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5′-Halogenated analogs of oxymorphindole

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Abstract—The presence of a 6,7-fused indole group in the indolomorphinans was considered to be responsible for the delta opioid selectivity for this class of ligands. Herein is shown that 5′-halogenated analogs of oxymorphindole are opioids with little selectivity for delta receptors over mu opioid receptors.

The delta opioid selective antagonist naltrindole (**1**)[1] has been employed to show that selective delta opioid antagonists have broad clinical potential.[2,3] However, increasing evidence indicates that delta opioid antagonists modulate the effects of mu opioid agonists,[4] including the interesting finding that naltrindole prevents the development of tolerance and dependence to morphine.[5,6] Subsequent studies with peptidic ligands showed that a dual profile of mu opioid agonism and delta opioid antagonism gave rise to mu opioid-mediated antinociception without the development of tolerance or dependence.[7] Ananthan extended these studies to a non-peptidic dual profile ligand **2**, but the results are difficult to interpret due to low mu opioid agonist efficacy and potency, and the need to administer the drug icv.[6,8]

As part of our studies into developing non-peptide ligands with a dual profile of potent mu opioid agonism and delta opioid antagonism as potential analgesics lacking tolerance and dependence, we previously reported that the presence of a 6,7-fused indolic group does not necessarily result in delta opioid selectivity.[9] This is in contrast to accepted structure–activity relationships, where the indole is considered responsible for delta selectivity.[2] As a continuation of these studies to develop indole-containing dual mu/delta opioid ligands, we focused on analogs of the 17-methyl indolomorphinans with halogen substituents on the indolic ring. This focus was chosen based on the facts that 17-methyl opioids tend to display mu opioid agonism[10] and the compound of Ananthan et al.[8] possessed halogen substitution on an aromatic ring which can be considered equivalent to the indole (Fig. 1).

Oxymorphone was converted to the desired products (**3**–**7**) in good yield through standard indole formation with the appropriate halogenated phenylhydrazine[11] and were converted to the HCl salts.[12] Pharmacological assays were performed by the Drug Evaluation Committee using their standard procedures,[13] and the results are shown in Table 1.

Consistent with previous studies,[1,14] oxymorphindole (**3**) showed excellent affinity and selectivity for delta receptors. The introduction of 5′-halogen substituents reduced delta opioid affinity between 3- and 10-fold, and increased mu opioid affinity for all compounds. This leads to compounds with greatly reduced preference for delta opioid receptors. Interestingly, as the size of the halogen increased, the effect on binding affinity and selectivity was relatively small with the 5′-iodo substituted analog (**7**) exhibiting similar binding pharmacology to the 5-fluoro substituted analog (**4**). This suggests that electronic contributions dominate over steric and lipophilic contributions for binding. The lack of good selectivity between mu and delta opioid receptors is the desired result for the development of dual profile ligands, but all compounds were shown to be inactive in mouse antinociceptive assays in which full mu agonists would be detected (tail flick, hot plate, and antiwrithing assays), and also inactive as morphine (mu) antagonists (tail flick vs morphine). GTPγS functional assays were performed on the 5′-fluoro substituted **4**, and showed low potency and efficacy as a mu opioid

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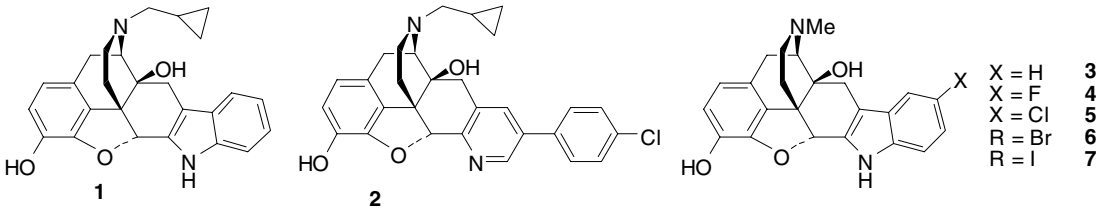

Figure 1. Delta opioid selective ligands.

Table 1. Binding affinities at opioid receptors and mouse antinociceptive data ($n = 3$)

	K_i (nM) ± SEM				Mouse[d]
	Mu[a]	Delta[b]	Kappa[c]	Mu/delta	
OMI (**3**)	105 ± 23	0.9 ± 0.2	515 ± 35	115	Inactive
F (**4**)	21 ± 4.7	2.3 ± 0.1[e]	310 ± 43	9	Inactive
Cl (**5**)	47 ± 9.9	5.1 ± 1.2	360 ± 36	9	Inactive
Br (**6**)	71 ± 23	8.6 ± 0.4	250 ± 45	8	Inactive
I (**7**)	66 ± 13	3.8 ± 0.3	160 ± 46	17	Inactive

[a] Displacement of ^{3}[H]-DAMGO.
[b] Displacement of ^{3}[H]-*p*-Cl-DPDPE.
[c] Displacement of ^{3}[H]-U69,593 from cloned receptors.
[d] Mouse antinociceptive data in tail flick, hot plate, antiwrithing, and tail flick versus morphine assays, as described (maximum dose, 30 mg/kg).[13]
[e] GTPγS efficacy data: mu EC_{50} = 1080 nM; 34% stimulation. Delta EC_{50} = 16 nM; 16% stimulation.

agonist, yet retained potent low delta opioid efficacy. This result is consistent with the mouse data, suggesting that the low mu efficacy of the compounds is responsible for their lack of activity in mice.

This work shows that 5′-halogen substitution leads to less delta selective ligands. Studies are currently underway to realize their potential for development into compounds with the desired profile of mu agonism and delta antagonism.

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