Supporting Information

C7β-Methyl analogues of the orvinols: The discovery of kappa opioid antagonists with nociceptin/orphanin FQ peptide (NOP) receptor partial agonism and low, or zero, efficacy at mu opioid receptors.

Juan Pablo Cueva[1#], Christopher Roche[1], Mehrnoosh Ostovar[1], Vinod Kumar[1#], Mary J. Clark[2], Todd M. Hillhouse[2], John W. Lewis[1], John R. Traynor[2], Stephen M. Husbands[1*]

[1]Department of Pharmacy and Pharmacology, University of Bath, Bath, BA2 7AY, UK; [2]Department of Pharmacology, University of Michigan, Ann Arbor, Michigan.

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1: Full characterisation of final compounds

General Procedures

A. Arylmagnesium halide addition:

To a solution of aldehyde **4b** or **11** in dry THF (10 mL/mmol of aldehyde) were added 3 eq. of Bu_4NBr followed by 2 eq. of arylmagnesium halide as solution in THF. The solution was then heated at reflux for 48 h, cooled to RT and quenched with 0.05 mL of water. The mixture was allowed to stir for 5 min then filtered over Celite. The solids were washed with hot THF, and the solution was removed of its solvent by rotary evaporation. The remaining residue was partitioned between EtOAc (20 mL) and water (10 mL). The water layer was extracted twice with 5 mL of EtOAc. The pooled organic solvent was washed twice with 5 mL of water, once with brine, dried over $MgSO_4$, filtered and dried under reduced pressure. The residue was dissolved in a minimum amount of Et_2O to induce crystallization. The crystals were collected by filtration, and dried under vacuum.

B. Swern oxidation/$LiAlH_4$ reduction of secondary alcohols:

A solution of oxalyl chloride (1.25 eq.) in CH_2Cl_2 (3 mL/mmol) was cooled to -78° C in a one-neck flask. Into this flask was added dropwise, a solution of dry DMSO (2.6 eq.) in CH_2Cl_2 (3 mL/mmol). The solution stirred for 5 min and then a solution N-CPCnorthevinol **5** or **12** in CH_2Cl_2 (2 mL/mmol) was added. The mixture stirred for 20 min and then Et_3N (5 eq.) was added. The reaction was removed from the cold bath, stirred for 1 h and water was added. The mixture was shaken, the organic layer was separated and washed with a saturated solution of NH_4Cl, then with a concentrated solution of $NaHCO_3$. The solution was washed once more with brine, dried over magnesium sulfate, filtered, and the solvents removed under reduced pressure to yield crude **6** or **13** as a clear solid.

This material was dissolved in dry THF (10 mL/mmol) and added to a stirring suspension of $LiAlH_4$ (4 eq.) in dry THF (5 mL/mmol) at 0° C. The suspension was allowed to warm up to RT and was stirred for 24 h. The reaction was cooled to 0° C and quenched with water in THF. The mixture was filtered, rinsing the solids with hot THF. The solution was subjected to rotary evaporation to yield an oil that was subjected to silica gel column chromatography eluting with 15% EtOAc in petroleum ether to yield two constituents, **7** or **14** (major product) as a high R_f component, and **5** or **12** (minor product), with lower R_f.

C. *O*-Demethylation using NaSPr/HMPA:

A solution of thevinol **7**, **9**, **14,** or **16** in dry HMPA (6 mL/mmol) was added sodium propanethiolate (6 eq.). The reaction was stirred for 3 h at 115 °C, then cooled to RT and quenched with 7 mL/mmol of a concentrated solution of NH_4Cl. The mixture was extracted three times with Et_2O. The organic layer was then extracted five times with water, once with brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The residue was then subjected to silica gel flash column chromatography eluting with a gradient of EtOAc in petroleum ether. The fractions containing the compound of interest were then evaporated to dryness and dissolved in a 2 M solution of HCl in EtOH, and then induced to crystallize upon addition of EtOAc. The crystals were collected by filtration, and dried under vacuum.

***N*-Cyclopropylcarbonyl-7α-formyl-7β-methyl-6,14-endo-ethenotetrahydronorthebaine (4b)**

To a suspension of 13.61 g (37.29 mmol) N-CPCnorthebaine in 20 mL of methacrolein was added 3.49 g of $LiBF_4$. The resulting solution was stirred for 16 h at RT. Into this solution were added 30 mL of CH_2Cl_2 and the mixture was extracted with water (10 mL x 3) and brine (5 mL). The solution was dried, filtered and removed of solvent on a rotary evaporator to afford a dark red syrup. This material was subjected to silica gel flash column chromatography eluting with 50% EtOAc in petroleum ether to afford 5.91 g of the faster running component **4a** (***N*-Cyclopropylcarbonyl-7β-formyl-7α-methyl-6,14-*endo*-ethenotetrahydronorthebaine)** as white solid ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (s, 1H), 6.67 (d, 1H, *J* = 8.0 Hz), 6.57 (d, 1H, *J* = 8.0 Hz), 6.14-6.07 (2d, 1H), 5.57 (d, 1H, *J* = 12.0 Hz), 5.33 (d, 1H, *J* = 8.0 Hz), 4.76 (d, 1H, 0.4H), 4.57-4.53 (m, 1.6H), 4.15-4.10 (m, 1H), 3.85 (s, 3H), 3.72 (s, 3H), 3.42 (dt, 1H, J_a = 12.0 Hz, J_b = 4.0 Hz), 3.11-3.05 (dd, 1H, J_a = 8.0 Hz, J_b = 4.0 Hz), 2.88-2.83 (m, 1H), 2.43-2.35 (dt, 1H, J_a = 12.0 Hz, J_b = 8.0 Hz), 1.85-1.76 (m, 1H), 1.69-1.65 (m, 1H), 1.09-1.03 (m, 5H), 0.91-0.76 (m, 2H). ESIMS: m/z 436 ($M+H^+$, 100) and 4.11 g of a slower running component, ***N*-Cyclopropylcarbonyl-7α-formyl-7β-methyl-6,14-endo-ethenotetrahydronorthebaine (4b)** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 0.5H), 9.45 (s, 0.5H), 6.69 (d, 1H, *J* = 8.0 Hz), 6.59 (d, 1H, *J* = 8.0 Hz), 6.14 (t, 1H), 5.57 (dd, 1H, J_a = 12.0 Hz, J_b = 8.0 Hz), 5.35 (d, 0.5H, *J* = 4.0 Hz), 4.93 (s, 1H), 4.80 (d, 0.5H, *J* = 8.0 Hz), 4.64 (dd, 1H, J_a = 8.0 Hz, J_b = 4.0 Hz), 4.15 (dd, 1H, J_a = 8.0 Hz, J_b = 4.0 Hz), 3.85 (s, 3H), 3.72 (2s, 3H), 3.49 (dt, 1H), 3.31-3.21 (m, 2H), 2.37-2.26 (dt, 0.5H), 2.27-2.15 (dt, 0.5H), 2.06-1.72 (m, 3H), 1.35 (s, 3H), 1.08 (m, 2H), 0.82 (m, 2H). At RT the ^{1}H NMR spectra of this compound in d_6-DMSO has two signals at δ

9.408 (s, 0.5H) and δ 9.375 (s, 0.5H) which coalesce when running the ^{1}H NMR experiment at 360° K. ESIMS: m/z 436 ($M+H^+$, 100).

***N*-Cyclopropylcarbonyl-6,14-*endo*-etheno-7β-methyl-nornepenthol (5a)**
General procedure **A** was followed using 500 mg of **4b** to yield 442 mg of **5a** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.19 (m, 5H), 6.68-6.63 (2d, 1H), 6.55-6.49 (2d, 1H), 6.19 (d, 0.55H, *J* = 12.0 Hz), 5.98 (d, 0.45H, *J* = 8.0 Hz), 5.41 (d, 0.55H, *J* = 12.0 Hz), 5.29-5.22 (m, 1H), 5.01 (s, 1H), 4.80 (d, 1H, *J* = 4.0 Hz), 4.66-4.53 (m, 1H), 4.12 (dd, 0.45H, *J* = 4.0 Hz, *J* = 8.0 Hz), 3.84 (2s, 3H), 3.72 (2s, 3H), 3.49-3.39 (m, 0.45H), 3.20-3.11 (dd, 0.55H, *J* = 4.0 Hz, *J* = 8.0 Hz), 3.08-2.89 (m, 2H), 2.82-2.78, (d, 0.55H), 2.46 (d, 0.45H), 2.39 (dt, 0.45H), 2.24 (dt, 0.55H), 2.10 (d, 0.55H, *J* = 12.0 Hz), 2.03 (d, 0.45H, *J* = 12.0 Hz), 1.89-1.69 (m, 3H), 1.27 (s, 1.35H), 1.12 (s, 1.65H), 1.10-0.91 (m, 2H), 0.88-0.78 (m, 2H). ESIMS: m/z 514 ($M+H^+$, 100).

***N*-Cyclopropylmethyl-6,14-*endo*-etheno-7β-methyl-norisonepenthol (7a).**
General procedures **B** was followed using 439 mg of **5a** to yield, after chromatography, 201 mg of the faster eluting component **7a** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.20 (m, 5H), 6.64 (d, 1H, *J* = 8 Hz), 6.50 (d, 1H, *J* = 8 Hz), 6.20 (dd, 1H, J_a = 8 Hz, J_b = 4 Hz), 5.58 (d, 1H, *J* = 8 Hz), 5.28 (s, 1H), 5.08 (s, 1H), 4.69 (s, 1H), 3.85 (s, 6H), 3.40 (d, 1H, *J* = 8 Hz), 3.07 (d, 1H, *J* = 20 Hz), 2.66 (m, 1H), 2.39 (dd, 1H, J_a = 8 Hz, J_b = 20 Hz), 2.35-2.22 (m, 4H), 2.01 (d, 1H, *J* = 16 Hz), 1.75-1.71 (m, 1H), 1.41 (s, 3H), 1.32-1.28 (d, 1H, *J* = 16 Hz), 0.73-0.68 (m, 1H), 0.52-0.42 (m, 2H), 0.09-0.02 (m, 2H). ESIMS: m/z 500 ($M+H^+$, 100).

***N*-Cyclopropylmethyl-6,14-*endo*-etheno-7β-methyl-nornepenthol (9a).**
General procedure **B** ($LiAlH_4$ reduction) was followed using 439 mg of **5a** to yield, after chromatography, 139 mg of the slower eluting component **9a** as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.17 (m, 5H), 6.59 (d, 1H, *J* = 8 Hz), 6.46 (d, 1H, *J* = 8 Hz), 6.02 (d, 1H, *J* = 8 Hz), 5.35 (d, 1H, *J* = 8 Hz), 5.01 (s, 1H), 4.78 (s, 1H), 3.82 (s, 3H), 3.70 (s, 3H), 3.52 (d, 1H, *J* = 4 Hz), 3.08 (d, 1H, *J* = 20 Hz), 2.78-2.68 (m, 2H), 2.44-2.25 (m, 6H), 1.94 (d, 1H, *J* = 16 Hz), 1.75-1.72 (m, 1H), 1.21 (s, 3H), 0.85 (m, 1H), 0.54 (m, 2H), 0.14 (m, 2H). ESIMS: m/z 500 ($M+H^+$, 100).

(1′R, 5α, 6R, 7R, 14α)-1′-phenyl-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-ethenomorphinan-7-yl)-methan-1′-ol (8a)
General procedure C was followed using 184 mg of **7a** to yield 103 mg of **8a** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.37 (d, 1H, *J* = 8 Hz), 7.32-7.23 (m, 3H), 6.62 (AB system, 1H), 6.56 (d AB system, 1H), 6.22 (d, 1H, *J* = 8 Hz), 5.61 (d, 1H, *J* = 12 Hz), 5.22 (s, 1H), 4.47 (s, 1H), 4.35 (d, 1H, *J* = 8 Hz), 3.86 (s, 3H), 3.40-3.30 (m, 3H), 3.15 (dt, 1H, J_a = 12 Hz, J_b = 4 Hz), 3.09-2.97 (m, 2H), 2.47 (dt, 1H, J_b = 12 Hz, J_a = 4 Hz), 2.10 (dd, 1H, J_a = 16 Hz, J_b = 4 Hz), 1.87 (AB system, 1H), 1.67 (AB system, 1H), 1.50 (s, 3H), 1.07 (m, 1H), 0.83 (m, 1H), 0.74 (m, 1H), 0.51-0.43 (m, 2H). ESIMS: m/z 486 ($M+H^+$, 100).

(1′S, 5α, 6R, 7R, 14α)-1′-phenyl-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-etheno-morphinan-7-yl)-methan-1′-ol (10a)
General procedure **C** was followed using 161 mg of **9a** to yield 56 mg of **10a** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.30-7.18 (m, 5H), 6.59 (AB system, 2H), 6.31 (d, 1H, *J* = 8.9 Hz), 5.51 (d, 1H, *J* = 8.9 Hz), 5.02 (s, 1H), 4.66 (s, 1H), 4.45 (d, 1H, *J* = 6.8 Hz), 3.50-3.40 (m, 3H), 3.38-3.32 (m, 1H), 3.20 (dt, 1H, J_a = 14 Hz, J_b = 9.7 Hz), 3.16-3.04 (m, 2H), 2.53 (dt, 1H, J_a = 14 Hz, J_b = 5.2 Hz), 2.16 (AB system, 2H), 2.11 (dd, 1H), 1.28 (s, 3H), 1.21-1.13 (m, 1H), 0.92-0.84 (m, 1H), 0.84-77 (m, 1H), 0.57 (m, 2H). ESIMS: m/z 486 ($M+H^+$, 100).

By a similar method, the following ligands were prepared:
(1′R, 5α, 6R, 7R, 14α)-1′-(2-methylphenyl)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-etheno-morphinan-7-yl)-methan-1′-ol (8b)
^{1}H NMR (400 MHz, CD_3OD) δ 7.65 (d, 1H, *J* = 7.3 Hz), 7.25-7.15 (m, 3H), 6.67-6.47 (AB system, 2H), 5.80 (d, 1H, *J* = 8.9 Hz), 5.26 (s, 1H), 5.08 (s, 1H), 4.23 (d, 1H, *J* = 6.4 Hz), 3.94 (s, 3H), 3.43 -3.33 (m, 3H), 3.12 (m, 1H), 3.03-2.83 (m, 1H), 2.52 (dt, 1H, J_b = 13.7 Hz, J_a = 5.4 Hz), 2.27 (s, 3H), 2.16-2.04 (bd, 1H), 1.95 (d, 1H, *J* = 13.5 Hz), 1.61 (s, 3H), 1.23 (d, 1H, *J* = 13.5 Hz), 1.07 (m, 1H), 0.82 (m, 1H), 0.72 (m, 1H), 0.49-0.37 (m, 2H). ESIMS: m/z 500 ($M+H^+$, 100).

(1′S, 5α, 6R, 7R, 14α)-1′-(2-methylphenyl)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-etheno-morphinan-7-yl)-methan-1′-ol (10b)

^{1}H NMR (400 MHz, CD_3OD) δ 7.16 (d, 2H, *J* = 8.0 Hz), 7.08 (d, 2H, *J* = 8.0 Hz), 6.59 (d, 1H, *J* = 8.0 Hz), 6.54 (d, 1H, *J* = 8.0 Hz), 6.29 (d, 1H, *J* = 8.6 Hz), 5.49 (s, 1H *J* = 9.0 Hz), 5.02 (s, 1H), 4.63 (s, 1H), 4.45 (bd, 1H), 3.47 (s, 3H), 3.46-3.31 (m, 2H), 3.32-3.06 (m, 3H), 2.52 (dt, 1H, J_a = 18.0 Hz, J_b = 5.0 Hz), 2.30 (s, 3H), 2.14 (s, 2H), 2.10-2.06 (m, 1H), 1.24 (s, 3H), 1.18 (m, 1H), 0.89-0.78 (m, 2H), 0.51 (m, 2H). ESIMS: m/z 500 ($M+H^+$, 100).

(1′R, 5α, 6R, 7R, 14α)-1′-(3-methylphenyl)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-etheno-morphinan-7-yl)-methan-1′-ol (8c)

^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (d, 1H, *J* = 7.4 Hz), 7.18-7.13 (m, 3H), 6.64-6.57 (AB system, 2H), 6.33 (d, 1H, *J* = 8.9 Hz), 5.54 (d, 1H, *J* = 8.9 Hz), 5.35 (s, 1H), 5.11 (s, 1H), 4.52 (d, 1H, *J* = 6.8 Hz), 3.72 (s, 3H), 3.51-3.32 (m, 3H), 3.29-3.20 (dt, 1H, J_b = 13.0 Hz, J_a = 4.0 Hz), 3.17-3.09 (m, 2H), 2.59 (dt, 1H, J_b = 13.7 Hz, J_a = 5.4 Hz), 2.45 (d, 1H, *J* = 14.6 Hz), 2.39 (s, 3H), 2.22 (d, 1H, *J* = 14.6 Hz), 2.11 (bd, 1H), 1.23 (m, 1H), 1.11 (s, 3H), 0.92-0.85 (m, 2H), 0.57 (m, 1H). ESIMS: m/z 500 ($M+H^+$, 100).

(1′S, 5α, 6R, 7R, 14α)-1′-(3-methylphenyl)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-etheno-morphinan-7-yl)-methan-1′-ol (10c)

^{1}H NMR (400 MHz, CD_3OD) δ 7.17-7.06 (m, 3H), 6.59 (d, 1H, *J* = 8.0 Hz), 6.54 (d, 1H, *J* = 8.0 Hz), 6.31 (d, 1H, *J* = 9.1 Hz), 5.50 (d, 1H, *J* = 8.7 Hz), 5.02 (s, 1H, *J* = 9.0 Hz), 4.64 (s, 1H), 4.44 (bd, 1H), 3.45 (s, 3H), 3.46-3.31 (m, 2H), 3.23-3.05 (m, 3H), 2.52 (dt, 1H, J_a = 15.5 Hz, J_b = 5.8 Hz), 2.32 (s, 3H), 2.11 (m, 2H), 1.25 (s, 3H), 1.18 (m, 1H), 0.93-0.77 (m, 2H), 0.53 (m, 2H). ESIMS: m/z 500 ($M+H^+$, 100).

(1′R, 5α, 6R, 7R, 14α)-1′-(4-methylphenyl)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-etheno-morphinan-7-yl)-methan-1′-ol (8d)

^{1}H NMR (400 MHz, CD_3OD) δ 7.25 (d, 1H, *J* = 8.0 Hz), 7.12 (d, 1H, *J* = 7.6 Hz), 6.59 (AB system, 2H), 6.23 (d, 1H, *J* = 8.8 Hz), 5.62 (d, 1H, *J* = 8.8 Hz), 5.21 (s, 1H), 4.69 (s, 1H), 4.34 (d, 1H, *J* = 6.4 Hz), 3.87 (s, 3H), 3.40-3.32 (m, 3H), 3.14 (dt, 1H, J_a = 13.1 Hz, J_a = 2.4 Hz), 3.12-2.99 (m, 2H), 2.48 (dt, 1H, J_b = 5.2 Hz, J_a = 14.3 Hz), 2.30 (s, 3H), 2.10 (dd, 1H, J_a = 14.3 Hz, J_b = 3.2 Hz), 1.87 (AB system, 1H), 1.64 (d, AB system, 1H), 1.50 (s, 3H), 1.07 (m, 1H), 0.83 (m, 1H), 0.74 (m, 1H), 0.52-0.40 (m, 2H). ESIMS: m/z 500 ($M+H^+$, 100).

(1′S, 5α, 6R, 7R, 14α)-1′-(4-methylphenyl)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-etheno-morphinan-7-yl)-methan-1′-ol (10d)

^{1}H NMR (400 MHz, CD_3OD) δ 7.16 (d, 2H, *J* = 8.0 Hz), 7.08 (d, 2H, *J* = 8.0 Hz), 6.59 (d, 1H, *J* = 8.1 Hz), 6.54 (d, 1H, *J* = 8.1 Hz), 6.29 (d, 1H, *J* = 8.6 Hz), 5.49 (s, 1H, *J* = 9.0 Hz), 5.02 (s, 1H), 4.63 (s, 1H), 4.45 (bd, 1H), 3.47 (s, 3H), 3.46-3.31 (m, 2H), 3.32-3.06 (m, 3H), 2.52 (dt, 1H, J_a = 18.3 Hz, J_b = 5.0 Hz), 2.30 (s, 3H), 2.14 (s, 2H), 2.10-2.06 (m, 1H), 1.24 (s, 3H), 1.18 (m, 1H), 0.89-0.78 (m, 2H), 0.51 (m, 2H). ESIMS: m/z 500 ($M+H^+$, 100).

(1′R, 5α, 6R, 7R, 14α)-1′-(4-fluorophenyl)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-etheno-morphinan-7-yl)-methan-1′-ol (8e)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.26 (m, 2H), 7.01–6.92 (m, 2H), 6.56 (d, 1H, *J* = 8.0 Hz), 6.44 (d, 1H, *J* = 8.1 Hz), 6.15 (d, 1H, *J* = 8.9 Hz), 5.56 (d, 1H, *J* = 8.9 Hz), 5.40 (s, 1H), 5.35 (bs, 1H), 5.08 (s, 1H), 4.69 (s, 1H), 3.80 (s, 3H), 3.39 (d, 1H, *J* = 6.4 Hz), 3.05 (d, 1H, *J* = 18.3 Hz), 2.70–2.61 (m, 1H), 2.43–2.19 (m, 5H), 2.01 (d, 1H, *J* = 13.9 Hz), 1.73 (d, 1H, *J* = 12.4 Hz), 1.38 (s, 3H), 1.28–1.16 (m, 1H), 0.78–0.64 (m, 1H), 0.55–0.38 (m, 2H), 0.14–-0.01 (m, 2H). ESIMS: m/z 504 ($M+H^+$, 100).

(1′S, 5α, 6R, 7R, 14α)-1′-(4-fluorophenyl)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-etheno-morphinan-7-yl)-methan-1′-ol (10e)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, 2H, Ja = 6.0, Jb = 2.6 Hz), 7.00–6.91 (m, 2H), 6.58 (d, 1H, *J* = 8.0 Hz), 6.44 (d, 1H, *J* = 8.1 Hz), 6.00 (dd, 1H, *Ja* = 8.8 Hz, *Jb* = 1.0 Hz), 5.38 (d, 1H, *J* = 8.8 Hz), 5.03 (d, 1H *J* = 1.1 Hz), 4.77 (d, 1H, d, *J* = 3.9 Hz), 4.46 (bs, 1H), 3.68 (s, 3H), 3.52 (d, 1H, *J* = 6.5 Hz), 3.08 (d, 1H, *J* = 18.4 Hz), 2.77–2.66 (m, 2H), 2.46–2.27 (m, 6H), 1.88 (d, 1H *J* = 13.4 Hz), 1.78–1.71 (m, 1H), 1.18 (s, 3H), 0.91–0.81 (m, 1H), 0.60–0.47 (m, 2H), 0.19–0.08 (m, 2H). ESIMS: m/z 504 ($M+H^+$, 100).

(1′R, 5α, 6R, 7R, 14α)-1′-(4-propylthiophenyl)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-etheno-morphinan-7-yl)-methan-1′-ol (8f)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 4H), 6.56 (d, 1H, *J* = 8.0 Hz), 6.44 (d, 1H, *J* = 8.1 Hz), 6.19–6.11 (m, 1H), 5.55 (d, 1H, J = 8.9 Hz), 5.36 (s, 1H), 5.35 (s, 1H), 5.08 (s, 1H), 4.66 (s, 1H), 3.80 (s, 3H), 3.39 (d, 1H, *J* = 6.4 Hz), 3.05 (d, 1H, *J* = 18.3 Hz), 2.88 (t, 2H, *J* = 7.2 Hz), 2.70–2.61 (m, 1H), 2.43–2.19 (m, 5H), 2.01 (d, 1H, *J* = 13.9 Hz), 1.77–1.59 (m, 2H), 1.38 (s, 3H), 1.28–1.16 (m, 1H), 1.01 (t, 3H, *J* =7.3 Hz), 0.78–0.64 (m, 1H), 0.55–0.38 (m, 2H), 0.14–-0.01 (m, 2H). ESIMS: m/z 560 ($M+H^+$, 100).

***N*-Cyclopropylcarbonyl-7α-formyl-7β-methyl-6,14-endo-ethanotetrahydronorthebaine (11)**

The aldehyde **4b** (500 mg) was dissolved in 15 mL of EtOH. Into this solution was added 30 mg of 10% Pd on carbon. The mixture was shaken in a Parr hydrogenator under 100 psi of H_2 for 12 h. The mixture was filtered and the solvents removed under reduced pressure to yield 510 mg of **11** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 0.6H), 9.69 (s, 0.4H), 6.76 (d, 1H, *J* = 8.1 Hz), 6.61 (d, 1H, *J* = 8.1 Hz), 4.9 (d, 0.4H, *J* = 6.9 Hz), 4.82 (s, 0.6H), 4.81 (s, 0.4H), 4.52 (dd, 0.6H, J_a = 14 Hz, J_b = 5.7 Hz), 4.34 (d, 0.6H *J* = 6.8 Hz), 4.04 (dd, 0.4H J_a = 15, J_b = 6 Hz), 3.89 (s, 3H), 3.48 (s, 1.8H), 3.46 (s, 1.2H), 3.34 (td, 0.4H J_a = 13.4, J_b = 3.2 Hz), 3.05 (dd, 0.6H J_a = 18.5 Hz, J_b = 6.9 Hz), 2.97 (dd, 0.4H, J_a = 18.7 Hz, J_b = 7.2 Hz), 2.87 (d, 0.6H *J* = 18.7 Hz), 2.81 (td, 0.6H J_a = 13.7, J_b = 4.1 Hz), 2.71 (d, 0.4H *J* = 18.8 Hz), 2.42–2.37 (m, 1H), 2.27 (td, 0.4H J_a = 13.1 Hz, J_b = 5.7 Hz), 2.16 (td, 0.6H J_a = 13.2 Hz, J_b = 5.8 Hz), 1.80–1.60 (m, 3.6H), 1.5 (dd, 0.4H J_a = 13.7 Hz, J_b = 3.7 Hz), 1.33–1.18 (m, 5H), 1.15–1.06 (m, 1H), 1.03–0.94 (m, 2H), 0.84–0.71 (m, 2H). ESIMS: m/z 438 ($M+H^+$, 100).

***N*-Cyclopropylcarbonyl-6,14-*endo*-ethano-7β-methyl-nornepenthol (12a).**

General procedure **A** was followed using 515 mg of **11** to yield 336 mg of **12a** as white crystals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.23 (m, 5H), 6.78-6.75 (2d, 1H), 6.61-6.58 (2d, 1H), 5.06 (d, 0.55H, *J* = 2.6 Hz), 4.99 (d, 0.45H, *J* = 2.6 Hz), 4.91-4.87 (m, 1H), 4.51-4.46 (dd, 0.55H, J_a = 5.4 Hz, Jb = 13.7 Hz), 4.35-4.34 (d, 0.55H, *J* = 6.8 Hz), 4.03-3.98 (d, 0.45H, J_a = 4.9 Hz, J_b = 13.5 Hz), 3.92-3.914 (2s, 3H), 3.53 (s, 1.65H), 3.48 (s, 1.35H), 3.38-3.30 (dt, 0.55H, J_a = 3.8 Hz, J_b = 8.6 Hz), 3.11-3.04 (dd, 0.55H, J_a = 6.9 Hz, J_b = 18.3 Hz), 3.02-2.96 (dd, 0.45H, J_a = 6.9 Hz, J_b = 18.5 Hz), 2.92-2.88 (d, 0.55H, *J* = 18.3 Hz), 2.49-2.44 (m, 1H), 2.36-2.29 (dt, 0.45Hz, J_a = 5.6 Hz, J_b = 12.9 Hz), 2.25-2.17 (dt, 0.55Hz, J_a = 6.0 Hz, J_b = 13.2 Hz), 2.03-1.90 (m, 2H), 1.86-1.80 (m, 0.45Hz), 1.76-1.51 (m, 6H), 1.10-0.69 (m, 7H).
ESIMS: m/z 516 ($M+H^+$, 100).

(1′R, 5α, 6R, 7R, 14α)-1′-phenyl-1′-(4,5-epoxy-7,8-dihydro-3,6-dimethoxy-7β-methyl 17-cyclopropylmethyl-6,14-etheno-morphinan-7-yl)-methan-1′-ol (14a).

General procedure **B** was followed using 473 mg of **12a** to yield a clear oil. Crystallization from CH_2Cl_2/Et_2O gave 133 mg of **14** as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.34-7.30 (m, 2H), 7.27-7.24 (m, 1H), 6.73 (d, 1H, *J* = 8.4 Hz), 6.57 (d, 1H, *J* = 8.0 Hz), 5.76 (s, 1H), 5.03 (s, 1H), 4.96 (s, 1H), 3.91 (s, 3H), 3.64 (s, 3H), 3.01-2.94 (m, 2H), 2.57 (d, 1H, *J* = 6.8 Hz), 2.29 (dd, 1H, J_a = 6.8 Hz, J_b = 18.3 Hz), 2.24-2.20 (m, 3H), 1.95 (dd, 1H, J_a = 4 Hz, J_b = 14.3 Hz), 1.90-1.77 (m, 2H), 1.60-1.52 (m, 2H), 1.40-1.28 (m, 4H), 0.95 (m, 1H), 0.68 (m, 1H), 0.51-0.39 (m, 2H), 0.08-0.01 (m, 2H). ESIMS: m/z 502 ($M+H^+$, 100).

(1′S, 5α, 6R, 7R, 14α)-1′-phenyl-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-ethanomorphinan-7-yl)-methan-1′-ol (17)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.36 (m, 2H), 7.31-7.27 (m, 2H), 7.25-7.21 (m, 1H), 6.74 (d, 1H, *J* = 8.4 Hz), 6.64 (d, 1H, *J* = 8.0 Hz), 5.02 (s, 1H), 4.95 (d, 1H, *J* = 2.4 Hz), 4.00 (d, 1H, *J* = 7.2 Hz), 3.47 (s, 3H), 3.39-3.22 (m, 3H), 3.12-3.00 (m, 2H), 2.95 (dd, 1H, *J* = 19.4, 7.0 Hz), 2.67 (d, 1H, *J* = 12.8 Hz), 2.50 (td, 1H, *J* = 13.8, 5.6 Hz), 2.15 (t, 1H, *J* = 12.2 Hz), 2.00 (dd, 1H, *J* = 12.6, 4.2 Hz), 1.90-1.79 (m, 2H), 1.70-1.62 (m, 1H), 1.20-1.12 (m, 1H), 0.92 (s, 3H), 0.89-0.77 (m, 3H), 0.53-0.47 (m, 2H). HMRS: calc for $C_{31}H_{38}NO_4$ ($[M+H]^+$) 488.2801, found 488.2949.

(1′R, 5α, 6R, 7R, 14α)-1′-phenyl-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-ethanomorphinan-7-yl)-methan-1′-ol (15a) .

General procedure **C** was followed using 133 mg of **14** to yield 75 mg of **15a** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.42 (m, 2H), 7.35–7.28 (m, 2H), 7.28–7.20 (m, 1H), 6.61 (d, 1H, *J* = 8.0 Hz), 6.47 (d, 1H, *J* = 8.0 Hz), 5.98 (s, 1H), 5.05 (s, 1H), 4.95 (d, 1H, *J* = 1.6 Hz), 3.59 (s, 3H), 2.98 (d, 1H, *J* = 6.4 Hz), 2.93 (d, 1H, *J* = 18.3 Hz), 2.63–2.50 (m, 1H), 2.32–2.13 (m, 5H), 1.95 (dd, 1H, J_a = 14.2 Hz, J_b = 3.9 Hz), 1.89–1.71 (m, 2H), 1.59–1.44 (m, 2H), 1.35–1.21 (m, 4H), 0.97–0.81 (m, 1H,), 0.75–0.60 (m, 1H), 0.52–0.36 (m, 2H), 0.10–-0.03 (m, 2H). ESIMS: m/z 488 ($M+H^+$, 100).

(1′R, 5α, 6R, 7R, 14α)-1′-(2-methylphenyl)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-ethanomorphinan-7-yl)-methan-1′-ol (15b)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, 1H, *J* = 7.8, 1.2 Hz), 7.22 (td, 1H, *J* = 7.4, 1.5 Hz), 7.17 (td, 1H, *J* = 7.3, 1.5 Hz), 7.13 (dd, 1H, *J* = 7.5, 1.7 Hz), 6.69 (d, 1H, *J* = 8.0 Hz), 6.52 (d, 1H, *J* = 8.0 Hz), 5.47 (s, 1H), 5.49 (s, 1H), 5.04 (s, 1H), 4.83 (bs, 1H), 3.61 (s, 3H), 2.94 (d, 1H, *J* = 18.1 Hz), 2.93 (d, 1H, *J* = 6.5 Hz), 2.61-2.57 (m, 1H), 2.47 (s, 3H), 2.31-2.18 (m, 5H), 1.99 (dd, 1H, *J* = 14.3, 3.9 Hz), 1.87-1.83 (m, 2H), 1.56 (d, 1H, *J* = 10.1 Hz), 1.43-1.33 (m, 4H), 1.25 (d, 1H, *J* = 14.3 Hz), 0.95-0.83 (m, 1H), 0.71-0.62 (m, 1H), 0.48-0.38 (m, 2H), 0.07-0.02 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) 145.4, 139.7, 137.7, 136.1, 133.4, 130.8, 130.6, 128.4, 127.4, 125.7, 119.9, 116.8, 94.8, 82.6, 73.8, 60.3, 59.3, 53.7, 53.5, 46.2, 44.5, 43.8, 38.6, 35.9, 33.6, 28.9, 23.1, 21.8, 18.3, 17.70, 9.6, 4.3, 3.8. HMRS: calc. for $C_{32}H_{40}N_1O_4$ ($[M+H]^+$) 502.2952, found 502.3045.

(1′R, 5α, 6R, 7R, 14α)-1′-(3-methylphenyl)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-ethanomorphinan-7-yl)-methan-1′-ol (15c)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (s, 1H), 7.23-7.18 (m, 2H), 7.07 (d, 1H, *J* = 6.8 Hz), 6.70 (d, 1H, *J* = 8.0 Hz), 6.53 (d, 1H, *J* = 8.0 Hz), 5.72 (s, 1H), 5.00 (s, 2H), 4.75 (bs, 1H), 3.61 (s, 3H), 2.99 (d, 1H, *J* = 6.9 Hz), 2.95 (d, 1H, *J* = 19.7 Hz), 2.62-2.54 (m, 1H), 2.36 (s, 3H), 2.30-2.19 (m, 5H), 1.96 (dd, 1H, *J* = 14.3, 4.9 Hz), 1.87-1.76 (m, 2H), 1.58-1.54 (m, 2H), 1.35-1.26 (m, 4H), 0.96-0.86 (m, 1H), 0.74-0.64 (m, 1H), 0.50-0.39 (m, 2H), 0.08-0.00 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.4, 141.2, 137.7, 137.2, 133.4, 131, 128.5, 128.4, 127.6, 127.5, 120, 116.8, 94.8, 82.4, 80.4, 60.3, 59.3, 53.4, 46.2, 43.9, 43.4, 39.8, 35.9, 33.7, 29.7, 23.1, 21.9, 18.2, 17.2, 9.60, 4.4, 3.8. HMRS: calc for $C_{32}H_{40}N_1O_4$ ($[M+H]^+$) 502.2952, found 502.3086.

(1′R, 5α, 6R, 7R, 14α)-1′-(4-methylphenyl)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-ethanomorphinan-7-yl)-methan-1′-ol (15d)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, 2H, *J* = 8.0 Hz), 7.12 (d, 2H, *J* = 8.0 Hz), 6.66 (d, 1H, *J* = 8.0 Hz), 6.50 (d, 1H, *J* = 8.0 Hz), 5.85 (s, 1H), 5.47 (bs, 1H), 5.01 (s, 1H), 4.97 (s, 1H), 3.60 (s, 3H), 2.98 (d, 1H, *J* = 6.5 Hz), 2.94 (d, 1H, *J* = 18.5 Hz), 2.61-2.55 (m, 1H), 2.34 (s, 3H), 2.28-2.18 (m, 5H), 1.95 (dd, 1H, *J* = 14.0, 4.0 Hz), 1.84-1.76 (m, 2H), 1.55-1.50 (m, 2H), 1.32-1.25 (m, 4H), 0.94-0.86 (m, 1H), 0.72-0.64 (m, 1H), 0.50-0.41 (m, 2H), 0.07-0.00 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145, 137.7, 137.5, 136.8, 132.9, 129.9, 128, 127.8, 119.5, 116.5, 94.2, 81.9, 79.9, 60, 58.9, 53, 45.7, 43.5, 43, 39.4, 35.5, 33.3, 29.3, 23.8, 22.6, 21, 17.8, 16.80, 9.2, 4, 3.4. HMRS: calc $C_{32}H_{39}NO_4Na$ ($[M+Na]^+$) 524.2777, found 524.2812.

(1′R, 5α, 6R, 7R, 14α)-1′-(4-fluorophenyl)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-ethanomorphinan-7-yl)-methan-1′-ol (15e)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (2H, dd, *J* = 8.5, 5.5 Hz), 7.00 (2H, t, *J* = 8.8 Hz), 6.62 (1H, d, *J* = 8.0 Hz), 6.49 (1H, d, *J* = 8.5 Hz), 6.00 (1H, s), 5.03 (1H, s), 4.95 (1H, d, *J* = 2.0 Hz), 3.59 (3H, s), 2.99 (1H, d, *J* = 6.5 Hz), 2.94 (1H, d, *J* = 18.5 Hz), 2.61-2.54 (1H, m), 2.28-2.19 (5H, m), 1.95 (1H, dd, *J* = 14.0, 4.0 Hz), 1.85-1.73 (2H, m), 1.58-1.51 (1H, m), 1.46 (1H, d, *J* = 14.5 Hz), 1.29-1.23 (4H, m), 0.97-0.87 (1H, m), 0.72-0.64 (1H, m), 0.50-0.40 (2H, m), 0.08-0.00 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163, 161.1, 145.0, 137.6, 132.8, 131.4, 131.3, 127.6, 119.5, 116.62, 114.2, 114.0, 93.9, 81.9, 79.4, 59.9, 58.8, 45.6, 43.5, 42.9, 39.4, 35.4, 33.3, 29.3, 22.6, 17.7, 16.7, 9.1, 4.0, 3.4. HMRS: calc for $C_{31}H_{37}NO_4F$ ($[M+H]^+$) 506.2701, found 506.2682.

(1′R, 5α, 6R, 7R, 14α)-1′-(4-methoxyphenyl)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-ethanomorphinan-7-yl)-methan-1′-ol (15f)

White solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (2H, d, *J* = 8.68 Hz), 6.84 (2H, d, *J* = 8.68 Hz), 6.68 (1H, d, *J* = 8.00 Hz), 6.50 (1H, d, *J* = 8.00 Hz), 5.77 (1H, s), 5.01-4.98 (2H, m), 3.81 (3H, s), 3.59 (3H, s), 2.99-2.93 (2H, m), 2.56 (1H, d, *J* = 5.88 Hz), 2.30-2.20 (5H, m), 1.94-1.91 (1H, m), 1.82-1.78 (2H, m), 1.53-1.51 (1H, m), 1.48 (1H, d, *J* = 14.1 Hz), 1.29-1.23 (4H, m), 0.94-0.91 (1H, m), 0.67-0.64 (1H, m), 0.47-0.42 (2H, m), 0.05-0.02 (2H, m). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 158.76, 144.91, 137.33, 132.92, 130.91, 127.94, 119.54, 116.4, 112.7, 94.27, 81.89, 79.55, 59.96, 58.86, 55.2, 53.06, 45.71, 43.46, 43.09, 39.42, 35.47, 33.29, 29.28, 22.6, 17.78, 16.72, 9.18, 4.02, 3.42. HRMS: calc for $C_{32}H_{39}NO_5Na$ ($[M+Na]^+$) 540.2726, found 540.2731.

(1′R, 5α, 6R, 7R, 14α)-1′-(3-chlorophenyl)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-ethanomorphinan-7-yl)-methan-1′-ol (15g)

White solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (bs, 1H), 7.36-7.30 (m, 1H), 7.29-7.22 (m, 2H), 6.67 (d, 1H, *J* = 8.0 Hz), 6.52 (d, 1H, *J* = 8.0 Hz), 6.00 (s, 1H), 5.02 (s, 1H), 4.96 (d, 1H, *J* = 2.0 Hz), 3.60 (s, 3H), 3.02 (d, 1H, *J* = 6.5 Hz), 2.96 (d, 1H, *J* = 18.3 Hz), 2.66-2.55 (m, 1H), 2.33-2.16 (m, 5H), 1.99 (dd, 1H, *J* = 3.9, 14.2 Hz), 1.89-1.70 (m, 2H), 1.61-1.52 (m, 1H), 1.49 (d, 1H, *J* = 14.3 Hz), 1.28 (s, 3H), 0.99-0.87 (m, 1H), 0.77-0.64 (m, 1H), 0.54-0.40 (m, 2H), 0.11-0.01 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 142.8, 137.5, 133.3, 132.8, 129.9, 128.5, 128.2, 127.7, 127.5, 119.6, 116.6, 93.9, 81.9, 79.6, 59.9, 58.8, 53.1, 45.6, 43.5, 42.9, 39.3, 35.5, 33.3, 29.2, 22.7, 17.7, 16.8, 9.1, 4.0, 3.4. HRMS: calc. for $C_{31}H_{36}ClNNaO_4$ ($[M+Na]^+$) 544.223056, found 544.2218.

(1′R, 5α, 6R, 7R, 14α)-1′-(3-fluorophenyl)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-ethanomorphinan-7-yl)-methan-1′-ol (15h)

White solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.18 (m, 3H), 6.97 (m, 1H), 6.69 (d, 1H, *J* = 8.0 Hz), 6.53 (d, 1H, *J* = 8.0 Hz), 5.92 (s, 1H), 5.03 (s, 1H), 4.98 (s, 1H), 3.61 (s, 3H), 3.02 (d, 1H, *J* = 6.5 Hz), 2.96 (d, 1H, *J* = 18.3 Hz), 2.60 (m, 1H), 2.33-2.17 (m, 5H), 1.98 (dd, 1H, *J* = 3.9, 14.4 Hz), 1.81 (m, 2H), 1.54 (m, 2H), 1.26 (s, 3H), 1.00-0.82 (m, 2H), 0.75-0.65 (m, 1H), 0.54-0.40 (m, 2H), 0.11-0.00 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 143.5, 137.4, 132.8, 128.6, 128.5, 127.9, 125.7, 125.6, 119.6, 116.9, 116.7, 116.5, 114.3, 114.1, 94.1, 81.9, 79.6, 59.9, 58.8, 53.1, 45.7, 43.5, 42.9, 39.3, 35.4, 33.2, 29.7, 29.3, 22.6, 17.7, 16.8, 9.1, 4.1, 3.4. HRMS: calc. for $C_{31}H_{36}FNNaO_4$ ($[M+Na]^+$) 528.252607, found 528.2552.

(1′R, 5α, 6R, 7R, 14α)-1′-(3-thiophenyl)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-ethanomorphinan-7-yl)-methan-1′-ol (15i)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25-7.22 (m, 2H), 7.19-7.17 (m, 1H), 6.69 (d, 1H, *J* = 8.08 Hz), 6.52 (d, 1H, *J* = 8.08 Hz), 5.64 (s, 1H), 5.14 (s, 1H), 4.98 (s, 1H), 4.68 (bd, 1H), 3.60 (s, 3H), 2.98 (d, 1H, *J* = 6.36 Hz), 2.93 (d, 1H, *J* = 18.4 Hz), 2.58 (d, 1H, *J* = 6.72 Hz), 2.30-2.16 (m, 5H), 2.08 (dd, 1H, *J*= 14.2 Hz, *J* = 4.04 Hz), 1.83-1.71 (m, 2H), 1.56-1.49 (m, 2H), 1.30 (s, 3H), 1.21-1.18 (m, 1H), 0.93-0.88 (m, 1H), 0.73-0.69 (m, 1H), 0.49-0.44 (m, 2H), 0.06-0.04 (m, 2H). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 145.11, 142.54, 137.26, 132.9, 128.81, 128.06, 123.96, 123.55, 119.58, 116.38, 94.21, 81.78, 76.62, 59.92, 58.79, 53.03, 45.72, 43.56, 42.97, 40.09, 35.54, 33.35, 29.34, 22.66, 17.81, 16.89, 9.21, 4.09, 3.28. HRMS: calc. for $C_{29}H_{35}NO_4SNa$ ($[M+Na]^+$) 516.2184, found 516.2212.

(1′R, 5α, 6R, 7R, 14α)-1′-(3-methyl-2-thiophenyl)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-ethanomorphinan-7-yl)-methan-1′-ol (15j)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20 (d, 1H, *J* = 5.12 Hz*)*, 6.76 (d, 1H, *J* = 5.12 Hz), 6.68 (d, 1H, *J* = 8.08 Hz), 6.51 (d, 1H, *J* = 8.08 Hz), 5.45 (s, 2H), 5.01 (s, 1H), 4.80 (bd, 1H), 3.58 (s, 3H), 2.96-2.92 (m, 2H), 2.59 (m, 1H), 2.29-2.21 (m, 8H), 2.11 (dd, 1H, *J* = 14.2 Hz*, J* = 4.04 Hz), 1.85-1.77 (m, 2H), 1.61-1.55 (m, 1H), 1.52 (s, 3H), 1.28-1.24 (m, 2H), 0.97-0.87 (m, 1H), 0.72-0.66 (m, 1H), 0.46-0.41 (m, 2H), 0.04- 0.02 (m, 2H). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 144.92, 138.41, 137.29, 134.55, 132.87, 128.75, 127.99, 124.09, 119.57, 116.4, 94.22, 81.9, 73.5, 59.91, 58.9, 53.08, 45.87, 44.1, 43.43, 39.27, 35.5, 33.33, 29.01, 22.68, 17.94, 17.09, 15.67, 9.18, 3.93, 3.38. HRMS: calc. for $C_{30}H_{38}NO_4S$ ($[M+H]^+$) 508.2521, found 508.2571.

(1′R, 5α, 6R, 7R, 14α)-1′-(5-chloro-2-thiophenyl)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-ethanomorphinan-7-yl)-methan-1′-ol (15k)

White solid: ^{1}H NMR ($CDCl_3$, 400MHz) δ 6.79 (d, 1H, *J* = 3.80 Hz), 6.76 (d, 1H, *J* = 3.80 Hz), 6.69 (d, 1H, *J* = 8.08 Hz), 6.52 (d, 1H, *J* = 8.08 Hz), 5.16 (s, 1H), 5.87 (s, 1H), 4.96 (s, 1H), 4.63 (bd, 1H), 3.57 (s, 3H), 2.98 (d, 1H, *J* = 6.36 Hz), 2.93 (d, 1H, *J* = 18.4 Hz), 2.61 (d, 1H, *J*=7.08 Hz), 2.28-2.23 (m, 6H), 1.80-1.77 (m, 1H), 1.68-1.66 (m, 1H), 1.52-1.44 (m, 2H), 1.32 (s, 3H), 1.20-1.19 (m, 1H), 0.94-0.87 (m, 1H), 0.75-0.73 (m, 1H), 0.50-0.46 (m, 2H), 0.07-0.06 (m, 2H). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 144.87, 144.32, 137.25, 132.76, 129.14, 128.05, 125.23, 124.82, 119.67, 116.44, 94.04, 81.67, 77.58, 59.94, 58.82, 53.05, 45.73, 43.45, 42.99, 40.39, 35.58, 33.38, 29.27, 22.85, 17.69, 16.8, 9.25, 3.98, 3.39. HRMS: calc. for $C_{29}H_{34}NO_4SClNa$ ($[M+Na]^+$) 550.1795, found 550.1823.

(1′R, 5α, 6R, 7R, 14α)-1′-(2-thiophenyl)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-ethanomorphinan-7-yl)-methan-1′-ol (15l)

White solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26-7.24 (m, 1H), 7.04-7.03 (m, 1H), 6.98-6.95 (m, 1H), 6.69 (d, 1H, *J* = 8.08 Hz), 6.52 (d, 1H, *J* = 8.08 Hz), 5.31 (s, 1H), 5.85 (s, 1H), 4.98 (s, 1H), 4.68 (bd, 1H), 3.59 (s, 3H), 2.99 (d, 1H, *J* = 6.36 Hz), 2.93 (d, 1H, *J* = 18.4 Hz), 2.59 (d, 1H, *J* = 6.72 Hz), 2.31-2.18 (m, 6H), 1.84-1.71 (m, 2H), 1.52-1.47 (m, 1H), 1.35 (s, 3H), 1.21-1.17 (m, 2H), 0.95-0.86 (m, 1H), 0.75-0.70 (m, 1H), 0.51-0.42 (m, 2H), 0.06-0.05 (m, 2H). ^{13}C NMR, 100 MHz,

($CDCl_3$) δ 145.27, 144.9, 137.25, 132.86, 128.08, 126.22, 125.71, 124.66, 119.62, 116.4, 94.15, 81.75, 76.62, 59.92, 58.79, 53.05, 45.74, 43.51, 43.1, 40.39, 35.59, 33.38, 29.28, 22.7, 17.77, 16.77, 9.23, 4.04, 3.34. HRMS: calc for $C_{29}H_{35}NO_4SNa$ ($[M+Na]^+$) 516.2184, found 519.2155.

(1′R, 5α, 6R, 7R, 14α)-1′-(3-furyl)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl 17-cyclopropylmethyl-6,14-ethanomorphinan-7-yl)-methan-1′-ol (15m).

^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (bs, 1H), 7.37 (t, 1H, *J* = 1.6 Hz), 6.68 (d, 1H, *J* = 8.0 Hz), 6.54-6.50 (m, 2H), 5.74 (s, 1H), 5.02 (s, 1H), 4.97 (d, 1H, *J* = 2.3 Hz), 3.59 (s, 3H), 3.05-2.90 (m, 2H), 2.68-2.58 (m, 1H), 2.37-2.17 (m, 6H), 1.88-1.64 (m, 2H), 1.62-1.52 (m, 1H), 1.42-1.34 (m, 1H), 1.31 (m, 3H), 1.22-1.11 (m, 1H), 0.95-0.85 (m, 1H), 0.79-0.70 (m, 1H), 0.55-0.42 (m, 2H), 0.12-0.03 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 142.1, 141.0, 137.5, 132.8, 127.8, 125.5, 119.6, 116.5, 111.3, 93.9, 81.7, 73.7, 59.9, 58.7, 53.0, 45.7, 43.6, 42.7, 40.5, 35.5, 33.4, 29.3, 22.6, 17.7, 16.8, 9.2, 4.1, 3.3. HRMS: calc. for $C_{29}H_{35}NNaO_5$ 500.241293, found 500.2439.

2: Micro analysis and HPLC

	Calculated			Found		
	C	**H**	**N**	**C**	**H**	**N**
8a: C31H35NO4.HCl.1.5H2O	67.8	7.16	2.55	68.3	7.57	2.84
8b: C32H37NO4.HCl	71.7	7.14	2.61	71.8	6.94	2.71
8c: C32H37NO4.HCl.0.5H2O	70.5	7.21	2.57	70.9	7.24	2.57
8d: C32H37NO4.HCl	71.7	7.14	2.61	71.5	7.25	2.76
8e: C31H34FNO4.HCl.1.5H2O	65.7	6.75	2.47	65.6	7.24	2.64
10a: C31H35NO4.HCl	71.3	6.95	2.68	71.2	6.85	2.50
10b: C32H37NO4.HCl.0.5H2O	70.5	7.21	2.57	70.8	7.46	2.78
10c: C32H37NO4.HCl.2H2O	67.1	7.40	2.45	66.6	6.91	2.43
10d: C32H37NO4.HCl.2H2O	67.1	7.40	2.45	66.8	7.09	2.88
10e: C31H34FNO4.HCl.H2O	66.7	6.68	2.51	66.7	7.20	2.94
15a: C31H37NO4.HCl	71.0	7.31	2.67	70.9	7.43	2.63
15b: [a]						
15c: C32H39NO4.HCl	71.3	7.38	2.75	71.4	7.49	2.60
15d: [b]						
15e: C31H36FNO4.HCl	68.6	6.77	2.71	68.7	6.88	2.58
15f: C32H39NO5.HCl	69.4	7.28	2.53	69.5	7.38	2.61
15g: C31H36ClNO4.HCl	66.7	6.68	2.51	66.5	6.61	2.65
15h: C31H36FNO4.HCl.3H20	62.5	7.27	2.35	62.1	6.36	3.01
15i: C29H35NO4S.HCl.1.4H2O	62.7	7.04	2.52	62.9	6.97	2.33
15j: C30H37NO4S.HCl	66.2	7.04	7.15	66.2	7.15	2.66
15k: C29H34NClO4S.HCl	61.7	6.25	2.48	61.8	6.32	2.57
15l: C29H35NO4S.HCl	65.7	6.84	2.64	65.5	6.89	2.54
15m: C29H35NO5.HCl.3H2O	61.3	7.45	2.47	61.7	6.94	2.65
17: C31H37NO4.HCl.H2O	69.8	7.38	2.63	70.0	7.88	2.63

[a]15b: Retention time, solvent system A: 7.4 min, > 95% purity by peak area; Retention time, solvent system B: 11.4 min, > 95% purity by peak area

[b]15d: Retention time, solvent system A: 8.5 min, > 95% purity by peak area; Retention time, solvent system B: 13.4 min, > 95% purity by peak area

Run A - MeCN:0.03% TFA 36:64

Run B - MeCN:0.03% TFA 32:68

HPLC: Integrated HPLC: Shimadzu LC-2010AHT, Column: Dionex Acclaim 15 cm C18 column, Temp: 25 degrees C, Wavelength of detection: 220 nm.

3: Pharmacology

All tissue culture reagents were purchased from Gibco Life Sciences (Grand Island, NY, USA). Radioactive compounds were purchased from Perkin-Elmer (Waltham, MA, USA).

Cell Lines and Membrane Preparations

C6-rat glioma cells stably transfected with a rat μ (C6-MOPr) or rat δ (C6-DOPr) opioid receptor,[6] Chinese hamster ovary (CHO) cells stably expressing a human κ (CHO-KOPr) opioid receptor[22] and HEK 293 cells expressing the human NOP receptor (HEK-NOP) were used for all in vitro assays. Cells were cultured and membranes prepared as previously described.[23] Receptor numbers were determined as: MOPr 2100 fmols/mg, DOPr 955 fmols/mg, KOPr 825 fmols/mg, NOPr 1130 fmols/mg.

Radioligand Binding Assays

Competitive displacement assays were performed as previously described [23] using 0.2 nM [^{3}H]diprenorphine (1.85 TBq/mmol)(for MOP, DOP and KOP) or [^{3}H]nociceptin (4.27TBq/mmol), and cell membrane suspension (20 μg of protein) in 50 mM Tris-HCl buffer (pH 7.4) with various concentrations of test compounds. Assays were performed at room temperature for 1 h to allow binding to reach equilibrium then filtered through glass-fiber filter mats using a Brandel cell harvester and rinsed six times with ice-cold wash buffer (50 mM Tris-HCl. pH 7.4). Filter mats were dried, scintillation mixture was added, and radioactivity retained on the filters was counted in a Wallac MicroBeta (PerkinElmer). K_i values were calculated using nonlinear regression analysis to fit a logistic equation to the competition data using GraphPad Prism. The results presented are the mean ± standard error from at least three separate assays performed in duplicate.

Stimulation of [^{35}S]GTPγS Binding

Agonist stimulation of [^{35}S]guanosine 5′-*O*-[γ-thio]triphosphate ([^{35}S]GTPγS, 1250 Ci, 46.2 TBq/mmol) binding was measured as described previously.[21, 24] Briefly, membranes (10–20 μg of protein/well) were incubated for 1 h at room temperature in GTPγS buffer (50 mM Tris-HCl, 100 mM NaCl, 5 mM $MgCl_2$, pH 7.4) containing 0.1 nM [^{35}S]GTPγS, 30 μM guanosine diphosphate (GDP), and varying concentrations of test compounds. Stimulation of [^{35}S]GTPγS was compared with 10 μM standard compounds [D-Ala^2,*N*-MePhe^4,Gly-ol]enkephalin (DAMGO) at MOPr, D-Pen^{2,5}-enkephalin (DPDPE) at DOPr, U69,593 at KOPr or nociceptin at NOPr. The reaction was terminated by rapidly filtering through GF/C filters and washing 10 times with cold GTPγS buffer. Retained radioactivity was measured as described above. The results are presented as the mean ± standard error from at least three separate assays performed in duplicate; maximal stimulation and EC_{50} values were determined using nonlinear regression analysis with GraphPad Prism. Antagonist affinities were determined as K_e values using a single concentration of test compound according to the formula $K_e = \frac{[\text{peptide}]}{\text{DR} - 1}$