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Synthesis and Opioid Activity of Novel 6-ketolevorphanol Derivatives

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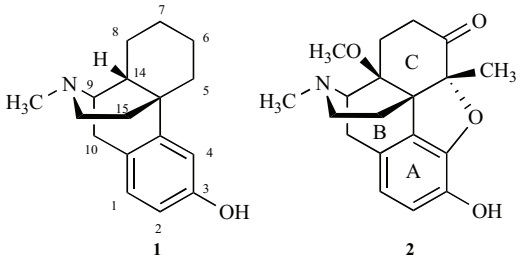
Abstract: Novel 6-ketolevorphanol analogs with diverse substitution patterns at ring C were synthesized and their binding affinities at the μ, δ and κ opioid receptors were investigated. The *in vitro* activity of the new analogs was then evaluated in the functional assay based on the electrically-stimulated contractions of the mouse ileum. It was shown that analogs with $\Delta^{7,8}$ bond had no significant potency at any of the opioid receptor types. In contrast, analogs with the saturated ring C were either potent κ agonist or antagonist depending on the absence or presence of the hydroxyl group in position 14.

Keywords: Analgesics, Opioid receptors, Binding Assay, Agonist, Antagonist.

INTRODUCTION

Current treatment of pain is based on the concept elaborated by the World Health Organization, according to which pain medications are categorized into three groups depending on their potency [1]. In the first group there are non-opioid drugs such as aspirin and other non-steroidal anti-inflammatory agents. The second group consists of weak opioids (e.g. codeine) and their combinations with non-opioid pain-killers. The most powerful analgesics, strong opioids, are in the third group and are represented by natural and semi-synthetic morphinans (e.g. morphine, hydromorphone, oxymorphone, oxycodone, levorphanol) and synthetic opioids (e.g. fentanyl and methadone). Levorphanol (**1**) was originally synthesized by Grewe and co-workers in the course of investigations aimed at the total synthesis of morphine [2]. This work was extended by Schnider and Hellerbach [3] who developed a synthetic route for the efficient production of levorphanol (**1**) which is a highly potent and clinically valuable analgesic. Levorphanol (**1**) has twice the activity of morphine, greater duration of effect and less frequent or severe side-effects [4] and is a full κ agonist [5]. Recently, compound **1** is considered an underestimated and neglected opioid both, in medicinal practice (due to its higher price compared with morphine) and in pharmaceutical research, despite its remarkable and unusual pharmacological profile (Fig. **1**) [6].



1 **2**

Fig. (1). Structure of strong opioids.

The high μ, δ and κ opioid receptor affinity of levorphanol (with K_i values 0.21, 4.2 and 2.3 nM, respectively [4]) and the development of synthetic methods of functionalization, encouraged us for extending structure-activity relationship data of this compound. In general for morphinans, significantly increased opioid receptor affinity was observed for derivatives with substituents at C14 and with short-chain alkyl groups at the 5β-position [7]. Also catalytic hydrogenation of the $\Delta^{7,8}$ bond in morphinans afforded analogs with increased analgesic activity [8]. For example, 14β-methoxymetopon (2) is a very potent μ-opioid receptor-selective analgesic with an unusual pharmacological profile and remarkable intrinsic activity [7]. Considering strictly the ketomorphinan structure, several important approaches were reported in the past for successful derivatizations [9].

In Fig. (**2**) six representative structures are presented for this backbone. Compounds **3a** and **3b** without the 3-hydroxyl function were found to be equipotent and six times more potent in *in vivo* hot plate tests (HPT) as morphine, respectively [10]. Derivatives **3c** and **3d** having only the keto

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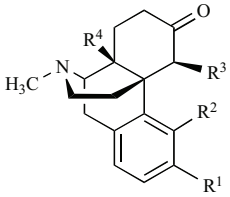


	R^1	R^2	R^3	R^4
3a	H	OH	H	OH
3b	H	OMe	H	OH
3c	H	OMe	H	H
3d	OMe	OMe	H	H
3e	OMe	OMe	Me	H

Fig. (2). Structures of representative ketomorphinans.

function in ring C were proven to be three times as potent in the HPT as morphine [11], while **3e** with the 5β-methyl substituent had a 1.5 times increased potency comparing with morphine [12]. These results also prompted us to further extend the available structure-activity data on this field allowing more accurate assumptions on future drug design. In agreement with this, we report here the synthesis and *in vitro* characterization of 5β- and 14β-substituted ketolevorphanol congeners.

RESULTS AND DISCUSSION

The synthetic route to new 5β-alkylmorphinans **17a,b-20a,b** was based on a recently published strategy [13], which allows the preparation of diversely functionalized morphinans without the 4,5-epoxy moiety. Our present work confirmed that this procedure could be extended for compounds with diverse substitution patterns at ring C.

Starting 5β-alkyl congeners of thebaine **4a,b** were synthesized as described by Boden *et al.* [14]. Preparation of these compounds involved formation of thebaine anion at low temperature (-78°C) and subsequent reaction of this nucleophile with alkyl halides.

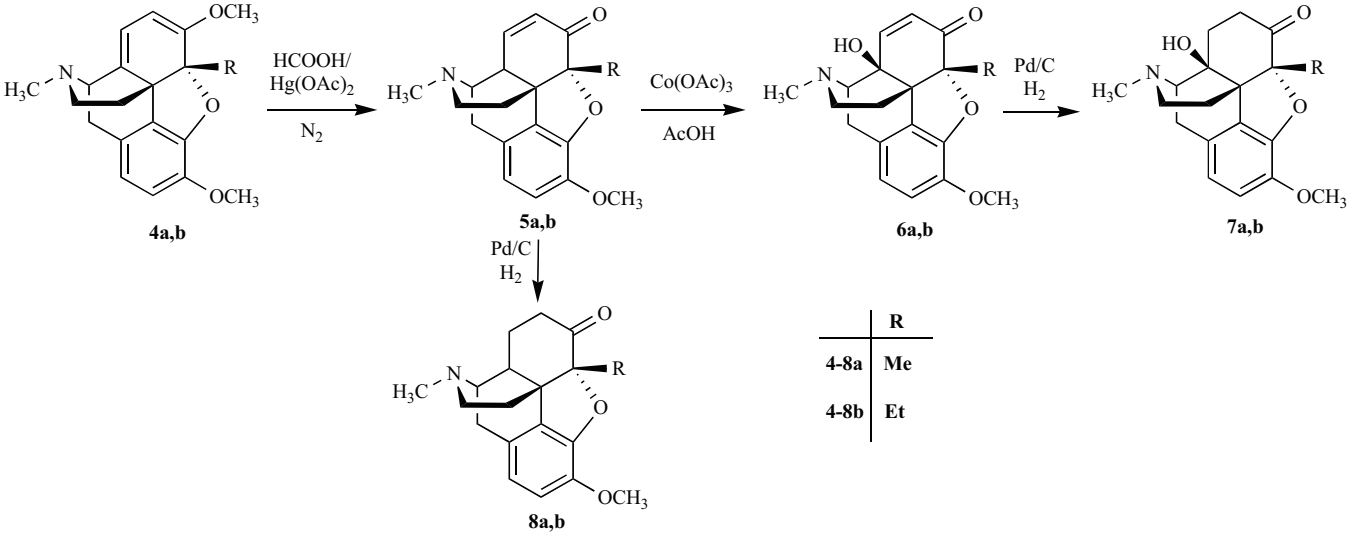
5β-Alkylthebaines **4a,b** were then converted into the corresponding 5-substituted codeinones **5a,b** using the methodology first reported by Dauben *et al.* [15] and adapted for 5-methylthebaine by Boden *et al.* [14] (Scheme **1**). The procedure utilizes mercury(II)-acetate in formic acid for the transformation of the dienyl enolether of ring C into the α,β-unsaturated ketone. Compounds **5a** and **5b** were obtained in 67% and 60% yields, respectively.

Fully stereoselective hydroxylation of **5a,b** at position 14 was accomplished applying the procedure elaborated by Coop and Rice [16]. Treatment of **5a,b** with cobalt(III)-acetate in acetic acid, followed by the purification of the crude product by column chromatography furnished pure 14β-hydroxyl congeners **6a** and **6b** in 44% and 47% yields, respectively. In the next step, the $\Delta^{7,8}$ bonds in both 5-alkyl codeinones **5a,b** and 5-alkyl-14-hydroxycodeinones **6a,b** were hydrogenated using 10 % palladium on charcoal as a catalyst to give dihydrocodeinones **7a,b** and **8a,b**, respectively, in very good yields.

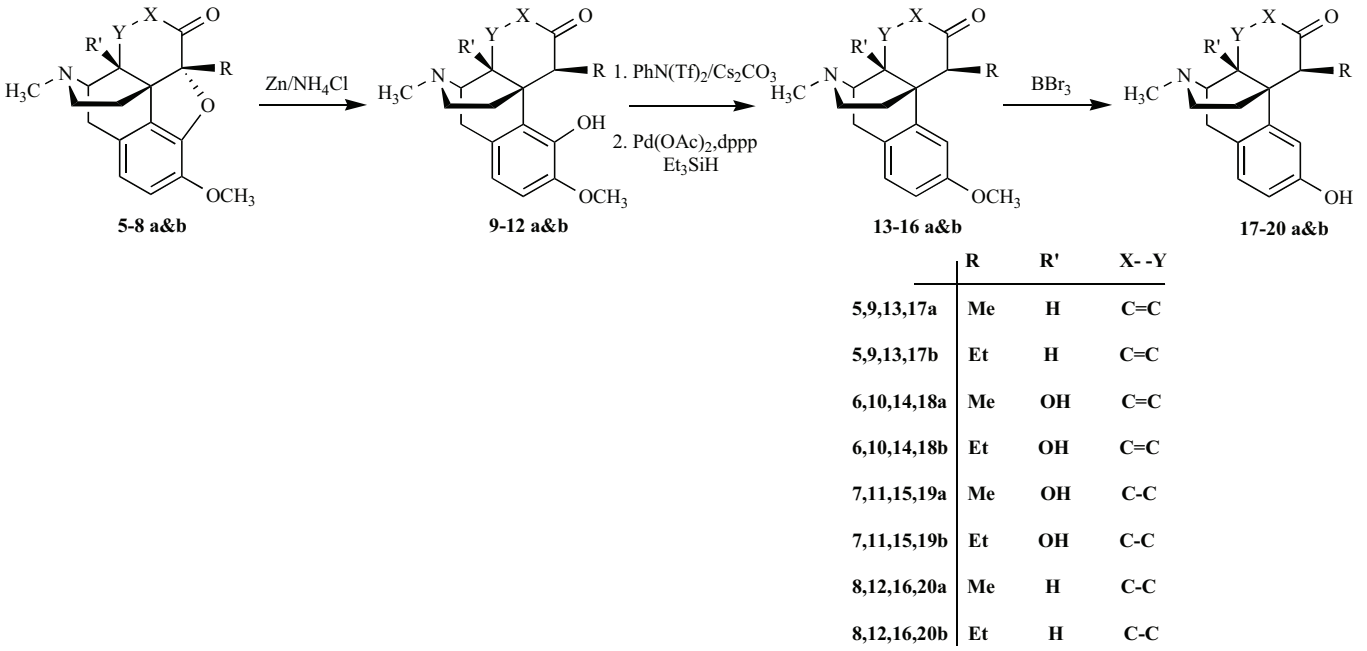
These transformations allowed us to prepare several pentacyclic 4,5-epoxymorphinans **5a,b-8a,b** with diversely functionalized ring C. Finally, all obtained pentacyclic morphinans **5a,b-8a,b** were transformed into target tetracyclic 5-alkylmorphinans **17a,b-20a,b** using the strategy described by Hupp and Neumeyer [13] (Scheme **2**).

Opening of O-C5 ether bond was performed using zinc under acidic conditions. Treatment of the obtained phenols **9a,b-12a,b** with *N*-phenyl-bis(trifluoromethanesulfonate) amide in the presence of cesium carbonate gave triflates which were used without further purification in the next step. These triflates were cleaved to morphinones **13a,b-16a,b** using palladium acetate, diphenylphosphinopropane (dppp), and 5 equivalents of triethylsilane at 60 °C for 4 h under inert atmosphere. In the last step, the targeted 3-hydroxymorphinones **17a,b-20a,b** were obtained by standard *O*-demethylation of morphinones **13a,b-16a,b** using a dichloromethane solution of BBr_3.

Yields of the three main steps of the conversion of 4,5-epoxymorphinans **5a,b-8a,b** into tetracyclic 5-alkylmorphinans **17a,b-20a,b** were summarized in Table **1**. Generally compounds with of $\Delta^{7,8}$ bond were obtained in somewhat lower overall yields than their saturated counterparts.



Scheme 1. Synthesis route to 5β-alkyl-codeinones with diverse ring C pattern.



	R	R'	X- -Y
5,9,13,17a	**Me**	**H**	**C=C**
5,9,13,17b	**Et**	**H**	**C=C**
6,10,14,18a	**Me**	**OH**	**C=C**
6,10,14,18b	**Et**	**OH**	**C=C**
7,11,15,19a	**Me**	**OH**	**C-C**
7,11,15,19b	**Et**	**OH**	**C-C**
8,12,16,20a	**Me**	**H**	**C-C**
8,12,16,20b	**Et**	**H**	**C-C**

Scheme 2. General synthesis of 5β-alkylmorphinans **17-20 a,b**.

Table 1. Comparison of Isolated Yields for the 3 Main Steps of the Conversion of 4,5-epoxymorphinans 5-8a,b into Tetracyclic 5-alkylmorphinans 17-20a,b

Transformations	Isolated YIELDS* (%) for		
	Reductive Opening of the Ether Bridge	Triflation and Removal of 4-OH Function	*O*-demethylation
5a → 9a → 13a	47	53	74
5b → 9b → 13b	51	57	65
6a → 10a → 14a	44	61	63
6b → 10b → 14b	59	60	59
7a → 11a → 15a	69	59	78
7b → 11b → 15b	64	71	74
8a → 12a → 16a	61	54	75
8b → 12b → 16b	67	54	80

*Reported yields are averages of 3 runs

The synthesis of phenol **12a** gave rise to fine crystals which were found to be suitable for X-ray analysis (Fig. **3**, deposited in the Cambridge Crystallographic Data Centre under deposition number CCDC 820388). This study allowed us to confirm the orientation of 5β-substituent and the relative position of 5β-methyl and 6-keto functions.

Potency and selectivity of new analogs **17a,b-20a,b** towards μ, δ, and κ opioid receptors were evaluated by radioligand binding assays according to the known procedures [17]. Rat brain membranes were used as a source of μ and δ receptors, and guinea pig brain membranes as a source of κ receptors. IC_{50} values at μ, δ and κ opioid receptors, determined against [^{3}H][DAMGO, [^{3}H][Ile^{5,6}]deltorphin-2 and [^{3}H]U69,593, respectively, were collected in Table **2**.

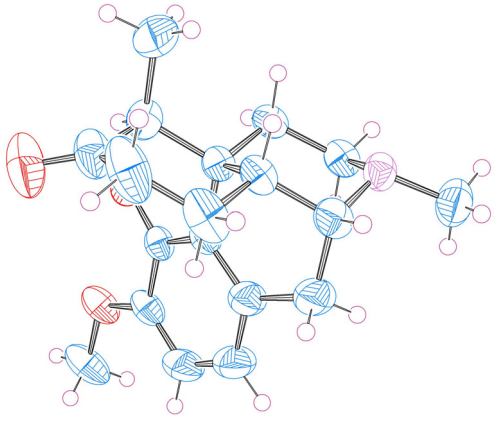


Fig. (3). ORTEP view of compound **12a** at 50% probability level.

Table 2. Opioid Receptor Binding Affinities of 5β-alkylmorphinans 17a,b-20 a,b

Compound	IC_{50} [nM]			Selectivity	
	μ[a]	δ[b]	κ[c]	κ/μ	κ/δ
17a	435±39	>1000	>1000	>2.30	-
17b	351±28	>1000	>1000	>2.85	-
18a	>1000	>1000	>1000	-	-
18b	>1000	>1000	730±58	<0.73	<0.73
19a	1.34±0.12	>1000	15.2±1.6	11.3	<0.02
19b	16.8±1.1	>1000	21.1±2.2	1.26	<0.02
20a	16.7±1.5	>1000	11.5±1.3	0.69	<0.01
20b	38.1±0.4	162±14	24.9±2.2	0.65	0.15
Levorphanol (**1**)	1.28±0.11	16.8±1.4	9.27±1.0	7.24	0.55

All values are expressed as mean ± S.E.M. of three determinations performed in duplicate.
[a]Determined against [^{3}H]DAMGO.
[b]Determined against [^{3}H][Ile^{5,6}]deltorphin-2.
[c]Determined against [^{3}H]U69,593

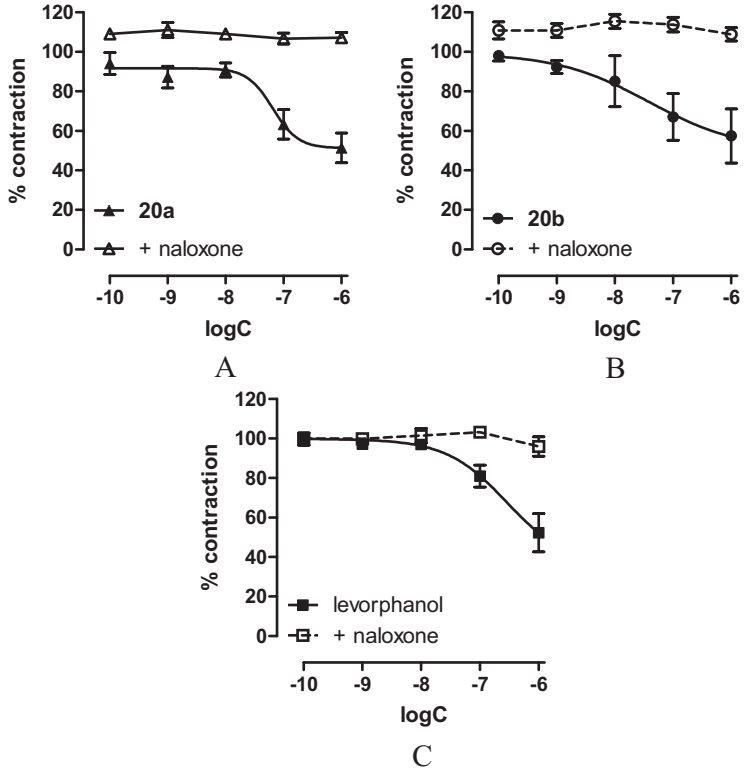


Fig. (4). Concentration–response curves showing the longitudinal smooth muscle contraction in mouse ileum induced by compounds **1**, **20a,b** (10^{-10}–10^{-6} M) alone or in the presence of non-selective opioid receptor antagonist naloxone (10^{-6} M). Data represent mean±SEM for n=6–10 experiments.

For comparison, opioid binding data for levorphanol (**1**) were also included. Structurally, new analogs differed by the presence of the $\Delta^{7,8}$ bond and OH group at the C14. Additionally, there was either a methyl or ethyl group at the 5β position, however none of these alkyl groups influenced the binding more than the other.

Compounds **17a,b** and **18a,b** with $\Delta^{7,8}$ bond all displayed a very poor binding at opioid receptors, whether they had the OH group at C14 or not. It seems that α,β-unsaturated ketone function in the ring C represents a more rigid structure that cannot fit into the binding pocket of the receptor. On the contrary, analogs **19a,b** and **20a,b** with saturated ring C showed significant potency at the μ and κ opioid receptors, but did not bind to the δ receptor.

Then, we examined the effect of compounds which had high potency at the μ and κ opioid receptors (**19a,b** and **20 a,b**), on electrically-stimulated contractions of the mouse ileum, to test the *in vitro* activity of these drugs in a tissue

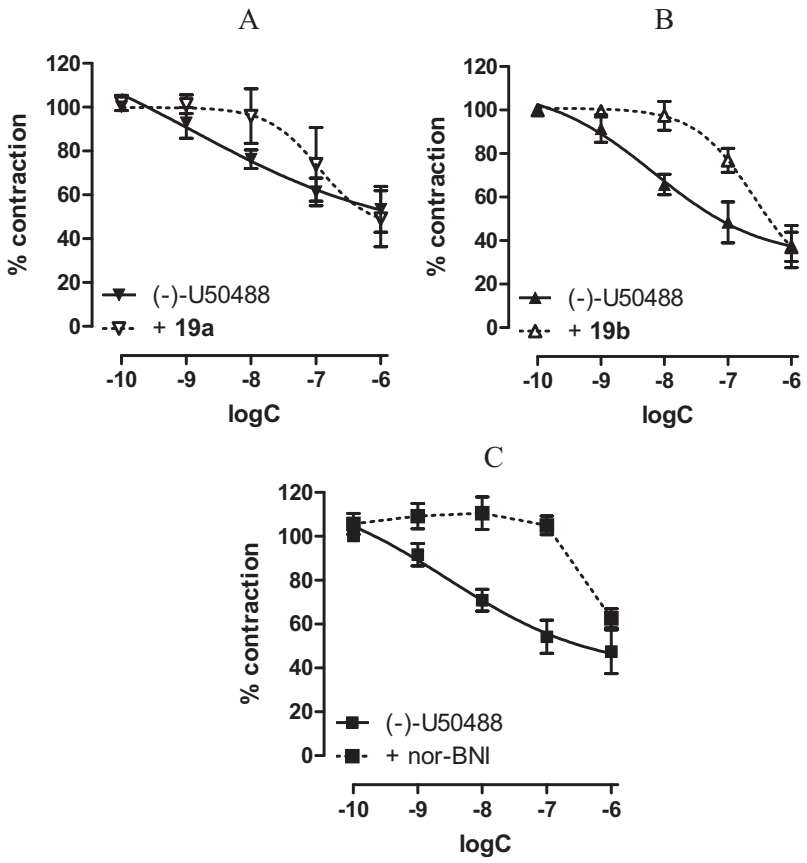


Fig. (5). Concentration–response curves showing the longitudinal smooth muscle contraction in mouse ileum induced by (-)-U50488 κ agonist (10^{-10}–10^{-6} M) alone or in the presence of compounds **19a,b** and the potent κ antagonist nor-BNI (10^{-6} M). Data represent mean±SEM for n=6–10 experiments.

where opioid effects are well characterized. Electrical stimulation of ileal preparations results in activation of cholinergic neurons, which leads to twitch contractions of the smooth muscular tissue [18]. The opioid-induced inhibition of electrically-stimulated twitch contractions provides a good functional assay for opioid activity.

Analogs **20a,b,** similarly to levorphanol (**1**), concentration-dependently reduced the amplitude of electrically-induced twitch contractions (Fig. **3A-C**) and the EC_{50} values were in the nanomolar range (Table **3**). The inhibitory effect of **1** and agonists **20a,b** on smooth muscle contractility was blocked by the opioid receptor antagonist naloxone (10^{-6} M), indicating that the effects of these compounds were mediated by the opioid receptors (Fig. **4A-C**).

Table 3. Agonist Potency of Levorphanol (1) and Analogs 20a and 20b

Compound	EC_{50} [nM]
20a	64.7 ± 5.8
20b	27.8 ± 3.1
Levorphanol (**1**)	16.1 ± 2.5

Compounds **19a,b** did not influence the smooth muscle contractions in mouse ileum tissue but blocked the effect exerted by the κ agonist (-)-U50,488 (Fig. **5A,B**). These data suggest that **19a,b** acted as antagonist at the κ opioid receptors in the mouse ileum. A well known κ antagonist, norbinaltorphimine (nor-BNI), was used for comparison (Fig. **5C**). The pA_2 values for analogs **19a,b** and nor-BNI are shown in Table **4**. Compound **19b** exerted the same, concentration-dependent, antagonist effect at the κ opioid receptor as nor-BNI (Fig. **6**), while **19a** was only a weak antagonist.

CONCLUSIONS

In conclusion we have studied the structure-activity relationship of several new congeners of levorphanol (**1**). Ketolevorphanols **17a,b-20a,b** modified in ring C were prepared by extending a previously published procedure for 5β-substituted 4,5-epoxymorphinans. The pharmacological properties of the novel derivatives at the opioid receptors were evaluated by both binding studies and *in vitro* functional measurements based on the electrically-stimulated contractions of the mouse ileum. Analogs **17a,b** and **18a,b** with $\Delta^{7,8}$ bond had no significant potency at any of the opioid receptor types. In contrast, analogs **19a,b-20a,b,** with the saturated ring C, showed interesting pharmacological properties. Depending on the absence or presence of the hydroxyl group at position 14, they were either potent κ agonist (**20a,b)** or antagonist (**19a,b**), respectively. The potency of

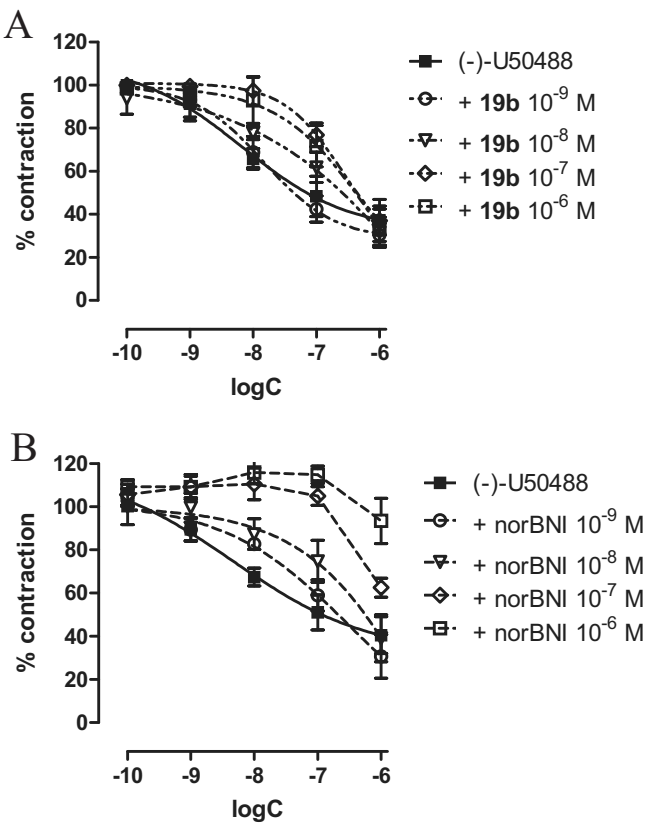


Fig. (6). Concentration–response curves showing the longitudinal smooth muscle contraction in mouse ileum induced by (-)-U50488 κ agonist (10^{-10}–10^{-6} M) alone or in the presence of compound **19b** and the potent κ agonist nor-BNI in the given concentrations.

Table 4. Antagonist Potency of nor-BNI and Analogs 19a and 19b at the κ Opioid Receptor

Compound	pA_2^*
19a	8.70
19b	10.99
nor-BNI	10.91

*Determined against (-)-U50488

19b was comparable to the potency of nor-BNI, a well-known, selective κ opioid receptor antagonist.

Experimental Part

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Thin layer chromatography was performed on precoated Merck 5554 Kieselgel 60 F_{254} foils using 80% CH_2Cl_2/20% CH_3OH mobile phase. The spots were visualized with Dragendorff's reagent. ^{1}H NMR spectra were recorded at 400 MHz using a Bruker Avance DRX400 spectrometer; chemical shifts were reported in ppm (δ) from internal TMS for all the undoubtedly identifiable signs. Coupling constants (*J*) were measured in Hz. Mass spectra were recorded on a Varian MAT 44 S apparatus. IR spectra were recorded with a Mattson Galaxy Series FTIR 3000 spectrometer (in cm^{-1}). Elemental analyses (C, H) were obtained on a Carlo Erba 1108 analyzer.

General Procedure for the Conversion of 5β-alkylthebaines 4a,b into 5-substituted Codeines 5a,b

To a stirred solution of 5-alkylthebaine (1.7 mmol) in 3 M formic acid (500 mL) mercuric acetate (1.7 mmol, 550 mg) was added and the mixture was stirred under nitrogen at room temperature for 12 h. After this period of time saturated K_2CO_3 solution (600 mL) was added carefully, and the mixture was extracted with CH_2Cl_2 (4 x 60 mL). The combined extracts were washed with water and brine, and solvent was evaporated to yield red residue which was passed through a silica gel column (eluent CH_2Cl_2/CH_3OH = 8/2) to give pure **5a** or **5b**.

5β-Methylcodeinone (**5a**)

This compound was obtained in 67% yield. The physical and spectral data were found to be in accordance with previously published ones [19].

5β-Ethylcodeinone (**5b**)

Yield: 60%. M.p.: 167-169°C; IR (KBr) 1686 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=6.64-6.57 (3H, m, H1, H2, H8); 6.09 (1H, d, H7, $J_{7\text{-}8}$=10.2); 3.85 (3H, s, C3-OCH_3); 2.43 (3H, s, N-CH_3); 1.97 (2H, q, C5-CH_2, *J*=4.4); 0.99 (3H, t, CH_2-**CH_3**, *J*=4.5); MS (ESI) m/z 326 $[M+1]^+$.

General Procedure for the Oxidation of 5β-alkylcodeinones 5a,b to 5β-alkyl-14β-hydroxy-codeinones 6a,b

$Co(OAc)_3$ (1.35 mmol, 319 mg), prepared as previously reported [22] was added to a solution of 5β-alkylcodeinone (1.35 mmol) in acetic acid (4 mL). After stirring for 24h at r.t. additional $Co(OAc)_3$ (1.35 mmol, 319 mg) was added and the solution was stirred for 4h. The mixture was diluted with water (30 mL), excess of the oxidant was destroyed with saturated $NaHSO_3$ solution. Then the pH of the reaction mixture was adjusted to 8 by addition of saturated solution of $NaHCO_3$. The products were extracted with dichloromethane (3 x 50 mL), washed with brine (100 mL), and dried. After removal of the solvent, crude product was purified by column chromatography (eluent CH_2Cl_2/CH_3OH = 9/1) to give pure **6a** or **6b**.

14β-Hydroxy- 5β-methylcodeinone (**6a**)

This compound was obtained in 44% yield. The physical and spectral data were found to be in accordance with previously published ones [20].

5β-Ethyl-14β-hydroxycodeinone (**6b**)

Yield: 47%. M.p.: 212-214°C; IR (KBr) 1687 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=6.87 (1H, d, H8, $J_{7\text{-}8}$=10.2), 6.64 (2H, dd, H1, H2, $J_{1\text{-}2}$=8.1); 6.11 (1H, d, H7, $J_{7\text{-}8}$=10.2); 3.83 (3H, s, C3-OCH_3); 2.41 (3H, s, N-CH_3); 2.01 (2H, q, C5-CH_2, *J*=4.2); 1.07 (3H, t, CH_2-**CH_3**, *J*=4.3); MS (ESI) m/z 342 $[M+1]^+$.

Hydrogenation of $\Delta^{7,8}$ of Substituted Codeinones 5a,b and 14-hydroxy-codeinones 6a,b

A mixture of 1 mmol of the unsaturated codeinone, 90 mg of Pd/C (10%) and 200 mL of ethanol (96%) was hydrogenated at 35 psi (r.t.) for 10 h. The obtained mixture was filtered through a short pad of Celite and washed with 3x10

mL of dichloromethane:methanol=8:2. The resulting organic solution was concentrated to dryness under vacuum. The crude compound was found in every case pure enough to step forward without purification.

5β-Methyl-dihydrocodeinone (**7a**)

This compound was obtained in 87% yield. The physical and spectral data were found to be in accordance with previously published ones [14].

5β-Ethyl-dihydrocodeinone (**7b**)

Yield: 90%. M.p.: 139-140.5°C; IR (KBr) 1719 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=6.61 (2H, dd, H1, H2, $J_{1\text{-}2}$=8.0); 3.87 (3H, s, C3-OCH_3); 2.41 (3H, s, N-CH_3); 1.99 (2H, q, C5-CH_2, J=4.0); 1.07 (3H, t, CH_2-**CH_3**, J=4.2); MS (ESI) m/z 328 $[M+1]^+$.

14β-Hydroxy-5β-methyl-dihydrocodeinone (**8a**)

This compound was obtained in 83% yield. The physical and spectral data were found to be in accordance with previously published ones [21].

5β-Ethyl-14β-hydroxy-dihydrocodeinone (**8b**)

Yield: 88%. M.p.: 174-175°C; IR (KBr) 1722 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=6.63 (2H, dd, H1, H2, $J_{1\text{-}2}$=8.1); 3.81 (3H, s, C3-OCH_3); 2.47 (3H, s, N-CH_3); 2.05 (2H, q, C5-CH_2, J=4.3); 1.00 (3H, t, CH_2-**CH_3**, J=4.3); MS (ESI) m/z 344 $[M+1]^+$.

Ether Ring Opening Procedure

To a 100 mL round bottom flask was added 4,5-epoxymorphinan (1 mmol) and n-PrOH:H_2O=8:1 (9 mL). Then ammonium chloride (640 mg, 11.9 mmol) was added and the mixture was brought to reflux. Once at reflux, zinc dust (520 mg, 8 mmol) was added over 5 min and the mixture was allowed to reflux overnight. The solvent was removed and water was added to the residue and basified using NH_4OH. The basic aqueous mixture was extracted with DCM (3 x 10 mL). The organics were combined, dried using anhydrous sodium sulphate and concentrated. Column chromatography was used to purify the product (eluent CH_2Cl_2/CH_3OH = 9/1).

(-)-5β,17-Dimethyl-4-hydroxy-3-methoxy-7,8-didehydromorphinan-6-one (**9a**)

M.p.: 189-191°C; IR (KBr) 1679 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=6.59-6.48 (3H, m, H1, H2, H8); 6.13 (1H, d, H7, $J_{7\text{-}8}$=9.9); 3.89 (3H, s, C3-OCH_3); 2.44 (3H, s, N-CH_3); 1.19 (3H, d, C5-CH_3, J=6.9); MS (ESI) m/z 314 $[M+1]^+$.

(-)-5β-Ethyl-4-hydroxy-3-methoxy-17-methyl-7,8-didehydromorphinan-6-one (**9b**)

M.p.: 177-178°C; IR (KBr) 1681 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=6.66-6.57 (3H, m, H1, H2, H8); 6.09 (1H, d, H7, $J_{7\text{-}8}$=10.9); 3.82 (3H, s, C3-OCH_3); 2.47 (3H, s, N-CH_3); 1.91 (2H, q, C5-CH_2, J=4.1); 1.10 (3H, t, CH_2-**CH_3**, J=4.2); MS (ESI) m/z 328 $[M+1]^+$.

(-)-4,14β-Dihydroxy-5β,17-dimethyl-3-methoxy-7,8-didehydromorphinan-6-one (**10a**)

M.p.: 197-199°C; IR (KBr) 1689 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=6.66-6.54 (3H, m, H1, H2, H8); 6.09 (1H, d, H7, $J_{7\text{-}8}$=10.3); 3.81 (3H, s, C3-OCH_3); 2.45 (3H, s, N-CH_3); 1.20 (3H, d, C5-CH_3, J=7.1); MS (ESI) m/z 330 $[M+1]^+$.

(-)-4,14β-Dihydroxy-5β-ethyl-3-methoxy-17-methyl-7,8-didehydromorphinan-6-one (**10b**)

M.p.: 184-186°C; IR (KBr) 1691 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=6.59-6.52 (3H, m, H1, H2, H8); 6.05 (1H, d, H7, $J_{7\text{-}8}$=9.8); 3.87 (3H, s, C3-OCH_3); 2.47 (3H, s, N-CH_3); 1.85 (2H, q, C5-CH_2, J=4.4); 1.06 (3H, t, CH_2-**CH_3**, J=4.3); MS (ESI) m/z 344 $[M+1]^+$.

(-)-5β,17-dimethyl-4-hydroxy-3-methoxy-morphinan-6-one (**11a**)

M.p.: 201-203°C; IR (KBr) 1721 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=6.61 (2H, dd, H1, H2, $J_{1\text{-}2}$=8.4); 3.86 (3H, s, C3-OCH_3); 2.45 (3H, s, N-CH_3); 1.20 (3H, d, C5-CH_3, J=7.2); MS (ESI) m/z 316 $[M+1]^+$.

(-)-5β-Ethyl-4-hydroxy-3-methoxy-17-methyl-morphinan-6-one (**11b**)

M.p.: 191-193.5°C; IR (KBr) 1717 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=6.66 (2H, dd, H1, H2, $J_{1\text{-}2}$=8.1); 3.82 (3H, s, C3-OCH_3); 2.39 (3H, s, N-CH_3); 1.90 (2H, q, C5-CH_2, J=4.1); 0.99 (3H, t, CH_2-**CH_3**, J=4.0); MS (ESI) m/z 330 $[M+1]^+$.

(-)-4,14β-Dihydroxy-5β,17-dimethyl-3-methoxy-morphinan-6-one (**12a**)

M.p.: 206-208°C; IR (KBr) 1717 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=6.59 (2H, dd, H1, H2, $J_{1\text{-}2}$=8.1); 3.79 (3H, s, C3-OCH_3); 2.41 (3H, s, N-CH_3); 1.18 (3H, d, C5-CH_3, J=7.0); MS (ESI) m/z 332 $[M+1]^+$.

(-)-4,14β-Dihydroxy-5β-ethyl-3-methoxy-17-methyl-morphinan-6-one (**12b**)

M.p.: 184-185.5°C; IR (KBr) 1714 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=6.66 (2H, dd, H1, H2, $J_{1\text{-}2}$=7.9); 3.87 (3H, s, C3-OCH_3); 2.47 (3H, s, N-CH_3); 1.86 (2H, q, C5-CH_2, J=4.2); 0.95 (3H, t, CH_2-**CH_3**, J=4.4); MS (ESI) m/z 346 $[M+1]^+$.

Triflation of the Phenolic 4-OH Function and Catalytic Removal of Triflate

The phenol (1 mmol) and cesium carbonate (385 mg, 1.45 mmol) were mixed with THF (3 mL). Then N-phenylbis(trifluoromethanesulfonate)amide (450 mg, 1.26 mmol) was added and the mixture stirred at 70°C overnight. The THF was removed and the residue was dissolved in DCM, washed with water, dried using anhydrous sodium sulphate and concentrated. The crude was found pure enough to use in the next step without further purification. The triflate (0.04 mmol), 9 mg of $Pd(OAc)_2$ (0.04 mmol) and 17 mg of diphenylphosphinopropane (dppp) (0.04 mmol) was dissolved in anhydrous DMF (2.00 mL) and stirred under inert atmosphere. Then triethylsilane (35 µL, 0.20 mmol) was added dropwise with a syringe. The mixture was heated at 60°C for 4 h. The DMF was then removed and the residue was dissolved in DCM (10.0 mL). The organics were washed with sat. sodium bicarbonate solution (5.00 mL) and were dried using anhydrous sodium sulphate and concentrated. Column chromatography was used to purify the product (eluent CH_2Cl_2/CH_3OH = 95/5).

(-)-5β,17-Dimethyl-3-methoxy-7,8-didehydromorphinan-6-one (**13a**)

M.p.: 231-232°C; IR (KBr) 1680 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=6.80-6.61 (3H, m, H1, H4, H8); 6.47 (1H, dd, H2, *J*=8.3, 2.7); 6.11 (1H, d, H8, $J_{7\text{-}8}$=10.0); 3.87 (3H, s, C3-OCH_3); 2.41 (3H, s, N-CH_3); 1.17 (3H, d, C5-CH_3, *J*=6.8); MS (ESI) m/z 298 $[M+1]^+$.

(-)-5β-Ethyl-3-methoxy-17-methyl-7,8-didehydromorphinan-6-one (**13b**)

M.p.: 192-194°C; IR (KBr) 1688 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=6.73-6.58 (3H, m, H1, H4, H8); 6.41 (1H, dd, H2, *J*=8.1, 2.9); 6.07 (1H, d, H7, $J_{7\text{-}8}$=10.4); 3.81 (3H, s, C3-OCH_3); 2.39 (3H, s, N-CH_3); 1.81 (2H, q, C5-CH_2, *J*=4.1); 1.05 (3H, t, CH_2-**CH_3**, *J*=4.0); MS (ESI) m/z 312 $[M+1]^+$.

(-)-5β,17-Dimethyl-14β-hydroxy-3-methoxy-7,8-didehydromorphinan-6-one (**14a**)

M.p.: 209-210.5°C; IR (KBr) 1679 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=6.76-6.61 (3H, m, H1, H4, H8); 6.37 (1H, dd, H2, *J*=7.9, 3.0); 6.05 (1H, d, H7, $J_{7\text{-}8}$=10.4); 3.81 (3H, s, C3-OCH_3); 2.46 (3H, s, N-CH_3); 1.23 (3H, d, C5-CH_3, *J*=7.3); MS (ESI) m/z 314 $[M+1]^+$.

(-)-5β-Ethyl-14β-hydroxy-3-methoxy-17-methyl-7,8-didehydromorphinan-6-one (**14b**)

M.p.: 179-181°C; IR (KBr) 1679 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=6.73-6.61 (3H, m, H1, H4, H8); 6.43 (1H, dd, H2, *J*=8.0, 2.9); 6.11 (1H, d, H7, $J_{7\text{-}8}$=10.1); 3.87 (3H, s, C3-OCH_3); 2.44 (3H, s, N-CH_3); 1.79 (2H, q, C5-CH_2, *J*=4.5); 0.95 (3H, t, CH_2-**CH_3**, *J*=4.4); MS (ESI) m/z 328 $[M+1]^+$.

(-)-5β,17-Dimethyl-3-methoxy-morphinan-6-one (**15a**)

M.p.: 168-170°C; IR (KBr) 1723 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=6.68-6.61 (2H, m, H1, H4); 6.50 (1H, dd, H2, *J*=8.1, 1.9); 3.81 (3H, s, C3-OCH_3); 2.42 (3H, s, N-CH_3); 1.16 (3H, d, C5-CH_3, *J*=7.4); MS (ESI) m/z 300 $[M+1]^+$.

(-)-5β-Ethyl-3-methoxy-17-methyl-morphinan-6-one (**15b**)

M.p.: 168-170°C; IR (KBr) 1723 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=6.70-6.64 (2H, m, H1, H4); 6.48 (1H, dd, H2, *J*=8.0, 2.2); 3.87 (3H, s, C3-OCH_3); 2.46 (3H, s, N-CH_3); 1.81 (2H, q, C5-CH_2, *J*=4.1); 0.97 (3H, t, CH_2-**CH_3**, *J*=4.2); MS (ESI) m/z 314 $[M+1]^+$.

(-)-5β,17-Dimethyl-4β-hydroxy-3-methoxy-morphinan-6-one (**16a**)

M.p.: 211-213°C; IR (KBr) 1719 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=6.71-6.64 (2H, m, H1, H4); 6.51 (1H, dd, H2, *J*=7.8, 2.0); 3.85 (3H, s, C3-OCH_3); 2.47 (3H, s, N-CH_3); 1.19 (3H, d, C5-CH_3, *J*=7.1); MS (ESI) m/z 316 $[M+1]^+$.

(-)-5β-Ethyl-14β-hydroxy-3-methoxy-17-methyl-morphinan-6-one (**16b**)

M.p.: 199°C (decomp.); IR (KBr) 1730 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=6.66-6.57 (2H, m, H1, H4); 6.43 (1H, dd, H2, *J*=7.9, 2.1); 3.80 (3H, s, C3-OCH_3); 2.41 (3H, s, N-CH_3); 1.82 (2H, q, C5-CH_2, *J*=4.4); 1.05 (3H, t, CH_2-**CH_3**, *J*=4.3); MS (ESI) m/z 330 $[M+1]^+$.

BBr_3-mediated *O*-demethylation of 3-methoxymorphinans

A solution of well-dried 3-methoxymorphinan (1 mmol) in 10 ml of CH_2Cl_2 was added during 2 min to a well-stirred 1 M dichloromethane solution of BBr_3 (18 mL) at 0°C. The temperature of in the mixture then allowed rising to room temperature and stirred for further 15 min. The reaction mixture which consisted of a suspension of white solid (in CH_2Cl_2) was then poured into a well-stirred mixture of 8 g of ice and 20 ml of concentrated (28-30%) NH_4OH. The two-phase system was kept at -5 to 0°C for 0.5 h (continuous stirring) and filtered. The resulting crystalline material was washed thoroughly with small portions of cold CH_2C1_2 and H_2O and dried to give the desired deprotected morphinan. The pure base was turned into hydrochloride salt form by the addition of HCl gas adsorbed in ether.

(-)-5β,17-Dimethyl-3-hydroxy-7,8-didehydromorphinan-6-one.HCl (**17a.HCl**)

M.p.: 148-150°C; IR (KBr) 1676 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d6) δ=10.10-9.91 (2H, NH^+, 3-OH, br s); 6.74-6.65 (2H, m, H1, H4); 6.53-6.49 (2H, m, H2, H8); 6.10 (1H, d, H7, $J_{7\text{-}8}$=10.0); 2.83 (3H, s, N-CH_3); 1.15 (3H, d, C5-CH_3, *J*=6.9); MS (ESI) m/z 284 $[M+1]^+$; calculated for $C_{18}H_{21}NO_2$.HCl: C, 67.60; H, 6.93; found: C, 67.54; H, 6.99.

(-)-5β-Ethyl-3-hydroxy-17-methyl-7,8-didehydromorphinan-6-one.HCl (**17b.HCl**)

M.p.: >250°C; IR (KBr) 1691 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d6) δ=10.55-9.83 (2H, NH^+, 3-OH, br s); 6.77-6.71 (2H, m, H1, H4); 6.57-6.43 (2H, m, H2, H8); 6.17 (1H, d, H7, $J_{7\text{-}8}$=10.4); 2.86 (3H, s, N-CH_3); 1.88 (2H, q, C5-CH_2, *J*=4.1); 1.01 (3H, t, CH_2-**CH_3**, *J*=4.3); MS (ESI) m/z 298 $[M+1]^+$; calculated for $C_{19}H_{23}NO_2$.HCl: C, 68.35; H, 7.25; found: C, 68.24; H, 7.30.

(-)-3,14β-Dihydroxy-5β,17-dimethyl-7,8-didehydromorphinan-6-one.HCl (**18a.HCl**)

M.p.: 249-251°C; IR (KBr) 1683 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d6) δ=9.90-9.73 (2H, NH^+, 3-OH, br s); 6.73-6.68 (2H, m, H1, H4); 6.59-6.50 (2H, m, H2, H8); 6.35 (1H, d, H7, $J_{7\text{-}8}$=10.0); 2.79 (3H, s, N-CH_3); 1.20 (3H, d, C5-CH_3, *J*=7.2); MS (ESI) m/z 300 $[M+1]^+$; calculated for $C_{18}H_{21}NO_3$.HCl: C, 64.38; H, 6.60; found: C, 64.19; H, 6.69.

(-)-3,14β-Dihydroxy-5β-ethyl-17-methyl-7,8-didehydromorphinan-6-one.HCl (**18b.HCl**)

M.p.: >250°C; IR (KBr) 1682 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d6) δ=9.79-9.43 (2H, NH^+, 3-OH, br s); 6.72-6.54 (2H, m, H1, H4); 6.54-6.49 (2H, m, H2, H8); 6.35 (1H, d, H7, $J_{7\text{-}8}$=10.1); 2.80 (3H, s, N-CH_3); 1.87 (2H, q, C5-CH_2, *J*=4.2); 1.06 (3H, t, CH_2-**CH_3**, *J*=4.3); MS (ESI) m/z 314 $[M+1]^+$; calculated for $C_{19}H_{23}NO_3$.HCl: C, 65.23; H, 6.91; found: C, 65.37; H, 6.98.

(-)-5β,17-Dimethyl-3-hydroxy-morphinan-6-one.HCl (**19a.HCl**)

M.p.: >250°C; IR (KBr) 1730 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d6) δ=10.06-9.81 (2H, NH^+, 3-OH, br s); 6.73-6.68 (2H, m, H1, H4); 6.35 (1H, dd, H2, *J*=8.0, 1.9); 2.76 (3H, s, N-CH_3); 1.17 (3H, d, C5-CH_3, *J*=7.0); MS (ESI) m/z 286

$[M+1]^+$; calculated for $C_{18}H_{23}NO_2$.HCl: C, 67.17; H, 7.52; found: C, 67.31; H, 7.66.

(-)-5β-Ethyl-3-hydroxy-17-methyl-morphinan-6-one.HCl (**19b.HCl**)

M.p.: >250°C; IR (KBr) 1727 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d6) δ=9.86-9.65 (2H, NH^+, 3-OH, br s); 6.77-6.71 (2H, m, H1, H4); 6.41 (1H, dd, H2, *J*=8.2, 2.1); 2.84 (3H, s, N-CH_3); 1.77 (2H, q, C5-CH_2, *J*=4.1); 0.96 (3H, t, CH_2-**CH_3**, *J*=4.3); MS (ESI) m/z 300 $[M+1]^+$; calculated for $C_{19}H_{25}NO_2$.HCl: C, 67.94; H, 7.80; found: C, 67.82; H, 7.91.

(-)-3,14β-Dihydroxy-5β,17-dimethyl-morphinan-6-one.HCl (**20a.HCl**)

M.p.: 176-178°C (Decomp.); IR (KBr) 1721 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d6) δ=10.01-9.73 (2H, NH^+, 3-OH, br s); 6.78-6.69 (2H, m, H1, H4); 6.38 (1H, dd, H2, *J*=8.1, 1.8); 2.81 (3H, s, N-CH_3); 1.15 (3H, d, C5-CH_3, *J*=7.1); MS (ESI) m/z 302 $[M+1]^+$; calculated for $C_{18}H_{23}NO_3$.HCl: C, 63.99; H, 7.16; found: C, 63.89; H, 7.29.

(-)-3,14β-Dihydroxy-5β-ethyl-17-methyl-morphinan-6-one.HCl (**20b.HCl**)

M.p.: >250°C; IR (KBr) 1727 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d6) δ=9.91-9.71 (2H, NH^+, 3-OH, br s); 6.79-6.71 (2H, m, H1, H4); 6.44 (1H, dd, H2, *J*=8.0, 2.1); 2.80 (3H, s, N-CH_3); 1.72 (2H, q, C5-CH_2, *J*=4.0); 1.00 (3H, t, CH_2-**CH_3**, *J*=4.1);MS (ESI) m/z 316 $[M+1]^+$; calculated for $C_{19}H_{25}NO_3$.HCl: C, 64.85; H, 7.45; found: C, 64.81; H, 7.69.

Crystallographic Details of Compound 12

X-ray data were collected on a Bruker-Nonius MACH3 diffractometer at 293 K, Mo Kα radiation λ=0.71073 Å, ω motion. The structure was solved using the SIR-92 software [23] and refined on F2 using SHELX-97 program [24], publication material was prepared with the WINGX-97 suite [25]. All non-hydrogen atoms were refined anisotropically. Crystallographic data (excluding structure factors) for structure **12a** have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 820388. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Crystal Data

$C_{19}H_{25}NO_3$	V = 1721.5 (3) Å^3
M_r = 315.4	Z = 4
Orthorhombic, $P2_12_12_1$	Mo $K\alpha$ radiation, λ = 0.71073 Å
a = 8.845 (1) Å	μ = 0.08 mm−1
b = 11.589 (1) Å	T = 293 K
c = 16.794 (1) Å	0.45 × 0.25 × 0.2 mm

Pharmacology

Radioligand binding assay. The opioid receptor binding assays were performed using rat brain (for the μ and δ receptors) or guinea pig brain (for the κ receptor) membrane preparations, as reported in detail elsewhere [17]. Binding affinities for the μ, δ and κ opioid receptors were determined by displacing [^{3}H]DAMGO, [^{3}H][Ile$_{5,6}$]deltorphin-2 and [^{3}H]U69,593 respectively. Briefly, crude membrane preparations, isolated from Wistar rat brains or guinea pig brains, were incubated at 25°C for 120 min. with appropriate concentration of a tested peptide in the presence of 0.5 nM radioligand in a total volume of 0.5 ml of Tris/HCl (50 mM, pH 7.4), containing MgCl2 (5 mM), EDTA (1 mM), NaCl (100 mM), and bacitracin (20 mg/L). Non-specific binding was determined in the presence of naloxone (1 μM). Incubations were terminated by rapid filtration through Whatman GF/B (Brentford, UK) glass fiber strips, which had been presoaked for 2 h in 0.5 % polyethylamine, using Millipore Sampling Manifold (Billerica, USA). The filters were washed three times with 4 ml of ice-cold Tris buffer solution. The bound radioactivity was measured in Packard Tri-Carb 2100 TR liquid scintillation counter (Ramsey, MN, USA) after overnight extraction of the filters in 4 ml of Perkin Elmer Ultima Gold scintillation fluid (Wellesley, MA, USA). Three independent experiments for each assay were carried out in duplicate.

Animals

Male Swiss albino mice (CD1, Charles River, Canada), weighing 20-26 g, were used throughout the studies. The animals were housed at a constant temperature (22°C) and maintained under a 12-h light/dark cycle in sawdust coated plastic cages with access to standard laboratory chow and tap water *ad libitum*. Animal use for these studies was approved by the University of Calgary Animal Care Committee and the experiments were performed in accordance with institutional animal ethics committee guidelines that follow the guidelines established by the Canadian Council on Animal Care.

Isolated Smooth Muscle Strips

The experiments were performed as described elsewhere [26]. Mice were sacrificed by cervical dislocation. Full-thickness (1 cm) segments of the distal ileum were removed and kept in ice-cold oxygenated Krebs-Ringer Solution (mmol/L: NaCl 119, KCl 4.7, KH_2PO_4 1.2, $NaHCO_3$ 25, $MgSO_4$ 1.5, $CaCl_2$ 2.5, and glucose 11). Luminal contents were gently flushed. The preparations were mounted between two platinum electrodes and placed in separate organ baths (25 mL; 37°C; oxygenated with 95% O_2 / 5% CO_2). Using a silk thread, one end of each preparation was attached to the bottom of the organ bath, while the other end was connected to a FT03 force displacement transducer (Grass Technologies, West Warwick, RI, USA). 0.5 g tension was applied and the preparations were allowed to equilibrate for 30 min. Changes in tension were amplified by a P11T Compact Transducer Amplifier (Grass Technologies, West Warwick, RI, USA) and recorded on personal computer using the PolyView software (Polybytes Inc., Chedar Rapids, Iowa, USA). All experiments lasted less than 3 h and each preparation was used for a single experiment only. Electrical field stimulation (EFS; 8 Hz, 24 V, stimulus duration 0.5 msec, train duration 10 sec) was applied by a S88X Dual Output Square Pulse Stimulator (Grass Technologies, West Warwick, RI, USA). Compounds (10^{-10}– 10^{-6} M) were added cumulatively into the organ baths and effects on the EFS

induced contractions were recorded. Each concentration was allowed to incubate for 10 minutes.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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