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Kappa opioid agonists as targets for pharmacotherapies in cocaine abuse

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Abstract

Kappa opioid receptors derive their name from the prototype benzomorphan, ketocyclazocine (**1a**) 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. Recent evidence suggests that agonists and antagonists at kappa opioid receptors may modulate the activity of dopaminergic neurons and alter the neurochemical and behavioral effects of cocaine. Kappa agonists blocked the effects of cocaine in squirrel monkeys in studies of cocaine discrimination and scheduled-controlled responding. Studies in rhesus monkeys suggested that kappa opioids may antagonize the reinforcing effects of cocaine. These studies prompted the synthesis and evaluation of a series of kappa agonists related to the morphinan, L-cyclorphan (**3a**) and the benzomorphan, L-cyclazocine (**2**). We describe the synthesis and preliminary evaluation of a series of morphinans, structural analogs of cyclorphan **3a–c**, the 10-keto morphinans **4a** and **b**, and the 8-keto benzomorphan **1b**, structurally related to ketocyclazocine (**1a**). In binding experiments L-cyclorphan (**3a**), the cyclobutyl (**3b**), the tetrahydrofurfuryl **3c** and the 10-keto **4b** analogs had high affinity for *mu* (μ), *delta* (δ) and *kappa* (κ) opioid receptors. Both **3a** and **3b** were more selective for the κ receptor than the μ receptor. However, **3b** was 18-fold more selective for the κ receptor in comparison to the δ receptor, while cyclorphan (**3a**) had only a 4-fold greater affinity for the κ receptor in comparison to the δ receptor. The cyclobutyl compound **3b** was found to have significant μ agonist properties, while **3a** was a μ antagonist. All compounds were also examined in the mouse tail flick and writhing assay. Compounds **3a** and **3b** were κ agonists. Correlating with the binding results, compound **3a** had some δ agonist properties, while **3b** was devoid of any activity at the δ receptor. In addition, compounds **3a** and **3b** had opposing properties at the μ opioid receptor. The cyclobutyl compound **3b** was found to have significant μ agonist properties, while **3a** was a μ antagonist.

Keywords: Morphinans; Benzomorphans; Kappa, delta and mu receptor affinity

1. Introduction

Cocaine abuse continues to be a major public health concern in the United States (National Institutes of Health, 1996). A current goal of preclinical research has been to characterize the neurobiological and pharmacological determinants of cocaine's high abuse potential and to develop drugs that could be used in the treatment of cocaine abuse. One approach to develop such drugs has been the observation that cocaine blocks the reuptake of the neurotransmitter dopamine (DA) (Koe, 1976; Taylor and Ho, 1978; Reith, 1988), and the extensive literature which suggests that cocaine's reinforcing effects are mediated by increases in extracellular dopamine levels in the mesolimbic dopamine system (Ritz et al., 1987; Koob and Bloom, 1988; Johanson and Fischman, 1989; Kuhar et al., 1991; Woolverton and Johnson, 1992). Dopamine receptor antagonists have been evaluated for their potential utility in treating cocaine abuse (Mello and Negus, 1996) but such agents produce extrapyramidal motor effects and other unwanted effects that complicate their use in the treatment of cocaine dependence.

Compounds acting on other receptors may provide an alternative means of modifying the neurobiological and behavioral effects of cocaine by indirectly modulating the

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activity of dopaminergic systems. For example, a growing body of evidence suggests that agonists and antagonists at *kappa* (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 (Mansour et al., 1987, 1988, 1994) as well as dynorphin (Hokefelt et al., 1984), an endogenous opioid peptide with high affinity for kappa receptors (Chavkin et al., 1982). In contrast to cocaine, kappa agonists have been shown to decrease striatal dopamine levels in rats (DiChiara and Imperato, 1988; Donzanti et al., 1992; Spanagel et al., 1992; Devine et al., 1993). Kappa agonists also attenuated cocaine-induced increases in dopamine levels in the nucleus accumbens. Kappa agonists also produce antagonism of the discriminating stimulus effects of cocaine in squirrel monkeys (Spealman and Bergman, 1992; Spealman and Bergman, 1994).

These findings suggest that activation of kappa opioid receptors may functionally antagonize some 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 (Archer et al., 1996).

The kappa antagonist norbinaltorphimine (nor-BNI) (Portoghese et al., 1987) was found to have no effect on cocaine self-administration but blocked the effects of the kappa agonists on cocaine self-administration (Glick et al., 1995; Negus et al., 1997). The structures of the known receptor selective kappa agonists are shown in Fig. 1. These agonists can be grouped into three chemical classes: (1) the arylacetamides such as spiradoline and enadoline; (2) the morphinan, L-cyclorphan (**3a**) and (3) the benzomorphans such as cyclazocine (**2**) and ethylketocyclazocine (**1b**). Although kappa opioid agonists have been found to attenuate some neurochemical and behavioral effects of cocaine, they also produce unwanted side-effects such as dysphoria and sedation that may compromise their clinical utility as medications for the treatment of cocaine dependence. We wish to describe here the synthesis and

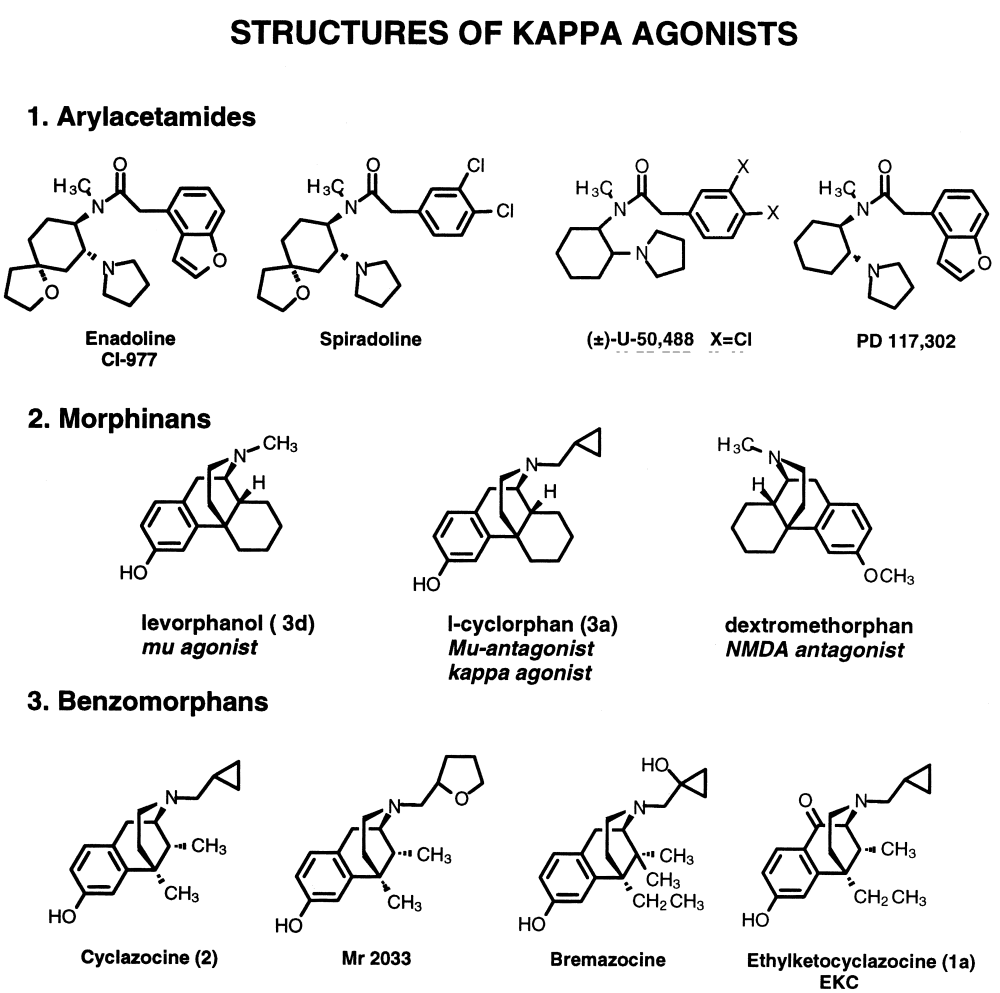


Fig. 1. Structures of kappa agonists.

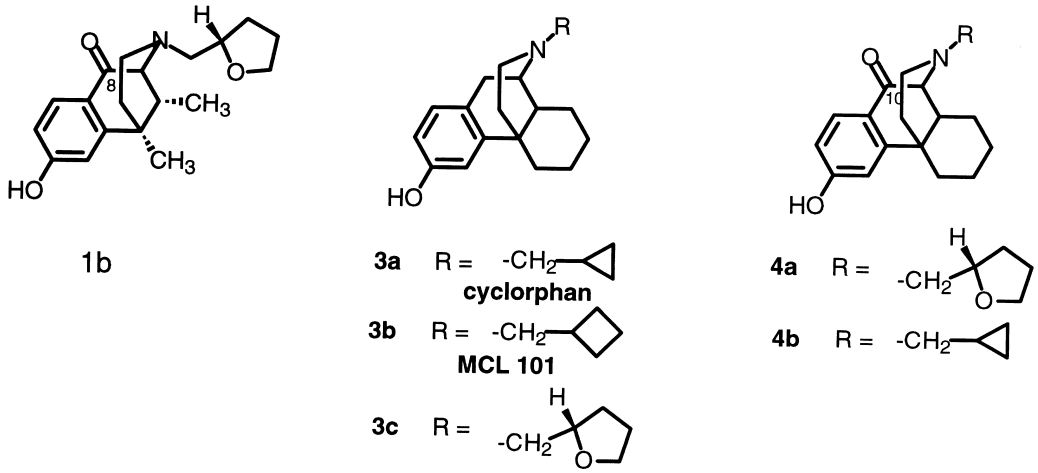


Fig. 2. Structures of synthesized morphinans and benzomorphans.

preliminary evaluation of a series of morphinans (**3a–c**), structural analogs of cyclorphan **3a**, the 10-keto morphinans **4a** and **b**, and the 8-keto benzomorphan **1b**, an analog of ketocyclazocine **1a** (Fig. 2).

2. Experimental procedures

The synthesis of the morphinans **3a–c** and the 10-keto derivatives **4a–b** are shown in Scheme 1. The experimental details of the syntheses of these compounds will be reported elsewhere (Neumeyer et al., 1999). The compounds were all prepared from commercially available levorphanol **3d** which was converted to the *O*-methyl ether 6 and *N*-dealkylated to norlevorphanol methyl ether **7**. Alternatively, levorphanol (**3d**) was directly *N*-dealkylated to norlevorphanol (**8**).

The intermediate **8** was *N*-and-Odiacylated with cyclopropane carbonyl chloride in triethylamine. The crude diacyl compound **9a** was further reduced with lithium aluminum hydride to yield known cyclorphan (**3a**) previously prepared (Gates and Montzka, 1964) from (−)-3-hydroxymorphinan.

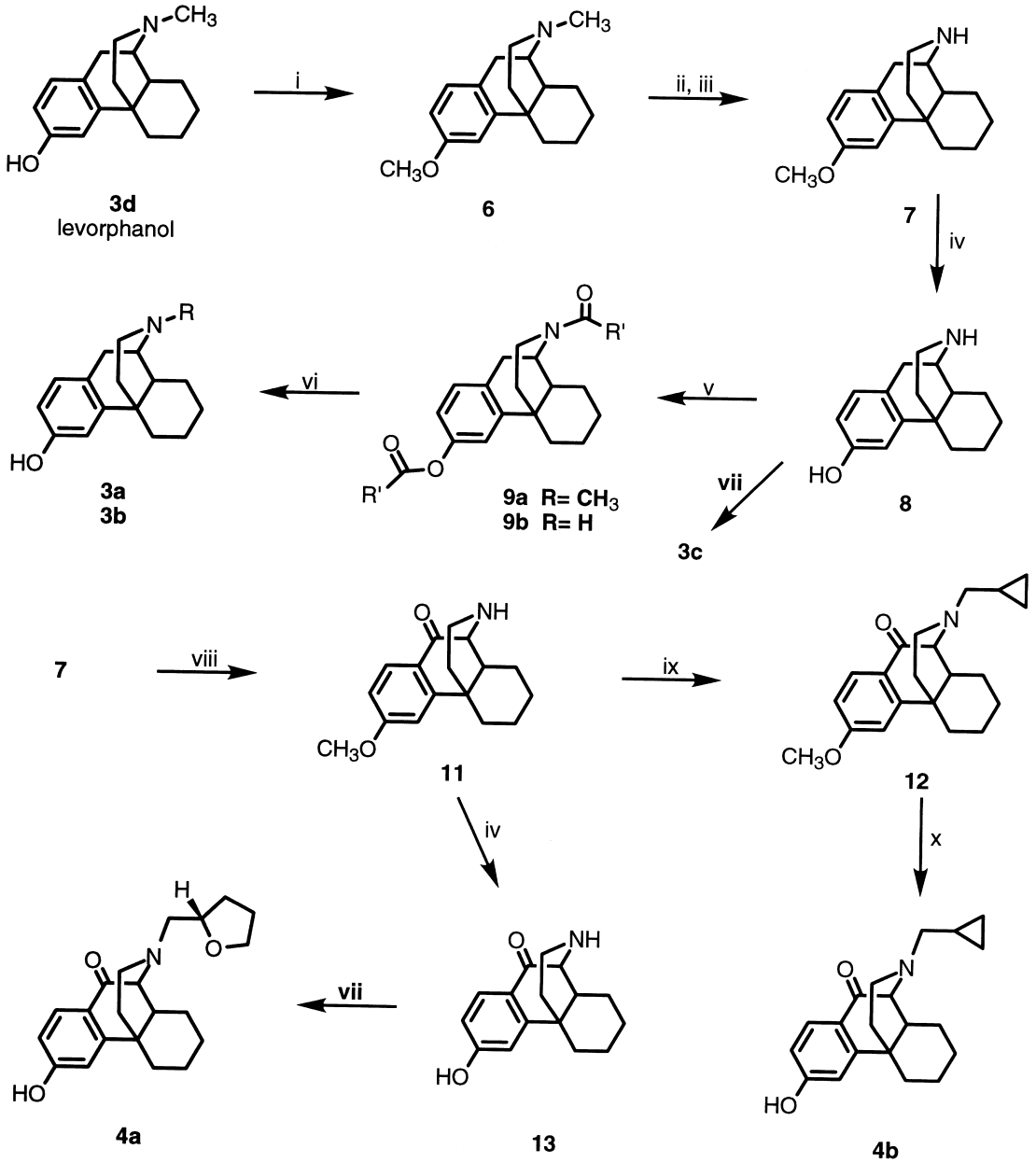
The free base **3a** was further converted to the mandelate salt, a white crystalline product. The cyclobutyl analog **3b** was similarly prepared from **8** and converted to the crystalline mandelate salt. The (*S*) *N*-tetrahydrofurfuryl derivative **3c** was prepared from (*S*) tetrahydrofurfuryl (1*R*) camphor-10-sulfonate (**10**) as previously reported (Mertz et al., 1997). The 10-keto morphinans were prepared by the oxidation (Michne and Albertson, 1972) of the morphinan **7** with CrO_3/H_2SO_4 followed by alkylation with cyclopropyl methyl 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 (1979).

The 8-keto benzomorphan derivative **1b** was prepared from (−)5,9-α-dimethyl-2′-hydroxy-6,7-benzomorphan (**14**) [(−)-nor-metazocine] (Tullar et al., 1967) as outlined in Scheme 2. Protection of the amine with ditertiarybutyl dicarbonate (boc) and *O*-methylation with dimethylsulfate led to **16**. Acid hydrolysis followed by oxidation of **17** with CrO_3/H_2SO_4 (Michne and Albertson, 1972) 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.

2.1. Determination of K_1 values at μ, δ and κ opioid receptors

Frozen guinea pig 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 39,000 × *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 39,000 × *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 (1976), 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 [^{3}H]DAMGO (μ), 0.2 nM [^{3}H]naltrindole (δ) or 1 nM [^{3}H]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 [^{3}H]DAMGO or [^{3}H]U69,593 were incubated at 25°C for 60 min. To measure binding to δ receptors, 5 ml $MgCl_2$ and 1 mM PMSF were included with [^{3}H]naltrindole and the test compound. These samples were incubated at 25°C for 3 h. Binding was terminated by filtering samples through Schleicher &



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.

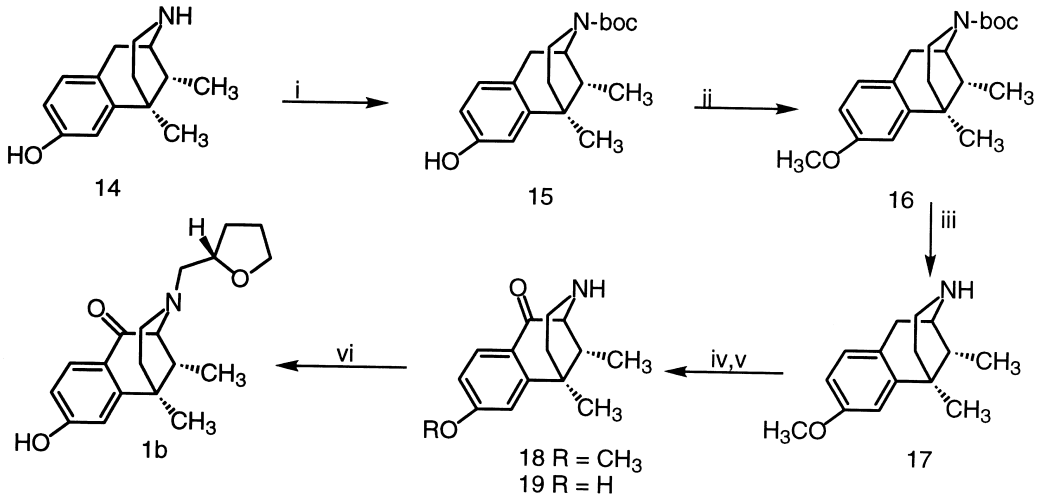
Scheme 1.

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 [^{3}H]naltrindole and [^{3}H]U69,593 binding, the filters were soaked in 0.25% polyethylenimine for at least 60 min before use.

IC_{50} values were determined using the least squares fit to a logarithm–probit analysis (Cheng and Prusoff, 1973). The K_d values for [^{3}H]DAMGO, [^{3}H]naltrindole, and [^{3}H]U69,593 binding to guinea pig membranes were 0.45 nM, 0.086 nM, and 0.46 nM, respectively (Table 1).

2.2. Mouse antinociceptive assays

All antinociceptive experiments used male, ICR mice (20–24 g, Harlan Sprague Dawley). Mice were kept in groups of eight in a temperature controlled room with a 12-h light–dark cycle. Food and water were available ad



Scheme 2.

libitum until the time of the experiment. Intracerebroventricular injections were made directly into the lateral ventricle (Haley and McCormick, 1957). The volume of all i.c.v. 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.

2.3. Tail-flick assay

The tail flick assay was performed as previously described (McLaughlin et al., 1999). The thermal nociceptive stimulus was 55°C water, with the latency to tail flick or withdrawal taken as the endpoint (Vaught and Takemori, 1979). After determining control latencies, the mice received graded i.c.v. doses of either (−)cyclorphan or MCL-101. Morphine sulfate, DPDPE, U50, 488, (−) cyclorphan, and MCL-101 were given as single i.c.v. injections with antinociceptive effect measured 20 min after injection. In the antagonist study, various doses of (−)cyclorphan and MCL-101 were co-administered with 3-nmol morphine by i.c.v. 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 were each given with the agonist in the same injection. β-FNA, the μ-selective antagonist, was injected 24 h before agonist injection. A cut-off 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

Table 1
K_i inhibition values μ, δ and κ opioid binding to guinea pig brain membranes by kappa opioids
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 M naloxone. Data are the mean values S.E.M. from three experiments, performed in triplicate.

Compound	[^{3}H]DAMGO (μ)	[^{3}H]Naltrindole (δ)	[^{3}H]U69,593 (κ)	Selectivity κ:μ	Selectivity κ:δ
	K_i (nM ± S.E.)				
U50,488	220 ± 5.6	2500 ± 170	0.36 ± 0.056	610	6900
(−)Cyclazocine (**2**)	0.10 ± 0.03	0.58 ± 0.06	0.052 ± 0.0009	2	11
(−)Cyclorphan (**3a**)	0.092 ± 0.005	0.22 ± 0.01	0.053 ± 0.003	2	4
Morphinan (**3b**) (MCL-101)	0.12 ± 0.012	1.3 ± 0.06	0.073 ± 0.012	2	18
Morphinan (**3c**)	0.010 ± 0.002	0.27 ± 0.02	0.15 ± 0.01	0.066	2
Levorphanol (**3d**)	0.21 ± 0.017	4.2 ± 0.45	2.3 ± 0.26	0.09	2
Morphinan (**4a**)	0.38 ± 0.004	1.0 ± 0.18	0.18 ± 0.019	2	6
Morphinan (**4be**)	240 ± 89	150 ± 71	24 ± 1.6	1	6
Benzomorphan (**1b**)	2900 ± 58	> 100,000	720 ± 57	4	

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 × (test latency − control latency)/(15 − control latency).

2.4. Mouse writhing assay

Since antinociception of κ opioid agonists has been difficult to evaluate in the tail-flick test (Porreca et al., 1987), we also investigated the action of (−)cyclorphan and MCL-101 in the mouse acetic acid writhing test (Xu et al., 1996). After receiving graded i.c.v. doses of opioid agonists and antagonists at various times, an i.p. injection of 0.6% acetic acid (10 ml/kg) was administered to each mouse. Five min after administration, the number of writhing signs displayed by each mouse was counted for an additional 5 min. Antinociception for each tested mouse were calculated by comparing the test group to a control group in which mice were treated with i.c.v. vehicle solution.

3. Results and discussion

All compounds were examined for their affinity and selectivity at μ, δ and κ opioid receptors in Guinea Pig brain membranes labeled with [^{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 and selectivity were examined further in the tail flick and acetic-acid writhing tests in mice.

In the warm-water tail flick test, (−)cyclorphan (**3a**) produced 37 ± 10% antinociception after an i.c.v. dose of 100 nmol. In contrast, MCL-101 (**3b**) produced a full dose–response curve. In the 55°C warm-water tail flick test an ED_{50} value and 95% confidence limits of 7.3 (5.7–9.4) nmol were obtained for MCL-101, with testing taking place 20 min after an i.c.v. injection.

Because MCL-101 (**3b**) generated a full dose–response curve in the tail flick test, the receptor selectivity of the agonist effect was determined by using selective antagonists. In the tail flick test, antinociception induced by MCL-101 (**3b**) was mediated by both κ and μ opioid receptors.

The effect of (−)cyclorphan (**3a**) and MCL-101 (**3b**) were also characterized in the writhing test. Both (−)cyclorphan and MCL-101 produced full dose–response curves in the writhing test, with ED_{50} values and 95% C.L. of 0.65 (0.35–1.2) nmol 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 (−)cyclorphan and MCL-101 in the writhing test was also determined. (−)Cyclorphan produced antinociception that was mediated by κ and δ opioid receptors. In contrast, MCL-101 produced antinociception that was mediated by κ and μ receptors, which is in agreement with the results from the tail flick assay. The receptor selectivity results in the writhing assay correlated with the binding results in Table 1, which showed that (−)cyclorphan had a higher affinity than MCL-101 for the δ receptor.

Because (−)cyclorphan 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 (−)cyclorphan. Antinociception was determined 20 min later. (−)Cyclorphan at a dose of 1 nmol, completely antagonized morphine-induced antinociception, indicating that (−)cyclorphan was a potent μ antagonist. In contrast, MCL-101 was a weak μ agonist, with only partial antagonism of morphine-induced antinociception, at a dose that did not produce antinociception by itself.

To determine the receptor selectivity of the antagonism induced by (−)cyclorphan, mice were co-injected with either the μ agonist, morphine, the κ-selective agonist, U50,488, or the δ-selective peptide DPDPE along with 1-nmol (−)cyclorphan. (−)Cyclorphan did not antagonize antinociception mediated by either the δ or the κ receptors, but did antagonize morphine-induced antinociception, demonstrating that (−)cyclorphan was a μ-selective antagonist.

4. Conclusions

The binding results demonstrate that MCL-101, like (−)cyclorphan, had high affinity for μ, δ and κ opioid receptors. Both compounds were approximately 2-fold more selective for the κ receptor than the μ receptor. However, MCL-101 was 18-fold more selective for the κ receptor in comparison to the δ receptor, while (−)cyclorphan had only a 4-fold greater affinity for the κ receptor in comparison to the δ receptor. This finding was confirmed in the antinociceptive tests, which demonstrated that (−)cyclorphan produced some antinociception that was mediated by the δ receptor, while MCL-101 did not produce agonist or antagonist effects at the δ receptor. MCL-101 had significant μ agonist properties, while (−)cyclorphan was a μ antagonist. So, while their affinity for the μ receptor is comparable, they produce different effects at the μ opioid receptor. However, the two compounds had comparable κ agonist properties. In summary, both MCL-101 and (−)cyclorphan were κ agonists. (−)Cyclorphan produced some antinociception mediated by the δ opioid receptor; this property was not shared with

MCL-101. While having similar affinity for the μ opioid receptor, (−)cyclorphan and MCL-101 had opposing effects at the μ receptor. MCL-101 was a μ agonist, while (−)cyclorphan was a μ antagonist. Recent findings from our laboratories (Mello and Negus, 1996; Negus et al., 1997) that some kappa agonists have a selective effect on cocaine self-administration by rhesus monkeys with minimal effects on food self-administration, supports our ongoing studies with these novel kappa agonists to carry out a comprehensive behavioral analysis of the interactions of these potential medications with cocaine. Such studies will help to define the clinical approach and suggest the relative effectiveness of these compounds as anti-cocaine medications.

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