7-Spiroindanyl Derivatives of Naltrexone and Oxymorphone as Selective Ligands for δ Opioid Receptors

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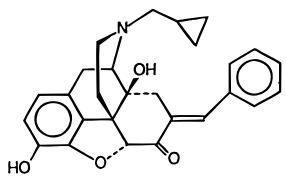
A series consisting of spiroindanyl (**5**−**7**), benzospiroindanyl (**8**−**10**), and spiroperinaphthyl (**11**) derivatives of naltrexone and oxymorphone were synthesized in order to investigate the role of an orthogonal-oriented "address" for δ opioid receptors. All of the ligands exhibited a preference for δ receptors in vitro. The 7-benzospiroindanyl derivative **8** (BSINTX) was the most selective δ opioid receptor antagonist in vitro. In mice BSINTX antagonized the δ_1-selective agonist, [D-Pen^2,D-Pen^5]enkephalin without significantly affecting the antinociceptive potency of δ_2, μ, and κ agonists. The results of this study are consistent with an orthogonally-oriented address favoring δ_1 activity.

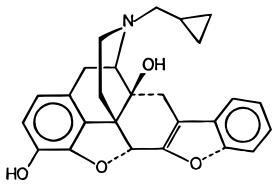
Introduction

It is now firmly established that there are at least three major types of receptors (μ, κ, μ) that have high affinity for endogenous opioid peptides.[1] The enkephalins appear to be generally accepted as the endogenous ligands for δ opioid receptors, and in vivo pharmacological studies now suggest the presence of two subtypes: δ_1 and δ_2.[2,3]

Two nonpeptide antagonists, 7-benzylidenenaltrexone[4] (**1**, BNTX) and naltriben[2] (**2**, NTB), are presently widely employed as δ_1 and δ_2 antagonists, respectively. BNTX selectively antagonizes the agonist effect of [D-Pen^2,D-Pen^5]enkephalin (DPDPE), while NTB selectively blocks [D-Ser^2,D-Leu^5]enkephalin-Thr^6 (DSLET) and deltorphin II. The fact that the preferred conformation of the benzylidene phenyl group is approximately orthogonal to ring C of BNTX led to the suggestion that this orientation favors δ_1 activity.[5] In contrast, the aromatic group of the δ_2 antagonist, NTB, is coplanar to ring C.

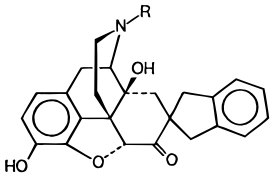


1, BNTX



2, NTB

Subsequent studies involved the synthesis of 7-spiroindanyloxymorphone (**3**, SIOM) and 7-spiroindanylnaltrexone (**4**, SINTX).[6,7] The rationale for the design of these ligands was to rigidly hold the benzene moiety of the indanyl substituent in an orthogonal position relative to ring C of the morphinan because molecular dynamics simulations of the δ_1 agonist, DPDPE,[8−10] revealed that many of the conformations of its Phe^4 phenyl group matched BNTX better than NTB. The fact that SIOM was more potently antagonized by BNTX than by NTB in vivo was consistent with the orthogonal orientation of its "address". Although SINTX was found to be a potent and selective δ antagonist in vitro, its in vivo profile, while favoring δ_1 receptors, had relatively low antagonist selectivity.



3, R = CH_3 (SIOM)
4, R = $CH_2CH(CH_2)_2$ (SINTX)

In this paper we present the synthesis and biological evaluation of a series of compounds (**5**−**11**) that contain substituted spiroindanyl (**5**−**7**), benzospiroindanyl (**8**-**10**), and spiroperinaphthyl (**11**) groups in an effort to explore the structure−selectivity relationship of ligands that possess an orthogonal aromatic system relative to ring C of the morphinan.

Chemistry

The target compounds **5**−**11** were prepared (Scheme 1) from *O*-benzyl-protected derivatives of naltrexone (**12**) or oxymorphone (**13**) by double alkylation with bis-(bromomethyl) derivatives of methoxybenzene (**14**, **15**) or naphthalene (**16**−**18**). The alkylation was effected with a combination of lithium hexamethyldisilazane (LHMDS) and 12-crown-4 in tetrahydrofuran (THF). The yields of the benzyl-protected spiro intermediates **5a**−**11a** were in the range of 42−83%. In the absence of crown ether, no product was obtained, and starting material was recovered when the reaction was conducted in THF.

The *O*-benzyl group of the intermediates **5a**−**11a** was removed by catalytic hydrogenation (Pd−C) to afford target compounds **5**−**11**. Compounds **5**−**7** and **10** were obtained as mixtures of two C-7 epimers which were present in approximately equal amounts.

The bis(bromomethyl) derivatives of anisole (**14**, **15**) and naphthalene (**16**−**18**) that were employed in the double alkylation reaction were prepared using two different methods. Compounds **14**−**16** were obtained from the corresponding dimethyl derivatives using

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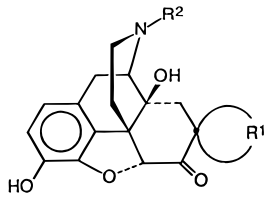
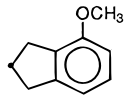
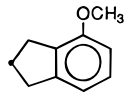
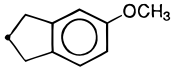
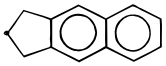
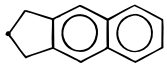
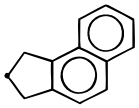
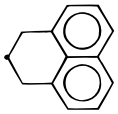
Chart 1



	R1	R2
5		$CH_2CH(CH_2)_2$
6		CH_3
7		$CH_2CH(CH_2)_2$
8		$CH_2CH(CH_2)_2$
9		CH_3
10		$CH_2CH(CH_2)_2$
11		$CH_2CH(CH_2)_2$

N-bromosuccinimide and benzoylperoxide in carbon tetrachloride (method 1). The bis(bromomethyl)naphthalenes **17** and **18** were prepared by reduction of the corresponding dicarboxylic acid or anhydride with lithium aluminum hydride in THF followed by treatment of the diols **17a** and **18a** with phosphorous tribromide (method 2).

Biological Results

Smooth Muscle Preparations. The opioid activity of **5**−**11** was evaluated on the electrically-stimulated guinea pig ileum[11] (GPI) and the mouse vas deferens[12] (MVD) preparations as reported previously.[13] The ligands were incubated with the preparation for 15 min prior to testing. The standard agonists morphine (M), ethylketazocine (EK), and [D-Ala^2,D-Leu^5]enkephalin[14] (DADLE) were employed when testing for antagonist activity. They are selective μ, κ, and δ opioid agonists, respectively. Three or more replicate determinations were carried out for each compound. The antagonist potency is expressed as an IC_{50} ratio, which is the IC_{50} of the agonist in the presence of the antagonist (100 nM) divided by the control IC_{50} in the same preparation. Ligands that were not full agonists were tested at a concentration of 1 μM, and the agonist activity is expressed as a percent of the maximal response. SIOM (**3**) and SINTX (**4**) were employed as reference compounds.

All of the cyclopropylmethyl-substituted target compounds (**5**, **7**, **8**, **10**, **11**) were δ-selective antagonists in the MVD preparation, with IC_{50} ratios ranging from 12 to 85 for DADLE (Table 1). The most δ-selective antagonist in the series was the benzoindanyl analog **8** (BSINTX) which was more selective than SINTX. Most of the cyclopropyl-substituted compounds exhibited partial agonist activity in the smooth muscle preparations. This ranged up to 14% in the MVD and 52% in the GPI. The *N*-methyl derivative **6** was found to be a full agonist in the MVD and GPI, with a potency in the MVD about the same as that of SIOM (**3**).

In Vivo Studies. Compounds **5**, **6**, **8**, and **9** were evaluated for opioid agonist or antagonist activity using the tail-flick[15] procedure in ICR mice. The *o*-methoxyspiroindan **6** exhibited agonist activity (icv), with an ED_{50} of 71 (57−90) nmol/mouse. The benzospiroindan analogs **8** and **9** were inactive as agonists at 80 nmol/mouse icv and 60 μmol/kg sc, respectively.

The ability of **5**, **8**, and **9** to antagonize the antinociceptive effect of selective agonists is reported as ED_{50} ratios in Table 2. Administration of **5**, **8**, or **9** was timed so that the peak antagonistic effect (20 min) coincided with the center of the observation period. The ED_{50} values of the standard agonists [D-Pen^2,D-Pen^5]enkephalin[16] (DPDPE), [D-Ser^2,Leu^5]enkephalin-Thr^6[17] (DSLET), morphine, and *trans*-(±)-dichloro-*N*-methyl-*N*-(2-pyrrolidinylcyclohexyl)benzeneacetamide[18] (U50488) were determined alone and in the presence of **5**, **8**, or **9**. At a dose of 10 nmol icv, **8** antagonized the δ_1 agonist, DPDPE, without significant antagonism of the δ_2-, μ-, or κ-selective ligands. Compound **5** was nonselective, as suggested by ED_{50} ratios that were greater than unity for all of the standard agonists. The oxymorphone

Table 1. Opioid Agonist and Antagonist Potencies of 7-Spiroindanyl Derivatives of Naltrexone and Oxymorphone

	GPI			MVD			
	antagonism IC_{50} ratio		agonism[b] IC_{50}	antagonism IC_{50}	agonism[b] IC_{50}	antagonist selectivity ratio[c]	
compd	M (μ)	EK (κ)	(nM) or % max resp	ratio DADLE (δ)	(nM) or % max resp	δ/μ	δ/κ
3 (SIOM)	1.2 ± 0.5	0.99 ± 0.33	55 ± 11%	*d*	23 (±9) nM		
4 (SINTX)	24.9 ± 4.3	1.95 ± 0.47	16 ± 9%	130 ± 30	−8 ± 6%	5.2	67
5	6.2 ± 1.1	2.40 ± 0.37	−4.5 ± 5.3%	85 ± 15	−18 ± 13%	13.7	35
6	*d*	*d*	148 ± 51 nM	*d*	27 ± 9 nM		
7	6.9 ± 1.7	2.8 ± 0.6	−52 ± 49%	11.8 ± 2.4	0.6 ± 9%	1.7	4.2
8 (BSINTX)	3.4 ± 1.2	0.24 ± 0.04	52 ± 2%	48 ± 11	4.9 ± 6.5%	14.1	48
9	0.58 ± 0.08	1.2 ± 0.4	13.4 ± 6.7%	1.1 ± 0.3	57 ± 6%	1.0	1.0
10	1.0 ± 0.3	1.7 ± 0.7	13.9 ± 4.5%	25 ± 6	14 ± 8%	25	14.7
11	0.93 ± 0.10	0.78 ± 0.22	11.2 ± 6.3%	12.6 ± 2.5	17.6 ± 2.7%	12.6	12.6

[a] Ratio of agonist IC_{50} values with and without antagonist present. [b] Partial agonist activity is expressed as the percentage inhibition of contraction at a concentration of 1 μM. Full agonist activity is expressed as an IC_{50} (nM). [c] The δ IC_{50} ratio divided by the μ or κ IC_{50} ratio; if the IC_{50} ratio is less than unity a minimum value of 1 is employed in the calculation. [d] Not determined due to full agonist activity.

Scheme 1

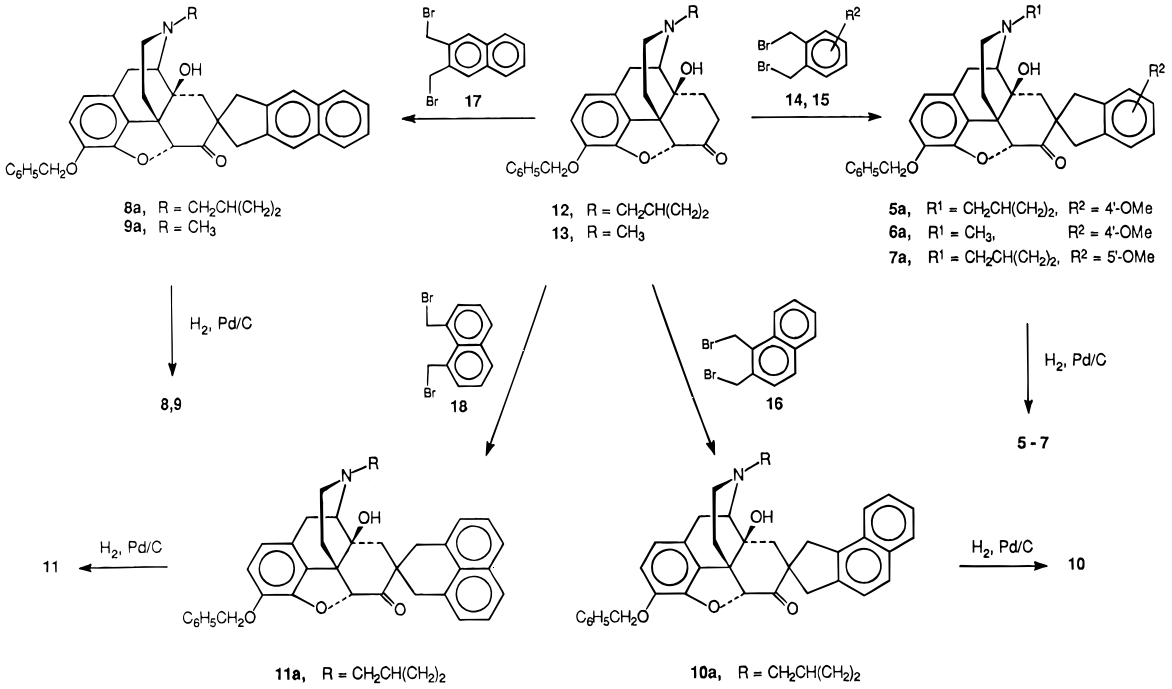


Table 2. Antagonism of the Antinociceptive Effect of Opioid Agonists by **5**, **8**, and **9** in Mice

	ED_{50} ratio (95% confidence limits)[a]			
compd[b]	DPDPE (δ_1)[c]	DSLET (δ_2)[c]	morphine (μ)[d]	U50488 (κ)[d]
1 (BNTX)[e]	7.2 (5.2−10.5)	0.91 (0.37−2.0)	0.80 (0.47−2.1)	1.2 (1.0−1.6)
5	5.6 (3.4−9.1)	4.3 (2.6−8.3)	2.5 (1.2−6.7)	3.4 (1.9−7.7)
8 (BSINTX)	4.4 (2.6−7.1)	1.5 (1.0−2.2)	0.8 (0.3−1.6)	0.8 (0.3−2.3)
9	1.5 (1.0−2.1)	0.9 (0.7−1.3)	2.0 (1.4−2.9)	3.0 (1.9−5.3)

[a] ED_{50} ratio = ED_{50} of agonist in the presence of icv-administered antagonist divided by the control ED_{50}. [b] Compounds **5** and **9** were tested as HCl salts at a dose of 5 nmol; **8** was tested as the phosphate salt at a dose of 10 nmol. [c] Administered icv. [d] Administered sc. [e] Taken from ref 4.

Table 3. Opioid Receptor Binding

	K_i, nM		
compd[b]	[^{3}H]NTI (δ)	[^{3}H]DAMGO (μ)	[^{3}H]U69594 (κ)
3[a]	2.75 ± 0.42 (3)	14.3 ± 3.9 (8)	>3000 (2)
4[b]	0.25 ± 0.06 (6)	1.53 ± 0.62 (3)	>3000 (3)
5	0.028 ± 0.013 (3)	0.44 ± 0.11 (3)	>3000 (2)
6	5.49 ± 1.47 (4)	9.24 ± 3.06 (3)	>3000 (2)
8	*c*	7.81 ± 1.56 (4)	1029 ± 369 (4)
9	31.6 ± 14.4 (3)	125 ± 48 (3)	>3000 (4)

[a] Data obtained from ref 6. [b] Data obtained from ref 7. [c] Apparent noncompetitive inhibition of [^{3}H]NTI binding.

derivative **9** appeared to marginally antagonize the κ antagonist, U50488, with little or no antagonism of other selective agonists.

Binding. Opioid receptor binding data for compounds **5**, **6**, **8**, and **9** were obtained with ICR mouse brain membranes using a modification of the procedure of Werling et al.[19] Binding was evaluated by competition of the compounds with the following selective radioligands: [^{3}H]naltrindole[20,21] ([^{3}H]NTI) (δ), [^{3}H][D-Ala^2,-Glyol^5]enkephalin[17] ([^{3}H]DAMGO) (μ), and [^{3}H]-5α,7α,8β-(−)-*N*-methyl-N-(1-pyrroldinyl)-1-oxaspiro[4.5]dec-8-yl-benzeneacetamide[22] ([^{3}H]U69593).

The K_i values are reported in Table 3. The binding of BSINTX (**8**) to δ sites could not be determined due to the very flat competition curve over a 9 decade concentration range. This was characterized by the inhibition of [^{3}H]NTI binding (40% bound) at exceptionally low concentrations (10^{-16} M) of **8**. One possible explanation for this result could be a noncompetitive type of interaction. While the ligands exhibited greater affinity for δ receptors, the binding of **6** and **9** was not much greater than to μ receptors. Compound **5** possessed the highest δ_1/μ selectivity ratio, with a value of 17. It can be noted that the cyclopropylmethyl compounds **4**, **5**, and **8** more effectively inhibited [^{3}H]NTI binding when compared to the methyl analogs **3**, **6**, and **9**. All four ligands had very low affinity for κ receptors.

Discussion

In an effort to explore the conformational role of the "address" moiety in conferring δ selectivity to nonpeptide opioid ligands, we have previously reported on the conformationally-restricted 6-spiroindanyl opiates **3** and **4** and their substantially greater preference for δ receptors relative to the corresponding parent compounds oxymorphone and naltrexone.[6,7] It was concluded that both coplanar and orthogonal conformations (relative to ring C of the opiate) of the aromatic address moiety are capable of conferring δ antagonist activity. However, the δ_1 agonism appeared to be associated with an orthogonal-like conformation of the address. The present study was undertaken to investigate further the role of an orthogonally-oriented address moiety with regard to the nature of the aromatic group.

The attachment of a methoxy substituent to the 6-spiroindanyl group (**5**−**7**) or the replacement of the benzene moiety with naphthalene (**8**−**11**) afforded ligands

with reduced δ agonist and antagonist potency relative to the unsubstituted spiro prototypes **3** and **4** when tested in smooth muscle preparations. However, because these modifications generally reduced μ and κ antagonist components to a greater degree than δ antagonist potency, the δ/μ and δ/κ selectivity ratios are in most cases greater.

Two of the more potent compounds (**5**, **8**) in the cyclopropylmethyl series were evaluated for antagonist activity in mice. Although the binding data indicated **5** to be a high-affinity, δ-selective ligand, its in vivo profile showed it to be nonselective. In contrast to **5**, the benzospiroindanyl derivative **8** (BSINTX) antagonized only the antinociceptive effect of the δ_1 agonist, DPDPE. No K_i value could be determined for BSINTX because of the flat binding curve that spanned a nine decade concentration range. It was observed that even at a concentration of 10^{-16} M BSINTX, the maximum percentage of [^{3}H]NTI bound was only 40% and in marked contrast with the normal binding curves obtained from competition with μ and κ radioligands. The results suggest that the binding sites for [^{3}H]NTI and BSINTX on the δ receptor may differ.

Although BSINTX (**8**) was a partial agonist in the GPI, with no agonist activity in the MVD, it exhibited no significant agonist activity in vivo. The *N*-methyl analog **9** also was inactive as an agonist in vivo, but in contrast to BSINTX, it displayed nonselective antagonist activity in mice. The binding selectivity of **9** was low for δ receptors, but because of the unusual binding of **8**, a direct comparison of these compounds was not possible. The spiroindanyl analog **6** exhibited agonist activity in mice consistent with full agonist activity in both smooth muscle preparations. The finding that **6** had approximately the same affinity for δ and μ receptors suggests that the in vivo agonist activity was mediated through both δ and μ receptors.

The marked difference in affinity between **5** and **6** (~200-fold) for δ sites and the dramatic disparity between the binding of **8** and **9** suggests profoundly different modes of interaction with δ receptors for the *N*-methyl and *N*-cyclopropylmethyl analogs. The reported[7] different conformational requirement for the "address" moiety of δ agonists and antagonists also is consistent with the present study in that it may also be due to different modes of interaction with the receptor.

In conclusion, the present study has uncovered a selective δ_1 opioid receptor antagonist, BSINTX (**8**). The δ_1 selectivity of BSINTX appears in part to be a consequence of its orthogonal aromatic "address" moiety. In this connection, it has been suggested from prior studies that factors such as differential access to δ receptor subtypes might also contribute to such selectivity.[23] Finally, while the in vitro and in vivo pharmacology suggests that BSINTX mediates its antagonist activity through δ receptors, it appears that BSINTX might not share the same recognition site as the prototypical δ antagonist naltrindole (NTI).

Experimental Section

Melting points were determined in open capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. Analyses were performed by M-H-W Laboratories, Phoenix, AZ. NMR spectra were recorded at ambient temperature on a GE 300 MHz spectrometer. Mass spectra were obtained on a Finnigan 40000, a AEIMS-30, or a VG7070EHF spectrometer. All reagents and solvents were reagent grade. Naltrexone and oxymorphone were supplied by Mallinckrodt.

Method 1: Bis(bromomethyl)aryl Derivatives from Dimethylanisole and Dimethylnaphthalene. 2,3-Bis(bromomethyl)anisole (14). A mixture of 2,3-dimethylanisole (5.0 g, 36.5 mmol), *N*-bromosuccinimide (13.0 g, 73.4 mmol), and benzoyl peroxide (40 mg) in carbon tetrachloride (75 mL) was refluxed for 15 h. The resulting succinimide was removed by filtration, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (chloroform−hexane, 1:4) and then recrystallized from ether−hexane to afford **14** (5.4 g, 68%): mp 78−79 °C; ^{1}H NMR ($CDCl_3$) δ 3.82 (3H, s), 4.63 (2H, s), 6.84 (1H, dd, J = 8.4, 2.4 Hz), 6.91 (1H, d, J = 2.4 Hz), 7.30 (1H, d, J = 8.4 Hz).

3,4-Bis(bromomethyl)anisole (15): yield 65%; mp 49−50 °C; ^{1}H NMR ($CDCl_3$) δ 3.90 (3H, s), 4.62 (2H, s), 4.75 (2H, s), 6.87 (1H, d, J = 8.4 Hz), 6.98 (1H, d, J = 8.4 Hz), 7.27 (1H, t, J = 8.4 Hz).

1,2-Bis(bromomethyl)naphthalene (16): yield 82%; mp 149−150 °C; ^{1}H NMR ($CDCl_3$) δ 4.77 (2H, s), 5.10 (2H, s), 7.43 (1H, d, J = 8.7 Hz), 7.54 (1H, m), 7.64 (1H, m), 7.85 (2H, m), 8.15 (1H, d, J = 8.7 Hz).

Method 2: Bis(bromomethyl)naphthalenes from Naphthalenedicarboxylic Acids. 2,3-Bis(hydroxymethyl)naphthalene (17a). To a suspension of LAH (1.7 g, 44.2 mmol) in THF (50 mL) was added a solution of dimethyl 2,3-naphthalenedicarboxylate (5.4 g, 22.1 mmol) in THF (20 mL), and the mixture was refluxed for 18 h. The cooled mixture was poured into ice−water, neutralized with 1 N HCl, and extracted with EtOAc. The extract was washed with water, dried over anhydrous $MgSO_4$, and concentrated. The crystals of **17a** (2.8 g, 67%), were collected and dried in vacuo: mp 160−161 °C, ^{1}H NMR ($CDCl_3$) δ 4.67 (4H, d, J = 4.8 Hz), 5.23 (2H, t, J = 4.8 Hz), 7.42 (2H, m), 7.85 (4H, m).

1,8-Bis(hydroxymethyl)naphthalene (18a): yield from 1,8-naphthalic anhydride, 53%; mp 157−158 °C; ^{1}H NMR (DMSO-d_6) δ 5.05 (4H, d, J = 6.0 Hz), 5.25 (2H, d, J = 6.0 Hz), 7.42 (2H, d, J = 8.0 Hz), 7.59 (2H, d, J = 8.0 Hz), 7.83 (2H, d, J = 8.0 Hz).

2,3-Bis(bromomethyl)naphthalene (17). To a solution of **17a** (2.0 g, 10.6 mmol) in THF (30 mL) was added PBr_3 (3.8 g, 14.2 mmol), and the mixture was refluxed for 1 h and then cooled. The mixture was diluted with water, and the product was extracted with EtOAc. The extract was washed with aqueous sodium bicarbonate solution and dried and the solvent removed. The residue was recrystallized from chloroform−hexane to afford **17** (2.7 g, 81%): mp 147−148 °C; ^{1}H NMR ($CDCl_3$) δ 4.89 (4H, s), 4.52 (2H, m), 7.81 (2H, m), 7.87 (2H, s).

1,8-Bis(bromomethyl)naphthalene (18): from **18a** using the same procedure, yield 83%; mp 131−132 °C; ^{1}H NMR ($CDCl_3$) δ 5.31 (4H, s), 7.46 (2H, t, J = 14.7 Hz), 7.63 (2H, d, J = 14.7 Hz), 7.89 (2H, d, J = 14.7 Hz).

3-*O*-Benzyl-7-(4′-methoxy-2′-spiroindanyl)naltrexone (5a). To a solution of hexamethyldisilazane (0.4 mL, 1.8 mmol) and 12-crown-4 (0.24 g, 1.38 mmol) in THF (4 mL) was added a 2.5 M solution of *n*-BuLi in hexane (0.54 mL, 1.38 mmol) at −78 °C with stirring. After the mixture stirred for 10 min, a solution of 3-*O*-benzylnaltrexone (200 mg, 0.46 mmol) in THF (2 mL) was added followed by a solution of 3,4-bis(bromomethyl)anisole (**15**) (320 mg, 1.5 mmol). The mixture was allowed to stand for 15 min at room temperature and then refluxed for 3 h. The cooled mixture was diluted with brine, and the product was extracted with EtOAc. The extract was washed with brine and dried, and the solvent was removed. The residue was chromatographed on silica gel (hexane−EtOAc, 4:1) to afford a mixture of **5a** epimers (217 mg, 83%): high-resolution MS (FAB) ($M + H^+$) 564.2772 (calcd for $C_{36}H_{38}NO_5$ 564.2750); ^{1}H NMR ($CDCl_3$) δ 0.14 (2H, m, H-20β, H-21β), 0.55 (2H, m, H-20α, H-21α), 0.85 (1H, m, H-19), 1.56 (1H, d, J = 12.3 Hz, H-15), 1.70 (1H, br s, 14-OH), 1.83 (1H, d, J = 13.5 Hz, H-8), 2.06 (1H, d, J = 13.5 Hz, H-8), 2.10 (1H, m, H-15), 2.37 (1H, d, J = 17.1 Hz, indan CH_2), 2.35−2.55 (3H, m, H-16, H-18), 2.58 (1H, hidden, H-10), 2.71 (1H, d, J = 8.4 Hz), 3.03 (1H, d, J = 18.3 Hz, H-10), 3.13 (1H, d, J = 4.8 Hz,

H-9), 3.21 and 3.23 (1H, d, J = 17.1 Hz, indan CH_2), 3.52 and 3.54 (1H, d, J = 17.1 Hz, indan CH_2), 3.75 (1H, d, J = 17.1 Hz, indan CH_2), 3.78 and 3.80 (3H, s, OMe), 5.01 and 5.06 (1H, s, H-5), 5.21 (1H, d, J = 12.3 Hz, Bz CH_2), 5.36 (1H, d, Bz aromatic H), 6.74 (1H, d, J = 7.5 Hz, H-2), 6.78 (1H, d, J = 7.5 Hz, Bz aromatic H).

3-*O*-Benzyl-7-(4′-methoxy-2′-spiroindanyl)oxymorphone (6a): yield 25%; FAB-MS m/z 524 $[M + H]^+$; ^{1}H NMR ($CDCl_3$) δ 7.38 (m, 5H, Bz aromatic H), 7.08 (m, 1H, indan aromatic H), 6.77 (m, 1H, indan aromatic H), 6.74 (d, 1H, J = 8.4 Hz, H-2), 6.62 (d, 1H, J = 7.8 Hz, indan aromatic H), 6.58 (d, 1H, J = 8.4 Hz, H-1), 5.38 (d, 1H, J = 11.7 Hz, Bz CH_2), 5.21 (d, 1H, J = 11.7 Hz, Bz CH_2), 5.05 and 5.00 (2s, 1H, H-5), 3.80 and 3.77 (2s, 3H, OCH_3), 3.75 (m, 2H, indan CH_2), 3.52 and 3.21 (m, 2H, indan CH_2), 3.13 (d, 1H, J = 18.9 Hz, H-10β), 2.82 (d, 1H, J = 5.4 Hz, H-9), 2.39 (s, 3H, NCH_3).

3-*O*-Benzyl-7-(5′-methoxy-2′-spiroindanyl)naltrexone (7a): yield 83%; ^{1}H NMR ($CDCl_3$) δ 0.15 (2H, m, H-20β, H-21β), 0.55 (2H, m, H-20α, H-21α), 0.86 (1H, m, H-19), 1.25 (1H, br s, OH), 1.57 (1H, d, J = 9.9 Hz, H-15), 1.82 and 1.83 (1H, d, J = 13.2 Hz, H-8), 2.04 (1H, d, J = 13.2 Hz, H-8), 2.11 (1H, t, J = 10.8 Hz, H-15), 2.33 (1H, d, J = 14.4 Hz, indan CH_2), 2.40 (2H, m, H-18), 2.48 (1H, m, H-16), 2.58 (1H, dd, J = 18.3, 3.6 Hz, H-10), 2.71 (1H, d, J = 11.1 Hz), 3.03 (1H, d, J = 18.3 Hz, H-10), 3.13 (1H, d, J = 4.8 Hz, H-9), 3.18 and 3.20 (1H, d, J = 16.8 Hz, indan CH_2), 3.43 and 3.46 (1H, d, J = 16.8 Hz, indan CH_2), 3.79 (1H, d, J = 16.8 Hz, indan CH_2), 4.07 (3H, s, OMe), 5.02 (1H, s, H-5), 5.21 (1H, d, J = 12.3 Hz, Bz CH_2), 5.36 (1H, d, J = 12.3 Hz, Bz CH_2), 6.58 (1H, d, J = 8.4 Hz, H-1), 6.63−6.75 (2H, m, indan aromatic H), 6.74 (1H, d, J = 8.4 Hz, H-2), 6.74 (1H, d, J = 8.4 Hz, indan aromatic H), 7.04 (1H, m, indan aromatic H), 7.25−7.50 (5H, m, Bz aromatic H).

3-*O*-Benzyl-7-(5′,6′-benzo-2′-spiroindanyl)naltrexone (8a): yield 68%; ^{1}H NMR ($CDCl_3$) δ 0.15 (2H, m, H-20β, H-21β), 0.55 (2H, m, H-20α, H-21α), 0.86 (1H, m, H-19), 1.59 (1H, d, J = 12.3 Hz, H-15), 1.87 (1H, br s, 14-OH), 1.87 (1H, d, J = 14.7 Hz, H-8), 2.05 (1H, d, J = 14.7 Hz, H-8), 2.13 (1H, t, J = 9.6 Hz, H-15), 2.39 (2H, m, H-16), 2.54 (1H, d, J = 15.9 Hz, indan CH_2), 2.54 (2H, hidden, H-18), 2.66 (1H, m, H-10), 3.04 (1H, d, J = 18.3 Hz, H-10), 3.14 (1H, d, J = 3.6 Hz, H-9), 3.40 (1H, d, J = 16.3 Hz, indan CH_2), 3.64 (1H, d, J = 16.3 Hz, indan CH_2), 3.95 (1H, d, J = 15.9 Hz, indan CH_2), 5.03 (1H, s, H-5), 5.21 (1H, d, J = 11.1 Hz, Bz CH_2), 5.35 (1H, d, J = 11.1 Hz, Bz CH_2), 6.59 (1H, d, J = 8.7 Hz, H-1), 6.75 (1H, d, J = 8.7 Hz, H-2), 7.25−7.50 (7H, m, naphthyl H, Bz aromatic H), 7.60 (2H, s, naphthyl H), 7.72 (2H, m, naphthyl H).

3-*O*-Benzyl-7-(5′,6′-benzo-2′-spiroindanyl)oxymorphone (9a): yield 48%; mp 207 °C; FAB-MS m/z 544 $[M + H]^+$; ^{1}H NMR ($CDCl_3$) δ 7.73−7.70 (m, 2 H, naphthyl H), 7.60 (s, 2H, naphthyl H), 7.47 (m, 2H, naphthyl H), 7.39−7.21 (m, 5H, Bz aromatic H), 6.76 (d, 1H, J = 7.8 Hz, H-2), 6.61 (d, 1H, J = 8.4 Hz, H-1), 5.35 (d, 1H, J = 11.7 Hz, Bz CH_2), 5.21 (d, 1H, J = 11.7 Hz, Bz CH_2), 5.02 (s, 1H, C-5), 3.93 (d, 1H, J = 17.1 Hz, indan CH_2), 3.63 (d, 1H, J = 15.9 Hz, indan CH_2), 3.40 (d, 1H, J = 17.1 Hz, indan CH_2), 3.14 (d, 1H, J = 18.3 Hz, H-10β), 2.85 (m, 1H, H-9), 2.41 (s, 3H, NCH_3).

3-*O*-Benzyl-7-(4′,5′-benzo-2′-spiroindanyl)naltrexone (10a): yield 42%; ^{1}H NMR ($CDCl_3$) δ 0.14 (2H, m, H-20β, H-21β), 0.50 (2H, m, H-20α, H-21α), 0.87 (1H, m, H-19), 1.43 (1H, d, J = 14.4 Hz, H-15), 1.90 and 1.93 (1H, d, 14.2 Hz, H-8), 2.12 (1H, br s, 14-OH), 2.15 (1H, J = 14.2 Hz, H-8), 2.25−2.80 (6H, m, H-10, H-15, H-16, H-18, indan CH_2), 2.54 (2H, hidden, H-18), 3.05 (1H, d, J = 18.6 Hz, H-10), 3.15 (1H, d, J = 4.8 Hz, H-9), 3.36 and 3.56 (1H, d, J = 17.0 Hz, indan CH_2), 3.74 and 3.99 (1H, d, J = 15.8 Hz, indan CH_2), 4.18 (1H, d, J = 16.2 Hz, indan CH_2), 5.07 and 5.08 (1H, s, H-5), 5.22 (1H, d, J = 12.0 Hz, Bz CH_2), 5.35 (1H, d, J = 12.0 Hz, Bz CH_2), 6.59 (1H, d, J = 8.2 Hz, H-1), 6.75 and 6.76 (1H, d, J = 8.2 Hz, H-2), 7.20−7.60 (8H, m, naphthyl H, Bz aromatic H), 7.60−7.90 (3H, s, naphthyl H).

3-*O*-Benzyl-7-(2′,3′-dihydro-2′-spiroperinaphthenyl)naltrexone (11a): yield 79%; ^{1}H NMR ($CDCl_3$) δ 0.06 (2H, m, H-20β, H-21β), 0.48 (2H, m, H-20α, H-21α), 0.76 (1H, m, H-19), 1.48 (1H, d, J = 13.2 Hz, H-8), 1.60 (1H, dd, J = 12.3, 2.4 Hz, H-15), 1.79 (1H, d, J = 13.2 Hz, H-8), 2.05 (1H, m , H-15), 2.29 (2H, m, H-18), 2.45 (1H, hidden, H-16), 2.50 (1H, br s, 14-OH), 2.52 (1H, d, J = 18.3 Hz, H-10), 2.57 (1H, d, J = 15.9 Hz, naphthyl CH_2), 2.72 (1H, dd, J = 12.3, 5.1 Hz, H-16), 2.91 (1H, s, H-9), 2.94 (1H, d, J = 18.3 Hz, H-10), 3.42 (1H, d, J = 15.9 Hz, naphthyl CH_2), 3.45 (1H, d, J = 15.9 Hz), 3.92 (1H, d, J = 15.9 Hz, naphthyl CH_2), 5.04 (1H, s, H-5), 5.24 (1H, d, J = 12.0 Hz, Bz CH_2), 5.34 (1H, d, J = 12.0 Hz, Bz CH_2), 6.55 (1H, d, J = 8.4 Hz, H-1), 6.76 (1H, d, J = 8.4 Hz, H-2), 7.13 (1H, d, J = 3.6 Hz, naphthyl H), 7.20−7.60 (8H, m, Bz aromatic H, naphthyl H), 7.66 (1H, d, J = 8.4 Hz, naphthyl H), 7.70 (1H, d, J = 8.7 Hz, naphthyl H).

7-(4′-Methoxy-2′-spiroindanyl)naltrexone (5). A solution of **5a** (170 mg, 0.3 mmol) in EtOH with a few drops of 1 N HCl was stirred for 10 h with 10% Pd−C under H_2 at atmospheric pressure. The catalyst was removed by filtration, and the filtrate was evaporated. To the residue were added EtOAc and aqueous sodium bicarbonate solution, and the mixture was shaken. The organic layer was separated, dried, and evaporated. The residue was chromatographed on silica gel (hexane−EtOAc, 2:1) to afford **5** (90 mg, 63%), which was dissolved in EtOH and treated with a few drops of HCl. The solution was evaporated, the residue was again dissolved in EtOH, and Et_2O was added. The resulting solid was collected, washed with Et_2O, and dried to afford an epimeric mixture of **5**·HCl (75 mg, 75%): mp 225−230 °C dec; HRMS (FAB) ($M + H^+$) 474.2281 (calcd for $C_{29}H_{32}NO_5$ 474.2280); ^{1}H NMR ($CDCl_3$) δ 0.13 (2H, m, H-20β, H-21β), 0.54 (2H, m, H-20α, H-21α), 0.85 (1H, m, H-19), 1.52 (1H, d, J = 12.0 Hz, H-15), 1.82 (1H, d, J = 9.0 Hz, H-8), 2.04 (1H, d, J = 9.0 Hz, H-8), 2.04 (1H, d, J = 9.0 Hz, H-8), 2.12 (1H, t, J = 12.0 Hz, H-15), 2.29 (1H, d, J = 15.9 Hz, indan CH_2), 2.32−2.50 (3H, m, H-16, H-18), 2.57 (1H, dd, J = 18.3, 4.8 Hz, H-10), 2.70 (1H, d, J = 8.7 Hz, H-16), 3.03 (1H, d, J = 18.3 Hz, indan CH_2), 3.14 (1H, d, J = 2.7 Hz, H-9), 3.18 and 3.21 (1H, d, J = 15.6 Hz, indan CH_2), 3.47 and 3.50 (1H, d, J = 15.6 Hz, indan CH_2), 3.74 (1H, d, J = 18.3 Hz, indan CH_2), 3.77 and 3.80 (3H, s, OMe), 4.96 and 4.99 (1H, s, H-5), 6.60 (1H, d, J = 8.7 Hz, H-1), 6.63 (1H, d, J = 8.4 Hz, indan aromatic H), 6.73 (1H, d, J = 8.7 Hz, H-2), 6.75 (1H, hidden, indan aromatic H), 7.10 (1H, t, J = 8.4 Hz, indan aromatic). Anal. ($C_{29}H_{31}NO_5$·HCl) C, H, N.

7-(4′-Methoxy-2′-spiroindanyl)oxymorphone (6): yield 58%; FAB-MS m/z 434 $[M + H]^+$, 432 $[M - H]^-$; ^{1}H NMR ($CDCl_3$) δ 7.09 (t, 1H, J = 7.8 Hz, indan aromatic H), 6.76 and 6.63 (2d, 2H, J = 7.8 Hz, indan aromatic H), 6.74 (d, 1H, J = 8.4 Hz, H-2), 6.58 (d, 1H, J = 8.7 Hz, H-1), 4.97 (s, 1H, H-5), 3.80 and 3.76 (2s, 3H, OCH_3), 3.54 and 3.50 (2d, 1H, J = 15.9 Hz, indan CH_2), 3.22 and 3.18 (2d, 1H, J = 17.4 Hz, indan CH_2), 3.11 (d, 1H, J = 18.9 Hz, H-10β), 2.84 (d, 1H, J = 5.4 Hz, H-9), 2.37 and 2.36 (2s, 3H, NCH_3); ^{13}C NMR ($CDCl_3$) δ 210.67 (C-6), 156.46 and 156.28 (indan C-1), 120.38 and 120.35 (C-1), 118.88 and 118.81 (C-2), 117.38 and 117.08 (indan C-2), 89.83 and 89.78 (C-5), 65.37 (C-14), 55.91 and 55.78 (OCH_3). Anal. ($C_{26}H_{27}NO_5$·HCl·1.5H_2O) C, H, N.

7-(5′-Methoxy-2′-spiroindanyl)naltrexone (7): yield 63%; ^{1}H NMR ($CDCl_3$) δ 0.14 (2H, m, H-20β, H-21β), 0.54 (2H, m, H-20α, H-21α), 0.85 (1H, m, H-19), 1.25 (1H, s, OH), 1.53 (1H, dd, J = 13.2, 2.4 Hz, H-15), 1.81 and 1.82 (1H, d, J = 13.4 Hz, H-8), 2.03 (1H, d, J = 14.4 Hz, H-8), 2.13 (H, dt, J = 12.3, 2.4 Hz, H-15), 2.32 (1H, d, J = 15.9 Hz, indan CH_2), 2.39 (2H, m, H-18), 2.46 (1H, dd, J = 12.3, 3.6 Hz, H-16), 2.56 (1H, dd, J = 19.5, 6.0 Hz, H-10), 2.70 (1H, dd, J = 12.3, 3.6 Hz, H-16), 3.03 (1H, d, 3.40) or 3.42 (1H, d, J = 15.9 Hz, indan CH_2), 3.76 (3H, s, OMe), 3.78 (1H, d, J = 14.7 Hz, indan CH_2), 4.95 and 4.96 (1H, s, H-5), 6.59 (1H, d, J = 8.7 Hz, H-1), 6.64−6.72 (2H, m, indan aromatic H), 6.73 (1H, d, J = 8.7 Hz, H-2), 7.03 (1H, t, J = 7.2 Hz, indan aromatic CH); HRMS (FAB) $(M + H)^+$ 474.2281 (calcd for $C_{29}H_{32}NO_5$ 474.2280). Anal. ($C_{29}H_{31}NO_5$·HCl·2H_2O) C, H, N.

7-(5′,6′-Benzo-2′-spiroindanyl)naltrexone (8): yield 68%; ^{1}H NMR ($CDCl_3$) δ 0.14 (2H, m, H-20β, H-21β), 0.54 (2H, m, H-20α, H-21α), 0.85 (1H, m, H-19), 1.25 (1H, s, 14-OH), 1.51 (1H, dd, J = 12.3, 2.4 Hz, H-15), 1.86 (1H, d, J = 14.7 Hz, H-8), 2.04 (1H, d, J = 14.7 Hz, H-8), 2.12 (1H, dt, J = 12.3, 3.6 Hz, H-15), 2.39 (2H, m, H-18, H-16), 2.53 (1H, d, J = 16.8 Hz, indan CH_2), 2.56 (1H, dd, J = 18.3, 6.0 Hz, H-10), 2.69 (1H, d, J = 18.3 Hz, H-16), 3.03 (1H, d, J = 18.3 Hz, H-10),

3.13 (1H, d, J = 4.8 Hz, H-9), 3.37 (1H, d, J = 16.8 Hz, indan CH_2), 3.58 (1H, d), 6.60 (1H, d, J = 8.7 Hz, H-1), 6.73 (1H, d, J = 8.7 Hz, H-2), 7.37 (2H, m, naphthyl H), 7.59 (2H, s, naphthyl H), 7.73 (2H, m, naphthyl H); HRMS (FAB) $(M + H)^+$ 494.2334 (calcd for $C_{32}H_{32}NO_4$ 494.2331). Anal. ($C_{32}H_{31}NO_4 \cdot H_2O$) C, H, N.

7-(5′,6′-Benzo-2′-spiroindanyl)oxymorphone (9): yield 75%; mp 235 °C; FAB-MS 454 $[M + H]^+$; ^{1}H NMR ($CDCl_3$) δ 7.74−7.71 (m, 2H, naphthyl H), 7.52 (s, 2H, naphthyl H), 7.32−7.29 (m, 2H, naphthyl H), 6.64 (d, 1H, J = 8.1 Hz, H-2), 6.53 (d, 1H, J = 7.8 Hz, H-1), 4.82 (s, 1H, H-5), 3.75 (d, 1H, J = 16.8 Hz, indan CH_2), 3.40 (d, 1H, J = 15.9 Hz, indan CH_2), 3.32 (d, 1H, J = 17.7 Hz, indan CH_2), 3.06 (d, 1H, J = 18.9 Hz, H-10β), 2.96 (d, 1H, J = 5.4 Hz, H-9), 2.39 (s, 3H, NCH_3). Anal. ($C_{29}H_{27}NO_4$) C, H, N.

7-(4′,5′-Benzo-2′-spiroindanyl)naltrexone (10): ^{1}H NMR ($CDCl_3$) δ 0.16 (2H, m, H-20β, H-21β), 0.56 (2H, m, H-20α, H-21α), 0.87 (1H, m, H-19), 1.56 (1H, dd, J = 14.4, 2.4 Hz, H-15), 1.83 and 1.95 (1H, d, J = 14.2 Hz, H-8), 2.15 (2H, m, H-8, 14-OH), 2.30−2.80 (6H, m, H-10, H-15, H-16, H-18, indan CH_2), 3.05 (1H, d, J = 18.6 Hz, H-10), 3.18 (1H, d, J = 4.8 Hz, H-9), 3.30 and 3.52 (1H, d, J = 16.8 Hz, indan CH_2), 3.68 and 3.95 (1H, d, J = 15.8 Hz, indan CH_2), 4.18 (1H, d, J = 17.0 Hz), 4.98 and 5.02 (1H, s, H-5), 6.60 (1H, d, J = 8.2 Hz, H-1), 6.74 (1H, d, J = 8.2 Hz, H-2), 7.20−7.60 (4H, m, naphthyl H), 7.65 (1H, m, naphthyl H), 7.90 (1H, m, naphthyl H); HRMS (FAB) $(M + H)^+$ 494.2334 (calcd for $C_{32}H_{32}NO_4$ 494.2331). Anal. ($C_{32}H_{31}NO_4 \cdot HCl \cdot 1.5H_2O$) C, H, N.

7-(2′,3′-Dihydro-2′-spiroperinaphthenyl)naltrexone (11): yield 74%; ^{1}H NMR ($CDCl_3$) δ 0.06 (2H, m, H-20β, H-21β), 0.48 (2H, m, H-20α, H-21α), 0.76 (1H, m, H-19), 1.48 (1H, d, J = 14.4 Hz, H-8), 1.57 (1H, d, J = 12.9 Hz, H-15), 1.79 (1H, d, J = 14.4 Hz, H-8), 2.09 (1H, dt, J = 2.4, 12.0 Hz, H-15), 2.30 (2H, m, H-18), 2.44 (1H, hidden, H-16), 2.50 (1H, br s, OH), 2.51 (1H, dd, J = 18.3, 2.4 Hz, H-10), 2.57 (1H, dd, J = 15.9 Hz, naphthyl CH_2), 2.70 (1H, dd, J = 12.3, 3.9 Hz, H-16), 2.91 (1H, s, H-9), 2.94 (1H, d, J = 18.3 Hz, H-10), 3.39 (1H, d, J = 14.4 Hz, naphthyl CH_2), 3.43 (1H, d, J = 14.4 Hz, naphthyl CH_2), 3.93 (1H, d, J = 15.9 Hz, naphthyl CH_2), 4.99 (1H, d, J = 2.4 Hz, H-5), 6.10 (1H, br s, aromatic OH), 6.57 (1H, dd, J = 8.4, 2.4 Hz, H-1), 6.73 (1H, dd, J = 8.4, 2.4 Hz, H-2), 7.10−7.75 (6H, m, naphthyl); HRMS (FAB) $(M + H)^+$ 474.2350 (calcd for $C_{32}H_{32}NO_4$ 494.2331). Anal. ($C_{32}H_{31}NO_4 \cdot HCl$) C, H, N.

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