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Efficient solid-phase synthesis of quinazoline-2,4-diones with various substituents on aromatic rings

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Abstract—We have developed a method for the solid-phase synthesis of quinazoline-2,4-diones with various substituents on the aromatic ring. Although there have been numerous reports of the solid-phase synthesis of quinazoline-2,4-diones, they were not applicable to the synthesis of the quinazoline-2,4-diones with electron-withdrawing substituents on the aromatic ring. Considering the poor nucleophilicity of the amino group of anthranilic acids, coupling of anthranilic acids to solid-supported amines was investigated without protecting the amino group. Various anthranilamides were prepared using anthranilic acids with electron-withdrawing substituents because a wide range of anthranilic acids are commercially available. These anthranilamides were successfully cyclized with carbonyldiimidazole to give quinazoline-2,4-diones with high purity.

1. Introduction

Solid-phase organic synthesis of non-peptide compounds is emerging as an important tool for drug discovery.[1] The synthesis of heterocyclic compounds on solid-support, in particular, has been a focus of recent investigation because of their applications toward a variety of drug targets. Among various heterocycles, quinazolines are particularly attractive pharmacophores because of their wide range of bioactivities.[2] As a part of our project to develop efficient synthetic methods for quinazoline derivatives,[3] we investigated the solid-phase synthesis of quinazoline-2,4-diones. Among numerous reports of the solid-phase synthesis of quinazoline-2,4-diones,[4] we are especially interested in the synthesis of quinazoline-2,4-diones using primary anilines as starting materials,[3d,5] because the bioactivities of similar pharmacophores such as 4-quinazolinones,[3b,6] 2-thioxoquinazolin-4-ones,[3a,c] benzimidazolone,[7] and hydantoin[8] can be compared efficiently. (Fig. 1) Although solid-phase syntheses of quinazoline-2,4-diones with limited substituents on the aromatic ring have been achieved,[3d,4] the synthesis of quinazoline-2,4-diones with various substituents on the aromatic ring was found to be difficult with the previous methods. For example, synthesis of quinazoline-2,4-diones **3** via urea **2** which was synthesized from **1** using methyl anthranilates and *p*-nitrophenyl chloroformate was reported.[5] (Scheme 1) However, we found the formation of the urea bond of **2** was difficult for methyl anthranilates with electron-withdrawing substituents due to the poor nucleophilicity thereof (data not shown). 2-Methoxycarbonyl phenylisocyanate[5] or isatoic acid[6] was also used for the preparation of **2**. However, the commercial availability of these reagents is very limited. On the other hand, the synthesis of **5** has been achieved using 2-nitrobenzoic acids (Scheme 2).[6] In this case, various byproducts were formed during the process of the reduction of the nitro group of **4** depending on the 2-nitrobenzoic acid used. Fmoc-anthranilic acids instead of 2-nitrobenzoic acids have been used for the preparation of **5**.[9] However, the preparation of the requisite Fmoc-anthranilic acids decreases the total efficiency of the synthesis. Acknowledging the poor nucleophilicity of the amino group of anthranilic acids, we considered that protection of the amine with an Fmoc group or a nitro group would not be necessary. In fact, it is known that solid-phase synthesis of benzodiazepines was achieved using anthranilic acids[10] without protecting the amine. In this report, we have investigated a synthetic strategy for quinazoline-2,4-diones using various commercially available anthranilic acids with various substituents on the aromatic ring.

2. Results and discussion

First, **6** was prepared by reductive amination[11] of Lantern[12] with 1-aminomethylnaphthalene (Scheme 3). Although **6** was used for all the compounds in this report, various amines can be used for this reductive amination to offer the first diversity point.[13] Then, **6** was reacted with 4-nitrophenylacetic acid **7**/*N*,*N*′-diisopropylcarbodiimide (DIC)/1-hydroxy-7-azabenzotriazole (HOAt)/NMP, followed by the treatment with $SnCl_2 \cdot 2H_2O$/EtOH/NMP to

Keywords: solid-phase synthesis; quinazoline-2,4-dione; anthranilic acid; heterocycle.

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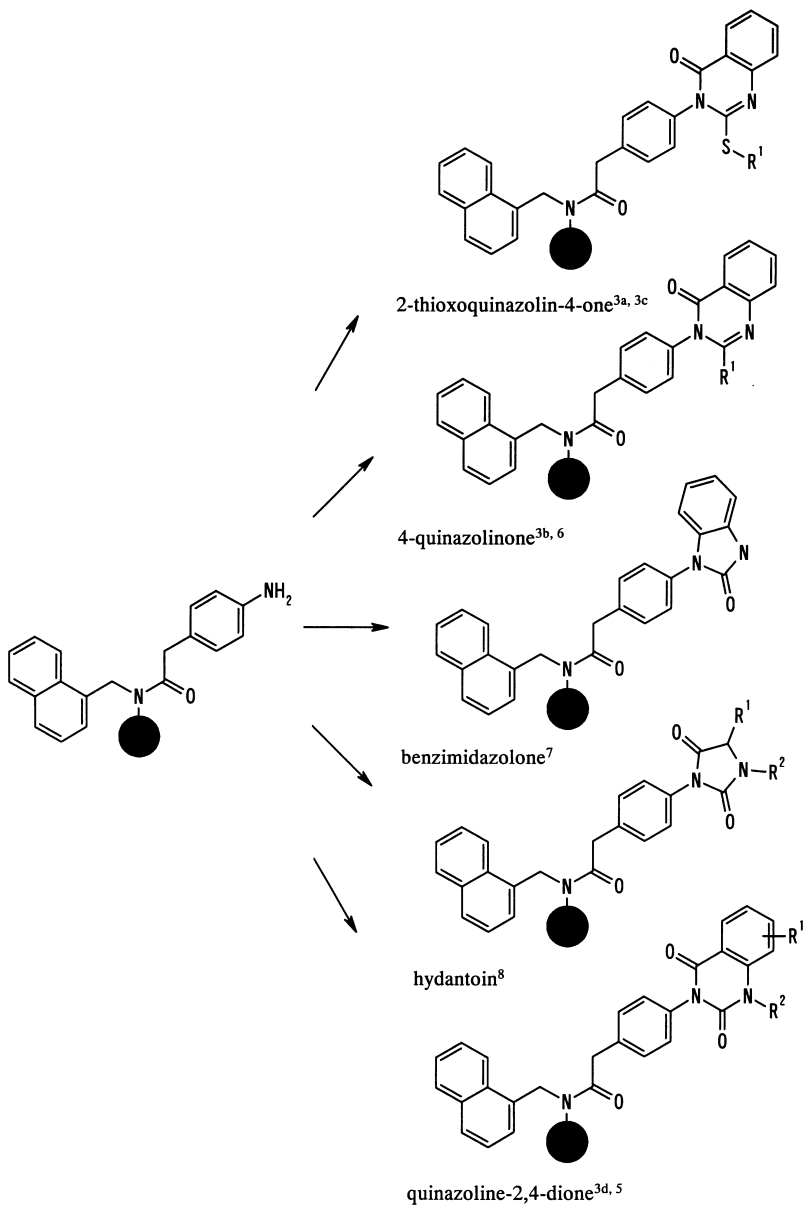
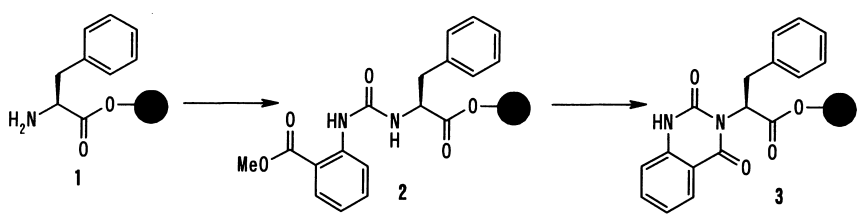
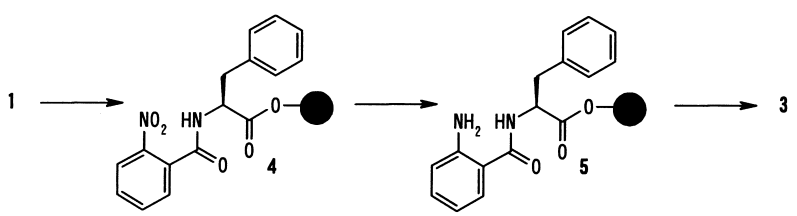


Figure 1.



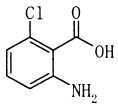
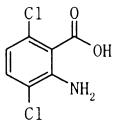
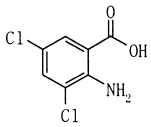
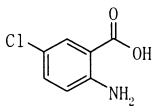
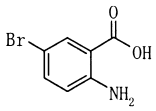
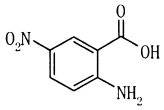
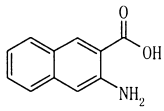
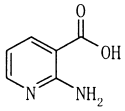
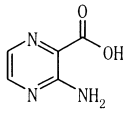
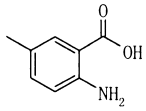
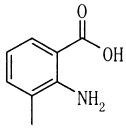
Scheme 1.



Scheme 2.

give **8**. Various solid-supported amines can be prepared using other building blocks instead of **7** (the second diversity point) as described later. Coupling of **8** with anthranilic acids **9** using *N*,*N*′-diisopropylcarbodiimide (DIC)/1-hydroxy-7-azabenzotriazole (HOAt) gave **10**. Pre-activation of **9** was important to prevent **8** from reacting with DIC to give a guanidinyl byproduct. Next, carbonylation with carbonyldiimidazole (CDI, **11**) was attempted. Because of the poor nucleophilicity of anthranilic acids, this carbonylation was found to be difficult under mild reaction conditions. After extensive investigation, quinazolidine-2,4-diones **13** were found to be obtained with high purity by treating **10** with CDI/decalin at 95°C.[3d] As shown in Table 1, various quinazolidine-2,4-diones **13** were obtained with this method. Quinazolidine-2,4-diones were obtained with high purity using halogen-substituted (entry a–e) and nitro-substituted (entry f) anthranilic acids, and 3-amino-2-naphthoic acid (entry g). In the case of 2-aminonicotinic acid and 3-aminopyrazine-2-carboxylic acid, the nucleophilicity of the amines was decreased due to the adjacent nitrogen atom, giving quinazolidine-2, 4-dione analogues with high purity (entry h, i). When anthranilic acids with electron-donating substituents were used, quinazolidine-2,4-diones were obtained with lower purity (entry j, k). Several solid-supported arylamines were also prepared by coupling nitrobenzene derivatives with **6**, followed by reduction of the nitro group (Schemes 3 and 4). After the sequence of reactions, quinazolidine-2,4-diones were obtained with good purity from these arylamines (Table 2, entry l–o). Furthermore, solid-supported alkylamines were (entry p,q) prepared by reacting **6** with Fmoc amino acids/DIC/HOAt/NMP, followed by treatment with 20% piperidine/NMP. Quinazolidine-2,4-diones were obtained with excellent purity from these solid-supported alkylamines, showing that the procedure is quite general and is suitable for the preparation of an array of compounds. The structures of all the products in this manuscript were confirmed by ^{1}H NMR and LC-MS (ESI mass spectrometer).

Table 1. Synthesis of quinazoline-2,4-diones with various substituents on the aromatic ring

Entry	Anthranylic acid **9**	**13**	
		Purity[a] (%)	Yield[b] (%)
a		>95	92
b		>95	97
c		>95	95
d		>95	93
e		>95	94
f		>95	99
g		>95	80
h		91	100
i		>95	100
j		68	99
k		77	86

[a] Reverse-phase HPLC was carried out using water/acetonitrile (0.04% TFA) linear gradients from 5 to 98% organic component over 5 min. Flow rate: 2 mL/min. Column: waters symmetry C_{18} (3.5 μm) 4.6×50 mm. HPLC purities were determined by summation of integrated HPLC peak areas at (210+2N) nm, N=0–45.

[b] Crude yields based on the theoretical loading weight of target molecules.

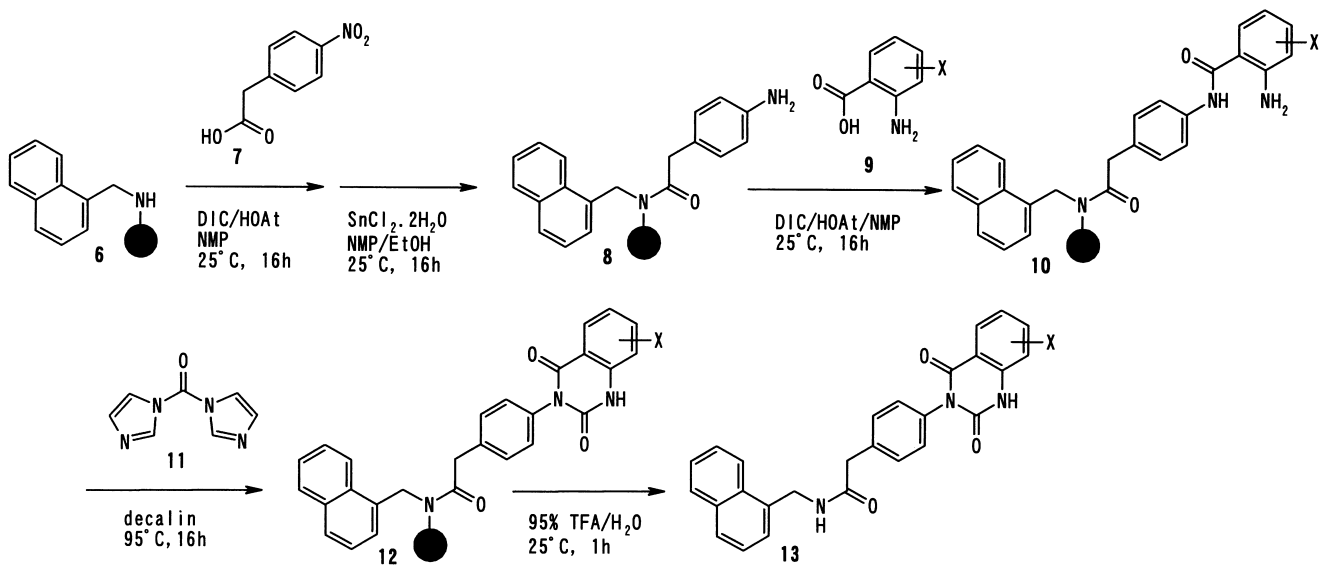
3. Conclusion

In conclusion, solid-phase synthesis of quinazolidine-2,4-diones with various substituents on the aromatic ring was investigated. Quinazolidine-2,4-diones with electron-withdrawing substituents were obtained with high purity by coupling anthranilic acids to solid-supported amines without protecting the amines of the anthranilic acids, followed by cyclization with CDI. A variety of quinazolidine-2,4-diones can be synthesized as this method worked well with both solid-supported aryl and alkylamines, and **12** or **15** can be further alkylated according to the previous report.[14] This synthesis with Synphase Lanterns can be easily scaled-up to obtain several hundred milligrams of the target compounds.

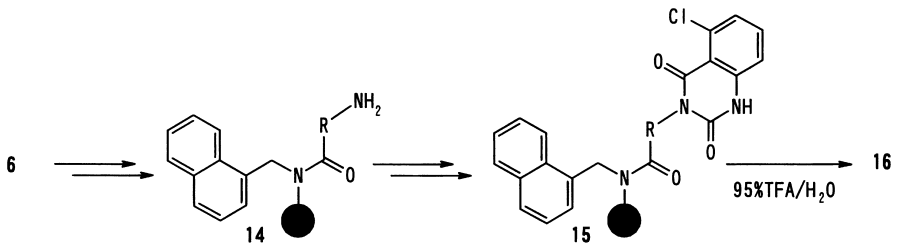
4. Experimental

4.1. General

4.1.1. General procedure for preparation of 2-[4-(5-chloro-2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)-phenyl]-*N*-(1-naphthylmethyl)acetamide (13a). (Syn-Phase™ Lanterns was put into a 2.5 mL syringe.[15] 1-Aminomethylnaphthalene/$NaCNBH_3$/NMP/AcOH (150 μL/32 mg/1.0 mL/10 μL) was added to the syringe, and the syringe was shaken for 16 h at 25°C, then for 6 h at 50°C using FlexChem Incubator.[16] The Lantern was washed with MeOH (2 mL×3), DMF (2 mL×3) and DCM (2 mL×3), and



Scheme 3.



Scheme 4.

dried under vacuum for 1 h. After 4-nitrophenylacetic acid (73 mg) was pre-activated with *N*,*N*′-diisopropylcarbodiimide (DIC)/1-hydroxy-7-azabenzotriazole (HOAt)/NMP (29 μL/55 mg/1.2 mL) at 25°C for 1 h, this solution was added to the syringe and the syringe was shaken at 25°C for 16 h. The Lantern was washed with DMF (2 mL×3) and DCM (2 mL×3), and dried under vacuum for 1 h. The Lantern was treated with $SnCl_2{\cdot}2H_2O$/NMP/EtOH (1.0 g/2.0 mL/100 μL) at 25°C for 16 h, and washed with DMF (2 mL×3), DCM (2 mL×3), and dried under vacuum for 1 h. Then, the Lantern was reacted with 6-chloroanthranilic acid/DIC/HOAt/NMP (124 mg/56 μL/98 mg/2 mL) at 45°C for 16 h and washed with DMF (2 mL×3) and CH_2Cl_2 (2 mL×3). To the Lantern was added CDI/decalin (100 mg/2.0 mL) and the mixture was heated to 95°C with gentle shaking for 16 h. The Lantern was washed with DMF (2 mL×3) and CH_2Cl_2 (2 mL×3), and dried under vacuum for 3 h. The Lantern was treated with 95%TFA/H_2O for 1 h and the solution was concentrated with Genevac evaporater.[17] The residue was dissolved with 50% CH_3CN/H_2O and lyophilized to give the product (Table 1, entry 1) in 92% yield (15 mg) based on the theoretical loading weight of the target molecule. ^{1}H NMR (Varian VXR-300S, 300 MHz, DMSO-d_6) δ 3.57 (s, 2H), 4.76 (d, J=5.7 Hz, 2H), 7.18–7.27 (m, 3H), 7.38 (d, J=7.5 Hz, 2H), 7.44–7.68 (m, 6H), 7.86 (dd, J=6.9, 2.1 Hz, 1H), 7.94–7.97 (m, 1H), 8.03–8.07 (m, 1H), 8.66 (brt, J=5.7 Hz, 1H), 11.65 (s, 1H). MS *m*/*z* 470, 472 $[MH]^+$. Anal. calcd for: $C_{27}H_{20}ClN_3O_3(1/3H_2O)$: C 68.15, H 4.38, N 8.83; found: C 68.38, H 4.53, N 8.98. Mp 295–298°C.

4.1.2. 2-[4-(5,8-Dichloro-2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)phenyl]-*N*-(1-naphthylmethyl)acetamide (13b). Prepared as described above, using 3,6-dichloroanthranilic acid. (17.1 mg, 97%) ^{1}H NMR (DMSO-d_6) δ 3.55 (s, 2H), 4.74 (d, J=5.1 Hz, 2H), 7.23 (d, J=8.4 Hz, 2H), 7.27 (d, J=8.7 Hz, 1H), 7.38 (d, J=8.1 Hz, 2H), 7.42–7.57 (m, 4H), 7.78 (d, J=9.0 Hz, 1H), 7.84 (dd, J=6.9, 2.1 Hz, 1H), 7.92–7.95 (m, 1H), 8.01–8.05 (m, 1H), 8.65 (brt, J=5.1 Hz, 1H), 10.99 (s, 1H). MS *m*/*z* 504, 506 $[MH]^+$. Anal. calcd for: $C_{27}H_{19}Cl_2N_3O_3(1/3H_2O)$: C 63.55, H 3.88, N 8.23; found: C 63.36, H 3.96, N 8.15. Mp 293–298°C.

4.1.3. 2-[4-(6,8-Dichloro-2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)phenyl]-*N*-(1-naphthylmethyl)acetamide (13c). Prepared as described above, using 3,5-dichloroanthranilic acid. (16.6 mg, 95%) ^{1}H NMR (DMSO-d_6) δ 3.57 (s, 2H), 4.76 (d, J=5.7 Hz, 2H), 7.25 (d, J=7.8 Hz, 2H), 7.39 (d, J=8.4 Hz, 2H), 7.46–7.56 (m, 4H), 7.83–7.88 (m, 2H), 7.94–7.97 (m, 1H), 8.02–8.06 (m 2H), 8.68 (brt, J=5.7 Hz, 1H), 11.31 (s, 1H). MS *m*/*z* 504, 506 $[MH]^+$. Anal. calcd for: $C_{27}H_{19}Cl_2N_3O_3(H_2O)$: C 62.08, H 4.05, N 8.04; found: C 61.96, H 4.16, N 7.81. Mp 310–312°C.

4.1.4. 2-[4-(6-Chloro-2,4-dioxo-1,2,3,4-tetrahydro-3(2*H*)-quinazolinyl)phenyl]-*N*-(1-naphthylmethyl)acetamide (13d). Prepared as described above, using 5-chloroanthranilic acid. (15.3 mg, 93%) ^{1}H NMR (DMSO-d_6) δ 3.57 (s, 2H), 4.76 (d, J=5.7 Hz, 2H), 7.24 (d, J=8.4 Hz, 2H), 7.25 (d, J=8.7 Hz, 1H), 7.39 (d, J=8.4 Hz, 2H), 7.44–7.58 (m, 4H), 7.76 (dd, J=8.7, 2.7 Hz, 1H), 7.86 (dd, J=6.9,

2.1 Hz, 1H), 7.88 (d, *J*=2.4 Hz, 1H), 7.94–7.97 (m, 1H), 8.03–8.07 (m, 1H), 8.68 (brt, *J*=5.7 Hz, 1H), 11.68 (s, 1H). MS *m/z* 470, 472 $[MH]^+$. Anal. calcd for: $C_{27}H_{20}ClN_3O_3(1/5H_2O)$: C 68.48, H 4.34, N 8.87; found: C 68.34, H 4.36, N 8.94. Mp 330–332°C.

4.1.5. 2-[4-(6-Bromo-2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)phenyl]-*N*-(1-naphthylmethyl)acetamide (13e). Prepared as described above, using 5-bromoanthranilic acid. (16.9 mg, 94%) ^{1}H NMR (DMSO-d_6) δ 3.57 (s, 2H), 4.76 (d, *J*=5.7 Hz, 2H), 7.20 (d, *J*=8.7 Hz, 1H), 7.24 (d, *J*=8.4 Hz, 2H), 7.39 (d, *J*=8.4 Hz, 2H), 7.44–7.58 (m, 4H), 7.86 (dd, *J*=6.9, 2.1 Hz, 1H), 7.87 (dd, *J*=8.4, 2.4 Hz, 1H), 7.94–7.97 (m, 1H), 8.00 (d, *J*=2.1 Hz, 1H), 8.03–8.07 (m, 1H), 8.68 (brt, *J*=5.7 Hz, 1H), 11.69 (s, 1H). MS *m/z* 515, 516 $[MH]^+$. Anal. calcd for: $C_{27}H_{20}BrN_3O_3(1/3H_2O)$: C 62.33, H, 4.00, N 8.08; found: C 62.37, H 4.01, N 8.17. Mp 310–312°C.

4.1.6. 2-[4-(6-Nitro-2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)phenyl]-*N*-(1-naphthylmethyl)acetamide (13f). Prepared as described above, using 5-nitroanthranilic acid. (16.6 mg, 99%) ^{1}H NMR (DMSO-d_6) δ 3.57 (s, 2H), 4.76 (d, *J*=5.7 Hz, 2H), 7.27 (d, *J*=8.4 Hz, 2H), 7.39–7.58 (m, 7H), 7.86 (dd, *J*=6.9, 2.1 Hz, 1H), 7.94–7.97 (m, 1H), 8.03–8.07 (m, 1H), 8.54 (dd, *J*=9.3, 2.7 Hz, 1H), 8.65 (d, *J*=2.7 Hz, 1H), 8.68 (brt, *J*=5.7 Hz, 1H), 12.18 (s, 1H). MS *m/z* 481 $[MH]^+$. Anal. calcd for: $C_{27}H_{20}N_4O_5(3/4H_2O)$: C 65.65, H 4.39, N 11.34; found: C 65.60, H 4.24, N 11.20. Mp 291–294°C.

4.1.7. 2-[4-(2,4-Dioxo-1,2,3,4-tetrahydrobenzo[*g*]quinazolin-3-yl)phenyl]-*N*-(1-naphthylmethyl)acetamide (13g). Prepared as described above, using 3-amino-2naphthoic acid. (13.7 mg, 80%) ^{1}H NMR (DMSO-d_6) δ 3.57 (s, 2H), 4.76 (d, *J*=5.7 Hz, 2H), 7.29 (d, *J*=8.4 Hz, 2H), 7.40 (d, *J*=8.4 Hz, 2H), 7.44–7.65 (m, 7H), 7.86 (dd, *J*=6.9, 2.1 Hz, 1H), 7.93–7.98 (m, 2H), 8.03–8.07 (m, 1H), 8.14 (d, *J*=7.8 Hz, 1H), 8.68 (brt, *J*=5.7 Hz, 1H), 8.71 (s, 1H), 11.62 (s, 1H). MS *m/z* 486 $[MH]^+$. Anal. calcd for: $C_{31}H_{23}N_3O_3(1/5H_2O)$: C 76.12, H 4.82, N 8.59; found: C 76.19, H 4.83, N 8.63. Mp 324–325°C.

4.1.8. 2-[4-(2,4-Dioxo-1,2,3,4-tetrahydropyrido[2,3]pyrimidin-3-yl)phenyl]-*N*-(1-naphthylmethyl)acetamide (13h). Prepared as described above, using 2-aminonicotinic acid. (15.1 mg, 100%) ^{1}H NMR (DMSO-d_6) δ 3.57 (s, 2H), 4.76 (d, *J*=5.7 Hz, 2H), 7.26 (d, *J*=8.4 Hz, 2H), 7.30 (dd, *J*=7.8, 4.8 Hz, 1H), 7.39 (d, *J*=8.4 Hz, 2H), 7.44–7.58 (m, 4H), 7.86 (dd, *J*=6.9, 2.1 Hz, 1H), 7.94–7.97 (m, 1H), 8.03–8.07 (m, 1H), 8.32 (dd, *J*=8.1, 2.1 Hz, 1H), 8.66 (dd, *J*=4.8, 1.8 Hz, 1H), 8.68 (brt, *J*=5.7 Hz, 1H), 12.05 (s, 1H). MS *m/z* 437 $[MH]^+$. Anal. calcd for: $C_{26}H_{20}N_4O_3(1/5H_2O)$: C 70.96, H 4.67, N 12.73; found: C 70.68, H 4.69, N 12.66. Mp 310–312°C.

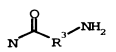
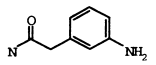
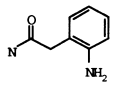
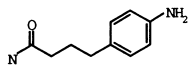
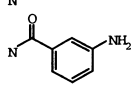
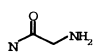
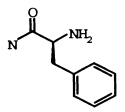
4.1.9. 2-[4-(2,4-Dioxo-1,2,3,4-tetrahydro-3-pteridinyl)-phenyl]-*N*-(1-naphthylmethyl)acetamide (13i). Prepared as described above, using 3-aminopyrazine-2-carboxylic acid. (15.3 mg, 100%) ^{1}H NMR (DMSO-d_6) δ 3.57 (s, 2H), 4.76 (d, *J*=5.7 Hz, 2H), 7.26 (d, *J*=8.4 Hz, 2H), 7.41 (d, *J*=8.4 Hz, 2H), 7.44–7.58 (m, 4H), 7.86 (dd, *J*=6.9, 2.1 Hz, 1H), 7.94–7.97 (m, 1H), 8.03–8.07 (m, 1H), 8.58 (d, *J*=2.1 Hz, 1H), 8.68 (brt, *J*=5.7 Hz, 1H), 8.72 (d, *J*=2.4 Hz, 1H), 12.30 (s, 1H). MS *m/z* 438 $[MH]^+$. Anal. calcd for: $C_{25}H_{19}N_5O_3(4/3H_2O)$: C 65.08, H 4.73, N 15.18; found: C 65.02, H 4.37, N 14.79. Mp 288–290°C.

4.1.10. 2-[4-(6-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)phenyl]-*N*-(1-naphthylmethyl)acetamide (13j). Prepared as described above, using 5-methylanthranilic acid. (15.5 mg, 99%) ^{1}H NMR (DMSO-d_6) δ 2.35 (s, 3H), 3.57 (s, 2H), 4.76 (d, *J*=5.7 Hz, 2H), 7.14 (d, *J*=8.7 Hz, 1H), 7.22 (d, *J*=8.4 Hz, 2H), 7.38 (d, *J*=8.4 Hz, 2H), 7.43–7.58 (m, 5H), 7.75 (s, 1H), 7.81–7.88 (m, 1H), 7.94–7.97 (m, 1H), 8.03–8.07 (m, 1H), 8.68 (brt, *J*=5.7 Hz, 1H), 11.47 (s, 1H). MS *m/z* 450 $[MH]^+$. Anal. calcd for: $C_{28}H_{23}N_3O_3(1/2H_2O)$: C 73.35, H 5.28, N 9.16; found: C 73.07, H 5.21, N 9.43. Mp 326–327°C.

4.1.11. 2-[4-(8-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)phenyl]-*N*-(1-naphthylmethyl)acetamide (13k). Prepared as described above, using 3-methylanthranilic acid. (13.5 mg, 86%) ^{1}H NMR (DMSO-d_6) δ 2.40 (s, 3H), 3.57 (s, 2H), 4.76 (d, *J*=5.7 Hz, 2H), 7.14 (t, *J*=7.8 Hz, 1H), 7.24 (d, *J*=8.4 Hz, 2H), 7.39 (d, *J*=8.4 Hz, 2H), 7.44–7.58 (m, 5H), 7.81–7.88 (m, 2H), 7.94–7.97 (m, 1H), 8.03–8.07 (m, 1H), 8.68 (brt, *J*=5.7 Hz, 1H), 10.79 (s, 1H). MS *m/z* 450 $[MH]^+$. Anal. calcd for: $C_{28}H_{23}N_3O_3(3/4H_2O)$: C 72.63, H 5.33, N 9.08; found: C 72.31, H 5.19, N 9.07. Mp 293.5–294°C

4.1.12. 2-[3-(5-Chloro-2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)phenyl]-*N*-(1-naphthylmethyl)acetamide (16l). Table 2. Prepared as described above, using 3-nitrophenylacetic acid. (14.6 mg, 89%) ^{1}H NMR

Table 2. Synthesis of 5-chloro-quinazoline-2,4-diones from various solid-supported amines

Entry	14	16	
		Purity[a] (%)	Yield[b] (%)
l		90	89
m		93	84
n		>95	79
o		92	76
p		>95	81
q		>95	83

[a] Reverse-phase HPLC was carried out using water/acetonitrile (0.04% TFA) linear gradients from 5% to 98% organic component over 5 min. Flow rate: 2 mL/min. Column: Waters Symmetry C_{18} (3.5 μm) 4.6×50 mm. HPLC purities were determined by summation of integrated HPLC peak areas at (210+2N) nm, N=0–45.

[b] Crude yields based on the theoretical loading weight of target molecules.

(DMSO-d_6) δ 3.55 (s, 2H), 4.76 (d, J=5.7 Hz, 2H), 7.17–7.54 (m, 10H), 7.63 (t, J=8.1 Hz, 1H), 7.83 (d, J=6.9 Hz, 1H), 7.90 (d, J=8.7 Hz, 1H), 8.04 (d, J=8.1 Hz, 1H), 8.68 (brt, J=5.7 Hz, 1H), 11.69 (s, 1H). MS m/z 470, 472 $[MH]^+$. Anal. calcd for: $C_{27}H_{20}ClN_3O_3(1/2H_2O)$: C 67.71, H 4.42, N 8.77; found: C 67.45, H 4.41, N 8.74. Mp 282–283°C.

4.1.13. 2-[2-(5-Chloro-2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)phenyl]-*N*-(1-naphthylmethyl)acetamide (16m). Prepared as described above, using 2-nitrophenylacetic acid. (13.8 mg, 84%) ^{1}H NMR (DMSO-d_6) δ 3.38 (s, 2H), 4.62 (d, J=5.1 Hz, 2H), 7.20–7.29 (m, 3H), 7.32–7.41 (m, 4H), 7.49–7.55 (m, 3H), 7.61 (t, J=8.1 Hz, 1H), 7.82 (d, J=8.4 Hz, 1H), 7.90–7.99 (m, 2H), 8.34 (brt, J=5.7 Hz, 1H), 11.67 (s, 1H). MS m/z 470, 472 $[MH]^+$. Anal. calcd for: $C_{27}H_{20}ClN_3O_3(1/3H_2O)$: C 68.15, H 4.38, N 8.83; found: C 68.35, H 4.56, N 8.94. Mp 144–154°C.

4.1.14. 4-[4-(5-Chloro-2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)phenyl]-*N*-(1-naphthylmethyl)butanamide (16n). Prepared as described above, using 4-nitrophenylbutyric acid. (13.7 mg, 79%) ^{1}H NMR (DMSO-d_6) δ 1.89 (m, 2H), 2.24 (t, J=7.8 Hz, 2H), 2.62 (t, J=7.2 Hz, 2H), 4.75 (d, J=5.7 Hz, 2H), 7.17–7.27 (m, 6H), 7.44–7.64 (m, 5H), 7.85 (dd, J=6.9, 2.1 Hz, 1H), 7.93–7.96 (m, 1H), 8.08–8.12 (m, 1H), 8.41 (brt, J=5.4 Hz, 1H), 11.65 (s, 1H). MS m/z 498, 500 $[MH]^+$. Anal. calcd for: $C_{29}H_{24}ClN_3O_3(1/5H_2O)$: C 69.44, H 4.90, N 8.38; found: C 69.31, H 4.94, N 8.35. Mp 267–268°C.

4.1.15. 3-(5-Chloro-2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)-*N*-(1-naphthylmethyl)benzamide (16o). Prepared as described above, using 3-nitrobenzoic acid. (12.1 mg, 76%) ^{1}H NMR (DMSO-d_6) δ 4.97 (d, J=5.7 Hz, 2H), 7.21 (dd, J=8.4, 1.2 Hz, 1H), 7.26 (dd, J=8.1, 0.9 Hz, 1H), 7.48–7.70 (m, 7H), 7.83–7.87 (m, 2H), 7.94–8.00 (m, 2H), 8.18 (d, J=7.8 Hz, 1H), 9.12 (brt, J=5.4 Hz, 1H), 11.72 (s, 1H). MS m/z 456, 458 $[MH]^+$. Anal. calcd for: $C_{26}H_{18}ClN_3O_3(1/2H_2O)$: C 67.17, H 4.12, N 9.04; found: C 66.97, H 4.27, N 8.90. Mp 331–332°C.

4.1.16. 2-(5-Chloro-2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)-*N*-(1-naphthylmethyl)acetamide (16p). Prepared as described above, using Fmoc-Gly-OH. (11.1 mg, 81%) ^{1}H NMR (DMSO-d_6) δ 4.54 (s, 1H), 4.76 (d, J=5.7 Hz, 1H), 7.17 (d, J=6.6 Hz, 1H), 7.26 (d, J=7.8 Hz, 1H), 7.44–7.62 (m, 5H), 7.83–7.87 (m, 1H), 7.93–7.96 (m, 1H), 8.05–8.08 (m, 1H), 8.68 (brt, J=6.0 Hz, 1H), 11.66 (s, 1H). MS m/z 394, 396 $[MH]^+$. Anal. calcd for: $C_{21}H_{16}ClN_3O_3(1/5H_2O)$: C 63.47, H 4.16, N 10.57; found: C 63.45, H 4.23, N 10.50. Mp 323–325°C.

4.1.17. (2*S*)-2-(5-Chloro-2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)-*N*-(1-naphthylmethyl)-3-phenylpropanamide (16q). Prepared as described above, using Fmoc-L-Phe-OH. (14.0 mg, 83%) ^{1}H NMR (DMSO-d_6) δ 3.33 (dd, J=14.1, 9.9 Hz, 1H), 3.60 (dd, J=13.8, 5.1 Hz, 1H), 4.74 (d, J=5.4 Hz, 2H), 5.64 (q, J=5.4 Hz, 1H), 7.02–7.19 (m, 7H), 7.40–7.56 (m, 5H), 7.80 (d, J=7.8 Hz, 1H), 7.90–7.93 (m, 1H), 8.05–8.09 (m, 1H), 8.50 (t, J=5.4 Hz, 1H), 11.44 (s, 1H). MS m/z 484, 486 $[MH]^+$. Anal. calcd for: $C_{28}H_{22}ClN_3O_3(3/2H_2O)$: C 65.82, H, 4.93, N 8.22; found: C 65.63, H 4.50, N 8.04. Mp 137–138°C.

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12. The type of Lantern used in this communication was SP-PS-D-BAL, loading 35 μmol/Lantern.
13. The following amines were confirmed to work with this method: isopropylamine, allylamine, cyclobutylamine, furfurylamine, piperonylamine, phenethylamine, 2,2-diphenylethylamine.
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15. Disposable polypropylene/polyethylene syringes are available from Aldrich (Milwaukee, WI).
16. FlexChem rotating oven, Model 404, http://www.robsci.com.
17. Genevac HT-8 available from Genevac Limited (Farthing Road, Ipswich, IP1 5AP, UK).