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Technical Note

Chemical Development of ZD9331: Synthesis of a Bromomethylquinazolinone Avoiding a Nonselective Radical Bromination

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Abstract:

An efficient regiospecific synthesis of ZD9331 Pivaloyloxymethyl (POM) Bromide (4) has been accomplished via ZD9331 Quinacetate HCl (15) avoiding a nonselective bromination. The original route used a radical bromination on a substrate with three methyl groups, which generated a range of bromomethyl derived compounds that carried through to the final active pharmaceutical ingredient (API). A strategy, based on the Zinin reaction, was developed to synthesize the required bromomethyl compound in a regioselective manner. This approach was successfully scaled to manufacture a tonne of material.

Introduction

ZD9331 (**1**) (Figure 1) is a nonpolyglutamable thymidalate synthase (TS) inhibitor, for the potential treatment of gastric cancer and solid tumors. Raltitrexed (**2**) (Figure 1) had already been launched as a TS inhibitor for the treatment of colorectal cancer; ZD9331 has a range of advantages over Raltitrexed, centered mainly around increased potency, by virtue of a more effective transport mechanism to solid tumors. ZD9331 originated from a collaboration between Zeneca, the Institute of Cancer Research (Sutton, UK), and BTG International Limited (BTG).[1] Details of ZD9331's pharmacological profile are cited in a previous paper.[2]

A particular problem with the original medicinal chemistry route[3] (Scheme 1) was a radical bromination of ZD9331 POM Quinazolinone (**3**), predominantly giving the bromomethyl intermediate **4**; but as there are three positions capable of undergoing a free radical bromination, a mixture of regioisomeric compounds was isolated after the subsequent alkylation of ZD9331 Propargylaniline (**8**) (Scheme 2). ZD9331 Pyrroloquinazolinone (**17**), derived from the dibrominated intermediate **6**, was particularly problematic as it is highly crystalline; hence its concentration increased through subsequent processing. As the final active pharmaceutical ingredient (API) is amorphous, control of **17** in the isolated API was extremely difficult in early scale-up. No effective method to separate it from ZD9331 POM Quinazolinone ester (**7**) could be devised without recourse to chromatography. The regioisomer derived from intermediate **5** was lost to the mother liquors upon isolation of **7**. The design of an alternative synthetic strategy was constrained by the fact that ZD9331 had already been subject to extensive toxicological screening, so any new impurities would have to be qualified by further toxicity testing; any new approach would have to meet this demanding constraint.

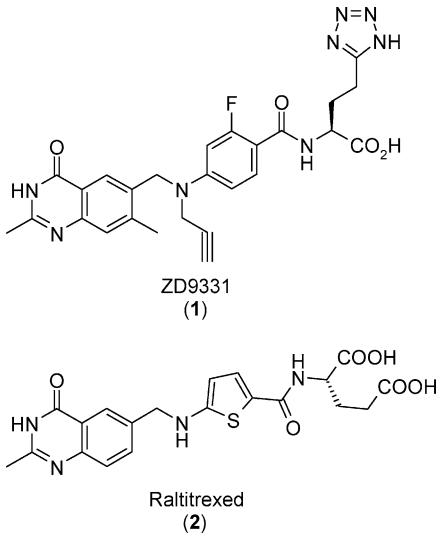

Figure 1.

Results and Discussion

Retrosynthetic analysis of the ZD9331 POM Bromide (**4**) (Scheme 3) identified that the methyl group, requiring activation as an electrophile, was para to an amino group, potentially accessed by reduction of a nitro group. Such an arrangement is set up to use a known feature of the Zinin reaction, first published in 1842, where a nitro group can be reduced, and concomitantly a para or ortho methyl group is oxidized to an aldehyde in one step using sodium polysulfide in aqueous sodium hydroxide.[4,5] Compound **9** was prepared

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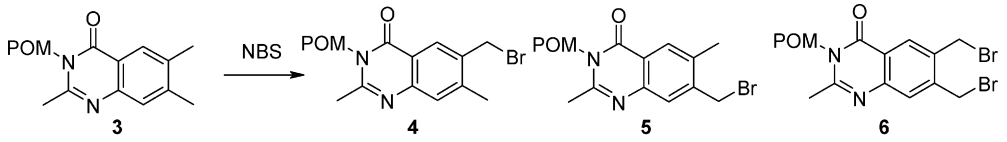
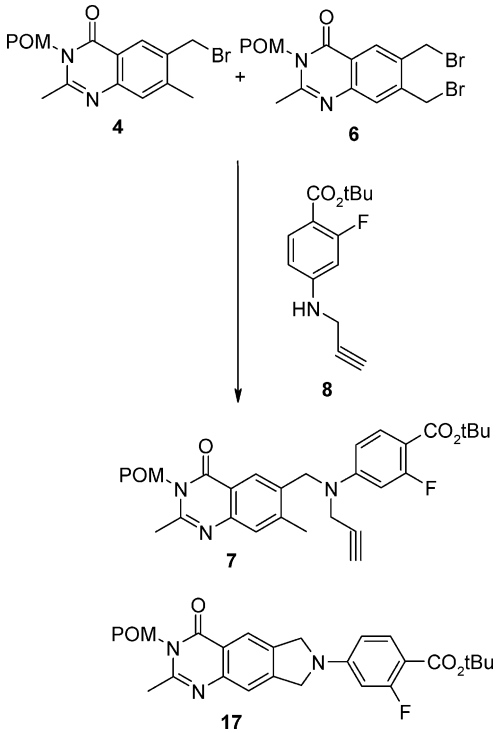
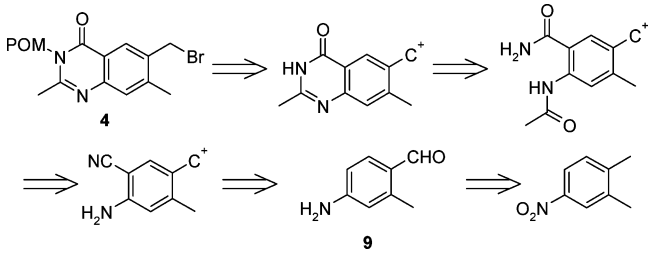
Scheme 1



Scheme 2

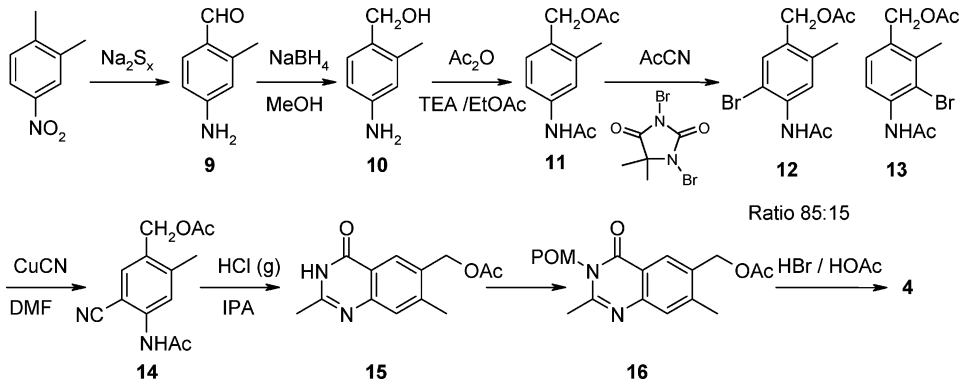


Scheme 3



using the procedure well exemplified in the literature;[6] an insight into the mechanism of the reaction is given in the paper by Yoshiro Ogata et al.[7] The challenge was to elaborate **9** through to the desired ZD9331 POM Bromide (**4**). The synthesis was designed by adapting the previous strategy of bromination and then functional group interconversion to a nitrile, followed by ring closure under acidic conditions to give the quinazolinone skeleton[8] (Scheme 4). A review of the synthesis of quinazolinones has recently been published by Patrick J. Guiry et al.[9] Initially it was hoped that the aldehyde group would be amenable to this strategy, ultimately allowing coupling via a reductive amination, rather than an alkylation of **8**. Bromination of **9** gave a 60:40 mixture of the 5- and 6-bromo compounds, so this approach was abandoned. A practical strategy (Scheme 4) was designed by reduction of **9** to **10** with sodium borohydride, as described by Youichi Shiokawa et al.[10] followed by acetylation of both the alcohol and amino groups to give intermediate **11**. Bromination of **11** gave an 85:15 mixture of the 3- and 5-bromo compounds; fortunately, **13** was lost to the mother liquors on workup, because otherwise this strategy would not have been any more efficient than the original free radical bromination approach. 1,3-Dibromo-5,5-dimethylhydantoin was the preferred reagent over *N*-bromosuccinimide as it has two available bromines. Acetylation and bromination were telescoped into one stage to improve the overall efficiency. Cyanation of **12** with copper cyanide in dimethylformamide (DMF) gave a relatively low strength for compound **14** (83% w/w), which was contaminated with unreacted **12** and residual solvent. However **12** could be removed in subsequent crystallisations. Ring closure of **14** with hydrogen chloride in 2-propanol gave **15** as a single regioisomer, although care had to be taken to prevent ingress of moisture as this led to high levels of the related hydroxymethyl compound. As described elsewhere[2] after protection with a POM group, the acetoxy compound was reacted with hydrogen bromide in acetic acid to yield **4**. As expected, **4** reacted cleanly with **8** to give the key intermediate **7**.

Scheme 4



Conclusion

Thus exploiting 19th century chemistry overcame an inherent weakness in the first scaled synthesis, namely an impurity that increases in concentration through subsequent processing, always a difficult challenge, but particularly in this case where the final API is amorphous.

Experimental Section

Reagents were purchased from standard suppliers.

NMR spectra were run at 270 MHz in d_6-DMSO solution and are reported in parts per million downfield from internal TMS.

HPLC analyses were conducted using a HiChrome RPB column 25 cm × 0.46 cm, solvent system acetonitrile/water/TFA 1200/800/1 (v/v/v), flow rate 1 mL/min, and detection at 235λ.

ZD9331 Bromide (12). Triethylamine (63 mL, 0.45 mole) was added in one portion to a slurry of ZD9331 Alcohol (**10**, 54 g, 0.3 mol equiv), in ethyl acetate (540 mL) at ambient temperature. The slurry was heated to 50 °C, acetyl chloride (30 mL, 0.42 mol equiv) was added over 2 h, and after a further 30 min the mixture was cooled to 20 °C. The slurry was extracted sequentially with water (2 × 270 mL) and saturated brine (270 mL). The ethyl acetate extract was solvent swapped into acetonitrile by distillation. The acetonitrile solution of 4-(acetylamino)-2-methylphenyl acetate (**11**) was treated with a solution of 1,3-dibromo-5,5-dimethylhydantoin (48.6 g, 0.17 mol equiv) in acetonitrile (380 mL) at 50 °C, and after 60 min the reaction mixture was cooled to 20 °C and poured into water (1350 mL). ZD9331 Bromide (**12**) was isolated by filtration, washed with water, and dried to constant weight at 50 °C in vacuo. The regioisomer 4-(acetylamino)-3-bromo-2-methylphenyl acetate (**13**) was lost to the aqueous acetonitrile wash to yield the product ZD9331 Bromide (**12**, 56 g 62%) with HPLC purity typically 98% w/w.

^{1}H NMR δ (DMSO-d_6): 2.1 (s, 3H), 2.2 (s, 3H), 2.3 (s, 3H), 5.0 (s, 2H), 7.6 (s, 1H) 7.4 (s, 1H), 9.5 (s, 1H).

ZD9331 Nitrile (14). ZD9331 Bromide (**12**, 50 g, 0.167 mol), copper(I) cyanide (14.2 g, 0.159 mol), and dimethylformamide (100 mL) were heated at 90 °C under an atmosphere of nitrogen. After 6 h the mixture was cooled to 60 °C and treated portionwise with zinc powder (13.1 g, 0.2 mol), and then the slurry was reheated to 90 °C, screened through Celite, cooled to 50 °C, and diluted with water (400 mL). On cooling to 20 °C the product was isolated by filtration, washed with water, and dried to constant weight at 50 °C in vacuo to yield the product ZD9331 Nitrile (**14**, 41.4 g 84%) with HPLC purity typically 83% w/w.

^{1}H NMR δ (DMSO-d_6): 2.1 (s, 3H), 2.25 (s, 3H), 2.5 (s, 3H), 5.3 (s, 2H), 7.6 (s, 1H), 7.9 (s, 1H), 10.3 (s, 1H).

ZD9331 Quinacetate HCl (15). Hydrogen chloride gas (0.12 kg, 3.29 mol) was added over 60 min to a slurry of ZD9331 Nitrile (**14**, 0.67 kg, 2.7 mol) in propan-2-ol (6.7 L). On cooling to 30 °C ZD9331 Quinacetate HCl (**15**) crystallised out of solution. The product was isolated by filtration, washed with propan-2-ol, and dried to constant weight at 50 °C in vacuo to yield the product ZD9331 Quinacetate HCl (**15**, 0.662 kg 87%) with HPLC purity typically 94% w/w.

^{1}H NMR δ (DMSO-d_6): 2.1 (s, 3H), 2.4 (s, 3H), 2.7 (s, 3H), 5.2 (s, 2H), 7.7 (s, 1H), 8.1 (s, 1H).

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