Novel Delta-Opioid-Receptor-Selective Ligands in the 14-Alkoxy-Substituted Indolo- and Benzofuromorphinan Series

by **Dauren Biyashev**[a]), **Krisztina Monory**[a]), **Sandor Benyhe**[a]), **Johannes Schütz**[b]), **Martin Koch**[b]), **Helmut Schmidhammer***[b]), and **Anna Borsodi**[a])

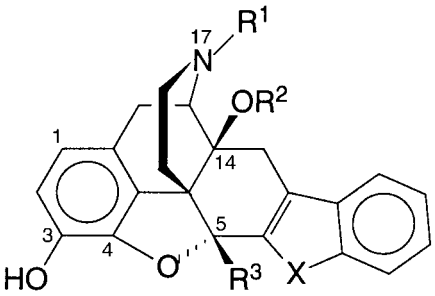
[a]) Institute of Biochemistry, Biological Research Center, Hungarian Academy of Sciences, Szeged H-6701
[b]) Division of Pharmaceutical Chemistry, Department of Pharmacy, University of Innsbruck, Innrain 52a, A-6020 Innsbruck

Several new indolo- and benzofuromorphinans substituted at the positions 5 and 14 were prepared and tested *in vitro* by means of opioid-receptor binding and functional ([^{35}S]GTPγS binding) assays. All compounds **1**–**11** displayed high affinity for δ opioid-binding sites (*Table 1*). Compound **4** proved to be an agonist, and all other compounds were antagonists. The presence of a Me group at position 5 induced no change in δ affinity (see **1** *vs.* **3**), but decreased the μ and κ affinities. An EtO group at position 14 conferred a very high affinity and also high selectivity to δ opioid receptors (see **2** and **10**). Chain elongation of the 14-alkoxy group resulted in compounds with reduced δ affinity and selectivity (see **4** and **11** and also **5**–**9**). The results of the present study indicate that the 5- and 14-positions of indolo- and benzofuromorphinans represent critical sites that could be a trigger to develop new compounds with increased δ affinity and/or selectivity.

Introduction. – Opioid agonists acting through μ opioid receptors (one of the three commonly accepted major classes of opioid receptors [1]) are used clinically for pain treatment. However, they can cause severe side effects such as respiratory depression, constipation, nausea, vomiting, and, moreover, their chronic use results in tolerance and dependence [2]. The clinical use of κ opioid agonists is very much limited due to their dysphoric and psychotomimetic properties [3]. δ Opioid agonists, while having analgesic properties, induce weaker physical dependence [4]. Therefore, δ opioid-receptors appear to represent important therapeutic targets for the development of novel safer analgesic agents [5]. It was shown that δ opioid receptors are involved in the regulation of the immune system [6]. While δ agonists tend to be immunostimulants, δ antagonists display potent immunosuppressive activity. There are also data suggesting that δ opioid antagonists can be used for treatment of alcohol and drug addiction [7].

Among the ligands acting at δ opioid receptors, there are peptides as well as non-peptide opioid compounds. Nonpeptide opioids are preferred as pharmacological tools, since they can generally penetrate the central nervous system and are less subject to metabolic degradation. There is much emphasis on the development of new selective antagonists that, except for medicinal purposes, can be also used to evaluate the selectivity of new agonists and to study the interaction of endogenous ligands with different opioid receptors [8]. By means of the 'message-address' concept, selective opioid ligands with antagonist activity were developed. Based on the naltrexone structure, the addition of an 'address' element, such as an indole or benzofuran moiety, resulted in two δ-selective antagonists, naltrindole (NTI) and naltriben (NTB), respectively [9].

Further studies to increase our understanding of the δ opioid-receptor system and its involvement in physiological processes require the development of stable, highly δ-selective nonpeptide ligands. Our approach toward this goal was to modify the structure and to investigate the structure-activity relationships of some newly developed indolo- and benzofuromorphinans. The prototypical members of these series were the two antagonists NTI and NTB. In the present study, we aimed at improving the selectivity and/or affinity of the indolo- and benzofuromorphinans with focus on their 5- and 14-positions. Methylation at position 5 was reported to play an important role in decreasing μ antagonism and thus increasing δ selectivity, while a 14-EtO group in indolomorphinans was found to be somewhat superior to either a 14-MeO group or a 14-PrO group concerning δ antagonism [10]. In this study, we mainly assessed the effect of 14-*O*-benzyl and 14-*O*-naphthylmethyl substitutions on δ affinity, selectivity, and antagonism. Furthermore, we investigated the influence of indolo *vs.* benzofuro fusion on opioid-binding properties. Here we describe the design and structure-activity relationships of the 14-alkoxy-substituted indolo- and benzofuromorphinans. Opioid-binding profiles and agonist/antagonist activities were determined in rat-brain homogenates for **1**–**11** by means of receptor binding and functional ([^{35}S]GTPγS binding) assays.



NTI	R^1 = cpm, R^2 = R^3 = H, X=NH
NTB	R^1 = cpm, R^2 = R^3 = H, X=O
1	R^1 = cpm, R^2 = R^3 = Me, X=NH
2	R^1 = cpm, R^2 = Et, R^3 = H, X=NH
3	R^1 = cpm, R^2 = Me, R^3 = H, X=NH
4	R^1 = Me, R^2 = $MeCH_2CH_2$, R^3 = Me, X=NH
5	R^1 = cpm, R^2 = 3-$NO_2C_6H_4CH_2$, R^3 = H, X=O
6	R^1 = cpm, R^2 = 2,6-$Cl_2C_6H_3CH_2$, R^3 = H, X=O
7	R^1 = cpm, R^2 = 2-$ClC_6H_4CH_2$, R^3 = H, X=NH
8	R^1 = cpm, R^2 = 2-naphthylmethyl, R^3 = H, X=O
9	R^1 = cpm, R^2 = 2-$FC_6H_4CH_2$, R^3 = H, X=O
10	R^1 = cpm, R^2 = Et, R^3 = H, X=O
11	R^1 = R^2 = H_2C=$CHCH_2$, R^3 = H, X = CH_2=$CHCH_2N$

cpm = cyclopropylmethyl

Chemistry. – Compound **13** was prepared from 5,14-*O*-dimethyloxycodone (**12**) [10] by 3-*O*-methyl ether cleavage with BBr_3. Compounds **4** and **17** were synthesized from 5,14-*O*-dimethyloxymorphone (**13**) and *N*-allyl-14-*O*-(propoxy)morphone (**14**) [11], respectively, by a *Fischer* indole synthesis (*Scheme*). The 14-*O*-alkylation of compound **15** [12] and 14-*O*,*N*(indole)-dialkylation of compound **17** in DMF in the presence of NaH as a base afforded compounds **16** and **18**, respectively. The 3-(methoxymethoxy) group of **16** and the 3-benzyloxy group of **18** were cleaved by a dilute HCl solution in MeOH to give compounds **10** and **11**, respectively. The syntheses of compounds **1**–**3** [10] and **5**–**9** [12] have already been described.

Biochemical Evaluation. – Compounds **1**–**11** were characterized in terms of affinities and selectivities to opioid receptors in rat-brain membranes by means of receptor binding assays. The following type-selective opioid radioligands were used:

[^{3}H][Ile^{5,6}]deltorphin II (δ) [13], [^{3}H][D-Ala^2,(N–Me)Phe^4,Gly^5-ol]enkephalin ([^{3}H]DAMGO; μ), and [^{3}H]ethylketocyclazocine ([^{3}H]EKC; κ) (*Table 1*). In addition to the novel ligands, two more compounds have been studied: NTI and NTB. The binding data expressed as inhibition-constant (K_i) values are shown in *Table 1*. All compounds **1**–**11** displayed high affinity towards δ opioid-binding sites and less affinity for μ and κ opioid-receptors. Compounds **3**–**9** and **11** had comparatively low δ selectivity with affinities for δ binding sites in the nanomolar range. Compounds **1** and **2** had high δ selectivity, with slightly lower μ/δ and higher κ/δ selectivity ratios than those of NTI. The 14-EtO-substituted benzofuromorphinan **10** showed higher affinity for δ binding sites compared to NTB, what resulted in a *ca.* 6-fold increased μ/δ selectivity. Compound **6** showed decrease of both affinity and selectivity for δ binding sites as compared to NTB. The δ selectivity of compounds **1**–**3** has been previously established in the mouse *vas deferens* bioassay [10].

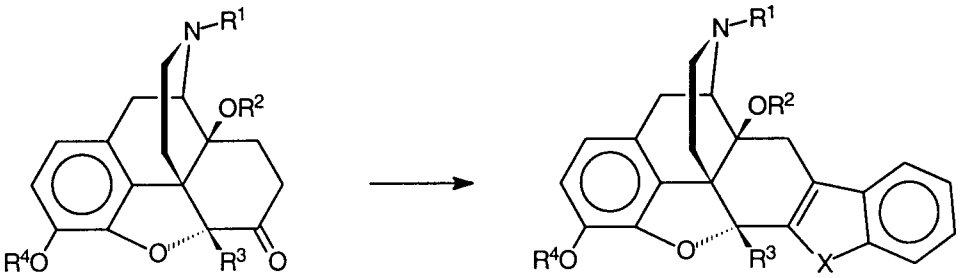
Table 1. *Affinities of Ligands* **1**–**11** *in Opioid-Receptor Binding Assays in Rat-Brain Membranes*

	K_i [nM][a])			Selectivity ratio	
	μ[b])	δ[c])	κ[d])	μ/δ	κ/δ
NTI	30.40 ± 0.70	0.09 ± 0.04	27.52 ± 2.41	338	306
NTB[e])	80.8 ± 2.3	0.54 ± 0.09		150	
1	283.55 ± 25.27	1.15 ± 0.85	420.52 ± 141.27	247	366
2	96.90 ± 34.80	0.40 ± 0.08	313.00 ± 98.90	242	783
3	68.70 ± 11.10	1.44 ± 0.40	103.00 ± 21.60	48	72
4	241.98 ± 22.21	9.02 ± 3.62	218.89 ± 68.08	27	24
5	419.00 ± 42.80	10.90 ± 1.24	373.00 ± 125.00	38	34
6	158.00 ± 9.68	30.80 ± 4.03	64.90 ± 5.02	5	2
7	164.79 ± 1.54	8.00 ± 0.31	130.50 ± 13.16	21	16
8	53.30 ± 11.10	4.60 ± 1.16	350.00 ± 123.00	12	76
9	138.52 ± 18.66	9.90 ± 4.36	148.66 ± 25.22	14	15
10	116.00 ± 12.40	0.12 ± 0.05	253.00 ± 65.10	967	2108
11	187.38 ± 17.80	4.66 ± 3.29	116.52 ± 19.31	40	25

[a]) Mean ± s.e.m. [b]) [^{3}H]DAMGO. [c]) [^{3}H][Ile^{5,6}]deltorphin II. [d]) [^{3}H]EKC in the presence of 100 nM DAMGO and [D-Ala^2,Leu^5]enkephalin for blocking μ and δ binding sites. [e]) Data from [14].

Examination of the chemical structures, binding affinities, and selectivities of the newly developed opioid compounds reveals certain structure-activity relationships for the investigated compounds. First, the presence of a 5-Me group induced no change in δ affinity, but decreased the μ and κ affinities, thus increasing μ/δ and κ/δ selectivity ratios (see *Table 1*; **1** *vs.* **3**). Second, the substitution at position 14 is a very important determinant in increasing δ selectivity. An EtO group at this position confers a very high affinity and also high selectivity to δ opioid-receptors (see **2** and **10**). Chain elongation of the 14-alkoxy group (see **4** and **11**) and introduction of benzyloxy and naphthylmethoxy groups at position 14 (see **5**–**9**) resulted in compounds with reduced δ affinity and selectivity. A benzofuro moiety (see **10**) seems to be superior to an indolo moiety (see **2**) regarding to both δ affinity and selectivity in this class of compounds. *N*-Substitution at the indole moiety (see **11**) does not seem to have much influence on δ affinity and selectivity.

Scheme



12 $R^1 = R^3 = R^4 = Me$, $R^2 = Pr$ [10]
13 $R^1 = R^3 = Me$, $R^2 = Pr$, $R^4 = H$
14 $R^1 = CH_2=CHCH_2$, $R^2 = R^3 = H$, $R^4 = Bn$ [11]
4 $R^1 = R^3 = Me$, $R^2 = Pr$, $R^4 = H$, $X = NH$
15 $R^1 = cpm$, $R^2 = R^3 = H$, $R^4 = MeOCH_2$, $X = O$ [12]
16 $R^1 = cpm$, $R^2 = Et$, $R^3 = H$, $R^4 = MeOCH_2$, $X=O$
10 $R^1 = cpm$, $R^2 = Et$, $R^3 = R^4 = H$, $X=O$
17 $R^1 = CH_2=CHCH_2$, $R^2 = R^3 = H$, $R^4 = Bn$, $X=NH$
18 $R^1 = R^2 = CH_2=CHCH_2$, $R^3 = H$, $R^4 = Bn$, $X=CH_2=CHCH_2N$
11 $R^1 = R^2=CH_2=CHCH_2$, $R^3 = R^4 = H$, $X=CH_2=CHCH_2N$

cpm = cyclopropylmethyl, Bn = benzyl

We also aimed to establish the agonist/antagonist properties of the new ligands. The *in vitro* effect produced by Na^+ ions on opioid-binding [15] in displacement experiments with [^{3}H]naloxone [16] was used (*Table 2*). According to their Na^+ indices, all new ligands, except **4**, were antagonists. Compound **4**, with a Me group at the morphinan N-atom showed agonistic features. Functional [^{35}S]GTPγS binding assays were performed to evaluate the ability of the newly synthesized compounds to stimulate the activity of G-proteins (*Table 3*). Compound **4** was able to stimulate [^{35}S]GTPγS binding in a dose-

Table 2. *Agonist/Antagonist Profile of Compounds* **1**–**11** *in Opioid-Binding Assays in Rat-Brain Membranes*

	K_i, [^{3}H]Naloxone [nM][a])		Na^+ Index[b])[c])
	− NaCl	+ NaCl	
NTI	15.17 ± 1.20	6.90 ± 0.28	0.5
NTB[d])	44	44	1
1	135.25 ± 21.06	347.56 ± 176.92	2.6
2	44.90 ± 9.44	33.10 ± 5.43	0.7
3	24.00 ± 3.70	15.30 ± 1.79	0.6
4	289.97 ± 48.56	4488.27 ± 2012.52	15.5
5	359.00 ± 45.90	306.00 ± 17.20	0.9
6	188.00 ± 30.90	132.00 ± 23.80	0.7
7	107.59 ± 12.94	67.72 ± 1.93	0.6
8	138.00 ± 37.00	158.00 ± 22.20	1.1
9	81.58 ± 15.23	71.02 ± 4.69	0.9
10	58.30 ± 10.70	49.10 ± 7.03	0.8
11	95.14 ± 15.60	78.73 ± 4.73	0.8

[a]) Mean ± s.e.m. [b]) Na^+ Index = $K_i(+ Na^+)/K_i(- Na^+)$. [c]) Na^+ Index ≥ 10 for full agonists, Na^+ index ≤ 1 for full antagonists. [d]) Data from [14].

Table 3. *Effect of Compounds* **1**–**11** *on [^{35}S]GTPγS-Binding in Rat-Brain Membranes*

	% Stimulation/inhibition over basal activity[a])[b])
Nonstimulated basal activity	100
4	126 ± 4
[Ile^{5,6}]deltorphin II (δ opioid agonist)	117 ± 1
[Ile^{5,6}]deltorphin II + naloxone	102 ± 4
[Ile^{5,6}]deltorphin II + NTI	97 ± 3
[Ile^{5,6}]deltorphin II + **1**	104 ± 3
[Ile^{5,6}]deltorphin II + **2**	103 ± 3
[Ile^{5,6}]deltorphin II + **3**	96 ± 4
[Ile^{5,6}]deltorphin II + **5**	94 ± 5
[Ile^{5,6}]deltorphin II + **6**	97 ± 3
[Ile^{5,6}]deltorphin II + **7**	103 ± 2
[Ile^{5,6}]deltorphin II + **8**	102 ± 3
[Ile^{5,6}]deltorphin II + **9**	95 ± 3
[Ile^{5,6}]deltorphin II + **10**	94 ± 3
[Ile^{5,6}]deltorphin II + **11**	100 ± 5

[a]) Mean ± s.e.m. [b]) Ligands used at 10 μM concentration.

dependent manner with an $EC_{50} = 497.2 \pm 138.9$ nM. In accordance with their antagonist character – established also by the binding assays (Na^+ indices) – all other tested compounds produced no change in [^{35}S]GTPγS binding (data not shown). These ligands were evaluated in inhibiting the response produced by the δ-selective agonist Ile^{5,6}deltorphin II. All of the newly developed compounds were able to decrease significantly the stimulatory effect produced by this opioid agonist (*Table 3*).

The pharmacological properties of the investigated compounds correlate very well with their structures. It is well-known that the nature of the substituent at the morphinan N-atom is very important concerning the opioid agonist/antagonist features of the compound. The δ-selective agonist **4** possesses a Me group at N(17), whereas the antagonists NTI, NTB, **1**–**3**, and **5**–**11** have 'antagonist' substituents such as cyclopropylmethyl or allyl at this position.

Taken together, the results of the present study indicate that the positions 5 and 14 of indolo- and benzofuromorphinans represent critical sites that could be a trigger to develop new compounds with increased δ affinity and/or selectivity.

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Experimental Part

General. M.p.s: *Kofler* melting-point microscope; uncorrected. IR Spectra: *Mattson Galaxy-Series-FTIR-3000* spectrometer; in cm^{-1}. ^{1}H-NMR Spectra: *Varian Gemini-2000* spectrometer; δ in ppm rel. to $SiMe_4$ as internal reference, *J* in Hz. Mass spectra: *Finnigan-Mat SSQ-7000* apparatus. Elemental analyses were performed at the Institute of Physical Chemistry, University of Vienna, Vienna, Austria.

4,5α-Epoxy-3-hydroxy-5β,17-dimethyl-14β-propoxymorphinan-6-one (**13**). A mixture of **12** [10] (2.70 g, 7.27 mmol), 1,2-dichloroethane (370 ml), and 1M BBr_3 soln. (54 ml, 54 mmol) in 1,2-dichloroethane was stirred at 0° for 2 h, then poured on ice (90 g) and conc. NH_4OH soln. (20 ml), and extracted with CH_2Cl_2 (3 × 230 ml).

The combined org. layers were washed with brine (300 ml), dried (Na_2SO_4), and evaporated to give a beige foam (2.40 g), which was crystallized from a little MeOH: 1.48 g (57%) of **13**. Beige crystals. M.p. 193–195°. IR (KBr): 3376 (OH), 1726 (CO). ^{1}H-NMR ($CDCl_3$): 6.67 (*d*, *J* = 8.1, 1 arom. H); 6.52 (*d*, *J* = 8.1, 1 arom. H); 2.37 (*s*, MeN); 1.57 (*s*, Me); 0.96 (*t*, *J* = 7.2, *Me*CH_2CH_2O). EI-MS: 357 (M^+). Anal. calc. for $C_{21}H_{27}NO_4$ (357.43): C 70.56, H 7.61, N 3.92; found: C 70.50, H 7.88, N 3.92.

*4,5α-Epoxy-5β,17-dimethyl-14β-propoxy-1′*H*-indolo[2′,3′:6,7]morphinan-3-ol Methanesulfonate* (**4**·$MeSO_3H$). A mixture of **13** (350 mg, 0.98 mmol), phenylhydrazine hydrochloride (210 mg, 1.45 mmol), and AcOH (12 ml) was refluxed for 20 h, evaporated, alkalinized with conc. NH_4OH soln., and extracted with CH_2Cl_2 (3 × 50 ml). The combined org. layer was washed with H_2O (3 × 60 ml), dried (Na_2SO_4), and evaporated to give a brown foam (0.36 g), which was converted to the methanesulfonate in the usual way: 0.15 g (29%) of **4**·$MeSO_3H$. Beige crystals. M.p. >270° (dec.). IR (KBr): 3203 (OH). ^{1}H-NMR ($(D)_6$DMSO): 11.29 (*s*, NH); 9.13 (*s*, OH); 8.47 (*s*, NH^+); 7.39–6.91 (*m*, 4 arom. H); 6.58 (*s*, 2 arom. H); 2.97 (*s*, MeN); 1.86 (*s*, Me); 0.57 (*t*, *J* = 7.3, *Me*CH_2CH_2O). EI-MS: 430 (M^+). Anal. calc. for $C_{27}H_{30}N_2O_3 \cdot MeSO_3H \cdot 0.7\ H_2O$ (539.27): C 62.36, H 6.62, N 5.19, S 5.95; found: C 62.36, H 6.50, N 5.20, S 6.02.

17-(Cyclopropylmethyl)-4,5α-epoxy-14β-ethoxy-3-(methoxymethoxy)benzofuro[2′,3′:6,7]morphinan (**16**). A mixture of **15** [12] (300 mg, 0.64 mmol), NaH (36 mg, 1.50 mmol; obtained from 60% NaH dispersion (60 mg) in oil by washing with hexane), and anh. DMF (6 ml) was stirred at 0° for 30 min. Diethyl sulfate (153 mg, 0.99 mmol) was added at once, and stirring was continued for 15 min at 0° and then for 3 h at r.t. Excess NaH was destroyed with MeOH and H_2O, the mixture extracted with AcOEt (3 × 30 ml), the combined org. layer washed with H_2O (2 × 30 ml) and brine (30 ml), dried (Na_2SO_4), and evaporated, and the residue (390 mg of brown oil) purified by CC (silica gel, CH_2Cl_2/MeOH/conc. NH_4OH soln. 240 : 10 : 1) to give a colorless foam (320 mg), which was crystallized from MeOH: 270 mg (87%) of **16**. Colorless crystals. M.p. 114–116°. ^{1}H-NMR ($CDCl_3$): 7.48–7.14 (*m*, 4 arom. H); 6.83 (*d*, *J* = 8.2, 1 arom. H); 6.57 (*d*, *J* = 8.2, 1 arom. H); 5.63 (*s*, H–C(5)); 5.16 (*d*, *J* = 6.6, 1 H, OCH_2O); 5.05 (*d*, *J* = 6.6, 1 H, OCH_2O); 3.41 (*s*, *Me*OCH_2O); 1.13 (*t*, *J* = 6.8, *Me*CH_2O); 0.86–0.80 (*m*, CH); 0.55–0.47 (*m*, CH_2); 0.14–0.09 (*m*, CH_2). EI-MS: 487 (M^+). Anal. calc. for $C_{30}H_{33}NO_5$ (487.59): C 73.90, H 6.82, N 2.87; found: C 73.97, H 6.81, N 2.87.

17-(Cyclopropylmethyl)-4,5α-epoxy-14β-ethoxybenzofuro[2′,3′:6,7]morphinan-3-ol (**10**). A soln. of **16** (200 mg, 0.41 mmol) in MeOH (4 ml) and 1M HCl (2 ml) was refluxed for 1 h, cooled, and evaporated. The residue was treated with H_2O (50 ml), alkalinized with conc. NH_4OH soln., and extracted with AcOEt (3 × 20 ml). The combined org. layer was washed with H_2O (2 × 30 ml) and brine (30 ml), dried (Na_2SO_4), and evaporated, and the residue (150 mg brown oil) purified by CC (silica gel, CH_2Cl_2/MeOH/conc. NH_4OH soln. 240 : 10 : 1) to give a colorless foam (120 mg), which was crystallized from MeOH: 85 mg (47%) of **10**. Colorless crystals. M.p. 142–144°. IR (KBr): 3400 (OH). ^{1}H-NMR ($CDCl_3$): 7.48–7.16 (*m*, 4 arom. H); 6.63 (*d*, *J* = 8.0, 1 arom. H); 6.54 (*d*, *J* = 8.0, 1 arom. H); 5.64 (*s*, H–C(5)); 1.17 (*t*, *J* = 6.7, *Me*CH_2O); 0.82–0.76 (*m*, CH); 0.62–0.56 (*m*, CH_2); 0.16–0.10 (*m*, CH_2). EI-MS: 443 (M^+). Anal. calc. for $C_{30}H_{33}NO_5 \cdot 0.1\ H_2O$ (445.35): C 75.52, H 6.61, N 3.15; found: C 75.46,H 6.61, N 3.12.

*17-Allyl-3-(benzyloxy)-4,5α-epoxy-1′*H*-indolo[2′,3′:6,7]morphinan-14β-ol Hydrochloride* (**17**·HCl). A mixture of **14** [11] (2.70 g, 5.96 mmol), phenylhydrazine hydrochloride (1.25 g, 8.64 mmol), and AcOH (40 ml) was refluxed for 4 h, evaporated, alkalinized with conc. NH_4OH soln., and extracted with CH_2Cl_2 (3 × 100 ml). The combined org. layer was washed with H_2O (3 × 100 ml) and brine (80 ml), dried (Na_2SO_4), and evaporated, and the residue converted into the hydrochloride in the usual way: 1.43 g (46%) of **17**·HCl. Yellow crystals. M.p. 190–195°. ^{1}H-NMR ($(D)_6$DMSO): 11.39 (*s*, NH); 9.36 (*s*, NH^+); 7.40–6.90 (*m*, 9 arom. H); 6.87 (*d*, *J* = 8.2, 1 arom. H); 6.70 (*d*, *J* = 8.2, 1 arom. H); 6.40 (*s*, OH–C(14)); 5.95 (*m*, 1 olef. H); 5.78 (*s*, H–C(5)); 5.60 (*m*, 2 olef. H); 5.06 (*d*, *J* = 11.6, 1 H, PhCH_2O); 4.97 (*d*, *J* = 11.6, 1 H, PhCH_2O). EI-MS: 490 (M^+). Anal. calc. for $C_{32}H_{30}N_2O_3 \cdot HCl \cdot 0.3\ Et_2O$ (549.30): C 72.60, H 6.24, N 5.10; found: C 72.96, H 6.50, N 4.72.

*1′,17-Diallyl-14β-(allyloxy)-3-(benzyloxy)-4,5α-epoxy-1′*H*-indolo[2′,3′:6,7]morphinan Hydrochloride* (**18**·HCl). A mixture of **17**·HCl (1.30 g, 2.47 mmol), NaH (0.60 g, 25.00 mmol; obtained from 60% NaH dispersion (1.00 g) in oil by washing with hexane), and anh. DMF (50 ml) was stirred at 0° for 15 min. Allyl bromide (0.89 g, 7.36 mmol) was added at once and stirring continued for 3.5 h at 0°. Excess NaH was destroyed with ice, the mixture poured on H_2O (150 ml) and extracted with CH_2Cl_2 (3 × 70 ml), the combined org. layer washed with H_2O (2 × 100 ml), dried (Na_2SO_4), and evaporated, and the residue converted to the hydrochloride in the usual way: 1.04 g (70%) of **18**·HCl. Beige crystals. M.p. 140–145°. ^{1}H-NMR ((D_6)DMSO): 9.16 (*s*, NH^+); 7.42–6.98 (*m*, 9 arom. H); 6.90 (*d*, *J* = 8.2, 1 arom. H); 6.75 (*d*, *J* = 8.2, 1 arom. H); 6.06 (*s*, H–C(5)); 5.65 (*m*, 3 olef. H); 5.20–4.80 (*m*, 6 olef. H, PhCH_2O). CI-MS: 571 ($[M+1]^+$). Anal. calc. for $C_{38}H_{38}N_2O_3 \cdot HCl \cdot 1.2\ H_2O$ (628.82): C 72.58, H 6.64, N 4.45; found: C 72.47, H 6.44, N 4.60.

*1′,17-Diallyl-14β-(allyloxy)-4,5α-epoxy-1′*H*-indolo[2′,3′:6,7]morphinan-3-ol Hydrochloride* (**11**·HCl). A soln. of **18**·HCl (400 mg, 0.66 mmol) in MeOH (6 ml) and conc. HCl soln. (4 ml) was refluxed for 12 h, cooled, and evaporated. The residue was treated with H_2O (50 ml), alkalinized with conc. NH_4OH soln., and extracted with CH_2Cl_2 (3×30 ml). The combined org. phase was washed with H_2O (2×50 ml), dried (Na_2SO_4), and evaporated, and the residue converted to the hydrochloride in the usual way: 190 mg (56%) of **11**·HCl. Yellow crystals. M.p. $>200°$ (dec.). ^{1}H-NMR ($(D)_6$DMSO): 9.29, 9.05 (2*s*, OH, NH^+); 7.42–6.95 (*m*, 4 arom. H); 6.67 (*d*, $J = 8.2$, 1 arom. H); 6.62 (*d*, $J = 8.2$, 1 arom. H); 5.92 (*s*, H–C(5)); 5.62 (*m*, 3 olef. H); 5.20–4.80 (*m*, 6 olef. H, PhCH_2O). CI-MS: 481 ($[M+1]^+$). Anal. calc. for $C_{31}H_{32}N_2O_3 \cdot HCl \cdot 1.4\ H_2O$ (542.29): C 68.66, H 6.65, N 5.17; found: C 68.56, H 6.42, N 4.99.

Opioid-Receptor Binding Assays. Rat-brain membrane was prepared as previously described [17]. Opioid-receptor binding assays were performed as described in [14][18].

[^{35}S]GTPγS Binding Assays. Experiments were performed as previously described [19].

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