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Facile solid phase synthesis of 1,2-disubstituted-6-nitro-1,4-dihydroquinazolines using a tetrafunctional scaffold

Xiaobing Wang,[a] Aimin Song,[a] Seth Dixon,[b] Mark J. Kurth[b] and Kit S. Lam[a,*]

[a]*Division of Hematology and Oncology, Department of Internal Medicine, UC-Davis Cancer Center, 4501 X Street, Sacramento, CA 95817, USA*
[b]*Department of Chemistry, One Shields Avenue, UC-Davis, CA 95616, USA*

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Abstract—Solid phase synthesis of 1, 2-disubstituted-6-nitro-1,4-dihydroquinazolines is described. The new tetrafunctional scaffold *N*-Alloc-3-amino-3-(2-fluoro-5-nitrophenyl)propionic acid was prepared by nitration of 3-amino-3-(2-fluorophenyl)propionic acid. The scaffold was anchored to Rink resin via its carboxylic group and treated with primary amines to displace the arylfluorine followed by cyclization with aryl isothiocyanates in the presence of DIC upon Alloc deprotection to afford 1,2-disubstituted-6-nitro-1,4-dihydroquinazolines in high yield.
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Quinazoline rings represent a novel heterocyclic class of pharmacophores for biological interaction. Some quinazolines have been identified as antibacterial drug[1] as well as potent and selective inhibitors of a variety of kinases such as Src kinase,[2] erbB1 (via ATP binding site),[3] CDK4/D1 and CDK2/E.[4] Because of its valuable pharmaceutical properties, synthesis of quinazolines has gained considerable interest in the field of medicinal chemistry. Many synthetic approaches have been reported using conventional solution phase synthesis.[5] Since solution phase synthesis usually requires tedious workup after each reaction step, several research groups have developed new methods for the synthesis of quinazolines on solid support.[6] Trifunctional scaffolds of *o*- or *p*-nitro arylfluorines, for example, 4-fluoro-3-nitrobenzoic acid[7] and 2-fluoro-5-nitrobenzaldehyde,[8] have been used as precursors to generate quinazolines because of efficient displacement of arylfluorine by nucleophiles. However, in solid phase synthesis, one of the three functional groups on the scaffolds has to be used as a handle to tether it to the solid support. Consequently only the two remaining functional groups are used for diversity generation. There is a need for developing methods to synthesize quinazoline libraries with great diversity. Here, we report on the synthesis of a novel tetrafunctional scaffold that can be used to prepare 1,2-disubstituted-6-nitro-1,4-dihydroquinazolines via solid phase synthesis.

Ideally, such a tetrafunctional scaffold should be conveniently prepared by introducing a nitro group to an arylfluoro-containing amino acid so that similar chemistry used for the trifunctional scaffolds would be applicable for this scaffold. We reasoned that 3-amino-3-(2-fluorophenyl)propionic acid could be the appropriate amino acid for this purpose because it is easy to prepare. Scheme 1 illustrates the synthetic route of the tetra-functional scaffold. 3-Amino-3-(2-fluorophenyl)propionic acid **1** was first prepared by one-pot condensation of 2-fluorobenzaldehyde and malonic acid in the presence of ammonium acetate under reflux overnight.[9] The resulting β-amino acid was then treated by the conventional nitration agent, HNO_3/H_2SO_4 (1:1) at 0 °C for 6 h to yield pure 3-amino-3-(2-fluoro-5-nitrophenyl) propionic acid **2** (>97%) in high yield (87.5%). FT-IR (1519, 1354 cm^{-1}) and MS (M+H = 229.4) analysis demonstrated the presence of a nitro group on product **2**. ^{13}C NMR data, in which nitro-substituted carbon at δ 144.50 ppm showed only one single peak, indicated no fluorine–carbon coupling interaction on this carbon, revealing that the nitration occurred at *para*-position with respect to the arylfluorine. The free amino acid **2**

Keywords: Tetrafunctional scaffold; Quinazoline; Solid phase synthesis.
* Corresponding author. Tel.: +1 916 734 8012; fax: +1 916 734 7946; e-mail: kit.lam@ucdmc.ucdavis.edu

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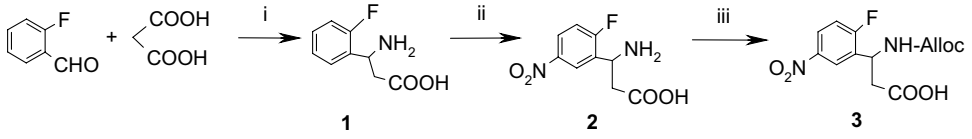


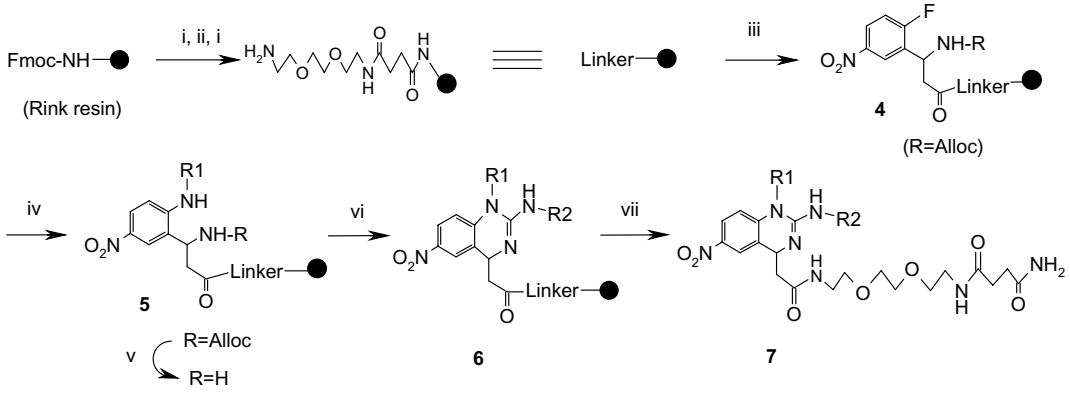
Scheme 1. Synthetic route of *N*-Alloc-3-amino-3-(2-fluoro-5-nitrophenyl)propionic acid. Reagents and conditions: (i) ammonium acetate (2.2 equiv), EtOH, reflux, overnight; (ii) HNO_3/H_2SO_4 (1:1), 0 °C, 6 h; (iii) Alloc-OSu, $NaHCO_3$, overnight.

was readily protected with Alloc-OSu in aqueous $NaHCO_3$ solution to afford *N*-Alloc-3-amino-3-(2-fluoro-5-nitrophenyl)propionic acid **3**.

To demonstrate the utility of this new scaffold for drug-like heterocyclic compound synthesis, we designed a simple solid phase synthetic route to prepare 1,2-disubstituted-6-nitro-1,4-dihydroquinazolines (Scheme 2). To ensure that all products are soluble in aqueous solution for biological screening and characterization, we purposely incorporated a hydrophilic linker, (2,2′-ethylenedioxy)-bis(ethylamine) monosuccinamide[10] on Rink resin prior to the quinazoline synthesis. Scaffold **3** was anchored to the resin via carboxyl group in the presence of DIC. The arylfluorine of the resin-bound scaffold **4** was then displaced with a primary amine to afford a resin-bound aniline **5**. In order to optimize the reaction, three basic conditions, DIEA alone, DIEA with a catalytic amount of DMAP and DBU alone were investigated. The resulting compounds were released from the resin by 95% trifluoroacetic acid in H_2O and analyzed by HPLC and MS, respectively. Although the MS results demonstrated that fluorine displacement could occur under all conditions, the HPLC results suggested that the second condition was more desirable. Therefore, for synthesis of the desired quinazolines, DIEA with catalytic amount of DMAP was used as the base in the S_NAr displacement step. After the arylfluorine displacement, the Alloc-protected amino group on the scaffold was liberated by palladium reagent.[11] The DIC-mediated cyclization[12] between the resin-bound diamine and an aryl isothiocyanate was carried out to give resin-bound 1,2-disubstituted-6-nitro-1,4-dihydroquinazolines **6**. The desired quinazolines **7** were obtained by 95% TFA (in H_2O) cleavage for 2 h in high yield and purity. The results are summarized in Table 1, which shows that either aliphatic or aryl R^1 group on **5** give the corresponding product in good yield. However, no desired product was obtained when the aliphatic isothiocyanates (**7j–k**) were used in the cyclization step as previously reported.[12a]

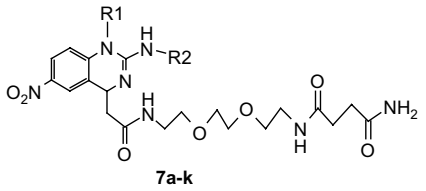
In summary, we have developed an easy method to prepare a novel tetrafunctional scaffold, *N*-Alloc-3-amino-3-(2-fluoro-5-nitrophenyl)propionic acid, that can be subsequently transformed to 1,2-disubstituted-6-nitro-1,4-dihydroquinazolines on solid support, with high yield and satisfactory purity. Since the scaffold has four functional groups, it enables one to extend this synthetic route to generate large diverse combinatorial libraries at positions of 1,2,4,6 of the quinazoline skeleton. For example, for a four point diversity library, an amino acid can be placed between the quinazolines and the solid support prior to the coupling of the scaffold to resin and the nitro group of quinazolines **6** can be reduced by $SnCl_2$ to generate a free amine for coupling of another building block.

Synthesis of 3-amino-3-(2-fluoro-5-nitrophenyl)propionic acid **2**: 2-fluorobenzaldehyde (30.0 g, 0.24 mol), malonic acid (27.5 g, 0.26 mol) and ammonium acetate (41.0 g, 0.53 mol) were mixed in 50 mL of ethanol and heated under reflux overnight. The reaction mixture was cooled to room temperature. The white solid was

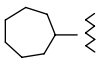
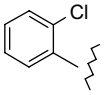
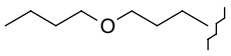
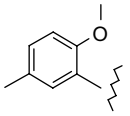
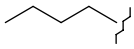
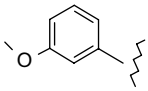
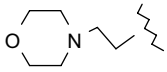
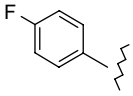
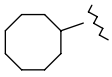
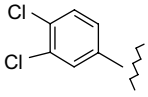
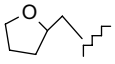
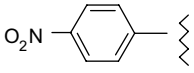
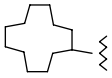
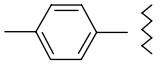
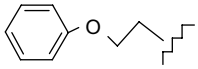
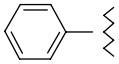
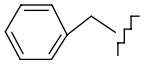
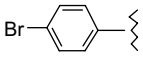
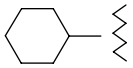
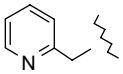


Scheme 2. Solid phase synthesis of 1,2-disubstituted-6-nitro-1,4-dihydroquinazolines. Reagents and conditions: (i) 25% piperidine, 15 min; (ii) *N*-Fmoc-2,2′-ethylenedioxy-bis(ethylamine) monosuccinamide (3 equiv), DIC (3 equiv); (iii) *N*-Alloc-3-amino-3-(2-fluoro-5-nitrophenyl)propionic acid (3 equiv), HOBt (3 equiv), DIC (3 equiv); (iv) R_1NH_2 (3 equiv), DIEA (3 equiv), DMAP (0.05 equiv), overnight; (v) $Pd(PPh_3)_4$ (0.24 equiv), $PhSiH_3$ (20 equiv), DCM, 1 h; (vi) R_2NCS (3 equiv), DIC (3 equiv), overnight; (vii) TFA/H_2O (95:5), 2 h.

Table 1. Synthesis of compounds **7a**–**k** via Scheme 2



7a-k

Entry	R_1	R_2	Crude yield[a] (%)	Purity[b] (%)	MS[c] (found, M+H$^+$)
7a			90	100	686.3
7b			75	65	714.4
7c			82	83	642.4
7d			71	70	687.3
7e			85	92	734.1
7f			77	97	685.2
7g			85	100	736.2
7h			73	94	676.4
7i			77	90	724.3
7j		$CH_3(CH_2)_2$[d]	—	—	—
7k		$CH_3(CH_2)_3$[d]	—	—	—

[a] Yield of the crude product was based on Rink resin substitution.
[b] Purity was detected by RP-HPLC at $\lambda = 254$ nm.
[c] Molecular weight was measured by MALDI-TOF MS.
[d] No desired product was obtained.

collected by filtration and washed with ethanol three times (3×50 mL) and ether two times (2×50 mL). The dry solid (26.0 g, purity >97%) was added into an ice-chilled mixture of HNO_3/H_2SO_4 (100 mL/100 mL) and stirred for 6 h in ice bath. The yellowish solution was poured into 600 mL of ice and neutralized with NaOH to pH = 6. The mixture was allowed to warm to room temperature. The precipitate was collected by suction–filtration, washed with water (25 mL), ethanol (3×50 mL), and ether (50 mL). Weight: 28.0 g, yield: 87.5%, purity: >97%, mp 222–228 °C. FT-IR (selected, cm^{-1}): 1519, 1354. MS (M+H$^+$): 229.4. ^{1}H NMR (500 MHz, D_2O): δ 8.38 (t, 1H), 8.32 (m, 1H), 7.40 (t, 1H), 4.95 (t, 1H), 2.95 (m, 2H). ^{13}C NMR (500 MHz, D_2O): δ 176.5, 165.5 (d, $^1J_{CF} = 246$ Hz), 144.5, 132.2 (d, $^2J_{CF} = 23.0$ Hz), 127.6 (d, $^3J_{CF} = 10.6$ Hz), 124.9 (d, $^3J_{CF} = 8.4$ Hz), 117.9 (d, $^2J_{CF} = 24.8$ Hz), 46.8, 39.1.

Synthesis of *N*-Alloc-3-amino-3-(2-fluoro-5-nitrophenyl) propionic acid **3**: To the solution of 3-amino-3-(2-fluoro-5-nitrophenyl)propionic acid (10.0 g, 0.044 mol) in aqueous $NaHCO_3$ (9.2 g, 0.11 mol) solution was dropwise added Alloc-OSu (8.7 g, 0.044 mol) solution in DMF. The mixture was stirred at room temperature overnight and washed with ethyl acetate twice (2×40 mL). The aqueous solution was neutralized with HCl to pH = 3. The solidified powder was collected by filtration, washed with water (5×50 mL) and dried

in vacuo. Weight: 9.0 g, yield: 66%, purity: 98%, mp 139–140 °C. FT-IR (selected, cm^{-1}): 1531, 1346. MS ($M+H^+$): 313.5. ^1H NMR (DMSO-d_6, 500 MHz): δ 12.5 (s, 1H), 8.37 (d, 1H), 8.22 (m, 1H), 8.14 (d, 1H), 7.49 (t, 1H), 5.89 (m, 1H), 5.29 (m, 2H), 5.17 (d, 1H), 4.48 (m, 2H), 2.75 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 171.8, 164.5 (d, $^1J_{CF}$ = 250 Hz), 155.8, 144.9, 134.1, 132.5 (d, $^2J_{CF}$ = 16.4 Hz), 125.9 (d, $^3J_{CF}$ = 10.4 Hz), 124.7 (d, $^3J_{CF}$ = 6.2 Hz), 117.8 (s), 117.6 (d,$^2J_{CF}$ = 22.1 Hz), 65.3, 45.9, 40.0.

Typical procedure: synthesis of *N*-{2-[2-(2-{2-[2-(2-chloro-phenylamino)-1-cycloheptyl-6-nitro-1,4-dihydro-quinazolin-4-yl] acetylamino}ethoxy) ethoxy] ethyl}-succinamide **7a**: Swollen Rink resin (0.1 g, 0.54 mmol/g) was deprotected with 25% piperidine for 15 min and coupled with *N*-Fmoc-2,2′-ethylenedioxy-bis (ethylamine) monosuccinamide (3 equiv)/DIC (3 equiv). After Fmoc-deprotection with 25% piperidine, the resin was coupled with **3** (3 equiv)/DIC (3 equiv), followed by incubation with cycloheptylamine (3 equiv)/DIEA (3 equiv)/DMAP (0.05 equiv) overnight. After Alloc-deprotection with $Pd(PPh_3)_4$ (0.24 equiv)/$PhSiH_3$ (20 equiv) in DCM for 1 h, the beads were incubated with 2-chlorophenyl isothiocyanate (3 equiv)/DIC (3 equiv) overnight. The resulting beads were thoroughly washed with DMF (3×10 mL), MeOH (3×10 mL), DCM (3×10 mL) and incubated with 95% TFA/H_2O for 2 h. The cleavage solution was collected by filtration and evaporated (30 mg), yield: 90%, purity: 100%. MS ($M+H^+$): 686.3. ^1H NMR (DMSO-d_6 500 MHz): δ 8.23 (d, 2H), 8.08 (t, 1H), 7.84 (t, 1H), 7.59 (d, 1H), 7.51 (t, 2H), 7.34 (t, 1H), 7.27 (d, 2H), 6.71 (s, 1H), 3.40–3.34 (m, 6H), 3.23 (m, 2H), 3.18 (m, 3H), 3.10 (m, 2H), 2.78 (m, 2H), 2.27 (s, 5H), 2.0–0.8 (br m, 12H). ^{13}C NMR (DMSO-d_6): δ 182.1, 174.2, 172.2, 169.8, 164.8, 144.5, 140.2, 136.1, 132.3, 130.3, 128.3, 127.9, 125.7, 124.8, 119.1, 116.4, 70.18, 70.14, 69.81, 69.65, 50.2, 40.75, 40.58, 40.41, 40.35, 40.28, 40.08, 39.91, 39.75, 39.21, 39.18, 31.2, 31.1.

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