N-Benzylnaltrindoles as Long-Acting δ-Opioid Receptor Antagonists

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The indolic nitrogen of the δ-opioid receptor antagonist, naltrindole (1), was derivatized with benzyl or substituted benzyl to afford a series (2–9) that retained δ-opioid receptor antagonist activity and selectivity *in vitro*. The two most potent members (2 and 8) of the series were evaluated in mice and were found to produce δ-selective antagonism of [D-Ser²,Leu⁵]enkephalin-Thr⁶ which lasted 5 days. N-Benzylnaltrindole (2) should be useful as a δ_2-selective antagonist for *in vivo* studies where prolonged action is desired.

The heterogeneity of opioid receptors is well established, and it is generally accepted that there are at least three types of opioid receptors (μ, κ, and δ).[1] The development of selective opioid ligands[2] has contributed immensely to the pharmacologic characterization of opioid receptors, and recently three receptor types have been cloned.[3-6] Among the nonpeptide antagonists that are recognized by enkephalin receptors (δ), naltrindole[7] (1, NTI) is one of the most potent, and it is presently widely used as a pharmacologic tool.[8] More recently, the naltrindole-related ligands, naltriben[9] (NTB), naltrindole-5′-isothiocyanate[10] (5′-NTII), and 7-benzylidenenaltrexone[11] (BNTX), have been reported to be useful in the pharmacologic characterization of δ-opioid receptor subtypes.[12-22]

As structure–activity relationship studies[23] of naltrindole have revealed that the indolic nitrogen is tolerant to substitution, the present study was undertaken in an effort to explore the effect of such substitution on δ selectivity. In this connection, N-benzyl-substituted analogues were investigated because the combination of different substituents and positional isomerism might afford more selective ligands. Here we report that members of the benzyl series (2–9) are potent δ antagonists *in vitro* and that two of the compounds (2 and 8) possess ultralong-lasting δ-opioid antagonism *in vivo*.

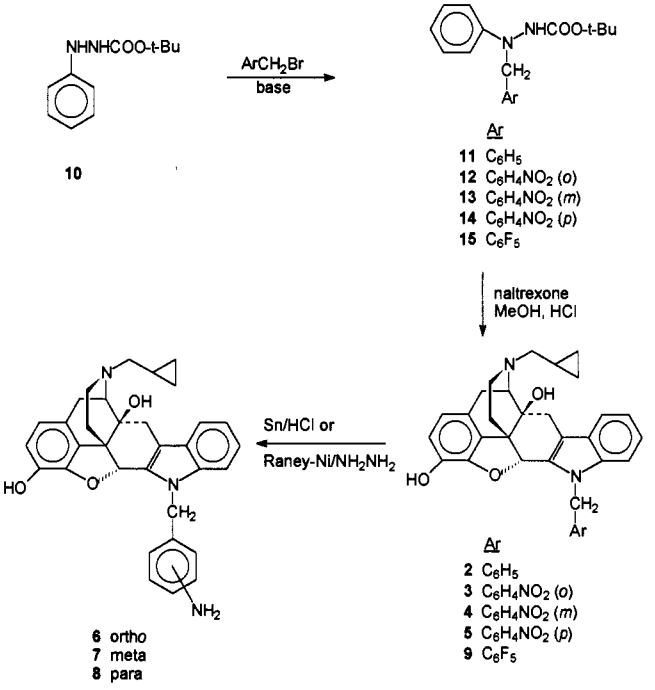
Chemistry

The N-benzyl derivatives 2–9 were synthesized as outlined in Scheme 1. Condensation of Boc-phenylhydrazine 10 with different substituted benzyl bromides afforded the Boc-N^1-benzyl-N^1-phenylhydrazines 11–15, which were reacted with naltrexone in refluxing methanolic HCl to yield the expected[13] N-benzylnaltrindoles 2–5 and 9. The Boc group was cleaved *in situ* under these reaction conditions. Reduction of the nitro group in 3–5 to the corresponding amines 6–8 was accomplished either with Raney nickel and hydrazine or with tin and HCl.

Biological Results

Smooth Muscle Preparations. The N-benzylnaltrindoles 2–9 were tested on the electrically stimulated guinea pig ileal longitudinal muscle[25] (GPI) and mouse vas deferens[26] (MVD) preparations as described previously

Scheme 1



(Table 1).[27] Morphine (M) and ethylketazocine (EK) were employed in the GPI, and [D-Ala²,D-Leu⁵]enkephalin[28] (DADLE) and morphine were employed in the MVD. These agonists are selective for μ-, κ-, and δ-opioid receptors, respectively. Opioid antagonism is expressed as an IC_{50} ratio, which is the IC_{50} of agonist in presence of antagonist (100 nM), divided by the control IC_{50} in the same preparation. The standard incubation time of the ligands was 15 min.

The more potent N-substituted naltrindoles (2, 4, and 6–8) possessed DADLE IC_{50} ratios and selectivity ratios that were >100 (Table 1). The benzyl and p-aminobenzyl derivatives (2 and 8, respectively) were the most potent δ antagonists in the series, but their IC_{50} ratios were somewhat lower than the parent compound, naltrindole (1). The remaining less potent members of the series (3, 5, and 9) have IC_{50} ratios in the range of 30–50, with selectivity ratios ≤ 50. All of the compounds were inactive as agonists in the GPI at a concentration of 1 μM. Some exhibited partial agonism amounting to not greater than 19% in the MVD.

***In Vivo* Studies.** Because compounds 2 and 8 exhibited the most potent δ antagonist activity *in vitro*, they were

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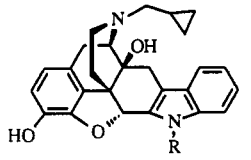
Table 1. Opioid Antagonist Potencies of *N*-Benzylnaltrindole and Its Analogues in the MVD and GPI Preparations



compd	R	IC$_{50}$ ratio[a] DADLE (δ)	M (μ)	EK (κ)	selectivity ratio[b] δ/μ	δ/κ
1	H	459 ± 104	11.2 ± 1.8	1.3 ± 0.2	41	353
2	$CH_2C_6H_5$	208 ± 28	1.6 ± 0.8	0.4 ± 0.1	131	208
3	$CH_2C_6H_4(o\text{-}NO_2)$	31 ± 6	2.3 ± 0.3	0.8 ± 0.3	13	31
4	$CH_2C_6H_4(m\text{-}NO_2)$	112 ± 29	0.9 ± 0.2	0.6 ± 0.2	112	112
5	$CH_2C_6H_4(p\text{-}NO_2)$	38 ± 9	0.5 ± 0.2	0.4 ± 0.03	38	38
6	$CH_2C_6H_4(o\text{-}NH_2)$	120 ± 20	1.0 ± 0.2	0.9 ± 0.1	120	120
7	$CH_2C_6H_4(m\text{-}NH_2)$	148 ± 36	1.3 ± 0.3	1.5 ± 0.4	111	100
8	$CH_2C_6H_4(p\text{-}NH_2)$	288 ± 37	2.7 ± 0.6	1.5 ± 0.3	106	188
9	$CH_2C_6F_5$	52 ± 11.4	1.4 ± 0.2	0.7 ± 0.4	37	52

[a] IC$_{50}$ ratios ± SE were determined ($n \geq 3$) in the presence of 100 nM of the antagonist after 15 min of incubation. [b] Selectivity ratios were calculated using the value 1 where IC$_{50}$ ratios are <1.

Table 2. Antagonism of Opioid Agonists by 2 and 8 24 h after Administration in Mice

compd	ED$_{50}$ ratio (95% confidence limit)[a] DSLET (δ_2)	DPDPE (δ_1)	morphine (μ)	U50488 (κ)
2	10.0 (5.6–16.7)	1.3 (0.9–1.9)	1.2 (0.7–2.3)	0.77 (0.41–1.39)
8	5.9 (3.3–10.0)	–	1.1 (0.6–2.0)	0.64 (0.31–1.11)

[a] The ED$_{50}$ ratio represents the ED$_{50}$ of agonist in the presence of 5 nmol icv of 2 or 8 divided by the control ED$_{50}$ (DSLET, 2.9 pmol/mouse; DPDPE, 0.46 nmol/mouse; morphine, 1.6 μmol/kg; U50488, 3.7 μmol/kg).

evaluated further in mice using the abdominal stretch assay[29] as described previously.[30] The peptide agonists were administered icv, and the nonpeptide agonists were given by the sc route. The solution of 2 was warmed prior to injection in order to prevent precipitation. At 90 min after icv administration, 2 (5 nmol) antagonized the antinociceptive effect of the selective δ_2 agonist, [D-Ser^2, Leu^5]enkephalin-Thr^6 [12,28] (DSLET), with an ED$_{50}$ ratio of 3.1 (1.9–5.3). No significant antagonism of the δ_1 agonist, [D-Pen^2,D-Pen^5]enkephalin[12,31] (DPDPE), was observed [ED$_{50}$ ratio, 1.0 (0.7–1.4)]. Interestingly, 24 h after administration of 2, its ED$_{50}$ ratio for DSLET increased to 10, and there were no significant differences from control values of the ED$_{50}$ ratios for DPDPE, morphine, or the κ agonist, 2-(3,4-dichlorophenyl)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]acetamide[32] (U50488) (Table 2). Compound 8 also was δ-selective, but its ED$_{50}$ ratio for DSLET was less than that of 2.

The antagonist effect of 2 and 8 was monitored over a 7-day period. As illustrated in Figure 1, the ED$_{50}$ ratios for 2 and 8 peaked at 24 h. The ratios were significantly greater than unity through day 5 [2, 6.7 (4.0–11.1); 8, 2.2 (1.3–3.7)], but after 1 week no statistical differences from control values were evident.

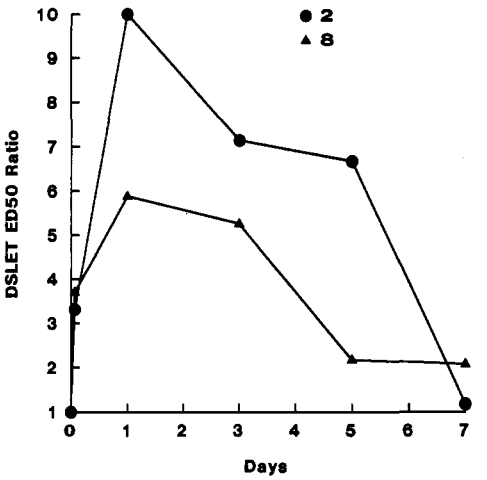


Figure 1. The time course of antagonism of DSLET by compounds 2 and 8 after icv administration (5 nmol/mouse).

Discussion

Substitution of a benzyl group on the indolic nitrogen of naltrindole (1, NTI) afforded a series of compounds with high antagonist potency and selectivity at δ-opioid receptors. Compound 2 was about half as potent as NTI and possessed improved δ selectivity over NTI in smooth muscle preparations. The increased selectivity of 2 was due to its lower potency at μ receptors. The nitro and amino derivatives retained δ antagonist activity and selectivity, but with the exception of 8, all had lower potency than the benzyl compound 2. The limited *in vitro* data did not reveal any correlation between δ antagonist potency and the position of substitution on the benzyl group. However, in general, the amino-substituted compounds 6–8 were more potent than the corresponding nitro analogues 3–5. The pentafluorobenzyl derivative 9 was found to be less potent and less selective than its unsubstituted congener 2.

The two most potent members (2 and 8) of the series were evaluated in mice for antagonist selectivity, and the data revealed that both compounds are selective δ antagonists. Moreover, since DSLET but not DPDPE was antagonized by *N*-benzylnaltrindole (2, Table 2), it appears that 2 is selective for the putative δ_2-opioid receptor. Both DSLET and [D-Ala^2,Leu^5]deltorphin have been shown to mediate antinociceptive activity through this δ receptor subtype, and these agonists are selectively antagonized by naltriben (NTB) and by naltrindole-5′-isothiocyanate (5′-NTII).[9,13] The δ_1-selective agonists include ligands such as DPDPE, DADLE, and (7-spiroindanyloxy)morphone[33] (SIOM), and they are selectively antagonized by 7-benzylidenenaltrexone[11] (BNTX) and by [D-Ala^2,Leu^5]enkephalin-Cys^6 [13,34] (DALCE). It is noteworthy that *N*-benzylnaltrindole (2) possesses greater *in vivo* δ_2 selectivity and longer duration of action than that reported[9] for the standard δ_2 antagonist, NTB.

Both 2 and 8 possessed peak activity 24 h after icv administration and a duration of action of 5 days. This is in marked contrast to NTI (1), whose duration of action

was reported to be 18–24 h.[12] The *in vivo* antagonist potency of **2** was substantially greater than that of **8** throughout the 5-day period when its ED_{50} ratios were significantly greater than unity. One possible explanation for the difference between **2** and **8** may be related to the greater lipophilicity of **2**. Thus, if the δ_2 receptor is located in a lipophilic compartment, the concentration of **2** may be greater than that of **8**.

In conclusion, *N*-benzylnaltrindole (**2**) is a potent δ_2-selective opioid receptor antagonist with a long duration of action. It therefore may serve as a useful tool in the pharmacologic characterization of δ_2-opioid receptor function. In addition, the fact that the *in vitro* δ antagonist activity is retained with the aminobenzyl derivatives (**6–8**) suggests that the amino group may serve as a point of attachment for the incorporation of electrophilic or photolyzable moieties in the design of affinity labels.

Experimental Section

Melting points were determined in open capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ, and are within ±0.4% of the theoretical values. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature on an IBM Bruker, AC-300, AC-200, or GE-300 instrument, and the chemical shifts are recorded (ppm) relative to TMS. Mass spectra were obtained on a Finnigan 4000, VG 7070-HF, or AEI MS-30 instrument. IR spectra were obtained from samples in KBr pellets from a Nicolet 5DXC FT-IR spectrometer, and peak positions are expressed as cm^{-1}. Column chromatography was carried out on silica gel 60 (230–400 mesh) from E. Merck. Preparative TLC was carried out on E. Merck 1-mm or 2-mm silica gel 60 F_{254} plates. HPLC separations were performed on a Beckman Model 110-A system using a 10-μm (Rsil, Alltech) semipreparative (10 mm × 250 mm) silica gel column, or 5-μm (Ultrasphere, Beckman) analytical (4.6 mm × 250 mm) silica gel column. All TLC data were determined using plastic backed sheets with silica gel (Machery Nagel), and the eluents $CHCl_3$–MeOH–NH_4OH are denoted by CMA. Visualization was achieved with either UV or I_2 vapor. Reagents and solvents were reagent grade and were used without prior purification. Chemicals were obtained from Aldrich Chemical Co., Milwaukee, WI. Naltrexone hydrochloride was a generous gift from Mallinckrodt Chemical Works, St. Louis, MO. Hydrochloride salts were prepared by addition of ethyl acetate–HCl or methanolic HCl to a solution of free base in ethyl acetate, followed by filtering, and drying *in vacuo*.

General Procedure for the Benzylation of Boc-phenylhydrazine. A mixture of Boc-phenylhydrazine[35] (1 mmol), benzyl bromide (1.0 mmol), and 1,8-bis(dimethylamino)naphthalene (Proton Sponge) (214 mg, 1 mmol) were dissolved in freshly distilled THF (10 mL) and refluxed under nitrogen for 24 h with stirring. The hydrogen bromide salt of Proton Sponge which precipitated during the course of the reaction was removed by filtration and washed with THF (10 mL). The filtrate was concentrated, washed with cold methanol until it was pure on TLC, and dried *in vacuo*. The pure product was obtained by crystallization from methanol. A higher boiling solvent, dioxane, was employed with *o*-nitrobenzyl bromide and with pentafluorobenzyl bromide.

N^1-Phenyl-N^1-benzyl-N^2-(*tert*-butoxycarbonyl)hydrazine (11): yield 238 mg, 80%; mp 94–96 °C; TLC, R_f 0.64 (CA, 100:1); ^{1}H-NMR (DMSO-d_6) δ 9.21 (s, 1 H, NH), 7.13–7.40 (m, 7 H, Ar), 6.68–6.73 (m, 3 H, Ar), 4.59 (s, 2 H, benzylic CH_2), 1.38 (s, 9 H, *t*-Bu); IR (cm^{-1}) 1704 (carbonyl); EI-MS *m/z* 298 (M^+).

N^1-Phenyl-N^1-(*o*-nitrobenzyl)-N^2-(*tert*-butoxycarbonyl)hydrazine (12): yield 215 mg, 62.5%; mp 104–108 °C; TLC, R_f 0.66 (CA, 100:1); ^{1}H-NMR (DMSO-d_6) δ 8.12 (d, J = 7.9 Hz, 1 H, Ar H ortho to the nitro group), 7.75–7.71 (m, 3 H, Ar), 7.21 (t, J = 7.8 Hz, 2 H, Ar), 6.8–6.71 (m, 3 H, Ar), 4.99 (s, 2 H, benzylic protons), 1.39 (s, 9 H, *t*-Bu); EI-MS *m/z* 343 (M^+).

N^1-Phenyl-N^1-(*m*-nitrobenzyl)-N^2-(*tert*-butoxycarbonyl)hydrazine (13): yield 295 mg, 86%; mp 127 °C; TLC, R_f 0.69 (CA, 100:1); ^{1}H-NMR (DMSO-d_6) δ 9.29 (s, 1 H, NH), 8.28 (s, 1 H, Ar), 8.12 (d, J = 8.0 Hz, 1 H, Ar), 7.88 (d, J = 8.0 Hz, 1 H, Ar), 7.64 (t, J = 7.9 Hz, 1 H, Ar), 7.21 (t, J = 7.8 Hz, 2 H, Ar), 6.78 (m, 3 H, Ar), 4.72 (s, 2 H, benzylic protons), 1.37 (s, 9 H, *t*-butyl); IR, (cm^{-1}) 1716 (amide carbonyl); EI-MS *m/z* 343 (M^+).

N^1-Phenyl-N^1-(*p*-nitrobenzyl)-N^2-(*tert*-butoxycarbonyl)hydrazine (14): yield 209 mg, 61%; mp 162–164 °C; TLC, R_f 0.66 (CA, 100:1); ^{1}H-NMR (DMSO-d_6) δ 9.33 (s, 1 H, NH), 7.93 (dd, 4 H, Ar), 7.17 (t, J = 7.7 Hz, 2 H, Ar), 6.73 (m, 3 H, Ar), 4.76 (s, 2 H, benzylic protons), 1.38 (s, 9 H, *t*-Bu); IR, (cm^{-1}) 1715 (carbonyl); EI-MS *m/z* 343 (M^+).

N^1-Phenyl-N^1-(pentafluorobenzyl)-N^2-(*tert*-butoxycarbonyl)hydrazine (15): yield 351 mg, 45.23%; TLC, R_f 0.68 (CA, 100:1); IR, cm^{-1} 1736 (ester carbonyl); EI-MS *m/z* 343 (M^+).

General Procedure for the Fischer Indole Synthesis. Naltrexone hydrochloride (377.5 mg, 1 mmol) was dissolved in 3 M HCl (5 mL), and to this solution was added 1 mmol of the hydrazine derivative (**12–15** and **18**) dissolved in methanolic HCl (5 mL). The mixture was refluxed for 7 h with stirring. Upon cooling of the reaction mixture, the solid which precipitated was filtered and recrystallized from ethanol. The crystals were washed with ether (3 mL) and dried *in vacuo* to afford the pure indole product. In some cases trace impurities necessitated dry column chromatography (CMA, 98:2:1). In case of the pentafluorobenzyl derivative **9**, $CHCl_3$–hexane–NH_4OH (80:20:1) was employed for purification.

1′-Benzyl-17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (2): yield 408 mg, 81%; mp >265 °C dec; TLC, R_f 0.67 (CMA, 98:2:1); ^{1}H-NMR (DMSO-d_6) δ 9.27 (s, 1 H, phenolic OH), 7.38 (d, J = 7.7 Hz, 1 H, Ar), 7.21–7.31 (m, 5 H, Ar), 7.07 (t, J = 7.1 Hz, 1 H, Ar), 6.98 (t, J = 7.4 Hz, 1 H, Ar), 6.67 (d, J = 8.1 Hz, 1 H, H_1), 6.61 (d, J = 8.1 Hz, 1 H, H_2, H_1 and H_2 appear as a quartet), 5.83 (s, 1 H, H_5), 5.51 (dd, J = 16.4 Hz, 2 H, benzylic protons); EI-MS *m/z* 504 (M^+). Anal. ($C_{33}H_{32}N_2O_3$) C, H, N.

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,14-dihydroxy-1′-(*o*-nitrobenzyl)indolo[2′,3′:6,7]morphinan (3): yield 375 mg, 68%; mp (HCl) > 240 °C dec; TLC, R_f 0.68 (CMA, 99:1:1); ^{1}H-NMR (DMSO-d_6) δ 8.87 (s, 1 H, phenolic OH), 8.21 (d, J = 6.3 Hz, 1 H, Ar), 7.52–7.42 (m, 3 H, Ar), 7.27 (d, J = 7.62 Hz, 1 H, Ar), 7.01–6.99 (m, 2 H, Ar), 6.6–6.4 (m, 2 H, H_1 and H_2), 6.13 (d, J = 6.47 Hz, 1 H, Ar), 5.93 (dd, J = 18.7 Hz, 2 H, benzylic protons), 5.62 (s, 1 H, H_5); EI-MS *m/z* 549 (M^+). Anal. ($C_{33}H_{31}N_3O_5$·HCl) C, H, N.

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,14-dihydroxy-1′-(*m*-nitrobenzyl)indolo[2′,3′:6,7]morphinan (4): yield 370 mg, 67%; mp >250 dec; TLC, R_f 0.56 (CMA, 98:2:1); ^{1}H-NMR (DMSO-d_6) δ 8.82 (s, 1 H, phenolic OH), 8.08 (d, J = 7.5 Hz, 1 H, Ar), 7.95 (s, 1 H, Ar), 7.50–7.58 (m, 2 H, Ar), 7.42 (d, J = 7.8 Hz, 1 H, Ar), 7.25 (d, J = 8.1 Hz, 1 H, Ar), 7.07 (t, J = 7.0 Hz, 1 H, Ar), 6.97 (t, J = 7.4 Hz, 1 H, Ar), 6.50–6.53 (m, 2 H, H_1 & H_2), 5.72 (s, 1 H, C_5), 5.68 (dd, J = 17.3 Hz, 2 H, benzylic protons); FAB MS *m/z* 550 $(MH)^+$, 548 $(M - H)^-$. Anal. ($C_{33}H_{31}N_3O_5$) C, H, N.

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,14-dihydroxy-1′-(*p*-nitrobenzyl)indolo[2′,3′:6,7]morphinan (5): yield 527 mg, 96%; mp >250 °C dec; TLC, R_f 0.67 (CMA, 98:2:1); ^{1}H-NMR (DMSO-d_6) δ 9.3 (s, 1 H, phenolic OH), 7.81 (dd, 4 H, Ar), 7.41 (d, J = 7.7 Hz, 1 H, Ar), 7.23 (d, J = 8.1 Hz, 1 H, Ar), 7.09 (t, J = 7.4 Hz, 1 H, Ar), 7.01 (t, J = 7.5 Hz, 1 H, Ar), 6.8–6.0 (m, 2 H, H_1 & H_2), 5.92 (s, 1 H, C_5), 5.69 (dd, J = 17.2 Hz, 2 H, benzylic protons); EI-MS *m/z* 549 (M^+). Anal. ($C_{33}H_{31}N_3O_5$) C, H, N.

1′-(*o*- or *m*-Aminobenzyl)-17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,14-dihydroxyindolo[2′,3′:6,7]morphinan. To a stirred solution of compound **3** or **4** (146.4 mg, 0.25 mmol) in a mixture of absolute ethanol (2 mL) and THF (1 mL) maintained at 50 °C was added Raney nickel. To this was added hydrazine hydrate (0.15 mL, 3.0 mmol) diluted with THF (1 mL), and the reaction was monitered by TLC. Small portions of Raney nickel were added until the evolution of gases ceased and conversion of the starting material was completed. The reaction was completed in 2 h and was allowed to stir for additional half hour prior to workup. The mixture was filtered to remove the Raney nickel, and the filtrate was evaporated to a gummy residue. Addition of ether (2 mL) produced a precipitate which was filtered to afford a pure product. In some cases chromatographic purification was required (CA, 100:1).

1′-(*o*-Aminobenzyl)-17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (6): yield 115 mg, 89%; mp (HCl) >225 °C dec; TLC, R_f 0.41 (CMA, 98:2:1); ^{1}H-NMR (DMSO-d_6) δ 9.0 (s, 1 H, phenolic OH), 7.44 (d, J = 7.7 Hz, 1 H, Ar), 7.185 (d, J = 8.2 Hz, 1 H, Ar), 7.07 (t, J = 7.5 Hz, 1 H, Ar), 7.0–6.92 (m, 2 H, Ar), 6.728 (d, J = 7.9 Hz, 1 H, Ar), 6.55 (d, J = 8.2 Hz, 1 H, H_1), 6.51 (d, J = 8.2 Hz, 1 H, H_2, H_1 and H_2 appear as a quartet), 6.36 (t, J = 7.5 Hz, 1 H, Ar), 6.144 (d, J = 7.6 Hz, 1 H, Ar), 5.45 (s, 1 H, H_5), 5.35 (dd, J = 17.3 Hz, 2 H, benzylic protons), 5.20 (s, 2 H, NH_2); FAB MS m/z 520 $(MH)^+$. Anal. ($C_{33}H_{33}N_3O_3$·HCl) C, H, N.

1′-(*m*-Aminobenzyl)-17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (7): yield 102 mg, 79%; mp >200 °C dec; TLC, R_f 0.36 (CMA, 98:2:1); ^{1}H-NMR (DMSO-d_6) δ 9.03 (s, 1 H, phenolic OH), 7.40 (d, J = 7.7 Hz, 1 H, Ar), 7.33 (d, J = 8.2 Hz, 1 H, Ar), 7.09 (t, J = 7.5 Hz, 1 H, Ar), 6.93–6.99 (m, 2 H, Ar), 6.40–6.57 (m, 5 H, Ar), 5.59 (s, 1 H, H_5), 5.36 (dd, J = 16.3 Hz, 2 H, benzylic protons), 4.97 (s, 2 H, NH_2); EI-MS m/z 519 (M^+). Anal. ($C_{33}H_{33}N_3O_3$·HCl·MeOH) C, H, N.

1′-(*p*-Aminobenzyl)-17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (8). To a stirred solution of **5** (585.5 mg, 1 mmol) in methanolic HCl (5 mL) was added granular tin (1.75 g), and the reaction mixture was refluxed for 5 h with stirring. It was then filtered to remove the unreacted tin. The solvent was evaporated and the crude product extracted with ethyl acetate:water (1:1) which was basified with NH_4OH. Pure **8** was obtained by dry column chromatography (CMA, 98:2:1): yield 303.6 mg, 59%; mp >200 °C dec; TLC, R_f 0.5 (CMA, 98:2:1); ^{1}H-NMR (DMSO-d_6) δ 8.96 (s, 1 H, phenolic OH), 7.37 (d, J = 7.0 Hz, 1 H, Ar), 7.32 (d, J = 7.0 Hz, 1 H, Ar), 7.06 (t, J = 8.1 Hz, 1 H, Ar), 7.0 (d, J = 8.4 Hz, 2 H, Ar), 6.94 (t, J = 7.7 Hz, 1 H, Ar), 6.46–6.56 (m, 4 H, Ar), 5.61 (s, 1 H, C_5), 5.30 (dd, J = 15.8 Hz, 2 H, benzylic protons); FAB MS m/z 520 $(MH)^+$. Anal. ($C_{33}H_{33}N_3O_3$·HCl·MeOH) C, H, N.

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,14-dihydroxy-1′-(pentafluorobenzyl)indolo[2′,3′:6,7]morphinan (9): yield 301 mg, 51%; mp >140 °C dec; TLC, R_f 0.72 (CMA, 98:2:1); ^{1}H-NMR (DMSO-d_6) δ 8.82 (s, 1H, phenolic OH), 7.54 (d, J = 8.2 Hz, 1H, Ar), 7.42 (d, J = 7.6 Hz, 1H, Ar), 7.2 (t, J = 7.7 Hz, 1H, Ar), 7.02 (t, J = 7.5 Hz, 1H, Ar), 6.46 (s, 2H, H_1 & H_2), 5.73 (s, 1H, H_5), 5.72 (dd, J = 16.7 Hz, 2H, benzylic protons); ^{19}F-NMR (DMSO-d_6) δ (ppm values referenced to $CFCl_3$ in acetone-d_6) 21 (t, 1F), 14.35 (t, 2F), −142 (d, 2F); FAB MS m/z 595 $(MH)^+$, 593 $(M - H)^-$. Anal. ($C_{33}H_{31}N_3O_5$) C, H, N.

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