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Selective alkylation of a 6,7-dihydroxyquinazoline

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Abstract—A convenient 3-step multi-parallel process for the preparation of 4-(3-chloro-2-fluoroanilino)-6,7-bisalkoxyquinazolines is highlighted.

In recent years, inhibition of receptor tyrosine kinases (RTKs) has been the focus of much research in the pharmaceutical industry.[1] 4-Anilinoquinazolines have emerged as an important class of potent and selective inhibitors of RTKs and numerous compounds are currently in clinical development for the treatment of cancer (Fig. 1). The small molecule tyrosine kinase inhibitors *gefitinib*[2] and *erlotinib*[1] have been approved for the treatment of non-small cell lung cancer refractory to chemotherapy.[3]

In our recent efforts to explore variation at positions C-6 and C-7 of the ring nucleus to further investigate the structure–activity relationships, we became interested in preparing a library of quinazolines containing extended ether side chains at both positions. Herein,

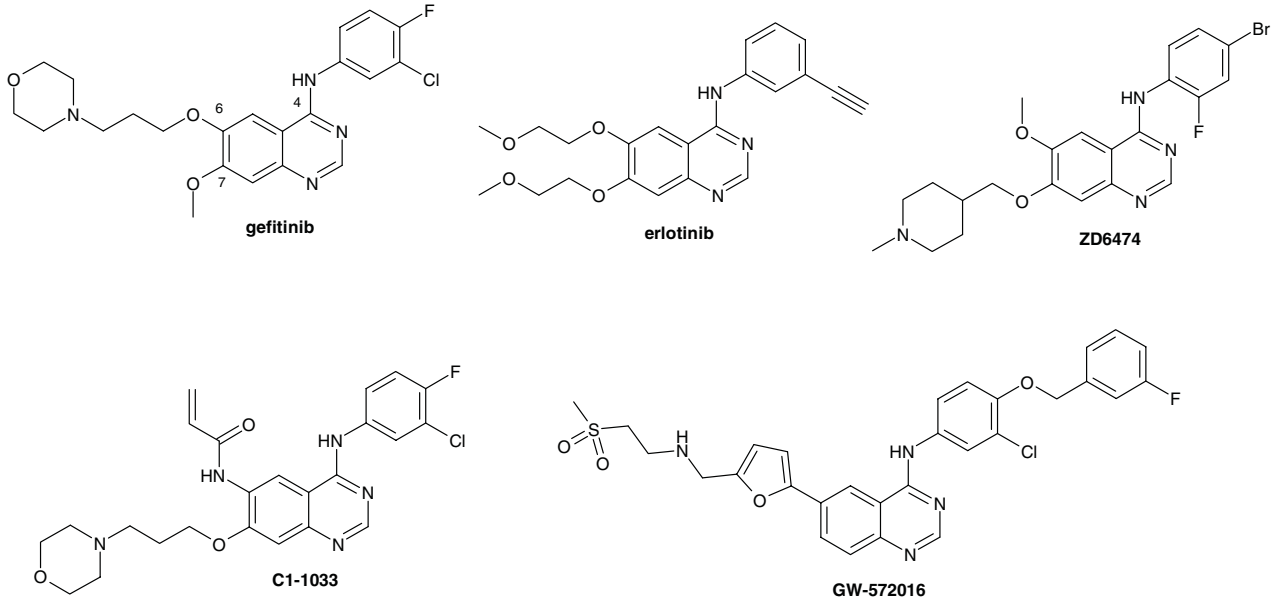

Figure 1. Examples of anilinoquinazolines in clinical development.

Keywords: Selective; *Mitsunobu*; Quinazoline.
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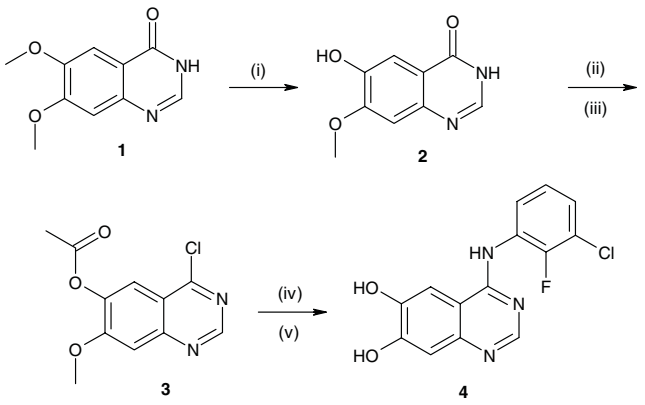


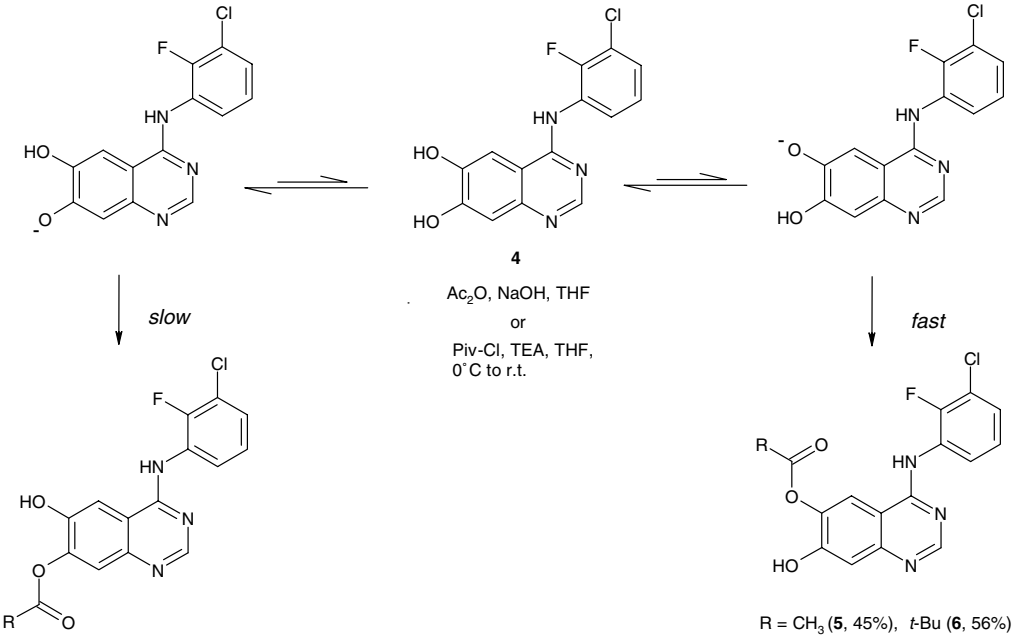
Scheme 1. Synthesis of 4-(3-chloro-2-fluoroanilino)-6,7-dihydroxyquinazoline. Conditions: (i) methionine, $MeSO_3H$, 100 °C, 3 h, 45%; (ii) Ac_2O, pyridine, 100 °C, 100%; (iii) $SOCl_2$, reflux, 16 h, 70%; (iv) 3-chloro-2-fluoroaniline, *i*-PrOH, reflux, 98%; (v) pyridinium hydrochloride, 150 °C, 3 h, 67%.

we communicate the facile and parallel chemistry employed to achieve this important class of kinase inhibitors from the corresponding bis-phenol precursor **4** (Scheme 1).

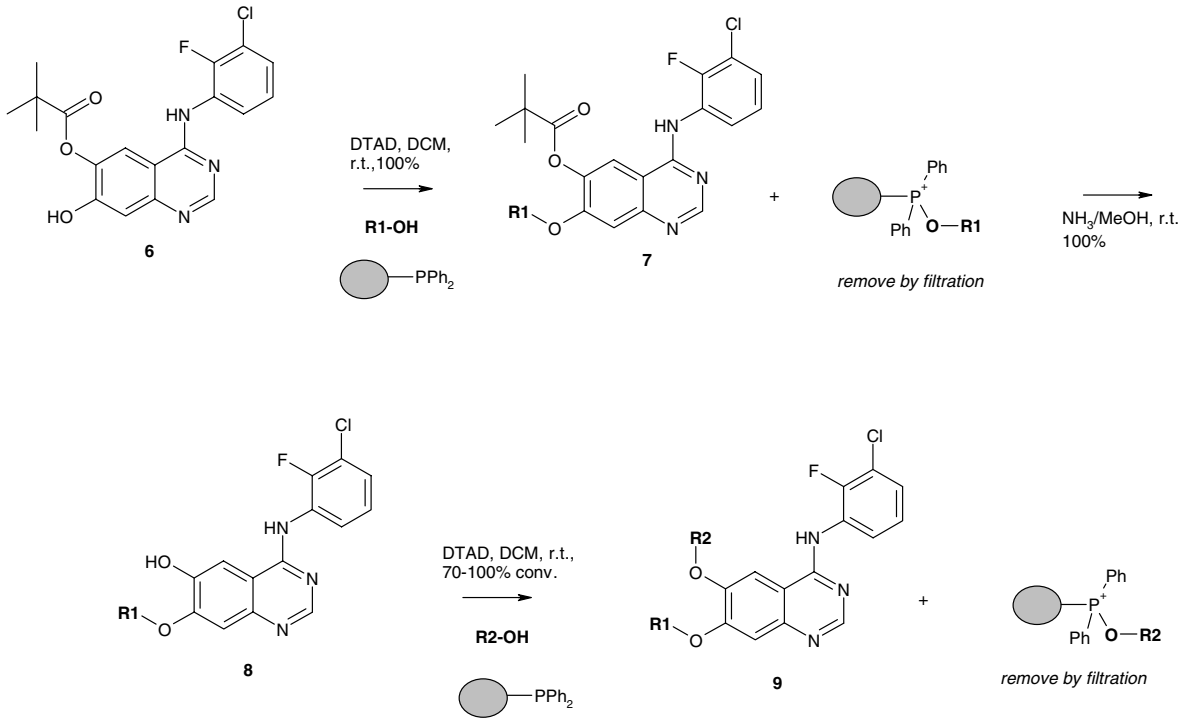
The synthesis of **4** was realised from 6,7-dimethoxyquinazolone **1**.[4] Deprotection of the methyl ether at C-6 was achieved using methionine in the presence of methanesulfonic acid.[5] The resulting C-6-phenol **2** was subsequently acetylated and chlorinated to afford the corresponding 4-chloroquinazoline **3**. Substitution of **3** with 3-chloro-2-fluoroaniline was achieved in excellent yield in *i*-PrOH at reflux. Cleavage of the second methyl ether at C-7, with simultaneous unmasking of the C-6-phenol to afford the requisite bis-phenol **4** was achieved in good yield using pyridium hydrochloride under melt conditions (Scheme 1).

We hypothesised that differentiating between the two phenols should be achievable due to the large difference in acidity between the C-7-phenol ($pK_a = 7.6$), whose delocalisation base can be stabilised by conjugation into the quinazoline ring, and the C-6-phenol ($pK_a = 10.02$) which cannot be stabilised by the quinazoline.[6] However, initial attempts to apply standard *Mitsunobu* chemistry[7] failed. No sign of any selective alkylation was observed despite attempts looking at both the mode of addition and solvent choice. We eventually chose to selectively esterify **4** with a view to preparing an intermediate, which could be utilised in a 3-step approach to prepare a differentially alkylated 6,7-bis-alkoxyquinazoline library. Selective acylation at C-6 was achieved using acetic anhydride in the presence of one equivalent of sodium hydroxide (Scheme 2).

We postulate that the excellent degree of regioselectivity can be explained by the Curtin-Hammet principle.[8] While based upon the differences in pK_a, the phenoxide at C-7 must be dominant, the rate of acylation of C-6-O^- is much greater than that of C-7-O^- thus driving the equilibrium towards the C-6-OAc (Scheme 2). Although the yield of 6-AcO-7-OH-quinazoline was acceptable, the resulting precursor proved to be somewhat unstable to the *Mitsunobu* alkylation conditions employed (di-*tert*-butylazadicarboxylate, triphenylphosphine, alcohol, DCM, 0 °C to rt). A signification quantity of bis-phenol **4** was observed, presumably through attack of the acylhydrazide anion generated by reaction of triphenylphosphine with the azadicarboxylate. However, the C-6-OAc derivative **5** did allow us to isolate our first examples of bis-alkylated products in acceptable overall yields.[9] In order to eliminate the observed in situ deprotection at C-6, we turned to the increase steric bulk offered by a pivalate protecting group, which also served to increase solubility in the reaction solvent (Scheme 2).[10]

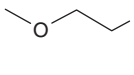
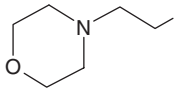
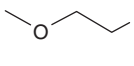
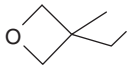
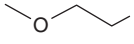
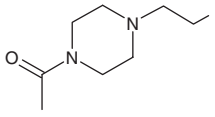
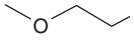
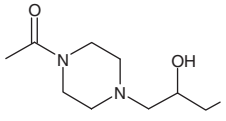
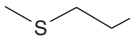
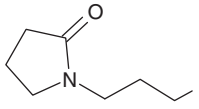
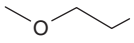
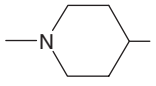
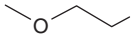
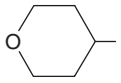
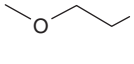
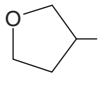
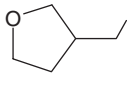


Scheme 2. Possible mechanistic explanation of the excellent regioselective acylation at C-6.



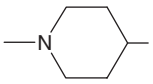
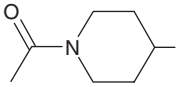
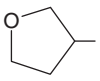
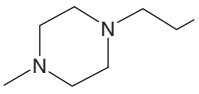
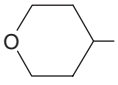
Scheme 3. Double-*Mitsunobu* transformation of **6** to 6,7-heteroalkylatedanilinoquinazolines **9**.

Table 1. Selected examples given in isolated yields after purification by preparative LCMS[13]

Entry	R1	R2	Conversion (LCMS) (7-,8-,9)	Yield (%)
1			100-,95-,85	55
2			100-,96-,91	78
3[a]			100-,96-,94-,93	53
4[a]			100-,96-,94-,92	45
5			80-,70-,65	43
6			98-,90-,81	44
7			98-,90-,76	51
8			98-,90-,70	59
9			98-,90-,75	50

(*continued on next page*)

Table 1 (*continued*)

Entry	R1	R2	Conversion (LCMS) (7-,8-,9)	Yield (%)
10			98-,90-,92	67
11			98-,90-,86	62
12			96-,96-,86	55
13			100-,94-,84	58
14			93-,77-,71	65

[a] The final *Mitsunobu* steps were carried out, with excellent conversions, using 2-bromoethanol and glycidinol, respectively. The resulting bromide and epoxide were treated with an excess of *N*-acetylpiperazine in DMF at 90 °C and in IPA at 90 °C, respectively, before purification.

The introduction of the C-6-OPiv greatly reduced the problem of in situ deprotection and the desired C-7-alkoxyquinazolines **7** were isolated in excellent yields. Subsequent deprotection of the C-6-OPiv was effected by treatment of the intermediate **7** with 7N methanolic ammonia in quantitative yield. This permitted the isolation of **8** not only in excellent overall yield but, after concentration, in a state of sufficient purity to carry out the final *Mitsunobu* alkylation. In essence, the process simply requires two filtrations and concentrations, and was automated to provide a large library of 6,7-bis-alkoxy-(2-chloro-3-fluoroanilino)quinazolines **9** (Scheme 3).

Although the reaction can be carried out entirely in solution in a 3-step-one-pot manner with simple concentrations between steps,[11] we have found the introduction of polymer-supported triphenylphosphine is beneficial to (a) improve the yield of **9**; (b) eliminate competing *N*-alkylation through steric hindrance;[12] (c) completely eliminate any in situ deprotection in the first step and consequential contamination with homo-alkylated product; and (d) to reduce mass of crude product charges on the column and thus aid separation. The author would like to emphasise that the choice of resin appears critical when adopting this approach where a large degree of diversity is introduced. High loading polystyrene-supported triphenylphosphines (~3 mmol/g) were generally acceptable for preparing un-hindered primary ether libraries where all the alcohol reacted thus was captured on the polymer during the first *Mitsunobu* step and none was carried through to the final *Mitsunobu* alkylation. However, for ether libraries where at least one of the side chains was derived from a secondary alcohol, high loading resins were not efficient in ensuring complete reaction in the initial *Mitsunobu* alkylation, that is, unreacted alcohol 'leached' through to the final *Mitsunobu* step resulting, in certain cases, in significant quantities of homo-alkylated product.

We found that lower loading polymer-supported triphenylphosphines (1–1.2 mmol/g) resulted in excellent conversions in both steps and little or no homo-alkylated product was formed. A small selection of hetero-bis-alkylated final compounds can be seen in Table 1.

The reaction conditions are indeed tolerant of a wide variety of functionality, as one would expect of the versatile *Mitsunobu* alkylation. Alcohols containing basic functionality (e.g., entries **1** and **10**), hindered secondary alcohols (e.g., entries 12 and **14**), alcohols containing electrophilic sites (e.g., entries **4** and **5**) can all be transformed in acceptable to excellent overall yields with this simple 3-step process.

Acknowledgements

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6. The pK_as of **4** were determined by mutli-wavelength spectrophotometry on a Sirius GlpKa, sweeping the pH from 2.5 to 11.5 and returning to 2.5. The analyte was composed of 2 mg of **4** and was dissolved in 200 μl of DMSO; 7.5 μl of this solution was diluted with 250 μl of a buffer solution containing 0.2 g of KH_2PO_4 dissolved in 100 ml of water.
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8. Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111.
9. On average, exposure of **7** to solution-phase *Mitsunobu* conditions resulted in formation of 15–20% of bis-phenol by LCMS. This figure could not be significantly improved upon by changing the order of addition of *Mitsunobu* reagents.
10. The regiochemistry of the 6-OPiv-7-OH intermediate **6** was determined by NMR experiments. In comparison, to the parent bis-phenol **4**, the proton at C-5 shifted 0.5 ppm downfield (as opposed to C-8 proton which did not move) and a NOE was observed between the C-5 proton and the aniline N–H.
11. Solution-based alkylation of **6** resulted in a 52% overall yield of 6,7-heteroalkylated final compound. The main impurities, as judged by LCMS, were homoalkylated product (5–10%) and *N*-alkylation of the desired compound (5%). Both impurities are practically eliminated using polymer-supported triphenylphosphine suggesting that access to the reactive sites on the polymer is dictated by steric hindrance.
12. Charette, A. B.; Janes, M. K.; Boezio, A. A. *J. Org. Chem.* **2001**, *66*, 2178.
13. Typically: To a stirred suspension of polymer-supported triphenylphosphine (3 equiv), the first alcohol (3 equiv) in DCM (5 ml/g of resin) at 0 °C, was added di-tert-azadicarboxylate (DTAD, 3 equiv) followed by **6**. The reaction mixture was slowly agitated for 1 h at room temperature, filtered and the filtrate was concentrated. The residue (containing **7**) was dissolved in methanolic ammonia (7 N) and stirred for 5 h, concentrated to dryness, re-dissolved in THF and re-concentrated to dryness. Phenol **8** was subsequently added to a stirred suspension of polymer-supported triphenylphosphine (4 equiv), the second alcohol (4 equiv), and DTAD (4 equiv) at 0 °C. The reaction mixture was slowly agitated for 1 h at room temperature, concentrated and purified by preparative LCMS to afford the desired 6,7-bis-alkylatedquinazolines **9** in acceptable to excellent overall yields.