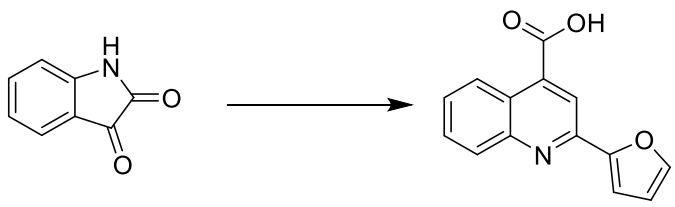
Supporting Information

Supporting Information Contents: Synthetic protocols and analytical data of Schemes S1 through S10

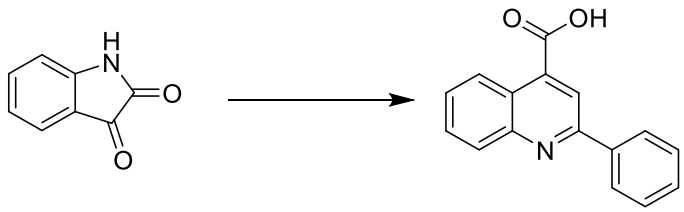
Scheme S1



(i) **(ii)**

2-(furan-2-yl)quinoline-4-carboxylic acid (ii). Isatin (i) (1.5 g, 10.20 mmol) and 2-acetylfuran (1.23 mL, 12.23 mmol, 1.2 eq.) were dissolved in EtOH (20.4 mL). KOH (1.72 g, 30.6 mmol, 3 eq.) was added, and the reaction was heated at reflux for 23 hours. Upon completion, the reaction was cooled to ambient temperature and concentrated. The residue was dissolved in H_2O and extracted 2× with Et_2O. The aqueous layer was cooled in an ice bath and acidified to pH 1 with concentrated HCl. The resulting precipitate was collected via filtration and was washed copiously with cold H_2O to afford KM-4-216-ppt (1.107 g, 49% yield). **^{1}H NMR** (400 MHz, d_6-acetone) δ 9.61 (br s, 1H), 8.81 (dd, *J* = 8.7, 1.4 Hz, 1H), 8.46 (s, 1H), 8.22 (d, *J* = 8.5 Hz, 1H), 7.93 – 7.80 (m, 2H), 7.69 (ddd, *J* = 8.4, 6.8, 1.3 Hz, 1H), 7.56 (d, *J* = 3.5 Hz, 1H), 6.75 (dd, *J* = 3.5, 1.8 Hz, 1H). **^{13}C NMR** (101 MHz, d_6-acetone) δ 167.0, 166.6, 157.1, 149.6, 143.5, 143.1, 139.5, 139.2, 131.1, 130.8, 130.7, 129.7, 128.23, 128.16, 126.2, 124.5, 124.3, 120.3, 120.2, 117.6, 108.5.

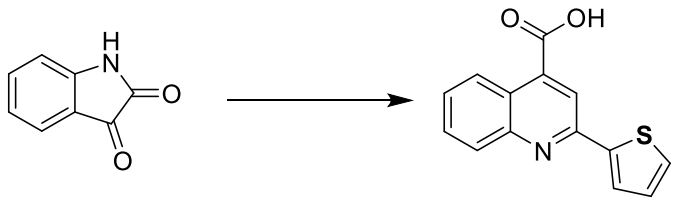
Scheme S2



(i) **(iii)**

2-phenylquinoline-4-carboxylic acid (iii). Isatin (i) (0.5 g, 3.40 mmol) and acetophenone (0.48 mL, 4.08 mmol, 1.2 eq.) were dissolved in EtOH (6.8 mL). KOH (0.572 g, 10.19 mmol, 3 eq.) was added, and the reaction was heated at reflux for 24 hours. Upon completion, the reaction was cooled to ambient temperature and concentrated. The residue was dissolved in H_2O and extracted 2× with Et_2O. The aqueous layer was cooled in an ice bath and acidified to pH 1 with concentrated HCl. The resulting precipitate was collected via filtration and was washed copiously with cold H_2O. The wet precipitate was dissolved in EtOAc dried over Na_2SO_4, filtered, and concentrated to afford KM-4-224-xtr (213 mg, 25% yield). **^{1}H NMR** (400 MHz, d_6-acetone) δ 8.35 (dd, *J* = 8.6, 0.7 Hz, 1H), 8.59 (s, 1H), 8.42 – 8.30 (m, 2H), 8.25 – 8.16 (m, 1H), 7.86 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.70 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.63 – 7.53 (m, 3H).

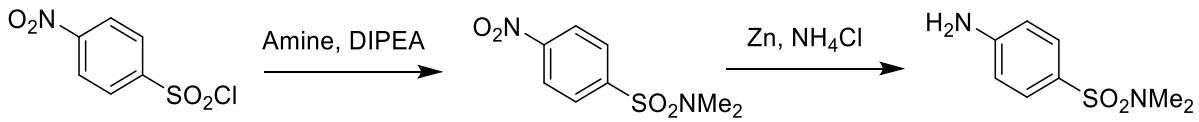
Scheme S3



(i) **(iv)**

2-(thiophen-2-yl)quinoline-4-carboxylic acid (iv). Isatin (i) (0.5 g, 3.40 mmol) and 2-acetylthiophene (0.44 mL, 4.08 mmol, 1.2 eq.) were dissolved in EtOH (6.8 mL). KOH (0.572 g, 10.19 mmol, 3 eq.) was added, and the reaction was heated at reflux for 6 days. Upon completion, the reaction was cooled to ambient temperature and concentrated. The residue was dissolved in H_2O and extracted 2× with Et_2O. The aqueous layer was cooled in an ice bath and acidified to pH 1 with concentrated HCl. The resulting precipitate was collected via filtration and was washed copiously with cold H_2O. The wet precipitate was dissolved in EtOAc dried over Na_2SO_4, filtered, and concentrated to afford KM-4-234-org (837 mg, 91% yield). **^{1}H NMR** (400 MHz, d_6-acetone) δ 8.76 (dd, *J* = 8.7, 1.4 Hz, 1H), 8.49 (s, 1H), 8.31 (d, *J* = 8.4 Hz, 1H), 8.29 – 8.25 (m, 1H), 7.86 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.78 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.70 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.28 (dd, *J* = 5.0, 3.8 Hz, 1H). **^{13}C NMR** (101 MHz, d_6-acetone) δ 166.6, 159.5, 149.2, 143.0, 142.6, 130.6, 129.9, 128.1, 127.4, 126.0, 124.6, 123.5, 120.6, 120.3, 120.2, 108.5, 25.2.; APCI MS *m/z*: 425.1 (M+H)+, $C_{20}H_{17}N_4O_3S_2$ requires 425.1.

Scheme S4

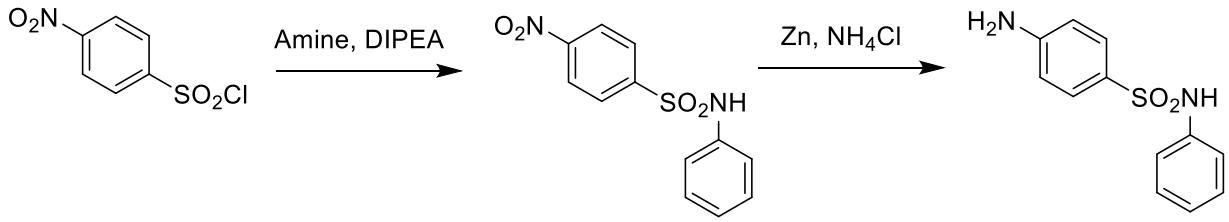


(v)

4-amino-N,N-dimethylbenzenesulfonamide (v). 4-Nosyl chloride (0.200 g, 0.9024 mmol) was dissolved in DCM (3 mL). Dimethylamine (0.5 mL, 2.0 M in THF, 1.1 eq.) and DIPEA (0.17 mL, 0.9926 mmol, 1.1 eq) were added and the reaction was stirred at ambient temperature overnight. Upon completion, the reaction was diluted with H_2O and the layers were separated. The aqueous layer was washed 2× more with DCM, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford sulfonamide KM-4-232 (208 mg, 98%). The nitrophenyl intermediate was dissolved in acetone/H_2O (18 mL, 5:1). Zinc dust (0.568 g, 8.686 mmol, 10 eq.) and NH_4Cl (0.697 g, 13.03 mmol, 15 eq.) were added and the reaction was stirred for 2 hours. The mixture was diluted with H_2O and extracted 3× with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude mixture was purified (SiO_2, 0–30%

EtOAc/DCM) to afford aniline KM-4-238-1 (61 mg, 35%) and hydroxylamine intermediate KM-4-238-2 (91 mg). **^{1}H NMR** (400 MHz, d_6-acetone) δ 7.46 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 5.51 (s, 1H), 2.58 (s, 6H). **^{13}C NMR** (101 MHz, CD_3OD) δ 171.1, 167.9, 151.1, 149.3, 143.9, 143.3, 138.9, 131.6, 129.9, 129.2, 128.6, 126.4, 125.8, 125.1, 121.0, 120.4, 109.4.; APCI MS *m/z*: 411.1 (M+H)+, $C_{19}H_{15}N_4O_3S_2$ requires 411.1.

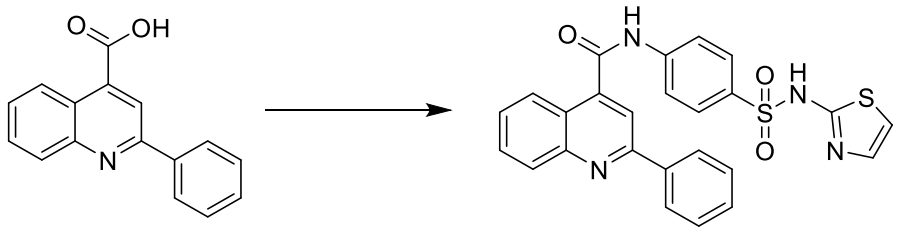
Scheme S5



(vi)

4-amino-N-phenylbenzenesulfonamide (vi). 4-Nosyl chloride (0.200 g, 0.9024 mmol) was dissolved in DCM (3 mL). Aniline (0.09 mL, 0.9926 mmol, 1.1 eq.) and DIPEA (0.17 mL, 0.9926 mmol, 1.1 eq) were added and the reaction was heated at 55 °C overnight. Upon completion, the reaction was diluted with H_2O and the layers were separated. The aqueous layer was washed 2× more with DCM, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford sulfonamide KM-4-242 (151 mg, 60%). The nitrophenyl intermediate was dissolved in acetone/H_2O (12 mL, 5:1). Zinc dust (0.352 g, 5.390 mmol, 10 eq.) and NH_4Cl (0.432 g, 8.085 mmol, 15 eq.) were added and the reaction was stirred for two days. The mixture was diluted with H_2O and extracted 3× with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude mixture was purified (SiO_2, 0–00% EtOAc/DCM) to afford aniline KM-4-246-1 (71 mg, 53%). **^{1}H NMR** (400 MHz, d_6-acetone) δ 7.52 – 7.38 (m, 2H), 7.28 – 7.11 (m, 4H), 7.01 (tt, *J* = 7.0, 2.1 Hz, 1H), 6.73 – 6.57 (m, 2H), 5.44 (br s, 1H). **^{13}C NMR** (101 MHz, d_6-acetone) δ 166.2, 153.7, 149.0, 148.89, 148.86, 146.0, 143.7, 143.5, 131.51, 131.45, 129.8, 128.2, 126.2, 124.1, 120.5, 116.2, 113.5, 112.2, 38.3.; APCI MS *m/z*: 422.2 (M+H)+, $C_{22}H_{20}N_3O_4S$ requires 422.1.

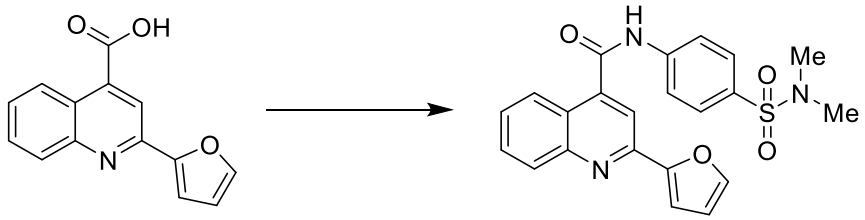
Scheme S6



(iii) **(vii)**

2-phenyl-*N*-(4-(*N*-(thiazol-2-yl)sulfamoyl)phenyl)quinoline-4-carboxamide (vii). Compound (iii) (0.075 g, 0.3008 mmol) was dissolved in DMF (0.75 mL). EDCI (0.069 g, 0.3610 mmol, 1.2 eq.) and HOBt (0.049 g, 0.3610 mmol, 1.2 eq) were added, followed by sulfathiazole (0.085 g, 0.3309 mmol, 1.1 eq.). The reaction was capped and stirred at ambient temperature for 5 days. The reaction was diluted with satd. aq. $NaHCO_3$ and extracted 3× with EtOAc. The combined organic layers were concentrated and purified (SiO_2, 0–30–75–100% EtOAc/Hexane) to afford KM-4-236-2 (25 mg, 17% yield.). **^{1}H NMR** (400 MHz, d_6-acetone) δ 11.30 (br s, 0.4H), 10.22 (s, 1H), 8.39 (s, 1H), 8.39 – 8.35 (m, 2H), 8.32 (dd, *J* = 8.4, 0.6 Hz, 1H), 8.19 (dd, *J* = 8.5, 0.9 Hz, 1H), 8.09 – 7.99 (m, 2H), 7.97 – 7.89 (m, 2H), 7.85 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.66 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.62 – 7.47 (m, 4H), 7.25 (d, *J* = 4.7 Hz, 1H), 6.80 (d, *J* = 4.7 Hz, 1H).

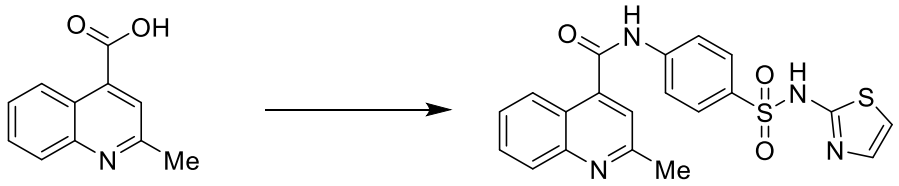
Scheme S7



(ii) **(viii)**

N-(4-(N,N-dimethylsulfamoyl)phenyl)-2-(furan-2-yl)quinoline-4-carboxamide (viii). KM-4-223 (0.050 g, 0.209 mmol, 1.07 eq.) was dissolved in DCM (1 mL) and 4 drops DMF. The mixture was cooled to 0 °C, and oxalyl chloride (0.021 mL, 0.2531 mmol, 1.3 eq) was added. The mixture was stirred for 1 hr. KM-4-238 (0.039 g, 0.1947 mmol, 1 eq.) and DIPEA (0.073 mL, 0.418 mmol, 2 eq.) were added and the reaction was stirred at ambient temperature overnight. The reaction was diluted with satd. aq. $NaHCO_3$ and extracted 3× with DCM. The combined organic layers were concentrated and purified (SiO_2, 0–30–50–100% EtOAc/Hexane) to afford a mixture of products and aniline starting material. This mixture was dissolved in DCM and washed 3× with 1M HCl to remove the aniline. The resulting mixture was repurified (SiO_2, 0–40% EtOAc/Hexane, then 0–10% MeOH/DCM) to afford KM-4-250-flush (20 mg, 24% yield.). **^{1}H NMR** (400 MHz, d_6-acetone) δ 10.44 (s, 1H), 8.31 (dd, *J* = 8.4, 1.3 Hz, 1H), 8.26 (s, 1H), 8.22 – 8.11 (m, 3H), 7.93 – 7.81 (m, 4H), 7.68 (td, *J* = 7.4, 6.7, 1.2 Hz, 1H), 7.55 (d, *J* = 2.2 Hz, 1H), 6.75 (dd, *J* = 3.5, 1.6 Hz, 1H), 2.71 (s, 6H).

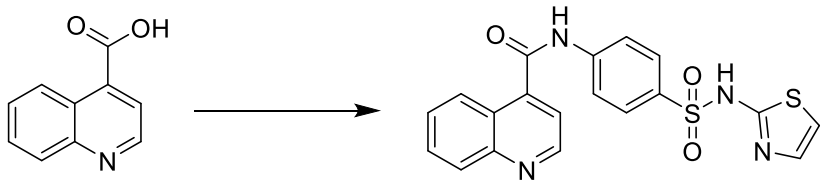
Scheme S8



(ix) **(x)**

2-methyl-*N*-(4-(*N*-(thiazol-2-yl)sulfamoyl)phenyl)quinoline-4-carboxamide (x). 2-Methyl-quinoline-4-carboxylic acid (ix) (0.100 g, 0.534 mmol) was dissolved in DMF (1 mL). HATU (0.244 mg, 0.641 mmol, 1.2 eq) was added. To that mixture was added sulfathiazole (0.164 mg, 0.641 mmol, 1.2 eq.) and DIPEA (0.28 mL, 1.60 mmol, 3 eq.). The reaction was heated to 90 °C for 23 h, then continued to stir at ambient temperature for 24 h. The reaction was diluted with satd. aq. $NaHCO_3$ and extracted 3× with EtOAc. The combined organic layers were washed with satd. aq.NaCl, concentrated and purified (SiO_2, 0–10–15% MeOH/DCM) to afford the expected product contaminated with DIPEA. This mixture was dissolved in DCM and washed 3× with satd. aq. NH_4Cl to remove the amine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford KM-4-261-3 (19.6 mg, 9% yield). **^{1}H NMR** (400 MHz, d_6-acetone) δ 11.34 (br s, 1H), 10.10 (s, 1H), 8.22 (dd, *J* = 8.6, 1.4 Hz, 1H), 8.02 (d, *J* = 6.2 Hz, 1H), 8.00 (d, *J* = 6.6 Hz, 2H), 7.91 (d, *J* = 8.7 Hz, 2H), 7.77 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.65 (s, 1H), 7.59 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.24 (d, *J* = 4.7 Hz, 1H), 6.79 (d, *J* = 4.7 Hz, 1H), 2.72 (s, 3H).

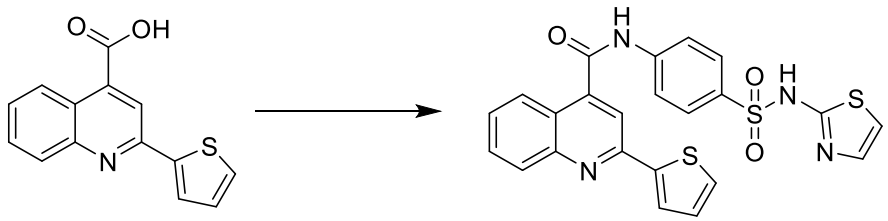
Scheme S9



(xi) **(xii)**

***N*-(4-(N-(thiazol-2-yl)sulfamoyl)phenyl)quinoline-4-carboxamide (xii)**. 4-Quinolinecarboxylic acid (xi) (0.100 g, 0.577 mmol) was dissolved in DMF (1.2 mL). HATU (0.264 mg, 0.693 mmol, 1.2 eq) was added. To that mixture was added sulfathiazole (0.177 mg, 0.693 mmol, 1.2 eq.) and DIPEA (0.30 mL, 1.73 mmol, 3 eq.). The reaction was heated to 90 °C for 23 h, then continued to stir at ambient temperature for 24 h. The reaction was diluted with satd. aq. $NaHCO_3$ and extracted 3× with EtOAc. The combined organic layers were washed with satd. aq.NaCl, concentrated and purified (SiO_2, 0–10–15% MeOH/DCM) to afford the expected product contaminated with DIPEA. This mixture was dissolved in DCM and washed 3× with satd. aq. NH_4Cl to remove the amine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford KM-4-263-3 (20 mg, 8% yield). **^{1}H NMR** (400 MHz, d_6-acetone) δ 11.27 (br s, 1H), 10.13 (s, 1H), 9.02 (d, *J* = 4.3 Hz, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 8.13 (d, *J* = 9.0 Hz, 1H), 8.01 (d, *J* = 8.7 Hz, 2H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.83 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.75 (d, *J* = 4.3 Hz, 1H), 7.68 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.24 (d, *J* = 4.7 Hz, 1H), 6.79 (d, *J* = 4.7 Hz, 1H).

Scheme S10



(iv) **(xiii)**

***N*-(4-(N-(thiazol-2-yl)sulfamoyl)phenyl)-2-(thiophen-2-yl)quinoline-4-carboxamide (xiii)**. Compound (iv) (0.100 g, 0.392 mmol) was dissolved in DMF (0.8 mL). HATU (0.179 mg, 0.470 mmol, 1.2 eq) was added. To that mixture was added sulfathiazole (0.120 mg, 0.470 mmol, 1.2 eq.) and DIPEA (0.20 mL, 1.18 mmol, 3 eq.). The reaction was heated to 90 °C for 23 h, then continued to stir at ambient temperature for 11 d. The reaction was diluted with satd. aq. $NaHCO_3$ and extracted 3× with EtOAc. The combined organic layers were washed with satd. aq. NH_4Cl, 2× 1 M HCl, 2× satd. aq. $NaHCO_3$, and 2× satd. aq. NaCl. The organic layer was dried Na_2SO_4, filtered, concentrated and purified (SiO_2, 0–10–15% MeOH/DCM) to afford KM-4-271-2 (6.7 mg, 3.5% yield). **^{1}H NMR** (400 MHz, d_6-acetone) δ 11.28 (br s, 1H), 10.20 (s, 1H), 8.32 (s, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 8.05 – 7.99 (m, 3H), 7.93 (d, *J* = 8.8 Hz, 2H), 7.81 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.70

(dd, *J* = 5.1, 1.1 Hz, 1H), 7.62 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.25 (d, *J* = 4.7 Hz, 1H), 7.24 – 7.21 (m, 1H), 6.80 (d, *J* = 4.7 Hz, 1H).