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Technical Notes

Trouble with Potassium Carbonate and Centrifuges: Mass Transfer and Scale-Up Effects in the Manufacture of ZD9331 POM Quinacetate

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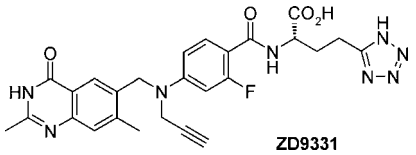
Abstract:

Manufacture of ZD9331 pivaloyloxymethyl (POM) quinacetate, was progressively scaled up from large-scale lab to pilot plant to full-scale production. The specific surface area of the potassium carbonate used for the deprotonation was found to be critical as successive increases in the mass transfer area were counteracted by the reduced mass transfer efficiency, linked to the reactor size and impeller effectiveness. Furthermore, a change from a pressure filter to a centrifuge meant that the washing efficiency was similarly limited by mass transfer, with the rate of dissolution of the undesired regioisomer on the centrifuge being too low for the shorter wash time. These problems were overcome, resulting in two successful manufacturing campaigns with over 1 tonne of POM quinacetate produced well within specification in eight batches.

Introduction

ZD9331 is a thymidylate synthase inhibitor[1,2] which originated from a collaboration between Zeneca, the Institute of Cancer Research (Sutton, UK), and BTG International Limited (BTG). AstraZeneca developed ZD9331 for the treatment of a range of solid tumours[2] including advanced[3,4] and refractory solid tumours.[5−7] These included potential treatments for advanced breast cancer,[7] colorectal cancer,[4] gastric cancer,[8] nonsmall cell lung cancer,[7] ovarian cancer,[2,7,9] and pancreatic cancer.[10] In addition to providing a potential treatment for a number of poorly treated cancers, ZD9331 also offered a benign side effect profile which could have helped with patient tolerance during the therapeutic regime.[6−8] BTG owns the rights to ZD9331 and are performing clinical trials additional to those listed above.



ZD9331

Previous manufacturing campaigns of ZD9331 had been conducted at Macclesfield. Campaign 4 had delivered 23 kg which was formulated for phase 3 clinical trials whilst the phase 2B trials were ongoing. During this time, a much improved route to the key intermediate quinacetate·HCl was developed[11,12] which was taken on trial in the Macclesfield large-scale lab. This delivered 1.5 kg of bulk drug as campaign 5A. Due to this late change, a pilot-plant campaign (5B) was conducted to provide bridging toxicity cover in case of an altered impurity profile and to assess potential scale-up issues with the new route. This campaign delivered 67 kg of bulk drug (Table 1).

Due to plant capacity constraints within ex-Zeneca at the time, the final stages of the manufacturing campaigns were to be out-sourced to contractors, specifically those who could contain cytotoxic products within their facilities. DOTTIKON EXCLUSIVE SYNTHESIS AG was chosen as the contractor for four of the last six steps[13] of full-scale manufacture (400−600 kg) which would include the technology transfer (TT)

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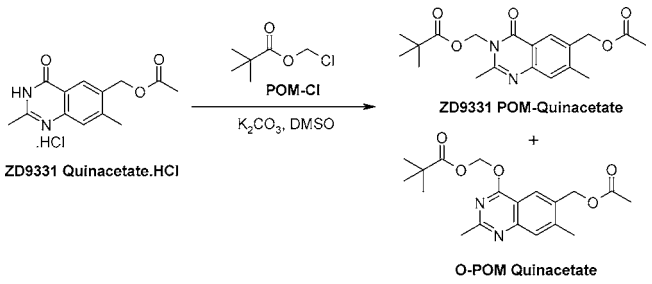
Table 1

campaign	quantity of bulk drug (kg)	site	notes
4	23	AZ pilot plant	old route
5A	1.5	AZ large-scale lab	new route trial
5B	67	AZ pilot plant	AZ pilot trial
pilot	52[a]	DOTTIKON pilot plant	DOTTIKON pilot trial
establishment	610[a]	DOTTIKON plant 10	full scale

[a] POM quin acid delivered.

Scheme 1



and establishment campaigns. Given the limited experience of scale-up of the new route, DOTTIKON ES were keen to get manufacturing experience of all stages and decided to run a pilot-scale TT campaign on a scale similar to that of campaign 5B. The first stage of this route was pivaloyloxymethyl (POM) quinacetate (Scheme 1).

This note discusses the difficulty of adjusting to pilot- and full-scale plant constraints during technology transfer between sites and within sites, even when key parameters are identified in advance and process adjustments are incorporated. In particular, mass transfer issues are particularly sensitive to equipment characteristics and process scale. Two such problems on the POM quinacetate process and their resolution in time and to quality, within the constraints of a TT/establishment campaign, are discussed.

Results and Discussion

The Initial Process. The POM quinacetate process used for campaigns 5A and 5B was slightly modified prior to transfer to DOTTIKON ES, the exact details of which are recorded in the Experimental Section as the initial lab process. In summary, quinacetate·HCl was slurried in DMSO with 2.6 equiv of K_2CO_3 for 4 h at 50 °C to neutralize the HCl salt and effect deprotonation. Pivaloyloxymethyl chloride (POM-Cl) was added over a period of 2.5 h at 30 °C, from which a 3:1 ratio of the N- to O-protected POM quinacetates was produced. This ratio had resisted improvements in selectivity despite much work.[14] A water/isohexane drown-out precipitated the mixed products which were isolated on a pressure filter and copiously washed with water to remove the high inorganic content. Further slurry washing with 2-propanol (IPA) removed the bulk of the undesired O-POM quinacetate down to <1% in all cases. The overall yield of desired POM quinacetate was typically 63%.

In view of the heterogeneous nature of this reaction, some investigations had already been conducted on the specific surface area (SSA) of the K_2CO_3 used. This had shown on the lab scale that K_2CO_3 with less than 1200 cm^2/g SSA would fail to deprotonate fully, leading to an incomplete reaction. Reagent of above 1600 cm^2/g SSA was set as a tentative minimum specification for future batches.[15]

The Pilot-Plant Campaign. DOTTIKON ES planned to run four batches of POM quinacetate in their pilot plant based on 25 kg of quinacetate·HCl input. Due to raw material delivery issues and tight plant scheduling, the desired grade of K_2CO_3 was not available for the first batch. A lower grade (600 cm^2/g SSA) batch already on site was used instead, resulting in almost no desired reaction. After a 72 h hold at ambient temperature, only ~40% deprotonation had occurred as determined by lab user trial of a portion removed from the batch. After this time, a second full charge (2.6 equivalents) of higher-grade K_2CO_3 (2700 cm^2/g SSA) was added to the batch in addition, and processing continued as normal from the 4 h deprotonation hold time at 50 °C. This batch was successfully rescued with no impact on yield or quality, despite a much extended hold time (3 days) and a double charge of K_2CO_3. The second batch also used the higher-grade K_2CO_3 input, but the delivery had fallen short, leaving K_2CO_3 of only 1200 cm^2/g SSA for the third and fourth batches. As this was a non-GMP pilot trial purely for scale-up experience and earlier lab work suggested K_2CO_3 of this grade should be adequate, a calculated risk was taken for the final two batches, both of which were successful. An overall yield of 63% was achieved with excellent quality of 98.5% for the combined four batches.[16] The O-POM quinacetate impurity was seen at 0.3%, and inorganics were well within specification, despite the necessary overcharge on batch 1.

The Establishment Campaign. With a successful pilot campaign showing that K_2CO_3 of lower SSA (1200 cm^2/g) than the proposed specification (1600 cm^2/g SSA) could be used, few problems were anticipated in scaling up 7-fold into a 10,000-L reactor (DOTTIKON ES Plant 10; 166 kg input of quinacetate·HCl). All batches would use the high grade K_2CO_3 with SSA of 2700 cm^2/g now that availability had been assured before the start of manufacture. However, the first batch was slow to deprotonate as determined by lab user trial. Although the grade of K_2CO_3 was correct, it was soon realised that the low fill volume in the larger reactor did not cover the second mid-level impeller. This was largely due to the big difference required between the reaction volume and the drown-out volume. A large drown-out volume required a large reactor but with a low minimum stirrable volume (MSV) to accommodate the initially small

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(16) The four pilot batches were combined into a single batch for convenience due to the size of the dryer. Analysis of individual batch 1 prior to drying showed that it would comfortably have passed the specification for O-POM quinacetate and inorganic content.

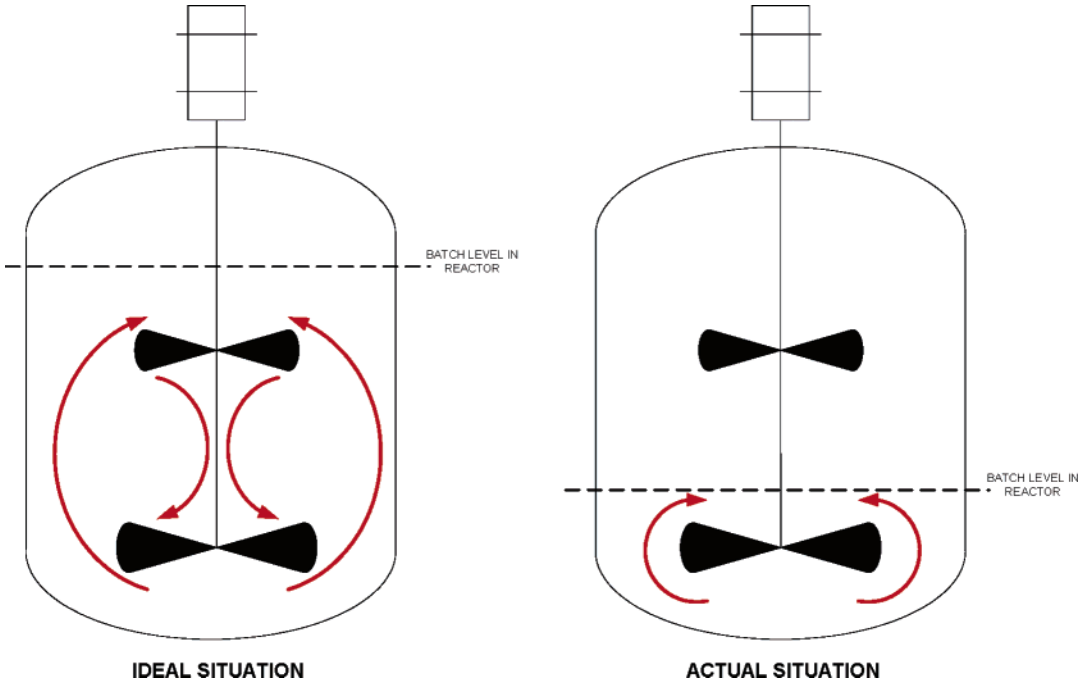
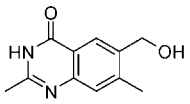


Figure 1.

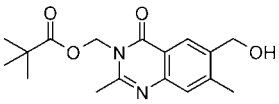
reaction volume. The Plant 10 reactor was ideal for these awkward requirements, and the provision of a mid-level impeller was seen as advantageous. Unfortunately, the agitation requirements were more demanding for this process; consequently, agitation was thought to be much less efficient on scale-up (see ref 17 for a discussion of this type of issue). This was observed with the dense K_2CO_3 being radially mixed at the bottom of the reactor and the bulk of the material not being suspended, rather than being axially mixed by the combined action of the low and mid-level impellers (Figure 1). Thus, the intimate mixing of K_2CO_3 with the quinacetate·HCl was not achieved, and hence, deprotonation was slower than expected, despite the high SSA (2700 cm^2/g).

Impeller agitators can handle a wide viscosity range, typically operating at 60−150 rpm. Normal operating speed is 90 rpm, but this stage was initially performed at 75 rpm on scale. In high-viscosity applications, this type of agitator may be used successfully without baffles, but at lower viscosities, baffles are essential to convert the radial flow into an axial component and hence provide increased agitation intensity. In this case, the axial flow would normally be provided by the mid-mounted impeller if the solvent level in the reactor was high enough. The angle of this impeller would force material down towards the bottom-mounted impeller and ideally increase the agitation intensity sufficiently to suspend the K_2CO_3.

Whilst various modeling studies and calculations could have been conducted to investigate this problem, including an assessment of the Zweitering off-bottom criterion to determine the minimum suspension speed,[18] an immediate practical solution was required. No other plant was available, and the batch size could not be sufficiently increased to cover the mid-level impeller during the reaction phase due to the large drown-out volume required later. However, by adding half the charge (1.3 equiv) of additional K_2CO_3 with an even higher SSA (4800 cm^2/g), and increasing the agitation rate from 75 to 90 rpm (at which rate suspension of the solids was observed), the first batch was completely deprotonated and the reaction proceeded as normal. Fortunately, there was no significant increase in hydrolysis of the acetate group from quinacetate or POM quinacetate to quinalcohol or POM quinalcohol respectively, even on holding the alkaline slurry at 50 °C.



Quinalcohol



POM-Quinalcohol

Centrifuge versus Pressure Filter. Although the reaction was successful, the isolation now proved problematic. All previous manufactures had isolated POM quinacetate using pressure filters, including the DOTTIKON ES pilot trial. The crude product cake was slurry washed on the filter with two charges of IPA, isolating the damp solid between each time. These washes were very efficient at removing O-POM quinacetate by dissolving it out of the product cake, such that less than 1% was typically left from the initial 3:1 mixture with the desired POM quinacetate. However, a late change in plant accommodation had necessitated the use of

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reactors linked only to centrifuges. Centrifuges are very efficient at removing solvent from the product cake by displacement, but they are much less efficient for slurry washes because the residence time of the wash solvent in the crude cake is often too short. Due to the large drown-out volume, each batch was discharged to the centrifuge in two portions. When so washed, the first half of batch 1 had a high level of POM quinacetate of 3.36%, although within the specification of 4% w/w, but the second half failed at 6.43%. The water wash had already been increased to account for the increased K_2CO_3 charge, and consequently, the inorganic content of both portions was well within specification.

By the time these results had been obtained, batch 2 was already underway using the very high grade SSA K_2CO_3 (4800 cm^2/g), and proceeded to completion with no issues. The IPA washes were increased from two to three 3-vol washes to help improve removal of the undesired regioisomer, and the single water wash was also replaced by two 3-vol washes to pre-empt less efficient inorganic removal. When combined, both half-batch portions of batch 2 had an O-POM quinacetate level of 0.91%, and inorganics were well within specification. However, despite these changes, batch 3 also failed the O-POM quinacetate specification at 7.20% for its second isolated portion when using the centrifuge (the first portion had only 1.58%).[19] Since this was the establishment campaign and there was a requirement to reliably manufacture consecutive batches within the specified operating limits, the manufacture was temporarily halted, and alternatives were considered.

The ideal solution would have been to use a pressure filter, but this was not available on the plant in use. DOTTIKON ES did not have a portable pressure filter which was big enough to accommodate such large batch volumes, nor could one be rented in a short time. Even so, this would have resulted in many multiple isolations per batch. However, the drown-out vessel itself could be used as a surrogate pressure filter for agitation purposes. The low MSV of the Plant 10 vessel was again beneficial, as the IPA slurry wash could still be agitated even though it was very concentrated. Batch 4 was started, and although deprotonation was slow, requiring 12.5 h, lab use tests indicated that the deprotonation was proceeding at a worthwhile rate. After the aqueous drown-out, the batch was isolated as before on the centrifuge in two portions, but applying only the aqueous washes. The two damp portions were recharged to the IPA-rinsed drown-out vessel and stirred with IPA (5 vols) for 2−2.5 h to mimic slurry washing on a pressure filter. This provided time and good mixing to dissolve the O-POM quinacetate. Re-isolation of the damp product was again achieved on the centrifuge. A small, second IPA displacement wash in the centrifuge was followed by two isohexane displacement washes to aid drying, also conducted in the centrifuge, to give the product POM quinacetate of excellent quality (0.13% O-POM quinacetate).

(19) An analysis of the damp weights discharged from the centrifuge for both portions of batches 1−3 indicated that the second portion was significantly heavier than the first one, probably because of discharging a slurry. Consequently, the second portion contained a greater mass of O-POM quinacetate that was subjected to the same wash volume as the first portion, hence, the probable cause of the failure. The fact that both portions of batch 2 passed specification indicates the wash process was not far from successful conditions, but it would not have been very robust.

Table 2

batch	strength % w/w	O-POM quinacetate % w/w	largest other impurity % w/w	total all impurities % w/w
specification	>90%	<4	<1	<10
1a	95.7	3.36	0.37	3.72
1b	93.9	6.43[a]	0.27	6.70
2[b]	98.7	0.91	0.17	1.28
3a	96.1	1.58	0.56	2.65
3b	91.7	7.20[a]	0.48	7.77
4	98.6	0.13	0.07	1.39
5	99.1	0.15	0.09	0.88
6	100.1	0.12	0.08	0.20
7	100.1	0.12	0.08	0.20
8	99.1	0.15	0.12	0.90
1 re-treat[b]	99.5	0.43	0.18	0.61
3 re-treat[b]	99.0	0.11	0.13	1.02

[a] Out of specification. [b] Portions combined as a single batch.

The Final Process

With these changes made to allow for the reduced effective agitation on full scale and the lack of a pressure filter, batches 5−8 were run using the final process as described in the Experimental Section. The only other concession made was to increase the deprotonation time from 4 to 8 h and rely on a validated in-process test for complete deprotonation. However, no further problems were encountered, and batches 5−8 gave product of excellent quality as can be seen from the results in Table 2. Furthermore, both failed batches 1 and 3 were successfully reprocessed by applying the IPA slurry washing technique in the drown-out vessel as a separate retreatment process.[20] This gave POM quinacetate of comparable quality with only a modest reduction in yield.

Conclusions

Even though we were aware of the potential issues with this stage and had preceded it with laboratory studies, technology transfer of this manufacture exposed the vulnerability of heterogeneous reactions to mixing issues on scale-up and the importance of considering all aspects of mass transfer-limited operations. Successive increases in the reagent surface area were counteracted by the reduced mass transfer efficiency (linked to the reactor size and impeller effectiveness). The washing efficiency was similarly limited by mass transfer, with the rate of dissolution of the undesired O-POM quinacetate on the centrifuge being too low for the shorter wash time. All these problems were readily solved, and two manufacturing campaigns were successfully run on scale at the contractor. In total, just over 1 tonne of POM quinacetate was produced in eight batches with an overall yield of 61%. Two failed batches were easily and success-

(20) Both portions of each batch were reprocessed together to simplify the batch histories, even though their first portions had been within specification.

fully retreated. Overall quality was >99% with O-POM quinacetate levels typically at ~0.1%, and with all other quality aspects (including inorganics) well within specification.

Epilogue

The three other stages performed at DOTTIKON ES all proceeded on both pilot- and full-scale manufacture without issue, despite some high batch numbers and technical challenges. This proved to be a highly successful TT/establishment campaign that delivered a high-quality intermediate (POM quin acid) above both the target quantity and quality, which in turn supported the TT/validation campaign for the final two stages at the other contractor.

Experimental Section

HPLC Method. Reaction mixtures and products were analysed by reverse phase HPLC on Hewlett-Packard 1050 or 1100 instruments using the following isocratic method. Column, Hichrom RPB, 250 mm × 4.6 mm i.d.; eluent, 1:1 acetonitrile:aqueous buffer (made up of 1.0 g $(NH_4)_2HPO_4$ dissolved in water (500 mL) and adjusted to pH 7 with concentrated phosphoric acid); wavelength 235 nm; flow rate 1.5 mL/min; injection volume 10 μL; run time 30 min. Typical retention times were as follows, with relative retention times (RRT) in parentheses: quinacetate, 2.12 (0.30); POM quinalcohol, 3.40 (0.48); POM quinacetate, 7.08 (1.00); O-POM quinacetate, 12.68 (1.79) min. The longest running of several very minor impurities had an RRT of 3.30. Reaction samples were made up from 200 μL of liquors, and standards from 10 to 20 mg dried material, in 100 mL of diluent composed of 1:1 acetonitrile:water.

SSA Measurements. SSAs were determined by a Fisher subsieve analyser, which measures the back pressure of a gas flow through a compacted sample and converts this reading to a porosity measurement with a related SSA value. Analytical test sieves were also investigated at the time but found to be unusable after the first analysis due to the hygroscopic nature of K_2CO_3.

Initial Production Process (Laboratory Scale). Potassium carbonate (13.34 g, 2.60 mol equiv) and dimethyl sulfoxide (105 mL, 10 vols) were charged to a nitrogen-purged reactor and heated to 50 °C with mechanical agitation. ZD9331 quinacetate·HCl (10.5 g, 1.0 mol equiv) was charged in three equal portions (3.5 g each) at 1 h intervals. (There is a 1 K exotherm on each addition at this scale, but no noticeable change of form or evolution of CO_2). The reaction mixture was held at 50 °C for 4 h with continued agitation, before cooling to 30 °C. Chloromethyl pivalate (7.45 mL, 1.35 mol equiv) was added over 2.5 h at 30 °C. (A stable foam is formed during this addition; on large scale, the agitation rate is reduced to minimize its formation). The reaction mixture was stirred at 30 °C for 3.5 h or until less than 1% quinacetate remained. The reaction mixture was transferred over typically 60 min to a second reactor containing a stirred mixture of deionised water (136.5 mL, 13.0 vols) and isohexane (84. 0 mL, 8.0 vols) at 30 °C. (The drown-out is exothermic with an adiabatic temperature rise of 21 K. The final reaction temperature was 43 °C in this case. The addition time is not critical and precipitation of the product is instantaneous). The first reactor was rinsed with dimethyl sulfoxide (5.3 mL, 0.5 vols) and transferred by line wash to the drown-out reactor. The combined reaction mixture was stirred for 30 min before the product was isolated by filtration on a glass sinter in the lab (a centrifuge was used on both plants). The filter cake was slurry washed with deionised water (42 mL, 4.0 vols each) at 20 °C and pulled dry, then washed by displacement with IPA (21 mL, 2.0 vols) and pulled dry. The filter cake was slurry washed with further IPA (42 mL, 4.0 vols) and allowed to soak for 15 min before deliquoring. Finally, the filter cake was washed by displacement with isohexane (21 mL, 4.0 vols), deliquored, discharged and dried at 50 °C to constant weight in a vacuum oven to yield the product ZD9331 POM quinacetate as a fine white solid (8.0 g, 60%). HPLC purity typically 98−100% w/w.

Final Production Process (Laboratory Scale). Potassium carbonate (13.34 g, 2.60 mol equiv) and dimethyl sulfoxide (105 mL, 10 vols) were charged to a nitrogen-purged reactor and heated to 50 °C with mechanical agitation. ZD9331 quinacetate·HCl (10.5 g, 1.0 mol equiv) was charged in three equal portions (3.5 g each) at 1 h intervals. (There is a 1 K exotherm on each addition at this scale, but no noticeable change of form or evolution of CO_2). The reaction mixture was held at 50 °C for 8 h with continued agitation, before cooling to 30 °C. Chloromethyl pivalate (7.45 mL, 1.35 mol equiv) was added over 2.5 h at 30 °C. (A stable foam is formed during this addition; on large scale, the agitation rate is reduced to minimize its formation). The reaction mixture was stirred at 30 °C for 3.5 h or until less than 2% quinacetate remains. The reaction mixture was transferred over typically 60 min to a second reactor containing a stirred mixture of water (136.5 mL, 13.0 vols) and isohexane (84. 0 mL, 8.0 vols) at 10−15 °C. (The drown-out is exothermic with an adiabatic temperature rise of 21 K. The final reaction temperature was 32 °C in this case, which is ideal for the next step since it helps to dissolve the inorganics. The addition time is not critical, and precipitation of the product is instantaneous.) The first reactor was rinsed with dimethyl sulfoxide (5.3 mL, 0.5 vols) and transferred by line wash to the drown-out reactor. The combined reaction mixture was stirred for 30 min before the product was isolated by filtration on a glass sinter in the lab (a centrifuge is used in the plant). The filter cake was washed by displacement at 20 °C three times with deionised water (31.5 mL, 3.0 vols each). (A small IPA wash may follow on plant-scale operation to suppress microbial growth if short-term storage of the damp product is required). The wet product cake was discharged from the filter or centrifuge and recharged to a clean nitrogen-purged reactor. IPA (52.5 mL, 5.0 vols) was charged and the resulting slurry stirred at 20−25 °C for 2.5 h before isolation of the product as before. The reactor was rinsed with IPA (8.4 mL, 0.8 vols) and used to wash the filter cake by displacement. The filter cake was washed by displacement twice with isohexane (21 mL, 2.0 vols each) at 20 °C, discharged and dried at 50 °C to constant

weight in a vacuum oven to yield the product ZD9331 POM quinacetate as a fine white solid (8.5 g, 63%). HPLC purity typically 98−100% w/w.

Acknowledgment

We are grateful to BTG International Limited and DOTTIKON EXCLUSIVE SYNTHESIS AG for permission to disclose this research. This stage was originally developed by Richard Wisedale and John Horbury (AstraZeneca, PR&D, Avlon). Our research developed on their initial investigations of K_2CO_3 particle size (with Claire Ancell), which has since been followed up by Adrian Clarke and Stuart Williams (AstraZeneca, PR&D, Avlon).

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