Placement of hydroxy moiety on pendant of peptidomimetic scaffold modulates mu and kappa opioid receptor efficacy.

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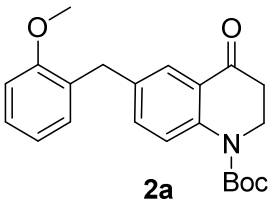
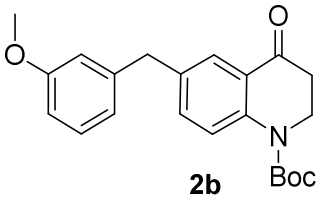
Supplementary Information



2a

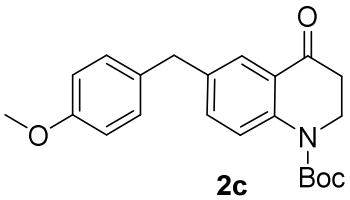
***Tert*-butyl 6-(2-methoxybenzyl)-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (2a).** **2a** was synthesized following general procedure A using **1** (150 mg, 0.44 mmol, 1.0 eq), (2-methoxyphenyl)boronic acid (0.134 mg, 0.88 mmol, 2.0 eq), K_2CO_3 (183 mg, 1.3 mmol, 3.0 eq), and Pd(dppf)Cl_2 (32 mg, 0.04 mmol, 0.1 eq). The contents were placed in a microwave tube and reacted in a microwave with max temp of 110°C, max power of 250 W for 30 min, with the "Powermax" option enabled. Once crude mixture was filtered through Celite, the solvent was removed and the residue was purified via silica gel chromatography to yield title compound **2a** (105 mg, 64.8%) as clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 2.2 Hz, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.26 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 7.4 Hz, 1H), 6.79 – 6.72 (m, 2H), 4.02 (t, *J* = 6.3 Hz, 2H), 3.85 (s, 2H), 3.70 (s, 3H), 2.63 (t, *J* = 6.3 Hz, 2H), 1.45 (d, *J* = 1.3 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.19, 157.11, 152.67, 141.97, 136.78, 134.63, 130.12, 128.78, 127.55, 127.06, 124.60, 123.45, 120.40, 110.32, 81.82, 55.15, 44.15, 38.90, 35.13, 28.17.



2b

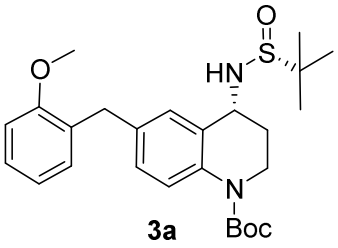
***Tert*-butyl 6-(3-methoxybenzyl)-4-oxo-3,4-dihydroquinoline-1(2 *H*)-carboxylate (2b).** **2b** was synthesized following general procedure A using **1** (150 mg, 0.44 mmol, 1.0 eq), (3-methoxyphenyl)boronic acid (0.134 mg, 0.88 mmol, 2.0 eq), K_2CO_3 (183 mg, 1.3 mmol, 3.0 eq), and Pd(dppf)Cl_2 (32 mg, 0.04 mmol, 0.1 eq). The contents were placed in a microwave tube and reacted in a microwave with max temp of 110°C, max power of 250 W for 30 min, with the "Powermax" option enabled. Once crude mixture was filtered through Celite, the solvent was removed and the residue was purified via silica gel chromatography to yield title compound **2b** (72 mg, 44.4%) as clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (q, *J* = 5.9, 4.4 Hz, 1H), 7.68 (dt, *J* = 9.6, 4.8 Hz, 1H), 7.32 (dt, *J* = 8.5, 2.8 Hz, 1H), 7.20 (tq, *J* = 9.8, 6.3, 4.8 Hz, 1H), 6.82 – 6.65 (m, 3H), 4.18 – 4.06 (m, 2H), 3.92 (t, *J* = 5.3 Hz, 2H), 3.82 – 3.69 (m, 3H), 2.80 – 2.67 (m, 2H), 1.61 – 1.45 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.20, 159.68, 152.68, 142.35, 141.92, 136.63, 134.56, 129.47, 127.08, 124.72, 123.78, 121.18,

114.63, 111.43, 82.02, 55.08, 44.20, 41.09, 38.92, 28.23.



2c

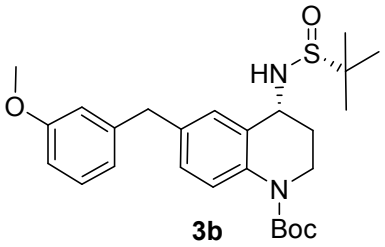
***Tert*-butyl 6-(4-methoxybenzyl)-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (2c). 2c** was synthesized following general procedure A using **1** (150 mg, 0.44 mmol, 1.0 eq), (4-methoxyphenyl)boronic acid (0.134 mg, 0.88 mmol, 2.0 eq), K_2CO_3 (183 mg, 1.3 mmol, 3.0 eq), and Pd(**dppf**)Cl_2 (32 mg, 0.04 mmol, 0.1 eq). The contents were placed in a microwave tube and reacted in a microwave with max temp of 110°C, max power of 250 W for 30 min, with the "Powermax" option enabled. Once crude mixture was filtered through Celite, the solvent was removed and the residue was purified via silica gel chromatography to yield title compound **2c** (110 mg, 67.9%) as clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 2.2 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.21 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.73 (d, *J* = 8.3 Hz, 2H), 4.03 (t, *J* = 6.3 Hz, 2H), 3.80 (s, 2H), 3.67 (s, 3H), 2.65 (t, *J* = 6.3 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.23, 157.97, 152.66, 142.20, 137.27, 134.45, 132.41, 129.67, 126.88, 124.67, 123.72, 115.90, 114.62, 113.88, 81.97, 55.12, 44.16, 40.14, 38.88, 28.18.



3a

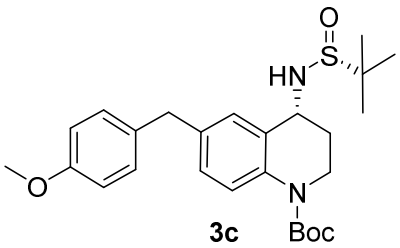
***Tert*-butyl (*R*)-4-(((*R*)-*tert*-butylsulfinyl)amino)-6-(2-methoxybenzyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (3a). 3a** was synthesized following general procedure B using **2a** (105 mg, 0.28 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (104 mg, 0.86 mmol, 3.0 eq), and $Ti(OEt)_4$ (0.359 mL, 1.71 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing $NaBH_4$ (65 mg, 1.71 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound **3a** (60 mg, 44.4%) as clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.5 Hz, 1H), 7.22 – 7.14 (m, 2H), 7.13 – 7.05 (m, 2H), 6.90 – 6.81 (m, 2H), 4.52 (bs, 1H), 3.99 – 3.87 (m,

3H), 3.82 (s, 3H), 3.61 – 3.50 (m, 1H), 3.30 (s, 1H), 2.24 – 2.12 (m, 1H), 1.99 – 1.90 (m, 1H), 1.50 (s, 9H), 1.20 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.19, 153.57, 136.54, 136.24, 130.21, 129.35, 128.98, 128.68, 128.34, 127.43, 123.79, 120.43, 110.35, 80.99, 55.59, 55.27, 50.25, 39.95, 35.09, 29.33, 28.31, 22.57.



3b

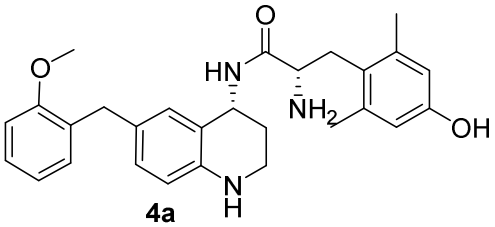
***Tert*-butyl (*R*)-4-(((*R*)-*tert*-butylsulfinyl)amino)-6-(3-methoxybenzyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (3b). 3b** was synthesized following general procedure B using **2b** (72 mg, 0.2 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (71 mg, 0.59 mmol, 3.0 eq), and $Ti(OEt)_4$ (0.246 mL, 1.18 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing $NaBH_4$ (44 mg, 1.18 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound **3b** (44 mg, 47.3%) as clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 8.4 Hz, 1H), 7.22 – 7.16 (m, 2H), 7.07 (dd, J = 8.5, 2.2 Hz, 1H), 6.78 (d, J = 7.7 Hz, 1H), 6.75 – 6.70 (m, 2H), 4.52 (q, J = 3.5 Hz, 1H), 3.94 (dt, J = 12.9, 4.5 Hz, 1H), 3.88 (s, 2H), 3.77 (s, 3H), 3.61 – 3.53 (m, 1H), 3.33 (s, 1H), 2.18 (dq, J = 14.1, 4.0 Hz, 1H), 2.02 – 1.90 (m, 1H), 1.50 (s, 9H), 1.20 (s, 9H).^{13}C NMR (126 MHz, $CDCl_3$) δ 159.63, 153.50, 142.41, 136.50, 136.37, 129.37, 128.93, 128.54, 128.53, 123.96, 121.23, 114.61, 111.33, 81.05, 55.62, 55.07, 50.41, 41.16, 40.01, 29.41, 28.28, 22.53.



3c

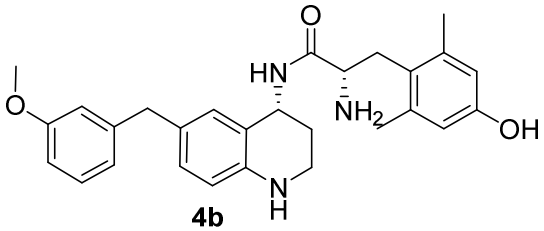
***Tert*-butyl (*R*)-4-(((*R*)-*tert*-butylsulfinyl)amino)-6-(4-methoxybenzyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (3c). 3c** was synthesized following general procedure B using **2c** (110 mg, 0.3 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (109 mg, 0.9 mmol, 3.0 eq), and $Ti(OEt)_4$ (0.377 mL, 1.80 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was

converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing $NaBH_4$ (68 mg, 1.8 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound **3c** (136 mg, 96.5%) as clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.5 Hz, 1H), 7.16 (d, *J* = 2.0 Hz, 1H), 7.10 – 7.06 (m, 2H), 7.03 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.81 – 6.76 (m, 2H), 4.50 (q, *J* = 3.6 Hz, 1H), 3.91 (dt, *J* = 12.9, 4.6 Hz, 1H), 3.83 (s, 2H), 3.74 (s, 3H), 3.62 – 3.51 (m, 1H), 3.39 (bs, 1H), 2.16 (dq, *J* = 13.7, 4.3 Hz, 1H), 1.95 – 1.89 (m, 1H), 1.48 (s, 9H), 1.18 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.78, 153.40, 136.93, 136.25, 132.88, 129.74, 129.61, 128.70, 128.46, 128.30, 123.83, 113.75, 113.72, 80.90, 55.54, 55.04, 50.38, 40.11, 39.96, 29.34, 28.16, 22.43.



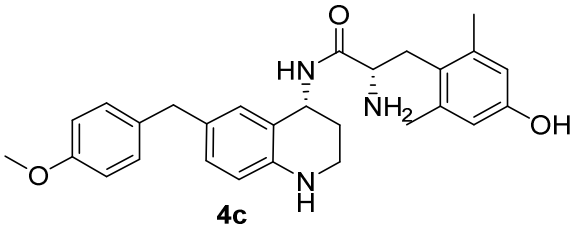
4a

(*S*)-2-Amino-3-(4-hydroxy-2,6-dimethylphenyl)-*N*-((*R*)-6-(2-methoxybenzyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide (4a). 4a was synthesized following general procedure C using **3a** (60 mg, 0.13 mmol, 1.0 eq) and conc. HCl (5 drops). After removing solvent, residue was re-suspended in Et_2O, and solid crashed out. After washing the solid 3 x with fresh Et_2O, the remaining Et_2O was decanted off, yielding a white solid amine hydrochloride salt (51 mg). The synthesis was completed by following general procedure D with newly formed (*R*) amine intermediate (51 mg, 0.13 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **4a** as a TFA salt. Not all final product was purified, therefore no yield was calculated. ^{1}H NMR (500 MHz, CD_3OD) δ 7.14 (ddd, *J* = 9.2, 7.5, 1.8 Hz, 1H), 6.97 – 6.93 (m, 2H), 6.88 (ddd, *J* = 8.0, 6.0, 1.5 Hz, 2H), 6.80 (td, *J* = 7.5, 1.1 Hz, 1H), 6.57 (d, *J* = 8.3 Hz, 1H), 6.48 (s, 2H), 4.92 (t, *J* = 4.4 Hz, 1H), 3.85 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.81 – 3.72 (m, 5H), 3.25 (dd, *J* = 13.7, 11.5 Hz, 1H), 3.01 (dt, *J* = 13.4, 5.1 Hz, 2H), 2.52 (td, *J* = 11.7, 2.7 Hz, 1H), 2.27 (s, 6H), 1.80 – 1.69 (m, 1H), 1.54 (dd, *J* = 12.8, 5.9 Hz, 1H). No ^{13}C data acquired. HPLC (gradient A): retention time 26.5. ESI-MS 482.2 $[M+Na]^+$.



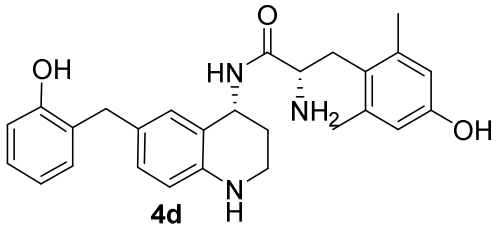
4b

(*S*)-2-Amino-3-(4-hydroxy-2,6-dimethylphenyl)-*N*-((*R*)-6-(3-methoxybenzyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide (4b). 4b was synthesized following general procedure C using **3b** (44 mg, 0.093 mmol, 1.0 eq) and conc. HCl (5 drops). After removing solvent, residue was re-suspended in Et_2O, and solid crashed out. After washing the solid 3 x with fresh Et_2O, the remaining Et_2O was decanted off, yielding a white solid amine hydrochloride salt (38 mg). The synthesis was completed by following general procedure D with newly formed (*R*) amine intermediate (38 mg, 0.13 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **4b** as a TFA salt. Not all final product was purified, therefore no yield was calculated. ^{1}H NMR (500 MHz, CD_3OD) δ 7.90 (dd, *J* = 9.0, 1.1 Hz, 0H), 7.76 (d, *J* = 1.4 Hz, 0H), 7.43 (dt, *J* = 8.8, 1.6 Hz, 0H), 7.15 – 7.09 (m, 1H), 6.95 (s, 1H), 6.91 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.70 (t, *J* = 6.5 Hz, 2H), 6.65 (d, *J* = 2.3 Hz, 1H), 6.62 (d, *J* = 8.3 Hz, 1H), 6.48 (s, 2H), 4.96 – 4.91 (m, 1H), 3.85 (dd, *J* = 11.6, 5.1 Hz, 1H), 3.77 (s, 2H), 3.72 (d, *J* = 1.1 Hz, 3H), 3.28 – 3.21 (m, 1H), 3.02 (ddd, *J* = 18.3, 14.0, 4.8 Hz, 2H), 2.55 (td, *J* = 11.9, 2.4 Hz, 1H), 2.27 (s, 7H), 1.80 – 1.70 (m, 1H), 1.57 – 1.48 (m, 1H). No ^{13}C data acquired. HPLC (gradient A): retention time 25.6. ESI-MS 482.2 $[M+Na]^+$.



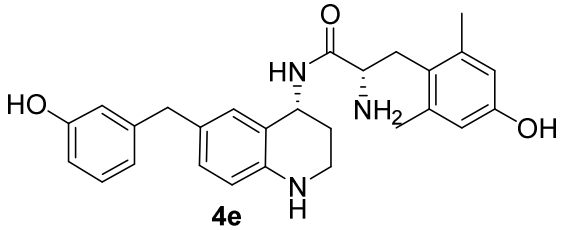
4c

(*S*)-2-Amino-3-(4-hydroxy-2,6-dimethylphenyl)-*N*-((*R*)-6-(4-methoxybenzyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide (4c). 4c was synthesized following general procedure C using **3c** (136 mg, 0.29 mmol, 1.0 eq) and conc. HCl (5 drops). After removing solvent, residue was re-suspended in Et_2O, and solid crashed out. After washing the solid 3 x with fresh Et_2O, the remaining Et_2O was decanted off, yielding a white solid amine hydrochloride salt (117 mg). The synthesis was completed by following general procedure D with newly formed (*R*) amine intermediate (117 mg, 0.13 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **4c** as a TFA salt. Not all final product was purified, therefore no yield was calculated. ^{1}H NMR (500 MHz, CD_3OD) δ 7.09 (d, *J* = 2.0 Hz, 1H), 7.05 – 7.01 (m, 3H), 6.86 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.80 – 6.76 (m, 2H), 6.49 (s, 2H), 5.00 (t, *J* = 4.8 Hz, 1H), 3.89 (ddd, *J* = 11.6, 5.2, 1.2 Hz, 1H), 3.80 (s, 2H), 3.73 (d, *J* = 1.3 Hz, 3H), 3.29 – 3.22 (m, 1H), 3.16 (dt, *J* = 12.8, 4.4 Hz, 1H), 3.05 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.72 – 2.65 (m, 1H), 2.27 (s, 6H), 1.87 (ddt, *J* = 14.7, 10.5, 4.0 Hz, 1H), 1.63 – 1.54 (m, 1H). Not all final product was purified, therefore no yield was calculated. No ^{13}C data acquired. HPLC (gradient A): retention time 24.7. ESI-MS 482.2 $[M+Na]^+$.



4d

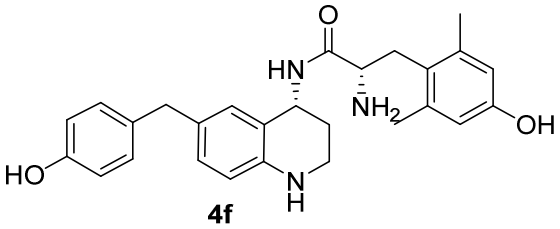
(*S*)-2-Amino-3-(4-hydroxy-2,6-dimethylphenyl)-*N*-((*R*)-6-(2-hydroxybenzyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide (4d). 4d was synthesized following general procedure C using **3a** (60 mg, 0.13 mmol, 1.0 eq) and conc. HCl (5 drops). After removing solvent, residue was re-suspended in Et_2O, and solid crashed out. After washing the solid 3 x with fresh Et_2O, the remaining Et_2O was decanted off, yielding a white solid amine hydrochloride salt (38 mg). The synthesis was completed by following a modified version general procedure E with newly formed (*R*) amine intermediate (38 mg, 0.13 mmol, 1.0 eq). After coupling to diBoc-Dmt, instead of using TFA:DCM to deprotect, .a 1M solution of BBr_3 in DCM (0.316 mL, 5.0 eq) was slowly added to the reaction vessel to remove the boc groups and cleave the methyl ether. Once completely added, solution stirred for 3 h. After 3 h, solvent was removed under reduced pressure and residue was resuspended in MeOH, then solvent was moved. This process was repeated 3 x to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **4d** as a TFA salt. Not all final product was purified, therefore no yield was calculated. ^{1}H NMR (500 MHz, CD_3OD) δ 7.12 (d, *J* = 2.4 Hz, 1H), 7.07 (dd, *J* = 8.1, 2.4 Hz, 1H), 7.02 – 6.97 (m, 1H), 6.96 – 6.92 (m, 1H), 6.81 (dd, *J* = 8.3, 2.9 Hz, 1H), 6.76 – 6.67 (m, 2H), 6.49 (d, *J* = 2.7 Hz, 2H), 4.99 (q, *J* = 4.3 Hz, 1H), 3.85 (tdd, *J* = 14.7, 11.5, 4.3 Hz, 3H), 3.25 (ddd, *J* = 14.4, 11.5, 3.0 Hz, 1H), 3.07 – 3.00 (m, 1H), 2.70 – 2.60 (m, 1H), 2.27 (d, *J* = 2.9 Hz, 6H), 1.87 (ddt, *J* = 14.3, 10.6, 4.0 Hz, 1H), 1.59 (dd, *J* = 12.8, 6.2 Hz, 1H). No ^{13}C data acquired. HPLC (gradient A): retention time 21.3. ESI-MS 468.2 $[M+Na]^+$.



4e

(*S*)-2-Amino-3-(4-hydroxy-2,6-dimethylphenyl)-*N*-((*R*)-6-(3-hydroxybenzyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide (4e). 4e was synthesized following general procedure C using **3b** (44 mg, 0.093 mmol, 1.0 eq) and conc. HCl (5 drops). After removing solvent, residue was re-suspended in Et_2O, and solid crashed out. After washing the solid 3 x with fresh Et_2O, the remaining Et_2O was decanted off, yielding a white solid amine hydrochloride salt (38 mg). The synthesis was completed by following a modified version general procedure E with newly formed (*R*) amine intermediate (38 mg,

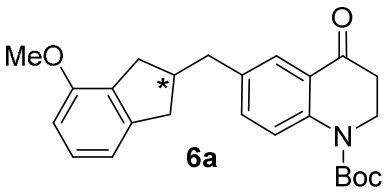
0.13 mmol, 1.0 eq). After coupling to diBoc-Dmt, instead of using TFA:DCM to deprotect, a 1M solution of BBr_3 in DCM (0.132 mL, 5.0 eq) was slowly added to the reaction vessel to remove the boc groups and cleave the methyl ether. Once completely added, solution stirred for 3 h. After 3 h, solvent was removed under reduced pressure and residue was resuspended in MeOH, then solvent was moved. This process was repeated 3 x to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **4e** as a TFA salt. Not all final product was purified, therefore no yield was calculated. ^{1}H NMR (500 MHz, CD_3OD) δ 7.03 (td, *J* = 7.8, 1.3 Hz, 1H), 7.00 (s, 1H), 6.97 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.69 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.62 – 6.55 (m, 2H), 6.54 (d, *J* = 2.0 Hz, 1H), 6.48 (s, 2H), 4.99 – 4.93 (m, 1H), 3.91 – 3.83 (m, 1H), 3.75 (s, 2H), 3.29 – 3.22 (m, 1H), 3.08 (dt, *J* = 12.2, 4.2 Hz, 1H), 3.02 (dd, *J* = 13.6, 5.1 Hz, 1H), 2.59 (t, *J* = 11.3 Hz, 1H), 2.30 – 2.24 (m, 6H), 1.83 – 1.74 (m, 1H), 1.54 (dd, *J* = 11.5, 4.8 Hz, 1H). No ^{13}C data acquired. HPLC (gradient A): retention time 20.5. ESI-MS 468.2 $[M+Na]^+$.



4f

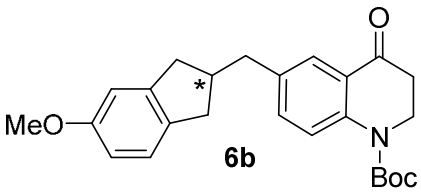
(*S*)-2-Amino-3-(4-hydroxy-2,6-dimethylphenyl)-*N*-((*R*)-6-(4-hydroxybenzyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide (4f). 4f was synthesized following general procedure C using **3c** (136 mg, 0.029 mmol, 1.0 eq) and conc. HCl (5 drops). After removing solvent, residue was re-suspended in Et_2O, and solid crashed out. After washing the solid 3 x with fresh Et_2O, the remaining Et_2O was decanted off, yielding a white solid amine hydrochloride salt (38 mg). The synthesis was completed by following a modified version general procedure E with newly formed (*R*) amine intermediate (117 mg, 0.13 mmol, 1.0 eq). After coupling to diBoc-Dmt, instead of using TFA:DCM to deprotect, a 1M solution of BBr_3 in DCM (0.375 mL, 5.0 eq) was slowly added to the reaction vessel to remove the boc groups and cleave the methyl ether. Once completely added, solution stirred for 3 h. After 3 h, solvent was removed under reduced pressure and residue was resuspended in MeOH, then solvent was moved. This process was repeated 3 x to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **4f** as a TFA salt. Not all final product was purified, therefore no yield was calculated. ^{1}H NMR (500 MHz, CD_3OD) δ 7.05 (s, 1H), 7.01 (d, *J* = 8.7 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 2H), 6.80 (d, *J* = 8.2 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 2H), 6.49 (s, 2H), 4.99 (t, *J* = 4.7 Hz, 1H), 3.88 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.76 (s, 2H), 3.26 (t, *J* = 12.7 Hz, 1H), 3.14 (dt, *J* = 12.7, 4.2 Hz, 1H), 3.03 (dd, *J* = 13.7, 5.2 Hz, 1H), 2.69 – 2.61 (m, 1H), 2.27 (s, 6H), 1.85 (tt, *J* = 11.0, 4.2 Hz, 1H), 1.56 (d, *J* =

14.9 Hz, 1H). No ^{13}C data acquired. HPLC (gradient A): retention time 18.9. ESI-MS 468.2 $[M+Na]^+$.



6a

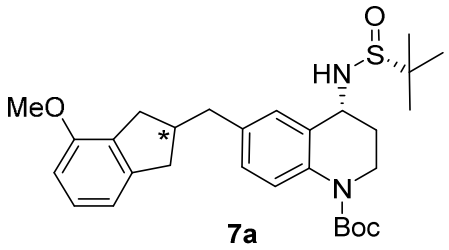
***Tert*-butyl 6-((4-methoxy-2,3-dihydro-1*H*-inden-2-yl)methyl)-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (6a). 6a** was synthesized following general procedure F using **5a** (118 mg, 0.384 mmol, 1.0 eq), Boc_2O (101 mg, 0.46 mmol, 2.0 eq), DMAP (5 mg, 0.038 mmol, 0.1 eq), DIPEA (0.08 mL, 0.46 mmol, 2.0 eq). The reaction stirred at reflux for 16 h. Once enough starting material was converted to product, the crude yellow oil was purified using silica gel chromatography to yield the title compound **6a** (83 mg, 53.2%) as a clear, colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 2.3 Hz, 1H), 7.71 (d, J = 8.6 Hz, 1H), 7.36 (dd, J = 8.3, 2.1 Hz, 1H), 7.11 (t, J = 7.8 Hz, 1H), 6.79 (d, J = 7.4 Hz, 1H), 6.65 (d, J = 8.1 Hz, 1H), 4.15 (t, J = 6.3 Hz, 2H), 3.80 (s, 3H), 2.99 (dt, J = 16.0, 6.4 Hz, 2H), 2.81 – 2.72 (m, 5H), 2.71 – 2.62 (m, 1H), 2.61 – 2.52 (m, 1H), 1.57 (d, J = 1.4 Hz, 9H), 1.53 (d, J = 4.3 Hz, 1H), 1.47 (d, J = 1.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.22, 155.91, 152.71, 144.80, 142.14, 137.02, 134.62, 130.34, 127.57, 126.96, 124.67, 123.56, 116.87, 107.77, 81.92, 55.02, 44.24, 40.75, 40.71, 39.04, 38.95, 35.20, 28.23.



6b

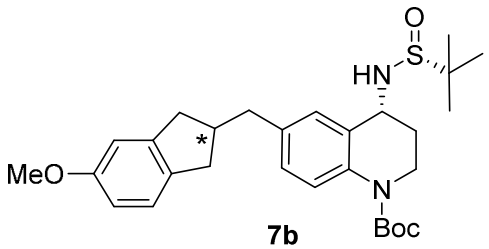
***Tert*-butyl 6-((5-methoxy-2,3-dihydro-1*H*-inden-2-yl)methyl)-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (6b). 6b** was synthesized following general procedure F using **5b** (100 mg, 0.325 mmol, 1.0 eq), Boc_2O (85 mg, 0.39 mmol, 2.0 eq), DMAP (4 mg, 0.033 mmol, 0.1 eq), DIPEA (0.068 mL, 0.39 mmol, 2.0 eq). The reaction stirred at reflux for 16 h. Once enough starting material was converted to product, the crude yellow oil was purified using silica gel chromatography to yield the title compound **6b** (47 mg, 35.3%) as a clear, colorless oil. Not all final product was purified, therefore no yield was calculated. ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.39 – 7.30 (m, 1H), 7.05 (d, J = 8.1 Hz, 1H), 6.73 (s, 1H), 6.68 (d, J = 7.9 Hz, 1H), 4.15 (t, J = 6.3 Hz, 2H), 3.76 (s, 3H), 2.93 (ddd, J = 18.8, 10.9, 4.1 Hz, 2H), 2.75 (d, J = 6.9 Hz, 6H), 2.60 (ddd, J = 20.8, 14.5, 4.4 Hz, 3H), 1.56 (s, 11H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.28, 158.58, 152.74, 144.39, 142.18, 137.04, 134.86, 134.64, 126.95, 124.86, 124.68, 123.58, 111.94, 110.05, 81.98, 55.33, 44.27, 41.64, 40.63, 39.01, 38.97, 37.88,

28.26.



7a

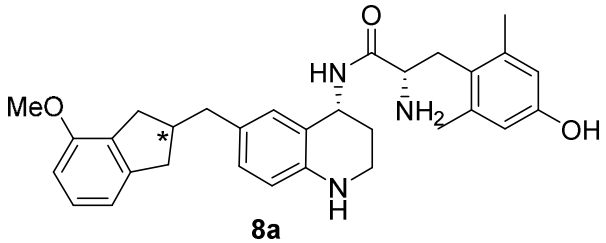
***Tert*-butyl (4*R*)-4-(((*R*)-*tert*-butylsulfinyl)amino)-6-((4-methoxy-2,3-dihydro-1*H*-inden-2-yl)methyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (7a). 7a** was synthesized following general procedure B using **6a** (83 mg, 0.20 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (74 mg, 0.61 mmol, 3.0 eq), and $Ti(OEt)_4$ (0.325 mL, 1.22 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*. Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing $NaBH_4$ (46 mg, 1.22 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound **7a** (43 mg, 41.3%) as an off-white solid and a mixture of inseparable diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.5 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 7.11 (t, *J* = 7.9 Hz, 2H), 6.79 (d, *J* = 7.5 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 4.57 (q, *J* = 3.1 Hz, 1H), 4.52 (s, 1H), 4.03 – 3.94 (m, 1H), 3.80 (d, *J* = 2.7 Hz, 3H), 3.62 – 3.52 (m, 1H), 3.04 – 2.91 (m, 2H), 2.74 (s, 3H), 2.70 – 2.62 (m, 1H), 2.61 – 2.52 (m, 1H), 2.19 (dt, *J* = 13.0, 3.9 Hz, 1H), 2.03 – 1.93 (m, 1H), 1.53 (s, 10H), 1.44 (s, 3H), 1.22 (s, 11H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.95, 153.56, 145.04, 136.90, 136.34, 130.54, 129.01, 128.68, 128.66, 128.37, 127.54, 123.79, 116.93, 107.77, 81.07, 55.59, 55.10, 55.08, 50.35, 40.91, 40.87, 40.83, 40.03, 40.01, 39.15, 35.29, 35.27, 29.55, 28.33, 24.16, 22.59.



7b

***Tert*-butyl (4*R*)-4-(((*R*)-*tert*-butylsulfinyl)amino)-6-((5-methoxy-2,3-dihydro-1*H*-inden-2-yl)methyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (7b). 7b** was synthesized following general procedure B using **6b** (139 mg, 0.41 mmol, 1.0 eq), (*R*)-2-methylpropane-2-sulfinamide (47 mg, 0.12 mmol, 3.0 eq), and $Ti(OEt)_4$ (0.145 mL, 0.69 mmol, 6.0 eq) to form the (*R*)-*tert*-butanesulfinyl imine intermediate *in situ*.

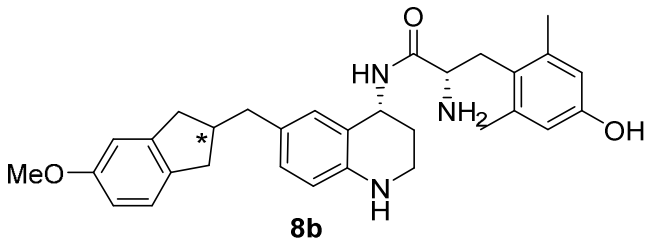
Once sufficient ketone was converted into imine intermediate (after 48 h), the reaction mixture was transferred via cannula to a round bottom flask containing $NaBH_4$ (26 mg, 0.69 mmol, 6.0 eq) and 20 mL of THF in a xylenes dry ice bath, after addition, the solution was stirred at room temperature for 3 h before being quenched with MeOH. Once resultant solid was removed, crude residue was purified using silica gel chromatography to yield the title compound as clear, colorless oil (25 mg, 44.0%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.5 Hz, 1H), 7.19 (s, 1H), 7.07 (dd, *J* = 19.0, 8.3 Hz, 2H), 6.73 (s, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 4.62 – 4.49 (m, 1H), 4.12 (q, *J* = 7.2 Hz, 0H), 3.99 (dt, *J* = 13.5, 4.5 Hz, 1H), 3.77 (s, 3H), 3.63 – 3.52 (m, 1H), 3.30 (s, 1H), 3.00 – 2.86 (m, 2H), 2.72 (s, 3H), 2.67 – 2.52 (m, 2H), 2.18 (dt, *J* = 13.5, 4.2 Hz, 1H), 2.00 (ddd, *J* = 20.6, 11.7, 4.1 Hz, 2H), 1.53 (s, 9H), 1.22 (s, 11H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.54, 153.54, 144.58, 144.56, 136.88, 136.35, 135.07, 135.04, 129.01, 128.65, 128.38, 124.85, 124.84, 123.74, 111.88, 111.86, 110.06, 81.05, 55.58, 55.35, 50.44, 41.81, 40.68, 40.06, 39.11, 39.09, 37.97, 37.95, 29.65, 28.32, 24.16, 22.57.



8a

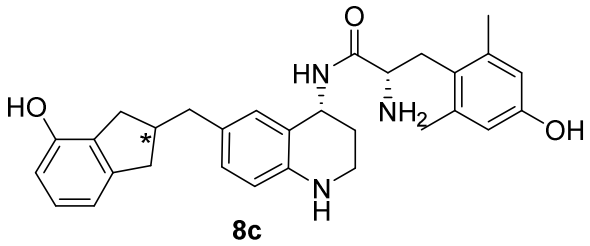
(2*S*)-2-Amino-3-(4-hydroxy-2,6-dimethylphenyl)-*N*-((4*R*)-6-((4-methoxy-2,3-dihydro-1*H*-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide (8a). 8a was synthesized following general procedure C using **7a** (43 mg, 0.084 mmol, 1.0 eq) and conc. HCl (3 drops). After removing solvent, residue was re-suspended in Et_2O, and solid crashed out. After washing the solid 3 x with fresh Et_2O, the remaining Et_2O was decanted off, yielding a white solid amine hydrochloride salt (15 mg). The synthesis was completed by following general procedure D with newly formed (*R*) amine intermediate (25 mg, 0.073 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **8a** (35 mg, 79.5%) as a white powder and the TFA salt of an inseparable mixture of diastereomers. ^{1}H NMR (500 MHz, CD_3OD) δ 7.18 – 7.11 (m, 2H), 7.06 (td, *J* = 7.8, 4.9 Hz, 1H), 6.95 (dd, *J* = 8.2, 4.7 Hz, 1H), 6.76 – 6.71 (m, 1H), 6.67 (dd, *J* = 8.3, 4.9 Hz, 1H), 6.50 (d, *J* = 4.9 Hz, 2H), 5.07 (q, *J* = 5.0 Hz, 1H), 3.90 (dt, *J* = 11.1, 5.2 Hz, 1H), 3.76 (d, *J* = 4.8 Hz, 3H), 3.31 (s, 2H), 3.28 – 3.18 (m, 2H), 3.06 (dt, *J* = 13.6, 5.1 Hz, 1H), 2.90 (dddd, *J* = 32.8, 17.5, 11.7, 5.8 Hz, 2H), 2.82 – 2.74 (m, 1H), 2.64 (s, 1H), 2.59 (dt, *J* = 15.3, 5.5 Hz, 1H), 2.48 (dt, *J* = 15.9, 5.2 Hz, 1H), 2.28 (d, *J* = 4.9 Hz, 6H), 1.99 – 1.87 (m, 1H), 1.59 (dq, *J* = 11.6, 5.8, 5.2 Hz, 1H). ^{13}C NMR (126 MHz, CD_3OD) δ 168.95, 157.37, 145.84, 145.80, 140.07, 134.95, 131.89, 131.86, 131.25, 131.20, 130.89, 130.85, 128.80, 127.63, 123.34, 121.21, 117.85, 117.83, 116.41, 108.96, 108.94, 55.52, 53.39, 45.19, 45.17, 42.33, 42.25,

41.91, 41.89, 40.15, 39.87, 39.59, 39.56, 36.24, 35.96, 31.82, 28.10, 20.44. HPLC (gradient A): retention time 31.7. ESI-MS 522.1 $[M+Na]^+$



8b

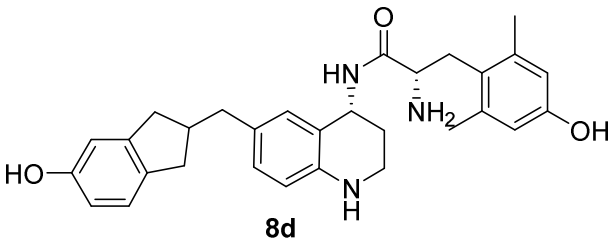
(2*S*)-2-Amino-3-(4-hydroxy-2,6-dimethylphenyl)-*N*-((4*R*)-6-((5-methoxy-2,3-dihydro-1*H*-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)propanamide (8b). **8b** was synthesized following general procedure C using **7b** (26 mg, 0.057 mmol, 1.0 eq) and conc. HCl (3 drops). After removing solvent, residue was re-suspended in Et_2O, and solid crashed out. After washing the solid 3 x with fresh Et_2O, the remaining Et_2O was decanted off, yielding a white solid amine hydrochloride salt (15 mg). The synthesis was completed by following general procedure D with newly formed (*R*) amine intermediate (15 mg, 0.044 mmol, 1.0 eq) to yield crude product which was purified by semipreparative HPLC and lyophilized to yield the title compound **8b** (19 mg, 70.4%) as a white fluffy powder and as a TFA salt of a mixture of inseparable diastereomers. No ^1H or ^{13}C data acquired. Instead, product formation was verified using mass spectrometry. HPLC (gradient A): retention time 30.1. ESI-MS 500.1 $[M+H]^+$ and 522.1 $[M+Na]^+$.



8c

(2*S*)-2-Amino-*N*-((4*R*)-6-((4-hydroxy-2,3-dihydro-1*H*-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (8c). To a round bottom flask already containing **8a** (25 mg, 0.043 mmol, 1.0 eq) was added anhyd DCM and then reaction vessel was placed under vacuum for 10 min, then flooded with Ar. A 1M BBr_3 solution in DCM (0.2 mL, 0.172 mmol, 4.0 eq) was slowly added to the reaction vessel. Once completely added, solution stirred for 3 h. After 3 h, solvent was removed under reduced pressure and residue was resuspended in MeOH, then solvent was moved. This process was repeated 3 x. The crude mixture was purified using semipreparative HPLC to yield title compound **8a** (15 mg, 62.5%) as a white fluffy powder and the TFA salt of an inseparable mixture of diastereomers. Additional starting material, **7a**, was recovered but not included in final yield calculation. ^1H NMR (500 MHz, CD_3OD) δ 8.18 – 8.14 (m, 0H), 7.05 – 6.98 (m, 2H), 6.94 – 6.88 (m, 1H), 6.72 (d, J = 8.1 Hz, 1H), 6.63 (d, J = 7.3 Hz, 1H), 6.52 (dd, J = 7.9, 2.7 Hz,

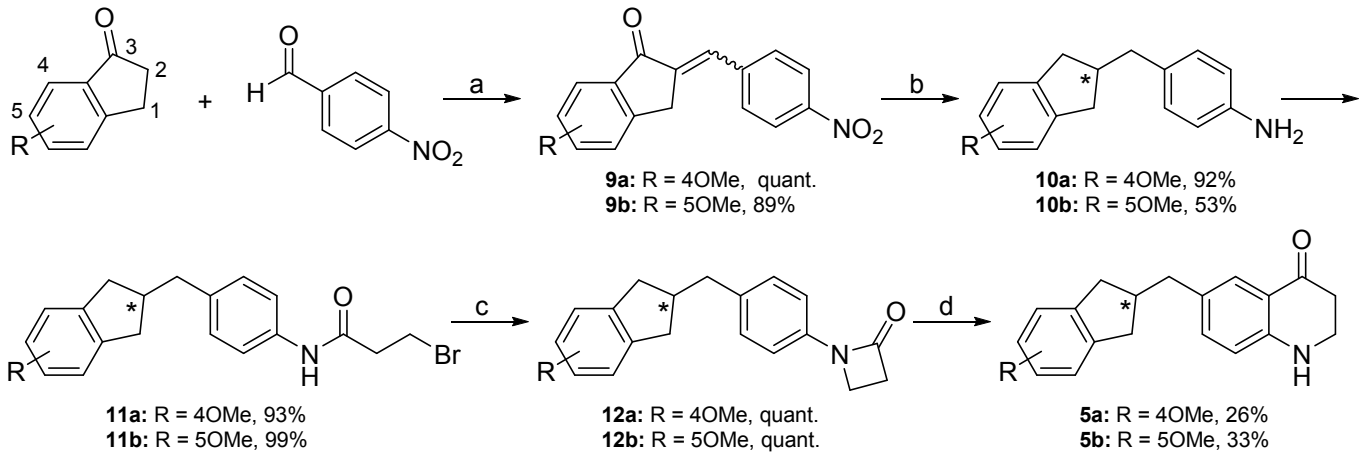
1H), 6.49 (d, *J* = 1.9 Hz, 2H), 5.01 (q, *J* = 4.2 Hz, 1H), 3.90 – 3.82 (m, 1H), 3.28 – 3.21 (m, 1H), 3.15 – 3.07 (m, 1H), 3.02 (ddd, *J* = 13.8, 5.4, 1.9 Hz, 1H), 2.95 – 2.78 (m, 2H), 2.62 (dq, *J* = 27.1, 16.4, 13.4 Hz, 5H), 2.52 – 2.44 (m, 1H), 1.82 (d, *J* = 12.8 Hz, 1H), 1.61 – 1.50 (m, 1H). No ^{13}C data acquired. HPLC (gradient A): retention time 25.9. ESI-MS 508.1 $[M+Na]^+$.



8d

(2*S*)-2-Amino-*N*-((4*R*)-6-((5-hydroxy-2,3-dihydro-1*H*-inden-2-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-hydroxy-2,6-dimethylphenyl)propanamide (8d). To a round bottom flask already containing **8b** (13 mg, 0.024 mmol, 1.0 eq) was added anhyd DCM and then reaction vessel was placed under vacuum for 10 min, then flooded with Ar. A 1M BBr_3 solution in DCM (0.125 mL, 0.090 mmol, 4.0 eq) was slowly added to the reaction vessel. Once completely added, solution stirred for 3 h. After 3 h, solvent was removed under reduced pressure and residue was resuspended in MeOH, then solvent was moved. This process was repeated 3 x. The crude mixture was purified using semipreparative HPLC to yield title compound **8d** (1.3 mg, 10%) as a white fluffy powder and the TFA salt of an inseparable mixture of diastereomers. Title compound was 80% pure, an additional 15% was the methoxy starting material (**8a**), and the entity of remaining 5% impurity was undetermined. Title compound formation was verified by mass spectrometry. No ^1H or ^{13}C data acquired. Instead, product formation was verified using mass spectrometry. HPLC (gradient A): retention time 31.7. ESI-MS 508.1 $[M+Na]^+$. Retention times of impurities are 24.8 (starting material **8a**) and 28.1 (unknown impurity).

Synthesis of 5a and 5b.



(a) KOH, MeOH, RT, 1 h (b) H_2, Pd/C, 50 psi, 2-3 drops HCl, MeOH, RT, 24 h (c) 3-bromopropionyl chloride, K_2CO_3, DCM, RT, 3 h (d) NaO*t*Bu, DMF, RT, 3 h (e) TfOH, DCE, RT, 3 h

Notes regarding the synthesis:

1.) The numbering of the 1-indanone starting material is not the conventional IUPAC numbering. The 1-indanone is numbered in the manner above because, once the final product is constructed, the carbons are numbered in this way according to the IUPAC convention.
2.) These molecules are synthesized as racemic mixtures through **5a** and **5b**.
3.) The syntheses followed the general procedures reported in Ref. 9 and Ref. 25. The first synthesis of the THQ core with a 2-methylindanyl pendant (in Ref. 9) uses the Fries Rearrangement sequence outlined in Ref. 25 (original literature using the Fries rearrangement sequence).

General Procedure G for synthesis of aldol adducts.[9] To a reaction vessel containing MeOH (375 mL) was added KOH. After dissolution, 1-indanone was added and allowed to dissolve. Next, *p*-nitrobenzaldehyde was added to the reaction mixture and allowed to stir for 1 h. Solvent was removed under reduced pressure and the residual solid was washed with cold H_2O (50 mL) and filtered to yield a homogeneous, tan powder as the pure product.

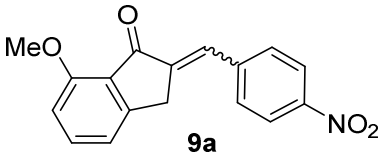
General Procedure H for synthesis *p*-substituted anilines.[9] To a hydrogenation vessel was added 10% Pd/C catalyst (1.5 g) followed by the slow addition of MeOH (120 mL). The aldol intermediate was dissolved in minimal MeOH and added to the vessel, followed by concentrated HCl (5.8 mL). The reaction vessel was placed on the hydrogenator under 50 psi of H_2 gas and allowed to shake for 24 h. The reaction mixture was then filtered through a pad of Celite, and solvent was removed under reduced

pressure. The crude residue was extracted twice with DCM (150 mL) from 2 M NaOH (200 mL), and the combined organic layers were subsequently washed 2 × $NaHCO_3$ (100 mL), 1 × brine (100 mL), dried under $MgSO_4$, filtered, and concentrated. The crude residue was purified using silica gel chromatography to yield the pure product.

General procedure I for the synthesis of the 3-Bromo-*N*-propanamides. [9, 25] To a flame-dried round bottom flask under Ar was added the aniline compound (1.0 eq) and K_2CO_3 (2.05 eq). The reaction vessel was placed back under vacuum and anhyd. DCE was added via syringe. The reaction solution stirred under vacuum for 5 min. After 5 min, the reaction vessel was then flooded with Ar and 3-bromopropionyl chloride (1.02 eq) was added via syringe. The reaction stirred under Ar at RT for 1 h and was monitored by TLC using a ninhydrin stain for disappearance of aniline compound. Once the reaction was complete, it was quenched with dI H_2O and the layers separated. The organic layer was washed with dI H_2O (1 x 50 mL) followed by brine (1 x 30 mL), then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield the pure product.

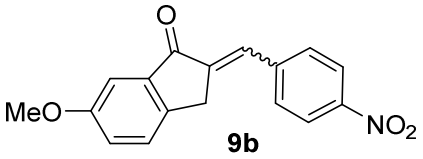
General procedure J for the synthesis of phenylazetidin-2-ones. [9, 25] To a round bottom flask already containing the dried, desiccated 3-bromo-*N*-propanamide (1.0 eq) was added NaO*t*Bu (1.05 eq). The reaction vessel was placed under vacuum and anhyd. DMF was added via syringe. The solution stirred under vacuum for 5 min, and then was flooded with Ar. The reaction stirred under Ar at RT for up to 3 h and was monitored by TLC. Once complete, the solvent was removed under reduced pressure and the resulting crude residue was re-suspended in DCM and dI H_2O, and the layers separated. The organic layer was washed once with dI H_2O (1 x 30 mL), then brine (1 x 30 mL), then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield the crude product, which was then purified using silica gel chromatography to yield the pure product.

General procedure K for the synthesis of 2,3-dihydroquinolin-4(1*H*)-ones.[9, 25] To the round bottom flask already containing the dried, desiccated phenylazetidin-2-ones (1.0 eq) was added anhyd. DCE under vacuum. The reaction vessel stirred under vacuum for 5 min then was flooded with Ar. Next, triflic acid (TfOH) (3.0 eq) was added via syringe. The reaction stirred under Ar at RT for up to 3 h and was monitored by TLC. Once complete, the reaction was quenched with dI H_2O (20 mL) and solid K_2CO_3 (one spatula full) and the layers separated. The organic layer was washed once with dI H_2O (1 x 30 mL), then sat. $NaHCO_3$ (1 x 30 mL), then brine (1 x 30 mL), then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield the crude product, which was then purified using silica gel chromatography to yield the pure product.



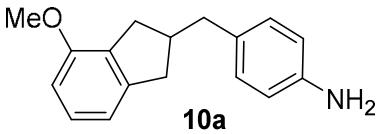
9a

4-Methoxy-2-(4-nitrobenzylidene)-2,3-dihydro-1*H*-inden-1-one (9a). 9a was synthesized according to general procedure G starting from commercially available 4-methoxy-2,3-dihydro-1*H*-inden-1-one (0.500 g, 3.1 mmol, 1.0 eq) and *p*-Nitrobenzaldehyde (0.559 g, 3.7 mmol, 1.2 eq) to yield the title compound **9a** (0.881 g, 96.8%) as a mustard yellow powder. No ^{1}H ^{13}C data was collected. Product was taken on to the next step (formation of **10a**) without additional isolation, purification, or characterization.



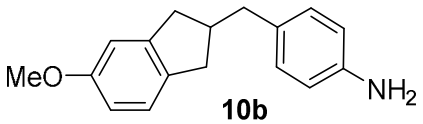
9b

5-Methoxy-2-(4-nitrobenzylidene)-2,3-dihydro-1*H*-inden-1-one (9b). 9b was synthesized according to general procedure G starting from commercially available 5-methoxy-2,3-dihydro-1*H*-inden-1-one (0.500 g, 3.1 mmol, 1.0 eq) and *p*-Nitrobenzaldehyde (0.559 g, 3.7 mmol, 1.2 eq) to yield the title compound **9b** (0.809 g, 88.9%) as a mustard yellow powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 – 8.28 (m, 2H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.81 – 7.76 (m, 2H), 7.62 (t, *J* = 2.3 Hz, 1H), 7.04 – 6.96 (m, 2H), 4.06 – 4.02 (m, 2H), 3.93 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.91, 165.71, 152.25, 141.87, 139.09, 130.96, 130.79, 129.61, 126.58, 124.06, 115.69, 109.98, 109.73, 55.78, 32.42.



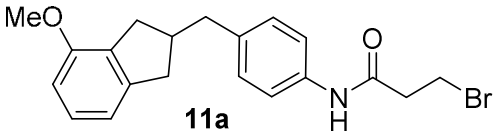
10a

4-((4-Methoxy-2,3-dihydro-1*H*-inden-2-yl)methyl)aniline (10a). 10a was synthesized according to general procedure H starting from **9a** (0.881 g, 2.98 mmol, 1.0 eq) to yield the title compound **10a** (698 mg, 92.3 %) as a light orange solid. ^{1}H NMR (400 MHz, CDCl3) δ 7.11 (td, *J* = 7.8, 3.5 Hz, 1H), 7.03 – 6.97 (m, 2H), 6.80 (dd, *J* = 7.4, 3.6 Hz, 1H), 6.65 (td, *J* = 8.6, 2.6 Hz, 3H), 4.12 (qd, *J* = 7.1, 3.5 Hz, 1H), 3.84 – 3.78 (m, 3H), 3.02 – 2.93 (m, 2H), 2.76 – 2.62 (m, 4H), 2.58 (ddd, *J* = 16.2, 6.4, 4.1 Hz, 1H), 2.05 (d, *J* = 3.3 Hz, 1H), 1.30 – 1.22 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.00, 145.32, 144.23, 144.21, 131.53, 130.79, 129.87, 129.64, 127.48, 127.48, 116.97, 116.96, 115.28, 115.19, 107.75, 60.38, 55.13, 41.31, 40.88, 39.10, 35.34, 21.04, 14.19.



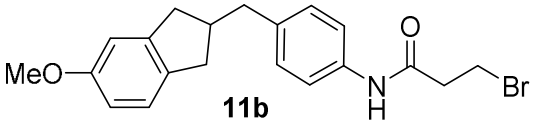
10b

4-((5-Methoxy-2,3-dihydro-1*H*-inden-2-yl)methyl)aniline (10b). 10b was synthesized according to general procedure H starting from **9b** (809 mg, 0.27 mmol, 1.0 eq) to yield the title compound **10b** (365 mg, 52.6 %) as a light orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (q, *J* = 7.7 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 2H), 6.77 – 6.68 (m, 1H), 6.66 (d, *J* = 9.7 Hz, 1H), 6.58 (dt, *J* = 8.6, 4.5 Hz, 2H), 3.72 (d, *J* = 5.4 Hz, 3H), 3.58 – 3.41 (m, 2H), 2.88 (tt, *J* = 13.8, 6.5 Hz, 2H), 2.60 (dtq, *J* = 29.1, 22.1, 7.2 Hz, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.42, 144.75, 144.23, 135.23, 131.31, 129.49, 124.78, 115.07, 111.71, 110.01, 55.24, 42.11, 40.63, 39.02, 37.87.



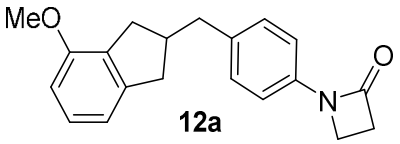
11a

3-Bromo-*N*-(4-((4-methoxy-2,3-dihydro-1*H*-inden-2-yl)methyl)phenyl)propanamide (11a). 11a was synthesized according to general procedure I starting from **10a** (698mg, 2.76 mmol, 1.0 eq) to yield the title compound **11a** (997 mg, 93.2%) as white, waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.1 Hz, 2H), 7.22 (s, 1H), 7.18 (d, *J* = 7.9 Hz, 2H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 7.4 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 3.80 (d, *J* = 1.7 Hz, 3H), 3.72 (t, *J* = 6.8 Hz, 2H), 3.01 – 2.91 (m, 5H), 2.75 (s, 3H), 2.62 (ddd, *J* = 40.6, 14.7, 5.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.90, 167.70, 156.01, 155.80, 145.07, 137.98, 135.21, 130.57, 129.42, 127.60, 120.12, 116.96, 107.83, 55.15, 41.14, 41.05, 40.72, 39.12, 35.33, 27.14.



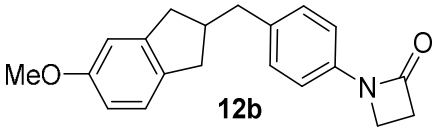
11b

3-Bromo-*N*-(4-((5-methoxy-2,3-dihydro-1*H* -inden-2-yl)methyl)phenyl)propanamide (11b). 11b was synthesized according to general procedure I starting from **10b** (365 mg, 1.4 mmol, 1.0 eq) to yield the title compound **11b** (554 mg, 99%) as a tan solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 4.6 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.73 (d, *J* = 2.3 Hz, 1H), 6.70 – 6.66 (m, 1H), 3.77 (d, *J* = 1.3 Hz, 3H), 3.72 (t, *J* = 6.4 Hz, 2H), 2.97 – 2.86 (m, 5H), 2.73 (s, 3H), 2.60 (ddd, *J* = 21.4, 14.8, 5.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.76, 158.58, 144.61, 137.97, 135.24, 135.08, 129.38, 124.91, 120.14, 111.90, 110.10, 55.40, 41.93, 40.98, 40.68, 39.09, 37.95, 27.14.



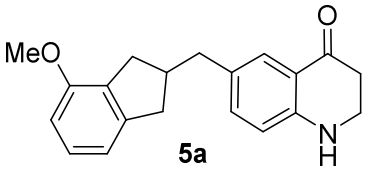
12a

1-(4-((4-Methoxy-2,3-dihydro-1*H*-inden-2-yl)methyl)phenyl)azetidin-2-one (12a). 12a was synthesized according to general procedure J starting from **11a** (997 mg, 2.57 mmol, 1.0 eq) to yield the title compound **12a** (789 mg, quant.) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.31 – 7.27 (m, 2H), 7.20 – 7.16 (m, 2H), 7.11 (t, *J* = 7.7 Hz, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 3.80 (d, *J* = 1.3 Hz, 4H), 3.61 (dh, *J* = 4.6, 2.6 Hz, 2H), 3.10 (tt, *J* = 4.6, 2.2 Hz, 2H), 2.98 (d, *J* = 6.4 Hz, 1H), 2.95 (t, *J* = 1.8 Hz, 6H), 2.88 (q, *J* = 1.2 Hz, 4H), 2.74 (d, *J* = 3.3 Hz, 3H), 2.65 (dd, *J* = 15.5, 5.6 Hz, 1H), 2.60 – 2.53 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.22, 162.45, 155.93, 144.97, 136.97, 136.49, 130.47, 129.42, 129.23, 127.55, 127.52, 119.93, 116.89, 116.08, 107.76, 55.07, 41.10, 41.07, 41.02, 39.03, 37.95, 36.41, 35.98, 35.22, 31.36.



12b

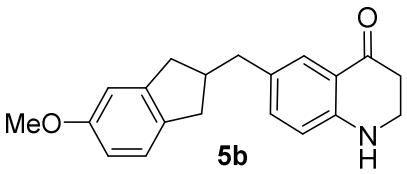
1-(4-((5-Methoxy-2,3-dihydro-1 *H* -inden-2-yl)methyl)phenyl)azetidin-2-one (12b). 12b was synthesized according to general procedure J starting from **11b** (544 mg, 1.43 mmol, 1.0 eq) to yield the title compound **12b** as a solid (439 mg, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 0H), 7.33 – 7.27 (m, 2H), 7.20 – 7.14 (m, 2H), 7.06 (d, *J* = 8.1 Hz, 1H), 6.76 – 6.72 (m, 1H), 6.71 – 6.65 (m, 1H), 3.77 (d, *J* = 1.1 Hz, 3H), 3.62 (td, *J* = 4.5, 1.2 Hz, 2H), 3.11 (td, *J* = 4.5, 1.1 Hz, 2H), 2.95 (d, *J* = 1.2 Hz, 1H), 2.95 – 2.86 (m, 4H), 2.73 (d, *J* = 2.7 Hz, 4H), 2.60 (ddd, *J* = 20.9, 15.1, 5.7 Hz, 3H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.25, 158.57, 144.57, 137.02, 136.55, 135.04, 129.43, 124.88, 116.11, 111.87, 110.09, 55.37, 42.00, 40.99, 39.05, 37.98, 37.91, 36.03.



5a

6-((4-Methoxy-2,3-dihydro-1*H*-inden-2-yl)methyl)-2,3-dihydroquinolin-4(1*H*)-one (5a). 5a was synthesized according to general procedure K starting from **12a** (789 mg, 2.57 mmol, 1.0 eq) to yield that title compound **5a** (205 mg, 25.9%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (t, *J* = 1.8 Hz, 1H), 7.16 (dt, *J* = 8.5, 1.8 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 7.4 Hz, 1H), 6.66 – 6.58 (m, 2H), 3.79 (d, *J* = 1.4 Hz, 3H), 3.57 – 3.48 (m, 2H), 3.01 – 2.92 (m, 2H), 2.76 – 2.60 (m, 7H), 2.55 (dd, *J* = 16.0, 6.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.89, 155.92, 150.47, 145.04, 136.10, 130.87, 130.53, 127.51, 127.05,

119.18, 116.92, 115.91, 107.76, 55.06, 42.39, 40.95, 40.57, 39.02, 38.17, 35.20.



5b

6-((5-Methoxy-2,3-dihydro-1*H*-inden-2-yl)methyl)-2,3-dihydroquinolin-4(1*H*)-one (5b). 5b was synthesized according to general procedure K starting from **12b** (514 mg, 1.67 mmol) to yield the title compound as a viscous yellow oil (172 mg, 33.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 2.1 Hz, 1H), 7.16 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.74 – 6.72 (m, 1H), 6.67 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.63 (d, *J* = 8.3 Hz, 1H), 3.77 (s, 3H), 3.57 (t, *J* = 6.9 Hz, 2H), 2.92 (td, *J* = 15.9, 6.9 Hz, 2H), 2.74 – 2.65 (m, 6H), 2.60 (ddd, *J* = 22.3, 15.1, 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.86, 158.57, 150.43, 144.66, 136.12, 135.14, 131.06, 127.15, 124.90, 119.33, 115.91, 111.90, 110.09, 55.40, 42.51, 41.92, 40.48, 39.04, 38.24, 37.90.