45%): mp 225–229 °C, $^1$H NMR (DMSO) δ 8.37 (s, 1 H), 8.11 (d, 1 H), 8.01 (d, 1 H), 7.83 (t, 1 H), 7.71 (t, 1 H), 4.06 (s, 2 H). Anal. ($C_{12}H_9NO_4$·0.6$H_2O$) C, H, N.

**2-Carboxycoumaran-3-acetic Acid (59).** Methyl 2-(methoxycarbonyl)coumaran-3-acetate was prepared by a previously described procedure.[30] The diester (1 g, 4.0 mmol) was saponified as described for compound **8** to yield the diacid as a colorless oil. Product **59** was crystallized from acetone/cyclohexane (850 mg, 96%): mp 172–175 °C; $^1$H NMR (DMSO) δ 12.84 (br s, 2 H), 7.22 (m, 2 H), 6.87 (m, 2 H), 4.91 (d, 1 H), 3.85 (m, 1 H), 2.70 (m, 2 H). Anal. ($C_{11}H_{10}O_5$) C, H.

**2-Carboxybenzofuran-3-acetic Acid (60).** Diacid **60** was prepared by a previously described procedure,[30] but the crude product was obtained directly upon acidification of a basic extract, without isolation of the reported contaminating brown oils. The crude diacid was recrystallized from acetone/cyclohexane to provide **60** (53% yield): mp 237–242 °C (lit.[30] mp 230 °C dec); $^1$H NMR (DMSO) δ 12.80 (br s, 2 H), 7.80 (d, 1 H), 7.68 (d, 1 H), 7.51 (t, 1 H), 7.35 (t, 1 H), 4.10 (s, 2 H). Anal. ($C_{11}H_8O_5$) C, H.

**Radioreceptor Assays. Inhibition of [$^3$H]Glycine Binding.** Strychnine-insensitive [$^3$H]glycine binding to the NMDA receptor-associated recognition site was performed with Triton X-100-washed synaptic plasma membranes (SPM) prepared from rat forebrain (30–45 day old, male Sprague-Dawley; Sasco, St. Charles, MO) as described previously.[34] The assay was initiated by the addition of 0.2–0.4 mg of SPM to an incubation containing 10 nM [$^3$H]glycine (49.0 Ci/mmol; New England Nuclear, Boston, MA), and various concentrations, in triplicate, of the appropriate test compounds in a total volume of 1 mL, with all additions made in 50 mM of Tris/acetate, pH 7.4. Following a 10-min incubation at 2 °C, the bound radioactivity was separated from the free by either centrifugation (12000g for 15 min at 4 °C) or vacuum filtration through Whatman GF/B filters using a Brandel MB-18 Harvester. The radioactivity associated with the SPM was quantitated using liquid scintillation spectrometry. Nonspecific binding was defined in the presence of 100 μM glycine. $K_i$ values were determined from logit–log transformations of the binding data.

**Inhibition of [$^3$H]Glutamate, [$^3$H]Kainate, and [$^3$H]AMPA Binding.** The [$^3$H]glutamate, [$^3$H]kainate, and [$^3$H]AMPA radioreceptor assays were carried out by using the methods described previously.[30,31] $K_i$ values were determined from logit–log transformations of the binding data.

**Modulation of [$^3$H]MK-801 Binding.** The modulation of [$^3$H]MK-801 binding was performed as described earlier.[32] Briefly, the synaptic plasma membranes (SPM) were treated with Triton X-100 (0.04% v/v) and then extensively washed with 50 mM Tris acetate, pH 7.4. The assay incubation was initiated by the addition of SPM (0.2–0.4 mg) to 5 nM [$^3$H]MK-801, 10 nM L-glutamate, and the appropriate concentration of the test compound in 50 mM Tris acetate, pH 7.4. After 30 min at 25 °C, the samples were filtered through polyethylenimine treated (0.05% v/v) Whatman GF/B filters and then washed four times with 2 mL of cold buffer. Radioactivity associated with the filter was determined by liquid scintillation spectrometry and nonspecific binding defined with 60 μM MK-801.

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# Role of the Spacer in Conferring κ Opioid Receptor Selectivity to Bivalent Ligands Related to Norbinaltorphimine

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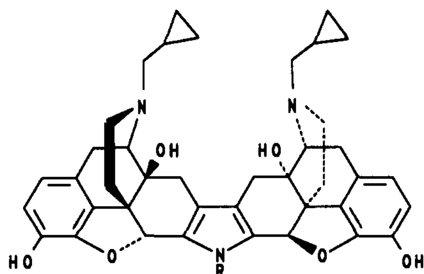
The thiophene **2** and pyran **3** analogues of the κ-selective opioid antagonist norbinaltorphimine (**1a**, norBNI) were synthesized and tested in an effort to determine the contribution of the spacer to the interaction of bivalent ligands at different opioid receptor types. Both **2** and **3** were found to be selective κ opioid receptor antagonists in smooth muscle preparations, and they bound selectively to κ-recognition sites. The thiophene analogue **2** displayed binding selectivity that was of the same order of magnitude as that of **1a**, while **3** was considerably less selective for κ site. This is consistent with the fact that the second pharmacophore in **1a** and **2** displayed a greater degree of superposition than **1a** and **3**. The results of this study suggest that the pyrrole moiety of norBNI functions primarily as an inert spacer to rigidly hold the basic nitrogen in the second pharmacophore at an "address" subsite that is unique for the κ opioid receptor.

Norbinaltorphimine (**1a**, norBNI) and binaltorphimine (**1b**, BNI) are bivalent ligands that are highly selective for κ opioid receptors.[1-3] They contain two naltrexone-derived




pharmacophores linked through a pyrrole spacer which is fused with ring C of the morphinan structure. The structure–activity relationship of related compounds has revealed that only one pharmacophore is required for κ antagonist selectivity.[4,5] We have suggested that the κ selectivity arises as a consequence of the pyrrole moiety holding the second half of the molecule in a specific, rigid orientation with respect to the first half, thereby facilitating its interaction with a subsite (the "address") of the κ receptor recognition locus.[5,6]

In an effort to determine whether the pyrrole moiety functions merely as a spacer or is a requirement for κ opioid

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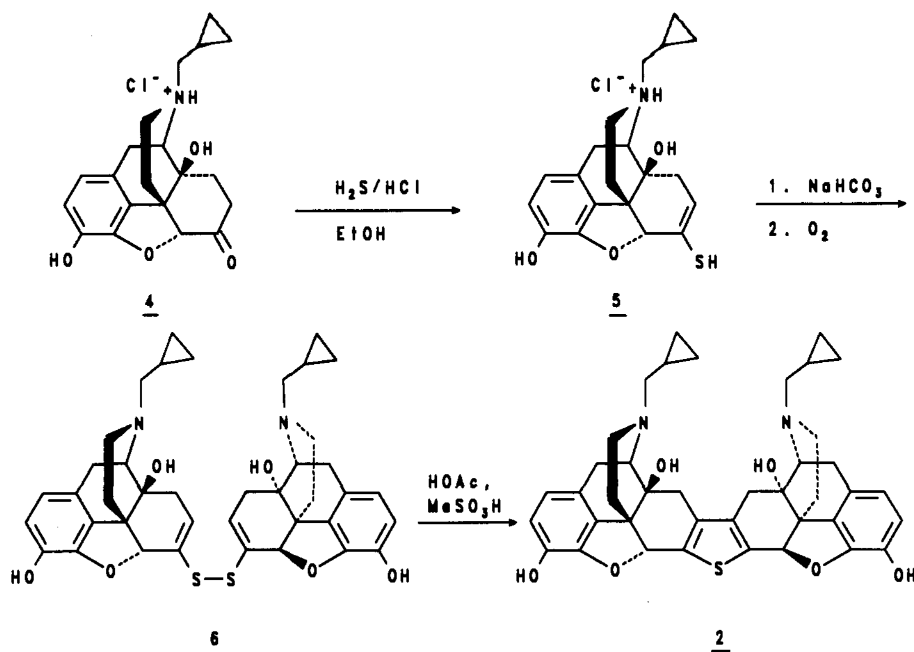
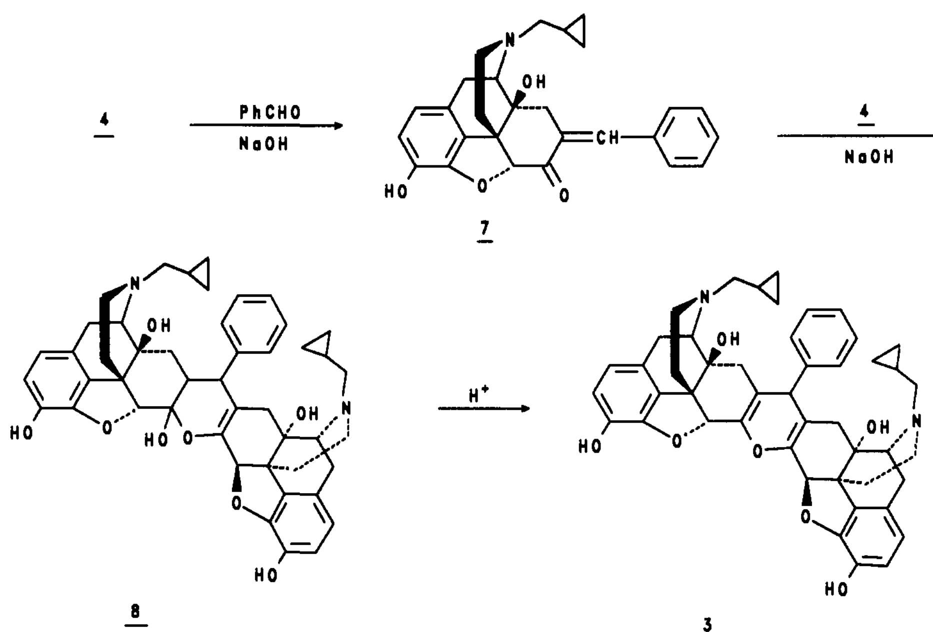
**Scheme I**




**Scheme II**




antagonist selectivity, we have replaced it with thiophene (2) and with pyran (3). Testing of 2 and 3 in vitro has revealed that they are κ-selective antagonists. The results of these studies support the idea that the pyrrole moiety of 1 functions primarily as a spacer.

## Chemistry

Synthesis of thiophene analogue 2 was accomplished in three steps (Scheme I). To a suspension of naltrexone hydrochloride in absolute ethanol was added liquid $H_2S$, and the mixture was saturated with HCl gas at −78 °C to afford the crude enethiol 5. After conversion to the free base, 5 was air-oxidized to the disulfide 6, and then this product was refluxed in glacial acetic acid containing methanesulfonic acid for 3 days to afford the desired product 2.

The pyran analogue 3 was synthesized (Scheme II) by allowing a mixture of naltrexone (4) and benzaldehyde in methanolic 1 N NaOH to stand at 24 °C for 18 h to afford the hemiketal 8. Since the $\alpha,\beta$-unsaturated ketone 7 was isolated in moderate yield when the reaction was conducted at 0 °C for 3 h, it seems likely that 7 is an intermediate in the formation of the hemiketal 8. Acid-catalyzed dehydration of 8 gave the corresponding pyran 3.

## In Vitro Studies

Compounds 2, 3, 6, and 7 were tested on the electrically stimulated guinea pig ileal longitudinal muscle[7] (GPI) and mouse vas deferens[8] (MVD) preparations as described previously.[9] The compounds were incubated with the preparations 15 min prior to testing with either morphine

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**Table I.** Opioid Antagonist Potencies in the GPI and MVD Preparations[a]

| | $\kappa^b$ | | | $\mu^b$ | | | $\delta^c$ | | | Ke ratio | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| antagonist | agonist | $IC_{50}$ ratio | Ke, nM | agonist | $IC_{50}$ ratio | Ke, nM | agonist | $IC_{50}$ ratio | Ke, nM | $\mu/\kappa$ | $\delta/\kappa$ |
| 1 (norBNI) | EK | 181 ± 7 (3) | 0.55 | M | 8.3 ± 1.8 (4) | 14 | DADLE | 10.4 ± 2.9 (3) | 10.6 | 25 | 19 |
| | U50488H | 473 ± 167 (4) | 0.21 | DMAGO | 5.6 ± 1.4 (3) | 22 | -- | | | 110 | -- |
| 2 | EK | 39 ± 10 | 2.6 | M | 3.5 ± 0.8 (4) | 41 | DADLE | 4.0 ± 0.7 (3) | 33 | 16 | 13 |
| | U50488H | 33 ± 5 (3) | 3.1 | DAMGO | 1.9 ± 0.6 (4) | ≥103 | DPDPE | 1.2 ± 0.2 (4) | ≥556 | ≥33 | ≥179 |
| 3 | EK | 39 ± 11 (4) | 2.6 | M | 3.6 ± 1.4 (3) | 39 | DADLE | 3.8 ± 0.8 (3) | 36 | 15 | 14 |
| 6 | EK[d] | 9.7 (2)[e] | 3.5 | M[d] | 14.6 (3) | 2.2 | DADLE | 8.6 ± 2.4 (4) | 13.2 | 0.6 | 3.9 |
| 7 | EK | 2.0 ± 0.1 (3) | 100 | M | 13.1 ± 0.9 (3) | 8.3 | DADLE | 35 ± 5 (3) | 2.9 | 0.08 | 0.35 |
| 4 (naltrexone) | EK | 19 ± 6 (4) | 5.5 | M | 98 ± 24 (4) | 1.0 | DADLE | 5.1 ± 1.3 (3) | 24 | 0.2 | 4.4 |
| | U50488H | 3.7 ± 0.7 (4) | 37 | DAMGO | 18 ± 6 (3)[f] | 1.2 | DPDPE | 2.4 ± 0.3 (4) | 69 | 0.03 | 1.9 |

[a] The concentration of the antagonist was 100 nM unless specified. [b] GPI preparation. [c] MVD preparation. [d] The concentration of 6 in the presence of agonist was 30 nM. [e] This ratio is an estimate because the maximum agonist response in the presence of 6 was 63%. [f] Concentration of naltrexone, 20 nM.

**Table II.** Maximal Inhibition or Stimulation by Ligands on the GPI and MVD Preparations[a]

| compd | GPI | MVD |
|---|---|---|
| 1a (norBNI) | 14 | 16 |
| 2 | -17 | -26 |
| 3 | -24 | 9 |
| 6 | 40 | 15 |
| 7 | -8 | -35 |

[a] Values are an average of three determinations at 1 μM concentration; negative values signify increase in amplitude (stimulation) of muscle twitch.

(M), [D-Ala[2],MePhe[4],Gly-ol[5]]enkephalin[10] (DAMGO), ethylketazocine (EK), *trans*-(±)-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide[11] (U50488H), [D-Ala[2],D-Leu[5]]enkephalin[12] (DADLE), or [D-Pen[2],D-Pen[5]]enkephalin[13] (DPDPE). These agonists are selective for μ (M, DAMGO), κ (EK, U50488H), and δ (DADLE, DPDPE) opioid receptors. The μ- and κ-selective agonists were tested on the GPI, and the δ-selective agonists were tested on the MVD. Concentration-response curves were obtained in the absence (control) and presence of the antagonist in the same preparation and were expressed as $IC_{50}$ values. The $IC_{50}$ ratio represents the $IC_{50}$ in the presence of the antagonist divided by the control $IC_{50}$ value in the same tissue. The $IC_{50}$ ratios (Table I) were employed to calculate the antagonist potency expressed as $Ke = [\text{antagonist}]/(IC_{50}\text{ ratio} - 1)$.

Both the thiophene **2** and pyran **3** analogues of norBNI (**1**) were more potent antagonists of κ-selective agonists than of μ- or δ-selective agonists. They were 5-10 times less potent than norBNI (**1a**) as κ antagonists, but their selectivity ratios were in the same range as norBNI because they were also less potent antagonists of μ and δ agonists.

Because the disulfide **6** exhibited partial agonist activity at 1 μM (40%), it was tested as an antagonist at 30 nM, which is lower than the standard concentration (100 nM) employed. Compound **6** displayed a noncompeptitive component, in that EK afforded a maximal agonist response of 63% in its presence. Consequently the Ke value of **6** at κ receptors is considered to be only an estimate. Interestingly, **6** was considerably more potent as a morphine antagonist (Ke = 2.2 nM) than any of the other bivalent ligands. Intermediate **7** was found to be a δ-selective antagonist (Ke = 2.9 nM), in that it was 3 and 35 times less potent at κ and μ receptors, respectively.

**Table III.** Opioid Receptor Binding of Bivalent Ligands

| | Ki, nM | | | Ki ratio | |
|---|---|---|---|---|---|
| compd | μ | δ | κ | μ/κ | δ/κ |
| 1a (norBNI) | 47 (35-64) | 39 (10-153) | 0.26 (0.07-0.09) | 181 | 150 |
| 1b (BNI)[a] | 18 (1.4-222) | 58 (20-170) | 0.41 (0.04-4.5) | 44 | 141 |
| 2 | 189 (105-339) | 77 (65-92) | 1.4 (1.2-1.6) | 135 | 55 |
| 3 | 29 (12-67) | 10 (2.6-42) | 2.6 (2.3-2.9) | 11 | 4 |

[a] This represents revised binding data for **1b** which was reported[2] to be nonselective, presumably due to decomposition.

**Table IV.** Antagonism by Compound **2** of the Antinociceptive Effect of Opioid Agonists in Mice[a]

| | $ED_{50}$, mg/kg | | |
|---|---|---|---|
| agonist[b] | control | treated[c] | $ED_{50}$ ratio[d] |
| EK | 0.038 (0.032-0.045) | 0.13 (0.11-0.16) | 3.4 (2.7-4.4) |
| U50488H | 1.5 (0.66-2.5) | 11.2 (4.6-18.4) | 7.5 (3.0-16.9) |
| M | 0.91 (0.36-2.1) | 5.4 (2.5-11.2) | 5.9 (1.9-19.4) |

[a] Acetic acid writhing assay. [b] Administered sc. [c] Treated icv with 100 nmol of 2·HCl in 5 μL of saline. [d] Treated $ED_{50}$ divided by the control $ED_{50}$.

The agonist activity of the compounds (1 μM) was evaluated on the guinea pig ileum (GPI) and mouse vas deferens (MVD) preparations (Table II). In the GPI, compounds **2**, **3**, and **7** produced no significant agonist effect, but rather displayed increased muscle twitch (stimulation). The 40% maximal inhibition of the GPI twitch for **6** suggests that it is a partial agonist. In the MVD, some of the ligands exhibited a significant agonist effect. However, it was observed that both **2** and **7** enhanced the contraction of the MVD preparation.

Opioid receptor binding of **1-3** was performed with guinea pig brain membranes by using a modification[2] of the procedure of Werling et al.[14] The radioligands employed were [$^3$H]DAMGO for μ receptors, [$^3$H]EK in the presence of 1 μM unlabeled DAMGO for κ receptors, and [$^3$H]DADLE in the presence of 1 μM unlabeled DAMGO for δ receptors. All compounds bound selectively to κ sites (Table III). The binding selectivities of **1a**, **1b**, and **2** were of similar magnitude, while the pyran analogue **3** possessed considerably lower selectivity. Also, the affinity of the standard compound, norBNI (**1a**), is 5-10 times greater than those of **2** and **3** for κ receptors.

### In Vivo Activity of 2

The thiophene compound **2** was tested icv in the mouse writhing assay as described by Hayashi and Takemori.[15] Administration of **2** and standard agonists was timed so that the peak effect (60 min) coincided with the center of

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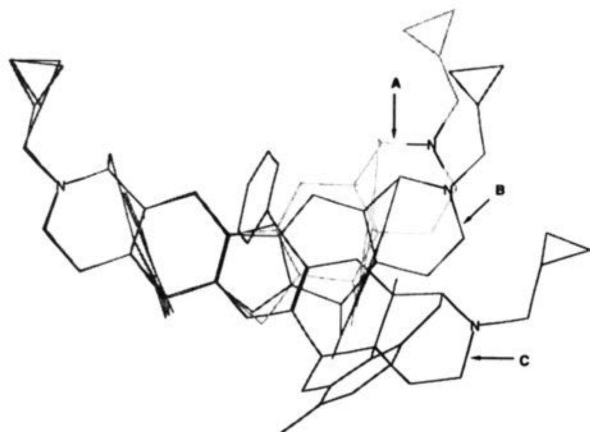



**Figure 1.** Superposition of norBNI (**1a**) (B) with its thiophene **2** (A) and pyran **3** (C) analogues. The distances of the basic nitrogens of **2** and **3** from that of **1a** are 1.3 and 3.8 Å, respectively.

the observation period. It was found that the peak action of **2** at an icv dose of 100 nmol was 60 min, which is similar to that observed for norBNI (**1a**).[2] The animals were then tested at four dose levels of agonists (M, EK, U50488H) administered sc. The results of these studies (Table IV) showed no significant differences in $ED_{50}$ ratios in the presence of **2**.

## Discussion

The data obtained from smooth muscle studies (Table I) show that bivalent ligands **2** and **3** possess Ke selectivity ratios that are only slightly lower than those of the standard, norBNI (**1a**). These similar Ke ratios reflect the proportionately lower potencies of **2** and **3** at all three opioid receptor types when compared to **1a**.

The binding data (Table III) are consistent with the in vitro pharmacology, in that **2** and **3** are κ-selective ligands. It can be noted that the Ki ratios of bivalent ligand **2** are substantially greater than those of **3**, which contains the pyran spacer. This is due primarily to the greater binding affinity of **3** to μ and δ receptors. We view the binding data as a more reliable index of recognition at opioid receptors than pharmacologic data because of the complexity of the signal transduction process.

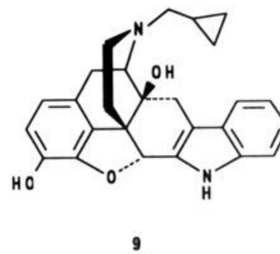
Superposition of **1a**, **2**, and **3** (Figure 1) illustrates that the different spacers give rise to different orientations of the second pharmacophores. In this regard, **1a** and **2** bear the closest relationship to one another, and this is reflected by the Ki ratios (Table III) that are of comparable magnitude. The geometry of the pyran spacer gives rise to a more angular displacement of the second pharmacophore in **3**, which leads to lower affinity at κ sites and increased affinity at μ and δ sites. The net result is the substantially lower binding selectivity ratios for **3** for κ sites.

Since structure–activity relationship studies of norBNI-related ligands have indicated that only one pharmacophore is essential for κ selectivity, we have suggested that the key determinant for such selectivity is the basic nitrogen in the second half of the molecule.[5,6] Moreover, we have entertained the possibility that this basic nitrogen mimics one of the basic residues at positions 6 or 7 of the endogenous, κ-selective opioid peptide dynorphin. The results of the present study provide additional support for this idea, in that the basic nitrogens of ligands **2** and **3** are positioned within a distance of 1.3 and 3.9 Å, respectively, from the basic nitrogen of norBNI (**1a**) (Figure 1).

This model, which is an adaptation of the message–address concept,[16] envisages the κ opioid receptor to contain a message subsite that recognizes one of the antagonist pharmacophores and an address subsite that recognizes the protonated amine function in the second half of the bivalent ligand. The message portion of dynorphin, which is considered to be critical for signal transduction, is $Tyr^1$. The address, starting with $Phe^4$, is connected to the message component by a spacer, $Gly^2$-$Gly^3$, and confers the κ selectivity to dynorphin by increasing affinity for κ sites with a concomitant decrease at μ and δ sites.

Of significance is the fact that the disulfide-containing bivalent ligand **6** is not a κ-selective antagonist. This may be a consequence of its greater conformational mobility relative to the bivalent ligands (**2**, **3**) with rigid spacers. Accordingly, **6** would be able to conformationally adapt to μ and δ receptors through rotation of the disulfide moiety. This would account for the greater potency of **6** at μ and δ receptors when compared to the rigid ligands (**1a**, **2**, **3**). We suggest that **2** and **3** derive a portion of their κ selectivity by virtue of their rigid structures which sterically interfere with binding at μ and δ sites.

Of interest is the observation that the benzylidene intermediate **7** is a δ-selective opioid antagonist. Since **7** contains a phenyl group in the vicinity of the benzene moiety of naltrindole (**9**),[17,18] a highly δ-selective antagonist,




this may account for its selectivity. The δ-receptor antagonist potency and selectivity of **7** are lower than those of **9** by more than 1 order of magnitude. This may be a consequence of the greater conformational flexibility of **7** and the orientation of its phenyl group with respect to its pharmacophore.

When compound **2** was tested for its ability to reverse antinociception in mice, no significant difference of $ED_{50}$ ratios was observed between the κ- and μ-selective agonists U50488H and morphine, respectively. The reason for the absence of selectivity in vivo is unknown. The standard compound, norBNI (**1a**), does exhibit selective antagonism[2] under the same conditions, although its selectivity ratios are considerably lower than those determined in vitro. The much greater complexity of the brain, including the possibility of opposing neural pathways, may contribute to the lower in vivo selectivity.

## Experimental Section

Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by M-W-H Laboratories, Phoenix, AZ. Magnetic resonance spectra were obtained on IBM-Bruker AC-300 (300 MHz, $^1H$ NMR; 75 MHz, $^{13}C$ NMR) and IBM-Bruker AC-200 (200 MHz, $^1H$ NMR; 50 MHz, $^{13}C$ NMR) spectrometers, and chemical shifts are reported as δ values (ppm) relative to TMS. IR spectra were recorded on a Nicollet 5DXC FT-IR spectrometer, and peak position are expressed in $cm^{-1}$. Mass spectra were obtained on AEI MS 30, Finnigan 4000 Cl, and VG 70,70 EHF

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instruments. All TLC data were determined with E. Merck Art. 5554 DC-Alufolien Kieselgel 60 $F_{254}$. Column chromatography was carried out on E. Merck silica gel 60 (230–400 mesh). Reagents were purified according to known procedures. Naltrexone was obtained from Mallinckrodt.

**6,6′-Dithiobis[17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxymorphinan-3,14β-diol] (6).** Naltrexone hydrochloride (4) (3.1407 g, 8.312 mmol) was suspended in absolute ethanol (150 mL) and stirred in a dry ice–acetone bath for 20 min. Liquid hydrogen sulfide (20 mL) was added, and hydrogen chloride gas was bubbled through the solution for 50 min at −78 °C to give a homogeneous colorless solution. The solution was stirred at −78 °C for an additional 2 h. Argon was bubbled through the solution at −78 °C for 3 h and then the solution was allowed to warm to 23 °C. Solvent was removed in vacuo to give a glass, which after drying under vacuum for 8 h afforded 3.19 g of crude enethiol 5: MS *m/e* 357.139 ($M^+$, EI, calcd 357.140); $^1H$ NMR (DMSO, 200 MHz) δ 5.01 (s, $H_5$), 6.07 (d, $H_7$). The crude product 5 (1.5941 g) was dissolved in water (10 mL) and shaken with ethyl acetate (25 mL) and a saturated sodium bicarbonate solution (25 mL). The organic phase was washed with a saturated sodium bicarbonate solution (10 mL) and brine (5 mL). The combined aqueous solution was extracted with ethyl acetate (2 × 25 mL). The organic extracts were dried ($MgSO_4$), filtered, and concentrated to give an oil, which was dissolved in methanol (50 mL) and ethyl ether (25 mL). The solution was stirred with exposure to air at 23 °C overnight to afford a suspension. The precipitate was collected by filtration, washed with methanol (8 mL), and dried in vacuo to give the disulfide 6 (579.1 mg, 48%): $^1H$ NMR (DMSO-$d_6$/methanol-$d_4$, 300 MHz) δ 0.2–0.25 (m, 4 H, $H_{20}$, $H_{21}$, $H_{20'}$, and $H_{21'}$), 0.56–0.61 (m, 4 H, $H_{20}$, $H_{21}$, $H_{20'}$ and $H_{21'}$), 0.8–1.0 (m, 2 H, $H_{19}$ and $H_{19'}$), 1.56 (d, 2 H, $J$ = 10.1 Hz, $H_{15}$ and $H_{15'}$), 2.12 (d, 2 H, $J$ = 18.0 Hz), 2.21–2.33 (m, 6 H), 2.43–2.46 (d, 4 H), 2.61–2.78 (m, 4 H), 3.12 (d, 2 H, $J$ = 18.6 Hz, $H_{10}$ and $H_{10'}$), 3.21 (d, 2 H, $J$ = 5.9 Hz, $H_9$ and $H_{9'}$), 5.01 (s, 2 H, $H_5$ and $H_{5'}$), 6.24 (d, 2 H, $J$ = 3.8 Hz, $H_7$ and $H_{7'}$), 6.59 (d, 2 H, $J$ = 8.1 Hz, $H_1$ and $H_{1'}$), 6.66 (d, 2 H, $J$ = 8.1 Hz, $H_2$ and $H_{2'}$); $^{13}C$ NMR (acetone-$d_6$, 50 MHz) δ 3.84 and 4.19 ($C_{20}$, $C_{21}$, $C_{20'}$, and $C_{21'}$), 9.71 ($C_{19}$ and $C_{19'}$), 23.03 ($C_{10}$ and $C_{10'}$), 31.54 ($C_{15}$ and $C_{15'}$), 34.40 ($C_8$ and $C_{8'}$), 44.13 ($C_{16}$ and $C_{16'}$), 47.28 ($C_{13}$ and $C_{13'}$), 59.56 ($C_{18}$ and $C_{18'}$), 61.79 ($C_9$ and $C_{9'}$), 70.73 ($C_{14}$ and $C_{14'}$), 87.12 ($C_5$ and $C_{5'}$), 117.67 ($C_2$ and $C_{2'}$), 119.26 ($C_1$ and $C_{1'}$), 125.06 ($C_{11}$ and $C_{11'}$), 129.58 ($C_{12}$ and $C_{12'}$), 131.72 ($C_6$ and $C_{6'}$), 138.90 ($C_4$ and $C_{4'}$), 140.50 ($C_7$ and $C_{7'}$), 143.78 ($C_3$ and $C_{3'}$); IR (KBr) 3395, 1618, 1641, 1511, 1459 $cm^{-1}$; MS *m/e* 713 ($M + H^+$, FAB); $R_f$ = 0.66 (silica gel and MeOH–$NH_4OH$–hexanes–EtOAc, 4:1:15:30); mp 170–180 °C. Anal. ($C_{40}H_{44}N_2O_6S_2$) C, H, N.

**17,17′-Bis(cyclopropylmethyl)-6,6′-epithio-4,5α:4′,5′α-diepoxy[7,7′-bimorphinan]-3,3′,14β,14′β-tetrol (2).** The disulfide 6 (154.2 mg, 0.2163 mmol) in acetic acid (2.0 mL) was heated to reflux, and methanesulfonic acid (58 μL, 85.9 mg, 0.894 mmol) was added. The solution was refluxed for 73 h to give a homogeneous brown solution, and acetic acid was then removed in vacuo. The residue was dissolved in methanol (1 mL) and shaken with ethyl acetate (20 mL) and a saturated sodium bicarbonate solution (20 mL). The ethyl acetate layer was separated and aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic solution was dried ($MgSO_4$), filtered, and concentrated, and the brown residue was purified by flash chromatography (silica gel; MeOH–$NH_4OH$–hexane–EtOAc, 4:1:35:65) to give 2 (56.1 mg, 38%) which was crystallized from chloroform: $^1H$ NMR (acetone-$d_6$, 300 MHz) δ 0.13–0.16 (m, 4 H, $H_{20}$, $H_{21}$, $H_{20'}$, and $H_{21'}$), 0.47–0.51 (m, 4 H, $H_{20}$, $H_{21}$, $H_{20'}$, and $H_{21'}$), 0.85–0.88 (m, 2 H, $H_{19}$ and $H_{19'}$), 1.63 (d, 2 H, $J$ = 10.1 Hz, $H_{15}$ and $H_{15'}$), 2.18–2.28 (m, 8 H), 2.40–2.43 (d, 4 H), 2.71–2.83 (dd, 4 H), 3.12 (d, 2 H, $J$ = 18.5 Hz, $H_{10}$ and $H_{10'}$), 3.24 (d, 2 H, $J$ = 6.0 Hz, $H_9$ and $H_{9'}$), 5.43 (s, 2 H, $H_5$ and $H_{5'}$), 6.50 (d, 2 H, $J$ = 8.1 Hz, $H_1$ and $H_{1'}$), 6.60 (d, 2 H, $J$ = 8.1 Hz, $H_2$ and $H_{2'}$); $^{13}C$ NMR (acetone-$d_6$, 50 MHz) δ 3.95 and 4.25 ($C_{20}$, $C_{21}$, $C_{20'}$, and $C_{21'}$), 9.99 ($C_{19}$ and $C_{19'}$), 23.56 ($C_{10}$ and $C_{10'}$), 32.27 and 32.44 ($C_{15}$, $C_8$, $C_{15'}$, and $C_{8'}$), 44.46 ($C_{16}$ and $C_{16'}$), 48.69 ($C_{13}$ and $C_{13'}$), 59.93 ($C_{18}$ and $C_{18'}$), 63.01 ($C_9$ and $C_{9'}$), 72.36 ($C_{14}$ and $C_{14'}$), 86.64 ($C_5$ and $C_{5'}$), 118.07 ($C_2$ and $C_{2'}$), 119.42 ($C_1$ and $C_{1'}$), 125.60 ($C_{11}$ and $C_{11'}$), 131.61 ($C_{12}$ and $C_{12'}$), 138.19 ($C_7$ and $C_{7'}$), 135.80 ($C_6$ and $C_{6'}$), 140.83 ($C_4$ and $C_{4'}$), 144.6 ($C_3$ and $C_{3'}$); IR (neat) 3363, 1516, 1695, 1639, 1616, 1505, 1456 $cm^{-1}$; MS *m/e* 678.273 ($M^-$, CI, calcd 678.277), 679 ($M + H^+$, FAB), $R_f$ = 0.40 (silica gel, MeOH–$NH_4OH$–hexanes–EtOAc, 4:1:14:30); mp >230 °C dec. Anal. ($C_{40}H_{42}N_2O_6S{\cdot}H_2O$) C, H, N.

**7,7′-Benzylidene-6,6′-epoxybis[17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxymorphinan-3,14β-diol] (3).** A solution of naltrexone hydrochloride (4) (310 mg, 0.82 mmol), benzaldehyde (0.3 mL, 2.83 mmol), and sodium hydroxide (1 N, 3 mL) in methanol (3 mL) was allowed to stand at 24 °C for 18 h. After neutralization with 1 N hydrochloric acid, the resulting precipitate was collected, washed with ether, and dried to give crude hemiketal 8 (200 mg, 65%): IR (KBr, $cm^{-1}$) 3402, 3078, 3001, 2924, 2832, 1630; FAB MS 771.4 ($M^+$ + 1, +VE), 769.7 ($M^+$ − 1, −VE). The product was used in the following reaction without further purification.

Product 8 (100 mg, 0.13 mmol) and methanesulfonic acid (0.1 mL, 1.04 mmol) in DMF (4 mL) and toluene (10 mL) were stirred under reflux with a Dean-Stark trap for 20 h. The mixture was concentrated to dryness in vacuo, and chloroform, saturated sodium bicarbonate, and methanol were added. After filtration of the mixture, the resulting filtrate was extracted with chloroform (3×). The combined chloroform layers were washed with brine, dried, and concentrated to give a crude product, which was purified by preparative TLC (silica gel; 10% methanol–chloroform) to afford the pyran 3 (76 mg, 78%): $R_f$ 0.57 (BuOH–acetone–$H_2O$, 2:1:1), 0.3 ($CHCl_3$–MeOH–acetone 19:0.7:0.1); IR (KBr, $cm^{-1}$) 3404, 2994, 2825, 1637, 1616; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 0.05–0.13 (m, 4 H), 0.43–0.54 (m, 4 H), 0.69–0.75 (m, 2 H), 1.55 (m, 2 H), 1.62 (m, 2 H), 1.70 (d, $J$ = 11.5 Hz, 1 H), 1.85 (d, $J$ = 16.1 Hz, 1 H), 2.1–2.43 (m, 10 H), 3.6–3.7 (m, 3 H), 2.75–3.06 (m, 3 H), 3.41 (s, 1 H), 5.15 (s, 1 H), 5.17 (s, 1 H), 6.39 (d, $J$ = 8.2 Hz, 1 H), 6.56 (d, $J$ = 8.2 Hz, 1 H), 6.70 (d, $J$ = 8.1 Hz, 1 H), 6.76 (d, $J$ = 8.1 Hz, 1 H), 6.89–6.92 (m, 2 H), 7.09–7.13 (m, 3 H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 3.73, 3.90, 3.93, 4.11, 9.33, 9.37, 22.69, 22.92, 30.84, 30.92, 31.56, 32.81, 34.96, 36.61, 43.39, 43.52, 46.93, 47.09, 59.50, 61.13, 61.32, 70.31, 70.47, 86.64, 87.12, 110.10, 110.73, 117.48, 117.69, 119.04, 119.26, 124.52, 127.05, 128.34, 128.39, 130.70, 130.76, 139.22, 139.29, 139.68, 140.43, 141.49, 142.85, 143.02; FAB MS 753.5 (+VE, $M^+$ + 1), 752.5 (−VE, $M^+$). Anal. ($C_{47}H_{48}O_7N_2{\cdot}2HCl{\cdot}H_2O$) C, H, N, Cl.

**7-Benzylidene-7-dehydronaltrexone (7).** To a stirred solution of naltrexone hydrochloride (200 mg, 0.53 mmol) in MeOH (8 mL) were added sodium hydroxide (1 N, 4 mL) and benzaldehyde (0.5 mL, 3.7 mmol) in an ice bath. The mixture was refrigerated for 14 h. The mixture was neutralized with 1 N HCl and extracted with $CHCl_3$ (3×). The combined organic layers were washed with brine, dried, and concentrated to afford a crude product which was purified on a Sephadex Column (CH-20, MeOH) to give 7 (113 mg, 50%): mp 230 °C dec; $R_f$ 0.60 ($CHCl_3$–MeOH–acetone, 19:0.5:0.1); IR (liquid film, $cm^{-1}$) 1685, 1611; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 0.12–0.15 (m, 2 H), 0.52–0.58 (m, 2 H), 0.79–0.90 (m, 1 H), 1.64 (d, $J$ = 11.9 Hz, 1 H), 2.22–2.50 (m, 6 H), 2.63–2.77 (m, 2 H), 3.01 (d, $J$ = 15.3 Hz, 1 H), 3.13 (d, $J$ = 18.6 Hz, 1 H), 3.21 (d, $J$ = 6.2 Hz, 1 H), 4.72 (s, 1 H), 6.63 (d, $J$ = 8.1 Hz, 1 H), 6.75 (d, $J$ = 8.1 Hz, 1 H), 9.85 (m, 5 H); MS *m/e* 429 ($M^+$, EI). 7·HCl: $R_f$ 0.72 (butanol–acetone–$H_2O$, 2:1:1); mp 210 °C dec. Anal. ($C_{27}H_{27}O_4N{\cdot}HCl$) C, H, N, Cl.

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