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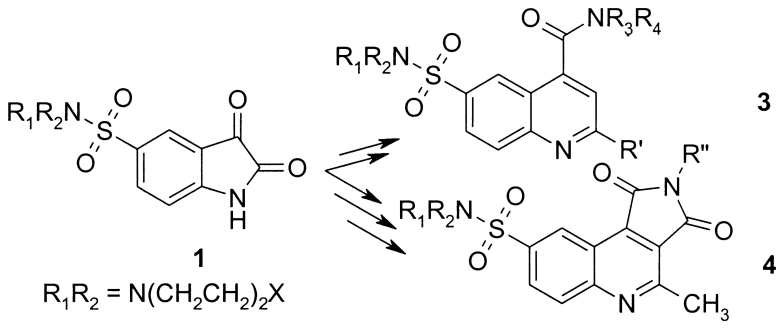

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New Scaffolds for Combinatorial Synthesis. II. 6-Sulfamoylquinolinecarboxylic Acids

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Starting from 5-sulfamoylisatins, 6-sulfamoyl-4-quinolinecarboxylic acids and 2-methyl-6-sulfamoylquinoline-3,4-dicarboxylic acids were prepared by the Pfitzinger reaction. These acids and diacids were then converted to the corresponding amide and imide libraries. A patent based on these new combinatorial chemical libraries has been applied for. All the newly synthesized compounds are crystalline substances that were purified by recrystallization from suitable solvents and characterized primarily by ^{1}H NMR, ^{13}C NMR, and mass spectrometry.

Introduction

Interest in the combinatorial synthesis of small molecules for the generation and optimization of leads for a variety of purposes is growing steadily. Therefore, the search for original scaffolds for the generation of new multifunctional combinatorial libraries is a timely problem.[1]

In a further search for new scaffolds[2−6] with multiple reaction sites, we looked into the possibility of synthesizing 6-sulfamoylquinoline-5-carboxylic acids (**2**) by the Pfitzinger reaction starting from 5-sulfamoylisatins **1**. The new scaffolds **2** were used for the preparation of amide and imide libraries which contain the new pharmacophores 6-sulfamoylquinoline-4-carboxamide **3** and 6-sulfamoylquinoline-3,4-dicarboximide **4** (Figure 1).

It should be noted that numerous derivatives of 4-quinolinecarboxylic acid, for example, carboxylic acids **5**{*1*−*3*} and amides **6**{*1*−*4*} (Figure 2), have been described as promising therapeutic agents for the treatment of various human diseases.[7−10] They exhibit their versatile physiological activities as CNS-active and oncolytic drugs or as agents for the treatment of pulmonary disorders, arrhythmia, hypertension, angina pectoris, and myocardial infarction. The profile of biological action depends on the nature of the substituents around the core moiety, and it is known that positions 2, 3, and 6 of the quinoline system are usually crucial for the manifestation of bioactivity. Some representative compounds of this type are discussed below.

Brequinar sodium **5**{*1*} inhibits dihydroorotate dehydrogenase and subsequent de novo pyrimidine biosynthesis. It has shown dose-dependent antineoplastic activity against several mouse and human tumor models.[11,12] 4-Quinolinecarboxylic acid **5**{*2*} has been reported as an antiarthritic and immunosuppressive agent that produces a significant reduction of adjuvant-induced arthritis and inhibits progressive joint destruction in rats.[13] Another example of a therapeutically significant substituted 4-quinolinecarboxylic acid is compound **5**{*3*}, which is claimed to be an angiotensin II receptor antagonist that is useful for the treatment of hypertension, congestive heart failure, ocular hypertension, and CNS disorders such as cognition disorders, anxiety, and depression.[14] Esters of acid **5**{*3*} possess the same therapeutic activity profile.[15]

Amide derivatives of 4-quinolinecarboxylic acids are another important class of biologically active agents. A typical member of this group is compound **6**{*1*}, which is claimed to be an antihypertensive agent and a potent potassium channel opener.[16] Amide **6**{*2*} is an agent for the treatment of pulmonary and CNS disorders and a nonpeptide tachykinin NK3 receptor antagonist.[17] A series of related chiral analogues, exemplified by compound **6**{*3*}, have been recently claimed as potent, selective, competitive, and orally active nonpeptide tachykinin NK3 receptor antagonists that are useful for the treatment of pulmonary, CNS, and neurodegenerative disorders.[8,18,19] They are also applicable as pharmacological tools for elucidating the function and pathophysiological role of NK3 receptors.[8,18] Guanidine derivative **6**{*4*} has been described as an inhibitor of Na^+/H^+ exchange, useful for the treatment of arrhythmia, hypertension, angina pectoris, and myocardial infarction.[20]

These examples show the high potential of variously substituted derivatives of 4-quinolinecaboxylic acids and their amides in the design of novel therapeutics. In this paper, we report the synthesis of modified analogues of **5** and **6** that bear a 6-sulfonamide moiety. This modification, frequently used in drug design, may lead to the discovery of novel physiologically active agents with improved pharmacokinetics and selectivity of action.

Results and Discussion

We have explored the reactions of 5-sulfamoylisatins **1**{*1,2*} with various ketones: acetophenones **7**{*1*−*4*}, methyl heteroaryl ketones **7**{*5*−*9*}, acetone **7**{*10*}, cyclohexanone **7**{*11*}, 1,3-cyclohexandione **7**{*12*}, and acetoacetic ester **7**{*13*}. 6-Sulfamoyl-4-quinolinecarboxylic acids **2**{*1*−*9*} were obtained by boiling isatins **1**{*1,2*} with ketones 7{*1,5*−*9*} and KOH in water/ethanol and subsequent adjustment of

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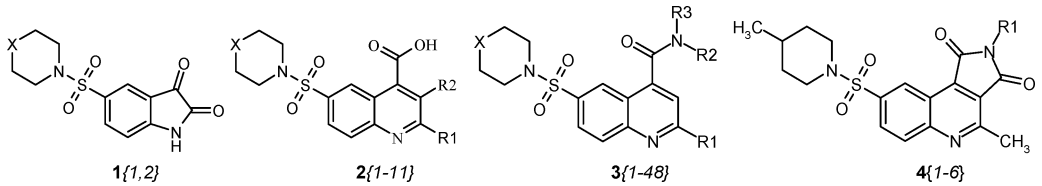


Figure 1. 5-Sulfamoylisatins **1**, 6-sulfamoyl-4-quinolinecarboxylic acids **2**, 6-sulfamoyl-4-quinolinecarboxamides **3**, and 6-sulfamoylquinoline-3,4-dicarboximides **4**. **1**−**3**: X = C−CH_3, O. **2**: R1 = alkyl, aryl, hetaryl; R2 = H, COOH; R1 + R2 = $(CH_2)_4$. **3**: R1 = phenyl, 2-thiophenyl, 2- and 4-pyridyl; R2, R3 = H, alkyl, aryl. and other; R2 + R3 = $(CH_2)_n$, n = 4−6; R2 + N + R3 = heterocyclyl. **4**: R1 = alkyl, cycloalkyl, heterocyclyl.

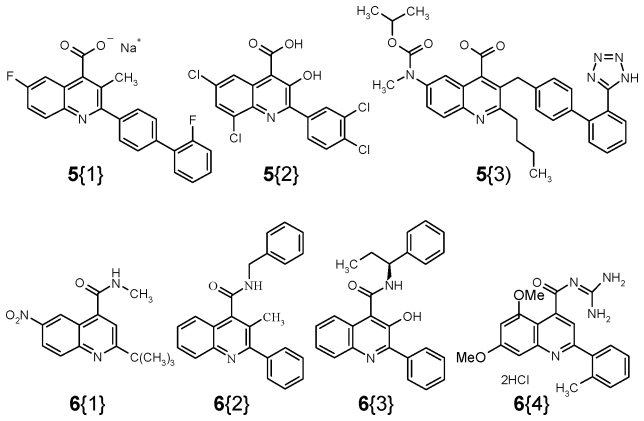


Figure 2. Examples of derivative 4-quinolinecarboxylic acids **5** and some amides **6**, which show physiological activity.

pH, filtering or extraction, and recrystallization (Scheme 1). The yields of the recrystallized acids varied from ∼1.5% to 80%, depending primarily on the stability of the ketones under the reaction conditions. The highest yield was achieved with 3-acetylpyridine **7**{*6*}, and the lowest, with 2-acetyl-5-methylfuran **7**{*9*}. With 4-(*N*,*N*-dimethylamino)acetophenone **7**(*2*), 3-nitroacetophenone **7**{*3*}, 4-nitroacetophenone **7**{*4*}, acetone **7**{*10*}, and 1,3-cyclohexandione **7**{*12*}, it was impossible to obtain the corresponding pure quinolinecarboxylic acids because of the large amounts of resin-like reaction byproducts.

Subjecting isatin **1**{*1*} and cyclohexanone, **7**{*11*}, to the Pfitzinger reaction conditions, we obtained a 57% yield of 7-(4-methylpiperidinosulfonyl)-1,2,3,4-tetrahydro-9-acridinecarboxylic acid, **2**{*10*}. Similarly, the reaction of **1** with ethyl acetoacetate **7**{*13*} led to a 39% yield of 2-methyl-6-(4-methylpiperidinosulfonyl)quinoline-3,4-dicarboxylic acid **2**{*11*}.

The new scaffolds **2** were used to obtain 6-sulfamoyl-4-quinolinecarboxamide library **3**{*1*−*48*} and 2-methyl-6-(4-methylpiperidinosulfonyl)quinoline-3,4-dicarboximide library **4**{*1*−*6*}. Library **3** was prepared by reacting the acid imidazolides or acid chlorides derived from **2**{*1,3,5,7*} with various primary, **8**, or secondary, **9**, amines. Heating dicarboxylic acid **2**{*11*} with acetic anhydride led to anhydride **10**, which was then heated with primary amines **8**{*5,7,25,27,29,30*} in toluene and in the presence of triethylamine to generate library **4**. Some members of these two libraries are shown in Figure 3.

It should be noted that the boiling of isatin **1**{*1*} in a large excess of acetone, **7**{*10*}, in aqueous ammonia led to 2-methyl-6-(4-methylpiperidinosulfonyl)-4-quinolinecarboxamide (**12**) (Scheme 2). The intermediate product of this reaction is probably acid **11**, which reacts with ammonia to yield amide **12**. The relatively low yield in this reaction (34%) is offset by the simple and convenient isolation of the desired product **12**. Unfortunately, our attempts to replace ammonia by amines **8 or 9** did not lead to the corresponding amides. The Hoffmann rearrangement of amide **12** produced a low yield (8%) of 4-amino-2-methyl-6-(4-methylpiperidinosulfonyl)quinoline (**13**), and our attempt to obtain acid **11** by oxidative deamination of amide **12** with HNO_2 was not successful.

Conclusions

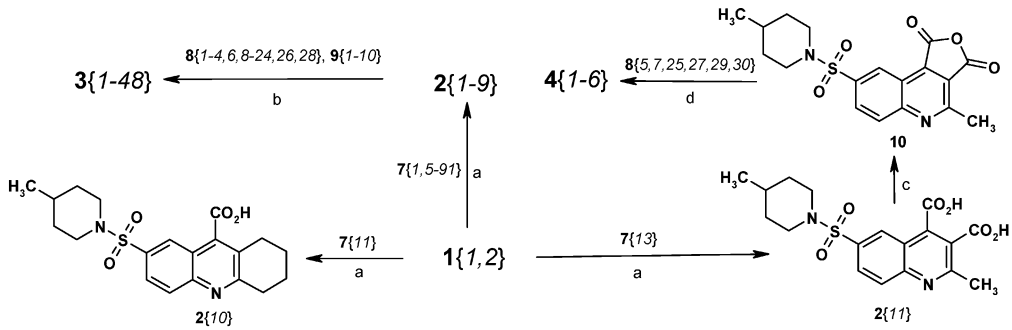
We have reported the synthesis of modified analogues of physiologically active 4-quinolinecarboxylic acids **5** and amides **6**. These analogues, **2**, bear a 6-sulfamoyl-4-quinolinecarboxylic acid moiety and were utilized as new scaffolds for the preparation of the new 6-sulfamoyl-4-quinolinecarboxamide library **3** and 6-sulfamoylquinolinedicarboximide library **4.** This modification, frequently used in drug design, may lead to discovery of novel physiologically active agents with improved pharmacokinetics and selectivity of action.

Experimental Section

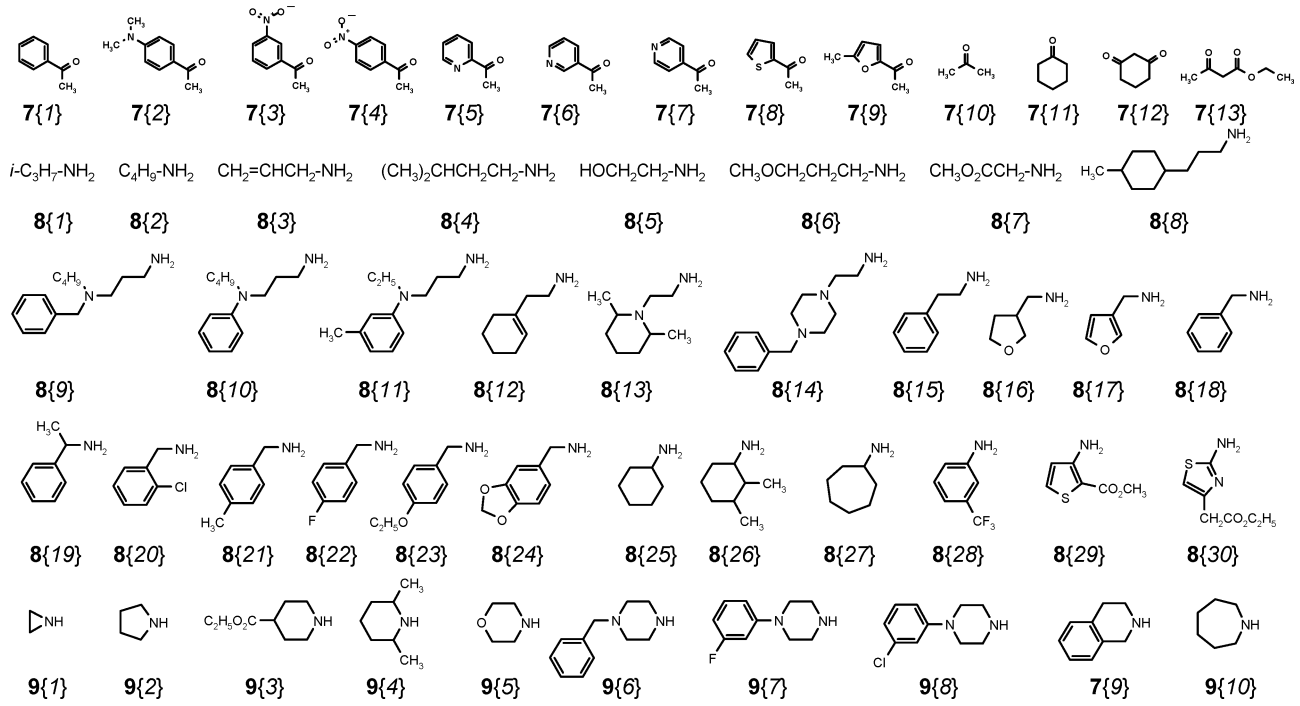
General Information. All solvents and reagents were obtained from commercial sources and used without further purification. Anhydrous toluene was obtained by distillation over sodium metal. The solid KOH used was at least 85% pure. 1,1′-Carbonyldiimidazole (CDI) and diversity reagents **7**{*1,3*−*8,10*−*12*}, **8**, and **9** were purchased from Acros Organics. Diversity reagents **7**{*9,13*} were obtained from Sigma-Aldrich Co. Diversity reagent **7**{*2*} is a commercial product of Chemical Diversity, Inc. The synthesized library compounds were purified by recrystallization from ethyl acetate (**2**{*1*}), methanol (**2**{*2*−*4,7,8*}, **3**{*2*}), dichloromethane (**2**{*5,6*}, **12**), hexane (**4**{*2*}), or dichloromethane/hexane (**3**{*1*}, **13**, **4**{*1,3*−*6*}). Melting points (mp) were determined on a Büchi model B-520 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz in DMSO-d_6 on a Varian model VXR-400 spectrometer. ^{13}C NMR spectra were measured in DMSO-d_6 at 75.47 MHz on a Bruker model AM-300 spectrometer or at 125.76 MHz on a Bruker model DRX-500 spectrometer. Chemical shifts are reported in δ units (parts per million) downfield from TMS as an internal standard. Low-resolution, electron-impact mass spectra (MS) were measured at 70 eV and 250 °C (ionization chamber temperature) on a Kratos model MS-890 mass spectrometer.

Analytical TLC was carried out either on 5 × 15 cm aluminum plates precoated with Silufol UV_{254} (Kavalier, Czech Republic), or on 5 × 10 cm glass plates precoated

Scheme 1. Synthesis of the 6-Sulfamoyl-4-quinolinecarboxylic Acid Library **2**, the 6-Sulfamoyl-4-quinolinecarboxamide Library **3**, and the 6-(4-Methylpiperidinosulfonyl)quinoline-3,4-dicarboxamide Library **4**



(a) EtOH - H_2O, KOH; reflux. (b) method A: *i* - DCM, CDI, reflux 0.5-8 h.; *ii* - **8** or **9**, r.t., 5 h. method B: *i* - DCM, $SOCl_2$, TEA, r.t. 2-3 h.; *ii* - **8** or **9**, TEA, r.t., 2-4 h. (c) Ac_2O, reflux 1-2 h. (d) toluene, TEA, reflux 48 h.



with a 0.25-mm layer of silica gel 60 F_{254} (Merck, Germany). The plates were visualized with UV light at 254 nm. Flash chromatography was carried out on silica gel L with particle size 5−40 μm (Chemapol, Czech Republic). HPLC analysis was performed on a Gilson model 714 gradient HPLC system equipped with a UV detector (215 and 254 nm) and fitted with a C_{18} column (100 × 4 mm). Elution was carried out using a linear gradient, beginning with water and ending with 5:95, v/v, water/acetonitrile, at a flow rate of 0.15 mL/min and an analysis cycle time of 25 min. The LC/MS data indicated that all the synthesized compounds were >95% pure at 254 nm.

General Procedure for the Synthesis of 2-Substituted 6-(4-Methylpiperidinosulfonyl)-4-quinolinecarboxylic Acids, 2{*1*−9**}.** To a solution of 0.97 g (10.21 mmol) of KOH in 15 mL of water, 10 mL of ethanol was added while stirring at room temperature, followed by 1.57 g (5.11 mmol) of sulfamoylisatin **1,** and upon dissolving, a solution of 6.13 mmol of ketone **7**{*1,5*−*11*} in 5 mL of ethanol. The resulting mixture was stirred and heated at reflux for 5−8 h, and the reaction progress was followed by TLC (silica gel; chloroform/methanol, 19:1, v/v) as follows: A 0.1-mL aliquot of the reaction mixture was diluted with 1 mL of water, acidified to pH 3.0 with 5% hydrochloric acid, and extracted with 0.25 mL of ethyl acetate. The organic layer was then separated and chromatographed. Upon completion of the reaction, the reaction mixture was concentrated on the rotary evaporator (to remove most of the alcohol), cooled, and filtered. (In some instances, e.g., **2**{*2*−*4*}, precipitation of the moderately soluble potassium quinolinecarboxylates occurred after concentration and cooling of the reaction mixture. In these cases, the residue was dispersed in a sufficient amount of water and filtered again.) The filtrate was then acidified to pH 2.0−3.0 with 10% hydrochloric acid. The precipitate was filtered, washed with water, and dried first in air and then in a vacuum desiccator over anhydrous $CaCl_2$. For a finely divided precipitate, the reaction product was extracted using a suitable solvent (generally ethyl acetate, chloroform, or dichloromethane), and the resulting extract was dried with anhydrous Na_2SO_4 and evaporated in vacuo on a rotary evaporator. The isolated acids **2**{*1*−*9*} were recrystallized from a suitable solvent as

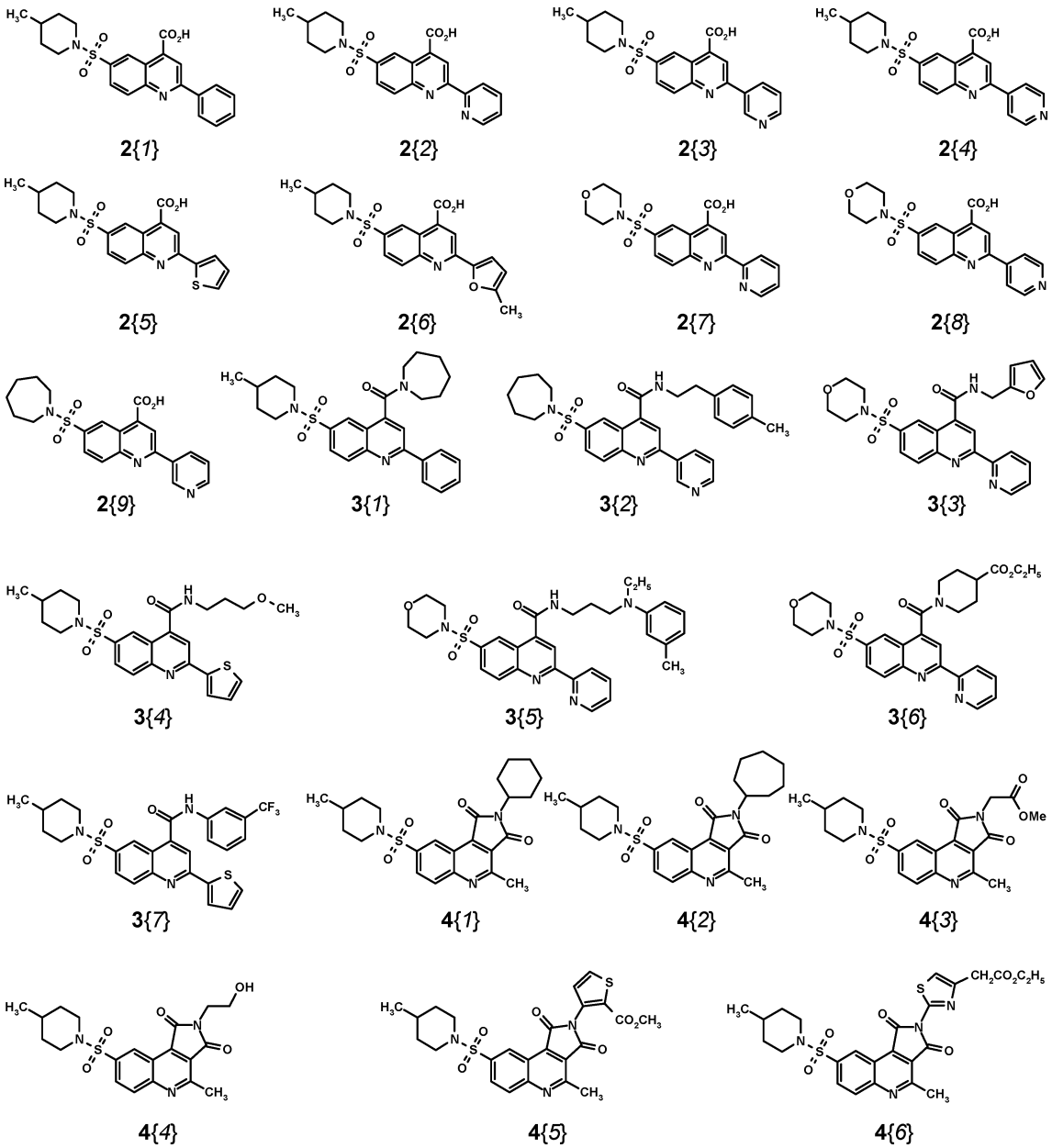
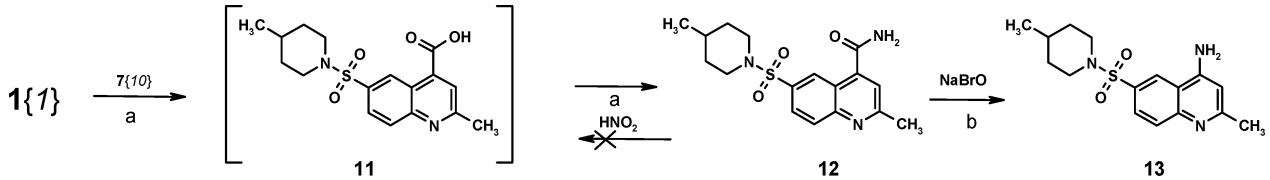


Figure 3. Examples of synthesized 6-sulfamoyl-4-quinolinecarboxylic acids **2**, 6-sulfamoyl-4-quinolinecarboxamides **3**, and 6-sulfamoylquinoline-3,4-dicarboximides **4**.

Scheme 2. Synthesis of 2-Methyl-6-(4-methylpiperidinosulfonyl)-4-quinolinecarboxamide **12** and 4-Amino-2-methyl-6-(4-methylpiperidinosulfonyl)quinoline **13**



(a) NH_3 - H_2O, reflux. (b) H_2O, 75 °C, 1 h.

indicated above. Acids **2**{*1*−*9*} are white or off-white, crystalline substances that are soluble in chloroform, dichloromethane, and ethyl acetate; moderately soluble in alcohol and acetone; poorly soluble in ether; and insoluble in hexane.

6-(4-Methylpiperidinosulfonyl)-2-phenyl-4-quinolinecarboxylic acid, 2{*1*}: yield 31%; mp 242−245 °C (dec); ^{1}H NMR δ 0.91 (d, J = 5.50 Hz, 3H), 1.16−1.38 (m, 3H), 1.71 (d, J = 11.30 Hz, 2H), 2.28−2.38 (m, 2H), 3.75 (d, J = 11.70 Hz, 2H), 7.45−7.63 (m, 3H), 8.01 (dd, J = 0.90 Hz, J = 8.40 Hz, 1H), 8.25−8.34 (m, 3H), 8.62 (s, 1H,), 9.26 (br s, 1H); ^{13}C NMR δ 21.24, 29.15, 32.85, 45.91, 120.59, 122.43, 125.87, 126.66, 127.08, 128.62, 130.18, 130.69, 134.16, 136.79, 137.63, 148.94, 157.95, 166.17; MS m/z 410 ($M^{\bullet+}$).

6-(4-Methylpiperidinosulfonyl)-2-(2-pyridyl)-4-quinolinecarboxylic acid, 2{*2*}: yield 59%; mp >300 °C; ^{1}H

NMR δ 0.91 (d, $J = 4.80$ Hz, 3H), 1.20−1.38 (m, 3H), 1.71 (d, $J = 9.90$ Hz, 2H), 2.27−2.38 (m, 2H), 3.77 (d, $J = 11.60$ Hz, 2H), 7.46−7.52 (m, 1H), 7.93−7.99 (m, 1H), 8.01 (dd, $J = 1.40$ Hz, $J = 8.25$ Hz, 1H), 8.30 (d, $J = 8.90$ Hz, 1H), 8.69 (d, $J = 8.25$ Hz, 1H), 8.76 (d, $J = 4.40$ Hz, 1H), 9.24 (s, 1H), 9.33 (br s, 1H); ^{13}C NMR δ 21.24, 29.17, 32.88, 46.01, 121.03, 121.41, 123.91, 125.54, 126.41, 127.07, 131.26, 135.10, 137.48, 137.65, 149.22, 149.55, 153.64, 157.66, 166.67; MS *m*/*z* 410 ($M^{\bullet+}$).

6-(4-Methylpiperidinosulfonyl)-2-(3-pyridyl)-4-quinolinecarboxylic acid, 2{*3*}: yield 80%; mp >300 °C; ^{1}H NMR δ 0.90 (d, $J = 5.30$ Hz, 3H), 1.17−1.38 (m, 3H), 1.71 (d, $J = 12.50$ Hz, 2H), 2.29−2.40 (m, 2H), 3.75 (d, $J = 11.20$ Hz, 2H), 7.55−7.61 (m, 1H), 8.05 (dd, $J = 1.00$ Hz, $J = 8.70$ Hz, 1H), 8.34 (d, $J = 8.70$ Hz, 1H), 8.60−8.74 (m, 2H), 8.68 (s, 1H), 9.25 (s, 1H), 9.46 (br s, $J = 1.00$ Hz, 1H); ^{13}C NMR δ 21.22, 29.18, 32.90, 45.99, 121.01, 123.02, 123.97, 126.29, 127.22, 131.22, 132.89, 135.04, 138.50, 148.54, 149.36, 151.08, 156.60, 166.65; MS *m*/*z* 410 ($M^{\bullet+}$).

6-(4-Methylpiperidinosulfonyl)-2-(4-pyridyl)-4-quinolinecarboxylic acid, 2{*4*}: yield 68%; mp >300 °C; ^{1}H NMR δ 0.92 (d, $J = 4.80$ Hz, 3H), 1.22−1.35 (m, 3H), 1.71 (d, $J = 9.90$ Hz, 2H), 2.28−2.38 (m, 2H), 3.78 (d, $J = 11.80$ Hz, 2H), 8.04 (dd, $J = 1.75$ Hz, $J = 8.85$ Hz, 1H), 8.22 (dd, $J = 1$ Hz, $J = 4.75$ Hz, 2H), 8.32 (d, $J = 8.85$ Hz, 1H), 8.69 (s, 1H), 8.76 (dd, $J = 1$ Hz, $J = 4.75$ Hz, 2H), 9.31 (d, $J = 1.75$ Hz, 1H); ^{13}C NMR δ 21.22, 29.14, 32.84, 45.88, 120.59, 121.05, 123.13, 125.87, 126.88, 130.99, 135.02, 138.24, 143.73, 148.77, 149.95, 155.73, 165.98; MS *m*/*z* 410 ($M^{\bullet+}$).

6-(4-Methylpiperidinosulfonyl)-2-(2-thienyl)-4-quinolinecarboxylic acid, 2{*5*}: yield 27%; mp >255 °C; ^{1}H NMR δ 0.91 (d, $J = 5.00$ Hz, 3H), 1.21−1.34 (m, 3H), 1.70 (d, $J = 10.70$ Hz, 2H), 2.26−2.36 (m, 2H), 3.75 (d, $J = 10.20$ Hz, 2H), 7.21 (m, $J = 3.85$ Hz, $J = 3.10$ Hz, 1H), 7.65 (d, $J = 3.85$ Hz, 1H), 7.95 (dd, $J = 1.00$ Hz, $J = 8.90$ Hz, 1H), 8.02 (d, $J = 3.10$ Hz, 1H), 8.18 (d, $J = 8.90$ Hz, 1H), 8.52 (s, 1H), 9.20 (br s, 1H); ^{13}C NMR δ 21.19, 29.12, 32.80, 45.95, 191.79, 122.71, 126.35, 127.22, 128.90, 129.04, 130.23, 131.43, 133.91, 138.55, 143.21, 149.25, 154.10, 166.67; MS *m*/*z* 410 ($M^{\bullet+}$).

2-(5-Methyl-2-furyl)-6-(4-methylpiperidinosulfonyl)-4-quinolinecarboxylic acid, 2{*6*}: yield 1.5%; mp >255 °C; ^{1}H NMR δ 0.88 (d, $J = 5.00$ Hz, 3H), 1.30 (m, 3H), 1.70 (d, $J = 10.65$ Hz, 2H), 2.32 (m, 2H), 2.50 (s, 3H), 3.75 (d, $J = 10.15$ Hz, 2H), 6.26 (d, $J = 3.45$ Hz), 7.28 (d, $J = 3.45$ Hz, 1H), 7.94 (dd, $J = 1.00$ Hz, $J = 8.90$ Hz, 1H), 8.12 (d, $J = 8.90$ Hz, 1H), 8.41 (s, 1H), 9.23 (br s, 1H); MS *m*/*z* 414 ($M^{\bullet+}$).

6-Morpholinosulfonyl-2-(2-pyridyl)-4-quinolinecarboxylic acid, 2{*7*}: yield 77%; mp >300 °C; ^{1}H NMR δ 2.96−3.12 (m, 4H), 3.61−3.76 (m, 4H), 7.44−7.52 (m, 1H), 7.91−8.00 (m, 1H), 8.02 (dd, $J = 1.80$ Hz, $J = 9.10$ Hz, 1H), 8.32 (d, $J = 9.10$ Hz, 1H), 8.70 (d, $J = 7.90$ Hz, 1H), 8.76 (d, $J = 4.70$ Hz, 1H), 9.27 (s, 1H), 9.38 (br s, 1H).

6-(1-Azepanylsulfonyl)-2-(3-pyridyl)-4-quinolinecarboxylic acid, 2{*9*}: yield 96%; mp >300 °C; ^{1}H NMR δ 1.50−1.63 (m, 4H), 1.65−1.78 (br s, 4H), 3.27−3.90 (br s, 4H), 7.55−7.64 (m, 1H), 8.10 (dd, $J = 1.80$ Hz, $J = 8.30$ Hz, 1H), 8.32 (d, $J = 8.30$ Hz, 1H), 8.63−8.76 (m, 2H), 8.66 (s, 1H), 9.26 (br s, 1H), 9.46 (s, 1H).

7-(4-Methylpiperidinosulfonyl)-1,2,3,4-tetrahydro-9-acridinecarboxylic acid, 2{*10*}: The general procedure used in the preparation of **2**{*1*−*9*} was followed here, too, except that 15 mmol of KOH per 1 mmol of sulfamoylisatin **1**{*1*} was employed. Yield 57%; mp >300 °C; ^{1}H NMR δ 0.91 (d, $J = 4.70$ Hz, 3H), 1.17−1.34 (m, 3H), 1.69 (d, $J = 9.50$ Hz, 2H), 1.88−2.05 (m, 4H), 2.18−2.32 (m, 2H), 2.98−3.17 (m, 4H), 3.71 (d, $J = 11.30$ Hz, 2H), 7.84 (dd, $J = 1.00$ Hz, $J = 8.70$ Hz, 1H), 8.04 (d, $J = 8.70$ Hz, 1H), 8.14 (br s, 1H); ^{13}C NMR δ 21.20, 21.70, 21.88, 26.41, 29.18, 32.82, 33.59, 45.95, 121.26, 124.78, 125.98, 128.04, 129.27, 133.67, 139.70, 146.51, 162.66, 167.74; MS *m*/*z* 388 ($M^{\bullet+}$).

2-Methyl-6-(4-methylpiperidinosulfonyl)-3,4-quinolinedicarboxylic acid, 2{*11*}: The general procedure used in the preparation of **2**{*1*−*9*} was followed here, too, except that 30 mmol of KOH per 1 mmol of sulfamoylisatin **1**{*1*} was employed; ethanol/water (1:1, v/v) was used in such an amount that for 3.00 g of KOH, there resulted 10 mL of the mixture; and the reaction time was at least 15 h. Upon acidifying the reaction filtrate to pH 2.0−3.0 with 10% hydrochloric acid, **2**{*11*} precipitated as a gel that could not be filtered using conventional techniques. Acid **2**{*11*} was extracted by centrifugal separation at 6000 rpm for 30 min. The centrifugate was discarded, and the precipitate **2**{*11*} was washed with water, followed by centrifuging under identical conditions until a negative chloride ion test was obtained. The product was dried in a desiccator over P_2O_5 and then recrystallized from anhydrous methanol. Yield 39%; mp 212−214 °C; ^{1}H NMR δ 0.90 (d, $J = 5.90$ Hz, 3H), 1.16−1.36 (m, 3H), 1.69 (d, $J = 12.30$ Hz, 2H), 2.24−2.33 (m, 2H), 2.83 (s, 3H), 3.71 (d, $J = 11.90$ Hz, 2H), 7.99 (dd, $J = 1.75$ Hz, $J = 9.00$ Hz, 1H), 8.15 (d, $J = 9.00$ Hz, 1H), 8.46 (d, $J = 1.75$ Hz, 1H); ^{13}C NMR δ 21.24, 24.25, 29.14, 32.83, 45.96, 120.68, 125.99, 126.64, 127.92, 130.31, 134.63, 139.50, 148.11, 158.59, 166.67, 167.70; MS *m*/*z* 392 ($M^{\bullet+}$).

2-Substituted 6-Sulfamoyl-4-quinolinecarboxamides, Chemset 3. Method A. 1.1 equiv of CDI was added at room temperature to a vigorously stirred suspension of 1 equiv of acid **2** in anhydrous dichloromethane (40 mL per 1 g of **2**). Stirring was continued until the acid dissolved completely (0.5 h to several hours, depending on the structure of **2**). Formation of the imidazolide was monitored by TLC (silica gel; chloroform/methanol, 19:1, v/v). Upon formation of the imidazolide, 1.1 equiv of amine **8** or **9** was added, and stirring continued at room temperature. If the reaction failed to go to completion within 5 h (as indicated by TLC), the reaction mixture was then boiled. The reaction mixture was then poured, with stirring, into a 2% aqueous solution of Na_2CO_3. The organic layer was separated and washed one more time with 1% aqueous Na_2CO_3, then with water, twice with 1% hydrochloric acid, again with water, then dried with anhydrous Na_2SO_4 and concentrated in vacuo until dry. In cases in which the purity of the synthesized amide was unsatisfactory (as shown by TLC), flash chromatography (silica gel, CH_2Cl_2, then CH_2Cl_2/CH_3OH 99:1) was used for further purification. Maximum yield: 40%.

Method B. First, 1.20 equiv of $SOCl_2$ was added at room temperature to a stirred dispersion of 1.00 equiv of acid **2** in anhydrous CH_2Cl_2 (in this case, the starting acid dissolved readily). Then 1.50 equiv of triethylamine was added, and stirring was continued until the reaction proceeded to completion (2−3 h as shown by TLC; silica gel; chloroform/methanol, 19:1, v/v). Then 1.05 equiv of amine **8** or **9** and another 0.90 equiv of triethylamine were added. The reaction mixture was then stirred until completion of the reaction (as verified by TLC), whereupon the mixture was worked up as described above. This method gave rise to a product of a rather good purity. If necessary, the product was recrystallized from a suitable solvent. The yield was ∼60%.

1-Azepanyl(6-(4-methylpiperidinosulfonyl)-2-phenyl-4-quinolyl)methanone, 3{*1*}: produced by method A; yield 37%; mp 217−219 °C; ^{1}H NMR δ 0.92 (d, J = 5.30 Hz, 3H), 1.19−1.37 (m, 3H), 1.46−1.80 (m, 8H), 1.87−1.98 (m, 2H), 2.28−2.36 (m, 2H), 3.23−3.34 (m, 2H), 3.74 (d, J = 11.50 Hz, 2H), 2.83 (s, 3H), 3.71 (d, J = 11.90 Hz, 2H), 3.62−3.98 (m, 1H), 7.47−7.57 (m, 3H), 7.98 (dd, J = 1.60 Hz, J = 8.75 Hz, 1H), 8.08 (d, J = 1.60 Hz, 1H), 8.12 (s, 1H), 8.26 (d, J = 8.75 Hz, 1H), 8.29−8.34 (m, 2H); ^{13}C NMR δ 21.19, 25.83, 27.10, 28.43, 29.13, 32.83, 44.68, 45.88, 48.81, 116.22, 121.83, 124.00, 126.92, 127.21, 128.51, 130.00, 130.79, 133.72, 137.02, 144.70, 148.35, 157.97, 165.63; MS m/z 394 ($M^{\bullet+}$ − $C_6H_{12}N$), 365 ($M^{\bullet+}$ − C_6H_{12}-NCO), 330 ($M^{\bullet+}$ − $C_6H_{12}NSO_2$).

***N*-(4-Methylphenethyl)-6-(1-azepanylsulfonyl)-2-(3-pyridyl)-4-quinolinecarboxamide, 3{*2*}:** produced by method A; yield 80%; mp 246−247 °C; ^{1}H NMR δ 1.60 (br s, 4H), 1.72 (br s, 4H), 2.32 (s, 3H), 2.99 (m, 2H), 3.32 (br s, 4H), 3.57−3.72 (m, 2H), 7.07 (d, J = 0.80 Hz, 2H), 7.19 (d, J = 0.80 Hz, 2H), 7.52−7.58 (m, 1H), 8.04 (dd, J = 1.00 Hz, J = 8.90 Hz, 1H), 8.20 (s, 1H), 8.25 (d, J = 8.90 Hz, 1H), 8.60−8.70 (m, 2H), 8.80 (br s, 2H), 9.45 (s, 1H).

***N*-(2-Furylmethyl)-6-morpholinosulfonyl-2-(2-pyridyl)-4-quinolinecarboxamide 3{*3*}:** produced by method A; yield 53%; mp 255−257 °C; ^{1}H NMR δ 2.90−3.10 (m, 4H), 3.60−3.80 (m, 4H), 4.60 (d, J = 5.10 Hz, 2H), 6.33 (d, J = 1.00 Hz, 1H), 6.42 (d, J = 1.00 Hz, 1H), 7.55−7.61 (m, 2H), 8.03−8.10 (m, 2H), 8.35 (d, J = 8.20 Hz, 1H), 8.65−8.75 (m, 1H), 8.60 (br s, J = 1.00 Hz, 1H), 8.75−8.83 (m, 1H), 8.78 (s, 1H), 9.58 (t, J = 5.10 Hz, 1H).

***N*-(3-Methoxypropyl)-6-(4-methylpiperidinosulfonyl)-2-(2-thienyl)-4-quinolinecarboxamide 3{*4*}:** produced by method A; yield 14%; mp 241−242 °C; ^{1}H NMR δ 0.91 (d, J = 5.00 Hz, 3H), 1.20−1.40 (m,), 1.70 (d, J = 10.80 Hz, 2H), 1.88 (t, J = 7.00 Hz, 2H), 2.22−2.38 (m, 2H), 3.32 (s, 3H), 3.40−3.54 (m, 4H), 3.75 (d, J = 10.80 Hz, 2H), 7.22 (m, J = 3.90 Hz, J = 3.10 Hz, 1H), 7.63 (d, J = 3.90 Hz,), 7.93 (dd, J = 1.10 Hz, J = 9.20 Hz, 1H), 8.01 (d, J = 3.10 Hz, 1H), 8.14 (d, J = 9.20 Hz, 1H), 8.17 (s, 1H), 8.67 (d, J = 1.10 Hz, 1H), 8.80 (t, J = 4.50 Hz, 1H).

***N*-(3-(*N*′-Ethyl-3-methylanilino)propyl)-6-morpholinosulfonyl-2-(2-pyridyl)-4-quinolinecarboxamide 3{*5*}:** produced by method A; yield 50%; mp 206−208 °C; ^{1}H NMR δ 1.02 (t, J = 3.20 Hz, 3H), 1.90 (t, J = 3.10 Hz, 3H), 2.20 (s, 3H), 2.90−3.05 (m, 4H), 3.35−3.45 (m, 4H), 3.49 (q, J = 3.20 Hz, 3H), 3.60−3.70 (m, 4H), 6.35 (d, J = 7.30 Hz, 1H), 6.48 (s, 1H), 6.49 (d, J = 7.30 Hz, 1H), 6.99 (t, J = 7.30 Hz, 1H), 7.54−7.61 (m, 1H), 8.00−8.10 (m, 2H), 8.35 (d, J = 9.45 Hz,), 8.63−8.73 (m, 1H), 8.74 (br s, 1H), 8.75−8.80 (m, 1H), 8.82 (s, 1H), 9.07 (t, J = 6.30 Hz, 1H).

Ethyl 1-(6-Morpholinosulfonyl-2-(2-pyridyl)-4-quinolylcarbonyl)-4-piperidinecarboxylate 3{*6*}: produced by method A; yield 54%; mp 112−115 °C; ^{1}H NMR δ 1.17−4.80 (br m, 9H), 1.22 (t, J = 6.40 Hz, 3H), 3.00 (m, 4H), 3.67 (m, 4H), 4.10 (q, J = 6.40 Hz, 3H), 4.40−5.80 (m, 1H), 7.46−7.54 (m, 1H), 7.94−8.05 (m, 1H), 8.04 (dd, J = 1.00 Hz, J = 9.90 Hz, 1H), 8.09−8.20 (m, 1H), 8.34 (d, J = 9.90 Hz, 1H), 8.62 (br s, 1H), 8.66−8.80 (m, 2H).

***N*-(3-Trifluoromethylphenyl)-6-(4-methylpiperidinosulfonyl)-2-(4-pyridyl)-4-quinolinecarboxamide, 3{*7*}:** produced by method B; yield 56%, mp 235−237 °C; ^{1}H NMR δ 0.93 (d, J = 5.30 Hz, 3H), 1.22−1.38 (m, 3H), 1.73 (d, J = 11.10 Hz, 2H), 2.30−2.42 (m, 2H), 3.79 (d, J = 11.40 Hz, 2H), 7.43 (dd, J = 1.00 Hz, J = 7.60 Hz, 1H), 7.59 (m, 1H), 8.07 (dd, J = 1.70 Hz, J = 8.95 Hz, 1H), 8.15 (dd, J = 1.00 Hz, J = 8.20 Hz, 1H), 8.22 (br s, 1H), 8.31 (d, J = 5.70 Hz, 2H), 8.35 (d, J = 8.95 Hz, 1H), 8.59 (s, 1H), 8.75−8.82 (m, 3H), 11.08 (s, 1H); ^{13}C NMR δ 21.16, 29.14, 32.80, 45.93, 116.27, 119.10, 120.71, 121.45, 123.03, 123.64, 125.64, 127.51, 129.32, 129.74, 130.18, 131.41, 135.00, 139.25, 143.08, 144.23, 148.88, 150.57, 156.21, 164.51; MS m/z 554 ($M^{\bullet+}$).

General Procedure for the Synthesis of 2-Substituted 4-Methyl-8-(4-methylpiperidinosulfonyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3-diones, Chemset 4{*1*−*6*}. Anhydride **10** was added to a stirred solution of amine **8**{*1*−*6*} and triethylamine (TEA) in anhydrous toluene. The molar ratios used were 1.0:1.0:0.1 of **10**/**8**/TEA, whereas 20 mL of toluene was utilized per 1 g of **10**. The reaction mixture was heated at reflux for at least 48 h, and its progress was monitored by TLC (silica gel; chloroform/methanol, 19:1, v/v). Upon completion of the reaction, the mixture was concentrated to dryness on a rotary evaporator, dispersed in CH_2Cl_2, and filtered. The filtrate was washed three times with 3% aqueous NaOH and water, and then three times with dilute hydrochloric acid (1:3, v/v) The dichloromethane layer was dried with anhydrous Na_2SO_4 and filtered, the solvent was stripped on a rotary evaporator, and the residual crude product was recrystallized from a suitable solvent as specified at the beginning of the Experimental Section. Where required, flash chromatography (silica gel; CH_2Cl_2 then CH_2Cl_2/CH_3OH, 99:1, v/v) was used to purify the product further. The resulting products **4**{*1*−*6*} are crystalline substances varying in color from white to orange-yellow. They are soluble in most organic solvents, poorly soluble in hexane, and insoluble in water.

2-Cyclohexyl-4-methyl-8-(4-methylpiperidinosulfonyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3-dione, 4{*1*}: yield 19%; mp 223−225 °C; ^{1}H NMR δ 0.91 (d, J = 5.70 Hz, 3H), 1.17−1.50 (m, 6H), 1.64−1.83 (m, 5H), 1.91 (d, J = 11.60 Hz, 2H), 2.10−2.24 (m, 2H), 2.29−2.40 (m, 2H), 3.01 (s, 3H), 3.78 (d, J = 11.60 Hz, 2H), 4.00−4.12 (m, 1H), 8.11 (dd, J = 1.20 Hz, J = 8.80 Hz, 1H), 8.24 (d, J = 8.80 Hz, 1H), 9.05 (br s, 1H); ^{13}C NMR δ 20.76, 21.50, 24.63, 25.22, 28.88, 29.18, 32.63, 45.60, 50.48, 118.93,

122.93, 124.21, 128.69, 130.09, 136.23, 136.37, 150.79, 157.02, 167.07, 167.19; MS *m*/*z* 455 ($M^{\bullet+}$).

2-Cycloheptyl-4-methyl-8-(4-methylpiperidinosulfonyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3-dione, 4{*2*}: yield 42%; mp 221−222 °C; ^{1}H NMR δ 0.89 (d, J = 6.40 Hz, 3H), 1.14−1.40 (m, 3H), 1.45−2.00 (m, 12H), 2.13−2.26 (m, 2H), 2.29−1.40 (m, 2H), 2.98 (s, 3H), 1.95 (m, 2H), 2.31 (m, 2H), 3.74 (d, J = 11.30 Hz, 2H), 4.16−4.27 (m, 1H), 8.13 (dd, J = 1.45 Hz, J = 9.05 Hz, 1H), 8.26 (d, J = 9.05 Hz, 1H), 9.02 (br s, 1H); ^{13}C NMR δ 21.11, 21.81, 24.94, 27.34, 29.16, 32.05, 32.88, 45.93, 52.29, 119.21, 123.28, 124.52, 128.99, 130.36, 136.18, 136.74, 151.01, 157.30, 167.17, 167.31; MS *m*/*z* 469 ($M^{\bullet+}$).

Methyl 2-[4-Methyl-8-(4-methylpiperidinosulfonyl)-1,3-dioxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-2-yl]acetate, 4{*3*}: yield 23%; mp 128−130 °C; ^{1}H NMR δ 0.93 (d, J = 5.40 Hz, 3H), 1.21−1.37 (m, 3H), 1.72 (d, J = 10.90 Hz, 2H), 2.30−2.41 (m, 2H), 3.05 (s, 3H), 3.74−3.82 (m, 2H), 3.79 (s, 3H), 4.48 (s, 2H), 8.13 (dd, J = 1.73 Hz, J = 9.05 Hz, 1H), 8.24 (d, J = 9.05 Hz, 1H), 9.02 (d, J = 1.73 Hz, 1H); ^{13}C NMR δ 21.21, 22.01, 29.11, 32.81, 45.89, 118.74, 122.81, 124.05, 129.08, 130.12, 135.00, 136.26, 150.74, 156.99, 166.07, 166.15, 167.11; MS *m*/*z* 445 ($M^{\bullet+}$).

2-(2-Hydroxyethyl)-4-methyl-8-(4-methylpiperidinosulfonyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3-dione, 4{*4*}: yield 25%; mp 134−136 °C; ^{1}H NMR δ 0.92 (d, J = 5.10 Hz), 1.21−1.36 (m, 3H), 1.71 (d, J = 11.50 Hz, 2H), 2.30−2.40 (m, 2H), 3.03 (s, 3H), 3.67 (t, J = 5.50 Hz, 2H), 3.74−3.82 (m, 4H), 8.10 (dd, J = 1.63 Hz, J = 9.00 Hz, 1H), 8.22 (d, J = 9.00 Hz, 1H), 9.05 (d, J = 1.63 Hz, 1H); ^{13}C NMR δ 21.21, 21.91, 29.00, 32.81, 40.52, 45.91, 57.69, 118.75, 123.05, 124.08, 128.75, 130.04, 135.55, 136.51, 150.51, 156.75, 166.91, 167.06; MS *m*/*z* 417 ($M^{\bullet+}$).

Methyl 3-[4-Methyl-8-(4-methylpiperidinosulfonyl)-1,3-dioxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-2-yl]-2-thiophenecarboxylate, 4{*5*}: yield 17%; mp 234−236 °C; ^{1}H NMR δ 0.93 (d, J = 5.70 Hz, 3H), 1.22−1.36 (m, 3H), 1.71 (d, J = 11.60 Hz, 2H), 2.33−2.42 (m, 2H), 3.08 (s, 3H), 3.75−3.82 (m, 2H), 3.79 (s, 3H), 7.26 (d, J = 5.25 Hz, 1H), 7.95 (d, J = 5.25 Hz, 1H), 8.16 (dd, J = 1.67 Hz, J = 9.00 Hz, 1H), 8.29 (d, J = 9.00 Hz, 1H), 9.07 (d, J = 1.67 Hz, 1H); ^{13}C NMR δ 21.21, 22.11, 29.12, 32.82, 45.89, 52.25, 118.82, 122.91, 124.08, 126.36, 128.18, 129.25, 130.24, 131.80, 132.52, 135.99, 136.36, 150.18, 157.22, 159.68, 164.96, 165.06; MS *m*/*z* 513 ($M^{\bullet+}$).

Ethyl 2-(2(4-Methyl-8-(4-methylpiperidinosulfonyl)-1,3-dioxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-2-yl)-1,3-thiazol-4-yl)acetate, 4{*6*}: yield 11%; mp 175−177 °C; ^{1}H NMR δ 0.93 (d, J = 5.30 Hz, 3H), 1.23−1.35 (m, 3H), 1.31 (t, J = 7.00 Hz, 3H), 1.72 (d, J = 11.70 Hz, 2H), 2.31−2.40 (m, 2H), 3.08 (s, 3H), 3.80 (d, J = 11.10 Hz, 2H), 3.84 (s, 2H), 4.17 (q, J = 7.00 Hz, 2H), 7.49 (s, 1H), 8.16 (dd, J = 1.00 Hz, J = 9.15 Hz, 1H), 8.28 (d, J = 9.15 Hz, 1H), 9.09 (br s, 1H); ^{13}C NMR δ 14.12, 21.22, 22.15, 29.14, 32.80, 36.46, 45.93, 60.30, 116.79, 118.78, 122.75, 124.13, 129.24, 130.19, 135.88, 136.24, 145.49, 149.98, 150.66, 157.29, 163.85, 163.99, 169.10; MS *m*/*z* 542 ($M^{\bullet+}$).

4-Methyl-8-(4-methylpiperidinosulfonyl)-1,3-dihydrofuro[3,4-*c*]quinoline-1,3-dione, 10. A suspension of 1.35 g (3.43 mmol) of diacid **2**{*11*} in 15 mL of acetic anhydride was stirred at 100 °C until the diacid dissolved completely. The resulting dark solution was cooled and allowed to stand a few hours at 0 °C. The precipitate was filtered, washed with anhydrous ether and hexane, and then dried in vacuo at 50−60 °C. A 0.69-g (54%) portion of anhydride **10** was obtained as an off-white, crystalline substance; mp 141−143 °C. Anhydride **10** was readily hydrolyzable by atmospheric moisture, and was thus utilized as soon as it was prepared. For the same reason, we were unable to get a satisfactory ^{1}H NMR spectrum of anhydride **10**. Because of the easy hydrolysis of anhydride **10** by water present in DMSO-d_6, we were only able to observe the spectrum of acid **2**{*11*}. The use of other solvents, known to be free of water, to record the ^{1}H NMR spectrum was not possible because of the poor solubility of **10** in them. MS *m*/*z* 373 ($M^{\bullet+}-1$).

2-Methyl-6-(4-methylpiperidinosulfonyl)-4-quinolinecarboxamide, 12. An 85-mL (1.20 mol) portion of 25% aqueous ammonia was added at room temperature to a stirred suspension of 2.29 g (7.43 mmol) of **1** in 17 mL of acetone (13.31 g, 229.20 mmol). A homogeneous dark-red solution resulted that became lighter within a few minutes. The reaction mixture was stirred and heated at gentle reflux for 15 h. Two hours after the start of the reaction, the product began to precipitate. On cooling, the precipitate was filtered, washed with water to neutral pH, dried, and recrystallized twice from CH_2Cl_2. Amide **12** is an off-white, crystalline substance that is moderately soluble in most organic solvents, but insoluble in hexane or water; yield 0.89 g (34%); mp >255 °C; ^{1}H NMR δ 0.91 (d, J = 5.30 Hz, 3H), 1.20−1.34 (m, 3H), 1.70 (d, J = 10.40 Hz, 2H), 2.24−2.33 (m, 2H), 2.77 (s, 3H), 3.73 (d, J = 11.30 Hz, 2H), 7.63 (s, 1H), 7.72 (br s, 1H), 7.89 (dd, J = 1.70 Hz, J = 8.75 Hz, 1H), 8.07 (d, J = 8.75 Hz, 1H), 8.14 (br s, 1H), 8.75 (dd, J = 1.75 Hz, 1H); ^{13}C NMR δ 21.20, 24.99, 29.15, 37.78, 45.94, 121.26, 121.75, 126.09, 126.60, 129.98, 133.27, 142.51, 148.68, 161.89, 167.72; MS *m*/*z* 347 ($M^{\bullet+}$).

2-Methyl-6-(4-methylpiperidinosulfonyl)-4-quinolinamine, 13. An aqueous solution of NaOBr was prepared by mixing at −5 °C a solution of 1.51 g (37.75 mmol) of NaOH in 50 mL of water with 2.11 g (13.20 mmol) of Br_2, and holding the resulting mixture at 0 °C for 45 min. A suspension of 0.55 g (1.58 mmol) of carboxamide **12** in 40 mL of cold water was added in one portion to a stirred, 10-mL solution of NaOBr (2.64 mmol) that was held at 0 °C. The reaction mixture was stirred at 75 °C, cooled, and then extracted with CH_2Cl_2 (4 × 15 mL). The combined dichloromethane extracts were dried with anhydrous Na_2SO_4 and eluted through a flash chromatography column (silica gel; CH_2Cl_2 then CH_2Cl_2/CH_3OH, 1:49, v/v). Recrystallization from dichloromethane/hexane yielded 0.04 g (8%) of pure **13**. Aminoquinoline **13** is a white, crystalline substance that is soluble in most organic solvents, but insoluble in hexane or water. mp 239−241 °C; ^{1}H NMR δ 0.89 (d, J = 5.20 Hz, 3H), 1.15−1.35 (m, 3H), 1.65 (d, J = 10.20 Hz, 2H),

2.19 (m, 2H), 2.50 (s, 3H), 3.70 (d, $J = 11.25$ Hz, 2H), 6.53 (s, 1H), 7.30 (br s, 2H), 7.75 (dd, $J = 1.00$ Hz, $J = 8.70$ Hz, 1H), 7.83 (d, $J = 8.70$ Hz, 1H), 8.58 (br s, $J = 1.00$ Hz, 1H); MS *m*/*z* 319 ($M^{\bullet+}$).

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Supporting Information Available. ^{1}H NMR spectra of chemsets **2**, **3**, and **4** and compounds **12** and **13**; ^{13}C NMR spectra of chemsets **2**, **3**, and **4**, and compound **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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