# 14-Desoxy Analogues of Naltrindole and 7-Spiroindanyloxymorphone: The Role of the 14-Hydroxy Group at δ Opioid Receptors

Tushar A. Kshirsagar, Xinqin Fang, and Philip S. Portoghese*

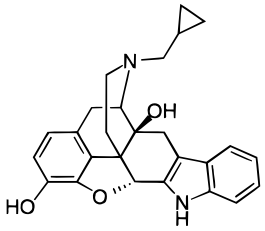
*Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455*

*Received April 3, 1998*

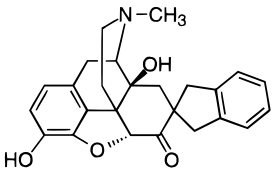
The 14-hydroxy group is known to increase the antagonist potency of μ-selective opioid ligands. To investigate the role of this group at the δ opioid receptor, the 14-desoxy analogues (**7** and **9**) of the δ-selective ligands, naltrindole (**1**, NTI) and spiroindanyloxymorphone (**2**, SIOM), have been synthesized and tested. The in vitro pharmacologic activities of **7** and **9** suggest that the 14-hydroxy group plays an important role in determining the δ selectivity and potency of NTI and SIOM.

## Introduction

Peptide and nonpeptide opioid ligands mediate their pharmacological effect through interaction with membrane-bound G protein-coupled receptors.[1] The fact that there are different types of opioid receptors, namely, μ, κ, and δ, has stimulated the design of a variety of selective ligands as pharmacologic tools. Nonpeptide ligands have proved useful in both in vitro and in vivo studies,[1] and in this regard, naltrindole[2] (**1**, NTI) and 7-spiroindanyloxymorphone (**2**, SIOM)[3] are examples of δ-selective antagonist and δ-selective agonist ligands. The selectivity of these ligands for δ receptors has been ascribed to the benzene moiety which functions as an "address".[4]



**1**



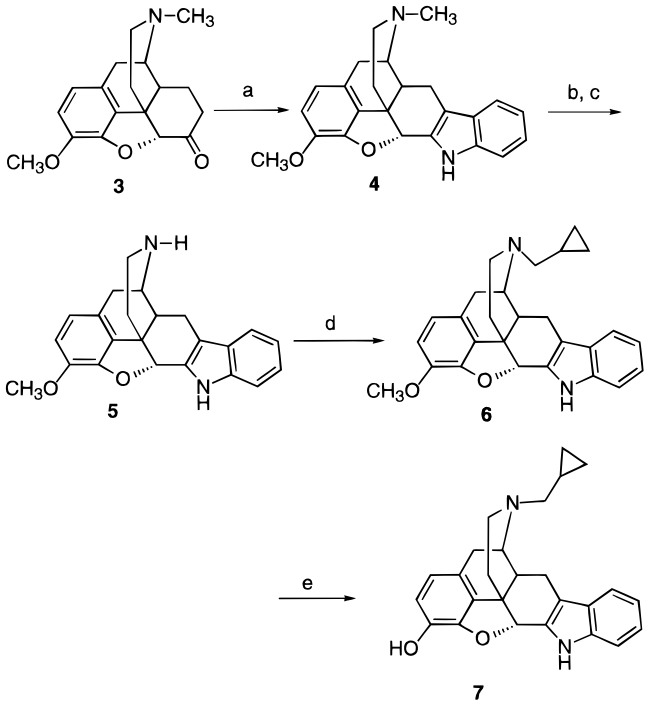
**2**

Structure−activity relationship studies of these ligands have focused primarily on the "address" moiety and on the tertiary nitrogen (N-17).[5−14] Since the role of the 14-hydroxy group has not been reported, the present study was carried out to determine how this group affects potency and selectivity at δ opioid receptors. The results indicate that the presence of the 14-hydroxy group is important for the antagonist potency and selectivity of NTI and essential for the δ agonist efficacy of SIOM.

## Chemistry

The synthesis of **7** was carried out via the Fischer indole reaction as depicted in Scheme 1. Hydrocodone (**3**) was refluxed with phenylhydrazine in methanolic HCl to yield the corresponding indole **4** in 92% yield. The indole **4** was N-demethylated using vinyl chloroformate to afford **5** (20%) which was N-alkylated with cyclopropylmethyl bromide to give **6** (65%). The cleavage of the methyl ether in **6** using boron tribromide yielded the target compound **7** (66%).

**Scheme 1**[a]



[a] (a) Phenylhydrazine, methanolic HCl, reflux, 10 h; (b) vinyl chloroformate, $K_2CO_3$, reflux, 36 h; (c) 2 N HCl, EtOH; (d) cyclopropylmethyl bromide, $Na_2CO_3$, reflux, 14 h; (e) $BBr_3$, $CH_2Cl_2$.

The key step in the synthesis of compound **9** was the base-promoted double alkylation of hydrocodone (**3**) with α,α′-dibromo-*o*-xylene to generate a spiro center at C-7 on the morphinone ring system (Scheme 2). The cyclization reaction was problematic because of quaternization of the tertiary amine group (N-17) of **3**. This difficulty was partially circumvented by using hexamethylphosphoramide (HMPA) as a polar aprotic cosolvent to enhance the nucleophilicity of the enolate intermediate toward the dibromide. Thus, in the absence of HMPA, only 3% yield of desired product **8** was isolated, while in its presence **8** was isolated in 10% yield. Treatment of methyl ether **8** with boron tribromide afforded the target compound **9** (49%).

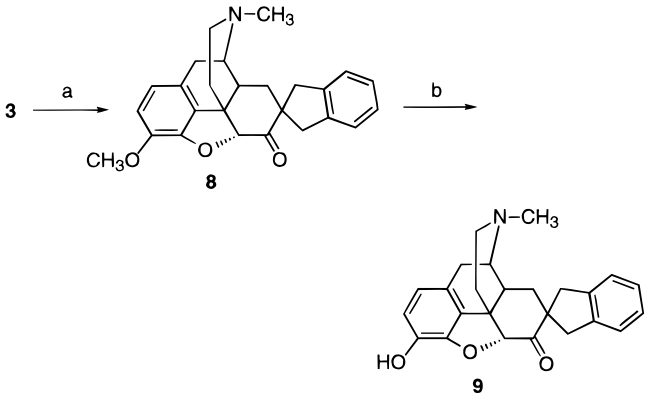
S0022-2623(98)00209-X CCC: $15.00 © 1998 American Chemical Society
Published on Web 06/16/1998

**Table 1.** Opioid Agonist and Antagonist Activities in Smooth Muscle Preparations

| | MVD | | | GPI | | |
|---|---|---|---|---|---|---|
| | agonism $IC_{50}$[a] or % | antagonism $IC_{50}$ ratio[b] | | agonism $IC_{50}$[a] or % | antagonism $IC_{50}$ ratio[b] | |
| compd | max response[c] | DADLE ($\delta$) | $K_e$ | max response[c] | morphine ($\mu$) | EK ($\kappa$) |
| **1** (NTI) | 37.1 ± 8.6% | 152.0 ± 34.0[d] | 0.13 | 7.6 ± 10.1% | 7.8 ± 1.6 | 5.4 ± 0.8 |
| **2**[e] (SIOM) | 22.0 ± 9.0 nM | *f* | | 55 ± 11% | 1.2 ± 0.5 | 1.0 ± 0.3 |
| **7** | 22.6 ± 11.0% | 34.6 ± 10.3 | 2.98 | 16.85 ± 4.89% | 2.01 ± 1.10 | 1.64 ± 0.35 |
| **9** | 58.6 ± 7.9% | 0.85 ± 0.3 | | 153 ± 39 nM | *f* | *f* |

[a] The $IC_{50}$ (±SE) is the concentration of the agonist required for half-maximal response of the preparation ($n \geq 3$). [b] Unless otherwise specified, the $IC_{50}$ ratio is the $IC_{50}$ in the presence of antagonist (100 nM) divided by the control $IC_{50}$ value ($n \geq 3$). [c] Percent of maximal agonist response (±SE) at 1 mM. [d] Reference 5; concentration of **1** was 20 nM. [e] Reference 9. [f] Not determined due to strong agonism.

**Scheme 2**[a]




[a] (a) α,α′-Dibromo-*o*-xylene, $LiN(SiMe_3)_2$, 12-crown-4, HMPA, THF; (b) $BBr_3$, $CH_2Cl_2$; 2 N HCl.

## Biological Results

**Smooth Muscle Preparations.** The target compounds were evaluated for opioid agonist and antagonist activity in the electrically stimulated mouse vas deferens[15] (MVD) and the guinea pig ileum[16] (GPI) preparations as previously described.[17] The agonist activity (Table 1) was determined by the ability of the compound to decrease the twitch height of the electrically stimulated smooth muscle. Initially a dose of 1 $\mu$M was employed, and if the compound showed full agonist behavior, then 4−6 different concentrations were employed to construct a dose−response curve. Testing for antagonist activity (Table 1) was carried out by preincubating the muscle preparation with the test compound for 15 min prior to testing with a standard agonist, [D-Ala$^2$,D-Leu$^5$]enkephalin[18] (DADLE), in the MVD. Morphine and ethylketazocine (EK) were employed in the GPI. The antagonist potency is expressed as the $IC_{50}$ ratio, which is the $IC_{50}$ of the standard agonist in the presence of the test compound divided by the control $IC_{50}$ of the agonist alone. When this ratio was significantly greater than 1, the antagonist potency was expressed as the $K_e$ value which is calculated as $K_e$ = [antagonist]/($IC_{50}$ ratio − 1).

The 14-desoxy compound **7** exhibited partial agonist activity in the GPI and the MVD similar to that of the analogous prototypical ligand, NTI.[5] Its antagonist potency in the MVD was 23-fold less than that of NTI. In the GPI preparation, **7** showed marginal antagonist activity. In contrast to the 14-hydroxy analogue **2**,[3] compound **9** was a partial agonist in the MVD. In the GPI, **9** was found to be a full agonist and it exhibited wash-resistant activity (16% recovery of twitch height after 40 washes). The agonist effect was only partially antagonized by treatment with the $\kappa$-antagonist, norbinaltorphimine (norBNI), whereas treatment with the naltrexone produced complete recovery.

## Discussion

Both compounds (**7**, **9**) lacking the 14-hydroxy group displayed lower $\delta$ agonist and antagonist potencies in the MVD assay when compared with their corresponding analogues, NTI (**1**) and SIOM (**2**). Thus, the $\delta$ antagonist potency of NTI was greater than 20-fold that of its analogue **7**, and in contrast to the $\delta$ agonist activity of SIOM (**2**), its analogue **9** behaved as a partial agonist. These data are in harmony with reports[19] on the potency-enhancing effect of the 14-hydroxy group of other opiate-derived ligands and indicate that the 14-hydroxy group may play an important role in modulating the potency of both $\delta$ agonists and antagonists. In particular, the partial $\delta$ agonist character of **9** suggests that the 14-hydroxy group is an important contributor to the efficacy of **2** at $\delta$ receptors. On the other hand, the presence of a 14-hydroxy group in the spiroindanyl opiates appears to have the opposite effect at $\mu$ opioid receptors, as suggested by the partial agonist character of **2** and the full agonist activity of **9** which appear to be mediated through $\mu$ receptors.

Although the design of SIOM as a $\delta$-selective agonist was based on the preferred conformations of the Phe$^4$ residue in several $\delta$-selective enkephalin analogues,[3] the structural relationship between the 7-spiroindanyl series and other classes of nonpeptide $\delta$ agonists[20,21] is unclear. It appears that there are no obvious structural features in other nonpeptide $\delta$ agonist ligands that correspond or may substitute for the 14-hydroxy of SIOM. The fact that the 14-hydroxy is in an axial conformation and vicinal to the protonated basic nitrogen of these opiates suggests that it may enhance activity by electronically stabilizing ion-pair formation at the receptor. Indeed, Scherrer[22] has made a good case for analogous stabilization of ion-pair formation for a variety of amines containing neighboring electronegative groups.

In conclusion, the 14-hydroxy group is an important determinant of receptor selectivity for NTI and SIOM. In the case of NTI, this selectivity is derived largely from the ability of the 14-hydroxy group to increase antagonist potency at $\delta$ receptors. With respect to SIOM, it appears to be a requirement for $\delta$ agonist efficacy. The apparent generality of the potency-enhancing effect of the 14-hydroxy may arise from electronic stabilization of ion-pair formation of the ligand at the receptor. This information should be useful in the design of opiate ligands that are selective for $\delta$ opioid receptors.

## Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on Analtech silica gel GHLF glass plates. Column chromatography was performed with silica gel (200−400 mesh; Aldrich Chemicals). Chromatographic solvent systems are reported as volume/volume. All reagents and solvents employed were reagent grade and were used without further purification. Infrared spectra were recorded on a Perkin-Elmer 281 spectrometer. Nuclear magnetic resonance spectra were recorded on a GE Omega 300-MHz NMR instrument or on a Varian 300-MHz NMR instrument at room temperature (18−20 °C). The $\delta$ (ppm) scale was in reference to the deuterated solvent. The coupling constants are reported in Hz. The mass spectra were obtained from the Mass Spectrometry Laboratory of the Department of Chemistry, University of Minnesota. Microanalyses were performed by MHW Laboratories, Phoenix, AZ. Where indicated by the symbols of the elements, analyses were within ±0.4% of the theoretical values unless otherwise indicated.

**6,7-Didehydro-4,5α-epoxy-3-methoxy-17-methyl-6,7:2′,3′-indolomorphinan (4).** Hydrocodone (**3**) (500 mg, 1.75 mmol) was dissolved in methanolic HCl (25 mL), and phenylhydrazine hydrochloride (429 mg, 3 mmol) was added with stirring. The reaction mixture was refluxed for 10 h. The precipitate obtained was filtered, washed with $CHCl_3$ (4 × 10 mL), and dried to give **4**·HCl (586 mg, 92%): $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.21−7.35 (m, 2H, H-4′ and H-7′), 7.09 (m, 1H, indole ring), 6.9 (m, 1H, indole ring), 6.59 (m, 2H, H-1 and H-2), 5.75 (s, 1H, H-5); FABMS *m*/*z* 359 (M + 1).

**6,7-Didehydro-4,5α-epoxy-3-methoxy-6,7:2′,3′-indolomorphinan (5).** Compound **4**·HCl (574 mg, 1.46 mmol) was dissolved in dichloroethane, and $K_2CO_3$ (700 mg, 5 mmol) was added. The reaction mixture was stirred in an inert atmosphere, and vinyl chloroformate (0.8 mL, 9 mmol) was added dropwise. After the mixture refluxed for 36 h, it was filtered. The filtrate was evaporated to dryness and dissolved in EtOH (10 mL). To this solution was added 2 N HCl (5 mL), and the mixture was refluxed for 2 h. The solvent was evaporated, and the residue was neutralized with saturated $NaHCO_3$ solution. The product was extracted with EtOAc (4 × 50 mL). The extracts were combined, washed with brine, dried over $Na_2SO_4$, and filtered, and the solvent was evaporated to yield **5**. The pure compound **5** (100 mg, 20%) was obtained by passing it through a column of silica gel ($CHCl_3$/MeOH, 90:10): $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.27 (m, 2H, H-4′ and H-7′), 7.02 (m, 1H, indole ring), 6.88 (m, 1H, indole ring), 6.49 (m, 2H, H-1 and H-2), 5.60 (s, 1H, H-5); FABMS *m*/*z* 345 (M + 1).

**17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3-methoxy-6,7:2′,3′-indolomorphinan (6).** Compound **5** (320 mg, 0.9 mmol) was dissolved in EtOH (30 mL), and $NaHCO_3$ (1.5 g, 17.85 mmol) was added. To the mixture was added cyclopropylmethyl bromide (0.48 mL, 5 mmol), and the reaction mixture was refluxed under nitrogen for 14 h. The mixture was then concentrated, and water (50 mL) was added to the residue. The product was extracted with $CHCl_3$ (4 × 30 mL). The combined extracts were dried over $Na_2CO_3$, evaporated, and chromatographed through a silica gel column ($CHCl_3$/MeOH, 95:5) to yield **6** (239 mg, 65%). The free base was converted to the HCl salt with ethereal HCl: mp > 250 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.40 (m, 1H, H-4′), 7.28 (m, 1H, H-7′), 7.16 (m, 1H, indole ring), 7.05 (m, 1H, indole ring), 6.65 (m, 2H, H-1 and H-2), 5.74 (s, 1H, H-5), 0.95 (m, 1H, H-19), 0.58 (m, 2H, H-20 and H-21), 0.20 (m, 2H, H-20 and H-21); FABMS *m*/*z* 413.3 (M + 1).

**17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-6,7:2′,3′-indolomorphinan (7).** A solution of $BBr_3$ in $CH_2Cl_2$ (1 M, 5 mL, 5 mmol) was added dropwise to a cooled stirred solution of **6** (239 mg, 0.58 mmol) in $CH_2Cl_2$ (20 mL) with continuous stirring. The mixture was stirred at room temperature for 1 h, and then 2 N HCl (15 mL) was added. The mixture was refluxed for 30 min and the reaction was quenched with saturated $NaHCO_3$ solution. The product was extracted with $CH_2Cl_2$ (4 × 50 mL), the extracts were combined and dried, and the solvent was evaporated. The residue was purified by passing through a column of silica gel ($CHCl_3$/MeOH, 90:10) to yield **7** (152 mg, 66%), TLC $R_f$ ($CHCl_3$/MeOH, 19:1) = 0.2, and converted to the HCl salt: mp > 250 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.32 (m, 2H, H-4′ and H-7′), 7.09 (m, 1H, indole ring), 6.95 (m, 1H, indole ring), 6.54 (m, 2H, H-1 and H-2), 5.62 (s, 1H, H-5), 0.95 (m, 1H, H-19), 0.58 (m, 2H, H-20 and H-21), 0.20 (m, 2H, H-20 and H-21); FABMS *m*/*z* 399.3 (M + 1). Anal. ($C_{26}H_{26}N_2O_2$·HCl·$H_2O$) C, H, N.

**4,5α-Epoxy-17-methyl-3-methoxymorphinan-6-one-7-spiro-2′-indan (8).** To a stirred solution of hexamethylphosphoramide (5 mL) and 12-crown-4 (3.58 mL, 22.1 mmol) in dry THF (10 mL) was added lithium bis(trimethylsilyl)amide (1.0 M solution in THF, 22.1 mL, 22.1 mmol) under argon. After 2 min, hydrocodone **3** (free base, 2.2 g, 7.35 mmol) in dry THF (25 mL) was added via syringe, and the resulting solution was stirred at room temperature for 5 min. α,α′-Dibromo-*o*-xylene (4.85 g, 18.4 mmol) in THF (10 mL) was introduced via syringe, and the reaction mixture was refluxed at 65 °C (oil bath) for 12 h. Upon cooling, the mixture was poured into water (150 mL) and extracted with chloroform (80 mL × 3), and the combined organic layers were thoroughly washed with brine, dried over anhydrous $Na_2SO_4$, filtered through Celite, and evaporated. The residue was separated by column chromatography on silica gel, eluting with 1−5% methanol and 1% $NH_3$ in chloroform, to afford **8** (280 mg, 10% yield) (the sample contained a small amount of impurity and was carried to the next step without further purification): TLC $R_f$ ($CHCl_3$/MeOH, 97:3) = 0.24; mp 224−226 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.2−7.0 (m, 4H, indan CH), 6.77 (d, 1H, $J$ = 8.4 Hz, H-2), 6.60 (d, 1H, $J$ = 8.4 Hz, H-1), 4.84 (s, 1H, H-5), 3.85 (s, 3H, OMe), 3.64 (d, 1H, $J$ = 16.3 Hz, indan $CH_2$), 3.32 (m, 1H, H-9), 3.25 (d, 1H, $J$ = 15.6 Hz, indan $CH_2$), 3.02 (d, 1H, $J$ = 16.3 Hz, indan $CH_2$), 2.90 (d, 1H, $J$ = 18.6 Hz, H-10$\beta$), 2.68 (m, 1H, H-14), 2.49 (s, 3H, NMe), 2.37 (m, 1H, H-10α), 2.29 (d, 1H, $J$ = 15.6 Hz, indan $CH_2$), 2.20 (m, 1H, H-8$\beta$), 1.8−1.7 (m, 2H), 1.38 (t, 1H, $J$ = 14.3 Hz, H-8α); HRMS (FAB) calcd for $C_{26}H_{28}NO_3$ (M + H) 402.2069, found 402.2073.

**4,5α-Epoxy-3-hydroxy-17-methylmorphinan-6-one-7-spiro-2′-indan (9).** To a stirred, cold solution of the methyl ether **8** (255 mg, 0.635 mmol) in dichloromethane (25 mL, freshly distilled over $CaH_2$) at 0 °C was added boron tribromide (1.0 M solution in dichloromethane, 2.0 mL, 2.0 mmol) via syringe under argon atmosphere. The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 90 min. Hydrochloric acid (2 N HCl, 20 mL) was added, and the resulting mixture was heated to reflux for 1 h. After cooling to room temperature, the mixture was adjusted to pH 8.5 with aqueous $NaHCO_3$ solution, and then extracted with chloroform (60 mL × 4). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated under vacuum. The remaining solid was purified by flash chromatography on silica gel (5% MeOH, 1% $NH_3$ in chloroform), to afford **9** (120 mg, 49%): TLC $R_f$ ($CHCl_3$/MeOH, 95:5) = 0.18; mp 235−236 °C; IR ($CHCl_3$) 1719.1 cm$^{-1}$ (C=O); $^1$H NMR ($CDCl_3$) $\delta$ 8.1 (br, 1H, OH), 7.13−7.04 (m, 4 H, indan CH), 6.74 (d, 1H, $J$ = 8.1 Hz, H-2), 6.61 (d, 1H, $J$ = 8.1 Hz, H-1), 4.82 (s, 1H, H-5), 3.62 (d, 1H, $J$ = 16.2 Hz, indan $CH_2$), 3.31 (m, 1H, H-9), 3.24 (d, 1H, $J$ = 15.6 Hz, indan $CH_2$), 3.00 (d, 1H, $J$ = 16.2 Hz, indan $CH_2$), 2.92 (d, 1H, $J$ = 18.5 Hz, H-10$\beta$), 2.67 (m, 1H, H-14), 2.55 (m, 1H), 2.47 (s, 3 H, NMe), 2.37 (m, 1H, H-10α), 2.30 (d, 1H, $J$ = 15.6 Hz, indan $CH_2$), 2.22−2.17 (m, 1H, H-8$\beta$), 1.81−1.69 (m, 2H), 1.40 (t, 1H, $J$ = 14.0 Hz, H-8α), 1.26−1.36 (m, 1H); $^{13}$C NMR-DEPT ($CDCl_3$) $\delta$ $CH_3$ (42.23), $CH_2$ (46.32, 40.06, 39.52, 36.33, 34.67, 19.97), CH (126.87, 126.61, 124.49, 124.39, 120.06, 118.61, 89.79, 58.74, 37.74), quaternary carbons (208.89, 144.17, 141.74, 140.01, 138.70, 126.41, 123.88, 56.52 (C-7), 46.80); HRMS (FAB) calcd for $C_{25}H_{26}NO_3$ (M + H) 388.1913, found 388.1909. The free base was converted to its hydrochloride salt by treatment with ethereal HCl. Anal. ($C_{25}H_{25}NO_3$·HCl) C, H, N.

**Acknowledgment.** This work was supported by the National Institutes on Drug Abuse. We thank Mike Powers, Veronika Phillips, and Reynold Francis for capable technical assistance.

## References

(1) Dhawan, B. N.; Cesselin, F.; Raghubir, R.; Reisine, T.; Bradley, P. B.; Portoghese, P. S.; Hamon, M. International Union of Pharmacology. XII. Classification of Opioid Receptors. *Pharmacol. Rev.* **1996**, *48*, 567−592.

(2) Portoghese, P. S.; Sultana, M.; Takemori, A. E. Naltrindole, A Highly Selective and Potent Non-peptide δ Opioid Receptor Antagonist. *Eur. J. Pharmacol.* **1988**, *146*, 185−186.

(3) Portoghese, P. S.; Moe, S. T.; Takemori, A. E. A Selective δ1 Opioid Receptor Agonist Derived from Oxymorphone. Evidence for Separate Recognition Sites for δ1 Opioid Receptor Agonists and Antagonist. *J. Med. Chem.* **1993**, *36*, 2572−2574.

(4) Portoghese, P. S.; Sultana, S.; Nagase, H.; Takemori, A. E. Application Of The Message-Address Concept In The Design Of Highly Potent And Selective Non-peptide δ Opioid Antagonists. *J. Med. Chem.* **1988**, *31*, 281−282.

(5) Portoghese, P. S.; Sultana, M.; Takemori, A. E. Design of Peptidomimetic δ Opioid Receptor Antagonist Using The Message-Address Concept. *J. Med. Chem.* **1990**, *33*, 1714−1720.

(6) Portoghese, P. S.; Nagase, H.; MaloneyHuss, K. E.; Lin, C.-E.; Takemori, A. E. Role of Spacer and Address Components in Peptidomimetic δ Opioid Receptor Antagonists Related to Naltrindole (NTI). *J. Med. Chem.* **1991**, *34*, 1715.

(7) Portoghese, P. S.; Sultana, M.; Nelson, W. L.; Klein, P.; Takemori, A. E. δ Opioid Antagonist Activity and Binding of Regioisomeric Isothiocyanate. Derivatives of Naltrindole: Evidence for δ Opioid Receptor Subtypes. *J. Med. Chem.* **1992**, *35*, 4086−4091.

(8) Portoghese, P. S.; Larson, D. L.; Sultana, M.; Takemori, A. E. Opioid Agonist and Antagonist Activities of Morphindoles Related to Naltrindole. *J. Med. Chem.* **1992**, *35*, 4325−4329.

(9) Portoghese, P. S.; Sultana, M.; Moe, S. T.; Takemori, A. E. Synthesis of Naltrexone-Derived δ-Opioid Antagonists. Role of Conformation of the δ-Address Moiety. *J. Med. Chem.* **1994**, *37*, 579−585.

(10) Portoghese, P. S.; Ohkawa, S.; Moe, S. T.; Takemori, A. E. Synthesis and δ-Opioid Receptor Antagonist Activity of a Naltrindole Analogue with a Regioisomeric Indole Moiety. *J. Med. Chem.* **1994**, *37*, 1886−1888.

(11) Portoghese, P. S.; Farouz-Grant, F.; Sultana, M.; Takemori, A. E. 7′-Substituted Amino Acid Conjugates of Naltrindole. Hydrophilic Groups as Determinants of Selective Antagonism of $\delta_1$ Opioid Receptor-mediated Antinociception in Mice. *J. Med. Chem.* **1995**, *38*, 402−407.

(12) Ohkawa, S.; DiGiacomo, B.; Larson, D. L.; Takemori, A. E.; Portoghese, P. S. 7-Spiroindanyl Derivatives of Naltrexone and Oxymorphone as Selective Ligands for Delta Opioid Receptors. *J. Med. Chem.* **1997**, *40*, 1720−1725 1997.

(13) Farouz-Grant, F.; Portoghese, P. S. Pyrrolomorphinans as δ Opioid Receptor Antagonists. The Role of Steric Hindrance in Conferring Selectivity. *J. Med. Chem*, **1997**, *40*, 1977−1981.

(14) Fang, X.; Larson, D. L.; Portoghese, P. S. 7-Spirobenzocyclohexyl Derivatives of Naltrexone Oxymorphone, and Hydromorphone as Selective Opioid Receptor Ligands. *J. Med. Chem.* **1997**, *40*, 3064−3070.

(15) Henderson, G.; Hughes, J.; Kosterlitz, H. W. A New Example of a Morphine-Sensitive Neuro-Effector Junction: Adrenergic Transmission in the Mouse Vas Deferens. *Br. J. Pharmacol.* **1972**, *46*, 746−766.

(16) Rang, H. P. Stimulant actions of Volatile Anaesthetics on Smooth Muscle. *J. Pharmacol. Ther.* **1965**, *22*, 356−365.

(17) Portoghese, P. S.; Takemori, A. E. TENA. A Selective Kappa Opioid Receptor Antagonist. *Life Sci.* **1986**, *36*, 801−805.

(18) Fournie-Zaluski, M.-C.; Gacel, G.; Maigret, B.; Premilat, S.; Roques, B. P. Structural Requirements for Specific Recognition of Mu or Delta Opiate Receptors. *Mol. Pharmacol.* **1981**, *20*, 484−491.

(19) Casy, A. F.; Parfitt, R. T. 4,5-Epoxymorphinans. *Opioid Analgesics*; Plenum Press: New York, 1986; Chapter I, pp 54−68.

(20) Knapp, R. J.; Landsman, R.; Waite, S.; Malatynska, E.; Varga, E.; Haq, W.; Hruby, V. J.; Roeska, W. R.; Nagase, H.; Yamamura, H. I. Properties of TAN-67, a Nonpeptidic δ Opioid Receptor Agonist, at Cloned Human δ and μ Opioid Receptor. *Eur. J. Pharmacol.* **1995**, *291*, 129−134.

(21) Calderon, S. N.; Rothman, R. B.; Porreca, F.; Flippen-Anderson, J. L.; McNutt, R. W.; Xu, H.; Smith, L. E.; Bilsky, E. J.; Davis, P.; Rice, K. C. Probes for Narcotic Receptor Mediated Phenomenon. 19. Synthesis of (+)-4-[(aR)-a-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide (SNC80): a Highly Selective Nonpeptide δ Receptor Agonist. *J. Med. Chem.* **1994**, *37*, 2125−2128.

(22) Scherrer, R. A. Factors Affecting Ion-Pair Partitioning and "Octanol p$K_a$". 11th European QSAR Meeting, Lausanne, 1996.

JM980209B