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A Decarboxylative Traceless Linker Approach for the Solid Phase Synthesis of Quinazolines

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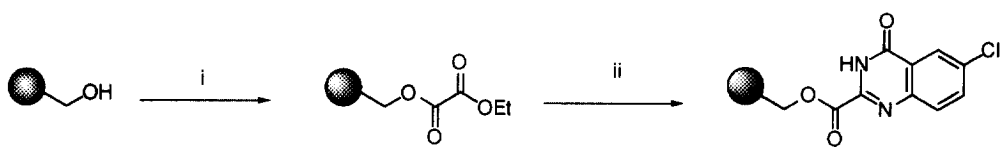
Abstract. A decarboxylative traceless linker strategy for the cleavage of resin-bound quinazolines has been developed using hydroxymethylpolystyrene (HMPS) resin derivatised as the ethyl oxalate. Methods for the solid phase synthesis of the linker, quinazoline formation, functionalisation and cleavage are described.

The central position of protein phosphorylation in signal transduction[1] gives protein kinases important regulatory roles in many biological processes, including in cellular differentiation. Deregulated kinase activity is associated with proliferative diseases such as cancer and psoriasis,[2] and consequently protein kinases have become important therapeutic targets.[3] The quinazolines are among the most potent of the protein kinase inhibitors that compete for binding at the ATP site.[4] Several 4-substituted quinazolines are picomolar inhibitors of EGF-R tyrosine protein kinase.

In this Paper we report an approach to the synthesis of quinazolines on solid phase. One important consideration in our strategy was the choice of the site of attachment of the heterocyclic nucleus to the resin bead. A key observation was that many of the most potent quinazolines are unsubstituted at C-2.[5] This was therefore chosen as the point of attachment of a traceless linker. There have been several reports of traceless linkers, mainly using silicon, sulfur or phosphorus-based chemistry.[6] Our approach was to exploit the facile decarboxylation of a carboxyl group on a carbon between two nitrogens in an aromatic heterocycle.[7] There has recently been a report of a traceless linker based around the decarboxylation of a 3-keto acid.[8]



1 2

Scheme 1. i) ethyl oxalyl chloride (5 eq.), CH_2Cl_2, DMAP (0.15 eq.), NEt_3 (5 eq.), 0-25 °C, 2 h, ii) 2-amino-5-chlorobenzamide (5 eq.), dioxan, CSA monohydrate (1 eq.), 110 °C, 48 h, 60% yield.

Our synthetic approach was to assemble 2-carboxyquinazolinones on resin (Scheme 1) and functionalise them at C-4 via the chloroquinazoline (Scheme 3) using an approach that had been amply demonstrated in solution for quinazolinones.[5] The 2-carboxyquinazolinone **2** was made in two steps (Scheme 1). Ethyl oxalyl chloride was reacted with hydroxymethylpolystyrene (0.70 mmol / g,[9] 2 % cross-

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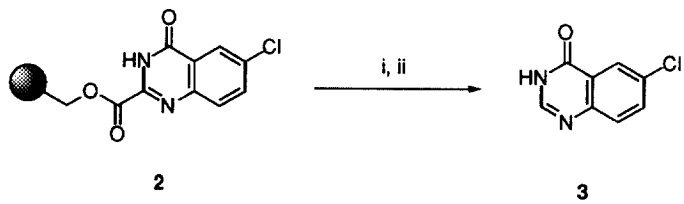
linked, NovaBiochem) providing a stable ethyl oxalate linkage **1**.[10] The ethyl oxalate was then reacted with the benzamide in the presence of camphor-sulphonic acid monohydrate (CSA) at 110 °C to form a quinazolinone **2**.[11] The loading of the resin was determined to be 60% by elemental analysis of nitrogen.

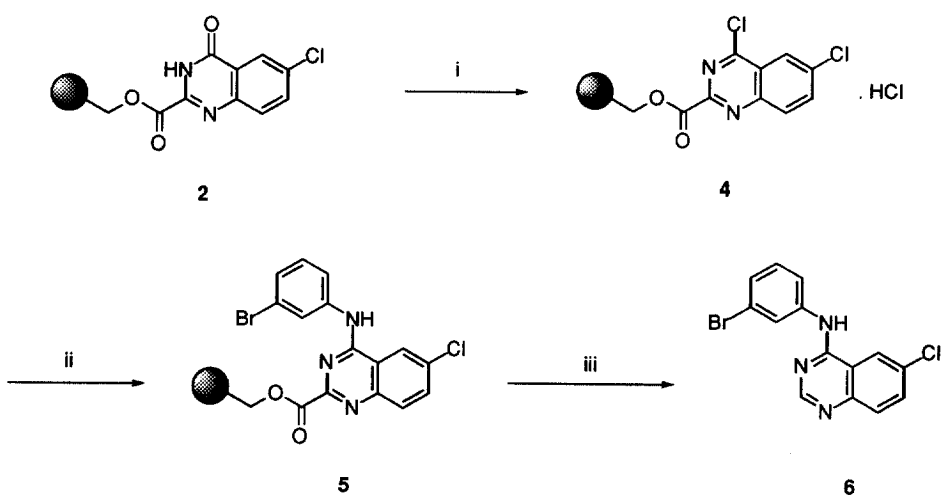
At this stage we demonstrated that the resin-bound quinazolinone could be cleaved from the resin using trimethylsilyl iodide[12] (Scheme 2). The liberated quinazolinone carboxylic acid underwent decarboxylation to form **3** upon treatment with 1 M HCl.



2 **3**

Scheme 2. i) Me_3SiCl, NaI, MeCN, dioxan, 75 °C, 18 h, ii) HCl, reflux, 2 h, 64% yield determined from the loading of **2** (97% purity).[13]

The resin-bound quinazolinone **2** was activated by heating at reflux in thionyl chloride for 2 hours to form the 4-chloroquinazoline hydrochloride **4** (Scheme 3). This intermediate was then reacted with 3-bromoaniline to give the 4-anilino-substituted quinazoline **5**.[14] Treatment of **5** with TMSI for 72 h at 75 °C effected both cleavage of the ester linkage and decarboxylation of the liberated quinazoline to give **6** in 69% yield[15] (95% purity).[12]



2 **4**

5 **6**

Scheme 3. i) $SOCl_2$/DMF, reflux, 3 h, ii) 3-bromoaniline (5 eq.), i-PrOH/DMF/HCl, rt, 18 h, iii) TMSCl/NaI/MeCN/dioxan, 75 °C, 72 h

We have shown how the ethyl oxalate group provides both a linking ester group and the C-2 of the quinazoline. Facile protocols for attachment of the ethyl oxalate to the resin, cyclisation of benzamides, functionalisation and finally cleavage, have been demonstrated. We envisage that this strategy can be generalised to the synthesis of other classes of heterocycles on solid phase.

Acknowledgements

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9. Resin loading was determined by treating the resin with Fmoc-Cl (5.0 equiv.) in dichloromethane in the presence of pyridine (5.0 eq.) for 18 h. The reactive hydroxyl groups were photometrically determined from the amount of Fmoc chromophore released upon treatment of the Fmoc-resin with 20% piperidine in DMF.
10. *Preparation of ethyl oxalate linker* **1**. To hydroxymethylpolystyrene (2.3 g) swelled in dry dichloromethane (30 ml), was added dry triethylamine (290 µl, 1.1 eq.) and catalytic DMAP (0.15 eq.). The mixture was cooled to 0 °C and ethyl oxalyl chloride (1.5 ml) was added dropwise. The reaction was shaken at room temperature overnight and resin was then filtered, washed with dichloromethane (8 x 20 ml), diethyl ether (5 x 20 ml) and dried *in vacuo*. The loading (determined by C and H analysis) was 0.9 mmol / g (100 %)

11. *Preparation of resin-bound-quinazolinones* **2**. To functionalised hydroxypolystyrene resin **1** (1.7 g) swelled in dioxane (5 ml) was added 2-amino-5-chlorobenzamide (1.49 g, 3.5 eq.) and camphor-sulphonic acid (0.6 g, 1 eq.) and the mixture was heated at reflux for 72 h. On cooling, the resin was filtered, washed with DMF (5 x 20 ml), dioxane (5 x 20 ml), dichloromethane (5 x 20 ml) and diethyl ether (5 x 20 ml), and dried *in vacuo*. The loading (determined by N analysis) 60%.
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13. The purity was determined by C-18 reverse phase HPLC using a Columbus 50 x 2 mm C18 column (0-100% CH_3CN in H_2O containing 0.1% TFA), monitored at 254 nm using a UV detector and by a SEDEX Evaporative Light Scattering Detector.
14. *Preparation of amino substituted quinazoline* **5**. To resin **2** (200 mg) swollen in anhydrous DMF (5 ml) was added thionyl chloride (5 ml) and the mixture was heated at reflux for 3 h. The resin was filtered and re-swollen in DMF (5 ml). 3-bromoaniline (150 µl, 5 eq.) in propan-2-ol (5 ml) was added along with conc. HCl (4 drops) and the reaction was shaken at room temperature overnight. The resin was filtered, washed with DMF (5 x 20 ml), dichloromethane (5 x 20 ml), diethyl ether (5 x 20 ml) and dried *in vacuo*.
15. *Cleavage of the amino substituted quinazolines from resin* **6**. To resin **5** (73 mg) swollen in 1,4-dioxan (4 ml) and MeCN (4 ml) was added NaI (100 mg) and trimethylsilyl chloride (200 µl). The mixture was heated at 75 °C for 72 h, and then filtered. The filtrate was concentrated *in vacuo* and taken up in water, and the product was extracted with dichloromethane (3 x 10 ml), washed with aqueous $Na_2S_2O_4$, dried over $MgSO_4$ and concentrated *in vacuo* to give 4-(3-bromoanilino)-6-chloroquinazoline (69%). ^1H NMR [$(CD_3)_2SO$] δ 9.89 (s, 1H), 8.72 (d, 1H, J = 2.9 Hz), 8.67 (s, 1H), 8.21 (s, 1H), 7.90 (m, 3H), 7.35 (m, 2H). ES-MS: 333.9, 335.9 (MH^+).