Liquid-Phase Synthesis with Solid-Phase Workup: Application to Multistep and Combinatorial Syntheses

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Combinatorial chemistry[1] is emerging as an important new tool for medicinal chemistry. In general, combinatorial chemistry is performed with the substrate attached to a solid support, and this fact has triggered extensive work in reaction condition optimization[2] for solid phase. Reaction optimization is doubly important in solid-phase combinatorial chemistry since the reaction must not only be applicable to a wide variety of substrates and reactants but also must be as complete as possible since the intermediates of a multistep synthesis usually remain admixed with the reaction side products. The method development lead time, the limitation in reaction concentration, and the difficulty in monitoring the reactions are some of the reasons behind the important thrust for liquid-phase synthetic methods applicable to combinatorial chemistry.

In liquid-phase methods and strategies, the innovation lies mostly with the isolation of the product from the reaction mixture. The method of Boger[3] uses the acidic or basic properties of the desired molecule as a handle for separating it from the reaction mixture. The method of Kim,[4] on the other hand, assembles many desired molecules into a supermolecule and uses the size of this assembly as a means of separation. The methods of Janda[5] and Curran[6] both attach the molecule of interest to a solubility control device and use the special solubility properties of these devices to isolate the desired material from reaction mixtures. In the former case, a poly(ethylene glycol) unit is used as a precipitation device. In the latter case, a fluorous phase soluble unit allows for the liquid−liquid extraction of the desired material (or reagents) from the reaction mixture.

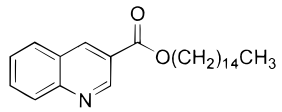
With the solubility control device concept in mind, we sought a low molecular weight group that would have switchable solubility properties to allow separation on demand and that would allow reaction monitoring and intermediate characterization by standard methods. Herein, we describe our work on the use of a quinoline unit to effect separation of the desired reaction products from the reaction mixtures by simple precipitation.

Table 1. Precipitation of 1 with Sulfuric Acid from Various Solvents

	solvent (0.2 M compound **1**)	recovered yield of **1**[a] (%)
1	AcOEt	89
2	CH_2Cl_2	91
3	DME	83
4	CH_3CN	82
5	DMF	oil[b]
6	DMF/AcOEt/H_2O[c]	71
7	DMF/ CH_2Cl_2	81
8	MeOH	56
9	MeOH/AcOEt/H_2O[c]	71
10	EtOH	65
11	EtOH/AcOEt/H_2O[c]	71
12	$CHCl_3$	86
13	THF	88

[a] Yield after precipitation and neutralization recovery. [b] The bisulfate salt separated from the mixture as an oil. [c] The hydrophilic solvent was first removed by aqueous extraction, followed by precipitation from ethyl acetate−ether.

The quinoline group is a stable, low molecular weight, and "neutral" group, with normal solubility properties in standard reaction solvents. However, protonation dramatically affects the solubility of the molecule. Using molecule **1** as a model,[7] efficient precipitation conditions from various solvents were sought. Protonation of **1** with



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mineral acids, in particular phosphoric and sulfuric acid, showed promise. It appeared from these preliminary experiments that the presence of ether in the mixture was helpful to induce effective precipitation. The quinoline substitution pattern was explored with the 2-, 4-, and 8-positional isomers of **1**. When the quinoline unit was attached by its 3-position, the protonated form was more insoluble, and the solid was easier to handle. It was noted at this point that sulfuric acid provided better behaved solids than phosphoric acid and was therefore used throughout the rest of this study.

Table 1 summarizes the results of precipitating **1** from various commonly used reaction solvents. Using a procedure which calls for an ether dilution of the mock reaction mixture, followed by slow addition of 1 mol of sulfuric acid per mole of **1**, most of the common reaction solvents gave satisfactory results. A recovery problem arose with DMF and alcoholic solvents. This problem was solved in two different ways. In a first procedure, an extraction method was applied (entries 6, 9, and 11) where the mock reaction mixture was diluted with an ethyl acetate−water mixture, the organic phase was separated, and the compound was precipitated from that

(1) Ellman, J. A. *Acc. Chem. Res.* **1996**, *29*, 132−143 and references therein.

(2) For a review of this type of optimization, see: Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *13*, 4527−4554.

(3) Cheng, S.; Comer, D. D.; Williams, J. P.; Myers, P. L.; Boger, D. L. *J. Am. Chem. Soc.*, **1996**, *118*, 2567−2573.

(4) Kim, R. M.; Manna, M.; Hutchins, S. M.; Griffin, P. R.; Yates, N. A.; Bernick, A. M.; Chapman, K. T. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 10012−10017.

(5) Han, H.; Wolfe, M. M.; Brenner, S.; Janda, K. D. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 6419−6423. See also: Bayer, E.; Mutter, M. *Nature*, **1972**, *237*, 512−513.

(6) Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823−826.

(7) This work exemplifies the concept with two ester linkers between the molecule of interest and the quinoline precipitation device. Other linkers such as silicon-based traceless linkers may also be compatible with this method and are being investigated. Boehm, T. L.; Showalter, H. D. H. *J. Org. Chem.* **1996**, *61*, 6498−6499. Chenera, B.; Finkelstein, J. A.; Veber, D. F. *J. Am. Chem. Soc.* **1995**, *117*, 11999−12000. Han, Y.; Walker, S. D.; Young, R. N. *Tetrahedron Lett.* **1996**, *16*, 2703−2706.

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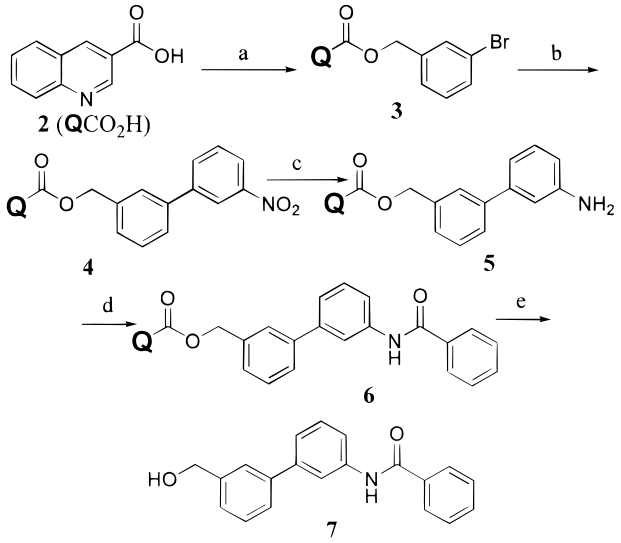
Scheme 1[a]



[a] Key: (a) 3-bromobenzyl alcohol, EDCI, CH_2Cl_2, 92%; (b) 3-nitrobenzeneboronic acid, $Pd(PPh_3)_4$, DME, 83%; (c) Fe, NH_4Cl, $EtOH-H_2O$, 89%; (d) benzoyl chloride, Et_3N, CH_2Cl_2, 91%; (e) LiOH, $THF-H_2O$, 85%.

phase after dilution with ether. A second procedure (entry 7) simply involved a 4-fold dilution with methylene chloride of the mock reaction mixture (from 0.5 M in DMF to 0.12 M), followed by the standard ether dilution to 0.08 M and acid precipitation. Under these conditions, the compound precipitated in better yield and the solid had useful mechanical properties.

The second phase of the isolation procedure, after the isolation the precipitated quinolinium salt from the reaction mixture, consists in neutralizing the salt to return the molecule back to the soluble form. We found that addition of 5% $NaHCO_3$ and AcOEt to the solid quinolinium salt resulted in a rapid neutralization of the salt in all cases. Evaporation of the organic layer yielded the desired free base quinoline.

The usefulness of the quinoline precipitation device was tested in a multistep synthesis (Scheme 1). Several features of this synthesis are noteworthy. All of the purification steps were accomplished by sulfuric acid precipitation only, which gave high yields and very expedient workups. The progress of the reactions was monitored by TLC, and the reaction intermediates were characterized by NMR and MS. The overall yield of this sequence was 53%, and the compound was 98% pure ($\lambda = 260$) by HPLC. The quinoline moiety **2** was recovered in the alkaline aqueous phase, leaving the desired compound **7** in solution. It was also demonstrated that **2** could be separated from **7** by acid precipitation. The recovered **2** was of sufficient purity for reuse without further purification.

It is interesting that **5**, which has an aniline group of basicity comparable to the quinoline group, and therefore offers two different sites for protonation, underwent precipitation under the same 1:1 H_2SO_4:quinoline ratio as the other intermediates of the sequence, with no observable difference.

This method was also applied to the synthesis of mixtures of compounds (Scheme 2). The first step of this sequence was the individual coupling of the phenol acids to the chloromethylquinoline **4**.[8] The seven quinoline phenols were obtained in somewhat less than expected yields (68%−82%), their recovery being complicated by their low solubility in the standard bicarbonate/ethyl acetate resolubilization procedure. The seven compounds were then mixed and split into seven benzyl bromide coupling reactions. The progress of the coupling reactions was monitored on TLC by disappearance of the group of more polar spots and appearance of a group of less polar spots. After precipitative workup, the desired products were freed from their quinoline group by saponification. The quinoline alcohol moiety was precipitated out with sulfuric acid, leaving the mixture of seven compounds in solution. LC-MS analysis of these mixtures showed the presence of all seven desired compounds in all seven reaction mixtures, with 0.1 and 2% contamination from 3-quinolinemethanol.

In conclusion, the quinoline precipitation device offers normal organic compound solubility in the neutral state, but very high insolubility as the bisulfate salt. This feature, along with its low molecular weight, makes it possible to handle quinoline intermediates exactly like any other organic intermediate (reactions under standard solution conditions, TLC, NMR, MS, flash chromatography, ion exchange isolation[9]) when necessary, but offers the advantages of a solid-phase workup upon treatment with sulfuric acid. Using ester linkers as examples, the usefulness of the quinoline as a separation device has been demonstrated in multistep and combinatorial syntheses. Further investigation of the scope and limitations of this method and application of the concept to reagents are in progress.

Experimental Section

Pentadecyl 3-Quinolinecarboxylate (1). To a solution of pentadecanol (7.9 g, 34 mmol), 3-quinolinecarboxylic acid (4.0 g, 23 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.9 g, 25 mmol) in methylene chloride (40 mL) was added DMAP (0.1 g, 2.3 mmol). After 3 h of stirring at ambient temperature, the reaction mixture was washed with water (40 mL) and diluted with ether (30 mL). Addition of H_2SO_4 (1.26 mL, 23.0 mmol) under rapid stirring deposited a white precipitate. After filtration, the solid was taken with AcOEt (40 mL) and 5% $NaHCO_3$ (30 mL). Evaporation of the organic layer gave 7.1 g (80%) of **1**. ^{1}H NMR (500 MHz, acetone-d_6): δ 0.85 (t, $J = 4.1$ Hz, 3H), 1.28 (m, 28H), 7.72 (t, $J = 4.8$ Hz, 1H), 7.95 (t, $J = 4.8$ Hz, 1H), 8.18 (m, 4H), 8.9 (s, 1H), 9.35 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.6, 149.3, 149.2, 147.3, 138.3, 131.8, 129.3, 128.8, 127.4, 126.4, 122.7, 78.8, 65.1, 60.9, 32.6, 31.4, 29.2, 29.1, 28.8, 28.7, 28.2, 25.6, 25.5, 22.2, 13.9 ppm. MS(EI): 370.1 (M^+, 100), 174.1 (33), 197.1 (10). IR ($CHCl_3$): 2900, 2820, 1720, 1290 cm^{-1}. An analytical sample was prepared by flash chromatography (AcOEt:hexane 1:4). Anal. Calcd for $C_{25}H_{32}NO_2$: C, 78.28; H, 9.72; N, 3.65. Found: C, 77.96; H, 10.16; N, 3.63.

3-Bromobenzyl-3-quinoline Carboxylate (3). To a solution of 3-bromobenzyl alcohol (3.3 mL, 27 mmol), 4.0 g of 3-quinolinecarboxylic acid (4.0 g, 23 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (5.3 g, 27 mmol) in methylene chloride (50 mL) was added DMAP (0.1 g, 2.3 mmol). After 3 h of stirring at ambient temperature, the reaction mixture was washed with water (40 mL) and diluted with ether (30 mL). Addition of H_2SO_4 (1.26 mL, 23 mmol) under rapid stirring deposited a white precipitate. After filtration, the solid was taken with AcOEt (40 mL) and 5% $NaHCO_3$ (30 mL). Evaporation of the organic layer gave 7.3 g (92%) of **3**. ^{1}H NMR (500 MHz, acetone-d_6): δ 5.32 (s, 2H), 7.48 (t, $J = 4.8$ Hz, 1H),

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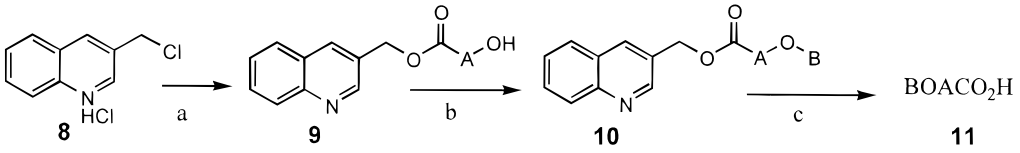
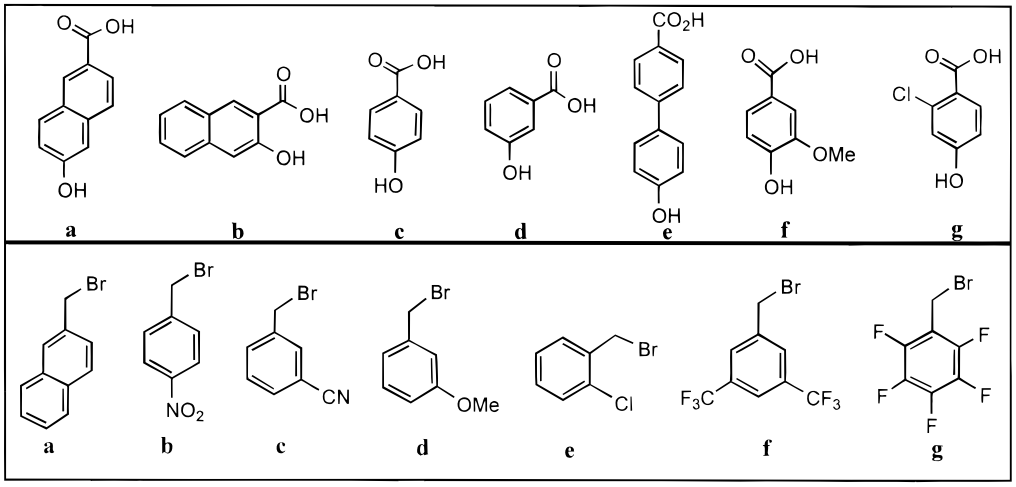
Scheme 2



a) phenolacid (below), Hunig's base, DMF; b) K_2CO_3, acetone, benzylbromide (below); c) LiOH, THF, H_2O



7.58 (t, J = 4.5 Hz, 2H), 7.77 (t, J = 5.2 Hz, 1H), 7.8 (s, 1H), 7.95 (t, J = 5.1 Hz, 1H), 8.16 (m, 2H), 9.0 (s, 1H), 9.4 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 164.7, 149.5, 149.3, 138.9, 138.7, 132.5, 131.3, 130.9, 129.8, 128.9, 127.9, 127.3, 126.6, 122.5, 121.9, 65.8 ppm. IR ($CHCl_3$): 1720, 1620, 1370, 1280 cm^{-1}. HRMS(FAB): calcd for $C_{17}H_{13}NO_2Br$ 342.0011, found 342.0128.

3′-Nitrobiphenyl-3-quinoline Carboxylate (4). To a solution of compound **3** (0.37 g, 1.1 mmol) in DME (4 mL) were added $Pd(PPh_3)_4$ (0.03 g, 0.03 mmol), Na_2CO_3 (1.35 mL of 2 M, 2.71 mmol), and *p*-nitroboronic acid (0.37 g, 2.1 mmol). After 4 h at 75 °C the reaction mixture was washed with water (10 mL) and CH_2Cl_2 (15 mL). The precipitation procedure described for compound **1** using H_2SO_4 (58 μL, 1.1 mmol) and ether (5 mL) gave 0.35 g of **4** (83%). ^{1}H NMR (500 MHz, acetone-d_6): δ 5.58 (s, 2H), 7.6−7.93 (m, 5H), 7.91 (t, J = 8.5 Hz, 1H), 8.01 (s, 1H), 8.15−8.25 (m, 4H), 8.5 (s, 1H), 9.05 (s, 1H), 9.4 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 154.4, 154.2, 145.4, 145.2, 144.7, 143.7, 141.6, 139.7, 137.4, 136.7, 134.4, 133.7, 132.7, 132.6, 132.5, 131.6, 131.5, 131.4, 127.5, 124.5, 123.7, 71.6 ppm. IR ($CHCl_3$): 1720, 1540, 1350, 1285 cm^{-1}. HRMS(FAB): calcd for $C_{23}H_{17}N_4O_2$ 385.1188, found 385.1184.

3′-Aminobiphenyl-3-quinoline Carboxylate (5). To a solution of compound **4** (0.11 g, 0.43 mmol) in EtOH (1.5 mL) and H_2O (0.5 mL) were added NH_4Cl (0.02 g, 0.55 mmol) and iron (0.12 g, 0.5 mmol). After 3 h at 60 °C, the reaction mixture was filtered through Celite and diluted with ether (4 mL). The precipitation procedure described for compound **1** using H_2SO_4 (21 μL, 0.43 mmol) gave 0.105 g of **5** (95%). ^{1}H NMR (500 MHz, acetone-d_6): δ 4.7 (bs, 2H), 5.52 (s, 2H), 6.66 (d, J = 2.5 Hz, 1H), 6.89 (d, J = 5 Hz, 1H), 6.98 (s, 1H), 7.14 (t, J = 7.8 Hz, 2H), 7.52 (m, 2H), 7.59 (d, J = 2.5 Hz, 1H), 7.69 (t, J = 7.8 Hz, 1H), 7.76 (s, 1H), 7.91 (t, J = 7.2 Hz, 1H), 8.14 (m, 2H), 8.98 (s, 1H), 9.4 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 164.8, 149.5, 149.3, 141.5, 140.7, 138.7, 136.4, 132.4, 129.8, 129.6, 128.8, 127.8, 127.2, 126.6, 122.63, 114.63, 113.5, 112.4, 66.9 ppm. IR (neat): 3460, 3360, 1710, 1600, 1290 cm^{-1}. HRMS(FAB): calcd for $C_{23}H_{19}N_2O_2$ 355.1447, found 355.1431.

3′-(Benzoylamino)biphenyl-3-quinoline Carboxylate (6). To a solution of compound **5** (0.066 g, 0.18 mmol), in CH_2Cl_2 (0.7 mL) was added NEt_3 (26 μL, 0.19 mmol), and benzoyl chloride (24 μL, 0.19 mmol). After 4 h at 25 °C, the reaction mixture was washed with CH_2Cl_2 (0.5 mL) and with ether (0.5 mL). The precipitation procedure described for compound **1** using H_2SO_4 (9 μL, 0.18 mmol) gave 0.080 g of **6** (92%). ^{1}H NMR (500 MHz, acetone-d_6): δ 5.57 (s, 2H), 7.45 (d, J = 2.5 Hz, 2H), 7.5−7.62 (m, 5H), 7.68 (m, 2H), 7.9 (m, 3H), 8.05 (d, J = 2.5 Hz, 1H), 8.16 (d, J = 4.8 Hz, 1H), 8.21 (d, J = 4.8 Hz, 1H), 8.28 (s, 1H), 9.05 (s, 1H), 9.4 (s, 1H), 9.59 (bs, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 165.9, 164. 9, 149.5, 149.3, 140.5, 140.4, 139.8, 138.8, 136.8, 134.9, 132.5, 131.9, 129.9, 129.5, 128.9, 128.6, 127.9, 127.8, 127.6, 126.8, 126.7, 126.6, 122.7, 122.3, 119.7, 118.9, 66.9 ppm. An analytical sample was prepared by flash chromatography (AcOEt:hexane 1:4). IR (neat): 3300, 1650, 1610, 1550, 1290 cm^{-1}. HRMS(FAB): calcd for $C_{30}H_{22}N_2O_2$ 459.1709, found 459.1709.

***N*-(3′-(Hydroxymethyl)biphenyl-3-yl)benzamide (7).** To a solution of compound **6** (0.051 g, 0.11 mmol) in THF (1 mL) was added LiOH (2 M, 0.8 mL, 0.17 mmol). After 1 h at 55 °C, the reaction mixture was washed with ether (5 mL), extracted, and evaporated to give 28 mg of **7** (85%). ^{1}H NMR (500 MHz, acetone-d_6): δ 4.29 (t, J = 5.8 Hz, 1H), 4.71 (d, J = 6 Hz, 2H), 7.35 (d, J = 8 Hz, 1H), 7.41 (m, 3H), 7.55 (m, 4H), 7.67 (s, 1H), 7.88 (d, J = 4.8 Hz, 1H), 8.05 (d, J = 7.8 MHz, 1H), 8.17 (s, 1H), 9.62 (bs, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 166.1, 143.6, 141.1, 140.5, 140.2, 135.2, 132.1, 129.6, 129.2, 128.8(2), 128.0-(2), 126.1, 125.4, 125.0, 122.4, 119.7, 118.9, 63.2 ppm. MS(EI): 304 (M^+, 100). IR (neat): 3300, 1640, 1600, 1540, 1305 cm^{-1}. An analytical sample was prepared by flash chromatography (AcOEt:hexane1:4). Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 78.99; H, 5.71; N, 4.47.

General Procedure for 9a−g. To a solution of the desired phenol acid (3.50 mmol) in DMF (2 mL) was added 3-(chloromethyl)quinoline hydrochloride (1.46 mmol) and Hunig's base (3.21 mmol). After the reaction was stirred overnight at 80 °C, one of the two work up procedures was followed (see individual preparation): (A) to the reaction mixture was added CH_2Cl_2 (3 mL), H_2SO_4 (1.46 mmol), and then slowly ether (10 mL), under rapid stirring; (B) the reaction mixture was diluted with water (8 mL) and CH_2Cl_2 (5 mL); after phase separation, addition of H_2SO_4 (1.46 mmol) and then slowly, ether (10 mL), under rapid stirring.

After filtration, the solid was dissolved with 50 mL of AcOEt and 20 mL of 5% $NaHCO_3$. Evaporation of the organic layer gave the corresponding compounds **9a**−**g**.

3-{[(6-Hydroxy-2-naphthyl)carbonyloxy]methyl}-quinoline (9a). Work up procedure: A. Yield: 68%. ^{1}H NMR (500 MHz, acetone-d_6): δ 5.64 (s, 2H), 7.26 (dd, J = 2.7 Hz, 6.5 Hz, 1H), 7.36 (s, 1H), 7.62 (t, J = 7.2 Hz, 1H), 7.77 (q, J = 1.4 Hz, 2.4 Hz, 2H), 7.88 (m, 3H), 8.07 (d, J = 7.8 Hz, 1H), 8.46 (s, 1H), 8.59 (s, 1H), 9.10 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6):

δ 166.2, 158.9, 151.0, 147.4, 137.6, 135.4, 131.3, 130.9, 129.9, 129.6, 128.8, 128.3, 127.5, 127.1, 126.5, 126.4, 125.2, 123.2, 120.3. 108.9, 64.2 ppm. MS(EI): 330.1 (M^+, 100), 160 (20). IR ($CHCl_3$): 1695, 1620, 1470, 1270 cm^{-1}. Anal. Calcd for $C_{21}H_{15}NO_2$: C, 76.58; H, 4.59; N, 4.25. Found: C, 76.01; H, 4.51; N, 4.31.

3-{[(3-Hydroxy-2-naphthyl)carbonyloxy]methyl}-quinoline (9b). Work up procedure: B. Yield: 82%. ^{1}H NMR (500 MHz, acetone-d_6): δ 5.76 (s, 2H), 7.33 (t, J = 3.8 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.62 (t, J = 7.2 Hz, 1H), 7.80 (m, 2H), 7.93 (d, J = 8.2 Hz, 1H), 8.01 (d, J = 7.9 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 8.52 (s, 1H), 8.67 (s, 1H), 9.13 (s, 1H), 10.3 (bs, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 165.7, 155.8, 151.1, 148.4, 147.4, 137.7, 135.9, 135.8, 130.4, 130.1, 129.9, 129.0, 128.8, 128.32, 128.1, 127.3, 127.1, 125.9, 123.2, 119.6, 65.4 ppm. MS-(EI): 330.1 (M^+, 80), 160 (100). IR (neat): 3400, 1720, 1590, 1490, 1250 cm^{-1}. Anal. Calcd for $C_{21}H_{15}NO_3$: C, 76.58; H, 4.59; N, 4.25. Found: C, 76.88; H, 4.49; N, 4.18.

3-{[(4-Hydroxyphenyl)carbonyloxy]methyl}quinoline (9c). Work up procedure: A. Yield: 70%. ^{1}H NMR (500 MHz, acetone-d_6): δ 5.55 (s, 2H), 6.92 (d, J = 3.0 Hz, 1H), 7.59 (t, J = 7.1 Hz, 1H), 7.76 (t, J = 7.1 Hz, 1H), 7.96 (d, J = 3.2 Hz, 1H), 7.98 (d, J = 8.2 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 8.40 (s, 1H), 9.03 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 165.6, 162.4, 150.9, 147.3, 135.3, 131.9, 130.0, 129.7, 128.8, 128.3, 127.4, 127.2, 120.9, 120.1, 115.6, 63.8 ppm. MS(EI): 280.1 (M^+, 100), 160.1 (10), 142 (40). IR (neat): 3400, 1705, 1605, 1595, 1290 cm^{-1}. Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.03; H, 4.89; N, 4.77.

3-{[(3-Hydroxyphenyl)carbonyloxy]methyl}quinoline (9d). Work up procedure: B. Yield: 76%. ^{1}H NMR (500 MHz, acetone-d_6): δ 5.58 (s, 2H), 7.09 (dd, J = 1.0 Hz, 1.6 Hz, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.52 (m, 2H), 7.62 (t, J = 5.6 Hz, 1H), 7.76 (t, J = 5.6 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 8.42 (s, 1H), 8.68 (bs, 1H), 9.05 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 165.8, 157.8, 150.9, 147.4, 135.5, 130.8, 130.1, 129.4, 128.8, 128.3, 127.5, 127.2, 120.8, 120.2, 115.9, 64.3 ppm. MS(EI): 280.1 (M^+, 100), 160.1 (30), 142 (8). IR ($CHCl_3$): 3400, 1715, 1590, 1280 cm^{-1}. Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.051; H, 4.85; N, 4.92.

3-{[(4-Hydroxybiphenyl)carbonyloxy]methyl}-quinoline (9e). Work up procedure: A. Yield: 71%. ^{1}H NMR (500 MHz, acetone-d_6): δ 5.62 (s, 2H), 6.94 (d, J = 4.8 Hz, 1H), 7.58 (m, 3H), 7.75 (m, 3H), 7.99 (d, J = 8.1 Hz, 1H), 8.07 (d, J = 8.1 Hz, 1H), 8.11 (d, J = 4.8 Hz, 1H), 8.45 (s, 1H), 8.57 (bs, 1H), 9.07 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 165.7, 158.2, 150.9, 147.3, 145.1, 135.4, 130.2, 130.1, 129.5, 129.4, 128.8, 128.3, 127.4, 127.2,127.1, 126.1, 116.1, 64.3 ppm. MS(EI): 356.1 (M^+, 100). IR ($CHCl_3$): 1705, 1490, 1450, 1270 cm^{-1}. Anal. Calcd for $C_{23}H_{17}NO_3$: C, 77.73; H,4.82; N,3.94. Found: C, 77.53; H, 4.75; N, 3.93.

3-{[(4-Hydroxy-3-methoxyphenyl)carbonyloxy]methyl}-quinoline (9f). Work up procedure: A. Yield: 79%. ^{1}H NMR (500 MHz, acetone-d_6): δ 3.88 (s, 3H), 5.56 (s, 2H), 6.90 (d, J = 8.3 Hz, 1H), 7.61 (m, 3H), 7.75 (t, J = 5.5 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 8.02 (d, J = 8.3 Hz, 1H), 8.4 (bd, 2H), 9.04 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 165.6, 151.9, 150.9, 147.6, 147.3, 135.3, 130.1, 129.7, 128.8, 128.4, 127.4, 127.2, 120. 3, 115.4, 112.7, 63.8 ppm. MS(EI): 310 (M^+, 100), 160 (15), 142 (12). IR ($CHCl_3$): 1710, 1290 cm^{-1}. Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.4; H, 4.94; N, 4.39.

3-{[(2-Chloro-4-hydroxyphenyl)carbonyloxy]methyl}-quinoline (9g). Work up procedure: A. Yield: 71%. ^{1}H NMR (500 MHz, acetone-d_6): δ 5.56 (s, 2H), 6.87 (d, J = 8.7 Hz, 1H), 6.97 (s, 1H), 7.61 (t, J = 7.1 Hz, 1H), 7.76 (t, J = 7.0 Hz, 1H), 7.90 (d, J = 8.7 Hz, 1H), 7.98 (d, J = 8.2 Hz, 1H), 8.05 (d, J = 8.1 Hz, 1H), 8.41 (s, 1H), 9.04 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 164.2, 161.8, 150.9, 147.3, 135.5, 134.7, 133.9, 130.0, 129.4, 128.8, 128.3, 127.4, 127.2, 119.1, 117.8, 114.6, 64.3 ppm. MS(EI): 313.9 (M^+, 100), 160 (20). IR ($CHCl_3$): 1715, 1600, 1560, 1290 cm^{-1}. Anal. Calcd for $C_{17}H_{12}ClNO_3$: C, 65.08; H, 3.86; N, 4.46. Found: C, 65.08; H, 4.05; N, 4.47.

Mixtures 10 and 11. To an equimolar mixture solution of compounds **9a**−**g** (0.47 mmol total concentrated) in acetone (2 mL) were added the desired benzyl bromide (0.85 mmol) and K_2CO_3 (0.52 mmol). After the reaction was stirred overnight stirring at 55 °C, CH_2Cl_2 (3 mL) was added, and the precipitation procedure described for compound **1** using H_2SO_4 (0.472 mmol) gave the corresponding compounds **10a**−**g**. The seven mixtures were taken separately in 2 mL of THF and 2 M LiOH (0.872 mmol). After 1 h at 55 °C, the precipitation procedure described for compound **1** was used adding H_2SO_4 (excess), ether (3 mL), and H_2O (3 mL). The organic layer was evaporated to yield an average of 50% with a maximum of 77% and a minimum of 48% from the mixture of **9a**−**g**. The seven mixtures were analyzed by HPLC and MS (negative ion) to show the presence of the expected molecular ion for the compounds **11a**−**g**.

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Supporting Information Available: NMR spectra for precipitated compounds **3**−**7** and **9a**−**g** as well as HPLC and LC-MS data for the mixture **11a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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