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Fumaroylamino-4,5-epoxymorphinans and Related Opioids with Irreversible μ Opioid Receptor Antagonist Effects

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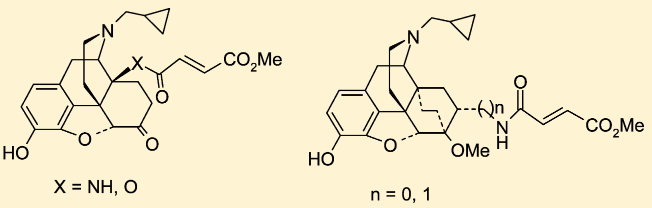
Supporting Information



ABSTRACT: We have previously shown that cinnamoyl derivatives of 14β-amino-17-cyclopropylmethyl-7,8-dihydronormorphinone and 7α-aminomethyl-6,14-endoethanonororipavine have pronounced pseudoirreversible μ opioid receptor (MOR) antagonism. The present communication describes the synthesis and evaluation of fumaroylamino analogues of these cinnamoylamino derivatives together with some related fumaroyl derivatives. The predominant activity of the new ligands was MOR antagonism. The fumaroylamino analogues (**2a**, **5a**) of the pseudoirreversible antagonist cinnamoylamino morphinones and oripavines (**2b**, **5b**) were themselves irreversible antagonists in vivo. However the fumaroylamino derivatives had significantly higher MOR efficacy than the cinnamoylamino derivatives in mouse antinociceptive tests. Comparison of **2a** and **5a** with the prototypic fumaroylamino opioid β-FNA (**1a**) shows that they have similar MOR irreversible antagonist actions but differ in the nature of their opioid receptor agonist effects; **2a** is a predominant MOR agonist and **5a** shows no opioid receptor selectivity, whereas the agonist effect of β-FNA is clearly κ opioid receptor (KOR) mediated.

INTRODUCTION

Investigation of the pharmacology associated with the individual opioid receptors, μ (MOR), κ (KOR), and δ (DOR), has been majorly advanced by the availability of antagonists selective for each of them. For MOR, one of the most well used antagonists has been β-FNA (**1a**, Chart 1),[1] which owes its selectivity to the presence of the fumaroylamino group preferentially interacting covalently as a Michael acceptor with the amino group of Lys233 in the MOR.[2] β-FNA also has KOR agonist activity of short duration.[1] Our interest in this field has been primarily in epoxymorphinan structures with cinnamoylamino substituents.[3−7] Though the 6β-cinnamoylamino analogue (**1b**) of **1a** had predominantly KOR agonist activity in vivo,[8] the *p*-chloro- and *p*-methylcinnamoylamino derivatives (**1c**, **1d**) had a profile more similar to that of **1a**.[9]

In contrast the 14-cinnamoylaminodihydromorphinones clocinnamox (C-CAM, **2c**) and methcinnamox (M-CAM, **2d**) had no significant opioid receptor agonist activity in vitro or in vivo but were MOR-selective antagonists of greater potency and longer duration than **1a**.[7] Though there was no evidence of covalent binding to MOR, **2c** and **2d** were able to cause long-term inhibition of MOR more effectively than **1a** and have been categorized as pseudoirreversible MOR antagonists.[7,10] The oripavine-related cinnamoylaminomethyl derivative **5b** has an opioid receptor profile similar to those of **2c** and **2d**.[6,11]

One of our particular aims in this field has been to discover compounds with a profile not dissimilar to that of the opiate abuse treatment agent buprenorphine.[12] Buprenorphine is a partial agonist at MOR with a long duration of action. When the agonist action is blunted, which occurs following repeated dosing when tolerance has developed, buprenorphine becomes a pseudoirreversible antagonist[13] that can block the actions of subsequently administered opiates. In addition to this activity at the MOR, buprenorphine is an antagonist at KOR and DOR. There has recently been interest in a combination of buprenorphine with sufficient naltrexone to essentially eliminate the MOR partial agonist effect, creating a functional MOR/KOR/DOR antagonist.[14] This combination could be used to prevent relapse in recovering opiate addicts. Since the cinnamoylamino (**2**) derivatives had also shown similar irreversible MOR antagonist characteristics compared to buprenorphine and also bound to KOR and DOR, it was of interest to determine what effect replacement of the cinnamoylamino group by a fumaroylamino moiety would have on their activity and whether ligands with profiles of interest for the treatment of drug abuse, or prevention of relapse to drug taking, could be obtained. Significant similarities between the

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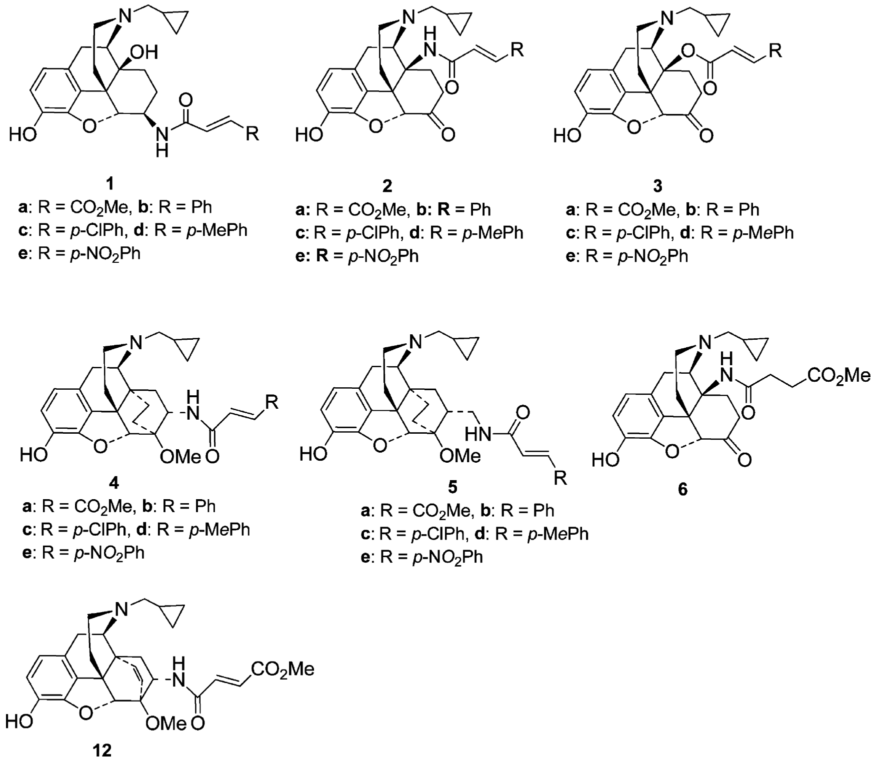
Chart 1

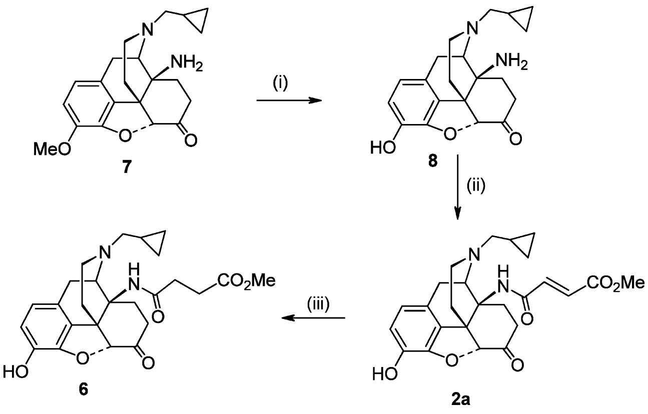


series have been found, while some notable differences in pharmacological profile were also noted.

SYNTHESIS

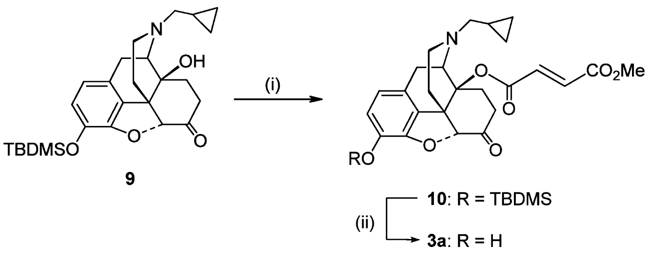
2a, **4a**, and **5a** were prepared by acylation of the known primary amines (**8**, **11a**, **11b**)[3,6] with methyl (3-chloroformyl)acrylate (Schemes 1 and 3), while hydrogenation of **2a** yielded **6** in respectable yield (Scheme 1). Acylation of TBDMS-protected naltrexone (**9**) with methylfumaroyl anhydride followed by removal of the protecting group allowed access to **3a** (Scheme 2).

Scheme 1[a]



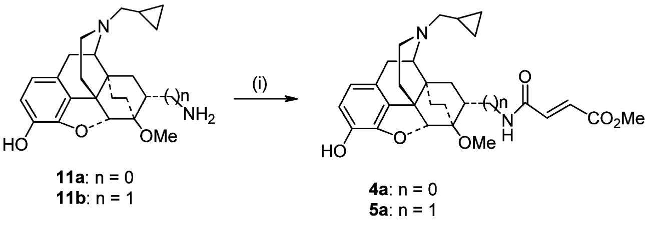
[a](i) BBr_3, CH_2Cl_2 (50%); (ii) $MeO_2CCHCHCOCl$, Na_2CO_3, THF, H_2O (81%); (iii) H_2, Pd/C, MeOH (62%).

Scheme 2[a]



[a](i) $(MeO_2CCHCHCO)_2O)$, toluene, heat (69%); (ii) 6 M HCl, MeOH (37%).

Scheme 3[a]



[a](i) $MeO_2CCHCHCOCl$, NEt_3, CH_2Cl_2 (**4a**, 65%; **5a**, 48%).

RESULTS

Opioid receptor binding studies were conducted in Hartley guinea pig brain membranes in which the displaced radioligands were [^{3}H]DAMGO (MOR), [^{3}H]Cl-DPDPE (DOR), and [^{3}H]U69593 (KOR) using previously reported procedures.[14] The results are shown in Table 1; the four fumaroyl derivatives (**2a**, **3a**, **4a**, **5a**) and one dihydrofumaroyl derivative (**6**) all showed high affinity for all three opioid receptors, although **4a** had lower affinity at MOR than the other ligands, while **3a** had lower affinity at DOR and had a binding profile quite similar to that of **1a**.

Table 1. Opioid Receptor Binding Affinities (K_i, nM) for Ligands in Hartley Guinea Pig Brain Membrane

ligand	K_i, nM[a]		
	MOR	DOR	KOR
2a	0.24 ± 0.03	1.50 ± 0.57	0.50 ± 0.01
3a	0.2 ± 0.05	6.0 ± 2.05	0.80 ± 0.15
6	0.7 ± 0.15	1.6 ± 0.3	0.5 ± 0.05
4a	2.8 ± 0.15	2.6 ± 0.01	1.9 ± 0.6
5a	0.9 ± 0.05	0.7 ± 0.01	2.8 ± 0.05
4b[b]	0.9 ± 0.35	1.1 ± 0.35	1.3 ± 0.45
5b[b]	0.7 ± 0.25	0.7 ± 0.05	2.6 ± 0.01
1a (β-FNA)[b]	0.4 ± 0.05	7.7 ± 2.4	0.9 ± 0.05
buprenorphine[c]	1.3 ± 0.15	1.6 ± 0.07	1.5 ± 0.25

[a] The selective radioligands used were [^{3}H]DAMGO (MOR), [^{3}H]Cl-DPDPE (DOR), [^{3}H]U69593 (KOR). [b] Data from ref 6. [c] Data from ref 14.

Functional opioid receptor activity was determined in vitro in electrically stimulated isolated tissue bioassays.[14] In the guinea pig ileum (GPI) which has populations of MOR and KOR but not DOR, the new ligands were either partial agonists (**2a**, **3a**, **5a**) or had no opioid receptor agonist activity (**4a**, **6**) (data not shown). The partial agonist activity of **2a** showed the highest level of efficacy (54% inhibition of the electrically stimulated twitch) which was inhibited by the selective MOR antagonist CTAP.[15] The partial agonist activity of **3a** (30−40% of maximum) was prevented by norBNI[16] but not by CTAP, indicating that it was KOR mediated. The partial agonist activity of **5a** (maximum 36% at 40 nM) was not prevented by CTAP or norBNI, which may suggest it is of irreversible character.

The mouse vas deferens (MVD) expresses populations of all three opioid receptors but is most sensitive to DOR agonist activity. None of the new ligands showed agonist activity in this assay, but they all displayed potent antagonist activity against selective agonists for MOR (DAMGO), DOR (DPDPE), and KOR (U69593) (Table 2). All the tested new ligands (**3a**, **4a**, **5a**, **6**) were potent MOR antagonists with subnanomolar K_e values. They were only slightly less potent KOR antagonists but significantly less potent (10- to 100-fold) DOR antagonists. Whereas there was little difference between binding affinities (K_i) and antagonist potencies (K_e) for the 7α-aminooripavine derivative (**4a**), for the 7α-aminomethyl derivative (**5a**) MOR and KOR antagonist potencies were very much higher than MOR and KOR binding affinities. This indicates that **5a** binds much more tightly to opioid receptors under physiological conditions than **4a**.

Table 2. Antagonist Activity (K_e, nM) for test Compounds at Opioid Receptors Determined in Mouse Vas Deferens

ligand	K_e, nM[a]		
	MOR	DOR	KOR
3a	0.83 ± 0.04	6.84 ± 2.00	ND
6	0.20 ± 0.02	3.89 ± 0.99	1.05 ± 0.13
4a	0.72 ± 0.11	6.20 ± 3.28	1.89 ± 0.17
5a	0.021 ± 0.002	1.25 ± 0.38	0.047 ± 0.005
3b[b]	0.02 ± 0.007	0.25 ± 0.06	0.19 ± 0.06
4b[c]	0.56 ± 0.15	0.94 ± 0.14	1.24 ± 0.12
5b[c]	0.008 ± 0.0006	0.044 ± 0.005	0.052 ± 0.003

[a] The selective agonists used were DAMGO (MOR), DPDPE (DOR), U69593 (KOR). ND = not determined. Buprenorphine is an agonist in the mouse vas deferens with an EC_{50} of 21 nM (ref 14). [b] Data from ref 21. [c] Data from ref 6.

The new ligands were evaluated in mouse antinociceptive tests using thermal (warm water tail withdrawal, TW) and chemical (acetic acid induced writhing, AW) stimuli using procedures reported previously.[7] In TW, only **2a** showed any antinociceptive activity. In the 50 °C TW assay it had substantial agonist activity, reaching 60% of the maximum effect at the highest dose tested (100 mg/kg) (Figure 1) with about half the potency of morphine. With water at 55 °C, **2a** had reduced agonist effect, giving 30% response at 100 mg/kg, whereas the same dose of morphine showed 100% response.

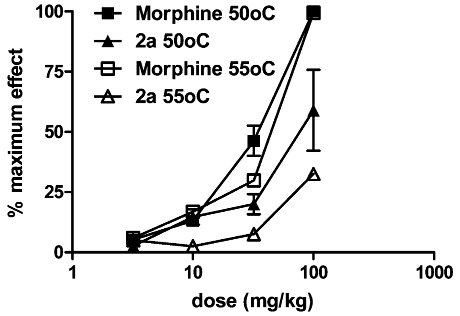


Figure 1. Agonist effect of **2a** and morphine in the mouse warm water tail withdrawal assay at 50 and 55 °C.

Given our interest in compounds that display initial agonist activity followed by antagonism and in view of its substantial agonist effect, the antagonist effect of **2a** on the morphine dose−response curve using 55 °C water was measured 24 h after **2a** was administered. At a dose of 10 mg/kg **2a**, the morphine curve was shifted 6-fold to the right, whereas a dose of 100 mg/kg **2a** totally flattened the morphine response (Figure 2). At a shorter time point (30 min), the 10 mg/kg dose had less effect than at 24 h, suggesting a slow onset of antagonist activity (data not shown). The higher dose had very long duration, remaining effective for at least 9 days (Figure 3). The morphine dose−response curve in TW was also substantially flattened by doses of 32 mg/kg **3a** and **5a** administered 30 min before morphine, whereas the effect of the same dose of **6** and **4a** was to shift the morphine curve 10-fold and 30-fold, respectively, to the right in essentially parallel fashion. When **3a**, **4a**, and **6** were administered with 24 h pretreatment, the morphine dose−response curve in each case was shifted about 4-fold to the right, whereas in an equivalent experiment **5a** produced a 30-fold rightward shift. Thus, as MOR

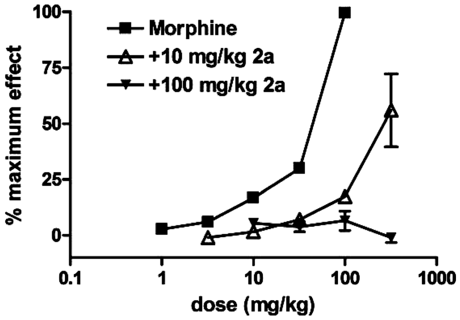


Figure 2. Antagonist activity of **2a** after 24 h of pretreatment (10 and 100 mg/kg) on morphine antiniciceptive activity in the mouse warm water tail withdrawal assay (55 °C).

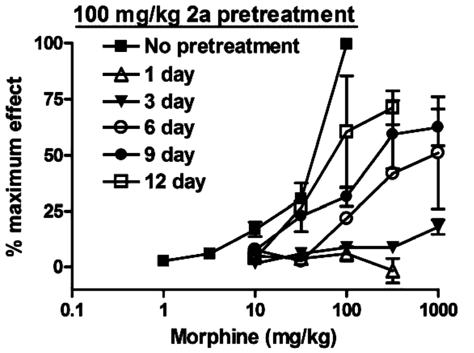


Figure 3. Duration of antagonist effect of **2a** (100 mg/kg) on morphine antinociceptive activity in the mouse warm water tail withdrawal assay.

antagonists, **2a** and **5a** are both of long duration and appear to have irreversible characteristics whereas **3a**, **4a**, and **6** are less impressive as irreversible MOR antagonists and may be essentially reversible, as predicted by the in vitro data where the K_i in binding was the same as the K_e in the functional assays for **3a**, **4a**, and **6**, indicating reversible binding.

Although **3a**, **4a**, **5a**, and **6** had no antinociceptive activity in TW, **5a** and **6** as well as **2a** had significant activity in AW. **2a** at a dose of 10 mg/kg inhibited writhing to 90% of the maximum possible inhibition, as did **6** at 32 mg/kg; **5a** at the same dose showed 80% inhibition. By use of selective antagonists for the individual opioid receptors, the antinociceptive effect of **2a** in AW was shown to be predominantly MOR-mediated, with some DOR involvement, whereas that due to **5a** had significant contributions from all three opioid receptors. This is illustrated in Figure 4 for **2a**. **3a** and **4a** had no antinociceptive activity in AW; in the case of **3a** this was in contrast to partial agonist activity in vitro in GPI. However, the latter was of low efficacy and mediated by KOR agonism.

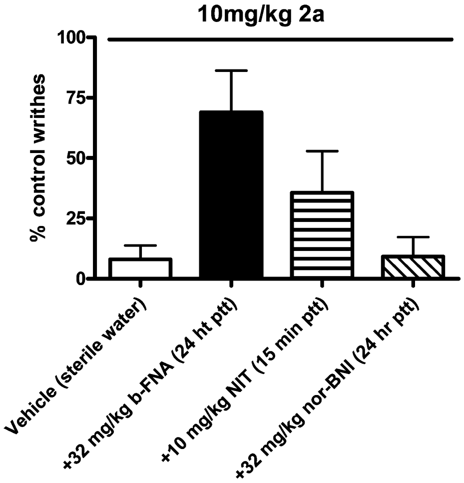


Figure 4. Effect of selective opioid antagonists on the antinociceptive effect of **2a** in the mouse antiwrithing assay.

The opioid receptor antagonist profile of the new ligands was also investigated in vivo in the AW assay. All the ligands tested (**2a**, **3a**, **4a**, **5a**) had opioid receptor antagonist activity when administered at a dose of 32 mg/kg, 24 h before determination of the effect of ED_{100} doses of selective opioid receptor agonists for MOR (morphine), KOR (bremazocine), and DOR (BW373-U86) (Table 3). In this assay the three fumaroylamino derivatives (**2a**, **4a**, **5a**) showed preference for MOR antagonism whereas the naltrexone derivative (**3a**), which had overall the least opioid receptor antagonist activity, had no selectivity.

Table 3. Percent Inhibition[a] by New Ligands of the Effect of an ED_{100} Dose of Selective Agonists[b] in AW

	% inhibition		
ligand	morphine	BW373U86	bremazocine
2a	62	31	5
3a	10	15	30
4a	70	28	20
5a	95	10	25

[a] Doses of 32 mg/kg of test ligands administered 24 h earlier. [b] The agonists used were morphine (MOR), BW373U86 (DOR), and bremazocine (KOR). Buprenorphine is a full agonist in the AW test with an EC_{50} of 0.11 (0.04−0.29) nM (Jiminez-Gomez and Traynor, unpublished).

The 14-fumaroylaminomorphinone derivative (**2a**) was evaluated in the morphine-dependent rhesus monkey model.[17] In withdrawn monkeys, **2a** at doses of 0.1 and 0.5 mg/kg did not substitute for morphine or attenuate withdrawal (data not shown) but in nonwithdrawn monkeys at a dose of 2.0 mg/kg it precipitated withdrawal symptoms that lasted longer than those produced by a standard dose of naloxone (0.05 mg/kg) (Figure 5).

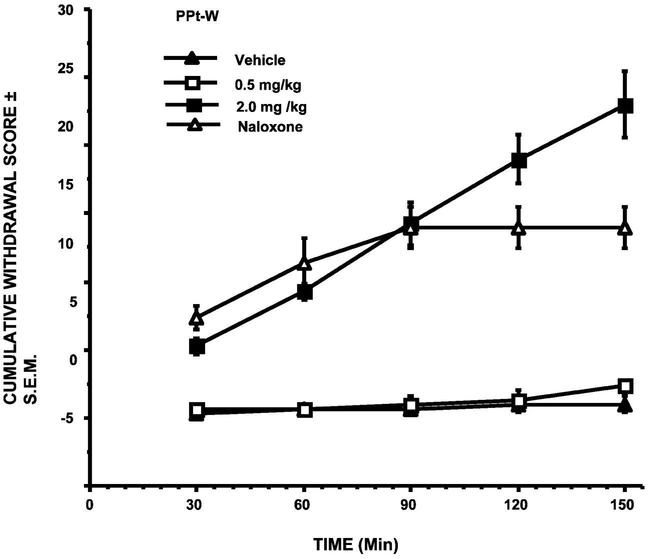


Figure 5. Substitution of **2a** for morphine in nonwithdrawn morphine dependent monkeys.

DISCUSSION AND STRUCTURE−ACTIVITY RELATIONSHIPS

We showed that replacement of the carbomethoxy group of (**1a**) with aryl groups gave new 6*β*-cinnamoylamino ligands (**1b**−**e**) of which the *p*-chloro and *p*-methyl derivatives had profiles similar to that of **1a**[9] and the unsubstituted cinnamoylamino and *p*-nitro analogues had predominant KOR agonist activity.[8] These relationships of cinnamoylamino to fumaroylamino derivatives motivated the present investigation of fumaroylamino derivatives (**2a**, **4a**, **5a**) related to our previously reported cinnamoylamino derivatives (**2b**−**e**, **4b**−**e**, **5b**−**e**).[4−6]

In the series of 14-cinnamoylamino-7,8-dihydromorphinones (**2b**−**e**) the dominant in vitro and in vivo activity was MOR antagonism.[7,17] In the current investigation it has been shown that the equivalent fumaroylamino derivative (**2a**) is a MOR partial agonist because in TW it had substantial MOR efficacy, but it also developed a long-lasting morphine antagonism having irreversible characteristics. In this respect it most closely resembled the *p*-nitrocinnamoylamino derivative (**2e**), the only member of the 14-cinnamoylaminodihydromorphinone series to have substantial agonist and MOR antagonist activity in TW.[5] Next most similar to **2a** among the 14-cinnamoylamino derivatives was the unsubstituted cinnamoylamino derivative (**2b**), although the latter was somewhat less effective than **2a** as a pseudoirreversible MOR antagonist and as a MOR agonist in vivo.[5] **2c** and **2d**, the chloro- and methylcinnamoylamino derivatives, are quite different from **2a** in having no opioid receptor agonist activity.

The 7*α*-fumaroylaminomethyl oripavine derivative (**5a**) had a profile similar to that of the 14-fumaroylaminodihydromorphinone derivative (**2a**), although the antinociceptive efficacy and the duration of in vivo MOR antagonism by **5a** were somewhat less impressive than those of **2a**. However, **5a** was able to flatten the morphine dose−response curve (up to 1000 mg/kg morphine) in the TW assay after 30 min of pretreatment, again suggestive of irreversible-like effects (Supporting Information). The cinnamoylaminomethyl oripavine derivatives (**5b**−**e**) related to **5a** all lacked the latter's opioid receptor partial agonist character, being opioid receptor antagonists in vivo.[11] However, in GPI the *p*-chlorocinnamoylaminomethyl derivative (**5c**) and the *p*-nitrocinnamoylaminomethyl derivative (**5e**) like **5a** had partial opioid receptor agonist activity. **5a** and the cinnamoylamino analogues (**5b**−**e**) were all opioid receptor antagonists in MVD, and it can be concluded that they all have predominant MOR antagonist activity of pseudoirreversible nature.[18]

The other fumaroylamino derivative (**4a**) was also part of an oripavine structure, but the pharmacophore was directly attached to the bridged C-ring rather than to a methylene spacer as in **5a**. It profiled as an opioid receptor antagonist without agonist actions both in vitro and in vivo. It had a substantial, long-duration morphine antagonist effect in TW and AW, but this did not appear to be pseudoirreversible. The MOR antagonist activity of **4a** was similar to that of the *p*-methylcinnamoylamino analogue (**4d**), but **4d** had significant opioid receptor agonist activity in AW. Only the *p*-nitro analogue (**4e**) shared **4a**'s lack of opioid receptor agonist activity, but it had even less MOR antagonist activity.[18]

It is of interest to compare the profile of **4a** with that of the 6,14-etheno analogue (**12**), designated NIH 10236, reported by Rothman et al.[19] **12** was found to have wash resistant in vitro binding in rat brain membranes to MOR and DOR, whereas these receptors and KOR were "alkylated" when equivalent studies were carried out in vivo with intracerebroventricular administration of **12**. The authors concluded that "multiple factors complicate the use of alkylating agents for in vivo selectivity studies". Our studies with **4a** suggest that it is a poor alkylating agent and thus a poor irreversible antagonist.

The action of **1a** as an irreversible MOR antagonist can be attributed to the fumaroylamino group acting as a Michael acceptor which in physiological conditions reacts with a sufficiently reactive nucleophile of the MOR, forming a covalent bond.[20] It is noteworthy that molecular modeling indicates that the double bond of the fumaroylamino group in **2a** and **5a** is conjugated to either the amide or ester functionality (dihedral angle near 0° or 180°), whereas there is a lack of conjugation to either in **4a**.[21] This might explain the lack of irreversible characteristics displayed by **4a** in vivo, as lack of reactivity would prevent Michael addition and hence covalent bond formation. Recently the crystal structure of the MOR bound to **1a** has been reported.[22] We have investigated whether the current ligands (**2a**, **4a**, **5a**) can overlay the structure of **1a** in the binding pocket while also interacting with the nucleophilic residue (Lys233) that **1a** covalently binds to. The results suggest that none of the current series appear to be able to interact with this or other lysine residues without adopting a very different binding conformation to **1a**, and so it is not clear that they would interact with the receptor in an analogous fashion to **1a**.

The remaining new 14-substituted derivatives (**3a**, **6**) were synthesized for comparison with the 14-fumaroylamino derivative (**2a**). The 14-dihydrofumaroylamino derivative (**6**) had a substantially lower level of antinociceptive activity than **2a**. It had only reversible MOR antagonist activity in TW, but it was a low potency antinociceptive agent in AW. The lack of irreversible antagonist activity for the dihydrofumaroylamino derivative supports the view that the irreversible antagonist activity of 14-fumaroylaminodihydromorphinone (**2a**) is the result of covalent binding to MOR via Michael addition to the fumaroylamino group.[21] The 14-fumaroyloxy derivative (**3a**) had weak KOR partial agonist activity in GPI but no antinociceptive activity in TW or AW. It was a powerful morphine antagonist in TW but of relatively short duration. Thus, the fumaroyloxy pharmacophore of **3a** failed to match either the MOR agonist or MOR antagonist profile of the fumaroylamino group in **2a**. **3a** can also be compared to the 14-cinnamoyloxy derivatives (**3b**−**d**).[23] The latter group had substantially higher potency in MVD as opioid receptor antagonists than **3a** (e.g., **3b** in Table 2). In fact, the MOR profile of **3a** is somewhat similar to that of its parent, naltrexone, i.e., a potent reversible MOR antagonist; it is possible that **3a** is metabolized in vivo to naltrexone.

In other studies short chain ester groups have been substituted for lipophilic aryl groups in active molecules in order to reduce duration of action, since they offer similar levels of lipophilicity but are more easily metabolized in vivo.[24] Comparison of fumaroylamino derivatives with equivalent cinnamoylamino derivatives can be seen in this light; in the current series there is no evidence that the presence of a methyl ester moiety leads to a shortened duration of action. This may be due to inhibition of metabolic esterase activity by conjugation in the fumaroylamides.

■ CONCLUSIONS

The fumaroylamino derivatives reported herein have predominant MOR antagonist activity that in the cases of the 14-substituted morphinone (**2a**) and 7-aminomethyl oripavine (**5a**) has irreversible character like the equivalent cinnamoylamino derivatives (**2b**−**e**, **5b**−**e**). The present study confirms the general similarity of the effects of the two pharmacophores, but the particular substituent in the cinnamoylamino group offering the closest similarity to the fumaroylamino derivative varies between series and in particular there seems to be a greater level of in vivo MOR agonist activity in the fumaroylamino series. Comparison of **2a** and **5a** with the prototype fumaroylamino opioid *β*-FNA (**1a**) shows that the new ligands have similar MOR irreversible antagonism. However, like *β*-FNA they have shorter duration agonist effects, but the agonism of **2a** is predominantly mediated by the MOR and the agonism of **5a** is less clearly defined whereas *β*-FNA's agonist effects are clearly KOR-mediated. The profile of **2a**, MOR agonist activity followed by irreversible antagonism, might have made it of interest in the search for alternatives to buprenorphine. However, **2a**'s MOR effects compare unfavorably with buprenorphine's, particularly the agonist effects. The MOR agonist activity of **2a** is of shorter duration and of lower efficacy and potency. The MOR irreversible antagonism of **2a** matches that of buprenorphine but again of lower potency.

EXPERIMENTAL SECTION

Column chromatography was performed under gravity over silica gel 60 (35−70 μm) purchased from Merck. Analytical TLC was performed using aluminum-backed plates coated with Kieselgel 60 F_{254} from Merck. The chromatograms were visualized using UV light (UVGL-58, short wavelength), ninhydrin (acidic), or potassium permanganate (basic). Melting points were carried out using a Reichert-Jung Thermo Galen Kopfler block or a Gallenkamp MFB-595 melting point apparatus and are uncorrected. High and low resolution electron impact (EI) mass spectra were recorded using EI ionization at 70 eV, on a VG AutoSpec instrument equipped with a Fisons autosampler. ^{1}H NMR and ^{13}C NMR spectra were recorded using a JEOL 270 (operating at 270 MHz for ^{1}H and 67.8 MHz for ^{13}C) spectrometer. Chemical shifts (δ) are measured in ppm. Spectra were referenced internally using TMS as the standard. Only diagnostic peaks have been quoted for proton NMR. Microanalysis was performed with a Perkin-Elmer 240C analyzer. Infrared spectroscopy was performed on a Perkin-Elmer 782 instrument. Chemicals and solvents were purchased from Aldrich Chemical Company. Compounds were submitted for testing as their oxalate salts, formed by adding 1 equiv of oxalic acid to an ethanolic solution of the ligand. Ligands were >95% pure by microanalysis.

***N*-Cyclopropylmethyl-7,8-dihydro-14*β*-[3′-(methoxycarbonyl)propenamido]normorphinone (2a).** A suspension of 14*β*-amino-*N*-cyclopropylmethyl-7,8-dihydronormorphinone (**8**) (1.19g, 3.48 mmol), methyl 3-(chlorocarbonyl)propanoate (681 mg, 4.59 mmol), and sodium carbonate (450 mg) in THF (27 mL) and water (3 mL) was stirred at room temperature for 2.5 h. Water (20 mL) was then added and the reaction mixture extracted with CH_2Cl_2 (2 × 50 mL). The extracts were combined, dried ($MgSO_4$), filtered, and evaporated to dryness before column chromatography (silica gel, CH_2Cl_2/CH_3OH, 19:1) to give the product as a white solid (1.27 g, 81%), mp 228−231 °C. ^{1}H NMR δ 0.19 (2H, m), 0.59 (2H, m), 0.88 (1H, m), 3.82 (3H, s), 4.98 (1H, s), 6.60 (1H, d), 6.75 (1H, d), 6.87(1H, d), 7.05 (1H, d), 7.52 (1H, brs); ^{13}C NMR δ 3.8, 4.1, 9.3, 21.5, 29.2, 29.9, 36.8, 44.1, 48.8, 52.2, 57.1, 59.2, 59.4, 89.7, 118.3, 119.8, 124.3, 128.0, 129.9, 137.5, 139.0, 143.5, 164.4, 166.2, 209.2.

***N*-Cyclopropylmethyl-7,8-dihydro-14*β*-[3′-(methoxycarbonyl)propanamido]normorphinone (6).** A suspension of *N*-cyclopropylmethyl-7,8-dihydro-14*β*-[3′-methoxycarbonyl)-propenamido]normorphinone oxalate (**2a**) (203 mg, 0.35 mmol) and 10% Pd/C (150 mg) in CH_3OH (30 mL) was hydrogenated at 15 psi until H_2 uptake ceased. The catalyst was removed by filtration through Celite and the filtrate evaporated. The residue was purified by column chromatography (CH_2Cl_2/CH_3OH, 19:1) to give **6** as a clear oil (98 mg, 62%). ^{1}H NMR δ 0.20 (2H, m), 0.54 (2H, m), 0.85 (1H, m), 3.70 (3H, s), 4.85 (1H, s), 6.58 (1H, d), 6.72 (1H, d), 7.16 (1H, s); ^{13}C NMR δ 3.7, 4.1, 9.3, 21.6, 29.2, 29.7, 31.5, 34.5, 36.8, 44.3, 48.6, 51.9, 56.3, 59.3, 59.9, 89.7, 118.1, 119.6, 124.1, 128.3, 139.1, 143.6, 172.6, 173.6, 208.6; EIMS 454 (M^+, 100%).

3-*O*-(*tert*-butyldimethylsilyl)-*N*-cyclopropylmethyl-7,8-dihydro-14*β*-[3′-(methoxycarbonyl)propenoyloxy]normorphinone (10). A solution of 3-*O*-(*tert*-butyldimethylsilyl)naltrexone (**9**)[25] (690 mg, 1.5 mmol) and monomethylfumaroyl anhydride (630 mg, 2.60 mmol) in dry toluene (12 mL) was heated to reflux under N_2 for 3 h. After cooling, the reaction mixture was washed with dilute $NaHCO_3$ (aq) (2 × 5 mL) and water (5 mL), dried ($MgSO_4$), filtered and the solvent evaporated. The residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH, 49:1) to yield (**10**) as a pale yellow solid (597 mg, 69%). ^{1}H NMR δ 0.03 (2H, m), 0.19 (3H, s), 0.29 (3H, s), 0.45 (2H, m), 0.68 (1H, m), 1.01 (9H, s), 3.83 (3H, s), 4.72 (1H, s), 6.56 (1H, d), 6.65 (1H, d), 6.90 (1H, d), 6.99 (1H, d); ^{13}C NMR δ −4.7, −4.5, 3.8, 3.9, 9.5, 18.2, 23.2, 25.7, 26.9, 30.4, 35.5, 43.8, 51.0, 52.3, 55.2, 59.2, 84.1, 89.4, 119.3, 122.6, 126.0, 128.4, 133.0, 135.1, 138.0, 146.7, 163.6, 165.4, 206.4; EIMS 567 (M^+, 99%).

***N*-Cyclopropylmethyl-7,8-dihydro-14*β*-[3′-(methoxycarbonyl)propenoyloxy]normorphinone (3a).** A solution of 3-*O*-(*tert*-butyldimethylsilyl)-*N*-cyclopropylmethyl-7,8-dihydro-14*β*-[3′-(methoxycarbonyl)propenoyloxy]normorphinone (**10**) (570 mg, 1.00 mmol) and 6 M HCl (1.2 mL) in methanol (12 mL) was stirred at room temperature for 1 h, then neutralized ($NaHCO_3$), and all solvents were then removed in vacuo. The residue was dissolved in CH_2Cl_2, filtered, dried ($MgSO_4$), filtered and the solvent again removed in vacuo. Silica gel chromatography (CH_2Cl_2/CH_3OH, 24:1) yielded **3a** as a clear oil (166 mg, 37%). ^{1}H NMR δ 0.05 (2H, m), 0.48 (2H, m), 0.72 (1H, m), 3.82 (3H, s), 4.98 (1H, s), 6.62 (1H, d), 6.76 (1H, d), 6.92(1H, d), 7.02 (1H, d); ^{13}C NMR δ 3.7, 4.0, 9.27, 23.1, 25.7, 27.0, 30.0, 35.6, 43.9, 51.2, 55.3, 59.2, 84.1, 89.9, 118.5, 120.0, 124.5, 127.9, 133.0, 135.1, 139.2, 143.5, 163.7, 165.5, 208.5; EIMS 453 (M^+, 100%).

***N*-Cyclopropylmethyl-6,14-endoethano-7*α*-(methoxyfumaroylamino)tetrahydronororipavine (4a).** To a solution of 7*α*-amino-*N*-cyclopropylmethyl-6,14-endoethanotetrahydronororipavine (**11a**) (0.43 g, 1.1 mmol) in dry CH_2Cl_2 (100 mL) was added triethylamine (0.45 g, 4.5 mmol). To this mixture, under N_2, was added a solution of methyl (3-chloroformyl)acrylate (0.16 g, 1.1 mmol) in CH_2Cl_2 (10 mL) dropwise over 45 min. Stirring was continued for 1 h before removal of the solvent in vacuo. Purification by column chromatography ($CH_2Cl_2/CH_3OH/NH_3$ (conc), 94:5:1) gave **4a** (0.35 g, 63%). ^{1}H NMR δ 0.08 (2H, m), 0.45 (2H, m), 3.33 (3H, s), 3.82 (3H, s), 4.60 (1H, s), 6.52 (1H, d), 6.70 (1H, d), 6.89 (1H, d), 7.11 (1H, d); ^{13}C NMR δ 3.6, 3.7, 9.3, 19.8, 22.8, 28.6, 35.0, 35.4, 37.1, 43.4, 45.6, 45.9, 49.8, 52.3, 58.4, 59.9, 76.3, 76.9, 87.9, 117.1, 119.8, 127.4, 129.7, 132.0, 137.0, 137.8, 145.6, 163.8, 166.7; EIMS 494 (M^+, 100%); EI-HRMS calcd for $C_{28}H_{34}N_2O_6$ 494.241 69, found 494.240 81.

***N*-Cyclopropylmethyl-6,14-endoethano-7*α*-(methoxyfumaroylaminomethyl)tetrahydronororipavine (5a).** A solution of 7*α*-aminomethyl-*N*-cyclopropylmethyl-6,14-endoethanotetrahydronororipavine (**11b**)[4] (0.22g, 0.55 mmol) was treated as described for **4a** (above) to yield, after column chromatography ($CH_2Cl_2/CH_3OH/NH_3$ (conc), 94:5:1) **5a** (0.13 g, 48%). ^{1}H NMR δ 0.14 (2H, m), 0.50 (2H, m), 3.57 (3H, s), 3.82 (3H, s), 4.46 (1H, s), 6.50 (1H, d), 6.69 (1H, d), 6.96 (3H, m); EIMS 467 (M+, 100%); EI-HRMS calcd for $C_{29}H_{36}N_2O_6$ 508.257 34, found 508.256 57.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental procedures and characterization data and figure showing antagonist activity of **5a** in TW assay. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

MOR, μ opioid receptor; DOR, δ opioid receptor; KOR, κ opioid receptor; β-FNA, β-funaltrexamine; CTAP, D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH_2; norBNI, norbinaltorphimine; TW, warm water tail withdrawal assay; AW, acetic acid induced writhing assay

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