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Selective κ-Opioid Antagonists Related to Naltrindole. Effect of Side-Chain Spacer in the 5′-Amidinoalkyl Series

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Abstract—The study of κ-opioid receptor function in vivo has been hampered by the limited choice of selective κ-antagonists. Recently discovered κ-antagonists have not yet been utilised in vivo. We here report the synthesis and in vitro evaluation of a new amidine derivative of naltrindole. It showed substantially greater κ-selectivity in binding assays than known analogues with shorter spacer in the amidine side chain. This indicates that in nor-BNI and related selective κ-antagonists, the second basic centre may not be ideally located.

Introduction

The effective study of receptor pharmacology requires the availability of a range of selective antagonists. In the opioid field there is only one commercially available selective κ-antagonist, nor-BNI (**1**). This dimer of naltrexone linked through a pyrrole spacer has been widely studied but when used in vivo it presents an undesirable pharmacokinetic profile with very slow onset and very long duration of action.[1] Though other selective κ-antagonists related to nor-BNI and naltrindole (NTI, **2**) have been reported,[2–4] their advantages over nor-BNI have not outweighed the relative inaccessibility so that they have not been used for in vivo studies. We aimed to synthesise derivatives of 5′-6′-pyrido-NTI (**4**) and for this required 5′-(2-aminoethyl)NTI (**3**) as a precursor. Since the amidine derivative (**5a**) had proved to have greater κ-antagonist selectivity than nor-BNI in smooth muscle preparations[3] it was decided to use **3** as a source of the homologue (**5b**). We here report its synthesis and in vitro pharmacological evaluation. In the displacement binding assay, **5b** was very much more selective for κ-opioid receptors than nor-BNI or **5a** but this superiority was not confirmed in the [^{35}S]GTPγS functional assay.

Synthesis

The synthetic route to **5b** is shown in Scheme 1. 4-Hydrazinobenzyl cyanide[5] was used in the Fischer-indole synthesis with naltrexone (**7**) to give **8** which was reduced ($RaNi/H_2$) to the aminoethyl derivative (**3**). This was converted into the butyl amidine (**5b**) by reaction with ethyl pentanimidate hydrochloride.[6] The product was isolated by preparative TLC on silica gel plates (eluant DCM:MeOH:NH_4OH, 84:15:1).

Pharmacology

The amidine (**5b**) and precursor amine (**3**) were evaluated in binding assays in chinese hamster ovary (CHO) cells transfected with cloned human receptors.[7] The displaced radioligands were [^{3}H]-DAMGO (μ), [^{3}H]-Cl-DPDPE (δ) and [^{3}H]-U69593 (κ). The results are shown in Table 1. The new ligands displayed high affinity for κ-receptors and substantial selectivity. The primary amine (**3**) was less κ-selective than nor-BNI but the amidine was much more selective than either nor-BNI or the equivalent amidinomethyl derivative (**5a**).

Functional opioid activity was determined by stimulation of [^{35}S]GTPγS in cloned human opioid receptors transfected into CHO cells (Table 2).[7,8] Neither **3** nor **5b** stimulated [^{35}S]GTPγS for any type of opioid receptor but were antagonists of selective agonists, DAMGO,

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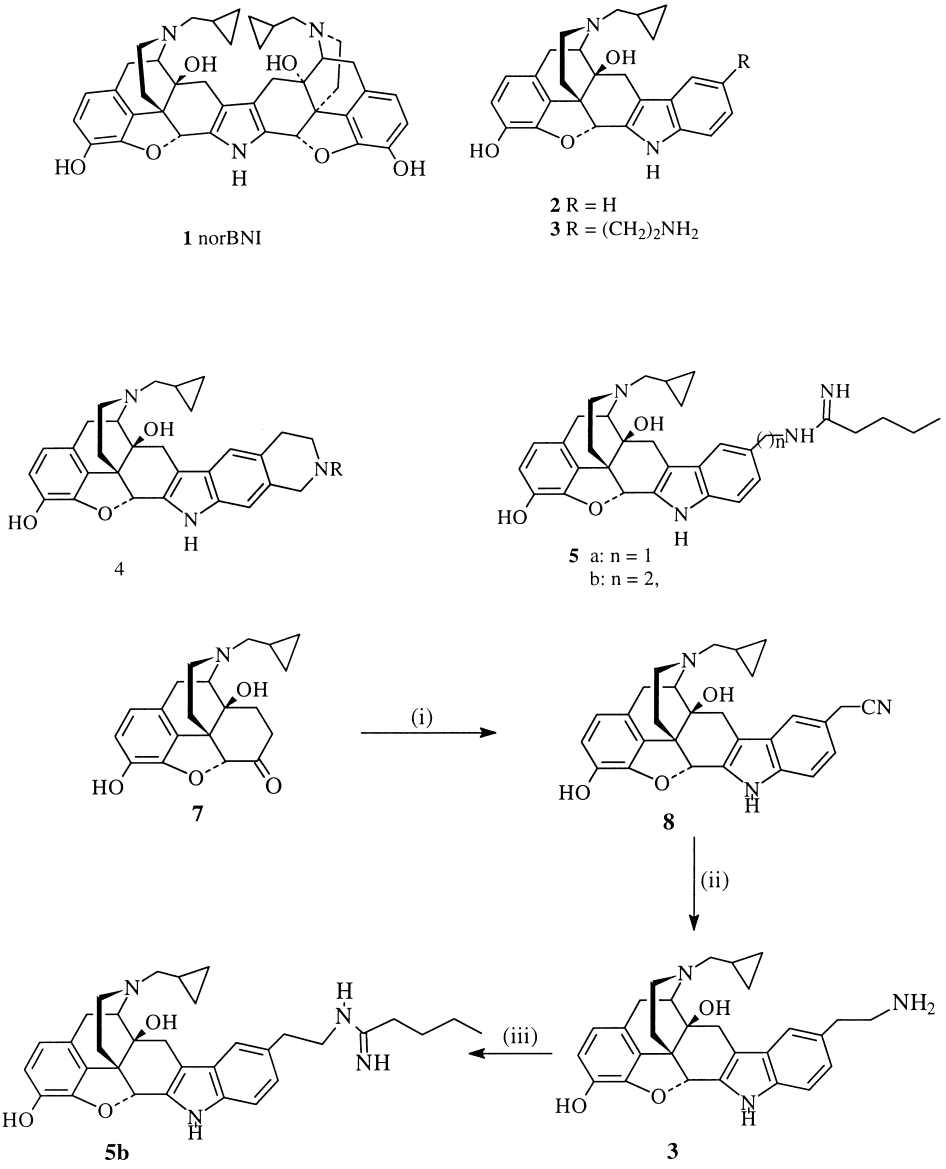

Scheme 1. (i) 4-Hydrazinobenzyl cyanide, HOAc, 1.5 h, 46%; (ii) RaNi/H_2, EtOH, NH_3, 4 h, 55%; (iii) $CH_3(CH_2)_3C(NH)OCH_2CH_3$·HCl, EtOH, N_2, 48 h, 20%.

Cl-DPDPE and U69593 for μ-, δ- and κ-receptors respectively. The K_e value for **3** as a κ-receptor antagonist was an order of magnitude greater than its K_i in the binding assay and it was also more selective for the κ-receptor in the functional assay. The κ-antagonist potency of the amidine (**5b**) was equivalent to its κ-binding affinity but potency as a μ and δ antagonist was substantially higher than its binding affinity for these receptors, resulting in very much reduced κ-selectivity. For nor-BNI the K_e at the κ-receptor was approximately five-fold higher than its K_i in the binding assay and unlike amidine **5b** its κ-selectivity was substantially greater in the functional assay than in the binding assay.

Table 1. Affinities in opioid receptor displacement binding assays

Ligand	K_i (nM)±SEM				
	μ	δ	κ	μ/κ	δ/κ
3	29.6±2.7	28.2±3.5	1.08±0.5	27	26
5b	219.2±84.5	38.2±4.9	0.30±0.2	730	127
5a[a]	3.5	5.5	0.061	57	90
1 (nor-BNI)	21.0±5.0	5.7±0.9	0.2±0.05	105	28

[a]Taken from Ref. 3 in guinea pig brain membranes, confidence limits not given. All values are the average of two experiments each carried out in triplicate. Displaced ligands were [^{3}H]DAMGO (μ), [^{3}H]Cl-DPDPE (δ), [^{3}H]U69,593 (κ).

Discussion

In binding assays the new pentylamidine (**5b**) showed much higher κ-selectivity than nor-BNI and its close analogue (**5a**). This suggests that the second basic centre in nor-BNI and **5a** is not optimally situated for κ-selectivity in application of the message-address principle.[9,10] However, the considerably lower κ-antagonist selectivity of **5b** in the [^{35}S]GTPγS assay together with the low yield in its synthesis suggests that a serious alternative to nor-BNI as the κ-antagonist of choice has still to be found.

Table 2. Opioid receptor antagonist activity in the [^{35}S]GTPγS assay[a]

Ligand	K_i (nM)±s.e.m				
	μ	δ	κ	μ/κ	δ/κ
3	17.4±1.2	3.79±0.49	0.12±0.05	*145*	32
5b	5.33±0.63	3.31±0.54	0.17±0.05	31	20
1 (nor-BNI)	18.9±1.8	4.42±0.38	0.039±0.004	484	113

[a]Each value represents the average of two experiments each carried out in triplicate. Standard agonists used were DAMGO (μ), Cl-DPDPE (δ), U69,593 (κ).

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