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Solid-phase synthesis of quinazolin-4(3*H*)-ones with three-point diversity†

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Abstract—A versatile method for the solid-phase synthesis of differentially substituted quinazolin-4(3*H*)-ones has been developed using immobilized arylguanidines. The latter were obtained by treating the amino group of polymer-linked anthranilamide with isothiocyanates followed by coupling with secondary amines in the presence of DIC. Finally a cyclative cleavage strategy was applied to give the desired compounds in high yields and purities. © 2002 Published by Elsevier Science Ltd.

The preparation of combinatorial libraries of heterocyclic compounds by solid-phase synthesis is of great interest for accelerating lead discovery in pharmaceutical research. There has been an emphasis on the preparation of heterocycles with extensive chemical diversity, which can give rise to structural members with more desirable physical and biological properties. Furthermore, these structurally diverse libraries can easily be clustered into subsets and screening through in vitro ADME tests may provide high quality data for building, testing and refining predictive models.[1]

Among the various classes of heterocyclic compounds, quinazolin-4(3*H*)-ones form an important component of pharmacologically active compounds, as they are associated with a wide spectrum of biological activities ranging from anticonvulsant[2] and antibacterial[3] to antidiabetic.[4] Therefore, the development of efficient strategies for the combinatorial and parallel synthesis on a solid support of this interesting target allowing the introduction of a high degree of molecular diversity has attracted considerable attention. In earlier strategies, solid-phase syntheses of quinazolin-4(3*H*)-ones were carried out either by the cyclocondensation of anthranilic acid with amino acids and aldehydes[5] or by aza-Wittig mediated annulation involving *o*-azidobenzoic acid.[6] Other methods reported recently involve cyclocondensation of 2-nitrobenzyl chloride with aryl amines[7] and thioureas with isatoic anhydride.[8] In this communication we report an efficient method for the solid-phase synthesis of quinazolin-4(3*H*)-ones with three-point diversity from versatile building blocks, which include substituted anthranilic acids, isothiocyanates and disubstituted secondary amines. The present investigation is in continuation of our ongoing interest in the design and synthesis of combinatorial libraries of small organic molecules[9–13] and natural products of medicinal importance[14,15] with high chemical diversity.

The solid-phase synthesis of quinazolin-4(3*H*)-ones is outlined in Scheme 1. Monitoring the progress of reactions on solid-phase by single bead FTIR and cleavage of numerous 2–5 mg of resin bound samples with subsequent LC–MS analysis of the resultant products accompanied each step during optimization of the reaction conditions. The final compounds were subjected to purification using high throughput LC–MS (Lachrom 8000; Merck) and characterized by ^{1}H NMR.

In the first step, Fmoc-anthranilic acid was loaded on to Rink Amide AM resin [Copoly (styrene–1%DVB) Novabiochem, bead size 200–400 mesh; 0.63 mmol/g)] using the 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluranium tetrafluoroborate (TBTU) and 1-hydroxybenzotriazole (HOBt) procedure. The completion of loading was monitored by a negative Kaiser test. Wang resin was not chosen in order to avoid premature cyclization or transesterification during the guanylation step. This was followed by removal of the Fmoc group with 25% piperidine–DMF and treatment of the resulting amine with isothiocyanate in DMF for 16 h at rt to give thiourea **2** in high yield and purity. The reaction progress could be qualitatively monitored by the analysis of a single bead FTIR spec-

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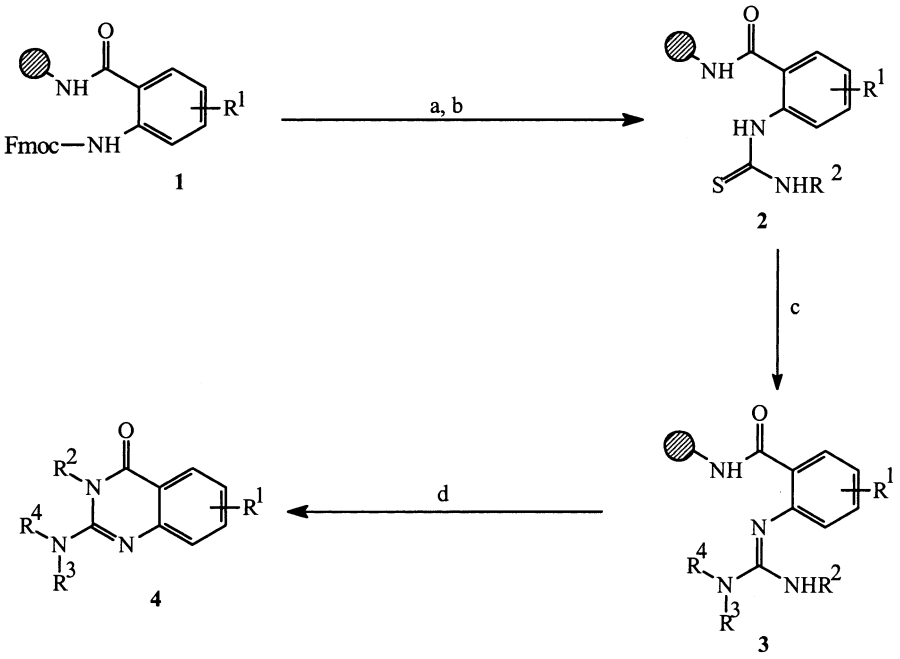

Scheme 1. *Reagents and conditions*: (a) 25% piperidine/DMF, (b) isothiocyanates, 16 h, rt, (c) secondary amine, DIC, 16 h, rt, (d) 10% AcOH/DCM, 16 h, rt.

Table 1. Purity and ESMS of some representative quinazolin-4(3*H*)-ones

R^1	R^2	HNR^3, R^4	ESMS $(M+H)^+$	Yield*/purity (%)
Anthranilic acid	$PhCH_2$	$R^3=C_4H_9$, $R^4=CH_3$	322.27	62/80
Anthranilic acid	Ph	$R^3=C_4H_9$, $R^4=CH_3$	308.40	60/92
Anthranilic acid	$PhCH_2$	$R^3=R^4=$morpholine	322.20	54/72
Anthranilic acid	Ph	$R^3=R^4=N$-methylpiperazine	321.53	59/88
3-Amino-2-naphthoic acid	$PhCH_2$	$R^3=R^4=N$-methylpiperazine	385.13	67/90
Anthranilic acid	C_2H_5	$R^3=R^4=N$-methylpiperazine	273.73	60/70
Chloroanthranilic acid	C_2H_5	$R^3=R^4=$4-benzylpiperidine	382.03	50/70
Chloroanthranilic acid	Ph	$R^3=R^4=$4-benzylpiperidine	430.07	52/72
3-Amino-2-naphthoic acid	Et	$R^3=C_4H_9$, $R^4=CH_3$	310.10	61/75
Anthranilic acid	$PhCH_2$	$R^3=R^4=$4-benzylpiperidine	410.73	54/70
Anthranilic acid	Ph	$R^3=R^4=$4-benzylpiperidine	396.47	53/85
3-Amino-2-naphthoic acid	Ph	$R^3=R^4=$4-benzylpiperidine	446.13	65/90

* Isolated yields following purification by LC–MS.

trum by following the disappearance of the N–H stretch at 3459 cm^{-1} and the appearance of a C=S stretch between 1130 and 1400 cm^{-1}. Condensation of **2** with a secondary amine was carried out in the presence of DIC for 16 h at rt to give immobilized substituted guanidine **3**. FTIR revealed the disappearance of the band due to the C=S stretch and the appearance of a C–H stretch between 2800 and 3300 cm^{-1} due to alkanes. Finally, intermediates **3** were smoothly cyclized to quinazolin-4(3*H*)-ones by treating the resin with a mixture of 10% AcOH–DCM at rt for 16 h. The desired heterocycle **4** was obtained in high yield and purity. To investigate further the scope and limitation of our strategy, we synthesized a library of 36 compounds using three anthranilic acid derivatives, three isothiocyanates and four secondary amines using an automated multiple organic synthesizer (Advanced Chemtech). The compounds were obtained in good yields with purities ranging from 70 to 93% (Table 1). The compounds were characterized using LC–MS and ^1H NMR.[16]

In summary we have developed a versatile approach for the solid-phase synthesis of quinazolin-4(3*H*)-ones with three-point diversity from polymer bound aryl guanidines. It can be successfully used for the generation of large libraries of quinazolin-4(3*H*)-ones using an automated synthesizer.

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16. General experimental procedure for **4**: The Fmoc group of the Rink Amide AM resin (100 mg; 0.063 mmol) was removed by treating with 25% piperidine in DMF (1 ml) twice for 5 and 25 min. The resin was drained and washed with DMF (9×5 ml). The resin so obtained was coupled with Fmoc anthranilic acid (3-fold) in the presence of TBTU (3-fold) and HOBt for 16 h. The resin was then washed sequentially with DMF, DCM and finally with ether to give **1**. Completion of the reaction was confirmed by a negative Kaiser test. The Fmoc group of **1** was removed in a similar manner as described above and the resulting free amine was treated with benzylisothiocyanate (10 fold) in DCM (1 ml) for 16 h at rt. Thereupon the resin was washed successively with DMF (3×2 min), MeOH (3×2 min), DCM (3×2 min) and finally dried in vacuo to give **2**. Next the resin **2** was coupled with a secondary amine (5-fold) in the presence of DIC (1 M). After shaking at rt for 16 h, the resin was successively washed with DMF (3×2 min), 0.1% AcOH/DCM (2×2 min), MeOH (3×2 min), DCM (3×2 min) and finally dried in vacuo to give **3**. Finally, resin **3** was subjected to cyclative cleavage with a mixture of 10% AcOH in DCM (1 ml) for 16 h at rt. The resulting mixture was filtered and evaporated to dryness in vacuo. The residue was dissolved in ^{t}BuOH/water (4:1) and freeze dried to give the desired quinazolin-4-ones **4**.

3-Benzyl-2-(4-methyl-piperazin-1-yl)-3*H*-quianzolin-4-one: LC–MS purity 93% (C18 reverse-phase column (10×50 mm, 5 μm) with a linear gradient 10–98% MeOH in water (v/v) over 11 min, flow rate 6.0 ml/min), ^{1}H NMR (300 MHz, CD_3OD): δ 8.07, 8.05 (d, 1H, $J=7.8$ Hz, Ar-H); 7.69 (t, 1H, $J=7.5$ Hz, Ar-H); 7.55, 7.52 (d, 1H, $J=8.1$ Hz, Ar-H); 7.35 (t, 1H, $J=7.5$ Hz, Ar-H); 7.26–7.13 (m, 5H, 5×Ar-H); 5.33 (s, 2H, CH_2Ph); 3.14–3.17 (m, 4H, 2×CH_2N); 2.53 (m, 4H, 2×CH_2N); 2.29 (s, 3H, CH_3N), ESI-MS: $m/z=335$ $[M+H]^+$.

3-Benzyl-2-(butyl-methyl-amino)-3*H*-benzo[*g*]quinazolin-4-one: LC–MS purity 88% (C18 reverse-phase column (10×50 mm, 5 μm) with a linear gradient 10–98% MeOH in water (v/v) over 11 min, flow rate 6.0 ml/min), ^{1}H NMR (300 MHz, CD_3OD): δ 8.73 (s, 1H, Ar-H); 8.04–8.02 (d, 1H, $J=8.4$ Hz, Ar-H); 8.02 (s, 1H, Ar-H); 7.94–7.97 (d, 1H, $J=8.4$ Hz, Ar-H); 7.59 (t, 1H, $J=7.2$ Hz, Ar-H); 7.48 (t, 1H, $J=7.2$ Hz, Ar-H); 7.16–7.28 (m, 5H, 5×Ar-H); 5.40 (s, 2H, CH_2Ph); 3.13 (t, 2H, $J=7.2$ Hz, N-CH_2); 2.88 (s, 3H, N-CH_3); 1.48–1.58 (q, 2H, $J=6.12$ Hz, CH_2); 1.11–1.18 (m, 2H, CH_2); 0.82 (t, 3H, $J=7.35$ Hz, CH_3), ESI-MS: $m/z=372.20$ $[M+H]^+$.