7-Arylidenenaltrexones as Selective δ_1 Opioid Receptor Antagonists

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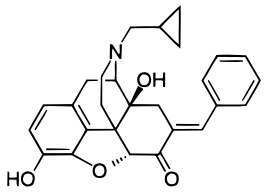
A series of 7-arylidinenaltrexones (**2a**−**m**) related to the prototypical δ_1-selective antagonist, 7-benzylidenenaltrexone **1** (BNTX), have been synthesized in an effort to develop more selective ligands. Testing in smooth muscle preparations revealed that members of the series exhibited varying degrees of selectively for δ receptors, with the *o*-methoxy (**2e**) and *o*-chloro (**2j**) congeners being most potent and most selective (Ke ∼ 0.8 nm). Evaluation of **1**, **2e**, and **2f** sc in mice using the tail-flick procedure indicated that they are selective δ_1 opioid receptor antagonists in the lower dose range. At high doses these ligands, including BNTX, exhibited decreased δ_1 selectivity due to increases in the ED_{50} ratios of [D-Ser^2,Leu^5]enkephalin-Thr^6 and morphine. It is concluded that **2e** and **2f** possess in vivo selectivity similar to that of BNTX, but are less potent as δ_1 antagonists.

Introduction

It is generally accepted that there are at least three major types of homologous opioid receptors (μ, δ, and κ) that are members of the rhodopsin subfamily of G protein-coupled receptors.[1] A number of putative subtypes of the three major receptor types have been reported, but definitive evidence for their existence is lacking. The availability of selective opioid ligands has played an important role in the cloning and pharmacologic characterization of opioid receptors, and in this regard, a variety of highly selective ligands have been developed as tools to sort out the effects mediated by these receptors.[1]

7-Benzylidenenaltrexone[2] **1** (BNTX) is one of several antagonists with in vivo pharmacologic selectivity for the putative δ_1 opioid receptor subtype.[3,4] The "address"[5] component that apparently confers the in vivo selectivity is the phenyl group of the benzylidene moiety.[6] Studies with conformationally restricted com-



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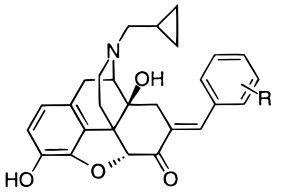
pounds have suggested that an orthogonal-like conformation of this group confers a preference for δ_1 antagonist or agonist activity in mice.[7,8] Here we present the synthesis and pharmacologic evaluation of a series of BNTX analogues (**2a**−**m**) modified in an effort to increase the in vivo potency and selectivity of ligands for δ_1 opioid receptors.

Chemistry

The synthesis of the BNTX derivatives (**2a**−**m**) was accomplished by aldol condensation of naltrexone (**3**) with a large excess (25 equiv) of the appropriately substituted aromatic aldehyde using sodium hydroxide as a base. The large excess of aldehyde prevented the formation of dimerized cycloaddition products.[9] Dimer formation was observed when 7 equiv of aldehyde was used. The reactions were conducted over periods of 1−10 days at room temperature or at 0 °C. The yields ranged from 26 to 84% (Table 1). All of the target compounds are presumed to be the more stable *E*-isomers, as is the case for BNTX and other 7-arylidinenaltrexones.[10,11]

Table 1. Physical Data for 7-Arylidenenaltrexones



compd	R	mp (°C)	reaction temp (°C)	reaction time (days)	yield (%)
2a	*p*-NO_2	225−235 (decomp)	0	3	78
2b	*m*-NO_2	220−230 (decomp)	0	3	64
2c	*p*-MeO	212−220 (decomp)	rt	7	39
2d	*m*-MeO	210−225 (decomp)	rt	3	59
2e	*o*-MeO	208−215 (decomp)	rt	10	72
2f	*p*-Me	222−238 (decomp)	rt	7	33
2	*p*-F	215−225 (decomp)	0	7	84
2h	*m*-F	207−220 (decomp)	rt	1	76
2i	*o*-F	215−225 (decomp)	rt	1	57
2j	*o*-Cl	210−225 (decomp)	rt	7	48
2k	*p*-COOMe	230−238 (decomp)	rt	2	70
2l	1-naph	215−220 (decomp)	rt	5	26
2m	2-naph	220−225 (decomp)	rt	5	26

Biological Results

Smooth Muscle Preparations. The target compounds (**2a**−**m**) were tested on the electrically stimulated guinea pig ileal longitudinal muscle[12] (GPI) and mouse vas deferens[13] (MVD) preparations as described previously.[14] The compounds (100 nM) were incubated with the preparations 15 min prior to testing with either morphine (M), ethylketazocine (EK), or [D-Ala^2,D-Leu^5]-enkephalin[15] (DADLE). These agonists are selective for

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Table 2. Opioid Antagonist Potencies of Substituted 7-Arylidenenaltrexones in Smooth Muscle Preparations

	IC_{50} ratio ± SEM[a]			selectivity ratio	
compd	M (μ)	EK (κ)	DADLE (δ)	δ/μ	δ/κ
1 (BNTX)[b]	13.1 ± 0.9	2.0 ± 0.1	35.0 ± 5	2.7	17.5
2a	4.42 ± 1.33 (4)	1.07 ± 0.28 (3)	1.9 ± 0.44 (3)	0.4	1.9
2b	1.15 ± 0.12 (4)	0.50 ± 0.04 (3)	5.18 ± 1.37 (6)	5.2	5.2
2c	3.75 ± 0.89 (6)	0.92 ± 0.18 (3)	5.52 ± 0.61 (5)	1.5	5.5
2d	6.44 ± 0.91 (3)	0.95 ± 4.3 (4)	18.0 ± 4.3 (4)	2.8	18.0
2e	8.49 ± 2.04 (8)	1.05 ± 0.23 (6)	120 ± 32 (3)	14.1	120
2f	7.05 ± 1.74 (8)	2.45 ± 5.6 (3)	22.3 ± 5.6 (3)	3.2	9.1
2g	2.23 ± 1.08 (4)	1.86 ± 0.46 (4)	2.01 ± 0.50 (3)	0.9	1.1
2h	7.83 ± 0.84 (3)	1.26 ± 0.18 (3)	16.3 ± 2.8 (6)	2.1	12.9
2i	3.86 ± 0.86 (3)[c]	1.65 ± 0.15 (3)[c]	17.0 ± 4.3 (4)[c]	4.4	10.3
2j	1.34 ± 0.42 (3)[c]	0.85 ± 0.44 (3)[c]	130 ± 48 (7)	130	130
2k	3.81 ± 1.13 (5)	0.62 ± 0.39 (3)	14.6 ± 2.2 (3)	3.8	14.6
2l	1.23 ± 0.09 (3)	1.85 ± 0.17 (3)	12.7 ± 3.1 (10)	10.3	6.9
2m	3.32 ± 0.82 (7)	1.07 ± 0.3 (3)	11.6 ± 2.9 (6)	3.5	11.6

[a] The morphine (M) and ethylketazocine (EK) IC_{50} ratios were obtained from the GPI, and the IC_{50} ratios for DADLE were obtained on MVD. Values are expressed as means ± SEM with the number of experiments in parentheses. [b] Data obtained from ref 9. [c] Incubation time was 30 min.

Table 3. Antagonism of the Antinociceptive Effect of Opioid Agonists by Subcutaneously Administered 7-Arylidenenaltrexones in Mice

	dose	ED_{50} ratio (95% confidence limits)[a]			
compd	(μmol/kg)	DPDPE (δ_1)	DSLET (δ_2)	morphine (μ)	U50488 (κ)
1 (BNTX)	1.25	3.3 (2.3−4.8)	1.69 (1.03−2.79)	0.88 (0.65−1.16)[b]	0.82 (0.77−0.87)[b]
	16	16.8 (5.2−58.2)	9.6 (5.1−17.4)	5.7 (4.5−7.2)	1.8 (0.6−5.0)
2e	5	2.0 (1.4−2.9)	0.80 (0.49−1.31)	1.03 (0.49−2.20)	0.47 (0.22−0.94)
	16	11.1 (7.3−17.6)	6.8 (2.0−26.3)	5.8 (2.6−18.4)	0.84 (0.35−1.95)
2j	5	3.7 (2.5−5.6)	0.87 (0.51−1.49)	0.53 (0.25−1.13)	0.73 (0.33−1.53)
	16	11.4 (7.5−18.1)	7.2 (1.9−26.6)	7.1 (2.6−21.2)	0.90 (0.37−2.03)

[a] ED_{50} ratio = ED_{50} of agonist in the presence of sc-administered antagonist divided by the control ED_{50}. [b] Tested in the presence of 1.34 μmol/kg sc of **1**.

μ (M), κ (EK), and δ (DADLE) opioid receptors. Morphine and EK were employed in the GPI, and DADLE was used in the MVD. Antagonist potencies are expressed as IC_{50} ratios (IC_{50} of the agonist in the presence of the test compound divided by the control IC_{50} in the same preparation). The selectivity ratio represents the DADLE IC_{50} ratio divided by the M or EK IC_{50} ratio. When the IC_{50} ratio was less than unity or not distinctly different from unity, the selectivity ratio was calculated using an IC_{50} ratio value of 1.

With the exception of the *p*-nitro- and *p*-fluorobenzylidenes (**2a**, **2g**), all of the members of the series more potently antagonized the δ-selective agonist, DADLE (Table 2). The most potent, δ-selective ligands were the *o*-methoxy (**2e**) and *o*-chloro (**2j**) derivatives, with IC_{50} ratios in the 120−130 range. Both of these ligands were substantially more potent and δ-selective than the standard δ_1 antagonist, BNTX **1**. The *m*-methoxyl (**2d**), *p*-methyl (**2f**), *p*-carbomethoxy (**2k**), and naphthyl (**2l,m**) analogues were of intermediate potency and more comparable to BNTX. The remaining members of the series, including the *m*-nitro (**2b**) and *p*-methoxy (**2c**) derivatives, possessed low δ antagonist potency and selectivity.

In Vivo Studies. The two most potent δ antagonists, **2e** and **2j**, were evaluated in male ICR mice using the tail-flick assay.[16] Mice were pretreated sc with the test compounds so that the peak antagonist activity coincided with the peak antinociceptive response to the selective agonists. The nonpeptide agonists, morphine (μ) and *trans*-(±)-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)-cyclohexyl]benzeneacetamide[17] (U50488) (κ), were administered sc; the peptide agonists, [D-Pen^{2,5}]enkephalin[18] (DPDPE) (δ_1) and [D-Ser^2,Leu^5]enkephalin-Thr^6 (DSLET)[19] (δ_2), were injected icv.

All of the ligands were δ_1 selective at low doses (1−5 μmol/kg). The antagonist potencies of **2e**, **2j**, and BNTX at different doses are shown in Table 3. However, at 16 μmol/kg greatly diminished selectivity was observed. This was due to concomitant increases of the ED_{50} ratios for DPDPE, DSLET, and morphine. Judging from the DPDPE ED_{50} ratios produced by **2e** (2.0 at 5 μmol/kg) and **2f** (3.7 at 5 μmol/kg), BNTX (ratio = 3.3 at 1.25 μmol/kg) is approximately 4 times more potent at δ_1 receptors.

Discussion

It has been reported that an orthogonal-like aryl "address" moiety favors δ_1 opioid agonist or antagonist selectivity in vivo.[7,8] Because the ortho-substituted congeners (**2e** and **2j**) in the present series were more δ-selective and more potent than BNTX **1** in smooth muscle preparations, we have investigated their activities in mice. What is more, since ortho substitution would be expected to increase the population of orthogonal-like aryl rotamers through unfavorable interaction with the neighboring carbonyl group or methylene protons, it was conceivable that this might enhance δ_1 opioid receptor selectivity.

In vivo testing of **2e** and **2j** (5 μmol/kg sc), however, revealed that although **2e** and **2j** were δ_1-selective, they were less potent than the unsubstituted ligand, BNTX **1** (1.25 μmol/kg). Interestingly, at a higher dose (16 μmol/kg), δ_1 selectivity was greatly reduced as a consequence of significant increases in the DSLET and morphine ED_{50} ratios. Thus, a dosing window for

optimal δ_1 selectivity clearly is evident from the present in vivo study. In view of the fact that only a single dose (usually icv) of BNTX has been employed in numerous reports, it is not known if a dose window exists for routes of administration other than sc.

The finding that **2e** and **2j** are more potent than BNTX as δ antagonists in the MVD, but less potent in mice, may be due to the presence of different δ receptor subtypes in the smooth muscle preparation versus the central nervous system.[20] A less likely possibility is differential bioavailability between the unsubstituted (BNTX) and substituted (**2e,j**) congeners.

Finally, the presence of a dose-dependent change in the selectivity of the standard δ_1 opioid receptor antagonist, BNTX,[21] suggests that this ligand should be used as a pharmacologic tool only in a low dose range to minimize antagonism at other opioid receptors.

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 4000, an AEIMS-30, or a VG70780EHF spectrometer. All reagents and solvents were reagent grade. Naltrexone was supplied by Mallinckrodt, St. Louis, MO.

7(*E*)-(4-Nitrobenzylidene)naltrexone Hydrochloride (2a). To a solution of naltrexone hydrochloride (100 mg, 0.26 mmol) and 4-nitrobenzaldehyde (1.0 g, 6.6 mmol) in MeOH (40 mL) was added N−NaOH (2 mL). The mixture was maintained for 3 days at 0 °C, then diluted with water, acidified with N−HCl, and washed with ether. The aqueous layer was made alkaline with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The extract was washed with water, dried, and evaporated. The residue was chromatographed on silica gel (hexanes−EtOAc, 1:1) to afford **2a** (102 mg, 78%). The compound **2a** was dissolved in ethanol and a few drops of concentrated HCl was added. The solution was concentrated, and ether was added. The resulting solid was collected, washed with ether, and dried to afford **2a**·HCl (100 mg). NMR (free base) δ ppm (in $CDCl_3$): 0.14 (2H, m, H-20b, H-21b), 0.55 (2H, m, H-20a, H-21a), 0.85 (1H, m, H-19), 1.68 (1H, d, J = 10.8 Hz, H-15), 2.20−2.50 (5H, m, H-8, H-15, H-16, H-18), 2.60 (1H, broad s, 14-OH), 2.70 (2H, m, H-10, H-16), 2.89 (1H, d, J = 15.9 Hz, H-8), 3.17 (1H, dd, J = 19.5 and 7.5 Hz, H-10), 3.20 (1H, d, J = 7.5 Hz, H-9), 4.71 (1H, s, H-5), 5.13 (1H, broad s, 3-OH), 6.65 (1H, d, J = 7.5 Hz, H-1), 6.76 (1H, d, J = 7.5 Hz, H-2), 7.51 (2H, d, J = 8.9 Hz, aromatic H), 7.60 (1H, s, vinylic H), 8.22 (2H, d, J = 8.9 Hz, aromatic H). Exact mass calcd for $C_{27}H_{27}N_2O_6$ $(M + H)^+$ 475.1869, found 475.1883. Anal. ($C_{27}H_{26}N_2O_6$·HCl·H_2O) C, H, N.

7(*E*)-(3-Nitrobenzylidene)naltrexone Hydrochloride (2b). NMR (free base) δ ppm (in $CDCl_3$): 0.13 (2H, m, H-20b, H-21b), 0.53 (2H, m, H-20a, H-21a), 0.83 (1H, m, H-19), 2.00−2.50 (6H, m, H-8, H-15, H-16, H-18, 14-OH), 2.50−2.80 (2H, m, H-10, H-16), 2.91 (1H, d, J = 14.7 Hz, H-8), 3.15 (1H, dd, J = 18.3 and 6.0 Hz, H-10), 3.21 (1H, hidden, H-9), 4.71 (1H, s, H-5), 5.00 (1H, broad s, 3-OH), 6.57 (1H, d, J = 7.2 Hz, H-1), 6.65 (1H, d, J = 7.2 Hz, H-2), 7.40−7.70 (3H, m, aromatic H, vinylic H), 8.00−8.30 (2H, m, aromatic H). Exact mass calcd for $C_{27}H_{27}N_2O_6$ $(M + H)^+$ 475.1865, found 475.1865. Anal. ($C_{27}H_{26}N_2O_6$·HCl·$1.4H_2O$) C, H, N.

7(*E*)-(4-Methoxybenzylidene)naltrexone Hydrochloride (2c). NMR (free base) δ ppm (in $CDCl_3$): 0.13 (2H, m, H-20b, H-21b), 0.54 (2H, m, H-20a, H-21a), 0.84 (1H, m, H-19), 1.25 (1H, s, 14-OH), 1.25 (1H, hidden, H-15), 1.65 (1H, d, J = 11.1 Hz, H-15), 2.20−2.50 (5H, m, H-8, H-16, H-18), 2.68 (1H, dd, J = 18.3 and 7.2 Hz, H-10), 2.71 (1H, dd, J = 12.3 and 4.8 Hz, H-16), 3.01 (1H, d, J = 15.9 Hz, H-8), 3.15 (1H, d, J = 18.3 Hz, H-10), 3.23 (1H, d, J = 6.0 Hz, H-9), 3.82 (3H, s, OMe), 4.69 (1H, s, H-5), 5.10 (1H, broad s, 3-OH), 6.63 (1H, d, J = 7.2 Hz, H-1), 6.74 (1H, d, J = 7.2 Hz, H-2), 6.88 (2H, d, J = 8.4 Hz, H-23), 7.31 (2H, d, J = 8.4 Hz, H-24), 7.66 (1H, d, J = 2.4 Hz, vinylic H). Exact mass calcd for $C_{28}H_{30}NO_5$ $(M + H)^+$ 460.2124, found 460.2129. Anal. ($C_{28}H_{29}NO_5$·HCl·$1.5H_2O$) C, H, N.

7(*E*)-(3-Methoxybenzylidene)naltrexone Hydrochloride (2d). NMR (free base) δ ppm (in $CDCl_3$): 0.14 (2H, m, H-20b, H-21b), 0.56 (2H, m, H-20a, H-21a), 0.845 (1H, m, H-19), 1.25 (1H, s, 14-OH), 1.25 (1H, hidden, H-15), 1.64 (1H, d, J = 11.1 Hz, H-15), 2.37 (4H, m, H-8, H-16, H-18), 2.71 (2H, m, H-10, H-16), 3.08 (2H, m, H-8, H-9), 3.15 (1H, d, J = 13.5 Hz, H-10), 3.79 (3H, s, OMe), 4.69 (1H, s, H-5), 5.10 (1H, broad s, 3-OH), 6.65 (1H, d, J = 6.3 Hz, H-1), 6.77 (1H, d, J = 6.3 Hz, H-2), 6.89 (2H, m, aromatic H), 7.26 (2H, m, aromatic H), 7.62 (1H, s, vinylic H). Exact mass calcd for $C_{28}H_{30}NO_5$ $(M + H)^+$ 460.2124, found 460.2129. Anal. ($C_{28}H_{29}NO_5$·HCl·H_2O) C, H, N.

7(*E*)-(2-Methoxybenzylidene)naltrexone Hydrochloride (2e). NMR (free base) δ ppm (in $CDCl_3$): 0.13 (2H, m, H-20b, H-21b), 0.51 (2H, m, H-20a, H-21a), 0.83 (1H, m, H-19), 1.64 (1H, d, J = 12.3 Hz, H-15), 2.20−2.50 (6H, m, H-8, H-15, H-16, H-18, 14-OH), 2.70 (2H, m, H-10, H-16), 2.94 (1H, d, J = 15.9 Hz, H-8), 3.12 (1H, d, J = 17.1 Hz, H-10), 3.18 (1H, m, H-9), 3.80 (3H, s, OMe), 4.69 (1H, s, H-5), 5.10 (1H, broad s, 3-OH), 6.64 (1H, d, J = 8.4 Hz, H-1), 6.75 (1H, d, J = 8.4 Hz, H-2), 6.87 (2H, d, J = 8.7 Hz, aromatic H), 6.91 (1H, t, J = 8.7 Hz, aromatic H), 7.17 (1H, d, J = 8.7 Hz, aromatic H), 7.31 (1H, t, J = 8.7 Hz, aromatic H), 7.83 (1H, d, J = 2.4 Hz, vinylic H). Exact mass calcd for $C_{28}H_{30}NO_5$ $(M + H)^+$ 460.2124, found 460.2124. Anal. ($C_{28}H_{29}NO_5$·HCl·H_2O) C, H, N.

7(*E*)-(4-Methylbenzylidene)naltrexone Hydrochloride (2f). NMR (free base) δ ppm (in $CDCl_3$): 0.12 (2H, m, H-20b, H-21b), 0.52 (2H, m, H-20a, H-21a), 0.83 (1H, m, H-19), 1.63 (1H, d, J = 12.0 Hz, H-15), 2.20−2.50 (4H, m, H-8, H-15, H-16, H-18), 2.36 (3H, s, Me), 2.60−2.80 (2H, m, H-10, H-16), 3.02 (1H, d, J = 15.9 Hz, H-8), 3.13 (1H, d, J = 16.5 Hz, H-10), 3.24 (1H, d, J = 4.8 Hz, H-9), 4.69 (1H, s, H-5), 5.10 (2H, broad s, 3-OH, 14-OH), 6.62 (1H, d, J = 8.4 Hz, H-1), 6.74 (1H, d, J = 8.4 Hz, H-2), 7.15 (1H, d, J = 7.2 Hz, aromatic H), 7.23 (1H, d, J = 7.2 Hz, aromatic H), 7.64 (1H, m, vinylic H). Exact mass calcd for $C_{28}H_{30}NO_4$ $(M + H)^+$ 444.2174, found 444.2198. Anal. ($C_{28}H_{29}NO_4$·HCl·$1.7H_2O$) C, H, N.

7(*E*)-(4-Fluorobenzylidene)naltrexone Hydrochloride (2g). NMR (free base) δ ppm (in $CDCl_3$): 0.13 (2H, m, H-20b, H-21b), 0.54 (2H, m, H-20a, H-21a), 0.84 (1H, m, H-19), 1.25 (1H, s, 14-OH), 1.66 (1H, d, J = 10.5 Hz, H-15), 2.20−2.50 (5H, m, H-8, H-15, H-16, H-18), 2.67 (1H, dd, J = 18.6 and 6.0 Hz, H-10), 2.72 (1H, dd, J = 10.8 and 3.6 Hz, H-16), 2.96 (1H, d, J = 14.7 Hz, H-8), 3.14 (1H, d, J = 18.3 Hz, H-10), 3.22 (1H, d, J = 6.0 Hz, H-9), 4.69 (1H, s, H-5), 5.10 (1H, broad s, 3-OH), 6.64 (1H, d, J = 8.4 Hz, H-1), 6.74 (1H, d, J = 8.4 Hz, H-2), 7.05 (2H, t, J = 8.4 Hz, aromatic H), 7.33 (2H, dd, J = 8.4 and 6.3 Hz, aromatic H), 7.61 (1H, d, J = 2.4 Hz, vinylic H). Exact mass calcd for $C_{27}H_{27}NO_4F$ $(M + H)^+$ 448.1924, found 448.1928. Anal. ($C_{28}H_{26}NO_4F$·HCl·$2H_2O$) C, H, N.

7(*E*)-(3-Fluorobenzylidene)naltrexone Hydrochloride (2h). NMR (free base) δ ppm (in $CDCl_3$): 0.13 (2H, m, H-20b, H-21b), 0.53 (2H, m, H-20a, H-21a), 0.84 (1H, m, H-19), 1.64 (1H, d, J = 10.8 Hz, H-15), 2.20−2.50 (4H, m, H-8, H-15, H-16, H-18), 2.60−2.80 (2H, m, H-10, H-16), 2.97 (1H, d, J = 15.9 Hz, H-8), 3.15 (1H, d, J = 17.1 Hz, H-10), 3.24 (1H, d, J = 6.0 Hz, H-9), 4.69 (1H, s, H-5), 4.85 (2H, broad s, 3-OH, 14-OH), 6.63 (1H, d, J = 8.4 Hz, H-1), 6.75 (1H, d, J = 8.4 Hz, H-2), 6.90−7.15 (3H, m, aromatic H), 7.20−7.40 (1H, m, aromatic H), 7.56 (1H, d, J = 2.4 Hz, vinylic H). Exact mass calcd for $C_{27}H_{27}NO_4F$ $(M + H)^+$ 448.1924, found 448.1901. Anal. ($C_{27}H_{26}NO_4F$·HCl·H_2O) C, H, N.

7(*E*)-(2-Fluorobenzylidene)naltrexone Hydrochloride (2i). NMR (free base) δ ppm (in $CDCl_3$): 0.12 (2H, m, H-20b, H-21b), 0.53 (2H, m, H-20a, H-21a), 0.83 (1H, m, H-19), 1.63 (1H, d, J = 12.3 Hz, H-15), 2.20−2.50 (4H, m, H-8, H-15, H-16, H-18), 2.60−2.80 (2H, m, H-10, H-16), 2.83 (1H, d, J = 11.7 Hz, H-8), 3.13 (1H, d, J = 18.3 Hz, H-10), 3.21 (1H, d, J = 5.1

Hz, H-9), 4.71 (1H, s, H-5), 4.95 (2H, broad s, 3-OH, 14-OH), 6.63 (1H, d, J = 8.4 Hz, H-1), 6.75 (1H, d, J = 8.4 Hz, H-2), 7.00−7.15 (2H, m, aromatic H), 7.25−7.35 (2H, m, aromatic H), 7.63 (1H, m, vinylic H). Exact mass calcd for $C_{27}H_{27}NO_4F$ $(M + H)^+$ 448.1924, found 448.1926. Anal. ($C_{27}H_{26}NO_4F \cdot HCl \cdot H_2O$) C, H, N.

7(*E*)-(2-Chlorobenzylidene)naltrexone Hydrochloride (2j). NMR (free base) δ ppm (in $CDCl_3$): 0.13 (2H, m, H-20b, H-21b), 0.51 (2H, m, H-20a, H-21a), 0.85 (1H, m, H-19), 1.64 (1H, d, J = 11.1 Hz, H-15), 2.20−2.60 (4H, m, H-8, H-15, H-16, H-18), 2.60−3.00 (3H, m, H-8, H-10, H-16), 3.12 (1H, d, J = 19.5 Hz, H-10), 3.24 (1H, m, H-9), 4.60 (2H, broad s, 3-OH, 14-OH), 4.71 (1H, s, H-5), 6.62 (1H, d, J = 8.4 Hz, H-1), 6.77 (1H, d, J = 8.4 Hz, H-2), 7.20−7.40 (4H, m, aromatic H), 7.66 (1H, d, J = 2.4 Hz, vinylic H). Exact mass calcd for $C_{28}H_{27}NO_4Cl$ $(M + H)^+$ 464.1628, found 464.1612. Anal. ($C_{28}H_{26}NO_4Cl \cdot HCl \cdot 1.7H_2O$) C, H, N.

7(*E*)-(4-Methoxycarbonylbenzylidene)naltrexone Hydrochloride (2k). NMR (free base) δ ppm (in $CDCl_3$): 0.14 (2H, m, H-20b, H-21b), 0.55 (2H, m, H-20a, H-21a), 0.85 (1H, m, H-19), 1.66 (1H, d, J = 10.8 Hz, H-15), 2.20−2.50 (5H, m, H-8, H-15, H-16, H-18, 14-OH), 2.60−2.80 (2H, m, H-10, H-16), 2.96 (1H, d, J = 15.9 Hz, H-8), 3.15 (1H, d, J = 15.9 Hz, H-10), 3.20 (1H, hidden, H-9), 3.91 (3H, s, COOMe), 4.70 (1H, s, H-5), 6.65 (1H, d, J = 8.4 Hz, H-1), 6.76 (1H, d, J = 8.4 Hz, H-2), 7.40 (2H, d, J = 8.4 Hz, aromatic H), 7.63 (1H, d, J = 2.4 Hz, vinylic H), 8.02 (2H, d, J = 8.4 Hz, aromatic H). Exact mass calcd for $C_{29}H_{30}NO_6$ $(M + H)^+$ 488.2073, found 488.2072. Anal. ($C_{29}H_{29}NO_6 \cdot HCl \cdot 0.3H_2O$) C, H, N.

7(*E*)-(1-Naphthylidene)naltrexone Hydrochloride (2l).[11] NMR (free base) δ ppm (in $CDCl_3$): 0.10 (2H, m, H-20b, H-21b), 0.50 (2H, m, H-20a, H-21a), 0.79 (1H, m, H-19), 1.65 (1H, d, J = 10.8 Hz, H-15), 2.20−2.50 (4H, m, H-8, H-15, H-16, H-18), 2.61 (1H, dd, J = 18.3 and 6.0 Hz, H-10), 2.71 (1H, m, H-16), 2.88 (1H, d, J = 14.7 Hz, H-8), 3.09 (1H, d, J = 18.3 Hz, H-10), 3.15 (1H, hidden, H-9), 4.60 (2H, broad s, 3-OH, 14-OH), 4.77 (1H, s, H-5), 6.63 (1H, d, J = 8.8 Hz, H-1), 6.77 (1H, d, J = 8.8 Hz, H-2), 7.30−7.60 (4H, m, aromatic H), 7.70−8.00 (3H, m, aromatic H), 8.17 (1H, d, J = 2.4 Hz, vinylic H). Exact mass calcd for $C_{32}H_{30}NO_4$ $(M + H)^+$ 480.2174, found 480.2179. Anal. ($C_{32}H_{29}NO_4 \cdot HCl$) C, H, N.

7(*E*)-(2-Naphthylidene)naltrexone Hydrochloride (2m). NMR (free base) δ ppm ($CDCl_3$): 0.12 (2H, m, H-20b, H-21b), 0.50 (2H, m, H-20a, H-21a), 0.82 (1H, m, H-19), 1.62 (1H, d, J = 10.8 Hz, H-15), 2.20−2.50 (4H, m, H-8, H-15, H-16, H-18), 2.73 (2H, m, H-10, H-16), 3.14 (2H, m, H-8, H-10), 3.27 (1H, m, H-9), 4.70 (2H, broad s, 3-OH, 14-OH), 4.71 (1H, s, H-5), 6.65 (1H, d, J = 8.7 Hz, H-1), 6.78 (1H, d, J = 8.7 Hz, H-2), 7.40−7.55 (3H, m, aromatic H), 7.70−8.00 (5H, m, aromatic H), 7.79 (1H, vinylic H). Exact mass calcd for $C_{32}H_{30}NO_4$ $(M + H)^+$ 480.2174, found 480.2164. Anal. ($C_{32}H_{29}NO_4 \cdot HCl \cdot 1.5H_2O$) C, H, N.

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