# A Remarkable Change of Opioid Receptor Selectivity on the Attachment of a Peptidomimetic κ Address Element to the δ Antagonist, Natrindole: 5′-[($N^2$-Alkylamidino)methyl]naltrindole Derivatives as a Novel Class of κ Opioid Receptor Antagonists

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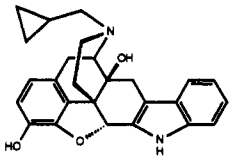
*Received November 11, 1992*

The selectivities of the prototypical δ and κ opioid receptor antagonists, naltrindole (1, NTI) and norbinaltorphimine (2, norBNI) have been attributed to the



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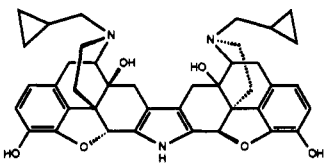

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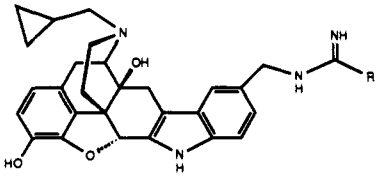
presence of nonpeptide "address" mimics which bear a functional relationship to key elements in the putative δ and κ addresses of enkephalin and dynorphin, respectively.[1,2] Accordingly, the design of 1 employed a model that envisaged the Phe[4] phenyl group of enkephalin as a critical part of the δ address.[3] Similarly, the address element conferring selectivity in 2 has been suggested to be a basic function that mimics the guanidinium moiety of Arg[7] in dynorphin.[4] Here we report on a dramatic and unprecedented change of opioid receptor selectivity from δ to κ, simply by the modification of NTI with a basic group which functions as a κ address, using the above model. This molecular modification affords a new class of highly selective κ opioid receptor antagonists (3–5).

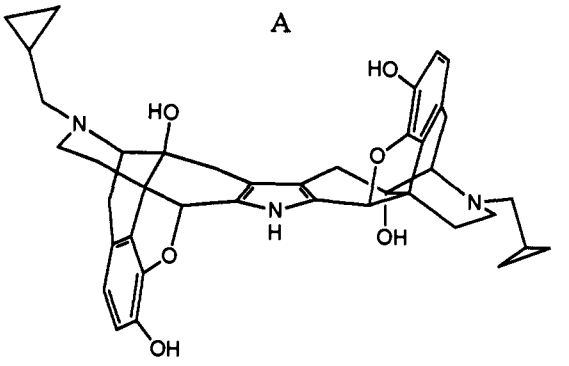


3, R = $CH_2CH_3$

4, R = $(CH_2)_2CH_3$

5, R = $(CH_2)_3CH_3$

The design rationale for the series involved the attachment of a basic group to the 5′ position of NTI in order



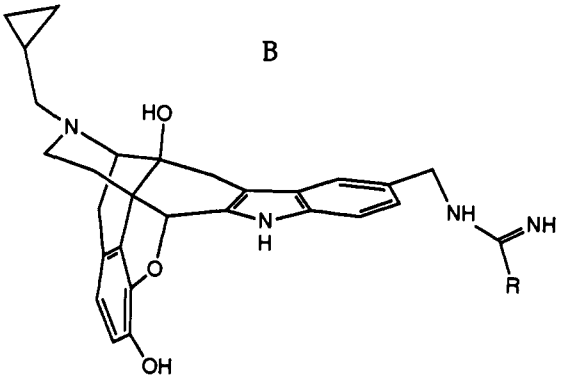


**Figure 1.** Comparison of a 3-dimensional representation of norbinaltorphimine 2 (A) with that of 5′-[($N^2$-alkylamidino)-methyl]naltrindole (3–5) (B). Note that the basic groups in the right hand part of these molecules are in similar orientations with respect to the antagonist pharmacophore.

to approximate the distance between one of the antagonist pharmacophores of 2 and its second basic group which has been suggested[4] to function as a κ address mimic. Alignment of the antagonist pharmacophore and the basic amidine group of 3–5 with those of norBNI (2) is illustrated in Figure 1. In this context the indole moiety functions as a rigid spacer to hold the amidine group in a location similar to that of the right-hand basic group of 2.

Another consideration in the design was based on structure–activity relationship studies which showed that δ-antagonist potency decreased on substitution of the indole moiety of NTI at the 5′-position.[3] Thus, 5′-substitution of NTI with an appropriate basic group should simultaneously suppress δ-antagonist potency and greatly enhance κ-antagonist potency.

Compounds 3–5 in the series were synthesized as outlined in Scheme I. Reaction of naltrexone (6) with 4-hydrazinobenzonitrile[5] under Fischer indole conditions afforded the 5′-nitrile 7, which was reduced to the primary amine 8 using Raney Ni. The amidines 3–5 were prepared by reacting 8 with the appropriate imidate esters.[6,7]

The pharmacological data (Table I) clearly show the dramatic change in the selectivity of NTI (1) upon modification with a 5′-[(alkylamidino)methyl] substituent. It can be noted that little, if any, of the δ antagonism of NTI is associated with these derivatives 3–5 and that there is a concomitant increase in the κ antagonist potency. Interestingly, 5 possesses greater in vitro κ antagonist potency and selectivity in smooth muscle than does norBNI (2). The opioid receptor binding data for the most potent compound, 5, is consistent with the κ selectivity (Table II).

Studies in mice indicated that 5 is a selective κ antagonist

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**Scheme I**

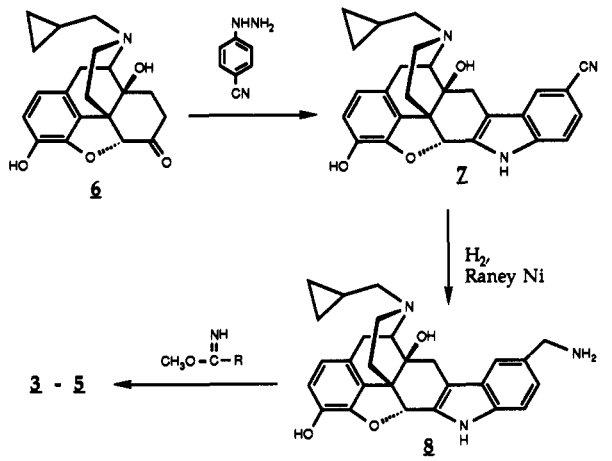


**Table I.** Antagonist Potencies in Smooth Muscle Preparations

| | IC50 ratios[a] (±SEM) | | | selectivity ratio | |
|---|---|---|---|---|---|
| compd | EK (κ)[b] | M (μ)[b] | DADLE (δ)[c] | κ/μ | κ/δ |
| 1 (NTI) | 1.3 ± 0.2 | 11.2 ± 1.8 | 459 ± 104 | (δ/μ, 41) | (δ/κ, 353) |
| 2 (norBNI)[d] | 181 ± 7 | 8.3 ± 1.8 | 10.4 ± 2.9 | 22 | 17 |
| 3 | 159 ± 43 | 11.3 ± 2.6 | 2.28 ± 0.57 | 14 | 69 |
| 4 | 185 ± 58 | 19.3 ± 5.3 | 3.00 ± 0.51 | 10 | 62 |
| 5 | 439 ± 100 | 15.7 ± 4.0 | 4.71 ± 1.06 | 28 | 93 |

[a] The $IC_{50}$ of the agonist in the presence of the antagonist (100 nM) divided by the $IC_{50}$ of the agonist alone in the same preparation. The number of replicate assays ≥ 3. [b] Determined in the guinea pig ileum preparation[11] using ethylketazocine (EK) or morphine (M). [c] Determined in the mouse vas deferens preparation[12] using [D-Ala²,D-Leu⁵]enkephalin (DADLE). [d] Data taken from ref 13.

**Table II.** Opioid Receptor Binding[a] of 5

| | $K_i$, nM[b] | | | $K_i$ selectivity ratio | |
|---|---|---|---|---|---|
| compd | κ[c] | μ[d] | δ[e] | μ/κ | δ/κ |
| 5 | 0.061 | 3.5 | 5.5 | 57 | 90 |
| 2 (norBNI)[f] | 0.28 | 47 | 43 | 181 | 150 |

[a] Guinea pig brain membranes were employed using a modification of the method of Werling et al.[14] [b] Values are geometric means of at least three replicate experiments. [c] [³H]U69593.[15] [d] [³H][D-Ala²,-MePhe⁴,Gly-ol⁶]enkephalin[16] (DAMGO). [e] [³H]DPDPE.[9] [f] Data from ref 17.

in vivo. At a dose of 4 mg/kg sc, 5 increased the antinociceptive $ED_{50}$ dose of the κ selective agonist, *trans*-(±)-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide[8] (U-50,488) by a factor of 3.77 (2.96–4.76) whereas insignificant increases were observed for the δ agonist, [D-Pen²,D-Pen⁵]enkephalin[9] (DPDPE), and the μ-selective agonist, morphine.

In conclusion, the data are consistent with the idea that the indole moiety in this series functions as a rigid scaffold to orient the amidine group to an address subsite on the κ opioid receptor. It has been suggested[2] that this subsite may recognize the guanidine group of Arg⁷ which is believed to be important for the recognition of dynorphin at κ-opioid receptors.[10] This study also suggests that a relatively simple group may be employed to mimic a key residue in an amino acid address sequence. The general implications of this study are that selective peptidomimetics may be designed when the class of peptides is organized into message and address domains and there is sufficient structure–activity information to determine the key amino acid residue(s) that functions as an address.

**Acknowledgment.** We thank Michael Powers, Veronika Doty, Joan Naeseth, and Mary Lunzer for in vitro and in vivo testing of the compounds. This work was supported by the National Institute on Drug Abuse.

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