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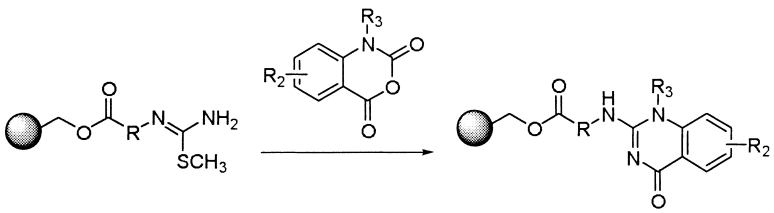

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Combinatorial Synthesis of Heterocycles: Solid-Phase Synthesis of 2-Amino-4(1*H*)-quinazolinone Derivatives

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A new solid-phase synthesis of various substituted 2-amino-4(1*H*)-quinazolinones from a resin bound amine component is described. The amine was readily converted to the corresponding polymer bound *S*-methylthiopseudourea. Condensation with different substituted isatoic anhydrides afforded 2-amino-4(1*H*)-quinazolinone derivatives. The method is amenable for combinatorial library generation.

Introduction

Solid-phase organic synthesis[1] has gained significant popularity due to its application in parallel and combinatorial synthesis for drug discovery.[2] Given the ubiquitous nature of the 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] Quinazolinones are an important class of molecules with physiological significance and pharmaceutical utility.[5] It is reported that 2-(arylamino)-4(3*H*)-quinazolinones **A** work as an inhibitor of the enzyme aldose reductase,[6] which prevents the onset of diabetic complications, and some 2-amino-4(3*H*)-quinazolinones **B** show antihypertensive activity[7] as well (Figure 1).

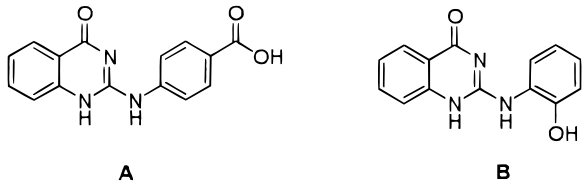
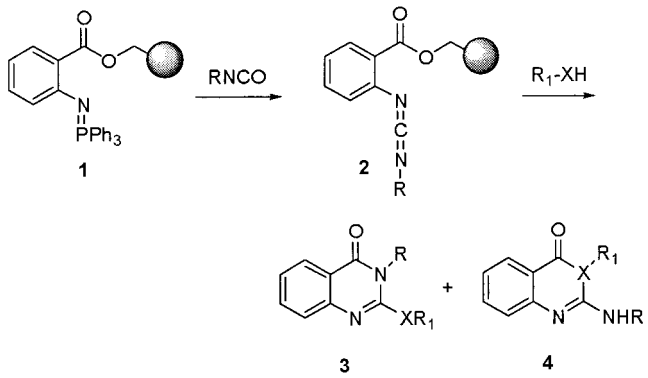


Figure 1.

A solid-phase synthesis of 3*H*-quinazolin-4-ones has been reported recently.[8] The synthesis is based on an aza Wittig reaction, and the scope of the method is limited since the reactive carbodiimide intermediate **2** gives a 1:1 mixture of **3** and **4** when sterically less hindered primary amines (R_1-XH = benzylamine or phenethylamine or butylamine) were used. (Scheme 1).

Scheme 1



To prepare a combinatorial library of quinazolinones with a high degree of diversity in the exocyclic amino region required for our biological evaluation, we considered the synthesis utilizing the isatoic anhydride chemistry.[9] Using this method a combinatorial quinazolinone synthesis is feasible since a number of isatoic anhydrides are commercially available or can be readily generated.[10] 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 2, Fmoc protected amino acid **5** was attached to the Wang resin **6**[11] 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 **7** in quantitative yield. The Fmoc group was removed using 20% piperidine in DMF. The free amine **8** was reacted with Fmoc-isothiocyanate **9**[12] in methylene chloride to give the Fmoc protected thiourea **10**. It was deprotected using 20% piperidine in DMF to give the thiourea **11**, which was converted to the corresponding *S*-methylthiopseudourea **12** by reacting with methyl iodide. Reaction of this resin bound compound with isatoic anhydride **13** in a polar aprotic solvent like *N*,*N*-dimethylacetamide (DMAC) led to the formation of the quinazolinone ring **14** on the resin. Upon treatment with trifluoroacetic acid in methylene chloride the required 2-amino substituted quinazoline-4-ones **15** were isolated.

Representative compounds produced by this synthesis are listed in Table 1. The purities of the crude product as assessed by HPLC[13] peak area were generally in the 60−85% range.[14] Aliphatic amino acids like the β-alanine (entry **15k**) also underwent efficient condensation with the isatoic anhydride. The reaction of *S*-methylpseudothiourea with N-substituted isatoic anhydride was equally efficient, providing a third point for diversification. Although the substituents R_2 and

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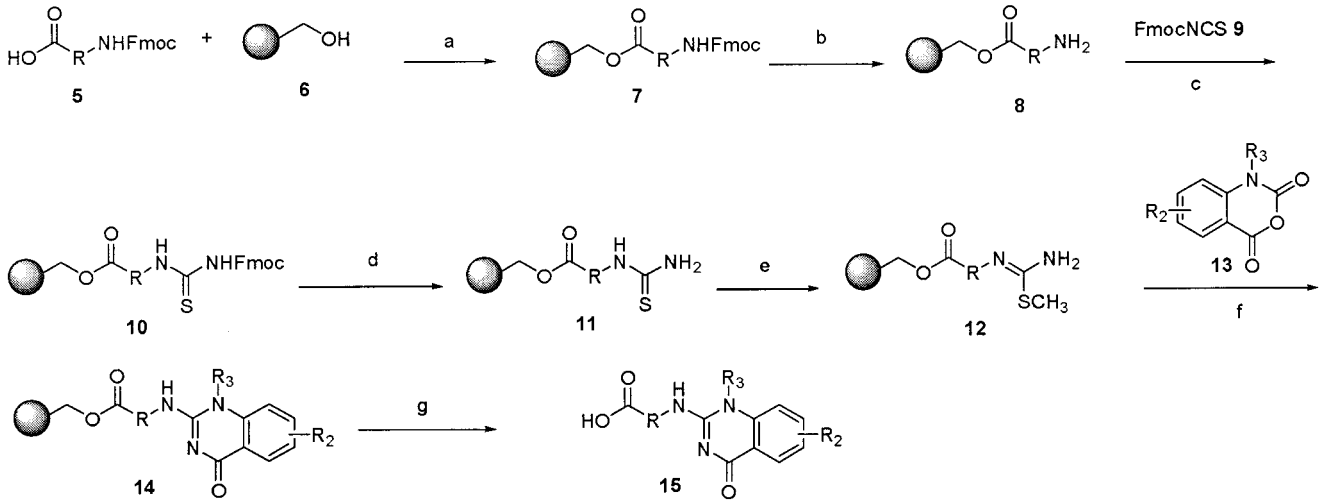
Scheme 2[a]



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

R_3 on the quinazolinone are derived from the isatoic anhydride component, considering the ease of synthesis of isatoic anhydrides, R_2 and R_3 can be introduced independently for the purpose of combinatorial library generation.

Conclusion

Described in this paper is a new solid-phase synthesis for 2-amino-1,4-dihydroquinazolin-4-one derivatives. The synthetic design includes three variable groups R_1-R_3 which are included in the scaffold: R_1 from an amine component, and R_2 and R_3 from an isatoic anhydride component. The procedure is quite general and is suitable for the preparation of combinatorial libraries.

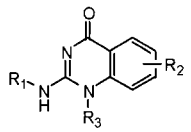
Experimental Section

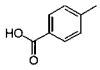
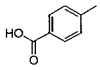
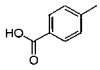
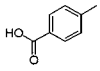
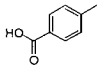
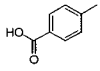
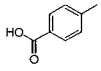
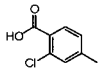
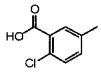
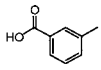
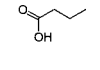
4-[(4-Oxo-1,4-dihydroquinazolin-2-yl)amino]benzoic Acid (15a). Step 1: Fluorenylmethyloxycarbonyl Isothiocyanate (9). The compound was prepared from fluorenylmethyloxycarbonyl chloride and potassium thiocyanate according to the procedure of Kearney et al.[12] ^{1}H NMR ($CDCl_3$): δ 7.75 (d, J = 7.5 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 (7a). Wang Resin (**6**) (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 (**5a**) (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 (**7a**) (5.5 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.

Table 1. Solid-Phase Synthesis of 2-Amino-1,4-dihydroquinazolin-4-one Derivatives



Entry	R_1	R_3	R_2	LC (min) MS (M+H)	Yield* (%)
15a		H	H	2.250 282.0	85
15b		CH_3	H	1.937 296.0	85
15c			H	2.412 322.0	92
15d			H	2.106 372.1	89
15e		H	Cl	2.185 316.0	80
15f		H	Br	2.300 360.0	95
15g		H	NO_2	2.059 327.0	90
15h			H	2.744 356.0	85
15i			H	2.430 356.0	88
15j			H	2.196 322.1	95
15k			H	1.601 274.1	90

[a] Crude yield based on loading of the amino acid on the resin as determined by elemental analysis.

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 (**8a**) (5.5 mmol) was added a solution of Fmoc-isothiocyanate (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 (**10a**) (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), 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 and filtered, and the filtrate was concentrated. MS: $[M + H]^+$ $m/z = 197$.

Step 6: Preparation of the Resin-Bounded Methyl Thiourea. To the resin-bounded thiourea (**11a**) (5.5 mmol) in anhydrous DMF (50 mL) was added MeI (6.85 mL, 0.11 mol). After 0.5 h, 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), 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 and filtered, and the filtrate was concentrated. MS: $[M + H]^+$ $m/z = 211$.

Step 7: Reaction with Isatoic Anhydride. A mixture of the resin (**12a**) (200 mg, 0.22 mmol; loading: 1.1 mmol/g), prepared as described in step 6, and isatoic anhydride (85 mg, 1.1 mmol) in anhydrous *N*,*N*-dimethylacetamide was heated at 80 °C 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). The resin was treated with 50% TFA/CH_2Cl_2 for 1 h and filtered, and the filtrate was concentrated to give 4-[(4-oxo-1, 4-dihydroquinazolin-2-yl)amino]benzoic acid. ^{1}H NMR (DMSO-d_6): δ 7.27 (t, 1H), 7.48 (d, 1H), 7.68 (t, 1H), 7.85−7.95 (AB quartet, 4H), 7.99 (d, 1H), 9.04 (s, 1H), 10.90 (s, 1H), 12.65 (s, 1H).

4-[(1-Methyl-4-oxo-1,4-dihydroquinazolin-2-yl)amino]-benzoic Acid (15b). The resin product was prepared according to step 7 of example 1 from 4-aminobenzoic acid methyl isothiourea on Wang resin and *N*-methylisatoic anhydride. ^{1}H NMR (DMSO-d_6): δ 3.45 (s, 3H), 7.40 (t, 1H), 7.46 (d, 1H), 7.65 (d, 1H), 7.84 (t, 1H), 7.95 (d, 2H), 8.03 (d, 2H), 10.30 (s, 1H), 12.70(s, 1H).

4-[(1-Allyl-4-oxo-1,4-dihydroquinazolin-2-yl)amino]benzoic Acid (15c). The resin product was prepared according to step 7 of example 1 from 4-aminobenzoic acid methyl isothiourea on Wang resin and *N*-allylisatoic anhydride. ^{1}H NMR (DMSO-d_6): δ 4.92 (m, 2H), 5.20 (m, 2H), 5.94−6.03 (m, 1H), 6.96 (t, 1H), 7.22 (d, 1H), 7.34 (d, 1H), 7.69 (t, 1H), 7.88 (d, 2H), 7.97 (d, 2H), 10.35 (s, 1H), 12.70 (s, 1H).

4-[(1-Benzyl-4-oxo-1,4-dihydroquinazolin-2-yl)amino]-benzoic Acid (15d). The resin product was prepared according to step 7 of example 1 from 4-aminobenzoic acid methyl isothiourea on Wang resin and *N*-benzylisatoic anhydride. ^{1}H NMR (DMSO-d_6): δ 5.56 (s, 2H), 7.18−7.37 (m, 8H), 7.60 (t, 1H), 7.88 (d, 2H), 7.97 (d, 2H), 10.45 (s, 1H), 12.60(s, 1H).

4-[(6-Chloro-4-oxo-1,4-dihydroquinazolin-2-yl)amino]-benzoic Acid (15e). The resin product was prepared according to step 7 of example 1 from 4-aminobenzoic acid methyl isothiourea on Wang resin and 5-chloroisatoic anhydride. ^{1}H NMR (DMSO-d_6): δ 7.50 (d, 1H), 7.72 (dd, 1H), 7.85−7.95 (m, 5H), 9.60 (s, 1H), 11.20 (s, 1H), 12.70 (s, 1H).

4-[(6-Bromo-4-oxo-1,4-dihydroquinazolin-2-yl)amino]-benzoic Acid (15f). The resin product was prepared according to step 7 of example 1 from 4-aminobenzoic acid methyl isothiourea on Wang resin and 5-bromoisatoic anhydride. ^{1}H NMR (DMSO-d_6): δ 7.43 (d, 1H), 7.82 (dd, 1H), 7.85−7.94 (AB quartet, 4H), 8.04 (d, 1H), 9.70 (s, 1H), 11.40 (s, 1H), 12.70 (s, 1H).

4-[(6-Nitro-4-oxo-1,4-dihydroquinazolin-2-yl)amino]-benzoic Acid (15g). The resin product was prepared according to step 7 of example 1 from 4-aminobenzoic acid methyl isothiourea on Wang resin and 5-nitroisatoic anhydride. ^{1}H NMR (DMSO-d_6): δ 7.60 (d, 1H), 7.86−7.98 (AB quartet, 4H), 8.43 (dd, 1H), 8.70 (d, 1H), 9.46 (s, 1H), 11.48 (s, 1H), 12.72 (s, 1H).

4-[(1-Allyl-4-oxo-1,4-dihydroquinazolin-2-yl)amino]-2-chlorobenzoic Acid (15h). The resin product was prepared according to step 7 of example 1 from 2-chloro-4-aminobenzoic acid methyl isothiourea on Wang resin and *N*-allylisatoic anhydride. ^{1}H NMR (DMSO-d_6): δ 4.89 (m, 2H), 5.09−5.22 (dd, 2H), 5.92−6.02 (m, 1H), 7.21 (t, 1H), 7.33 (d, 1H), 7.65−7.73 (m, 2H), 7.79 (d, 1H), 7.98 (dd, 1H), 8.10 (t, 1H), 8.73 (s, 1H), 11.60 (s, 1H), 12.90 (s, 1H).

5-[(1-Allyl-4-oxo-1,4-dihydroquinazolin-2-yl)amino]-2-chlorobenzoic Acid (15i). The resin product was prepared according to step 7 of example 1 from 2-chloro-5-aminobenzoic acid methyl isothiourea on Wang resin and *N*-allylisatoic anhydride. ^{1}H NMR (DMSO-d_6): δ 4.92 (m, 2H), 5.10−5.27 (dd, 2H), 5.97−6.07 (m, 1H), 7.32 (t, 1H), 7.41 (d, 1H), 7.51 (d, 1H), 7.58 (m, 1H), 7.75 (t, 1H), 8.00 (d, 2H), 8.90 (s, 1H), 11.70 (s, 1H), 13.20 (s, 1H).

3-[(1-Allyl-4-oxo-1,4-dihydroquinazolin-2-yl)amino]benzoic Acid (15j). The resin product was prepared according to step 7 of example 1 from 3-aminobenzoic acid methyl isothiourea on Wang resin and *N*-allylisatoic anhydride. ^{1}H NMR (DMSO-d_6): δ 4.95 (m, 2H), 5.14−5.28 (dd, 2H), 5.97−6.07 (m, 1H), 7.30 (t, 1H), 7.43−7.49 (m, 2H), 7.71−7.77 (m, 2H), 7.93−8.02 (m, 3H), 8.87 (s, 1H), 11.60 (s, 1H), 13.10 (s, 1H).

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References and Notes

(1) (a) Lorsbach, B. A.; Kurth, M. J. Carbon−Carbon Bond Forming Solid-Phase Reactions. *Chem. Rev.* **1999**, *99*, 1549−1581. (b) 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. (c) Hermkens, P. H. H.; Ottenheijim, H. C. J.; Rees, D. Solid-Phase Organic Reactions II: A Review of the Literature Nov 95−Nov 96. *Tetrahedron* **1997**, *53*, 5643−5678. (d) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449−472. (e) Hermkens, P. H. H.; Ottenheijim, H.

C. J.; Rees, D. Solid-Phase Organic Reactions: A Review of the Recent Literature. *Tetrahedron* **1996**, *52*, 4527−4554. (f) 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) Hall, S. E. Recent Advances in Solid-Phase Synthesis. *Mol. Diversity* **1999**, *4*, 131−142. (b) 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) Fry, D. W.; Kraker, A. J.; McMichael, A.; Ambroso. L. A.; Nelson, J. M.; Leopold, W. R.; Connors, R. W.; Bridges, A. J. *Science* **1994**, *265*, 1093. (b) Laszlo, S. E. d.; Chang, R. S.; Cheng, T. B.; Faust, K. A.; Greenlee, W. J.; Kivlighn, S. D.; Lotti, V. J.; O'Malley, S. S.; Schorn. T. W.; Siegl, P. K.; Tran, J.; Zingaro, G. J. *Biorg. Chem. Med. Lett.* **1995**, *5*, 1359. (c) Johne, S. *Pharmazie* **1981**, *36*, 583.

(6) DeRuiter, J.; Brubaker, A. N.; Millen, J.; Riley, T. N. Design and Synthesis of 2-(Arylamino)-4(3*H*)-quinazolinones as Novel Inhibitors of Rat Lens Aldose Reductase. *J. Med. Chem.* **1986**, *29*, 627−629.

(7) (a) Hess, H.-J.; Cronin, T. H.; Scriabine, A. Antihypertensive 2-Amino-4(3H)-quinaolinones. *J. Med. Chem.* **1968**, *11*, 130−136. (b) Hussain, M. A.; Chiu, A. T.; Price, W. A.; Timmermans, P. B.; Shefter, E. Antihypertensive Activity of 2[(2-Hydroxyphenyl)amino]-4(3*H*)-quinazolinone. *Pharm. Res.* **1988**, *5*, 242−244.

(8) Villalgordo, J. M.; Obrecht, D.; Chucholowsky A. Solid-Phase Synthesis of 3*H*-Quinazolin-4-ones Based on an Aza Wittig-Mediated annulation Strategy. *Synlett* **1998**, 1405−1407.

(9) Coppola, G. M.; Hardtmann, G. E.; Pfister, O. R. Chemistry of 2*H*-3,1-Benzoxazine-2,4(1*H*)-dione (Isatoic Anhydride). 2. Reactions with Thiopseudoureas and Carbanions. *J. Org. Chem.* **1976**, *41*, 825−831.

(10) Coppola, G. M. The Chemistry of Isatoic Anhydride. *Synthesis* **1980**, 505−536.

(11) Wang, S. *J. Am. Chem. Soc.* **1973**, *95*, 1328−1333.

(12) Kearney, P. C.; Fernandez, M.; Flygare, J. A. Solid-Phase Synthesis of 2-Aminothiazoles. *J. Org. Chem*. **1998**, *63*, 196−200.

(13) LC conditions: HP 1100, 23 °C, 10 μL injected. Column: YMC-ODS-A 4.6 × 50, 5 μm. Gradient A: 0.05% TFA/water; B: 0.05% TFA/acetonitrile. Time 0 & 1 min: 98% A & 2% B. Time 7 min: 10% A & 90% B. Time 8 min: 10% A & 90% B. Time 8.9 min: 98% A & 2% B. Post time: 1 min. Flow rate: 2.5 mL/min. Detection: 215 and 254 nm, DAD.

(14) Analysis of the crude product indicated the presence of unreacted methyl thioureas **12** as the only other major component.

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