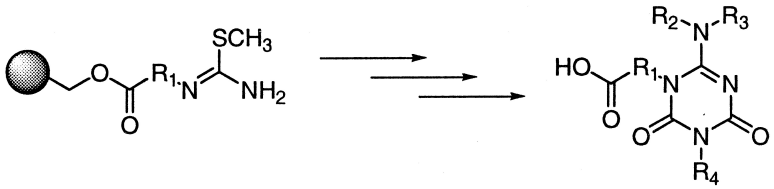
JOURNAL OF combinatorial CHEMISTRY

Article

Combinatorial Synthesis of Heterocycles: Solid-Phase Synthesis of 6-Amino-2,4-dioxo-3,4-dihydro-1,3,5-triazine Derivatives

Ariamala Gopalsamy, and Hui Yang

J. Comb. Chem., **2001**, 3 (3), 278-283• DOI: 10.1021/cc000091w • Publication Date (Web): 05 April 2001



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 1 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Journal of Combinatorial Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Combinatorial Synthesis of Heterocycles: Solid-Phase Synthesis of 6-Amino-2,4-dioxo-3,4-dihydro-1,3,5-triazine Derivatives

Ariamala Gopalsamy* and Hui Yang

Chemical Sciences Division, Wyeth-Ayerst Research, Pearl River, New York 10965

Received October 11, 2000

A new solid-phase synthesis of trisubstituted 6-amino-2,4-dioxo-3,4-dihydro-1,3,5-triazines from a resin-bound amine component is described. The amine was readily converted to the corresponding polymer-bound *S*-methylthiopseudourea, which upon reaction with secondary amines gave the disubstituted guanidines. Cyclization of the polymer-bound guanidines with chlorocarbonylisocyanate afforded the triazinediones. The third point of diversity was introduced by the Mitsunobu reaction. The method is amenable for iterative combinatorial library generation.

Introduction

Solid-phase organic synthesis[1] has gained significant popularity because of its application in parallel and combinatorial synthesis for drug discovery.[2] Given the ubiquitous nature of a wide variety of heterocyclic moieties among biologically active species, it is not surprising that synthesis of heterocycles[3] has been a primary focus for solid-phase organic transformations, in particular nitrogen heterocycles.[4] Triazinediones are an important class of molecules with pharmaceutical[5] and agricultural[6] utility. It is reported that 6-acylaminotetrahydro-1,3,5-triazine-2,4-dione derivatives (**A**) show analgesic properties[5a] and in addition 1,3,5-triazine-2,4-dione derivatives (**B**) possess herbicidal properties[6a] (Figure 1).

To prepare a combinatorial library of triazinediones with a high degree of diversity required for our biological evaluation, we considered an iterative combinatorial synthesis utilizing chlorocarbonyl isocyanate cyclization chemistry.[7] By use of this method, combinatorial synthesis of disubstituted triazinediones can be readily accomplished; they are an interesting class of compounds themselves with an acidic NH for additional interaction with the biological target or they can be readily converted to trisubstituted triazinediones. A wide array of amines can be readily converted to *S*-methylthiopseudourea by simple manipulations. We used the amino acids attached to the solid support as the amine component to optimize the synthesis.

Results and Discussion

As outlined in Scheme 1, Fmoc-protected amino acid **1** was attached to the Wang resin **2**[8] using 1-hydroxybenzotriazole (HOBT) and *N*,*N*-diisopropylcarbodiimide (DIC) as coupling reagents in the presence of *N*,*N*-dimethylaminopyridine (DMAP) in *N*,*N*-dimethylformamide (DMF) to give the resin-bound, Fmoc-protected amino acid **3** in quantitative yield. The Fmoc group was removed using 20% piperidine in DMF. The free amine **4** was reacted with Fmoc isothiocyanate **5**[9] in methylene chloride to give the Fmoc-protected thiourea **6**. It was deprotected using 20% piperidine in DMF

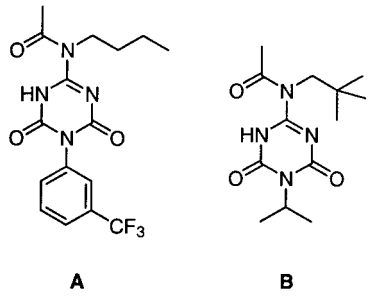


Figure 1.

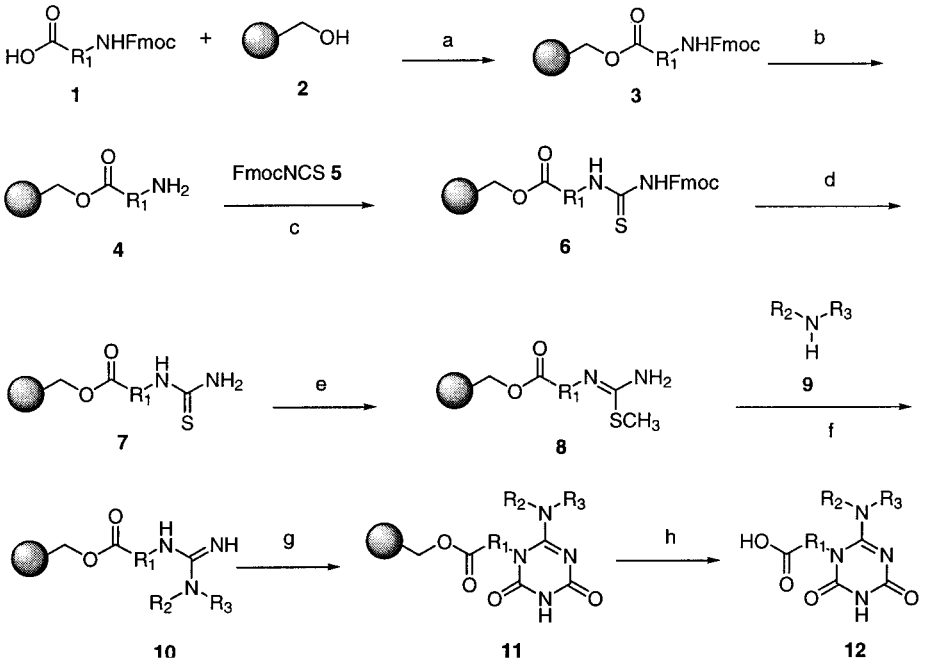
to give the thiourea **7**, which was converted to the corresponding *S*-methylthiopseudourea **8** by reacting with methyl iodide. Reaction of this resin-bound compound with amine **9** in DMSO at elevated temperature led to the displacement of the methylthio group to give the resin-bound guanidine **10**. Cyclization of **10** was carried out using chlorocarbonylisocyanate to give the disubstituted triazinediones **11** on the resin. At this stage resin **11** was treated with trifluoroacetic acid in methylene chloride to isolate disubstituted triazinediones **12** (for examples, see entries **12a**−**d** of Table 1).

On the other hand, a third point of diversity element can be introduced into the resin-bound disubstituted triazinediones **11** by reacting with alcohol **13** under Mitsunobu[10] conditions to give resin-bound trisubstituted triazinediones **14**. Upon treatment with trifluoroacetic acid in methylene chloride, the required trisubstituted triazinediones **15** were isolated (Scheme 2).

An array of 60 compounds (4 × 3 × 5) were generated starting from 4-amino-, 3-amino-, 2-chloro-5-amino-, and 2-chloro-4-aminobenzoic acids as amine components. Piperidine, *N*-ethylbenzylamine, and *N*,*N*-di-*n*-propylamine were used as the secondary amine components. 4-Bromo-, 4-benzyloxy-, 4-trifluoromethyl-, 2-phenyl-, and 3,4-dimethylbenzyl alcohols were used for the Mitsunobu reaction. Representative compounds produced by this synthesis are listed in Table 1. The purities of the crude product as assessed by HPLC[11] peak area were generally in the 60−85% range.

10.1021/cc000091w CCC: $20.00
Published on Web 04/05/2001

Scheme 1[a]



[a] Reagents and conditions: (a) HOBT, DIC, DMAP, DMF, RT, 18 h; (b) 20% piperidine/DMF, room temperature, 2 × 10 min; (c) CH_2Cl_2, RT, 20 min; (d) 20% piperidine/DMF, 1 × 10 min, 1 × 30 min; (e) MeI, DMF, room temperature, 18 h; (f) DMSO, 80 °C, 24 h; (g) ClCONCO, THF, room temperature, 2 h; (h) 50% CF_3COOH/CH_2Cl_2, room temperature, 1 h.

While anilines were used in this array, use of aliphatic amine-like β-Ala during optimization gave the cyclized product **12** in 65% yield. Secondary amines were used to displace the methylthio group, leading to guanidines to avoid regioisomers during cyclization. Both cyclic and acyclic amines worked well. While benzyl alcohols were used in the array, optimization using allyl alcohol also gave a very clean conversion (~95%). However, hindered isopropyl alcohol gave only (~45% conversion). The substituents R_1, R_2, R_3, and R_4 on the triazinediones are derived from three different components, which are readily available and can be introduced independently for the purpose of combinatorial library generation.

Conclusion

Described in this paper is a new solid-phase synthesis for 1,3,5-triazine-2,4-dione derivatives. The synthetic design includes four variable groups R1−R4, which are included in the scaffold, R1 from a primary amine component, R2 and R3 from a secondary amine component, and R4 from an alcohol component. The procedure is quite general and is suitable for the preparation of combinatorial libraries.

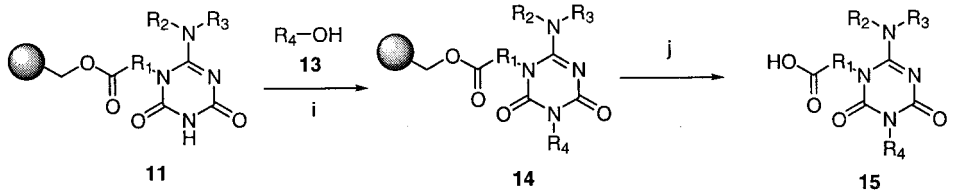
Experimental Section

4-(3-(4-Bromobenzyl)-2,4-dioxo-6-piperidin-1-yl-3,4-dihydro-1,3,5-triazin-1(2H)-yl)benzoic Acid (15a). Step 1. Fluorenylmethyloxycarbonyl Isothiocyanate (5). The title compound was prepared from fluorenylmethyloxycarbonyl chloride and potassium thiocyanate according to the procedure of Kearney et al.[9] ^{1}H NMR ($CDCl_3$): δ 7.75 (d, J = 7.5 Hz, 2H), 7.56 (d, J = 7.5 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.32 (t, J = 7.5 Hz, 2H), 4.44 (d, J = 7.4 Hz, 2H), 4.23 (t, J = 7.4 Hz, 1H). IR(cm^{-1}): 1963.32 (N=C=S stretch).

Step 2. Attachment of *N*-Fmoc-4-aminobenzoic Acid to Wang Resin (3a). Wang Resin (**2**) (Ana Spec 100−200 mesh, 1% cross-linked; loading, 1.1 mmol/g; 5 g, 5.5 mmol) was swollen in anhydrous DMF (20 mL). A solution of *N*-Fmoc-4-aminobenzoic acid (**1a**) (7.9 g, 22 mmol), HOBT (3.37 g, 22 mmol), DMAP (268.8 mg, 2.2 mmol), and DIC (3.4 mL, 22 mmol) in anhydrous DMF (30 mL) was added to the resin. The mixture was shaken at room temperature on an orbital shaker overnight. The mixture was filtered, and the resin was washed with DMF (3 × 50 mL), MeOH (3 × 50 mL), and CH_2Cl_2 (3 × 50 mL) and dried.

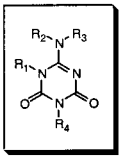
Step 3. Deprotection of Fmoc Group. The resin (**3a**) (5.5

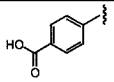
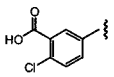
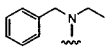
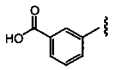
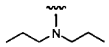
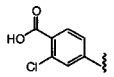
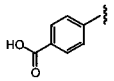
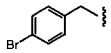
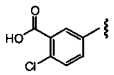
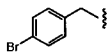
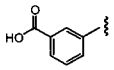
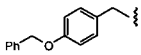
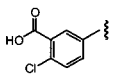
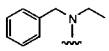
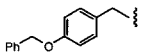
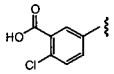
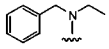
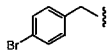
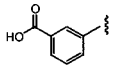
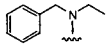
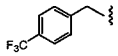
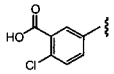
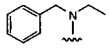
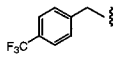
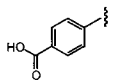
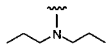
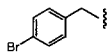
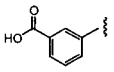
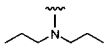
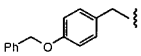
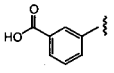
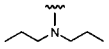
Scheme 2[a]



[a] Reagents and conditions: (i) TMAD, Bu_3P, THF−CH_2Cl_2 (1:1), room temperature, 18 h; (j) 50% CF_3COOH/CH_2Cl_2, room temperature, 1 h.

Table 1. Solid Phase Synthesis of 6-Amino-2,4-dioxo-3,4-dihydro-1,3,5-triazine Derivatives



Entry	R_1	R2-N-R_3	R_4	LC (min) MS (M+H)	Yield[a] (%)
12a			H	1.773 317	78
12b			H	2.315 401	73
12c			H	2.128 333	63
12d			H	1.814 351	72
15a				2.793 485	58
15b				2.957 519	62
15c				3.157 513	61
15d				3.518 597	70
15e				3.272 569	67
15f				3.218 525	58
15g				3.338 559	66
15h				3.101 501	70
15i				3.009 529	64
15j				3.266 499	62

[a] Isolated yield after HPLC purification[12] based on loading of the amino acid on the resin as determined by elemental analysis.

mmol), prepared as described in step 2 above, was treated with a solution of 20% piperidine in DMF (2 × 50 mL, 10 min for the first time and 30 min for the second time) to remove the Fmoc protecting group from the resin. The mixture was filtered, and the resin was washed with DMF (3 × 50 mL), MeOH (3 × 50 mL), and CH_2Cl_2 (3 × 50 mL).

Step 4. Reaction with Fmoc Isothiocyanate. To the 4-aminobenzoic acid on Wang resin (**4a**) (5.5 mmol) was added a solution of Fmoc isothiocyanate (**5**) (3.09 g, 11 mmol, prepared as described in step 1) in anhydrous CH_2Cl_2 (50 mL). After 20 min, the mixture was filtered and washed with CH_2Cl_2 (5 × 50 mL).

Step 5. Deprotection of Fmoc Group. The resin (**6a**) (5.5 mmol) obtained from step 4 was reacted again with a solution of 20% piperidine in DMF (2 × 50 mL, 10 min for the first time and 30 min for the second time) to produce the thiourea. The mixture was filtered, and the resin was washed with DMF (3 × 50 mL), MeOH (3 × 50 mL), CH_2Cl_2 (3 × 50 mL), and dried. To confirm that the reaction occurred, 100

mg of resin was treated with 50% TFA/CH_2Cl_2 for 1 h, the solution was filtered, and the filtrate was concentrated. LC/MS analysis showed the correct $M^+ + H$, 197.

Step 6. Preparation of the Resin-Bounded Methyl Thiourea. To the resin-bound thiourea (**7a**) (5.5 mmol) in anhydrous DMF (50 mL) was added MeI (6.85 mL, 0.11 mol). After half an hour, the mixture was filtered and treated again with an equal amount of MeI in DMF overnight. The mixture was then filtered, and the resin was washed with DMF (3 × 50 mL), MeOH (3 × 50 mL), and CH_2Cl_2 (3 × 50 mL) and dried. To confirm that the reaction occurred, 100 mg of resin was treated with 50% TFA/CH_2Cl_2 for 1 h, the solution was filtered, and the filtrate was concentrated. LC/MS analysis showed the correct $M^+ + H$, 211.

Step 7. Displacement of the Methylthio Group with Piperidine. A mixture of the resin (**8a**) (200 mg, 0.22 mmol; loading 1.1 mmol/g), prepared as described in step 6, and piperidine (87 μL, 0.88 mmol) in anhydrous dimethyl sulfoxide (4 mL) was heated at 80 °C for 24 h. The mixture was then filtered, and the resin was washed with DMSO (3 × 4 mL), MeOH (3 × 4 mL), and CH_2Cl_2 (3 × 4 mL) and dried. To confirm that the reaction occurred, 100 mg of resin was treated with 50% TFA/CH_2Cl_2 for 1 h, the solution was filtered, and the filtrate was concentrated. LC/MS analysis showed the correct $M^+ + H$, 248.

Step 8. Formation of 1,3,5-Triazine-2,4-dione. The resin (**10a**) (0.22 mmol) obtained from step 7 was swollen in anhydrous THF (4 mL), and 70.8 μL (0.88 mmol) of chlorocarbonylisocyanate was subsequently added. This reaction was allowed to shake at room temperature for 2 h. The mixture was filtered, and the resin was washed with THF (3 × 4 mL) and CH_2Cl_2 (3 × 4 mL) and dried. To confirm that the reaction occurred, 100 mg of resin was treated with 50% TFA/CH_2Cl_2 for 1 h, the solution was filtered, and the filtrate was concentrated. LC/MS analysis showed the correct $M^+ + H$, 317. ^{1}H NMR (DMSO-d_6): δ 1.21 (m, 4H), 1.38−1.40 (m, 2H), 3.10−3.14 (m, 4H), 7.57 (d, 2H), 8.03 (d, 2H), 11.10 (s, 1H), 13.15 (s, 1H).

Step 9. Mitsunobu Reaction with 4-Bromobenzyl Alcohol. To the resin **11a** (0.22 mmol) in 1:1 THF/CH_2Cl_2 (4 mL) was added tetramethylazodicarboxamide (189.4 mg, 1.1 mmol), followed by 4-bromobenzyl alcohol (205.7 mg, 1.1 mmol). Finally, tributylphosphine (275 μL, 1.1 mmol) was added. The resulting reaction mixture was rotated at room temperature overnight. The mixture was filtered, and the resin was washed with THF (3 × 4 mL), MeOH (3 × 4 mL), and CH_2Cl_2 (3 × 4 mL) and finally cleaved from resin with 50% TFA/CH_2Cl_2 (4 mL) for 1 h. The solution was filtered, and the filtrate was concentrated to 4-(3-(4-bromobenzyl)-2,4-dioxo-6-piperidin-1-yl-3,4-dihydro-1,3,5-triazin-1(2H)-1(2H)-yl)benzoic acid. LC/MS analysis showed the correct $M^+ + H$, 485.30. ^{1}H NMR (DMSO-d_6): δ 1.22−1.23 (m, 4H), 1.39−1.40 (m, 2H), 3.12−3.16 (m, 4H), 4.87 (s, 2H), 7.30 (d, 2H), 7.51 (d, 2H), 7.61 (d, 2H), 8.03 (d, 2H), 13.25 (s, 1H).

5-(3-(4-Bromobenzyl)-2,4-dioxo-6-piperidin-1-yl-3,4-dihydro-1,3,5-triazin-1(H)-yl)-2-chlorobenzoic acid (15b). The resin product was prepared according to steps 7 and 8 above from 2-chloro-5-aminobenzoic acid methyl isothiourea on Wang resin and piperidine followed by the cyclization. A sample of resin was treated with 50% TFA/CH_2Cl_2 to yield 2-chloro-5-(2,4-dioxo-6-piperidin-1-yl-3,4-dihydro-1,3,5-triazin-1(2H)-yl)benzoic acid. ^{1}H NMR (DMSO-d_6): δ 1.23 (m, 4H), 1.40−1.41 (m, 2H), 3.10−3.11 (m, 4H), 7.61−7.69(m, 2H), 7.90 (d, 1H), 11.10 (s, 1H), 13.10 (s, 1H).

The final Mitsunobu reaction followed by cleavage was carried out as described above (step 9) using 4-bromobenzyl alcohol. ^{1}H NMR (DMSO-d_6): δ 1.12−1.24 (m, 4H), 1.41−1.42 (m, 2H), 3.05−3.14 (m, 4H), 4.86 (s, 2H), 7.30 (d, 2H), 7.50 (d, 2H), 7.68(m, 2H), 7.97 (d, 1H), 13.20 (s, 1H).

3-(3-[4-(Benzyloxy)benzyl]-2,4-dioxo-6-piperidin-1-yl-3,4-dihydro-1,3,5-triazin-1(H)-yl)benzoic acid (15c). The resin product was prepared according to steps 7−9 from 3-aminobenzoic acid methyl isothiourea on Wang resin and piperidine followed by the cyclization. The Mitsunobu reaction was carried out using *p*-benzyloxybenzyl alcohol. ^{1}H NMR (DMSO-d_6): δ 1.18 (m, 4H), 1.39 (m, 2H), 3.10−3.12 (m, 4H), 4.82 (s, 2H), 5.07 (s, 2H), 6.94 (d, 2H), 7.27 (d, 2H), 7.31−7.44 (m, 5H), 7.61 (t, 1H), 7.72 (d, 1H), 7.96 (d, 1H), 8.02 (d, 1H), 13.30 (s, 1H). ESI-FTMS (exact mass) MH^+ Calcd for $C_{29}H_{28}N_4O_5$: 513.21325. Found: 513.21209.

5-(6-[Benzyl(ethyl)amino]-3-[4-(benzyloxy)benzyl]-2,4-dioxo-3,4-dihydro-1,3,5-triazin-1(H)-yl)-2-chlorobenzoic acid (15d). The resin product was prepared according to steps 7−9 from 2-chloro-5-aminobenzoic acid methyl isothiourea on Wang resin and *N*-ethylbenzylamine followed by the cyclization. The Mitsunobu reaction was carried out using *p*-benzyloxybenzyl alcohol. ^{1}H NMR (DMSO-d_6): δ 0.72 (t, 3H), 3.00 (q, 2H), 4.42 (s, 2H), 4.82(s, 2H), 5.08 (s, 2H), 6.94 (d, 2H), 7.16 (d, 2H), 7.25−7.34 (m, 5H), 7.34−7.44 (m, 5H), 7.59 (d, 1H), 7.66 (dd, 1H), 7.95 (d, 1H), 13.45 (s, 1H). ESI-FTMS (exact mass) MH^+ Calcd for $C_{33}H_{29}ClN_4O_5$: 597.18992. Found: 597.18905.

5-(6-[Benzyl(ethyl)amino]-3-(4-bromobenzyl)-2,4-dioxo-3,4-dihydro-1,3,5-triazin-1(H)-yl)-2-chlorobenzoic acid (15e). The resin product was prepared according to steps 7−9 from 2-chloro-5-aminobenzoic acid methyl isothiourea on Wang resin and *N*-ethylbenzylamine followed by the cyclization. The Mitsunobu reaction was carried out using 4-bromobenzyl alcohol. ^{1}H NMR (DMSO-d_6): δ 0.73 (t, 3H), 3.00 (q, 2H), 4.45 (s, 2H), 4.86 (s, 2H), 7.17 (d, 2H), 7.23−7.32 (m, 5H), 7.51 (d, 2H), 7.59 (d, 1H), 7.68 (dd, 1H), 7.97 (d, 1H), 13.45(s, 1H). ESI-FTMS (exact mass) MH^+ Calcd for $C_{26}H_{22}BrClN_4O_4$: 569.05857. Found: 569.05751.

3-(6-[Benzyl(ethyl)amino]-2,4-dioxo-3-[4-(trifluoromethyl)benzyl]-3,4-dihydro-1,3,5-triazin-1(H)-yl)benzoic Acid (15f). The resin product was prepared according to steps 7−9 from 3-aminobenzoic acid methyl isothiourea on Wang resin and *N*-ethylbenzylamine followed by the cyclization. The Mitsunobu reaction was carried out using *p*-trifluoromethylbenzyl alcohol. ^{1}H NMR (DMSO-d_6): δ 0.65 (t, 3H), 2.99 (q, 2H), 4.45 (s, 2H), 4.99 (s, 2H), 7.18−7.31 (m, 5H), 7.56 (d, 2H), 7.59 (d, 1H), 7.69 (d, 2H), 7.76 (d, 1H), 7.92 (d, 1H), 8.06 (t, 1H), 13.30 (s, 1H). ESI-FTMS (exact mass) MH^+ Calcd for $C_{27}H_{23}F_3N_4O_4$: 525.17442. Found: 525.17238.

5-(6-[Benzyl(ethyl)amino]-2,4-dioxo-3-[4-(trifluoromethyl)benzyl]-3,4-dihydro-1,3,5-triazin-1(H)-yl)-2-chlorobenzoic Acid (15g). The resin product was prepared according to steps 7−9 from 2-chloro-5-aminobenzoic acid methyl isothiourea on Wang resin and *N*-ethylbenzylamine followed by the cyclization. The Mitsunobu reaction was carried out using *p*-trifluoromethylbenzyl alcohol. ^{1}H NMR (DMSO-d_6): δ 0.74 (t, 3H), 3.02 (q, 2H), 4.44 (s, 2H), 4.98 (s, 2H), 7.17−7.31 (m, 5H), 7.55−7.70 (m, 6H), 7.99 (d, 1H), 13.40 (s, 1H). ESI-FTMS (exact mass) MH^+ Calcd for $C_{27}H_{22}ClF_3N_4O_4$: 559.13544. Found: 559.13362.

4-(3-(4-Bromobenzyl)-6-(dipropylamino)-2,4-dioxo-3,4-dihydro-1,3,5-triazin-1(H)-yl)benzoic Acid (15h). The resin product was prepared according to steps 7 and 8 from 4-aminobenzoic acid methyl isothiourea on Wang resin and dipropylamine followed by the cyclization. A sample of resin was treated with 50% TFA/CH_2Cl_2 as in step 8 to yield 4-(6-(dipropylamino)-2,4-dioxo-3,4-dihydro-1,3,5-triazin-1(2H)-yl)benzoic acid. ^{1}H NMR (DMSO-d_6): δ 0.64 (t, 6H), 1.18−1.30 (m, 4H), 2.98 (t, 4H), 7.55 (d, 2H), 8.04 (d, 2H), 11.00 (s, 1H), 13.22 (s, 1H).

The final Mitsunobu step (step 9) was carried out using 4-bromobenzyl alcohol. ^{1}H NMR (DMSO-d_6): δ 0.63 (t, 6H), 1.18−1.30 (m, 4H), 3.00 (t, 4H), 4.86 (s, 2H), 7.29 (d, 2H), 7.50 (d, 2H), 7.59 (d, 2H), 8.04 (d, 2H), 13.28 (s, 1H).

3-(3-[4-(Benzyloxy)benzyl]-6-(dipropylamino)-2,4-dioxo-3,4-dihydro-1,3,5-triazin-1(H)-yl)benzoic acid (15i). The resin product was prepared according to steps 7−9 from 3-aminobenzoic acid methyl isothiourea on Wang resin and dipropylamine followed by the cyclization. The final Mitsunobu reaction was carried out using *p*-benzyloxybenzyl alcohol. ^{1}H NMR (DMSO-d_6): δ 0.61 (t, 6H), 1.15−1.23 (m, 4H), 2.98 (t, 4H), 3.81 (s, 2H), 4.73 (s, 2H), 6.72 (d, 1H), 7.00 (m, 2H), 7.11−7.25 (m, 5H), 7.61−7.70 (m, 2H), 7.97−8.02 (m, 2H), 9.37 (s, 1H), 13.30(s, 1H). ESI-FTMS (exact mass) MH^+ Calcd for $C_{30}H_{32}N_4O_5$: 529.24455. Found: 529.24285.

3-(3-([1,1′-Biphenyl]-2-ylmethyl)-6-(dipropylamino)-2,4-dioxo-3,4-dihydro-1,3,5-triazin-1(H)-yl)benzoic Acid (15j). The resin product was prepared according to steps 7−9 from 3-aminobenzoic acid methyl isothiourea on Wang resin and dipropylamine followed by the cyclization. The final Mitsunobu reaction was carried out using 2-biphenylmethanol. ^{1}H NMR (DMSO-d_6): δ 0.62 (t, 6H), 1.17−1.24 (m, 4H), 3.00 (t, 4H), 4.84 (s, 2H), 7.19−7.20 (m, 2H), 7.24−7.45 (m, 7H), 7.61 (t, 1H), 7.66 (dd, 1H), 7.98 (d, 2H), 13.30(s, 1H). ESI-FTMS (exact mass) MH^+ Calcd for $C_{29}H_{30}N_4O_4$: 499.23398. Found: 499.23193.

Acknowledgment. We thank Dr. John Ellingboe for helpful suggestions and Dr. Keiko Tabei for high-resolution mass spectometry data.

Supporting Information Available. NMR spectra of compounds **15a**−**15j**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Wendeborn, S.; De Mesmaeker, A.; Brill, W.; Berteina, S. Synthesis of Diverse and Complex Molecules on the Solid Phase. *Acc. Chem. Res*. **2000**, *33*, 215−224. (b) Lorsbach, B. A.; Kurth, M. J. Carbon−Carbon Bond Forming Solid-Phase Reactions. *Chem. Rev.* **1999**, *99*, 1549−1581. (c) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. Solid-Phase Organic Reactions. III. A Review of the Literature Nov 96−Dec 97. *Tetrahedron* **1998**, *54*, 15385−15443. (d) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. Solid-Phase Organic Reactions II: A Review of the Literature Nov 95−Nov 96. *Tetrahedron* **1997**, *53*, 5643−5678. (e) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449−472. (f) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. Solid-Phase Organic Reactions: A Review of the Recent Literature. *Tetrahedron* **1996**, *52*, 4527−4554. (g) Ellman, J. A. Design, Synthesis, and Evaluation of Small-Molecule Libraries. *Acc. Chem. Res.* **1996**, *29*, 132−143.

(2) (a) Andres, C. J.; Denhart, D. J.; Deshpande, M. S.; Gillman, K. W. Recent Advances in the Solid Phase Synthesis of Drug-Like Heterocyclic Small Molecules. *Comb. Chem. High Throughput Screening* **1999**, *2*, 191−210. (b) Peng, G.; Sohn, A.; Gallop, M. A. Stereoselective Solid-Phase Synthesis of a Triaza Tricyclic Ring System: A New Chemotype for Lead Discovery. *J. Org. Chem.* **1999**, *64*, 8342−8349. (c) Fink, B. E.; Mortensen, D. S.; Stauffer, S. R.; Aron, Z. D.; Katzenellenbogen, J. A. Novel Structural Templates for Estrogen-Receptor Ligands and Prospects for Combinatorial Synthesis of Estrogens. *Chem. Biol.* **1999**, *6*, 205−219.

(3) (a) Franzen, R. G. Recent Advances in the Preperation of Heterocycles on Solid Support: A Review of the Literature. *J. Comb. Chem*. **2000**, *2*, 195−214. (b) Gopalsamy, A.; Yang, H. Combinatorial Synthesis of Heterocycles: Solid-Phase Synthesis of 2-Amino-4(1H)-quinazolinone Derivatives. *J. Comb. Chem*. **2000**, *2*, 378−381. (c) Hall, S. E. Recent Advances in Solid Phase Synthesis. *Mol. Diversity* **1999**, *4*, 131−142. (d) Corbett, J. W. Recent Progress in Solid Phase Heterocycle Syntheses. A Review. *Org. Prep. Proced. Int.* **1998**, *30*, 489−550.

(4) (a) Chiu, C.; Tang, Z.; Ellingboe, J. W. Solid-Phase Synthesis of 2,4,6-Trisubstituted Pyridines. *J. Comb. Chem*. **1999**, *1*, 73−77. (b) Gopalsamy, A.; Pallai, P. V. Combinatorial Synthesis of Heterocycles: Solid Phase Synthesis of 2-Arylquinoline-4-carboxylic Acid Derivatives. *Tetrahedron Lett*. **1997**, *38*, 907−910. (c) Pernerstorfer, J.; Schuster, M.; Blechert, S. A Solid-Phase Synthesis of Functionalized 6-, 7- and 8-Membered Azacycles via Olefin Metathesis. *Synthesis* **1999**, *1*, 138−144. (d) Shao, H.; Colucci, M.; Tong, S.; Zhang, H.; Castelhano, A. L. A Practical Solid Phase Synthesis of Quinazoline-2,4-diones. *Tetrahedron Lett.* **1998**, *39*, 7235−7238. (e) Park, K.-H.; Olmstead, M. M.; Kurth, M. J. Diastereoselective Solid-Phase Synthesis of Novel Hydantoin- and Isoxazoline-Containing Heterocycles. *J. Org. Chem.* **1998**, *63*, 6579−6585.

(5) (a) Brown, E. D. Analgesic 6-acylaminotetrahydro-1,3,5-2,4-dione derivatives, pharmaceutical compositions thereof, and process for their manufacture. European Patent EP 5911, 1979. (b) Pawlak, D.; Adamkiewicz, M.; Malyszko, J.; Takada, A. Vascular and cardiac effect of DV-7028, a selective, 5-HT2-receptor antagonist in rats. *J. Cardiovasc. Pharmacol*. **1998**, *32*, 266−273. (c) Hall, I. H.; Taylor, K.; Izydore, R. A.; Coleman, D. E.; Mitchell, J. A.; Cummings, R. The cytotoxic action of 1,3,5-triazabicyclo-[3.1.0]hexane-2,4-diones and 1,3,5-triazine-4,6-(1H,5H)-diones in murine and human tumor cells. *Pharmazie* **1998**, *53*, 398−405.

(6) (a) Kay, I. T. Substituted triazinedions, their preperation and use as herbicides. British Patent GB1464248, 1974. (b) Walker, K. A.; Ridley, S. M.; Lewis, T.; Harwood, J. L. A new class of herbicide which inhibits acetyl-CoA carboxylase in sensitive plant species. *Phytochemistry* **1990**, *29*, 3743−3747. (b) Sato, J.; Fukuda, K.; Ito, K.; Suzuki, K.; Nawamaki, T.; Watanabe, S. Preperation of 3-phenyl-1,3,5-triazine-2,4-

(1H,3H)-dione derivatives as selective herbicides. Japanese Patent JP03077874, 1991.
(7) Hagemann, H. Synthesis and reactions of N-chlorocarbonyl isocyanate. *Angew. Chem., Int. Ed. Engl*. **1977**, *16*, 743−750.
(8) Wang, S. *p*-Alkoxybenzyl Alcohol Resin and *p*-Alkoxybenzyloxycarbonylhydrazide Resin for Solid-Phase Synthesis of Protected Peptide Fragments. *J. Am. Chem. Soc.* **1973**, *95*, 1328−1333.
(9) Kearney, P. C.; Fernandez, M.; Flygare, J. A. Solid-Phase Synthesis of 2-Aminothiazoles. *J. Org. Chem*. **1998**, *63*, 196−200.
(10) Thomas, A. R.; Chapman, K. T. Solid phase synthesis of aryl ethers via mitsunobu reaction. *Tetrahedron Lett.* **1995**, *36*, 3789−3792.
(11) LC Conditions: HP 1100, 23 °C, 10 μL injected; column YMC-ODS-A 4.6 × 50 mm, 5 μm; gradient A, 0.05% TFA/water; gradient B, 0.05% TFA/acetonitrile; time 0 and 1 min, 98% A and 2% B; 7 min, 10% A and 90% B; 8 min, 10% A and 90% B; 8.9 min, 98% A and 2% B; post time, 1 min; flow rate, 2.5 mL/min; detection, 215 and 254 nm, DAD.
(12) Semiprep HPLC: Gilson with Unipoint software; column, Phenomenex C18 Luna 21.6 mm × 60 mm, 5 μM; solvent A, water (0.02% TFA buffer); solvent B, acetonitrile (0.02% TFA buffer); solvent gradient, 0 min, 5% B; 2.5 min, 5% B; 12 min, 95% B; hold, 95% B 3 min; flow rate, 22.5 mL/min; detection, 215 and 254 nm.

CC000091W