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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 3-SUBSTITUTED 3-DESOXYNALTRINDOLE DERIVATIVES

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Abstract: The 3-unsubstituted and substituted analogs of naltrindole (NTI) were synthesized using palladium-catalyzed transformations, and their binding affinity to opioid receptors was determined. Although the 3-desoxy analog showed comparable δ selectivity with that of NTI, all of the novel compounds possessed low affinity for δ receptors indicating the important role of the 3-oxygen atom of NTI for interaction with δ-opioid receptors.
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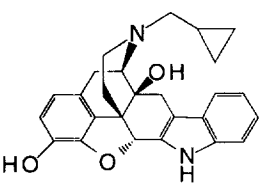
In recent years, mu (μ), delta (δ), and kappa (κ) opioid receptors have been cloned and sequenced.[1] It is known that each receptor mediates distinct pharmacological events,[2,3] and δ opioid receptor antagonists have been suggested to be potentially useful for the treatment of drug abuse, alcoholism, as appetite suppressants, and to block the rewarding brain stimulation response induced by cocaine.[4,5] It has also been shown that δ receptor agonists produce some antinociception with minimal undesirable morphine-like side-effects.[6-9] From these studies, it is apparent that more selective and potent nonpeptidic δ agonists and antagonists would be extremely useful to further our knowledge of the biological effects mediated by the δ-receptor system.

Naltrindole (**1**) (NTI) is a nonpeptide that has been found to have high affinity for the δ-opioid receptor and is reasonably selective for that receptor.[10] It acts as a δ opioid receptor antagonist and kappa agonist.[11] NTI served as the model for the modification of a "message-address" concept[12,13] in which the conformationally constrained indolic benzene was postulated to function as the address portion, affording ligand selectivity to the δ receptor.[10]



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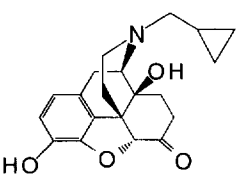

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NTI shows greater δ selectivity than naltrexone (**2**) because of its reduced affinity for μ and κ receptors and the higher δ affinity conferred by the indole moiety; NTI is now commonly used as a pharmacological tool in opioid research. Many attempts have been made to develop more selective and higher affinity ligands for the

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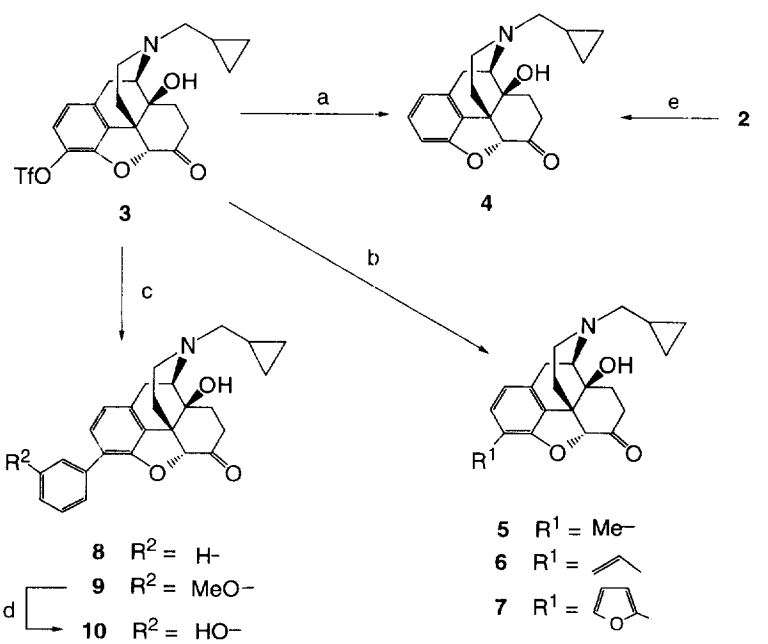
δ receptor by modification of the indole area of NTI,[14-17] and of the 14-hydroxyl group in the molecule.[18] We were led to explore the structure–activity relationships of alkyl and aryl substituents at the 3-position in 3-desoxynaltrindole because of our finding that 3-desoxynaltrindole, a compound without the 3-hydroxyl group, had μ/δ selectivity comparable with NTI. Its affinity for the δ opioid receptor was, however, considerably less than NTI (**11**, Table 1). There is, insofar as we are aware, no *a priori* way of discerning whether the structure–activity relationships applicable to μ opioid receptor ligands are necessarily pertinent to δ opioid receptor ligands. Thus, as part of our studies on the design and synthesis of ligands with higher affinity and greater selectivity for the δ opioid receptor, we decided to investigate the effect of replacing the 3-hydroxyl group with various alkyl, alkenyl, and aryl substituents at the 3-position on the 3-desoxy aromatic ring of NTI (**12–17**) on receptor recognition and selectivity.

Chemistry

The target compounds (**11–17**) were obtained from the appropriately substituted morphinan-6-ones (Scheme 1, **4–10**) by the Fischer indole synthesis.

Scheme 1[a]

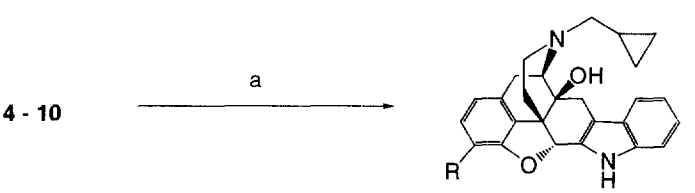


[a]Key: (a) Bu_3N, HCOOH, $Pd(PPh_3)_2Cl_2$, DPPP, DMF, 80 °C, 16 h, 68%; (b) Me_4Sn or R^1SnBu_3, $Pd(PPh_3)_2Cl_2$, LiCl, PPh_3, DMF, 120 °C, 0.5~6 h, 39~83%; (c) 3-$(R^2)C_6H_4B(OH)_2$, $Ph(PPh_3)_4$, LiCl, 2M Na_2CO_3, EtOH, DME, reflux, 4~6 h, 80~85%; (d) BBr_3, $CHCl_3$, rt, 15 min, 85%; (e) i. 5-Chloro-1-phenyl-1*H*-tetrazole, K_2CO_3, DMF, rt, 48 h; ii. H_2 (40 psi), Pd/C, AcOH, 35 °C, 5 h, 86%.

We introduced various substituents in the 3-position through a palladium-catalyzed reduction (Scheme 1, path a) or a cross-coupling reaction (Scheme 1, path b or c) of the trifluoromethanesulfonate (**3**, Scheme 1). The precursor for compound **11** (**4**) was also prepared (Scheme 1, path e) by hydrogenation of the tetrazoyl ether of naltrexone (**2**). The key intermediate **3**[19] was readily obtained from **2** by treatment with trifluoromethanesulfonic anhydride and triethylamine in dichloromethane (0 °C, 3 h, 76%). The conversion of **3** to the 3-deoxy analog (**4**) was perfomed by treatment with tributylamine and formic acid in the presence of bis(triphenylphosphine)palladium(II) chloride [$Pd(PPh_3)_2Cl_2$] - 1,3-bis(diphenylphosphino)propane (DPPP) as a catalytic system in DMF.[20,21] The palladium-catalyzed cross-coupling of **3** with tetramethyltin using conditions reported by Saá, *et al.*[22,23] for sterically hindered, electron-rich aryl triflates gave **5** in 83% yield.[24] Compounds **6** and **7** were synthesized by the cross-coupling with tributyl(vinyl)tin and tributyl(2-furyl)tin, respectively. On the other hand, the cross-coupling of **3** with trimethyl(phenyl)tin proceeded with limited success. The 3-aryl substituted compounds **8** and **9** were synthesized by palladium-catalyzed cross-couplings of the corresponding arylboronic acid with **3**.[25-27] Further, **9** was *O*-demethylated by treatment with boron tribromide[28] in chloroform to give **10**.

Finally, the conversions of **4–10** to the indole compounds (**11–17**) were easily perfomed by treatment with phenylhydrazine hydrochloride and *p*-toluenesulfonic acid monohydrate in refluxing ethanol (Scheme 2). All novel indole compounds showed 4 aromatic indole protons in the ^1H spectra (300MHz), in the range of δ 6.9–7.5.

Scheme 2[a]



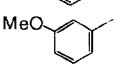
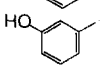
[a]Key: (a) $PhNHNH_2 \cdot HCl$, *p*-$TsOH \cdot H_2O$, EtOH, reflux, 1.5~6 h, 22~72%.

Results and Discussion

The affinities of the 3-unsubstituted and the various 3-substituted 3-desoxynaltrindole ligands, and a standard drug, NTI, for μ, δ, and κ opioid receptors were determined using radioligand binding assays (Table 1). Binding to μ opioid receptors from rat brain membranes was evaluated using [^{3}H][D-Ala^2,MePhe^4,Gly-ol^6]enkephalin[29] ([^{3}H]DAMGO), and to δ opioid receptors using [^{3}H][D-Pen^2,D-Pen^5]enkephalin[30] ([^{3}H]DPDPE) with 100 nM DAMGO to block μ receptors. Binding to κ receptors from guinea pig brain membranes was determined with [^{3}H](5α,7α,8β)-(-)-*N*-methyl-*N*-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-ylbenzene-acetamide[31] ([^{3}H]U69593).

Compound **11**, in which the 3-hydroxyl group of NTI has been removed, showed more than a 160-fold decrease in its affinity for all three opioid receptors, compared with NTI, and its δ selectivity (μ/δ>162, κ/δ=312), however, remained similar to that of NTI (μ/δ=124, κ/δ=140). Compounds with small alkyl substituents such as methyl (**12**) or vinyl (**13**) showed a further twofold loss in affinity over the unsubstituted compound **11**, and their δ selectivities were similarly reduced. The presence of an aromatic ring in the 3-position (**14–17**) was detrimental to interaction with any opioid receptor.

Table 1. Inhibition of Radioligand Binding to Rat Brain μ and δ Receptors and Guinea Pig Brain κ Receptors by Naltrindole and Its 3-Unsubstituted (**11**) and Substituted Analogs **12–17**, and Their Melting Points

Compound	R =	mp (°C) HCl salt	*Ki* (nM) ± SD		
			[^{3}H]DADLE (δ)	[^{3}H]DAMGO (μ)	[^{3}H]U69593 (κ)
11	H-	251-254	35 ± 1.5	> 5,682	10,903 ± 680
12	Me-	259-262	71 ± 8	> 5,682	> 6,803
13		> 260	61 ± 5	> 5,682	17,628 ± 2,443
14		> 255	959 ± 40	> 5,682	> 6,803
15		250-254	10,588 ± 835	> 5,682	> 6,803
16		237-243	> 6,667	> 5,682	> 6,803
17		> 260	1,605 ± 85	> 5,682	> 6,803
NTI (1)	HO-		0.217 ± 0.047	27 ± 1.25	30.4 ± 3.6

It has been previously noted that the 3-hydroxyl function is very important for high binding affinity to μ or δ opioid receptors in the NTI-like series,[14] or in the epoxymorphinan and related series of compounds. A 3-methoxy analog, in these classes of molecules, always appears to show lower δ or μ receptor affinity and, generally, less μ/δ selectivity. Clearly, elimination of the 3-hydroxyl and substitution at the 3-position with alkyl, alkenyl and aryl groups does not lead to compounds with improved affinity or selectivity, possibly due to either the steric effect of the bulky substituents (the affinity of the smaller, methyl and vinyl, analogs was higher than that of the bulkier ones), or their inability to hydrogen bond to the receptor, or both. We are currently synthesizing and exploring the SAR of different 3-substituted ether analogs of NTI to see whether a hydrogen bond acceptor moiety at the 3-position would improve affinity.

In conclusion, it was shown that palladium-catalyzed transformation is efficient for the synthesis of 3-substituted analogs of 3-desoxy NTI. Although the 3-desoxy analog **11** showed comparable δ selectivity with

NTI, all of the novel compounds possessed low affinity for δ receptors. These results indicate the important role of the oxygen atom in NTI for interaction with δ-opioid receptors.

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