Synthesis and Opioid Receptor Affinity of Morphinan and Benzomorphan Derivatives: Mixed κ Agonists and μ Agonists/Antagonists as Potential Pharmacotherapeutics for Cocaine Dependence[†]

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This report concerns the synthesis and preliminary pharmacological evaluation of a novel series of κ agonists related to the morphinan (−)-cyclorphan **(3a)** and the benzomorphan (−)-cyclazocine **(2)** as potential agents for the pharmacotherapy of cocaine abuse. Recent evidence suggests that agonists acting at κ opioid receptors may modulate the activity of dopaminergic neurons and alter the neurochemical and behavioral effects of cocaine. We describe the synthesis and chemical characterization of a series of morphinans **3a–c**, structural analogues of cyclorphan [(−)-3-hydroxy-*N*-cyclopropylmethylmorphinan *S*(+)-mandelate, **3a**], the 10-keto-morphinans **4a,b,** and the 8-ketobenzomorphan **1b**. Binding experiments demonstrated that the cyclobutyl analogue **3b** [(−)-3-hydroxy-*N*-cyclobutylmethylmorphinan *S*(+)-mandelate, **3b**, MCL-101] of cyclorphan **(3a)** had a high affinity for μ, δ, and κ opioid receptors in guinea pig brain membranes. Both **3a,b** were approximately 2-fold more selective for the κ receptor than for the μ receptor. However **3b** (the cyclobutyl analogue) was 18-fold more selective for the κ receptor in comparison to the δ receptor, while cyclorphan **(3a)** had only 4-fold greater affinity for the κ receptor in comparison to the δ receptor. These findings were confirmed in the antinociceptive tests (tail-flick and acetic acid writhing) in mice, which demonstrated that cyclorphan **(3a)** produced antinociception that was mediated by the δ receptor while **3b** did not produce agonist or antagonist effects at the δ receptor. Both **3a,b** had comparable κ agonist properties. **3a,b** had opposing effects at the μ receptor: **3b** was a μ agonist whereas **3a** was a μ antagonist.

Introduction

κ Opioid receptors derive their name from the prototype benzomorphan, ketocyclazocine (**1a**) (Chart 1), which was found to produce behavioral effects that were distinct from the behavioral effects of morphine but that were antagonized by the opioid antagonist, naltrexone.[1] Compounds from several structural classes, including benzomorphans, arylacetamides, and morphinans have been found to possess κ opioid agonist activity. A growing body of evidence suggests that agonists at κ opioid receptors may modulate the activity of dopaminergic neurons and alter the neurochemical and behavioral effects of cocaine. The nucleus accumbens contains high levels of both κ opioid receptors[2–4] and dynorphin,[5] an endogenous opioid peptide with high affinity for κ receptors.[6] In contrast to cocaine, κ agonists have been shown to decrease striatal dopamine levels in rats.[7–9] κ Agonists also attenuated cocaine-induced increases in dopamine levels in the nucleus accumbens.[10] Behaviorally, the administration of κ agonists

in rodents has been reported to block or decrease cocaine-induced hyperactivity,[11,12] sensitization to cocaine-induced hyperactivity and stereotypies,[13] and cocaine-induced place preferences.[11,13,14] κ Agonists also blocked the effects of cocaine in squirrel monkeys in assays of cocaine discrimination[15,16] and scheduled-controlled responding. These findings suggest that activation of κ opioid receptors may functionally antagonize some abuse-related effects of cocaine, possibly by inhibiting the release of dopamine from dopaminergic neurons, and may provide a new approach to the continuing search for effective treatment medications for cocaine abuse and dependence.[17] In an effort to evaluate this hypothesis, the effects of eight benzomorphan and arylacetamide κ agonists on cocaine self-administration in rhesus monkeys were examined.[18,19] Most of these κ agonists produced dose-dependent decreases in cocaine self-administration. Moreover, all κ agonists that reduced cocaine self-administration were compounds with relatively high efficacy for κ receptors, whereas a low-efficacy κ agonist (cyclazocine, **2**) and a κ antagonist (*nor*-binaltorphimine) were ineffective. Interestingly, however, nonselective κ agonists such as ethylketocyclazocine (**1c**), which produce μ receptor-mediated effects in addition to their κ agonist effects, decreased cocaine self-administration more effectively and with fewer
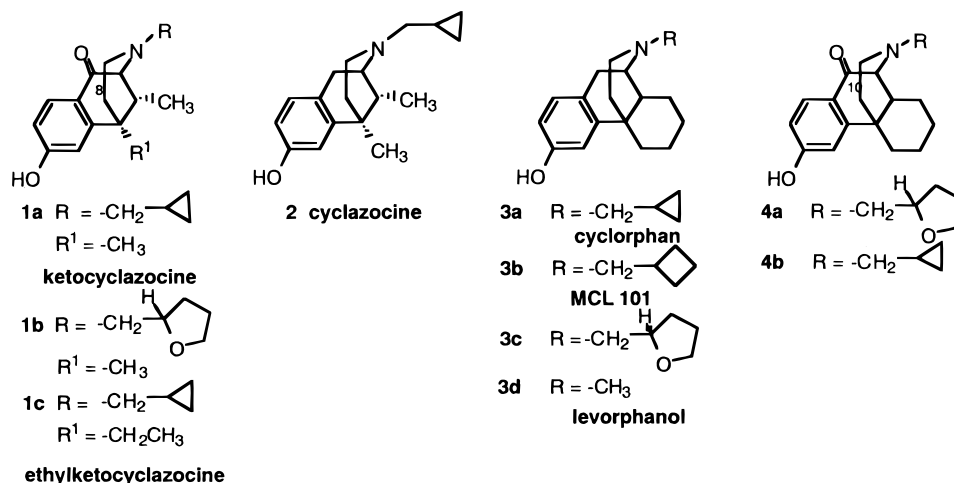
Chart 1. Structures of κ Agonists

undesirable side effects than highly selective κ agonists. Antagonism studies also suggested that κ agonists which are partial agonists at the μ receptor such as ethylketocyclazocine (**1c**) may be especially effective in decreasing cocaine self-administration in rhesus monkeys.[18] Specifically, naloxone completely blocked the effects of ethylketocyclazocine on cocaine self-administration, but the κ-selective antagonist, *nor*-binaltorphimine, was only partially effective. In contrast, both naloxone and *nor*-binaltorphimine completely blocked the effects of the highly selective κ agonist U-50,488 on cocaine self-administration.[15,16,18,19] Taken together, these earlier findings suggested that nonselective κ agonists with additional activity at μ receptors may be especially promising candidate medications for the treatment of cocaine abuse.

Ethylketocyclazocine (**1c**) has intermediate efficacy at μ receptors and functions as a κ agonist/μ partial agonist. The development of other κ agonists with higher or lower efficacy at μ receptors would permit further evaluation of the most favorable combination of κ and μ opioid receptor-mediated effects for the reduction of cocaine self-administation. Because both morphinans and benzomorphans are known to include compounds with mixed activity at μ and κ receptors, the purpose of the present study was to develop novel morphinan and benzomorphan κ agonists as candidate drug abuse treatment medications. Accordingly, we describe here the synthesis and preliminary evaluation of a series of morphinans (**3a**−**c**), structural analogues of cyclorphan **3a**, the 10-ketomorphinans **4a,b**, and the 8-ketobenzomorphan **1b**, structurally related to ketocyclazocine (**1a**). The structures of these compounds are shown in Chart 1.

Chemistry

The synthesis of the morphinans **3a**−**c** and the 10-keto derivatives **4a,b** is shown in Scheme 1. The compounds were all prepared from commercially available (−)-3-hydroxy-*N*-methylmorphinan (levorphanol, **3d**) which was converted to the *O*-methyl ether **6** and N-dealkylated to (−)-3-methoxymorphinan **(7)**. Alternatively, **3d** was directly N-dealkylated to **8**.

The intermediate **8** was N- and O-diacylated with cyclopropanecarbonyl chloride in the presence of tri-

ethylamine. The crude diacyl compound **9a** was further reduced with lithium aluminum hydride to yield **3a,b** previously prepared by Gates and Montzka[20] from (−)-3-hydroxymorphinan. **3a,b** were further converted to their white crystalline mandelate salts. The (*S*)-*N*-tetrahydrofurfuryl derivative **3c** was prepared from (*S*)-tetrahydrofurfuryl (1*R*)-camphor-10-sulfonate **(10)** by methods previously reported.[21] The 10-ketomorphinans were prepared by the oxidation[22] of the morphinan **7** with CrO_3/H_2SO_4 followed by alkylation with cyclopropylmethyl bromide and O-demethylation to yield **4b** (Scheme 1). O-Demethylation of **11** to form **13** followed by alkylation with (*S*)-tetrahydrofurfuryl (1*R*)-camphor-10-sulfonate **(10)** led to **4a**. The assignment of the stereochemistry of **4a** was based on the work of Merz and Stockhaus.[23]

The 8-ketobenzomorphan derivative **1b** was prepared from (−)-5,9-α-dimethyl-2-hydroxy-6,7-benzomorphan **(14)** [(−)-*nor*-metazocine][24] as outlined in Scheme 2. Protection of the amine with di-*tert*-butyl dicarbonate (Boc) and O-methylation with dimethyl sulfate led to **16**. Acid hydrolysis followed by oxidation of **17** with CrO_3/H_2SO_4 by the procedure of Michne and Albertson[22] led to **18**. O-Demethylation and alkylation with 5-tetrahydrofurfuryl (1*R*)-camphor-10-sulfonate **(10)** gave **1b** which was isolated as the HCl salt.

Results

All compounds were examined for their affinity and selectivity at μ, δ, and κ opioid receptors in guinea pig brain membranes using the selective radioligands, [^{3}H]-DAMGO (μ), [^{3}H]naltrindole (δ), and [^{3}H]U69,593 (κ) (Table 1). The antinociceptive activity of the two morphinans with the highest affinity at the κ receptor was examined further in the tail-flick and acetic acid writhing tests in mice.

55° Warm-Water Tail-Flick Test. In the warm-water tail-flick test, (−)-cyclorphan **(3a)** produced $37 \pm 10\%$ antinociception after an icv dose of 100 nmol. In contrast, **3b** produced a full dose−response curve with an ED_{50} value and 95% confidence limits (CL) of 7.3 (5.7−9.4) nmol with testing taking place 20 min afer an icv injection.

Because **3b** generated a full dose−response curve in the tail-flick test, the receptor selectivity of the agonist

Scheme 1[a]
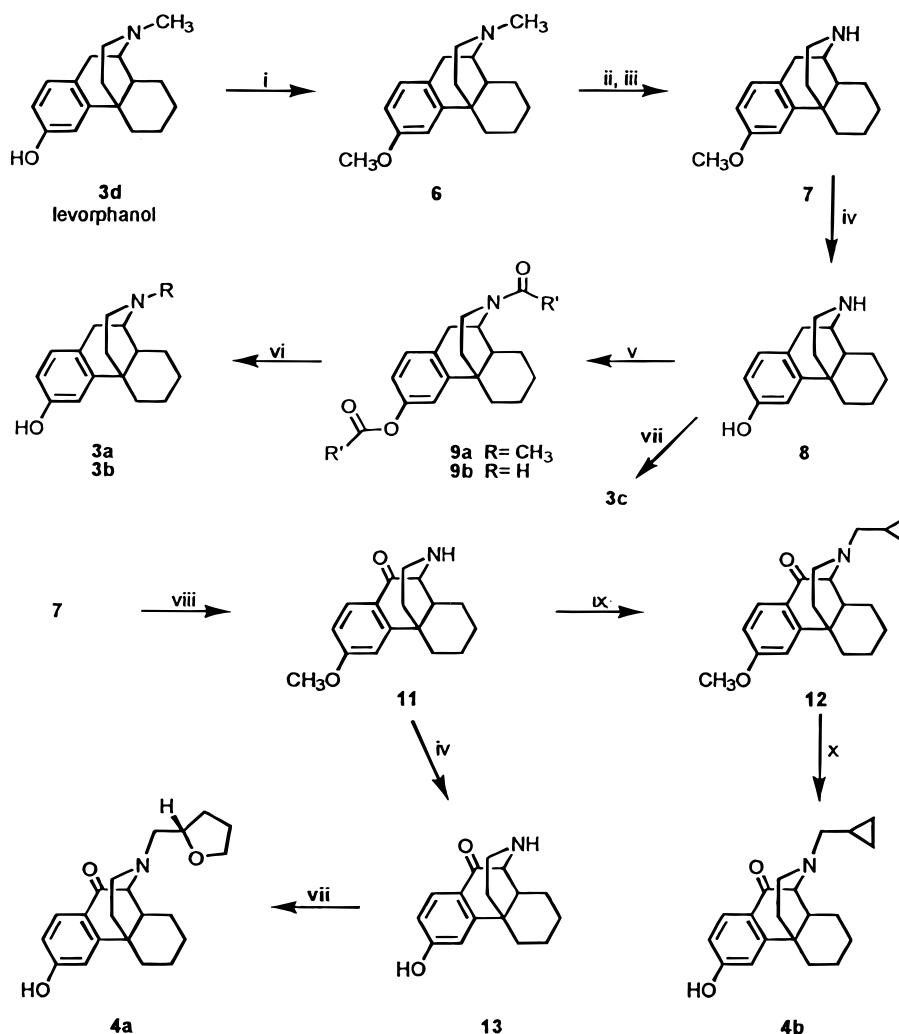
[a] Reagents: (i) CH_2N_2; (ii) 1-chloroethyl chloroformate; (iii) MeOH; (iv) HBr/HOAc; (v) R′COCl; (vi) LiAlH$_4$; (vii) (S)-tetrahydrofurfuryl (1R)-camphor-10-sulfonate (**10**); (viii) $CrO_3-H_2SO_4$; (ix) cyclopropylmethyl bromide; (x) BBr_3/CH_2Cl_2.

Scheme 2[a]
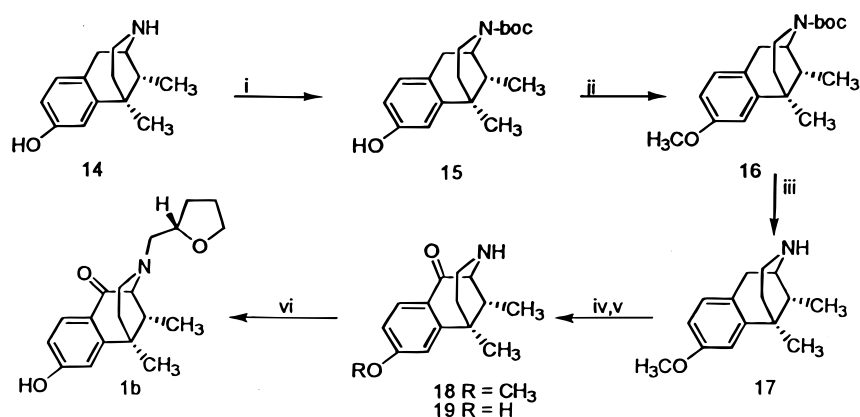
[a] Reagents: (i) (t-Boc)$_2$O, K_2CO_3, dioxane, H_2O; (ii) $(CH_3O)_2SO_2$, NaOH, H_2O; (iii) HCl, H_2O/EtOAc; (iv) CrO_3, H_2SO_4; (v) 48% HBr; (vi) (S)-tetrahydrofurfuryl (1R)-camphor-10-sulfonate.

effect was determined by using selective antagonists. Figure 1 shows that in the tail-flick test, antinociception induced by **3b** was mediated by both κ and μ opioid receptors.

Acetic Acid Writhing Test. Because κ agonists often do not produce full dose−response curves in the warm-water tail-flick test,[25] the effects of **3a,b** were character-

ized in the writhing test. Both **3a,b** produced full dose−response curves in the writhing test, with ED$_{50}$ values and 95% CL of 0.65 (0.35−1.2) and 0.79 (0.48−1.3) nmol, respectively, demonstrating that in this assay the two compounds were equipotent.

The receptor selectivity for antinociception produced by **3a,b** in the writhing test was also determined. Figure

Table 1. K_i Value Inhibition of μ, δ, and κ Opioid Binding to Guinea Pig Brain Membranes by Test Compounds[a]

compound	K_i (nM $\pm$ SE)			selectivity κ:μ	selectivity κ: δ
	[³H]DAMGO (μ)	[³H]naltrindole (δ)	[³H]U69,593 (κ)		
U50,488	220 $\pm$ 5.6	2500 $\pm$ 170	0.36 $\pm$ 0.056	610	6900
ethylketocyclazocine **(1c)**	0.78 $\pm$ 0.1	3.4 $\pm$ 0.41	0.62 $\pm$ 0.11	1	5
(−)-cyclazocine **(2)**	0.10 $\pm$ 0.03	0.58 $\pm$ 0.06	0.052 $\pm$ 0.0009	2	11
(−)-cyclorphan **(3a)**	0.092 $\pm$ 0.005	0.22 $\pm$ 0.01	0.053 $\pm$ 0.003	2	4
MCL-101 **(3b)**	0.12 $\pm$ 0.012	1.3 $\pm$ 0.06	0.073 $\pm$ 0.012	2	18
3c	0.010 $\pm$ 0.002	0.27 $\pm$ 0.02	0.15 $\pm$ 0.01	0.066	2
levorphanol **(3d)**	0.21 $\pm$ 0.017	4.2 $\pm$ 0.45	2.3 $\pm$ 0.26	0.09	2
4a	0.38 $\pm$ 0.004	1.0 $\pm$ 0.18	0.18 $\pm$ 0.019	2	6
4b	240 $\pm$ 89	150 $\pm$ 71	24 $\pm$ 1.6	1	6
1b	2900 $\pm$ 58	>100000	720 $\pm$ 57	4	

[a] Guinea pig brain membranes, 0.5 mg of protein/sample, were incubated with 12 different concentrations of the compounds in the presence of receptor-specific radioligands at 25 °C, in a final volume of 1 mL of 50 mM Tris-HCl, pH 7.5. Nonspecific binding was determined using 1 μM naloxone. Data are the mean values SEM from three experiments, performed in triplicate.
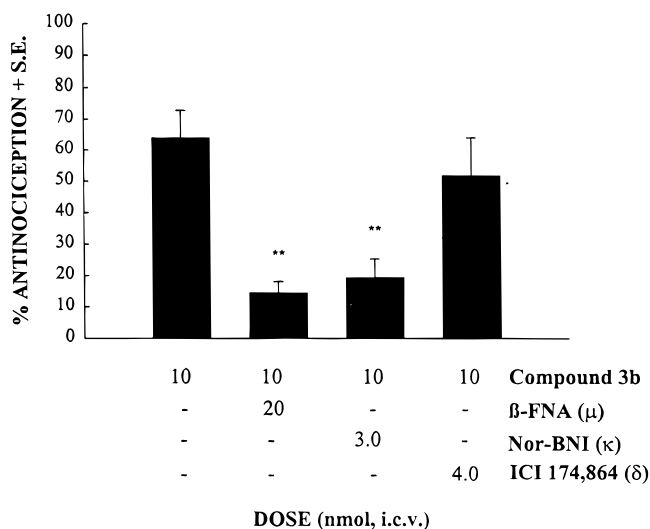

Figure 1. Receptor selectivity of antinociception induced by **3b** in the tail-flick test. Mice were pretreated either with the μ-selective antagonist β-FNA for 24 h or with the κ antagonist *nor*-BNI or the δ antagonist ICI 174,864, which were co-injected with MCL-101 **(3b)**, 20 min before testing. Each group contained 10 mice. Data are the mean $\pm$ SE. **P < 0.01, in comparison to the **3b** alone group.

2A shows that **3a** produced antinociception that was mediated by κ and δ opioid receptors. In contrast, **3b** produced antinociception that was mediated by κ and μ receptors, as shown in Figure 2B, and is in agreement with the results from the tail-flick assay *(*Figure 1*)*. The receptor selectivity results in the writhing assay correlated with the binding results in Table 1, which showed that **3a** had a higher affinity than **3b** for the δ receptor.

Antagonist Properties of (−)-Cyclorphan (3a) and Compound 3b. Because **3a** did not produce a full dose−response curve in the 55 °C warm-water tail-flick test, experiments were performed to determine if it would antagonize morphine-induced antinociception. Mice were co-injected with 3 nmol of morphine and varying doses of **3a**. Antinociception was determined 20 min later. Figure 3A shows that **3a** at a dose of 1 nmol completely antagonized morphine-induced antinociception, indicating that **3a** was a μ antagonist. In contrast, **3b** was a weak μ antagonist, with only partial antagonism of morphine-induced antinociception, at a dose that did not produce antinociception by itself *(*Figure 3*)*.
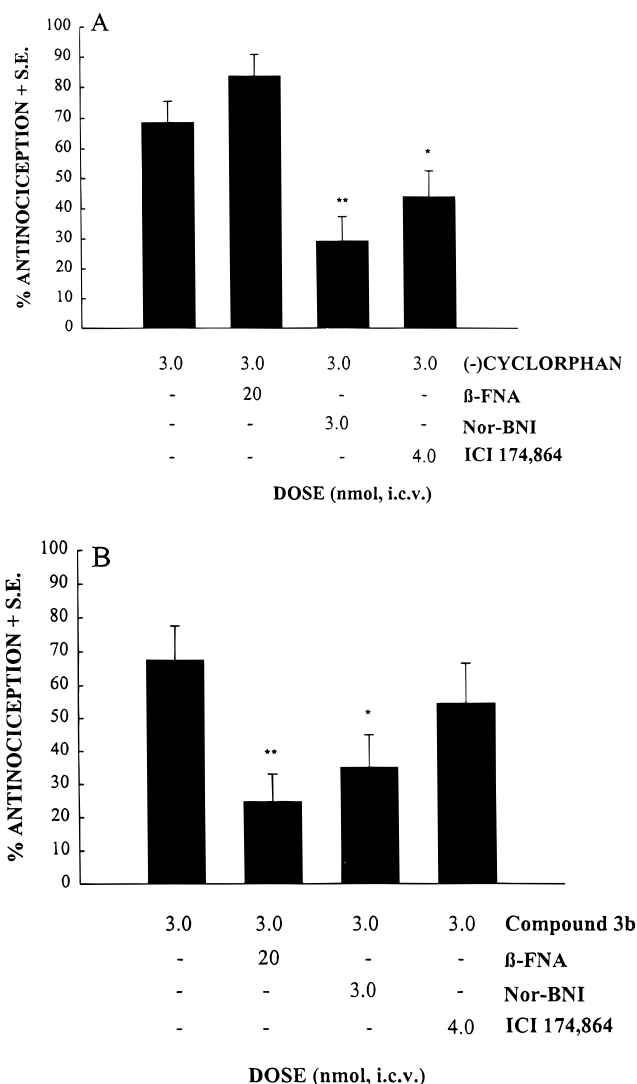

Figure 2. Receptor selectivity of antinociception induced by (−)-cyclorphan **(3a)** (A) and **3b** (B) in the writhing test. Mice were pretreated either with the μ-selective antagonist β-FNA for 24 h or with the κ antagonist *nor*-BNI or the δ antagonist ICI 174,864, which were co-injected with (−)-cyclorphan or **3b**. After 20 min, the number of writhes was measured and compared to a control group of mice that received icv saline. Each group contained 10 mice. Data are the mean $\pm$ SE. *P < 0.05, **P < 0.01, in comparison to the (−)-cyclorphan (A) or **3b** (B) alone group.

To determine the receptor selectivity of the antagonism induced by **3a**, mice were co-injected with either
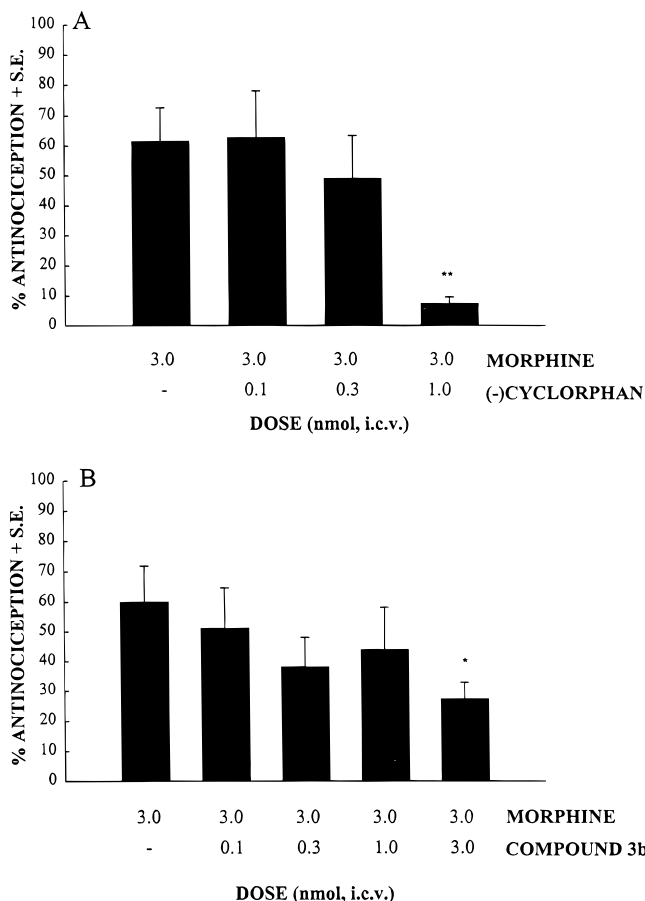
Figure 3. Antinociceptive effects of icv morphine (3 nmol, −20 min), alone or co-administered to mice with increasing doses of icv (−)-cyclorphan (**3a**) (A) or **3b** (B) in the mouse tail-flick assay. Data are the mean ± SE. *$P < 0.05$, **$P < 0.01$, in comparison to the morphine alone group.
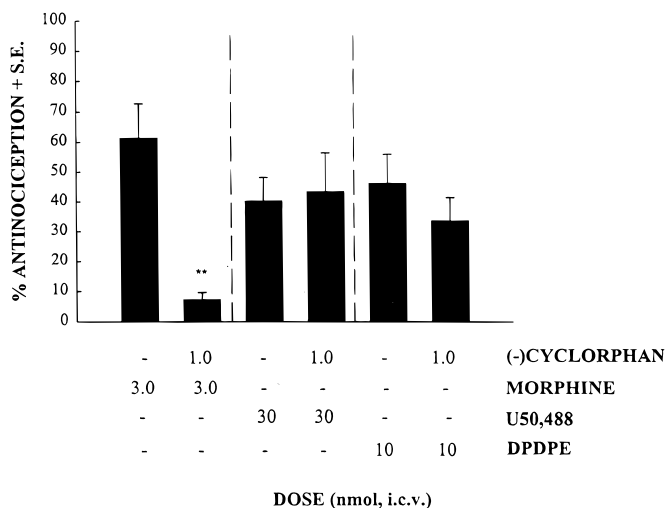

Figure 4. Antinociceptive effects of icv morphine (3 nmol), U50,488 (30 nmol), or DPDPE (10 nmol) in untreated mice and mice co-administered with a single icv dose of (−)-cyclorphan (1 nmol) in the warm-water tail-flick assay. Testing was performed 20 min after the co-administration of the compounds. **$P < 0.01$, in comparison to the morphine alone group.

the μ agonist, morphine, the κ-selective agonist, U50,-488, or the δ-selective peptide, DPDPE, along with 1-nmol of (−)-cyclorphan (**3a**). Figure 4 shows that **3a** did not antagonize antinociception mediated by either

the δ or κ receptors but did antagonize morphine-induced antinociception, demonstrating that **3a** was a μ-selective antagonist.

Conclusions

The major findings of this study were that cyclorphan (**3a**) and **3b** (the *N*-cyclobutylmethyl analogue of **3a**) had similar agonist effects mediated by κ opioid receptors but produced different effects at μ opioid receptors. Specifically, both cyclorphan (**3a**) and **3b** had high affinity for κ opioid receptors and produced agonist effects mediated by κ opioid receptors in mice. Both compounds also bound to μ opioid receptors with affinities approximately 2-fold lower than their affinities for κ receptors. However, cyclorphan (**3a**) had low efficacy at μ receptors and acted as a μ *antagonist*, whereas **3b** had higher efficacy at μ receptors and acted as a μ *agonist*. In addition to these effects at κ and μ receptors, cyclorphan (**3a**) also produced δ receptor-mediated agonist effects, whereas **3b** did not produce agonist or antagonist effects at δ receptors.

These findings confirm and extend previous studies that have evaluated opioid receptor binding profiles and pharmacological activities of different N-substituted morphinans. For example, in the present study, conversion of the N-substituent from *N*-methyl (levorphanol, **3d**) to *N*-cyclopropylmethyl (cyclorphan, **3a**) increased binding affinity to μ, κ, and δ receptors, and this increase in affinity was most pronounced for κ receptors. Consequently, levorphanol (**3d**) had 10−20-fold selectivity for μ vs κ and δ receptors, whereas cyclorphan (**3a**) had approximately 2−4-fold selectivity for κ vs μ and δ receptors. Moreover, the conversion of the N-substituent from *N*-methyl to *N*-cyclopropylmethyl also decreased μ agonist efficacy, and cyclorphan acted as a μ antagonist. Previous studies also found that conversion of the N-substituent from *N*-methyl to *N*-cyclopropylmethyl increased μ, κ, and δ receptor affinity and decreased μ receptor efficacy for morphinans [i.e. levorphanol (**3d**) and cyclorphan (**3a**)] as well as for morphine itself (i.e. morphine and *N*-cyclopropylmethyl-*nor*-morphine) and benzomorphans (i.e. metazocine and cyclazocine).[26] Previous in vivo preclinical studies also reported that cyclorphan (**3a**) displayed agonist effects at κ receptors and low-efficacy effects at μ receptors in both pigeons and primates.[27−30]

In the present study, further conversion of the N-substituent from *N*-cyclopropylmethyl to *N*-cyclobutylmethyl had little effect on receptor affinity or selectivity but increased μ agonist efficacy. To our knowledge, previous studies have not provided a detailed pharmacological evaluation of this conversion in the morphinan series. However, earlier studies did find that **3b** was approximately 40 times more potent than morphine in suppressing abstinence in morphine-dependent monkeys, and this finding is consistent with the conclusion that **3b** has potent μ agonist effects.[31] Moreover, conversion of the N-substituent from *N*-cyclopropylmethyl to *N*-cyclobutylmethyl has also been found to increase μ agonist efficacy in other related chemical classes including the 14-hydroxymorphinans,[31] the *nor*-oxymorphones,[32] and the 5-phenylbenzomorphans.[33]

The present study also evaluated the effects of two other modifications to cyclorphan (**3a**). First, addition

of a 10-keto group to cyclorphan (**3a**) to produce **4b** decreased affinity at κ, μ, and δ receptors. Similarly, addition of a 10-keto group to the benzomorphan cyclazocine to form ketocyclazocine also produced a decrease in affinity for κ, μ, and δ receptors.[34] Second, the further substitution of *N*-cyclopropylmethyl to *N*-furfurylmethyl to form **4a** increased binding affinities to κ, μ, and δ receptors. Thus, **4a** retained high affinity for opioid receptors. Interestingly, the comparable benzomorphan **1b** did not retain affinity for opioid receptors.

Recent findings from our laboratory[18,19] that some κ agonists selectively decrease cocaine self-administration by rhesus monkeys with minimal effects on food self-administration support our further chemical and behavioral studies with these and other mixed κ/μ opioids as potential anticocaine medications.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary tube apparatus and are reported uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker AC300 spectrometer using tetramethylsilane as an internal reference. All optical rotations were measured at the sodium D line using a Rudolph polarimeter (model DP 1A31, 10-cm cell). Elemental analyses, performed by Atlantic Microlabs, Atlanta, GA, were within $\pm0.4\%$ of theoretical values. Analytical thin-layer chromatography (TLC) was carried out on 0.2-mm Kieselgel 60F 254 silica gel plastic sheets (EM Science, Newark) and visualization was performed by illumination with 254-nm UV light or by exposure to iodine vapor. Flash chromatography was used for the routine purification of reaction products. The column output was monitored with TLC. HPLC apparatus consisted of a Rainin-Rabbit-HP pump, a Rheodyne injector, column (Phenomenex Bondclone C18, 3.9 × 300 mm; or EMerk Aluspher RP select B250-4), and a variable wavelength UV detector.

(−)-3-Methoxy-*N*-methylmorphinan (6). (−)-3-Hydroxy-*N*-methylmorphinan (levorphanol) (**3d**) free base was made from levorphanol tartrate (Mallinckrodt) by treating with NaHCO$_3$(aq) and extraction with CHCl$_3$. To a solution of KOH (8 g) in water (8 mL) and EtOH (25 mL) was added a solution of Diazald (20 g) in ether (200 mL) at 65 °C. The resulting mixture was subjected to distillation and the ether solution of CH$_2$N$_2$ was collected in an ice-bath trap. Additional ether (50 mL) was added to maintain the distillation. This process was stopped when the distillate solution became colorless (a total of ~120 mL was collected). It was then added to a solution of **3d** (2.4 g, 9.3 mmol) in MeOH (25 mL) in a pressure tube. The resulting solution was sealed and allowed to stay at room temperature overnight. Pressure was released with caution. Solvent was removed under reduced pressure to afford crude **6** (2.5 g, 99%) (lit.[35] mp 109–111 °C). TLC [CHCl$_3$−MeOH− NH$_3$H$_2$O (1% in MeOH), 80−20].

(−)-3-Methoxymorphinan (7). The N-dealkylation was carried out by the procedure of Olfoson et al.[36] A mixture of **6** (5.2 g, 19.2 mmol), α-chloroethyl chloroformate (18 mL, 166 mmol), 1,2-dichloroethane (80 mL), and NaHCO$_3$ (2.4 g) was allowed to reflux for 48 h. Upon filtration, the filtrate was concentrated to dryness under reduced pressure. MeOH (500 mL) was added, and the mixture was heated to reflux for 3 h. Solvent was removed under reduced pressure, and the remaining material was taken up with CHCl$_3$ (50 mL). It was washed with NaOH (1.8 N, 10 mL) and water (to pH 7), dried (MgSO$_4$), and concentrated to dryness to afford an oil **7** (5.1 g, 90%). ^{1}H NMR (CDCl$_3$, free base): δ 1−1.6 (m, 8H), 2.05 (m, 1H), 2.18 (m, 1H), 2.37 (m, 1H), 2.75 (m, 1H), 3.1−3.25 (m, 3H), 3.72 (m, 1H), 3.8 (s, 3H), 6.75−6.81 (m, 2H), 7.09−7.12 (d, $J = 8.3$ Hz, 1H).

10-Keto-3-methoxymorphinan (11). To a solution of **7** (0.7 g, 2.38 mmol) in 17 mL of dilute H$_2$SO$_4$ (prepared by cautiously adding 3 mL of H$_2$SO$_4$ to 34 mL of water) was added a solution of CrO$_3$ in the remaining 17 mL of dilute H$_2$SO$_4$. The resulting suspension was heated to reflux for 2 h. TLC (9:1:0.01 CH$_2$Cl$_2$−MeOH−NH$_4$OH) analysis indicated the disappearance of the starting material. Upon cooling, NH$_3$ (37%, 8 mL) was added, and the resulting emulsion was extracted with ether (3 × 50 mL). Upon filtration the ether extracts were washed with water, dried (MgSO$_4$), and concentrated to dryness to afford **11** (0.6 g, 92%). ^{1}H NMR (CDCl$_3$): δ 0.9−1.7 (m, 7H), 1.76−1.88 (m, 1H), 1.90−2.1 (m, 2H), 2.31−2.4 (m, 1H), 2.54−2.65 (m 1H), 2.71−2.79 (m, 1H), 3.22 (d, $J = 3.3$ Hz, 1H), 3.89 (s, 3H), 6.82−6.88 (m, 2H), 8.07 (d, $J = 8.6$ Hz).

10-Keto-3-methoxy-*N*-cyclopropylmethylmorphinan (12). A mixture of **11** (250 mg, 0.92 mmol), cyclopropylmethyl bromide (0.1 mL, 1.03 mmol), and NaHCO$_3$ (0.12 g, 1.4 mmol) in dry DMF (3 mL) was heated under nitrogen at 75 °C for 4 h. Solvent was removed under reduced pressure. The remaining material was taken up with CHCl$_3$ (25 mL), washed with water (2 × 25 mL), dried (MgSO$_4$), and concentrated to dryness to afford **12** (250 mg, 87%). ^{1}H NMR (CDCl$_3$): δ 0.02−0.15 (m, 2H), 0.45−0.49 (m, 2H), 0.82−0.98 (m, 1H), 1.03−1.7 (m, 9H), 1.86−2.03 (m, 3H), 2.08−2.15 (m, 1H), 2.66−2.74 (m, 1H), 2.9− 2.98 (m, 1H), 3.2 (d, $J = 2.9$ Hz, 1H), 3.87 (s, 3H), 6.8−6.86 (m, 2H), 8.0 (d, $J = 8.5$ Hz, 1H).

10-Keto-3-hydroxy-*N*-cyclopropylmethylmorphinan (4b). To a solution of **12** (220 mg, 0.67 mmol) in CH$_2$Cl$_2$ (15 mL) was added a solution of BBr$_3$ in CH$_2$Cl$_2$ (1 M, 2.8 mL, 2.8 mmol), and the resulting solution was stirred at room temperature overnight. TLC (CHCl$_3$−EtOH, 95:5) indicated a major transformation. MeOH (20 mL) was added, and the resulting solution was allowed to reflux for 2 h. Solvent was removed under reduced pressure. The remaining material was taken up with CHCl$_3$ (30 mL), washed with saturated NaHCO$_3$ (to pH 8) and water, dried (MgSO$_4$), and concentrated to dryness. Column separation (silica gel, 30 g) eluting with CHCl$_3$−EtOH (99:1) afforded **4b** (150 mg, 71%). ^{1}H NMR (CDCl$_3$): δ 0.01−0.28 (m, 2H), 0.45−0.48 (m, 2H), 0.85−0.94 (m, 1H), 1.08−1.7 (m, 8H), 1.9−2.17 (m, 4H), 2.3−2.38 (m, 1H), 2.7−2.79 (m, 1H), 2.93−3.01 (m, 1H), 3.24 (d, $J = 2.8$ Hz, 1H), 6.75−6.78 (m, 2H), 7.97 (d, $J = 9.2$ Hz, 1H). Compound **4b** (150 mg, 0.48 mmol) was dissolved in EtOH (1 mL) and treated with ethereal HCl (1 M, 0.5 mL). Solvent was removed under reduced pressure. The remaining material was washed with ether and collected as **4b HCl** (100 mg, 60%): mp 174 °C (sublime). Anal. (C$_{20}$H$_{25}$NO$_2$HCl·0.75H$_2$O) C,H,N.

(−)-3-Hydroxymorphinan (8). The procedure of Portoghese[37] was modified by using phenyl chloroformate for the synthesis of **8** from **3d** in 69% yield: mp 273−274 °C (lit.[37] mp 260−262 °C).

(−)-3-Hydroxy-*N*-cyclopropylmethylmorphinan Mandelate ((−)-Cyclorphan Mandelate) (3a). To 7.1 g of **8** dissolved in 400 mL of anhydrous CH$_2$Cl$_2$ were added cyclopropanecarbonyl chloride (9.4 g) and triethylamine 64 mL. The reaction mixture was stirred and allowed to reflux for 14 h. After cooling, 130 mL of water and 50 mL of ice were added and the mixture was extracted with HCl (concentrated HCl 40 mL in 300 mL H$_2$O), washed with 200 mL of H$_2$O, and dried over K$_2$CO$_3$ and the solvent removed to yield 12.5 g of crude diacyl compound (**9a**) as an oil. Without purification, the oil was dissolved in 385 mL of anhydrous tetrahydrofuran, and 87 mL of 1 M lithium aluminum hydride in tetrahydrofuran was added. The mixture was stirred at room temperature under N$_2$ overnight. To the reaction mixture was added 44 mL of EtOAc and the mixture was stirred for an additional 10 min, followed by the addition of 10 mL of H$_2$O with stirring. The mixture was then stirred vigorously with a solution of ammonium L-tartrate (290 g in 700 mL of H$_2$O) for 1 h. The aqueous layer was extracted three times with 150-mL portions of CH$_2$Cl$_2$. The organic layers were combined and dried over sodium sulfate. The solvent was removed under reduced pressure to yield 8.9 g of an oil, to which 7 mL of EtOAc was added and the oil triturated until crystals formed. The product was refrigerated, filtered, and washed with small volumes of

cold EtOAc to yield 4.5 g (51.8%) of crystalline free base: mp 187.5−189 °C (lit.[20] mp 187.5−189 °C).

The free base of **3a** was converted to the *S*(+)-mandelate salt and recrystallized from isopropyl ether/ETOH. The product obtained 17 g, mp 189−190 °C, is a white crystalline powder: $[\alpha]^{25}_D$ −7.28° (MeOH, *c* 1.5). Anal. ($C_{20}H_{27}NO\cdot C_8H_8O_3$) C,H,N.

(−)-3-Hydroxy-*N*-cyclobutylmethylmorphinan *S*(+)-Mandelate (3b). This compound was prepared as described for **3a** from **8** and cyclobutanecarbonyl chloride to yield a crystalline base, mp 217.5−218 °C (lit.[20] mp 219.2−219.8 °C), which was converted to the *S*(+)-mandelate salt **3b**: mp 201−202 °C. Anal. ($C_{21}H_{29}NO\cdot C_8H_8O_3$) C,H,N.

(−)-3-Hydroxy-*N*-[(*S*)-tetrahydrofurfuryl]morphinan Hydrochloride (3c). A mixture of 0.65 g (2 mmol) of **8**, 0.79 g (2 mmol) of **10,** and $NaHCO_3$ (0.6 g, 7 mmol) in DMF (10 mL) was stirred at 120 °C for 7 h. Solvent was removed under reduced pressure. The remaining material was taken up with $CHCl_3$ (15 mL) and washed with water (to neutral), and the organic layer was concentrated to dryness. The residue was applied to a silica gel column (30 g) and eluted with $CHCl_3$−EtOH (95/5) to afford 0.4 g (58%). ^{1}H NMR ($CDCl_3$): δ 1−1.7 (m, 6H), 1.8−2.1 (m, 5H), 2.15−2.32 (m, 3H), 2.35−2.42 (t, *J* = 7.2 Hz, 1H), 2.65−2.7 (m, 3H), 2.84−2.99 (m, 2H), 3.14−3.23 (m, 1H), 3.38−3.43 (t, *J* = 7.2 Hz, 1H), 3.7−3.8 (m, 1H), 3.85−3.92 (m, 1H), 4.05−4.15 (m, 1H), 6.61−6.66 (m, 1H), 6.74−6.77 (m, 1H), 6.94−6.98 (d, *J* = 7.3 Hz, 1H). Compound **3c** (400 mg, 1.17 mmol) was dissolved in EtOH (2 mL) and treated with 1 M etheral HCl (1.5 mL, 1.5 mmol). Solvent was removed under reduced pressure. The residue **3c** was recrystalized from EtOH−ether to afford 190 mg (42%): mp 170 °C dec; $[\alpha]^{25}_D$ −33.6° (MeOH, *c* 0.8). Anal. ($C_{21}H_{29}NO_2\cdot HCl\cdot 0.25H_2O$) C,H,N.

(−)-(*S*)-Tetrahydrofurfuryl (1*R*)-Camphor-10-sulfonate (10).[21] A solution of (1*R*)-camphor-10-sulfonyl chloride (75 g, 300 mmol) in 60 mL of anhydrous pyridine was stirred in an ice bath. To this solution was added tetrahydrofurfuryl alcohol (30.6 g, 300 mmol) dropwise over a period of 25 min. The resulting mixture was stirred at 25 °C for 20 h. Then the mixture was poured into 600 mL of ice−water, extracted with 3 × 250 mL of ether. The combined ether layer was washed with 1 × 100 mL of water, 2 × 100 mL of 2 N HCl, and brine, dried, and evaporated. The residue was recrystallized from CCl_4−petroleum ether (35−65 °C). After three crystallizations 18.1 g (16%) of (−)-(*S*)-tetrahydrofurfuryl (1*R*)-camphor-10-sulfonate was obtained: mp 66−67 °C; $[\alpha]^{25}_D$ −14.7° (MeOH, *c* 1).

(−)-10-Keto-3-hydroxy-*N*-[(*S*)-tetrahydrofurfuryl]mor-phinan Hydrochloride (4a). A mixture of **13** (1.5 g, 4.4 mmol), **10** (1.54 g, 4.8 mmol), and $NaHCO_3$ (0.74 g, 8.8 mmol) in DMF (15 mL) was stirred at 120 °C for 12 h. Solvent was removed under reduced pressure. The residue was taken up with $CHCl_3$ (25 mL), washed with NH_4Cl (10%, 10 mL) to pH 5, followed by washing with water (2 × 20 mL). The $CHCl_3$ layer was separated and concentrated to dryness under reduced pressure. Column separation (silica gel, 45 g) eluting with $CHCl_3$−EtOH (96/4) afforded **4a** (290 mg, 19%). ^{1}H NMR ($CDCl_3$): δ 1.04−1.68 (m, 6H), 1.78−2.09 (m, 4H), 2.14−2.31 (m, 2H), 2.39 (t, *J* = 9.7 Hz, 1H), 2.64−2.8 (m, 3H), 2.85−2.99 (m, 2H), 3.15−3.24 (m, 1H), 3.39 (t, *J* = 6.4 Hz, 1H), 3.7−3.79 (m, 1H), 3.85−3.93 (m, 1H), 4.05−4.14 (m, 1H), 6.62−6.77 (m, 1H), 6.74 (m, 1H), 6.94−6.97 (d, *J* = 7.4 Hz, 1H). Compound **4a** (290 mg, 0.85 mmol) was dissolved with EtOH (1.5 mL) and treated with etheral HCl (1 M, 0.9 mL, 0.9 mmol). Solvent was removed to dryness. The residue was recrystalized from EtOH−ether to afford **4a HCl** (200 mg, 62%): mp 255 °C dec; $[\alpha]_D{}^{25}$ −0.13° (MeOH, *c* 0.75). Anal. ($C_{21}H_{28}NO_3HCl\cdot 0.25H_2O$) C,H,N.

(+)-*N*-[(*S*)-Tetrahydrofurfuryl]-8-keto-*nor*-metazo-cine (1b). A mixture of (−)-*nor*-metazocine (RBI) **(14)** (11.6 g, 40 mmol) and K_2CO_3 (11 g, 80 mmol) in water (160 mL) was stirred at 25 °C. To this was added a solution of di-*tert*-butyl dicarbonate (8.7 g, 40 mmol) in dioxane (80 mL) dropwise and the stirring was continued at 25 °C for 16 h. The

precipitated solid was filtered, washed with water, and dried to give 13 g of **15** as a white solid. The t-Boc derivative **15** was dissolved in 2 N NaOH (100 mL) and was treated with 10 mL of dimethyl sulfate. The mixture was stirred at 25 °C for 6 h and was extracted with ether (3 × 50 mL). The ether extract was washed with 2.5 N NaOH and brine and evaporated to an oil. The oil was dissolved in EtOAc (100 mL) and mixed with 6 N HCl (100 mL) and the mixture was stirred at 50 °C for 16 h. The volatiles were removed under vacuum to give a foam **17** as the hydrochloride salt (8 g, 80% from **15**).

Dilute sulfuric acid was prepared by dissolving 54 mL of concentrated H_2SO_4 in 600 mL of ice−water. Compound **17** (8 g) was dissolved in 300 mL of this acid to give an orange solution. To this was added a solution of CrO_3 (7.2 g, 72 mmol) in 300 mL of the dilute sulfuric acid in one portion. The resulting mixture was stirred at 100 °C for 2 h, cooled in ice, basified with NH_4OH, and extracted with ether (4 × 100 mL). The ether extract was washed with brine, dried, and evaporated to a reddish brown oil 6.0 g (82%). Without further purification 2 g of the product **18** was O-demethylated by treating with 25 mL of 48% HBr at reflux for 2.5 h. The solution was evaporated and the residue was dissolved in water and basified with NH_4OH to give 900 mg of **19** as a tan solid. A mixture of compound **19** (1.0 g, 4.3 mmol), $NaHCO_3$ (600 mg, 7.1 mmol), *S*-tetrahydrofurfuryl (1*R*)-camphor-10-sulfonate (**10**) (1.52 g, 4.80 mmol), and anhydrous DMF (50 mL) was heated at 100 °C for 16 h. DMF was removed in vacuum and the residue in water was extracted with ether, dried, and evaporated. The residue was purified by column chromatography (silica gel, CH_2Cl_2:MeOH:NH_4OH, 90:9:1) to give **1b** which was isolated as the HCl salt: yield 75 mg (5%); mp 212−214 °C; $[\alpha]^{25}_D$ +59.0° (CH_3OH, *c* 0.2). ^{1}H NMR (CD_3-OD): δ 0.97−0.99 (d, 3H), 1.51 (s, 3H), 1.53−1.65 (m, 1H), 1.75−1.85 (br d, 1H), 1.9−2.0 (m, 2H), 2.1−2.5 (m, 3H), 2.78−2.9 (m, 1H), 2.96−3.1 (m, 1H), 3.22−3.35 (m, 3H), 3.8−4.0 (m, 2H), 4.04 (br s, 1H), 4.55−4.65 (m, 1H), 6.84−6.87 (m, 2H), 7.95−8.0 (d, 1H). Anal. ($C_{19}H_{25}NO_3\cdot HCl\cdot 0.25C_4H_{10}O$) C,H,N.

Determination of K_1 Values at μ, δ, and κ Opioid Receptors. Guinea pig brain membranes were prepared from frozen guinea pig brains, obtained from Harlan Bioproducts (Indianapolis, IN). Brains were thawed and homogenized in 10 times the wet weight of tissue in cold 50 mM Tris-HCl, pH 7.5, followed by centrifugation at 39000*g* for 20 min at 4 °C. The membranes were resuspended in the original volume of buffer and incubated at 37 °C for 30 min, followed by centrifugation at 39000*g* for 20 min at 4 °C. The membranes were resuspended at a protein concentration of 8−12 mg/mL in 50 mM Tris-HCl, pH 7.5, and stored at −80 °C until use. The protein concentration of membranes was determined by the method of Bradford,[38] using bovine serum albumin as standard.

Guinea pig brain membranes, 500 μg of membrane protein, were incubated with 12 different concentrations of the compound in the presence of either 0.25 nM [3H]DAMGO (μ), 0.2 nM [3H]naltrindole (δ), or 1 nM [3H]U69,593 (κ) in a final volume of 1 mL of 50 mM Tris-HCl, pH 7.5 at 25 °C. Naloxone at a final concentration of 1 μM was used to measure nonspecific binding. Samples incubated with either [3H]-DAMGO or [3H]U69,593 were incubated at 25 °C for 60 min. To measure binding to δ receptors, 5 mL of $MgCl_2$ and 1 mM PMSF were included with [3H]naltrindole and the test compound. These samples were incubated at 25 °C for 3 h. Binding was terminated by filteirng samples through Schleicher & Scheull No. 32 glass fiber filters. The filters were subsequently washed three times with 3 mL of cold 50 mM Tris-HCl, pH 7.5, and were counted in 2 mL of Ecoscint A scintillation fluid. For [3H]naltrindole and [3H]U69,593 binding, the filters were soaked in 0.25% poly(ethylenimine) for at least 60 min before use.

IC_{50} values were detrmined using the least-squares fit to a logarithm probit analysis reported by Cheng and Prusoff.[39] The K_d values for [3H]DAMGO, [3H]naltrindole, and [3H]U69,593 binding to guinea pig membranes were 0.45, 0.086, and 0.46 nM, respectively.

Mouse Antinociceptive Assays. All antinociceptive experiments used male, ICR mice (20–24 g; Harlan Sprague–Dawley, Inc., Indianapolis, IN). Mice were kept in groups of 8 in a temperature-controlled room with a 12-h light–dark cycle. Food and water were available ad libitum until the time of the experiment. Intracerebroventricular injections were made directly into the lateral ventricle according to the modified method of Haley and McCormick.[40] The volume of all icv injections was 5 μL, using a 10-μL Hamilton microliter syringe. The mouse was lightly anesthetized with ether, an incision was made in the scalp, and the injection was made 2 mm lateral and 2 mm caudal to bregma at a depth of 3 mm.

Tail-Flick Assay. The tail-flick assay was performed as described in McLaughlin et al.[41] The thermal nociceptive stimulus was 55 °C water, with the latency to tail-flick or withdrawal taken as the endpoint.[42] After determining control latencies, the mice received graded icv doses of either **3a** or **3b**. Morphine sulfate, DPDPE, U50,488, **3a**, and **3b** were given as single icv injections with antinociceptive effect measured 20 min after injection. In the antagonist study, various doses of **3a** and **3b** were co-administered with 3 nmol of morphine by icv injection, 20 min before testing. In the receptor selectivity studies, either the κ-selective antagonist, *nor*-BNI, or the δ-selective antagonist, ICI 174,864, was each given with the agonist in the same injection. β-FNA, the μ-selective antagonist, was injected 24 h before agonist injection. A cutoff time of 15 s was used; if the mouse failed to display a tail-flick in that time, the tail was removed from the water and the animal assigned a maximal antinociceptive score of 100%. Mice who showed no response within 5 s in the initial control test were eliminated from the experiment. At each time point, antinociception was calculated according to the following formula: % antinociception = $100 \times$ (test latency − control latency)/(15 − control latency).

Mouse Writhing Assay. Since antinociception of κ opioid agonists has been difficult to evaluate in the tail-flick test,[25] we also investigated the action of **3a,b** in the mouse acetic acid writhing test, which was performed as described in Xu et al.[43] After receiving graded icv doses of opioid agonists and antagonists at various times, an ip injection of 0.6% acetic acid (10 mL/kg) was administered to each mouse. Five minutes after administration, the number of writhing signs displayed by each mouse was counted for an additional 5 min. Antinociception for each tested mouse was calculated by comparing the test group to a control group in which mice were treated with icv vehicle solution.

Statistics. IC$_{50}$ values for the radioligand binding experiments were calculated by least-squares fit to a logarithm probit analysis. Saturation [³H]DAMGO binding data were analyzed by nonlinear regression analysis using the LIGAND program.[44] All dose–response lines were analyzed, using the regression methods described by Tallarida and Murray.[45] Regression lines, D$_{50}$ (dose producing 50% antinociception) values, and 95% confidence limits were determined with each individual data point.[45] All data points shown are the mean of 7–10 mice, with standard error of the mean represented by error bars.

Chemicals. [³H]DAMGO (60 Ci/mmol) and [³H]U69,593 (64 Ci/mmol) were purchased from Amersham (Arlington Heights, IL). [³H]Naltrindole (40 Ci/mmol) was obtained from New England Nuclear (Boston, MA). Morphine sulfate was purchased from Mallinckrodt Chemical Co. (St. Louis, MO). DPDPEP, U50,488, *nor*-BNI, ICI 174,964, and β-FNA were purchased from Research Biochemicals International (Natick, MA).

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