Synthesis and pharmacological evaluation of novel C-8 substituted tetrahydroquinolines as balanced-affinity mu/delta opioid ligands for the treatment of pain

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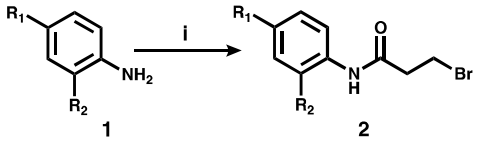
*General Procedure **(i)** for Preparation of Acyl Bromides **2a-h***



2a	R_1 = Bn	R_2 = H	**2e**	R_1 = H	R_2 = *n*-Bu
2b	R_1 = H	R_2 = Me	**2f**	R_1 = H	R_2 = *t*-Bu
2c	R_1 = Br	R_2 = Et	**2g**	R_1 = Br	R_2 = F
2d	R_1 = H	R_2 = *n*-Pr	**2h**	R_1 = H	R_2 = CF_3

2a. *N-(4-benzylphenyl)-3-bromopropanamide.* **2a** was synthesized following **General Procedure (i):** To a flame-dried round-bottom flask under inert atmosphere was added 4-benzylaniline (3.65 g, 19.92 mmol, 1.00 equiv.), followed by dichloromethane (200 mL), then K_2CO_3 (3.56 g, 25.78 mmol, 1.30 equiv.). After 10 minutes, 3-bromopropionyl chloride (2.11 mL, 20.91 mmol, 1.05 equiv.) was added slowly via syringe. Reaction was monitored by TLC in 40% ethyl acetate, 60% hexanes. Ninhydrin stain was used to help monitor disappearance of aniline starting material. After 3 hours, reaction was quenched with deionized water. Organics were separated and dried over $MgSO_4$, then filtered and concentrated under vacuum. Product was used without further purification. Yield: 6.37 g, 100%. ^{1}H NMR (500 MHz, CDCl3) δ 7.43 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 7.3 Hz, 1H), 7.16 (dd, *J* = 7.9, 5.8 Hz, 4H), 3.95 (s, 2H), 3.71 (t, *J* = 6.6 Hz, 2H), 2.92 (t, *J* = 6.6 Hz, 2H).

2b. *3-bromo-N-(o-tolyl)propanamide.* **2b** was synthesized following General Procedure (i) from *o*-toluidine (1.00 g, 5.38 mmol, 1.00 equiv.), K_2CO_3 (2.23 g, 16.14 mmol, 3.00 equiv.) and 3-bromopropionyl chloride (0.57 mL, 5.64 mmol, 1.05 equiv.). Yield: 1.72 g, 100%. ^{1}H NMR (500 MHz, CDCl3) δ 7.57 (d, *J* = 7.6 Hz, 2H), 7.16 (d, *J* = 7.5 Hz, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 3.66 (t, *J* = 6.5 Hz, 2H), 2.91 (t, *J* = 6.5 Hz, 2H), 2.22 (s, 3H). ^{13}C NMR (500 MHz, CDCl3) δ 168.64, 135.16, 130.76, 130.64, 126.63, 126.03, 124.38, 40.21, 27.57, 18.02.

2c. *3-bromo-N-(4-bromo-2-ethylphenyl)propanamide*. **2c** was synthesized following General Procedure (i) from 4-bromo-2-ethylaniline (1.41 g, 7.05 mmol, 1.00 equiv.), K_2CO_3 (1.95 g, 14.10 mmol, 2.00 equiv.) and 3-bromopropionyl chloride (0.75 mL, 7.35 mmol, 1.05 equiv.). Yield: 2.36 g, 100%. ^{1}H NMR (500 MHz, CDCl3) δ 7.67 (d, *J* = 8.4 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.07 (s, 1H), 3.72 (t, *J* = 5.8 Hz, 2H), 2.97 (t, *J* = 6.3 Hz, 2H), 2.60 (q, *J* = 7.5 Hz, 2H), 1.24 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (500 MHz, CDCl3) δ 168.32, 137.66, 133.70, 131.62, 129.82, 125.79, 119.24, 40.80, 27.41, 24.33, 13.93.

2d. *3-bromo-N-(2-propylphenyl)propanamide.* **2d** was synthesized following General Procedure (i) from 2-propylaniline (1.00 g, 7.40 mmol, 1.00 equiv.), K_2CO_3 (3.07 g, 22.2 mmol, 3.00 equiv.) and 3-bromopropionyl chloride (0.78 mL, 7.77 mmol, 1.05 equiv.). Yield: 1.73 g, 86%. ^{1}H NMR (500 MHz, CDCl3) δ 7.70 (q, *J* = 6.9, 5.8 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 3.72 (td, *J* = 7.0, 6.5, 3.1 Hz, 2H), 2.96 (dq, *J* = 7.1, 3.8, 3.3 Hz, 2H), 2.56 (t, *J* = 7.9 Hz, 2H), 1.62 (h, *J* = 7.6 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (500 MHz, CDCl3) δ 168.28, 134.56, 129.63, 126.67, 125.91, 124.54, 40.55, 33.47, 27.46, 23.12, 14.06.

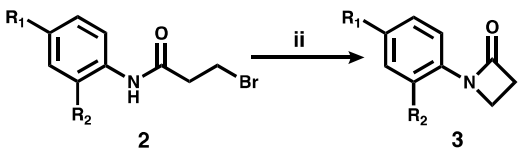
2e. *3-bromo-N-(2-butylphenyl)propanamide.* **2e** was synthesized following General Procedure (i) from 2-butylaniline (1.00 g, 6.70 mmol, 1.00 equiv.), K_2CO_3 (2.78 g, 20.1 mmol, 3.00 equiv.) and 3-bromopropionyl chloride (0.71 mL, 7.03 mmol, 1.05 equiv.). Yield: 1.725 g, 91%. ^{1}H NMR (500 MHz, CDCl3) δ 7.74 (d, *J* = 7.9 Hz, 1H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.17 – 7.10 (m, 2H), 3.73 (t, *J* = 6.5 Hz, 2H), 2.97 (t, *J* = 6.5 Hz, 2H), 2.59 (t, *J* = 7.9 Hz, 2H), 1.57 (h, *J* = 9.8, 8.7 Hz, 2H), 1.39 (h, *J* = 7.4 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (500 MHz, CDCl3) δ 168.13, 134.53, 134.36, 129.57, 126.67, 125.86, 124.31, 40.67, 32.10, 31.18, 27.42, 22.61, 13.96.

2f. *3-bromo-N-(2-(tert-butyl)phenyl)propanamide.* **2f** was synthesized following General Procedure (i) from 2-(*tert*-butyl)aniline (0.96 g, 6.41 mmol, 1.00 equiv.), K_2CO_3 (2.66 g, 19.2 mmol, 3.00 equiv.) and 3-bromopropionyl chloride (0.68 mL, 6.73 mmol, 1.05 equiv.). Yield: 1.82 g, 100%. ^{1}H NMR (500 MHz, CDCl3) δ 7.54 (d, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.26 – 7.16 (m, 2H), 3.75 (t, *J* = 6.6 Hz, 2H), 2.98 (t, *J* = 6.5 Hz, 2H), 1.42 (s, 13H). ^{13}C NMR (500 MHz, CDCl3) δ 168.21, 143.07, 134.64, 128.39, 127.55, 126.87, 126.65, 40.80, 34.65, 30.82, 27.24.

2g. *3-bromo-N-(4-bromo-2-fluorophenyl)propanamide.* **2g** was synthesized following General Procedure (i) from 4-bromo-2-fluoroaniline (1.0 g, 5.26 mmol, 1.00 equiv.), K_2CO_3 (1.49 g, 10.8 mmol, 2.05 equiv.) and 3-bromopropionyl chloride (0.54 mL, 5.37 mmol, 1.05 equiv.). Yield: 1.71 g, 100%. ^{1}H NMR (500 MHz, CDCl3) δ 8.18 (t, *J* = 8.5 Hz, 1H), 7.33 (s, 1H), 7.24 – 7.18 (m, 3H), 3.63 (t, *J* = 6.5 Hz, 2H), 2.93 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 167.85, 152.96, 127.83, 127.80, 125.13, 122.80, 118.55, 118.37, 116.22, 40.63, 26.36.

2h. *3-bromo-N-(2-(trifluoromethyl)phenyl)propanamide.* **2h** was synthesized following General Procedure (i) from 2-(trifluoromethyl)aniline (2.00 g, 12.4 mmol, 1.00 equiv.), K_2CO_3 (5.14 g, 37.2 mmol, 3.00 equiv.) and 3-bromopropionyl chloride (1.31 mL, 13.0 mmol, 1.05 equiv.). Yield: 3.68 g, 100%. ^{1}H NMR (500 MHz, $_{CDCl3}$) δ 8.17 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.57 (t, *J* = 7.9 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 1H), 3.71 (t, *J* = 6.6 Hz, 2H), 2.99 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 168.31, 134.75, 133.71, 133.06, 127.45, 126.26, 125.10, 40.86, 26.53.

*General Procedure **(ii)** for Preparation of β-Lactams **3a-h***



2 3

3a	R_1 = Bn	R_2 = H	**3e**	R_1 = H	R_2 = *n*-Bu
3b	R_1 = H	R_2 = Me	**3f**	R_1 = H	R_2 = *t*-Bu
3c	R_1 = Br	R_2 = Et	**3g**	R_1 = Br	R_2 = F
3d	R_1 = H	R_2 = *n*-Pr	**3h**	R_1 = H	R_2 = CF_3

3a. *1-(4-benzylphenyl)azetidin-2-one.* **3a** was synthesized following **General Procedure (ii):** To a flame-dried round-bottom flask under inert atmosphere was added sodium *tert*-butoxide (2.02 g, 21.02 mmol, 1.05 equiv.), then DMF (60 mL) and stirred 10 min before slowly adding a solution of **2a** (6.37g, 20.02 mmol, 1.00 equiv.) dissolved in DMF (60 mL) at ambient temperature via syringe. Monitored reaction by TLC, in 40% ethyl acetate, 60% hexanes. Desired product showed a moderate decrease in Rf relative to starting material. After stirring 1 hour, reaction mixture was concenctrated under vacuum, then resuspended in dichloromethane. Extracted reaction mixture with deionized water and aqueous sodium bicarbonate, then separated organics and dried over $MgSO_4$. Filtered and reconcentrated organics onto silica, then purified by flash chromatography. Yield: 4.25 g, 90%. ^{1}H NMR (500 MHz, CDCl3) δ 7.29 (d, *J* = 8.1 Hz, 3H), 7.20 (d, *J* = 7.3 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 4H), 3.95 (s, 2H), 3.60 (t, *J* = 4.5 Hz, 2H), 3.10 (t, *J* = 4.5 Hz, 2H).

3b. *1-(o-tolyl)azetidin-2-one.* **3b** was synthesized following General Procedure (ii) from **2b** (1.72 g, 5.36 mmol, 1.00 equiv.) and NaO*t*Bu (540 mg, 5.63 mmol, 1.05 equiv.). Yield: 1.18 g, 92%. ^{1}H NMR (500 MHz, CDCl3) δ 7.28 (td, *J* = 8.6, 6.9, 0.8 Hz, 1H), 7.09 (t, *J* = 6.9 Hz, 2H), 7.03 (td, *J* = 7.6, 7.2, 1.5 Hz, 1H), 3.60 (t, *J* = 4.4 Hz, 2H), 2.97 (t, *J* = 4.5 Hz, 2H), 2.28 (s, 3H). ^{13}C NMR (500 MHz, CDCl3) δ 165.27, 136.19, 131.08, 130.79, 126.06, 125.76, 125.75, 122.03, 41.04, 35.99, 18.87.

3c. *1-(4-bromo-2-ethylphenyl)azetidin-2-one*. **3c** was synthesized following General Procedure (ii) from **2c** (2.56 g, 7.64 mmol, 1.00 equiv.) and NaO*t*Bu (734 mg, 7.64 mmol, 1.00 equiv.). Yield: 1.89 g, 97%. ^{1}H NMR (500 MHz, CDCl3) δ 7.36 (d, *J* = 2.1 Hz, 1H), 7.33 – 7.29 (m, 1H), 3.75 – 3.69 (m, 2H), 3.13 (td, *J* = 4.5, 1.3 Hz, 2H), 2.71 (q, *J* = 7.5 Hz, 2H), 1.22 (td, *J* = 7.5, 1.3 Hz, 3H). ^{13}C NMR (500 MHz, CDCl3) δ 165.77, 139.73, 135.09, 132.52, 129.62, 124.88, 119.92, 42.03, 36.81, 25.12, 14.34.

3d. *1-(2-propylphenyl)azetidin-2-one*. **3d** was synthesized following General Procedure (ii) from **2d** (1.56 g, 5.78 mmol, 1.00 equiv.) and NaO*t*Bu (583 mg, 6.07 mmol, 1.05 equiv.). Yield: 1.10 g, 100%. ^{1}H NMR (500 MHz, CDCl3) δ 7.35 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.20 (td, *J* = 6.2, 5.4, 2.0 Hz, 2H), 7.16 (dd, *J* = 7.2, 1.6 Hz, 1H), 3.74 – 3.69 (m, 2H), 3.14 – 3.09 (m, 2H), 2.71 – 2.63 (m, 2H), 1.61 (h, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (500 MHz, CDCl3) δ 165.86, 136.45, 136.02, 130.55, 126.64, 126.62, 123.68, 42.03, 36.59, 34.35, 23.64, 14.20.

3e. *1-(2-butylphenyl)azetidin-2-one*. **3e** was synthesized following General Procedure (ii) from **2e** (1.725 g, 6.06 mmol, 1.00 equiv.) and NaO*t*Bu (613 mg, 6.37 mmol, 1.05 equiv.). Yield: 1.23 g, 100%. ^{1}H NMR (500 MHz, CDCl3) δ 7.35 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.20 (td, *J* = 8.4, 7.9, 2.1 Hz, 2H), 7.17 – 7.13 (m, 2H), 3.71 (td, *J* = 4.4, 0.9 Hz, 2H), 3.11 (td, *J* = 4.4, 1.0 Hz, 2H), 2.74 – 2.65 (m, 2H), 1.56 (p, *J* = 7.9, 7.5 Hz, 2H), 1.37 (h, *J* = 7.3 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (500 MHz, CDCl3) δ 165.82, 136.71, 135.97, 130.49, 126.63, 126.57, 123.70, 42.02, 36.57, 32.70, 32.00, 22.71, 14.08.

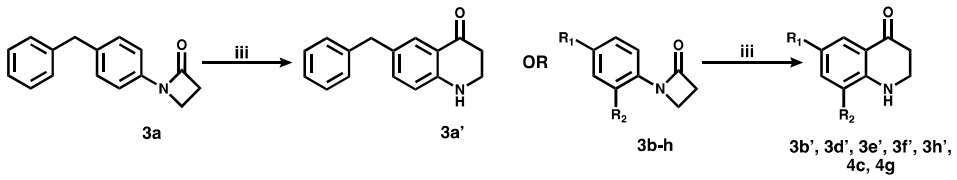
3f. *1-(2-(tert-butyl)phenyl)azetidin-2-one*. **3f** was synthesized following General Procedure (ii) from **2f** (1.90 g, 6.67 mmol, 1.00 equiv.) and NaO*t*Bu (673 mg, 7.00 mmol, 1.05 equiv.). Yield: 1.36 g, 100%. ^{1}H NMR (500 MHz, CDCl3) δ 7.46 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.26 (s, 1H), 7.23 (td, *J* = 7.4, 1.5 Hz, 1H), 7.13 (dd, *J* = 7.6, 1.6 Hz, 1H), 3.64 (td, *J* = 4.3, 1.1 Hz, 2H), 3.10 (td, *J* = 4.3, 1.0 Hz, 2H), 1.41 (d, *J* = 0.9 Hz, 9H). ^{13}C NMR (500 MHz, CDCl3) δ 168.19, 148.84, 135.79, 130.22, 128.65, 127.52, 127.15, 44.52, 36.68, 35.20, 31.35.

3g. *1-(4-bromo-2-fluorophenyl)azetidin-2-one*. **3g** was synthesized following General Procedure (ii) from **2g** (1.71 g, 5.26 mmol, 1.00 equiv.) and NaO*t*Bu (530 mg, 5.30 mmol, 1.05 equiv.). Yield: 1.00 g, 78%. ^{1}H NMR (500 MHz, CDCl3) δ 7.91 (t, *J* = 8.6 Hz, 1H), 7.25 – 7.15 (m, 2H), 3.87 (q, *J* = 4.4 Hz, 2H), 3.15 (t, *J* = 4.6 Hz, 2H). ^{13}C NMR

(500 MHz, CDCl3) δ 165.40, 152.52, 150.53, 127.71, 127.68, 125.66, 125.58, 122.06, 122.03, 119.69, 119.51, 115.66, 115.59, 42.07, 42.01, 38.39, 38.38.

3h. *1-(2-(trifluoromethyl)phenyl)azetidin-2-one*. **3h** was synthesized following General Procedure (ii) from **2h** (3.38 g, 12.56 mmol, 1.00 equiv.) and NaO*t*Bu (1.27 g, 13.19 mmol, 1.05 equiv.). Yield: 1.62 g, 60%. ^{1}H NMR (500 MHz, CDCl3) δ 7.98 (d, *J* = 8.1 Hz, 1H), 7.64 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.52 (td, *J* = 7.8, 1.5 Hz, 1H), 7.30 – 7.21 (m, 1H), 3.84 (td, *J* = 4.6, 1.2 Hz, 2H), 3.14 (t, *J* = 4.7 Hz, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 166.86, 135.88, 135.87, 132.95, 132.94, 127.00, 126.95, 125.58, 125.55, 124.66, 122.49, 43.89, 43.86, 43.82, 43.79, 37.24.

*General Procedure **(iii)** for Cyclization of Intermediates **3a-h***



3b, 3b'	R_1 = H	R_2 = Me
3c, 4c	R_1 = Br	R_2 = Et
3d, 3d'	R_1 = H	R_2 = *n*-Pr
3e, 3e'	R_1 = H	R_2 = *n*-Bu
3f, 3f'	R_1 = H	R_2 = *t*-Bu
3g, 4g	R_1 = Br	R_2 = F
3h, 3h'	R_1 = H	R_2 = CF_3

Note: Intermediates **4c** and **4g** contained R_1 = Br from the starting aniline, **3c** and **3g** go directly to **4c** and **4g** with no aryl bromination step (**iv**)

3a'. *6-benzyl-2,3-dihydroquinolin-4(1H)-one.* **3a'** was synthesized following **General Procedure (iii):** To a round-bottom flask containing intermediate **3a** (3.75 g, 15.80 mmol, 1 equiv.) dissolved in dichloroethane (150 mL) under inert atmosphere was slowly added TfOH (4.18 mL, 47.40 mmol, 3 equiv.). After 1 hour, TLC in 40% ethyl acetate, 60% hexanes showed a decrease in Rf. Reaction was quenched with deionized water, then diluted with dichloromethane. Separated organics and dried over $MgSO_4$, then filtered and concentrated organics onto silica and purified by flash chromatography. Yield: 3.34 g, 90%. ^{1}H NMR (500 MHz, CDCl3) δ 7.72 (d, *J* = 2.1 Hz, 1H), 7.30 – 7.23 (m, 2H), 7.20 – 7.15 (m, 3H), 7.12 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.60 (d, *J* = 8.4 Hz, 1H), 4.34 (s, 1H), 3.86 (s, 2H), 3.54 (td, *J* = 7.1, 2.0 Hz, 2H), 2.68 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 193.92, 150.73, 141.35, 136.19, 130.89, 128.86, 128.59, 127.37, 126.18, 119.34, 116.35, 77.16, 42.53, 41.08, 38.30. Intermediate **3a'** was then brominated following General Procedure (iv) to give **4a**.

3b'. *8-methyl-2,3-dihydroquinolin-4(1H)-one.* **3b'** was synthesized following General Procedure (iii) from **3b** (1.18 g, 4.9 mmol, 1 equiv.) and TfOH (1.3 mL, 14.7 mmol, 3 equiv.). Yield: 606 mg, 52%. ^{1}H NMR (500 MHz, CDCl3)

δ 7.75 (d, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 7.1 Hz, 1H), 6.65 (t, *J* = 7.5 Hz, 1H), 4.40 (s, 1H), 3.60 (t, *J* = 6.9 Hz, 2H), 2.68 (t, *J* = 6.9 Hz, 2H), 2.15 (s, 3H). ^{13}C NMR (500 MHz, CDCl3) δ 194.16, 150.47, 135.73, 125.61, 122.87, 119.10, 117.26, 77.16, 42.18, 37.92, 16.95. Intermediate **3b'** was then brominated following General Procedure (iv) to give **4b**.

4c. *6-bromo-8-ethyl-2,3-dihydroquinolin-4(1H)-one*. **4c** was synthesized following General Procedure (iii) from **3c** (1.89 g, 7.42 mmol, 1 equiv.) and TfOH (1.31 mL, 14.85 mmol, 2 equiv.). Yield: 640 mg, 34%. ^{1}H NMR (500 MHz, CDCl3) δ 7.88 (d, *J* = 2.4 Hz, 1H), 7.29 (d, *J* = 2.3 Hz, 1H), 4.40 (s, 1H), 3.61 (t, *J* = 7.0 Hz, 3H), 2.69 (t, *J* = 7.1 Hz, 3H), 2.46 (q, *J* = 7.5 Hz, 3H), 1.27 (t, *J* = 7.5 Hz, 4H). ^{13}C NMR (500 MHz, CDCl3) δ 192.87, 148.71, 135.93, 130.97, 127.91, 120.59, 110.25, 42.13, 37.69, 23.30, 12.53.

3d'. *8-propyl-2,3-dihydroquinolin-4(1H)-one*. **3d'** was synthesized following General Procedure (iii) from **3d** (1.10 g, 5.8 mmol, 1 equiv.) and TfOH (1.54 mL, 17.4 mmol, 3 equiv.). Yield: 1.06 g, 100%. ^{1}H NMR (500 MHz, CDCl3) δ 7.77 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.18 (dd, *J* = 7.2, 1.5 Hz, 1H), 6.70 (t, *J* = 7.6 Hz, 1H), 3.72 (s, 1H), 3.60 (dd, *J* = 7.6, 6.3 Hz, 2H), 2.69 (dd, *J* = 7.5, 6.4 Hz, 2H), 2.46 – 2.41 (m, 2H), 1.65 (h, *J* = 7.4 Hz, 2H), 1.01 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (500 MHz, CDCl3) δ 194.22, 149.96, 134.78, 127.18, 125.74, 119.59, 117.47, 77.16, 42.32, 38.04, 32.84, 21.59, 14.20. Intermediate **3d'** was then brominated following General Procedure (iv) to give **4d**.

3e'. *8-butyl-2,3-dihydroquinolin-4(1H)-one*. **3e'** was synthesized following General Procedure (iii) from **3e** (1.23 g, 6.06 mmol, 1.00 equiv.) and TfOH (1.64 mL, 18.58 mmol, 3.07 equiv.). Yield: 1.174 g, 95%. ^{1}H NMR (500 MHz, CDCl3) δ 7.80 – 7.74 (m, 1H), 7.19 (t, *J* = 7.2 Hz, 1H), 6.70 (q, *J* = 7.7 Hz, 1H), 4.44 (s, 1H), 3.61 (q, *J* = 7.3 Hz, 2H), 2.70 (q, *J* = 7.3 Hz, 2H), 2.47 (q, *J* = 7.8 Hz, 2H), 1.61 (h, *J* = 7.6 Hz, 2H), 1.42 (hept, *J* = 7.5 Hz, 2H), 0.97 (q, *J* = 7.5 Hz, 3H). ^{13}C NMR (500 MHz, CDCl3) δ 194.23, 194.21, 149.95, 134.69, 134.67, 127.38, 125.71, 125.69, 119.59, 117.49, 42.35, 42.33, 38.06, 38.04, 30.57, 30.56, 30.52, 30.51, 22.81, 22.80, 14.08, 14.07. Intermediate **3e'** was then brominated following General Procedure (iv) to give **4e**.

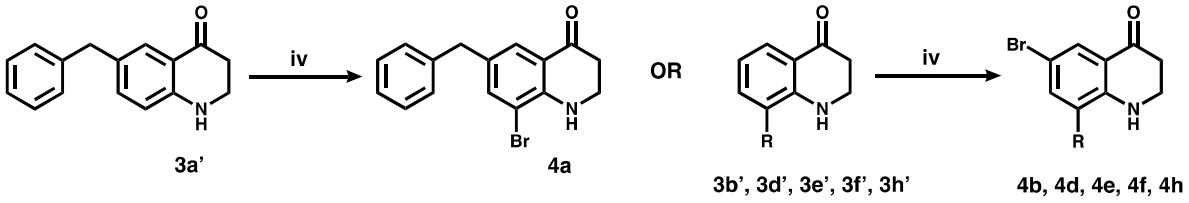
3f'. *8-(tert-butyl)-2,3-dihydroquinolin-4(1H)-one*. **3f'** was synthesized following General Procedure (iii) from **3f** (1.36 g, 6.71 mmol, 1.00 equiv.) and TfOH (1.78 mL, 20.14 mmol, 3.00 equiv.). Yield: 1.02 g, 75%. ^{1}H NMR (500

MHz, CDCl3) δ 7.83 (ddd, *J* = 7.8, 1.6, 0.7 Hz, 1H), 7.37 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.70 (td, *J* = 7.7, 1.6 Hz, 1H), 3.66 – 3.56 (m, 2H), 2.69 (ddd, *J* = 7.7, 6.8, 1.5 Hz, 2H), 1.43 (d, *J* = 1.2 Hz, 9H). ^{13}C NMR (500 MHz, CDCl3) δ 194.44, 150.68, 134.42, 132.18, 126.36, 120.68, 117.42, 42.24, 38.03, 34.28, 30.05. Intermediate **3f'** was then brominated following General Procedure (iv) to give **4f**.

4g. *6-bromo-8-fluoro-2,3-dihydroquinolin-4(1H)-one*. **4g** was synthesized following General Procedure (iii) from **3g** (1.0 g, 4.1 mmol, 1 equiv.) and TfOH (1.09 mL, 12.3 mmol, 3 equiv.). Yield: 508 mg, 51%. ^{1}H NMR (500 MHz, CDCl3) δ 7.76 (t, *J* = 1.7 Hz, 1H), 7.27 – 7.23 (m, 1H), 4.65 (s, 1H), 3.64 (td, *J* = 7.5, 7.1, 2.0 Hz, 2H), 2.73 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 191.33, 152.16, 150.20, 140.23, 140.13, 125.60, 122.79, 122.62, 121.78, 108.04, 107.97, 41.94, 37.80.

3h'. *8-(trifluoromethyl)-2,3-dihydroquinolin-4(1H)-one*. **3h'** was synthesized following General Procedure (iii) from **3h** (1.62 g, 7.52 mmol, 1.00 equiv.) and TfOH (2.00 mL, 22.56 mmol, 3.00 equiv.). Yield: 850 mg, 52%. ^{1}H NMR (500 MHz, CDCl3) δ 8.05 (ddd, *J* = 7.9, 1.7, 0.9 Hz, 1H), 7.60 (ddd, *J* = 7.6, 1.7, 0.8 Hz, 1H), 6.77 (td, *J* = 7.7, 0.9 Hz, 1H), 5.06 (s, 1H), 3.69 – 3.63 (m, 2H), 2.77 – 2.71 (m, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 192.59, 148.70, 132.75, 132.71, 132.66, 132.62, 132.22, 125.64, 123.47, 120.74, 116.46, 41.72, 37.44. Intermediate **3h'** was then brominated following General Procedure (iv) to give **4h**.

*General Procedure **(iv)** for Aromatic Bromination to Produce Aryl Bromides **4a-h***



4a. *6-benzyl-8-bromo-2,3-dihydroquinolin-4(1H)-one.* **4a** was synthesized from **3a'** following **General Procedure (iv):** To a round-bottom flask containing **3a'** (501 mg, 2.11 mmol, 1.00 equiv.), dissolved in dichloromethane (20 mL) under inert atmosphere was added *N*-bromosuccinimide (375 mg, 2.11 mmol, 1.00 equiv.) at ambient temperature. After 30 minutes, TLC in 40% ethyl acetate, 60% hexanes showed complete conversion. Reaction was reconcentrated onto silica and was purified by flash chromatography. Yield: 640 mg, 96%. ^{1}H NMR (500 MHz,

CDCl3) δ 7.70 (d, *J* = 2.0 Hz, 1H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 2H), 7.22 – 7.17 (m, 1H), 7.15 (d, *J* = 7.5 Hz, 2H), 4.89 (s, 1H), 3.83 (s, 2H), 3.60 (td, *J* = 7.2, 2.1 Hz, 2H), 2.69 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 193.10, 147.40, 140.62, 138.57, 131.31, 128.81, 128.70, 127.07, 126.41, 120.28, 110.32, 77.16, 41.92, 40.75, 37.55.

4b. *6-bromo-8-methyl-2,3-dihydroquinolin-4(1H)-one.* **4b** was synthesized following General Procedure (iv) from **3b'** (120 mg, 0.74 mmol, 1.00 equiv.) and NBS (139 mg, 0.78 mmol, 1.05 equiv.). Yield: 170 mg, 95%. ^{1}H NMR (500 MHz, CDCl3) δ 7.85 (d, *J* = 2.3 Hz, 1H), 7.28 (dd, *J* = 2.3, 1.1 Hz, 1H), 4.34 (s, 1H), 3.61 (t, *J* = 7.0 Hz, 2H), 2.71 – 2.65 (m, 2H), 2.13 (s, 3H). ^{13}C NMR (500 MHz, CDCl3) δ 192.79, 149.26, 137.96, 127.94, 125.36, 120.28, 109.76, 42.07, 37.60, 16.80.

4d. *6-bromo-8-propyl-2,3-dihydroquinolin-4(1H)-one*. **4d** was synthesized following General Procedure (iv) from **3d'** (294 mg, 1.55 mmol, 1.00 equiv.) and NBS (282 mg, 1.58 mmol, 1.02 equiv.). Yield: 350 mg, 84%. ^{1}H NMR (500 MHz, CDCl3) δ 7.87 (d, *J* = 2.3 Hz, 1H), 7.26 (s, 1H), 4.42 (s, 1H), 3.63 – 3.56 (m, 2H), 2.68 (td, *J* = 7.0, 1.1 Hz, 2H), 2.44 – 2.37 (m, 2H), 1.70 – 1.59 (m, 2H), 1.01 (td, *J* = 7.3, 1.1 Hz, 3H). ^{13}C NMR (500 MHz, CDCl3) δ 192.90, 148.83, 136.97, 129.68, 127.97, 120.67, 110.07, 77.16, 42.11, 37.68, 32.56, 21.40, 14.14.

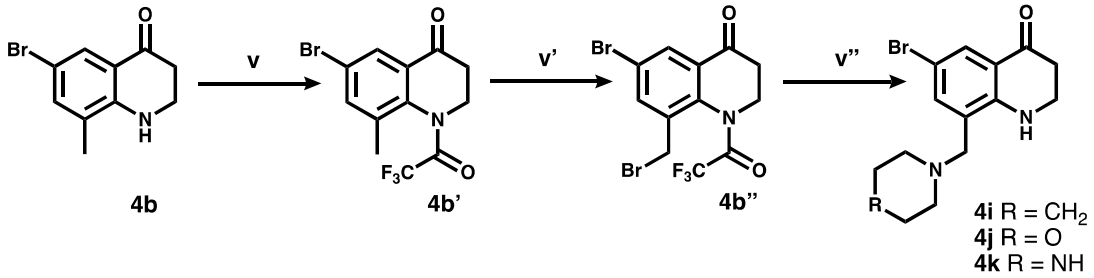
4e. *6-bromo-8-butyl-2,3-dihydroquinolin-4(1H)-one.* **4e** was synthesized following General Procedure (iv) from **3e'** (485 mg, 2.46 mmol, 1.00 equiv.) and NBS (446 mg, 2.51 mmol, 1.05 equiv.). Yield: 575 mg, 85%. ^{1}H NMR (500 MHz, CDCl3) δ 7.86 (dd, *J* = 2.5, 1.0 Hz, 1H), 7.26 (s, 1H), 4.44 (s, 1H), 3.63 – 3.55 (m, 2H), 2.68 (td, *J* = 7.0, 1.1 Hz, 2H), 2.47 – 2.38 (m, 2H), 1.64 – 1.54 (m, 2H), 1.41 (h, *J* = 7.4 Hz, 2H), 0.96 (td, *J* = 7.3, 1.0 Hz, 3H). ^{13}C NMR (500 MHz, CDCl3) δ 193.15, 149.07, 137.11, 130.17, 128.14, 120.89, 110.31, 42.36, 37.92, 30.56, 30.51, 23.00, 14.29.

4f. *6-bromo-8-(tert-butyl)-2,3-dihydroquinolin-4(1H)-one.* **4f** was synthesized following General Procedure (iv) from **3f'** (500 mg, 2.46 mmol, 1.00 equiv.) and NBS (460 mg, 2.58 mmol, 1.05 equiv.). Yield: 570 mg, 82%. ^{1}H NMR (500 MHz, CDCl3) δ 7.92 (d, *J* = 2.4 Hz, 1H), 7.41 (d, *J* = 2.4 Hz, 1H), 4.73 (s, 1H), 3.61 (t, *J* = 7.0 Hz, 2H),

2.72 – 2.63 (m, 2H), 1.41 (s, 9H). ^{13}C NMR (500 MHz, CDCl3) δ 192.86, 149.20, 136.79, 134.67, 128.30, 121.49, 110.17, 77.16, 41.78, 37.37, 34.17, 29.59.

4h. *6-bromo-8-(trifluoromethyl)-2,3-dihydroquinolin-4(1H)-one*. **4h** was synthesized following General Procedure (iv) from **3h'** (850 mg, 3.95 mmol, 1.00 equiv.) and NBS (739 mg, 4.15 mmol, 1.05 equiv.). Yield: 1.00 g, 86%. ^{1}H NMR (500 MHz, CDCl3) δ 8.13 (d, *J* = 2.4 Hz, 1H), 7.68 (d, *J* = 2.5 Hz, 1H), 5.07 (s, 1H), 3.70 – 3.63 (m, 2H), 2.78 – 2.70 (m, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 191.23, 147.36, 135.24, 135.19, 135.15, 135.10, 134.57, 124.64, 122.47, 122.03, 108.56, 41.55, 37.08.

*General Procedures **(v)**, **(v')**, and **(v'')**, for N-Trifluoroacetyl Protection, Benzylic Bromination & Substitution of **4b** to Produce Intermediates **4i**, **4j**, and **4k**.*



For conversion of **3b** to **4b**, see above

4b'. *6-bromo-8-methyl-1-(2,2,2-trifluoroacetyl)-2,3-dihydroquinolin-4(1H)-one.* **4b'** was synthesized following **General Procedure (v):** To a round-bottom flask containing intermediate **4b** (1.17 g, 4.89 mmol, 1 equiv.) dissolved in dichloromethane (50 mL) under inert atmosphere was added trifluoroacetic anhydride (1.37 mL, 9.78 mmol, 2 equiv.) at 0°C . After 4 hours, reaction was reconcentrated onto silica and was purified by flash chromatography, yielding intermediate **4b'** as a white crystalline solid. Yield: 1.54 g, 95%. ^{1}H NMR (400 MHz, CDCl3) δ 7.99 (d, *J* = 2.2 Hz, 1H), 7.63 (d, *J* = 2.3 Hz, 1H), 4.52 (dd, *J* = 14.6, 5.2 Hz, 1H), 3.88 (td, *J* = 13.9, 3.9 Hz, 1H), 3.03 – 2.79 (m, 2H), 2.17 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 191.77, 139.79, 139.42, 139.10, 136.84, 129.86, 128.58, 128.36, 121.85, 117.65, 114.79, 77.16, 46.17, 40.13, 39.99, 18.70, 18.48.

4b''. *6-bromo-8-(bromomethyl)-1-(2,2,2-trifluoroacetyl)-2,3-dihydroquinolin-4(1H)-one.* **4b''** was synthesized following **General Procedure (v'):** To a round-bottom flask containing intermediate **4b'** (478 mg, 1.42 mmol, 1.00

equiv.) under inert atmosphere was added *N*-bromosuccinimide (266 mg, 1.49 mmol, 1.05 equiv.) and benzoyl peroxide (34 mg, 0.14 mmol, 0.1 equiv.), followed by degassed, Ar-sparged CCl_4 (15 mL). Reaction was heated to reflux for 6 hours. Reaction was cooled to -20°C, and precipitate was filtered from solution (washing with additional CCl_4 at -20°C). Filtrate was then reconcentrated onto silica and purified by manually-packed silica column chromatography using 10% ethyl acetate, 90% hexanes, as flash chromatography did not provide sufficient separation. Brominated intermediate **4b''** was isolated as a white crystalline solid. Yield: 232 mg, 40%. ^{1}H NMR (500 MHz, CDCl3) δ 8.11 (t, *J* = 2.6 Hz, 1H), 7.82 (t, *J* = 2.8 Hz, 1H), 4.62 – 4.52 (m, 1H), 4.41 (dd, *J* = 11.7, 3.0 Hz, 1H), 4.32 (dd, *J* = 11.8, 3.0 Hz, 1H), 3.92 (tt, *J* = 14.4, 3.5 Hz, 1H), 3.00 (dddd, *J* = 16.7, 13.7, 5.7, 3.0 Hz, 1H), 2.94 – 2.85 (m, 1H). ^{13}C NMR (500 MHz, CDCl3) δ 191.09, 138.90, 136.23, 134.42, 131.08, 130.77, 129.92, 128.99, 122.30, 77.16, 46.11, 46.08, 39.92, 28.94.

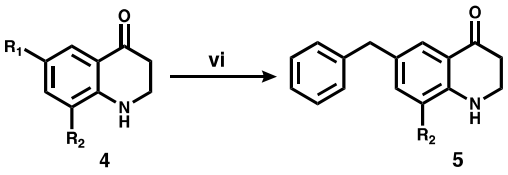
4i. *6-bromo-8-(piperidin-1-ylmethyl)-1-(2,2,2-trifluoroacetyl)-2,3-dihydroquinolin-4(1H)-one.* **4i** was synthesized following **General Procedure (v''):** To a round-bottom flask containing intermediate **4b''** (140 mg, 0.34 mmol, 1 equiv.) under inert atmosphere was added K_2CO_3 (140 mg, 1.02 mmol, 3 equiv.) and piperidine (0.04 mL, 0.41 mmol, 1.2 equiv.), followed by DMF (5 mL) at ambient temperature. After 12 hours, reaction was reconcentrated onto silica and was purified by flash chromatography. *N*-trifluoroacetyl group was partially removed during reaction, so **4i** was carried forward as a 1:1 molar equiv. mixture of N-TFA protected (60 mg, 0.14 mmol) and deprotected (45 mg, 0.14 mmol) intermediates. Net yield: 0.28 mmol, 82%. Unprotected: ^{1}H NMR (500 MHz, CDCl3) δ 7.87 (d, *J* = 2.6 Hz, 1H), 7.50 (s, 1H), 7.17 (d, *J* = 2.6 Hz, 1H), 3.54 (t, *J* = 7.1 Hz, 2H), 3.44 (s, 2H), 2.63 (t, *J* = 7.1 Hz, 2H), 2.34 (s, 4H), 1.54 (q, *J* = 5.8 Hz, 4H), 1.45 (s, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 192.97, 151.75, 137.64, 128.90, 125.72, 120.35, 108.66, 77.16, 62.11, 54.04, 41.38, 37.47, 26.23, 24.28. TFA-protected: ^{1}H NMR (500 MHz, CDCl3) δ 7.97 (d, *J* = 2.4 Hz, 1H), 7.83 (s, 1H), 4.43 (dd, *J* = 14.3, 5.4 Hz, 1H), 3.77 (d, *J* = 15.8 Hz, 1H), 3.27 (dd, 2H), 2.96 – 2.72 (m, 2H), 2.17 (s, 4H), 1.54 – 1.40 (m, 4H), 1.35 (q, *J* = 6.1 Hz, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 191.76, 182.72, 139.46, 138.55, 137.67, 129.98, 129.33, 121.93, 119.74, 117.45, 115.15, 112.87, 60.76, 54.74, 45.98, 40.04, 25.82, 24.25.

4j. *6-bromo-8-(morpholinomethyl)-1-(2,2,2-trifluoroacetyl)-2,3-dihydroquinolin-4(1H)-one.* **4j** was synthesized following General Procedure (v'') from intermediate **4b''** (250 mg, 0.60 mmol, 1 equiv.), and morpholine (3 mL,

excess.); K_2CO_3 was not used here. No loss of trifluoroacetic protecting group observed. Yield: 160 mg, 63% ^{1}H NMR (500 MHz, CDCl3) δ 8.09 (d, *J* = 2.4 Hz, 1H), 7.95 (d, *J* = 2.3 Hz, 1H), 4.53 (d, *J* = 14.3 Hz, 1H), 3.88 (d, *J* = 13.8 Hz, 1H), 3.70 (t, *J* = 4.7 Hz, 4H), 3.41 (s, 2H), 2.96 (ddd, *J* = 18.8, 13.4, 5.5 Hz, 1H), 2.88 (ddd, *J* = 18.5, 3.9, 1.7 Hz, 1H), 2.37 (s, 4H). ^{13}C NMR (500 MHz, CDCl3) δ 191.46, 139.50, 138.53, 130.11, 129.88, 122.18, 77.16, 66.72, 60.08, 53.72, 46.11, 40.04.

4k. *6-bromo-8-(piperazin-1-ylmethyl)-1-(2,2,2-trifluoroacetyl)-2,3-dihydroquinolin-4(1H)-one.* **4k** was synthesized following General Procedure (v'') from **4b''** (280 mg, 0.67 mmol, 1 equiv.), K_2CO_3 (251 mg, 1.35 mmol, 2 equiv.), and monoBoc-piperazine (187 mg, 1.35 mmol, 2 equiv.). Some loss of trifluoroacetic protecting group observed, but not isolated. Yield: 212 mg, 75%. ^{1}H NMR (500 MHz, CDCl3) δ 7.99 (d, *J* = 2.2 Hz, 1H), 7.85 (d, *J* = 2.4 Hz, 1H), 4.51 – 4.38 (m, 1H), 3.77 (t, *J* = 14.0 Hz, 1H), 3.38 – 3.29 (m, 4H), 2.91 – 2.84 (m, 1H), 2.79 (ddd, *J* = 18.6, 3.7, 1.7 Hz, 1H), 2.21 (t, *J* = 5.0 Hz, 4H), 1.38 (s, 9H). ^{13}C NMR (500 MHz, CDCl3) δ 191.48, 154.81, 139.39, 138.36, 136.59, 130.05, 129.69, 122.08, 119.68, 117.38, 115.09, 79.88, 59.83, 53.09, 46.02, 43.33, 39.99, 28.51.

*General Procedure **(vi)** for Suzuki Coupling in the Synthesis of **5a-l***



4a	R_1 = Bn	R_2 = Br		**5a**	R_2 = Bn
4b	R_1 = Br	R_2 = Me		**5b**	R_2 = Me
4c	R_1 = Br	R_2 = Et		**5c**	R_2 = Et
4d	R_1 = Br	R_2 = *n*-Pr		**5d**	R_2 = *n*-Pr
4e	R_1 = Br	R_2 = *n*-Bu		**5e**	R_2 = *n*-Bu
4f	R_1 = Br	R_2 = *t*-Bu		**5f**	R_2 = *t*-Bu
4g	R_1 = Br	R_2 = F		**5g**	R_2 = F
4h	R_1 = Br	R_2 = CF_3		**5h**	R_2 = CF_3
4i	R_1 = Br	R_2 = methylpiperidine	(from **3b**)	**5i**	R_2 = methylpiperidine
4j	R_1 = Br	R_2 = methylmorpholine	(from **3b**)	**5j**	R_2 = methylmorpholine
4k	R_1 = Br	R_2 = methylpiperazine	(from **3b**)	**5k**	R_2 = methylpiperazine
				5l	R_2 = EtPh (from **4a**)

5a. *6,8-dibenzyl-2,3-dihydroquinolin-4(1H)-one.* **5a** was synthesized following **General Procedure (vi):** To a round-bottom flask containing **4a** (236 mg, 0.75 mmol, 1 equiv.), under inert atmosphere was added degassed, argon-sparged 3:1 acetone/water (12 mL), followed by $Pd(dppf)Cl_2$ (55 mg, 0.08 mmol, 0.1 equiv.), benzyl boronic acid pinacol ester (0.50 mL, 2.24 mmol, 2 equiv.), and K_2CO_3 (310 mg, 2.24 mmol, 3 equiv.), then heated to reflux (85°C) overnight. After 12 hours, reaction mixture was cooled to ambient temperature and diluted with ethyl acetate and aqeuous sodium bicarbonate. Organics were isolated, dried over $MgSO_4$, filtered and reconcentrated onto silica.

Crude reaction mixture was purified by flash chromatography. Yield: 210 mg, 86%. ^{1}H NMR (500 MHz, CDCl3) **δ** 7.72 (d, *J* = 2.0 Hz, 1H), 7.34 – 7.24 (m, 5H), 7.19 (dd, *J* = 7.7, 4.7 Hz, 3H), 7.14 (d, *J* = 7.5 Hz, 2H), 7.07 (d, *J* = 2.1 Hz, 1H), 4.20 (s, 1H), 3.89 (s, 2H), 3.86 (s, 2H), 3.43 (t, *J* = 7.0 Hz, 2H), 2.63 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 194.17, 149.04, 141.42, 138.31, 137.54, 130.25, 128.99, 128.85, 128.60, 128.32, 126.91, 126.20, 126.16, 125.69, 119.86, 42.25, 41.13, 37.92, 37.68.

5b. *6-benzyl-8-methyl-2,3-dihydroquinolin-4(1H)-one.* **5b** was synthesized following General Procedure (vi) from **4b** (300 mg, 1.25 mmol, 1 equiv.), benzyl boronic acid pinacol ester (0.56 mL, 2.50 mmol, 2 equiv.), K_2CO_3 (518 mg, 3.75 mmol, 3 equiv.) and Pd(dppf)Cl_2 (88 mg, 0.12 mmol, 0.1 equiv.). Yield: 223 mg, 71%. ^{1}H NMR (500 MHz, CDCl3) δ 7.64 (d, *J* = 2.1 Hz, 1H), 7.30 – 7.23 (m, 2H), 7.20 – 7.15 (m, 3H), 7.04 – 7.02 (m, 1H), 3.84 (s, 2H), 3.59 (t, *J* = 7.0 Hz, 2H), 2.68 (t, *J* = 6.9 Hz, 2H), 2.10 (s, 3H). ^{13}C NMR (500 MHz, CDCl3) δ 194.24, 149.08, 141.53, 136.80, 130.14, 128.86, 128.59, 126.14, 125.32, 123.34, 119.11, 42.42, 41.17, 38.06, 25.00, 17.05.

5c. *6-benzyl-8-ethyl-2,3-dihydroquinolin-4(1H)-one.* **5c** was synthesized following General Procedure (vi) from **4c** (200 mg, 0.79 mmol, 1 equiv.), benzyl boronic acid pinacol ester (0.35 mL, 1.57 mmol, 2 equiv.), K_2CO_3 (326 mg, 2.36 mmol, 3 equiv.) and Pd(dppf)Cl_2 (58 mg, 0.08 mmol, 0.1 equiv.). Yield: 120 mg, 57%.^{1}H NMR (400 MHz, CDCl3) δ 7.64 (d, *J* = 2.1 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.20 – 7.13 (m, 3H), 7.05 (d, *J* = 2.1 Hz, 1H), 4.39 – 4.31 (m, 1H), 3.86 (s, 2H), 3.57 (td, *J* = 7.1, 1.7 Hz, 2H), 2.71 – 2.64 (m, 2H), 2.44 (q, *J* = 7.5 Hz, 2H), 1.22 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 194.38, 148.55, 141.51, 134.74, 134.71, 130.14, 128.99, 128.81, 128.55, 126.09, 125.24, 125.18, 119.27, 75.12, 42.38, 41.23, 38.07, 24.98, 24.94, 23.58, 12.87, 12.85.

5d. *6-benzyl-8-propyl-2,3-dihydroquinolin-4(1H)-one*. **5d** was synthesized following General Procedure (vi) from **4d** (102 mg, 0.38 mmol, 1 equiv.), benzyl boronic acid pinacol ester (0.17 mL, 0.76 mmol, 2 equiv.), K_2CO_3 (157 mg, 1.14 mmol, 3 equiv.) and Pd(dppf)Cl_2 (28 mg, 0.04 mmol, 0.1 equiv.), with the exception that the reaction was run in a microwave at 110^{o}C for 30 minutes. Yield: 35 mg, 32%. ^{1}H NMR (500 MHz, CDCl3) δ 7.65 (d, *J* = 2.1 Hz, 1H), 7.27 (dd, *J* = 8.5, 6.6 Hz, 2H), 7.20 – 7.17 (m, 3H), 7.03 (d, *J* = 2.1 Hz, 1H), 3.86 (s, 2H), 3.58 (t, *J* = 7.0 Hz, 2H), 2.68 (t, *J* = 6.5 Hz, 2H), 2.41 (t, *J* = 3.9 Hz, 2H), 1.62 (h, *J* = 7.5 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H).

5e. *6-benzyl-8-butyl-2,3-dihydroquinolin-4(1H)-one*. **5e** was synthesized following General Procedure (vi) from **4e** (300 mg, 1.06 mmol, 1 equiv.), benzyl boronic acid pinacol ester (0.47 mL, 2.12 mmol, 2 equiv.), K_2CO_3 (440 mg, 3.18 mmol, 3 equiv.) and Pd(dppf)Cl_2 (81 mg, 0.11 mmol, 0.1 equiv.), except reaction was run in microwave at 110°C for 30 minutes. Yield: 78 mg, 25%. ^{1}H NMR (500 MHz, CDCl3) δ 7.64 (d, *J* = 2.1 Hz, 1H), 7.26 (s, 2H), 7.18 (td, *J* = 8.6, 7.8, 3.5 Hz, 3H), 7.03 (d, *J* = 2.1 Hz, 1H), 3.86 (s, 2H), 3.58 (d, *J* = 7.0 Hz, 2H), 2.70 – 2.67 (m, 2H), 2.41 (d, *J* = 7.8 Hz, 2H), 1.59 – 1.52 (m, 2H), 1.41 – 1.35 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (500 MHz, CDCl3) δ 194.25, 141.53, 135.81, 134.70, 128.84, 128.58, 127.96, 126.55, 126.12, 125.76, 125.40, 42.52, 41.23, 38.11, 30.68, 30.64, 22.83, 14.06.

5f. *6-benzyl-8-(tert-butyl)-2,3-dihydroquinolin-4(1H)-one.* **5f** was synthesized following General Procedure (vi) from **4f** (300 mg, 1.06 mmol, 1 equiv.), benzyl boronic acid pinacol ester (0.47 mL, 2.12 mmol, 2 equiv.), K_2CO_3 (440 mg, 3.18 mmol, 3 equiv.) and Pd(dppf)Cl_2 (81 mg, 0.11 mmol, 0.1 equiv.), except reaction was run in microwave at 110°C for 2 hours. Yield: 87 mg, 28%. ^{1}H NMR (500 MHz, CDCl3) δ 7.70 (d, *J* = 2.1 Hz, 1H), 7.40 – 7.37 (m, 1H), 7.30 – 7.25 (m, 2H), 7.22 (d, *J* = 2.1 Hz, 1H), 7.19 (d, *J* = 7.7 Hz, 2H), 3.87 (s, 2H), 3.62 – 3.57 (m, 2H), 2.69 – 2.65 (m, 2H), 1.39 (d, *J* = 1.0 Hz, 9H). ^{13}C NMR (500 MHz, CDCl3) δ 194.52, 149.25, 141.50, 133.32, 129.81, 128.83, 128.56, 126.08, 125.87, 120.60, 117.41, 42.34, 41.45, 38.10, 34.27, 30.06.

5g. *6-benzyl-8-fluoro-2,3-dihydroquinolin-4(1H)-one.* **5g** was synthesized following General Procedure (vi) from **4g** (75 mg, 0.31 mmol, 1 equiv.), benzyl boronic acid pinacol ester (0.14 mL, 0.61 mmol, 2 equiv.), K_2CO_3 (128 mg, 0.92 mmol, 3 equiv.) and Pd(dppf)Cl_2 (23 mg, 0.03 mmol, 0.1 equiv.). Yield: 29 mg, 37%. ^{1}H NMR (500 MHz, CDCl3) δ 7.54 – 7.51 (m, 1H), 7.32 – 7.24 (m, 2H), 7.22 – 7.19 (m, 1H), 7.18 – 7.14 (m, 2H), 6.94 (dd, *J* = 11.7, 1.9 Hz, 1H), 4.52 (s, 1H), 3.86 (s, 2H), 3.61 (td, *J* = 7.5, 7.1, 1.8 Hz, 2H), 2.75 – 2.68 (m, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 192.90, 152.40, 150.47, 140.70, 139.68, 139.57, 130.23, 128.89, 128.73, 126.45, 122.43, 120.44, 120.30, 42.29, 41.10, 38.20.

5h. *6-benzyl-8-(trifluoromethyl)-2,3-dihydroquinolin-4(1H)-one.* **5h** was synthesized following General Procedure (vi) from **4h** (300 mg, 1.02 mmol, 1 equiv.), benzyl boronic acid pinacol ester (0.45 mL, 2.04 mmol, 2 equiv.), K_2CO_3 (423 mg, 3.06 mmol, 3 equiv.) and Pd(dppf)Cl_2 (73 mg, 0.10 mmol, 0.1 equiv.). Yield: 110 mg, 35%. ^{1}H

NMR (500 MHz, CDCl3) δ 7.92 (d, *J* = 2.2 Hz, 1H), 7.44 (d, *J* = 2.2 Hz, 1H), 7.29 (dd, *J* = 8.2, 6.9 Hz, 2H), 7.23 – 7.18 (m, 1H), 7.17 – 7.14 (m, 2H), 4.96 (s, 1H), 3.89 (s, 2H), 3.64 (td, *J* = 7.0, 2.3 Hz, 2H), 2.75 – 2.67 (m, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 192.72, 147.26, 140.45, 133.27, 132.02, 129.55, 128.81, 126.54, 120.84, 41.84, 40.82, 37.57.

5i. *6-benzyl-8-(piperidin-1-ylmethyl)-2,3-dihydroquinolin-4(1H)-one*. **5i** was synthesized following General Procedure (vi) from mixture of **4i** previously described (105 mg, 0.28 mmol, 1 equiv.), benzyl boronic acid pinacol ester (0.10 mL, 0.43 mmol, 1.5 equiv.), K_2CO_3 (120 mg, 0.86 mmol, 3 equiv.) and Pd(dppf)Cl_2 (21 mg, 0.028 mmol, 0.1 equiv.). Yield: 88 mg, 92%. ^{1}H NMR (500 MHz, CDCl3) δ 7.58 (d, *J* = 2.1 Hz, 1H), 7.18 (d, *J* = 7.0 Hz, 2H), 7.14 – 7.06 (m, 3H), 6.85 (d, *J* = 2.1 Hz, 1H), 3.76 (s, 2H), 3.46 (d, *J* = 7.5 Hz, 2H), 3.36 (s, 2H), 2.56 (d, *J* = 7.0 Hz, 2H), 2.29 – 2.20 (m, 4H), 1.46 (p, *J* = 5.4 Hz, 4H), 1.37 (s, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 194.42, 151.61, 141.51, 136.59, 129.02, 128.82, 128.54, 126.33, 126.09, 119.16, 75.12, 62.58, 54.09, 54.03, 41.75, 41.06, 37.90, 26.26, 24.97, 24.38.

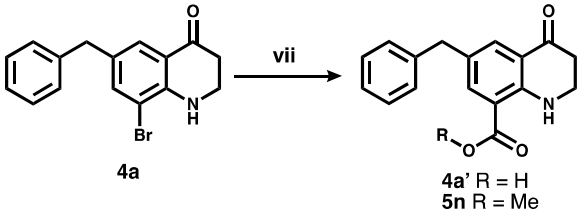
5j. *6-benzyl-8-(morpholinomethyl)-2,3-dihydroquinolin-4(1H)-one.* **5j** was synthesized following General Procedure (vi) from **4j** (160 mg, 0.38 mmol, 1 equiv.), benzyl boronic acid pinacol ester (0.13 mL, 0.57 mmol, 1.5 equiv.), K_2CO_3 (160 mg, 1.14 mmol, 3 equiv.) and Pd(dppf)Cl_2 (30 mg, 0.04 mmol, 0.1 equiv.). Yield: 75 mg, 60%. ^{1}H NMR (500 MHz, CDCl3) δ 7.68 (d, *J* = 2.1 Hz, 1H), 7.26 (s, 2H), 7.22 – 7.13 (m, 3H), 6.96 (d, *J* = 2.2 Hz, 1H), 3.83 (s, 2H), 3.68 (t, *J* = 4.7 Hz, 4H), 3.56 (p, *J* = 5.9 Hz, 2H), 3.47 (s, 2H), 2.65 (dd, *J* = 7.7, 6.5 Hz, 2H), 2.43 – 2.37 (m, 4H). ^{13}C NMR (500 MHz, CDCl3) δ 194.16, 151.08, 141.36, 136.94, 129.29, 128.78, 128.75, 128.56, 128.53, 128.35, 126.77, 126.14, 119.35, 77.16, 67.10, 62.16, 53.22, 53.15, 41.75, 41.01, 37.83, 24.96.

5k. *6-benzyl-8-(piperazin-1-ylmethyl)-2,3-dihydroquinolin-4(1H)-one*. **5k** was synthesized following General Procedure (vi) from **4k** (212 mg, 0.50 mmol, 1 equiv.), benzyl boronic acid pinacol ester (0.22 mL, 1.00 mmol, 2 equiv.), K_2CO_3 (207 mg, 1.50 mmol, 3 equiv.) and Pd(dppf)Cl_2 (37 mg, 0.05 mmol, 0.1 equiv.). Yield: 84 mg, 39%. ^{1}H NMR (500 MHz, CDCl3) δ 7.69 (d, *J* = 2.1 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.20 – 7.14 (m, 3H), 6.94 (d, *J* = 2.2 Hz, 1H), 6.83 (s, 1H), 3.84 (s, 2H), 3.55 (ddd, *J* = 7.7, 5.3, 2.0 Hz, 2H), 3.48 (s, 2H), 3.45 – 3.36 (m, 4H), 2.68 –

2.61 (m, 2H), 2.35 (s, 4H), 1.45 (s, 9H). ^{13}C NMR (500 MHz, CDCl3) δ 194.18, 178.30, 154.82, 151.11, 141.40, 136.90, 129.39, 128.83, 128.61, 126.84, 126.19, 122.69, 119.45, 80.00, 61.88, 52.54, 41.79, 41.05, 37.88, 28.54.

5l. *6-benzyl-8-phenethyl-2,3-dihydroquinolin-4(1H)-one.* **5l** was synthesized following General Procedure (vi) from **4a** (130 mg, 0.41 mmol, 1 equiv.), phenethyl boronic acid MIDA ester (161 mg, 0.62 mmol, 1.5 equiv.), K_2CO_3 (171 mg, 1.24 mmol, 3 equiv.) and Pd(dppf)Cl_2 (30 mg, 0.04 mmol, 0.1 equiv.). Yield: 65 mg, 46%. ^{1}H NMR (500 MHz, CDCl3) δ 7.67 (d, *J* = 2.1 Hz, 1H), 7.26 (s, 4H), 7.24 – 7.18 (m, 2H), 7.15 (dd, *J* = 9.7, 7.7 Hz, 4H), 7.02 (d, *J* = 2.1 Hz, 1H), 3.85 (s, 2H), 3.39 (td, *J* = 7.7, 7.1, 2.1 Hz, 2H), 2.93 – 2.87 (m, 2H), 2.73 (t, *J* = 7.7 Hz, 2H), 2.66 – 2.60 (m, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 194.30, 148.77, 141.43, 141.25, 136.03, 130.18, 128.79, 128.65, 128.55, 128.48, 126.93, 126.40, 126.09, 125.71, 119.56, 42.37, 41.14, 37.97, 35.30, 32.85.

*General Procedure (**vii**) for Carbonylation of **4a** to the Carboxylic Acid Intermediate **4a'** and Methyl Ester **5n***

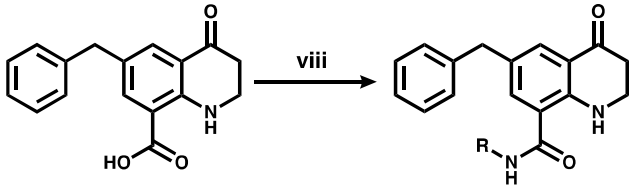


4a'. *6-benzyl-4-oxo-1,2,3,4-tetrahydroquinoline-8-carboxylic acid.* **4a'** was synthesized following **General Procedure (vii):** To a flame-dried glass microwave tube containing degassed 4:1 DMF:H_2O (5 mL) under inert atmosphere was added **4a** (305 mg, 0.97 mmol, 1 equiv.), K_2CO_3 (200 mg, 1.45 mmol, 1.5 equiv.) and Pd(dppf)Cl_2 (71 mg, 0.097 mmol, 0.1 equiv.). To a separate 30 mL pressure tube containing 2M NaOH (15 mL) stirring, with a port from the septum of the pressure tube leading into the reaction solution, was added oxalyl chloride (1 mL total volume). Carbon monoxide generated *in situ* from the decomposition of oxalyl chloride bubbled through the vented reaction mixture 10 minutes. Vent was replaced with a balloon filled with CO, and heated at 80°C for 5 hours. After cooling to ambient temperature, reaction solvents were removed under vacuum and residue was resuspended in ethyl acetate and water at pH 1. Organics were isolated, dried with $MgSO_4$, filtered, and reconcentrated onto silica. Reaction was purified by flash chromatography. Yield: 150 mg, 55%. ^{1}H NMR (500 MHz, CDCl3) δ 8.04 (s, 1H), 8.00 (d, *J* = 2.4 Hz, 1H), 7.98 (d, *J* = 2.3 Hz, 1H), 7.30 – 7.26 (m, 2H), 7.21 – 7.15 (m, 3H), 3.88 (s, 2H), 3.65 (t, *J* =

7.1 Hz, 2H), 2.73 – 2.68 (m, 2H), 2.12 (s, 1H). ^{13}C NMR (500 MHz, CDCl3) δ 193.29, 172.27, 152.62, 140.82, 139.57, 134.93, 128.79, 128.75, 128.29, 126.41, 120.42, 111.83, 40.83, 37.24.

5n. *methyl 6-benzyl-4-oxo-1,2,3,4-tetrahydroquinoline-8-carboxylate.* **5n** was synthesized following General Procedure (vii) from **4a** (220 mg, 0.70 mmol, 1 equiv.), oxalyl chloride (1 mL, excess), K_2CO_3 (142 mg, 1.04 mmol, 1.5 equiv.) and Pd(dppf)Cl_2 (51 mg, 0.07 mmol, 0.1 equiv.) in 1:1 DMF:MeOH. Yield: 103 mg, 50%. ^{1}H NMR (500 MHz, CDCl3) δ 7.93 (s, 2H), 7.30 – 7.26 (m, 2H), 7.21 – 7.14 (m, 3H), 3.86 (s, 2H), 3.85 (s, 3H), 3.63 (td, *J* = 7.1, 2.4 Hz, 2H), 2.69 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 192.93, 167.99, 152.05, 140.82, 133.83, 128.61, 128.55, 127.84, 126.28, 120.14, 112.39, 51.81, 40.71, 40.70, 37.17.

*General Procedure (**viii**) for Amide Coupling of **4a'** to Produce **5m, 5o, 5p***



4a'

5m R = Et
5o R = Ph
5p R = Bn

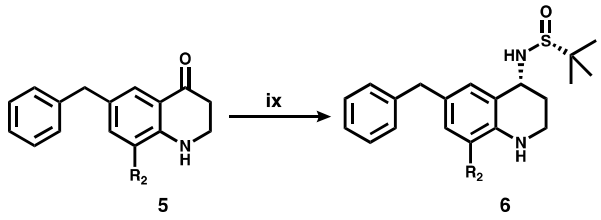
5m. *6-benzyl-N-ethyl-4-oxo-1,2,3,4-tetrahydroquinoline-8-carboxamide.* **5m** was synthesized following **General Procedure (viii):** To a pear-shaped flask containing intermediate **4a'** (78 mg, 0.28 mmol, 1.0 equiv.) dissolved in DMF (3 mL) under inert atmosphere was added PyBOP (172 mg, 0.33 mmol, 1.2 equiv.), ethylamine hydrochloride (27 mg, 0.33 mmol, 1.2 equiv.) and DIPEA (0.15 mL, 0.84 mmol, 3.0 equiv.), and stirred at ambient temperature. After 3 hours, solvent was removed under reduced pressure and reconcentrated residue onto silica. Purified by flash chromatography. Product was highly fluorescent under long-wave UV (285 nm) light. Yield: 66 mg, 77%. ^{1}H NMR (500 MHz, CDCl3) δ 7.86 (d, *J* = 2.0 Hz, 1H), 7.31 – 7.27 (m, 3H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 2H), 3.87 (s, 2H), 3.59 (td, *J* = 7.8, 7.2, 2.3 Hz, 2H), 3.42 (p, *J* = 7.1, 6.5 Hz, 2H), 2.67 (t, *J* = 7.1 Hz, 2H), 1.23 (t, *J* = 7.3 Hz, 3H).

5o. *6-benzyl-4-oxo-N-phenyl-1,2,3,4-tetrahydroquinoline-8-carboxamide.* **6o** was synthesized following General Procedure (viii) from **4a'** (40 mg, 0.14 mmol, 1.0 equiv.), aniline (0.02 mL, 0.18 mmol, 1.2 equiv.), PyBOP (94 mg,

0.18 mmol, 1.2 equiv.) and DIPEA (0.07 mL, 0.42 mmol, 3.0 equiv.). Product was highly fluorescent under 385 nm light. Yield: 30 mg, 60%. ^{1}H NMR (500 MHz, CDCl3) δ 7.89 (d, *J* = 1.8 Hz, 1H), 7.85 (s, 1H), 7.53 (dt, *J* = 8.8, 1.8 Hz, 2H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 3H), 7.27 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.23 – 7.17 (m, 1H), 7.16 (d, *J* = 7.1 Hz, 3H), 3.88 (d, *J* = 1.8 Hz, 2H), 3.59 (tt, *J* = 7.8, 1.8 Hz, 2H), 2.67 (t, *J* = 6.8 Hz, 2H). ^{13}C NMR (500 MHz, CDCl3) δ 193.52, 167.11, 151.49, 140.71, 137.50, 133.96, 132.34, 129.40, 129.21, 129.02, 128.79, 128.01, 126.51, 125.05, 120.95, 120.71, 120.51, 117.83, 77.16, 40.96, 40.85, 37.39.

5p. *N,6-dibenzyl-4-oxo-1,2,3,4-tetrahydroquinoline-8-carboxamide.* **5p** was synthesized following General Procedure (viii) from **4a'** (43 mg, 0.15 mmol, 1.0 equiv.), benzylamine (0.02 mL, 0.18 mmol, 1.2 equiv.), PyBOP (95 mg, 0.18 mmol, 1.2 equiv.) and DIPEA (0.13 mL, 0.75 mmol, 5 equiv.). Yield: 40 mg, 70%. ^{1}H NMR (500 MHz, CDCl3) δ 8.06 (s, 1H), 7.86 (d, *J* = 2.1 Hz, 1H), 7.38 – 7.30 (m, 5H), 7.29 – 7.23 (m, 2H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.15 – 7.10 (m, 2H), 6.51 (t, *J* = 5.9 Hz, 1H), 4.57 (d, *J* = 5.7 Hz, 2H), 3.84 (s, 2H), 3.58 (td, *J* = 7.6, 7.2, 2.3 Hz, 2H), 2.66 (t, *J* = 7.1 Hz, 2H), 1.22 (s, 1H). ^{13}C NMR (500 MHz, CDCl3) δ 193.62, 168.60, 151.49, 140.78, 138.05, 133.96, 132.03, 128.91, 128.74, 128.70, 127.89, 127.77, 127.73, 126.39, 120.40, 117.30, 43.88, 40.95, 40.78, 37.40, 22.22.

*General Procedure (**ix**) for Reductive Amination in the Preparation of Chiral Sulfinamides **6a-q***



5 6

5a	R_2 = Bn	**6a**	R_2 = Bn
5b	R_2 = Me	**6b**	R_2 = Me
5c	R_2 = Et	**6c**	R_2 = Et
5d	R_2 = *n*-Pr	**6d**	R_2 = *n*-Pr
5e	R_2 = *n*-Bu	**6e**	R_2 = *n*-Bu
5f	R_2 = *t*-Bu	**6f**	R_2 = *t*-Bu
5g	R_2 = F	**6g**	R_2 = F
5h	R_2 = CF_3	**6h**	R_2 = CF_3
5i	R_2 = methylpiperidine	**6i**	R_2 = methylpiperidine
5j	R_2 = methylmorpholine	**6j**	R_2 = methylmorpholine
5k	R_2 = methylpiperazine	**6k**	R_2 = methylpiperazine
5l	R_2 = EtPh	**6l**	R_2 = EtPh
5m	R_2 = CONHEt	**6m**	R_2 = CONHEt
5n	R_2 = COOMe	**6n**	R_2 = COOEt
5o	R_2 = CONHPh	**6o**	R_2 = CONHPh
5p	R_2 = CONHBn	**6p**	R_2 = CONHBn
4a	R_2 = Br	**6q**	R_2 = Br (from **4a**)

6a. *(R)-N-((R)-6,8-dibenzyl-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide.* **6a** was synthesized following **General Procedure (ix):** To a pear-shaped flask containing intermediate **5a** (70 mg, 0.21 mmol, 1 equiv.) under inert atmosphere was added (R)-2-methyl-2-propanesulfinamide (104 mg, 0.86 mmol, 4 equiv.), followed by THF (3 mL) at ambient temperature. Reaction mixture was cooled to 0°C before adding $Ti(OEt)_4$ (0.27 mL, 1.28 mmol, 6 equiv.). Upon reaching ambient temperature, reflux condenser under inert atmosphere was affixed and reaction was heated to reflux. After 48 hours, reaction was cooled to ambient temperature, then transferred to a round-bottom flask containing $NaBH_4$ (50 mg, 1.28 mmol, 6 equiv.) under inert atmosphere in THF (3 mL) at -78°C via syringe. Reaction flask was warmed to ambient temperature, and after 3 hours was quenched with saturated aqeuous NaCl. Reaction mixture was diluted with ethyl acetate and saturated aqeuous ammonium chloride. Organics were isolated and dried over $MgSO_4$, filtered and concentrated onto silica. Crude reaction mixture was purified by flash chromatography. Product had a much lower Rf than starting material by TLC in 80% ethyl acetate, 20% hexanes. Yield: 38 mg, 41%. ^{1}H NMR (500 MHz, CDCl3) δ 7.31 – 7.21 (m, 4H), 7.21 – 7.11 (m, 5H), 7.06 (d, *J* = 2.0 Hz, 1H), 6.81 (d, *J* = 2.0 Hz, 1H), 4.57 – 4.48 (m, 1H), 3.84 (d, *J* = 3.0 Hz, 2H), 3.77 (s, 2H), 3.25 (td, *J* = 11.8, 2.7 Hz, 1H), 3.15 (dt, *J* = 11.7, 3.9 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.81 (tt, *J* = 13.2, 3.9 Hz, 1H), 1.19 (s, 9H). ^{13}C NMR (500 MHz, CDCl3) δ 141.97, 141.31, 139.10, 131.26, 129.81, 129.21, 128.81, 128.75, 128.53, 128.46, 126.50, 125.91, 124.70, 121.02, 77.16, 55.42, 49.86, 41.15, 37.88, 36.68, 28.28, 22.76.

6b. *(R)-N-((R)-6-benzyl-8-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide.* **6b** was synthesized following General Procedure (ix) from **5b** (75 mg, 0.30 mmol, 1 equiv.), (R)-2-methyl-2-propanesulfinamide (106 mg, 0.90 mmol, 3 equiv.), and $Ti(OEt)_4$ (0.38 mL, 1.80 mmol, 6 equiv.), then $NaBH_4$ (68 mg, 1.80 mmol, 6 equiv.). Yield: not calculated. ^{1}H NMR (500 MHz, CDCl3) δ 7.29 – 7.22 (m, 1H), 7.20 – 7.12 (m, 3H), 7.00 (d, *J* = 2.0 Hz, 1H), 6.80 (d, *J* = 2.5 Hz, 1H), 4.54 (q, *J* = 3.0 Hz, 1H), 3.82 (d, *J* = 2.7 Hz, 2H), 3.40 (td, *J* = 11.8, 2.8 Hz, 1H), 3.31 (dt, *J* = 11.4, 4.0 Hz, 1H), 2.12 – 2.06 (m, 1H), 2.04 (s, 3H), 1.89 (dddd, *J* = 16.7, 8.1, 4.1, 2.1 Hz, 1H), 1.21 (s, 9H). ^{13}C NMR (500 MHz, CDCl3) δ 142.09, 141.30, 130.69, 129.79, 128.86, 128.50, 125.94, 122.12, 120.17, 116.96, 55.42, 49.71, 41.19, 36.77, 28.34, 22.80, 22.25, 17.31.

6c. *(R)-N-((R)-6-benzyl-8-ethyl-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide.* **6c** was synthesized following General Procedure (ix) from **5c** (100 mg, 0.38 mmol, 1 equiv.), (R)-2-methyl-2-

propanesulfinamide (137 mg, 1.13 mmol, 3 equiv.), and $Ti(OEt)_4$ (0.47 mL, 2.26 mmol, 6 equiv.), then $NaBH_4$ (85 mg, 2.26 mmol, 6 equiv.). Yield: not calculated. ^{1}H NMR (500 MHz, CDCl3) δ 7.28 – 7.23 (m, 2H), 7.21 – 7.16 (m, 2H), 7.16 – 7.14 (m, 1H), 6.99 (d, *J* = 2.0 Hz, 1H), 6.83 (d, *J* = 2.0 Hz, 1H), 4.54 (q, *J* = 2.7, 2.2 Hz, 1H), 3.84 (d, *J* = 2.4 Hz, 2H), 3.38 (td, *J* = 11.8, 2.8 Hz, 1H), 3.33 – 3.26 (m, 1H), 2.38 (q, *J* = 7.5 Hz, 2H), 2.08 (dq, *J* = 13.6, 3.2 Hz, 1H), 1.89 (ttd, *J* = 12.1, 3.9, 1.2 Hz, 1H), 1.23 (t, *J* = 6.3 Hz, 3H), 1.20 (s, 9H). ^{13}C NMR (500 MHz, CDCl3) δ 142.10, 140.76, 129.83, 128.85, 128.52, 128.49, 128.48, 127.72, 125.92, 120.36, 55.42, 55.31, 49.81, 47.33, 41.31, 36.72, 28.35, 24.98, 23.80, 23.73, 22.80, 22.65, 12.84.

6d. *(R)-N-((R)-6-benzyl-8-propyl-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide.* **6d** was synthesized following General Procedure (ix) from **5d** (88 mg, 0.31 mmol, 1 equiv.), (R)-2-methyl-2-propanesulfinamide (115 mg, 0.95 mmol, 3 equiv.), and $Ti(OEt)_4$ (0.40 mL, 1.89 mmol, 6 equiv.), then $NaBH_4$ (71 mg, 1.89 mmol, 6 equiv.). Yield: 20 mg, 17%. ^{1}H NMR (500 MHz, CDCl3) δ 7.21 – 7.18 (m, 1H), 7.16 (d, *J* = 2.4 Hz, 2H), 7.12 – 7.08 (m, 1H), 7.00 (d, *J* = 2.3 Hz, 1H), 6.95 (s, 1H), 6.76 (d, *J* = 1.9 Hz, 1H), 4.45 (d, *J* = 3.0 Hz, 1H), 3.79 – 3.75 (m, 2H), 3.29 (d, *J* = 3.0 Hz, 1H), 3.25 (dt, *J* = 11.5, 4.2 Hz, 2H), 2.27 (t, *J* = 7.8 Hz, 4H), 2.02 (dq, *J* = 13.7, 3.4 Hz, 2H), 1.84 – 1.76 (m, 2H), 1.55 (qd, *J* = 7.2, 4.5 Hz, 3H), 1.15 (d, *J* = 0.9 Hz, 17H), 0.93 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (500 MHz, CDCl3) δ 141.26, 131.32, 130.35, 129.62, 128.78, 128.67, 128.61, 128.44, 128.35, 128.26, 128.12, 125.82, 121.94, 108.32, 55.39, 49.57, 41.12, 36.44, 32.65, 27.75, 22.64, 21.17, 14.13.

6e. *(R)-N-((R)-6-benzyl-8-butyl-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide.* **6e** was synthesized following General Procedure (ix) from **5e** (78 mg, 0.27 mmol, 1 equiv.), (R)-2-methyl-2-propanesulfinamide (97 mg, 0.80 mmol, 3 equiv.), and $Ti(OEt)_4$ (0.34 mL, 1.60 mmol, 6 equiv.), then $NaBH_4$ (61 mg, 1.60 mmol, 6 equiv.). Yield: 89 mg, 84%. ^{1}H NMR (500 MHz, CDCl3) δ 7.20 – 7.14 (m, 1H), 7.11 (d, *J* = 7.3 Hz, 2H), 7.11 – 7.03 (m, 1H), 6.92 (d, *J* = 2.0 Hz, 1H), 6.73 (d, *J* = 2.0 Hz, 1H), 6.58 (t, *J* = 7.5 Hz, 1H), 4.47 (q, *J* = 3.8, 3.3 Hz, 1H), 3.76 (d, *J* = 2.3 Hz, 2H), 3.38 – 3.17 (m, 2H), 2.31 (dt, *J* = 21.0, 7.9 Hz, 2H), 2.02 (ddq, *J* = 13.3, 6.5, 3.2 Hz, 1H), 1.89 – 1.79 (m, 1H), 1.58 – 1.41 (m, 2H), 1.41 – 1.26 (m, 2H), 1.14 (dd, *J* = 5.0, 1.0 Hz, 9H), 0.88 (ddd, *J* = 12.4, 7.8, 6.8 Hz, 3H). ^{13}C NMR (500 MHz, CDCl3) δ 142.12, 131.41, 130.49, 129.57, 128.85, 128.81, 128.53, 128.49, 128.39, 125.92, 120.50, 117.03, 55.44, 49.88, 41.28, 36.77, 30.83, 30.67, 28.42, 23.01, 22.82, 14.11.

6f. *(R)-N-((R)-6-benzyl-8-(tert-butyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide.* **6f** was synthesized following General Procedure (ix) from **5f** (87 mg, 0.30 mmol, 1 equiv.), (R)-2-methyl-2-propanesulfinamide (109 mg, 0.90 mmol, 3 equiv.), and $Ti(OEt)_4$ (0.38 mL, 1.80 mmol, 6 equiv.), then $NaBH_4$ (68 mg, 1.80 mmol, 6 equiv.). Yield: 27 mg, 23%. ^{1}H NMR (500 MHz, CDCl3) δ 7.18 (s, 1H), 7.14 – 7.10 (m, 2H), 7.10 – 7.06 (m, 1H), 6.93 (s, 2H), 6.57 (tt, *J* = 7.7, 2.1 Hz, 1H), 4.45 (d, *J* = 7.2 Hz, 1H), 3.81 – 3.72 (m, 2H), 3.34 – 3.21 (m, 2H), 2.02 – 1.95 (m, 1H), 1.81 (tdd, *J* = 16.7, 8.4, 4.1 Hz, 1H), 1.31 – 1.25 (m, 9H), 1.16 – 1.11 (m, 9H). ^{13}C NMR (500 MHz, CDCl3) δ 142.01, 141.55, 133.25, 131.16, 129.43, 129.16, 129.13, 128.92, 128.84, 128.71, 128.66, 128.45, 127.33, 127.17, 126.46, 126.34, 125.88, 121.13, 116.66, 77.16, 55.40, 50.33, 41.45, 36.56, 29.91, 29.70, 28.06, 22.80.

6g. *(R)-N-((R)-6-benzyl-8-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide.* **6g** was synthesized following General Procedure (ix) from **5g** (25 mg, 0.10 mmol, 1 equiv.), (R)-2-methyl-2-propanesulfinamide (36 mg, 0.30 mmol, 3 equiv.), and $Ti(OEt)_4$ (0.12 mL, 0.60 mmol, 6 equiv.), then $NaBH_4$ (23 mg, 0.60 mmol, 6 equiv.). Yield: 16 mg; 53%. ^{1}H NMR (500 MHz, CDCl3) δ 7.27 (t, *J* = 7.6 Hz, 2H), 7.22 – 7.14 (m, 3H), 6.92 (s, 1H), 6.70 (dd, *J* = 12.0, 1.8 Hz, 1H), 4.55 (q, *J* = 3.3 Hz, 1H), 4.07 (s, 1H), 3.83 (d, *J* = 3.7 Hz, 2H), 3.36 (td, *J* = 11.6, 2.9 Hz, 1H), 3.30 (dt, *J* = 11.4, 4.2 Hz, 1H), 2.11 (dq, *J* = 13.7, 3.4 Hz, 1H), 1.97 – 1.88 (m, 1H), 1.62 (s, 1H), 1.22 (d, *J* = 0.7 Hz, 9H). ^{13}C NMR (500 MHz, CDCl3) δ 141.34, 131.91, 129.73, 128.88, 128.62, 126.23, 125.41, 122.55, 114.87, 114.73, 110.15, 55.58, 49.28, 41.10, 36.09, 28.36, 22.79.

6h. *(R)-N-((R)-6-benzyl-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide.* **6h** was synthesized following General Procedure (ix) from **5h** (110 mg, 0.36 mmol, 1 equiv.), (R)-2-methyl-2-propanesulfinamide (132 mg, 1.08 mmol, 3 equiv.), and $Ti(OEt)_4$ (0.45 mL, 2.16 mmol, 6 equiv.), then $NaBH_4$ (82 mg, 2.16 mmol, 6 equiv.). Yield: 128 mg, 86%. ^{1}H NMR (500 MHz, CDCl3) δ 7.30 – 7.24 (m, 3H), 7.20 – 7.15 (m, 4H), 4.59 (s, 1H), 4.54 (q, *J* = 3.3 Hz, 1H), 3.90 – 3.79 (s, 2H), 3.41 (td, *J* = 12.0, 3.1 Hz, 1H), 3.34 (dt, *J* = 7.8, 4.0 Hz, 1H), 2.10 (dq, *J* = 13.8, 3.5 Hz, 1H), 1.88 (ddt, *J* = 17.0, 12.9, 3.9 Hz, 1H), 1.22 (s, 9H). ^{13}C NMR (500 MHz, CDCl3) δ 141.13, 140.96, 134.78, 128.80, 128.68, 127.21, 126.30, 122.16, 55.63, 49.84, 40.86, 36.30, 27.23, 22.77.

6i. *(R)-N-((R)-6-benzyl-8-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide.* **6i** was synthesized following General Procedure (ix) from **5i** (88 mg, 0.26 mmol, 1 equiv.), (R)-2-methyl-2-propanesulfinamide (96 mg, 0.79 mmol, 3 equiv.), and $Ti(OEt)_4$ (0.33 mL, 1.58 mmol, 6 equiv.), then $NaBH_4$ (60 mg, 1.58 mmol, 6 equiv.). Yield: 85 mg, 74%. Carried forward without characterization.

6j. *(R)-N-((R)-6-benzyl-8-(morpholinomethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide.* **6j** was synthesized following General Procedure (ix) from **5j** (75 mg, 0.22 mmol, 1 equiv.), (R)-2-methyl-2-propanesulfinamide (81 mg, 0.66 mmol, 3 equiv.), and $Ti(OEt)_4$ (0.28 mL, 1.34 mmol, 6 equiv.), then $NaBH_4$ (51 mg, 1.34 mmol, 6 equiv.). Yield: 31 mg, 31%. ^{1}H NMR (500 MHz, CDCl3) δ 7.26 (s, 2H), 7.18 – 7.13 (m, 3H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.74 (d, *J* = 2.1 Hz, 1H), 4.52 (q, *J* = 3.3 Hz, 1H), 3.81 (d, *J* = 3.2 Hz, 2H), 3.67 (t, *J* = 4.7 Hz, 4H), 3.46 (d, *J* = 12.8 Hz, 1H), 3.36 – 3.33 (m, 1H), 3.32 – 3.23 (m, 2H), 2.37 (t, *J* = 10.1 Hz, 4H), 2.10 – 2.02 (m, 1H), 1.89 – 1.79 (m, 1H), 1.21 (s, 9H). ^{13}C NMR (500 MHz, CDCl3) δ 143.41, 141.97, 131.00, 129.99, 128.86, 128.79, 128.46, 125.93, 121.35, 120.64, 116.06, 67.17, 62.46, 53.22, 49.92, 41.08, 36.19, 28.37, 22.78.

6k. *(R)-N-((R)-6-benzyl-8-(piperazin-1-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide.* **6k** was synthesized following General Procedure (ix) from **5k** (84 mg, 0.19 mmol, 1 equiv.), (R)-2-methyl-2-propanesulfinamide (71 mg, 0.58 mmol, 3 equiv.), and $Ti(OEt)_4$ (0.24 mL, 1.16 mmol, 6 equiv.), then $NaBH_4$ (44 mg, 1.16 mmol, 6 equiv.). Yield: 83 mg, 80%. ^{1}H NMR (500 MHz, CDCl3) δ 7.27 – 7.23 (m, 2H), 7.20 – 7.12 (m, 3H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.72 (d, *J* = 2.0 Hz, 1H), 4.53 (q, *J* = 3.3 Hz, 1H), 3.82 (d, *J* = 3.3 Hz, 2H), 3.52 – 3.43 (m, 1H), 3.39 (q, *J* = 6.7, 4.9 Hz, 4H), 3.33 (d, *J* = 13.1 Hz, 2H), 3.27 (ddd, *J* = 11.7, 8.1, 3.4 Hz, 1H), 2.35 – 2.30 (m, 4H), 2.13 – 2.02 (m, 1H), 1.85 (tt, *J* = 13.0, 12.5, 4.0 Hz, 1H), 1.45 (s, 9H), 1.22 (s, 9H). ^{13}C NMR (500 MHz, CDCl3) δ 154.87, 143.41, 141.97, 130.94, 129.99, 128.92, 128.81, 128.49, 125.95, 121.54, 120.68, 79.81, 62.11, 55.45, 52.53, 49.92, 41.10, 36.18, 28.52, 28.36, 22.80, 22.63.

6l. *(R)-N-((R)-6-benzyl-8-phenethyl-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide.* **6l** was synthesized following General Procedure (ix) from **5l** (65 mg, 0.19 mmol, 1 equiv.), (R)-2-methyl-2-propanesulfinamide (70 mg, 0.57 mmol, 3 equiv.), and $Ti(OEt)_4$ (0.24 mL, 1.14 mmol, 6 equiv.), then $NaBH_4$ (44 mg, 1.14 mmol, 6 equiv.). Yield: 61 mg, 72%. Carried forward without characterization.

6m. *(R)-6-benzyl-4-(((R)-tert-butylsulfinyl)amino)-N-ethyl-1,2,3,4-tetrahydroquinoline-8-carboxamide*. **6m** was synthesized following General Procedure (ix) from **5m** (64 mg, 0.21 mmol, 1 equiv.), (R)-2-methyl-2-propanesulfinamide (76 mg, 0.62 mmol, 3 equiv.), and $Ti(OEt)_4$ (0.26 mL, 1.24 mmol, 6 equiv.), then $NaBH_4$ (47 mg, 1.24 mmol, 6 equiv.). Yield: 61 mg, 71%. ^{1}H NMR (500 MHz, CDCl3) δ 7.58 (s, 1H), 7.30 – 7.22 (m, 2H), 7.19 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.15 (dd, *J* = 5.6, 3.1 Hz, 3H), 7.04 (d, *J* = 2.0 Hz, 1H), 5.96 (s, 1H), 4.51 (q, *J* = 2.9 Hz, 1H), 3.83 (s, 2H), 3.39 (qd, *J* = 7.3, 4.9 Hz, 3H), 3.31 (ddd, *J* = 11.9, 5.8, 3.5 Hz, 1H), 3.09 (s, 1H), 2.07 (dt, *J* = 7.0, 3.7 Hz, 1H), 1.83 (tt, *J* = 13.2, 4.1 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.20 (s, 9H). ^{13}C NMR (500 MHz, CDCl3) δ 169.55, 144.90, 141.55, 134.37, 130.65, 129.68, 128.86, 128.76, 128.59, 128.49, 127.73, 126.85, 126.18, 125.96, 121.93, 115.25, 115.01, 55.53, 50.17, 40.90, 35.53, 26.92, 22.78, 22.76, 15.01.

6n. *ethyl (R)-6-benzyl-4-(((R)-tert-butylsulfinyl)amino)-1,2,3,4-tetrahydroquinoline-8-carboxylate.* **6n** was synthesized following General Procedure (ix) from **5n** (42 mg, 0.14 mmol, 1 equiv.), (R)-2-methyl-2-propanesulfinamide (52 mg, 0.42 mmol, 3 equiv.), and $Ti(OEt)_4$ (0.18 mL, 0.85 mmol, 6 equiv.), then $NaBH_4$ (32 mg, 0.85 mmol, 6 equiv.). NMR indicated conversion of **6n** methyl ester to an ethyl ester in **7n**. Yield: 48 mg, 83%. ^{1}H NMR (500 MHz, CDCl3) δ 7.75 (d, *J* = 3.8 Hz, 1H), 7.62 (d, *J* = 2.2 Hz, 1H), 7.21 – 7.16 (m, 2H), 7.15 – 7.07 (m, 4H), 4.44 (q, *J* = 3.0 Hz, 1H), 4.21 (qd, *J* = 7.1, 1.5 Hz, 2H), 3.75 (s, 2H), 3.36 (m, 1H), 3.29 (dt, *J* = 12.0, 4.0 Hz, 1H), 3.00 (s, 1H), 2.02 (dqd, *J* = 13.6, 3.3, 1.1 Hz, 1H), 1.81 – 1.71 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.12 (s, 9H). ^{13}C NMR (500 MHz, CDCl3) δ 168.50, 146.63, 141.63, 136.18, 131.87, 128.72, 128.54, 126.63, 126.08, 121.61, 109.73, 60.37, 55.52, 50.03, 40.89, 35.53, 26.55, 22.73, 14.47.

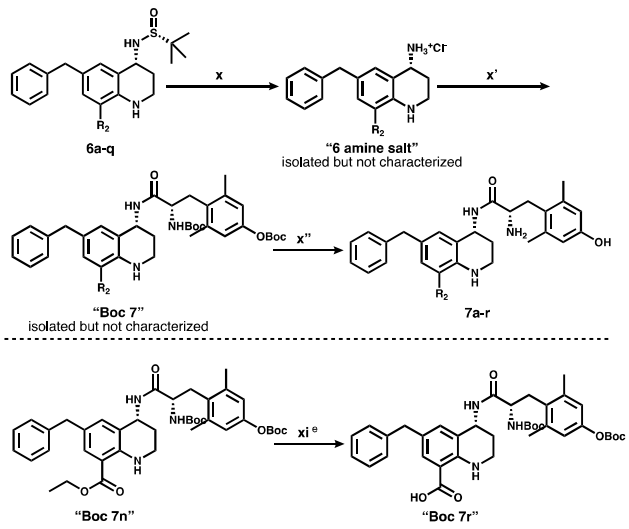
6o. *(R)-6-benzyl-4-(((R)-tert-butylsulfinyl)amino)-N-phenyl-1,2,3,4-tetrahydroquinoline-8-carboxamide.* **6o** was synthesized following General Procedure (ix) from **5o** (42 mg, 0.12 mmol, 1 equiv.), (R)-2-methyl-2-propanesulfinamide (43 mg, 0.36 mmol, 3 equiv.), and $Ti(OEt)_4$ (0.15 mL, 0.72 mmol, 6 equiv.), then $NaBH_4$ (28 mg, 0.72 mmol, 6 equiv.). Yield: 45 mg, 81%. ^{1}H NMR (500 MHz, CDCl3) δ 7.52 (d, *J* = 1.3 Hz, 1H), 7.50 (t, *J* = 1.1 Hz, 1H), 7.37 – 7.32 (m, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.23 – 7.21 (m, 2H), 7.21 – 7.18 (m, 2H), 7.18 – 7.16 (m, 1H), 7.13 (ddt, *J* = 7.6, 6.9, 1.1 Hz, 1H), 4.53 (t, *J* = 2.8 Hz, 1H), 3.87 (d, *J* = 2.9 Hz, 2H), 3.41 (td, *J* = 12.2, 3.3 Hz, 1H), 3.33 (dq, *J* = 7.9, 4.0 Hz, 1H), 3.11 (t, *J* = 1.7 Hz, 1H), 2.08 (dd, *J* = 13.7, 3.5 Hz, 1H), 1.86 (td, *J* = 12.9, 6.5

Hz, 1H), 1.21 (s, 9H). ^{13}C NMR (500 MHz, CDCl3) δ 167.95, 145.34, 141.35, 137.90, 134.96, 129.12, 128.81, 128.68, 127.81, 127.15, 126.31, 124.62, 122.25, 120.78, 114.91, 55.60, 50.21, 40.91, 35.59, 26.80, 22.76.

6p. *(R)-N,6-dibenzyl-4-(((R)-tert-butylsulfinyl)amino)-1,2,3,4-tetrahydroquinoline-8-carboxamide.* **6p** was synthesized following General Procedure (ix) from **5p** (40 mg, 0.11 mmol, 1 equiv.), (R)-2-methyl-2-propanesulfinamide (40 mg, 0.32 mmol, 3 equiv.), and $Ti(OEt)_4$ (0.14 mL, 0.65 mmol, 6 equiv.), then $NaBH_4$ (25 mg, 0.65 mmol, 6 equiv.). Yield: 43 mg, 84%. ^{1}H NMR (500 MHz, CDCl3) δ 7.71 – 7.65 (m, 1H), 7.38 – 7.28 (m, 5H), 7.29 – 7.23 (m, 3H), 7.18 – 7.15 (m, 2H), 7.15 – 7.11 (m, 2H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.26 (s, 1H), 4.56 (dd, *J* = 5.7, 2.7 Hz, 2H), 4.52 (d, *J* = 3.1 Hz, 1H), 3.87 – 3.74 (m, 2H), 3.45 – 3.38 (m, 1H), 3.33 (dq, *J* = 11.9, 4.2 Hz, 1H), 3.09 (s, 1H), 2.11 – 2.04 (m, 1H), 1.84 (ddt, *J* = 16.2, 12.7, 4.1 Hz, 1H), 1.21 (s, 9H). ^{13}C NMR (500 MHz, CDCl3) δ 169.48, 145.21, 141.45, 134.69, 128.89, 128.79, 128.62, 127.87, 127.76, 127.67, 126.88, 126.22, 122.10, 114.50, 55.57, 50.19, 43.81, 40.87, 35.56, 26.85, 22.78.

6q. *(R)-N-((R)-6-benzyl-8-bromo-1,2,3,4-tetrahydroquinolin-4-yl)-2-methylpropane-2-sulfinamide.* **6q** was synthesized following General Procedure (ix) from **4a** (80 mg, 0.25 mmol, 1 equiv.), (R)-2-methyl-2-propanesulfinamide (92 mg, 0.76 mmol, 3 equiv.), and $Ti(OEt)_4$ (0.32 mL, 1.52 mmol, 6 equiv.), then $NaBH_4$ (58 mg, 1.52 mmol, 6 equiv.). Yield: 71 mg, 67%. ^{1}H NMR (500 MHz, CDCl3) δ 7.29 – 7.25 (m, 2H), 7.20 – 7.15 (m, 4H), 7.06 (d, *J* = 1.9 Hz, 1H), 4.52 (q, *J* = 3.2 Hz, 1H), 4.50 (s, 1H), 3.81 (s, 2H), 3.41 (tdd, *J* = 11.9, 3.0, 1.1 Hz, 1H), 3.37 – 3.32 (m, 1H), 2.98 (s, 1H), 2.13 – 2.06 (m, 1H), 1.93 – 1.84 (m, 1H), 1.21 (s, 9H). ^{13}C NMR (500 MHz, CDCl3) δ 141.27, 140.26, 132.57, 130.70, 129.96, 128.85, 128.62, 126.23, 121.86, 109.13, 55.58, 49.86, 40.80, 36.61, 27.91, 22.

*General Procedures (**x, x', x'',** and **xi**) for Sulfinamide Cleavage, Amide Coupling, Boc-Deprotection and Ester Hydrolysis to Produce Final Compounds **7a-r***



6a	R_2 = Bn	**7a**	R_2 = Bn
6b	R_2 = Me	**7b**	R_2 = Me
6c	R_2 = Et	**7c**	R_2 = Et
6d	R_2 = *n*-Pr	**7d**	R_2 = *n*-Pr
6e	R_2 = *n*-Bu	**7e**	R_2 = *n*-Bu
6f	R_2 = *t*-Bu	**7f**	R_2 = *t*-Bu
6g	R_2 = F	**7g**	R_2 = F
6h	R_2 = CF_3	**7h**	R_2 = CF_3
6i	R_2 = methylpiperidine	**7i**	R_2 = methylpiperidine
6j	R_2 = methylmorpholine	**7j**	R_2 = methylmorpholine
6k	R_2 = methylpiperazine	**7k**	R_2 = methylpiperazine
6l	R_2 = EtPh	**7l**	R_2 = EtPh
6m	R_2 = CONHEt	**7m**	R_2 = CONHEt
6n	R_2 = COOEt	**7n**	R_2 = COOEt
6o	R_2 = CONHPh	**7o**	R_2 = CONHPh
6p	R_2 = CONHBn	**7p**	R_2 = CONHBn
6q	R_2 = Br	**7q**	R_2 = Br
		7r [e]	R_2 = COOH (from **6n**)

7a. *(S)-2-amino-N-((R)-6,8-dibenzyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide.* **7a** was synthesized following **General Procedure (x):** To a pear-shaped flask containing **6a** (26 mg, 0.06 mmol, 1 equiv.) was added dioxane (15 mL), followed by concentrated HCl (0.12 mL, excess) at ambient temperature. After 1 hour, solvent was removed and residual oil was washed with diethyl ether. Reaction flask was cooled to 0°C, then ether was decanted leaving the amine salt as a white solid. Carried forward without further purification or characterization. **General Procedure (x')**: To a pear-shaped flask under inert atmosphere was added **6a** amine salt (22 mg, 0.06 mmol, 1 equiv.), di-Boc-Dmt (33 mg, 0.078 mmol, 1.3 equiv.), PyBOP (42 mg, 0.078 mmol, 1.3 equiv.), and 6-Cl HOBt (14 mg, 0.078 mmol, 1.3 equiv.), followed by DMF (10 mL) and DIPEA (0.13 mL, 0.71 mmol, 12 equiv.) at ambient temperature. After stirring 6 hours, solvent was removed under vacuum and residual oil was loaded onto silica. Boc-protected intermediates were purified by flash chromatography, but were generally not characterized by NMR. **General Procedure (x'')**: Isolated Boc-protected product was suspended in DCM (9 mL), and TFA was added (3 mL). After 1 hour, solvent was removed under vacuum and product was resuspended in a solution of 99.9% acetonitrile, 0.1% TFA, then diluted with deionized water. Final products were purified by reverse-phase semi-preparative HPLC. Final yield not calculated. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.20 (dd, J = 8.0, 2.7 Hz, 1H), 7.27 – 7.21 (m, 2H), 7.21 – 7.15 (m, 3H), 7.08 (ddd, J = 23.4, 11.4, 7.1 Hz, 5H), 6.90 (d, J = 3.0 Hz, 1H), 6.71 (d, J = 2.7 Hz, 1H), 6.47 (d, J = 2.3 Hz, 2H), 5.02 – 4.97 (m,

1H), 3.86 (dt, *J* = 11.5, 3.6 Hz, 1H), 3.78 (s, 2H), 3.76 (s, 2H), 3.24 (td, *J* = 12.5, 11.4, 1.9 Hz, 1H), 3.09 (dt, *J* = 12.4, 4.1 Hz, 1H), 3.02 (dt, *J* = 13.9, 3.4 Hz, 1H), 2.55 (t, *J* = 12.0 Hz, 1H), 2.26 (s, 6H), 1.75 (ddt, *J* = 17.8, 10.7, 3.3 Hz, 1H), 1.51 (dd, *J* = 12.9, 5.4 Hz, 1H). HPLC (gradient A): retention time = 44.3 min. ESI-MS 520.3[M + H]+ and 542.3 [M + Na]+.

7b. *(S)-2-amino-N-((R)-6-benzyl-8-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide*. **7b** was synthesized following General Procedures (x) from **6b** (0.30 mmol, 1 equiv.) and concentrated HCl (0.03 mL, excess). Carried forward without characterization following General Procedure (x') from **6b** amine salt (20 mg, 0.070 mmol, 1 equiv.), di-Boc-Dmt (31 mg, 0.076 mmol, 1.1 equiv.), PyBOP (40 mg, 0.076 mmol, 1.1 equiv.), and 6-Cl HOBt (13 mg, 0.076 mmol, 1.1 equiv.), followed by DIPEA (0.12 mL, 0.70 mmol, 10 equiv.). Boc-deprotected following General Procedure (x''). Final yield not calculated. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.22 (td, J = 7.5, 2.0 Hz, 2H), 7.13 (td, J = 8.7, 4.2 Hz, 3H), 7.01 (s, 1H), 6.94 (s, 1H), 6.49 (s, 2H), 4.98 (m, 1H), 3.90 – 3.82 (m, 1H), 3.83 (s, 2H), 3.26 (dd, J = 13.6, 11.6 Hz, 1H), 3.25 – 3.19 (m, 1H), 3.02 (dd, J = 13.5, 5.6 Hz, 1H), 2.76 – 2.64 (m, 1H), 2.27 (s, 6H), 2.14 (s, 3H), 1.90 – 1.78 (m, 1H), 1.63 – 1.54 (m, 1H). HPLC (gradient A): retention time = 28.4 min. ESI-MS 466.3 [M + Na]+.

7c. *(S)-2-amino-N-((R)-6-benzyl-8-ethyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide***.** **7c** was synthesized following General Procedure (x) from **6c** (0.38 mmol, 1 equiv.) and concentrated HCl (0.03 mL, excess). Carried forward without characterization following General Procedure (x') from **6c** amine salt (45 mg, 0.15 mmol, 1 equiv.), di-Boc-Dmt (67 mg, 0.16 mmol, 1.1 equiv.), PyBOP (85 mg, 0.16 mmol, 1.1 equiv.), and 6-Cl HOBt (28 mg, 0.16 mmol, 1.1 equiv.), followed by DIPEA (0.26 mL, 1.50 mmol, 10 equiv.). Boc-deprotected following General Procedure (x''). Final yield not calculated. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.21 (t, *J* = 7.5 Hz, 2H), 7.11 (t, *J* = 8.8 Hz, 3H), 6.77 (d, *J* = 6.1 Hz, 2H), 6.48 (s, 2H), 4.92 (t, *J* = 3.9 Hz, 1H), 3.84 (dd, *J* = 11.6, 5.1 Hz, 1H), 3.76 (s, 2H), 3.29 – 3.22 (m, 1H), 3.09 – 3.02 (m, 1H), 2.99 (dd, *J* = 13.7, 5.1 Hz, 1H), 2.48 (t, *J* = 11.1 Hz, 1H), 2.38 (q, *J* = 7.5 Hz, 2H), 2.27 (s, 6H), 1.70 (t, *J* = 12.7 Hz, 1H), 1.56 – 1.48 (m, 1H), 1.11 (td, *J* = 7.5, 0.9 Hz, 3H). HPLC (gradient A): retention time = 32.1. ESI-MS 480.3 [M + Na]+.

7d. *(S)-2-amino-N-((R)-6-benzyl-8-propyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide*. **7d** was synthesized following General Procedures (x) from **6d** (19 mg, 0.05 mmol, 1 equiv.) and concentrated HCl (0.02 mL, excess). Carried forward without characterization following General Procedure (x') from **6d** amine salt (16 mg, 0.050 mmol, 1 equiv.), di-Boc-Dmt (23 mg, 0.055 mmol, 1.1 equiv.), PyBOP (29 mg, 0.055 mmol, 1.1 equiv.), and 6-Cl HOBt (19 mg, 0.055 mmol, 1.1 equiv.), followed by DIPEA (0.09 mL, 0.50 mmol, 10 equiv.) and stirred 18 hours. Boc-deprotected following General Procedure (x''). Final yield not calculated. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.21 (td, J = 7.3, 1.4 Hz, 2H), 7.16 – 7.08 (m, 3H), 6.85 (dt, J = 5.3, 2.7 Hz, 2H), 6.48 (s, 2H), 4.96 (d, J = 5.1 Hz, 1H), 3.86 (ddd, J = 11.6, 5.2, 2.3 Hz, 1H), 3.80 (d, J = 2.4 Hz, 2H), 3.25 (t, 1H), 3.11 (d, J = 4.0 Hz, 1H), 3.01 (ddd, J = 13.5, 5.3, 2.0 Hz, 1H), 2.58 (tt, J = 10.6, 2.5 Hz, 1H), 2.39 (td, J = 7.9, 3.0 Hz, 2H), 2.27 (s, 7H), 1.76 (dddd, J = 17.9, 14.1, 9.1, 5.3 Hz, 1H), 1.59 – 1.48 (m, 3H), 0.93 (td, J = 7.3, 1.4 Hz, 3H). HPLC (gradient A): retention time = 37.1 min. ESI-MS 494.3 [M + Na]+.

7e. *(S)-2-amino-N-((R)-6-benzyl-8-butyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide*. **7e** was synthesized following General Procedure (x) from **6e** (82 mg, 0.21 mmol, 1 equiv.) and concentrated HCl (0.03 mL, excess). Carried forward without characterization following General Procedure (x') from **6e** amine salt (68 mg, 0.21 mmol, 1 equiv.), di-Boc-Dmt (93 mg, 0.23 mmol, 1.1 equiv.), PyBOP (118 mg, 0.23 mmol, 1.1 equiv.), and 6-Cl HOBt (38 mg, 0.23 mmol, 1.1 equiv.), followed by DIPEA (0.40 mL, 2.1 mmol, 10 equiv.) and stirred 18 hours. Boc-deprotected following General Procedure (x''). Final yield not calculated. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.23 – 7.18 (m, 2H), 7.14 – 7.08 (m, 3H), 6.82 (dq, J = 6.6, 2.2 Hz, 2H), 6.48 (s, 2H), 4.95 (d, J = 4.5 Hz, 1H), 3.86 (ddd, J = 11.6, 5.1, 1.9 Hz, 1H), 3.79 (d, J = 2.3 Hz, 2H), 3.25 (ddd, J = 13.3, 11.6, 1.2 Hz, 1H), 3.11 (dq, J = 12.2, 4.0 Hz, 1H), 3.01 (ddd, J = 13.7, 5.2, 1.8 Hz, 1H), 2.56 (tt, J = 12.2, 3.0 Hz, 1H), 2.40 (td, J = 7.6, 2.6 Hz, 2H), 2.27 (d, J = 1.2 Hz, 6H), 1.79 – 1.70 (m, 1H), 1.56 – 1.44 (m, 2H), 1.34 (hept, J = 7.2, 6.6 Hz, 2H), 0.91 (td, J = 7.3, 1.2 Hz, 3H). HPLC (gradient A): retention time = 40.9 min. ESI-MS 508.3 [M + Na]+.

7f. *(S)-2-amino-N-((R)-6-benzyl-8-(tert-butyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide.* **7f** was synthesized following General Procedure (x) from **6f** (27 mg, 0.068 mmol, 1 equiv.) and concentrated HCl (0.02 mL, excess). Carried forward without characterization following General

Procedure (x') from **6f** amine salt (22 mg, 0.068 mmol, 1 equiv.), di-Boc-Dmt (31 mg, 0.074 mmol, 1.1 equiv.), PyBOP (39 mg, 0.074 mmol, 1.1 equiv.), and 6-Cl HOBt (13 mg, 0.074 mmol, 1.1 equiv.), followed by DIPEA (0.12 mL, 0.67 mmol, 10 equiv.), stirring 18 hours before Boc-deprotecting. Boc-deprotected following General Procedure (x''). Final yield not calculated. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.23 – 7.17 (m, 2H), 7.14 – 7.07 (m, 3H), 6.91 (d, J = 2.2 Hz, 1H), 6.75 (d, J = 2.2 Hz, 1H), 6.49 (d, J = 2.1 Hz, 2H), 4.92 (s, 1H), 3.90 – 3.81 (m, 1H), 3.75 (s, 2H), 3.25 (ddd, J = 13.7, 11.6, 2.3 Hz, 1H), 3.09 (d, J = 12.4 Hz, 1H), 2.99 (ddd, J = 13.8, 5.3, 2.2 Hz, 1H), 2.48 (t, J = 12.1 Hz, 1H), 2.27 (d, J = 2.2 Hz, 6H), 1.67 (t, J = 13.1 Hz, 1H), 1.47 (d, J = 13.3 Hz, 1H), 1.29 (d, J = 2.3 Hz, 9H). HPLC (gradient A): retention time = 44.7 min. ESI-MS 486.3[M + H]+ and 508.3 [M + Na]+.

7g *(S)-2-amino-N-((R)-6-benzyl-8-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide.* **7g** was synthesized following General Procedure (x) from **6g** (19 mg, 0.05 mmol, 1 equiv.) and concentrated HCl (0.03 mL, excess). Carried forward without characterization following General Procedure (x') from **6g** amine salt (55 mg, 0.14 mmol, 1 equiv.), di-Boc-Dmt (60 mg, 0.15 mmol, 1.1 equiv.), PyBOP (73 mg, 0.15 mmol, 1.1 equiv.), and 6-Cl HOBt (24 mg, 0.15 mmol, 1.1 equiv.), followed by DIPEA (0.25 mL, 1.4 mmol, 10 equiv.). Boc-deprotected following General Procedure (x''). Final yield not calculated. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.25 – 7.19 (m, 2H), 7.11 (d, J = 7.7 Hz, 2H), 6.70 (s, 1H), 6.63 (d, J = 12.1 Hz, 1H), 6.48 (s, 2H), 4.93 (s, 1H), 3.84 (dd, J = 11.6, 4.7 Hz, 1H), 3.75 (s, 2H), 3.25 (t, J = 12.6 Hz, 1H), 3.19 – 3.13 (m, 1H), 3.03 (d, J = 8.0 Hz, 1H), 3.00 (d, J = 11.7 Hz, 1H), 2.46 (t, J = 11.7 Hz, 1H), 2.31 – 2.23 (m, 7H), 1.68 (t, J = 12.6 Hz, 1H), 1.50 (d, J = 13.4 Hz, 1H). HPLC (gradient A): retention time = 35.2 min. ESI-MS 470.2 [M + Na]+.

7h. *(S)-2-amino-N-((R)-6-benzyl-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide. 7***h** was synthesized following General Procedure (x) from **6h** (128 mg, 0.31 mmol, 1 equiv.) and concentrated HCl (0.05 mL, excess). Carried forward without characterization following General Procedure (x') from **6h** amine salt (48 mg, 0.140 mmol, 1 equiv.), di-Boc-Dmt (63 mg, 0.154 mmol, 1.1 equiv.), PyBOP (78 mg, 0.154 mmol, 1.1 equiv.), and 6-Cl HOBt (26 mg, 0.154 mmol, 1.1 equiv.), followed by DIPEA (0.25 mL, 1.40 mmol, 10 equiv.). Boc-deprotected following General Procedure (x''). Final yield not calculated. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.21 (d, J = 8.0 Hz, 1H), 7.26 – 7.21 (m, 2H), 7.17 – 7.13 (m, 1H), 7.13 – 7.08 (m, 3H), 7.06 (d, J = 2.1 Hz, 1H), 6.50 – 6.46 (m, 2H), 4.95 (q, J = 4.2 Hz, 1H), 3.84 (dd, J = 11.6, 5.0 Hz, 1H), 3.79 (s,

2H), 3.25 (dd, *J* = 13.6, 11.6 Hz, 1H), 3.08 (dtd, *J* = 12.6, 4.3, 1.2 Hz, 1H), 3.01 (dd, *J* = 13.7, 5.0 Hz, 1H), 2.50 – 2.41 (m, 1H), 1.70 – 1.60 (m, 1H), 1.50 (dq, *J* = 13.2, 3.7 Hz, 1H). ^{13}C NMR (500 MHz, cd_3od) δ 168.36, 157.38, 142.65, 142.38, 140.00, 135.67, 129.64, 129.48, 128.97, 127.69, 127.12, 123.27, 121.87, 116.46, 53.39, 46.76, 41.44, 37.53, 31.94, 28.05, 20.44. HPLC (gradient A): retention time = 42.1 min. ESI-MS 498.24 [M + H]+.

7i. *(S)-2-amino-N-((R)-6-benzyl-8-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide*. **7i** was synthesized following General Procedure (x) from **6i** (85 mg, 0.19 mmol, 1 equiv.) and concentrated HCl (0.05 mL, excess). Carried forward without characterization following General Procedure (x') from **6i** amine salt (37 mg, 0.090 mmol, 1 equiv.), di-Boc-Dmt (41 mg, 0.099 mmol, 1.1 equiv.), PyBOP (52 mg, 0.099 mmol, 1.1 equiv.), and 6-Cl HOBt (17 mg, 0.099 mmol, 1.1 equiv.), followed by DIPEA (0.16 mL, 0.90 mmol, 10 equiv.). Boc-deprotected following General Procedure (x''). Final yield not calculated. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.25 – 7.20 (m, 2H), 7.16 – 7.10 (m, 3H), 7.01 (d, *J* = 2.0 Hz, 1H), 6.96 (d, *J* = 2.1 Hz, 1H), 6.47 (s, 2H), 4.93 (dt, *J* = 7.9, 4.2 Hz, 1H), 4.15 – 4.02 (m, 2H), 3.88 (dd, *J* = 11.6, 5.0 Hz, 1H), 3.79 (s, 2H), 3.37 (d, *J* = 12.4 Hz, 2H), 3.26 (dd, *J* = 13.6, 11.6 Hz, 1H), 3.07 (dt, *J* = 12.4, 4.2 Hz, 1H), 3.02 (dd, *J* = 13.7, 5.1 Hz, 1H), 2.95 – 2.84 (m, 2H), 2.54 – 2.45 (m, 1H), 2.27 (s, 6H), 1.89 (d, *J* = 14.7 Hz, 2H), 1.80 (d, *J* = 12.8 Hz, 1H), 1.71 (m, 2H), 1.65 (m, 1H), 1.53 (q, *J* = 4.2 Hz, 1H), 1.49 (m, 1H). HPLC (gradient A): retention time = 27.6min. ESI-MS 527.3[M + H]+ and 549.3 [M + Na]+.

7j. *(S)-2-amino-N-((R)-6-benzyl-8-(morpholinomethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide*. **7j** was synthesized following General Procedure (x) from **6j** (31 mg, 0.070 mmol, 1 equiv.) and concentrated HCl (0.03 mL, excess). Carried forward without characterization following General Procedure (x') from **6j** amine salt (25 mg, 0.068 mmol, 1 equiv.), di-Boc-Dmt (31 mg, 0.075 mmol, 1.1 equiv.), PyBOP (39 mg, 0.075 mmol, 1.1 equiv.), and 6-Cl HOBt (13 mg, 0.075 mmol, 1.1 equiv.), followed by DIPEA (0.13 mL, 0.70 mmol, 10 equiv.). Boc-deprotected following General Procedure (x''). Final yield not calculated. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.24 – 7.17 (m, 2H), 7.15 – 7.09 (m, 3H), 7.01 (d, *J* = 2.1 Hz, 1H), 6.98 (d, *J* = 2.1 Hz, 1H), 6.47 (s, 2H), 4.92 (m, 1H), 4.17 (m, 2H), 3.88 (m, 1H), 3.88 (broad s, 4H), 3.78 (s, 2H), 3.26 (m, 1H), 3.19 (broad s, 4H), 3.07 (dt, *J* = 12.3, 4.3 Hz, 1H), 3.02 (dd, *J* = 13.7, 5.1 Hz, 1H), 2.49 (td, *J* = 11.9, 2.9 Hz, 1H), 2.27 (s,

6H), 1.64 (ddt, *J* = 13.0, 11.4, 4.1 Hz, 1H), 1.55 – 1.47 (m, 1H). HPLC (gradient A): retention time = 24.2 min. ESI-MS 551.3 [M + Na]+.

7k. *(S)-2-amino-N-((R)-6-benzyl-8-(piperazin-1-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide.* ***7k*** was synthesized following General Procedure (x) from **6k** (43 mg, 0.080 mmol, 1 equiv.) and concentrated HCl (0.015 mL, 0.18 mmol, 2 equiv.). Reaction was monitored by TLC for disappearance of **6k**, and solvent was removed after 12 minutes. Recovered 40 mg crude product. Carried forward without characterization following General Procedure (x') from **6k** amine salt (40 mg, 0.079 mmol, 1 equiv.), diBoc-Dmt (36 mg, 0.087 mmol, 1.1 equiv.), PyBOP (46 mg, 0.087 mmol, 1.1 equiv.), and 6-Cl HOBt (15 mg, 0.087 mmol, 1.1 equiv.), followed by DIPEA (0.14 mL, 0.79 mmol, 10 equiv.). Boc-deprotected following General Procedure (x''). Final yield not calculated. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.20 (t, *J* = 7.4 Hz, 2H), 7.14 – 7.07 (m, 3H), 6.88 (s, 1H), 6.74 (s, 1H), 6.48 (s, 2H), 4.94 (s, 1H), 3.84 (d, *J* = 10.0 Hz, 1H), 3.76 (s, 2H), 3.47 – 3.44 (m, 2H), 3.26 (m, 1H), 3.21 – 3.15 (m, 4H), 3.09 (d, *J* = 12.5 Hz, 1H), 3.01 (dd, *J* = 13.8, 5.0 Hz, 1H), 2.53 (m, 1H), 2.28 (s, 6H), 1.66 (t, *J* = 12.2 Hz, 1H), 1.56 – 1.47 (m, 1H), 1.29 (s, 4H). HPLC (gradient A): retention time = 21.7 min. ESI-MS 528.3[M + H]+ and 550.3 [M + Na]+.

7l. *(S)-2-amino-N-((R)-6-benzyl-8-phenethyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide*. **7l** was synthesized following General Procedure (x) from **6l** (61 mg, 0.14 mmol, 1 equiv.) and concentrated HCl (0.03 mL, excess). Carried forward without characterization following General Procedure (x') from **6l** amine salt (32 mg, 0.084 mmol, 1 equiv.), di-Boc-Dmt (38 mg, 0.093 mmol, 1.1 equiv.), PyBOP (49 mg, 0.093 mmol, 1.1 equiv.), and 6-Cl HOBt (16 mg, 0.093 mmol, 1.1 equiv.), followed by DIPEA (0.15 mL, 0.84 mmol, 10 equiv.). Boc-deprotected following General Procedure (x''). Yield after deprotection: 17 mg, 31% over 2 steps. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.12 (d, *J* = 7.9 Hz, 1H), 7.23 – 7.17 (m, 4H), 7.16 – 7.09 (m, 4H), 7.05 – 7.02 (m, 2H), 6.79 (d, *J* = 2.0 Hz, 1H), 6.70 (d, *J* = 2.0 Hz, 1H), 6.49 (s, 2H), 4.94 (q, *J* = 4.6 Hz, 1H), 3.86 (dd, *J* = 11.6, 5.0 Hz, 1H), 3.72 (s, 2H), 3.25 (dd, *J* = 13.6, 11.6 Hz, 1H), 3.06 (dt, *J* = 12.2, 4.3 Hz, 1H), 3.01 (dd, *J* = 13.6, 5.1 Hz, 1H), 2.81 (t, *J* = 7.6 Hz, 2H), 2.70 (td, *J* = 8.0, 7.5, 4.7 Hz, 2H), 2.51 (td, *J* = 11.8, 2.5 Hz, 1H), 2.28 (s, 6H), 1.76 – 1.67 (m, 1H), 1.55 – 1.47 (m, 1H). HPLC (gradient A): retention time = 45.3 min. ESI-MS 556.3 [M + Na]+.

7m. *(R)-4-((S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamido)-6-benzyl-N-ethyl-1,2,3,4-tetrahydroquinoline-8-carboxamide.* **7m** was synthesized following General Procedure (x) from **6m** (61 mg, 0.15 mmol, 1 equiv.) and concentrated HCl (0.03 mL, excess). Carried forward without characterization following General Procedure (x') from **6m** amine salt (41 mg, 0.12 mmol, 1 equiv.), di-Boc-Dmt (53 mg, 0.13 mmol, 1.1 equiv.), and PyBOP (68 mg, 0.13 mmol, 1.1 equiv.), followed by DIPEA (0.21 mL, 1.19 mmol, 10 equiv.). Boc-deprotected following General Procedure (x''). Final yield not calculated. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.21 (d, J = 7.9 Hz, 1H), 7.22 (t, J = 7.5 Hz, 2H), 7.14 (d, J = 3.9 Hz, 1H), 7.14 – 7.11 (m, 2H), 6.94 (d, J = 2.0 Hz, 1H), 6.47 (s, 2H), 4.92 – 4.87 (m, 0H), 3.82 (dd, J = 11.6, 5.1 Hz, 1H), 3.77 (s, 2H), 3.30 (s, 2H), 3.24 (dd, J = 13.5, 11.6 Hz, 1H), 2.99 (dd, J = 13.4, 4.9 Hz, 2H), 2.40 (td, J = 12.0, 2.6 Hz, 1H), 2.27 (s, 6H), 1.62 (ddt, J = 12.5, 8.3, 4.1 Hz, 1H), 1.50 (dd, J = 13.3, 3.6 Hz, 1H), 1.16 (t, J = 7.2 Hz, 3H). HPLC (gradient A): retention time = 32.5 min. ESI-MS 501.3[M + H]+ and 523.3 [M + Na]+.

7n. *ethyl (R)-4-((S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamido)-6-benzyl-1,2,3,4-tetrahydroquinoline-8-carboxylate.* **7n** was synthesized following General Procedure (x) from **6n** (48 mg, 0.12 mmol, 1 equiv.) and concentrated HCl (0.03 mL, excess). Yield: 40 mg, 99%. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.78 (d, J = 2.2 Hz, 1H), 7.29 – 7.24 (m, 3H), 7.20 – 7.14 (m, 3H), 4.48 (t, J = 4.2 Hz, 1H), 4.33 – 4.26 (m, 2H), 3.86 (s, 2H), 3.56 (dtd, J = 13.1, 4.6, 1.0 Hz, 1H), 3.45 – 3.37 (m, 1H), 2.17 – 2.10 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C NMR (500 MHz, cd_3od) δ 169.20, 147.37, 142.73, 136.75, 134.04, 129.74, 129.51, 128.39, 127.14, 117.52, 111.58, 111.41, 109.38, 61.54, 41.59, 36.22, 26.03, 14.62. Carried forward following General Procedure (x') from **6n** amine salt (30 mg, 0.086 mmol, 1 equiv.), di-Boc-Dmt (41 mg, 0.10 mmol, 1.15 equiv.), PyBOP (52 mg, 0.10 mmol, 1.15 equiv.), and 6-Cl HOBt (17 mg, 0.10 mmol, 1.15 equiv.), followed by DIPEA (0.16 mL, 0.92 mmol, 11 equiv.). Boc-deprotected following General Procedure (x''). Final yield not calculated. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.61 (d, J = 2.2 Hz, 1H), 7.23 (t, J = 7.5 Hz, 2H), 7.15 (d, J = 7.4 Hz, 1H), 7.13 – 7.09 (m, 2H), 7.03 (d, J = 2.2 Hz, 1H), 6.48 (s, 2H), 4.92 (t, J = 4.0 Hz, 1H), 4.24 (qd, J = 7.2, 1.4 Hz, 2H), 3.83 (dd, J = 11.6, 5.0 Hz, 1H), 3.76 (s, 2H), 3.25 (dd, J = 13.6, 11.6 Hz, 1H), 3.12 (dt, J = 12.7, 4.2 Hz, 1H), 3.00 (dd, J = 13.7, 5.1 Hz, 1H), 2.47 (td, J = 12.2, 3.2 Hz, 1H), 2.27 (s, 6H), 1.63 (tt, J = 11.9, 4.2 Hz, 1H), 1.52 (dq, J = 13.2, 3.8 Hz, 1H), 1.31 (t, J = 7.2 Hz, 3H). ^{13}C NMR (500 MHz, cd_3od) δ 168.25, 157.41, 147.68, 142.95, 140.00, 137.00, 135.31, 132.61, 129.62, 129.41, 127.01, 123.26,

121.33, 116.49, 61.28, 53.35, 47.06, 36.90, 31.94, 27.77, 20.43, 14.63. HPLC (gradient A): retention time = 43.1 min. ESI-MS 525.3 [M + Na]+.

7o. *(R)-4-((S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamido)-6-benzyl-N-phenyl-1,2,3,4-tetrahydroquinoline-8-carboxamide.* **7o** was synthesized following General Procedure (x) from **6o** (45 mg, 0.097 mmol, 1 equiv.) and concentrated HCl (0.03 mL, excess). Carried forward without characterization following General Procedure (x') from **6o** amine salt (24 mg, 0.061 mmol, 1 equiv.), di-Boc-Dmt (28 mg, 0.067 mmol, 1.1 equiv.), PyBOP (35 mg, 0.067 mmol, 1.1 equiv.), and 6-Cl HOBt (12 mg, 0.067 mmol, 1.1 equiv.), followed by DIPEA (0.10 mL, 0.61 mmol, 10 equiv.). Boc-deprotected following General Procedure (x''). Final yield not calculated. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.23 (d, J = 7.8 Hz, 1H), 7.59 – 7.53 (m, 2H), 7.42 (d, J = 2.1 Hz, 1H), 7.32 (t, J = 7.8 Hz, 2H), 7.23 (t, J = 7.6 Hz, 2H), 7.19 – 7.15 (m, 2H), 7.15 – 7.09 (m, 1H), 7.00 (d, J = 1.9 Hz, 1H), 6.48 (s, 2H), 4.96 – 4.90 (m, 1H), 3.85 (d, J = 5.1 Hz, 1H), 3.82 (s, 3H), 3.25 (dd, J = 13.6, 11.6 Hz, 1H), 3.09 – 2.96 (m, 2H), 2.44 (t, J = 11.7 Hz, 1H), 2.27 (s, 6H), 1.65 (tt, J = 12.2, 4.2 Hz, 1H), 1.57 – 1.48 (m, 1H). HPLC (gradient A): retention time = 43.0 min. ESI-MS 549.3[M + H]+ and 571.3 [M + Na]+.

7p. *(R)-4-((S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamido)-N,6-dibenzyl-1,2,3,4-tetrahydroquinoline-8-carboxamide.* **7p** was synthesized following General Procedure (x) from **6p** (43 mg, 0.090 mmol, 1 equiv.) and concentrated HCl (0.03 mL, excess). Carried forward without characterization following General Procedure (x') from **6p** amine salt (36 mg, 0.088 mmol, 1 equiv.), diBoc-Dmt (40 mg, 0.097 mmol, 1.1 equiv.), PyBOP (51 mg, 0.097 mmol, 1.1 equiv.), and 6-Cl HOBt (17 mg, 0.097 mmol, 1.1 equiv.), followed by DIPEA (0.15 mL, 0.88 mmol, 10 equiv.). Boc-deprotected following General Procedure (x''). Final yield not calculated. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.20 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 5.5 Hz, 4H), 7.25 – 7.19 (m, 3H), 7.16 – 7.11 (m, 3H), 6.95 (d, J = 2.0 Hz, 1H), 6.47 (s, 2H), 4.90 (s, 1H), 4.52 – 4.42 (m, 2H), 3.83 (dd, J = 11.6, 5.1 Hz, 1H), 3.77 (s, 2H), 3.24 (dd, J = 13.6, 11.6 Hz, 1H), 3.01 (td, J = 13.9, 4.7 Hz, 2H), 2.45 – 2.36 (m, 1H), 2.27 (s, 6H), 1.63 (tt, J = 12.4, 4.2 Hz, 1H), 1.55 – 1.46 (m, 1H). HPLC (gradient A): retention time = 42.0 min. ESI-MS 563.3[M + H]+ and 585.3 [M + Na]+.

7q. *(S)-2-amino-N-((R)-6-benzyl-8-bromo-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide.* **7q** was synthesized following General Procedure (x) from **6q** (71 mg, 0.17 mmol, 1 equiv.) and concentrated HCl (0.03 mL, excess). Carried forward without characterization following General Procedure (x') from **6q** amine salt (62 mg, 0.175 mmol, 1 equiv.), di-Boc-Dmt (78 mg, 0.192 mmol, 1.1 equiv.), PyBOP (99 mg, 0.192 mmol, 1.1 equiv.), and 6-Cl HOBt (32 mg, 0.192 mmol, 1.1 equiv.), followed by DIPEA (0.31 mL, 1.75 mmol, 10 equiv.), stirring 18 hours before Boc-deprotecting. Boc-deprotected following General Procedure (x''). Final yield not calculated. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.16 (d, J = 8.0 Hz, 1H), 7.26 – 7.20 (m, 2H), 7.17 – 7.12 (m, 1H), 7.12 – 7.08 (m, 3H), 6.86 (d, J = 2.0 Hz, 1H), 6.48 (s, 2H), 4.91 (dt, J = 7.9, 4.1 Hz, 1H), 3.83 (dd, J = 11.6, 5.0 Hz, 1H), 3.74 (s, 2H), 3.25 (dd, J = 13.6, 11.6 Hz, 1H), 3.12 – 3.04 (m, 1H), 3.00 (dd, J = 13.7, 5.0 Hz, 1H), 2.46 (td, J = 12.0, 3.0 Hz, 1H), 2.27 (s, 6H), 1.64 (ddt, J = 13.0, 11.6, 4.1 Hz, 1H), 1.50 (dq, J = 13.3, 3.8 Hz, 1H). ^{13}C NMR (500 MHz, cd_3od) δ 168.28, 157.38, 142.79, 141.86, 139.99, 133.41, 131.24, 130.77, 129.66, 129.43, 127.06, 123.26, 121.64, 116.45, 109.56, 53.39, 46.91, 41.45, 37.96, 31.94, 28.75, 20.45. HPLC (gradient A): retention time = 39.9 min. ESI-MS 508.16[M + H]+ and 510.16 [M + Na]+.

7r. *(R)-4-((S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)propanamido)-6-benzyl-1,2,3,4-tetrahydroquinoline-8-carboxylic acid.* **General Procedure (xi):** To a pear-shaped flask containing Boc **7n** (34 mg, 0.048 mmol, 1 equiv.) under inert atmosphere was added 1:1 THF/H_2O (6 mL), followed by LiOH (6 mg, 0.25 mmol, 5 equiv.) at ambient temperature, stirring for 6 hours. Solution was titrated to pH 1 with HCl, then organics were extracted with ethyl acetate. Organics were dried with $MgSO_4$, filtered, and reconcentrated. Crude product was then Boc-deprotected and purified by HPLC following General Procedure (x''). Final yield not calculated. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.62 (d, J = 2.2 Hz, 1H), 7.25 – 7.20 (m, 2H), 7.16 – 7.10 (m, 3H), 7.02 (d, J = 2.3 Hz, 1H), 6.48 (s, 2H), 4.92 (d, J = 5.4 Hz, 1H), 3.83 (dd, J = 11.6, 5.0 Hz, 1H), 3.75 (s, 2H), 3.25 (dd, J = 13.6, 11.6 Hz, 1H), 3.10 (dt, J = 12.2, 3.9 Hz, 1H), 3.00 (dd, J = 13.6, 5.0 Hz, 1H), 2.50 – 2.41 (m, 1H), 2.27 (s, 6H), 1.63 (tt, J = 12.0, 4.2 Hz, 1H), 1.52 (dq, J = 13.0, 3.6 Hz, 1H). HPLC (gradient A): retention time = 31.1 min. ESI-MS 474.3[M + H]+ and 496.3 [M + Na]+.