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Solid-Phase Synthesis of 1,3-Dialkyl Quinazoline-2,4-Diones

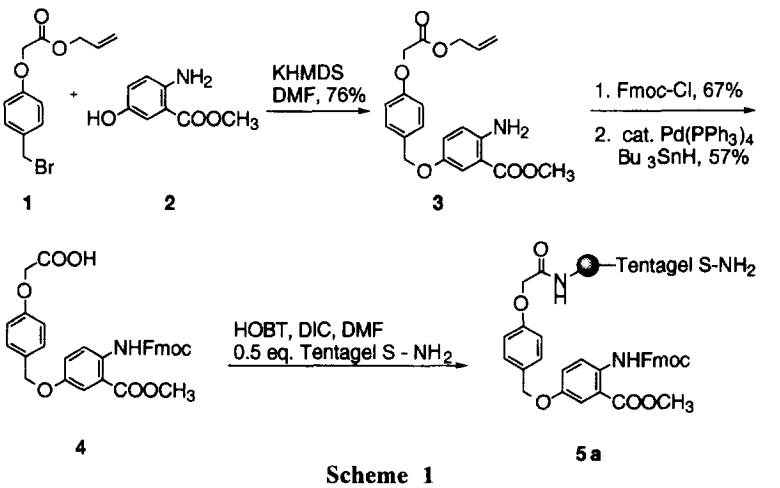
Brad O. Buckman* and Raju Mohan

New Lead Discovery
Berlex Biosciences
15049 San Pablo Ave, Richmond, CA 94804-0099

Abstract. A library of 1,3-dialkyl quinazoline-2,4-diones **9** has been synthesized on polymeric support by a three step approach. Addition of isocyanates or amines to a polymer-supported anthranilate derivative affords urea **6** which can be cyclized to 3-alkyl quinazolinedione **7**. N-Alkylation at the 1-position and cleavage from the resin affords **9a-o** in high yield and purity.

In the recent years, the desire to generate large numbers of diverse, novel, biologically active small molecules for drug discovery and development has caused the rapid growth of both combinatorial chemistry[1] and solid-phase organic synthesis.[2] A number of structural families known to possess high biological activity have been synthesized in this manner (e.g. benzodiazapines[3], β-lactams[4] and β-turn mimetics[5]). In recent years, quinazoline (benzopyrimidine) derivatives have attracted attention as pharmacophores,[6] especially as inhibitors of protein tyrosine kinases.[6b] In this communication, we wish to report the first solid-phase synthesis of 1,3-dialkyl quinazolinediones.

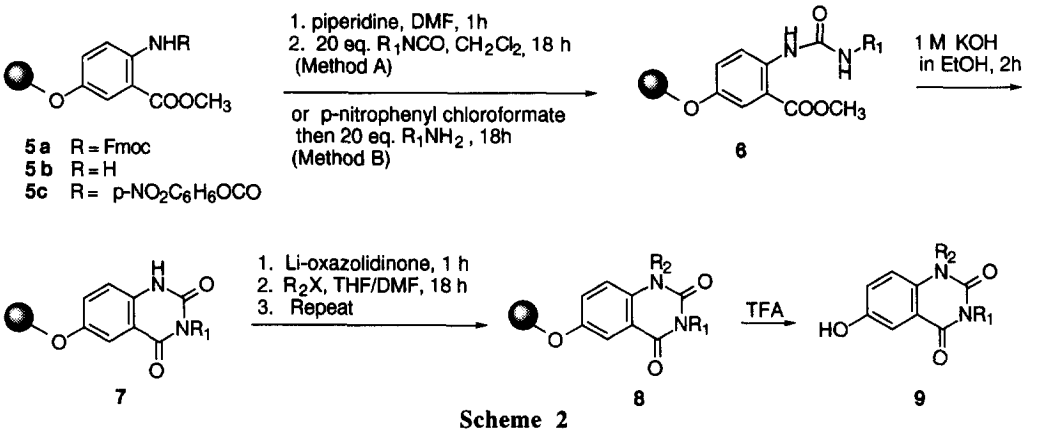
Our strategy towards 1,3-dialkyl quinazoline-2,4-dione **9** consists of three carbon-nitrogen bond-forming reactions on an anthranilate bound to solid support: urea formation, base-induced intramolecular cyclization, and N-alkylation. The nitrogen atoms at the 1 and 3 positions are used as sites for attachment of substituents R_1 and R_2. These substituents are derived from three readily available classes of reagents: isocyanates, primary amines and alkyl halides. This strategy allows a matrix synthesis of *m* isocyanates or primary amines and *n* alkyl halides to produce *m* x *n* compounds in a spatially distinct manner.[1b]



Scheme 1

The strategy for the solid-phase synthesis consists of an anthranilate derivative bound through a phenoxy functional group to a polymeric support. Since the synthesis uses strong base and protic solvents, we chose the acid cleavable linker ((4-hydroxymethyl)phenoxy)acetic acid and a Tentagel resin. As shown in Scheme 1, the potassium phenoxide of methyl 5-hydroxyanthranilate (**2**) (KHMDS, DMF, 0 °C) is added to benzyl bromide **1** to give anthranilate **3**.[7] Fmoc-protection of the free amine of **3** followed by removal of the allyl ester ($Pd(PPh_3)_4$, Bu_3SnH) affords carboxylic acid **4**.[7] Coupling to Tentagel S-NH_2 (loading ≈ 0.3 mmol/g, HOBT, DIC, DMF) gives polymer-bound Fmoc-protected anthranilate **5a**, which is the starting material for the quinazoline library formation.

The dialkyl quinazoline derivatives are synthesized from anthraniliate **5a**, as shown in Scheme 2. Removal of the Fmoc group from **5a** using 20% piperidine in DMF gives free amine **5b.** Subsequent addition of the isocyanate (20 eq R_1NCO, CH_2Cl_2, Method A[8]) forms urea **6**. The addition proceeds with alkyl, alkenyl and both electron-rich and deficient aryl isocyanates (R_1, Table 1). The resulting ureas **6** are cyclized in ethanolic KOH[9] to form 3-alkyl quinazolinediones **7**. The reaction proceeds nearly quantitatively for the addition and cyclization steps; < 2% of of **5b** or **6** are seen by HPLC. Treatment of **7** with lithium oxazolidinone[7] (THF, rt, 1.5 h) followed by addition of activated alkyl halides, such as alkyl iodides and benzylic or allylic bromides, gives di-alkyl quinazoline **8** bound to the solid support. Generally, the alkylation reactions do not proceed to completion either by using excess base, excess halide, or longer reaction times. However, by resubmitting the mixture to the alkylating conditions, < 5% of starting monoalkyl quinazoline **7** could be detected by HPLC. The final products are cleaved from the resin (95:5 TFA:H_20) to afford 1,3-dialkyl quinazoline-2,4-diones **9a-j** in > 80% yield by HPLC (Table 1).



Scheme 2

Alternatively, larger functional group diversity can be built into the quinazoline library by addition of primary amines to **5c** to generate urea **6** (Method B[8]). Thus, anthranilate **5b** is reacted with *p*-nitrophenylchloroformate to give reactive carbamate **5c**.[10] Addition of functionalized primary amines to *p*-nitrophenyl carbamate **5c** affords ureas **6** which are converted to quinazolines **9** as described above. Compounds **9k-o** were synthesized using this method (Table 1).

Table 1. 1,3-Dialkyl Quinazoline-2,4-Diones **9** from Solid-Phase Synthesis

Cmpd	R_1	R_2	yield (%)[a]
9a	o-methylphenyl	benzyl	94
9b	p-methoxyphenyl	benzyl	92
9c	methyl	1-(3-methylbutyl)	93
9d	allyl	ethyl	87
9e	p-fluorophenyl	methyl	95
9f	3,5-ditrifluoromethylphenyl	cinnamyl	94
9g	1-naphthyl	propyl	95
9h	phenyl	propyl	93
9i	p-nitrophenyl	benzyl	85
9j	benzyl	o-bromobenzyl	87
9k	4-(2-methylquinolinyl)	methyl	85
9l	1-(3-(1-imidazolyl))propyl	methyl	89
9m	1-(3-morpholinyl)propyl	ethyl	89
9n	1-(3-methylpiperazinyl)propyl	allyl	89
9o	3-pyridinyl	allyl	82

a) HPLC yield determined from area of peak corresponding to correct molecular weight by LC ES/MS.[11]

By choice of appropriate reagents from the commerical pool, quinazolines **9** with varied substituents R_1 and R_2 can be synthesized. Such substituents include alkyl, alkenyl, halo- and alkylaryl and heteroaryl. A representative selection of quinazolines synthesized are shown in Table 1. The products were analyzed for purity by HPLC (C_{18}, CH_3CN/H_2O), and give satisfactory LC/MS[11] and ^1H NMR data.[12]

In conclusion, we have developed a solid-phase synthesis of 1,3-dialkyl quinazoline-2,4-dione **9** which is derived from anthranilic acid derivatives **5** and commercially available amines or isocyanates and alkylating agents. The synthesis proceeds in high yield and purity and is amenable to automation. Therefore, this approach offers the potential of providing diverse libraries of quinazoline derivatives for assay in biological systems.

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8. General experimental procedure: **Method A:** Polymer (Tentagel S-NH_2) supported anthranilic acid derivative **5a** (0.20 g, 0.06 mmol) is slurried in 2 mL DMF . Piperidine (0.5 mL) is added and the reaction is shaken for 1 h to form free amine **5b**. The resin is rinsed with DMF then CH_2Cl_2. Methylene chloride (2 mL) is added and the isocyanate (1.16 mmol, 20 equiv.) is added. The reaction is shaken for 18 h to form urea **6**, then the resin is rinsed with CH_2Cl_2 and EtOH. 1M KOH in ethanol (2 mL) is added and the mixture is shaken for 1 h to give mono alkyl quinazoline **3**, then the resin is rinsed with EtOH and THF. THF (1 mL) is added to each vessel followed by lithium benzyloxazolidinone (3 mL, 0.3 M in tetrahydrofuran, 0.90 mmol, 15.5 equiv.). The reaction is shaken for 1.5 h. Alkylating reagent (R_2X) (2.32 mmol, 40 equiv.) is added followed by DMF (1 mL), and the reaction is shaken for 18 h. The resin is filtered and the addition of lithium benzyloxazolidinone and alkylating agent is repeated as above to give dialkyl quinazoline **4**. The resin is rinsed with THF, 1:1 THF/water, then THF again. Trifluoroacetic acid (95% in water, 2 mL) is added to the resin and shaken for 1 h. The resulting solution is filtered from the resin, diluted with water and lyophilized to provide quinazoline **9**. **Method B:** To free amine **5b** above is added 0.5 M p-nitrophenyl chloroformate and 0.5 M triethylamine in 1:1 THF/CH_2Cl_2 (2 mL) and the reaction is shaken for 18 h to form carbamate **5c**. The resin is rinsed with CH_2Cl_2, then a primary amine (2 mL of 0.5 M in CH_2Cl_2) is added and the reaction is haken for 12 h to form urea **6**. The resulting urea is treated as above to form **9.**
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11. LC ES/MS was performed on a Sciex API III Plus.
12. ^1H NMR (300MHz, DMSO-d_6) for **9a**: 2.15 (s, 3), 5.28 (br s, 2), 7.21-7.44 (m, 12).

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