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DELTA OPIOID BINDING SELECTIVITY OF 3-ETHER ANALOGS OF NALTRINDOLE

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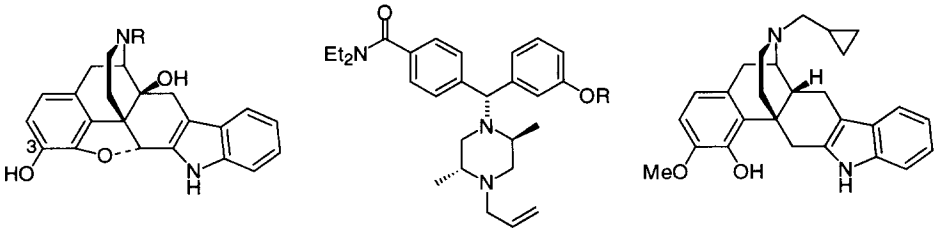
Abstract: Masking of the 3-phenol of naltrindole as a range of ethers caused a decrease in binding affinity at all three opiate receptors (μ, κ, δ), however for the methyl ether, the reduction in affinity at both μ and κ was greater than at δ, thereby increasing δ binding selectivity. © 1999 Published by Elsevier Science Ltd.

The delta (δ) opioid receptor has been associated with many biological processes.[1] In addition to the potential use of δ agonists as clinically useful analgesics lacking the detrimental side effects of mu (μ) and kappa (κ) agonists,[2,3] it has also been shown that δ antagonists may be useful for the treatment of cocaine abuse.[4,5] For further study of the δ opioid system and its interaction with other biological systems, metabolically stable nonpeptide δ selective ligands are required. One of our approaches towards the development of highly selective δ ligands has been to modify the structure of the indolomorphinans, a series of ligands developed by Portoghese that display moderate δ selectivity.[6] Some members of this series such as the δ antagonist naltrindole (**1**) and the δ partial agonist oxymorphindole (**2**) (Figure 1) are widely used pharmacological tools,[7] but their high affinity at both μ and κ receptors severely limit their potential medicinal use.[8]



1 R = cyclopropylmethyl
2 R = methyl

3 R = H
4 R = methyl

5

Figure 1. Structures of δ Selective Ligands

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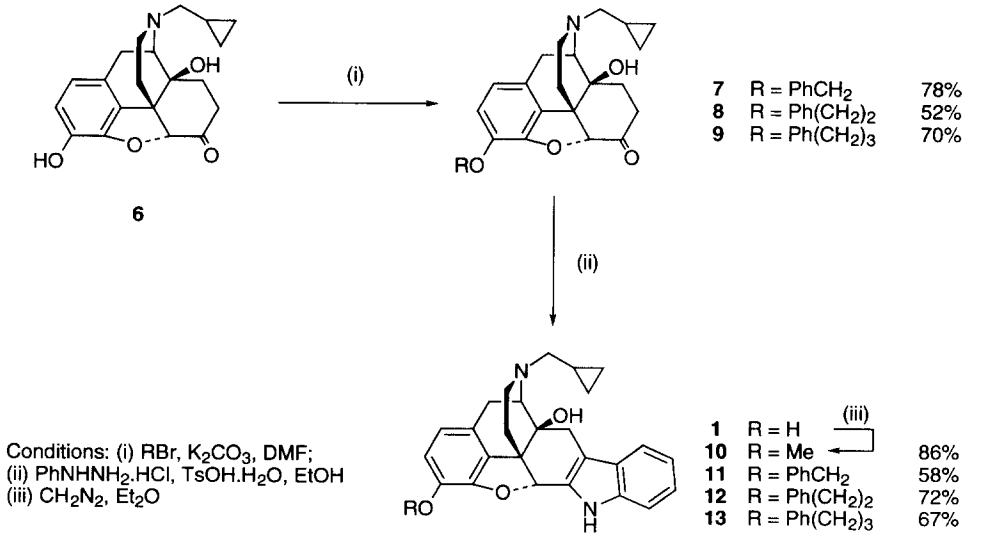
We considered that one method of improving the selectivity of the indolomorphinans would be to introduce groups into the opioid nucleus that are known to reduce μ affinity in other classes of opioids, with the aim of discovering a group that reduces μ and κ affinity, but not δ, thereby increasing δ binding selectivity. As part of these studies, we recently published a report showing that replacing the 3-phenol of **1** with an alkyl or aryl group greatly reduced both affinity and selectivity.[9] From this work, we suggested that an oxygen atom attached to C-3 is necessary for recognition at the δ receptor. However, there is conflicting data as to whether the free hydroxyl or the corresponding methyl ether gives rise to the greater selectivity. Portoghese[6] showed that masking the phenol of **1** as a methyl ether caused a decrease in δ antagonist potency and selectivity (MVD vs GPI),[10] whereas Loew showed that similar masking of the 3-phenol of **2** led to a greater decrease in μ affinity than δ, thereby increasing δ binding selectivity.[11] Our finding that masking the phenol of the moderately δ selective (+)-BW373U86 (**3**) as a methyl ether gave the highly selective SNC80 (**4**) (Figure 1),[12] together with our recent report that the 3-methyl ether/4-phenol substituted **5** (Figure 1) also possessed very high δ binding selectivity,[13,14] prompted us to reinvestigate the effect of a 3-ether substituent on binding and functional activity in the naltrindole series. Thus, a range of 3-ethers of **1** were prepared and evaluated in binding assays, and the most selective compound (**10**) evaluated in GTPγS functional assays.

Chemistry

A range of aryl alkyl ethers (**7**, **8**, and **9**) of **6** were prepared by reaction of **6** with the relevant aryl alkyl bromide and K_2CO_3 in DMF. The three ketones were converted into the corresponding indoles (**11–13**) by treatment with phenylhydrazine.HCl and $TsOH.H_2O$ in EtOH at reflux (Scheme 1). Methyl ether **10**[6] was prepared by the treatment of **1** with diazomethane. With the exception of **11**, the indoles were converted into water soluble salts,[15] and binding assays (Table 1) and GTPγS functional assays (Table 2) were performed as previously described.[9,13]



Scheme 1. Synthesis of 3-Ether Analogs of Naltrindole

Results

Table 1. Binding affinities of the 3-ether analogs of naltrindole

	K_i (nM) ± SEM					
	μ[a]	δ[b]	κ[c]	μ/δ	salt	mp
1[d]	27 ± 1.25	0.22 ± 0.05	30.4 ± 3.6	120		
10	2510 ± 510	6.57 ± 1.15	3911 ± 287	380	fumarate	170–173 °C[e]
11	396 ± 55	103 ± 6	728 ± 54	4	freebase	143–4 °C
12	>6250	1044 ± 121	>7042	7	oxalate	176–8 °C (dec)
13	>6250	99 ± 6	>5319	54	HCl	190–2 °C (dec)

[a]Displacement of [3]H]DAMGO; [b]Displacement of [3]H]DADL; [c]Displacement of [3]H]U69593; [d]Data from reference 9; [e]Lost solvent of crystallization to give an amorphous solid, which darkened with increasing temperature.

Table 2. Inhibition of opioid agonist stimulated [^{35}S] GTPγS binding

	Apparent Functional K_i (nM ± SD)			
	μ[a]	δ[b]	κ[c]	μ/δ
10	411 ± 53	9.0 ± 1.4	1760 ± 883	45
1[d]	3.20 ± 0.20	0.062 ± 0.006	8.85 ± .082	52

[a]Inhibition of DAMGO; [b]Inhibition of SNC80; [c]Inhibition of U69593, [d]Data from reference 13.

Analysis of these data indicates that masking the 3-phenol of naltrindole as an ether leads to a reduction in affinity at all three opioid receptor sites. However, the methyl ether **10** showed a greater reduction at μ and κ than at δ (three- and fourfold, respectively), thereby giving a ligand of improved binding selectivity (μ/δ = 380, κ/δ = 590). Although the aryl alkyl ether analogs generally possessed very poor affinity, these data show that greatest μ and κ affinity occurs with the 3-benzyl substituent (**11**) and that both benzyl and phenylpropyl substituents (**11** and **13**) lead to higher δ affinity than a phenethyl (**12**). In functional assays, there is an almost equal loss in antagonist potency at all three opioid receptors compared to naltrindole, leading to a compound of similar selectivity, but of greatly reduced potency.

Discussion

A 3-phenolic group is usually considered essential for high activity at opioid receptors. Indeed, the masking of the 3-phenol of naltrindole as a methyl ether led to a decrease in both affinity and antagonist potency at all three sites, but, in binding assays, the decrease at both μ and κ was greater than at δ, resulting in a threefold increase in δ selectivity. Thus, the binding is consistent with the work of Loew[11] and the SAR seen in the SNC80 series,[12] and the functional assays are consistent with Portoghese,[6] who showed that this same compound possessed poor δ antagonist potency and selectivity in functional assays. This work confirms that binding and functional data for these compounds appear not to correlate. This apparent discrepancy is actually in accord with our own findings with the 3-methoxy/4-phenolic compound **5**, which displayed excellent δ selectivity in binding assays (δ K_i = 7 nM; μ/δ = 1900), but possessed poor δ activity in MVD.[13] This suggests that for recognition, the δ receptor can tolerate changes in the A-ring to a greater extent than the μ receptor in the naltrindole series. However, masking the phenol as a methyl ether leads to poor activity in functional assays. Although the reason for this difference is

not known, it is clear that care must be taken when evaluating analogs of naltrindole with single digit nanomolar δ affinity. The effect of introducing an aryl alkyl ether group served to reduce affinity at all three receptors to a great extent, giving ligands of similar affinity to the 3-alkyl and 3-aryl analogs.[9] This suggests that a large lipophilic group attached to C-3 is very detrimental to binding and dominates over any aid to binding through hydrogen bonding from the receptor to the ether oxygen. Increasing the alkyl chain length reduced affinity at both μ and κ, whereas affinity at δ was similarly lost on moving from benzyl to phenethyl, but was regained on moving to phenylpropyl giving a ligand (**13**) of moderate selectivity. This suggests that a phenyl group three atoms removed from the 3-position occupies a position most detrimental to δ binding in the 3-ether series.

Conclusions

Masking of the 3-phenol of naltrindole as an ether gave rise to a reduction in affinity at all three opioid sites, however for the methyl ether the reduction at μ and κ was greater than at δ, giving a ligand of enhanced δ selectivity demonstrating that a 3-phenol is not required for high δ binding selectivity. The fact that this compound showed poor activity in functional assays[6] underscores the inconsistencies that exist between binding and functional assays.

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15. Freebase **11** was dissolved under the assay conditions by the addition of 1 equivalent of HCl. All spectra were consistent with the assigned structures and all novel compounds gave satisfactory microanalyses (CHN) within ±0.4%.