Supporting Information

Synthesis and Pharmacological Activities of 6-Glycine Substituted 14-Phenylpropoxymorphinans, a Novel Class of Opioids with High Opioid Receptor Affinities and Antinociceptive Potencies

Mariana Spetea,[†, §] Petra Windisch,[†, §] Yan Guo,[‡] Indre Bileviciute-Ljungar,[‡] Johannes Schütz,[†] Muhammad Faheem Asim, [†] Ilona P. Berzetei-Gurske,[&] Pal Riba,[+] Kornel Kiraly,[+] Susanna Fürst,[+] Mahmoud Al-Khrasani[+], and Helmut Schmidhammer[†,*]

[†]*Department of Pharmaceutical Chemistry, Institute of Pharmacy and Center for Molecular Biosciences Innsbruck, University of Innsbruck, Innrain 52a, A-6020 Innsbruck, Austria,* [‡]*Department of Physiology and Pharmacology, Karolinska Institutet, S-171 77 Stockholm, Sweden;* [&]*Biosciences Division, SRI International, 333 Ravenswood Avenue, Menlo Park, CA 94025,USA;* [+]*Department of Pharmacology and Pharmacotherapy, Medical Faculty, Semmelweis University, Nagyvarad ter 4, POB 370, H-1445 Budapest, Hungary.*

Table of Contents

General Procedure for the synthesis of esters 11, 12, 15 and 16 (11 and 12 as examples). Compound **4** (1.20 g; 2.86 mmol) was dissolved in a mixture of 80 mL anhydrous DMF and 8 mL anhydrous MeOH. Molecular sieve 4 Å (5 g) and glycine-*t*-butylester hydrochloride (2.40 g; 14.31 mmol) were added, and the mixture was stirred at room temperature for 6 h. After the addition of $NaCNBH_3$ (0.90 g; 14.31 mmol) the mixture was stirred for another 2 days. The molecular sieve was filtered off (Celite) and washed with CH_2Cl_2 (3 × 20 mL). The filtrate was washed with water (3 × 200 mL; 2 × 150 mL) and brine (1 × 150 mL) and dried (Na_2SO_4). The solvent was evaporated, and the crude product which contained a mixture of diastereoisomers was chromatographed. The products were obtained as white foam.

***tert*-Butyl [[4,5*α*-epoxy-3-hydroxy-17-methyl-14*β*-[(3-phenylpropyl)oxy]morphinan-6*α*-yl]amino]acetate (11) and *tert*-Butyl [[4,5*α*-epoxy-3-hydroxy-17-methyl-14*β*-[(3-phenylpropyl)oxy]morphinan-6*β*-yl]amino]acetate (12).** The crude product (1.42 g yellow oil) was separated by MPLC (silica gel; CH_2Cl_2/MeOH 10:1) to give 0.31 g **11** (20%) and 0.51 g **12** (32%), respectively. **11:** IR (KBr) 1735 (C=O). ^{1}H NMR ($CDCl_3$) δ 7.29–7.17 (m, 5 arom H); 6.66 (d, J = 8.3, 1 arom H); 6.47 (d, J = 8.3 1 arom H); 4.70 (d, J = 3.0, *H*-C(5)); 2.35 (s, C*H*$_3$N); 1.43 (s, t-Bu). MS (CI) *m/z* 535 $[M+1]^+$. Anal. ($C_{32}H_{42}N_2O_5 \cdot 0.4H_2O$) C, H, N. **12:** IR (KBr) 1734 (C=O). ^{1}H NMR ($CDCl_3$) δ 7.28–7.20 (m, 5 arom H); 6.67 (d, J = 8.2,1 arom H); 6.51 (d, J = 8.2, 1 arom. H); 4.55 (d, J = 7.0, *H*-C(5)); 2.36 (s, C*H*$_3$N); 1.42 (s, t-Bu). MS (CI) *m/z* 535 $[M+1]^+$. Anal. ($C_{32}H_{42}N_2O_5 \cdot 1H_2O$) C, H, N.

***tert*-Butyl [[17-cyclopropylmethyl-4,5*α*-epoxy-3-hydroxy-14*β*-[(3-phenylpropyl) oxy]morphinan-6*α*-yl]amino]acetate (15) and *tert*-Butyl [[17-cyclopropylmethyl-4,5*α*-epoxy-3-hydroxy-14*β*-[(3-phenylpropyl)oxy]morphinan-6*β*-yl]amino]acetate (16).** The mixture of the epimers (0.72 g yellow oil) was separated by MPLC (silica gel; CH_2Cl_2/MeOH/conc. NH_4OH 250:1:0.5) to give 23% of compound **15** and 23% of compound **16**. **15:** IR (KBr) 1735 (C=O). ^{1}H NMR ($CDCl_3$) δ 7.28–7.17 (m, 5 arom H); 6.66 (d, J = 8.1, 1 arom H); 6.45 (d, J = 8.1, 1 arom H); 4.70 (d, J = 4.2, *H*-C(5)); 1.44 (s, t-Bu); 0.75 (m, C*H*-cp); 0.44 (m, C*H*$_2$-cp); 0.07 (m, C*H*$_2$-cp). MS (CI) *m/z* 575 $[M+1]^+$. Anal. ($C_{35}H_{46}N_2O_5 \cdot 1.3H_2O \cdot 0.1NH_3$) C, H, N. **16:** IR (KBr) 1735 (C=O). ^{1}H NMR ($CDCl_3$) δ 7.27–7.18 (m, 5 arom H); 6.66 (d, J = 8.1,1 arom H); 6.50 (d, J = 8.1, 1 arom H); 4.49 (d, J = 7.2, *H*-C(5)); 1.44 (s, t-Bu); 0.67 (m, C*H*-cp); 0.42 (m, C*H*$_2$-cp); 0.06 (m, C*H*$_2$-cp) (cp = cyclopropyl). MS (CI) *m/z* 575 $[M+1]^+$. Anal. ($C_{35}H_{46}N_2O_5$) C, H, N.

Elemental analyses of compounds 11-18

Compd No	**% C calcd found**	**% H calcd found**	**% N calcd found**	**Calculated for M_r**
11	70.93 70.85	7.96 8.02	5.17 5.23	$C_{32}H_{42}N_2O_5 \cdot 0.4H_2O$ 541.91
12	69.31 69.29	8.03 7.85	5.05 4.86	$C_{32}H_{42}N_2O_5 \cdot 1.1H_2O$ 554.52
13·2HCl	57.42 57.46	6.85 7.25	4.78 4.47	$C_{28}H_{34}N_2O_5 \cdot 2HCl \cdot 1.9H_2O$ 585.74
14·2HCl	57.24 57.29	6.86 7.08	4.77 4.60	$C_{28}H_{34}N_2O_5 \cdot 2HCl \cdot 2H_2O$ 587.54
15	70.08 69.81	8.22 7.94	4.90 5.24	$C_{35}H_{46}N_2O_5 \cdot 1.3H_2O \cdot 0.1NH_3$ 599.89
16	73.14 73.12	8.07 8.01	4.87 4.84	$C_{35}H_{46}N_2O_5$ 574.76
17·2HCl	60.37 60.26	6.99 6.71	4.54 4.77	$C_{31}H_{38}N_2O_5 \cdot 2HCl \cdot 1.4H_2O$ 616.80
18·2HCl	59.84 59.86	7.03 6.88	4.50 4.40	$C_{31}H_{38}N_2O_5 \cdot 2HCl \cdot 1.7H_2O$ 622.21

Figure S1. Antinociceptive effects of *N*-methyl-14-phenylpropoxymorphinans **11-14** after sc administration in the tail-flick test in the rat. (A, left panel) Dose-dependent and time course of the antinociceptive response presented as % antinociceptive effect before drug administration. (B, right panel) Areas under the curves (AUC) of the respective time curves for the effect of vehicle (0) and different doses of test compounds are represented. Data are shown as mean ± SEM. **p*<0.05, ***p* <0.01 and ****p* < 0.001 vs vehicle control group.

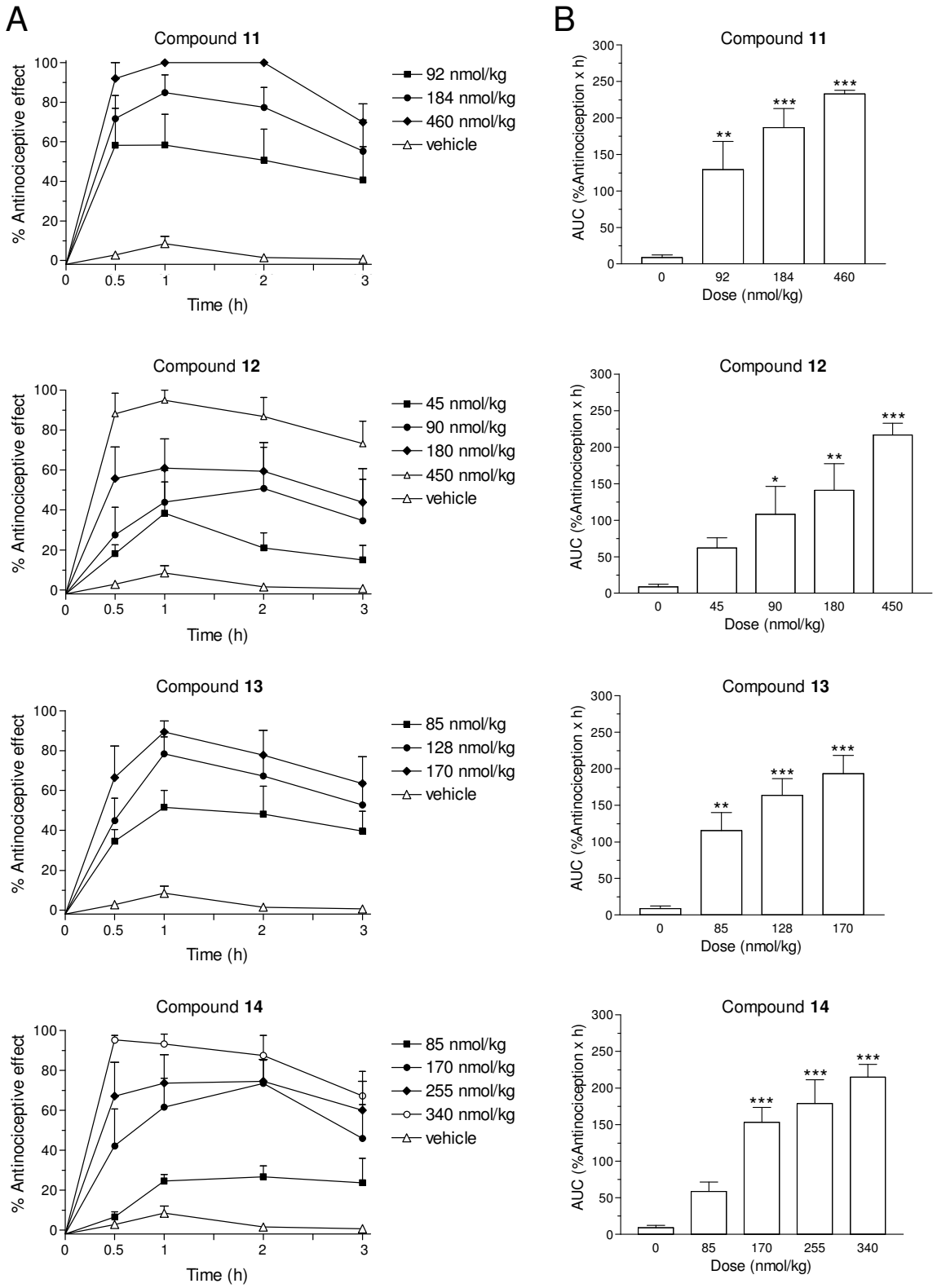

Figure S2. Antinociceptive effects of *N*-cyclopropylmethyl-14-phenylpropoxymorphinans **15-18** after sc administration in the tail-flick test in the rat. (A, left panel) Dose-dependent and time course of the antinociceptive response presented as % antinociceptive effect before drug administration. (B, right panel) Areas under the curves (AUC) of the respective time curves for the effect of vehicle (0) and different doses of test compounds are represented. Data are shown as mean ± SEM. **p*<0.05, ***p* <0.01 and ****p* < 0.001 vs vehicle control group.