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Three-point variation of a gefinitib quinazoline core

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ABSTRACT

A versatile four-step process describing the controlled systematic variation of a key quinazoline core from one intermediate is highlighted.

As an ATP-binding mimic, the quinazoline family has been of major interest to the pharmaceutical industry offering a relatively simple scaffold to probe and develop quickly a strong understanding of structure-activity relationships culminating in many candidate drug nominations.[1] Perhaps quinazolines substituted at C-4, C-6 and C-7 have emerged as one of the most important classes of quinazoline-based kinase inhibitors with *gefitinib*[2] and *erlotinib*[3] having already been approved for the treatment of non-small cell lung cancer refractory to chemotherapy[4] and AZD6474,[5] AZD2171 and KRN951 showing promising results in the clinic[6] (Fig. 1).

Despite numerous synthetic achievements in this domain and the intensive research carried out during the past decade up to the present day,[7] the synthesis of analogues in the C-4 substituted 6,7-bis(alkoxy)quinazoline family is rather rigid and this has somewhat been an inhibitory factor to fine-tuning structure-activity exploration and improving physico-chemical properties. Current methodology to access 'heterodialkoxy' C-4 substituted quinazolines relies upon effecting aryl methyl ether deprotections in order to reveal the corresponding phenols at C-6[8]or C-7[9] using, for example, pyridinium hydrochloride under melt conditions[10] or lithium iodide in 2,4,6-collidine at elevated temperatures.[11] However, retaining sensitive groups such as aryl ethers at C-4 under these harsh conditions is not possible.

In a recent Letter,[12] we described a novel route to differentially alkylate at C-7-OH then at C-6-OH using *Mitsunobu* alkylation conditions.[13] This route allowed us to access a large library of novel 6,7-heterodialkyl-oxyanilinoquinazolines. Herein, we take the chemistry back to yet another level and prove that systematic variation of all three-key points of this important family of kinase inhibitors can be performed in a very convenient manner allowing for an explosion in diversity. (Scheme 1).

The synthesis of **5** was realised from 6-AcO-7-OMe-quinazolone (**1**).[14] Double deprotection of the methyl ether at C-7 and the acetyl protecting group at C-6 of **1** was achieved using pyridinium hydrochloride under melt conditions. The resulting diol **2**[15] was subsequently protected with pivaloyl groups. We found the use of pivaloyl groups over acetyl protecting groups was essential in aiding purification of the subsequent chloride **3**, achieved by carefully treating the quinazolone precursor with an excess of $POCl_3$ in the presence of TEA at <50 °C. Deprotection of **3** via ammonolysis afforded the stable diol **4**, a useful and completely novel intermediate in itself for synthesising C-6,7-homodialkoxyquinazoline libraries. Finally, regioselective protection of **4** was achieved, as described in our previous Letter,[12] using pivaloyl chloride in the presence of TEA at room temperature to afford a good yield of the key intermediate **5** (Scheme 2).

In practise, exploitation of **5** was possible going in both directions. From the left-hand direction, *Mitsunobu* alkylation using DTAD and polymer-supported triphenylphosphine[16] afforded **6** in near quantitative conversions. The subsequent phenols **7** were revealed by ammonolysis of the 6-C-OPiv using methanolic ammonia at room temperature. The solutions were concentrated to dryness and the residues were exposed to the second *Mitsunobu* alkylation conditions to afford the 4-chloro-6,7-heterodialkoxyquinazolines **8** again with excellent conversions. The resin was removed and the filtrate was concentrated, dissolved in DMF and in the case of aniline substitutions, a catalytic quantity of dry HCl was added and the reaction mixtures were heated at 80 °C with the desired aniline for 2 h; in the case of phenols and thiophenols substitution, 3 equiv of potassium carbonate was added and the reaction mixtures were heated at 80 °C with the desired phenol or thiophenol for 2 h; and in the case of aliphatic amines, 3 equiv of the desired amine was

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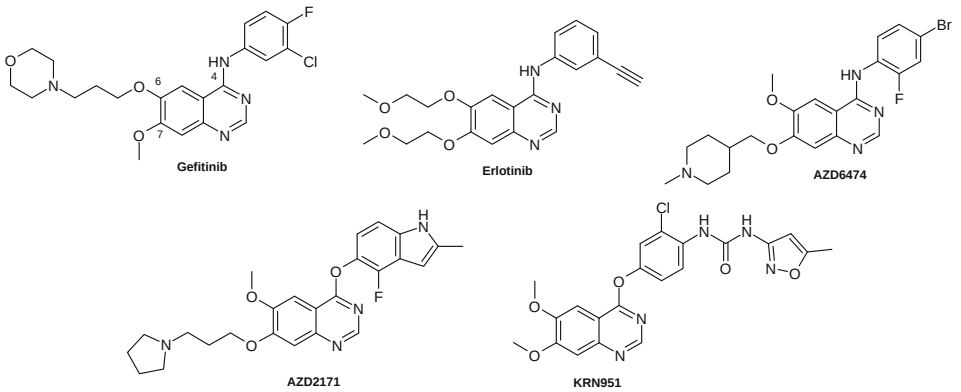
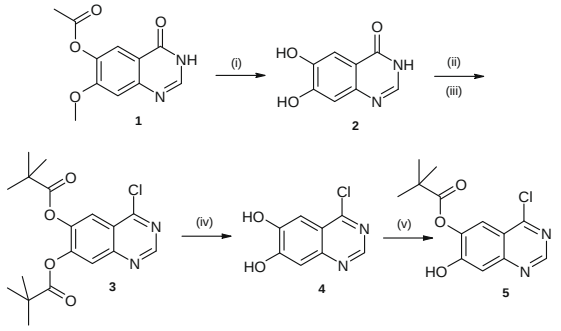
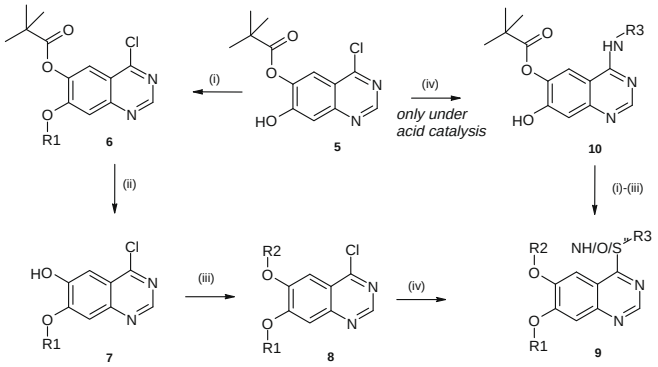


Figure 1. Examples of C4-substituted quinazolines on the market or in late-stage clinical development.



Scheme 1. Synthesis of 4-chloro-6-OPiv-7-OH-quinazoline. Reagents and conditions: (i) pyridinium hydrochloride, 170 °C, 3 h, 95%; (ii) Piv-Cl, TEA, DMF, rt, 2 h, 71%; (iii) $POCl_3$, TEA, toluene, rt, 40 °C, 3 h, 70%; (iv) NH_3/MeOH, rt, 2 h, 100%; (v) Piv-Cl, TEA, DMF, rt, 2 h, 57%.



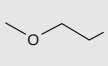
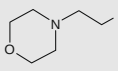
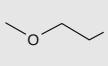
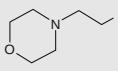
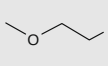
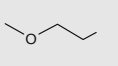
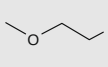
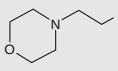
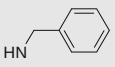
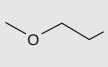
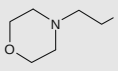
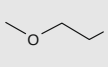
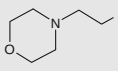
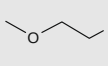
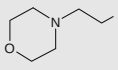
Scheme 2. Two routes to access **9**. Reagents and conditions: (i) R1-OH, DTAD, TPP, DCM, rt; (ii) NH_3/MeOH, rt, 2 h, 100%; (iii) R2-OH, DTAD, TPP, DCM, rt; (iv) R3-Ar-NH_2, cat. HCl, MeCN or DMF, 80 °C or R3-Ar-OH or R3-Ar-SH, K_2CO_3, DMF, 70 °C or excess R3-aliphatic amines, DMF, 80 °C, 38–75%.

added and the reaction mixtures were heated at 80 °C for 2 h. The resulting solution or suspensions were filtered and purified directly by preparative LC–MS to afford libraires of **9** in good yield for a four-step process. From the right-hand direction, application of similar aniline substitution conditions as described above in MeCN resulted in little or no in situ deprotection of the C-6-OPiv affording **10**. However, it was necessary to purify **10** by preparative LC–MS in order to carry out the double *Mitsunobu* alkylation process. All attempts to displace the C-4-Cl of **5** under basic conditions failed, as expected, resulting in deprotection of the C-6-OPiv and further degradation.

A short selection of simple compounds was made to illustrate this highly adaptable process which can be seen in Table 1. It is worth noting that by adapting this process, one can access libraries of **9** in 5 h as opposed to weeks using existing routes and introduce sensitive groups at C-4, for example, ethers (entries **7** and **8**) which would not be retained following existing methodology.

In conclusion, we have developed new, flexible and tolerant routes passing through novel and highly versatile quinazoline intermediates to thoroughly explore quinazoline substitution at C-4, C-6 and C-7 in a selective and rapid manner compared with existing methodology.

Table 1
Selected examples given in isolated yields after purification by preparative LC–MS[17]

Entry	Cpd	R1	R2	R3	Conversion (LC–MS) 5–6–7–8–9 (% purity at 254 nm)	Yield (%)
1[a]	**9a**				88-,100-,96-,93	49
2	**9a**				95-,100-,94-,98	51
3[b]	**9b**				93-,98-,100-,94	51
4[b]	**9c**				96-,92-,98-,93	60
5	**9d**				90-,98-,92-,66	42
6	**9e**				90-,98-,92-,81	75
7	**9f**				90-,98-,92-,71	58
8	**9g**				90-,98-,92-,64	38

[a] Final compound prepared going from right hand direction with after purification of **10**.
[b] Final compounds can also be prepared from intermediate **4**.

Acknowledgements

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Supplementary data

Detailed experimental procedures for the synthesis of all final compounds, intermediates with supporting ^{1}H NMR and LC–MS characterisation data are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.099.

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16. Free triphenylphosphine can be used for this chemistry[12] but for multi-parallel approaches where the end product is purified by mass-triggered preparative LC–MS using reverse-phase chromatography, the presence of large quantities of triphenylphosphine oxide can contaminate the final compounds depending on their polarity but more importantly 'drown' the mass detector resulting in loss of compound.
17. *Typical procedure*: To a stirred suspension of polymer-supported triphenylphosphine (3 equiv), and the first alcohol (3 equiv) in DCM (5 ml/g of resin) at 0 °C was added di-*tert*-butyl azadicarboxylate (DTAD, 3 equiv) followed by **5**. The reaction mixture was slowly agitated for 1 h at room temperature, filtered, and the filtrate was concentrated. The residue (containing **6**) was dissolved in methanolic ammonia (7 N) and stirred for 5 h, concentrated to dryness, re-dissolved in THF and re-concentrated to dryness. The phenol **7** 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 and concentrated to dryness. The resulting residue was exposed to the following conditions: (a) for the introduction of C-4-anilines (e.g., entry **2**), the residues were taken up in DMF and treated with 1.1 equiv of aniline and 0.2 equiv of HCl in dry 1,4-dioxane at 80 °C for 2 h; (b) for the introduction of C-4-aryl(thio)ethers, the residues were taken up in DMF and treated with (thio)phenol (3 equiv) and K_2CO_3 (3.3 equiv) at 80 °C for 2 h (entry **7**); (c) for the introduction of C4-aliphatic amines (entry **6**), the residues were taken up in DMF and treated with the desired amine (3 equiv) at 80 °C for 2 h. The reaction mixtures were cooled to room temperature, filtered and purified directly by preparative LC–MS to afford the desired C4-substituted 6,7-*bis*-alkyoxyquinazolines (**9**) in acceptable overall yields.