Synthesis and Biological Evaluation of 14-Alkoxymorphinans. 22.[1] Influence of the 14-Alkoxy Group and the Substitution in Position 5 in 14-Alkoxymorphinan-6-ones on in Vitro and in Vivo Activities

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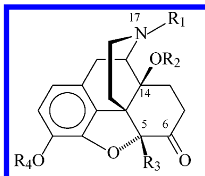
Novel 14-alkoxy-substituted (e.g. allyloxy, benzyloxy, naphthylmethoxy) morphinan-6-one derivatives were synthesized and biologically evaluated. Compounds **6**−**9** and **11** displayed affinities in the subnanomolar range to μ opioid receptors which were comparable to 14-*O*-methyloxymorphone (**1**) and 14-methoxymetopon (**3**), and higher than oxymorphone (**2**). Opioid binding affinity was sensitive to the character and length of the substituent in position 14. In smooth muscle preparations they behaved as potent agonists. Antinociceptive potencies of compounds **6**−**11** in the hot-plate test after sc administration in mice were considerably greater than the potency of morphine. In the colonic propulsion test, the most potent analgesic compound **7** showed negligible constipating activity at the analgesic dose. 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. Introduction of a 5-methyl group has no significant effect on in vitro biological activities, but resulted in decreased antinociceptive potency.

Introduction

Morphinans play an important role among therapeutically valuable opioids. They include powerful pain relieving agents such as naturally occurring alkaloids (e.g. morphine, codeine), semisynthetic derivatives (e.g. oxycodone, oxymorphone, buprenorphine), and synthetic analogues (e.g. levorphanol, butorphanol). The oxymorphone derivatives naloxone and naltrexone are clinically useful opioid antagonists. Naloxone reverses the potentially lethal respiratory depression caused by neurolept analgesia or opioid overdosage. Naltrexone is being used for maintenance of former opioid addicts after narcotic withdrawal and for the treatment of alcoholism.[2]

Introduction of a 14-alkoxy group into *N*-methylmorphinan-6-ones was described to significantly increase the antinociceptive potency.[2] Thus, 14-*O*-methyloxymorphone (compound **1**; Figure 1) was found to possess ca. 40-fold higher antinociceptive potency than its 14-hydroxy counterpart oxymorphone (**2**).[3] The 5-methyl analogue of **1**, namely 14-methoxymetopon (compound **3**; Figure 1), also exhibits high antinociceptive potency which is 24- to 20 000-fold greater than that of morphine following systemic administration, depending upon the analgesic test (hot-plate, tail-flick, or acetic acid writhing test) and the animal species used.[4−8] This enhanced potency is markedly increased with either spinal or supraspinal administration, where its analgesic potency is more than 1 million-fold greater than that of morphine.[8] Moreover, 14-methoxymetopon (**3**) was reported to elicit minimal physical dependence and tolerance compared to morphine.[4] It shows significantly lower potential to induce respiratory depression, hypotension, and bradycardia than sufentanil, another highly potent μ opioid analgesic.[9] In addition, the effects of 14-methoxymetopon on gastrointestinal transit, a potential measure of the ability of an opioid drug to produce constipation clinically, were far less pronounced than those observed with morphine.[8] The analogue 14-



1 $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$ (14-*O*-methyloxymorphone)
2 $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$ (oxymorphone)
3 $R_1 = R_2 = R_3 = CH_3$, $R_4 = H$ (14-methoxymetopon)
4 $R_1 = R_3 = CH_3$, $R_2 = C_2H_5$, $R_4 = H$ (14-ethoxymetopon)
5 $R_1 = R_3 = CH_3$, $R_2 = (CH_2)_3Ph$, $R_4 = H$ (PPOM)
6 $R_1 = CH_3$, R_2 = allyl, $R_3 = R_4 = H$
7 $R_1 = CH_3$, $R_2 = CH_2Ph$, $R_3 = R_4 = H$
8 $R_1 = R_3 = CH_3$, $R_2 = CH_2Ph$, $R_4 = H$
9 $R_1 = CH_3$, R_2 = 1-naphthylmethyl, $R_3 = R_4 = H$
10 $R_1 = CH_3$, $R_2 = CH_2Ph$-2,6-diCl, $R_3 = R_4 = H$
11 $R_1 = (CH_2)_2Ph$, $R_2 = C_2H_5$, $R_3 = CH_3$, $R_4 = H$
18 $R_1 = R_4 = CH_3$, $R_2 = CH_2Ph$, $R_3 = H$

Figure 1.

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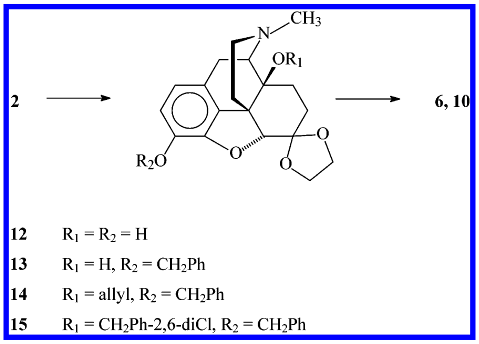
Scheme 1



12 $R_1 = R_2 = H$
13 $R_1 = H, R_2 = CH_2Ph$
14 R_1 = allyl, $R_2 = CH_2Ph$
15 $R_1 = CH_2Ph$-2,6-diCl, $R_2 = CH_2Ph$

ethoxymetopon (**4**) was reported to produce a slightly lower analgesic effect and to have similar low physical dependence scores and tolerance when compared to **3**.[4] The 5-demethyl analogue 14-*O*-methyloxymorphone (**1**) shows somewhat higher analgesic potency but more pronounced physical dependence.[3] The 14-phenylpropoxy analogue of 14-methoxymetopon (PPOM; compound **5**) exhibits an extremely high antinociceptive potency, which is considerably greater than that of etorphine in different analgesic tests in mice.[10]

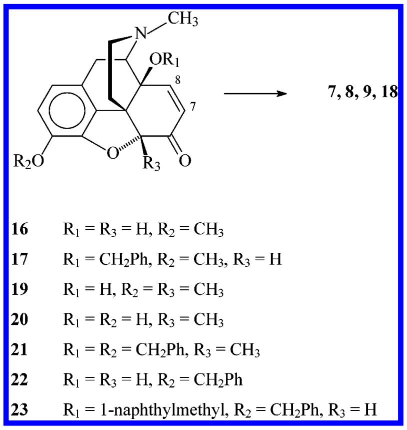
Further studies to increase our understanding of the μ opioid receptor system and its involvement in physiological processes require the development of nonpeptide ligands with high affinity and increased μ selectivity. Our approach toward this goal was to modify the structure and to investigate the structure−activity relationship of the newly developed compounds belonging to the 14-alkoxymorphinan-6-one series. In the present study, we mainly assessed the character and length of the substituent in position 14 on opioid affinity and selectivity. Furthermore, we investigated the influence of selected substituents in position 14 on in vitro agonist activity, antinociceptive potency and inhibition of gastrointestinal motility. We have synthesized *N*-methylmorphinan-6-ones substituted in position 14 with allyloxy (**6**), benzyloxy (**7**, **8**), 1-naphthylmethoxy (**9**), and 2,6-dichlorobenzyloxy (**10**) (Figure 1). In addition, the 14-ethoxy-substituted *N*-(2-phenlyethyl)morphinan-6-one **11** was prepared to investigate the influence of a *N*-phenylethyl group in this class of compounds. Moreover, the effect of a methyl group in position 5 on in vitro and in vivo activities was examined.

Chemistry

14-*O*-Allyloxymorphone (**6**) was prepared starting from oxymorphone (**2**). Prior to 14-O-allylation, the 3-OH and 6-keto groups were protected. First, ketal **12** was formed, which was 3-O-benzylated (**13**) and further 14-O-allylated with allyl bromide in *N,N*-dimethylformamide (DMF) in the presence of NaH as base to give compound **14**. Acid hydrolysis with HCl/MeOH yielded compound **6** (Scheme 1). The 2,6-dichlorobenzyloxy-substituted *N*-methylmorphinan-6-one **10** was synthesized analogously from 3-O-benzylated derivative **13** via compound **15** (Scheme 1).

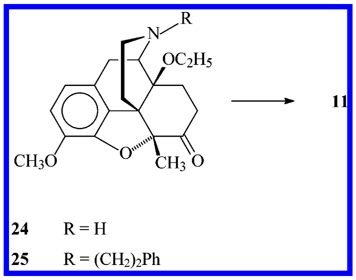
14-*O*-Benzyloxymorphone (**7**) was synthesized starting from 14-hydroxycodeinone (**16**), which was 14-O-benzylated to give compound **17** (Scheme 2). Catalytic hydrogenation over Pd/C afforded 14-*O*-benzyloxycodone (**18**) which was 3-O-demethylated with BBr_3 in CH_2Cl_2 to yield **7**. 14-Benzyloxymetopon (**8**) was prepared from 14-hydroxy-5-methylcodeinone (**19**)[11] employing a different route as compared to the synthesis of compound **7** (Scheme 2). Thus, compound **19** was first 3-O-demethylated using 48% HBr solution to give phenol **20** which was 3,14-bis-O-benzylated to afford compound **21**. The 3-*O*-benzyl protecting group was removed by catalytic hydrogenation over Pd/C to yield compound **8**.

Scheme 2



16 $R_1 = R_3 = H, R_2 = CH_3$
17 $R_1 = CH_2Ph, R_2 = CH_3, R_3 = H$
19 $R_1 = H, R_2 = R_3 = CH_3$
20 $R_1 = R_2 = H, R_3 = CH_3$
21 $R_1 = R_2 = CH_2Ph, R_3 = CH_3$
22 $R_1 = R_3 = H, R_2 = CH_2Ph$
23 R_1 = 1-naphthylmethyl, $R_2 = CH_2Ph, R_3 = H$

Scheme 3



24 R = H
25 $R = (CH_2)_2Ph$

The synthesis of compound **9** was accomplished starting from 3-O-benzylated 7,8-dehydromorphinan **22**,[12] which was treated with 1-bromomethylnaphthalene in DMF in the presence of NaH to give compound **23**. Catalytic hydrogenation over Pd/C yielded 14-*O*-(1-naphthylmethyl)oxymorphone (**9**) (Scheme 2).

The *N*-phenylethyl derivative **11** was prepared from 14-ethoxy-substituted N-nor morphinan **24**[13] by N-alkylation with 2-phenylethyl bromide (**24**) followed by ether cleavage of **25** with 48% HBr.

Results and Discussion

Opioid Receptor Binding Affinities. Opioid receptor binding affinities of compounds **6**−**11** were determined using previously described procedures.[14] The binding affinities to μ and δ receptors were determined by inhibition of binding of [^{3}H][D-Ala^2,Me-Phe^4,Gly-ol^5]-enkephalin ([^{3}H]DAMGO) and [^{3}H][Ile^{5,6}]deltorphin II to rat brain membranes. The affinities of the compounds to κ receptors were determined by displacement of [^{3}H]-U69,593 using guinea pig brain membranes. The μ, δ, and κ opioid receptor binding affinities expressed as inhibition constant (K_i) and selectivity ratios for compounds **6**−**11** and reference compounds are shown in Table 1.

As expected and in agreement with the previous determinations of the positive influence of 14-alkoxy substituents in morphinan-6-ones,[2,3,15] all of the tested 14-alkoxymorphinans, except **10**, showed very high μ opioid receptor affinity, with K_i values ranging between

Table 1. Opioid Receptor Binding Affinities and Selectivities of Compounds **6**−**11** and Reference Compounds

	K_i (nM) ± SEM			selectivity ratio	
compound	[^{3}H]DAMGO (μ)[a]	[^{3}H][Ile^{5,6}]deltorphin II (δ)[a]	[^{3}H]U69,593 (κ)[b]	δ/μ	κ/μ
6	0.61 ± 0.02	36.0 ± 1.5	33.8 ± 1.9	59	55
7	0.12 ± 0.01	2.14 ± 0.13	1.18 ± 0.11	18	10
8	0.18 ± 0.01	3.67 ± 0.40	2.46 ± 0.32	20	14
9	0.18 ± 0.02	2.92 ± 0.35	0.92 ± 0.08	16	5.1
10	10.3 ± 1.3	152 ± 15	33.2 ± 3.6	15	3.2
11	0.16 ± 0.02	3.14 ± 0.41	83.2 ± 5.4	20	520
1[c]	0.10 ± 0.01	4.80 ± 0.22	10.2 ± 2.0[a]	48	102
3[d]	0.15 ± 0.01	13.3 ± 0.2	25.2 ± 4.9[a]	89	168
oxymorphone (**2**)	0.97 ± 0.05	80.5 ± 5.5	61.6 ± 1.2	83	51
morphine[d]	6.55 ± 0.74	217 ± 19	113 ± 9[a]	33	17

[a] Rat brain membranes were used. [b] Guinea pig brain membranes were used. [c] Data taken from ref 24. [d] Data taken from ref 23.

0.12 and 0.61 nM (Table 1). Compounds **6**−**9** and **11** displayed a 10- to 54-fold enhanced affinity to the μ receptor in comparison to morphine, and comparable μ affinity to 14-*O*-methyloxymorphone (**1**) and 14-methoxymetopon (**3**). Moreover, they showed higher μ affinity than oxymorphone (**2**). Comparing 14-*O*-methyloxymorphone (**1**) with its 14-hydroxy analogue oxymorphone (**2**), it became apparent that a 14-methoxy group increased the affinity to opioid receptors in binding assays, as reported earlier using [^{3}H]naloxone.[3]

Following the pattern of structure−activity relationships, compounds **6** and **7** had comparable affinity to the μ receptor, but different binding affinities to δ and κ sites. It appears that an allyloxy group in position 14 is not favorable for interaction with δ and κ receptors, thus leading to an enhancement in μ selectivity. An examination of the affinities of the 14-arylalkoxy target compounds revealed that 2,6-dichloro substitution at the aromatic ring of the benzyloxy group in compound **10** has a detrimental effect on the affinity to all three opioid receptors compared to the 14-benzyloxy analogue **7** (Table 1). However, a 1-naphthylmethoxy group in position 14 in compound **9** did not affect the interaction with μ, δ, and κ receptors, displaying similar binding affinities as the benzyloxy-substituted counterpart **7**. We have found that in the series of morphinan-6-ones, the presence of larger groups such as 14-*O*-phenylpropyl (e.g. PPOM; compound **5**) markedly increases binding affinities to δ and κ opioid receptors while retaining the high affinity to the μ receptor.[10,16] Our present findings provide further evidence that opioid binding affinity is sensitive to the character and length of the substituent in position 14.

When comparing compounds **1** and **7** to their 5-methyl analogues **3** and **8**, respectively, it became apparent that the presence of a methyl group in position 5 has no major effect on μ affinity, while only a slight decrease in binding to δ and κ receptors was observed. Moreover, the 14-methoxy-substituted compounds **1** and **3** exhibited higher δ/μ and κ/μ selectivity ratios than the 14-benzyloxy-substituted **7** and **8**, indicating that a 14-methoxy group is superior to a 14-benzyloxy group regarding to μ selectivity in this class of compounds (Table 1).

Derivative **11** exhibited very high affinities to μ and δ opioid receptors, 0.16 and 3.14 nM, respectively, being comparable to those of 14-*O*-methyloxymorphone (**1**), but showed about 8-fold reduced affinity to the κ site. Thus, introduction of a *N*-phenylethyl group did not significantly alter the interaction with μ and δ receptors, but affected binding to the κ receptor.

Table 2. Opioid Agonist Activities of Compounds **6**−**11** and Reference Compounds in GPI and MVD Preparations

	IC$_{50}$ (nM) ± SEM		
compound	GPI	MVD	IC$_{50}$ MVD/IC$_{50}$ GPI
6	17.6 ± 2.1	63.0 ± 9.0	3.6
7	0.9 ± 0.1	1.5 ± 0.2	1.7
8	0.5 ± 0.1	2.3 ± 0.3	4.6
9	0.9 ± 0.1	0.8 ± 0.1	0.9
10	1000 ± 110	209 ± 25	0.2
11	1.9 ± 0.3	9.7 ± 1.1	5.1
1	2.0 ± 0.3	30.5 ± 5.0	15
3	6.1 ± 0.8	24.4 ± 3.1	4.0
morphine	311 ± 29	1600 ± 121	5.1

Table 3. Antinociceptive Potencies in the Hot-Plate Test and Colonic Bead Expulsion in Mice of Compounds **6**−**11** and Reference Compounds

compound	HP,[a] AD$_{50}$ (nmol/kg, sc)[c]	CBE,[b] ED$_{50}$ (nmol/kg, sc)[c]	ED$_{50}$ CBE/AD$_{50}$ HP
6	35 (27−46)	37 (27−51)	1.1
7	9.6 (9.0−10.3)	27 (25−28)	2.8
8	65 (60−71)	74 (69−80)	1.1
9	14.4 (14.2−14.6)	11.8 (8.4−12.9)	0.8
10	1640 (1040−2570)	2491 (2487−2494)	1.5
11	109 (81−146)	121 (100−148)	1.1
1	53 (48−58)	22 (21−24)	0.4
3	280 (273−285)	n.t.	–
morphine	6690 (4468−9348)	7622 (6336−9170)	1.1

[a] HP = hot-plate test. [b] CBE = colonic bead expulsion. [c] Effective dose 50% (95% confidence limits).

Biological Activities. Compounds **6**−**11** were further evaluated for the agonist activity in vitro on smooth muscle preparations and in vivo for the analgesic and constipating effects. The results of in vitro bioassays using guinea pig ileum (GPI) and mouse vas deferens (MVD) preparations[17,18] (Table 2) are in qualitative agreement with the binding data. Antinociceptive potencies of compounds **6**−**11** after subcutaneous (sc) administration were assessed in the hot-plate test (HP) in mice.[19]

As shown in Table 2, introduction of different substituents in position 14 in the morphinan-6-ones **6**−**9** and **11** afforded compounds that are potent agonists in the GPI (IC$_{50}$ = 0.5−17.6 nM) and in the MVD (IC$_{50}$ = 0.8−63 nM) and elicited analgesic potencies 60- to 700-fold higher than morphine. The 2,6-dichlorobenzyloxy-substituted derivative **10** showed a significant decrease in agonistic activity in the GPI and in analgesic potency (Tables 2 and 3). Substitution in position 14 with allyloxy (compound **6**) produced about 2- and 8-fold decrease in potency in the MVD and the GPI, respectively, when compared to the methoxy-substituted derivative **1** (Table 2), but left the analgesic potency unaffected (Table 3). However, the presence of a 14-benzyloxy group in **7** and a 14-(1-naphthylmethoxy) substituent in **9** yielded the most potent agonists in the GPI and MVD, which could be due to their very high affinities to all three opioid receptors, μ, δ, and κ. Simultaneous stimulation of the different opioid receptors could cooperate in the inhibition of the electrically stimulated twitch of the smooth muscle preparations produced by compounds **7** and **9**. Derivatives **7** and **9** also displayed the highest antinociceptive potency being about 700- and 460-fold, respectively, more potent than morphine, and about 4- to 5-fold more potent than 14-*O*-methyloxymorphone (**1**) in the hot-plate test in mice (Table 3). Thus, introduction of a benzyloxy or a 1-naphthylmethoxy group compared to a methoxy group in position 14 leads to increased analgesic potency. In an earlier study,[3] it was shown that introduction of a 14-methoxy group in oxymorphone markedly enhanced the antinociceptive potency as assessed in the hot-plate test in mice after sc administration. Recently, we have reported that the introduction of a 14-phenylpropoxy group gives rise to extremely potent analgesics in morphinan-6-ones having a methyl, cyclopropylmethyl, or allyl group at the morphinan nitrogen.[10,16] Thus, it became apparent that 14-arylalkoxy substitution increases analgesic potency compared to 14-alkoxymorphinans such as 14-*O*-methyloxymorphone (**1**).

2,6-Dicholoro substitution at the aromatic ring of the benzyloxy group in position 14 led to compound **10** which was less potent as agonist in the MVD and in the GPI, and a weaker analgesic, as compared to the aromatic unsubstituted analogue **7** (Tables 2 and 3). The decrease in agonist activity and in antinociceptive potency of analogue **10** compared to **7** correlates very well with the decrease in affinities to all three opioid receptors as determined in binding assays (Table 1).

Methylation in position 5 of compound **1** resulted in analogue **3** which showed about the same agonist potency as **1** in the MVD and a 3-fold decrease in the potency in the GPI. In the case of the 14-benzyloxy-substituted derivative **7**, introduction of a 5-methyl group resulted in 14-benzyloxymetopon (**8**) with comparable potencies in both smooth muscle preparations, while a 7-fold decrease in antinociceptive potency of compound **8** was observed (Tables 2 and 3). A similar decrease in potency has been detected with compound **3**, the 5-methyl analogue of 14-*O*-methyloxymorphone (**1**). This indicates that the presence of a methyl group in position 5 alters the antinociceptive potency in this class of compounds, although it does not significantly affect the in vitro biological activities.

Replacement of the *N*-methyl group in compound **1** with a *N*-phenylethyl substituent in **11** left the binding affinities at μ and δ opioid receptors unchanged, and it did not significantly alter the in vitro agonist activity and the in vivo antinociceptive potency (Tables 2 and 3).

It is well-recognized that the μ opioid system plays a primary role in the inhibitory control of gastrointestinal (GI) motility, one of the most frequent adverse effects of opioid analgesics.[20] Colonic bead expulsion in mice (CBI) was used to assess the effect on GI motility after sc administration.[21,21] All tested opioid compounds produced a dose-related inhibition of CBE with ED_{50} values ranging between 11.8 and 2491 nmol/kg (Table 3). On the basis of the in vitro biological data, these compounds show increased interaction with the μ receptor, which can explain the inhibitory effect on colonic propulsion.

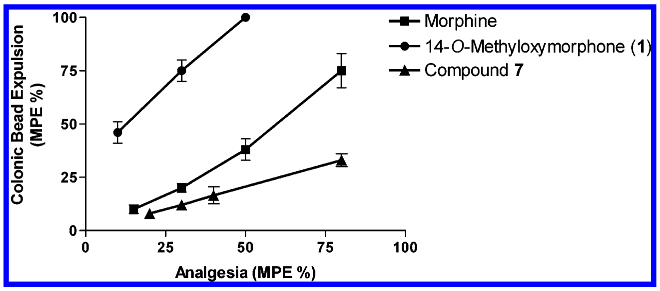


Figure 2. Analgesia versus colonic bead expulsion in mice of compound **7** and reference compounds.

The ratios of ED_{50} CBE vs AD_{50} HP were calculated, and the values around the unit indicate the induction of constipation at analgesic doses (Table 3). Interestingly, the most potent analgesic compound **7 (**ED_{50} CBE vs AD_{50} HP = 2.8) elicited negligible constipating activity at the analgesic dose (Figure 2). The 14-benzyloxy-substituted derivative **7** also appeared to be 2.5-fold less constipating than morphine and about 7-fold less constipating than 14-*O*-methyloxymorphone (**1**) after sc administration in mice. Compounds **6** and **8**−**11** showed similar constipating potency as morphine, but were about 1.5- to 3-fold less constipating than the reference compound **1**.

Conclusions

The present study on selected 14-alkoxy-substituted morphinan-6-ones 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, leading to qualitative and quantitative differences in biological and pharmacological activities.

Introduction of 14-alkoxy substitutents (e.g. allyloxy, benzyloxy, 1-naphthylmethoxy) led to compounds with high binding affinities to the μ receptor and generally potent agonist activities in smooth muscle preparations. Antinociceptive evaluation in the hot-plate test after sc administration in mice revealed that 14-arylalkoxy substitutents (benzyloxy, 1-naphthylmethoxy) are able to enhance considerably the antinociceptive potency in *N*-methylmorphinan-6-ones. A 14-allyloxy and a *N*-phenylethyl substituent had only minor influence on the analgesic potency. The 14-benzyloxy substitution gave rise to a compound which showed negligible constipating activity at the analgesic dose after sc administration. The 2,6-dichloro substitution of the 14-benzyloxy group decreased μ affinity, agonist and analgesic potencies. The presence of a methyl group in position 5 has no significant effect on μ affinity and in vitro agonist activities, but resulted in decreased antinociceptive potency compared to the 5-demethylated derivatives.

Taken together, the results of the present study indicate that the positions 5 and 14 of *N*-methylmorphinan-6-ones represent critical sites that could be a trigger to develop new compounds with increased μ affinity and/or selectivity and potent analgesic drugs with an improved side effect profile compared to currently available opioids.

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 measured using 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 (200 MHz) spectra were recorded using a Varian Gemini 200 spectrometer. Chemical shifts (δ) are reported in ppm (relative to $SiMe_4$ as internal standard), coupling constants (J) in Hz. Mass spectra were recorded with 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.

4,5α-Epoxy-3,14-dihydroxy-17-methylmorphinan-6-spiro-2′-(1,3-dioxolane) (12). A solution of oxymorphone (7.557 g, 19.76 mmol) and methanesulfonic acid (1.92 mL, 29.64 mmol) in 100 mL of ethylene glycol was stirred under N_2 at 80−90 °C (bath temperature) for 24 h. After addition of H_2O (200 mL) and alkalization with concentrated ammonia, the mixture was extracted with CH_2Cl_2 (1 × 60 mL, 2 × 20 mL). The combined organic layers were washed with H_2O (2 × 200 mL), dried (Na_2SO_4), and evaporated to give an oil which was treated with refluxing MeOH to afford crystalline material which was recrystallized twice from MeOH to yield 4.89 g (70%) of **12**: mp 252−254 °C. Anal. ($C_{19}H_{23}NO_5$) C, H, N.

3-Benzyloxy-4,5α-epoxy-14-hydroxy-17-methylmorphinan-6-spiro-2′-(1,3-dioxolane) (13). A mixture of **12** (4.5 g, 12.7 mmol), potassium carbonate (6.15 g, 44.45 mmol), benzyl bromide (1.8 mL, 15.24 mmol), and anhydrous DMF (38 mL) was stirred at 80−90 °C (bath temperature) for 42 h. The inorganic material was filtered off, and the filtrate was acidified with 2 N HCl (225 mL) and extracted with Et_2O (3 × 80 mL). The aqueous phase was alkalized with concentrated ammonia, extracted with CH_2Cl_2, washed with H_2O (2 × 80 mL) and brine (80 mL), dried (Na_2SO_4), and evaporated to yield 5.1 g of a brownish oily residue. Purification by column chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH 90:9:1) afforded a yellowish oil (2.34 g, 42%) of **13** which was used for the next synthetic step.

14-Allyloxy-3-benzyloxy-4,5α-epoxy-17-methylmorphinan-6-spiro-2′-(1,3-dioxolane) (14). NaH (1.22 g, 50.9 mmol) (obtained from 2.05 g of a 60% NaH dispersion in oil by washings with petroleum ether) was added to a solution of **13** (2.15 g, 4.94 mmol) in 15 mL of anhydrous DMF under N_2 at 0 °C (bath temperature) while stirring. After 20 min, allyl bromide (0.85 mL, 9.87 mmol) was added and the resulting mixture was stirred at room temperature for 6 h. Excess NaH was destroyed carefully by addition of small pieces of ice, and then the mixture was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (4 × 25 mL). The combined organic layers were washed with H_2O (3 × 35 mL) and brine (80 mL), dried (Na_2SO_4), and evaporated to yield 2.63 g (91%) of a reddish oil of **14** which was used without further purification for the next synthetic step.

14-Allyloxy-4,5α-epoxy-3-hydroxy-17-methylmorphinan-6-one Hydrochloride (6·HCl). A solution of **14** (2.44 g, 5.13 mmol) in MeOH (30 mL) and concentrated HCl (20 mL) was refluxed for 25 h and then poured on H_2O (15 mL). After alkalization with concentrated ammonia, the mixture was extracted with CH_2Cl_2 (1 × 40 mL, 2 × 15 mL), and the combined organic layers were washed with H_2O (2 × 15 mL) and brine (15 mL), dried (Na_2SO_4), and evaporated to give 1.53 g of a brown oil. Purification by column chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH 90:9:1) yielded a slightly red foam (610 mg) which was dissolved in Et_2O and treated with HCl/Et_2O to give crystalline material which was recrystallized from MeOH/Et_2O to afford 420 mg (22%) of pure **6**·HCl: mp 186−188 °C. Anal. ($C_{20}H_{23}NO_4\cdot HCl\cdot 1.1H_2O$) C, H, N.

3-Benzyloxy-14-(2′,6′-dichlorobenzyloxy)-4,5α-epoxy-17-methylmorphinan-6-spiro-2′-(1,3-dioxolane) (15). Compound **15** was prepared essentially by the procedure described for the synthesis of compound **14**. Yield **15**: 48%; mp 114−115 °C (MeOH). Anal. ($C_{33}H_{33}NO_5Cl_2\cdot 0.2MeOH$) C, H, N, Cl.

14-(2′,6′-Dichlorobenzyloxy)-4,5α-epoxy-3-hydroxy-17-methylmorphinan-6-one Hydrochloride (10·HCl). **10**·HCl was prepared essentially by the procedure described for the synthesis of **6**·HCl. Yield **10**·HCl: 48%; mp 187−189 °C (Et_2O). Anal. ($C_{24}H_{23}NO_4Cl_2\cdot HCl\cdot 1.3H_2O$) C, H, N.

14-Benzyloxycodeinone (14-Benzyloxy-4,5α-epoxy-7,8-didehydro-3-methoxy-17-methylmorphinan-6-one; 17). NaH (800 mg, 33.33 mmol) (obtained from 1.34 g of a 60% NaH dispersion in oil by washings with petroleum ether) was added to a solution of 14-hydroxycodeinone (**16**) (3.0 g, 9.57 mmol), in 120 mL of anhydrous DMF under N_2 at 0 °C (bath temperature) while stirring. After 20 min, benzyl bromide (1.71 mL, 14.44 mmol) was added and the resulting mixture was stirred at room temperature for 3 h. Excess NaH was destroyed carefully by addition of small pieces of ice, and then the mixture was diluted with H_2O (75 mL) and extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layers were washed with H_2O (3 × 50 mL), dried (Na_2SO_4), and evaporated to yield 4.28 g of a brownish semicrystalline residue, which was treated with 3 mL of boiling MeOH to yield 2.07 g (52%) of **17** (mp 170−177 °C). A small portion was recrystallized from MeOH: mp 177−182 °C. Anal. ($C_{25}H_{25}NO_4\cdot 0.3MeOH$) C, H, N.

14-*O*-Benzyloxycodone (14-Benzyloxy-4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one; 18). A mixture of **17** (1.0 g, 2.48 mmol), 10% Pd/C catalyst (150 mg), and EtOH (50 mL) was hydrogenated at room temperature and 35 psi for 4.5 h. The catalyst was filtered off, and the filtrate was evaporated. The crystalline residue (972 mg) was recrystallized from EtOH to yield 710 mg (72%) of **18**: mp 136−140 °C. Anal. ($C_{25}H_{27}NO_4$) C, H, N.

14-*O*-Benzyloxymorphone Salicylate (14-Benzyloxy-4,5α-epoxy-3-hydroxy-17-methylmorphinan-6-one Salicylate; 7·$C_7H_6O_3$). To a solution of **18** (1.0 g, 2.47 mmol) in 8 mL of CH_2Cl_2 was added a 1 M solution of BBr_3 in CH_2Cl_2 (14.8 mL) within 10 min at −15 °C (bath temperature) while stirring. After 5 min, 20 g of ice and 12 mL of concentrated ammonia were added and the resulting mixture was stirred at 0 °C (bath temperature) for 30 min. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated to yield 950 mg of a slightly brown foam which was purified by column chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH 90:9:1) to give 383 mg of **7** as a colorless foam which was dissolved in MeOH and converted into the salicylate (**7**·$C_7H_6O_3$) by addition of salicylic acid. Yield 374 mg (29%); mp 233−240 °C. Anal. ($C_{24}H_{25}NO_4\cdot C_7H_6O_3$) C, H, N.

14-Hydroxy-5-methylmorphinone Hydrobromide (7,8-Didehydro-4,5α-epoxy-3,14-dihydroxy-5,17-dimethylmorphinan-6-one Hydrobromide; 20·HBr). A solution of 14-hydroxy-5-methylcodeinone (**19**)[11] (2.7 g, 8.62 mmol) in 48% HBr solution (15 mL) was refluxed for 20 min. After the solution was evaporated, the residue (a brownish oil) was dissolved in MeOH and the solution was evaporated again. This procedure was repeated, the residue dissolved in a little MeOH, and Et_2O was added dropwise to obtain crystallization: 2.06 g (61%) of **20**·HBr was isolated. A small amount was recrystallized from MeOH/Et_2O to give an analytical sample: mp > 230 °C (dec). Anal. ($C_{18}H_{19}NO_4\cdot HBr\cdot 1.0H_2O$) C, H, N.

3-*O*-Benzyl-14-benzyloxy-5-methylmorphinone Hydrochloride (3,14-Dibenzyloxy-7,8-didehydro-4,5α-epoxy-5,-17-dimethylmorphinan-6-one Hydrochloride; 21·HCl). NaH (570 mg, 23.75 mmol) (obtained from 950 mg of a 60% NaH dispersion in oil by washings with petroleum ether) was added to a solution of **20**·HBr (850 mg, 2.16 mmol) in 25 mL of anhydrous DMF under N_2 at 0 °C (bath temperature) while stirring. After 20 min, benzyl bromide (0.64 mL, 5.4 mmol) was added and the resulting mixture was stirred at room temperature for 4 h. Excess NaH was destroyed carefully by addition of small pieces of ice, and then the mixture was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (1 × 150 mL, 2 × 50 mL). The combined organic layers were washed with H_2O (3 × 200 mL), dried (Na_2SO_4), and evaporated to yield 1.09 g of a brown oil which was converted into the hydrochloride salt in anhydrous Et_2O by addition of Et_2O/HCl to afford 937 mg (82%) of **21**·HCl: mp 150 °C. Anal. ($C_{32}H_{33}NO_4 \cdot HCl \cdot 1.0H_2O$) C, H, N Cl.

14-Benzyloxymetopon Hydrochloride (14-Benzyloxy-4,5α-epoxy-3-hydroxy-5,17-dimethylmorphinan-6-one Hydrochloride; 8·HCl). A mixture of **21**·HCl (850 mg, 1.6 mmol), 10% Pd/C catalyst (250 mg), and MeOH (25 mL) was hydrogenated at room temperature and 40 psi for 2.5 h. The catalyst was filtered off, and the filtrate was evaporated. The residue (680 mg yellowish foam) was crystallized from acetone/MeOH to yield 520 mg (73%) of colorless **8**·HCl: mp > 215 °C (dec). Anal. ($C_{25}H_{37}NO_4 \cdot HCl \cdot 0.8H_2O$) C, H, N, Cl.

3-*O*-Benzyl-7,8-didehydro-14-(1-naphthylmethoxy)morphinone Hydrochloride (3-Benzyloxy-7,8-didehydro-4,5α-epoxy-5,17-dimethyl-14-(1-naphthylmethoxy)morphinan-6-one Hydrochloride; 23·HCl). NaH (1.8 g, 75.1 mmol) (obtained from 3 g of a 60% NaH dispersion in oil by washings with petroleum ether) was added to a solution of 3-*O*-benzyl-14-hydroxymorphinone (**22**)[12] (5.87 g, 15.07 mmol) in 30 mL of anhydrous DMF under N_2 at 0 °C (bath temperature) while stirring. After 15 min, 1-bromomethylnaphthalene (5.0 g, 2.3 mmol) was added and the resulting mixture was stirred at room temperature for 90 min. Excess NaH was destroyed carefully by addition of small pieces of ice, and then the mixture was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (2 × 60 mL). The combined organic layers were washed with H_2O (2 × 20 mL) and brine (20 mL), dried (Na_2SO_4), and evaporated to yield 8.32 g of a slightly orange colored foam which was purified by column chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH 90:9:1) to afford 2.56 g of a colorless oil. A solution of this oil in ether was treated with Et_2O/HCl to yield 2.47 g (29%) of **23**·HCl: 136−138 °C. Anal. ($C_{35}H_{31}NO_4 \cdot HCl$) C, H, N, Cl.

14-*O*-(1-Naphthylmethyl)oxymorphone (4,5α-Epoxy-3-hydroxy-17-methyl-14-(1-naphthylmethoxy)morphinan-6-one; 9). A mixture of **23**·HCl (1.0 g, 1.9 mmol), glacial acetic acid (100 mL), and 10% Pd/C-catalyst (100 mg) was hydrogenated at room temperature for 8 h. The catalyst was filtered off, the filtrate evaporated, and the oily residue purified by column chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH 250:2:0.5) to afford 412 mg of a colorless foam which was crystallized from MeOH to yield 250 mg (30%) of **9**: mp 147−149 °C. Anal. ($C_{28}H_{27}NO_4 \cdot 0.8\ MeOH \cdot 0.1CH_2Cl_2$) C, H, N.

4,5α-Epoxy-14-ethoxy-3-methoxy-5-methyl-17-(2-phenylethyl)morphinan-6-one (25). A mixture of 4,5α-epoxy-14-ethoxy-3-methoxy-5-methylmorphinan-6-one hydrochloride (**24**·HCl)[13] (3.0 g, 7.88 mmol), potassium carbonate (3.9 g, 28.2 mmol), 2-phenylethyl bromide (1.41 mL, 10.4 mmol), and anhydrous DMF (20 mL) was stirred at 80 °C (bath temperature) for 2 h. After addition of H_2O (130 mL), the mixture was extracted with Et_2O (3 × 60 mL). The combined organic layers were washed with H_2O (3 × 70 mL), dried over Na_2SO_4, and evaporated to give 3.6 g of a yellow oil which was crystallized from MeOH to yield 2.1 g (70%) of **25**: mp 86−89 °C. Anal. ($C_{28}H_{33}NO_4$) C, H, N.

4,5α-Epoxy-14-ethoxy-3-hydroxy-5-methyl-17-(2-phenylethyl)morphinan-6-one Hydrobromide (11·HBr). A solution of **25** (1.5 g, 3.35 mmol) in 48% HBr solution (5 mL) was refluxed for 30 min and then evaporated. The residue was dissolved in MeOH and again evaporated. This procedure was repeated twice, and the crystalline residue (1.7 g) was recrystallized from MeOH to yield 950 mg of **11**·HBr: mp > 270 °C (dec). Anal. ($C_{27}H_{31}NO_4 \cdot HBr$) C, H, N, Br.

Opioid Receptor Binding Assays. Membranes were prepared from Sprague−Dawley rat or guinea pig brains as previously described.[14] Binding experiments were performed in 50 mM Tris-HCl buffer in a final volume of 1 mL containing 0.3−0.5 mg protein as described.[14] Rat brain homogenates were incubated either with [^{3}H]DAMGO (0.5 nM, 45 min, 35 °C) or [^{3}H][Ile^{5,6}]deltorphin II (0.5 nM, 45 min, 35 °C). Guinea pig brain homogenates were incubated with [^{3}H]U69,593 (1 nM, 30 min, 30 °C). Reactions were terminated by rapid filtration through Whatman GF/B pretreated with 0.1% polyethyleneimine ([^{3}H]U69,593) or GF/C ([^{3}H]DAMGO and [^{3}H]-[Ile^{5,6}]deltorphin II) glass fiber filters using a Brandel Cell Harvester, followed by three washings with 5 mL of ice-cold 50 mM Tris-HCl buffer. Nonspecific binding was defined in the presence of 10 μM unlabeled naloxone. All experiments were carried out in duplicate. The values presented are the mean ± SEM of 3−4 independent experiments. Competition inhibition constant (K_i) values were calculated with the GraphPad Prism (version 3.0, San Diego, CA) program.

Bioassays. Preparations of the myenteric plexus longitudinal muscle obtained from the small intestine of male guinea-pigs and preparations of mouse vas deferens were used for field stimulation with bipolar rectangular pulses of supramaximal voltage as described earlier.[17,18] The GPI is primarily a μ receptor preparation, even though the ileum does also contain κ receptors. In the MVD, the opioid effects are predominantly mediated through δ receptors, but μ and κ receptors also exist in the tissue. The agonists were evaluated for their ability to inhibit the electrically evoked twitch. The results are expressed as IC_{50} values obtained from concentration−response curves. The values presented are the mean ± SEM.

Hot-Plate Test in Mice. Male CD-1 mice (20−25 g) were housed at 22 ± 2 °C with food and water ad libitum. A standard light/dark circle was maintained with a time-regulated light period from 6:00 AM to 6:00 PM. Animals were used after a minimum of 4 days of acclimatization to the housing conditions. All experiments were conducted between 9:00 AM and 5:00 PM. The IASP guidelines on ethical standards for investigations of experimental pain in animals were followed. Compounds were dissolved in sterile Ringer's solution and administered to the mice in a volume of 0.05 mL/10 g of body weight. Each dose was tested in 10 animals after subcutaneous (sc) administration. Hot-plate latencies were determined by placing each mouse on a hot-plate kept at 55 ± 1 °C and observing the occurrence of nociceptive responses, licking of a paw or jumping.[17] Each animal served as its own control. Before drug administration, each animal was tested and the latency to hot-plate recorded (control latency, CL). Animals not responding within 3 s were not used. The latency to hot-plate of each drug injected animal was defined as the test latency (TL). To avoid tissue damage, animals with a test latency of more than 12 s (cutoff time) were removed from the nociceptive stimulus and assigned a TL of 12. For drawing the dose− and time−response curves, the antinociceptive response was expressed as MPE, calculated from the following equation: $\mathrm{MPE} = (\mathrm{TL} - \mathrm{CL})/(12 - \mathrm{CL}) \times 100$. Each dose was tested in 10 animals. AD_{50} was defined as the opioid dose that produced an analgesic peak effect equal to 50% MPE.

Colonic Propulsion Test. Male CD-1 mice (20−25 g) were used for the experiments which were performed essentially as previously described.[21,22] Five minutes after sc administration of the compounds at doses ranging from AD_{10} to AD_{80} (AD = analgesic dose), a single 3 mm glass bead was inserted into the distal colon of each mouse. The time required for expulsion of the glass bead was determined for each animal. Inhibition of colonic propulsion was measured as the increase in mean expulsion time (MET) of the glass bead and expressed as the percent of the maximum possible effect (MPE) according to the formula: $\mathrm{MPE} = (\mathrm{METp} - \mathrm{METv})/(120 - \mathrm{METv}) \times 100$. METp is the mean expulsion time in drug treated mice, METv is that in saline-treated mice (8.0 ± 1.2 min), and 120 is the cutoff time in minutes. ED_{50} was defined as the opioid dose that produced a peak effect equal to 50% MPE.

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Supporting Information Available: Spectroscopic data of compounds **12**, **13**, **14**, **6**, **15**, **10**, **17**, **18**, **7**, **20**, **21**, **8**, **23**, **9**, **25**, and **11** and elemental analyses data. This material is available free of charge via the Internet at http://pubs.acs.org.

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