# Structural Determinants of Opioid and NOP Receptor Activity in Derivatives of Buprenorphine

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Ⓢ *Supporting Information*

ABSTRACT: The unique pharmacological profile of buprenorphine has led to its considerable success as an analgesic and as a treatment agent for drug abuse. Activation of nociceptin/orphanin FQ peptide (NOP) receptors has been postulated to account for certain aspects of buprenorphine's behavioral profile. In order to investigate the role of NOP activation further, a series of buprenorphine analogues has been synthesized with the aim of increasing affinity for the NOP receptor. Binding and functional assay data on these new compounds indicate that the area around C20 in the orvinols is key to NOP receptor activity, with several compounds displaying higher affinity than buprenorphine. One compound, **1b**, was found to be a mu opioid receptor partial agonist of comparable efficacy to buprenorphine but with higher efficacy at NOP receptors.
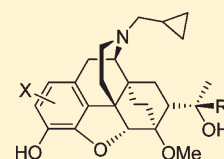
■ INTRODUCTION

The treatment of opiate abuse and dependence by detoxification, substitution, and maintenance with methadone, LAAM and, more recently, buprenorphine (**1a**)(Chart 1), is the most successful pharmacotherapeutic program of substance abuse treatment.[1] The pharmacological profile of buprenorphine has long been recognized as having some unique features.[2,3] Some of these effects are explicable by the slow onset and even slower offset of its interaction with mu opioid (MOP) receptors. These effects include its long duration of action and the mildness of the abstinence syndrome following its chronic administration and the delay in the appearance of these effects.[4] Of particular significance to its use as a pharmacotherapy for heroin addiction is its acute safety in overdosage, which clearly differentiates buprenorphine from the abused opiates and the therapeutic substitute, methadone. Though, as an MOP receptor partial agonist, buprenorphine would be expected to show a ceiling to its opiate effects, including respiratory depression, in fact, the level of opiate effects from very high doses are lower than that from intermediate doses, i.e., buprenorphine has bell-shaped dose—response curves for its opiate effects including respiratory depression, thus, explaining its exceptional acute safety.[5,6]

The mechanism of the bell-shaped dose—response curves for buprenorphine's MOP receptor effects in vivo has been the subject of considerable speculation. This has been addressed in a review of buprenorphine's basic pharmacology and the two most favored explanations recognized as being (a) an interaction with an opposing pronociceptive system and (b) an induction of autoinhibition at higher doses, which can be attributed to buprenorphine's slow offset kinetics.[6] The pronociceptive system in question is the NOP receptor (nociceptin/orphanin FQ receptor), a receptor to which most standard opioid ligands do not bind with any significant affinity.[7] Buprenorphine is therefore somewhat unusual among opioids in having moderate affinity at the NOP site.[7] Although the affinity is 2 orders of magnitude

Chart 1. Structures

1a: Buprenorphine

2: MC-CAM

10a: R = CH₃
10b: R = CH₂CH(CH₂)₂

3: Ro 64-6198
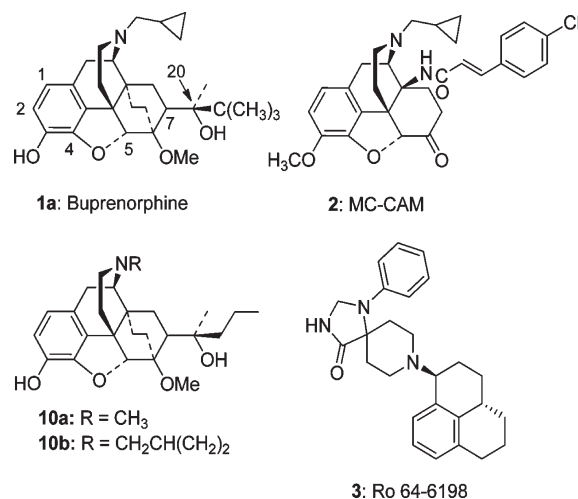
lower than the affinity for the MOP and KOP receptors, buprenorphine seems to have some agonist activity at NOP.[8−10] Lutfy and colleagues discovered that the bell-shaped antinociception curve lost its downward component in the presence of an NOP antagonist and in NOP knockout mice in the absence of an antagonist.[11] This finding led to the conclusion that NOP activation at high buprenorphine concentrations was the cause of the downward part of the dose—response curve. Further support for the influence of buprenorphine's NOP activity was supplied by the findings of Ciccocioppo and colleagues that low doses of buprenorphine enhanced alcohol consumption in rats but that high doses of buprenorphine reduced the consumption of alcohol.[12]
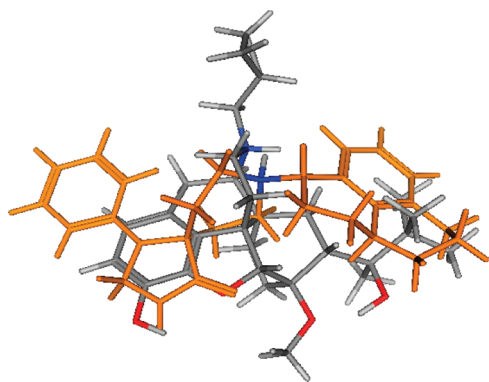
Figure 1. Overlay of buprenorphine (colored by atom type) with Ro 64-6198 (gold, except for the NH, which is colored by atom type).

Figure 2. Overlay of buprenorphine (colored by atom type) and Ro 64-6198 (gold, except for the NH, which is colored by atom type).

The reduced consumption produced by high buprenorphine dosage was additive with the opiate antagonist naltrexone's similar effect but inhibited by a selective NOP antagonist.

Though the case for NOP involvement to explain buprenorphine's bell-shaped dose—response curves in MOP receptor mediated behavioral assays is compelling, it seems unlikely that this is the whole story. This follows from the effect of the competitive MOP receptor antagonist naloxone on buprenorphine's antinociception bell-shaped dose—response curve.[13] Naloxone induced a parallel displacement of the dose—response curve to a higher dose range, without changing the bell-shape. This is only possible when all components of the curve are susceptible to the competitive interaction with naloxone. The antagonist has no measurable affinity for NOP; therefore, it could not affect the NOP component.[14,15]

The slow dissociation of buprenorphine from the MOP receptor, though not involving any covalent interactions with the receptor, corresponds to a pseudoirreversible binding. It can be hypothesized that pseudoirreversible binding is preceded by reversible binding during which time the ligand displays its agonist effects.[16] The prolonged occupation of the receptor produces receptor blockade, which is manifested as an antagonist effect of the ligand.[6,17] The lower MOP receptor agonist effect of higher doses of buprenorphine may be related to the observation by Bidlack and co-workers that the onset of the MOP receptor antagonist effect in ligands related to methoclocinnamox (MC-CAM, **2**: a ligand with a profile very similar to that of buprenorphine) is dose-dependent with higher doses having a very much faster onset.[18,19]

It is, therefore, unclear whether direct activation of NOP receptors is the mechanism by which buprenorphine produces a bell-shaped dose—response curve. This issue can be investigated by identifying and characterizing novel ligands with differing affinity and activity profiles at MOP and NOP receptors. Such ligands might also allow for the development of substitution therapies for opiate dependence with a duration of effect and acute safety comparable to those of buprenorphine but with, for example, a higher level of morphine-like effects to appeal to addicts for whom methadone is presently prescribed. Alternatively, it may allow for the identification of novel analgesics with low or no abuse potential and low tolerance development.
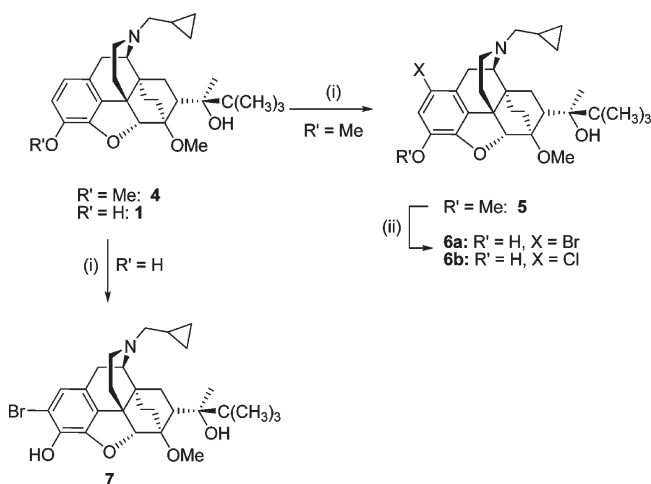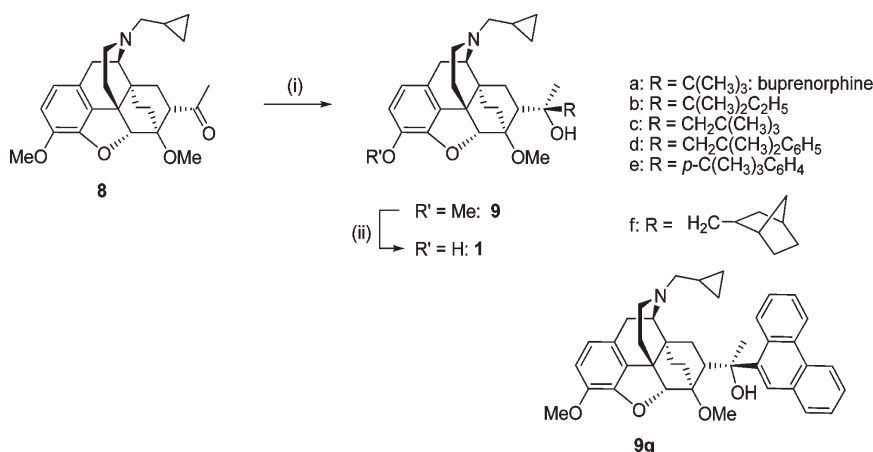
■ DESIGN AND SYNTHESIS

The majority of NOP receptor ligands can be described by a two-dimensional (2-D) pharmacophore as previously reported.[20]
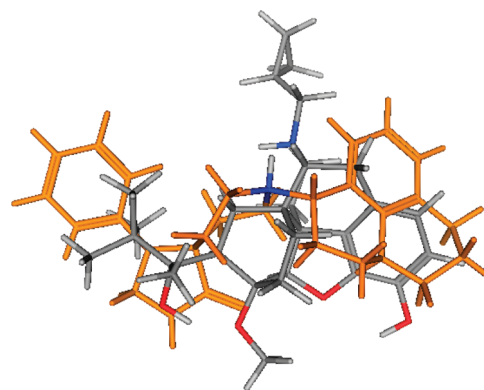
Scheme 1[a]

[a] (i) N-Bromosuccinimide, 0.1 N H$_2$SO$_4$, 38% or N-chlorosuccinimide, 0.1 N HCl, 45%; (ii) PrSNa, HMPA, 120 °C, 56—89%.

A major feature of the pharmacophore is the presence of a basic nitrogen to which is attached a large, lipophilic moiety. We have previously demonstrated that replacement of the N-cyclopropylmethyl group of buprenorphine with the lipophilic cyclooctylmethyl group found in selective NOP receptor antagonists such as J-113397,[15] resulted in a significant decrease in affinity for the NOP receptor[7] suggesting that the N-17 substituent of buprenorphine does not play the same role as the N-substituent in high affinity NOP receptor ligands and that an alternative group in the buprenorphine structure interacts with the lipophilic site. Alignment (using the flexible alignment feature of MOE, v.2005.06) of buprenorphine with known NOP receptor ligands (Figures 1 and 2 show alignments with Ro 64—6198 (**3**)[21]) indicates that either the t-butyl group (Figure 1) or the aromatic A-ring (Figure 2) of buprenorphine could be acting as the lipophilic group while still allowing the basic nitrogen to occupy a position similar to that in **3**. These alignments suggest that either increasing the steric bulk of the t-butyl substituent or adding a substituent to the aromatic ring of buprenorphine could provide compounds with increased affinity for NOP receptors.

To this end, 1-chloro- and 1-bromo-buprenorphine were prepared using methods previously reported for the halogenation of hydrocodone and oxycodone.[22] Thus, buprenorphine 3-O-

Scheme 2[a]

a: R = C(CH₃)₃: buprenorphine
b: R = C(CH₃)₂C₂H₅
c: R = CH₂C(CH₃)₃
d: R = CH₂C(CH₃)₂C₆H₅
e: R = p-C(CH₃)₃C₆H₄

R' = Me: **9**
R' = H: **1**

f: R =

9g

[a] (i) RMgBr, THF/Toluene, 15—45%; (ii) PrSNa, HMPA, 120 °C, 52—80%.

methyl ether (**4**) was halogenated using the appropriate N-halosuccinimide to give the 1-substituted thevinol (**5**) before 3-O-demethylation with propane thiolate (Scheme 1), while bromination of buprenorphine itself with N-bromosuccinimide gave 2-bromobuprenorphine (**7**) directly, analogous to a previous iodination of buprenorphine.[23] Attempts to synthesize 2-chlorobuprenorphine using an identical procedure with N-chlorosuccinimide failed to give the desired product due to, among other things, competing 6-O-demethylation.

Access to analogues of buprenorphine in which the t-butyl group is replaced by alternative bulky groups was by the standard procedure of Grignard addition to a ketone (**8**). This is a reaction that is low yielding (30—40%) for buprenorphine itself due to the size of the Grignard reagent. Unsurprisingly, it proved difficult to increase bulk without adversely affecting this addition step. p-(t-Butyl)phenylmagnesium bromide, phenanthren-9-ylmagnesium bromide, and t-pentylmagnesium chloride were prepared from their corresponding halides, and each gave the expected addition product (**9b,e**, **9g**) on reaction with (**8**) (Scheme 2). The attempted addition of (3-methylbut-2-en-2-yl)magnesium bromide or 1-methylcyclopentylmagnesium bromide failed to yield any of the desired tertiary alcohol. In the case of the alkyl and arylalkyl Grignard reagents, the addition of a methylene group to separate the reacting and bulky centers resulted, as expected, in a more facile Grignard addition (**9c,d,f**). The generally low yields (15—45%) were the result of rearrangements leading to C4-phenols and, in the reaction with t-pentylmagnesium chloride, the secondary alcohol product of Grignard reduction.[24] In each case, the thevinol (**9**) was then 3-O-demethylated to the corresponding orvinol (**1**) using propane thiolate. Despite numerous attempts, this step failed for **9g** (no reaction took place), and the corresponding orvinol could not be obtained.

■ RESULTS AND DISCUSSION

Binding affinities of the new compounds, plus various standards, were determined in Chinese hamster ovary (CHO) cells transfected with human receptor cDNA, as previously described;[25] the displaced selective radioligands were [³H]DAMGO, [³H]Cl-DPDPE, [³H]U69593, and [³H]N/OFQ for binding to the MOP, delta opioid (DOP), kappa opioid (KOP), and NOP receptors,

Table 1. Binding Affinities to Opioid and NOP Receptors

	K_i (nM) ± SEM[a]			
	NOP	mu	delta	kappa
nociceptin	0.08 ± 0.03	437 ± 13	2846 ± 512	147 ± 3.4
DAMGO	>10,000	1.59 ± 0.17	300 ± 59	306 ± 46
DPDPE	>10,000	504 ± 10	1.24 ± 0.09	>10,000
U69593	>10,000	>10,000	>10,000	1.6 ± 0.26
1a	77.4 ± 16	1.5 ± 0.8	6.1 ± 0.4	2.5 ± 1.2
1b	8.46 ± 1.3	2.14 ± 0.79	1.59 ± 0.28	5.63 ± 1.3
1c	18.5 ± 0.68	2.95 ± 0.65	1.27 ± 0.21	1.59 ± 0.25
1d	22.0 ± 0.55	2.19 ± 0.65	3.66 ± 0.92	4.15 ± 1.3
1e	133 ± 8.2	5.56 ± 1.3	3.03 ± 0.61	8.92 ± 0.34
1f	16.0 ± 1.5	11.4 ± 0.17	7.13 ± 1.3	9.87 ± 1.3
6a	237 ± 64	14.3 ± 0.88	6.79 ± 0.99	9.93 ± 3.7
6b	67.8 ± 20	13.2 ± 0.97	17.2 ± 0.26	45.6 ± 3.4
7	159 ± 1.4	10.5 ± 3.86	8.67 ± 0.81	35.5 ± 3.9

[a] Binding to cloned human opioid receptors transfected into CHO cells (method in ref 25). Values are the average of two experiments each carried out in duplicate. Tritiated ligands were [³H]DAMGO (MOP), [³H]Cl-DPDPE (DOP), [³H]U69593 (KOP), and [³H] N/OFQ.

respectively. Buprenorphine (**1a**) was found to bind with nanomolar affinity to MOP, KOP, and DOP receptors with around 50-fold lower affinity for NOP receptors compared to that for MOP receptors (Table 1). Halogenation at C-1 or C-2 (**6a**, **6b**, **7**) had little effect on NOP and DOP receptor affinity but resulted in somewhat lower affinity for MOP and KOP receptors. This might imply that the aryl ring of buprenorphine does not occupy the lipophilic site described within the NOP receptor pharmacophore. Because of this result, no further aryl ring substituted analogues were synthesized and evaluated and attention focused on the C20 group.

Of the analogues of **1a** with variation in the C20 substituent, **1b** and **1c**, having t-pentyl and neopentyl groups, are the closest in structure to **1a**, being homologues with one extra methylene group. Compared to **1a**, **1b** retained affinity at opioid receptors (all 1.6—5.6 nM) and was 1 order of magnitude higher in affinity at NOP receptors (8.5 nM versus 77 nM). Therefore, **1b** has essentially equivalent affinities for each of the opioid and NOP

Table 2. Stimulation (EC$_{50}$/nM and % Stimulation) of [^{35}S]GTPγS Binding to Opioid and NOP Receptors

	MOR		NOP		DOR		KOR	
	EC$_{50}$	% stim[a]	EC$_{50}$	% stim[a]	EC$_{50}$	% stim[a]	EC$_{50}$	% stim[a]
DAMGO	35.3 ± 0.53	100			6.86 ± 0.4	100		
nociceptin			8.1 ± 1.4	100			78.5 ± 8.80	100
1a	10.2 ± 2.2	28.7 ± 1.1	116 ± 88	21.0 ± 8.4	>10,000		>10,000	
1b	6.0 ± 2.1	20.1 ± 8.7	78.6 ± 49	48 ± 13		10.8 ± 6.8		0
1c	2.6 ± 1.2	26.5 ± 8.0		5.4 ± 3.4	50.1 ± 7.1	20.6 ± 0.6		16.9 ± 1.5
1d		16.8 ± 1.3	2380 ± 156	42.7 ± 21	3411 ± 819	42.7 ± 6.7	0.88 ± 0.58	33.7 ± 3.4
1e		0		9.3		0		0
1f	6.1 ± 2.7	67.7 ± 7.0	111 ± 10	58.2 ± 20	49.3 ± 4.6	61.3 ± 21	5.33 ± 1.8	52.4 ± 7.9
6a		18.6 ± 19.0		0		17.0 ± 4.8		0
6b		13.8 ± 4.8		0		0		12.4
7		17.1 ± 1.1		17.0 ± 1.9		12.9 ± 4.9		6.05 ± 3.6

[a] Percent maximal stimulation with respect to the standard agonists DAMGO (MOP), U69593 (KOP), DPDPE (DOP), and nociceptin (NOP). Values are the means of 5 or 6 experiments. EC$_{50}$ values were not calculated if the % stimulation was < 20%.

receptors. Compound **1c** behaves similarly in binding, though the effect at NOP receptors is not as profound, being 4- to 5-fold higher in affinity than **1a**. Once again, **1c** has high, nonselective affinity for the three opioid receptors comparable with that of **1a**. Compound **1d**, which is structurally related to **1c**, having a phenyl group in place of one of the methyls of the neopentyl group, has an affinity similar to that of **1c** for all four receptors and is 10-fold selective for MOP over NOP receptors. Compound **1f**, in which the C20 substituent is a bulky tricyclic group attached through a methylene spacer to C20, also shows increased affinity for NOP receptors compared to that of **1a** but couples this with a reduced affinity for opioid receptors such that it has near 10 nM affinity for each of the four receptors. The final ligand, **1e**, has the *t*-butyl group separated from C20 by a phenyl ring; it displays no increase in affinity for NOP receptors over **1a**, while having similar or slightly lower opioid receptor affinity. Overall, the binding data suggest that it is the C20 substituent of **1a** and related orvinols that occupy the putative lipophilic site in the NOP receptor, as required for high affinity binding.

The ligands were assessed for functional activity in the [^{35}S]GTPγS-binding assay in human receptor transfected CHO cells as described previously.[25] The results from these assays are shown in Table 2. Buprenorphine (**1a**) was confirmed as a low efficacy partial agonist at the MOP receptor with 29% stimulation relative to the standard MOP receptor agonist DAMGO and as a low potency (116 nM) and low efficacy (21% relative to nociceptin) partial agonist at NOP receptors. The data for **1a** is consistent with the suggestion that its in vivo profile is due to it having MOP receptor mediated effects at low doses with NOP receptor activation being noticeable at higher doses.[12,26]

The halogenated analogues (**6a**, **6b**, and **7**) had little efficacy at any receptor studied. Each had around half the efficacy of buprenorphine at the MOP receptors with only the 2-bromo analogue (**7**) demonstrating any efficacy at the NOP receptors. 1-Chlorobuprenorphine (**6b**) is interesting as a highly lipophilic, universal opioid and NOP receptor antagonist. In vitro, compound **6b** inhibited agonist stimulated [^{35}S]GTPγS activity at MOP, DOP, KOP, and NOP receptors (see Figure S1 in the Supporting Information). Its MOP receptor antagonist activity has been confirmed in vivo in mice, where it was found to have little to no efficacy in the tail flick assay up to a dose of 30 mg/kg (peak effect

of 15% at 30 mg/kg) and only reached a peak of 20% in the much lower stimulus intensity PPQ-induced antiwrithing assay in which even low efficacy partial agonists are active.[27] Compound **6b** did act as an antagonist versus morphine in the tail flick assay, AD$_{50}$ 4.7 mg/kg, which is comparable to that obtained with **1a** (AD$_{50}$ 1 mg/kg). However, **1a** was an agonist in both the tail flick (ED$_{50}$ 0.14 mg/kg) and PPQ-induced writing assays (ED$_{50}$ 0.016 mg/kg) confirming it as a partial agonist in vivo.

Of the C20 analogues of buprenorphine (**1a**), the one carbon homologues **1b** and **1c** displayed efficacy similar to that of **1a** at MOP receptors (all 20−29% relative to DAMGO) and were of very similar potency (2.6−10.2 nM). Quite substantial differences in efficacy were found between these three ligands at the NOP receptor (5−48% relative to nociceptin). Compound **1a** was of similar efficacy at the NOP receptor as at the MOP receptor, but an order of magnitude less potent at the former, while the homologue having a methylene between C20 and the *t*-butyl group (**1c**) had little or no efficacy at the NOP receptors. In contrast, **1b** was more efficacious, and of similar or higher potency, at the NOP receptors than was **1a**. As found with **1a**, **1b** was around 10-fold more potent at the MOP receptor compared to the NOP receptor. The low efficacy at MOP and KOP receptors displayed by **1b** and **1c** is notable due to their structural relationship to the *n*-propyl orvinols **10a** and **10b**. In the original orvinol and N-CPM nororvinol series, a C20 R-group three carbon atoms in length was associated with a peak in analgesic activity, through the activation of MOP or KOP receptors.[28] Both **1b** and **1c** have a substituted three carbon chain and yet have low efficacy at both MOP and KOP receptors indicating that the effect of branching in lowering efficacy at opioid receptors outweighs the higher efficacy associated with a three carbon-long chain. Compound **1d**, in which a phenyl ring replaces a methyl group in **1c**, had low efficacy at MOP receptors and only very low potency at NOP receptors. The most noticeable feature about **1d**'s profile in this assay was the increase in efficacy at KOP receptors, such that it was a potent low efficacy partial agonist. This compares with the equivalent phenethyl compound (**1**, R = (CH$_2$)$_2$Ph; unpublished) that demonstrates negligible efficacy at any of the opioid receptors under these conditions but was a partial agonist at NOP receptors (35% stimulation). Similarly, **1f** displayed KOP receptor partial agonist activity, suggesting that the introduction of the methylene group

between C20 and the bulky substituent leads to a rise in KOP receptor activation, as would be predicted from earlier studies.[29,30] Compound **1f** is profiled as a partial agonist at each of the four receptors, with highest potency at MOP and KOP receptors. Compound **1e** had little to no efficacy at any receptor, and like the 1-chloro analogue (**6b**), it may prove to be a universal opioid and NOP receptor antagonist.

Because **1b** has an in vitro profile similar to that of **1a**, but with higher affinity and efficacy for the NOP receptor, it was evaluated in an antinociceptive assay (tail flick) in the mouse and has been found to be an agonist of higher efficacy than buprenorphine and equivalent in efficacy to morphine.[31] This may indicate that the MOP receptor mediated effects of BU08028 predominate in vivo.

■ CONCLUSIONS

The notable rise in affinity at NOP receptors for compounds **1b**, **1c**, **1d**, and **1f**, but not with **6a**, **6b**, and **7**, indicates that it is the area around the C20 carbon of buprenorphine (**1a**) and analogues that fulfils the role of the large lipophilic group found in NOP receptor ligands. A methylene group inserted between the bulky lipophilic group and C20 (**1c**, **1d**, **1f**) led to an increase in efficacy at KOP receptors compared to that of **1a** with less consistent effects on MOP receptor activity. One compound, **1b**, profiled as an MOP receptor partial agonist of comparable efficacy to buprenorphine, but with higher efficacy at NOP receptors, is the subject of more extensive pharmacological evaluation in vivo.[31]

■ EXPERIMENTAL SECTION

Full details are available in the Supporting Information. Reagents and solvents were purchased from Aldrich or Lancaster and used as received. M.p.: Gallenkamp MFB-595 melting point apparatus, uncorrected. NMR Spectra: Jeol Delta-270-MHz instrument, ^{1}H at 270 MHz; Varian Mercury-400-MHz instrument, ^{1}H at 400 MHz, ^{13}C at 100 MHz, δ in ppm, J in Hz with TMS as an internal standard. ESIMS: micrOTOF (BRUKER). Microanalysis: Perkin-Elmer 240C analyzer. Ligands were tested as their hydrochloride salts and prepared by adding one equivalent of (5 N hydrochloric acid in isopropanol) to an ether solution of the compound. All compounds were >95% pure by microanalysis.

General Procedure A: Halogenation. Buprenorphine or buprenorphine 3-O-methyl ether (0.31 mmol), was dissolved in H_2SO_4 (0.1 N, 16 mL) for bromination or HCl (0.1 N, 4 mL) for chlorination, and N-halosuccinimide (0.37 mmol) was added in one portion. The reaction mixture was stirred until TLC indicated that the starting material had been consumed (approximately 3 h), and the mixture was then poured into a separatory funnel containing dichloromethane (17 mL). Sufficient aqueous sodium hydroxide (10%) solution was added to raise the pH of the aqueous layer to ca. 10, the organic layer was separated, and the aqueous layer was extracted further with three portions of 9:1 dichloromethane/methanol (10 mL). The organic extracts were combined and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography over silica gel eluting with a gradient from 5% to 10% ethyl acetate in hexane.

General Procedure B: Grignard Addition. The Grignard reagents were prepared from the corresponding bromides (6 mmol) by reaction with magnesium (218 mg, 9 mmol) in anhydrous THF (6 mL) containing a crystal of iodine. The Grignard reagents were titrated prior to use by adding 1 mL of the Grignard solution to a flask containing 1,10-phenanthroline (~2 mg) in anhydrous THF (2 mL)

(purple solution) and titrating with 1 M 2-butanol (anhydrous) in THF (end point, pale yellow solution).

A solution of the appropriate Grignard reagent (1 M in THF, 1.2 mL, 1.2 mmol) was treated dropwise at room temperature with a solution of N-cyclopropylmethyl-6,14-*endo*-ethanonorthevinone (**8**) (500 mg, 1.18 mmol) in anhydrous toluene (12 mL). After stirring at room temperature for 20 h, the reaction was quenched by the addition of a saturated aqueous ammonium chloride solution (20 mL). The phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with saturated aqueous sodium bicarbonate, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with a gradient from 10% to 30% ethyl acetate in hexane. R_f values are recorded from TLC eluted with 30:1:69 ethyl acetate/ammonia solution/hexane.

General Procedure C: 3-O-Demethylation. A solution of the appropriate methyl ether (0.1 mmol) in anhydrous HMPA (0.5 mL) under an inert atmosphere was treated with sodium hydride (8.5 mg, 0.35 mmol) followed by 1-propanethiol (32 μL, 0.35 mmol). After the addition was complete, the reaction mixture was heated to 120 °C and stirred until completion (~3 h). Upon cooling to room temperature, NH_4Cl (sat, aq) was added, and the mixture was extracted with diethyl ether. The organic extracts were washed with water (3×) and brine. The organic phase was dried over $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by column chromatography over silica gel.

The HCl salts were prepared by the addition of 5 N HCl in isopropanol (2 equiv) to a solution of the orvinol in diethyl ether. The white precipitate that formed was collected by filtration, washed with ether, and dried under high vacuum.

(2′R,5α,6R,7R,14α)-2′-(1-Bromo-17-cyclopropylmethyl-7,8-dihydro-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxy-morphinan-7-yl)-3′,3′-dimethylbutan-2′-ol (6a). Compound **5a** was treated as described in General Procedure C, and **6a** was isolated as a white solid (52 mg, 89%). R_f 0.20; ^{1}H NMR (270 MHz, CDCl₃) δ 0.10−0.14 (2H, d, J = 8.0 Hz), 0.48−0.50 (2H, t, J = 7.8, 8.9 Hz), 0.73−0.75 (1H, m), 1.22 (9H, s), 1.22−1.27 (1H, m), 1.34 (3H, s), 1.62−2.17 (6H, m), 2.19 −2.23 (3H, m), 2.30−2.32 (2H, d, J = 6.4 Hz), 2.58−2.60 (1H, m), 2.75−2.82 (1H, d, J = 18.1 Hz), 2.85−2.86 (1H, m), 3.01−3.03 (1H, d, J = 5 Hz), 3.50 (3H, s), 4.46 (1H, s), 5.84 (1H, s), 6.90 (1H, s). ESIMS m/z: 547 [M + 1]⁺. Anal. ($C_{29}H_{40}BrNO_4$·0.75H_2O) CHN.

(2′R,5α,6R,7R,14α)-2′-(1-Chloro-17-cyclopropylmethyl-7,8-dihydro-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxy-morphinan-7-yl)-3′,3′-dimethylbutan-2′-ol (6b). Compound **5b** was treated as described in General Procedure C, and **6b** was isolated as a white solid (8 mg, 56%). R_f 0.15; ^{1}H NMR (270 MHz, CDCl₃) δ 0.12−0.13 (2H, d, J = 8.0 Hz), 0.47−0.49 (2H, m), 0.49−0.51 (1H, m), 0.78−0.83 (4H, m), 1.03 (9H, s), 1.25−1.36 (4H, m), 1.56 (3H, brs), 1.68−1.97 (4H, m), 2.04−2.14 (3H, m), 2.32−2.34 (1H, d, J = 6.3 Hz), 2.61−2.65 (1H, m), 2.81−2.82 (2H, m), 3.02−3.03 (1H, d, J = 6.3 Hz), 3.51 (3H, s), 4.47 (1H, s), 5.77 (1H, s), 6.75 (1H, s). ESIMS m/z: 503 [M + 1]. Anal. ($C_{29}H_{40}ClNO_4$·HCl·0.75H_2O) CHN.

(2′R,5α,6R,7R,14α)-2′-(2-Bromo-17-cyclopropylmethyl-7,8-dihydro-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxy-morphinan-7-yl)-3′,3′-dimethylbutan-2′-ol (7). From buprenorphine (**1a**) using the halogenation procedure in General Procedure A, **7** was obtained as a white solid (70 mg, 60%). R_f 0.25; ^{1}H NMR (270 MHz, CDCl₃) δ 0.08−0.14 (2H, d, J = 8.0 Hz), 0.47−0.50 (2H, t, J = 7.8, 8.9 Hz), 0.99−1.07 (1H, m), 1.22 (9H, s), 1.23−1.27 (3H, m), 1.35 (3H, s), 1.61−2.12 (5H, m), 2.19 −2.30 (3H, m), 2.30−2.33 (2H, d, J = 6.4 Hz), 2.58−2.60 (1H, m), 2.75−2.82 (1H, d, J = 18.1 Hz), 2.85−2.86 (1H, m), 3.00−3.03 (1H, d, J = 5 Hz), 3.53 (3H, s), 4.45 (1H, s), 5.80 (1H, s), 6.90 (1H, s). ESIMS m/z: 547 [M + 1]⁺. Anal. ($C_{29}H_{40}BrNO_4$·0.45H_2O) CHN.

(1′*RS*,5α,6*R*,7*R*,14α)-2′-(17-Cyclopropylmethyl-7,8-dihy-dro-3,6-dimethoxy-4,5-epoxy-6,14-ethano-morphinan-7-yl)- 3′,3′-dimethylpentan-2′-ol (9b). General Procedure B was used to isolate 9b as a clear oil (428 mg, 15%). R_f 0.58; ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.08−0.11 (2H, m), 0.44−0.53 (2H, m), 0.81−0.86 (3H, m), 0.83−0.86 (3H, m), 0.89 (6H, s), 1.24−1.31 (2H, m), 1.34 (1H, s), 1.41 (3H, s), 1.55−1.80 (3H, m), 1.95−2.03 (2H, m), 2.27−2.34 (5H, m), 0.84 (1H, m), 2.79−2.84 (1H, t, $J = 9$ Hz), 2.94−2.98 (1H, m), 3.53 (3H, s), 3.86 (3H, s), 4.41 (1H, s), 5.96 (1H, s), 6.53 (1H, d, $J = 8.0$ Hz), 6.67 (1H, d, $J = 8.0$ Hz, m). ESIMS m/z: 496 $[M + 1]^+$.

(2′*R*,5α,6*R*,7*R*,14α)-2′-(17-Cyclopropylmethyl-7,8-dihy-dro-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxy-morphi-nan-7-yl)-3′,3′-dimethylpentan-2′-ol (1b). General Procedure C was used to isolate (1b) as a clear oil (182 mg, 80%). R_f 0.23; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.08−0.10 (2H, d, $J = 8.0$ Hz), 0.44−0.49 (2H, t, $J = 7.8, 8.9$ Hz), 0.65−0.69 (1H, m), 0.72−0.80 (1H, m), 0.86−0.90 (3H, m), 0.91 (6H, s), 1.03−1.06 (1H, m), 1.31−1.34 (2H, m), 1.35 (3H, s), 1.40−1.45 (1H, m), 1.60−1.75 (3H, m), 1.80−1.86 (1H, m), 1.93−2.00 (1H, m), 2.15−2.36 (5H, m), 2.57−2.62 (1H, dd, $J = 5$ Hz), 2.79−2.86 (1H, m), 2.93−2.96 (1H, d, $J = 17.0$ Hz), 2.96−2.98 (1H, d, $J = 7.0$ Hz), 3.51 (3H, s), 4.43 (1H, s), 5.95 (1H, s), 6.49 (1H, d, $J = 8.1$ Hz), 6.67 (1H, d, $J = 8.1$ Hz); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 3.2, 4.1, 9.1, 9.4, 18.3, 20.6, 21.4, 21.7, 22.8, 28.5, 29.5, 33.3, 35.5, 35.8, 42.7, 43.0, 43.6, 46.3, 52.4, 58.2, 59.4, 80.4, 80.8, 96.9, 116.3, 119.5, 128.3, 132.6, 137.2, 145.3. ESIMS m/z: 482 $[M + 1]^+$. Anal. (C$_{30}$H$_{43}$NO$_4$·0.3 H$_2$O) CHN.

(2′*R*,5α,6*R*,7*R*,14α)-2′-(17-Cyclopropylmethyl-7,8-dihy-dro-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxy-morphi-nan-7-yl)-4′,4′-dimethylpentan-2′-ol (1c). Isolated as a white solid, by using General Procedure C to yield 1c (20 mg, 52%). R_f 0.46; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.10−0.11 (2H, d, $J = 8.0$ Hz), 0.47−0.50 (2H, m), 0.72−0.75 (1H, m), 0.81−0.88 (2H, m), 1.08 (9H, s), 1.24 (2H, s), 1.44 (6H, m), 1.63−1.66 (1H, d, $J = 3$ Hz) 1.73−1.81 (2H, m), 1.84−2.04 (2H, m), 2.17−2.40 (4H, m), 2.61−2.65 (1H, m), 2.81−2.87 (1H, m), 2.94−2.99 (1H, d, $J = 18.1$ Hz), 2.99−3.00 (1H, d, $J = 5$ Hz), 3.50 (3H, s), 4.42 (1H, s), 5.14 (1H, s), 6.48−6.50 (1H, d, $J = 8.0$ Hz), 6.66−6.68 (1H, d, $J = 8.0$ Hz); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 3.4, 4.1, 9.4, 18.0, 22.6, 24.0, 29.8, 31.9, 32.0, 32.6, 35.5, 36.0, 47.1, 48.4, 52.0, 52.6, 58.2, 59.8, 78.2, 80.9, 97.5, 116.2, 119.4, 128.4, 132.4, 137.1, 145.4. ESIMS m/z: 482 $[M + 1]$. Anal. (C$_{30}$H$_{43}$NO$_4$·HCl·0.3H$_2$O) CHN.

(2′*R*,5α,6*R*,7*R*,14α)-2′-(17-Cyclopropylmethyl-7,8-dihy-dro-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxy-morphinan-7-yl)-4′-methyl-4′-phenylpentan-2′-ol (1d). General Procedure C was used to prepare 1d and was isolated as a clear oil (60 mg, 80%). R_f 0.34; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.13−0.14 (2H, d, $J = 8.1$ Hz), 0.52−0.53 (2H, m), 0.55−0.56 (1H, m), 0.85−0.96 (6H, m), 1.41 (3H, s), 1.52 (5H, m), 1.62−1.64 (2H, t, $J = 6.8$ Hz), 1.73−1.85 (3H, m), 2.03−2.07 (1H, d, $J = 14.5$ Hz), 2.16−2.35 (4H, m), 2.58−2.71 (2H, m), 2.92−2.96 (1H, d, $J = 18.4$ Hz), 2.95−2.96 (1H, m), 3.43 (3H, s), 4.27 (1H, s), 5.18 (1H, brs), 6.46−6.48 (1H, d, $J = 8.1$ Hz), 6.64−6.66 (1H, d, $J = 8.1$ Hz), 7.15−7.17 (1H, t, $J = 7.1$ Hz), 7.27−7.29 (2H, d, $J = 7.1$ Hz), 7.44−7.45 (2H, d, $J = 7.2$ Hz); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 3.5, 4.0, 9.4, 18.3, 22.6, 23.8, 29.6, 32.6, 33.4, 35.3, 35.9, 37.9, 43.5, 46.6, 46.8, 52.4, 52.7, 58.3, 59.9, 80.8, 96.9, 116.3, 119.4, 125.0, 126.1, 127.9, 128.1, 132.4, 137.1, 145.4, 150.5. ESIMS m/z: 544 $[M + 1]^+$. Anal. (C$_{35}$H$_{45}$NO$_4$·HCl·1.5H$_2$O) CHN.

(2′*R*,5α,6*R*,7*R*,14α)-1′-(4″-*t*-Butyl-phenyl)-1′-(17-cyclopro-pylmethyl-7,8-dihydro-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxy-morphinan-7-yl)-ethan-1′-ol (1e). Compound 1e was prepared using General Procedure C and was isolated as a white solid (50 mg, 79%). R_f 0.33; ^{1}H NMR (400 MHz, CDCl$_3$) δ −0.07−0.00 (2H, m), 0.31−0.33 (2H, d, $J = 8.0$ Hz), 0.68−0.72 (1H, m), 0.73−0.86 (1H, m), 0.86−0.92 (1H, m), 0.99−1.03 (1H, m), 1.31 (9H, s), 1.52−1.55 (1H, d, $J = 12.5$ Hz), 1.77 (6H, m), 1.81−1.84 (1H, m),

2.03−2.10 (1H, m), 2.13−2.20 (5H, m), 2.46−2.48 (1H, m), 2.77−278 (1H, m), 2.87−2.91 (1H, d, $J = 18.3$ Hz), 3.54 (3H, s), 4.43 (1H, s), 5.44 (1H, s), 6.44−6.46 (1H, d, $J = 8.0$ Hz), 6.61−6.63 (1H, d, $J = 8.0$ Hz), 7.32−7.33 (2H, d, $J = 4.7$ Hz), 7.34−7.35 (2H, d, $J = 4.7$ Hz); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 3.4, 3.5, 9.1, 17.8, 23.0, 23.4, 29.8, 31.3, 32.4, 34.3, 35.5, 36.0, 43.2, 47.0, 48.3, 52.7, 58.5, 59.2, 80.7, 97.2, 116.3, 119.4, 124.6, 125.6, 128.1, 132.3, 137.2, 144.0, 145.4, 149.3. ESIMS m/z: 544 $[M + 1]^+$. Anal. (C$_{35}$H$_{45}$NO$_4$) CHN.

(2′*R*,5α,6*R*,7*R*,14α)-2′-(17-Cyclopropylmethyl-7,8-dihy-dro-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxy-morphi-nan-7-yl)-1′-(bicyclo[2.2.1]heptan-1-yl)-propan-2′-ol (1f). General Procedure C was used to prepare 1f, isolated as a white solid (55 mg, 62%). R_f 0.23; ^{1}H NMR (400 MHz, MeOD) δ 0.16−0.18 (2H, m), 0.51−0.53 (2H, d, $J = 8.1$ Hz), 0.71−0.82 (3H, m), 1.14−1.35 (3H, m), 1.37−1.38 (15 H, m), 1.54−1.86 (7H, m), 2.22−2.39 (4H, m), 2.69 (1H, m), 2.99−3.00 (1H, m), 3.03−3.05 (1H, d, $J = 18.1$ Hz), 3.58 (3H, s), 4.36 (1H, s), 6.47−6.50 (1H, d, $J = 8.0$ Hz), 6.62−6.64 (1H, d, $J = 8.0$ Hz); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 4.0, 4.4, 10.2, 19.1, 23.8, 24.8, 29.6, 30.7, 32.9, 36.0, 37.2, 38.6, 39.8, 40.9, 43.5, 44.8, 46.9, 53.0, 60.8, 67.1, 69.2, 81.9, 97.9, 117.9, 120.4, 128.5, 133.6, 139.5, 147.3. ESIMS m/z: 520 $[M + 1]^+$. Anal. (C$_{33}$H$_{45}$NO$_4$·HCl·0.5H$_2$O) CHN.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Full experimental details (spectra and microanalysis data) plus figures detailing antagonist activity of 6b in vitro. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS USED

MOP receptor, mu opioid receptor; NOP receptor, nociceptin/ orphanin FQ receptor; MC-CAM, methoclocinnamox; CHO, Chinese hamster ovary; KOP receptor, kappa opioid receptor; DOP, delta opioid receptor

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