Structural Determinants of Opioid Activity in Derivatives of 14-Aminomorphinones: Effects of Changes to the Chain Linking of the C_{14}-Amino Group to the Aryl Ring

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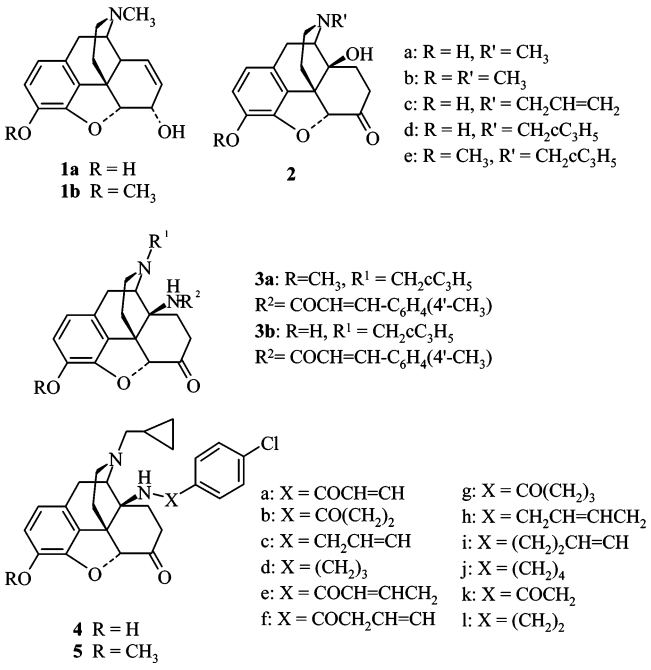
The 14-aminodihydromorphinone and codeinone series of opioid ligands have produced a number of ligands of substantial interest. To investigate the importance of the 14-substituent, a series of analogues in which the side chain length is varied and the amide and alkene functions are reduced have been prepared. Binding affinity, particularly at the μ-opioid receptor (MOR), was largely determined by the aromatic group of the side chain. In the [^{35}S]GTPγS functional assay, the ligands having a three-carbon side chain were more potent antagonists than their longer chain counterparts, while shorter, two-carbon chain analogues were of higher MOR efficacy, an effect that was confirmed in vivo. Wash-resistant binding was observed within this series and appeared to be unrelated to side-chain length.

Introduction

Among the close structural analogues of the opium alkaloids morphine (**1a**) and codeine (**1b**), the dihydromorphinones (**2**) have provided the major opportunities for therapeutic analogues and the starting materials for a series of opioid ligands selective for the individual types of opioid receptors.[1] Introduction of a hydroxyl at C_{14} provided the therapeutic analgesics oxymorphone (**2a**) and oxycodone (**2b**), but importantly, also in naloxone (**2c**) and naltrexone (**2d**), the first "pure" opiate antagonists[2] that have become indispensable pharmacological tools with therapeutic utility in treating narcotic overdose (naloxone) and in maintenance therapy for opiate dependence and alcoholism (naltrexone).[3,4]

For a number of years, we have studied derivatives in the formally similar 14-aminodihydromorphinone series (**3**) and, in particular, the cinnamoylamino derivatives (**4**).[5] The lead compounds from this series clocinnamox (C-CAM, **4a**)[6,7] and methocinnamox (M-CAM, **3b**)[8] are important pharmacological tools as selective irreversible antagonists for the μ-opioid receptor (MOR), having the advantage over the prototype MOR-irreversible antagonist β-FNA that they have no short-term agonist activity. The codeinone (MC-CAM, **5a**) equivalent of **4a** had long-duration potent antinociceptive activity and, when this had waned, irreversible MOR antagonist activity similar to that of **4a**.[9]

This report relates to analogues of **4a** and **5a**, in which the side chain has been extended or shortened (**4f**,**k**, **5e**,**f**,**k**), together with the equivalent ligands in which the side chain amide function (−NHCO−) has been reduced to the equivalent amine (−NHCH$_2$−) (**4h**,**i**,**l**, **5h**,**i**,**l**) and those having the alkene moiety reduced (**4g**,**j**, **5g**,**j**). Also included are the close relatives of **4a** and **5a** with saturated side chains (**4b**, **5b**) and with the amide carbonyl reduced (**4c**,**d**, **5c**,**d**), which were prepared earlier but not reported in any detail.[10]



Chemistry

N-Cyclopropylmethyl-14β-amino-7,8-dihydronormorphinone (**7a**) and the equivalent codeinone (**7b**) were prepared via ketals (**6**) from thebaine using established procedures (Scheme 1).[11,12] Acylated codeinone derivatives **5b**, **5f**, **5g**, and **5k** were prepared from **7b** and the appropriate acid chloride. Their phenolic counterparts **4f**, **4g**, and **4k** were prepared from **7a** by bisacylation with subsequent hydrolysis of the C_3-phenolic ester or for **4b** by 3-*O*-demethylation of **5b** (Scheme 1).

Direct alkylation of **7a** and **7b** using the corresponding alkyl bromides gave target compounds **4h**, **5h**, **4l**, and **5l** (Scheme 1). Direct alkylation of ethylene ketals **6a** and **6b**, with subsequent deprotection of the carbonyl group under acidic conditions, gave the 14β-alkylaminocodeinone/morphinone analogues **4i**, **5i**, **4j**, and **5j**. In these latter cases, this two-stage strategy gave superior results to the direct alkylation of **7a** and **7b** (Scheme 1). Compound **6a** was also used in the preparation of **5d**. Acylation of **6a** to give **8**, followed by LiAlH$_4$ reduction

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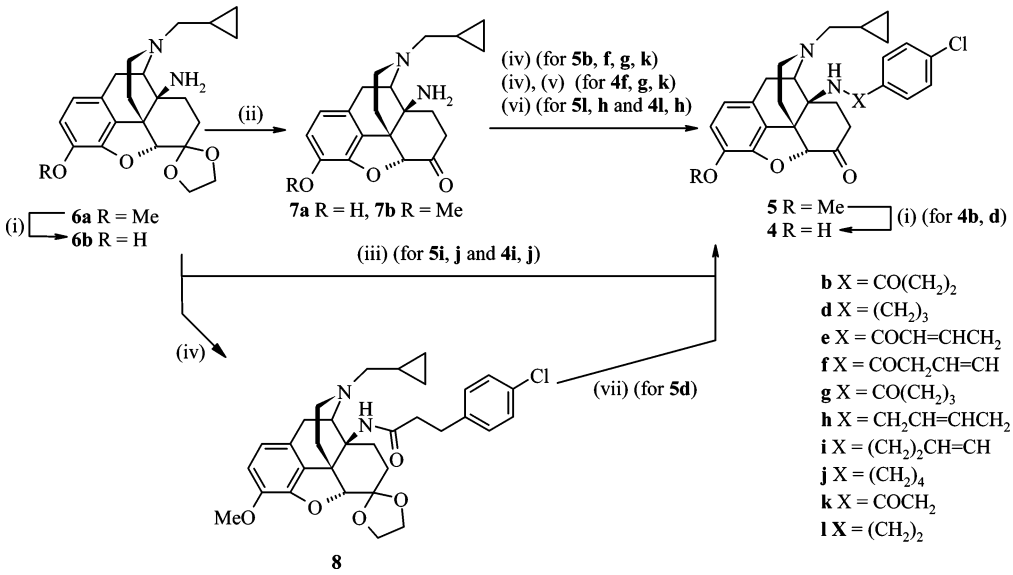
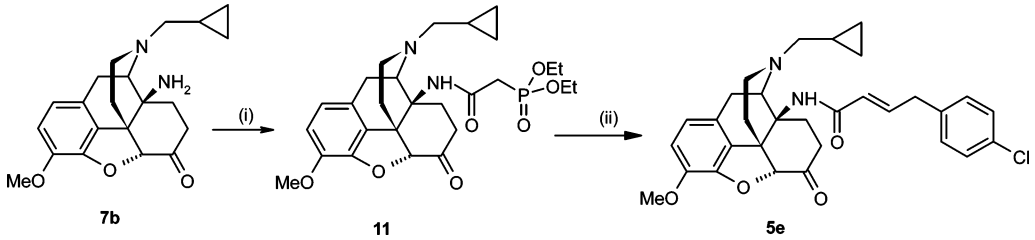
Scheme 1[a]



[a] Reagents and conditions: (i) BBr_3, DCM, −30 °C to rt, 0.5 h, 40% (**6a** to **6b**) or 40% (**7b** to **7a**); (ii) HCl (6 N), MeOH, reflux, 5 h, 50%; (iii) (a) alkyl bromide, K_2CO_3, DMF, 90 °C, 24 h; (b) HCl (6 N), MeOH, reflux, 5 h; (iv) acid chloride, NEt_3, DCM, rt, overnight; (v) K_2CO_3, MeOH, rt, overnight; (vi) alkyl bromide, K_2CO_3, DMF, 90 °C, 3 h; (vii) $LiAlH_4$, THF, reflux overnight, then HCl (1 N), MeOH, reflux, 5 h, 53%.

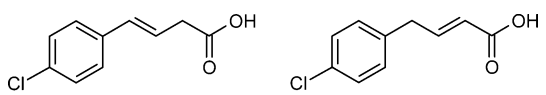
Scheme 2[a]



[a] Reagents and conditions: (i) $(EtO)_2P(O)CH_2COCl$, THF, −20 °C to rt, 0.5 h, 60%; (ii) (a) LDA, THF, −78 °C, 0.5 h, (b) 4-chlorophenylacetaldehyde, THF, −78 °C to rt, 1 h, 28%.

of the amide and deprotection of the C_6-carbonyl, gave **5d**, which could then be 3-*O*-demethylated to yield **4d**.

Having discovered that 4-(4′-chlorophenyl)-2-butenoic acid (**10**) could not readily be isolated, owing to its preference to isomerize to **9**, an alternative strategy to the routine acylation approach was required for the preparation of **5e** (Scheme 2). The protocol selected involved the formation of the α,β-unsaturated amide via a Horner−Wadsworth−Emmons-type reaction.[13] Acylation of **7b** using diethoxyphosphorylacetyl chloride[14,15] afforded **11**. Treatment of **11** with LDA at low temperature in the presence of 4-chlorophenylacetaldehyde afforded **5e** exclusively in the (*E*)-configuration.



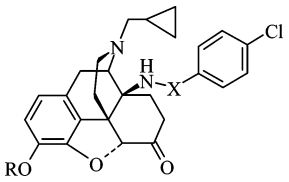
9 **10**

Results and Discussion

Affinity for the individual types of opioid receptors (OR) was determined in displacement binding assays in recombinant human opioid receptors transfected into chinese hamster ovary (CHO) cells; the displaced selective radioligands were [^{3}H]-DAMGO (MOR), [^{3}H]U69593 (κ; KOR), and [^{3}H]Cl-DPDPE (δ; DOR).[16] All the morphinone and codeinone ligands had high affinity for MOR, with the morphinones (**4**) having modestly higher (≤6-fold) affinity than the equivalent codeinones (**5**; Table 1). KOR affinity of the codeinones was also lower (≤59-fold) than that of the equivalent morphinones, as was DOR affinity (≤71-fold). Thus, the codeinones showed significant MOR over DOR selectivity (≤64-fold). MOR over KOR selectivity was generally modest, but the four-carbon chain arylalkyl substituents in **5i** and **5j** conferred a MOR selective profile, and the three-carbon chain analogues **5c** and **5d** were even more selective for MOR (Table 1).

Compounds **4a** and **5a** with a three-carbon chain C_{14} substituent have similar MOR and DOR affinities (Table 1), but the KOR affinity of **5a** is 12-fold lower than that of **4a**. The equivalent new ligands, with a four-carbon side chain (**4f**, **5e**, **5f**), generally had similar binding affinities to **4a** and **5a**, with the notable exception that the DOR affinity of **5e** was 50-fold lower and the DOR affinity of **5f** was more than 20-fold lower than that of **5a**. Among the new ligands there was relatively little effect on OR binding affinities resulting from differences of chain length, though the new three-carbon chain derivatives (**4b**, **4d**, **5b**, **5d**) generally showed higher affinity than their two- and four-carbon equivalents (**4g**, **4j**, **4k**, **4l**, **5g**, **5j**, **5k**, **5l**). There was a similar lack of substantial effect from introducing unsaturation into the side chain and replacing NHCO in the side chain with $NHCH_2$. It can be concluded that the predominant entity in the side chain for OR binding affinity is the aromatic group. The affinities of naltrexone (**3d**) were 25-fold (DOR), 320-fold (KOR), and 430-fold (MOR) greater than those of its 3-*O*-methyl ether (**3e**; Table 1). The big loss of KOR and MOR affinities resulting from 3-*O*-methylation of naltrexone is in sharp contrast to the modest differences in KOR and MOR

Table 1. Binding Affinities of Ligands to Human Opioid Receptor Transfected into CHO Cells[a]



			Ki/nM				
compd	R	X	DOR	KOR	MOR	DOR/MOR	KOR/MOR
5a	Me	COCH=CH	4.79 ± 0.73	16.4 ± 2.54	4.78 ± 0.58	1.0	3.4
5b	Me	$CO(CH_2)_2$	5.10 ± 0.14[b]	6.50 ± 0.26[b]	0.24 ± 0.05[b]	21.2	27.1
5c	Me	CH_2CH=CH	44.5 ± 4.6[b]	53.6 ± 0.95[b]	0.70 ± 0.10[b]	63.6	76.6
5d	Me	$(CH_2)_3$	31.3 ± 1.8[b]	78.6 ± 32.8[b]	0.59 ± 0.00[b]	53.0	133
5e	Me	$COCH$=$CHCH_2$	242 ± 50.0	25.2 ± 4.14	8.07 ± 1.84	30.0	3.1
5f	Me	$COCH_2CH$=CH	104 ± 21.7	21.5 ± 4.19	8.19 ± 0.94	12.7	2.6
5g	Me	$CO(CH_2)_3$	89.4 ± 20.0	7.51 ± 0.43	3.88 ± 1.07	23.0	1.9
5h	Me	CH_2CH=$CHCH_2$	94.9 ± 21.2	25.9 ± 5.9	6.76 ± 2.39	14.0	3.8
5i	Me	$(CH_2)_2CH$=CH	24.8 ± 5.15	33.5 ± 4.15	1.15 ± 0.27	21.6	29.1
5j	Me	$(CH_2)_4$	55.9 ± 1.67	41.5 ± 7.79	2.23 ± 0.80	25.1	18.6
5k	Me	$COCH_2$	51.9 ± 15.6	2.59 ± 0.22	2.64 ± 0.91	19.7	1.0
5l	Me	$(CH_2)_2$	33.8 ± 1.40	13.1 ± 2.29	1.33 ± 0.24	25.4	9.8
4a	H	COCH=CH	2.69 ± 0.23	1.41 ± 0.52	2.98 ± 0.22	0.9	0.5
4b	H	$CO(CH_2)_2$	0.60 ± 0.00[b]	0.65 ± 0.07[b]	0.04 ± 0.00[b]	15.0	16.2
4c	H	CH_2CH=CH	0.63 ± 0.08[c]	0.91 ± 0.12[c]	0.32 ± 0.03[c]	2.0	2.8
4d	H	$(CH_2)_3$	1.10 ± 0.00[b]	1.90 ± 0.85[b]	0.13 ± 0.08[b]	8.5	14.6
4f	H	$COCH_2CH$=CH	3.25 ± 0.28	4.94 ± 1.75	1.87 ± 0.45	1.7	2.6
4g	H	$CO(CH_2)_3$	3.85 ± 0.25	2.95 ± 0.16	1.34 ± 0.05	2.9	2.2
4h	H	CH_2CH=$CHCH_2$	6.65 ± 0.20	3.72 ± 0.05	1.89 ± 0.01	3.5	2.0
4i	H	$(CH_2)_2CH$=CH	2.10 ± 0.79	3.69 ± 1.31	1.00 ± 0.28	2.1	3.7
4j	H	$(CH_2)_4$	2.18 ± 0.30	5.27 ± 2.06	0.96 ± 0.35	2.3	5.5
4k	H	$COCH_2$	1.51 ± 0.17	1.00 ± 0.14	0.73 ± 0.00	2.0	1.4
4l	H	$(CH_2)_2$	1.91 ± 0.17	1.53 ± 0.05	0.86 ± 0.20	2.2	1.8
3d	H		10.8 ± 3.0	0.4 ± 0.1	0.2 ± 0.0	54.0	2.0
3d	H		6.5 ± 1.3[b]	0.6 ± 0.1[b]	0.4 ± 0.05[b]	16.2	1.5
3e	Me		272 ± 72	128 ± 23	85.6 ± 0.22	3.2	1.5

[a] Data are the average from two experiments, each carried out in triplicate. Tritiated ligands were [^{3}H]DAMGO(μ), [^{3}H]Cl-DPDPE(δ), and [^{3}H]U69593(κ). [b] Binding to guinea pig brain homogenates. [c] Displacement of ^{3}H-diprenorphine from membranes of C6mu cells, C6delta cells or CHOkappa cells.

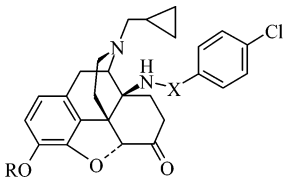
affinities between the series of morphinones (**4**) and codeinones (**5**). That the presence of a free 3-OH group is not necessary for high MOR affinity in series **4** and **5**, but is necessary in naltrexone-related ligands, confirms that the C_{14} substituent in **4** and **5** is relatively a more important determinant of MOR affinity than the C_3 substituent.[17]

In vitro OR functional activity of the new ligands was determined in assays in which stimulation of [^{35}S]GTPγS binding is measured for recombinant human OR transfected into CHO cells.[16,18] All the new ligands with four-carbon chain C_{14} substituents (**4f**−**4j**, **5e**−**5j**) were potent MOR antagonists (Table 2), with the codeinones having 4−7-fold lower potency than the morphinones. The only exception was **5f**, which was equipotent as a MOR antagonist to **4f**. The morphinones (**4f**−**4j**) were also potent DOR antagonists, whereas the codeinones were low potency DOR antagonists (**5g**, **5h**, **5j**) or low potency, low efficacy DOR partial agonists (**5f**, **5i**). Only the morphinones with saturated four-carbon chains in the C_{14} substituent (**4g**, **4j**) were KOR antagonists; those with unsaturated four-carbon chains (**4f**, **4h**, **4i**) were KOR low efficacy partial agonists of moderate potency. The codeinones (**5e**−**5j**) were all KOR partial agonists of generally low potency. As was found in the binding assays, the in vitro functional profiles of the morphinones (**4f**−**4j**) and codeinones (**5e**−**5j**) were relatively insensitive to the change of C_{14}-amide (NHCO) to amine ($NHCH_2$) and to the introduction of unsaturation into the side chain.

While the location of the double bond or degree of saturation did not appear to greatly influence the potency of the compounds having a four-carbon chain, differences were seen within the series having a three-carbon chain. All the ligands having a three-carbon chain (**4a**, **4b**, **4d** and **5a**, **5b**, **5d**) were antagonists at each of the opioid receptors, with the more flexible, saturated analogues (**4b**, **4d** and **5b**, **5d**) being more potent than their cinnamoyl counterparts (**4a**, **5a**). This was most noticeable at MOR and KOR, with antagonist potency at DOR least affected. Thus, **4b**, **4d**, and **5b** were more potent than **4a** and **5a** by around 20−40-fold at MOR and KOR and 10-fold at DOR. Compound **5d** was a slight exception, being more potent than **5a** by around 5-fold at each receptor. As expected, the morphinones (**4a**, **4b**, **4d**) were of higher antagonist potency than their codeinone counterparts (**5a**, **5b**, **5d**) at KOR and DOR, with little or no change seen at MOR. The most striking SAR is found in comparison of the new ligands with three-carbon side chains (**4b**, **4d**, **5b**, **5d**) with their four-carbon counterparts (**4g**, **4j**, **5g**, **5j**). At each of the three opioid receptors, the three-carbon chain analogues were very much more potent (20−150-fold) in the functional assay than their four-carbon homologues, suggesting that it is at three carbons that optimal antagonist potency is reached. In fact, the addition of the extra carbon in codeinones **5g** and **5j** results in the introduction of some efficacy at KOR.

The in vitro functional profiles of the new ligands with two-carbon chain C_{14} substituents were notable insofar as they were the only ligands tested that showed significant MOR efficacy in the [^{35}S]GTPγS assay (Table 2). Compounds **4k**, **4l**, **5k**, and **5l** were all potent MOR partial agonists, with the phenylacetyl-aminomorphinone (**4k**) having the greatest potency, with EC_{50} = 0.26 nM. The codeinones **5k** and **5l** had marginally higher MOR efficacy than the morphinones **4k** and **4l**, but **4k** was over thirty times more potent than **5k**. The difference in potency

Table 2. Agonist and Antagonist Effects of Ligands at Opioid Receptors Measured by the [^{35}S]GTPγS Binding Assay[a]



			IC_{50}/nM: % stim or Ke/nM		
compd	R	X	DOR	KOR	MOR
5a	Me	COCH=CH	7.16 ± 0.57; ANT	9.81 ± 0.88; ANT	0.97 ± 0.15; ANT
5b	Me	$COCH_2CH_2$	0.76 ± 0.11; ANT	0.29 ± 0.07; ANT	0.03 ± 0.003; ANT
5d	Me	$(CH_2)_3$	1.66 ± 0.17; ANT	1.87 ± 1.00; ANT	0.12 ± 0.01; ANT
5e	Me	$COCH=CHCH_2$	NT	26.2 ± 0.62; 23	12.1 ± 0.38; ANT
5f	Me	$COCH_2CH=CH$	118 ± 21.0; 32	106 ± 28.0; 41	1.27 ± 0.24; ANT
5g	Me	$CO(CH_2)_3$	79.9 ± 6.19; ANT	20.2 ± 8.3; 30	4.91 ± 0.54; ANT
5h	Me	$CH_2CH=CHCH_2$	96.8 ± 9.27; ANT	387 ± 47.0; 31	4.98 ± 0.59; ANT
5i	Me	$(CH_2)_2CH=CH$	148 ± 47.0; 29	208 ± 66.0; 43	1.64 ± 0.28; ANT
5j	Me	$(CH_2)_4$	61.1 ± 6.71; ANT	202 ± 47.7; 49	1.45 ± 0.22; ANT
5k	Me	$COCH_2$	88.7 ± 29.6; 32	9.07 ± 2.53; 89	8.84 ± 0.22; 39
5l	Me	$(CH_2)_2$	63.0 ± 16.0; 44	43.4 ± 11.5; 31	3.73 ± 0.91; 39
4a	H	COCH=CH	0.19 ± 0.02; ANT	0.10 ± 0.006; ANT	0.53 ± 0.13; ANT
4b	H	$CO(CH_2)_2$	0.03 ± 0.006; ANT	0.003 ± 0.001; ANT	0.028 ± 0.005; ANT
4d	H	$(CH_2)_3$	0.02 ± 0.002; ANT	0.006 ± 0.002; ANT	0.0125 ± 0.002; ANT
4f	H	$COCH_2CH=CH$	1.70 ± 0.45; ANT	13.8 ± 3.09; 33	1.84 ± 0.32; ANT
4g	H	$CO(CH_2)_3$	1.37 ± 0.21; ANT	0.59 ± 0.08; ANT	0.87 ± 0.10; ANT
4h	H	$CH_2CH=CHCH_2$	3.35 ± 0.42; ANT	3.45 ± 0.41; 24	1.21 ± 0.06; ANT
4i	H	$(CH_2)_2CH=CH$	1.17 ± 0.14; ANT	16.7 ± 2.34; 44	0.24 ± 0.04; ANT
4j	H	$(CH_2)_4$	0.67 ± 0.04; ANT	0.44 ± 0.06; ANT	0.29 ± 0.01; ANT
4k	H	$COCH_2$	2.41 ± 0.85; 50	1.12 ± 0.29; 23	0.26 ± 0.07; 29
4l	H	$(CH_2)_2$	1.59 ± 0.01; 27	0.34 ± 0.05; ANT	1.56 ± 0.57; 34
3d	H		5.44 ± 0.75; ANT	1.86 ± 0.16; ANT	0.59 ± 0.04; ANT
3e	Me		1000 ± 52; ANT	410 ± 104; ANT	96.3 ± 18; ANT

[a] Values are means from five or six experiments. NT = not tested. Efficacy is measured against the standards DPDPE (δ), U69593 (κ), and DAMGO (μ), and antagonist potency is recorded as Ke values versus the same standards. ANT = antagonist.

between **4l** and **5l** was only about 2-fold, in keeping with the MOR affinities in the binding assays (Table 1). Compounds **4k** and **4l** were also potent DOR partial agonists and had potent, very low efficacy, or antagonist KOR functional activity. The efficacy of the phenylethylaminomorphinone (**4l**) for DOR and KOR was somewhat lower than that of the phenylacetylaminomorphinone (**4k**). The equivalent codeinones (**5k**, **5e**) had low potency DOR partial agonist activity but, whereas **5l** was also a low potency KOR partial agonist, the phenylacetylaminocodeinone (**5k**) was a nearly full KOR agonist of significant potency (Table 2).

Three of the new 14-aminodihydromorphinones (**4f**, **4g**, **4k**) and **4a** (C-CAM) were investigated in membranes from C_6 cells expressing MOR to determine whether evidence could be found for irreversible binding to MOR. The test compound or vehicle-treated membranes were incubated in Tris-HCl buffer for 1 h at 25 °C, following which the membranes were collected by centrifugation, resuspended, incubated at 37 °C to promote the dissociation of the weakly bound ligand, and then collected by recentrifugation and twice further washed. This procedure was sufficient to cause complete washout of 10 μM of the reversible antagonist naloxone (**2c**), whereas the test compounds (**4a**, **4f**, **4g**, **4k**) remained bound to the membranes. This was confirmed in experiments in which the test compound or vehicle-treated membranes (15 μg) were incubated at 25 °C for 1 h with increasing concentrations of DAMGO in the presence of buffered [^{35}S]GTPγS to determine the effects of the ligand combinations on [^{35}S]GTPγS binding. The effects on DAMGO concentration-effect curves for incubation with the test ligands are shown in Figures 1 and 2. For **4a**, a concentration of 10 nM had a relatively small effect in suppressing the stimulation of [^{35}S]GTPγS binding produced by DAMGO (Figure 1); a concentration of 100 nM was fully effective (Figure 1). The homologue (**4f**) had a similar effect as **4a** at 10 nM concentration, but the phenylbutylamido derivative (**4g**) and phenylacetyl-

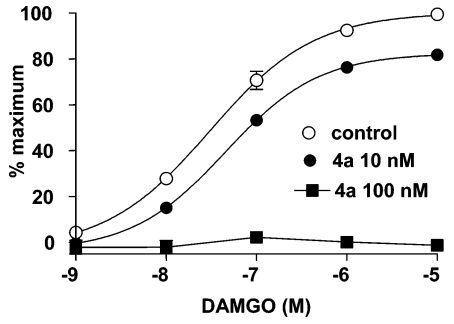


Figure 1. Effect of preincubation with C-CAM (**4a**) followed by extensive washing on the concentration effect curve for DAMGO in C6 cells expressing a mu-opioid receptor.

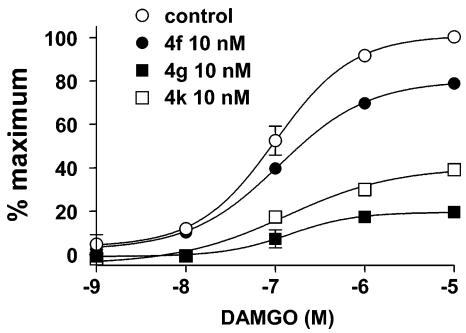


Figure 2. Effect of preincubation with C-CAM analogues (**4f**, **4g**, **4k**) followed by extensive washing on the concentration effect curve for DAMGO in C6 cells expressing a mu-opioid receptor.

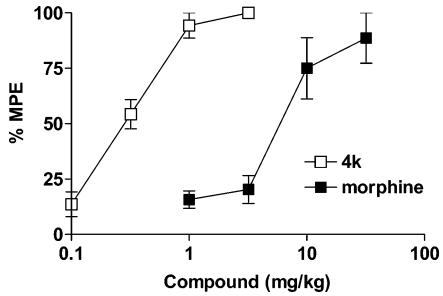


Figure 3. Agonist effect of **4k** compared to morphine in the 50 °C mouse tail-withdrawal test.

amino derivative (**4k**) at 10 nM concentration both produced a greater effect than **4a** (Figure 2). The effect of **4g** at 1 nM was at least as great as **4a** at 10 nM (data not shown). The flattening of the dose−response curve of an agonist in the presence of an antagonist is an indication that the antagonist binds irreversibly to the receptor responsible for the agonist effect,[19] and in this series, the magnitude of this effect was unrelated to side-chain length.

The phenylacetylaminomorphinone (**4k**) was investigated in vivo in the mouse tail withdrawal assay with water at 50 °C (Figure 3).[8] Compound **4k** was fully active in this assay at a dose of 1 mg/kg, representing 10 times greater potency than morphine. The antinociceptive effect of **4k** had gone by 24 h, and at that pretreatment time, **4k** did not affect the antinociceptive dose−effect curve of morphine, which would have indicated a delayed MOR-antagonist effect. The high efficacy agonist effect of **4k** in vivo is apparently at odds with its modest efficacy (29% of DAMGO) in the [^{35}S]GTPγS in vitro assay. However, such disparity between activity in vitro and in vivo for lipophilic ligands in the 14-substituted morphinone series has been noted elsewhere.[8] One explanation for this disparity is that the receptor reserve in the 50 °C water antinociceptive assay is substantially greater than in the MOR [^{35}S]GTPγS assay. Differences are also noted for antagonist activity where, for example, **4k** was a powerful noncompetitive antagonist of DAMGO in the [^{35}S]-GTPγS assay but had no discernible delayed antagonism in the tail withdrawal assay. More work is needed to better understand these disparities and whether the antagonism in vitro provides any beneficial effects in the search for MOR agonists with reduced abuse potential.

Conclusion

The lack of any agonist effect and the exceptional noncompetitive antagonism displayed in vivo by **4a** cannot be explained by covalent bond formation to the receptor[20,21] but seems likely to involve dominant lipophilic binding by the cinnamoyl aromatic group. This could involve binding of the aromatic group outside the helical loops of the receptor to the lipid bilayer. In that case, the interaction could be sensitive to the length of the C_{14} side chain. The data presented here indicate that, of the new ligands that were more extensively studied in vitro, MOR profiles of **4f** and **4g**, with 4 carbon C_{14} side chains, are similar to that of the three-carbon chain analogues such as **4a** and **4b**, whereas the ligand (**4k**) with a two-carbon chain is different in having substantial MOR-agonist activity that was confirmed in vivo. However, the in vitro data provide evidence that **4k** is a MOR partial agonist and show noncompetitive antagonist activity in suppressing the agonist effects of the selective MOR-agonist DAMGO. It is, therefore, unclear whether extra-helical binding is responsible for the profile of **4a** as a noncompetitive antagonist.

Experimental Section

Reagents and solvents were purchased from Aldrich or Lancaster and used as received. Melting point: Gallenkamp MFB-595 melting point apparatus; uncorrected. IR spectra: Perkin-Elmer 881 instrument, in cm^{-1}. NMR spectra: JEOL Lambda-270-MHz instrument: ^{1}H at 270 MHz, ^{13}C at 67.5 MHz, δ in ppm, and J in Hz, with TMS as an internal standard. EIMS: V.G.-Autospec instrument equipped with a Fisons autosampler; EI at 70 eV; m/z (rel %). Microanalysis: Perkin-Elmer 240C analyzer. Ligands were tested as their oxalate salts, prepared by adding 1 equiv of oxalic acid to an ethanolic solution of the compound.

General Procedure A: Preparation of Acid Chlorides and the in situ Acylation of *N*-Cyclopropylmethyl-14β-amino-7,8-dihydronorcodeinones/morphinones. A suspension of oxalyl chloride (8.8 equiv) and the corresponding carboxylic acid (1.1 equiv) in anhydrous toluene was heated at reflux for 1 h. The resulting solution was allowed to cool, and the solvent was removed in vacuo. The residue was dissolved in anhydrous dichloromethane and added dropwise to a solution of *N*-cyclopropylmethyl-14β-amino-7,8-dihydronorcodeinone (1 equiv) and triethylamine (1.1 equiv) in anhydrous dichloromethane, and the mixture stirred at room temperature overnight. The solvent was removed in vacuo, and the crude residue was purified by column chromatography (5% CH_3OH in CH_2Cl_2). In the acylation of *N*-cyclopropylmethyl-14β-amino-7,8-dihydronormorphinone, a second equivalent (total: 2 equiv) of the corresponding acid chloride was used to afford the bisacylated derivative. The crude residue was dissolved in methanol/water (9:1) before adding potassium carbonate (5 equiv), and the mixture was stirred at room temperature overnight. The solvent was removed in vacuo, and the crude residue was purified by column chromatography (5% CH_3OH in CH_2Cl_2).

General Procedure B: Alkylation of *N*-Cyclopropylmethyl-14β-amino-7,8-dihydronorcodeinones/morphinones and Their Ethylene Glycol Protected Derivatives. A stirring suspension of *N*-cyclopropylmethyl-14β-amino-7,8-dihydronorcodeinone/morphinone or its ethylene ketal-protected derivative (1 equiv), potassium carbonate (5 equiv), and the corresponding alkyl bromide (1.1 equiv) in dimethylformamide was heated at 90 °C for 3−12 h. The solvent was removed in vacuo and the crude residue purified by column chromatography (5% CH_3OH in CH_2Cl_2).

General Procedure C: Acid-Catalyzed Deprotection of *N*-Cyclopropylmethyl-14β-amino-7,8-dihydronorcodeinone/morphinone Ethylene Ketals. A solution of *N*-cyclopropylmethyl-14β-amino-7,8-dihydronorcodeinone/morphinone ethylene ketal in methanol and hydrochloric acid (6 N) was heated at reflux for 4 h. The solvent was removed in vacuo and the crude residue was basified with concentrated ammonia and extracted with dichloromethane. The combined organic extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and the crude residue was purified by column chromatography (5% CH_3OH in CH_2Cl_2).

***N*-Cyclopropylmethyl-14β-[3′-(4″-chlorophenyl)propanamido]-7,8-dihydronorcodeinone (5b).** Compound **7b** (1.57 g, 4.42 mmol) was treated with 3-(4-chlorophenyl)propanoyl chloride (912 mg, 4.90 mmol), as described in general procedure A, to afford **5b** as a white foam (1.75 g, 3.37 mmol, 76%). Anal. (oxalate salt; $C_{32}H_{35}N_2ClO_8$) C, H, N.

***N*-Cyclopropylmethyl-14β-[3′-(4″-chlorophenyl)propanamido]-7,8-dihydronormorphinone (4b).** A solution of BBr_3 (17 mL, 1 M, 17 mmol) in CH_2Cl_2 was added at −78 °C under N_2 to a solution of **5b** (1.48 g, 2.8 mmol) in CH_2Cl_2 (10 mL). The mixture was allowed to warm to −20 °C and stirred for 1 h before again cooling to −78°C and adding MeOH (30 mL). The mixture was then basified using 2 M NaOH (to pH 12) and then neutralized with dilute HCl. Extraction with CH_2Cl_2/MeOH (9:1, 3 × 20 mL), drying ($MgSO_4$), and evaporation gave a residue that was purified using column chromatography (CH_2Cl_2/MeOH, 19:1) to yield **4b** as a white solid (990 mg, 1.98 mmol, 69%). Anal. (free base; $C_{29}H_{31}N_2ClO_4.CH_3OH$) C, H, N.

***N*-Cyclopropylmethyl-14*β*-[3′-(4″-chlorophenyl)propanamido]-7,8-dihydronorcodeinone Ethylene Glycol Ketal (8).** Compound **6a** (1.65 g, 4.15 mmol), 3-(4-chlorophenyl)propanoyl chloride (0.97 g, 12.4 mmol), and NEt_3 (0.58 mL) in dry CH_2Cl_2 (10 mL) were stirred under N_2 for 3 h before evaporation to dryness and purification by silica gel column chromatography (CH_2Cl_2/MeOH, 19:1) to yield **8** as a white foam (1.92 g, 3.40 mmol, 82%).

***N*-Cyclopropylmethyl-14*β*-[3′-(4″-chlorophenyl)propylamino]-7,8-dihydronorcodeinone (5d).** A solution of **8** (2.87 g, 5.08 mmol) in dry THF (12 mL) was added to a suspension of $LiAlH_4$ (500 mg, 13.0 mmol) in dry THF (33 mL) under N_2. The mixture was refluxed for 24 h and cooled, and the reaction was quenched by the addition of Rochelle's salt. The THF was removed in vacuo, and CH_2Cl_2 and H_2O were added, with the organic layer being collected. The aqueous layer was further extracted with CH_2Cl_2/MeOH (9:1, 3 × 20 mL), and the combined extracts were dried ($MgSO_4$) and evaporated in vacuo to give a white foam that was immediately dissolved in MeOH (25 mL) and 1 M HCl (15 mL). After refluxing for 5 h, the solution was cooled and neutralized with Na_2CO_3, and the MeOH was evaporated. Extraction with CH_2Cl_2/MeOH (9:1, 3 × 15 mL), evaporation, and purification by silica gel column chromatography (CH_2Cl_2/MeOH, 19:1) gave **5d** as a white foam (1.37 g, 2.71 mol, 53%). Anal. (oxalate; $C_{32}H_{37}N_2ClO_7 \cdot 0.5H_2O$) C, H, N.

***N*-Cyclopropylmethyl-14*β*-[3′-(4″-chlorophenyl)propylamino]-7,8-dihydronormorphinone (4d).** Compound **5d** (1.1 g; 2.2 mmol) was treated with BBr_3 (13 mL, 1 M, 13 mmol) as described for **4b**. Column chromatography (CH_2Cl_2/MeOH, 19:1) yielded **4d** as a white solid. Anal. (oxalate; $C_{31}H_{35}N_2ClO_7 \cdot 0.5H_2O$) C, H, N.

***N*-Cyclopropylmethyl-14*β*-[4′-(4″-chlorophenyl)-3′-butenamido]-7,8-dihydronorcodeinone (5f).** Compound **7b** was treated with 4-(4′-chlorophenyl)-3-butenoyl chloride, as in general procedure A, to afford **5f** as a pale yellow solid (68 mg, 0.13 mmol, 64%). Anal. (oxalate; $C_{33}H_{35}N_2ClO_8 \cdot 0.5H_2O$) C, H, N.

***N*-Cyclopropylmethyl-14*β*-[4′-(4″-chlorophenyl)-3′-butenamido]-7,8-dihydronormorphinone (4f).** Compound **7a** was treated with 4-(4′-chlorophenyl)-3-butenoyl chloride, as in general procedure A, to afford **4f** as a white solid (50 mg, 0.10 mmol, 48%). Anal. (oxalate; $C_{32}H_{33}N_2ClO_8 \cdot 0.75H_2O$) C, H, N.

***N*-Cyclopropylmethyl-14*β*-[4′-(4″-chlorophenyl)-butanamido]-7,8-dihydronorcodeinone (5g).** Compound **7b** was treated with 4-(4′-chlorophenyl)butanoyl chloride, as in general procedure A, to afford **5g** as a yellow solid (76 mg, 0.14 mmol, 71%). Anal. (oxalate; $C_{33}H_{37}N_2ClO_8 \cdot 1H_2O$) C, H, N.

***N*-Cyclopropylmethyl-14*β*-[4′-(4″-chlorophenyl)-butanamido]-7,8-dihydronormorphinone (4g).** Compound **7a** was treated with 4-(4′-chlorophenyl)butanoyl chloride, as in general procedure A, to afford **4g** as a white solid (55 mg, 0.11 mmol, 53%). Anal. (oxalate; $C_{32}H_{35}N_2ClO_8 \cdot 0.75H_2O$) C, H, N.

***N*-Cyclopropylmethyl-14*β*-[4′-(4″-chlorophenyl)-2′-butenamido]-7,8-dihydronorcodeinone (5e).** To a solution of lithium diisopropylamide [butyllithium 2.5 M in hexanes (100 *μ*L, 0.24 mmol) and diisopropylamine (35 *μ*L, 0.24 mmol)] in tetrahydrofuran (1 mL) at −78 °C was added **11** (0.11 g, 0.20 mmol) in tetrahydrofuran (1 mL), and the mixture was stirred for 0.5 h, maintaining this temperature. A solution of 4-chlorophenylacetaldehyde (**9**; 0.04 g, 0.26 mmol) in tetrahydrofuran (1 mL) was added dropwise at −78 °C, and the resulting mixture was stirred at room temperature for 1 h. Water was added, and the aqueous layer was extracted with diethyl ether and then dichloromethane. The combined organic extracts were washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. Purification by column chromatography (5% CH_3OH in CH_2Cl_2) afforded **5e** as a white solid (30 mg, 0.06 mmol, 28%). Anal. (oxalate; $C_{33}H_{35}N_2ClO_8$) C, H, N.

***N*-Cyclopropylmethyl-14*β*-[2′-(4″-chlorophenyl)-ethanamido]-7,8-dihydronorcodeinone (5k).** Compound **7b** was treated with 2-(4′-chlorophenyl)acetyl chloride, as in general procedure A, to afford **5k** as a white solid (70 mg, 0.14 mmol, 69%). Anal. ($C_{31}H_{33}N_2ClO_8 \cdot 1.5H_2O$) C, H, N.

***N*-Cyclopropylmethyl-14*β*-[2′-(4″-chlorophenyl)-ethanamido]-7,8-dihydronormorphinone (4k).** Compound **7a** was treated with 2-(4′-chlorophenyl)acetyl chloride, as in general procedure A, to afford **4k** as a white solid (50 mg, 0.10 mmol, 51%). Anal. (oxalate; $C_{30}H_{31}N_2ClO_8 \cdot 0.5H_2O$) C, H, N.

***N*-Cyclopropylmethyl-14*β*-[2′-(4″-chlorophenyl)-ethanamino]-7,8-dihydronorcodeinone (5l).** Compound **7b** was treated with 2-(4′-chlorophenyl)ethyl iodide, as in general procedure B, to afford **5l** as a pale brown solid (47 mg, 0.10 mmol, 48%). Anal. (oxalate; $C_{31}H_{35}N_2ClO_7 \cdot 0.5CH_2Cl_2$) C, H, N.

***N*-Cyclopropylmethyl-14*β*-[2′-(4″-chlorophenyl)-ethanamino]-7,8-dihydronormorphinone (4l).** Compound **7a** was treated with 2-(4′-chlorophenyl)ethyl iodide, as in general procedure B, to afford **4l** as a white solid (35 mg, 0.07 mmol, 37%). Anal. (oxalate; $C_{30}H_{33}N_2ClO_7 \cdot 0.5CH_2Cl_2$) C, H, N.

***N*-Cyclopropylmethyl-14*β*-[4′-(4″-chlorophenyl)-3′-butenamino]-7,8-dihydronorcodeinone (5i).** Compound **6a** was treated with 4-(4′-chlorophenyl)-3-butenyl bromide, as in general procedure B, to afford *N*-cyclopropylmethyl-14*β*-[4′-(4″-chlorophenyl)-3′-butenamino]-7,8-dihydronorcodeinone ethylene ketal as a colorless oil (39 mg, 0.07 mmol, 50%).

This was treated as in general procedure C to afford **5i** as a pale yellow solid (21 mg, 0.04 mmol, 65%). Anal. (oxalate; $C_{33}H_{37}N_2ClO_7 \cdot 1.5H_2O$) C, H, N.

***N*-Cyclopropylmethyl-14*β*-[4′-(4″-chlorophenyl)-3′-butenamino]-7,8-dihydronormorphinone (4i).** Compound **6b** was treated with 4-(4′-chlorophenyl)-3-butenyl bromide, as in general procedure B, to afford *N*-cyclopropylmethyl-14*β*-[4′-(4″-chlorophenyl)-3′-butenamino]-7,8-dihydronormorphinone ethylene ketal as a colorless oil (77 mg, 0.14 mmol, 44%).

This was treated as in general procedure C to afford **4i** as a pale yellow solid (36 mg, 0.07 mmol, 54%). Anal. (oxalate; $C_{32}H_{35}N_2ClO_7 \cdot 1H_2O$) C, H, N.

***N*-Cyclopropylmethyl-14*β*-[4′-(4″-chlorophenyl)-2′-butenamino]-7,8-dihydronorcodeinone (5h).** Compound **7b** was treated with 4-(4′-chlorophenyl)-2-butenyl bromide, as in general procedure B, to afford **5h** as a yellow solid (82 mg, 0.16 mmol, 79%). Anal. (oxalate; $C_{33}H_{37}N_2ClO_7 \cdot 1.5H_2O$) C, H, N.

***N*-Cyclopropylmethyl-14*β*-[4′-(4″-chlorophenyl)-2′-butenamino]-7,8-dihydronormorphinone (4h).** Compound **7a** was treated with 4-(4′-chlorophenyl)-2-butenyl bromide, as in general procedure B, to afford **4h** as a yellow solid (70 mg, 0.14 mmol, 69%). Anal. (oxalate; $C_{32}H_{35}N_2ClO_7 \cdot 1.25H_2O$) C, H, N.

***N*-Cyclopropylmethyl-14*β*-[4′-(4″-chlorophenyl)-butanamino]-7,8-dihydronorcodeinone (5j).** Compound **6a** was treated with 4-(4′-chlorophenyl)butyl bromide, as in general procedure B, to afford *N*-cyclopropylmethyl-14*β*-[4′-(4″-chlorophenyl)-butanamino]-7,8-dihydronorcodeinone ethylene ketal as a colorless oil (51 mg, 0.09 mmol, 58%).

This was treated as in general procedure C to afford **5j** as a pale yellow solid (25 mg, 0.05 mmol, 63%). Anal. (oxalate; $C_{33}H_{39}N_2ClO_7 \cdot 1.25H_2O$) C, H, N.

***N*-Cyclopropylmethyl-14*β*-[4′-(4″-chlorophenyl)-butanamino]-7,8-dihydronormorphinone (4j).** Compound **6b** was treated with 4-(4′-chlorophenyl)butyl bromide, as in general procedure B, to afford *N*-cyclopropylmethyl-14*β*-[4′-(4″-chlorophenyl)-butanamino]-7,8-dihydronormorphinone ethylene ketal as a colorless oil (94 mg, 0.17 mmol, 49%).

This was treated as in general procedure C to afford **4j** as a pale yellow solid (40 mg, 0.08 mmol, 51%). Anal. (oxalate; $C_{32}H_{37}N_2ClO_7 \cdot 1.5H_2O$) C, H, N.

***N*-Cyclopropylmethyl-14*β*-(2-diethoxyphosphoryl-1-oxoethyl)-7,8-dihydronorcodeinone (11).** To a stirring solution of *N*-cyclopropylmethyl-14*β*-amino-7,8-dihydronorcodeinone (**7b**; 140 mg, 0.40 mmol) in tetrahydrofuran (3 mL) at −20 °C was added diethoxyphosphorylacetyl chloride (94 mg, 0.44 mmol) in tetrahydrofuran (1 mL). The mixture was allowed to warm and was stirred at room temperature for 0.5 h. Water was added, and the mixture was extracted with diethyl ether and then dichloromethane. The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, and the solvent was removed in

vacuo. Purification by column chromatography (5% CH_3OH in CH_2Cl_2) afforded **17** as a colorless oil (128 mg, 0.24 mmol, 60%).

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, mass spectra, infrared, melting point, and microanalysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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