Brief Articles

Effects of Substitution on the Pyrrole N Atom in Derivatives of Tetrahydronaltrindole, Tetrahydrooxymorphindole, and a Related 4,5-Epoxyphenylpyrrolomorphinan

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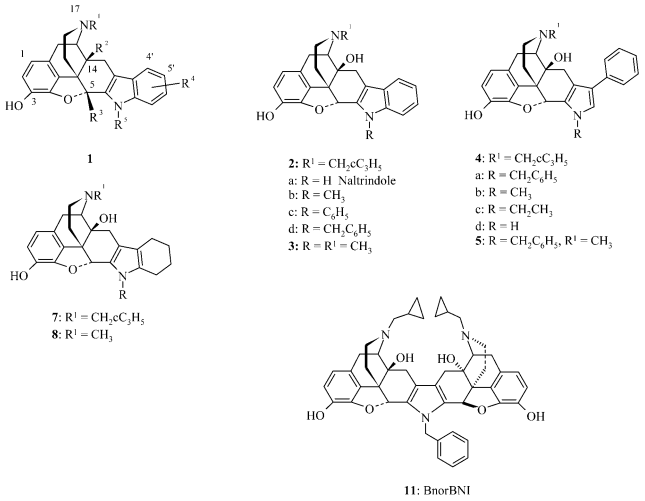
The effect of substitution of the pyrrolo- and indolo-N atoms in tetrahydronaltrindole (TNTI), tetrahydrooxymorphindole (TOMI), and 17-cyclopropylmethyl-3,14-dihydroxy-4,5-epoxy-4′-phenyl-6,7:2′,3′-pyrrolomorphinan (**4**) is reported. In opioid functional assays **4** were potent δ opioid receptor (DOR) antagonists while the TNTI derivatives (**7**) were potent DOR antagonists or low-efficacy DOR partial agonists without substantial selectivity. The TOMI derivatives (**8**) were DOR agonists with significant selectivity. In vivo the DOR antagonist activity of **7d** was confirmed, but the predominant agonist effect of **8d** was shown to be μ opioid receptor mediated.

Introduction

The 4,5-epoxyindolomorphinan structure (**1**) has been the basis of many selective ligands for δ opioid receptors (DOR) and κ opioid receptors (KOR).[1−3] Extensive investigations of SAR in **1** have particularly involved substitution at N_{17} (R^1), C_{14} (R^2), C_5 (R^3), and the indole aromatic ring (R^4).[1−10] Limited investigation of SAR for substitution on the indolic N (R^5) has been reported.[7−10] *N*-Methylnaltrindole (**2b**) and *N*-phenylnaltrindole (**2c**) had potent DOR antagonist activity in the mouse vas deferens (mvd) assay but were 8- and 25-fold less potent than naltrindole (NTI, **2a**) and substantially less DOR-selective.[7] However, *N*-benzylnaltrindole (BNTI, **2d**), though slightly less potent as a DOR antagonist than NTI, was of equivalent in vitro selectivity as a DOR antagonist. Moreover, BNTI antagonized the selective DOR agonist DSLET with very long duration after icv administration in the mouse acetic acid induced abdominal stretch assay (AS).[9]

We have recently used Michael addition chemistry on benzylimine derivatives of oxymorphones and oxycodones with nitrostyrenes to source 4,5-epoxy-4′-arylpyrrolomorphinans with pyrrole *N*-benzyl substitution (e.g., **4a**, **5**).[11] Lead **4a** was a selective antagonist in vitro and in vivo versus DOR agonist induced nociception and convulsions. The Michael addition between nitroolefins and oxymorphone imines (**6**) has now been extended to enable study in more detail of the effects of pyrrole N substitution in 4,5-epoxypyrrolomorphinans, particularly in derivatives of tetrahydronaltrindole (TNTI, **7**) and tetrahydrooxymorphindole (TOMI, **8**).



Chemistry

The preparation of *N*-methyltetrahydronaltrindole (**7a**) in 5% yield by Piloty synthesis from in situ generated naltrexone−methylimine was previously reported by Portoghese and co-workers.[12] In the present study **7a** was prepared in 70% yield and the series in 57−82% yield by refluxing in ethanol in situ generated oxymorphone imines (**6**) with 1-nitro-1-cyclohexene (Scheme 1). By this method a variety of pyrrole-N substituents could be introduced.

Results

The new ligands were evaluated in binding assays in human recombinant opioid receptors transfected into Chinese hamster ovary (CHO) cells in which the displaced radioligands were [^{3}H]DAMGO (MOR, μ opioid receptors), [^{3}H]Cl-DPDPE (DOR), and [^{3}H]U69593 (KOR) (Table 1).[13] The TNTI derivatives (**7a**−**f**) showed high

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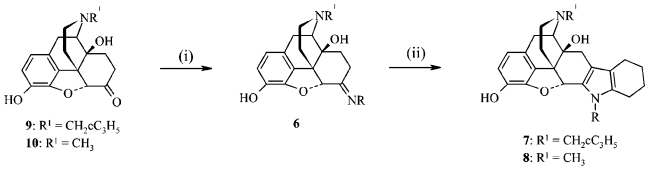
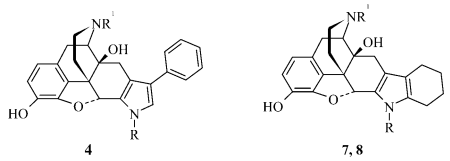
Scheme 1[a]



[a] (i) RNH_2, TsOH, EtOH; (ii) 1-nitro-1-cyclohexene.

Table 1. Binding Affinities to Cloned Human Opioid Receptors Transfected into (CHO Cells[a]



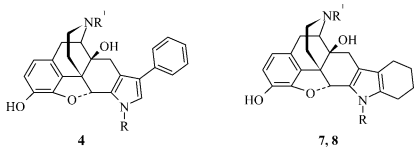
			$K_i \pm$ SEM (nM)		
	R^1	R	[^{3}H]DAMGO (MOR)	[^{3}H]U69593 (KOR)	[^{3}H]Cl-DPDPE (DOR)
4a	$CH_2cC_3H_5$	$C_6H_5CH_2$	16.8 ± 6.18	120 ± 9.61	13.7 ± 0.30
4b	$CH_2cC_3H_5$	CH_3	7.60 ± 0.35	18.5 ± 1.97	3.35 ± 1.13
4c	$CH_2cC_3H_5$	CH_3CH_2	8.75 ± 0.37	24.3 ± 1.55	2.95 ± 0.63
7a	$CH_2cC_3H_5$	CH_3	5.76 ± 0.87	4.11 ± 0.28	2.01 ± 0.01
7b	$CH_2cC_3H_5$	CH_3CH_2	5.06 ± 0.38	7.38 ± 0.43	1.65 ± 0.29
7c	$CH_2cC_3H_5$	$CH_2cC_3H_5$	2.52 ± 0.27	2.51 ± 0.50	1.81 ± 0.54
7d	$CH_2cC_3H_5$	$C_6H_5CH_2$	5.39 ± 0.72	6.29 ± 0.17	2.94 ± 0.79
7e	$CH_2cC_3H_5$	$cC_6H_{11}CH_2$	18.5 ± 5.15	24.9 ± 5.37	3.10 ± 1.12
7f	$CH_2cC_3H_5$	$C_6H_5(CH_2)_2$	7.46 ± 2.60	8.97 ± 0.47	1.80 ± 0.50
8a	CH_3	CH_3	25.2 ± 3.07	89.1 ± 8.03	1.63 ± 0.60
8b	CH_3	CH_3CH_2	25.8 ± 0.33	168 ± 12.0	2.67 ± 0.27
8d	CH_3	$C_6H_5CH_2$	88.9 ± 33.5	289 ± 19.1	18.1 ± 4.19
8e	CH_3	$cC_6H_{11}CH_2$	17.9 ± 0.81	262 ± 7.79	4.17 ± 1.06
8f	CH_3	$C_6H_5(CH_2)_2$	15.4 ± 2.89	163 ± 22.9	5.00 ± 0.83
2a, NTI	$CH_2cC_3H_5$	H	6.3 ± 2.3	10.1 ± 0.65	0.2 ± 0.05

[a] Data are the average from two experiments, each carried out in triplicate.

affinity for DOR with K_i's in the range 1.5−3.1 nM, higher than the affinity for KOR and MOR but with low levels of DOR selectivity. The equivalent derivatives of TOMI (**8a**,**b**,**d**−**f**) displayed similar high affinity for DOR with the exception of the *N*-benzyl derivative (**8d**) that had lowest affinity for all three opioid receptor types. Although limited, DOR-selectivity in the TOMI series, particularly over KOR, was superior to that in the TNTI series. In the 17(N)-cyclopropylmethyl-4,5-epoxy-4′-phenylpyrrolomorphinan series the affinities for DOR, KOR, and MOR of the 1′(N)-methyl and 1′-(N)-ethyl derivatives (**4b,c**) were similar and higher than those previously reported for the 1′(N)-benzyl derivative (**4a**).[11] The affinity for DOR of **4b** and **4c** was higher than for KOR and MOR, but selectivity for DOR was no more impressive than for **4a**.

Opioid receptor functional activity was determined for stimulation of [^{35}S]GTPγS binding in recombinant human opioid receptors transfected into CHO cells.[13] In DOR assays **7a**−**f** were potent antagonists (**7a,d**) or low-efficacy agonists of varying potency (Table 2). The 1′-(N)-ethyl (**7b**) and 1′(N)-cyclopropylmethyl (CPM; **7c**) derivatives had high potency DOR partial agonist activity, but the cyclohexylmethyl and phenethyl analogues (**7e**,**f**) were 20- to 30-fold less potent. All the TNTI derivatives (**7a**−**f**) displayed MOR antagonist effects of relatively high potency. The efficacy range for KOR activity in this series was greater than for DOR or MOR activity. In addition to **7a** and **7d**, which were antagonists for all opioid receptor types, **7c** was also a KOR antagonist. In contrast **7b**,**e**,**f** had very substantial KOR efficacy in the range 63−84% of the standard KOR agonist U69593. The selectivity for DOR of the two all-antagonist ligands (**7a**,**d**) was modest over MOR but substantial over KOR and in both cases greater than in the binding assays.

Table 2. [^{35}S]GTPγS Binding in Cloned Human Opioid Receptors



			EC_{50}/nM, % stim,[a] or (K_e/nM)[b]		
	R^1	R	MOR	KOR	DOR
4a	$CH_2cC_3H_5$	$C_6H_5CH_2$	(8.09 ± 1.86)	(21.6 ± 1.71)	(0.43 ± 0.09)
4b	$CH_2cC_3H_5$	CH_3	(4.04 ± 0.49)	(34.1 ± 4.20)	(0.62 ± 0.07)
4c	$CH_2cC_3H_5$	CH_3CH_2	(10.7 ± 2.19)	(44.0 ± 4.72)	(0.72 ± 0.08)
7a	$CH_2cC_3H_5$	CH_3	(4.30 ± 0.35)	(12.2 ± 1.03)	(0.47 ± 0.02)
7b	$CH_2cC_3H_5$	CH_3CH_2	(5.32 ± 0.34)	14.3 ± 1.03, 63	3.25 ± 1.21, 25
7c	$CH_2cC_3H_5$	$CH_2cC_3H_5$	(2.51 ± 0.13)	(11.8 ± 1.15)	3.89 ± 1.31, 32
7d	$CH_2cC_3H_5$	$C_6H_5CH_2$	(8.13 ± 0.71)	(49.8 ± 2.69)	(2.23 ± 0.40)
7e	$CH_2cC_3H_5$	$cC_6H_{11}CH_2$	(11.6 ± 0.70)	54.3 ± 3.13, 84	68.2 ± 18.7, 37
7f	$CH_2cC_3H_5$	$C_6H_5(CH_2)_2$	(5.66 ± 0.47)	13.8 ± 0.63, 76	110 ± 10.2, 36
8a	CH_3	CH_3	222 ± 82.5, 39	97.2 ± 6.56, 69	8.52 ± 3.10, 68
8b	CH_3	CH_3CH_2	175 ± 30.6, 41	98.2 ± 14.7, 66	10.3 ± 1.59, 76
8d	CH_3	$C_6H_5CH_2$	732 ± 34.4, 44	1754 ± 228, 43	9.87 ± 1.48, 85
8e	CH_3	$cC_6H_{11}CH_2$	130 ± 8.10, 57	153 ± 1.10, 85	13.0 ± 3.23, 90
8f	CH_3	$C_6H_5(CH_2)_2$	175±14.3, 71	131 ± 1.24, 76	12.0 ± 2.15, 59
2a	$CH_2cC_3H_5$	H	(4.26 ± 0.3)	(4.95 ± 0.32)	(0.11 ± 0.005)

[a] Percent maximal stimulation with respect to the standard agonists DAMGO (MOR), U69593 (KOR), and DPDPE (DOR). Mean of two experiments, each carried out in triplicate. [b] Values are the mean of five or six experiments versus DAMGO (MOR), U69593 (KOR), and DPDPE (DOR).

The DOR antagonist activity of the 1′(N)-benzyl derivative (**7d**) was confirmed in vivo. In the phenylquinone-induced abdominal stretch assay[14] **7d** showed significant antagonism of the selective DOR agonist SNC80, but complete antagonism was not achieved. The maximum antagonism achieved at 3 and 10 mg/kg **7d** sc was 54%. However, in this assay BNTI (**2d**) showed a very similar DOR antagonist effect with maximum antagonism of SNC80 (57%) at 1 mg/kg **2d** sc. In another in vivo test for DOR antagonist activity **7d** (10 mg/kg sc) administered 20 min before SNC80 (32 mg/kg) completely prevented SNC80-mediated convulsions.[15]

The 4,5-epoxypyrrolomorphinans (**4a**−**c**), which have the 17(N)-cyclopropylmethyl group in common with the TNTI derivatives (**7**), were antagonists for DOR, KOR, and MOR in the [^{35}S]GTPγS functional assays (Table 2). All three of these ligands had subnanomolar potency as DOR antagonists, ≥50-fold higher than their potency as KOR antagonists. DOR antagonist selectivity over MOR was less impressive but similar to the DOR selectivity of derivatives of TNTI (**7**). DOR antagonist potency and overall selectivity of **4a**−**c** was substantially better than in the binding assays. The differences between the individual 4,5-epoxypyrrolomorphinan derivatives (**4a**−**c**) were insignificant and smaller than between the equivalent derivatives of TNTI (**7a**,**b**,**d**).

The derivatives of TOMI (**8**) in [^{35}S]GTPγS assays displayed DOR agonist activity of substantial efficacy and potency (Table 2). Efficacy was 59−90% of the efficacy of the standard selective DOR agonist DPDPE with EC_{50} consistently close to 10 nM. KOR efficacy with respect to the selective agonist U69593 was in the range 43% (1′-benzyl) to 85% (1′-cyclohexylmethyl), but KOR potency was substantially lower than DOR potency,

typically by 1 order of magnitude and in the case of **8d** by nearly 180-fold. MOR efficacy and potency in this series were generally lower than DOR and KOR efficacy so that overall the TOMI derivatives profiled as moderately selective DOR agonists or partial agonists. The most promising example was **8d**, which had nearly full agonist activity at DOR with modest efficacy partial agonism at KOR and MOR. Moreover, the selectivity of its DOR agonist effects was impressive; **8d** as a DOR agonist was 178 times more potent than as a KOR partial agonist and 74 times more potent than as a MOR partial agonist.

On the basis of this in vitro profile, **8d** was investigated in vivo in abdominal stretch assays. With phenylquinone (PPQ) as the nociceptor, **8d** showed substantial antinociceptive activity (ED_{50} = 5.1 (2.5−9.8) mg/kg sc), but this was only weakly antagonized by pretreatment with the selective DOR antagonist NTI (**2a**) (maximum antagonism of 40% by 30 mg/kg sc NTI). Surprisingly the antinociceptive effect of **8d** was reversed by the MOR antagonist naltrexone. The AD_{50} of naltrexone for this reversal (0.02 mg/kg) strongly suggests that the action of **8d** in this in vivo assay is mediated by agonist actions at MOR. **8d** was unable to antagonize the effects of the selective DOR agonist SNC80 in the PPQ assay when administered sc, but when administered icv (10μg/brain) 24 h before SNC80 a >50% reversal of the agonist effect was achieved.

Discussion

The present study was performed to determine the SAR for substitution of the pyrrole-N atom in 4,5-epoxypyrrolomorphinan DOR opioid ligands. Though the 1′-unsubstituted 4,5-epoxy-4′-phenylpyrrolomorphinan (**4d**) has been reported,[16] it was not possible to obtain the parent pyrroles **7g** and **8g** by dealkylation of the TNTI or TOMI derivatives (**7**, **8**) or by modification of the Michael synthesis. We earlier showed that introducing the 1′(N)-benzyl group into **4d** to give **4a** markedly enhanced DOR antagonist activity.[11] In the present study the 1′(N)-methyl (**4b**) and 1′(N)-ethyl (**4c**) analogues had, like **4a**, subnanomolar DOR antagonist potency in the [^{35}S]GTPγS assay and also had similar DOR selectivity showing that the binding pocket for antagonist interaction of the 4,5-epoxypyrrolomorphinans with DOR can accommodate small and significantly larger 1′(N) substituents equally well. However, in the receptor binding assays, the smaller 1′(N) substituents of **4b** and **4c** were associated with higher affinity for all three opioid receptor types than the benzyl group in **4a**.

In the absence of the parent TNTI (**7g**) and TOMI (**8g**), the 1′(N)-methyl derivatives **7a** and **8a** are the appropriate standards against which to evaluate the other members of **7** and **8**, particularly because **7a** had previously been reported.[12] The present data and the published data for **7a** show some very pronounced differences. It was reported that **7a** had high affinity for DOR (K_i = 0.54 nM) and a high level of DOR selectivity (MOR/DOR 311, KOR/DOR 3762) in opioid receptor binding assays.[12] In the present study, the DOR affinity was about 4-fold lower, but MOR and KOR affinity was 30- and 500-fold higher, respectively, so that **7a** had only marginal binding selectivity for DOR. It is very difficult to explain such large differences even though the cell lines (CHO cells/guinea pig brain membranes), the receptors (recombinant individual/wild type mixed), and the displaced radioligands (DOR, [^{3}H]-ClDPDPE/[^{3}H]DPDPE; KOR, [^{3}H]U69593/[^{3}H]EKC in the presence of excess DAMGO) were all different in the two studies. In [^{35}S]GTPγS assays the DOR selectivity of **7a** as a DOR antagonist (KOR/DOR 26, MOR/DOR 9) was similar to the reported selectivity in isolated tissue assays (KOR/DOR 28, MOR/DOR 17).[12] However, the DOR antagonist potency of **7a** in the GTPγS assay was 20-fold higher than reported in the mvd assay.

In the present study, there was relatively little SAR for 1′(N) substitution in TNTI derivatives (**7**), particularly in the binding assays. Replacement of the 1′-methyl group in **7a** with larger alkyl and arylalkyl groups generally had little effect on binding affinities or antagonist potencies for opioid receptors. However, there were substantial variations in KOR functional activity in the TNTI series that are surprising and difficult to explain, particularly when comparing the methyl (**7a**) with ethyl (**7b**) and the benzyl (**7d**) with the phenethyl (**7f**) derivatives. The effect of the additional methylene group in both cases was to markedly enhance KOR efficacy from <20% (antagonism) to >60% of the efficacy of the standard KOR agonist U69593. The benzyl to cyclohexylmethyl comparison was similar, with the effect of reduction of the aromatic ring being to produce a nearly full KOR agonist (**7e**) from a KOR antagonist (**7d**).

Though there has been considerable investigation of the effects of piperidine N substitution in epoxymorphinan, morphinan and benzomorphan series,[17] comparison of *N*-methyl with *N*-CPM derivatives has not been thoroughly studied in recent times using modern in vitro assays. The most consistent and prominent effect of replacing NMe with *N*-CPM is a loss of MOR efficacy with a lesser attenuation of DOR and KOR efficacy.[18] In the present study the expected effect on MOR efficacy was clearly seen in a comparison of TOMI derivatives (**8**) with equivalent TNTI derivatives (**7**); the former derivatives were all MOR partial agonists, while the latter derivatives were all MOR antagonists. Substantial loss of DOR efficacy was also observed in the transformation of **8** to **7**, but the effect of the change on KOR efficacy was dependent on both 17- and 1′-N substitution. When the 1′-substituent was ethyl, cyclohexylmethyl, or phenethyl, KOR efficacy in the TOMI series (**8**) and TNTI series (**7**) was very similar, whereas when the 1′-N substituent was methyl or benzyl there was a dramatic and unexpected loss of KOR efficacy between **8a**,**d** and **7a**,**d**. The loss of KOR efficacy in the transformation of the 1′-*N*-benzyl derivatives **8d** to **7d** contrasts with the situation in the 4,5-epoxyphenylpyrrolomorphinan derivatives where the 17-methyl and 17-CPM derivatives with 1′-benzyl substitution (**4a**, **5**) were KOR antagonists.[11] The 1′-N substituted TOMI derivatives (**8**) in vitro were reasonably potent and somewhat selective DOR agonists or partial agonists. This activity was considerably greater than would have been expected from the report that the equivalent oxymorphindole derivative (**3**) had neither opioid agonist nor antagonist activity in isolated tissue assays.[7]

The DOR antagonist activity of the 1′(N)-benzyl TNTI derivative **7d** was confirmed in vivo by the reversal of the antinociceptive and convulsant effects of the selective DOR agonist SNC80. This antagonist effect of **7d** administered sc was not particularly impressive, but in the antinociceptive assay the effect of **7d** was equivalent

to that of BNTI (**2d**). Previous reports of the DOR antagonist activity of BNTI used the icv route.[9] The TOMI derivative **8d** showed good antinociceptive activity in the abdominal stretch assay when administered sc, but this activity was predominantly the result of a MOR agonist effect. This was surprising because in the [^{35}S]GTPγS assays the DOR agonist activity of **8d** appeared to be of higher efficacy and considerably higher potency than its MOR agonist activity. Though when administered sc the contribution of a DOR agonist effect to the antinociceptive effects of **8d** was small and there was no DOR antagonist effect, a distinct DOR antagonist effect of **8d** was observed on icv administration. Thus, **8d** has the profile in vivo of a MOR agonist when administered peripherally and a DOR antagonist on central administration. This is similar to our findings with 1′-benzylnorbinaltorphimine (BnorBNI; **11**), which was a MOR agonist on peripheral administration and a KOR antagonist on central administration.[19]

In conclusion, the previously presented evidence[11] for the enhancement of DOR activity by introduction of a pyrrolic *N*-benzyl group in a 4,5-epoxypyrrolomorphinan series has been confirmed for related series over a substantial range of N substituents. The TNTI (**7**) and TOMI (**8**) series represent further examples of DOR ligands of substantial affinity lacking the indolic aromatic DOR address system.[2,20]

Experimental Section

Reagents and solvents were purchased by Aldrich or Lancaster and used as received except naltrexone, which was supplied by the NIDA Drug Supply Program, and oxymorphone, which was prepared from oxycodone (Macfarlan Smith Ltd.) using a standard procedure.[21] **7** and **8** were prepared according to the procedure now described for **7d**, and compounds of type **4** were prepared using the method described for **4b**.

1′-Benzyl-17-cyclopropylmethyl-6,7-didehydro-3,14-dihydroxy-4,5α-epoxy-4′,5′,6′,7′-tetrahydroindolo[2′,3′:6,7]-morphinan (7d). Benzylamine (0.18 mL, 1.51 mmol) and *p*-tolunesulfonic acid monohydrate (1 mg) were added to a solution of naltrexone (0.50 g, 1.47 mmol) in dry EtOH (1.5 mL) and refluxed in the presence molecular sieves (4 Å) under nitrogen for 3 h. 1-Nitro-1-cyclohexene (0.17 mL, 1.5 mmol) was added, and the resulting solution was refluxed for 48 h before cooling and filtration. The EtOH was removed under reduced pressure, and the solid obtained was washed with hexane. Purification of the crude product by column chromatography using 1% MeOH/DCM gave **7d**. Yield 0.59 g (80%); R_f = 0.64; mp 245 °C; EIMS *m*/*z* (% rel intens): 508 (M^+, 100), 91 (50). Anal. ($C_{33}H_{36}N_2O_3$·2HCl·0.75H_2O) C, H, N.

17-Cyclopropylomethyl-6,7-didehydro-3,14-dihydroxy-4,5α-epoxy-1′-methyl-4′-phenylpyrrolo [2′,3′:6,7] morphinan (4b). Methylamine (2 M in MeOH) (2.2 mL, 0.004 mol), *p*-toluenesulfonic acid monohydrate (1 mg), and *trans*-*β*-nitrostyrene (0.65 g, 4 mmol) were added to a solution of naltrexone (1.5 g, 4.0 mmol) in dry EtOH (10 mL) and refluxed in the presence of molecular sieves (4 Å) under nitrogen for 4 h. It was then cooled and filtered. The EtOH was removed under reduced pressure, and purification by column chromatography using 0.5% MeOH/DCM gave the required compound (0.8 g, 40%). TLC (5% MeOH/DCM) R_f = 0.6; mp 256−260 °C; MS *m*/*z* (rel intens) 454 (M^+, 100%). Anal. ($C_{29}H_{30}N_2O_3$·2HCl) C, H, N.

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Supporting Information Available: Full experimental details, including spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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