronate ester (**5**) prepared by C-H borylation on multi-kilo scale. Preparation of the cross-coupling partner (**4**) using bromine/pyridine/methanol has highlighted the incompatibility of this reagent/solvent combination with tantalum, commonly used in the construction and repair of standard manufacturing vessels.

KEYWORDS: materials of construction; tantalum; bromine; methanol; C-H borylation; Suzuki-Miyaura

INTRODUCTION

$A_{2A}R$ antagonist[1] AZD4635 (**6**) (Scheme 1) is an investigational new drug currently in Phase IIa clinical trials for the treatment of solid tumors. Prior to in-licence of AZD4635 by AstraZeneca, clinical supplies had been delivered using a developed version of the discovery route (Scheme 1).[2,3] The 3-amino-1,2,4-triazine[4] based API is prepared in a convergent fashion *via* Suzuki-Miyaura coupling of aryl bromide (**4**) with pinacol boronate ester (**5**). These intermediates are respectively prepared by bromination of 3-amino-1,2,4-triazine (**3**) and iridium-mediated borylation of commercially available 2-chloro-6-methyl-pyridine (**7**). 3-Amino-1,2,4-triazine (**3**) is prepared by condensation of 1-(4-fluorophenyl)-2,2-dihydroxy-ethanone (**1**) with aminoguanidine bicarbonate (**2**).[5]



Scheme 1. Prior synthetic route to AZD4635 (**6**)

In advance of scale-up manufacture at AstraZeneca to deliver API for additional clinical supply and formulation development, assessment of the in-licensed process highlighted four key areas for improvement: (i) operability of the bromination stage to prepare **4**, minimizing operator exposure to bromine; (ii) the modest 59% yield of **6** from the Suzuki-Miyaura coupling; (iii) the use of scavenging to remove palladium in the API; and (iv) the lack of polymorph control in the final crystallisation of the API necessitating re-processing and low overall yield.

RESULTS AND DISCUSSION

3-Amino-1,2,4-triazine **3** was prepared with minor modifications to the in-licensed process. The process performed reliably on kilo lab scale (7 kg input **1**) with batch yields of 65-67% to deliver a total of 26 kg of **3**.

Development of bromination to prepare 4. Bromination of **3** was previously accomplished by treatment with excess bromine (2.50 mol eq)[6] in the presence of pyridine (3.00 mol eq) in methanol (8.00 rel vol) at 25°C. During the previous campaign this process was run on 2 kg scale (input **3**) to deliver **4** in 55% overall yield across 11 batches. The use of bromine in

methanol poses safety concerns due to a potential background reaction of bromine with the solvent.[7] Following process safety assessment, it was deemed the current procedure could be run safely without risk of uncontrollable exotherm up to 100 L scale, provided that the process concentration of bromine was not increased above 10% v/v.

The original process charged neat bromine *via* a pump, an option not available in the AstraZeneca kilo lab facility without significant operational modification. Furthermore, following the end of the reaction, solid product **4** was directly filtered from the bromine/pyridine/methanol slurry, this process could not be operated safely in the kilo lab due to potential operator exposure to unreacted bromine vapours when using open filtration equipment. In order to accommodate the bromination reaction, a method to safely charge bromine and quench the unreacted excess prior to isolation was developed. The exotherm upon bromine addition was controlled by charging aliquots of bromine *via* a nitrogen flushed charge bag to the cooled heterogeneous slurry of **3** in methanol/pyridine. Bromine was sourced in 1 kg bottles which allowed scaling such that an entire bottle could be opened inside an inert charge bag, the full contents charged to the reactor, and the bottle safely disposed. This reduced the number of operations performed with bromine and eliminated the requirement for any measurement by the process operator. Approximately 1 h after the bromine charge, HPLC showed an approximately 90–95% consumption of **3**. A further 21 h was required to progress to >98% consumption of **3**, possibly due to the precipitation of product **4**,[8] along with unreacted starting material **3**. This observed precipitation, typically within 1 h

of the bromine addition, presented a significant mixing challenge on laboratory scale, but was not an issue at 100 L kilo lab scale due to more efficient agitation.

Sodium thiosulfate was identified as a suitable reagent to quench any unreacted bromine at the end of the reaction, as indicated by visual decolourization of the deep red reaction mixture to a light cream (Figure 1). Due to the low solubility of sodium thiosulfate in methanol, it was charged as a solution in water to the thick reaction slurry causing a significant exotherm. Control of the exothermic quench was important, as at temperatures >25°C the formation of an unidentified by-product was observed. 0.34 mol eq (relative to **3**) of sodium thiosulfate was required to quench the excess bromine, consistent with the expected molar balance.[9] This suggests that bromine is not significantly consumed by side reactions, for example with the methanol solvent. The final conditions utilised 0.40 mol eq of sodium thiosulfate in water (1.00 rel vol), charged dropwise over 2 h, maintaining the internal temperature below 20°C.

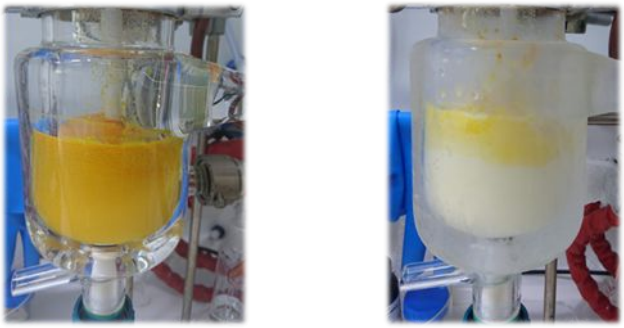


Figure 1. Photograph of lab-scale reaction mixture pre- (left) and during- (right) quench of bromine.

Following the quench, the solubility of **4** in the reaction mixture, *i.e.* the loss to the liquors upon filtration and isolation, was higher than expected based on the measured solubility of isolated **4**. Analysis of the pH during the sodium thiosulfate quench clearly showed a change in pH from 4 to 2, concurrent with the overall balanced equation for reduction of bromine by thiosulfate.[9] It was postulated that a protic salt of **4** was forming during the quench. Indeed, independent preparation and measurement of the solubility of the HBr salt of **4** revealed it had a significantly increased solubility in methanol/water mixtures relative to the freebase form, explaining the increased loss to liquors upon filtration and isolation.[10] The original process incorporated a direct filtration of the unquenched reaction mixture, followed by three methanol washes at –20°C to provide isolated material that was effective in the subsequent stage, but typically contained both pyridine.HBr, approximately 6–7% w/w, and bromine, approximately 2–3% (table 1 entry 1). Following the introduction of the quench procedure, the assay of **4** was significantly reduced (80% w/w by ^{1}H NMR).[11] This batch stalled in the

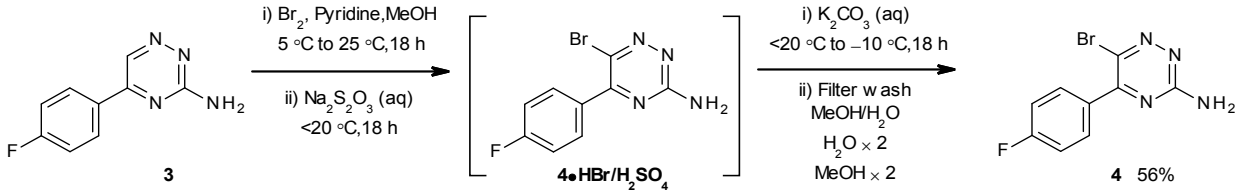
subsequent Suzuki-Miyaura reaction but could be restarted with a fresh charge of the palladium catalyst (table 1 entry 2). Aryl bromide **4** prepared using the original procedure was spiked with possible inorganic contaminants from the quench process which confirmed the need to remove these impurities during the isolation of **4** (Table 1 entry 3/4).[12]

entry	Inorganic spiked (charge based on **4**)	Outcome of Suzuki-Miyaura reaction
1	None (obtained *via* original process)	Complete conversion
2	None (obtained *via* quenched process)	Stalled conversion
3	Sodium thiosulfate (0.20 mol eq)	Stalled conversion
4	Potassium tetrathionite (0.10 mol eq)	Stalled conversion

Table 1. Spiking of inorganic contaminants into Suzuki-Miyaura coupling

To isolate the desired freebase form in higher yield, the pH following the thiosulfate quench was re-adjusted to 4–4.5 using an aqueous K_2CO_3 solution and held at -10°C, for at least 4 h to further maximise isolated yield. In order to obtain **4** in sufficient purity to allow successful

Suzuki-Miyaura coupling, a filter cake displacement washing sequence was developed that removed all significant impurities, residual pyridine salts, inorganics, and water (Scheme 2).[13] This fully developed process performed well on 120 g lab scale, delivering **4** in acceptable yield and purity (56% yield, 97% w/w).



Scheme 2. Developed synthetic sequence for the bromination of **3**.

Manufacture of 4. The manufacture of the first of two planned batches on 100 L scale was successfully carried out without any apparent issue using the developed process, providing 7 kg of **4** in 94% w/w purity at 56% yield. During manufacture of the second batch, a leak was observed from the reaction vessel which was subsequently traced to the thermopocket housing for the temperature control probe. Following removal of the thermopocket, extensive investigation was carried out into the origin of the leak. The thermopocket consists of a hollow bolt constructed from tantalum which seals against the glass lining of the vessel with a PTFE gasket. Analysis of the corrosion pattern of the bolt concluded that general corrosion attack of the bolt head had removed the sealing weld, allowing through leakage (Figure 2 (a)).

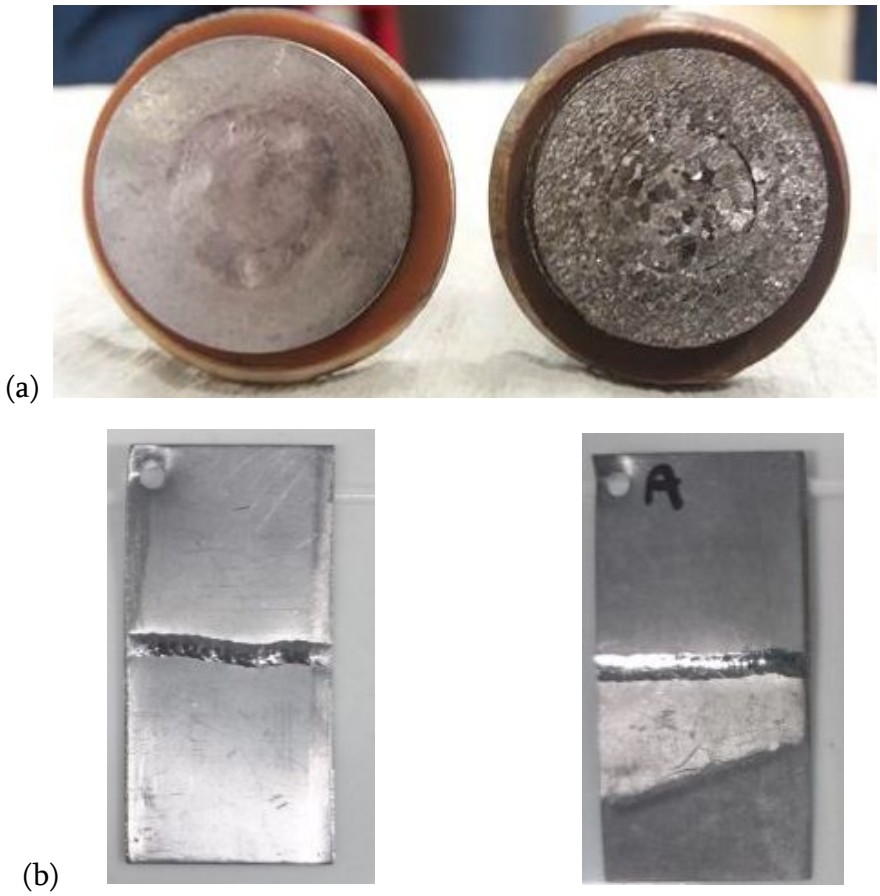


Figure 2. (a) Photograph comparing a used but not corroded thermopocket (left), to the leaking thermopocket showing signs of corrosion (right). **(b)** Photograph showing tantalum coupon after immersion in the reaction mixture (right). Compared with the control (left) there is visible corrosion below the weld line where the coupon has contacted the reaction mixture.

Concurrently, a laboratory user trial of **4** manufactured in the first kilo lab batch in the subsequent synthetic step showed the presence of hitherto unobserved insoluble material in the reaction mixture after successful Suzuki-Miyaura coupling to prepare **6**. Removal of this material by filtration and subsequent analysis by ICP-MS revealed that it was comprised of

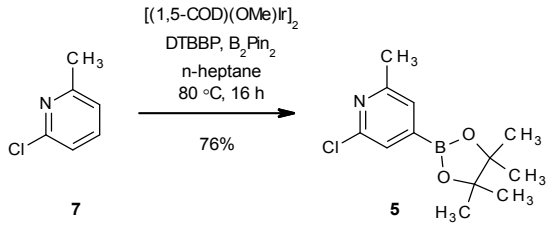
tantalum. The level of tantalum in the input batch of **4** was quantified as 558 ppm by ICP-OES analysis confirming the suspicion that the batch had been contaminated.[14]

In order to discern whether the bromination process to prepare **4** was responsible for the observed corrosion, tantalum coupon testing of the reaction mixture was carried out on laboratory scale by suspending a coupon in the reaction vessel, so that it contacted the reaction mixture below the weld line. The coupon was visibly corroded where it had contacted the reaction mixture and to a lesser extent where it had been exposed to vapours generated by the process, providing further evidence of the incompatibility of tantalum with the reaction mixture (Figure 2 (b)).

Standard materials of construction compatibility checks had not flagged any issue between tantalum and individual components, or by-products of the reaction mixture (bromine, pyridine, methanol, hydrobromic acid), suggesting that a combination of these components may be responsible. Detailed literature searching found reports that tantalum is not resistant to methanol solutions of 5% bromine containing less than 5% water, due to dissolution of the protective oxide coating. Based on the process charges used in the manufacture of **4** (bromine 2.50 mol eq, methanol 8.00 L/kg), the bromine content in methanol is 25% w/w (approximately 8% v/v) excluding the substrate **3** and pyridine. This suggests that the combination of bromine and methanol at the process concentration is responsible for the observed corrosion of tantalum, especially given the lack of added water to the process, although water is reported to only temper the corrosive effect to a limited extent.[15]

Although the tantalum compatibility issue prevented further manufacture of intermediate **4**, the stock already prepared was successfully processed through to API with implementation of an in-line filtration to remove insoluble tantalum material prior to isolation. This was successful in reducing tantalum to an acceptable limit of less than 1 ppm in the API (see Table 2).[16] Beyond component construction, tantalum is commonly used to repair damaged glass-lined steel vessels widely prevalent in manufacturing units, therefore work is on-going to develop alternative conditions for the bromination of **3** so as not to limit future manufacturing options.[17]

Scale-up of C-H borylation to prepare 5. Key Suzuki-Miyaura coupling partner **5** was prepared using a slightly modified version of the process used to deliver previous campaigns,[18] which has been adapted from the literature procedure (Scheme 3).[19,20,21]



7 5

Scheme 3. Preparation of boronate ester **5** by C-H borylation

Commercially available 2-chloro-6-methyl-pyridine (**7**) was charged to a pre-heated solution of (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (0.25 mol%), DTBBP (0.50 mol%) and (bispinacolato)diboron (0.70 mol eq) in n-heptane (10.00 L/kg) at 50°C. The batch was then heated further to 80°C and held for approximately 16 h to effect the conversion to **5**. The

product was isolated by concentration of the batch and cooling to initiate crystallisation. This process was successfully run on 6 kg input scale with isolation of the product in 76% overall yield across two batches. An essential consideration for accommodation of this process was checking the venting capacity of the reactor to ensure safe removal of hydrogen. This stoichiometric by-product is generated either directly, or from hydrolysis of pinacolborane upon exposure to atmospheric moisture during isolation of **5** on an open filter.[22]

Assembly of AZD4635. During the previous manufacturing campaign, incomplete conversion was observed during the final assembly of the API via Suzuki-Miyaura coupling, resulting in a moderate 59% yield. The reason for this was never discerned and user trials of lab batches of **4** prepared using the previous procedure (assay by ^{1}H NMR >95% w/w) with the standard coupling conditions showed no issue with the quality of **4**. Having established confidence in the input quality of **4** and the cross-coupling conditions, attention turned to the isolation and ultimate quality of Suzuki-Miyaura product **6**.

The previous delivery for clinical studies had relied on scavenging to remove palladium residues to an appropriate level in the final isolated API. Investigation was undertaken to assess the extent of metal removal in the isolation of AZD4635 following the Suzuki-Miyaura reaction, achieved *via* solvent swap from THF to ethanol and subsequent crystallisation. This demonstrated that the majority of both palladium and iridium (and boron) was removed in the crystallisation liquors and subsequent displacement washes.[13]

The developed process transferred well to manufacture in the kilo-scale laboratory at 4 kg input scale of **4**. The conversion target was achieved and AZD4635 was isolated in 85% overall yield across two batches. Residual iridium levels were within the range seen in laboratory development batches, whilst palladium levels were slightly higher than expected, although they could be adequately controlled in the subsequent crystallisation.

Crystallisation of AZD4635.

Despite the observation of some metal removal during the initial isolation of AZD4635 after the Suzuki-Miyaura coupling, it was evident that an additional crystallisation step would be required to safely control both palladium and iridium to within the specification limit of no more than 100 ppm.[23] Of equal consideration, following the Suzuki-Miyaura coupling, AZD4635 was not isolated as a pure crystalline form in laboratory development batches. Therefore control of the desired Form 1 must be provided by the final crystallisation.

The general approach to crystallisation development adopted by AstraZeneca comprises three stages: (i) solubility screen and solvent selection; (ii) process outline; and (iii) process exploration.[24] Solubility screening can be carried out using a variety of small scale (*i.e.* <5 mL) methods and equipment, whereas stages (ii) and (iii) are typically performed in jacketed vessels with overhead agitation in order to provide confidence that the process will reliably transfer to manufacturing equipment (*i.e.* >20 L) with control of API quality attributes (*e.g.* form and purity).

The solubility screen for AZD4635 Form 1 was performed using primarily ICH Class 3 and some Class 2 solvents by equilibrium methods.[13,25] Solubility *vs.* temperature data was generated for the subset of solvents with a solubility within the range 5-25 mg/mL at 25°C using turbidity measurement.[26] These single solvent systems showed a shallow response, indicating that an anti-solvent crystallisation would be the most appropriate method to obtain sufficient recovery. AZD4635 Form 1 had a much greater solubility in DMSO (>100 mg/mL at 25°C) than the other studied solvents and was therefore selected to be used in the new process in combination with an anti-solvent exhibiting the least solubility: 2-propanol (1 mg/mL at 25°C).

The process outline was determined experimentally as follows: AZD4635 was dissolved in DMSO/2-propanol (2:1, v/v) at elevated temperature to enable transfer into the crystallizer through a screening/polishing filter, before cooling to induce supersaturation and seeding with Form 1 to initiate crystallisation. The batch was then held for an extended period of time until the saturation state was reached. This was identified and monitored in the laboratory using PAT, specifically FBRM®; this technology indicated when the total particle counts had reached a steady maximum, which should be related to the saturated (*i.e.* equilibrium) state. At this point additional 2-propanol was charged in a controlled manner to promote further crystallisation, subsequently followed by a ramped cool to the isolation temperature. This process reliably delivered Form 1 in the lab in approximately 80% yield. Further process

exploration work then focused on understanding robustness of the process parameters (*e.g.* seeding temperature) and consistency in the output quality, particularly metal rejection.

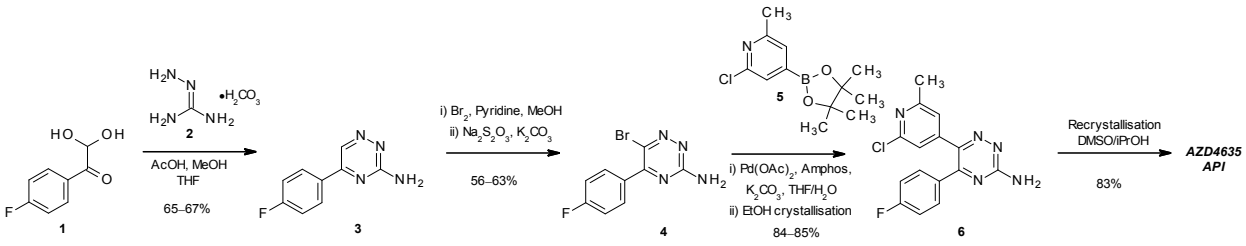
The crystallisation process developed transferred as expected to the kilo scale laboratory, where two input batches were combined to deliver 6.5 kg of AZD4635 Form 1 in 83% yield. Crucially, the crystallisation was also successful at reducing the levels of residual palladium and iridium to within specification without the requirement for scavenging (Table 2). Control of tantalum *via* in-line filtration during work-up of the Suzuki-Miyaura coupling was also confirmed by analysis of the output from that stage prior to the final crystallisation.

entry	Batch	Palladium (ppm)	Iridium (ppm)	Tantalum (ppm)
1	Input C660/1 (3.5 kg)	121	66	<1
2	Input C660/2 (4.4 kg)	129	69	<1
3	**Output C660/1**	**16**	**29**	**not analysed**

Table 2. Removal of metals *via* crystallisation of AZD4635

Campaign summary for AZD4635.

Overall, the campaign delivered 6.5 kg of AZD4635 prior to the suspension of further planned batches, due to observed corrosion of a tantalum component of a 100 L vessel during the bromination stage (Scheme 4). Stage 1 delivered a total of 26 kg of **3** in 65–67% yield, using a slightly modified procedure to that developed prior to in-licence. The subsequent bromination produced 15 kg of **4** in 56–63% yield, following significant re-design of the process to minimize potential operator exposure to bromine. Suzuki-Miyaura coupling of aryl bromide **4** and pinacol boronate ester **5**, followed by a modified isolation, gave 8 kg of AZD4635 in an improved 84-85% yield. Final stage crystallisation delivered the required form in 83% yield, while successfully reducing the levels of residual metals to within specification without the requirement for scavenging.



Scheme 4. Campaign summary.

CONCLUSION

AZD4635 was successfully prepared in 28% overall yield from **1**. The bromination of **3** to deliver cross-coupling partner **4** was successfully developed to introduce a quench of excess bromine whilst ensuring successful conversion in the key Suzuki-Miyaura coupling to prepare **6**. Pinacol boronate ester **5** was synthesized *via* scale-up of the iridium-mediated borylation of **7**. Both palladium and iridium metals were controlled through well-designed crystallisations of the API without the need for scavenging. Kilo-scale manufacture has highlighted that the combination of bromine and methanol is incompatible with reactor components constructed from tantalum at typical process concentrations. It is highly recommended that all possible combinations of reaction components are checked for compatibility with materials of construction and coupon tests are carried out where there is a lack of any existing data.

EXPERIMENTAL METHODS

General. All reactions were carried out in dry vessels under an atmosphere of dry nitrogen unless otherwise specified. All reagents and solvents were used as received without further purification unless specified.

*Synthesis of 5-(4-fluorophenyl)-1,2,4-triazin-3-amine (**3**).* 1-(4-Fluorophenyl)-2,2-dihydroxy-ethanone (**1**) (6.85 kg, 40.3 mol, 1.00 equiv), aminoguanidine bicarbonate (**2**) (6.03 kg, 44.3 mol, 1.10 equiv) and acetic acid (86.2 kg) were charged to a 100 L glass-lined reactor which had been purged with nitrogen. After addition, the mixture was heated to 73-77°C and then held for ≥20 h. The reaction mixture was cooled to 23-27°C over 3.5-4.5 h and then held for ≥1 h. The mixture was filtered and washed twice with methanol (10.8 kg). The cake was dried at 40°C under vacuum to constant weight to give 5-(4-fluorophenyl)-1,2,4-triazin-3-amine (**3**) as a grey powder (4.94 kg, 26.0 mol, 64.5%); ^{1}H NMR (400 MHz, DMSO-d6) δ 7.26 (br s, 2H), 7.37–7.43 (m, 2H), 8.23–8.26 (m, 2H) and 9.24 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d6) δ 164.38 (J = 249.9), 162.97, 153.84, 136.94, 130.50 (J = 2.9), 129.83 (J = 9.0), 116.15 (J = 21.9). Assay (QNMR) 95.0% w/w.

*Synthesis of 6-bromo-5-(4-fluorophenyl)-1,2,4-triazin-3-amine (**4**).* 5-(4-Fluorophenyl)-1,2,4-triazin-3-amine (**3**) (4.76 kg, 25.0 mol, 1.00 equiv), methanol (30.2 kg) and pyridine (5.94 kg, 75.1 mol, 3.00 equiv) were charged to a 100 L glass-lined reactor which had been purged with nitrogen. After addition the mixture was cooled to 3-7°C. Bromine (10.0 kg, 62.6 mol, 2.50 equiv) was then charged in 10 aliquots. The mixture was then warmed to to 23-27°C and held for ≥18 h. The reaction was considered complete when conversion of 5-(4-fluorophenyl)-1,2,4-triazin-3-amine (**3**) was ≥99%. The reaction mixture was cooled to 13-17°C. A solution of sodium thiosulfate (1.58 kg, 10.0 mol, 0.40 equiv) in water (15.2 kg) was added over ≥2 h keeping the batch temperature ≤20°C. A solution of potassium carbonate (4.22 kg, 30.5 mol, 1.22 equiv) in water (4.76 kg) was added over ≥2 h. The reaction mixture was cooled to -12 to -8°C over 0.5 - 1.5 h and then held for ≥4 h. The mixture was filtered and washed with pre-mixed methanol (7.84 kg) and water (9.91 kg) cooled to -12 to -8°C. The filter cake was then washed twice with water (19.0 kg) and twice with methanol (15.1 kg). The cake was dried at 40°C under vacuum to constant weight to give 6-bromo-5-(4-fluorophenyl)-1,2,4-triazin-3-amine (**4**) as an off-white powder (4.22 kg, 15.7 mol, 62.7%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.32–7.41 (m, 2H), 7.55 (s, 2H), 7.81–7.85 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d6) δ 115.29 (J = 21.9), 131.55 (J = 3.1), 131.81 (J = 9.0), 134.56, 157.39, 162.29, 163.37 (J = 248.8). Assay (QNMR) 95.6% w/w.

*Synthesis of 2-chloro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**5**).* (1,5-Cyclooctadiene)(methoxy)iridium(I) dimer (74.9 g, 113 mmol, 0.0025 equiv), 4,4'-di-tert-butyl-2,2'-bipyridine (60.7 g, 226 mmol, 0.0050 equiv), bis(pinacolato)diboron (8.03 kg, 31.6 mol, 0.70 equiv) and n-heptane (35.5 kg) were charged to a 100 L glass-lined reactor which had been purged with nitrogen. The reactor was purged three times with nitrogen, heated to 45-55°C with stirring and then held for 0.5-3 h. 2-Chloro-6-methyl-pyridine (**7**) (5.76 kg, 45.1 mol, 1.00 equiv) was then charged to the reactor, followed by a line wash with n-heptane (3.94 kg). The reactor was purged with nitrogen, heated to 75-85°C over 1-5 h then held for ≥16 h. The reaction mixture was cooled to 35-45°C over 1-5 h. The reaction was considered complete when conversion of 2-chloro-6-methyl-pyridine (**7**) was >95%. The batch was distilled under vacuum at 35-45°C until the concentration of *2*-chloro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**5**) was >225 mg/mL. The reaction mixture was cooled to 25-35°C over 1-3 h and then seeded if crystallisation had not already started. After holding for ≥1 h the reaction mixture was cooled to -15 to -10°C over 2-6 h. After holding for ≥1 h the mixture was filtered and washed twice with n-heptane (7.89 kg) cooled to -15 to -10°C. The cake was dried at 40°C under vacuum to constant weight to give 2-chloro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**5**) as an off-white powder (8.20 kg, 32.3 mol, 71.7%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.29 (s, 12H), 2.45 (s, 3H), 7.33 (s, 1H), 7.42 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.6, 84.7, 125.3, 126.8, 141.0, 149.5, 159.1; Assay (QNMR) 95.7% w/w.

*Synthesis of 6-(2-chloro-6-methylpyridin-4-yl)-5-(4-fluorophenyl)-1,2,4-triazin-3-amine (**6**).* 6-Bromo-5-(4-fluorophenyl)-1,2,4-triazin-3-amine (**4**) (4.37 kg, 16.2 mol, 1.00 equiv), 2-chloro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**5**) (4.11 kg, 16.2 mol, 1.00 equiv), potassium carbonate (3.36 kg, 24.3 mol, 1.50 equiv), 4-(di-*tert*-butylphosphino)-N,N-dimethylaniline (215 g, 810 mmol, 0.05 equiv), tetrahydrofuran (34.8 kg), water (17.5 kg) and palladium(II) acetate (72.8 g, 324 mmol, 0.02 equiv) were charged to a 100 L glass-lined reactor which had been purged with nitrogen. The reactor was purged three times with nitrogen, heating to 62-66°C with stirring and then held for 3-18 h. The reaction was considered complete when conversion of 6-bromo-5-(4-fluorophenyl)-1,2,4-triazin-3-amine (**4**) was >97% and conversion of 2-chloro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**5**) was >97%. The reaction mixture was cooled to 45-55°C and then filtered to remove insoluble tantalum residues. The aqueous phase was separated and then the organic phase was distilled under vacuum at 45-55°C to remove 21.0 L of solvent. Ethanol (34.9 L) was charged at such a rate that the batch temperature remained within the range 45-55°C. The batch was then distilled under vacuum at 45-55°C to remove 26.0 L of solvent. The reaction mixture was cooled to -2 to 2°C over 2-4 h and then held for ≥1 h. The mixture was filtered and washed with methyl *tert*-butyl ether (6.48 kg), twice with water (8.73 kg) and twice with ethanol (6.90 kg). The cake was dried at 40°C under vacuum to constant weight to give 6-(2-chloro-6-methylpyridin-4-yl)-5-(4-fluorophenyl)-1,2,4-triazin-3-amine as a white powder (4.32 kg, 13.7 mol, 84.5%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.41 (s, 3H), 7.16 (s, 1H), 7.24-7.31 (m, 3H), 7.4-7.51 (m, 2H), 7.71 (br s, 2H); ^{13}C NMR (101 MHz, DMSO-d6) δ 163.25 (*J* = 248.6), 161.87, 159.07, 155.89, 149.10, 147.86, 145.34, 129.96 - 132.28, 121.92, 120.60, 115.48 (*J* = 22.0), 23.56.Assay (QNMR) 98.3% w/w.

*Recrystallisation of 6-(2-chloro-6-methylpyridin-4-yl)-5-(4-fluorophenyl)-1,2,4-triazin-3-amine (**6**).* 6-(2-Chloro-6-methylpyridin-4-yl)-5-(4-fluorophenyl)-1,2,4-triazin-3-amine (**6**) (7.87 kg, 24.9 mol, 1.00 equiv), dimethyl sulfoxide (21.8 kg) and 2-propanol (7.80 kg) were charged to a 100 L glass-lined reactor which had been purged with nitrogen (dissolving vessel). The mixture was heated to 73-77°C and then held for ≥1 h to ensure dissolution. The solution was cooled to 70°C and then screened through a 5 μm filter into a pre-heated 100 L glass-lined reactor (crystallising vessel) which had been purged with nitrogen and then the batch temperature was adjusted as appropriate to 68-72°C. Dimethyl sulfoxide (1.73 kg) and 2-propanol (619 g) were charged to the dissolving vessel, heated to 70°C and then screened through the 5 μm filter into the crystallising vessel as a line wash. The solution was cooled to 49-53°C over ≥30 min and then 6-(2-chloro-6-methylpyridin-4-yl)-5-(4-fluorophenyl)-1,2,4-triazin-3-amine (**6**) seed was charged (31.5 g, 0.04 g/g). The mixture was held for ≥5 h to establish crystallisation and then 2-propanol (41.3 kg) was charged over ≥5 h. The mixture was cooled to 8-12°C over ≥2 h and then held for ≥5 h. The mixture was filtered and washed with pre-mixed dimethyl sulfoxide (4.33 kg) and 2-propanol (9.28 kg) that had been screened through a 5 μm filter into the crystallising vessel and then cooled to 8-12°C. The cake was washed with 2-propanol (12.4 kg) that had been screened through a 5 μm filter into the

crystallising vessel and then cooled to 3-7°C. The cake was dried at 40°C under vacuum to constant weight to give 6-(2-chloro-6-methylpyridin-4-yl)-5-(4-fluorophenyl)-1,2,4-triazin-3-amine as a white powder (6.51 kg, 20.6 mol, 82.7%; QNMR (100% w/w).

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ABBREVIATIONS

$A_{2A}R$, adenosine A_{2A} receptor; API, active pharmaceutical ingredient; DTBPP, 4,4'-di-*tert*-butyl-2,2'-bipyridine; Amphos, 4-(di-*tert*-butylphosphino)-*N*,*N*-dimethylaniline; PAT, process analytical technology; PTFE, polytetrafluoroethylene; ICP-MS, inductively coupled plasma mass spectrometry; ICP-OES, inductively coupled plasma optical emission spectrometry; FBRM®, Focused Beam Reflectance Measurement®

ASSOCIATED CONTENT

Supporting Information

pH profile during quench of bromination; solubility data for **4** and **4**.HBr; proposed mass balance for bromination and quench; purity data for **4** during cake washing; Pd, Ir and B content during initial isolation of **6**; solubility data for AZD4635 Form 1; ^{1}H and ^{13}C NMR spectra for **3**, **4**, **5**, and **6**.

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6. We believe an excess of bromine is required due to the competitive formation of pyridinium hydrobromide perbromide (pyridine.HBr_3). Pyridine.HBr_3 was found to be ineffective in the bromination of **3**. See Moon, M. P.; Crouch, D. R.; Pyridinium Hydrobromide Perbromide. Encyclopedia of Reagents for Organic Synthesis, **2008**

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8. Analysis by HPLC of the solid and filtrate samples independently, showed that the remaining starting material **3** is predominantly out of solution at this stage of the reaction

9. The overall equation for reduction of bromine by thiosulfate is

   $Na_2S_2O_3 + 4\ Br_2 + 5H_2O \rightarrow 2H_2SO_4 + 6HBr + 2NaBr$

10. We did not fully characterise the salt counterion of **4** in solution and cannot rule out formation of the hydrogen sulfate salt of **4**. See the supporting information for further details

11. This material contained approximately 5–10% of the salt form of **4** with the remaining mass balance unaccounted for

12. We did not attempt to characterize or quantify the residual inorganic content in the low assay batch. Tetrathionate ($S_4O_6^{2-}$) has been reported to degrade to S_8 under acidic conditions which may have further effected the subsequent Suzuki-Miyaura reaction. For example see Xiang, Y.; Caron, P-Y.; Lillie, B. M.; Vaidyanathan, R. Sulfur Contamination Due to Quenching of Halogenation Reactions with Sodium Thiosulfate: Resolution of Process Problems via Improved Quench Protocols. *Org. Process Res. Dev.,* **2008**, *12* (1), 116–119

13. See the supporting information for further details

14. We did not characterize or confirm the structure of the contaminating tantalum species

15. *Dechema-Werkstoff-Tabelle "Methanol" (Corrosion data sheets "Methanol") (in German)*; Dechema, D-6000: Frankfurt am Main, **1961**. In addition to the effect of water, further investigation would be required to unambiguously rule out the role of substrate **3**, pyridine, and/or the reaction solution post quench in effecting the observed corrosion

16. An acceptable limit was assigned based on a conservative estimate of the Permitted Daily Exposure for tantalum and the maximum clinical dose of API

17. During materials of construction assessment, no issues were flagged for glass-lined vessels, however Hastelloy was flagged as incompatible due to HBr generation. Subsequent coupon testing has confirmed incompatibility of the reaction mixture with Hastelloy C-22 and C-276; PTFE showed no issues.

18. n-Heptane replaced hexane or THF in the literature procedures to facilitate isolation of **5**. The two-stage heating process, with addition of the substrate **7** at 45-55°C, had been employed in previous manufacture of **5** prior to in-licence and was found to be robust in our hands. The process was modified to provide greater control in the crystallisation of **5**.

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22. The risk of potential static build-up in a non-conducting solvent such as n-heptane was mitigated by: (i) ensuring oxygen content was below the flammable range of solvent vapour/oxygen composition (<5% oxygen); (ii) glass-lined vessels were earthed using earthing plugs; (iii) avoiding vigorous agitation of non-conducting solvents; (iv) reducing addition rate when charging non-conducting solvents.

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