Supporting Information

Synthesis, Biological and Structural Explorations of New Zwitterionic Derivatives of 14-*O*-Methyloxymorphone, as Potent μ/δ Opioid Agonists and Peripherally Selective Antinociceptives

Mariana Spetea,[†]* Silvia B. Rief,[†§] Tanila Ben Haddou,[†§] Monika Fink,[†] Elka Kristeva,[†] Harald Mittendorfer,[†] Stefanie Haas,[†] Nora Hummer,[†] Valeria Follia,[†] Elena Guerrieri,[†] Muhammad Faheem Asim,[†] Sonja Sturm,[‡] Helmut Schmidhammer[†]*

[†]Department of Pharmaceutical Chemistry, Institute of Pharmacy and Center for Molecular Biosciences Innsbruck (CMBI), University of Innsbruck, Innrain 80-82, 6020 Innsbruck, Austria
[‡]Department of Pharmacognosy, Institute of Pharmacy, University of Innsbruck, Innrain 80-82, 6020 Innsbruck, Austria

Table of Contents

General procedure for the synthesis of 6-amino acid esters 24-41.

A mixture of 2.5 mmol of 14-*O*-methyloxymorphone hydrobromide, 5 mmol of the corresponding amino acid ester (hydrochloride salt), triethylamine (5 mmol), and 25 mL anhydrous methanol was stirred under inert conditions at room temperature for 3 hours. After addition of 2.5 mmol sodium cyanoborohydride, the mixture was stirred for 2 days at room temperature. The end of the reaction was monitored by TLC. After addition of water, the mixture was reduced in vacuo and treated with conc. ammonia solution until a pH of 11 was reached. The mixture was extracted several times with dichloromethane. The combined organic layers were washed with water and brine, dried over sodium sulfate and evaporated. The crude product (a mixture of α- and β-diastereoisomers) was separated and purified by column chromatography (MPLC; silica gel; dichloromethane/methanol) to yield the separated diastereoisomers usually in form of a colorless foam.

(2S)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6α-yl)amino]-3-hydroxypropionic acid *tert*-butyl ester (24a). 7% yield; ^{1}H-NMR (D_2O): δ 6.72 (d, J=8.0, 1 ar. H), 6.52 (d, J=8.0, 1 ar. H), 4.64 (d, J=2.6, H-C(5)), 3.22 (s, MeO), 2.40 (s, MeN), 1.45 (s, 9 H, *t*-Bu); MS (CI): m/z 461 (M^++1); IR (KBr): 1725 (C=O) cm^{-1}; Anal. $C_{25}H_{36}N_2O_6 \cdot 0.7H_2O$ (473.18): calc. C 63.46, H 7.97, N 5.92, found C 63.45, H 7.80, N 5.88.

(2S)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6β-yl)amino]-3-hydroxypropionic acid *tert*-butyl ester (24b). 28% yield; ^{1}H-NMR (D_2O): δ 6.72 (d, J=8.1, 1 ar. H), 6.59 (d, J=8.1, 1 ar. H), 4.46 (d, J=7.2, H-C(5)), 3.26 (s, MeO), 2.49 (s, MeN), 1.45 (s, 9 H, *t*-Bu); MS (CI): m/z 461 (M^++1); IR (KBr): 1725 (C=O) cm^{-1}; Anal. $C_{25}H_{36}N_2O_6 \cdot 0.9H_2O \cdot 0.4CH_2Cl_2$ (510.76): calc. C 59.73, H 7.62, N 5.48.

(2S)-2-[(4,5α-Epoxy-3,14β-dihydroxy-17-methylmorphinan-6α-yl)amino]-3-methylbutyric acid *tert*-butyl ester (25a). 8% yield; ^{1}H-NMR ($CDCl_3$): δ 6.71 (d, J=8.0, 1 ar. H), 6.51 (d, J=8.0, 1 ar. H), 4.65 (d, J=2.2, H-C(5)), 3.21 (s, MeO), 2.36 (s, MeN), 1.48 (s, *t*-Bu), 0.95 (d, J=7.0, CH*Me*), 0.93 (d, J=7.0, CH*Me*); MS (CI): m/z 473 (M^++1); IR (KBr): 1721 (C=O) cm^{-1}; Anal. $C_{27}H_{40}N_2O_5 \cdot 0.8H_2O$ (487.04): calc. C 66.59, H 8.61, N 5.75, found C 66.53, H 8.47, N 5.74.

(2S)-2-[(4,5α-Epoxy-3,14β-dihydroxy-17-methylmorphinan-6β-yl)amino]-3-methylbutyric acid *tert*-butyl ester (25b). 26% yield; ^{1}H-NMR ($CDCl_3$): δ 6.70 (d, J=8.4, 1 ar. H), 6.55 (d, J=8.4, 1 ar. H), 4.37 (d, J=7.6, H-C(5)), 3.23 (s, MeO), 2.43 (s, MeN), 1.43 (s, *t*-Bu), 0.92 (d, J=6.8, 2×CH*Me*); MS (CI): m/z 473 (M^++1); IR (KBr): 1721 (C=O) cm^{-1}; Anal. $C_{27}H_{40}N_2O_5 \cdot 0.8C_3H_8O$ (520.71): calc. C 67.82, H 8.98, N 5.38, found C 67.83, H 8.88, N 5.18.

(2S)-6-Benzyloxycarbonylamino-2-[(4,5α-epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6α-yl)amino]hexanoic acid *tert*-butyl ester (26a).15% yield; ^{1}H NMR ($CDCl_3$): δ 7.34 (s, 5 ar. H), 6.67 (d, *J*=8.1 Hz, *H*-C(1)), 6.53 (d, *J*=8.1 Hz, *H*-C(2)), 5.09 (s, 2 H, OCH_2Ph), 4.68 (d, *J*=2.8 Hz, *H*-C(5)), 3.21 (s, C*H*$_3$O), 2.38 (s, C*H*$_3$N), 1.47 (s, 9 H *t*-Bu); MS (CI): m/z 636 (M^++1); IR (KBr): 1724 (C=O) cm^{-1}; Anal. $C_{36}H_{49}N_3O_7 \cdot 0.8 H_2O$ (650.22): calc. C 66.50, H 7.84, N 6.46, found C 66.47, H 7.54, N 6.51.

(2S)-6-Benzyloxycarbonylamino-2-[(4,5α-epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6β-yl)amino]hexanoic acid *tert*-butyl ester (26b). 15% yield; ^{1}H NMR ($CDCl_3$): δ 7.34 (s, 5 ar. H), 6.70 (d, *J*=8.3 Hz, *H*-C(1)), 6.56 (d, *J*=8.3 Hz, *H*-C(2)), 5.09 (s, 2 H, OCH_2Ph), 4.36 (d, *J*=7.2 Hz, *H*-C(5)), 3.24 (s, C*H*$_3$O), 2.48 (s, C*H*$_3$N), 1.41 (s, 9 H *t*-Bu); MS (CI): m/z 636 (M^++1); IR (KBr): 1721 (C=O) cm^{-1}; Anal. $C_{36}H_{49}N_3O_7 \cdot 0.5CH_2Cl_2$ (678.27): calc. C 64.64, H 7.43, N 6.20, found C 64.41, H 7.47, N 6.22.

(2S)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6α-yl)amino]-3-(4-hydroxyphenyl)propionic acid *tert*-butyl ester (27a). 9% yield; ^{1}H-NMR ($CDCl_3$): δ 7.11 (d, J=8.7, 2 ar. H), 6.76 (d, J=8.7, 2 ar. H), 6.67 (d, J=8.2, 1 ar. H), 6.47 (d, J=8.2, 1 ar. H), 4.68 (d, J=3.4, H-C(5)), 3.16 (s, MeO), 2.34 (s, MeN), 1.34 (s, *t*-Bu); MS (CI): m/z 537 (M^++1); IR (KBr): 1724 (C=O) cm^{-1}; Anal. $C_{31}H_{40}N_2O_6 \cdot 1.1\ H_2O$ (556.49): calc. C 66.91 H 7.64 N 5.03, found C 66.70 H 7.29 N 4.82.

(2S)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6β-yl)amino]-3-(4-hydroxyphenyl)propionic acid *tert*-butyl ester (27b). 22% yield; ^{1}H-NMR ($CDCl_3$): δ 7.05 (d, J=8.4, 2 ar. H), 6.69 (m, 3 ar. H), 6.53 (d, J=8.0, 1 ar. H), 4.68 (d, J=3.4, H-C(5)), 3.19 (s, MeO), 2.38 (s, MeN), 1.34 (s, *t*-Bu); MS (CI): m/z 545 (M^++1); IR (KBr): 1723 (C=O) cm^{-1}; Anal. $C_{31}H_{40}N_2O_6 \cdot 1.0H_2O$ (554.69): C 67.13 H 7.63 N 5.05, found C 67.17 H 7.63 N 4.79.

(2S)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6α-yl)amino]-3-(1*H*-indol-3-yl)propionic acid *tert*-butyl ester (28a). 7% yield; ^{1}H-NMR ($CDCl_3$): δ 7.74-7.12 (m, 4 ar. H, 1 olef. H), 6.63 (d, J=8.0, 1 ar. H), 6.45 (d, J=8.0, 1 ar. H), 4.69 (d, J=3.0, H-C(5)), 3.14 (s, MeO), 2.35 (s, MeN), 1.39 (s, *t*-Bu). MS (CI): m/z 560 (M^++1); IR (KBr): 1724 (C=O) cm^{-1}; Anal. $C_{33}H_{41}N_3O_5 \cdot 0.9H_2O$ (575,92): calc. C 68.82, H 7.49, N 7.30, found C 68.83, H 7.25, N 7.12.

(2S)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6β-yl)amino]-3-(1*H*-indol-3-yl)propionic acid *tert*-butyl ester (28b). 40% yield; ^{1}H-NMR ($CDCl_3$): δ 7.59-7.06 (m, 4 ar. H, 1 olef. H), 6.67 (d, J=8.0, 1 ar. H), 6.53 (d, J=8.0, 1 ar. H), 4.39 (d, J=7.8, H-C(5)), 3.18 (s, MeO), 2.40 (s, MeN), 1.28 (s, *t*-Bu); MS (CI): m/z 560 (M^++1); IR (KBr): 1724 (C=O) cm^{-1}; Anal. $C_{33}H_{41}N_3O_5 \cdot 1.2H_2O$ (581,33): calc. C 68.18, H 7.53, N 7.23, found C 68.16, H 7.51, N 7.01.

(2S)-3-Carbamoyl-2-[(4,5α-epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6α-yl)amino]propionic acid *tert*-butyl ester (29a). 9% yield; ^{1}H-NMR ($CDCl_3$): δ 6.72 (d, J=8.0, 1 ar. H), 6.49 (d, J=8.0, 1 ar. H), 4.68 (d, J=3.6, H-C(5)), 3.19 (s, MeO), 2.34 (s, MeN), 1.46 (s, *t*-Bu); MS (CI): m/z 488 (M^++1); IR (KBr): 1724 (C=O) cm^{-1}; Anal. $C_{26}H_{37}N_3O_6 \cdot 1.0CH_2Cl_2$ (572.53): calc. C 56.64, H 6.87, N 7.34, found C 57.00 H 7.17 N 6.96.

(2S)-3-Carbamoyl-2-[(4,5α-epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6β-yl)amino]propionic acid *tert*-butyl ester (29b). 23% yield; ^{1}H-NMR ($CDCl_3$): δ 6.71 (d, J=8.0, 1 ar. H), 6.57 (d, J=8.0, 1 ar. H), 4.45 (d, J=7.2, H-C(5)), 3.87 (t, J=7.0, NHC*H*), 3.23 (s, MeO), 2.43 (s, MeN), 1.46 (s, *t*-Bu); MS (CI): m/z 488 (M^++1); IR (KBr): 1724 (C=O) cm^{-1}; Anal. $C_{26}H_{37}N_3O_6$ $0.9CH_2Cl_2$ (564.04): calc. C 57.28, H 6.93, N 7.45, found C57.49, H 7.12, N 7.11.

(2S)-4-Carbamoyl-2-[(4,5α-epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6α-yl)amino]butyric acid *tert*-butyl ester (30a). 7% yield (colorless oil); ^{1}H-NMR ($CDCl_3$): δ 6.71 (d, J=8.0, 1 ar. H), 6.49 (d, J=8.0, 1 ar. H), 4.65 (d, J=3.6, H-C(5)), 3.19 (s, MeO), 2.34 (s, MeN), 1.47 (s, *t*-Bu); MS (CI): m/z 502 (M^++1); IR (KBr): 1719 (C=O) cm^{-1}; Anal. $C_{27}H_{39}N_3O_6 \cdot 0.5CH_2Cl_2$ (544.09): calc. C 60.71, H 7.41, N 7.72, found C 60.54, H 7.24, N 7.55.

(2S)-4-Carbamoyl-2-[(4,5α-epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6β-yl)amino]butyric acid *tert*-butyl ester (30b). 13% yield; ^{1}H-NMR ($CDCl_3$): δ 6.72 (d, J=8.0, 1 ar. H), 6.56 (d, J=8.0, 1 ar. H), 4.40 (d, J=7.0, H-C(5)), 3.23 (s, MeO), 2.46 (s, MeN), 1.46 (s, *t*-Bu); MS (CI): m/z 502 (M^++1); IR (KBr): 1724 (C=O) cm^{-1}; Anal. $C_{27}H_{39}N_3O_6 \cdot 0.4CH_2Cl_2 \cdot 0.2H_2O$ (539.20): calc. C 61.04 H 7.51 N 7.79, found C 61.15 H 7.58 N 7.65.

(2S)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6α-yl)amino]pentanedioic acid di-*tert*-butyl ester (31a). 11% yield; ^{1}H-NMR ($CDCl_3$): δ 6.70 (d, J=8.0, 1 ar. H), 6.50 (d, J=8.0, 1 ar. H), 4.71 (d, J=3.8, H-C(5)), 3.21 (s, MeO), 2.35 (s, MeN), 1.48 (s, *t*-Bu), 1.45 (s, *t*-Bu); MS (CI): m/z 545 (M^++1); IR (KBr): 1728 (C=O) cm^{-1}; Anal. $C_{30}H_{44}N_2O_7 \cdot 0.8.H_2O$ (559.11): calc. C 64.45, H 8.22, N 5.01, found C 64.47, H 8.57, N 5.20.

(2S)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6β-yl)amino]pentanedioic acid di-*tert*-butyl ester (31b). 13% yield; ^{1}H-NMR ($CDCl_3$): δ 6.70 (d, J=8.3, 1 ar. H), 6.56 (d, J=8.3, 1 ar. H), 4.41 (d, J=7.0, H-C(5)), 3.21 (s, MeO), 2.40 (s, MeN), 1.45 (s, *t*-Bu), 1.43 (s, *t*-Bu); MS (CI): m/z 545 (M^++1); IR (KBr): 1728 (C=O) cm^{-1}; Anal. $C_{30}H_{44}N_2O_7 \cdot 0.7H_2O$ (557.30): calc. C 64.66, H 8.21, N 5.03, found C 64.69, H 8.49, N 4.95.

(2S)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6α-yl)amino]pentanedioic acid di-*tert*-butyl ester (32a). 11% yield; ^{1}H-NMR ($CDCl_3$): δ 6.71 (d, J=8.0, 1 ar. H), 6.50 (d, J=8.0, 1 ar. H), 4.62 (d, ^{3}J=4.0, ^{4}J=1.2, H-C(5)), 3.20 (s, MeO), 2.35 (s, MeN), 1.48 (s, *t*-Bu), 1.45 (s, *t*-Bu); MS (CI): m/z 559 (M^++1); IR (KBr): 1729 (C=O) cm^{-1}; Anal. $C_{31}H_{46}N_2O_7 \cdot 0.5H_2O$ (567,73): calc. C 65.58, H 8.34, N 4.93, found C 65.25, H 8.27, N 4.73.

(2S)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6β-yl)amino]pentanedioic acid di-*tert*-butyl ester (32b). 27% yield; ^{1}H-NMR ($CDCl_3$): δ 6.69 (d, J=8.2, 1 ar. H), 6.55 (d, J=8.0, 1 ar. H), 4.38 (d, J=7.4, H-C(5)), 3.20 (s, MeO), 2.38 (s, MeN), 1.47 (s, *t*-Bu), 1.45 (s, *t*-Bu); MS (CI): m/z 559 (M^++1); IR (KBr): 1729 (C=O) cm^{-1}; Anal. $C_{31}H_{46}N_3O_7 \cdot 0{,}3H_2O$ (564,12): calc. C 66.00, H 8.33, N 4.97, found C 65.95, H 8.58, N 4.95.

(2R)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6α–yl)amino]propionic acid *tert*-butyl ester (33a). 5% yield; ^{1}H-NMR ($CDCl_3$): δ 6.70 (d, J=8.0 Hz, 1 ar. H), 6.55 (d, J=8.0 Hz, 1 ar. H), 4.66 (d, J=3.2 Hz, C5-H), 3.22 (s, C14-OCH_3), 2.35 (s, C17-NCH_3), 1.48 (s, 9H, *t*-Bu); IR(KBr): 1728 (C=O) cm^{-1}

(2R)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6β–yl)amino]propionic acid *tert*-butyl ester (33b). 19% yield; ^{1}H-NMR ($CDCl_3$): δ 6.61 (d, J=8.1 Hz, 1 ar. H), 6.47 (d, J=8.1 Hz, 1 ar. H), 4.42 (d, J=7.0 Hz, C5-H), 3.12 (s, C14-OCH_3), 2.31 (s, C17-NCH_3), 1.31 (s, 9H, *t*-Bu); IR(KBr): 1718 (C=O) cm^{-1}

(2R)-2-[(4,5α-Epoxy-3,14β-dihydroxy-17-methylmorphinan-6α-yl)amino]-3-methylbutyric acid *tert*-butyl ester (34a). 46% yield; ^{1}H-NMR ($CDCl_3$): δ 6.67 (d, J=8.0, 1 ar. H), 6.50 (d, J=8.0, 1 ar. H), 4.61 (d, J=4.0, H-C(5)), 3.22 (s, MeO), 2.36 (s, MeN), 1.51 (s, *t*-Bu), 0.92 (d, J=7.0, CH*Me*), 0.90 (d, J=7.0, CH*Me*); MS (CI): m/z 473 (M^++1); IR (KBr): 1721 (C=O) cm^{-1}; Anal. $C_{27}H_{40}N_2O_5 \cdot 0{,}9H_2O$ (488.84): calc. C 66.34, H 8.62, N 5.73, found C 66.31, H 8.33, N 5.70.

(2R)-2-[(4,5α-Epoxy-3,14β-dihydroxy-17-methylmorphinan-6β-yl)amino]-3-methylbutyric acid *tert*-butyl ester (34b). 12% yield; ^{1}H-NMR ($CDCl_3$): δ 6.70 (d, J=8.2, 1 ar. H), 6.54 (d, J=8.0, 1 ar. H), 4.46 (d, J=6.6, H-C(5)), 3.24 (s, MeO), 2.45 (s, MeN), 1.36 (s, *t*-Bu), 1.02 (d, J=6.8, CH*Me*), 0.97 (d, J=6.8, CH*Me*); MS (CI): m/z 473 (M^++1); IR (KBr): 1721 (C=O) cm^{-1}; Anal. $C_{27}H_{40}N_2O_5 \cdot 0.8H_2O$ (487.04): calc. C 66.59, H 8.61, N 5.75, found C 66.61, H 8.59, N 5.58.

(2*R*)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methyl-morphinan-6α-yl)-amino]-3-phenylpropionic acid *tert*-butyl ester (35a). 5% yield; ^{1}H-NMR ($CDCl_3$): δ 7.19-7.26 (m, 5 ar. H), 6.67 (d, J=8.2, 1 ar. H), 6.49 (d, J=8.2, 1 ar. H), 4.62 (d, J=3.6, C5-H), 3.23 (s, C14-OCH_3), 2.34 (s, C17-NCH_3), 1.34 (s, 9H, *t*-Bu); IR (KBr): 1723 (C=O) cm^{-1}

(2*R*)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methyl-morphinan-6β-yl)-amino]-3-phenylpropionic acid *tert*-butyl ester (35b). 29% yield; ^{1}H-NMR ($CDCl_3$): δ 7.15-7.27 (m, 5 ar. H), 6.60 (d, J=8.1, 1 ar. H), 6.46 (d, J=8.1, 1 ar. H), 4.40 (d, J=6.8, C5-H), 3.19 (s, C14-OCH_3), 2.34 (s, C17-NCH_3), 1.21 (s, 9H, *t*-Bu); IR (KBr): 1722 (C=O) cm^{-1}

(2*S*)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methyl-morphinan-6α-yl)-amino]-2-cyclohexyl acetic acid *tert*-butyl ester (36a). 8% yield; ^{1}H-NMR ($CDCl_3$): δ 6.72 (d, J=7.8, 1 ar. H), 6.51 (d, J=7.8, 1 ar. H), 4.64 (d, J=2.6, C5-H), 3.20 (s, C14-OCH_3), 2.36 (s, C17-NCH_3), 1.48 (s, 9H, *t*-Bu), 1.63 (m, 10H, cyclohexyl); IR (KBr): 1723 (C=O) cm^{-1}

(2*S*)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methyl-morphinan-6β-yl)-amino]-2-cyclohexyl acetic acid *tert*-butyl ester (36b). 3% yield; ^{1}H-NMR ($CDCl_3$): δ 6.68 (d, J=8.0, 1 ar. H), 6.54 (d, J=8.0, 1 ar. H), 4.34 (d, J=7.6, C5-H), 3.20 (s, C14-OCH_3), 2.39 (s, C17-NCH_3), 1.41 (s, 9H, *t*-Bu), 1.70 (m, 10H, cyclohexyl); IR (KBr): 1722 (C=O) cm^{-1}

(2S)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6α-yl)amino]-2-ethylacetic acid *tert*-butyl ester (37a). 11% yield; ^{1}H-NMR ($CDCl_3$): δ 6.72 (d, J=8.3, 1 ar. H), 6.51 (d, J=8.3, 1 ar. H), 4.70 (d, J = 3.8, C5-H), 3.20 (s, C14-OCH_3), 2.38 (s, C17-NCH_3), 1.47 (s, 9H, *t*-Bu); IR (KBr): 1733 (C=O) cm^{-1}

(2S)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6β-yl)amino]-2-ethylacetic acid *tert*-butyl ester (37a). 11% yield; ^{1}H-NMR ($CDCl_3$): δ 6.69 (d, J=8.0, 1 ar. H), 6.55 (d, J=8.0, 1 ar. H), 4.37 (d, J=7.4, C5-H), 3.22 (s, C14-OCH_3), 2.43 (s, C17-NCH_3), 1.42 (s, 9H, *t*-Bu); IR (KBr): 1726 (C=O) cm^{-1}

3-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6α-yl)amino]propionic acid tert-butyl ester (38a). 12% yield; ^{1}H-NMR ($CDCl_3$): δ 6.64 (d, J=8.3, 1 ar. H), 6.48 (d, J=8.3, 1 ar. H), 4.68 (d, J=3.8, H-C(5)), 3.22 (s, MeO), 2.42 (s, MeN), 1.45 (s, *t*-Bu); MS (CI): m/z 445 (M^++1);

IR (KBr): 1724 (C=O) cm^{-1}; Anal. $C_{25}H_{36}$ $N_2O_5 \cdot 0.1H_2O$ (446.38): calc. C 67.27, H 8.1,7 N 6.28, found C 67.05, H 8.12, N 6.19.

3-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6β-yl)amino]propionic acid tert-butyl ester (38b). 23% yield; ^{1}H-NMR ($CDCl_3$): δ 6.64 (d, J=8.0, 1 ar. H), 6.54 (d, J=8.0, 1 ar. H), 4.51 (d, J=7.4, H-C(5)), 3.20 (s, MeO), 2.39 (s, MeN), 1.46 (s, *t*-Bu); MS (CI): m/z 445 (M^++1); IR (KBr): 1724 (C=O) cm^{-1}; Anal. $C_{25}H_{36}$ $N_2O_5 \cdot 0.4H_2O$ (451.78): calc. C 67.47, H 8.21, N 6.20, found C 66.50, H 8.44, N 6.21.

4-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6α-yl)amino]butyric acid tert-butyl ester (39a). 15% yield; ^{1}H-NMR ($CDCl_3$): δ 6.67 (d, J=8.2, 1 ar. H), 6.48 (d, J=8.2, 1 ar. H), 4.70 (d, J=3.6, H-C(5)), 3.22 (s, MeO), 2.34 (s, MeN), 1.44 (s, *t*-Bu); MS (CI): m/z 459 (M^++1); IR (KBr): 1726 (C=O) cm^{-1}; Anal.$C_{26}H_{38}N_2O_5 \cdot 0.5H2O$ (467.61): calc. C 66.78, H 8.41, N 5.99, found C 66.72, H 8.35, N 5.72.

4-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6β-yl)amino]butyric acid tert-butyl ester (39b). 53% yield; ^{1}H-NMR ($CDCl_3$): δ 6.68 (d, J=8.0, 1 ar. H), 6.55 (d, J=8.0, 1 ar. H), 4.43 (d, J=6.8, H-C(5)), 3.20 (s, MeO), 2.37 (s, MeN), 1.45 (s, *t*-Bu); MS (CI): m/z 459 (M++1); IR (KBr): 1726 (C=O) cm^{-1}; Anal.$C_{26}H_{38}N_2O_5 \cdot 0.6H_2O$ (469.41): calc. C 66.53, H 8.42, N 5.97, found C 66.67, H 8.41, N 5.74.

(2S)-2-[[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6α-yl)amino]-(2S)-3-methylbutyrylamino]-3-(4-hydroxyphenyl)propionic acid benzyl ester (40a). 19% yield; ^{1}H-NMR ($CDCl_3$): δ 7.34-6.49 (m, 11 ar. H), 5.13 (s, C*H*$_2$-Ph), 4.60 (d, J=3.6, H-C(5)), 3.17 (s, MeO), 2.42 (s, MeN), 0.90 (d, J=6.7, CH*Me*), 0.80 (d, J=6.7, CH*Me*); MS (CI): m/z 670 (M^++1); IR (KBr): 1737 (C=O) cm^{-1}; Anal. $C_{39}H_{47}N_3O_7 \cdot 1.5H_2O$ (696.85): calc. C 67.22, H 7.23, N 6.03, found C 67.25, H 7.11, N 5.93.

(2S)-2-[[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6β-yl)amino]-(2S)-3-methylbutyrylamino]-3-(4-hydroxyphenyl)propionic acid benzyl ester (40b). 20% yield; ^{1}H-NMR ($CDCl_3$): δ 7.32-6.55 (m, 11 ar. H), 5.21 (d, J=12.3, C*H*$_2$-Ph), 5.08 (d, J=12.3, C*H*$_2$-Ph), 4.30 (d, J=7.0, H-C(5)), 3.27 (s, MeO), 2.50 (s, MeN), 0.87 (d, J=6.8, CH*Me*), 0.67 (d, J=6.8, CH*Me*); MS (CI): m/z 670 (M^++1); IR (KBr): 1737 (C=O) cm^{-1}; Anal. $C_{39}H_{47}N_3O_7 \cdot 1.3H_2O$ (693.24): calc. C 67.57, H 7.21, N 6.06, found C 67.56, H 7.32, N 5.74.

2-[2-[(4,5α-epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6α-yl)amino]acetylamino]acetic acid benzyl ester (41a). 1% yield; ^{1}H-NMR ($CDCl_3$): δ 7.36 (s, 5 ar. H), 6.72 (d, J=8.2, 1 ar. H), 6.53 (d, J=8.2, 1 ar. H), 5.22 (s, C*H*$_2$-Ph), 4.62 (d, J=3.6, H-C(5)), 3.22 (s, MeO), 2.37 (s, MeN); MS (CI): m/z 522 (M^++1); IR (KBr): 1750 (C=O) cm^{-1}; Anal. $C_{29}H_{35}N_3O_6 \cdot 1.2H_2O$ (543.24): found C 64.12, H 6.94, N 7.74, found C 64.01, H 7.24, N 7.92.

2-[2-[(4,5α-epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6β-yl)amino]acetylamino]acetic acid benzyl ester (41b). 16% yield; ^{1}H-NMR ($CDCl_3$): δ 7.33 (s, 5 ar. H), 6.63 (d, J=8.2, 1 ar. H), 6.53 (d, J=8.2, 1 ar. H), 5.27 (d, J=12.4, C*H*$_2$-Ph), 5.10 (d, J=12.4, C*H*$_2$-Ph), 4.34 (d, J=7.4, H-C(5)), 3.19 (s, MeO), 2.36 (s, MeN); MS (CI): m/z 522 (M^++1); IR (KBr):

1750 (C=O) cm^{-1}; Anal. $C_{22}H_{29}N_3O_6 \cdot 2.0H_2O \cdot 1.0CH_3OH$ (499.56): calc. 55.30, 7.47, 8.41, found 55.33, 7.29, 8.27.

Table S1. Binding affinities of 6-amino acid (2a/b, 3a/b, 4a/b, 14a/b, 15a/b, 17a/b and 19a/b) and 6-dipeptide substituted derivatives (22a/b) at the human opioid receptors

compd	amino acid substitution at position 6	K_i (nM)[a]	
		MOR	DOR
2a	α-Gly	0.79 ± 0.08	18.2 ± 6.1
2b	β-Gly	0.90 ± 0.14	10.1 ± 2.7
3a	α-L-Ala	0.85 ± 0.06	26.0 ± 3.5
3b	β-L-Ala	2.01 ± 0.41	8.43 ± 2.1
4a	α-L-Phe	0.81 ± 0.20	3.61 ± 1.2
4b	β-L-Phe	4.15 ± 0.47	1.12 ± 0.23
14a	α-L-Glu	3.29 ± 0.61	24.0 ± 11.8
14b	β-L-Glu	28.7 ± 7.9	18.0 ± 3.5
15a	α-D-Ala	0.68 ± 0.08	14.9 ± 1.9
15b	β-D-Ala	1.61 ± 0.04	11.5 ± 2.6
17a	α-D-Phe	0.85 ± 0.01	5.26 ± 0.42
17b	β-D-Phe	1.84 ± 0.14	2.17 ± 0.26
19a	α-L-Abu	0.95 ± 0.13	38.0 ± 15.4
19b	β-L-Abu	2.10 ± 0.33	1.99 ± 0.84
22a	α-L-Val-L-Tyr	1.29 ± 0.13	1.46 ± 0.59
22b	β-L-Val-L-Tyr	0.64 ± 0.07	1.39 ± 0.13

[a]Determined in competition radioligand binding assays using CHO cell membranes expressing human MOR and DOR. Values represent the mean ± SEM of three independent experiments each performed in duplicate.