Cinnamoyl Derivatives of 7α-Aminomethyl-6,14-*endo*-ethanotetrahydrothebaine and 7α-Aminomethyl-6,14-*endo*-ethanotetrahydrooripavine and Related Opioid Ligands

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A new series of ligands has been synthesized where the cinnamoyl group of the 14-cinnamoylamino morphinones has been introduced to the 7α-substituent of the 6,14-bridged oripavine series. In vitro the compounds were mostly low efficacy partial agonists or antagonists with some selectivity for the mu opioid receptor, with evidence of mu efficacy in vivo. The similarity in SAR between these 6,14-bridged oripavines and the 14-cinnamoylamino series suggests a similar mode of interaction with the mu opioid receptor.

Introduction

The 6,14-bridged oripavines with 7α-substituents have been extensively studied and have yielded the important veterinary medicines etorphine (**1**) and diprenorphine (**2b**) as well as buprenorphine (**2c**) which has found use as a clinical analgesic and more recently as a treatment for opiate abuse and dependence (Chart 1).[1] As mu opioid receptor (MOR) antagonists equivalent to naltrexone,[2] β-FNA,[3] and clocinnamox (C-CAM, **3a**),[4] the *N*-cyclopropylmethylnororipavine series has provided the hydroxyethyl derivative (**2a**)[5] and the cinnamoylaminomethyl derivatives (**4**).[6] The latter are, like **3**, high potency irreversible MOR antagonists with no in vivo antinociceptive activity. The antagonists **2a**, **2b**, **3**, **4** all possess a cyclopropylmethyl group at N_{17} and in various opioid series it has been found that replacing this with a methyl group greatly increases efficacy, particularly at MOR.[7] We here report an investigation of a series of 17-methyl analogues (**5**, **6**) of **4** from which long acting MOR partial agonists could emerge as alternatives to buprenorphine in the treatment of opiate abuse and dependence.

Synthesis. 7α-Aminomethyl-6,14-*endo*-ethanotetrahydrothebaine (**11**) was prepared from the known thebaine adduct (**9**)[8] in three steps (Scheme 1). Treatment of **9** with hydroxylamine hydrochloride under reflux afforded the oxime, with subsequent reduction using lithium aluminum hydride leading to amine **10**. Catalytic hydrogenation of the olefin bond gave 7α-aminomethyl-6,14-*endo*-ethanotetrahydrothebaine (**11**) in an overall yield of 23%. Boron tribromide[9]-mediated 3-O-demethylation at room-temperature gave 7α-aminomethyl-6,14-*endo*-ethanotetrahydrooripavine (**12**).

Acylation of 7α-aminomethyl-6,14-*endo*-ethanotetrahydrothebaine (**11**) using the appropriate acid chloride gave target compounds **5a**−**f**, while EDC promoted coupling with the appropriate acid furnished **5g**−**i**. In the acylation of 7α-aminomethyl-6,14-*endo*-ethanotetrahydrooripavine (**12**) a second equivalent of the acid chloride was used to afford the bisacylated derivative as an intermediate, with subsequent hydrolysis giving the desired phenols **6a**−**f** (Scheme 1).

As expected the 7α-cinnamylaminomethyl analogues **7**, **8** could not be accessed directly via an alkylation using the corresponding cinnamyl bromide, owing to the predominant formation of the dialkylated tertiary amine product. Instead a reductive amination approach was utilized. A two-stage protocol, treating amines **11** and **12** with the corresponding cinnamaldehyde, followed by reduction of the imine intermediate using sodium borohydride, was employed (Scheme 1).

C_7,C_8 ring-constrained analogues **18a** and **18b** were prepared as depicted in Scheme 2. First, cycloaddition of thebaine (**13**) with *N*-benzylmaleimide gave rise to **14** in quantitative yield with sequential reduction (to give **15**) and debenzylation, performed under standard hydrogenolysis conditions, affording **16**. This latter step proceeded in poor yield and under these conditions the 6,14-etheno bridge was not reduced. Demethylation of **16** at C_3, was best performed with boron tribromide, affording **17** in good yield. BBr_3 is known to demethylate opioid ligands at both C_3 and C_6;[9] however, the authors suggested that selective demethylations at C_3 could be achieved with an aminomethyl group in the 7α-position, which forms a complex with the boron atom thus blocking the reaction at C-6. It would appear that the constrained aminomethyl moiety of **16** was behaving similarly to the nonconstrained example. In a similar manner to the synthesis of **5** and **6**, the secondary amine was acylated to give rise to **18a** and **18b** in moderate yield.

Results

In displacement binding assays in recombinant human opioid receptors in which the displaced radioligands were [^{3}H]DAMGO (MOR), [^{3}H]U69593 (KOR), and [^{3}H]Cl-DPDPE (DOR),[10] the new ligands (**5**, **6**) showed high affinity for MOR. This was particularly true for the oripavine derivatives (**6**) which all had subnanomolar MOR affinity (Table 1). They had affinity for KOR and DOR in the nanomolar range resulting in MOR selectivity which was higher for the unsubstituted cinnamoylamino ligand (**6a**) than for the substituted analogues (**6b**−**f**). MOR affinity of the thebaine derivatives (**5**) was lower than that of the oripavine derivatives (**6**). The reduction in affinity was least in the 2′-chloro derivative (**6c** to **5c**; 2.5-fold) and greatest in the 4′-methyl derivative (**6d** to **5d**; 51-fold). Reduction in KOR and DOR affinity in the thebaine derivatives (**5**) compared to the oripavine derivatives (**6**) was as great, or greater, than reduction in MOR affinity so that MOR selectivity was higher in **5** than in **6**. Greatest selectivity was shown by

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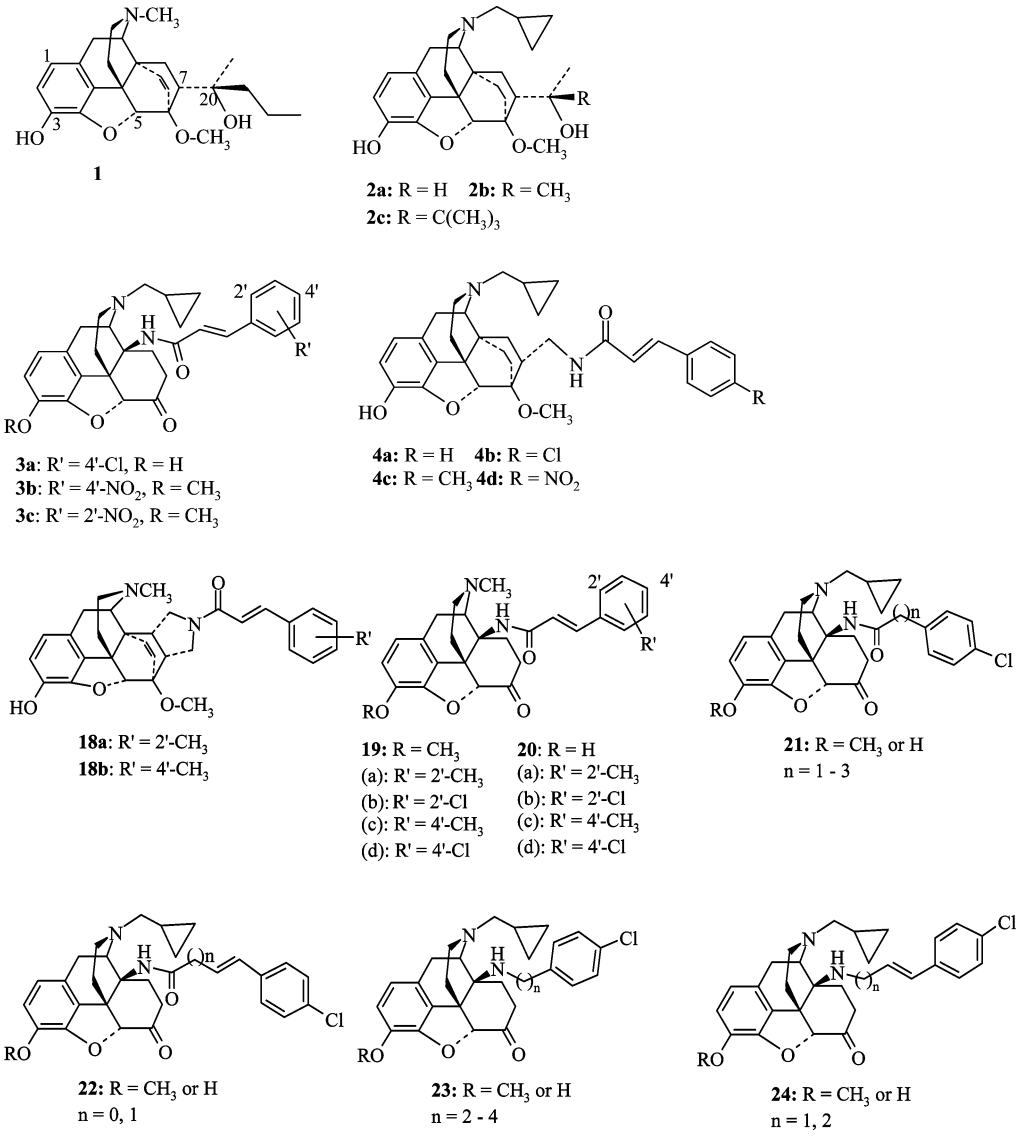
Chart 1. Structures



the 4′-nitro thebaine derivative (**5f**) which was 153-fold selective for MOR over DOR and 67-fold selective for MOR over KOR in the binding assays.

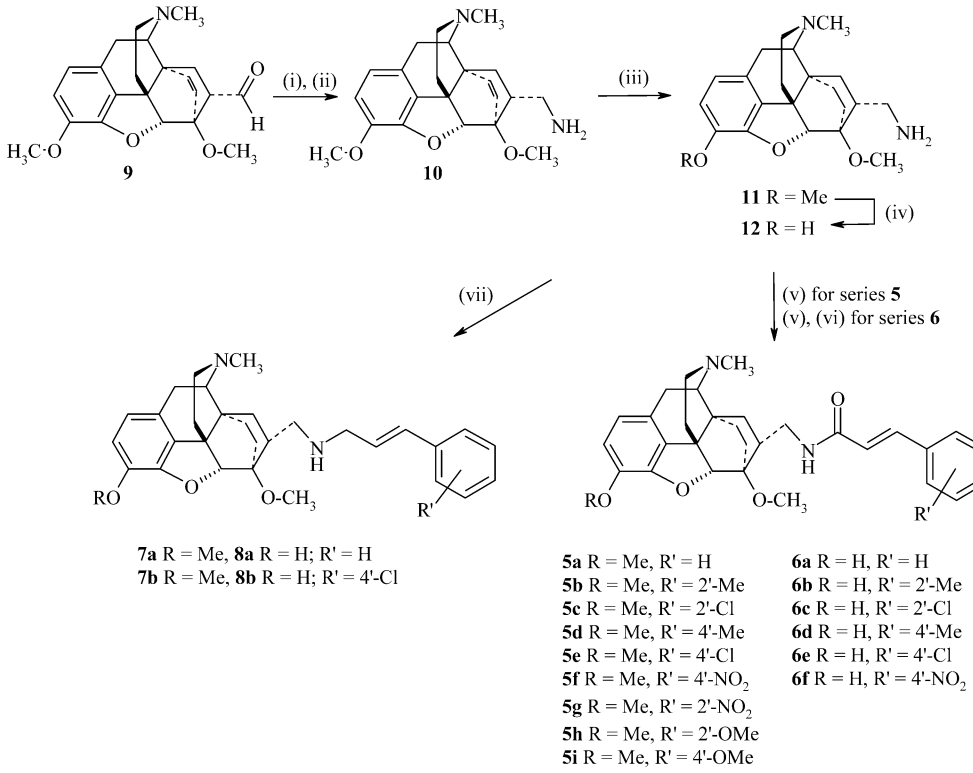
The in vitro assay used to determine opioid receptor functional activity was the [^{35}S]GTPγS stimulation assay which, like the binding assays, was performed on recombinant opioid receptors transfected into CHO cells.[10,11] Agonist efficacy at each opioid receptor was determined in comparison to the standard selective agonists DAMGO (MOR), U69593 (KOR), and DPDPE (DOR). In the MOR assay the oripavine derivatives (**6**) were potent low efficacy partial agonists with the exception of the 4′-methyl derivative (**6d**) which had very low MOR agonist efficacy (<20%) and was a potent antagonist of DAMGO (Table 2). The oripavine derivatives (**6**) were also KOR and DOR partial agonists of lower potency, in keeping with their OR binding affinities. The thebaine derivatives (**5**) showed greater potency as MOR partial agonists than as KOR and DOR partial agonists, though selectivity for MOR was less impressive than in the binding assays.

There was no great difference in MOR efficacy between the thebaine derivatives (**5**) and the equivalent oripavine derivatives (**6**) in the [^{35}S]GTPγS assays, but the potency of the thebaine-derived ligands was substantially lower (Table 2). KOR efficacy in the thebaine derivatives was higher than KOR efficacy in the equivalent oripavines for the unsubstituted (**5a**) and 2′-substituted derivatives (**5b**, **5c**) but lower for the 4′-substituted derivatives (**5d**, **5e**, **5f**). There was exceptional difference between the 2′-methyl thebaine derivative (**5b**; KOR agonist) and the equivalent oripavine derivative (**6b**; potent KOR antagonist).

The effect of replacing the amide carbonyl by methylene was investigated for the unsubstituted and 4′-chloro derivatives. In opioid receptor binding (Table 1) there was no great difference between the two series, but the amines (**7**, **8**) generally had lower affinity than the equivalent amides (**5**, **6**). The most significant feature in the [^{35}S]GTPγS assays (Table 2) was the higher MOR and KOR efficacy of the amine derivatives (**7a**, **7b**; **8a**, **8b**) when compared to the equivalent amides (**5a**, **5e**; **6a**, **6e**).

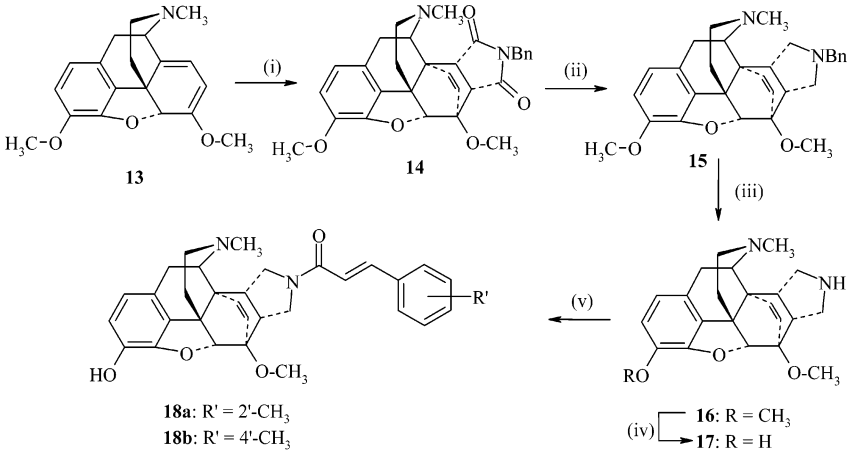
Binding affinities for the conformationally constrained analogues (**18a**, **18b**) were quite similar to those of the equivalent aminomethyl derivatives (**6b**, **6d**) (Table 1). In the functional assays (Table 2) **18a** and **18b** were moderately potent partial agonists for all three OR with no particular selectivity. The main differences from the equivalent aminomethyl derivatives (**6b**, **6d**) were in the KOR efficacy of the 2′-methyl-substituted ligands and in MOR efficacy of the 4′-methyl derivatives. In both cases the constrained analogues had substantially higher efficacy.

Scheme 1[a]



[a] Reagents and conditions: (i) $NH_2OH{\cdot}HCl$, EtOH/H_2O (1:1), reflux, 6 h, 78%; (ii) $LiAlH_4$, THF, reflux, overnight, 61%; (iii) H_2, Pd−C, EtOH, 50 °C, 40 psi, overnight, 60%; (iv) BBr_3, DCM, r.t., 0.25 h, 65%; (v) acid chloride, NEt_3, DCM, r.t., overnight; or acid, EDC, HOBt, DCM, r.t., overnight (vi); K_2CO_3, MeOH/H_2O (9:1), r.t., overnight; (vii) cinnamaldehyde, DCM, r.t., overnight, then $NaBH_4$, MeOH, r.t., 3 h.

Scheme 2[a]



[a] Reagents and conditions: (i) *N*-benzylmaleimide, toluene, reflux, 18 h, quantitative; (ii) $LiAlH_4$, THF, reflux, 16 h, 74%; (iii) 10% Pd/C, EtOH, HCl (concd), H_2 at 40 psi, 5 days, 22%; (iv) BBr_3, DCM, 15 min, 72%; (v) acid chloride, NEt_3, DCM, r.t., overnight.

Two of the new oripavine derivatives (**6b**, **6d**) were selected for evaluation in mouse antinociceptive assays (Table 3). **6b** in particular had a profile in [^{35}S]GTPγS assays similar to that of buprenorphine, i.e., moderate partial agonist at MOR and antagonist at KOR.[7] There was a difference at DOR where **6b** was a partial agonist and buprenorphine an antagonist,[7] but this was perceived not to be an important difference. Though no qualitative difference of antinociceptive effect between **6b** and **6d** was found (Table 3), there was a potency difference with the 2′-CH_3 (**6b**) derivative having 2−4-fold greater potency than the 4′-CH_3 (**6d**) derivative. Neither **6b** nor **6d** showed any antagonism of morphine when administered 30 min before the agonist in the tail flick assay (data not shown) whereas buprenorphine had AD_{50} 1.0 (0.3−3.3) mg/kg in this assay.[12] The substantial in vivo agonist effects of **6d** and the lack of demonstrable MOR antagonist effects is in contrast to the lack of any antinociceptive effect of the equivalent *N*-cyclopropylmethyl (N-CPM) derivative (**4c**) which is a powerful pseudoirreversible MOR antagonist.[6] Loss of MOR efficacy when N-Me is replaced by N-CPM is normal SAR in epoxymorphinan series of opioids.[7,13]

6b was further evaluated to determine duration of action in the mouse tail flick assay. An ED_{80} dose (3 mg/kg, s.c.) proved not to be long-acting with a duration of less than 2 h (Table 4). This is in contrast to the equivalent 14β-cinnamoylamino morphinone (**20a**) for which an ED_{80} dose had, in the same assay, a much longer duration of action, retaining 30% of its activity at 3 h and only becoming inactive at around 8 h.[19] At

Table 1. Binding Affinities of 7α-Cinnamoylamino- and 7α-Cinnamylamino-6,14-*endo*-ethanotetrahydrothebaine Derivatives and Corresponding Oripavine Derivatives to Cloned Human Opioid Receptors Transfected into Chinese Hamster Ovary (CHO) Cells[a]

			K_i (nM)		
ligand	R	R′	MOR	KOR	DOR
5a	CH_3	H	1.69 ± 0.34	23.7 ± 5.8	86.4 ± 16.4
5b	CH_3	2-CH_3	0.74 ± 0.20	21.0 ± 8.8	65.7 ± 23.0
5c	CH_3	2-Cl	0.63 ± 0.17	22.2 ± 6.2	94.1 ± 31.9
5d	CH_3	4-CH_3	11.8 ± 2.3	159 ± 54.0	246 ± 88
5e	CH_3	4-Cl	2.61 ± 0.18	155 ± 20.8	289 ± 105
5f	CH_3	4-NO_2	0.87 ± 0.07	58 ± 5.3	133 ± 2.3
5g	CH_3	2- NO_2	2.96 ± 0.91	29.8 ± 1.91	111 ± 0.40
5h	CH_3	2- OCH_3	1.98 ± 0.20	44.7 ± 2.74	87.9 ± 7.0
5i	CH_3	4- OCH_3	12.8 ± 3.24	109 ± 7.41	322 ± 37.4
6a	H	H	0.25 ± 0.04	5.30 ± 0.47	11.1 ± 0.46
6b	H	2-CH_3	0.14 ± 0.03	1.82 ± 0.06	3.41 ± 0.70
6c	H	2-Cl	0.25 ± 0.07	1.64 ± 0.12	7.59 ± 0.80
6d	H	4-CH_3	0.23 ± 0.01	3.11 ± 0.27	6.53 ± 1.84
6e	H	4-Cl	0.18 ± 0.01	1.85 ± 0.23	8.0 ± 0.42
6f	H	4-NO_2	0.19 ± 0.03	1.72 ± 0.04	5.38 ± 0.4
7a	CH_3	H	11.3 ± 0.14	26.4 ± 2.6	395 ± 100
7b	CH_3	4-Cl	34.2 ± 1.65	67.9 ± 19.7	741.55 ± 192
8a	H	H	0.39 ± 0.01	6.60 ± 0.86	38.6 ± 4.39
8b	H	4-Cl	0.68 ± 0.02	9.95 ± 2.03	60.3 ± 12.8
18a	H	2-CH_3	0.22 ± 0.0	0.52 ± 0.17	2.36 ± 0.61
18b	H	4-CH_3	0.48 ± 0.14	1.41 ± 0.22	4.83 ± 0.81
19b[b]	CH_3	2-Cl	0.68 ± 0.11	2.5 ± 0.32	0.58 ± 0.08
19d[b]	CH_3	4-Cl	0.60 ± 0.01	6.4 ± 2.0	1.0 ± 0.04
20b	H	2-Cl	0.15 ± 0.005	0.54 ± 0.20	0.08 ± 0.02
buprenorphine	-	-	1.5 ± 0.8	0.8 ± 0.09	4.5 ± 0.4
naltrexone	-	-	0.20 ± 0.01	0.40 ± 0.10	10.8 ± 3.00
morphine	-	-	1.1 ± 0.05	46.9 ± 14.5	140 ± 1.5

[a] K_i (nM) versus [^{3}H]DAMGO (mu), [^{3}H]U69593 (kappa), and [^{3}H]DPDPE (delta). Mean of two experiments, each carried out in triplicate. [b] Data from Nieland et al.[13] [c] All data supplied by NIDA Addiction Treatment Discovery Program.

Table 2. Functional Activity at Opioid Receptors from Stimulation of [^{35}S]GTPγS Binding

			EC_{50} (nM): % stimulation		
ligand	R	R′	MOR	KOR	DOR
5a	CH_3	H	41.5 ± 9.7; 34	131 ± 18; 51	160 ± 2.5; 74
5b	CH_3	2-CH_3	15.1 ± 3.6; 52	74.4 ± 18; 80	85.3 ± 22.3; 87
5c	CH_3	2-Cl	10.6 ± 1.8; 47	56.7 ± 12; 84	106 ± 14; 77
5d	CH_3	4-CH_3	47.4 ± 13; ANT	290 ± 4.8; 27	ND
5e	CH_3	4-Cl	32.3 ± 9.0; ANT	196 ± 5.7; ANT	ND
5f	CH_3	4-NO_2	26.0 ± 1.25; 24	133 ± 25; 22	214 ± 35; 90
5g	CH_3	2- NO_2	14.3 ± 1.28; 26	285 ± 19.3; 23	216 ± 18.8; 58
5h	CH_3	2-OCH_3	11.7 ± 0.88; 62	159 ± 7.11; 16	164 ± 45.2; 64
5i	CH_3	4-OCH_3	74.2 ± 4.17; 27	680 ± 115; 52	ND
6a	H	H	3.12 ± 1.2; 34	41.7 ± 2.6; 26	59.2 ± 13; 36
6b	H	2-CH_3	0.25 ± 0.04; 44	4.02 ± 0.50; ANT	7.23 ± 0.78; 63
6c	H	2-Cl	0.30 ± 0.08; 38	3.52 ± 0.09; 40	3.36 ± 0.18; 60
6d	H	4-CH_3	0.33 ± 0.02; ANT	9.88 ± 4.4; 43	15.9 ± 0.91; 51
6e	H	4-Cl	2.46 ± 0.86; 25	8.62 ± 0.04; 36	35.4 ± 0.03; 63
6f	H	4-NO_2	1.30 ± 0.32; 32	7.49 ± 1.4; 43	11.3 ± 0.48; 84
7a	CH_3	H	139 ± 17; 69	106 ± 34; 79	ND
7b	CH_3	4-Cl	149 ± 29; 34	233 ± 77; 75	ND
8a	H	H	5.51 ± 1.35; 93	1.78 ± 0.47; 88	26.2 ± 6.4; 33
8b	H	4-Cl	5.37 ± 0.41; 67	14.2 ± 3.7; 24	62.5 ± 11; 39
18a	H	2-CH_3	2.59 ± 0.46; 68	3.95 ± 0.88; 88	1.80 ± 0.07; 54
18b	H	4-CH_3	3.10 ± 0.34; 48	3.33 ± 0.22; 75	14.4 ± 0.38; 70
19b[b]	CH_3	2-Cl	0.50 ± 0.20; 108	8.5 ± 1.6; 78	2.2 ± 0.95; 110
19d[b]	CH_3	4-Cl	0.90 ± 0.45; 28	35 ± 11; 26	5.0 ± 1.2; 50
20b[b]	H	2-Cl	0.04 ± 0.005; 126	0.10 ± 0.03; 59	0.10 ± 0.005; 115
buprenorphine	-	-	14.8 ± 3; 18	> 10000; 0	ND
naltrexone	-	-	0.59 ± 0.04; ANT	1.9 ± 0.16; ANT	5.4 ± 0.75; ANT
morphine	-	-	15.6 ± 0.5; 93	484 ± 213; 62	316 ± 4.9; 103

[a] Percent maximal stimulation with respect to the standard agonists DAMGO (mu), U69593 (kappa), and DPDPE (delta). ANT indicates antagonist activity (K_e/nM) versus DAMGO, U69593, and DPDPE. Values are the mean of five or six experiments. ND indicates not determined. [b] Data from Nieland et al.[13] [c] All data supplied by NIDA Addiction Treatment Discovery Program.

105 min an ED_{80} dose of **6b** caused no antagonism of morphine's actions in the tail flick assay (data not shown).

Discussion

The primary objective of the study was to compare structure−activity relationships (SAR) for 7α-cinnamoylaminomethyl-thebaine and oripavine derivatives (**5**, **6**) with the equivalent 14-cinnamoylamino codeinone and morphinone derivatives (**19**, **20**). Of particular interest was the effect on MOR efficacy in the in vitro [^{35}S]GTPγS assays of orientation of methyl, chloro, and nitro substituents in the cinnamoyl aromatic ring. The 2′-methyl and 2′-chloro thebaine derivatives (**5b**, **5c**) clearly

Table 3. Antinociceptive Potencies of **6b** and **6d**[a]

ligand	tail flick ED_{50} (mg/ kg)	hot plate ED_{50} (mg/ kg)	phenylquinone writhing ED_{50} (mg/kg)
6b	1.76 (1.48−2.11)	1.00 (0.58−1.75)	0.63 (0.44−0.90)
6d	6.37 (2.57−15.80)	2.28 (1.34−3.88)	2.70 (1.74−4.20)
buprenorphine	0.4 (0.09−0.23)	0.035 (0.028−0.045)	0.016 (0.005−0.042)
morphine	5.8 (5.7−5.9)	0.98 (0.83−1.1)	0.23 (0.20−0.25)

[a] ED_{50} (95% confidence limits). Assays were performed by the Drug Evaluation Committee (DEC) of the College on Problems of Drug Dependence (CPDD). Full experimental details for these methods are given in ref 18.

Table 4. Duration of Action of an ED_{80} Dose of **6b** in the Mouse Tail Flick Assay[a]

minutes	% MPE ± SEM
20	83 ± 9.2
40	78 ± 11
60	57 ± 12
90	35 ± 7.6
105	31 ± 9.2
120	7.0 ± 5.1
150	2.0 ± 2.6

[a] Full experimental details for these methods are given in ref 18.

showed higher MOR and KOR efficacy than the 4′-substituted isomers (**5d**, **5e**) with the unsubstituted derivative (**5a**) coming in between. In this regard, the SAR for the new cinnamoylamino derivatives is similar to the SAR for the equivalent 14β-cinamoylamino-7,8-dihydrocodeinones (**19b**, **19d**; Table 2). In the thebaine series we were also able to compare the 2′-nitro- and 4′-nitrocinnamoyl derivatives (**5g**, **5f**). There was little difference in MOR and KOR efficacy and potency between **5g** and **5f** in contrast to the differences seen between the 2′- and 4′-chloro and -methyl thebaine derivatives (**5b**, **5c**, **5d**, **5e**). This difference of effect of substituent orientation was also seen in the 14-cinnamoylamino series where the 4′-nitro derivative (**3b**) had greater MOR efficacy and potency in vivo than the 2′-nitro derivative (**3c**).[13]

Though the 2′-substituted oripavine derivatives (**6b**, **6c**) had higher MOR efficacy in vitro than the 4′-substituted isomers (**6d**, **6e**), the differences were less marked than between the equivalent thebaine derivatives (**5b**, **5c**, **5d**, **5e**) and even less impressive when compared to the 14-cinnamoylamino derivatives (**19b**, **19d**). Despite these differences and the lower binding affinity and in vitro efficacy and potency of the thebaine and oripavine derivatives (**5**, **6**) when compared to the dihydrocodeinones (**19**) and dihydromorphinones (**20**), there is sufficient similarity of SAR between the series to make the general conclusion that the cinnamoyl aromatic rings in the 7α-position of the new series and the 14β-position of the codeinones and morphinones are also able to interact with MOR and KOR in a similar if not identical way.

The effects of replacing the amide carbonyl by methylene (in structures **7**, **8**) and in constraining the amine group in a pyrrolidine ring (in structures **18**) were not dramatic, but they generally showed higher MOR and KOR efficacy in [^{35}S]GTPγS assays than the unconstrained amides (**5**, **6**). This is in contrast with SAR in series of 14-amino-17-cyclopropylmethyl-7,8-dihydromorphinone derivatives (**21**−**24**) where over a range of side chain structures there was no significant difference in MOR efficacy in [^{35}S]GTPγS assays between the amide (e.g., **21**, **22**) and equivalent amine (**23**, **24**) side-chain structures.[14]

In vivo evaluation of **6b** and **6d** in mouse antinociceptive tests revealed them to be reasonably potent in assays using both thermal (tail flick and hot plate) and chemical (phenylquinone writhing) nociceptors. This suggests they have fairly high MOR efficacy since only MOR agonists respond well to thermal stimuli.[15] No MOR antagonism was observed in the tail flick assay using the standard protocol[18] where the test ligand is administered just prior to morphine, nor did **6b** act as a delayed antagonist once its agonist effects had diminished. Thus for **6d** there was substantial disparity between its MOR profile in vitro and in vivo. In the [^{35}S]GTPγS assay it was a potent MOR antagonist without agonist activity whereas in vivo it was a quite potent antinociceptive agent suggesting MOR efficacy equivalent to morphine. This kind of disparity has been found previously in the 14-cinnamoylamino series (**19**−**24**) and related to the lipophilicity of the side chain and its effect on the kinetics of MOR binding.[13,14] The predominant MOR agonism observed after peripheral administration in vivo would result from there being insufficient brain concentrations to effect significant receptor blockade. In vitro the test ligand is present in sufficient concentration to bind pseudoirreversibly via the lipophilic side chain so that its efficacy appears to be quite low.

The lack of an extended duration of action for **6b** in the tail flick assay is in contrast to that reported for **20a**, appearing to confirm the conclusions drawn from the in vitro assays that suggest a similar but nonidentical mode of binding to the receptor for the two series.

Experimental Section

Proton and carbon-13 nuclear magnetic resonance (NMR) spectra were obtained on a JEOL JNM-GX FT 300 MHz spectrometer. Chemical shifts (δ), with tetramethylsilane as a standard, are measured in parts per million (ppm) and coupling constants in hertz. Mass spectra were recorded on Fisons Autospectrometer using electron impac. Infra red (IR) spectra were obtained using a Perkin-Elmer 881 spectrometer. Microanalysis were obtained from a Carlo Erba EA 1108 analyzer, and the results were within ±0.4% of the theoretical values.

General Procedure A. 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 to rt and the solvent removed in vacuo. The residue was redissolved in anhydrous DCM and added dropwise to a solution of 7α-aminomethyl-6,14-*endo*-ethanotetrahydrothebaine (1.0 equiv) and triethylamine (1.1 equiv) in anhydrous DCM, and the mixture stirred at rt overnight. The solvent was removed in vacuo and the crude residue purified by column chromatography (5% MeOH in DCM). In the acylation of 7α-aminomethyl-6,14-*endo*-ethanotetrahydrooripavine, a second equivalent (2.2 equiv) of the corresponding acid chloride was used to afford the bis-acylated derivative. The crude residue was redissolved in methanol/water (9:1) before adding K_2CO_3 (5.0 equiv), and the mixture was stirred at room temperature overnight. The solvent was removed in vacuo and the crude residue purified by column chromatography (5% MeOH in DCM).

General Procedure B. EDC (2.0 equiv) was added to a stirred solution of the appropriate cinnamic acid (1.1 equiv) in DCM(5 mL), followed by HOBt (0.5 equiv). The reaction mixture was stirred for 10 min, and then 7α-aminomethyl-6,14-endo-ethanotetrahydrothebaine (**11**) (1.0 equiv) was added. After 16 h the solvent was removed in vacuo and the crude residue purified by column chromatography (DCM:MeOH:NH_4OH, 200:10:1) to afford the desired amides.

General Procedure C. To a solution of 7α-aminomethyl-6,14-*endo*-ethanotetrahydrothebaine/oripavine (1.0 equiv) in anhydrous CH_2Cl_2 was added the corresponding cinnamaldehyde (1.0 equiv), and the mixture was stirred at rt overnight. The solvent was removed in vacuo, the crude residue redissolved in MeOH and cooled to 0 °C, and sodium borohydride (3 equiv) added slowly, with further stirring for 3 h. The reaction was quenched through the addition of HCl (1 N), basified with NH_3 solution and extracted with DCM. The combined organic phases were washed with water and dried over $MgSO_4$, and the solvent was removed in vacuo. The crude residue was purified by column chromatography (5% MeOH in DCM).

7α-(Aminomethyl)-6,14-*endo*-ethenotetrahydrothebaine (10). A solution of **9**[8] (3.38 g, 9.21 mmol) and hydroxylamine hydrochloride (1.28 g, 18.43 mmol) in EtOH/water (60 mL, 1:1) was heated at reflux for 6 h. The solvent was removed in vacuo, and the mixture made basic with aqueous ammonia. The aqueous layer was extracted with DCM, the combined organic phases were washed with brine and dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo to afford the oxime intermediate as a solid (quant), which was used without further purification. A solution of the oxime (0.2 g, 0.52 mmol) in anhydrous THF (5 mL) was added to a slurry of LAH (0.06 g, 1.62 mmol) in anhydrous THF and the mixture heated at reflux under nitrogen overnight. The excess LAH was decomposed using sodium sulfate decahydrate, the mixture filtered through celite, and the solvent removed in vacuo to afford **10** as a white solid (1.62 g, 4.4 mmol, 48%).

7α-(Aminomethyl)-6,14-*endo*-ethanotetrahydrothebaine (11). A solution of **10** (0.16 g, 0.44 mmol) in EtOH (10 mL) was added to a slurry of 10% palladium-on-carbon (40% w/w) in EtOH (10 mL) and subsequently hydrogenated (40 psi) at 50 °C overnight. The mixture was then filtered through celite, the solvent removed in vacuo, and the crude residue purified by gravity elution chromatography (DCM:MeOH:NH_4OH, 83:15:2) to afford **11** as a white foam (100 mg, 0.27 mmol, 61%).

7α-[(4′-Chlorocinnamoyl)-aminomethyl]-6,14-*endo*-ethanotetrahydrothebaine (5e). 11 was treated with 4′-chlorocinnamoyl chloride as in general procedure A to afford **5e** as a white solid (147 mg, 0.27 mmol, 76%). Anal. (oxalate) ($C_{33}H_{37}N_2ClO_8 \cdot 2H_2O$) C, H, N.

7α-(Aminomethyl)-6,14-*endo*-ethanotetrahydrooripavine (12). To a solution of **11** (0.07 g, 0.20 mmol) in anhydrous dichloromethane (8 mL) was added a solution of boron tribromide (2.6 mL, 2.6 mmol, 1 M in CH_2Cl_2), and the mixture was stirred at room temperature under nitrogen for 15 min. The reaction was quenched with ice/ammonium hydroxide (1:1) and stirred for a further 30 min. Following extraction with chloroform/methanol (3:1), the organic layer was washed with brine and dried ($MgSO_4$) and the solvent removed in vacuo. Purification by gravity elution chromatography (DCM:MeOH:NH_4OH, 82.5:15:2.5) afforded **12** as a solid (52 mg, 0.14 mmol, 70%).

7α-[(4′-Chlorocinnamoyl)-aminomethyl]-6,14-*endo*-ethanotetrahydrooripavine (6e). 12 was treated with 4′-chlorocinnamoyl chloride as in general procedure A to afford **6e** as a white solid (76 mg, 0.15 mmol, 43%). Anal. (oxalate) ($C_{32}H_{35}N_2ClO_8 \cdot 2H_2O$) C, H, N.

7α-[(Cinnamyl)-aminomethyl]-6,14-*endo*-ethanotetrahydrooripavine (8a). 12 was treated with cinnamyl bromide as in general procedure C to afford **8a** as a white solid (109 mg, 0.23 mmol, 61%). Anal. (oxalate) ($C_{32}H_{38}N_2O_7 \cdot CH_2Cl_2 \cdot H_2O$) C, H, N.

1′-Benzyl-2′,5′-dioxo-[7α,8α:3′,4′]-pyrrolidino-6,14-*endo*-ethenotetrahydrothebaine (14). A mixture of thebaine (13) (1.6 g, 5.1 mmol) and *N*-benzylmaleimide (1.4 g, 7.7 mmol) in toluene (30 mL) was heated at reflux for 18 h. The solvent was removed in vacuo to afford **14** as an orange solid (quant), which was used without further purification.

1′-Benzyl-[7α,8α:3′,4′]-pyrrolidino-6,14-*endo*-ethenotetrahydrothebaine (15). To a slurry of LAH (0.58 g, 15.43 mmol) in anhydrous THF (10 mL) at rt under nitrogen was added **14** (2.16 g, 4.34 mmol) in anhydrous THF (20 mL), and the suspension was heated at reflux for 16 h. The mixture was then filtered through celite and the solvent removed in vacuo. The residue was then purified by gravity elution chromatography (DCM:MeOH, 97:3) to afford **15** as a white foam (1.52 g, 3.23 mmol, 74%).

[7α,8α:3′,4′]-Pyrrolidino-6,14-*endo*-ethenotetrahydrothebaine (16). To a solution of **15** (1.41 g, 3.0 mmol) in ethanol (10 mL) were added concentrated hydrochloric acid (0.62 mL, 7.52 mmol) and 10% palladium-on-carbon (40% w/w), and the mixture was hydrogenated (40 psi) at room temperature for 5 d. The mixture was then filtered through celite and the solvent removed in vacuo to afford **16** as a white solid (0.24 g, 0.64 mmol, 22%); with 63% recovery of starting material.

[7α,8α:3′,4′]-Pyrrolidino-6,14-*endo*-ethenotetrahydrooripavine (17). To a solution of **16** (0.07 g, 0.15 mmol) in anhydrous DCM (6 mL) at rt under nitrogen was added a solution of boron tribromide (2.0 mL, 2.0 mmol, 1 M in CH_2Cl_2), and the mixture was stirred for 15 min. The mixture was then quenched with ice/ammonia (50:50) and stirred for further 30 min. The organic layer was extracted with DCM:MeOH (3:1), the combined organic phases were washed with brine and dried over anhydrous $MgSO_4$, and the solvent removed in vacuo. The crude residue was then purified by gravity elution chromatography (DCM:MeOH:NH_4OH, 82.5:15:2.5) to afford **17** as a light brown foam (40 mg, 0.11 mmol, 72%).

1′-(*p*-Methylcinnamoyl)-[7α,8α:3′,4′]-pyrrolidino-6,14-*endo*-ethenotetrahydrooripavine (18b). 17 was treated as in general procedure A with purification by gravity elution chromatography ($CHCl_3$:CH_3OH:NH_4OH, 94:5:1) and preparative thin layer chromatography affording **18b** as a white solid (90 mg, 0.18 mmol, 43%). Anal. (HCl) ($C_{32}H_{35}N_2O_4Cl \cdot CHCl_3 \cdot 0.25H_2O$) C, H, N.

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

References

(1) Lewis, J. W.; Husbands, S. M. The Orvinols and Related Opioids − High Affinity Ligands with Diverse Efficacy Profiles. *Curr. Pharm. Des.* **2004**, *10*, 717−732.

(2) Resnick, R. B.; Volavka, J.; Freedman, A. M.; Thomas, M. Studies of EN-1639A (naltrexone): a new narcotic antagonist. *Am. J. Psychiatry* **1974**, *131*, 646−650.

(3) Portoghese, P. S.; Larson, D. L.; Sayre, L. M.; Fries, D. S.; Takemori, A. E. A novel opioid receptor site directed alkylating agent with reversible agonistic properties. *J. Med. Chem.* **1980**, *23*, 233−234.

(4) Comer, S. D.; Burke, T. F.; Lewis, J. W.; Woods, J. H. Clocinnamox: a novel, systemically active irreversible opioid antagonist. *J. Pharmacol. Exp. Ther.* **1992**, *262*, 1051−1056.

(5) Lewis, J. W. Ring C-bridged derivatives of thebaine and oripavine. In *Advances in Biochemical Psychopharmacology*; Braude, M. C.; Harris, L. S.; May, E. L.; Smith, J. P.; Villarreal, J. E., Eds.; Raven Press, New York, 1974; Vol 8, pp 123−136.

(6) Derrick, I.; Lewis, J. W.; Woods, J. H.; Broadbear, J.; Plumer, H. Cinnamoylamidomethyloripavines: Preliminary in-vivo evaluation of potential new affinity ligands for opioid receptors. *Analgesia* **1995**, *1*, 386−389.

(7) Husbands, S. M.; Lewis, J. W. Structural Determinants of Efficacy for κ-Opioid Receptors in the Orvinol Series: 7,7-Spiro Analogues of Buprenorphine. *J. Med. Chem.* **2000**, *43*, 139−141.

(8) Bentley, K. W.; Hardy, D. G. Novel analgesics and molecular rearrangements in the morphine-thebaine group. I. Ketones derived from 6,14-endo-ethenotetrahydrothebaine. *J. Am. Chem. Soc.* **1967**, *89*, 3267−3273.

(9) Kopcho, J. J.; Schaeffer, J. C. Selective O-demethylation of 7α-(aminomethyl)-6,14-endo-ethenotetrahydrothebaine. *J. Org. Chem.* **1986**, *51*, 1620−1622.

(10) Zaveri, N.; Polgar, W. E.; Olsen, C. M.; Kelson, A. B.; Grundt, P.; Lewis, J. W.; Toll, L. Characterization of opiates, neuroleptics and synthetic analogs at ORL-1 and opioid receptors. *Eur. J. Pharmacol.* **2001**, *428*, 29−36.

(11) Traynor, J. R.; Nahorski, S. R. Modulation by mu-opioid agonists of guanosine-5′-O-(3-[S-35]thio)triphosphate binding to membranes from human neuroblastoma SH-SY5Y cells. *Mol. Pharmacol.* **1995**, *47*, 848−854.
(12) Aceto, M. D.; Harris, L. S.; May, E. L. Dependence studies of new compounds in the rhesus monkey, rat and mouse. (1985). *NIDA Res. Monogr.* **1986**, *67*, 399−452. Compound designated NIH8805.
(13) Nieland, N. P. R.; Moynihan, H.; Carrington, S.; Broadbear, J.; Woods, J. H.; Traynor, J. R.; Husbands, S. M.; Lewis, J. W. Structural Determinants of Opioid Activity in Derivatives of 14-Aminomorphinones: Effect of Substitution in the Aromatic Ring of Cinnamoylaminomorphinones and codeinones. *J. Med. Chem.* **2006**, *49*, 5333−5338.
(14) Rennison, D.; Moynihan, H.; Traynor, J. R.; Lewis, J. W.; Husbands, S. M. Structural Determinants of Opioid Activity in Derivatives of 14-Aminomorphinones: Effects of Changes to the C14-amino to Aryl Ring Linker Chain. *J. Med. Chem.* **2006**, *49*, 6104−6110.
(15) Tyers, M. B. Classification of opiate receptors that mediate antinociception in animals. *Br. J. Pharmacol.* **1980**, *69*, 503−512.
(16) Piggot, N. G.; Derrick, I.; Moynihan, H. A.; Husbands, S. M.; Lewis, J. W. Modeling of fumaramido and cinnamoylamido derivatives in epoxymorphinans. Correlation with pharmacological profiles. *Analgesia* **1995**, *1*, 647−650.
(17) Derrick, I.; Husbands, S. M.; Broadbear, J.; Traynor, J. R.; Woods, J. H.; Lewis, J. W. Cinnamoyl derivatives of 7α-amino and 7α-(aminomethyl)-N-(cyclopropylmethyl)-6,14-endoethanotetrahydrooripavines are high potency opioid antagonists. *Helv. Chim. Acta* **2000**, *83*, 3122−3130.
(18) Aceto, M. D.; Harris, L. S.; Bowman, E. R. Etorphines: μ-opioid receptor-selective antinociception and low physical dependence capacity. *Eur. J. Pharmacol.* **1997**, *338*, 215−223.
(19) Aceto, M. D.; Bowman, E. R.; Harris, L. S.; May, E. L. Dependence studies of new compounds in the rhesus monkey, rat and mouse. (1999). *NIDA Res. Monogr.* **2000**, *180*, 346−404. Compound designated NIH10932.

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