Supporting Information

Structural Determinants of Opioid and NOP activity in Derivatives of Buprenorphine

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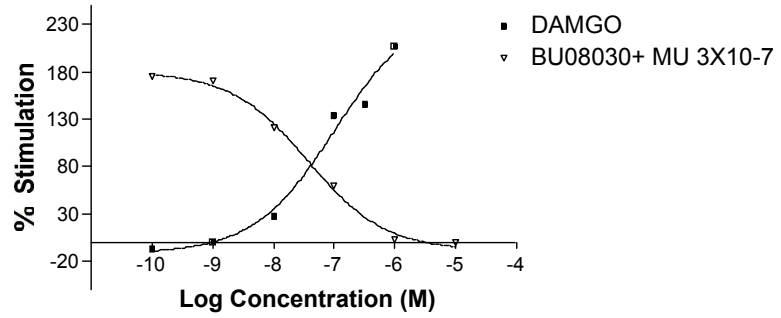

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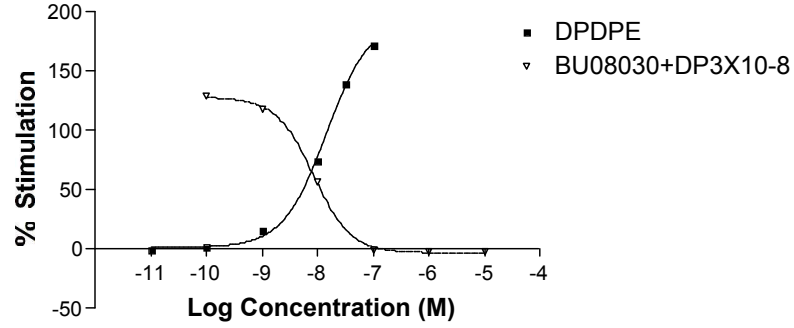

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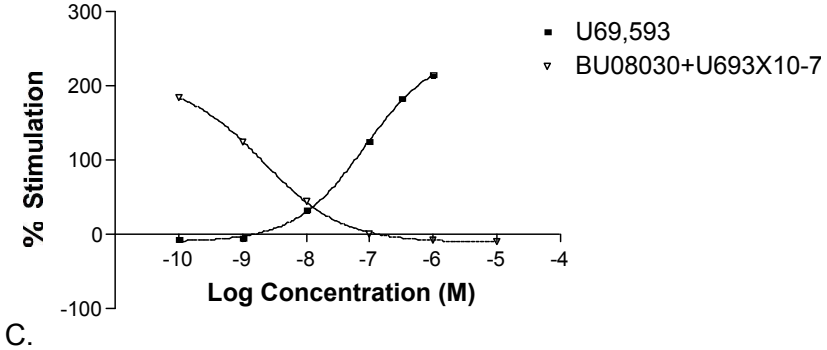

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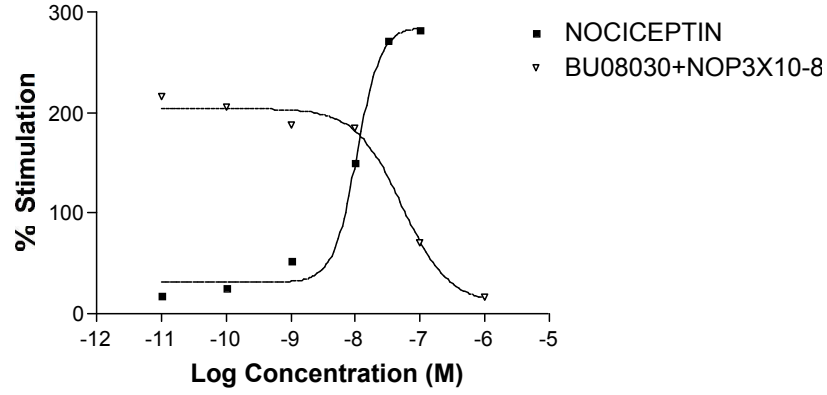

D.

Supplemental Figure S1. Ability of BU08030 (**6b**) to inhibit opioid receptor agonist-induced [^{35}S]GTPγS activity in vitro. Various concentrations of BU08030 (**6b**) were used to inhibit activity induced by 300 nM DAMGO (mu), 30 nM DPDPE (delta), 300 nM U69593 (kappa), and 30 nM N/OFQ (NOP). [^{35}S]GTPγS binding was conducted as described previously (Reference 25). Data are from individual experiments that were repeated at least twice at each site. IC_{50} values for

BU08030 (**6b**) were 37 nM, 8.4 nM, 2.1 nM, and 52 nM at mu, delta, kappa, and NOP receptors respectively.

Experimental Part

Reagents and solvents were purchased from *Aldrich* or *Lancaster* and used as received. M.p.: *Gallenkamp MFB-595* melting point apparatus; uncorrected. NMR Spectra: *Jeol Delta-270-MHz* instrument: ^{1}H at 270 MHz, and *Varian Mercury-400-MHz* instrument: ^{1}H at 400 MHz, ^{13}C at 100 MHz; δ in ppm, *J* in Hz with TMS as an internal standard. ESIMS: micrOTOF (BRUKER). Microanalysis: *Perkin-Elmer 240C* analyser. Ligands were tested as their hydrochloride salts, prepared by adding one equivalent of (5N hydrochloric acid in isopropanol) to an ether solution of the compound. All compounds were > 95% pure.

General Procedure A, halogenation: Buprenorphine or buprenorphine 3-O-methyl ether (0.31 mmol), was dissolved in H_2SO_4 (0.1 N, 16 mL) for bromination or HCl (0.1 N, 4 mL) for the chlorination, and the N-halosuccinimide (0.37 mmol) was added in one portion. The reaction mixture was stirred until TLC indicated the starting material had been consumed, (aprox. 3h), and the mixture was then poured into a separatory funnel containing dichloromethane (17 mL). Sufficient aqueous sodium hydroxide (10%) solution was added to raise the pH of the aqueous layer to ca. 10, the organic layer was separated and the aqueous layer was extracted further with three portions of 9:1 dichloromethane-methanol (10 mL). The organic extracts were combined and dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. The residue was purified by column chromatography over silica gel eluting with a gradient from 5% to 10% ethyl acetate in hexane.

General procedure B, Grignard addition: The Grignard reagents were prepared form the corresponding bromides (6 mmol) by reaction with magnesium (218 mg, 9 mmol) in anhydrous THF (6 ml) containing a crystal of iodine. The Grignard reagents were titrated prior to use by adding 1 ml of the Grignard solution to a flask containing 1,10-phenanthroline (~2 mg) in anhydrous THF (2 ml) (purple solution) and titrating with 1M 2-butanol (anhydrous) in THF (end point pale yellow solution).

A solution of the appropriate Grignard reagent (1 M in THF, 1.2 ml, 1.2 mmol) was treated dropwise at room temperature with a solution of *N*-cyclopropylmethyl-6,14-*endo*-ethanonorthevinone (**8**) (500 mg, 1.18 mmol) in anhydrous toluene (12 ml). After stirring at room temperature for 20 h, the reaction was quenched by addition of saturated aqueous ammonium chloride solution (20 ml). The phases were separated and the aqueous phase extracted with EtOAc. The combined organic phases were washed with saturated aqueous sodium bicarbonate, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with a gradient from 10% to 30% ethyl acetate in hexane. R_f values are recorded from TLC eluted with 30:1:69 ethyl acetate/ammonia solution/hexane.

General Procedure C, 3-O-demethylation: A solution of the appropriate methyl ether (0.1 mmol) in anhydrous HMPA (0.5 ml) under an inert atmosphere was treated with sodium hydride (8.5 mg, 0.35 mmol) followed by 1-propanethiol (32 µl, 0.35 mmol). After the addition was complete, the reaction mixture was heated to 120°C and stirred until completion (~ 3 h). On cooling to room temperature, NH_4Cl (sat, aq) was added and the mixture extracted with diethyl ether. The organic extracts were washed with water (3×) and brine. The organic phase was dried over $MgSO_4$ filtered and evaporated to dryness. The residue was purified by column chromatography over silica gel.

The HCl salts were prepared by the addition of 5N HCl in isopropanol (2 equiv.) to a solution of the orvinol in diethyl ether. The white precipitate which formed was collected by filtration, washed with ether and dried under high vacuum.

(2′R, 5α, 6R, 7R, 14α)-2′-(1-Bromo-17-cyclopropylmethyl-7,8-dihydro-3,6-dimethoxy-4,5-epoxy-6,14-ethano-morphinan-7-yl)-3′,3′-dimethylbutan-2′-ol (5a)

General procedure A using buprenorphine-3-O-methyl ether. **5a** isolated as a white solid (38%). R_f 0.47, ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.11-0.15 (2H, d, *J*=8.0 Hz), 0.47-0.48 (2H, m), 0.73-0.79 (1H, m), 1.01 (9H, s), 1.25-1.34 (2H, m), 1.36 (3H, s), 1.80-1.81 (1H, m), 1.85-1.95 (3H, m), 2.17 -2.20 (3H, m), 2.30-2.33 (2H, d, *J*=6.4 Hz), 2.57-2.59 (1H, m), 2.76-2.83 (1H, d, *J*= 18.1 Hz), 2.86-2.87 (1H, m), 3.01-3.02 (1H, d, *J*= 5.0 Hz), 3.53 (3H, s), 3.86 (3H, s), 4.43 (1H, s), 5.85 (1H, s), 6.86 (1H, s); ^{13}C NMR (68 MHz, $CDCl_3$) δ 3.4, 9.5, 18.1, 20.1, 24.6, 26.5, 29.7, 33.2, 35.7, 35.8, 40.4, 43.5, 43.8, 46.6, 52.7, 56.8, 58.3, 59.5, 79.4, 80.6, 97.1, 112.3, 116.5, 128,1, 134.2, 142.3, 146.3; ESIMS m/z: 561 $[M + 1]^+$.

(2′R, 5α, 6R, 7R, 14α)-2′-(1-Bromo-17-cyclopropylmethyl-7,8-dihydro-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxy-morphinan-7-yl)-3′,3′-dimethylbutan-2′-ol (6a)

5a was treated as described in General Procedure C .and **6a** isolated as a white solid (52 mg, 89%). R_f 0.20, ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.10-0.14 (2H, d, *J*=8.0 Hz), 0.48-0.50 (2H, t, *J*=7.8, 8.9 Hz), 0.73-0.75 (1H, m), 1.22 (9H, s), 1.22-1.27 (1H, m), 1.34 (3H, s), 1.62-2.17 (6H, m), 2.19 -2.23 (3H, m), 2.30-2.32 (2H, d, *J*=6.4 Hz), 2.58-2.60 (1H, m), 2.75-2.82 (1H, d, *J*= 18.1 Hz), 2.85-2.86 (1H, m), 3.01-3.03 (1H, d, *J*= 5 Hz), 3.50 (3H, s), 4.46 (1H, s), 5.84 (1H, s), 6.90 (1H, s); ESIMS m/z: 547 $[M + 1]^+$. Anal ($C_{29}H_{40}BrNO_4 \cdot 0.75H_2O$) CHN.

(2′R, 5α, 6R, 7R, 14α)-2′-(2-Bromo-17-cyclopropylmethyl-7,8-dihydro-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxy-morphinan-7-yl)-3′,3′-dimethylbutan-2′-ol (7)

From buprenorphine (**1a**) using the general halogenation procedure A yielding **7** as a white solid (70 mg, 60%). R_f 0.25, ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.08-0.14 (2H, d, *J*=8.0 Hz), 0.47-0.50 (2H, t, *J*=7.8, 8.9 Hz), 0.99-1.07 (1H, m), 1.22 (9H, s), 1.23-1.27 (3H, m), 1.35 (3H, s), 1.61-2.12 (5H, m), 2.19 - 2.30 (3H, m), 2.30-2.33 (2H, d, *J*=6.4 Hz), 2.58-2.60 (1H, m), 2.75-2.82 (1H, d, *J*= 18.1 Hz), 2.85-2.86 (1H, m), 3.00-3.03 (1H, d, *J*= 5 Hz), 3.53 (3H, s), 4.45 (1H, s), 5.80 (1H, s), 6.90 (1H, s); ESIMS m/z: 547 $[M + 1]^+$. Anal ($C_{29}H_{40}BrNO_4 \cdot 0.45H_2O$) CHN.

(2′R, 5α, 6R, 7R, 14α)-2′-(1-Chloro-17-cyclopropylmethyl-7,8-dihydro-3,6-dimethoxy-4,5-epoxy-6,14-ethano-morphinan-7-yl)-3′,3′-dimethylbutan-2′-ol (5b)

Buprenorphine-3-O-methyl ether was treated as in General Procedure A and **5b** isolated as a white solid (30 mg, 45%). R_f 0.42, ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.11-0.13 (2H, d, *J*=8.0 Hz), 0.48-0.52 (2H, m), 0.74-0.78 (1H, m), 0.86 (9H, s), 1.24-1.27 (2H, m), 1.55 (3H, s), 2.17-2.32 (7H, m), 2.67-2.82 (2H, m), 2.83-2.88 (1H, d, *J*= 18.1 Hz), 3.08-3.10 (1H, d, *J*= 5 Hz), 3.81 (3H, s), 3.99 (3H, s), 4.23 (1H, s), 5.29 (1H, s), 6.69 (1H, s); ESIMS m/z: 517 [M + 1].

(2′R, 5α, 6R, 7R, 14α)-2′-(1-Chloro-17-cyclopropylmethyl-7,8-dihydro-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxy-morphinan-7-yl)-3′,3′-dimethylbutan-2′-ol (6b)

5b was treated as described in General Procedure C and **6b** isolated as a white solid (8 mg, 56%). R_f 0.15, ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.12-0.13 (2H, d, *J*=8.0 Hz), 0.47-0.49 (2H, m), 0.49-0.51 (1H, m), 0.78-0.83 (4H, m), 1.03 (9H, s), 1.25-1.36 (4H, m), 1.56 (3H, brs), 1.68-1.97 (4H, m), 2.04-2.14 (3H, m), 2.32-2.34 (1H, d, *J*=6.3 Hz), 2.61-2.65 (1H, m), 2.81-2.82 (2H, m), 3.02-3.03 (1H, d, *J*= 6.3 Hz), 3.51 (3H, s), 4.47 (1H, s), 5.77 (1H, s), 6.75 (1H, s); ESIMS m/z: 503 [M + 1]. Anal ($C_{29}H_{40}ClNO_4 \cdot HCl \cdot 0.75H_2O$) CHN.

(1′RS, 5α, 6R, 7R, 14α)-2′-(17-Cyclopropylmethyl-7,8-dihydro-3,6-dimethoxy-4,5-epoxy-6,14-ethano-morphinan-7-yl)- 3′,3′-dimethylpentan-2′-ol (9b)

General Procedure B and **9b** isolated as a clear oil (428 mg, 15%). R_f 0.58 ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.08-0.11 (2H, m), 0.44-0.53 (2H, m), 0.81-0.86 (3H, m), 0.83-0.86 (3H, m), 0.89 (6H, s),

1.24-1.31 (2H, m), 1.34 (1H, s), 1.41 (3H, s), 1.55-1.80 (3H, m), 1.95-2.03 (2H, m), 2.27-2.34 (5H, m), 0.84 (1H, m), 2.79-2.84 (1H, t, *J*=9 Hz), 2.94-2.98 (1H, m), 3.53 (3H, s), 3.86 (3H, s), 4.41 (1H, s), 5.96 (1H, s), 6.53 (1H, d, *J*=8.0 Hz), 6.67 (1H, d, *J*=8.0 Hz, m); ESIMS m/z: 496 $[M + 1]^+$.

(1′RS, 5α, 6R, 7R, 14α)-1′-(4″-*t*-butylphenyl)-1′-(17-Cyclopropylmethyl-7,8-dihydro-3,6-dimethoxy-4,5-epoxy-6,14-ethano-morphinan-7-yl)-ethan-1′-ol (9e)

General Procedure B and **9e** isolated as a white solid (230 mg, 45%). R_f 0.50, ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.18-0.23 (2H, m), 0.54-0.63 (3H, m), 0.83-1.04 (4H, m), 1.27 (9H, s),1.29-1.50 (5H, m), 1.71 (1H, d, *J* = 10.1 Hz), 1.80 (3H, s), 2.37 (1H, brs), 2.58 -2.69 (3H, m), 2.97 (1H, d, *J* = 18.0 Hz), 3.16-3.18 (1H, m), 3.37 (3H, s), 3.84 (3H, s), 4.50 (1H, s), 6.53 (1H, d, *J* = 8.0 Hz), 6.69 (1H, d, *J* = 8.0 Hz), 7.30 (2H, d, *J* = 8.6 Hz), 7.50 (2H, d, *J* = 8.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 3.5, 5.1, 18.2, 22.9, 29.8, 31.3, 34.3, 35.9, 38.7, 44.9, 46.6, 51.9, 56.9, 58.8, 59.1, 78.0, 115.3, 119.4, 124.3, 126.3, 131.2, 142.4, 143.5, 147.3, 149.3; ESIMS m/z: 558 $[M + 1]^+$.

(1′RS, 5α, 6R, 7R, 14α)-1′-phenanthrene-1′-(17-cyclopropylmethyl-7,8-dihydro-3,6-dimethoxy-4,5-epoxy-6,14-ethano-morphinan-7-yl)-ethan-1′-ol (9g)

(9g) was prepared using General Procedure B, isolated as a white solid (130 mg, 36%). R_f 0.28, ^{1}H NMR (270 MHz, $CDCl_3$) δ -0.32-(-0.25) (2H, m), 0.06-0.08 (2H, m), 0.17-0.18 (1H, m), 0.78-0.86 (3H, m), 1.24-1.27 (2H, m), 1.48-1.49 (3H, m), 1.72-1.73 (1H, m), 1.97-2.07 (6H, m), 2.15-2.28 (2H, m), 2.74 (1H, d, *J* = 5.5 Hz), 2.91 (1H, d, *J* = 18.0 Hz), 3.06 (1H, t, *J* = 5.0 Hz), 3.67 (3H, s), 3.88 (3H, s), 4.96 (1H, s), 5.58 (1H, s), 6.49 (1H, d, *J* = 8.0 Hz), 6.68 (1H, d, *J* = 8.0 Hz), 7.54-7.65 (5H, m), 7.87 (1H, d, *J* = 8.0 Hz), 8.65 (1H, d, *J* = 8.2 Hz), 8.74-8.78 (1H, m), 9.37-9.41 (1H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 3.0, 3.6, 8.8, 18.4, 22.6, 26.4, 29.9, 32.8, 36.0, 43.1, 44.5, 47.0, 56.8, 57.8, 59.1, 80.5, 81.2, 97.3, 114.0, 119.0, 122.2, 123.1, 125.7, 126.1, 126.5, 128.0, 128.9, 130.4, 130.9, 131.6, 132.6, 139.1, 141.5, 146; . ESIMS m/z: 602 $[M + 1]^+$.

2-(Bromomethyl)bicyclo[2.2.1]heptane

A solution of 2-norbornamethanol (14.11 g, 100 mmol) in anhydrous diethyl ether (30 ml) at -78°C' was treated dropwise with phosphorus tribromide (3.5 ml, 37 mmol). The resulting solution was allowed to warm to room temperature and stirred overnight. Water was added (20 ml) and the phases separated. The aqueous phase was extracted with ether and the organic phases dried over $MgSO_4$ and filtered. The ether was then removed by distillation through a six-inch Vigreux column. The product was then distilled (b.p. 103.5-105°C at atmospheric pressure) affording GC-2-148 as a colourless liquid (14.06 g, 66%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.64-0.68 (1H, m), 0.96-0.11 (2H, m), 1.23-15.2 (4H, m), 1.54-1.91 (2H, m), 2.03-2.31 (3H, m), 3.02-3.3 (1H, m), 3.59-3.63 (1H, m).

(1′RS, 5α, 6R, 7R, 14α)-2′-(4″-methyl-4″-phenyl)-2′-(17-cyclopropylmethyl-7,8-dihydro-3,6-dimethoxy-4,5-epoxy-6,14-ethano-morphinan-7-yl)-pentan-2′-ol (9d)

General Procedure B was used to isolate (**9d**) as a white solid (88 mg, 23%). R_f 0.54, ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.10-0.14 (2H, d, *J*=8.0 Hz), 0.52-0.55 (2H, m), 0.56-0.67 (1H, m), 0.97-1.00 (5H, m), 1.18-1.20 (1H, m), 1.33 (2H, s), 1.40 (3H, s), 1.46 (3H, s), 1.66-1.83 (5H, m), 2.04-2.34 (4H, m), 2.56-2.70 (2H, m), 2.92-2.99 (1H, d, *J*=17.8 Hz), 2.96-2.99 (1H, d, *J*=7.8 Hz), 3.45 (3H, s), 3.84 (3H, s), 4.28 (1H, s), 5.20 (1H, s), 6.49-6.52 (1H, d *J*=8.1 Hz), 6.65-6.68 (1H, d *J*=8.1 Hz), 7.24-7.63 (5H, m); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 9.5, 14.3, 18.3, 21.1, 22.6, 23.8, 25.4, 29.6, 29.8, 32.7, 33.7, 35.5, 35.9, 38.1, 40.1, 43.6, 46.2, 47.1, 52.6, 52.9, 56.9, 58.3, 60.0, 60.4, 73.1, 78.5, 80.9, 96.8, 114.1, 119.1, 125.2, 126.2, 128.5, 150.7; ESIMS m/z: 558 $[M + 1]^+$.

(2′R, 5α, 6R, 7R, 14α)-2′-(17-Cyclopropylmethyl-7,8-dihydro-3,6-dimethoxy-4,5-epoxy-6,14-ethano-morphinan-7-yl)-1'-(bicyclo[2.2.1]heptan-1-yl)-propan-2′-ol (9f)

Procedure B to isolate **9f** as a white solid (90 mg, 27%). R_f 0.28, ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.07-0.11 (2H, m), 0.46-0.49 (2H, m), 0.55-0.60 (1H, m), 1.07-1.09 (1H, m), 1.09-1.13 (2H, m), 1.16-1.85 (19H, m), 2.03 (3H, s), 2.15-2.26 (4H, m), 2.58-2.59 (1H, m), 2.77-2.81 (1H, m), 2.94 (1H, d, *J*=18 Hz), 2.94-3.01 (1H, m), 3.52 (3H, s), 3.81 (3H, s), 4.39 (1H, s), 6.54 (1H, d, *J*=8.0 Hz), 6.69 (1H, d, *J*=8.0 Hz, m); ESIMS m/z: 534 $[M + 1]^+$.

(2′R, 5α, 6R, 7R, 14α)-1′-(4′′-*t*-butyl-phenyl)-1′-(17-cyclopropylmethyl-7,8-dihydro-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxy-morphinan-7-yl)-ethan-1′-ol (1e)

(1e) was prepared using General Procedure C. Isolated as a white solid (50 mg, 79%). R_f 0.33, ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.07-0.00 (2H, m), 0.31-0.33 (2H, d, *J*= 8.0 Hz), 0.68-0.72 (1H, m), 0.73-0.86 (1H, m), 0.86-0.92 (1H, m), 0.99-1.03 (1H, m), 1.31 (9H, s), 1.52-1.55 (1H, d, *J*= 12.5 Hz), 1.77 (6H, m), 1.81-1.84 (1H, m), 2.03-2.10 (1H, m), 2.13-2.20 (5H, m), 2.46-2.48 (1H, m), 2.77-278 (1H, m), 2.87-2.91 (1H, d, *J*=18.3 Hz), 3.54 (3H, s), 4.43 (1H, s), 5.44 (1H, s), 6.44-6.46 (1H, d, *J*= 8.0 Hz), 6.61-6.63 (1H, d, *J*=8.0 Hz), 7.32-7.33 (2H, d, *J*=4.7 Hz), 7.34-7.35 (2H, d, *J*=4.7 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.4, 3.5, 9.1, 17.8, 23.0, 23.4, 29.8, 31.3, 32.4, 34.3, 35.5, 36.0, 43.2, 47.0, 48.3, 52.7, 58.5, 59.2, 80.7, 97.2, 116.3, 119.4, 124.6, 125.6, 128.1, 132.3, 137.2, 144.0, 145.4, 149.3; ESIMS m/z: 544 $[M + 1]^+$. Anal ($C_{35}H_{45}NO_4$) CHN.

(2′R, 5α, 6R, 7R, 14α)-2′-(17-cyclopropylmethyl-7,8-dihydro-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxy-morphinan-7-yl)-1’-(bicyclo[2.2.1]heptan-1-yl)-propan-2′-ol (1f)

General Procedure C was used to prepare **(1f)**. Isolated as a white solid (55 mg, 62%). R_f 0.23, ^{1}H NMR (400 MHz, MeOD) δ 0.16-0.18 (2H, m), 0.51-0.53 (2H, d, *J*=8.1 Hz), 0.71-0.82 (3H, m), 1.14-1.35 (3H, m), 1.37-1.38 (15 H, m), 1.54-1.86 (7H, m), 2.22-2.39 (4H, m), 2.69 (1H, m), 2.99-3.00 (1H, m), 3.03-3.05 (1H, d, *J*=18.1 Hz), 3.58 (3H, s), 4.36 (1H, s), 6.47-6.50 (1H, d, *J*=8.0 Hz), 6.62-6.64 (1H, d, *J*=8.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 4.0, 4.4, 10.2, 19.1, 23.8, 24.8, 29.6, 30.7, 32.9, 36.0, 37.2, 38.6, 39.8, 40.9, 43.5, 44.8, 46.9, 53.0, 60.8, 67.1, 69.2, 81.9, 97.9, 117.9, 120.4, 128.5, 133.6, 139.5, 147.3; ESIMS m/z: 520 $[M + 1]^+$. Anal ($C_{33}H_{45}NO_4 \cdot HCl \cdot 0.5H_2O$) CHN

(2′R, 5α, 6R, 7R, 14α)-2′-(17-cyclopropylmethyl-7,8-dihydro-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxy-morphinan-7-yl)-3′,3’-dimethylpentan-2′-ol (1b)

Procedure C to isolate **1b**, as a clear oil (182 mg, 80%). R_f 0.23, ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08-0.10 (2H, d, *J*=8.0 Hz), 0.44-0.49 (2H, t, *J*=7.8, 8.9 Hz), 0.65-0.69 (1H, m), 0.72-0.80 (1H, m), 0.86-0.90 (3H, m), 0.91 (6H, s), 1.03-1.06 (1H, m), 1.31-1.34 (2H, m), 1.35 (3H, s), 1.40-1.45 (1H, m), 1.60-1.75 (3H, m), 1.80-1.86 (1H, m), 1.93-2.00 (1H, m), 2.15-2.36 (5H, m), 2.57-2.62 (1H, dd, *J*=5 Hz), 2.79-2.86 (1H, m), 2.93-2.96 (1H, d, *J*= 17.0 Hz), 2.96-2.98 (1H, d, *J*=7.0 Hz), 3.51 (3H, s), 4.43 (1H, s), 5.95 (1H, s), 6.49 (1H, d, *J*=8.1 Hz), 6.67 (1H, d, *J*=8.1 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.2, 4.1, 9.1, 9.4, 18.3, 20.6, 21.4, 21.7, 22.8, 28.5, 29.5, 33.3, 35.5, 35.8, 42.7, 43.0, 43.6, 46.3, 52.4, 58.2, 59.4, 80.4, 80.8, 96.9, 116.3, 119.5, 128.3, 132.6, 137.2, 145.3; ESIMS m/z: 482 $[M + 1]^+$.

(2′R, 5α, 6R, 7R, 14α)-2′-(17-cyclopropylmethyl-7,8-dihydro-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxy-morphinan-7-yl)-4′,4’-dimethylpentan-2′-ol (1c)

Isolated as a white solid, by using General procedure C to yield **1c** (20 mg, 52%). R_f 0.46, ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10-0.11 (2H, d, *J*=8.0 Hz), 0.47-0.50 (2H, m), 0.72-0.75 (1H, m), 0.81-0.88 (2H, m), 1.08 (9H, s), 1.24 (2H, s),1.44 (6H, m), 1.63-1.66 (1H, d, *J*= 3 Hz) 1.73-1.81 (2H, m), 1.84-2.04 (2H, m), 2.17-2.40 (4H, m), 2.61-2.65 (1H, m), 2.81-2.87 (1H, m), 2.94-2.99 (1H, d, *J*= 18.1 Hz), 2.99-3.00 (1H, d, *J*= 5 Hz), 3.50 (3H, s), 4.42 (1H, s), 5.14 (1H, s), 6.48-6.50 (1H, d, *J*= 8.0 Hz), 6.66-6.68 (1H, d, *J*= 8.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.4, 4.1, 9.4, 18.0, 22.6, 24.0, 29.8, 31.9, 32.0, 32.6, 35.5, 36.0, 47.1, 48.4, 52.0, 52.6, 58.2, 59.8, 78.2, 80.9, 97.5, 116.2, 119.4, 128.4, 132.4, 137.1, 145.4; ESIMS m/z: 482 [M + 1].

(2′R, 5α, 6R, 7R, 14α)-2′-(17-cyclopropylmethyl-7,8-dihydro-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxy-morphinan-7-yl)-4′-methyl-4’-phenylpentan-2′-ol (1d)

Procedure C to prepare (**1d**). Isolated as a clear oil (60 mg, 80%). R_f 0.34, ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13-0.14 (2H, d, *J*=8.1 Hz), 0.52-0.53 (2H, m), 0.55-0.56 (1H, m), 0.85-0.96 (6H, m), 1.41 (3H, s), 1.52 (5H, m), 1.62-1.64 (2H, t, *J*=6.8 Hz), 1.73-1.85 (3H, m), 2.03-2.07 (1H, d, *J*= 14.5 Hz), 2.16-2.35 (4H, m), 2.58-2.71 (2H, m), 2.92-2.96 (1H, d, *J*= 18.4 Hz), 2.95-2.96 (1H, m), 3.43 (3H, s), 4.27 (1H, s), 5.18 (1H, brs), 6.46-6.48 (1H, d, *J*= 8.1 Hz), 6.64-6.66 (1H, d, *J*= 8.1 Hz), 7.15-7.17 (1H, t, *J*=7.1 Hz), 7.27-7.29 (2H, d, *J*=7.1 Hz), 7.44-7.45 (2H, d, *J*=7.2 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.5, 4.0, 9.4, 18.3, 22.6, 23.8, 29.6, 32.6, 33.4, 35.3, 35.9, 37.9, 43.5, 46.6, 46.8, 52.4, 52.7, 58.3, 59.9, 80.8, 96.9, 116.3, 119.4, 125.0, 126.1, 127.9, 128.1, 132.4, 137.1, 145.4, 150.5; ESIMS m/z: 544 $[M + 1]^+$. Anal ($C_{35}H_{45}NO_4 \cdot HCl \cdot 1.5H_2O$) CHN

Elemental analyses of compounds 1b-7

Compd No	%C calcd found	%H calcd found	%N calcd found	Calculated for Mr
1b	73.92 73.9	9.02 8.98	2.87 2.80	$C_{30}H_{43}NO_4 \cdot 0.32\ H_2O$ 481.67
1c·HCl	68.82 68.9	8.59 8.62	2.68 2.74	$C_{30}H_{43}NO_4 \cdot HCl \cdot 0.3H_2O$ 481.67
1d·HCl	69.23 69.2	8.13 7.99	2.14 2.31	$C_{35}H_{45}NO_4 \cdot HCl \cdot 1.5H_2O$ 543.74
1e	77.31 77.46	8.34 8.50	2.58 2.40	$C_{35}H_{45}NO_4$ 543.74
1f·HCl	70.13 69.84	8.38 8.10	2.48 2.37	$C_{33}H_{45}NO_4 \cdot HCl \cdot 0.5H_2O$ 519.71
6a	62.19 62.2	7.47 7.39	2.50 2.43	$C_{29}H_{40}BrNO_4 \cdot 0.75H_2O$ 546.54
6b·HCl	63.09 62.98	7.76 7.63	2.54 2.46	$C_{29}H_{40}ClNO_4 \cdot HCl \cdot 0.75H_2O$ 502.09
7	62.80 62.9	7.43 7.30	2.53 2.38	$C_{29}H_{40}BrNO_4 \cdot 0.45H_2O$ 546.54