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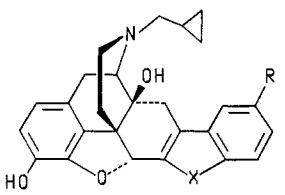
Communications to the Editor

Application of the Message–Address Concept in the Design of Highly Potent and Selective Non-Peptide δ Opioid Receptor Antagonists

Sir:

Progress in medicinal chemistry relies heavily on ligands as pharmacologic tools to evaluate selectivity of action. This is particularly relevant to opioid receptors, as there are at least three major receptor types (μ, κ, δ) that modulate a variety of physiologic processes.[1] Although highly selective opioid antagonists have been reported for μ[2,3] and κ[4] receptors, the fact that antagonist ligands for δ receptors are peptides[5] related to enkephalin limits their use as tools in vivo. Here we report on the design and structure–selectivity relationship of a series of highly selective and potent δ receptor opioid antagonists **1–6** that are nonpeptides.



	X	R
1	NH	H
2	NH	F
3	NH	OMe
4	NH	Me
5	NMe	H
6	O	H

The rationale for the design of these antagonists was based on the "message–address" concept[6,7] for the recognition of peptides by receptors and on the idea that the phenyl group of Phe[4] of leucine-enkephalin functions both as the address and part of the message for interaction with δ opioid receptors. Our finding[8] that the attachment of a δ receptor "address" segment of enkephalin to an opiate structure (e.g., oxymorphone) significantly altered receptor selectivity in a predictable fashion suggested that the "address" subsites are vicinal to the morphinan recognition locus that comprises the "message" component of the receptor. Accordingly, we have modified naltrexone by attachment of an aromatic ring that may mimic the phenyl group of Phe[4] of enkephalin. An important consideration in this approach was the conformational restriction of this group to an orientation that would permit binding with an address subsite that is unique to the δ receptor, while sterically hindering binding to address subsites associated with other opioid receptor types.

Since the conformational requirement of enkephalins at the δ opioid receptor was not known, our selection of target compounds was determined by the facility with which a conformationally restricted aromatic system could be introduced. Fusion of an indole or benzofuran to the C_{6-7} position of the morphinan skeleton of naltrexone proved to be the most direct route to obtaining such compounds. Indoles **1–5** were synthesized from naltrexone and the appropriate substituted phenylhydrazine under conditions of the Fischer indole synthesis.[9] The benzofuran **6** was obtained with *O*-phenylhydroxylamine under similar conditions.[10]

Table I. Opioid Antagonist Potencies of Indole and Benzofuran Derivatives of Naltrexone in the MVD and GPI

	K_e,[a] nM			selectivity	
compd	DADLE[b] (δ)	M[c] (μ)	EK[c] (κ)	μ/δ	κ/δ
1 (NTI)	0.21	32	58	152	276
2	2.0	61	46	31	23
3	5.7	63	13	11	2.3
4	4.2	*d*	*d*		
5	1.0	11	20	11	20
6	1.1	27	48	25	44
naloxone	40	2.2	16	0.06	0.4

[a] Derived from the Schild relationship (Schild, H. O. *Pharmacol. Rev.* **1957**, *9*, 242) and calculated from an average of at least three IC_{50} ratio determinations by using K_e = [antagonist]/(IC_{50} ratio − 1). [b] [D-Ala^2,D-Leu^5]enkephalin in the MVD preparation. [c] Morphine (M) or ethylketazocine (EK) in the GPI preparation. [d] No significant antagonism was observed from M or EK in the presence of 200 nM **4**.

(1) Martin, W. R. *Pharmacol. Rev.* **1983**, *35*, 283.
(2) Takemori, A. E.; Ikeda, M.; Portoghese, P. S. *Eur. J. Pharmacol.* **1986**, *123*, 387.
(3) Pelton, J. C.; Kazmierski, W.; Gulya, K.; Yamamura, H. I.; Hruby, V. J. *J. Med. Chem.* **1986**, *29*, 2370.
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(5) Cotton, R.; Giles, M. G.; Miller, L.; Shaw, J. S.; Timms, D. *Eur. J. Pharmacol.* **1984**, *97*, 331.
(6) Schwyzer, R. *Ann. N.Y. Acad. Sci.* **1977**, *297*, 3.
(7) Chavkin, C.; Goldstein, A. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 6543.
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(9) Naltrexone hydrochloride (1 mmol) and the appropriate aromatic hydrazine hydrochloride (2 mmol) were refluxed in glacial acetic acid or in methanol containing HCl for 3–6 h to afford hydrochloride salts of **1–5** in yields of 56–71%. Compounds were analytically pure (within ±0.4%) or chromatographically homogeneous and possessed spectral properties consistent with their assigned structures. NTI (**1**) was purified by column chromatography (silica gel/$CHCl_3$–MeOH–NH_4OH, 97:3:0.5) to give the pure base, which was converted to the HCl salt and crystallized from EtOH–$CHCl_3$, mp 270 °C dec.

(10) Obtained in 80% yield by refluxing an ethanolic solution containing equivalent amounts of naltrexone hydrochloride, *O*-phenylhydroxylamine hydrochloride, and methanesulfonic acid for 18 h.

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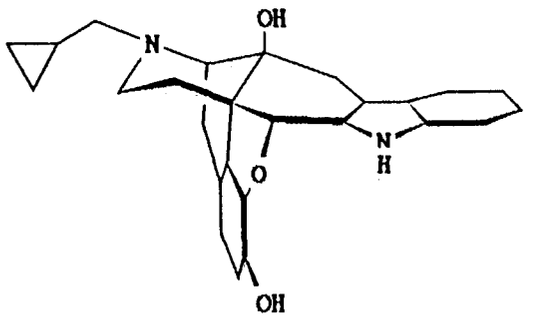
A



B

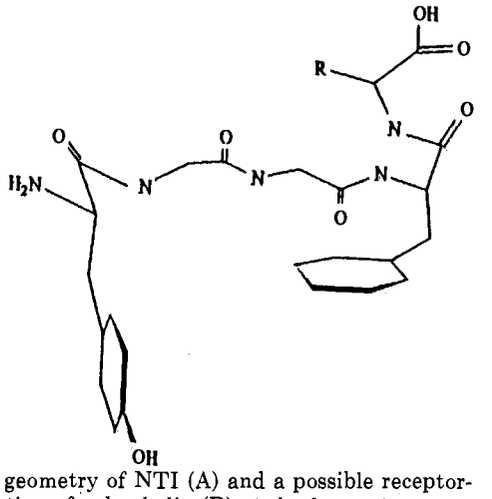
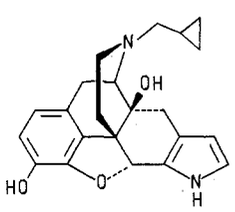


Figure 1. The geometry of NTI (A) and a possible receptor-bound conformation of enkephalin (B) at the δ receptor.

Testing was conducted on the guinea pig ileum[11] (GPI) and mouse vas deferens[12] (MVD) preparations by using opioid agonists that are selective[13] for δ, μ, and κ receptors (Table I). The unsubstituted indole **1** (naltrindole, NTI) clearly was the most δ-selective member of the series and was at least 5-fold more potent than other ligands at δ receptors. By comparison, the K_e value of the established δ antagonist, allyl$_2$Tyr-Aib-Aib-Phe-Leu[5] (ICI 174864), was determined to be 68 nM[14] or over 300 times that of NTI (**1**).

The fact that the benzofuran **6** also is δ-selective suggests that the pyrrole and furan moieties of these heterocyclic systems may function primarily by restricting the conformational mobility of the benzene ring. The necessity of the benzene ring was supported by our finding that the related pyrrole **7**[15] was not δ-selective.[16]



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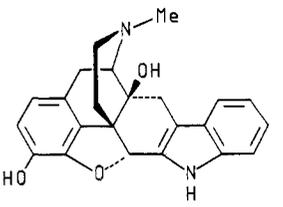
Significantly, the *N*-methyl analogue **8**[17] of NTI is active as an agonist in the MVD but not in the GPI.[18] This suggests that **8** is a δ-selective agonist. Thus, it is conceivable that the relative orientations of the conformationally fixed aromatic rings (Figure 1) are responsible for the δ selectivity. Moreover, δ-receptor-bound enkephalins may have their aromatic rings in a similar conformation.



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In conclusion, the "message–address" concept and conformationally fixed non-peptide message and address elements have been utilized as an approach to design highly selective and potent δ opioid receptor antagonists. These ligands are unique in that they are the first non-peptides that are highly δ-selective. The most potent member of the series, NTI (**1**), should find wide use as a pharmacologic tool, particularly for in vivo studies where the blood–brain barrier interferes with the penetration of peptide ligands into the CNS.[19]

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Registry No. **1**, 111555-53-4; **1**·HCl, 111469-81-9; **2**, 111555-54-5; **2**·HCl, 111469-82-0; **3**, 111555-55-6; **3**·HCl, 111469-83-1; **4**, 111555-56-7; **4**·HCl, 111469-84-2; **5**, 111555-57-8; **5**·HCl, 111469-85-3; **6**, 111555-58-9; **6**·HCl, 111469-86-4; **7**, 111469-87-5; **8**, 111469-88-6; $C_6H_5NHNH_2$·HCl, 59-88-1; 4-$FC_6H_4NHNH_2$·HCl, 823-85-8; 4-$MeOC_6H_4NHNH_2$·HCl, 19501-58-7; 4-$MeC_6H_4NHNH_2$·HCl, 637-60-5; $C_6H_5NMeNH_2$·HCl, 39232-92-3; $C_6H_5PMH_2$·HCl, 6092-80-4; $H_2NCH_2CH(OEt)_2$, 645-36-3; naltrexone hydrochloride, 16676-29-2; oxymorphone hydrochloride, 357-07-3.

(11) Rang, H. B. *Br. J. Pharmacol.* **1964**, *22*, 356.
(12) Henderson, G.; Hughes, J.; Kosterlitz, H. N. *Br. J. Pharmacol.* **1972**, *46*, 764.
(13) Herz, A. In *Trends in Medicinal Chemistry*; Mutschler, E., Winterfeldt, E., Eds.; VCH Verlagsgesellschaft: Weinheim, 1987; pp 338–350.
(14) ICI 174864 at 1 μM gave an IC_{50} ratio for DADLE of 15.6 ± 2.4.
(15) Prepared by refluxing a mixture of naltrexone hydrochloride, aminoacetaldehyde diethyl acetal, and methanesulfonic acid in DMF–benzene (1:1) with azeotropic removal of water for 14 h.
(16) The K_e values of **7** at μ, κ, and δ receptors are 0.7, 2.1, and 3.7 nM, respectively.
(17) Oxymorphone hydrochloride and phenylhydrazine hydrochloride were employed in a procedure identical with that described in ref 9.
(18) Compound **8** did not exhibit antagonist activity in the MVD or GPI. Its agonist activity in the GPI was 12 ± 4.4% at 1 μM; in the MVD it behaved as a partial agonist (65 ± 5% at 1 μM) with an IC_{50} of 100 nM.
(19) In preliminary studies, sc administration of NTI in mice has been found to antagonize the effect of the δ agonist ligand Tyr-D-Ser-Gly-Phe-Leu-Thr (IC_{50} ratio = 5.3) without affecting the ED_{50} of morphine (μ agonist) or U50488H (κ agonist).

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