**Supporting Information**

# Fumaroylamino-4,5-epoxymorphinans and related opioids with irreversible mu opioid receptor antagonist effects

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**Experimental**

Column chromatography was performed under gravity, over silica gel 60 (35-70μm) purchased from Merck. Analytical TLC was performed using aluminium-backed plates coated with Kieselgel 60 $F_{254}$, from Merck. The chromatograms were visualised using either UV light (UVGL-58, short wavelength), ninhydrin (acidic) or potassium permanganate (basic). Melting points were carried out using a Reichert-Jung Thermo Galen Kopfler block or a Gallenkamp MFB-595 melting point apparatus and are uncorrected. High and low resolution electron impact (EI) mass spectra were recorded using EI ionisation at 70eV, on a VG AutoSpec instrument, equipped with a Fisons autosampler. $^{1}$H NMR and $^{13}$C NMR spectra were recorded using a JEOL 270 (operating at 270 MHz for $^{1}$H and 67.8 MHz for $^{13}$C) spectrometer. Chemical shifts (δ) are measured in ppm. Spectra were referenced internally using TMS as the standard. Only diagnostic peaks have been quoted for proton NMR. Microanalysis was performed with a Perkin-Elmer 240C analyser. Infrared spectroscopy was performed on either a Perkin-Elmer 782 Instrument. Chemicals and solvents were purchased from Aldrich chemical company. Compounds were submitted for testing as their oxalate salts, formed by adding one equivalent of oxalic acid to an ethanolic solution of the ligand. Ligands were > 95% pure by microanalysis.

**N-Cyclopropylmethyl-7,8-dihydro-14β-[3'-(methoxycarbonyl)propenamido]normorphinone (2a)**

A suspension of 14β-amino-N-cyclopropylmethyl-7,8-dihydronormorphinone (**8**) (1.19g, 3.48 mmol), methyl 3-(chlorocarbonyl)propanoate (681 mg, 4.59 mmol) and sodium carbonate (450 mg) in THF (27 mL) and water (3 mL) was stirred at r.t. for 2.5 h. Water (20 mL) was then added and the reaction mixture extracted with $CH_2Cl_2$ (2 x 50 mL). The extracts were combined, dried ($MgSO_4$), filtered and evaporated to dryness before column chromatography (silica gel, $CH_2Cl_2$:$CH_3OH$ 19:1) to give the product as a white solid (1.27 g: 81%); m.p. 228-231°C; IR ($CHCl_3$) 3564, 3311, 1722, 1678, 1644 cm$^{-1}$; $^{1}$Hnmr δ 0.19 (2H, m, $NCH_2CH(CHHCHH)$), 0.59 (2H, m, $NCH_2CH(CHHCHH)$), 0.88 (1H, m, $NCH_2CH(CH_2CH_2)$), 3.82 (3H, s, CH3), 4.98 (1H, s, H-5), 6.60 (1H, d, J 8Hz, Aryl-H), 6.75 (1H, d, J 8Hz, Aryl-H), 6.87(1H, d, J 14Hz), 7.05 (1H, d, J 14Hz), 7.52 (1H, brs, NH); $^{13}$Cnmr δ 3.8, 4.1, 9.3, 21.5, 29.2, 29.9, 36.8, 44.1, 48.8, 52.2, 57.1, 59.2, 59.4, 89.7, 118.3, 119.8, 124.3, 128.0, 129.9, 137.5, 139.0, 143.5, 164.4, 166.2, 209.2; Anal. (oxalate salt) ($C_{27}H_{30}N_2O_{10}.2H_2O$) C, H, N.

**N-Cyclopropylmethyl-7,8-dihydro-14β-[3'-(methoxycarbonyl)propanamido]normorphinone (6)**

A suspension of N-cyclopropylmethyl-7,8-dihydro-14β-[3'-methoxycarbonyl)propenamido]normorphinone oxalate (**2a**) (203 mg, 0.35 mmol) and 10% Pd/C (150 mg) in $CH_3OH$ (30 mL) was hydrogenated at 15 psi until $H_2$ uptake ceased. The catalyst was removed by filtration through celite and the filtrate evaporated. The residue was purified by column chromatography ($CH_2Cl_2$:$CH_3OH$, 19:1) to give **6** as a clear oil (98 mg, 62%). IR ($CHCl_3$) 3562, 3325, 1726, 1672 cm$^{-1}$; $^{1}$H nmr δ 0.20 (2H, m, $NCH_2CH(CHHCHH)$), 0.54 (2H, m, $NCH_2CH(CHHCHH)$), 0.85 (1H, m, $NCH_2CH(CH_2CH_2)$), 3.70 (3H, s, $OCH_3$), 4.85 (1H, s, H-5), 6.58 (1H, d, J 10Hz, Aryl-H), 6.72 (1H, d, J 10Hz, Aryl-H), 7.16 (1H, s, NH); $^{13}$C nmr δ 3.7, 4.1, 9.3, 21.6, 29.2, 29.7, 31.5, 34.5, 36.8, 44.3, 48.6, 51.9, 56.3, 59.3, 59.9, 89.7, 118.1, 119.6, 124.1, 128.3, 139.1, 143.6, 172.6, 173.6, 208.6; EIMS 454 (M+, 100%); Anal. (oxalate salt) ($C_{27}H_{32}N_2O_{10}.1.5H_2O$) C, H, N.

**3-O-(tert-butyldimethylsilyl)-N-cyclopropylmethyl-7,8-dihydro-14β-[3'-(methoxycarbonyl)propenoyloxy]normorphinone** (**10**)

A solution of 3-O-(tert-butyldimethylsilyl)naltrexone (**9**)[25] (690 mg, 1.5 mmol) and monomethyl fumaroyl anhydride (630 mg, 2.60 mmol) in dry toluene (12 mL) was heated to reflux under $N_2$ for 3 h. After cooling the reaction mixture was washed with dilute $NaHCO_3$ (aq.) (2 x 5 mL) and water (5 mL), dried ($MgSO_4$), filtered and the solvent evaporated. The residue was purified by silica gel column chromatography ($CH_2Cl_2$:$CH_3OH$, 49:1) to yield () as a pale yellow solid (597 mg, 69%). IR ($CHCl_3$) 1715 $cm^{-1}$; $^1$H nmr $\delta$ 0.03 (2H, m, $NCH_2CH(CHHCHH)$), 0.19 (3H, s, SiCH3), 0.29 (3H, s, SiCH3), 0.45 (2H, m, $NCH_2CH(CHHCHH)$), 0.68 (1H, m, $NCH_2CH(CH_2CH_2)$), 1.01 (9H, s, 3 x $CH_3$), 3.83 (3H, s, $OCH_3$), 4.72 (1H, s, H-5), 6.56 (1H, d, J 10 Hz, Aryl-H), 6.65 (1H, d, J 10Hz, Aryl-H), 6.90 (1H, d, J 16Hz), 6.99 (1H, d, J 16Hz); $^{13}$C nmr  -4.7, -4.5, 3.8, 3.9, 9.5, 18.2, 23.2, 25.7, 26.9, 30.4, 35.5, 43.8, 51.0, 52.3, 55.2, 59.2, 84.1, 89.4, 119.3, 122.6, 126.0, 128.4, 133.0, 135.1, 138.0, 146.7, 163.6, 165.4, 206.4; EIMS 567 (M+, 99%); Anal. (oxalate salt) ($C_{31}H_{41}NO_7Si$) C, H, N.

**N-Cyclopropylmethyl-7,8-dihydro-14β-[3'-(methoxycarbonyl)propenoyloxy]normorphinone (3a)**

A solution of 3-O-(tert-butyldimethylsilyl)-N-cyclopropylmethyl-7,8-dihydro-14β-[3'-(methoxycarbonyl)propenoyloxy]normorphinone (**10**) (570 mg, 1.00 mmol) and 6M HCl (1.2 mL) in methanol (12 mL) was stirred at RT for 1 h, then neutralised ($NaHCO_3$) and all solvents then removed in vacuo. The residue was dissolved in $CH_2Cl_2$, filtered, dried ($MgSO_4$), filtered and the solvent again removed in vacuo. Silica gel chromatography ($CH_2Cl_2$:$CH_3OH$, 24:1) yielded **3a** as a clear oil (166 mg, 37%). IR ($CHCl_3$) 3567, 1723 $cm^{-1}$; $^1$H nmr $\delta$ 0.05 (2H, m, $NCH_2CH(CHHCHH)$), 0.48 (2H, m, $NCH_2CH(CHHCHH)$), 0.72 (1H, m, $NCH_2CH(CH_2CH_2)$), 3.82 (3H, s, CH3), 4.98 (1H, s, H-5), 6.62 (1H, d, J 10Hz, Aryl-H), 6.76 (1H, d, J 10Hz, Aryl-H), 6.92(1H, d, J 16Hz), 7.02 (1H, d, J 16Hz); $^{13}$C nmr $\delta$ 3.7, 4.0, 9.27, 23.1, 25.7, 27.0, 30.0, 35.6, 43.9, 51.2, 55.3, 59.2, 84.1, 89.9, 118.5, 120.0, 124.5, 127.9, 133.0, 135.1, 139.2, 143.5, 163.7, 165.5, 208.5; EIMS 453 (M+, 100%); Anal. (oxalate salt) ($C_{27}H_{29}NO_{11}.3H_2O$) C, N, requires H 5.90, found H 5.32.

**N-Cyclopropylmethyl-6,14-endoethano-7α-(methoxyfumaroylamino)tetrahydronororipavine (4a)**

To a solution of 7α-amino-N-cyclopropylmethyl-6,14-endoethanotetrahydronororipavine (**11a**) (0.43 g, 1.1 mmol) in dry $CH_2Cl_2$ (100 mL) was added triethylamine (0.45 g, 4.5 mmol). To this mixture, under $N_2$, was added a solution of methyl-(3-chloroformyl)acrylate (0.16 g, 1.1 mmol) in $CH_2Cl_2$ (10 mL) dropwise over 45 min, stirring was continued for 1 h before removal of the solvent in vacuo. Purification by column chromatography ($CH_2Cl_2$:$CH_3OH$:$NH_3$(conc.), 94:5:1) gave **4a** (0.35 g, 63%); IR ($CHCl_3$) 3410, 1723 $cm^{-1}$; $^1$H nmr $\delta$ 0.08 (2H, m, $NCH_2CH(CHHCHH)$), 0.45 (2H, m, $NCH_2CH(CHHCHH)$), 3.33 (3H, s, $CO_2CH_3$), 3.82 (3H, s, 6-$OCH_3$), 4.60 (1H, s, H-5), 6.52 (1H, d, J 8Hz, 1-H), 6.70 (1H, d, J 8Hz, 2-H), 6.89 (1H, d, J 16Hz, C=CH), 7.11 (1H, d, J 16Hz, C=CH); $^{13}$C nmr $\delta$ 3.6, 3.7, 9.3, 19.8, 22.8, 28.6, 35.0, 35.4, 37.1, 43.4, 45.6, 45.9, 49.8, 52.3, 58.4, 59.9, 76.3, 76.9, 87.9, 117.1, 119.8, 127.4, 129.7, 132.0, 137.0, 137.8, 145.6, 163.8, 166.7; EIMS 494 (M+, 100%); EI-HRMS calc. for $C_{28}H_{34}N_2O_6$ 494.24169, found 494.24081; Anal. (oxalate salt) ($C_{30}H_{36}N_2O_{10}.2.5H_2O$) C, H, N.

**N-Cyclopropylmethyl-6,14-endoethano-7α-(methoxyfumaroylaminomethyl)tetrahydronororipavine (5a)**

A solution of 7α-aminomethyl-N-cyclopropylmethyl-6,14-endoethano-tetrahydronororipavine (**11b**)[4] (0.22g, 0.55 mmol) was treated as described for **4a** (above) to yield, after column chromatography ($CH_2Cl_2$:$CH_3OH$:$NH_3$(conc.), 94:5:1) **5a** (0.13 g, 48%); IR ($CHCl_3$) 3578, 3387, 1725, 1672 $cm^{-1}$; $^1$H nmr $\delta$ 0.14 (2H, m, $NCH_2CH(CHHCHH)$), 0.50 (2H, m, $NCH_2CH(CHHCHH)$), 3.57 (3H, s, 6-$OCH_3$), 3.82 (3H, s,

$CH_3$), 4.46 (1H, s, H-5), 6.50 (1H, d, J 8Hz, 1-H), 6.69 (1H, d, J 8Hz, 2-H), 6.96 (3H, m, CH=CH and CONH); EIMS 467 (M+, 100%); EI-HRMS calc. for $C_{29}H_{36}N_2O_6$ 508.25734, found 508.25657; Anal. (oxalate salt) ($C_{31}H_{38}N_2O_{10}.1.5H_2O$) C, H, N.

**Microanalysis data**

| | C | | H | | N | |
|---|---|---|---|---|---|---|
| Compound | Calc' | Found | Calc' | Found | Calc' | Found |
| **2a**.oxalate.$2H_2O$ | 56.1 | 56.3 | 5.92 | 5.83 | 4.84 | 4.70 |
| **3a**.oxalate.$3H_2O$ | 54.3 | 54.0 | 5.90 | 5.32 | 2.34 | 2.33 |
| **4a**.oxalate.$2.5H_2O$ | 57.2 | 57.2 | 6.52 | 6.16 | 4.45 | 4.47 |
| **5a**.oxalate.$1.5H_2O$ | 59.5 | 59.2 | 6.56 | 6.29 | 4.48 | 4.42 |
| **6**.oxalate.$1.5H_2O$ | 56.7 | 56.7 | 6.17 | 6.28 | 4.90 | 4.42 |

Antagonist activity of 32 mg/kg **5a** after 24 h and 30 min pretreatment on morphine antinociceptive activity in the mouse warm water tail withdrawal assay (55$^{o}$C)