Synthesis and Biological Evaluation of 14-Alkoxymorphinans. 17. Highly δ Opioid Receptor Selective 14-Alkoxy-Substituted Indolo- and Benzofuromorphinans

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14-Alkoxy analogues of naltrindole and naltriben differently substituted in positions 5 and 17 and at the indole nitrogen (compounds **28**–**44**) have been synthesized in an effort to enhance the δ potency and/or δ selectivity and in order to further elaborate on structure–activity relationships of this class of compounds. Introduction of a 14-alkoxy instead of the 14-hydroxy group present in naltrindole resulted in somewhat lower δ binding affinity, while in many cases (compounds **31**, **34**, **37**, **40**, **41**, **44**, HS 378) the δ receptor selectivity was considerably increased. An ethoxy group in position 14 is superior to other alkoxy groups concerning δ affinity and selectivity (**34**, **41**, **42**, **44**, HS 378). In [³⁵S]GTPγS binding, compounds **34**, **41**, and HS 378 exhibited about one-tenth the antagonist potency of naltrindole at δ opioid receptors while their δ antagonist selectivity was considerably higher. 17-Methyl-substituted compounds **35** and **44** were found to be pure δ receptor agonists in this test.

Introduction

On the basis of pharmacological, behavioral, and biochemical studies, opioid receptors have been classified into three major types: μ, δ, and κ. They belong to the G-protein-coupled receptor superfamily.[1] Receptor type selective opioid agonists and antagonists are of interest both as pharmacological tools and as potential therapeutic agents. During the past 3 decades, one of the major aims of opioid pharmacology has been to develop opioids with high affinity and/or selectivity for each of the three receptor types.[2–5] Recently δ opioid receptors have been studied extensively and it was found that they are involved in many biological processes.[6] Besides the analgesic effect of δ agonists,[7,8] they show for instance stimulatory effects on respiration[9] or immunomodulatory effects[10–12] that were found to be immunostimulant.[13,14] δ Antagonists, like naltrindole (NTI, **1**, Figure 1), were found to have immunosuppressive potency and less toxicity than the presently used immunosuppressive compound cyclosporin.[15–17] Such agents can be used after organ transplantation to suppress the rejection of the foreign organ and also in the treatment of autoimmune diseases (e.g., rheumatoid arthritis).

In the search for selective non-peptide δ opioid receptor ligands, indolo- and benzofuromorphinans derived from the nonselective antagonist naltrexone display selectivity toward δ receptors. The prototype antagonists NTI[18] and naltriben (NTB, **2**)[19] also show some agonist effects,[20,21] while the 17-methyl analogue of
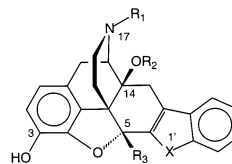

Figure 1. **1** (NTI): R₁ = CPM, R₂ = H, R₃ = H, X = NH. **2** (NTB): R₁ = CPM, R₂ = H, R₃ = H, X = O. **3** (OMI): R₁ = Me, R₂ = H, R₃ = H, X = NH. **4** (HS 378): R₁ = CPM, R₂ = Et, R₃ = Me, X = NH. CPM: cyclopropylmethyl.

naltrindole (oxymorphindole, OMI, **3**) clearly exhibits partial agonism.[22] Recently it was reported that modification of the substituent in position 17 (R₁) causes major changes in affinity, selectivity, and potency of the ligands.[23] For instance, it was apparent from this work that the effect of some 17-substituents (e.g., ethyl or pentyl) is dissimilar in ligands selective for δ or μ opioid receptors. The 17-ethyl and 17-pentyl analogues of NTI showed clear δ opioid antagonism. Structure–activity studies on NTI analogues focusing on the indolic benzene ring revealed that substituents in the 7′ position did not significantly alter δ affinity and δ selectivity, while substituents in 4′, 5′, and 6′ positions had major influence in affinity and subtype specificity.[18,22,24–30]

Introduction of a 14-ethoxy and a 5-methyl group onto the NTI molecule resulted in a pure opioid antagonist (HS 378, **4**) with somewhat lower δ potency but much higher δ selectivity in bioassays,[31] functional assay, and receptor binding.[32] Recently Spetea et al.[33] have found that HS 378 possesses an immunosuppressive potency in vitro on T-lymphocyte proliferation that is more than 10-fold higher compared to NTI. Introduction of a 14-ethoxy and a 5-methyl group onto the OMI molecule resulted in a pure δ opioid receptor agonist in the MVD.[31] Another study showed that a 5-methyl group

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Scheme 1[a]
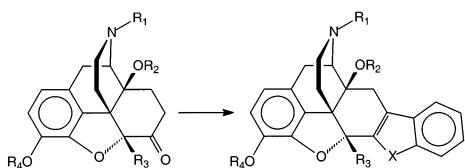
[a] For ketones. **5**:[35] R_1 = Me, R_2 = H, R_3 = Me, R_4 = Me, $\Delta.^{7,8}$ **6**: R_1 = Me, R_2 = dimethylallyl, R_3 = Me, R_4 = Me, $\Delta.^{7,8}$ **7**: R_1 = Me, R_2 = isoamyl, R_3 = Me, R_4 = Me. **8**:[32] R_1 = H, R_2 = Pr, R_3 = Me, R_4 = Me **9** R_1 = CPM, R_2 = Pr, R_3 = Me, R_4 = Me. **10**:[36] R_1 = H, R_2 = Et, R_3 = Me, R_4 = Me. **11**: R_1 = 2-phenylethyl, R_2 = Et, R_3 = Me, R_4 = Me. **12**: R_1 = CBM, R_2 = Et, R_3 = Me, R_4 = Me. **13**:[37] R_1 = H, R_2 = Me, R_3 = H, R_4 = Me. **14**: R_1 = CHM, R_2 = Me, R_3 = H, R_4 = Me. **15**: R_1 = Me, R_2 = isoamyl, R_3 = Me, R_4 = H. **16**: R_1 = CPM, R_2 = Pr, R_3 = Me, R_4 = H. **17**: R_1 = 2-phenylethyl, R_2 = Et, R_3 = Me, R_4 = H. **18**: R_1 = CBM, R_2 = Et, R_3 = Me, R_4 = H. **19**:[39] R_1 = allyl, R_2 = Me, R_3 = H, R_4 = H. **20**:[39] R_1 = allyl, R_2 = Et, R_3 = H, R_4 = H. **21**:[40] R_1 = Me, R_2 = Me, R_3 = Me, R_4 = H. For indoles/benzofuranes. **22**:[38] R_1 = CPM, R_2 = H, R_3 = H, R_4 = Bz, X = NH. **23**: R_1 = CPM, R_2 = allyl, R_3 = H, R_4 = Bz, X = *N*-allyl. **24**:[34] R_1 = allyl, R_2 = H, R_3 = H, R_4 = Bz, X = NH. **25**: R_1 = allyl, R_2 = Me, R_3 = H, R_4 = Bz, X = *N*-Me. **26**: R_1 = allyl, R_2 = CH$_2$Ph(2-Cl), R_3 = H, R_4 = Bz, X = *N*-CH$_2$Ph(2-Cl). **27**: R_1 = CHM, R_2 = Me, R_3 = H, R_4 = Me, X = NH. **28**: R_1 = CPM, R_2 = Pr, R_3 = H, R_4 = H, X = *N*-Pr. **29**: R_1 = allyl, R_2 = Me, R_3 = H, R_4 = H, X = *N*-Me. **30**: R_1 = Pr, R_2 = Me, R_3 = H, R_4 = H, X = *N*-Me. **31**:[34] R_1 = allyl, R_2 = allyl, R_3 = H, R_4 = H, X = *N*-allyl. **32**: R_1 = allyl, R_2 = CH$_2$Ph(2-Cl), R_3 = H, R_4 = H, X = *N*-CH$_2$Ph(2-Cl). **33**: R_1 = CHM, R_2 = Me, R_3 = H, R_4 = H, X = NH. **34**:[34] R_1 = CPM, R_2 = Et, R_3 = H, R_4 = H, X = O. **35**:[34] R_1 = Me, R_2 = Pr, R_3 = Me, R_4 = H, X = NH. **36**: R_1 = Me, R_2 = isoamyl, R_3 = Me, R_4 = H, X = NH. **37**: R_1 = CPM, R_2 = Pr, R_3 = Me, R_4 = H, X = NH. **38**: R_1 = 2-phenylethyl, R_2 = Et, R_3 = Me, R_4 = H, X = NH. **39**: R_1 = CBM, R_2 = Et, R_3 = Me, R_4 = H, X = NH. **40**: R_1 = allyl, R_2 = Me, R_3 = H, R_4 = H, X = NH. **41**: R_1 = allyl, R_2 = Et, R_3 = H, R_4 = H, X = NH. **42**: R_1 = allyl, R_2 = Et, R_3 = H, R_4 = H, X = O. **43**: R_1 = Me, R_2 = Me, R_3 = Me, R_4 = H, X = NH. **44**:[31] R_1 = Me, R_2 = Et, R_3 = Me, R_4 = H, X = NH. CPM = cyclopropylmethyl. CBM = cyclobutylmethyl. CHM = cyclohexylmethyl. Bz = benzyl.

did not change δ affinity but decreased μ and κ affinities, thus resulting in increased δ selectivity.[34]

In an attempt to enhance the δ potency and/or δ selectivity and in order to further elaborate on structure–activity relationships of 14-alkoxy-substituted indolo- and benzofuromorphinans, we prepared a series of compounds differently substituted in positions 5, 14, and 17 and at the indole nitrogen.

Chemistry

Compound **6** (Scheme 1) was prepared from 14-hydroxy-5-methylcodeinone (**5**)[35] by 14-*O*-alkylation with allyl bromide in anhydrous DMF in the presence of NaH as a base. Compound **7** was obtained by hydrogenation of compound **6** in glacial acetic acid. N-alkylation of compounds **8**,[32] **10**,[36] and **13**[37] in anhydrous DMF in the presence of K_2CO_3 afforded compounds **9**, **11**, **12**, and **14**, respectively. Compounds **15**, **16**, **17**, **18**, and **33** were synthesized from the corresponding 3-*O*-methyl ethers **7**, **9**, **11**, **12**, and **27**, respectively, by ether cleavage with HBr or BBr$_3$. Simultaneous alkylation of the 14-OH group and the indole-N in compounds **22**[38] and **24**[34] was performed with 7 equiv of NaH in anhydrous DMF to yield indoles **23**, **25**, and **26**, respectively. The 3-*O*-benzyl groups of **23**, **25**, and **26** were cleaved either by hydrogenation in EtOH (in the case of compound **25** the double bound of the 17-allyl group was hydrogenated, too) or by a dilute HCl solution in MeOH to afford compounds **28**, **29**, **30**, and **32**, respectively. Fischer

indole cyclization of ketones **14**, **15**, **16**, **17**, **18**, **19**,[39] **20**,[39] and **21**[40] with phenylhydrazine hydrochloride in glacial acetic acid gave indoles **27**, **36**, **37**, **38**, **39**, **40**, **41**, and **43**, respectively. Benzofuromorphinan **42** was prepared from compound **20**[39] using *O*-phenylhydroxylamine hydrochloride and methanesulfonic acid in MeOH. The syntheses of compounds **31**,[34] **34**,[34] **35**,[34] and **44**[31] have been previously described.

Biological Testing

Opioid Receptor Binding Assays. The binding affinities of the target compounds for δ and μ receptors were determined by inhibition of binding of [^{3}H]-DADLE[41] and [^{3}H]DAMGO[42] to rat brain membranes. The affinities for κ receptors were assessed by inhibition of binding of [^{3}H]U69,593[43] to guinea pig brain membranes. The results are shown in Table 1. These data show that introduction of a 14-alkoxy instead of the 14-hydroxy group present in NTI results in a somewhat lower δ affinity, while in many cases (compounds **31**, **34**, **37**, **40**, **41**, **44**, HS 378) the δ receptor selectivity was considerably increased. 14-Ethoxy substitution seems to be superior to 14-methoxy and 14-propoxy substitution.

[^{35}S]GTPγS Assays. The ability of compounds **34**, **41**, and HS 378 to inhibit [^{35}S]GTPγS binding in guinea pig caudate stimulated by selective opioid agonists was determined. The studies were conducted employing SNC80 (δ), DAMGO (μ), and U69,593 (κ) as selective agonists.[44] The results obtained are shown in Table 2.

Discussion and Conclusion

From the biological results obtained with the present series of compounds, the following conclusions can be drawn concerning the effects of various changes to the naltrindole and HS 378 molecules.

The present data show that introduction of a 14-alkoxy instead of the 14-hydroxy group present in NTI results in somewhat lower δ affinity, while in many cases (compounds **29**, **31**, **34**, **37**, **40**, **41**, **44**, HS 378) the δ receptor selectivity was considerably increased. 14-Ethoxy substitution seems to be somewhat superior to 14-methoxy and particularly 14-propoxy substitution. Introduction of a 14-isoamyloxy group results in lower δ affinity and selectivity, while a 14-allyloxy group is either detrimental to δ selectivity (compound **28**) or δ affinity (compound **31**). It also became apparent that the nature of X (O, NH, or *N*-Me) does not have much influence on affinity and selectivity. As reported earlier, a 5-methyl group is not necessary for high δ affinity.[33]

The replacement of the 17-cyclopropylmethyl group by 17-allyl or 17-Me has little influence on δ binding affinity and selectivity, while introduction of a 17-propyl or a 17-cyclobutylmethyl group results in lower δ affinity. 17-Cyclohexylmethyl and 17-(2-phenylethyl) groups decrease δ affinity considerably.

In [^{35}S]GTPγS binding, compounds **34**, **41**, and HS 378 exhibited about one-tenth the antagonist potency of NTI at δ opioid receptors, while their δ antagonist selectivity was considerably increased. Compounds **35** and **44** were found to be pure δ receptor agonists in this test. These data confirm once more the well-known fact that in this class of compounds a 17-Me group increases opioid

Table 1. Opioid Receptor Binding of Compounds **28−44** and Reference Compounds

| compd | K_i (nM) $\pm$ SEM | | | selectivity ratio | |
	[³H]DADLE (δ)	[³H]DAMGO (μ)	[³H]U69,593 (κ)	μ/δ	κ/δ
28	1.28 $\pm$ 0.30	14.8 $\pm$ 2.0	3.1 $\pm$ 0.5	12	2.4
29	1.97 $\pm$ 0.23	731 $\pm$ 82	149 $\pm$ 12	371	76
30	11.5 $\pm$ 1.5	106 $\pm$ 11	115 $\pm$ 29	9.2	10
31	7.3 $\pm$ 0.5	1001 $\pm$ 82	763 $\pm$ 54	137	105
32	151 $\pm$ 12	1231 $\pm$ 158	721429 $\pm$ 142	8.2	4800
33	370 $\pm$ 30	13978 $\pm$ 3377	3250 $\pm$ 231	38	8.8
34	1.18 $\pm$ 0.08	185 $\pm$ 9	94 $\pm$ 6	157	80
35	5.3 $\pm$ 0.3	30.0 $\pm$ 3.8	556 $\pm$ 36	5.7	105
36	12.8 $\pm$ 0.4	238 $\pm$ 25	1263 $\pm$ 116	19	99
37	5.3 $\pm$ 0.7	555 $\pm$ 47	504 $\pm$ 34	105	95
38	31.0 $\pm$ 3.3	14.0 $\pm$ 0.8	3639 $\pm$ 181	0.5	117
39	12.6 $\pm$ 1.2	409 $\pm$ 51	378 $\pm$ 36	32	30
40	3.80 $\pm$ 0.49	869 $\pm$ 61	233 $\pm$ 31	229	61
41	2.60 $\pm$ 0.13	1368 $\pm$ 117	349 $\pm$ 25	526	134
42	1.20 $\pm$ 0.13	22.8 $\pm$ 1.6	68 $\pm$ 5	19	57
43	3.95 $\pm$ 0.25	58 $\pm$ 5	1527 $\pm$ 137	15	387
44	3.90 $\pm$ 0.42	515 $\pm$ 48	725 $\pm$ 69	132	186
HS 378	4.4 $\pm$ 0.5	340 $\pm$ 29	134 $\pm$ 30	77	30
NTI	0.81 $\pm$ 0.06	13.0 $\pm$ 0.8	15.8 $\pm$ 4.0	16	20
OMI	2.0 $\pm$ 0.2	171 $\pm$ 15	395 $\pm$ 26	86	198

Table 2. Antagonist K_i Values of Compounds **34**, **41**, HS 378, and NTI Determined in the [³⁵S]GTPγS Assay in Guinea Pig Caudatae

| compd | K_i (nM) $\pm$ SEM | | |
	δ^a	μ^b	κ^c
34	0.88 $\pm$ 0.05	>10000^d	>10000^d
41	1.00 $\pm$ 0.08	>10000^d	>10000^d
HS 378	0.96 $\pm$ 0.07	>10000^d	>10000^d
NTI^e	0.062 $\pm$ 0.006	3.2 $\pm$ 0.2	8.9 $\pm$ 0.8

^{a} Antagonism of SNC80. ^{b} Antagonism of DAMGO. ^{c} Antagonism of U69,593. ^{d} The compounds were screened for antagonism at μ and κ opioid receptors, but they did not inhibit stimulation of 10 μM DAMGO or 10 μM U69,593, respectively, by at least 50% at that concentration. ^{e} Taken from ref 44.

agonism while 17-cyclopropylmethyl and 17-allyl groups increase opioid antagonism.

In conclusion, introduction of a 14-alkoxy group into the NTI molecule results in compounds with considerable higher δ opioid receptor selectivity.

Experimental Section

Melting points were measured on a Kofler melting point microscope and are uncorrected. IR spectra were recorded with a Mattson Galaxy series FTIR 3000 spectrometer (in cm^{-1}). ¹H NMR spectra were recorded on a Bruker AM 300 (300 MHz) or on a Varian Gemini 200 (200 MHz) spectrometer. Chemical shifts (δ) are reported in ppm (relative to SiMe$_4$ as internal standard), and coupling constants (J) are reported in hertz. Mass spectra were recorded on a Varian MAT 44S or on a Finnigan Mat SSQ 7000 apparatus. Elemental analyses were performed at the Institute of Physical Chemistry at the University of Vienna, Austria. For TLC, POLYGRAM SIL G/UV$_{254}$ precoated plastic sheets (Macherey-Nagel, Germany) were used, and for column chromatography, silica gel 60 (230−400 mesh ASTM, Fluka, Switzerland) was used.

7,8-Didehydro-4,5α-epoxy-3-methoxy-5β,17-dimethyl-14β-[(3-methylbut-2-enyl)oxy]morphinan-6-one (6). A mixture of **5**[35] (3.00 g, 9.16 mmol), NaH (0.45 g, 18.75 mmol, obtained from 0.75 g of 60% NaH dispersion in oil by washing with hexane), and anhydrous DMF (50 mL) was stirred at 0 °C. After 20 min, 3,3-dimethylallyl bromide (2.07 g, 13.89 mmol) was added at once and stirring was continued for 2 h at room temperature. Excess NaH was destroyed with ice and 120 mL of H$_2$O, the mixture was extracted with CH$_2$Cl$_2$ (3 $\times$ 70 mL), and the combined organic layers were washed with H$_2$O (3 $\times$ 100 mL) and brine (100 mL), dried (Na$_2$SO$_4$), and evaporated. The residue (3.67 g brown oil) was crystallized from MeOH to give 1.37 g (38%) of pure **6**: colorless crystals; mp 119−123 °C; IR (KBr) 1668 (C=O); ¹H NMR (DMSO-d_6) δ 7.21 (d, J = 10.1, 1 olef H), 6.66 (d, J = 8.0, 1 arom H), 6.62 (d, J = 8.0, 1 arom H), 6.08 (d, J = 10.1, 1 olef H), 5.23 (m, CH$_2$CH=C), 3.68 (s, CH$_3$O), 2.35 (s, CH$_3$N), 1.68 (s, C(CH$_3$)$_2$), 1.59 (s, C(CH$_3$)$_2$), 1.52 (s, CH$_3$−C(5)); EI-MS m/z 395 (M$^+$). Anal. (C$_{24}$H$_{29}$NO$_4$) C, H, N.

4,5α-Epoxy-3-methoxy-5β,17-dimethyl-14β-[(3-methylbutyl)oxy]morphinan-6-one (7). A mixture of **6** (1.34 g, 3.39 mmol), AcOH (30 mL), and 10% Pd/C (0.13 g) was hydrogenated at room temperature and 30 psi for 19 h. The catalyst was filtered off, and the filtrate was reduced, alkalinized with concentrated NH$_4$OH solution, and partitioned between H$_2$O (100 mL) and CH$_2$Cl$_2$ (3 $\times$ 60 mL). The combined organic layers were washed with H$_2$O (100 mL) and brine (100 mL), dried (Na$_2$SO$_4$), and evaporated to give 0.66 g (49%) of **7** as yellow oil, which was pure by TLC (CH$_2$Cl$_2$/MeOH/concentrated NH$_4$-OH solution, 90:9:1) and not crystallized for the next step. No elemental analysis was performed. IR (CCl$_4$) 1728 (C=O); ¹H NMR (CDCl$_3$) δ 6.64 (d, J = 8.2, 1 arom H), 6.58 (d, J = 8.2, 1 arom H), 3.87 (s, CH$_3$O), 2.36 (s, CH$_3$N), 1.61 (s, CH$_3$−C(5)), 0.96 (d, J = 2.7, C(CH$_3$)$_2$), 0.34 (d, J = 2.7, C(CH$_3$)$_2$); EI-MS m/z 399 (M$^+$).

General Procedure for the Synthesis of 9, 11, 12, and 14. A mixture of the corresponding N-nor compound (**8**·HCl,[32] **10**·HCl,[36] and **13**·HCl[37]), 4 equiv of K$_2$CO$_3$, 1.2 equiv of alkylation reagent, and anhydrous DMF was stirred under N$_2$ at 80 °C for 20 h. The inorganic material was filtered off, the filtrate was evaporated, and the residue was partitioned between H$_2$O and CH$_2$Cl$_2$. The combined organic layers were washed with H$_2$O and brine, dried (Na$_2$SO$_4$), and evaporated. The products were either crystallized from MeOH (**11**) or precipitated as hydrochloride from Et$_2$O (**9**, **12**, and **14**).

17-Cyclopropylmethyl-4,5α-epoxy-3-methoxy-5β-methyl-14β-propoxymorphinan-6-one hydrochloride (9·HCl): yellow powder; yield 55%; mp 156−158 °C; IR (KBr) 1723 (C=O); ¹H NMR (DMSO-d_6) δ 8.57 (s, NH$^+$), 6.85 (d, J = 8.2, 1 arom H), 6.75 (d, J = 8.2, 1 arom H), 3.79 (s, CH$_3$O), 1.51 (s, CH$_3$−C(5)), 0.87 (t, J = 7.4, CH$_3$CH$_2$); CI-MS m/z 412 (M$^+$ + 1). Anal. (C$_{25}$H$_{33}$NO$_4$·HCl·0.6H$_2$O) C, H, N, Cl.

4,5α-Epoxy-14β-ethoxy-3-methoxy-5α-methyl-17-[(2-phenyl)ethyl]morphinan-6-one (11): colorless crystals; yield 70%; mp 86−89 °C; IR (KBr) 1725 (C=O); ¹H NMR (CDCl$_3$) δ 7.30−7.13 (m, 5 arom H), 6.64 (d, J = 8.2, 1 arom H), 6.54 (d, J = 8.2, 1 arom H), 3.85 (s, CH$_3$O), 1.60 (s, CH$_3$−C(5)), 1.12 (t, J = 6.8, CH$_3$CH$_2$); CI-MS m/z 448 (M$^+$ + 1). Anal. (C$_{28}$H$_{33}$-NO$_4$) C, H, N.

17-Cyclobutylmethyl-4,5α-epoxy-14β-ethoxy-3-methoxy-5β-methylmorphinan-6-one hydrochloride (12·HCl): colorless crystals; yield 70%; mp 151−152 °C; IR (KBr) 1725

(C=O); ^{1}H NMR (DMSO-d_6) δ 8.61 (s, br, NH^+), 6.85 (d, J = 8.2, 1 arom H), 6.75 (d, J = 8.2, 1 arom H), 3.78 (s, CH_3O), 1.49 (s, CH_3−C(5)), 1.33 (t, J = 6.8, CH_3CH$_2$); CI-MS m/z 412 (M$^+$ + 1). Anal. (C$_{25}$H$_{33}$NO$_4$·HCl·1.5H$_2$O) C, H, N.

17-Cyclohexylmethyl-4,5α-epoxy-3,14β-dimethoxymorphinan-6-one hydrochloride (14·HCl): colorless crystals; yield 59%; mp 176 °C (dec); IR (KBr) 1723 (C=O); ^{1}H NMR (DMSO-d_6) δ 10.40 (s, br, NH^+), 6.75 (d, J = 8.8, 1 arom H), 6.67 (d, J = 8.8, 1 arom H), 3.92 (s, CH_3O−C(3)), 3.29 (s, CH_3O−C(14)); CI-MS m/z 412 (M$^+$ + 1). Anal. (C$_{25}$H$_{33}$NO$_4$·HCl) C, H, N.

General Procedure for the Synthesis of 15 and 17. A mixture of the corresponding 3-O-methyl ether (**7** and **11**) and 48% HBr was refluxed for 20 min and then evaporated. The residue was dissolved in MeOH and evaporated again to give a beige foam that was crystallized from MeOH.

4,5α-Epoxy-3-hydroxy-5β,17-dimethyl-14β-[(3-methylbutyl)oxy]morphinan-6-one hydrobromide (15·HBr): colorless crystals; yield 33%; mp >260 °C (dec); IR (KBr) 3427 (OH), 1724 (C=O); ^{1}H NMR (DMSO-d_6) δ 9.40 (s, OH), 8.35 (s, NH^+), 6.64 (s, 2 arom H), 2.94 (s, CH_3N), 1.48 (s, CH_3−C(5)), 0.95 (d, J = 2.6, C(CH_3)$_2$), 0.93 (d, J = 2.6, C(CH_3)$_2$); EI-MS m/z 385 (M$^+$). Anal. (C$_{23}$H$_{31}$NO$_4$·HBr·0.8H$_2$O) C, H, N.

4,5α-Epoxy-14β-ethoxy-3-hydroxy-5β-methyl-17-[(2-phenyl)ethyl]morphinan-6-one hydrobromide (17·HBr): colorless crystals; yield 63%; mp >270 °C (dec); IR (KBr) 1720 (C=O); ^{1}H NMR (DMSO-d_6) δ 9.38 (s, OH), 8.48 (s, NH^+), 7.38−7.25 (m, 5 arom H), 6.68 (d, J = 8.2, 1 arom H), 6.64 (d, J = 8.2, 1 arom H), 1.51 (s, CH_3−C(5)), 1.34 (t, J = 6.8, CH_3CH$_2$); CI-MS 434 (M$^+$ + 1). Anal. (C$_{27}$H$_{31}$NO$_4$·HBr) C, H, N, Br.

General Procedure for the Synthesis of 16, 18, and 33. A mixture of the corresponding 3-O-methyl ether (**9·HCl**, **12·HCl**, and **27·HBr**), 7 equiv of 1 M BBr$_3$ solution in CH$_2$Cl$_2$, and CH$_2$Cl$_2$ was stirred under N$_2$ at 0 °C for 1.5 h. The reaction was ended by adding ice and concentrated NH$_4$OH solution, and the mixture was extracted with CH$_2$Cl$_2$. The combined organic layers were washed with H$_2$O and brine, dried (Na$_2$SO$_4$), evaporated, and the products were crystallized from MeOH either as free base (**16** and **18**) or as hydrobromide (**33**).

17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-5β-methyl-14β-propoxymorphinan-6-one (16): beige crystals; yield 55%; mp 184−186 °C; IR (KBr) 3390 (OH), 1720 (C=O); ^{1}H NMR (CDCl$_3$) δ 10.24 (s, br, OH), 6.73 (d, J = 8.2, 1 arom H), 6.65 (d, J = 8.2, 1 arom H), 1.62 (s, CH_3−C(5)), 1.00 (t, J = 7.3, CH_3CH$_2$); CI-MS m/z 398 (M$^+$ + 1). Anal. (C$_{24}$H$_{31}$NO$_4$·0.6MeOH) C, H, N.

17-Cyclobutylmethyl-4,5α-epoxy-14β-ethoxy-3-hydroxy-5β-methylmorphinan-6-one (18): colorless crystals; yield 57%; mp 168−174 °C; IR (KBr) 3567 (OH), 1725 (C=O); ^{1}H NMR (DMSO-d_6) δ 9.07 (s, br, OH), 6.52 (d, J = 8.2, 1 arom H), 6.48 (d, J = 8.2, 1 arom H), 1.45 (s, CH_3−C(5)), 1.17 (t, J = 7.0, CH_3CH$_2$); EI-MS m/z 397 (M$^+$). Anal. (C$_{24}$H$_{31}$NO$_4$·0.9H$_2$O) C, H, N.

17-Cyclohexylmethyl-4,5α-epoxy-14β-methoxyindolo[2′,3′:6,7]morphinan-3-ol hydrobromide (33·HBr): colorless crystals; yield 14%; mp >250 °C (dec); ^{1}H NMR (DMSO-d_6) δ 11.33 (s, NH), 9.25 (s, NH^+), 7.34−6.95 (m, 4 arom H), 6.64 (s, 2 arom H), 5.85 (s, H−C(5)), 3.11 (s, CH_3O); CI-MS m/z 471 (M$^+$ + 1). Anal. (C$_{30}$H$_{34}$N$_2$O$_3$·HBr·0.7H$_2$O) C, H, N, Br.

General Procedure for the Synthesis of 23, 25, and 26. A mixture of the corresponding 14-OH indole (**22·HCl**[38] and **24·HCl**[34]), 7 equiv of NaH (obtained from 60% NaH dispersion in oil by washing with hexane), and anhydrous DMF was stirred at 0 °C. After 20 min, an amount of 3 equiv of alkylation reagent was added at once and stirring was continued for 2 h at 0 °C. Excess NaH was destroyed with ice and H$_2$O, the mixture was extracted with CH$_2$Cl$_2$, and the combined organic layers were washed with H$_2$O and brine, dried (Na$_2$SO$_4$), and evaporated. The residue was either precipitated as hydrochloride from Et$_2$O (**23** and **25**) or purified by column chromatography (silica gel, CH$_2$Cl$_2$/MeOH/concentrated NH$_4$OH solution, 290:9:0.1) and then crystallized from *i*-PrOH (**26**).

1′-Allyl-14β-allyloxy-3-benzyloxy-17-cyclopropylmethyl-4,5α-epoxyindolo[2′,3′:6,7]morphinan hydrochloride (23·HCl): colorless crystals; yield 86%; mp 182−185 °C; ^{1}H NMR (DMSO-d_6) δ 8.65 (s, NH^+), 7.43−6.99 (m, 9 arom H), 6.90 (d, J = 8.2, 1 arom H), 6.74 (d, J = 8.2, 1 arom H), 6.06 (s, H−C(5)); CI-MS m/z 585 (M$^+$ + 1). Anal. (C$_{39}$H$_{40}$N$_2$O$_3$·HCl·2.5H$_2$O) C, H, N.

17-Allyl-3-benzyloxy-4,5α-epoxy-14β-methoxy-1′-methylindolo[2′,3′:6,7]morphinan hydrochloride (25·HCl): colorless crystals; yield 59%; mp 173−178 °C; ^{1}H NMR (DMSO-d_6) δ 11.21 (s, br, NH^+), 7.42−7.04 (m, 9 arom H), 6.75 (d, J = 8.2, 1 arom H), 6.63 (d, J = 8.2, 1 arom H), 6.33 (m, 1 olef H), 5.85 (s, H−C(5)), 5.64 (m, 2 olef H), 3.86 (s, CH_3N), 3.28 (s, CH_3O); CI-MS m/z 519 (M$^+$ + 1). Anal. (C$_{34}$H$_{34}$N$_2$O$_3$·HCl·1.9H$_2$O) C, H, N.

17-Allyl-3-benzyloxy-1′-(2-chlorobenzyl)-14β-[(2-chlorobenzyl)oxy]-4,5α-epoxyindolo[2′,3′:6,7]morphinan (26): colorless crystals; yield 50%; mp 155−157 °C; ^{1}H NMR (CDCl$_3$) δ 7.43−6.87 (m, 17 arom H), 6.70 (d, J = 8.2, 1 arom H), 6.60 (d, J = 8.2, 1 arom H), 6.08−5.78 (m, 1 olef H), 5.71 (d, J = 18.4, 1 H, NCH$_2$(2-Cl−Ph)), 5.67 (s, H−C(5)), 5.55 (d, J= 18.4, 1 H, NCH$_2$(2-Cl−Ph)), 5.30−5.15 (m, 2 olef H), 4.91 (d, J = 12.8, 1 H, OCH$_2$(2-Cl−Ph)), 4.44 (d, J = 12.8, 1 H, OCH$_2$(2-Cl−Ph)); CI-MS m/z 739 (M$^+$ + 1). Anal. (C$_{46}$H$_{40}$N$_2$O$_3$Cl$_2$·0.3H$_2$O) C, H, N, Cl.

General Procedure for the Synthesis of 28 and 30. A mixture of the corresponding 3-O-benzyl ether (**23·HCl** and **25·HCl**), EtOH, and 10% Pd/C was hydrogenated at room temperature and 30 psi for 2 h. The catalyst was filtered off, the filtrate was evaporated, the residue was alkalinized with concentrated NH$_4$OH solution, and the result was partitioned between H$_2$O and CH$_2$Cl$_2$. The combined organic layers were washed with H$_2$O and brine, dried (Na$_2$SO$_4$), and evaporated. The residue was precipitated as hydrochloride either from Et$_2$O (**28**) or from acetone (**30**).

17-Cyclopropylmethyl-4,5α-epoxy-14β-propoxy-1′-propylindolo[2′,3′:6,7]morphinan-3-ol hydrochloride (28·HCl): colorless crystals; yield 73%; mp 212−215 °C; IR (KBr) 3376 (OH); ^{1}H NMR (DMSO-d_6) δ 8.40 (s, br, 2 H, OH, NH^+), 7.48−6.97 (m, 4 arom H), 6.67 (d, J = 8.1, 1 arom H), 6.61 (d, J = 8.1, 1 arom H), 6.01 (s, H−C(5)); CI-MS m/z 499 (M$^+$ + 1). Anal. (C$_{32}$H$_{38}$N$_2$O$_3$·HCl·2.1H$_2$O) C, H, N.

4,5α-Epoxy-14β-methoxy-1′-methyl-17-propylindolo[2′,3′:6,7]morphinan-3-ol hydrochloride (30·HCl): colorless crystals; yield 40%; mp 243−249 °C; IR (KBr) 3387 (OH); ^{1}H NMR (DMSO-d_6) δ 9.28 (s, OH), 8.97 (s, br, NH^+), 7.46−7.02 (m, 4 arom H), 6.67 (d, J = 8.2, 1 arom H), 6.62 (d, J = 8.2, 1 arom H), 6.05 (s, H−C(5)), 3.84 (s, CH_3N), 3.11 (s, CH_3O); CI-MS m/z 431 (M$^+$ + 1). Anal. (C$_{27}$H$_{30}$N$_2$O$_3$·HCl·2.4H$_2$O) C, H, N.

General Procedure for the Synthesis of 29 and 32. A mixture of the corresponding 3-O-benzyl ether (**25·HCl** and **26**), MeOH, and concentrated HCl was refluxed for 6 h, cooled to room temperature, alkalinized with concentrated NH$_4$OH solution, and partitioned between H$_2$O and CH$_2$Cl$_2$. The combined organic layers were washed with H$_2$O and brine, dried (Na$_2$SO$_4$), and evaporated. The residue was precipitated as hydrochloride from Et$_2$O.

17-Allyl-4,5α-epoxy-14β-methoxy-1′-methylindolo[2′,3′:6,7]morphinan-3-ol hydrochloride (29·HCl): colorless crystals; yield 92%; mp 182−185 °C; IR (KBr) 3387 (OH); ^{1}H NMR (DMSO-d_6) δ 9.33 (s, br, 2 H, OH, NH^+), 7.48−6.98 (m, 4 arom H), 6.68 (d, J = 8.2, 1 arom H), 6.62 (d, J = 8.2, 1 arom H), 6.05 (s, H−C(5)), 5.95 (m, 1 olef H), 5.64 (m, 2 olef H), 3.08 (s, CH_3O); CI-MS m/z 429 (M$^+$ + 1). Anal. (C$_{27}$H$_{28}$N$_2$O$_3$·HCl·1.1H$_2$O) C, H, N.

17-Allyl-1′-(2-chlorobenzyl)-14β-[(2-chlorobenzyl)oxy]-4,5α-epoxyindolo[2′,3′:6,7]morphinan-3-ol hydrochloride (32·HCl): colorless crystals; yield 37%; mp 141−142 °C; IR (KBr) 3412 (OH); ^{1}H NMR (DMSO-d_6) δ 9.33 (s, OH), 9.05 (s, NH^+), 7.62−6.92 (m, 12 arom H), 6.69 (s, 2 arom H), 6.05−5.97 (m, 1 olef H), 5.90 (s, NCH$_2$(2-Cl−Ph)), 5.76 (s, H−C(5)), 5.68−5.60 (m, 2 olef H), 4.71 (d, J = 12.9, 1 H, OCH$_2$(2-Cl−

Ph)), 4.59 (d, $J = 12.9$, 1 H, OCH_2(2-Cl−Ph)); CI-MS m/z 649 (M$^+$ + 1). Anal. (C$_{39}$H$_{34}$N$_2$O$_3$Cl$_2$·HCl·1.1H$_2$O) C, H, N, Cl.

General Procedure for the Synthesis of 27, 36−41, and 43. A mixture of the corresponding 6-keto compound (**14**·HCl, **15**·HBr, **16**, **17**·HBr, **18**, **19**,[39] **20**,[39] and **21**·Br[40]), 2 equiv of phenylhydrazine hydrochloride, and AcOH was refluxed for 24 h, evaporated, alkalinized with concentrated NH$_4$OH solution, and partitioned between H$_2$O and CH$_2$Cl$_2$. The combined organic layers were washed with H$_2$O and brine, dried (Na$_2$SO$_4$), and evaporated. The residue was either purified by column chromatography (silica gel, CH$_2$Cl$_2$/MeOH/concentrated NH$_4$OH solution 90:10:1) and then crystallized from MeOH as hydrobromide (**27**) or crystallized as methanesulfonate from MeOH (**36**, **37**, **40**, and **41**) or crystallized as free base from MeOH (**43**) or precipitated from Et$_2$O as hydrochloride (**38** and **39**).

17-Cyclohexylmethyl-4,5α-epoxy-3,14β-dimethoxyindolo[2′,3′:6,7]morphinan hydrobromide (27·HBr): colorless crystals; yield 18%; mp 226−232 °C; IR (KBr) 3398 (OH); ^{1}H NMR (DMSO-d_6) δ 11.37 (s, NH), 8.60 (s, br, NH^+), 7.37−6.95 (m, 4 arom H), 6.83 (d, $J = 8.4$, 1 arom H), 6.76 (d, $J = 8.4$, 1 arom H), 5.92 (s, H−C(5)), 3.68 (s, CH_3O−C(3)), 3.12 (s, CH_3O−C(14)); CI-MS 485 (M$^+$ + 1). Anal. (C$_{31}$H$_{36}$N$_2$O$_3$·HBr·0.2H$_2$O) C, H, N, Br.

4,5α-Epoxy-5β,17-dimethyl-14β-[(3-methylbutyl)oxy]indolo[2′,3′:6,7]morphinan-3-ol methanesulfonate (36·CH$_3$SO$_3$H): colorless crystals; yield 36%; mp >250 °C (dec); IR (KBr) 3406 (OH); ^{1}H NMR (DMSO-d_6) δ 11.27 (s, NH), 9.21 (s, OH), 8.46 (s, NH^+), 7.39−6.90 (m, 4 arom H), 6.58 (s, 2 arom H), 2.96 (s, CH_3N), 1.85 (s, CH_3−C(5)), 0.68 (d, $J = 5.4$, C(CH_3)$_2$), 0.34 (d, $J = 5.4$, C(CH_3)$_2$); CI-MS m/z 459 (M$^+$ + 1). Anal. (C$_{29}$H$_{34}$N$_2$O$_3$·CH$_3$SO$_3$H·1.0H$_2$O) C, H, N, S.

17-Cyclopropylmethyl-4,5α-epoxy-5β-methyl-14β-propoxyindolo[2′,3′:6,7]morphinan-3-ol methanesulfonate (37·CH$_3$SO$_3$H): colorless crystals; yield 36%; mp 295−298 °C; IR (KBr) 3539 (OH); ^{1}H NMR (DMSO-d_6) δ 11.31 (s, NH), 9.16 (s, OH), 8.01 (s, NH^+), 7.35−6.92 (m, 4 arom H), 6.59 (s, 2 arom H), 1.89 (s, CH_3−C(5)), 0.60 (t, $J = 7.0$, CH_3CH$_2$); FAB-MS m/z 471 (M$^+$ + 1). Anal. (C$_{30}$H$_{34}$N$_2$O$_3$·CH$_3$SO$_3$H) C, H, N, S.

4,5α-Epoxy-14β-ethoxy-5β-methyl-17-[(2-phenyl)ethyl]indolo[2′,3′:6,7]morphinan-3-ol hydrochloride (38·HCl): beige crystals; yield 51%; mp >225 °C (dec); IR (KBr) 3400 (OH); ^{1}H NMR (DMSO-d_6) δ 11.34 (s, NH), 9.19 (s, OH), 8.97 (s, NH^+), 7.35−6.91 (m, 9 arom H), 6.62 (d, $J = 8.4$, 1 arom H), 6.57 (d, $J = 8.4$, 1 arom H), 1.87 (s, CH_3−C(5)), 0.96 (t, $J = 6.9$, CH_3CH$_2$); CI-MS m/z 507 (M$^+$ + 1). Anal. (C$_{33}$H$_{34}$N$_2$O$_3$·HCl·1.8H$_2$O) C, H, N, Cl.

17-Cyclobutylmethyl-4,5α-epoxy-14β-ethoxy-5β-methylindolo[2′,3′:6,7]morphinan-3-ol hydrochloride (39·HCl): colorless crystals; yield 34%; mp >250 °C; IR (KBr) 3400 (OH); ^{1}H NMR (DMSO-d_6) δ 11.35 (s, br, NH), 9.22 (s, br, OH), 8.47 (s, br, NH^+), 7.35−6.95 (m, 4 arom H), 6.60 (d, $J = 8.2$, 1 arom H), 6.56 (d, $J = 8.2$, 1 arom H), 1.86 (s, CH_3−C(5)), 0.97 (t, $J = 7.0$, CH_3CH$_2$); EI-MS m/z 471 (M$^+$). Anal. (C$_{30}$H$_{34}$N$_2$O$_3$·HCl·1.5H$_2$O) C, H, N, Cl.

17-Allyl-4,5α-epoxy-14β-methoxyindolo[2′,3′:6,7]morphinan-3-ol methanesulfonate (40·CH$_3$SO$_3$H): colorless crystals; yield 42%; mp 258−261 °C; IR (KBr) 3416 (OH); ^{1}H NMR (DMSO-d_6) δ 11.32 (s, NH), 9.25 (s, br, OH), 8.96 (s, br, NH^+), 7.39−6.94 (m, 4 arom H), 6.67 (d, $J = 8.1$, 1 arom H), 6.63 (d, $J = 8.1$, 1 arom H), 5.92 (m, 1 olef H), 5.82 (s, H−C(5)), 5.64 (m, 2 olef H), 3.08 (s, CH_3O); CI-MS m/z 415 (M$^+$ +1). Anal. (C$_{26}$H$_{26}$N$_2$O$_3$·CH$_3$SO$_3$H·0.7H$_2$O) C, H, N, S.

17-Allyl-4,5α-epoxy-14β-ethoxyindolo[2′,3′:6,7]morphinan-3-ol methanesulfonate (41·CH$_3$SO$_3$H): colorless crystals; yield 51%; mp 275−278 °C; IR (KBr) 3425 (OH); ^{1}H NMR (DMSO-d_6) δ 11.30 (s, NH), 8.57 (s, br, NH^+), 7.37−6.93 (m, 4 arom H), 6.65 (d, $J = 8.1$, 1 arom H), 6.63 (d, $J = 8.1$, 1 arom H), 5.90 (m, 1 olef H), 5.83 (s, H−C(5)), 5.65 (m, 2 olef H), 0.97 (t, $J = 6.8$, CH_3CH$_2$); CI-MS m/z 429 (M$^+$ + 1). Anal. (C$_{27}$H$_{28}$N$_2$O$_3$·CH$_3$SO$_3$H·0.7H$_2$O) C, H, N, S.

4,5α-Epoxy-14β-methoxy-5β,17-dimethylindolo[2′,3′:6,7]morphinan-3-ol (43): beige crystals; yield 67%; mp 273−276 °C (dec); IR (KBr) 3300 (OH); ^{1}H NMR (DMSO-d_6) δ 11.10 (s, NH), 8.78 (s, OH), 7.32−6.91 (m, 4 arom H), 6.44 (s, 2 arom H), 3.32 (s, CH_3O), 2.33 (s, CH_3N), 1.81 (s, CH_3−C(5)); CI-MS m/z 403 (M$^+$ + 1). Anal. (C$_{25}$H$_{26}$N$_2$O$_3$·1.9MeOH) C, H, N.

17-Allyl-4,5α-epoxy-14β-ethoxybenzofuro[2′,3′:6,7]morphinan-3-ol salicylate (42·C$_7$H$_6$O$_3$). A mixture of **20**[5] (0.30 g, 0.84 mmol), *O*-phenylhydroxylamine hydrochloride (0.16 g, 1.10 mmol), methanesulfonic acid (0.1 mL, 1.04 mmol), and MeOH (10 mL) was refluxed for 6 days, evaporated, alkalinized with concentrated NH$_4$OH solution, and extracted with CH$_2$-Cl$_2$ (3 × 65 mL). The combined organic layers were washed with H$_2$O (3 × 100 mL) and brine (100 mL), dried (Na$_2$SO$_4$), and evaporated. The residue (0.31 g of brown foam) was crystallized as salicylate from MeOH/i-Pr$_2$O: beige crystals; yield 0.15 g (31%); mp 144−147 °C; IR (KBr) 3426 (OH); ^{1}H NMR (DMSO-d_6) δ 9.20 (s, OH), 9.06 (s, NH^+), 7.73−6.72 (m, 8 arom H), 6.55 (s, 2 arom H), 5.82 (m, 1 olef H), 5.64 (s, H−C(5)), 5.41−5.20 (m, 2 olef H), 0.94 (t, $J = 7.1$, CH_3CH$_2$); CI-MS m/z 430 (M$^+$ + 1). Anal. (C$_{27}$H$_{27}$NO$_4$·C$_7$H$_6$O$_3$·0.8H$_2$O) C, H, N.

Biological Assays. Receptor Binding Assays. These assays were performed as previously described.[41−43]

[^{35}S]GTPγS Functional Assays. These assays were performed as previously described.[23,44]

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