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N-Cyclohexylethyl-*N*-noroxymorphindole: A μ-Opioid Preferring Analogue of Naltrindole

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Abstract—The position of the indole in the indolomorphinans, which includes the δ opioid antagonist naltrindole, is considered to be responsible for the δ opioid selectivity for this class of ligands. Herein is described the *N*-cyclohexylethyl substituted *N*-nor-derivative, which is shown to be μ preferring. Thus, the nature of the N-substituent is equally important to the receptor selectivity for this class of ligands.

The discovery of the indolomorphinan naltrindole (**1**) (Fig. 1) as a δ opioid selective antagonist was a major advance in the field,[1] and allowed studies that have shown that δ antagonists have broad clinical potential.[2] δ Antagonists may be useful for the treatment of cocaine[3] and methamphetamine[4] and alcohol[5] abuse, and their immunosuppressive effects lead to the promise of useful treatments for preventing rejection in transplant therapy.[6] In addition, it has been shown that the δ opioid system modulates the μ opioid system, with δ antagonists preventing the development of tolerance and dependence to morphine.[7] Importantly, it has also been shown that peptidic ligands with a dual profile of μ agonism and δ antagonism give rise to μ mediated antinociception without the development of tolerance or dependence,[8] raising the possibility that a nonpeptidic ligand with such a profile would be a useful medication for the treatment of chronic pain. Indeed, Ananthan has recently described such a ligand, but it possessed low μ agonist potency.[9]

SAR studies in the indolomorphinans have concentrated on improving the δ antagonist selectivity of naltrindole or preparing agonist derivatives such as **2**;[1,10] studies have generally not concentrated on attempting to reduce the δ selectivity or to convert naltrindole from a μ antagonist[11] to a μ agonist. Herein, we present our unexpected preliminary results on the *N*-cyclohexylethyl substituted indolomorphinan **6**, which displays moderate μ selectivity and μ agonism.

The introduction of the 6,7-indole into naltrexone to give naltrindole (**1**) causes a reduction in μ affinity and an increase in δ affinity to give the observed δ selectivity.[1] It has been suggested that the position of this aromatic ring (the address) is critical for the δ binding selectivity of the indolomorphinans,[12] and ligands with such a substituent tend to display some degree of δ selectivity. However we,[13,14] and others,[15] have shown that changes in substituents at other positions of the opioid skeleton can seriously reduce the degree of selectivity, through increasing μ affinity and decreasing δ affinity.

Our interest into the effects of the N-substituent on the pharmacology of opioids recently led to our investigation of the effect of *N*-benzyl substituents.[16] Nonpeptidic opioids with *N*-benzyl substituents, unlike *N*-phenethyl,[17] possess very poor opioid activity, and we showed that *N*-benzyl-*N*-noroxymorphindole (**3**) was no exception and displayed low affinity at all three opioid receptors (Table 1). Consistent with other

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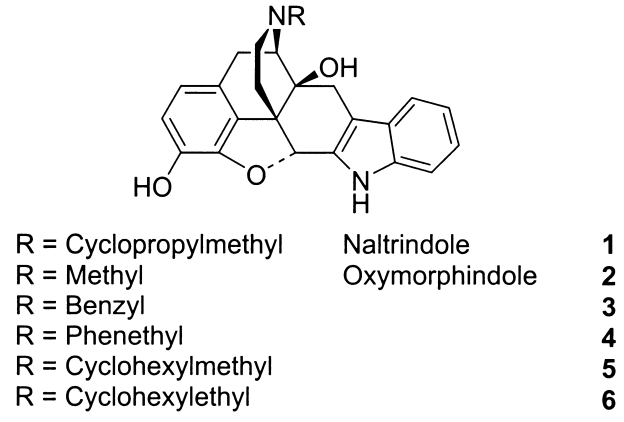


Figure 1. N-Substituted-*N*-noroxymorphindoles.

Table 1. Binding affinities of **3**, **5**, and **6** at opioid receptors

	K_i (nM) ± SEM			
	μ[a]	δ[b]	κ[c]	μ/δ
1 (Naltrindole)[d]	3.7	0.04	5.8	93
3 (Benzyl)[e]	5330±195	115±32	134±41	46
5 (Cyclohexylmethyl)	1925±563	94.5±13.6	1115±430	20
6 (Cyclohexylethyl)	7.3±1.2	181±35	378±72	0.04

[a]Displacement of [^{3}H]-DAMGO (C6 glioma cells expressing the cloned μ receptor).
[b]Displacement of [^{3}H]-*p*-Cl-DPDPE (C6 glioma cells expressing the cloned δ receptor).
[c]Displacement of [^{3}H]-U69,593 (CHO cells expressing the cloned κ receptor).
[d]Data from ref 21.
[e]Previously reported in monkey cortex.[16]

indolomorphinans, **3** did possess moderate δ binding selectivity (Table 1).[16] *N*-Phenethyl-*N*-noroxymorphindole (**4**) has been reported by Portoghese to possess only slight δ selectivity (eightfold over μ), but possess greater δ affinity than **3**.[18] Based on the fact that the differences between *N*-benzyl and *N*-phenethyl substituents cannot be explained for other opioid ligands, we decided to further our knowledge in the area by preparing the saturated analogues, *N*-cyclohexylmethyl and *N*-cyclohexylethyl, to investigate the differences between saturated and unsaturated rings in the indolomorphinan series.

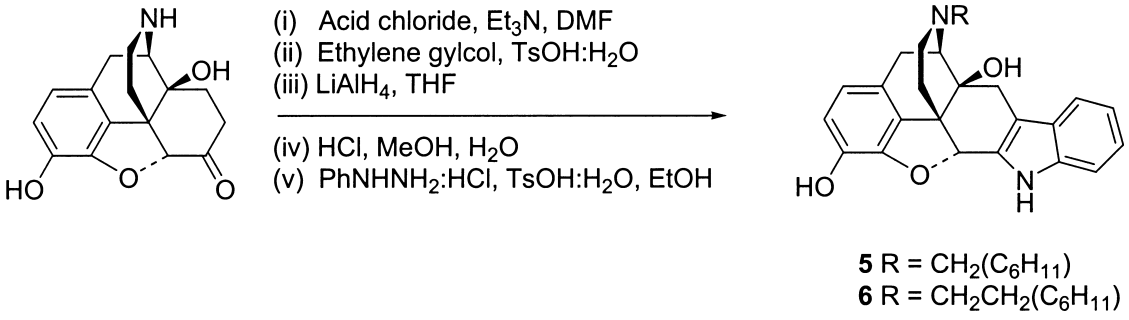
Synthesis

Oxycodone was converted to noroxymorphone (**7**) by standard methods.[19] Noroxymorphone was converted to the desired products (**5** and **6**) as shown in Scheme 1. Acylation with the relevant acid chloride, ethylene ketal formation, $LiAlH_4$ reduction, acid hydrolysis, and indole formation[13] gave the desired products in good yield, which were converted to the HCl salts.[20]

Results and Discussion

Pharmacological assays were performed by the Drug Evaluation Committee using their standard procedures,[16] and the results are shown in Tables 1 and 2. The *N*-cyclohexylmethyl derivative (**5**) displayed similar binding characteristics to the corresponding aromatic analogue **3**, being of low affinity at all three opioid receptors but somewhat δ preferring (Table 1). This demonstrates that the presence of an aromatic or a saturated six-membered ring one carbon removed from the nitrogen has little difference in the recognition of the indolomorphinans at the opioid receptors. Surprisingly, the corresponding *N*-cyclohexylethyl analogue (**6**) demonstrated high affinity and preference for μ receptors (K_i δ/μ = 25). Indeed, comparing **5** and **6**, it can be seen that increasing the N-substituent by one methylene increases μ affinity by over 200-fold, whereas the effects on δ and κ affinity are relatively minor. Comparing **6** to naltrindole (**1**), it can be seen that the loss of δ selectivity is due to a great decrease in δ affinity, not an increase in μ affinity. This shows that the effect of the N-substituent is more important than the indolic 'address' component in this case, and shows that the presence of a 6,7-fused indole does not necessarily lead to δ binding selectivity. These data also show that changing from an aromatic six-membered ring two carbons from the nitrogen to a saturated ring, causes a change from δ preferring[18] to μ preferring in binding assays.

The mouse antinociceptive assays (Table 2) were consistent with the binding studies; **5** was inactive as either an antinociceptive agent or a morphine antagonist. This shows that **5** displays a similar profile to the corresponding *N*-benzyl analogue **3**. Compound **6** showed potent antinociception in the mouse in all three assays,



Scheme 1. Preparation of N-substituted-*N*-noroxymorphindoles.

Table 2. Antinociceptive activity of **5** and **6** in the mouse[a]

	sc mg/kg[b]			
	TF[c]	TF vs M[d]	PPQ[e]	HP[f]
5 (Cyclohexylmethyl)	Inactive	Inactive	Inactive	Inactive
6 (Cyclohexylethyl)	3.86 (2.66–5.59)[g]	—	0.39 (0.17–0.86)	2.42 (1.57–3.73)

[a]**3** was inactive in all mouse assays.[16] 'Inactive' is stated when less than half of the mice were affected at 30 mg/kg.
[b]Parenthesized numbers represent 95% confidence limits.
[c]Tail flick: morphine sulfate = 0.73 (0.35–1.53).
[d]Tail flick vs morphine: naloxone = 0.04 (0.01–0.09).
[e]Paraphenylquinone: morphine sulfate = 0.4 (0.2–0.8).
[f]Hot plate: morphine sulfate = 3.1 (1.5–6.4).
[g]Naloxone AD_{50} = 0.1 (0.07–0.6), β-FNA (μg/brain) AD_{50} = 1.25 (0.51–3.07), norBNI Inactive, naltrindole Inactive.

being equipotent with morphine in the hot plate and antiwrithing, but fivefold less potent than morphine in the tail flick. The potent antinociceptive activity in the hot plate, coupled with the potent reversal of the antinociception seen in the tail flick by the μ preferring antagonist naloxone, strongly suggests the antinociceptive effects to be μ-mediated. This profile was confirmed by the reversal of the antinociception in the tail flick by a selective μ antagonist (β-FNA), but not by a κ or δ antagonist (norBNI and naltrindole, respectively).

This work shows that there is little difference between a saturated ring and an aromatic ring one carbon removed from the nitrogen, but there are differences when the ring is two carbons distant. Importantly, the *N*-cyclohexylethyl substituted indolomorphinan possesses a profile of μ preferring agonism, and suggests that ligands with a profile of μ agonism and δ antagonism can be developed in this series of ligands. Further studies to fully characterize the pharmacological profile of this unique ligand are currently underway.

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