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# A Traceless Approach for the Parallel Solid-Phase Synthesis of 2-(Arylamino)quinazolinones

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**Abstract:** A traceless approach for the parallel solid-phase synthesis of 2-arylamino-substituted quinazolinones is described. Acylation of MBHA resin with *o*-nitrobenzoic acid derivatives, followed by reduction of the nitro group with tin chloride, generated a resin-bound *o*-anilino derivative. Reaction of resin-bound *o*-anilino derivative with arylisothiocyanates yielded resin-bound thioureas, which reacted with amines in the present of Mukaiyama's reagent (2-chloro-1-methylpyridinium iodide) to afford resin-bound guanidines. Following intramolecular cyclization of the resin-bound guanidines during cleavage from the resin by HF/anisole (95/5) for 1.5 h at 0 °C, the desired products were obtained in good yield and purity.

Solid-phase parallel synthesis is used worldwide to generate libraries of small organic compounds to accelerate the drug discovery process.[1] Substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents.[2] As a result, an increasing range and number of pharmaceutically useful heterocyclic compounds recently have been prepared using solid-phase methodology.[3−6] This approach permits the rapid synthesis of large numbers of individual compounds, as well as mixture-based combinatorial libraries in a short time period and facilitates their use in high-throughput screening.[7] The quinazoline skeleton (Figure 1) is found in many biologically active compounds and is known to have useful therapeutic implications.[8] The 2-amino-substituted quinazolines have been shown to be potential histamine H2 antagonists,[9] thymidylate synthase inhibitors,[10] cognition enhancement agents,[11] and inhibitors of tumor necrosis factor.[12] Similarly, diarylguanidines have attracted attention in the field of medicinal chemistry due to the hydrogen-bonding acceptor and donor abilities of the guanidino group playing important roles in supramolecule formation and in bioactive substances.[13] Recently, several reports have described solid-phase syntheses of different quinazolinone derivatives.[14] However, one of the challenges of the solid-phase combinatorial synthesis of heterocyclic compounds is developing chemical routes that provide access to the target compounds without leaving any trace of the linker used for tethering the starting building blocks to the solid support. As part of our ongoing efforts directed toward the solid-phase synthesis of small molecule and heterocyclic compounds and the generation of combinatorial libraries of organic compounds,[15] we report here a novel traceless, chemoselective, approach for the solid-phase synthesis of 2-arylamino-substituted quinazolinone containing the diaryl

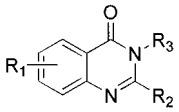


**FIGURE 1.** Quinazolinone skeleton.

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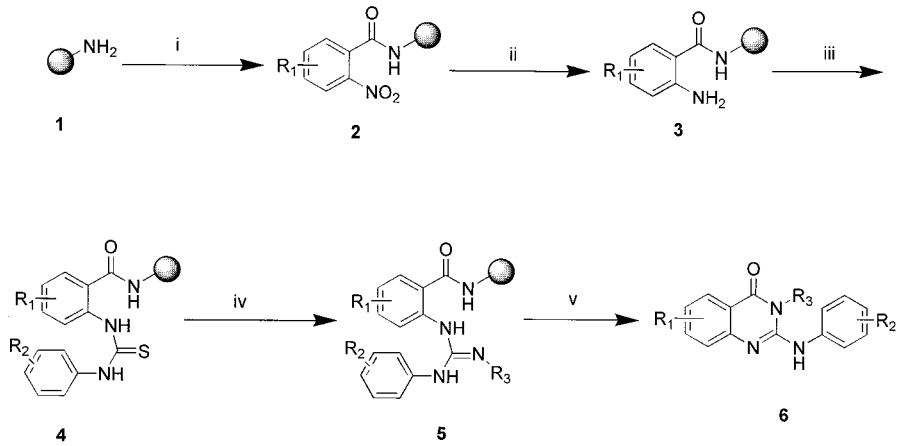
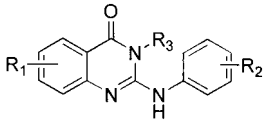
**SCHEME 1. Solid-Phase Synthesis of 2-Arylamino-Substituted Quinazolinones**[a]



[a] Reagents and conditions: (i) *o*-nitrobenzoic acid (6 equiv, 0.1 M), HOBT (6 equiv, 0.1 M), DIC (6 equiv, 0.1 M) in DMF, rt, overnight; (ii) $SnCl_2$ (20 equiv, 2 M) in DMF, rt, overnight; (iii) arylisothiocyanate (6 equiv, 0.1 M) in DCM, rt, overnight; (iv) Mukaiyama's reagent (6 equiv, 0.1 M), amine (6 equiv, 0.1 M) in DCM, rt, overnight; (V) HF, 0 °C, 1.5 h.

**TABLE 1. Individual 2-Arylamino-Substituted Quinazolinones 6**



| entry | product | $R_1$ | $R_2$ | $R_3$ | yield[a] | purity[b] | MW (found)[c] |
|---|---|---|---|---|---|---|---|
| 1 | **6a** | H | 2-Cl,4-$NO_2$ | $(CH_3)_2CHCH_2$ | 86 | 85 | 372.8 ($[M + H]^+$) |
| 2 | **6b** | H | 4-$NO_2$ | $(CH_3)_2CHCH_2CH_3CH$ | 89 | 82 | 366.4 ($[M + H]^+$) |
| 3 | **6c** | H | 2,3-di-Cl | $(CH_3)_2CHCH_2$ | 83 | 84 | 362.2 ($[M + H]^+$) |
| 4 | **6d** | H | 3-Cl | $(CH_3)_2CHCH_2$ | 91 | 76 | 327.1 ($[M + H]^+$) |
| 5 | **6e** | H | 4-CN | $(CH_3)_2CHCH_2$ | 88 | 81 | 318.3 ($[M + H]^+$) |
| 6 | **6f** | H | H | $(CH_3)_2CHCH_2$ | 86 | 58 | 293.1 ($[M + H]^+$) |
| 7 | **6g** | H | 4-$NO_2$ | $C_6H_5CH_2CH_2CH_2$ | 85 | 78 | 400.1 ($[M + H]^+$) |
| 8 | **6h** | H | 4-$NO_2$ | $CH_3(CH_2)_4CH_2$ | 88 | 82 | 366.4 ($[M + H]^+$) |
| 9 | **6i** | 5-$CH_3O$ | 4-$NO_2$ | $(CH_3)_2CHCH_2CH_3CH$ | 85 | 76 | 396.4 ($[M + H]^+$) |
| 10 | **6j** | 5-$(CH_2)_5N$ | 3,5-di-Cl | $CH_3(CH_2)_2CH_2$ | 86 | 67 | 445.4 ($[M + H]^+$) |
| 11 | **6k** | 5-$(CH_2)_5N$ | 4-$NO_2$ | $CH_3(CH_2)_2CH_2$ | 88 | 79 | 421.4 ($[M + H]^+$) |

[a] Percent yields are based on the weight of crude material and are relative to the initial loading of the resin. The isolated yields are listed in the Experimental Section. [b] The purity of the crude material was estimated based on analytical traces at $\lambda = 214$ nm. [c] Confirmed by mass spectra (ESI).

guanidine and quinazolinones functionalities encompassing three positions of diversity.

The parallel solid-phase synthesis of 2-amino-substituted quinazolinones was carried out on the solid-phase using the "tea-bag" methodology.[1b] The reaction sequence is illustrated in Scheme 1.

Starting from *p*-methylbenzhydrylamine (MBHA) resin **1**, a specific *o*-nitrobenzoic acid was coupled to the resin. Reduction of aromatic nitro group of the resin-bound *o*-nitrobenzamide **2** with tin(II) chloride yielded the corresponding *o*-aniline **3** (Scheme 1). The resin was dried and the resulting aniline **3** was reacted with an arylisothiocyanate to provide resin-bound thiourea **4**. The resin-bound thiourea **4** was reacted with Mukaiyama's reagent (2-chloro-1-methylpyridinium iodide) and a primary amine in dichloromethane at room-temperature overnight to give the corresponding guanidine **5**. The desired 2-amino-substituted quinazolinone **6** was obtained via intramolecular cyclization with concomitant cleavage from the resin using HF for 1.5 h at 0 °C in good yield and purity. The products were characterized by electrospray LC-MS under ESI conditions, as well as $^1H$ and $^{13}C$ NMR. Due to the difference of nucleophilicity in the two adjacent nitrogen atoms in guanidine **5,** the intramolecular cyclization was highly chemoselective. Thus, only one isomer of **6** was found by LC-MS and NMR spectra. The results are summarized in Table 1. We investigated the potential use of TFA as the cyclization/cleavage agent. No product or starting material **5** was released from the resin using a range of concentrations of TFA in dichloromethane (55−90%). It seems this type of reaction occurred only under the strong acidic conditions found when using HF.

We also investigated using 5-fluoro-2-nitrobenzoic acid as an *o*-nitrobenzoic acid derivative in order to increase the numbers of intermediate **2** (Scheme 2). Thus, resin-bound 5-piperidine-*o*-nitrobenzamide **2j**, obtained by

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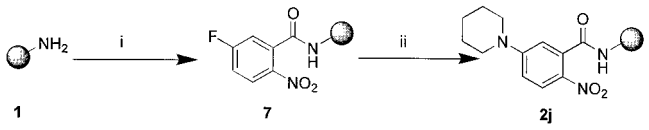
**SCHEME 2. Solid-Phase Synthesis of Resin-Bound 5-Piperidine-*o*-nitrobenzamide 2j**[a]




[a] Reagents and conditions: (i) 5-Fluoro-2-nitrobenzoic acid (6 equiv, 0.1 M), HOBT (6 equiv, 0.1 M), DIC (6 equiv, 0.1 M) in DMF, rt, overnight; (ii) piperidine (10 equiv, 0.1 M) in DMF, rt, overnight.

displacement of the fluoro group by piperidine of resin-bound 5-fluoro-*o*-nitrobenzamide **7**, also gave satisfactory results (**6j**, **6k**).

## Summary

In summary, we have demonstrated a traceless approach for the parallel solid-phase synthesis of *o*-arylamino-substituted quinazolinones from common building blocks, such as 2-nitrobenzonic acid derivatives ($R_1$), arylisocyanates ($R_2$), and amines ($R_3$). The reaction conditions are amenable to the synthesis of large combinatorial libraries.

## Experimental Section

NMR spectra were recorded at 500 and 125 MHz for $^1$H NMR and $^{13}$C NMR, respectively. NMR chemical shifts are expressed in ppm relative to the internal solvent peak. Coupling constants were calculated in hertz.

**General Procedure for the Synthesis of 2-Arylamino-Substituted Quinazolinones**. A 100 mg amount of *p*-methylbenzhydrylamine (MBHA) resin (1 mequiv/g, 100−200 mesh) was sealed within a polypropylene mesh packet, Reactions were carried out in polypropylene bottles. The resin was washed with dichloromethane (DCM), followed by neutralization with 5% diisopropylethylamine (DIEA) in DCM, and washed with DCM. An *o*-nitrobenzoic acid derivative (6 equiv, 0.1 M) was coupled to the resin using DIC and HOBt (6 equiv, 0.1 M each) in dimethylformamide (DMF) at room-temperature overnight, followed by washes with DMF (three times), DCM (two times), and methanol (three times). The resulting resin-bound *o*-nitrobenzamide was treated with tin(II) chloride dihydrate (20 equiv, 2 M) in DMF at room-temperature overnight, followed by washes with DMF (six times), DCM (three times), and methanol (three times). The resin was treated with arylisothiocyanate (6 equiv, 0.1 M) in anhydrous DCM overnight to yield resin-bound thiourea **4**. The resin was washed with DCM (two times), IPA (two times), and DCM (two times). The resin-bound thiourea was reacted with amine (6 equiv, 0.1 M) in the present of the Mukaiyama's reagent (2-chloro-1-methylpyridinium iodide) (6 equiv, 0.1 M) in anhydrous DCM overnight to afford a resin-bound guanidine. After being washed with DMF (three times), MeOH (three times), $CH_2Cl_2$ (three times), the resin was cleaved by HF at 0 °C for 1.5 h and the cyclization product **6** was extracted with 95% acetic acid in $H_2O$ and lyophilized. Following purification by RP-HPLC, the identity of the compounds was confirmed by LC-MS, $^1$H NMR, and $^{13}$C NMR.

**Synthesis of Resin-Bound 5-Piperidine-*o*-nitrobenzamide 2j**. A 100 mg amount of MBHA resin (1 mequiv/g, 100−200 mesh) was sealed within a polypropylene mesh packet. Reactions were carried out in polypropylene bottles. The resin was washed with dichloromethane (DCM), followed by neutralization with 5% diisopropylethylamine (DIEA) in DCM, and washed with DCM. 5-Fluoro-2-nitrobenzoic acid (6 equiv, 0.1 M) was coupled to the resin using DIC and HOBt (6 equiv, 0.1 M each) in dimethylformamide (DMF) at room-temperature overnight, followed by washes with DMF (three times), DCM (two times), and methanol (three times). The resulting resin-bound 5-fluoro-*o*-nitrobenzamide was treated with piperidine (10 equiv, 0.1 M) in DMF at room-temperature overnight to yield **2j**.

**2-(2-Chloro-4-nitrophenyl)-3-isobutylquinazolin-4(3*H*)-one (6a)**. Isolated yield: 45%. LC-MS (ESI) *m/z* 373.0 (M + H$^+$). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 0.83 (d, $J$ = 6.7 Hz, 6H), 1.96 (m, 1H), 3.06 (m, 1H), 3.20 (m, 1H), 6.48 (brs, 1H), 7.18 (t, $J$ = 7.6 Hz, 1H), 7.37 (d, $J$ = 8.2 Hz, 1H), 7.66−7.69 (m, 1H), 7.91−7.96 (m, 2H), 8.41−8.43 (m, 1H). 8.63 (m, 1H), $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 20.0, 27.1, 48.4, 116.0, 122.2, 124.0, 124.1, 125.6, 125.7, 126.5, 133.2, 134.2, 135.1, 138.4, 148.7, 148.9, 160.7.

**3-(1,3-Dimethylbutyl)-2-(4-nitrophenyl)quinazolin-4(3*H*)-one (6b)**. Isolated yield: 43%. LC-MS (ESI) *m/z* 367.0 (M + H$^+$). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 0.84 (d, $J$ = 6.7 Hz, 3H), 0.87 (d, $J$ = 6.7 Hz, 3H), 1.09 (d, $J$ = 6.4 Hz, 3H), 1.13−1.19 (m, 1H), 1.43−1.48 (m, 1H), 1.41−1.57 (m, 1H), 4.31−43.5 (m, 1H), 5.90 (brs, 1H), 7.18−7.21(t, $J$ = 7.4 Hz, 1H), 7.40−7.41 (d, $J$ = 7.8 Hz, 1H), 7.66−7.73 (m, 3H), 7.91−7.96 (m, 1H), 8.44−8.45 (m, 1H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 20.6, 22.4, 22.8, 24.5, 44.6, 45.7, 116.3, 122.5, 123.1, 125.3, 126.6, 131.0, 131.7, 134.9, 140.5, 148.2, 149.0, 161.2.

**2-[(2,3-Dichlorophenyl)amino]-3-isopropylquinazolin-4(3*H*)-one (6c)**. Isolated yield: 41%. LC-MS (ESI) *m/z* 363.9 (M + H$^+$). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 0.82 (d, $J$ = 3.1 Hz, 3H), 0.84 (d, $J$ = 3.4 Hz, 3H), 1.93−1.99 (m, 1H), 3.13−3.16 (m, 2H), 6.68 (brs, 1H), 7.18 (t, $J$ = 7.4 Hz, 1H), 7.39 (d, $J$ = 8.2 Hz, 1H), 7.58−7.93 (m, 5H), $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 19.9, 27.2, 48.44, 115.9, 122.5, 123.4, 126.7, 129.6, 130.3, 131.5, 132.0, 133.0, 133.9, 135.1, 149.2, 160.5.

**2-[(3-Chlorophenyl)amino]-3-isopropylquinazolin-4(3*H*)-one (6d)**. Isolated yield: 42%. LC-MS (ESI) *m/z* 328.0 (M + H$^+$). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 0.82(d, $J$ = 4.0 Hz, 3H), 0.84 (d, $J$ = 4.2 Hz, 3H), 1.92−1.97 (m, 1H), 3.10 (m, 1H), 3.21 (m, 1H), 7.20−7.93 (m, 9H), $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 19.9, 27.1, 48.5, 116.4, 126.7, 128.1, 129.6, 129.8, 131.6, 134.0, 134.9, 149.9.

**2-[(4-Cyanophenyl)amino]-3-isopropylquinazolin-4(3*H*)-one(6e)**. Isolated yield: 39%. LC-MS (ESI) *m/z* 319.0 (M + H$^+$). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 0.82(d, $J$ = 6.4 Hz, 6H), 1.92−1.97 (m, 1H), 3.14−3.17(t, $J$ = 6.6 Hz, 2H), 6.68 (brs, 1H), 7.24−8.12 (m, 8H), $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 19.9, 27.0, 48.6, 112.7, 116.2, 118.4, 123.0, 126.8, 130.8, 134.4, 135.1, 138.6, 149.7, 160.7.

**2-Anilino-3-isobutylquinazolin-4(3*H*)-one (6f)**. Isolated yield: 31%. LC-MS (ESI) *m/z* 294.0 (M + H$^+$). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 0.80(d, $J$ = 6.4 Hz, 6H), 1.91 (m, 1H), 3.12−3.15(t, $J$ = 6.5 Hz, 2H), 7.12 (brs, 1H), 7.37−7.91 (m, 9H), $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 19.8, 27.1, 48.6, 112.8, 116.9, 118.3, 122.8, 126.6, 131.8, 135.3, 136.2, 149.7, 160.7.

**2-[(4-Nitrophenyl)amino]-3-(3-phenylpropyl)quinazolin-4(3*H*)-one (6g)**. Isolated yield: 32%. LC-MS (ESI) *m/z* 401.1 (M + H$^+$). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 1.79−1.86(m, 2H), 2.55−2.58 (t, $J$ = 7.6 Hz, 2H), 3.33−3.36 (m, 2H), 6.45 (brs, 1H), 7.41−8.45 (m, 13H), $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 30.2, 34.26, 39.2, 120.5, 124.6, 125.4, 125.6, 126.7, 127.3, 127.6, 128.1, 128.3, 128.4, 129.8, 129.9, 135.3, 139.6, 140.2, 143.9, 148.9, 149.4, 160.2.

**3-Hexyl-2-[(4-nitrophenyl)amino]quinazolin-4(3*H*)-one (6h)**. Isolated yield: 37%. LC-MS (ESI) *m/z* 367.1 (M + H$^+$). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 0.84−0.86 (t, $J$ = 6.4 Hz, 3H), 1.24−1.27 (m, 6H), 1.49−1.52 (m, 2H), 3.27−3.31 (m, 2H), 6.36 (brs, 1H), 7.18−8.45 (m, 8H), $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 14.1, 22.8, 27.8, 30.6, 31.8, 39.1, 120.8, 124.8, 125.3, 125.7, 127.3, 127.5, 127.8, 128.2, 135.4, 139.8, 143.9, 148.9, 149.5, 160.3.

**3-(1,3-Dimethylbutyl)-6-methoxy-2-[(4-nitrophenyl)amino]quinazolin-4(3*H*)-one (6i)**. Isolated yield: 38%. LC-MS (ESI) *m/z* 397.2 (M + H$^+$). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 0.84−0.85 (d, $J$ = 6.6 Hz, 3H), 0.87−0.88 (d, $J$ = 6.6 Hz, 3H), 1.09−1.11 (d, $J$ = 6.5 Hz, 3H),1.15−1.20 (m, 1H), 1.43−1.49 (m, 1H), 1.49−1.55 (m, 1H), 3.81 (s, 3H), 4.25−4.27 (m, 1H), 6.15 (brs, 1H), 7.35−8.46 (m, 7H), $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 20.6, 22.4, 22.8, 24.6, 44.6, 45.6, 117.6, 125.3, 125.4, 125.8, 126.0, 131.0, 131.6, 134.8, 140.5, 148.2, 149.3, 160.5.

**3-Butyl-2-[(3,5-dichlorophenyl)amino]-6-piperidin-1-ylquinazolin-4(3*H*)-one (6j)**. Isolated yield: 32%. LC-MS (ESI) *m/z* 445.5 ($M + H^+$). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 0.86−0.89 (t, $J$ = 7.6 Hz, 3H), 1.24−1.29 (m, 2H), 1.47−1.53 (m, 2H),1.58 (brs, 2H), 1.74 (brs, 4H), 3.30−3.31 (m, 6H), 7.41−7.85 (m, 6H), $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 13.7, 19.4, 24.5, 30.6, 62.2, 69.7, 116.5, 122.2, 126.5, 128.7, 129.6, 134.9, 149.1, 170.5.

**3-Butyl-2-[(4-nitrophenyl)amino]-6-piperidin-1-ylquinazolin-4(3*H*)-one (6k)**. Isolated yield: 35%. LC-MS (ESI) *m/z* 422.1 ($M + H^+$). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 0.86−0.89 (t, $J$ = 7.6 Hz, 3H), 1.23−1.27 (m, 2H), 1.47−1.50 (m, 2H),1.59 (brs, 2H), 1.75 (brs, 4H), 3.28−3.33 (m, 6H), 7.44−7.47 (d, $J$ = 8.7 Hz, 1H), 7.72−7.74 (m, 4H), 8.45−8.47 (m, 2H), $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 13.7, 19.4, 24.4, 30.6, 116.5, 125.4, 126.5, 131.3, 148.2, 149.1, 160.7.

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**Supporting Information Available:** Copies of LC-MS of all compounds; $^1$H and $^{13}$C NMR spectra of compounds **6a**−**f**,**i**−**k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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