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3-Hydroxy-4-methoxyindolomorphinans as delta opioid selective ligands

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Abstract

Previous studies showed that 4-hydroxy-3-methoxyindolomorphinans had variable delta opioid affinity and selectivity. Herein we show that the 3,4-dimethoxy analogs possessed similar low affinity, whereas the 3-hydroxy-4-methoxy analogs showed excellent delta opioid affinity and selectivity comparable with the parent indolomorphinans.

In an attempt to improve the selectivity of the delta opioid indolomorphinans naltrindole (**1**) and oxymorphindole (**2**),¹ we previously showed that the corresponding 4-hydroxy-3-methoxyindolomorphinans (such as **3** and **4**) had widely differing selectivity over mu opioid receptors, with some being very selective and others possessing poor selectivity,² consistent with studies by others with similarly substituted opioids.³ The differences in affinity at delta receptors and selectivity over mu receptors compared to the indolomorphinans may be due to the presence of the 4-hydroxyl, the lack of a 3-hydroxyl, or the fact that modeling studies showed that opening the 4,5-bridge caused a shift in the relative position of the indole.² In addition, the 4-hydroxyl compounds proved prone to rapid oxidation and suffered from poor aqueous solubility potentially complicating the pharmacological data. Thus, for purposes of rational drug design and inclusion in our developing predictive pharmacophore model,⁴ aqueous soluble analogs of **3** and **4** are required which are less prone to oxidation and only have one functional group changed from the parent indolomorphinans **1** and **2**.

In order to remove the problems with oxidation the 4-hydroxyl was masked as a methyl ether to give 3,4-dimethoxyindolomorphinans (**6**, **8**) and formal 3-O-demethylation was envisioned to yield 3-hydroxy-4-methoxyindolomorphinans (**7**, **9**) which would be directly compared to the 3-hydroxy substituted parents **1** and **2**. A recent publication by Neumeyer focused on the similar class of 4-unsubstituted 3-hydroxyindolomorphinans (**5**) showing good affinity at delta opioid receptors,⁵ prompted us to publish our findings. A similar chemical manipulation on cyprodime led to a great increase in affinity at opioid receptors,⁶ lending strength to the hypothesis that 3-hydroxy-4-methoxyindolomorphinans would have high affinity, and the more exposed 3-hydroxyl was anticipated to allow greater aqueous solubility.⁷

The 3,4-dimethoxymorphinans were prepared as previously described utilizing reductive opening of the 4,5-bridge followed by 4-O-methylation,⁷ and converted to the indolomorphinans (**6**, **8**) (Figure 2) through standard Fisher indole conditions.² We previously showed that attempted selective demethylation of the unhindered 3-methoxyl over the 4-methoxyl in the morphinans series only gave 4-demethylation with L-Selectride due to

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coordination with the 6-oxygen function.⁷ Selective demethylation with L-Selectride was therefore attempted on dimethoxyindolomorphinan **7** which has a 6-nitrogen rather than an oxygen, but 4-O-demethylated product **4** was again obtained. The desired compounds were therefore prepared via the method of Schmidhammer,⁶ modified through the use of TMS-CHN₂ for the 4-O-methylation reaction.⁷ Standard Fisher indole formation conditions gave the desired products (**7**, **9**). All compounds were converted to HCl salts,⁸ and evaluated in competition assays at opioid receptors by the Drug Evaluation Committee following their standard assays,⁹ and the results are shown in Table 1.

No issues with solubility or oxidation when in solution were noted with the new compounds. As shown in Table 1, protecting the 4-hydroxyl as a methyl ether yielded no significant difference in the *N*-cyclopropylmethyl series, but did lead to a 5-fold increase in delta affinity in the *N*-methyl series (**8**). However, as anticipated, both series still displayed only moderate delta affinity. The 3-hydroxy-4-methoxy analogs (**7**, **9**) gave the expected increase in affinity at both mu and delta receptors to give high affinity, delta selective ligands. This shows that the position of the indolic group in the 4,5-opened analogs is appropriate for delta opioid affinity and selectivity. Compounds **7** and **9** had similar affinity at delta receptors as the corresponding compounds of Neumeyer,⁵ but displayed increased delta opioid selectivity. The current compounds differ from Neumeyer's compounds (**5**) by both a 4-methoxyl and a 14-hydroxyl group, and further studies are underway to determine which substituent is responsible for the difference in selectivity between the series to allow meaningful application to the predictive pharmacophore model.

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Figure 1.
Previously reported indolomorphinans

Figure 2.
4-O-Methyl indolomorphinans

Table 1

Binding affinities at opioid receptors (n=3)

	K_i (nM) $\pm$ SEM			
	μ^a	δ^b	κ^c	μ/δ
Naltrindole.HCl (1) ^d	27.0 $\pm$ 1.3	0.22 $\pm$ 0.13	30.4 $\pm$ 3.6	123
3 ^d	1850 $\pm$ 382	21.8 $\pm$ 7.0	3160 $\pm$ 205	85
6	1720 $\pm$ 140	19.0 $\pm$ 2.0	1440 $\pm$ 90	90
7	58.0 $\pm$ 19	0.40 $\pm$ 0.3	79.0 $\pm$ 22	145
Oxymorhindle.HCl (2)	105 $\pm$ 23	0.9 $\pm$ 0.2	515 $\pm$ 35	115
4 ^d	2850 $\pm$ 25	218 $\pm$ 33	>6700	13
8	7590 $\pm$ 660	41.0 $\pm$ 4.0	>7000	185
9	474 $\pm$ 220	4.50 $\pm$ 0.5	582 $\pm$ 160	105

^aDisplacement of [³H]-DAMGO^bDisplacement of [³H]-p-CI-DPDPE; (recombinant rat μ and δ receptors expressed in C6 rat glioma cells)^cDisplacement of [³H]-U69,593; (recombinant human κ receptors expressed in CHO cells).^dPreviously reported:² δ displacement using [³H]DADLE.