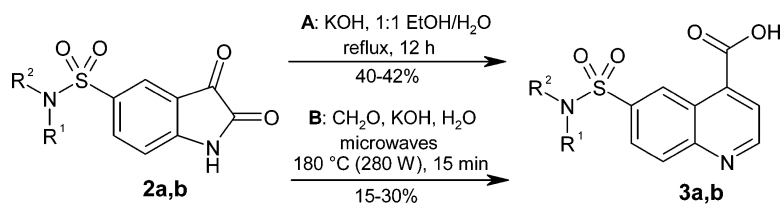**Article**

Parallel Liquid-Phase Synthesis of N-Substituted 6-Aminosulfonyl-2-oxo-1,2-dihydroquinoline-4-carboxamide and 6-Aminosulfonylquinoline-4-carboxamide Derivatives

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Parallel Liquid-Phase Synthesis of N-Substituted 6-Aminosulfonyl-2-oxo-1,2-dihydroquinoline-4-carboxamide and 6-Aminosulfonylquinoline-4-carboxamide Derivatives

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Two efficient strategies for solution-phase parallel synthesis of libraries of quinoline derivatives are described. The first synthetic pathway features the Pfitzinger reaction of isatin with diethyl malonate and sulfochlorination of the resulting 2-oxo-1,2-dihydroquinoline-4-carboxylate followed by generation of sulfonamide library. The second strategy employs the unusual behavior of 5-sulfamoylisatins in Pfitzinger reactions, which results in formation of 6-sulfamoyl-4-carboxyquinolines instead of the anticipated 2-oxo-1,2-dihydroquinoline structures. The obtained carboxylates appeared to be convenient synthetic intermediates for the generation of the corresponding carboxamide libraries. Using these reagents, the parallel solution-phase synthesis of more than 500 substituted quinoline and 2-oxo-1,2-dihydroquinoline derivatives has been accomplished on the 50−100-mg scale. Simple manual techniques for parallel reactions using special CombiSyn synthesizers were coupled with easy purification procedures to give high-purity final products. The scope and limitations of the developed approaches are discussed.

Introduction

Combinatorial synthesis of small organic molecules using solid- and liquid-phase approaches has evolved in the past few years to become a powerful tool for the rapid development of novel lead compounds and for the optimization of therapeutic efficacy.[1] Among the broad range of templates, heterocyclic scaffolds represent the most promising molecules as lead structures for the discovery of novel synthetic drugs.[2] In particular, 4-carboxy-substituted quinolines and 1,2-dihydroquinolines, present in the core of many physiologically active agents, display interesting therapeutic properties. Such compounds have been shown to inhibit several enzymes as well as to modulate the activity of many receptors. Thus, various quinoline-4-carboxamide derivatives were described as physiologically active compounds with a wide range of potential pharmaceutical applications.[3] Substituted 2-oxo-1,2-dihydroquinoline-4-carboxamides were reported as strong antagonists of tachykinin NK_2 and NK_3 receptors, potentially useful as analgesic and antiarthritic agents,[4] and 1-alkylated 1,2-dihydroquinoline-4-carboxylic acids were described as antagonists of serotonin 5-HT$_3$, NMDA, and AT$_1$ receptors.[5] Several 6-aminosulfonyl-2-oxo-1,2-dihydroquinolines which display neuroprotective, antistroke and anticancer activity[6] were described. The latter examples are of particular interest for our study. The sulfonamide moiety is an attractive functional group in medicinal chemistry, since there is the potential to design novel peptidomimetics with improved pharmacokinetic and
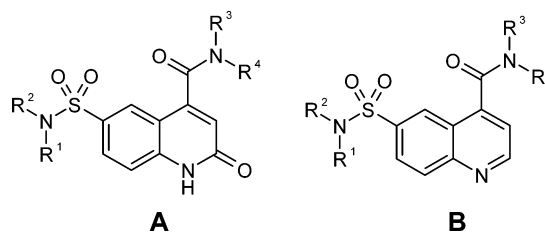

Figure 1. Combinatorial libraries of N-substituted 6-(aminosulfonyl)-2-oxo-1,2-dihydroquinoline-4-carboxamide **A** and 6-(aminosulfonyl)-quinoline-4-carboxamide **B** derivatives synthesized in this work.

pharmacodynamic parameters. The efficient introduction of this group is a topic of growing interest in organic chemistry.[7]

These recent examples have prompted us to explore 6-(aminosulfonyl)-quinoline-4-carboxamide and 6-(aminosulfonyl)-2-oxo-1,2-dihydroquinoline-4-carboxamide pharmacophoric scaffolds in a combinatorial format as promising sources of bioactive molecules. These scaffolds are perfectly suited for combinatorial library generation because they have rigid cores that possess up to three sites for the incorporation of diversity. In this paper, we describe the results of our systematic studies in the area of parallel solution-phase synthesis and characterization of combinatorial libraries of N-substituted 6-(aminosulfonyl)-2-oxo-1,2-dihydroquinoline-4-carboxamide **A** and 6-(aminosulfonyl)-quinoline-4-carboxamide **B** derivatives (Figure 1).

Synthesis of 6-(Aminosulfonyl)-2-oxo-1,2-dihydroquinoline-4-carboxylates. As part of our ongoing studies of chemistry of substituted 2-oxo-1,2-dihydroquinolines, we explored two alternate approaches to the synthesis of 2-oxo-1,2-dihydroquinoline-4-carboxylates **6**, which serve as gen-

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Scheme 1. Synthesis of 6-(Aminosulfonyl)-2-oxo-1,2-dihydroquinoline-4-carboxylates.
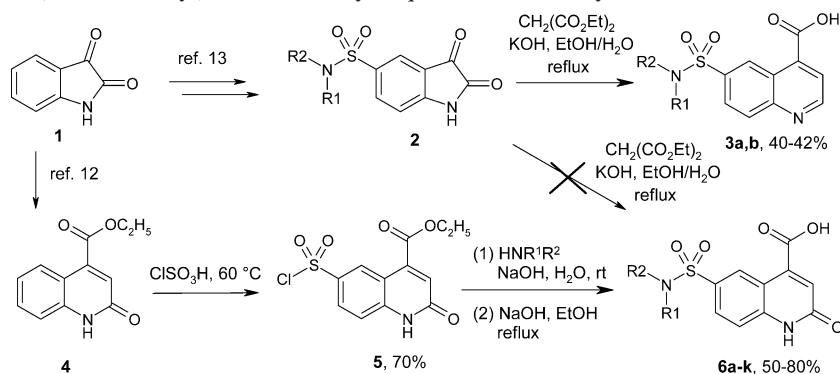
eral precursors for amide structures **A** (Scheme 1). The first approach to these structures includes generation of 5-sulfamoylisatins **2** from isatin **1** followed by Pfitzinger reaction[8] with diethyl malonate. The alternate strategy involves Pfitzinger reaction of isatin **1** with diethyl malonate. The resulting carboxylate **4** can be further converted into 6-sulfamoyl derivatives via the corresponding chlorosulfonate **5**.

Pfitzinger reaction of isatins with α-methylene carbonyl compounds is widely used for the synthesis of physiologically active derivatives of substituted quinoline-4-carboxylic acids.[3] For example, the interaction of various substituted derivatives of isatin with diethyl malonate under the conditions of Pfitzinger reaction leads to the formation of the corresponding 2-oxo-1,2-dihydroquinoline-4-carboxylic acids.[9] Recently, we described the Pfitzinger reaction of 5-sulfamoylisatins with acetone, methyl aryl ketones, methyl heteroaryl ketones, cyclohexanone, and acetoacetic acid esters.[10]

The key intermediates in the first synthetic strategy are N-substituted 5-sulfamoylisatins **2**. Recently, we described a convenient synthetic way to prepare these compounds which involves sulfochlorination of isatin followed by reaction of the resulting chlorosulfonate with various primary and secondary amines.[11] However, our attempts to obtain the carboxylate **6** using the Pfitzinger reaction of the corresponding N-substituted 5-sulfamoylisatins **2** with diethyl malonate were unsuccessful. Thus, 6-sulfamoylquinoline-4-carboxylic acid **3** was isolated as the major product instead of the anticipated 2-oxo-1,2-dihydroquinoline-4-carboxylic acid **6**. These observations are consistent with our recent data about an unusual behavior of 5-sulfamoylisatin in its interaction with diethyl malonate in ethanol.[12] More generally, we have observed that the presence of electron-withdrawing substituents in position 5 of isatin moiety increases the susceptibility of the isatin carbonyl group to nucleophilic attack and, thus, facilitates the formation of various reactive intermediates. The subsequent reactions of these intermediates are kinetically controlled and are often favorable over the classical Pfitzinger pathway.

Therefore, we directed our effort to the alternate strategy. As a starting compound, we used ethyl 2-oxo-1,2-dihydroquinoline-4-carboxylate **4**, readily synthesized from isatin **1** and diethyl malonate using the standard Pfitzinger scheme.[13] Chlorosulfonate **5** was synthesized by reacting **4** with chlorosulfonic acid. The reaction proceeded at 50−60 °C to smoothly afford the desired product in 70% yield. We used
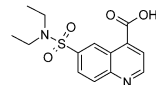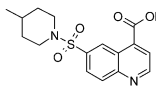
**Table 1.** 2-Oxo-1,2-dihydroquinoline-4-carboxylic Acids

ID	structure	yield, %	LCMS m/z, (M+1)	Purity (UV, 254 nm), %
6a		60	353	96
6b		55	381	95
6c		52	365	97
6d		75	323	98
6e		82	337	97
6f		78	351	97
6g		75	351	98
6h		65	351	97
6i		60	365	95

a similar synthetic approach to prepare various chlorosulfonate derivatives of isatin.[10,11]

Chlorosulfonate **5** was a convenient intermediate for synthesis of the desired 2-oxo-1,2-dihydroquinoline-4-carboxylates **6a−k**. The reaction between equimolar amounts of chlorosulfonate **5** and a variety of acyclic and cyclic aliphatic amines in the presence of NaOH proceeded at room temperature. Treatment of the reaction mixture with an excess of NaOH/EtOH, followed by filtration and acidification, gave

Table 2. 6-Sulfamoylquinoline-4-carboxylic Acids

	structure	yield, %		LCMS m/z, (M+1)	Purity (UV, 254 nm),[a] %
		method A	method B		
3a		41	15	309	96
3b		40	30	335	97

[a] For method A.

Scheme 2. Synthesis of 6-Sulfamoylquinoline-4-carboxylates.
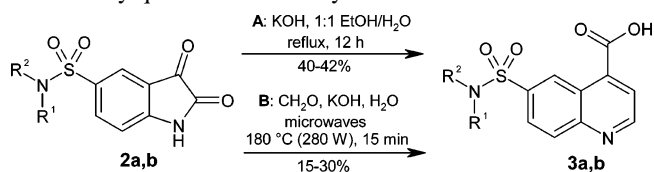
individual sulfonamides **6a**−**k** in good yields (50−80%) and purity (Table 1).

The structures of compounds **6a**−**k** were established by a combination of elemental analyses and mass, ^{1}H, and ^{13}C NMR spectroscopy. A series of NOE difference experiments provided full information about the substitution patterns. For example, for compound **6e**, the key experiment enabled us to assign all four protons of the quinolin-2-one ring by a single NOE difference spectrum. In this experiment, we observed the positive NOEs between the H-8 proton and H-7 and H-1 protons, which are consistent with the suggested molecular structure (see Supporting Information).

Synthesis of 6-Aminosulfonylquinoline-4-carboxylates. 6-Sulfamoylquinoline-4-carboxylic acids **3a,b** (Table 2) were isolated as the major products of reaction of the correspond-

ing N-substituted sulfamoylisatins **2** with diethyl malonate in the presence of ethanol under the conditions of the Pfitzinger reaction (Scheme 2, method A), instead of the anticipated 6-sulfamoyl-2-oxo-1,2-dihydroquinoline-4-carboxylic acids **6** (Scheme 1). The structures of the reaction products **3a,b** were established by NMR studies, including HMBC and HMQC correlations.[11] On the basis of the dynamic LC/MS analysis of the reaction mixture and analysis of reactions with isotopically labeled reagents, we hypothesized a possible mechanism for the observed transformations (Scheme 3). In the first step, 5-sulfamoylisatine **2** undergo alkali-mediated hydrolysis leading to its ring-opened form **7**. The product of hydrolysis reacts with ethanol under strong basic conditions yielding hemiacetal **8**. The intermolecular conversions within the hemiacetal lead to acetaldehyde and anions **9** and **10**. Acetaldehyde reacts in situ with the open-chain hydrolyzed forms of isatin **7** to afford 4-carboxyquinolines **3**. This condensation proceeds more rapidly than the competitive classical Pfitzinger reaction, and therefore, the products of condensation of **7** with malonate, 2-oxo-1,2-dihydroquinoline-4-carboxylic acids **6**, are not formed.

To experimentally confirm the suggested mechanism, we performed reactions of N-substituted sulfamoylisatins **2** with

Scheme 3. Mechanism of Conversion of 5-Sulfamoylisatins into 6-Sulfamoylquinoline-4-carboxylic Acids.
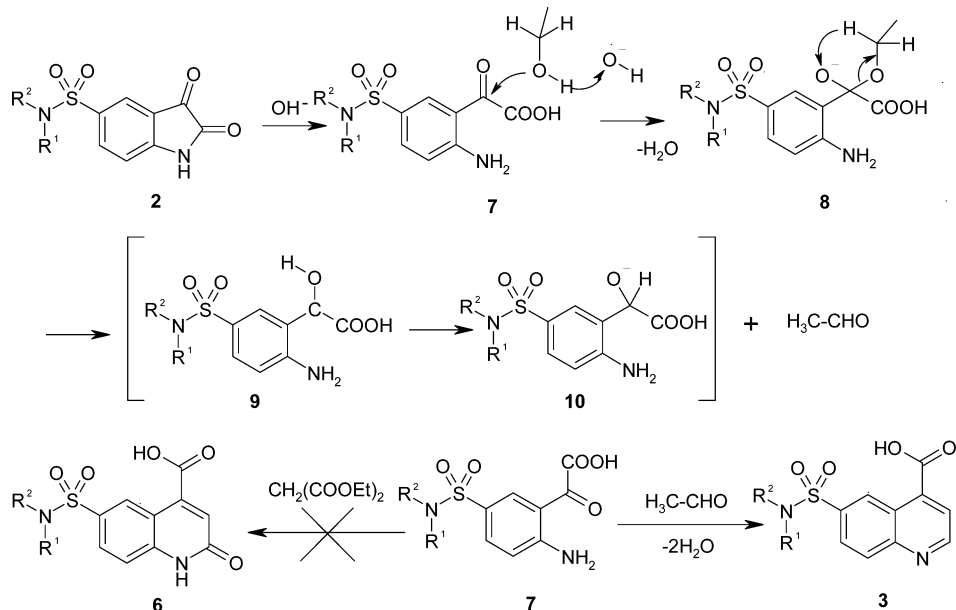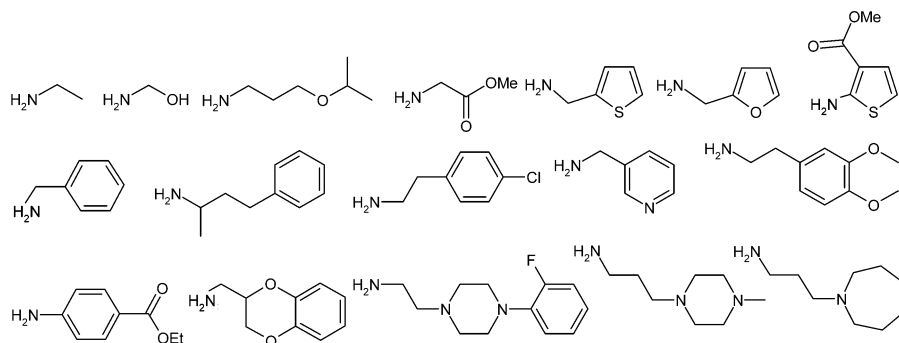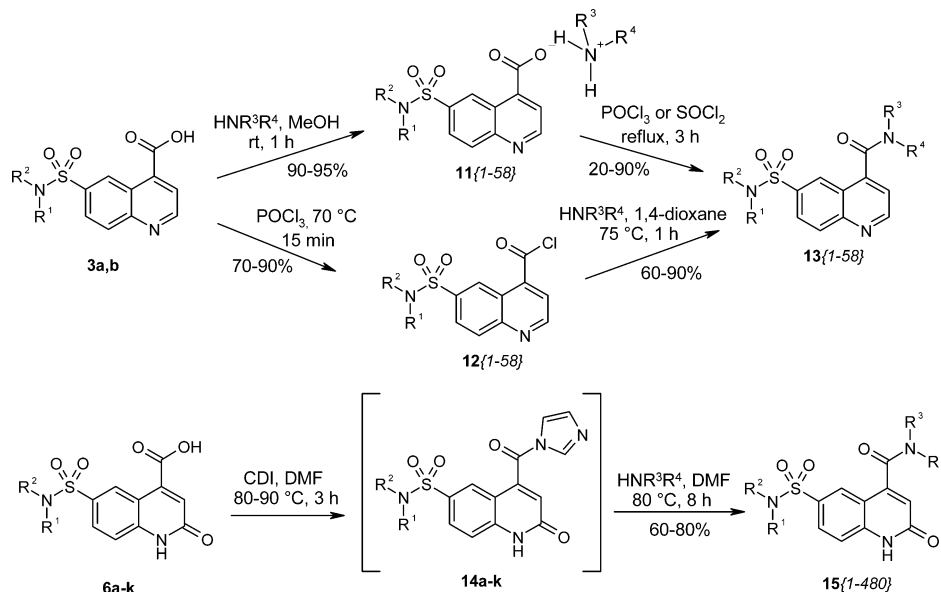
Figure 2. Representative examples of amines used as building blocks in the reactions with acids **3a,b** and **6a−k**.

Scheme 4. Synthesis of Carboxamide Libraries.

isotopically labeled reactants. In full accordance with our hypothesis, upon the reaction of **2** with ¹³C-ethanol under the described conditions, we observed the formation of ¹³C-labeled products.[14] We also studied the reaction of **2** with ¹³H₂(CO₂Et)₂ in the presence of unlabeled ethanol. On the basis of results of NMR spectroscopy, no ¹³C atoms were incorporated into the structure of the final product.

The same carboxylates **3a,b** can also be obtained using the reaction of 5-sulfamoylisatins with acetaldehyde (Scheme 2, method B). The microwave-assisted reaction conditions in the presence of aqueous KOH were found to be optimal for this transformation. However, the yields were only low to moderate (15−30%), which probably reflects the aforementioned complication of the reactions of 5-sulfamoylisatins. On the basis of these observations, pathway A is the method of choice for the synthesis of 6-sulfamoylquinoline-4-carboxylates.

Synthesis of Amide Libraries. Carboxylates **3a,b** and **6a−k** are useful precursors for synthesis of the corresponding carboxamide libraries (Scheme 4). Reaction of **3a,b** with primary and secondary amines HNR³R⁴ in methanol produced the corresponding ammonium salts **11**{*1−58*} in high yields (90−95%). On treatment with POCl₃ or SOCl₂ or heating at reflux in toluene with a catalytic amount of TsOH and azeotropic removal of water, these ammonium salts were converted into the corresponding amides **13**{*1−58*} in 20−

90% yields. Alternatively, carboxamides **13**{*1−58*} could be obtained via the reaction of amines HNR³R⁴ with the corresponding acid chlorides **12**{*1−58*} that were formed upon the reaction of acids **3a,b** with POCl₃.

The lactim−lactam tautomeric conversions within the 2-oxo-1,2-dihydroquinoline scaffold complicate the amide formation mediated by strong coupling reagents, such as SOCl₂ and POCl₃. Therefore, we used an alternate synthetic approach to amides **15**{*1−480*}, which were obtained by the reaction of carboxylates **6a−k** with primary and secondary amines via CDI-mediated (CDI, *N,N′*-carbonyldiimidazole) activation of the carboxylate group. The reactive imidazolide intermediates **14a−k** were obtained upon the treatment of acids **6a−k** with CDI in dimethylformamide and used in the reaction with amines HNR³R⁴ without purification. Due to relatively mild reaction conditions (75−80 °C, 8 h), easy separation procedures and high yields (60−80%), the described reaction scheme can be used in high-throughput combinatorial format.

The representative examples of primary and secondary amines used in the described transformations are shown in Figure 2. Several arbitrary examples of compounds from libraries **13**{*1−58*} and **15**{*1−480*} are shown in Figure 3.

All final amides within the two series **A** and **B** are stable crystalline compounds that were characterized by LC/MS and ¹H NMR spectroscopy. The spectral data gave satisfac-
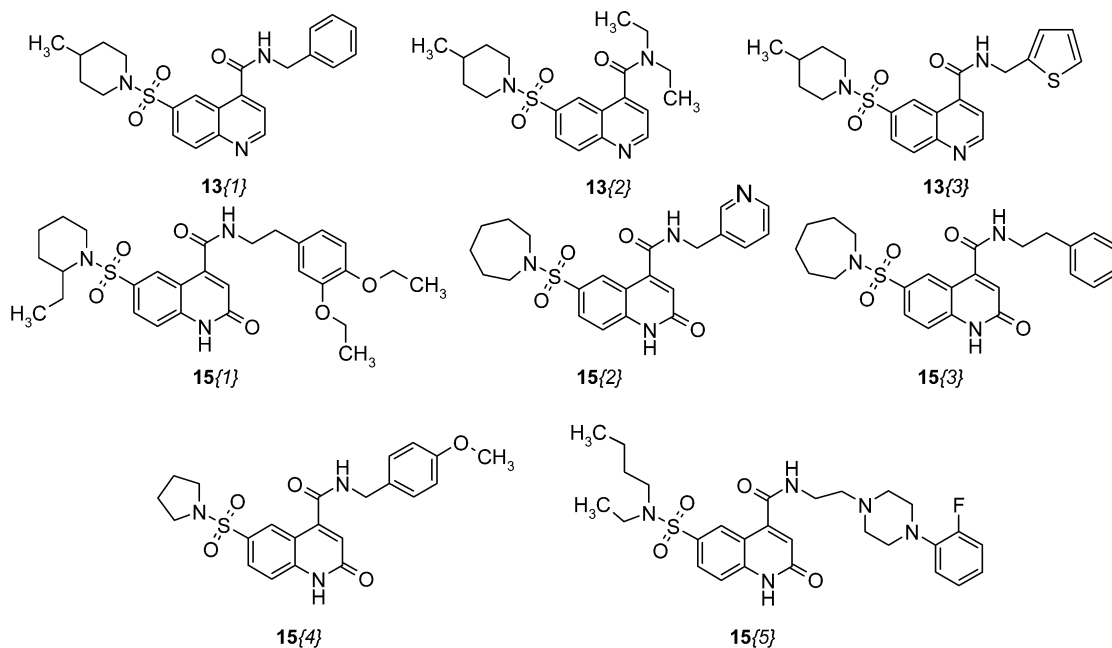
Figure 3. Examples of amides of general formula **A** and **B** synthesized in this work.

tory results consistent with the suggested molecular structures. The protons of the 2-oxo-1,2-dihydroquinoline and quinoline structures synthesized in this work are sometimes concealed by other signals, but usually clearly observed in the range of δ 6.60−9.30 ppm. The formation of carboxamides from the corresponding acids usually causes a definite upfield shift of 0.48−0.52 ppm for the H-3 and H-5 signals for the 2-oxo-1,2-dihydroquinoline series and the more substantial shift of 0.72−0.89 ppm for the H-3 and H-5 signals for the quinoline series; the other protons are not substantially influenced by the acid−amide conversion. The N[1]−H protons of the 2-oxo-1,2-dihydroquinoline scaffold are seen as broad singlets at δ 12.25−12.31 ppm. As expected, these signals disappear in the spectra of compounds from the quinoline series. The described signals can be used for identification of the synthesized compounds.

Conclusion

An efficient synthetic route was developed for the combinatorial synthesis of N-substituted 6-(aminosulfonyl)-2-oxo-1,2-dihydroquinoline-4-carboxamide and 6-(aminosulfonyl)quinoline-4-carboxamide libraries in solution. In all of the reactions investigated, the corresponding libraries were generated with low levels of impurities using standard laboratory techniques. Product yields varied according to reactant structures, but in most cases, the desired products were obtained in good-to-high yields. Biological evaluation of these libraries is currently in progress.

Experimental Section

General Information. Melting points (°C) were measured with a Koeffler melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60 F-254). ^{1}H NMR spectra were recorded on a Bruker AMX-400 or Varian spectrometer in DMSO-d_6 using TMS as an internal standard (chemical shifts in parts per million).

LC/MS spectra were recorded with a PE SCIEX API 150EX liquid chromatograph equipped with a UV detector (λ_{max} 215 and 254 nm) and using a C_{18} column (100 × 4 mm). Elution started with water and ended with acetonitrile/water (95:5, v/v) and used a linear gradient at a flow rate of 0.15 mL/min and an analysis cycle time of 25 min. According to LC/MS data, all the synthesized compounds have purity >95%.

All solvents and reagents were obtained from commercial sources and used without purification. Isatin **1** was purchased from Aldrich. Amines shown in Figure 2 were purchased from Acros Organics, Aldrich, or ChemDiv. N-Substituted 5-sulfamoylisatins **2** were prepared by reaction of isatin with chlorosulfonic acid, followed by reaction of the resulting chlorosulfonate with the corresponding amines, as reported in our recent article.[10] Ethyl 2-oxo-1,2-dihydroquinoline-4-carboxylate **4** was prepared from isatin and diethyl malonate as reported.[13]

The parallel liquid-phase reactions were performed using a laboratory synthesizer "CombiSyn-012−3000",[15] which provides some advanced opportunities for high-throughput solution-phase combinatorial synthesis. All the workup, isolation, purification and analytic procedures were carried out using a proprietary technology platform, which includes all the equipment required for parallel synthesis of large combinatorial libraries.[16] The microwave instrument used was a commercial household microwave oven (Moulinex FM1935G, frequency: 2450 MHz).

Ethyl 6-(Chlorosulfonyl)-2-oxo-1,2-dihydroquinoline-4-carboxylate 5. Ethyl carboxylate **4** (54 g, 0.25 mol) was added portionwise to chlorosulfonic acid (300 mL). The reaction mixture was stirred at room temperature for 1 h and then at 50−60 °C for 5 h. The reaction mixture was poured onto ice, and the formed precipitate was filtered off, washed with water, and dried in vacuo. The product was recrystallized from glacial acetic acid to give pure 6-chlorosulfonate **5** (55 g, 70%). mp 142−144 °C. ^{1}H NMR (DMSO, 400 MHz): δ 1.33 (t, J = 7.1, Hz 3H, CH$_3$), 3.02 (q, J = 6.7

Hz, 2H, CH$_2$), 7.12 (s, 1H, ArH), 7.60 (d, J = 8.7 Hz, 1H, ArH), 7.83 (d, J = 8.7 Hz, 1H, ArH), 8.89 (s, 1H, ArH), 12.6 (br s, 1H, NH).

General Procedure for the Synthesis of 2-Oxo-1,2-dihydro-6-sulfamoyl-4-carboxylic Acids 6a−k. A mixture of chlorosulfonate **5** (1.58 g, 5 mmol), amine HNR^{1}R^2 (6 mmol), NaOH (0.24 g), and water (25 mL) was stirred at room temperature for 3 h. NaOH (0.48 g, 12 mmol) and EtOH (25 mL) were added, and the reaction mixture was heated at reflux for 1 h. The solvent was evaporated, the crude residue was dissolved in water (15 mL), and the resulting solution was acidified by addition of 20% H$_2$SO$_4$ until pH 5 was reached. The formed precipitate was filtered out, washed with water, and recrystallized from ethanol to afford acid **6a−k** in 50−80% yield.

2-Oxo-6-(piperidin-1-ylsulfonyl)-1,2-dihydroquinoline-4-carboxylic Acid 6e. mp 222−224 °C. ^{1}H NMR (DMSO, 400 MHz): δ (ppm) 1.4−2.9 (m, 10H, 5CH$_2$), 7.1 (s, 1H, ArH), 7.51 (d, J = 8.7 Hz, 1H, ArH), 7.75 (d, J = 8.7 Hz, 1H, ArH), 8.72 (s, 1H, ArH), 12.4 (s, 1H, NH); ^{13}C NMR (Varian, 75 MHz): δ 26.2 (2C, piperidin), 25.2 (3C, piperidin), 54.7 (H$_2$C^4−N−C^{5}H$_2$), 116.2, 118.0, 126.1, 126.3, 129.1, 130.1, 140.4, 142.0, 161.6, 166.2 (10C, arom). LC/MS m/z 337 (M + 1).

6-[(4-Methylpiperidin-1-yl)sulfonyl]-2-oxo-1,2-dihydroquinoline-4-carboxylic Acid 6f. mp 316−319 °C. ^{1}H NMR (DMSO, 400 MHz): δ (ppm) 0.9 (s, 3H, CH$_3$), 1.21 (t, J = 5.4 Hz, 3H), 1.7 (d, J = 6.8 Hz, 2H), 2.21 (t, J = 7.2 Hz, 2H), 3.60 (d, J = 6.8 Hz, 2H), 7.05 (s, 1H, ArH), 7.5 (d, J = 8.5 Hz, 1H, ArH), 7.7 (d, J = 8.5 Hz, 1H, ArH), 8.7 (s, 1H, ArH), 12.4 (s, 1H, NH); ^{13}C NMR (Varian, 75 MHz): δ 21.9 (C^{1}H$_3$), 29.1 (HC^2−CH$_3$), 33.3 (H$_2$C^3−CH−C^{6}H$_2$), 64.4 (H$_2$C^4−N−C^{5}H$_2$), 116.0, 117.1, 126.2, 126.9, 129.3, 129.4, 140.6, 142.6, 162.5, 166.5 (10C, arom). LC/MS m/z 351 (M + 1).

6-[(3-Methylpiperidin-1-yl)sulfonyl]-2-oxo-1,2-dihydroquinoline-4-carboxylic Acid 6g. mp 342−343 °C. ^{1}H NMR (DMSO, 400 MHz) δ (ppm): 0.91 (s, 3H, CH$_3$), 0.97 (t, J = 7.0 Hz, 1H), 1.5−1.8 (m, 4H), 1.92 (t, J = 5.7 Hz, 1H), 2.21 (t, J = 5.8 Hz, 1H), 3.5 (t, J = 2.5 Hz, 2H), 7.07 (s, 1H, ArH), 7.51 (d, J = 8.5 Hz, 1H, ArH), 7.7 (d, J = 8.5 Hz, 1H, ArH), 8.71 (s, 1H, ArH), 12.3 (s, 1H, NH);^{13}C NMR (Varian, 75 MHz): δ 19.2 (C^{1}H$_3$), 26.0 (C^{4}H$_2$−CH$_2$−N), 31.2 (HC^2−CH$_3$), 33.2 (N−CH$_2$−CH(CH$_3$)−C^{3}H$_2$), 56.3 (H$_2$C^6−N−C^{5}H$_2$), 115.8, 117.2, 127.6, 127.7, 129.7, 130.0, 140.8, 141.4, 161.5, 165.3 (10C, arom). LC/MS m/z 351 (M + 1).

General Procedure for the Synthesis of 2-Oxo-1,2-dihydroquinoline-4-carboxamides 15{1−480}. 1,1′-Carbonyldiimidazole (49.4 g, 305 mmol) was added portionwise to a solution of acid **6a−k** (300 mmol) in DMF (100 mL). The resulting mixture was stirred at room temperature for 10 min and then at 80−90 °C for 3 h to accomplish the conversion of the initial acids into the corresponding imidazolide derivatives **14a−k**. The mixture was cooled to room temperature, and DMF was added until the total volume was 500 mL. All subsequent parallel reactions were performed using a laboratory synthesizer, CombiSyn-012-3000. In each individual reaction unit, the freshly prepared solution of

14a−k (5 mL) and a solution of amine HNR^{3}R^4 in dry DMF (3 mL) were loaded. The reaction mixture was stirred at 75−80 °C for 8 h and then cooled to room temperature. Water (50 mL) was added, and the formed precipitate was filtered out and recrystallized from ethanol−DMF to afford pure carboxamide **15{1−480}** in 60−80% yield.

***N*-[2-(3,4-Diethoxyphenyl)ethyl]-6-[(2-ethylpiperidin-1-yl)sulfonyl]-2-oxo-1,2-dihydroquinoline-4-carboxamide 15{1}.** mp 202−204 °C. ^{1}H NMR (400 MHz) δ (ppm): 0.89 (t, J = 7.3 Hz, 5H, CH$_2$CH$_3$), 1.1−1.8 (m, 8H, 4CH$_2$), 1.4 (s, 6H, 2CH$_3$, OCH$_2$CH$_3$), 1.45 (q, J = 7.3 Hz, 5H, CH$_2$-CH$_3$), 2.8 (t, J = 5.8 Hz, 2H, CH$_2$), 3.6 (d, J = 5.8 Hz, 2H, CH$_2$), 3.8 (q, J = 5.9 Hz, 1H, CH), 4.1 (m, 4H, 2CH$_2$), 6.55 (s, 1H, ArH), 6.7 (m, 3H, ArH), 7.49 (d, J = 8.7 Hz, 1H, ArH), 7.8 (d, J = 8.7 Hz, 1H, ArH), 8.3 (s, 1H, ArH), 8.7 (t, J = 6.4 Hz, 1H, CONH), 11.7 (s, 1H, NH). LC/MS m/z 556 (M + 1).

6-(Azepan-1-ylsulfonyl)-2-oxo-*N*-(pyridin-3-ylmethyl)-1,2-dihydroquinoline-4-carboxamide 15{2}. mp 341−343 °C. ^{1}H NMR (400 MHz): δ 1.5−1.7 (2s, 8H, 4CH$_2$), 3.2 (t, J = 5.7 Hz, 4H, 2CH$_2$), 4.50 (d, J = 5.2 Hz, 2H, CH$_2$), 6.7 (s, 1H, ArH), 7.2−7.3 (t, J = 6.0 Hz, 1H, ArH), 7.49 (d, J = 8.7 Hz, 1H, ArH), 7.71 (m, 2H, ArH), 7.75 (d, J = 8.7 Hz, 1H, ArH), 8.2 (s, 1H, ArH), 8.4 (s, 1H, ArH), 9.35 (t, J = 5.8 Hz, 1H, CONH). LC/MS m/z 441 (M + 1).

***N*-(2-Phenylethyl)-6-(azepan-1-ylsulfonyl)-2-oxo-1,2-dihydroquinoline-4-carboxamide 15{3}.** mp 296−297 °C. ^{1}H NMR (400 MHz): δ 1.5−1.7 (2s, 8H, 4CH$_2$), 2.9 (t, J = 7.0 Hz, 2H, CH$_2$), 3.2 (t, J = 5.5 Hz, 4H, 2CH$_2$), 3.50 (q, J = 5.7 Hz, 2H, CH$_2$), 6.62 (s, 1H, ArH), 7.2−7.3 (m, 5H, ArH), 7.50 (d, J = 8.6 Hz, 1H, ArH), 7.75 (d, J = 8.6 Hz, 1H, ArH), 8.25 (s, 1H, ArH), 8.80 (t, J = 6.9 Hz, 1H, ONH), 12.0 (s, 1H, NH). LC/MS m/z 454 (M + 1).

***N*-(4-Methoxybenzyl)-2-oxo-6-(pyrrolidin-1-ylsulfonyl)-1,2-dihydroquinoline-4-carboxamide 15{4}.** mp 330−332 °C, ^{1}H NMR (400 MHz): δ 1.7 (t, J = 4.1 Hz, 4H, 2CH$_2$), 3.15 (t, J = 7.2 Hz, 4H, 2CH$_2$), 3.8 (s, 3H, CH$_3$), 4.4 (t, J = 5.9 Hz, 2H, CH$_2$), 6.65 (s, 1H, ArH), 6.9 (d, J = 8.5 Hz, 2H, ArH), 7.3 (d, J = 8.5 Hz, 2H, ArH), 7.51 (d, J = 8.7 Hz, 1H, ArH), 7.82 (d, J = 8.7 Hz, 1H, ArH), 8.26 (s, 1H, ArH), 9.21 (t, J = 6.5 Hz, 1H, CONH), 12.2 (s, 1H, NH). LC/MS m/z 442 (M + 1).

6-{[Butyl(ethyl)amino]sulfonyl}-*N*-{2-[4-(2-fluorophenyl)piperazin-1-yl]ethyl}-2-oxo-1,2-dihydroquinoline-4-carboxamide 15{5}. mp 248−250 °C. ^{1}H NMR (400 MHz): δ 0.78−1.49 (t, J = 6.2 Hz, 5H, CH$_2$CH$_3$), 0.8−1.5 (q, J = 6.2 Hz, 5H, CH$_2$CH$_3$), 2.6 (t, J = 6.5 Hz, 2H, CH$_2$), 2.70 (s, 4H, 2CH$_2$), 3.01 (s, 6H, 3CH$_2$), 3.18 (d, J = 7.0 Hz, 2H, CH$_2$), 3.5 (d, J = 5.5 Hz, 2H, CH$_2$), 6.68 (s, 1H, ArH), 6.8−7.00 (m, 4H, ArH), 7.48 (d, J = 8.5 Hz, 1H, ArH), 7.78 (d, J = 8.5 Hz, 1H, ArH), 8.3 (s, 1H, ArH), 8.61 (s, 1H, CONH), 12.31 (s, 1H, NH). LC/MS m/z 558 (M + 1).

***N*-(2-Ethoxybenzyl)-6-[(2-ethylpiperidin-1-yl)sulfonyl]-2-oxo-1,2-dihydroquinoline-4-carboxamide 15{6}.** mp 170−172 °C, ^{1}H NMR (400 MHz): δ 0.87−0.89 (q, 3H, J = 4.6 Hz, CH$_3$), 1.46 (t, J = 7.4 Hz, 3H, CH$_3$), 1.46−1.48 (t, 2H, J = 4.6 Hz, CH$_2$), 3.6 (d, J = 3.2 Hz, 2H, CH$_2$), 3.8 (q, J = 5.4 Hz, 1H, CH), 4.1 (q, J = 7.4 Hz 2H, CH$_2$), 4.5 (d, J = 5.8 Hz, 2H, CH$_2$), 6.66 (s, 1H, ArH), 6.9 (m, 2H, ArH), 7.2

(m, 2H, ArH), 7.48 (d, *J* = 8.7 Hz, 1H, ArH), 7.8 (d, *J* = 8.7 Hz, 1H, ArH),), 9.00 (t, *J* = 6.7 Hz, 1H, CONH), 12.2 (s, 1H, NH). LC/MS *m/z* 498 (M + 1).

N-(sec-Butyl)-6-[(2-ethylpiperidin-1-yl)sulfonyl]-2-oxo-1,2-dihydroquinoline-4-carboxamide 15{7}. mp 282−283 °C. ¹H NMR (400 MHz): δ 0.89−0.91 (t, *J* = 6.0 Hz, 6H, 2CH₃), 1.13 (s, 1H, CH₃), 1.2−1.9 (m, 8H, 4CH₂), 1.45−1.47 (q, *J* = 6.0 Hz, 4H, 2CH₂), 3.8 (q, *J* = 5.8 Hz, 1H, CH), 6.52 (s, 1H, ArH), 7.5 (d, *J* = 8.7 Hz, 1H, ArH), 7.79 (d, *J* = 8.7 Hz, 1H, ArH), 8.28 (s, 1H, ArH), 8.7 (t, *J* = 7.1 Hz, 1H, CONH), 12.2 (s, 1H, NH). LC/MS *m/z* 420 (M + 1).

6-(Azepan-1-ylsulfonyl)-N-cyclohexyl-2-oxo-1,2-dihydroquinoline-4-carboxamide 15{8}. mp 302−304 °C. ¹H NMR (400 MHz): δ 1.1−1.48 (m, 6H, 3CH₂), 1.5−1.7 (2s, 8H, 4CH₂), 1.71 (d, *J* = 7.3 Hz, 2H, CH₂), 2.01(d, *J* = 7.3 Hz, 2H, CH₂), 3.19 (t, *J* = 5.5 Hz, 4H, 2CH₂), 3.8 (m, 1H, CH), 6.71 (s, 1H, ArH), 7.49 (d, *J* = 8.3 Hz, 1H, ArH), 7.70 (d, *J* = 8.3 Hz, 1H, ArH), 8.39 (s, 1H, ArH), 8.61 (d, *J* = 5.6 Hz, 1H, CONH). LC/MS *m/z* 432 (M + 1).

6-(Azepan-1-ylsulfonyl)-N-2,3-dihydro-1,4-benzodioxin-2-yl-2-oxo-1,2-dihydroquinoline-4-carboxamide 15{9}. mp 301−302 °C, ¹H NMR (400 MHz): δ 1.51−1.7 (2s, 8H, 4CH₂), 3.20 (t, *J* = 5.5 Hz, 4H, 2CH₂), 3.56 (m, 2H, CH₂), 3.71 (m, 2H, CH₂), 4.11 (m, 1H, CH), 4.43 (d, *J* = 5.4 Hz, 2H, CH₂), 6.65 (s, 1H, ArH), 6.75−6.83 (m, 4H, ArH), 7.48 (d, *J* = 8.7 Hz, 1H, ArH), 7.76 (d, *J* = 8.7 Hz, 1H, ArH), 8.31 (s, 1H, ArH), 9.11 (d, *J* = 5.7 Hz, 1H, CONH). LC/MS *m/z* 484 (M + 1).

2-Oxo-N-(2-pyrrolidin-1-ylethyl)-6-(pyrrolidin-1-ylsulfonyl)-1,2-dihydroquinoline-4-carboxamide 15{10}. mp 298−220 °C. ¹H NMR (400 MHz): δ 1.7 (s, 8H, 4CH₂), 2.6 (s, 4H, 2CH₂), 2.7 (s, 2H, CH₂), 3.21 (s, 4H, 2CH₂), 3.4 (q, *J* = 5.7 Hz, 2H, CH₂), 6.71 (s, 1H, ArH), 7.5 (d, *J* = 8.3 Hz, 1H, ArH), 7.80 (d, *J* = 8.3 Hz, 1H, ArH), 8.29 (s, 1H, ArH), 8.70 (t, *J* = 5.9 Hz, 1H, CONH), 12.25 (s, 1H, NH). LC/MS *m/z* 419 (M + 1).

N-Allyl-2-oxo-6-(pyrrolidin-1-ylsulfonyl)-1,2-dihydroquinoline-4-carboxamide 15{11}. mp 313−315 °C, ¹H NMR (400 MHz): δ 1.76 (s, 4H, 2CH₂), 3.8 (t, *J* = 5.7 Hz, 2H, CH₂), 4.09 (d, *J* = 5.2 Hz, 2H, CH₂), 4.22 (d, *J* = 5.6 Hz, 4H, 2CH₂), 4.84 (m, 1H, CH), 6.65 (s, 1H, ArH), 7.51 (d, *J* = 8.2 Hz, 1H, ArH), 7.82 (d, *J* = 8.2 Hz, 1H, ArH), 8.22 (s, 1H, ArH), 9.31 (s, 1H, CONH), 12.3 (s, 1H, NH). LC/MS *m/z* 362 (M + 1).

N-(2-Furylmethyl)-2-oxo-6-(pyrrolidin-1-ylsulfonyl)-1,2-dihydroquinoline-4-carboxamide 15{12}. mp 327−329 °C. ¹H NMR (400 MHz): δ 1.7 (s, 4H, 2CH₂), 3.13 (s, 4H, 2CH₂), 4.45 (s, 2H, CH₂), 6.35 (d, 2H, ArH), 6.67 (s, 1H, ArH), 7.49 (d, *J* = 8.4 Hz, 1H, ArH), 7.51 (d, 1H, ArH), 7.83 (d, *J* = 8.4 Hz, 1H, ArH), 8.22 (s, 1H, ArH), 9.30 (s, 1H, CONH), 12.21 (s, 1H, NH). LC/MS *m/z* 402 (M + 1).

6-[(Dibutylamino)sulfonyl]-2-oxo-N-(3-phenylpropyl)-1,2-dihydroquinoline-4-carboxamide 15{13}. mp 255−256 °C. ¹H NMR (400 MHz): δ 0.92 (s, 6H, 2CH₃), 1.41−1.44 (m, 8H, 4CH₂), 1.70−1.82 (dd, *J* = 8.8 Hz, 2H, CH₂), 2.21 (s, 3H, CH₃), 2.61 (m, 2H, CH₂), 3.07 (s, 4H, 2CH₂), 4.11 (m, 1H, CH), 6.68 (s, 1H, ArH), 7.05−7.32 (m, 5H, ArH), 7.49 (d, *J* = 8.7 Hz, 1H, ArH), 7.83 (d, *J* = 8.7 Hz, 1H,

ArH), 8.22 (s, 1H, ArH), 8.61 (d, *J* = 6.7 Hz, 1H, CONH), 12.3 (s, 1H, NH). LC/MS *m/z* 498 (M + 1).

N-(3-Cyclohex-1-en-1-ylpropyl)-6-[(dibutylamino)sulfonyl]-2-oxo-1,2-dihydroquinoline-4-carboxamide 15{14}. mp 255−256 °C. ¹H NMR (400 MHz): δ 0.92 (s, 6H, 2CH₃), 1.41 (s, 8H, 4CH₂), 1.70−1.82 (dd, *J* = 5.8 Hz, 2H, CH₂), 2.21 (s, 3H, CH₃), 2.61 (m, 2H, CH₂), 3.07 (s, 4H, 2CH₂), 4.11 (m, 1H, CH), 6.68 (s, 1H, ArH), 7.05−7.32 (m, 5H, ArH), 7.49 (d, *J* = 8.7 Hz, 1H, ArH), 7.83 (d, *J* = 8.7 Hz, 1H, ArH), 8.22 (s, 1H, ArH), 8.61 (d, *J* = 6.3 Hz, 1H, CONH), 12.3 (s, 1H, NH). LC/MS *m/z* 498 (M + 1).

N-{2-[Benzyl(methyl)amino]ethyl}-6-{[butyl(ethyl)amino]sulfonyl}-2-oxo-1,2-dihydroquinoline-4-carboxamide 15{15}. mp 206−208 °C. ¹H NMR (400 MHz): δ 0.8−1.1 (t, *J* = 8.7 Hz, 3H, CH₃), 1.5−1.54 (q, *J* = 7.1 Hz, 2H, CH₂), 2.2 (s, 3H, CH₃), 2.6 (s, 2H, CH₂), 3.1 (s, 4H, 2CH₂), 3.4 (d, *J* = 5.7 Hz, 2H, CH₂), 3.6 (s, 2H, CH₂), 6.63 (s, 1H, ArH), 7.1−7.3 (m, 5H, ArH), 7.5 (d, *J* = 8.5 Hz, 1H, ArH), 7.8 (d, *J* = 8.5 Hz, 1H, ArH), 8.29 (s, 1H, ArH), 8.65 (s, 1H, CONH), 12.30 (s, 1H, NH). LC/MS *m/z* 499 (M + 1).

6-{[Butyl(ethyl)amino]sulfonyl}-N-{3-[butyl(phenyl)amino]propyl}-2-oxo-1,2-dihydroquinoline-4-carboxamide 15{16}. mp 211−212 °C. ¹H NMR (400 MHz): δ 0.9−1.3 (t, *J* = 6.7 Hz, 1H, CH₃), 1.3 (m, 2H, CH₂), 1.65−1.67 (q, *J* = 6.7 Hz, 2H, CH₂), 1.9 (t, *J* = 4.9 Hz, 2H, CH₂), 3.1 (s, 6H, 3CH₂), 3.45 (s, 2H, CH₂), 3.36 (t, *J* = 5.6 Hz, 2H, CH₂), 6.49 (t, *J* = 7.9 Hz, 1H, ArH), 6.55 (d, *J* = 8.2 Hz, 2H, ArH), 6.65 (s, 1H, ArH), 7.1 (t, *J* = 7.6 Hz, 2H, ArH), 7.5 (d, *J* = 8.4 Hz, 1H, ArH), 7.8 (d, *J* = 8.4 Hz, 1H, ArH), 8.3 (s, 1H, ArH), 8.83 (s, 1H, CONH), 12.32 (s, 1H, NH). LC/MS *m/z* 541 (M + 1).

6-{[Butyl(ethyl)amino]sulfonyl}-N-(4-ethoxy-3-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-4-carboxamide 15-{17}. mp 229−230 °C. ¹H NMR (400 MHz): δ 0.8−1.2 (t, *J* = 7.5 Hz, 3H, CH₃), 1.4 (s, 3H, CH₃), 1.5−1.7 (q, *J* = 7.0 Hz, 2H, CH₂), 3.0 (q, *J* = 4.7 Hz, 2H, CH₂), 3.1−3.22 (m, 6H, 3CH₂), 3.73 (s, 3H, CH₃), 4.00 (d, *J* = 5.5 Hz, 2H, CH₂), 4.4 (d, *J* = 5.6 Hz, 2H, CH₂), 6.65 (s, 1H, ArH), 6.8 (s, 2H, ArH), 6.95 (s, 2H, ArH), 7.49 (d, *J* = 8.5 Hz, 1H, ArH), 7.8 (d, *J* = 8.5 Hz, 1H, ArH), 8.25 (s, 1H, ArH), 8.3 (s, 1H, CONH), 12.29 (s, 1H, NH). LC/MS *m/z* 516 (M + 1).

General Procedure for the Synthesis of 6-Sulfamoylquinoline-4-carboxylic Acids 3a,b. Method A. 5-Sulfamoylisatin **2a,b** (5 mmol) was added to a solution of 5.64 g (100.7 mmol) of KOH in ethanol−water (32 mL, 1:1, v/v). The resulting solution was heated at reflux for 8 h, then cooled to room temperature, and its pH was adjusted to ~1 by addition of 1 N HCl. The acidic solution was extracted with ethyl acetate (3 × 50 mL), and the organic extracts were combined and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography (eluent = 19:1 v/v CHCl₃/CH₃-OH) or by recrystallization from ethyl acetate. Yield 40−42%.

Method B. 5-Sulfamoylisatin **2a,b** (0.15 mmol) was dissolved in 2.5 N aqueous KOH solution (3 mL) in a 5-mL microwave vial. After the solution became clear, acetaldehyde (0.020 g, 0.45 mmol) was added. The vial was capped and irradiated in the microwave synthesizer at 80 °C for 15

min. The resulting solution was diluted with water (5 mL), and its pH was adjusted to ∼3 by addition of acetic acid. The acidified mixture was extracted with ethyl acetate (3 × 20 mL). The organic extracts were combined, washed with water (3 × 10 mL) and brine (1 × 10 mL), and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure, and the residue was purified as described in method A. Yield 15−30%.

6-(Diethylaminosulfonyl)quinoline-4-carboxylic Acid 3a. Yield 42% (method A). mp >300 °C (dec). IR 1705 cm⁻¹ ($\nu_{C=O}$). ¹H NMR (Varian, 300 MHz): δ 1.05 (t, J = 6.7 Hz, 6H, 2CH₃), 3.22 (q, J = 6.7 Hz, 4H, CH₂), 8.11 (d, J = 8.7 Hz, 1H, Ar), 8.13 (dd, J = 7.9 Hz, 1H, Ar), 8.30 (d, J = 8.7 Hz, 1H, Ar), 9.21 (d, J = 7.9 Hz, 1H, Ar), 9.30 (s, 1H, Ar), 14.2 (br s, 1H, OH); ¹³C NMR (Varian, 75 MHz): δ 14.5, 42.3, 124.7, 126.0, 126.7, 131.7, 136.9, 139.0, 149.6, 163.6, 167.1. MALDI-FTMS calcd [M + H] for C₁₄H₁₆N₂O₄S, 309.0909; found m/z 309.0901 [M + H].

6-(4-Methylpiperidine-1-sulfonyl)quinoline-4-carboxylic Acid 3b. Yield 40% (method B). mp >300 °C (dec). IR 1705 cm⁻¹ ($\nu_{C=O}$). ¹H NMR (Varian, 500 MHz): δ 0.83 (d, J = 6.3 Hz, 3H), 1.13−1.15 (m, 2H, CH₂), 1.26−1.28 (m, 1H, CH), 1.61 (d, J = 8.9 Hz, 2H, CH₂), 2.30 (t, J = 8.9 Hz, 2H, CH₂), 3.66 (d, J = 8.9 Hz, 2H, CH₂), 8.05 (d, J = 7.8 Hz, 1H, ArH), 8.12 (d, J = 7.5 Hz, 1H, ArH), 8.30 (d, J = 7.8 Hz, 1H, ArH), 9.21 (d, J = 7.5 Hz, 1H, ArH), 9.24 (s, 1H, ArH), 14.1 (br s, 1H, OH). ¹³C NMR (Varian, 125 MHz): δ 21, 29, 32, 46, 123, 126.5, 126.7, 131, 134, 136, 149, 153, 166. Anal. Calcd for C₁₆H₁₈N₂O₄S: C, 57.47%; H, 5.43%; N, 8.38%; S, 9.59%. Found: C, 57.75%; H, 5.84%; N, 8.55%; S, 10.05%. LC/MS m/z 335 (M + 1).

General Procedure for the Synthesis of Ammonium 6-Sulfonylquinoline-4-carboxylates 11{*1−58*}. Amine HNR³R⁴ (1 mmol) was added to a suspension of 0.06 g (0.19 mmol) of **3a,b** in methanol (1 mL). After the main portion of **3a,b** was dissolved (∼1 h), the reaction mixture was filtered, and the filtrate was evaporated to dryness under reduced pressure to give products **11{*1−58*}**. Yield 90−95%.

N,N,N-Triethylammonium 6-(4-Methylpiperidine-1-sulfonyl)quinoline-4-carboxylate 11{*1*}. Yield 91%, viscous oil. ¹H NMR (Varian, 500 MHz): δ 0.91 (d, J = 6.2 Hz, 3H, CH₃), 1.18−1.29 (m, 12H, 6CH₂), 1.69 (d, J = 8.7 Hz, 2H, CH₂), 2.26 (m, 2H), 3.04 (q, J = 7.6 Hz, 6H), 3.70 (d, J = 8.7 Hz, 2H, CH₂), 7.87−7.89 (m, 2H, ArH), 8.14 (s, J = 7.5 Hz, 1H, ArH), 9.01 (d, J = 7.7 Hz, 2H, ArH), 9.42 (s, 1H, NH).

N,N-Diethylammonium 6-(4-methylpiperidine-1-sulfonyl)quinoline-4-carboxylate 11{*2*}. Yield 94%. mp 304 °C (dec). ¹H NMR (Varian, 500 MHz): δ 0.80 (d, J = 6.4 Hz, 3H, CH₃), 1.15−1.16 (m, 3H, CH₃), 1.20 (t, J = 7.2 Hz, 6H, 3CH₂), 1.63 (d, J = 8.7 Hz, 2H, CH₂), 2.24−2.26 (m, 2H, CH₂), 2.92 (q, J = 7.5 Hz, 4H, 2CH₂), 3.63 (d, J = 8.7 Hz, 2H, CH₂), 7.69 (d, J = 7.5 Hz, 1H, ArH), 7.88 (d, J = 7.5 Hz, 1H, ArH), 8.14 (s, 1H, ArH), 8.97 (d, J = 7.7 Hz, 2H, ArH), 8.50−9.50 (br s, 2H), 9.31 (s, 1H, NH).

General Procedure for the Synthesis of 6-Sulfonylquinoline-4-carboxamides 13{*1−58*}. Method A: Using POCl₃. A 1.1-mmol portion of amine HNR³R⁴ was added to a suspension of 0.31 g (1.0 mmol) of **3a,b** in methanol (10

mL). The resulting mixture was heated at reflux for 5 min. Methanol was then removed under reduced pressure, and POCl₃ (5 mL) was added to the resulting dry residue of **11{*1−58*}**. The new reaction mixture was heated at gentle reflux for 3 h and allowed to cool back down to room temperature, and the solvent was evaporated to dryness under reduced pressure. This second residue was triturated with water (25 mL), and the pH of the resulting suspension was adjusted to ∼8 to 9 with powdered NaHCO₃. The suspension was then stirred for 1 h, and the precipitate was filtered, washed with water (2 × 10 mL), and extracted with CH₂Cl₂ (3 × 15 mL). The extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was evaporated under reduced pressure, and the residual crude product **139{*1−58*}** was recrystallized from dichloromethane/hexane. Yield 20−80% from **3a,b**.

Method B: Using TsOH. A 1.1-mmol portion of amine HNR³R⁴ was added to a suspension of 0.31 g (1.0 mmol) of **3b** in methanol (10 mL). The resulting mixture was stirred and boiled gently for 5 min, and the methanol was then evaporated to dryness under reduced pressure. Anhydrous toluene (15 mL) and *p*-toluenesulfonic acid (0.05 g, 0.25 mmol) were added to the dry residue of **11{*1−58*}**, and the new mixture was stirred and boiled for 60 h with simultaneous azeotropic distillation of water. After cooling, the reaction mixture was evaporated to dryness under reduced pressure, and the crude product was isolated by flash chromatography on silica gel. The column was eluted first with CH₂Cl₂ and then with a 19:1 v/v mixture of CH₂Cl₂−CH₃OH. Crude **13{*1−58*}** thus obtained was purified further by recrystallization from dichloromethane/hexane. Yield 20−80% from **3a,b**.

Method C: Using Acid Chlorides. 6-(4-Methylpiperidine-1-sulfonyl)quinoline-4-carboxylic Acid Chloride 12-{*2*}. A suspension of 0.20 g (0.66 mmol) of **3b** in POCl₃ (5 mL) was stirred at 70 °C until the dissolution of **3b** was completed (∼15 min). The resulting solution was then allowed to stand at ∼20 °C for 12 h. Concentration of the reaction mixture to dryness under reduced pressure resulted in a viscous liquid residue, which was washed with anhydrous ether (10 mL). The white crystalline solid that precipitated was quickly filtered and washed with hexane (3 × 10 mL) to yield 0.14 g (74%) of **12{*2*}**, mp 286−290 °C. Compound **12{*2*}** is extremely moisture-sensitive and should, therefore, be immediately used in the next reaction step.

6-(4-Methylpiperidine-1-sulfonyl)quinoline-4-carboxylic Acid Benzyl Amide 13{*4*}. A 1.32-mmol portion of benzylamine was added to a suspension of 0.66 mmol of acid chloride **12{*2*}** in anhydrous dioxane (5 mL), and the mixture was stirred at 75 °C for 1 h. The solvent was then evaporated to dryness under reduced pressure on a rotary evaporator. Water (15 mL) was added to the dry residue, and the precipitate was filtered, washed with water (2 × 10 mL), and dissolved in CH₂Cl₂ (3 × 10 mL). The dichloromethane extracts were combined, dried over anhydrous Na₂SO₄, filtered, and evaporated to dryness under reduced pressure. The crude product, **9{*4*}**, was recrystallized from dichloromethane/hexane.

6-(4-Methylpiperidine-1-sulfonyl)quinoline-4-carboxylic Acid Benzyl Amide 13{*1*}. Yield 41% (method A), 37% (method B), 63% (method C). mp 138−140 °C (from dichloromethane-hexane). ^{1}H NMR (Varian, 500 MHz): δ 0.94 (s, 3H, CH$_3$), 1.29−1.31 (m, 3H, CH$_3$), 1.70 (d, $J =$ 6.7 Hz, 2H, CH$_2$), 2.27−2.29 (m, 2H, CH$_2$), 3.70 (d, $J =$ 6.7 Hz, 2H, CH$_2$), 2.71 (d, $J =$ 6.7 Hz, 2H, CH$_2$), 7.25−7.43 (m, 5H, ArH), 7.74 (d, $J =$ 8.7 Hz, 1H, ArH), 7.98 (d, $J =$ 8.7 Hz, 1H, ArH), 8.23 (d, $J =$ 8.2 Hz, 1H, ArH), 8.74 (s, 1H, ArH), 9.11 (d, $J =$ 8.3 Hz, 1H, ArH), 9.32 (t, $J =$ 6.7 Hz, 1H). LC/MS *m/z* 424 (M + 1).

6-(4-Methylpiperidine-1-sulfonyl)quinoline-4-carboxylic Acid Diethyl Amide, 13{*2*}. Yield 52% (method A), 31% (method B). mp 127−129 °C (from cyclohexane). ^{1}H NMR (Varian, 500 MHz): δ 0.88 (s, 3H, CH$_3$), 1.01 (t, $J =$ 6.6 Hz, 3H, CH$_3$), 1.22−1.23 (m, 3H, CH$_3$), 1.31 (t, $J =$ 6.2 Hz, 3H, CH$_3$), 1.69 (d, $J =$ 7.4 Hz, 2H, CH$_2$), 2.27−2.29 (m, 2H, CH$_2$), 3.09−3.11 (m, 2H, CH$_2$), 3.65−3.67 (m, 2H, CH$_2$), 3.70 (d, $J =$ 5.5 Hz, 2H, CH$_2$), 7.56 (d, $J =$ 8.6 Hz, 1H, ArH), 7.98 (d, $J =$ 8.6 Hz, 1H, ArH), 8.04 (s, 1H, ArH), 8.24 (d, $J =$ 7.9 Hz, 1H), 9.07 (d, $J =$ 8.0 Hz, 1H). LC/MS *m/z* 390 (M + 1).

6-(4-Methylpiperidine-1-sulfonyl)quinoline-4-carboxylic Acid (Thien-2-ylmethyl) Amide, 13{*3*}. Yield 88% (method A). mp 139−141 °C (from dichloromethane-hexane). ^{1}H NMR (Varian, 500 MHz): δ 0.90 (d, $J =$ 6.5 Hz, 3H, CH$_3$), 1.25−1.26 (m, 3H, CH$_3$), 1.68 (d, $J =$ 7.2 Hz, 2H, CH$_2$), 2.26−2.28 (m, 2H, CH$_2$), 3.68 (d, $J =$ 7.9 Hz, 2H, CH$_2$), 4.73 (d, $J =$ 7.9 Hz, 2H, CH$_2$), 6.97 (t, $J =$ 8.2 Hz, 1H, ArH), 7.07 (d, $J =$ 8.2 Hz, 1H, ArH), 7.35 (d, $J =$ 8.5 Hz, 1H, ArH), 7.72 (d, $J =$ 7.6 Hz, 1H, ArH), 7.99 (d, $J =$ 8.5 Hz, 1H, ArH), 8.24 (d, $J =$ 7.6 Hz, 1H, ArH), 8.71 (s, 1H, ArH), 9.12 (d, $J =$ 8.2 Hz, 1H), 9.48 (t, $J =$ 7.0 Hz, 1H). LC/MS *m/z* 430 (M + 1).

6-(4-Methylpiperidine-1-sulfonyl)quinoline-4-carboxylic Acid (2-Chloroethyl) Amide, 13{*4*}. Yield 18% (method A). mp 159−160 °C (from dichloromethane-hexane). ^{1}H NMR (Varian, 500 MHz): δ 0.94 (d, $J =$ 6.5 Hz, 3H, CH$_3$), 1.31−1.33 (m, 3H, CH$_3$), 1.72 (d, $J =$ 7.4 Hz, 2H, CH$_2$), 2.30−2.33 (m, 2H, CH$_2$), 3.74−3.76 (m, 6H, 2CH$_3$), 7.69 (d, $J =$ 8.5 Hz, 1H, ArH), 8.54 (d, $J =$ 8.5 Hz, 1H, ArH), 8.18 (d, $J =$ 7.9 Hz, 1H, ArH), 8.72 (s, 1H, ArH), 9.01 (t, $J =$ 8.2 Hz, 1H), 9.06 (d, $J =$ 8.0 Hz, 1H). LC/MS *m/z* 396 (M + 1).

Supporting Information Available. ^{1}H NMR spectra of synthesized compounds from libraries **6a−k** and **15{*1−480*}** and NOE difference spectrum for compound **6e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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