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A Facile Synthesis of C_2,N_3-Disubstituted-4-quinazolone

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Abstract: A simple and efficient methodology for the synthesis of C_2,N_3-disubstituted-4 quinazolones from anilines and *N*-acylanthranilic acids was developed. The new cyclization conditions are much milder than any other reported protocols and resulted in excellent yields (87−98%) without chromatography.

It has long been known that 4-quinazolones (**1**) exhibit a wide spectrum of biological activities and were used as antihypertensives,[1,2] CNS depressants,[3,4] and antiinflammatories.[5] Recently, a group reported synthetic approaches leading to 2-hydroxymethyl-4-quinazolones (Figure 1, **2**), since one of its derivatives, 2-carbamoyloxymethyl-4(3*H*)-quinazolones (Figure 1, **3**), had shown potent hypotensive activity in anesthetized rabbits and in conscious spontaneously hypertensive rats.[2] The majority of reported 4-quinazolone syntheses proceeded from either anthranilic acid or its derivatives (**4**).[6] Niementowski developed a preparation of 4-quinazolones in 1895 by heating an anthranilic acid and an amide neat at temperatures exceeding 150 °C.[7] Grimmel modified the former synthesis by heating *N*-acetylanthranilic acids with anilines in toluene or xylene in the presence of condensing agents such as phosphorus trichloride, phosphorus oxychloride, or thionyl chloride.[8] Other methodologies included treating 2-aminobenzonitriles with urea hydrogen peroxide[9] and pyrolyzing *O*-acetylaminobenzamides.[6] There are several drawbacks in these reported syntheses: they are lengthy and low yielding, require difficult isolation techniques, or work only for simple

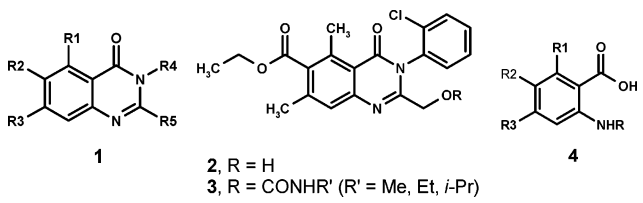
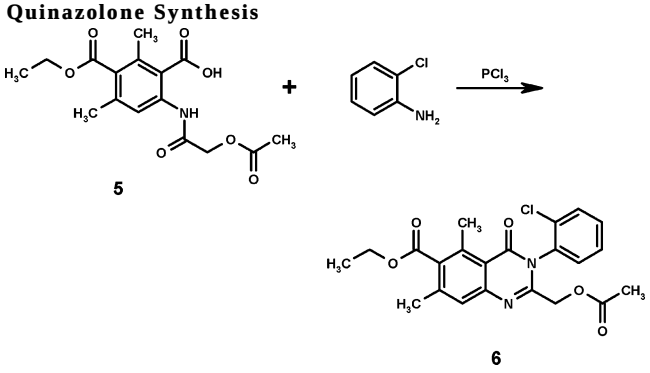


FIGURE 1.

TABLE 1. Solvent and Temperature Effects on Quinazolone Synthesis



entry	solvents	PCl_3 [equiv]	temp [°C]	yield (HPLC) [%]
1	toluene	0.34	110	10
2	toluene	2.0	110	20
3	CH_2Cl_2	2.0	40	17
4	THF	2.0	50	93
5	CH_3CN	2.0	50	95
6	CH_3CN	1.0	50	88
7	CH_3CN	2.0	70	95

quinazolones.[2,7,10] In this paper, we wish to report an optimization of Grimmel's conditions for the synthesis of C_2,N_3-disubstituted-4-quinazolones (**1**) from *N*-acylanthranilic acids (**4**, R = $COCH_2R''$).

Grimmel's 1946 paper reported that no detectable 2-acetoxymethyl-4-quinazolone (**1**, R_1, R_2, R_3 = H, R_4 = Ph, R_5 = CH_2OCOCH_3) had been formed when aniline and *N*-acetoxyacetylanthranilic acid (**4**, R = $COCH_2OCOCH_3$, R_1, R_2, R_3 = H) were refluxed in toluene or xylene in the presence of 0.34 equiv of PCl_3.[8] Interestingly, when we applied his protocol to *O*-chloroaniline and a trisubstituted *N*-acetoxyacetylanthranilic acid (**5**), a small amount (10%) of 4-quinazolone product (**6**) was generated (Table 1, entry 1). The identity of **6** was supported by ^{1}H NMR and elemental analysis of the purified product. This unexpected result encouraged us to explore his approach further. We noticed that when 2 equiv of PCl_3 were employed (entry 2), a large amount of sticky solid was coated on the inner wall of the glassware

* Corresponding authors.

(1) Hess, H.-J.; Cronin, T. H.; Scriabine, A. *J. Med. Chem.* **1968**, *11*, 130.

(2) (a) Ishikawa, M.; Azuma, H.; Eguchi, Y.; Sugimoto, A.; Ito, S.; Takashima, Y.; Ebisawa, H.; Moriguchi, S.; Kotoku, I.; Suzuki, H. *Chem. Pharm. Bull.* **1982**, *30*, 744. (b) Ishikawa, M.; Eguchi, Y. *Heterocycles* **1981**, *16*, 31.

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(5) (a) Leszkovsky, G.; Tardos, L. *Chem. Abstr.* **1965**, *62*, 16821g. (b) Saxena, S.; Verma, M.; Saxena, A. K.; Shanker, K. *Indian J. Pharm. Sci.* **1991**, *53*, 48.

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(8) Grimmel, H. W.; Guenther, A.; Morgan, J. F. *J. Am. Chem. Soc.* **1946**, *68*, 539.

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(10) (a) Bergman, J.; Brynolf, A. *Tetrahedron*, **1990**, *46*, 1295. (b) George, T.; Tahilramani, R.; Mehta, D. V. *Indian J. Chem.* **1971**, *9*, 1077. (c) Uskokovic, M.; Iacobelli, J.; Toome, V.; Wenner, W. *J. Org. Chem.* **1964**, *29*, 582. (d) Sutherland, D. R.; Tennant, G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 534. (e) Hennequin, L. F.; Boyle, F. T.; Wardleworth, J. M.; Marsham, P. R.; Kimbell, R.; Jackman, A. L. *J. Med. Chem.* **1996**, *39*, 695. (f) Bavetsias, V. *Synth. Commun.* **1998**, *28*, 4547. (g) Ager, I. R.; Harrison, D. R.; Kennewell, P. D.; Taylor, J. B. *J. Med. Chem.* **1977**, *20*, 379. (h) Yamada, Y.; Otsuka, M.; Tani, J.; Oine, T. *Chem. Pharm. Bull.* **1983**, *31*, 1158.

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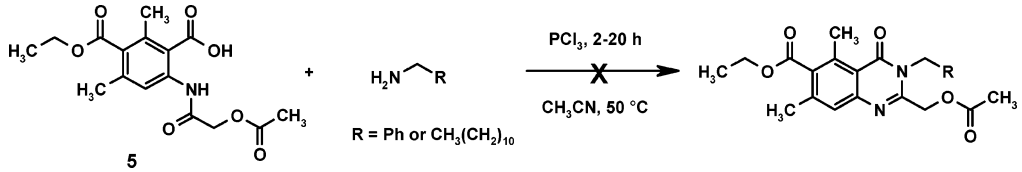
SCHEME 1. No Quinazolone Formation with an Aliphatic Amine



during the reaction. Subsequent workup was difficult and resulted in 15% isolated yield. According to HPLC and ^{1}H NMR analyses, the sticky precipitate contained a mixture of a plausible intermediate **7** (Figure 2) and product **6**. This suggested that low solubility of intermediate(s) in toluene may be one of the factors contributing to the low yield.

We envisioned that cyclization of anthranilic acid **8** with an aniline leading to quinazolone **9** was presumably promoted by two Lewis acids: PCl_3 employed and HCl generated in situ. We decided to investigate solvent and temperature effects on the efficiency of cyclization, hoping to identify an ideal combination that could optimize the solubilities of both HCl and intermediates and contribute eventually to higher conversion of quinazolone. As shown in Table 1, various solvents, temperatures, and amounts of PCl_3 were examined. Polar aprotic solvents, such as acetonitrile and tetrahydrofuran, appeared to be superior to less polar toluene and methylene chloride when 2 equiv of PCl_3 were used at 50 °C. Under these conditions, excellent conversions (93−95%) were achieved as indicated by HPLC analyses (entries 4 and 5). Attempts to reduce the amount of PCl_3 resulted in slightly lower yield (entry 6).

To probe the scope and limitations for 4-quinazolone synthesis using our newly developed protocol, a variety of anilines and acylanthranilic acids were examined employing the optimized conditions: 2 equiv of PCl_3/CH_3CN/50 °C. As is evident from Table 2, excellent isolated yields (87−98%) were obtained for all 4-quinazolones. The protocol was efficient for any combinations of substituted- or unsubstituted-acylanthranilic acids and electronic-rich or electronic-poor anilines. It is noteworthy that no 4-quinazolone was produced in the reaction involving an alkylamine, such as benzylamine or dodecylamine, and anthranilic acid **5** (Scheme 1).

2-Hydroxymethylquinazolones (**2**, **17**, and **18**) were obtained by the methanolysis reaction of the corresponding 2-acetoxymethylquinazolones (**6**, **10**, and **12**) with potassium carbonate in methanol (Table 3). In all cases, the methanolysis was fast (20 min) and efficient. Upon completion, water was added to the reaction mixture in several installments to initiate the precipitation of products with high quality (>98% HPLC). The products were isolated by filtration with excellent yields (90−96%) without chromatography.

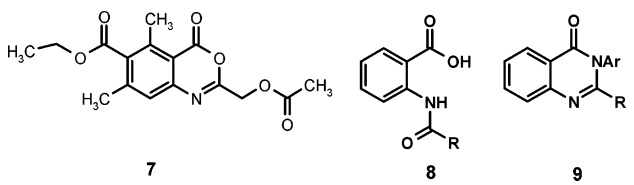


FIGURE 2.

In summary, we have developed a simple and efficient methodology for the synthesis of C_2,N_3-disubstituted-quinazolones from anilines and *N*-acylanthranilic acids. Our cyclization conditions are much milder than any reported protocols and resulted in excellent yields (87−98%) without chromatography.

Experimental Section

All reagents and solvents were purchased from commercial suppliers and used without further purification. Compound **15** is a known compound[11] that was synthesized in our lab and confirmed by ^{1}H NMR and MS spectra.

General Procedure for the Preparation of *N*-Acetoxyacetylanthranilic Acids. To a solution of anthranilic acid (0.1 mol) and Et_3N (0.4 mol) in THF was added acetoxyacetyl chloride (0.15 mol) under nitrogen atmosphere while keeping the temperature below 0 °C. The mixture was warmed to rt and stirred for 1 h. EtOAc and 10% aqueous citric acid were added to the mixture. The organic layer was separated, washed with water, and concentrated under vacuum to give an oily residue. Pure *N*-acetoxyacetylanthranilic acids were recrystallized from a mixture of EtOAc and cyclohexane.

4-Acetoxyacetylamino-2,6-dimethyl-1,3-benzenedicarboxylic acid 1-ethyl ester (5): mp 153−156 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.68 (br s, 1H), 10.41 (s, 1H), 8.16 (s, 1H), 4.60 (s, 2H), 4.28 (q, J = 7.2 Hz, 2H), 2.34 (s, 3H), 2.21 (s, 3H), 2.09 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H). Anal. Calcd for $C_{16}H_{19}NO_7$: C, 56.97; H, 5.68; N, 4.15. Found: C, 56.82; H, 5.60; N, 4.00.

***N*-(Acetoxyacetyl)anthranilic acid (11):** mp 156−160 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.52 (s, 1H), 8.78 (d, J = 8.5 Hz, 1H), 8.09 (d, J = 8.1 Hz, 2H), 7.62 (t, J = 7.9 Hz, 1H), 7.17 (t, J = 7.7 Hz, 1H), 4.75 (s, 2H), 2.28 (s, 3H). Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found: C, 55.66; H, 4.69; N, 5.76.

4-Acetylamino-2,6-dimethyl-1,3-benzenedicarboxylic acid 1-ethyl ester (13): mp 172−176 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.60 (s, 1H), 7.35 (s, 1H), 4.30 (q, J = 7.2 Hz, 2H), 2.35 (s, 1H), 1.95 (s, 1H), 1.30 (t, J = 7.2 Hz, 3H). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.15; H, 6.22; N, 5.05.

General Procedure for the Synthesis of 4-Quinazolone. To a solution of the acetylanthranilic acid (6 mmol) in CH_3CN was added a solution of the aniline (8 mmol) in CH_3CN (10 mL) at rt to give a white suspension. PCl_3 (12 mmol) was added via syringe, and the resulting mixture was warmed to 50 °C and stirred for an additional 2−20 h. The mixture was cooled to rt and diluted with EtOAc. The mixture was quenched by the addition of 1 N aqueous HCl solution. The organic layer was separated, washed with 10% aqueous $KHCO_3$ solution, and evaporated under vacuum to give an oil, which crystallized on standing. The crude products were recrystallized from ethanol/water (1:1).

2-Acetoxymethyl-5,7-dimethyl-3-(2-chlorophenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxylic acid ethyl ester (6): mp 124−127 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.75−7.50 (m, 5 H), 4.67 (q_{ab}, J = 18.8, 14.1 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 2.65 (s, 3H), 2.38 (s, 3H), 2.00 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H).

(11) Osborne A. G.; Goolamali, Z. *Spectrochim. Acta Part A* **2000**, *56*, 1079.

TABLE 2. Synthesis of 4-Quinazolones

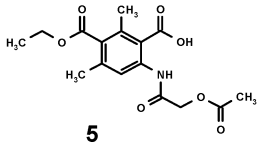
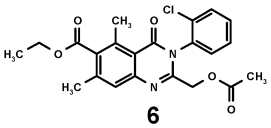
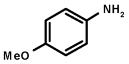
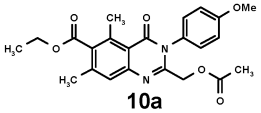
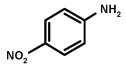
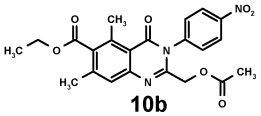
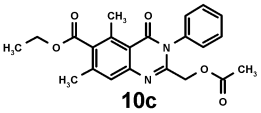
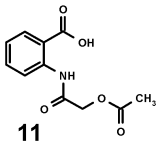
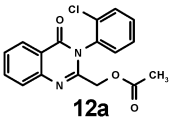
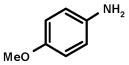
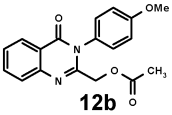
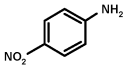
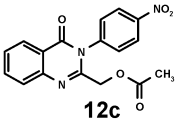
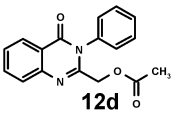
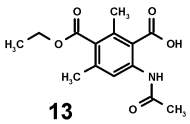
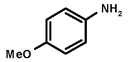
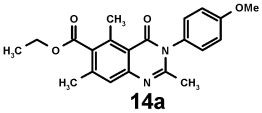
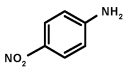
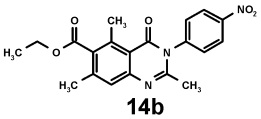
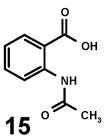
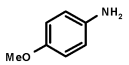
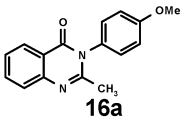
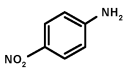
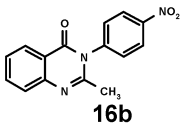
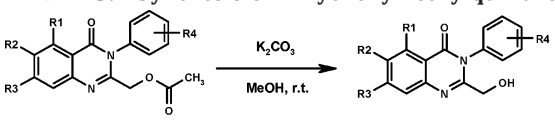
Entry	N-Acylanthranilic acids	Anilines	Quinazolones	Time [h]	Yield [%]
1	 **5**		 **6**	2	92
2	**5**		 **10a**	2	94
3	**5**		 **10b**	2	96
4	**5**		 **10c**	2	93
5	 **11**		 **12a**	2	96
6	**11**		 **12b**	2	97
7	**11**		 **12c**	2	98
8	**11**		 **12d**	2	96
9	 **13**		 **14a**	20	90
10	**13**		 **14b**	2	96
11	 **15**		 **16a**	20	87
12	**15**		 **16b**	20	89

TABLE 3. Synthesis of 2-Hydroxymethylquinazolones



Entry	Substrate	Product	Yield (Isolated) [%]
1	**6**	**2**	95
2	**10a**	**17a**	90
3	**10b**	**17b**	95
4	**10c**	**17c**	96
5	**12a**	**18a**	95
6	**12b**	**18b**	90
7	**12c**	**18c**	91
8	**12d**	**18d**	91

Anal. Calcd for $C_{22}H_{21}N_2O_5Cl$: C, 61.61; H, 4.94; N, 6.53; Cl, 8.27. Found: C, 61.56; H, 4.71; N, 6.45; Cl, 8.30.

2-Acetoxymethyl-3-(2-chlorophenyl)-4-oxo-3,4-dihydroquinazoline (12a): mp 83−86 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.25 (d, J = 6.2 Hz, 1H), 7.75 (m, 2H), 7.30−7.60 (m, 5H), 4.70 (q_{ab}, J = 32.0, 15.2 Hz, 2H), 2.00 (s, 3H). Anal. Calcd for $C_{17}H_{13}N_2O_3Cl$: C, 62.25; H, 4.00; N, 8.54; Cl, 10.81. Found: C, 61.99; H, 3.72; N, 8.48; Cl, 10.76.

2-Methyl-5,7-dimethyl-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxylic acid ethyl ester (14a): mp 104−106 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (s, 1H), 7.15 (d, J = 9.0 Hz, 2H), 7.05 (d, J = 9.0 Hz, 2H), 4.43 (q, J = 7.0 Hz, 2H), 3.85 (s, 3H), 2.75 (s, 3H), 2.42 (s, 3H), 2.23 (s, 3H), 1.40 (t, J = 7.0 Hz, 3H). Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.83; H, 6.05; N, 7.65. Found: C, 68.52; H, 5.88; N, 7.50.

2-Methyl-5,7-dimethyl-3-(4-nitrophenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxylic acid ethyl ester (14b): mp 177−178 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.35 (d, J = 9.0 Hz, 2H), 7.42 (d, J = 9.0 Hz, 2H), 7.32 (s, 1H), 4.35 (q, J = 7.0 Hz, 2H), 2.65 (s, 3H), 2.35 (s, 3H), 2.15 (s, 3H), 1.35 (t, J = 7.0 Hz, 3H). Anal. Calcd for $C_{20}H_{19}N_3O_5$: C, 62.98; H, 5.02; N, 11.02. Found: C, 62.98; H, 4.77; N, 10.95.

2-Methyl-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazoline (16a): mp 167−170 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.25 (d, J = 6.2 Hz, 1H), 7.75 (m, 2H), 7.48 (m, 1H), 7.20 (d, J = 9.0 Hz, 2H), 7.05 (d, J = 9.0 Hz, 2H), 3.85 (s, 3H), 2.35 (s, 3H). Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.08; H, 5.08; N, 10.58.

2-Methyl-3-(4-nitrophenyl)-4-oxo-3,4-dihydroquinazoline (16b): mp 190−193 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.35 (d, J = 9.0 Hz, 2H), 8.18 (d, J = 6.2 Hz, 1H), 7.75 (m, 2H), 7.62 (d, J = 6.2 Hz, 1H), 7.45 (d, J = 9.0 Hz, 2H), 2.18 (s, 3H). Anal. Calcd for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94; N, 14.94. Found: C, 64.00; H, 3.70; N, 14.99.

General Procedure for the Synthesis of 2-Hydroxymethyl-4-quinazolones. Method A: To a slurry of 2-acetoxymethyl-4-quinazolones (1 mmol) in MeOH (4 mL) at rt was added K_2CO_3 (2.5 mmol). The mixture was stirred at rt for an additional 20 min. Water (10 mL) was added slowly, and the product precipitated. The slurry was filtered and dried under vacuum.

Method B: To a slurry of 2-acetoxymethyl-4-quinazolones (1 mmol) in MeOH (4 mL) at rt was added K_2CO_3 (2.5 mmol). The mixture was stirred at rt for an additional 20 min. Water (10 mL) was added, followed by TBME (10 mL). The organic layer was separated, dried under $MgSO_4$, filtered, and concentrated under vacuum to give a foamy solid.

Method C: To a slurry of 2-acetoxymethyl-4-quinazolones (1 mmol) in MeOH (4 mL) at rt was added K_2CO_3 (2.5 mmol). The mixture was stirred at rt for an additional 20 min. Water (10 mL) was added, followed by TBME (10 mL). The organic layer was separated, dried under $MgSO_4$, and filtered. Hydrochloric acid (37%, 1 mmol) was added, and the resulting hydrochloride salt precipitates were filtered and dried under vacuum.

2-Hydroxymethyl-5,7-dimethyl-3-(2-chlorophenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxylic acid ethyl ester (2): Method B; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.65−7.50 (m, 5 H), 5.37 (t, J = 6.0 Hz, 1 H, O*H*), 4.39 (q, J = 7.2 Hz, 2H), 4.00 (dq_{ab}, J = 33.2, 15.1, 6.0 Hz, 2H), 2.64 (s, 3H), 2.38 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H). Anal. Calcd for $C_{20}H_{19}N_2O_4Cl$: C, 62.10; H, 4.95; N, 7.24; Cl, 9.16. Found: C, 62.11; H, 4.82; N, 7.09; Cl, 9.02.

2-Hydroxymethyl-5,7-dimethyl-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxylic acid ethyl ester hydrochloride salt (17a·HCl): Method C; mp 118−121 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.79 (s, 1H), 7.39 (d, J = 9.0 Hz, 2H), 7.12 (d, J = 9.0 Hz, 2H), 6.33 (b, 2H), 4.40 (q, J = 7.1 Hz, 2H), 4.16 (s, 2H), 3.84 (s, 3H), 2.64 (s, 3H), 2.40 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H). Anal. Calcd for $C_{21}H_{23}N_2O_5Cl$: C, 60.22; H, 5.53; N, 6.69. Found: C, 60.64; H, 5.71; N, 6.65.

2-Hydroxymethyl-5,7-dimethyl-3-(4-nitrophenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxylic acid ethyl ester (17b): Method A; mp 215−217 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.23 (d, J = 9.2 Hz, 2H), 7.36 (s, 1H), 7.26 (d, J = 9.2 Hz, 2H), 5.15 (s, 2H), 4.37 (q, J = 7.1 Hz, 2H), 2.69 (s, 3H), 2.31 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H). Anal. Calcd for $C_{20}H_{19}N_3O_6$: C, 60.45; H, 4.82; N, 10.57. Found: C, 60.37; H, 4.93; N, 10.66.

2-Hydroxymethyl-3-(2-chlorophenyl)-4-oxo-3,4-dihydroquinazoline (18a): Method B; mp 75−77 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.30−7.40 (m, 8H), 5.39 (t, J = 6.2 Hz, 1H), 4.05 (dq_{ab}, J = 30, 15, 6.2 Hz, 2H). Anal. Calcd for $C_{15}H_{11}N_2O_2Cl$: C, 62.84; H, 3.87; N, 9.77; Cl, 12.37. Found: C, 62.69; H, 3.76; N, 9.60; Cl, 12.59.

2-Hydroxymethyl-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazoline (18b): Method A; mp 163−166 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.14 (dd, J = 7.9, 1.1 Hz, 1H), 7.88 (td, J = 7.6, 1.5 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.55 (td, J = 7.5, 1.1 Hz, 1H), 7.35 (d, J = 8.9 Hz, 2H), 7.08 (d, J = 8.9 Hz, 2H), 5.16 (s, 1H), 4.07 (s, 2H), 3.83 (s, 3H). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00; N, 9.92. Found: C, 67.95; H, 4.97; N, 9.89.

2-Hydroxymethyl-3-phenyl-4-oxo-3,4-dihydroquinazoline (18d): Method A; mp 155−157 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.14 (dd, J = 7.9, 1.1 Hz, 1H), 7.89 (td, J = 7.0, 1.5 Hz, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.65−7.45 (m, 6H), 5.23 (s, 1H), 4.06 (s, 2H). Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.12; H, 5.00; N, 11.13.

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Supporting Information Available: Text giving analytical and spectral data for compounds **10a**, **10b**, **10c**, **12b**, **12c**, **12d**, **17c**, and **18c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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