Synthesis and Biological Evaluation of 14-Alkoxymorphinans. 18.[1] N-Substituted 14-Phenylpropyloxymorphinan-6-ones with Unanticipated Agonist Properties: Extending the Scope of Common Structure−Activity Relationships

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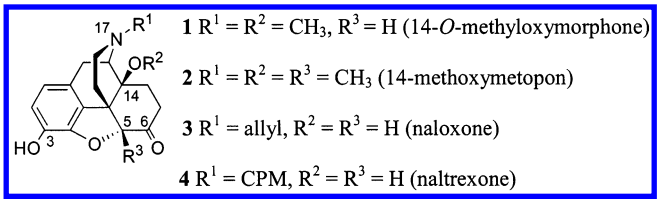
The synthesis, biological, and pharmacological evaluations of 14β-*O*-phenylpropyl-substituted morphinan-6-ones are described. The most striking finding of this study was that all of the compounds from the novel series of differently N-substituted 14β-*O*-phenylpropylmorphinans acted as powerful opioid agonists. Even with *N*-substituents such as cyclopropylmethyl and allyl, which are usually associated with distinct antagonist properties, only agonists were obtained. Compared to morphine, the *N*-cyclopropylmethyl derivative **15** showed considerably increased potency in the in vivo assays in mice (600-fold in the tail-flick assay, 60-fold in the paraphenylquinone writhing test, and 400-fold in the hot-plate assay). Remarkably, most of the new ligands were nonselective and exhibited binding affinities in the subnanomolar range at opioid receptors (μ, κ, δ), with the *N*-propyl derivative **19** displaying the highest affinity for the μ-receptor (K_i = 0.09 nM).

Introduction

Established and generally accepted structure−activity relationship (SAR) models have assigned critical importance in the development of opioid agonist/antagonist properties of morphinan-6-ones to the *N*-substituent.[2−4] Substituents such as cyclopropylmethyl (CPM) or allyl on the nitrogen have been commonly associated with an antagonist character in this series of opioids.[3] While 14-methoxy-*N*-methylmorphinan-6-ones (Figure 1) such as 14-*O*-methyloxymorphone[5,6] (**1**) and 14-methoxymetopon[7−11] (**2**) are known to act as agonists at the μ-opioid receptor, the replacement of the *N*-methyl group by an allyl or a CPM group typically results in a complete loss of agonist activity, thus leading to pure antagonists. Well-known examples are the nonselective opioid receptor antagonists naloxone (**3**), naltrexone (**4**) (Figure 1), and their 14-*O*-methyl and 14-*O*-ethyl derivatives.[4,5,12−14] In addition, there is no evidence for an increase of agonist activity upon methylation or ethylation of the C14-*O*.[12] In agreement with these results, the introduction of methyl and ethyl groups at the C14-*O* in morphinan derivatives was described as slightly enhancing the antagonist properties of the compounds. Thus, there is only some minor indication of any influence of the C14-*O* substituent in modulating the agonist and antagonist profile of morphinan-6-ones.[12,15]



1 $R^1 = R^2 = CH_3$, $R^3 = H$ (14-*O*-methyloxymorphone)

2 $R^1 = R^2 = R^3 = CH_3$ (14-methoxymetopon)

3 R^1 = allyl, $R^2 = R^3 = H$ (naloxone)

4 R^1 = CPM, $R^2 = R^3 = H$ (naltrexone)

Figure 1.

On the basis of these findings and also from the fact that the introduction of a 14-alkoxy group not only usually markedly increases the affinity to opioid receptors but also considerably enhances the antinociceptive potency of *N*-methyl-6-ketomorphinans,[5] we have decided to prepare several N-substituted 14β-phenylpropyloxymorphinan derivatives. In an effort to develop new partial opioid agonists that would interact with the μ-opioid receptor and hence might be subject to lesser side effects, we undertook the synthesis of this series. Furthermore, we were also interested in replacing the substitutent on the nitrogen with substituents that usually produce pure, potent antagonists, e.g., allyl or CPM, in order to increase the lipophilicity above the level of their analogues naloxone and naltrexone. Since opioid antagonists are used in the treatment of drug abuse, enhanced lipophilic properties would broaden their therapeutic scope, e.g., use in transdermal systems. The latter is known to be advantageous with regard to patients' compliance to the therapy and thus possibly to increase the success of the treatment.

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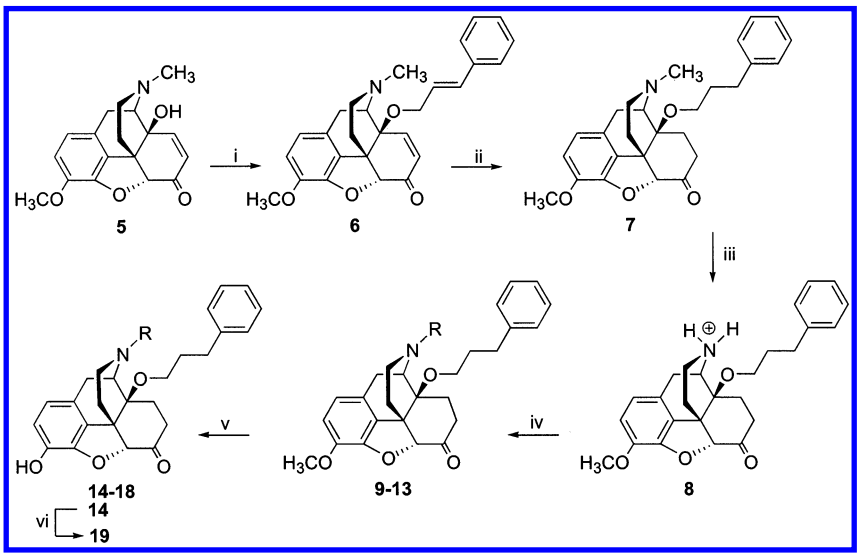
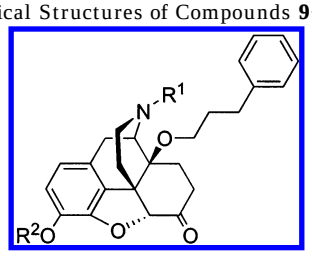
Scheme 1[a]



[a] (i) NaH, cinnamyl bromide, DMF; (ii) H_2/Pd/C; (iii) 1-chloroethyl chloroformate, $NaHCO_3$, $C_2H_4Cl_2$, reflux, MeOH, reflux; (iv) RX, K_2CO_3, DMF, 80 °C; (v) HBr 48%, reflux; (vi) H_2/Pd/C.

Table 1. Chemical Structures of Compounds **9**−**19**



R^1	compd for $R^2 = CH_3$	compd for $R^2 = H$
allyl	**9**	**14**
CPM[a]	**10**	**15**
CBM[b]	**11**	**16**
(±)-tetrahydrofurfuryl	**12**	**17**
2-phenylethyl	**13**	**18**
propyl		**19**

[a] CPM = cyclopropylmethyl. [b] CBM = cyclobutylmethyl.

Table 2. Results of in Vitro Radioligand Binding Studies of Compounds **12**−**19** in Comparison to 14-Methoxymetopon (**2**) and Morphine

	K_i (nM)			selectivity ratio	
compd	μ	δ	κ	κ/μ	δ/μ
12	3.80 ± 1.3	6.20 ± 0.2	61.4 ± 1.9	16.2	1.64
13	1.90 ± 0.4	5.40 ± 1.2	1.40 ± 0.7	0.74	2.84
14	0.20 ± 0.01	0.26 ± 0.07	0.11 ± 0.05	0.55	1.30
15[a]	0.34 ± 0.06	0.48 ± 0.05	0.41 ± 0.09	1.96	1.84
16	0.25 ± 0.07	0.46 ± 0.16	0.49 ± 0.25	1.96	1.84
17	0.20 ± 0.04	0.09 ± 0.02	0.08 ± 0.02	0.40	0.45
18	1.10 ± 0.4	1.25 ± 0.5	0.60 ± 0.2	0.55	1.14
19	0.09 ± 0.05	0.93 ± 0.18	0.37 ± 0.17	4.11	10.3
2	0.023 ± 0.008	40.9 ± 7.4	304 ± 52	13217	1178
morphine[a]	6.55 ± 0.74	217 ± 19	113 ± 9	17.3	33.1

[a] Binding data determined in rat brain membranes using [^{3}H]DAMGO (μ), [^{3}H]Ile^{5,6}deltorphin II (δ), and [^{3}H]U69593 (κ) in nM.[31]

Chemistry

The target derivatives **9**−**19** were synthesized from thebaine following a procedure shown in Scheme 1. 14-Hydroxycodeinone (**5**) is readily available from thebaine by oxidation with performic acid.[16] 14-O-Alkylation with cinnamyl bromide in DMF using NaH as a base gave 14-cinnamyloxycodeinone (**6**). Catalytic hydrogenation over Pd/C catalyst afforded the corresponding 7,8-dihydro-14β-phenylpropyloxy derivative **7**. N-Demethylation was accomplished by treatment of **7** with 1-chloroethyl chloroformate in 1,2-dichloroethane in the presence of $NaHCO_3$. Cleavage of the resulting carbamate intermediate to give **8** was performed in refluxing MeOH. Direct alkylation of the *N*-nor derivative **8** with various alkyl halides in DMF using K_2CO_3 as a base provided the N-substituted compounds **9**−**13**. 3-O-Demethylation with 48% HBr solution yielded derivatives **14**−**18**. Further catalytic hydrogenation of **14** over Pd/C catalyst afforded compound **19** (Table 1).

Results and Discussion

Opioid Receptor Binding. The binding affinities on compounds **12**−**19** were determined using a previously described method.[17] As expected and in agreement with the previous determination of the positive influence of 14-alkoxy substituents,[4,5] all of the newly synthesized compounds showed very high opioid receptor affinity. Among the tested ligands the 3-hydroxy analogues **14**−**19** displayed extremely low K_i values in the picomolar range (Table 2). Only the *N*-propyl derivative **19** showed moderate preference for μ over κ and δ receptors (4-fold and 10-fold, respectively); all other compounds completely lacked selectivity. Following the pattern of SARs in 4,5-epoxymorphinans, the presence of a 3-hydroxy group produces compounds with a much higher level of opioid potency than in the corresponding 3-methoxy derivatives, which usually show a significant drop in affinity and potency.[3,18] This also holds true for our compounds carrying a 3-methoxy group (**12**, **13**). However, although the opioid receptor affinity of the 3-methoxy derivatives **12** and **13** was considerably lower compared to that of their corresponding 3-hydroxy analogues **17** and **18**, these compounds still displayed high affinity for all opioid receptors in the low nanomolar range (1−60 nM, Table 2).

Antinociceptive Assays. Most surprisingly and in contrast to published data,[3−6,14] all of the compounds in this series appeared to be very potent opioid receptor

Table 3. Results of the in Vivo Activities of Compounds **12**−**19** in Comparison to Morphine and 14-Methoxymetopon (**2**)

	ED_{50} (95% confidence limit) (sc) in mice, mg/kg		
compd	TF[a]	PPQ[b]	HP[c]
12	0.76 (0.29−1.98)	*d*	0.7 (0.29−1.61)
13	0.08 (0.05−0.14)	0.006 (0.0027−0.0144)	0.06 (0.02−0.17)
14	0.006 (0.003−0.0107)	*d*	0.006 (0.0037−0.0094)
15	0.003 (0.0016−0.0062)	0.006 (0.0031−0.0125)	0.002 (0.0011−0.0047)
16	0.008 (0.0034−0.0197)	0.0003 (0.00002−0.006)	0.004 (0.0008−0.0172)
17	0.007 (0.004−0.014)	0.002 (0.0017−0.0041)	0.001 (0.0006−0.003)
18	0.11 (0.060−0.20)	0.009 (0.0041−0.027)	0.01 (0.0049−0.0282)
19	0.002 (0.0009−0.0027)	0.0009 (0.0005−0.0017)	0.002 (0.0008−0.0036)
2	0.03 (0.010−0.60)	0.009 (0.003−0.023)	0.03 (0.010−0.050)
morphine	1.9 (0.89−4.14)	0.40 (0.20−0.80)	0.85 (0.39−1.86)

[a] TF = tail-flick test. [b] PPQ = paraphenylquinone writhing test. [c] HP = hot-plate test. [d] Inconsistent dose response.

agonists in vivo (Table 3). All of the tested opioid ligands acted as antinociceptives in the mouse tail-flick test (TF), and their potency was considerably greater than that of morphine. In addition, they also displayed very high antinociceptive potency in the paraphenylquinone writhing test (PPQ) and hot-plate assay (HP) (Table 3).

The results for the *N*-allyl derivative **14** indicate distinct opioid agonist properties. Its potency is about 300-fold higher compared to that of morphine in the TF. The *N*-CPM analogue **15** is approximately 600 times more potent than morphine in the TF (ED_{50} = 0.003 mg/kg for **15**, compared with 1.9 mg/kg for morphine). The *N*-cyclobutylmethyl derivative **16** was more than 1300-fold more potent in the PPQ than morphine. Compound **17,** the *N*-tetrahydrofurfuryl derivative, also proved to be a very potent agonist (about 850 times more potent in the HP, 200 times more potent in the PPQ, and 270-fold more potent in the TF, respectively, compared to morphine). The antinociceptive activity of the *N*-phenethyl derivative **18** was slightly lower compared to that of the other analogues with a 3-hydroxy group in this series and was only about 17-fold higher compared to that of morphine in the TF. An *N*-phenethyl group was previously described to produce pure agonists in the series of morphinan-6-ones.[3] The *N*-propyl derivative **19** with the highest affinity of this series for the μ-opioid receptor was also shown to be an extremely potent antinociceptive agent. The in vivo assays revealed more than 400 times higher potency than morphine in the PPQ and also in the HP, respectively, and it was also found to be about 950-fold more potent than morphine in the TF. Although the tested compounds from the subset carrying a 3-methoxy group (**12**, **13**) displayed less pronounced antinociceptive properties compared to their 3-hydroxy analogues, the potencies were still notably high. Compound **13**, which showed the lowest opioid receptor affinity, was still significantly more potent than morphine. Most of the compounds in this series also surpassed 14-methoxymetopon (**2**) in potency, which was previously described as an extremely potent μ-opioid agonist.[8−10] Compound **19** displayed 10-fold greater potency in the PPQ and about 15-fold in TF and in HP compared to **2**, and derivative **16** was 30 times more potent than **2** in the PPQ. In alignment with these findings, none of the compounds showed measurable antagonist activity. All of the compounds were essentially inactive as antagonists in the TF assay versus morphine. None of the compounds exhibited sufficient antagonist activity to enable the determination of its AD_{50}.

Conclusions

Our present results on differently N-substituted 14β-*O*-phenylpropylmorphinan derivatives provide further evidence that the nature of the substituent at the oxygen in position 14 has a major impact on the ability of the compounds to bind to opioid receptors. These ligands exhibit significantly increased binding affinities at all opioid receptors without any specific preference for any one receptor type. It is remarkable that the presence of the 14-*O*-phenylpropyl substituent leads to an alteration of the pharmacological profile in this class of compounds. This substituent obviously annuls the decisive influence of the *N*-substituent on the determination of the antagonist properties of the new molecules. Even with *N*-substituents that usually produce compounds with distinct antagonist properties (e.g., allyl, CPM), only agonists were obtained. This discovery seems to revise the established structure−activity relationships and opens up an entirely new approach to the development of highly potent opioid agonists with exceptionally high binding affinities in the series of morphinan-6-ones.

Experimental Section

Thebaine was obtained from Tasmanian Alkaloids Ltd., Australia. Melting points were determined with a Kofler melting-point microscope. The ^{1}H NMR spectra were obtained on a Varian Gemini 200 spectrometer in DMSO-d_6 and tetramethylsilane (TMS) as internal standard. All chemical shift values were recorded as δ (ppm). Coupling constants J are given in hertz. IR spectra were taken on a Mattson Galaxy FTIR series 3000 in KBr pellets. Mass spectra were taken on a Varian MAT 44 S apparatus. Elemental analyses were performed at the Institute of Physical Chemistry of the University of Vienna and were within ±4% of theoretical values. Column chromatography was carried out on silica gel 60 (0.040−0.063 mm) from Fluka. TLC was performed on silica gel plates Polygram SIL G/UV254 with CH_2Cl_2/MeOH/NH_4OH, 90:9:1.

14-Cinnamyloxycodeinone (6). NaH (1.0 g, 40.4 mmol) obtained from 1.6 g of a 55−60% NaH dispersion in oil by washings with petroleum ether was added to a solution of 14-hydroxycodeinone[16] (**5**) (3.0 g, 9.6 mmol) in anhydrous DMF (100 mL) under N_2 at 5 °C. After 20 min, cinnamyl bromide (2.3 g, 11.6 mmol) was added and the resulting mixture was stirred at 5 °C for 30 min and then for 4.5 h at room temperature. Excess NaH was destroyed by addition of ice. H_2O (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried (Na_2SO_4), and evaporated to yield a brown oil that was crystallized from MeOH to afford **6** as colorless crystals (2.49 g, 60%): mp 214−217 °C; ^{1}H NMR (DMSO-d_6) δ 7.46−7.17 (m, 5H ar, phenyl), 7.19 (d, 1H olef, $^3J_{7/8}$ = 10.2 Hz, CH-8), 6.74/6.65 (2d, 2H ar, $^3J_{1/2}$ =

8.3 Hz, CH-1/2), 6.51−6.59 (m, 1H olef, O−CH_2−CH=C*H*−Phe), 6.34 (trans)/6.26 (cis) (2 ps-d, 1H olef, O−CH_2−C*H*=H−Phe, cis/trans = 1:1), 6.18 (d, 1H olef, $^3J_{7/8}$ = 10.2 Hz, CH-7), 4.85 (s, 1H, CH-5), 4.26/4.11 (2 d × d × d, 2H, for δ 4.11 ^2J = 13.7 Hz, ^3J = 5.6 Hz, ^4J = 0.5 Hz, O−CH_2−), 3.73 (s, 3H, O−CH_3), 2.36 (s, 3H, N-CH_3). Anal. ($C_{27}H_{27}NO_4$) C, H, N.

4,5α-Epoxy-3-methoxy-17-methyl-14*β*-(3-phenylpropyloxy)morphinan-6-one (7). A mixture of **6** (6.3 g, 14.6 mmol) and Pd/C (0.3 g, 20%) in acetic acid (200 mL) was hydrogenated at 30 psi and room temperature for 3 h. The catalyst was filtered off, and the filtrate was evaporated. The oily residue was then dissolved in H_2O and basified to pH 9 with NH_4OH. The product was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (3 × 70 mL), dried (Na_2SO_4), and evaporated to give a yellow oil, which was crystallized from MeOH to afford **7** as colorless crystals (4.9 g, 78%): mp 116−119 °C; ^{1}H NMR ($CDCl_3$) δ 7.35−7.15 (m, 5H ar, phenyl), 6.68 (d, 1H ar, $^3J_{1/2}$ = 8.2 Hz, CH-2), 6.60 (d, 1H ar, $^3J_{1/2}$ = 8.2 Hz, CH-1), 4.63 (s, 1H, CH-5), 3.89 (s, 3H, O−CH_3), 2.34 (s, 3H, N−CH_3); MS *m*/*z* (EI) 433 $[M]^+$. Anal. ($C_{27}H_{31}NO_4$) C, H, N.

7,8-Dihydro-14*β*-(3-phenylpropyloxy)norcodeinone Hydrochloride (8·HCl). A mixture of **7** (5.0 g, 11.5 mmol), $NaHCO_3$ (6.8 g, 80.9 mmol), ethyl chloroformate (7.5 mL, 67.5 mmol), and EtOH-free $ClCH_2CH_2Cl$ (30 mL) was stirred under reflux conditions for 17 h. The inorganic material was filtered off, and the filtrate was evaporated to give the carbamate derivative as a brown oil, which was not further purified and characterized. This oil was dissolved in MeOH (100 mL) and heated to reflux for 1 h. Evaporation and crystallization from acetone afforded **8**·HCl (4.9 g, 93%) as colorless crystals: mp >220 °C (dec); ^{1}H NMR ($CDCl_3$) δ 10.55/8.68 (2s, 2H, NH^+-17), 7.28−7.10 (m, 5H, phenyl), 6.75 (d, 1H, *J* = 8.3 Hz, CH-2), 6.71 (d, 1H, *J* = 8.3 Hz, CH-1), 4.41 (s, 1H, CH-5), 3.89 (s, 3H, 3-O−CH_3); MS *m*/*z* (EI) 419 $[M]^+$.

17-Allyl-4,5α-epoxy-3-methoxy-14*β*-(3-phenylpropyloxy)-morphinan-6-one Hydrochloride (9·HCl). A suspension of **8**·HCl (2.0 g, 4.8 mmol), K_2CO_3 (4.0 g, 28.9 mmol), and allyl bromide (0.6 mL, 6.6 mmol) in dry DMF (15 mL) was heated at 80 °C for 7 h. Then H_2O (200 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined CH_2Cl_2 portions were washed with H_2O (3 × 100 mL) and brine (2 × 100 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a crude oil that was chromatographed (silica gel, CH_2Cl_2/MeOH/NH_4OH (conc), 250:2:0.5), dissolved in ether, and converted into the hydrochloride salt. Recrystallization from 2-propanol afforded **9**·HCl (1.5 g, 69%) as colorless crystals: mp 129−130 °C; ^{1}H NMR (DMSO-d_6) δ 8.98 (s, 1H, NH^+-17), 7.30−7.18 (m, 5H, phenyl), 6.89 (d, 1H, *J* = 8.4 Hz, CH-2), 6.83 (d, 1H, *J* = 8.4 Hz, CH-1), 6.05−5.73 (m, 1H, NH^+−CH_2−C*H*=H_2), 5.69 (d, 1H, $^3J_{trans}$ = 18 Hz, NH^+−CH_2−CH=CHH_{cis}), 5.57 (d, 1H, $^3J_{cis}$ = 9.8 Hz, NH^+−CH_2−CH=CHH_{trans}), 4.94 (s, 1H, CH-5), 4.07 (ps-d, 1H, CH-9), 3.81 (s, 3H, 3-O−CH_3); MS *m*/*z* (CI) 460 $[M + 1]^+$. Anal. ($C_{29}H_{34}NO_4Cl$·$2H_2O$) C, H, N.

17-Cyclopropylmethyl-4,5α-epoxy-3-methoxy-14*β*-(3-phenylpropyloxy)morphinan-6-one Hydrochloride (10·HCl). Following the procedure described for **9**·HCl, a suspension of compound **8**·HCl (1.5 g, 3.6 mmol), K_2CO_3 (3.0 g, 21.7 mmol), and cyclopropylmethyl bromide (1.0 mL, 6.6 mmol) in dry DMF (10 mL) was heated at 80 °C for 4 h. Purification by column chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH (conc), 250:2:0.5) followed by formation of the hydrochloride salt from Et_2O gave **10**·HCl (0.6 g, 53%) as colorless crystals: mp 130−133 °C; ^{1}H NMR (DMSO-d_6) δ 8.30 (s, 1H, NH^+-17), 7.31−7.18 (m, 5H, phenyl), 6.88 (d, 1H, *J* = 8.4 Hz, CH-2), 6.78 (d, 1H, *J* = 8.4 Hz, CH-1), 4.96 (s, 1H, CH-5), 4.51 (ps-d, 1H, CH-9), 3.81 (s, 3H, 3-O−C*H*$_3$), 0.80−0.40 (m, 5H, *c*-propyl); MS *m*/*z* (EI) 473 $[M + 1]^+$. Anal. ($C_{29}H_{34}NO_4Cl$·$1H_2O$) C, H, N.

17-Cyclobutylmethyl-4,5α-epoxy-3-methoxy-14*β*-(3-phenylpropyloxy)morphinan-6-one Hydrochloride (11·HCl). Following the procedure described for **9**·HCl, a suspension of compound **8**·HCl (0.5 g, 1.2 mmol), K_2CO_3 (1.0 g, 7.2 mmol), and cyclobutylmethyl bromide (0.6 mL, 5.3 mmol) in dry DMF (7 mL) was heated at 80 °C for 24 h. Purification by column chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH (conc), 250:2:0.5) followed by formation of the hydrochloride salt from Et_2O gave **11**·HCl (0.4 g, 69%) as colorless crystals: mp 128−133 °C; ^{1}H NMR (DMSO-d_6) δ 8.48 (s, 1H, NH^+-17), 7.30−7.15 (m, 5H, phenyl), 6.87 (d, 1H, *J* = 8.4 Hz, CH-2), 6.77 (d, 1H, *J* = 8.4 Hz, CH-1), 4.93 (s, 1H, CH-5), 4.04 (ps-d, 1H, CH-9), 3.81 (s, 3H, 3-O−CH_3); MS *m*/*z* (CI) 488 $[M + 1]^+$. Anal. ($C_{31}H_{38}NO_4Cl$·$1.75H_2O$) C, H, N.

4,5α-Epoxy-3-methoxy-17-(2-methyltetrahydrofurfuryl)-14*β*-(3-phenylpropyloxy)morphinan-6-one Hydrochloride (12·HCl). Following the procedure described for **9**·HCl, a suspension of compound **8**·HCl (1.0 g, 2.4 mmol), K_2CO_3 (0.6 g, 4.4 mmol), and (±)-tetrahydrofurfuryl chloride (5.0 mL, 0.7 mmol) was heated at 150 °C for 15 h. Purification by column chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH (conc), 250:1.5:0.5 → 250:3.5:0.5) followed by formation of the hydrochloride salt from Et_2O gave **12**·HCl (0.6 g, 48%) as colorless crystals: mp 121−123 °C; ^{1}H NMR (DMSO-d_6) δ 8.18/7.64 (2s, 2 × 0.5H, NH^+-17, 2 epimeres 1:1), 7.08−6.96 (m, 5H, phenyl), 6.68−6.52 (m, 2H, CH-2, CH-1), 4.75, 4.73 (2s, 2 × 0.5H, CH-5); MS *m*/*z* (CI) 504 $[M + 1]^+$. Anal. ($C_{31}H_{38}NO_5Cl$·$0.5H_2O$) C, H, N.

4,5α-Epoxy-3-methoxy-17-(2-phenylethyl)-14*β*-(3-phenylpropyloxy)morphinan-6-one Hydrochloride (13·HCl). Following the procedure described for **9**·HCl, a suspension of compound **8**·HCl (1.0 g, 2.4 mmol), K_2CO_3 (3.0 g, 21.7 mmol), and 2-phenylethyl bromide (1.2 mL, 8.8 mmol) in dry DMF (10 mL) was heated at 80 °C for 12 h. Purification by column chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH (conc), 250:2:0.5) followed by formation of the hydrochloride salt from Et_2O gave **13**·HCl (0.5 g, 36%) as colorless crystals: mp 128−130 °C; ^{1}H NMR (DMSO-d_6) δ 8.84 (s, 1H, NH^+-17), 7.39−7.17 (m, 10H, 2 × phenyl), 6.89 (d, 1H, *J* = 8.2 Hz, CH-2), 6.79 (d, 1H, *J* = 8.4 Hz, CH-1), 4.95 (s, 1H, CH-5), 4.44 (ps-d, 1H, CH-9), 3.81 (s, 3H, 3-O−CH_3); MS *m*/*z* (CI) 524 $[M + 1]^+$. Anal. ($C_{29}H_{34}NO_4Cl$·$1H_2O$) C, H, N.

17-Allyl-4,5α-epoxy-3-hydroxy-14*β*-(3-phenylpropyloxy)-morphinan-6-one Hydrochloride (14·HCl). A solution of **9**·HCl (1.5 g, 3.0 mmol) in 48% HBr solution (5 mL) was refluxed for 15 min. Upon cooling, the solution was basified to pH 9 with concentrated NH_4OH and extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with H_2O (3 × 50 mL) and brine (2 × 50 mL), dried (Na_2SO_4), and evaporated. Purification by column chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH (conc), 250:2:0.5) followed by formation of the hydrochloride salt from Et_2O yielded **14**·HCl (0.5 g, 34%) as colorless crystals: mp >205 °C (dec); ^{1}H NMR (DMSO-d_6) δ 9.51 (s, 1H, 3-OH), 8.81 (s, 1H, NH^+-17), 7.30−7.16 (m, 5H, phenyl), 6.71 (d, 1H, *J* = 8.0 Hz, CH-2), 6.64 (d, 1H, *J* = 8.0 Hz, CH-1), 6.05−5.80 (m, 1H, N^+CH_2C*H*=H_2), 5.68 (d, 1H, $^3J_{trans}$ = 16 Hz, NH^+−CH_2−CH=CHH_{cis}), 5.55 (d, 1H, $^3J_{cis}$ = 10 Hz, NH^+−CH_2−CH=CHH_{trans}), 4.87 (s, 1H, CH-5), 4.04 (ps-d, 1H, CH-9); MS *m*/*z* (CI) 446 $(M + 1]^+$. Anal. ($C_{28}H_{32}NO_4Cl$·$0.75H_2O$) C, H, N.

17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14*β*-(3-phenylpropyloxy)morphinan-6-one Hydrochloride (15·HCl). This compound was prepared in 34% yield starting from **10**·HCl using the procedure described for **14**·HCl. Recrystallization of **15**·HCl from 2-propanol gave colorless crystals: mp 175−178 °C; ^{1}H NMR (DMSO-d_6) δ 9.52 (s, 1H, 3-OH), 8.20 (s, 1H, NH^+-17), 7.30−7.18 (m, 5H, phenyl), 6.71 (d, 1H, *J* = 8.0 Hz, CH-2), 6.64 (d, 1H, *J* = 8.0 Hz, CH-1), 4.89 (s, 1H, CH-5), 4.50 (ps-d, 1H, CH-9); MS *m*/*z* (CI) 460 $[M + 1]^+$. Anal. ($C_{29}H_{34}NO_4Cl$·$0.75H_2O$) C, H, N.

17-Cyclobutylmethyl-4,5α-epoxy-3-hydroxy-14*β*-(3-phenylpropyloxy)morphinan-6-one Hydrochloride (16·HCl). This compound was prepared in 24% yield starting from **11**·HCl using the procedure described for **14**·HCl: mp >227 °C (dec) (Et_2O); ^{1}H NMR (DMSO-d_6) δ 9.51 (s, 1H, 3-OH), 8.30 (s, 1H, NH^+-17), 7.29−7.18 (m, 5H, phenyl), 6.70 (d, 1H, *J* = 8.4 Hz, CH-2), 6.63 (d, 1H, *J* = 8.3 Hz, CH-1), 4.86 (s, 1H, CH-5), 3.99 (ps-d, 1H, CH-9); MS *m*/*z* (CI) 474 $[M + 1]^+$. Anal. ($C_{30}H_{36}NO_4Cl$·$0.75H_2O$) C, H, N.

4,5α-Epoxy-3-hydroxy-17-(2-methyltetrahydrofurfuryl)-14β-(3-phenylpropyloxy)morphinan-6-one Hydrochloride (17·HCl). This compound was prepared in 36% yield starting from **12**·HCl using the procedure described for **14**·HCl: mp 170−172 °C (Et_2O); ^{1}H NMR (DMSO-d_6) δ 9.45 (s, 1H, 3-OH), 8.45, 7.85 (2s, 2 × 0.5H, NH^+-17, epimeres 1:1), 7.30−7.21 (m, 5H, phenyl), 6.70−6.65 (m, 2H, CH-1, CH-2), 4.90/ 4.87 (2s, 2 × 0.5H, CH-5, epimeres 1:1); MS *m*/*z* (CI) 490 $[M + 1]^+$. Anal. ($C_{30}H_{36}NO_5Cl·1H_2O$) C, H, N.

4,5α-Epoxy-3-hydroxy-17-(2-phenylethyl)-14β-(3-phenylpropyloxy)morphinan-6-one Hydrochloride (18·HCl). This compound was prepared in 15% yield starting from **13**·HCl using the procedure described for **14**·HCl: mp >218 °C (dec) (Et_2O); ^{1}H NMR (DMSO-d_6) δ 9.51 (s, 1H, 3-OH), 8.80 (s, 1H, NH^+-17), 7.39−7.17 (m, 10H, 2 × phenyl), 6.72 (d, 1H, J = 8.4 Hz, CH-2), 6.66 (d, 1H, J = 8.3 Hz, CH-1), 4.87 (s, 1H, CH-5), 4.41 (ps-d, 1H, CH-9); MS *m*/*z* (CI) 510 $[M + 1]^+$. Anal. ($C_{33}H_{36}NO_4Cl·0.75H_2O$) C, H, N.

4,5α-Epoxy-3-hydroxy-14β-(3-phenylpropyloxy)-17-(*n*-propyl)morphinan-6-one Hydrochloride (19·HCl). A mixture of **14**·HCl (0.3 mg, 0.6 mmol), Pd/C (35 mg, 10%), and MeOH (50 mL) was hydrogenated at 30 psi and room temperature for 3 h. The catalyst was filtered off, and the filtrate was evaporated. Purification as the hydrochloride salt from Et_2O gave **19**·HCl as colorless crystals (0.3 g, 95%): mp 162−163 °C; ^{1}H NMR (DMSO-d_6) δ 9.51 (s, 1H, 3-OH), 8.50 (s, 1H, NH^+-17), 7.30−7.18 (m, 5H ar, phenyl), 6.75 (d, 1H ar, $^3J_{1/2}$ = 8.4 Hz, CH-2), 6.64 (d, 1H ar, $^3J_{1/2}$ = 8.4 Hz, CH-1), 4.86 (s, 1H, CH-5), 4.25 (ps-d, 1H, CH-9), 3.81 (s, 3H, N−$CH_2CH_2CH_3$); MS *m*/*z* (CI) 448.3 $[M + 1]^+$. Anal. ($C_{28}H_{34}NO_4Cl·0.5H_2O$) C, H, N.

Opioid Receptor Binding Assays. Details of the binding assay have been described previously.[17,19] Aliquots of a membrane preparation were incubated with [^{3}H]diprenorphine (0.3 nM) in the presence of different concentrations of the drug under investigation at 25 °C for 1 h. Specific (i.e., opioid-receptor-related) binding was determined as the difference in binding obtained in the absence and presence of 10 μM naloxone. The potency of the drugs in displacing the specific binding of [^{3}H]diprenorphine was determined from data using Graphpad Prism (GraphPAD, San Diego, CA) and converted into K_i values.[20] Opioid binding was performed in membranes from C_6 rat glioma cells expressing recombinant μ[21] or δ[22] (rat) and CHO cells expressing the recombinant κ[23] (human). The affinity (K_d) values of [^{3}H]diprenorphine at the receptors were the following: μ (0.15 nM), δ (0.45 nM), κ (0.25 nM).

In Vivo Assays. General Methods. ICR male mice (Harlan Sprague-Dawley, Inc., Indianapolis, IN) weighing 20−30 g were used, and each animal was tested only once. All drugs were administered by the subcutaneous route. At least 3 doses were tested, and 6−10 animals per dose were used.

Tail-Flick Test (TF) and Tail-flick vs Morphine (TF vs M) Assays.[24−26] The original procedures and their modifications have been described earlier.

Hot-Plate (HP) Assay. The original procedures and their modifications have been previously described.[26−28]

Phenylquinone Abdominal Writhing (PPQ) Assay. The original procedures and their modifications have been previously described.[26,29,30]

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