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Derivatives of 17-(2-Methylallyl)-substituted Noroxymorphone: Variation of the Delta Address and Its Effects on Affinity and Selectivity for the Delta Opioid Receptor

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Abstract—In an effort to establish the importance of the *N*-(2-methylallyl) substituent in the noroxymorphone series, several derivatives have been synthesized, retaining that *N*-substituent and modifying the δ address moiety. A few compounds showed moderate binding affinity and selectivity for the δ receptor; none displayed a pharmacological profile as exceptional as *N*-(2-methylallyl)noroxymorphindole. A second study showed that 3-*O*-methylation of all derivatives decreases binding affinity. The present results indicate that only a combination of the *N*-(2-methylallyl) group and an indole δ address provided high selectivity for the δ receptor. Published by Elsevier Science Ltd.

Naltrindole (NTI, **1**)[1] (Fig. 1) exhibits very high affinity for the opioid δ-receptor and is moderately selective (μ/δ affinity ratio = 120).[2] Since δ antagonists are reported to be potentially useful in the treatment of cocaine abuse,[3,4] and in the suppression of tolerance and dependence,[5] there is broad interest in new δ receptor antagonists more selective than NTI. We have recently reported the development of a new opioid ligand, *N*-(2-methylallyl)oxymorphindole (TU753, **2**), that exhibits high affinity, high antagonist potency, and impressively high selectivity for the δ receptor, proving that minor modifications of the *N*-substituent in NTI can lead to a significantly altered profile.[6] Thus, **2** is more selective than NTI in binding assays (see Table 1) and as an antagonist in the GTPγS assay and, as well, in smooth muscle (MVD/GPI) functional assays (NTI: μ/δ selectivity = 90; **2**: μ/δ selectivity = 2200).[6,7] In an effort to establish whether the *N*-methylallyl substituent was the determining factor for the biological activity of the molecule, we synthesized several derivatives of **2** by modifying the 'δ address', the part of the molecule that is considered unique for this subtype and, which functions to enhance the affinity of the ligand without contributing to signal transduction.[8]

δ address moieties have been studied extensively on NTI.[9] We decided to choose representative structures among a variety of referenced molecules bearing interesting pharmacological profiles, but also wanted to provide a broad range of different chemical entities that can be obtained in only one or two steps from the same starting material. Emphasis was hence laid on rigid (fused, conjugated or spiro-annulated) carbocycles and heterocyles. The moieties (*E*)-benzylidene, spiroindane, benzofuran and 3-(*p*-chlorophenyl)pyridine scaffolds were chosen for their high-affinity binding and δ-selectivity profile in the *N*-cyclopropylmethyl series.[9,10] A pyrazole was also prepared using a (dimethylamino)-methylene substituent, which will allow the future preparation of other *N*-heterocycles. The pyrazole moiety, lacking a necessary extension into the space that is crucial for the lipophilic δ address domain, served for comparison studies. Since several reactions required

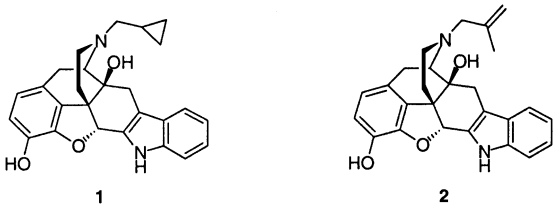

Figure 1. Structures of NTI and TU753.

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protection of the phenolic group (position 3), an *O*-methyl series was also synthesized and compared to the OH compounds.

Noroxymorphone (**3**) was *N*-alkylated with 3-bromo-2-methylpropene to afford *N*-(2-methylallyl)oxymorphone (**4**), the starting material for all following conversions (Scheme 1).

The indole (**2**), benzofuran (**6**), pyridine (**7**), and benzylidene (**8**) derivatives were prepared as suggested in the literature.[6,10–12] The spiroindane (**15**)[13] and pyrazole (**14**)[14] derivatives could not be directly obtained from **4**, but required phenolic *O*-protection to give **13**, which was accomplished by introducing a methyl group that could be cleaved afterwards with BBr_3.[14] All other compounds were *O*-methylated correspondingly.[15] It is worthy of note that step (iv) in Scheme 1, the pyrazole synthesis, required employment of allyl alcohol instead of the methanol used in the referenced literature.[14] It was observed that in the absence of unsaturated solvents, the hydrazine reagent would reduce the *N*-methallyl double bond entirely under the chosen conditions, probably by formation of a highly reactive diimide species. Allyl alcohol was an appropriate solvent to efficiently inhibit the reduction,[16] thus allowing complete conversion to the desired pyrazole (**10**). Whereas the indole (**5**), benzofuran (**6**), and pyridine (**7**) derivatives could be *O*-methylated easily with TMS-diazomethane,[14] this method was not applicable to the benzylidene compound (**8**). Experimental data suggested that the α,β-unsaturated ketone underwent cycloaddition with diazomethane[17] prior to or concomitantly with, *O*-methylation. Instead, phenyltrimethylammonium chloride was used, affording methyl derivative **11** in good yield.[18]

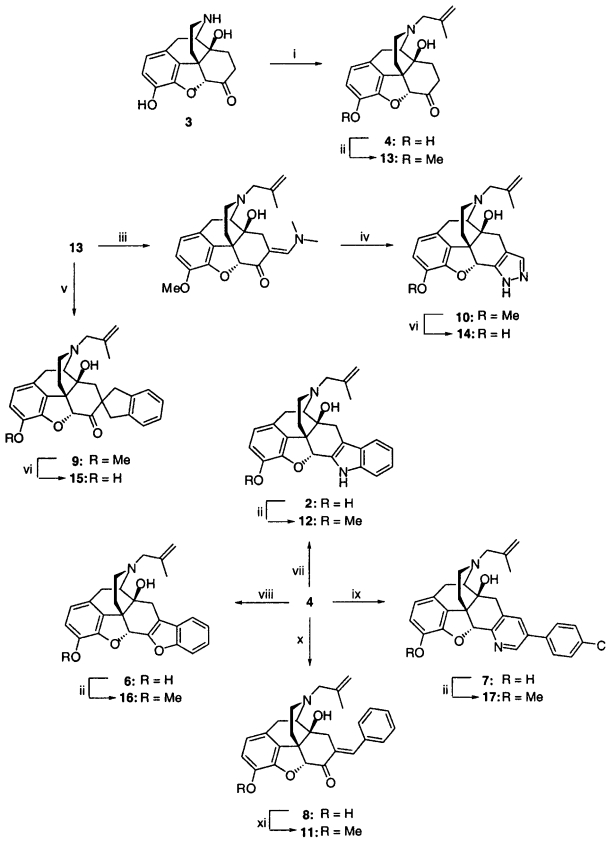
Radioligand binding assays at μ, κ, and δ opioid receptors were performed as previously described.[6] The affinities of all tested substances, as well as those of compounds **1** and **2**, are summarized in Table 1. Thus, moderate affinity for the δ receptor was observed in both benzofuran compounds, **6** ($K_i = 8.2$ nM, $\mu/\delta = 160$, $\kappa/\delta = 71$), and—to a lesser extent—its methylated derivative, **16** ($K_i = 44$ nM, $\mu/\delta = 140$, $\kappa/\delta = 230$). The latter had selectivity comparable to NTI. With the exception of **15** and **16**, all *O*-methylated compounds showed poor affinity and/or selectivity for the δ receptor. Compounds **7** and **15** exhibited moderate binding affinity and selectivity for the δ receptor, and the pyrazole derivative **14**, being devoid of a δ address moiety, unsurprisingly showed affinities for all three receptors.

Table 1. Opioid receptor binding affinity and selectivity of NTI (**1**), TU753 (**2**) and its δ address modified analogues **6**–**17**

	K_i (nM) (SEM)			Selectivity ratio	
	μ[a]	δ[b]	κ[c]	μ/δ	κ/δ
1[d]	27 ± 1.3	0.22 ± 0.05	30 ± 3.6	120	140
2[e]	7900 ± 820	4.7 ± 0.9	3800 ± 220	1700	810
6	1300 ± 40	8.2 ± 1.0	580 ± 30	160	71
7	> 6000	16 ± 1.0	300 ± 20	> 380	19
8	4500 ± 320	210 ± 20	4500 ± 520	21	21
9	> 6000	> 7200	> 7000	—	—
10	> 6000	2400 ± 200	3100 ± 220	> 2	1
11	> 6000	3400 ± 290	> 7000	> 1	> 2
12	> 6000	500 ± 90	> 14000	> 12	> 28
14	140 ± 9.0	40 ± 3.0	38 ± 3.0	4	1
15	2000 ± 230	41 ± 6.0	1000 ± 90	49	24
16	> 6000	44 ± 5.0	> 10000	140	230
17	> 6000	260 ± 30	3200 ± 350	23	12

[a]Displacement of [^{3}H]DAMGO.
[b]Displacement of [^{3}H]DADLE.
[c]Displacement of [^{3}H]U69,593.
[d]See ref 19.
[e]See ref 6.

The present study indicates that, although *N*-(2-methylallyl)noroxymorphindole has been shown to be more selective than its *N*-CPM analogue,[6] the *N*-(2-methylallyl) substituent does not appear to provide the same selectivity in our molecules with other δ address moieties. Rather, binding affinity and selectivity for the δ receptor in the investigated compounds decreased remarkably, with the exception of benzofuran derivative **6**, which had a binding affinity similar to that of indole **2**. Furthermore, the results obtained imply that 3-*O*-methylation is detrimental to either or both δ affinity and selectivity. It may be concluded that the unique



Scheme 1. (i) 3-Bromo-2-methylpropene, $NaHCO_3$, DMF, 80 °C, 2 h, 85%; (ii) TMS–CHN_2, Et_3N, MeOH/MeCN, 25 °C, 3 h, 93%; (iii) DMF dimethylacetal, 110 °C, 6 h, 71%; (iv) $H_2NNH_2 \cdot H_2O$, 2-propenol/H_2O, 110 °C, 2 h, 99%; (v) α,α′-dibromo-*o*-xylene, LiHMDS, 12-crown-4, THF, −78→60 °C, 48 h, 55%; (vi) BBr_3, CH_2Cl_2, 0→25 °C, 3 h, 83%; (vii) $PhNHNH_2 \cdot HCl$, MeOH/3 N HCl, 80 °C, 12 h, 97%; (viii) $PhONH_2 \cdot HCl$, $MeSO_3H$, EtOH, 78 °C, 18 h, 83%; (ix) *p*-$ClC_6H_4CH(CHO)_2$, NH_4OAc, AcOH, 110 °C, 48 h, 55%; (x) PhCHO, AcOH/pyrrolidine/toluene, 25 °C, 96 h, 86%; (xi) $PhNMe_3Cl$, K_2CO_3, DMF, 80 °C, 2 h, 82%.

pharmacological profile of TU753 (**2**) results from a combination of the *N*-2-methylallyl group and the indole moiety, and that the absence of either of them leads to a deterioration of that profile.

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