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Cinnamoyl Derivatives of 7 α -Aminomethyl-6,14-endoethanotetrahydrothebaine and 7 α -Aminomethyl-6,14-endoethanotetrahydrooripavine and Related Opioid Ligands

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Abstract

A new series of ligands has been synthesized where the cinnamoyl group of the 14-cinnamoylamino morphinones has been introduced to the 7 α -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 7 α -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.¹ As mu opioid receptor (MOR) antagonists equivalent to naltrexone,² β -FNA³ and clocinnamox (C-CAM, **3a**),⁴ the N-cyclopropylmethylnororipavine series has provided the hydroxymethyl derivative (**2a**)⁵ and the cinnamoylaminoethyl 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 N₁₇ 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

7 α -Aminomethyl-6,14-endoethanotetrahydrothebaine (**11**) was prepared from the known thebaine adduct (**9**)⁸ in 3 steps (Scheme 1). Treatment of **9** with hydroxylamine hydrochloride under reflux afforded the oxime, with subsequent reduction using lithium aluminium hydride leading to amine **10**. Catalytic hydrogenation of the olefin bond gave 7 α -aminomethyl-6,14-endoethanotetrahydrothebaine (**11**) in an overall yield of 23%. Boron tribromide⁹ mediated 3-O-demethylation at room temperature gave 7 α -aminomethyl-6,14-endoethanotetrahydrooripavine (**12**).

Acylation of 7 α -aminomethyl-6,14-endoethanotetrahydrothebaine (**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 7 α -aminomethyl-6,14-endoethanotetrahydrooripavine (**12**) a second equivalent of the acid chloride was used to afford the bis-acylated derivative as an intermediate, with subsequent hydrolysis giving the desired phenols **6a** – **f** (Scheme 1).

As expected the 7 α -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).

C₇,C₈ 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 C₃, was best performed with boron tribromide, affording **17** in good yield. BBr₃ is known to demethylate opioid ligands at both C₃ and C₆,⁹ however, the authors suggested that selective demethylations at C₃ could be achieved with an aminomethyl group in the 7 α -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 non-constrained 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 [³H]DAMGO (MOR), [³H]U69593 (KOR) and [³H]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**–**6f**). 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 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 [³⁵S]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 [³⁵S]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 [³⁵S]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.

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 [³⁵S]GTPγS assays similar to that of buprenorphine, ie 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 antagonist⁷ 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'-CH₃ (**6b**) derivative having 2–4-fold greater potency than the 4'-CH₃ (**6d**) derivative. Neither **6b** nor **6d** showed any antagonism of morphine when co-administered 30 min before the agonist in the tail flick assay (data not shown) whereas buprenorphine had AD₅₀ 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 But 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 ED₈₀ dose (3 mg/kg, s.c.) proved not to be long-acting with a duration of less than 2 hours (Table 4). This is in contrast to the equivalent 14β-cinnamoylamino morphinone (**20a**) for which an ED₈₀ dose had, in the same assay, a much longer duration of action, retaining 30% of its activity at 3 hours and only becoming inactive at around 8 hours.¹⁹ At 105 minutes an ED₈₀ 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-cinnamoylamino methylthebaine 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* [³⁵S]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 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-cinnamoylamino-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 [³⁵S]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 [³⁵S]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 protocol¹⁸ 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 [³⁵S]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 non-identical mode of binding to the receptor for the two series.

Experimental

Proton and carbon-13 nuclear magnetic resonance (n.m.r.) 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 (p.p.m.) and coupling constants in Hz. Mass spectra were recorded on Fisons Autospectrometer using electron impact. Infra red (I.R.) spectra were obtained using a Perkin-Elmer 881 spectrometer. Microanalysis were obtained from a Carlo Erba EA 1108 analyser, and the results were within $\pm 0.4\%$ of the theoretical values.

General Procedure A

A suspension of oxalyl chloride (8.8 eqv) and the corresponding carboxylic acid (1.1 eqv) 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 7 α -aminomethyl-6,14-endo-ethanotetrahydrothebaine (1.0 eqv) and triethylamine (1.1 eqv) 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 7 α -aminomethyl-6,14-endoethanotetrahydrooripavine, a second equivalent (2.2 eqv) 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 K₂CO₃ (5.0 eqv), and the mixture 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 eqv) was added to a stirred solution of the appropriate cinnamic acid (1.1 eqv) in DCM (5 mL), followed by HOBt (0.5 eqv). The reaction mixture was stirred for 10 mins and then 7 α -aminomethyl-6,14-endo-ethanotetrahydrothebaine (**11**) (1.0 eqv) was added. After 16 h the solvent was removed *in vacuo* and the crude residue purified by column chromatography (DCM:MeOH:NH₄OH, 200:10:1) to afford the desired amides.

General Procedure C

To a solution of 7 α -aminomethyl-6,14-endoethanotetrahydrothebaine/oripavine (1.0 eqv) in anhydrous CH₂Cl₂ was added the corresponding cinnamaldehyde (1.0 eqv) and the mixture stirred at rt overnight. The solvent was removed *in vacuo* and the crude residue redissolved in MeOH, cooled to 0 °C and sodium borohydride (3 eqv) added slowly, with further stirring for 3 h. The reaction was quenched through the addition of HCl (1 N), basified with NH₃ solution and extracted with DCM. The combined organic phases were washed with water, dried over MgSO₄ and the solvent removed *in vacuo*. The crude residue was purified by column chromatography (5% MeOH in DCM).

7 α -(Aminomethyl)-6,14-endoethenotetrahydrothebaine (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 and the combined organic phases washed with brine, dried over anhydrous MgSO₄ and the solvent 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 sulphate 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%).

7 α -(Aminomethyl)-6,14-endoethanotetrahydrothebaine (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 atm) 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:NH₄OH, 83:15:2) to afford **11** as a white foam (100 mg, 0.27 mmol, 61%).

7 α -[(4'-Chlorocinnamoyl)-aminomethyl]-6,14-endoethanotetrahydrothebaine (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) (C₃₃H₃₇N₂ClO₈·2H₂O) CHN.

7 α -(Aminomethyl)-6,14-endoethanotetrahydrooripavine (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, 1M in CH₂Cl₂) and the mixture 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, dried (MgSO₄) and the solvent removed *in vacuo*. Purification by gravity elution chromatography (DCM:MeOH:NH₄OH, 82.5:15:2.5) afforded **12** as a solid (52 mg, 0.14 mmol, 70%).

7 α -[(4'-Chlorocinnamoyl)-aminomethyl]-6,14-endoethanotetrahydrooripavine (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) (C₃₂H₃₅N₂ClO₈·2H₂O) CHN.

7 α -[(Cinnamyl)-aminomethyl]-6,14-endoethanotetrahydrooripavine (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) (C₃₂H₃₈N₂O₇·CH₂Cl₂·H₂O) CHN.

1'-Benzyl-2',5'-dioxo-[7 α ,8 α :3',4']-pyrrolidino-6,14-endoethenotetrahydrothebaine (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-[7 α ,8 α :3',4']-pyrrolidino-6,14-endoethenotetrahydrothebaine (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 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%).

[7 α ,8 α :3',4']-Pyrrolidino-6,14-endoethenotetrahydrothebaine (**16**)

To a solution of **15** (1.41 g, 3.0 mmol) in ethanol (10 mL) was added concentrated hydrochloric acid (0.62 mL, 7.52 mmol) and 10% palladium-on-carbon (40% w/w) and the mixture 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.

[7 α ,8 α :3',4']-Pyrrolidino-6,14-endoethenotetrahydrooripavine (**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, 1M in CH₂Cl₂) and the mixture 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 washed with brine, dried over anhydrous MgSO₄ and the solvent removed *in vacuo*. The crude residue was then purified by gravity elution chromatography (DCM:MeOH:NH₄OH, 82.5:15:2.5) to afford **17** as a light brown foam (40 mg, 0.11 mmol, 72%).

1'-(p-Methylcinnamoyl)-[7 α ,8 α :3',4']-pyrrolidino-6,14-endoethenotetrahydrooripavine (**18b**)

17 was treated as in general procedure A with purification by gravity elution chromatography (CHCl₃:CH₃OH:NH₄OH, 94:5:1) and preparative thin layer chromatography affording **18b** as a white solid (90 mg, 0.18 mmol, 43%). Anal. (HCl) (C₃₂H₃₅N₂O₄Cl·0.25 H₂O) CHN.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Reagents and Conditions: (i) NH₂OH.HCl, EtOH/H₂O (1:1), reflux, 6 h, 78%; (ii) LiAlH₄, THF, reflux, overnight, 61%; (iii) H₂, Pd-C, EtOH, 50 °C, 40 atm, overnight, 60%; (iv) BBr₃, DCM, r.t., 0.25 h, 65%; (v) Acid chloride, NEt₃, DCM, r.t., overnight; or Acid, EDC, HOBT, DCM, r.t., overnight (vi); K₂CO₃, MeOH/H₂O (9:1), r.t., overnight; (vii) Cinnamaldehyde, DCM, r.t., overnight, then NaBH₄, MeOH, r.t., 3 h.

Scheme 2.

Reagents and Conditions: (i) N-benzylmaleimide, toluene, reflux, 18 h, quantitative; (ii) LiAlH₄, THF, reflux, 16 h, 74%; (iii) 10% Pd/C, EtOH, HCl (conc.), H₂ at 40 psi, 5 days, 22%; (iv) BBr₃, DCM, 15 min, 72%; (v) Acid chloride, NEt₃, DCM, r.t., overnight.

Binding affinities of 7 α -cinnamoylamino- and 7 α -cinnamylamino-6,14-endoethanotetrahydrothebaine derivatives and corresponding oripavine derivatives to cloned human opioid receptors transfected into Chinese hamster ovary (CHO) cells.^a

Table 1

Ligand	R	R'	MOR	Ki (nM)	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

^aKi (nM) versus [³H]DAMGO (nM), [³H]U69593 (kappa) and [³H]DPDPE (delta). Mean of two experiments, each carried out in triplicate

^bdata from Nieland et al¹³

^call data supplied by NIDA Addiction Treatment Discovery Program.

Table 2
Functional activity at opioid receptors from stimulation of [³⁵S]GTPγS binding.

Ligand	R	R'	MOR EC ₅₀ (nM): % Stim'	KOR EC ₅₀ (nM): % Stim'	DOR EC ₅₀ (nM): % Stim'
5a	CH ₃	H	41.5±9.7	131±18	160±2.5
5b	CH ₃	2'-CH ₃	15.1±3.6	52	85.3±22.3
5c	CH ₃	2'-Cl	10.6±1.8	47	106±14
5d	CH ₃	4'-CH ₃	47.4±13	ANT	ND
5e	CH ₃	4'-Cl	32.3±9.0	ANT	ND
5f	CH ₃	4'-NO ₂	26.0±1.25	24	214±35
5g	CH ₃	2'-NO ₂	14.3±1.28	26	216±18.8
5h	CH ₃	2'-OCH ₃	11.7±0.88	62	164±45.2
5i	CH ₃	4'-OCH ₃	74.2±4.17	27	ND
6a	H	H	3.12±1.2	34	59.2±13
6b	H	2'-CH ₃	0.25±0.04	44	7.23±0.78
6c	H	2'-Cl	0.30±0.08	38	3.36±0.18
6d	H	4'-CH ₃	0.33±0.02	ANT	15.9±0.91
6e	H	4'-Cl	2.46±0.86	25	35.4±0.03
6f	H	4'-NO ₂	1.30±0.32	32	11.3±0.48
7a	CH ₃	H	139±17	69	ND
7b	CH ₃	4'-Cl	149±29	34	ND
8a	H	H	5.51±1.35	93	26.2±6.4
8b	H	4'-Cl	5.37±0.41	67	62.5±11
18a	H	2'-CH ₃	2.59±0.46	68	1.80±0.07
18b	H	4'-CH ₃	3.10±0.34	48	14.4±0.38
19b ^b	CH ₃	2'-Cl	0.50±0.20	108	2.2±0.95
19d ^b	CH ₃	4'-Cl	0.90±0.45	28	5.0±1.2
20b ^b	H	2'-Cl	0.04±0.005	126	0.10±0.005
Buprenorphine	-	-	14.8 ± 3	18	ND
Naltrexone	-	-	0.59±0.04	ANT	5.4±0.75
Morphine	-	-	15.6±0.5	93	316±4.9

^a Percent maximal stimulation with respect to the standard agonists DAMGO (mu), U69593 (kappa) and DPDPE (delta). ANT indicates antagonist activity (Ke/nM) versus the DAMGO, U69593 and DPDPE. Values are the mean of 5 or 6 experiments. ND indicates Not Determined.

^b data from Nieland et al ¹³

^c all data supplied by NIDA Addiction Treatment Discovery Program.

Table 3Antinociceptive 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)

^aED₅₀ (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 4Duration of action of an ED₈₀ dose of 6b in the mouse tail flick assay.

Minutes	% MPE $\pm$ SEM
20	83 $\pm$ 9.2
40	78 $\pm$ 11
60	57 $\pm$ 12
90	35 $\pm$ 7.6
105	31 $\pm$ 9.2
120	7.0 $\pm$ 5.1
150	2.0 $\pm$ 2.6

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