Synthesis and Biological Evaluation of 14-Alkoxymorphinans. 21.[1] Novel 4-Alkoxy and 14-Phenylpropoxy Derivatives of the μ Opioid Receptor Antagonist Cyprodime[⊥]

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The synthesis, biological, and pharmacological evaluation of novel derivatives of cyprodime are described. Their binding affinities at μ, δ, and κ opioid receptors were evaluated using receptor binding assay. It was observed that the affinity of these compounds was sensitive to the character and length of the substituent in position 4. Further prolongation of the 4-alkoxy group of cyprodime (**1**) and its 4-butoxy analogue **2** is detrimental for the μ opioid receptor affinity. Introduction of an arylalkoxy group at C-4 does not increase μ affinity in the case of benzyloxy, while a phenylpropoxy group reduces μ affinity. The δ and κ affinities were also reduced compared to the reference compounds. A significant increase in the affinity at the μ opioid receptors was achieved by introducing a 14-phenylpropoxy group. Increases in the affinity at δ and κ receptors were also observed. These findings provide further evidence that the nature of the substituent at position 14 has a major impact on the abilities of morphinans to interact with opioid receptors. In the [^{35}S]GTPγS binding assay, all tested compounds were partial agonists at μ and δ receptors. Compounds **8** and **17** showed antagonism at κ receptors, while compound **7** exhibited some partial agonist activity at this receptor. The novel derivatives of cyprodime containing a 14-phenylpropoxy group acted as potent antinociceptives. When tested in vivo, compounds **7**, **8**, and **17** were considerably more potent than morphine, with phenol **7** showing the highest antinociceptive potency (21-fold in the hot plate test, 38-fold in the tail flick test, and 300-fold in the paraphenylquinone writhing test) in mice. Introduction of a 14-phenylpropoxy substituent leads to a profound alteration in the pharmacological profile of this class of compounds.

Introduction

Cyprodime (**1**) was reported as the first nonpeptidic, competitively pure and specific μ opioid receptor antagonist.[2] Although cyprodime shows lower affinity at the μ opioid receptor than naloxone, its significantly increased μ selectivity makes it a very valuable tool in opioid research.[3−9] Cyprodime has been prepared in tritium-labeled form and has become a useful tool for radioligand binding assays especially because it is commercially available.[10] Cyprodime was shown to antagonize sufentanil-induced respiratory depression in the dog.[11] Coadministration of cyprodime with levodopa decreased dyskinesia in a primate model of Parkinson's disease without attenuation of the anti-Parkinsonian actions of levodopa.[12]

Removing the 6-keto function in cyprodime produced only a small reduction in μ antagonist potency but was accompanied by an increase in κ and δ antagonist potency, resulting in a decrease of μ selectivity.[13] An extensive study on cyprodime-related compounds revealed that several modifications to the cyprodime molecule (e.g., an additional methoxy group at C-3, different substituents at C-4, a 14-ethoxy group, an *N*-allyl group) yielded compounds with either less μ selectivity or partial agonist activity.[14] Increasing the chain length at C-4 by introduction of a butoxy group (compound **2**, Figure 1) resulted in increased affinity at μ receptors (ca. 2-fold) but very little change in either selectivity or intrinsic activity. Introduction of a hydroxy group at C-3 of cyprodime and analogues markedly enhanced affinity at all three opioid receptor types and retained pure antagonism, while selectivity for the μ opioid receptor was reduced.[15]

In an effort to investigate the effect of a further increase of the chain length at C-4 on opioid binding properties, we have synthesized 4-phenylpropoxy-, 4-benzyloxy-, and 4-hexyloxy-substituted cyprodime derivatives (compounds **4**−**6**; Figure 1). A 14-phenylpropoxy group was very recently found to significantly increase

[⊥] This paper is dedicated to Dr. Arnold Brossi on the occasion of his 80th birthday and to Prof. Dr. Leendert Maat on the occasion of his 70th birthday.

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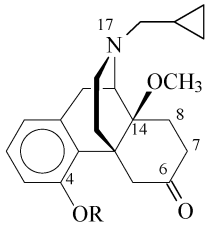


1 R = CH_3 (cyprodime)
2 R = n-C_4H_9
3 R = cinnamyl, $\Delta^{7,8}$
4 R = $(CH_2)_3Ph$
5 R = CH_2Ph
6 R = n-C_6H_{13}

Figure 1.

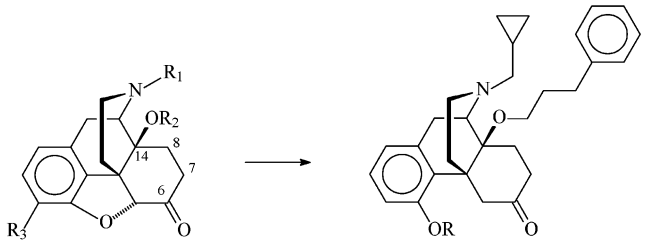
binding affinities of morphinan-6-ones at all three opioid receptor types.[16,17] In addition, it became apparent that a 14-phenylpropoxy group gives rise to highly potent analgesics also in morphinan-6-ones having a cyclopropylmethyl or allyl group at the morphinan nitrogen.[16] Another aim of the study was to investigate whether a 14-phenylpropoxy group would also convert cyprodime and analogues into opioid agonists with high affinity to all three receptor types. The 14-phenylpropoxy derivatives **7** and **8** were prepared and biologically and pharmacologically characterized.

Chemistry

To obtain the 4-phenylpropoxy analogue of cyprodime (compound **4**, Figure 1), 17-(cyclopropylmethyl)-4-hydroxy-14β-methoxymorphinan-6-one[14] was first 14-O-alkylated with cinnamyl bromide (3-bromo-1-phenyl-1-propene) in DMF in the presence of K_2CO_3 to afford compound **3**, which was subsequently hydrogenated over Pd/C to yield compound **4**. Compounds **5** and **6** were prepared analogously to the synthesis of compound **3** using benzyl chloride and hexyl iodide, respectively (Figure 1).

The synthesis of the 14-phenylpropoxy analogues of cyprodime (compounds **7**−**9**, **17**) started from 14-hydroxycodeinone (**10**, Scheme 1). **10** was 14-O-alkylated with cinnamyl bromide in DMF in the presence of NaH to give compound **11**, which was hydrogenated over Pd/C to afford 14-phenylpropoxy-substituted **12**. The 3-*O*-methyl ether of compound **12** was cleaved by refluxing in 48% HBr to obtain phenol **13**, which was converted into the phenyltetrazolyl ether **14** by reaction with 5-chloro-1-phenyl-1*H*-tetrazole[18] in DMF. Catalytic

Scheme 1



10 $R_1 = CH_3$, $R_2 = H$, $R_3 = OCH_3$, $\Delta^{7,8}$
11 $R_1 = CH_3$, R_2 = cinnamyl, $R_3 = OCH_3$, $\Delta^{7,8}$
12 $R_1 = CH_3$, $R_2 = (CH_2)_3Ph$, $R_3 = OCH_3$
13 $R_1 = CH_3$, $R_2 = (CH_2)_3Ph$, $R_3 = OH$
14 $R_1 = CH_3$, $R_2 = (CH_2)_3Ph$, R_3 = PTO
15 $R_1 = CH_3$, $R_2 = (CH_2)_3Ph$, $R_3 = H$
16 $R_1 = R_3 = H$, $R_2 = (CH_2)_3Ph$
17 R_1 = CPM, $R_2 = (CH_2)_3Ph$, $R_3 = H$

7 R = H
8 R = CH_3
9 R = n-C_4H_9

CPM = cyclopropylmethyl
PTO = phenyltetrazolyloxy

hydrogenation of **14** over Pd/C gave compound **15**, which was N-demethylated using 1-chloroethyl chloroformate.[19] The corresponding carbamate was cleaved by refluxing in MeOH/HCl to yield the *N*-normorphinan **16**, which was cyclopropylmethylated to afford **17**. The 4,5-ring opening of compound **17** with activated zinc in the presence of NH_4Cl in MeOH[14] gave phenol **7**, which was 4-O-alkylated with phenyltrimethylammonium chloride and butyl iodide, respectively, to afford compounds **8** and **9**.

Results and Discussion

Opioid Receptor Binding. The new compounds were evaluated in receptor binding assays in rat brain membranes by displacement of [^{3}H]DAMGO (μ), [^{3}H]-[Ile^{5,6}]deltorphin II (δ), and [^{3}H]U69,593 (κ).[20] Compounds **3**, **4**, and **6** exhibited lower affinity at the μ opioid receptor and decreased binding to δ and κ receptors compared to cyprodime and its analogue **2** (Table 1). Compounds **5** and **9** had affinities at the μ binding sites comparable to those of the reference compounds, but some increase in the affinities at δ and κ receptors was observed. The 14-phenylpropoxy-substituted compounds **7**, **8**, and **17** showed affinities in the subnanomolar range at the μ opioid receptor. Their interaction with the μ receptor was remarkably improved, being 2 orders of magnitude higher than that of the reference compounds. Among the tested compounds, the 14-phenylpropoxy derivative **8** and its

Table 1. Opioid Receptor Binding Affinities and Selectivities of Compounds **3**−**9** and **17** and Reference Compounds in Rat Brain Membranes

	$K_i \pm$ SEM (nM)			selectivity ratio	
compd	[^{3}H]DAMGO (μ)	[^{3}H][Ile^{5,6}]deltorphin II (δ)	[^{3}H]U69,593 (κ)	δ/μ	κ/μ
3	27.9 ± 0.8	841 ± 113	359 ± 16	30	13
4	43.3 ± 4.4	1412 ± 134	208 ± 61	33	4.8
5	11.6 ± 0.7	213 ± 17	56.8 ± 9.3	18	4.9
6	44.9 ± 1.7	1172 ± 120	441 ± 55	26	9.8
7	0.40 ± 0.05	5.06 ± 0.53	5.84 ± 0.69	13	15
8	0.34 ± 0.05	16.9 ± 0.547	7.36 ± 1.68	50	22
9	14.9 ± 2.2	232 ± 20	150 ± 47	16	10
17	0.84 ± 0.08	46.2 ± 4.9	22.8 ± 0.4	55	27
2	13.8 ± 0.8	765 ± 70	261 ± 38	55	19
cyprodime (**1**)	10.6 ± 0.7	414 ± 27	109 ± 4	39	10

Table 2. Stimulation of [^{35}S]GTPγS Binding by Compounds **7**, **8**, and **17** and Reference Compounds in Recombinant Human Opioid Receptors[a]

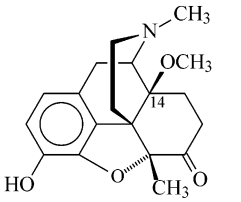
	μ opioid receptor		δ opioid receptor		κ opioid receptor	
compd	E_{max} (% maximal stimulation)	EC_{50} (nM)	E_{max} (% maximal stimulation)	EC_{50} (nM)	E_{max} (% maximal stimulation)	EC_{50} (nM)
7	35 ± 9.5	3.47 ± 0.86	49 ± 9.9	7.91 ± 0.34	45.8 ± 11.0	4.51 ± 0.13
8	35 ± 2.5	1.97 ± 0.89	22 ± 3.3	20.6 ± 9.3		>10000
17	43 ± 8.8	9.80 ± 1.25	17 ± 7.7	86.8 ± 2.4		>10000
2		>10000	22 ± 6.0	1613 ± 130		>10000
cyprodime (**1**)	33 ± 2.9	20.3 ± 1.8	18 ± 2.4	1105 ± 163	18.8 ± 6.4	117 ± 0.8

[a] Membranes from CHO cells that stably expressed μ, δ, or κ opioid receptors were incubated with varying concentrations of the compounds. EC_{50} values represent the concentration of compound necessary to produce 50% of the E_{max} value. Data represent the mean ± SEM.

Table 3. Antagonist K_e Values of Compounds **8** and **17** and Reference Compounds[a]

	K_e ± SEM (nM)	
compd	DAMGO (μ)	U69,593 (κ)
8	nt	2.52 ± 0.32
17	nt	8.54 ± 1.08
2	11.1 ± 0.7	120 ± 6
cyprodime (**1**)	12.4 ± 1.7	26.1 ± 5.0

[a] Membranes from CHO cells that stably expressed either μ or κ opioid receptors were incubated with DAMGO or U69,593 in the presence of varying concentrations of the compound. nt, not tested.



14-Methoxymetopon (HS 198)

Figure 2.

4-hydroxy analogue **7** displayed the highest μ affinities (K_i of 0.34 and 0.40 nM, respectively). Compared to cyprodime and analogue **2,** the affinities of compounds **7** and **8** were increased 30- to 40-fold at μ, 25- to 150-fold at δ, and 15- to 45-fold at κ receptors. Of the new derivatives, compounds **8** and **17** were the most selective for the μ opioid receptor with δ/μ selectivity ratios of 50 and 55, respectively, and κ/μ selectivity ratios of 22 and 27, respectively, which are equivalent to or higher than those of the reference compounds (Table 1).

Introduction of a phenylpropoxy and hexyloxy substituent at C-4 was detrimental to μ receptor affinity, while a benzyloxy group retained μ affinity but increased δ and κ affinity, thus resulting in less μ selectivity compared to cyprodime and analogue **2**. A phenylpropoxy substituent at C-14 was able to considerably increase the binding to the μ, δ, and κ receptors in the presence of a hydroxyl and methoxy group at C-4 (compounds **7** and **8**, respectively) and a 4,5-ether bridge (compound **17**). Enlarging the substituent at C-4 (butoxy group) in the presence of a phenylpropoxy substituent (compound **9**) resulted in reduction of affinity at μ, δ, and κ receptors.

[^{35}S]GTPγS Binding Assay. The three compounds (**7**, **8**, and **17**) with subnanomolar affinity values at the μ opioid receptor as determined in binding assays were tested in the [^{35}S]GTPγS binding assay.[20] They produced similar maximal stimulation of [^{35}S]GTPγS binding (E_{max}) to μ and δ receptors in comparison to cyprodime and analogue **2** (Table 2). The rank orders of the EC_{50} values substantially correlated with the K_i values obtained for the compounds in the binding assay with [^{3}H]DAMGO and [^{3}H][Ile^{5,6}]deltorphin II. All new derivatives were partial agonists at μ and δ receptors. Among the most potent compounds, **8** had the lowest EC_{50} value at the μ receptor and compound **7** had the lowest at the δ receptor. Only compound **7** exhibited some partial agonist activity at κ receptors (EC_{50} = 4.51 nM). Compounds **8** and **17** were tested for antagonism at κ receptors (Table 3), and they showed K_e values of 2.52 and 8.54 nM, respectively. Cyprodime and its analogue **2** were a low-efficacy partial agonist and antagonist, respectively, at all receptors in this functional assay (Table 2).

Antinociceptive Assays. Compounds **7**, **8**, and **17** of this series were tested for their antinociceptive potencies in vivo in the hot-plate (HP), the tail-flick (TF), and the paraphenylquinone writhing (PPQ) tests in mice (Table 4). All compounds were considerably more potent than morphine in all three in vivo assays. Derivative **7**, a partial agonist exhibiting the best affinity at the μ opioid receptor (K_i = 0.40 nM) and also good affinity at the δ and κ receptors, had the highest antinociceptive potency, with a potency 21-fold higher in the HP, 38-fold higher in the TF, and ca. 300-fold higher in the PPQ compared to morphine. When compared to the highly potent μ opioid agonist 14-methoxymetopon[16,20−25] (Figure 2), it became apparent that compound **7** exhibits similar potencies in all three assays. The antinociceptive

Table 4. Results of the in Vivo Activities of Compounds **7**, **8**, and **17** in Comparison to Morphine and 14-Methoxymetopon (HS 198)

	ED_{50} (sc, mg/kg)[a]		
compd	HP[b]	TF[c]	PPQ[d]
7	0.04 (0.013−0.143)	0.05 (0.015−0.17)	0.0014 (0.0004−0.005)
8	0.3 (0.094−0.96)	0.28 (0.15−0.5)	0.06 (0.019−0.197)
17	0.68 (0.29−1.6)	0.187 (0.054−0.640)	0.0094 (0.003−0.028)
HS 198[e]	0.03 (0.010−0.050)	0.03 (0.010−0.60)	0.009 (0.003−0.023)
morphine[e]	0.85 (0.39−1.86)	1.9 (0.89−4.14)	0.40 (0.20−0.80)

[a] Effective dose 50% (95% confidence limits). [b] HP = hot plate test. [c] TF = tail flick test. [d] PPQ = paraphenylquinone writhing test. [e] Taken from ref 16.

activities of the 4-methoxy derivative **8** and compound **17**, which display also high μ affinity and μ selectivity, were slightly lower compared to analogue **7**, which has a 4-hydroxy group. All of the compounds (**7**, **8**, and **17**) were essentially inactive as antagonists in the TF test versus morphine. None of the compounds exhibited sufficient antagonist activity to enable the determination of its AD_{50}. The novel derivatives of cyprodime containing a 14-phenylpropoxy group acted as potent antinociceptives. This is in agreement with our recent observations in other morphinan series.[16,17]

Conclusions

It was found that further prolongation of the 4-alkoxy group of cyprodime and its 4-butoxy analogue **2** is detrimental for μ opioid receptor affinity. Introduction of an arylalkoxy group at C-4 does not increase μ affinity in the case of benzyloxy, while a phenylpropoxy group at C-4 reduces μ affinity. The present study on different cyprodime derivatives provides further evidence that the nature of the substituent at position 14 has a major impact on the ability of morphinans to interact with opioid receptors. Introduction of a 14-phenylpropoxy group markedly increases binding affinities to μ and also to δ and κ receptors and gives rise to a significant increase in the agonist potency. The new derivatives containing a 14-phenylpropoxy group acted as potent antinociceptives. Thus, the presence of this substituent leads to a profound alteration in the pharmacological profile in this class of compounds.

Experimental Section

The required reagents as well as anhydrous DMF were purchased from Fluka, Switzerland, in the highest purities available. The solvents were distilled before usage. Melting points were determined 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 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 in Hz. Mass spectra were recorded 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 (eluent: CH_2Cl_2/MeOH/concentrated NH_4OH solution, 90:9:1), and for column chromatography, silica gel 60 (230−400 mesh ASTM, Fluka, Switzerland) was used.

17-(Cyclopropylmethyl)-14β-methoxy-4-{[(*E*)-3-phenylprop-2-enyl]oxy}morphinan-6-one Hydrochloride (3·HCl). A mixture of 17-(cyclopropylmethyl)-4-hydroxy-14β-methoxymorphinan-6-one[14] (1.00 g, 2.93 mmol), cinnamyl bromide (0.75 g, 3.81 mmol), K_2CO_3 (1.09 g, 7.91 mmol), and anhydrous DMF (5 mL) was stirred at room temperature for 24 h. After addition of H_2O (15 mL), the mixture was extracted with CH_2Cl_2 (5 × 20 mL), and the combined organic layers were washed with H_2O (2 × 100 mL) and brine (4 × 100 mL), dried (Na_2SO_4), and evaporated. The residue (920 mg of yellow-brown oil) was purified by column chromatography (silica gel, elution with CH_2Cl_2/MeOH/concentrated NH_4OH solution, 250:2.5:0.5) to afford a yellowish oil (833 mg of **3**, 62%). To obtain an analytical sample, a small portion of this oil was dissolved in Et_2O and **3**·HCl was precipitated with Et_2O/HCl: slightly yellow powder; mp 132−137 °C; IR (KBr) 1710 (C═O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.83 (s, br, ^+NH), 7.50−7.18 (m, 6 arom H), 6.96−6.53 (m, 2 arom H, 2 olef H), 4.79−4.74 (m, PhCH-CHCH_2), 3.43 (s, CH_3O); CI-MS m/z 458 ($M^+ + 1$). Anal. ($C_{30}H_{35}NO_3$·HCl·1.8H_2O) C, H, N.

17-(Cyclopropylmethyl)-14β-methoxy-4-[3-(phenylpropyl)oxy]morphinan-6-one Hydrochloride (4·HCl). A mixture of **3** (oil, 480 mg, 1.05 mmol), 10% Pd/C (60 mg), and MeOH (20 mL) was hydrogenated at room temperature and 35 psi for 45 min. The catalyst was filtered off, and the filtrate was evaporated. The residue (475 mg of brownish oil) was purified by column chromatography (silica gel, elution with CH_2Cl_2/MeOH/concentrated NH_4OH solution, 250:2.5:0.5) to afford a slightly yellow oil (190 mg of **4**, 62%). The hydrochloride salt was obtained in the usual way (Et_2O/HCl) to yield 191 mg (37%) of **4**·HCl: mp 185−192 °C; IR (KBr) 1710 (C═O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.91 (s, br, ^+NH), 7.34−7.16 (m, 12 arom H), 6.83−6.81 (m, 2 arom H), 3.43 (s, CH_3O); CI-MS m/z 460 ($M^+ + 1$). Anal. ($C_{30}H_{37}NO_3$·HCl·0.4H_2O) C, H, N.

4-Benzyloxy-17-(cyclopropylmethyl)-14β-methoxymorphinan-6-one Hydrochloride (5·HCl). A mixture of 17-(cyclopropylmethyl)-4-hydroxy-14 β-methoxymorphinan-6-one[14] (700 mg, 2.05 mmol), benzyl chloride (0.32 mL, 2.78 mmol), K_2CO_3 (770 mg, 5.59 mmol), and anhydrous DMF (5 mL) was stirred under N_2 at room temperature for 24 h. After addition of H_2O (15 mL), the mixture was extracted with CH_2Cl_2 (5 × 20 mL), and the combined organic layers were washed with H_2O (2 × 100 mL) and brine (4 × 100 mL), dried (Na_2SO_4), and evaporated. The residue (830 mg of yellow-brown oil) was purified by column chromatography (silica gel, elution with CH_2Cl_2/MeOH/concentrated NH_4OH solution, 250:4.5:0.5) to afford a yellowish oil (542 mg of **5**, 61%). A part of this oil (169 mg) was dissolved in Et_2O, and **5**·HCl was precipitated with Et_2O/HCl: colorless crystals (120 mg); mp 224−229 °C; IR (KBr) 1708 (C═O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.93 (s, br, ^+NH), 7.59−7.35 (m, 5 arom H), 7.22 (t, J = 8.0, 1 arom H), 6.97 (d, J = 8.0, 1 arom H), 6.85 (d, J = 8.0, 1 arom H), 3.42 (s, CH_3O); CI-MS m/z 432 ($M^+ + 1$). Anal. ($C_{28}H_{33}NO_3$·HCl·0.2H_2O) C, H, N.

17-(Cyclopropylmethyl)-4-hexyloxy-14β-methoxymorphinan-6-one Hydrochloride (6·HCl). A mixture of 17-(cyclopropylmethyl)-4-hydroxy-14β-methoxymorphinan-6-one[14] (400 mg, 1.17 mmol), *n*-hexyl iodide (0.35 mL, 2.36 mmol), K_2CO_3 (490 mg, 3.56 mmol), and anhydrous DMF (5 mL) was stirred under N_2 at 50 °C (bath temperature) for 2 h. The inorganic material was filtered off, and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 (50 mL), washed with H_2O (3 × 30 mL) and brine (1 × 30 mL), dried (Na_2SO_4), and evaporated. The remaining yellow oil (470 mg) was purified by column chromatography (silica gel, elution with CH_2Cl_2/MeOH/concentrated NH_4OH solution, 250:4:0.5) to afford a yellowish oil (389 mg of **6**, 78%). The hydrochloride salt was obtained in the usual way (Et_2O/HCl) to yield 417 mg (77%) of **6**·HCl: mp 134−142 °C; IR (KBr) 1724 (C═O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.11 (s, br, ^+NH), 7.20 (t, J = 8.0, 1 arom H), 6.86 and 6.81 (2 d, J = 8.0, 8.0, 2 arom H), 3.43 (s, CH_3O); CI-MS m/z 426 ($M^+ + 1$). Anal. ($C_{27}H_{39}NO_3$·HCl·0.9H_2O) C, H, N.

7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methyl-14β-{[(*E*)-3-phenylprop-2-enyl]oxy}morphinan-6-one (11). NaH (0.92 g, 38.30 mmol, obtained from 1.53 g of 60% NaH dispersion in oil after washings with petroleum ether) was added to a stirred solution of **10** (4.00 g, 12.77 mmol) in anhydrous DMF (100 mL) at 0 °C under N_2. After 30 min, a solution of cinnamyl bromide (3.27 g, 16.59 mmol) in anhydrous DMF (20 mL) was added slowly within 10 min, and the resulting mixture was stirred for another 30 min at 0 °C and 1.5 h at room temperature. Excess NaH was destroyed carefully by addition of small pieces of ice. Then the mixture was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (4 × 100 mL), and the combined organic layers were washed with H_2O (5 × 150 mL) and brine (150 mL), dried (Na_2SO_4), and evaporated. The residue (4.22 g, orange oil) crystallized spontaneously and was treated with boiling MeOH (10 mL) to yield 3.23 g (59%) of **11** (mp 210−215 °C). A small portion was recrystallized from MeOH to afford an analytical sample of **11**: mp 216−219 °C; ^1H NMR ($CDCl_3$) δ 7.38−7.22 (m, 5 arom H), 6.76 (d, J = 10.2, 1 olef H, *H*-C(8)), 6.69 (d, J = 8.3,

1 arom H), 6.61 (d, $J = 8.3$, 1 arom H), 6.55 (d, $J = 16.2$, 1 olef H), 6.32 (dt, $J = 16.2$, $J = 5.9$, 1 olef H), 6.23 (d, $J = 10.2$, 1 olef H, *H*-C(7)), 4.78 (s, *H*-C(5)), 3.84 (s, CH_3O), 2.51 (s, CH_3N). Anal. ($C_{27}H_{27}NO_4$) C, H, N.

4,5α-Epoxy-3-methoxy-17-methyl-14b-(3-phenylpropyloxy)morphinan-6-one (=14-*O*-(3-Phenylpropyl)oxycodone) (12). A mixture of **11** (12.70 g, 29.57 mmol) and 1.27 g Pd/C (10%) in glacial acetic acid (160 mL) was hydrogenated at room temperature and 40 psi for 1 h. The catalyst was filtered off, the filtrate was evaporated, the residue was alkalinized with concentrated NH_4OH solution and extracted with CH_2Cl_2 (4 × 70 mL). The combined organic layers were washed with H_2O (3 × 150 mL) and brine (3 × 150 mL), dried (Na_2SO_4), and evaporated. The residue (14 g of yellow-brown oil) was crystallized from MeOH to yield 10.14 g (79%) colorless needles of **12** (mp 116−118 °C). A small portion was recrystallized from MeOH to afford an analytical sample of **12**: mp 119−121 °C; ^{1}H NMR ($CDCl_3$) δ 7.35−7.15 (m, 5 arom H), 6.68 (d, $J = 8.2$, 1 arom H,), 6.60 (d, $J = 8.2$, 1 arom H,), 4.63 (s, *H*-C(5)), 3.89 (s, CH_3O), 2.34 (s, CH_3N). Anal. ($C_{27}H_{31}NO_4$) C, H, N.

4,5α-Epoxy-3-hydroxy-17-methyl-14β-[(3-phenylpropyl)oxy]morphinan-6-one Hydrochloride (13·HCl). A solution of **12** (10.1 g, 23.30 mmol) in 48% HBr (140 mL) was refluxed for 25 min. After cooling, the solution was poured on ice−water (100 mL), alkalinized with concentrated NH_4OH solution, and extracted with CH_2Cl_2 (5 × 120 mL). The combined organic layers were washed with H_2O (150 mL) and brine (4 × 100 mL), dried (Na_2SO_4), and evaporated. The residue (13.85 g of yellow-brown oil) was purified by column chromatography (silica gel, elution with CH_2Cl_2/MeOH/concentrated NH_4OH solution, 250/2.5/0.5) to afford a yellowish oil (6.48 g of **13**, 66%) which was used as such for the next step. For analysis, a small portion was converted into the hydrochloride salt in the usual way (Et_2O/HCl) to yield analytically pure **13**·HCl: mp 181−188 °C (dec); ^{1}H NMR (DMSO-d_6) δ 9.50 (s, O*H*), 8.68 (s, br, $^+$N*H*), 7.34−7.16 (m, 5 arom H), 6.70 (d, $J = 8.0$, 1 arom H), 6.65 (d, $J = 8.0$, 1 arom H), 4.87 (s, *H*-C(5)), 2.92 (d, $^+$NC*H*$_3$). Anal. ($C_{26}H_{29}NO_4$·HCl·1.5H_2O) C, H, N.

4,5α-Epoxy-17-methyl-14β-[(3-phenylpropyl)oxy]-3-[(1-phenyl-1*H*-tetrazole-5-yl)oxy]morphinan-6-one (14). A mixture of **13** (6.38 g, 15.20 mmol), K_2CO_3 (5.67 g, 41.06 mmol), 5-chloro-1-phenyl-1*H*-tetrazole (3.02 g, 16.73 mmol), and anhydrous DMF (40 mL) was stirred at room temperature for 23 h. After addition of H_2O (300 mL), the mixture was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were washed with H_2O (2 × 200 mL) and brine (3 × 250 mL), dried (Na_2SO_4), and evaporated. The residue (7.48 g yellowish oil) was purified by column chromatography (silica gel, elution with CH_2Cl_2/MeOH/concentrated NH_4OH solution, 250:2:0.5) to afford a yellow oil (6.41 g of **14**, 75%) which was used as such for the next step. A small portion was crystallized from Et_2O to give an analytical sample of **14**: mp 117−119 °C; IR (KBr): 1723 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.88−7.83 (m, 2 arom H), 7.73−7.62 (m, 3 arom H), 7.30−7.16 (m, 6 arom H), 6.85 (d, $J = 8$, 1 arom H), 4.93 (s, *H*-C(5)), 2.29 (s, CH_3N); CI-MS *m*/*z* 564 ($M^+ + 1$). Anal. ($C_{33}H_{33}N_5O_4$) C, H, N.

4,5α-Epoxy-17-methyl-14β-[(3-phenylpropyl)oxy]morphinan-6-one (15). A mixture of **14** (6.20 g, 11.00 mmol) and 2.48 g of Pd/C (10%) in glacial acetic acid (100 mL) was hydrogenated at 40 °C and 50 psi for 17 h. The catalyst was filtered off, the filtrate was reduced to 30 mL by evaporation, and ice−water (100 mL) was added. The solution was alkalinized with concentrated NH_4OH solution and extracted with CH_2Cl_2 (1 × 100 mL, 3 × 75 mL). The combined organic layers were washed with brine (4 × 200 mL), dried (Na_2SO_4), and evaporated. The residue (4.15 g of yellowish oil) was crystallized from little MeOH to yield 3.20 g (72%) of **15** as colorless crystals: mp 105−109 °C; IR (KBr) 1721 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.29−7.16 (m, 5 arom H), 7.04 (t, $J = 8.0$, 1 arom H), 6.73 (d, $J = 8.0$, 1 arom H), 6.64 (d, $J = 8.0$, 1 arom H), 4.75 (s, *H*-C(5)), 2.28 (s, CH_3N); CI-MS *m*/*z* 404 ($M^+ + 1$). Anal. ($C_{26}H_{29}NO_3$) C, H, N.

4,5α-Epoxy-14β-[(3-phenylpropyl)oxy]morphinan-6-one Hydrochloride (16·HCl). A mixture of **15** (3.20 g, 7.93 mmol), $NaHCO_3$ (3.33 g, 39.65 mmol), 1-chloroethyl chloroformate (4.32 mL, 39.65 mmol), and 1,2-dichloroethane (40 mL) was stirred at 60 °C (bath temperature) under N_2 for 13.5 h. The inorganic material was filtered off, and the filtrate was evaporated. The residue (3.7 g of yellow-brown oil, pure by TLC) was refluxed in a mixture of concentrated HCl (15 mL) and MeOH (35 mL) without further purification and characterization. Then the solution was evaporated and the residue was crystallized from MeOH/Et_2O to afford 2.77 g (82%) of **16**·HCl: mp >225 °C (dec); IR (KBr): 1729 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.25 (s, br, $^+$*H*N), 8.11 (s, br, $^+$*H*N), 7.34−7.12 (m, 5 arom H), 7.16 (t, $J = 8.0$, 1 arom H), 6.85 (d, $J = 8.0$, 1 arom H), 6.77 (d, $J = 8.0$ Hz, 1 arom H), 4.96 (s, *H*-C(5)); CI-MS *m*/*z* 390 ($M^+ + 1$). Anal. ($C_{25}H_{27}NO_3$·HCl·0.3H_2O) C, H, N.

17-(Cyclopropylmethyl)-4,5α-epoxy-14β-[(3-phenylpropyl)oxy]morphinan-6-one Hydrochloride (17·HCl). A mixture of **16**·HCl (2.36 g, 5.55 mmol), K_2CO_3 (2.13 g, 15.40 mmol), cyclopropylmethyl bromide (0.64 mL, 6.67 mmol), and anhydrous DMF (20 mL) was stirred at 80 °C (bath temperature) under N_2 for 8 h. The inorganic material was filtered off, and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 (150 mL), washed with H_2O (5 × 150 mL) and brine (150 mL), dried (Na_2SO_4), and evaporated. The residue (2.43 g of **17** as a yellowish oil, 99%) was used for the next step without further purification. A small portion was converted into the hydrochloride salt in the usual way (Et_2O/HCl) to yield an analytical sample of **17**·HCl: mp 145−150 °C; IR (KBr) 1726 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.26 (s, br, $^+$*H*N), 7.31−7.14 (m, 5 arom H), 7.18 (t, $J = 8.0$, 1 arom H), 6.85 (d, $J = 8.0$, 1 arom H), 6.78 (d, $J = 8.0$, 1 arom H), 4.96 (s, *H*-C(5)); CI-MS *m*/*z* 444 ($M^+ + 1$). Anal. ($C_{29}H_{33}NO_3$·HCl·0.9H_2O) C, H, N.

17-(Cyclopropylmethyl)-4-hydroxy-14β-[(3-phenylpropyl)oxy]morphinan-6-one Hydrochloride (7·HCl). To a refluxing mixture of **17** (1.2 g, 2.71 mmol), NH_4Cl (0.72 g, 13.46 mmol), and MeOH (50 mL) was added activated zinc powder (0.88 g, 13.46 mmol) in small portions while stirring. After the mixture was refluxed for 80 min, the inorganic material was filtered off and the filtrate was evaporated. The residue was dissolved in H_2O (50 mL) and alkalinized with concentrated NH_4OH solution, and the mixture was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with brine (5 × 100 mL), dried (Na_2SO_4), and evaporated to give 1.20 g (99%) of **7** as a yellowish oil which was used as such for the next step. A small portion was transformed into the hydrochloride salt in the usual way (Et_2O/HCl) to afford an analytical sample of **7**·HCl: mp >170 °C (dec); IR (KBr) 1709 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.82 (s, O*H*), 8.43 (s, br, $^+$N*H*), 7.30−7.20 (m, 5 arom H), 7.03 (t, $J = 8.0$, 1 arom H), 6.66 (m, 2 arom H); CI-MS *m*/*z* 446 ($M^+ + 1$). Anal. ($C_{29}H_{35}NO_3$·HCl·0.7H_2O) C, H, N.

17-(Cyclopropylmethyl)-4-methoxy-14β-[(3-phenylpropyl)oxy]morphinan-6-one Hydrochloride (8·HCl). A mixture of **7**·HCl (0.40 g, 0.90 mmol), K_2CO_3 (0.37 g, 2.69 mmol), phenyltrimethylammonium chloride (0.46 g, 2.69 mmol), and anhydrous DMF (6 mL) was stirred at 80 °C (bath temperature) under N_2 for 3.5 h. After the mixture was cooled, the inorganic material was filtered off, the filtrate was evaporated, and the residue was dissolved in CH_2Cl_2 (100 mL), washed with brine (4 × 150 mL), dried (Na_2SO_4), and evaporated. The residue (0.30 g of dark oil) was purified by column chromatography (silica gel, elution with CH_2Cl_2/MeOH/concentrated NH_4OH solution, 250:4:0.5) to afford a yellow oil (0.23 g) which was dissolved in Et_2O. Addition of Et_2O/HCl yielded 0.22 g (48%) of **8**·HCl: mp 121−126 °C; IR (KBr) (C=O) 1710 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.34 (s, br, $^+$N*H*), 7.30−7.16 (m, 5 arom. H), 7.22 (t, $J = 8.0$, 1 arom H), 6.88 (d, $J = 8.0$, 1 arom H), 6.82 (d, $J = 8.0$, 1 arom H); CI-MS *m*/*z* 460 ($M^+ + 1$). Anal. ($C_{30}H_{37}NO_3$·HCl·0.7H_2O) C, H, N.

4-(*n*-Butoxy)-17-(cyclopropylmethyl)-14β-[(3-phenylpropyl)oxy]morphinan-6-one Hydrochloride (9·HCl). A mixture of **7**·HCl (0.60 g, 1.34 mmol), K_2CO_3 (0.55 g, 4.01 mmol), *n*-butyl iodide (0.31 mL, 2.67 mmol), and anhydrous DMF (5 mL) was stirred at 90 °C (bath temperature) under N_2 for 7 h. After the mixture cooled, the inorganic material was filtered off, the filtrate was evaporated, and the residue was dissolved in CH_2Cl_2 (100 mL), washed with brine (3 × 150 mL), dried (Na_2SO_4), and evaporated. The residue (0.43 g of brown oil) was purified by column chromatography (silica gel, elution with CH_2Cl_2/MeOH/concentrated NH_4OH solution, 250:4:0.5) to afford a yellow oil (0.26 g) which was dissolved in Et_2O. Addition of Et_2O/HCl yielded 0.19 g (26%) of **9**·HCl: mp 172−177 °C; IR (KBr) (C=O) 1711 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.52 (s, br, ^+NH), 7.30−7.15 (m, 6 arom H), 6.86 (d, J = 8.0, 1 arom H), 6.80 (d, J = 8.0, 1 arom H), 3.95 (t, J = 6.4, (C4)OCH_2(CH_2)$_2CH_3$); CI-MS m/z 502 ($M^+ + 1$). Anal. ($C_{33}H_{43}NO_3$·HCl·0.5H_2O) C, H, N.

Opioid Receptor Binding Assays. Rat brain membrane preparations and binding assays were performed as described.[20]

[^{35}S]GTPγS Binding Assay. Membrane preparation from Chinese hamster ovary (CHO) cells transfected with human opioid receptors and binding assays were performed as described.[20]

In Vivo Antinocicieptive Tests have been performed as earlier described.[16,17]

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