δ Opioid Affinity and Selectivity of 4-Hydroxy-3-methoxyindolomorphinan Analogues Related to Naltrindole

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To investigate the effect of the introduction of a 4-phenolic substituent on the δ opioid affinity and selectivity of the indolomorphinans, a range of 4-phenolic analogues of naltrindole were prepared and evaluated in in vitro assays. Although the majority of the ligands displayed poor affinity for all three opioid receptors (μ, κ, δ), 17-cyclopropylmethyl-6,7-didehydro-4-hydroxy-3-methoxy-6,7:2′,3′-indolomorphinan (**13**) was an exception, displaying excellent δ binding selectivity (δ K_i = 7 nM, μ/δ = 1900, μ/κ = 1130). GTP-γ-S functional assays showed **13** to be a selective δ antagonist, albeit with lower potency than naltrindole. Although the reason for the unique profile of **13** could not be determined, these results validate our approach of introducing groups into the indolomorphinans that are known to reduce μ activity, to obtain increased δ selectivity.

Introduction

The discovery of the opioid receptor subtypes mu, kappa, and delta (μ, κ, δ) and the finding that traditional opioid analgesics act through the μ receptor[1] initially prompted research into the possibility that κ and δ agonists could be clinically useful analgesics lacking the detrimental side effects of μ agonists.[2,3] Studies on the δ receptor have, however, shown that in addition to analgesia,[4,5] the δ receptor is involved in many biological processes.[6] δ Agonists have been shown to have a stimulatory effect on respiration,[7] appear to act as antidiarrheals without affecting motility in the GI tract,[8,9] and are immunoregulators acting through δ-like binding sites on the surface of immune cells.[10−12] Unlike δ agonists which tend to be immunostimulants,[13−15] δ antagonists display potent immunosuppression and have the potential to be useful medications in transplant therapy.[16−18] It has also been shown that δ antagonists prevent the development of tolerance and dependence to μ agonists such as morphine,[19] a finding that has implications for the use of δ antagonists in the treatment of patients requiring chronic administration with μ agonists. In addition, recent findings that lung cancer cells express δ receptors, whereas normal lung cells do not, may allow for novel δ opioid-based diagnostic and therapeutic strategies in this area.[20]

Further studies to increase our understanding of the δ receptor system and its interactions with other systems in vivo require the development of metabolically stable non-peptide ligands with high δ selectivity and good CNS penetration. One of our approaches toward this goal has been to modify the structure and investigate the structure−activity relationship (SAR) of the indolomorphinans, a series of moderately δ-selective ligands developed by Portoghese.[21] The prototypical member of this series is the antagonist naltrindole (**1**) (Chart 1),[21] an indolomorphinan which was prepared from the nonselective naltrexone (**2**) by the introduction of an indolic moiety. This group served to reduce μ and κ affinity and increase δ affinity, thereby giving a ligand of moderate binding selectivity (μ/δ = 120 in our binding assays).[22] Although **1** has found many uses as a pharmacological tool,[23] its high affinity at both μ and κ receptors limits its utility. Indeed, the κ agonist profile of **1** can easily be observed in vivo,[24] a possible complication in such studies when high doses are employed.

Studies aimed at improving the selectivity of the indolomorphinans have mainly concentrated on modifying the indolic region, as this moiety is the portion of the ligand that confers the δ selectivity.[25−29] However, it has also been shown that changes in functionality in the opioid nucleus of the indolomorphinans modify their degree of selectivity. Loew[30] showed that an *N*-cyclopropylmethyl (N-CPM) substituent is superior to an *N*-methyl (N-Me) in terms of δ selectivity and, in the agonist N-Me series, ligands with a 14-hydroxyl group tend to be 2−3-fold more δ-selective than the corresponding 14-unsubstituted analogues, the latter recently corroborated by Portoghese in the antagonist N-CPM series.[31] On the basis of this work, we became interested in the systematic introduction of functionality into the opioid nucleus of **1** that is known to be detrimental to μ affinity, with the aim of discovering a group that reduces μ and κ affinity, but not δ, thereby increasing δ selectivity.

One obvious example would be masking the 3-phenol as a 3-methoxyl group, a modification shown in other classes of opioids to reduce μ affinity,[32] but previous work on 3-ethers of the indolomorphinans has led to conflicting results. In the N-Me series, Loew reported

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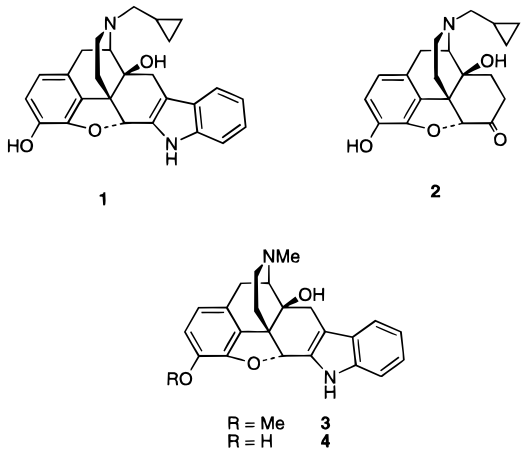
Chart 1. Structures of Naltrexone and Naltrindole Analogues



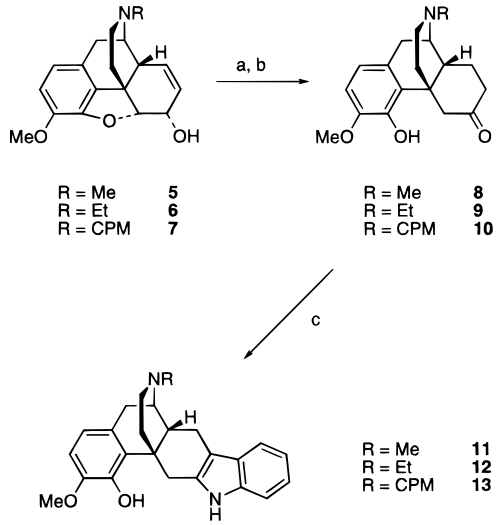
that **4** lost affinity at all three sites compared to phenol **3** (Chart 1), but the decrease at μ and κ was far greater than at δ giving rise to increased selectivity,[30] whereas Portoghese reported that in the N-CPM series, masking the 3-phenol of **1** as a methyl ether led to a ligand with poor selectivity and activity.[21] Although these reports appear to be contradictory, it is obvious that functionality in the A-ring can influence the δ affinity and selectivity in the naltrindole series of ligands. This led us to investigate the effect of introducing both a 4-phenolic and a 3-methoxyl substituent into this series, as 4-phenolic/3-methoxyl-substituted opioid ligands are known to possess extremely poor opioid activity in in vivo assays that predominantly measure μ agonism.[33,34] Because of the poor activity, in vitro assays have rarely been performed, but low μ affinity has been observed.[35] It was therefore expected that the combination of a 4-phenolic and 3-methoxyl group would lead to extremely low μ affinity in the indolomorphinans; because of the conflicting data above for the 3-ethers, the effect at δ receptors could not be predicted. This paper describes the synthesis, binding affinities, and μ/δ selectivities of a series of 4-phenolic analogues of naltrindole leading to the discovery of **13**, a highly δ-selective opioid ligand.

Chemistry

Codeine (**5**), *N*-ethylnorcodeine (**6**),[36] and *N*-cyclopropylmethylnorcodeine (**7**)[37] were converted to the corresponding dihydrothebainones **8**−**10** by treatment with BuLi, followed by catalytic hydrogenation.[38] Simple Fischer indole reaction with $PhNHNH_2$·HCl and TsOH in EtOH[22] gave only the 6,7-fused products **11**−**13** (Scheme 1). The regiochemistry of the products was determined by the presence of a doublet in the ^{1}H NMR spectra at 4.75 ppm, a signal that is known to correspond to the equatorial H-5 proton in 4-phenolic opioids.[39]

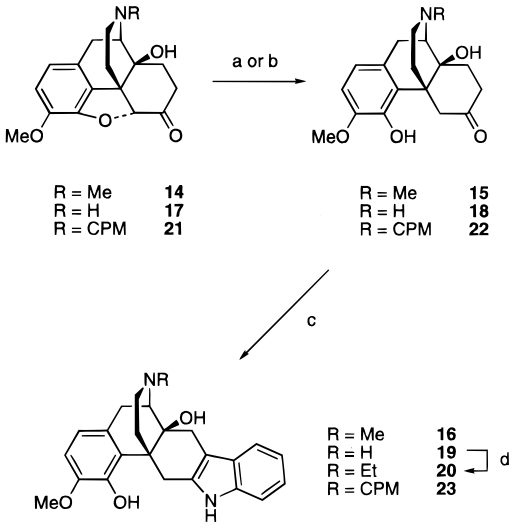
Oxycodone (**14**) was treated with Zn/HCl/AcOH to give the corresponding phenol **15**,[40] and again indole formation gave only the 6,7-fused isomer **16**. *N*-Norphenol **18** was prepared from noroxycodone (**17**)[41,42] by treatment with Zn/NH_4Cl and converted to *N*-norindole **19**, which was ethylated to give the *N*-ethyl (N-Et) analogue **20**. Naltrexone 3-methyl ether (**21**)[43] was converted to **23** under the same conditions as for **14** (Scheme 2).

Scheme 1[a]



[a] Conditions: (a) BuLi, THF; (b) H_2/Pd/C (10%), AcOH; (c) $PhNHNH_2$·HCl, TsOH, EtOH.

Scheme 2[a]



[a] Conditions: (a) Zn, HCl, AcOH; (b) Zn, NH_4Cl; (c) $PhNHNH_2$·HCl, TsOH, EtOH; (d) EtI, DMF, $NaHCO_3$.

Biological Results

Opioid Receptor Binding Assays. The binding affinities of the target compounds for μ and δ receptors were determined by inhibition of binding of [^{3}H]-DAMGO[44] and [^{3}H]DADLE[45] to rat brain membranes. The affinities of the compounds for κ receptors were determined by inhibition of binding of [^{3}H]U69,593[46] to guinea pig brain membranes. The results are shown in Table 1. These data show that the introduction of both a 4-phenolic and a 3-methyl ether group has a detrimental effect on affinity at all three opioid receptors for all members of this series compared to the parent indolomorphinans (**1**, **3**). However, **13** is unique in this series, the loss of affinity compared to **1** at μ and κ receptors being greater than the loss at δ, giving a ligand of excellent selectivity (μ/δ = 1900, κ/δ = 1130).

Bioassays in Smooth Muscle Preparations and GTP-γ-S Assays. Being the most selective compound in binding assays, **13** was chosen for further evaluation

Table 1. Opioid Receptor Binding Affinity of 4-Phenolic Analogues of Naltrindole

compound	K_i (nM) ± SEM			selectivity ratio	
	μ^a	δ^b	κ^c	μ/δ	κ/δ
1, naltrindole	27.0 ± 1.3	0.22 ± 0.13	30.4 ± 3.6	123	138
3, oxymorphindole	66 ± 5.6	0.80 ± 0.10	2170 ± 440	83	2700
11	2820 ± 850	94 ± 9	>6800	30	72
12	1350 ± 99	515 ± 65	3640 ± 254	3	7
13	13300 ± 695	7.0 ± 1.3	7920 ± 890	1900	1130
16	2850 ± 25	218 ± 33	>6700	13	31
20	797 ± 48	684 ± 40	>5300		8
23	1850 ± 382	21.8 ± 7.0	3160 ± 205	85	145

[a] Displacement of [^{3}H]DAMGO. [b] Displacement of [^{3}H]DADLE. [c] Displacement of [^{3}H]U69,593.

Table 2. Agonist Activity of **13** in Mouse Vas Deferens and Guinea Pig Ileum Preparations

compound	MVD IC_{50} (nM) ± SEM	GPI IC_{50} (nM) ± SEM
13	187.5 ± 57.9[a]	532 ± 48[b]
SNC80	2.73 ± 0.48	5457 ± 2052
1, naltrindole	*c, d*	*c*

[a] Dose−response curve shifted 12.9-fold by 1 mM ICI-174,864. [b] Dose−response curve shifted 6-fold by 1 μM naloxone. [c] Less than 20% inhibition. [d] 1 μM naltrindole shifted DPDPE dose−response curve 2698-fold.

of antagonist and agonist activity on electrically stimulated guinea pig ileal longitudinal muscle myenteric plexus (GPI) and mouse vas deferens (MVD) smooth muscle preparations using previously described bioassays.[47] As can be seen from Table 2, **13** displayed weak agonist activity in the MVD and very weak agonist activity in the GPI. The agonist activity in GPI was somewhat reversed with the μ-preferring antagonist naloxone (6-fold shift in the dose−response curve) indicating that the extremely weak agonism in this tissue was mediated through μ receptors. Challenging **13** in MVD with the δ-selective antagonist ICI-174,864 caused a 12.9-fold shift in the dose−response curve, indicating a δ agonist effect. The ability of **13** to inhibit GTP-γ-S binding in guinea pig caudate stimulated by selective opioid agonists was also determined. As can be seen from Table 3, **13** acts as a moderately potent δ antagonist with a selectivity equal to or greater than that of naltrindole.

Discussion

The 4-phenolic ligands displayed the expected poor affinity for μ receptors; however, in general they also had poor affinity for both κ and δ receptors giving rise to ligands of reduced affinity and selectivity compared to the parent indolomorphinans. This would tend to suggest that the combination of 4-phenol and 3-methoxyl groups is detrimental to δ activity; however, this is not the case for **13**, which has a 30-fold lower δ affinity than naltrindole but almost 500-fold lower μ affinity, rendering it one of the most δ opioid-selective nonpeptide ligands yet described as determined in displacement assays (μ/δ = 1900, κ/δ = 1130). The reason that **13** possesses such high selectivity whereas the other members of the series possess poor selectivity is unclear; molecular modeling (Tripos' Sybyl) showed negligible differences between the 4-phenolic ligands, in terms of the distances between the A-ring, basic nitrogen, and indolic group. However, it was noted that differences exist between the 4-phenolic ligands and the indolomorphinans; opening of the 4,5-bridge causes a change in the relative position of the indolic ring by about 2.3 Å,[48] possibly explaining the differences observed in the SAR of the current 4-phenolic ligands and the indolomorphinans. For both the N-Me (**11**, **16**) and N-CPM (**13**, **23**) analogues, it was observed that the presence of a 14-hydroxyl group was detrimental to δ selectivity and affinity, an effect particularly marked between the N-CPM analogues: 14-unsubstituted **13** possesses 3-fold higher δ affinity and 7-fold lower μ affinity than the 14-hydroxy **23**, leading to a difference in μ/δ selectivity of 22-fold. This contrasts with the findings of both Loew[30] and Portoghese,[31] who found that a 14-hydroxyl group enhanced δ selectivity and affinity in the indolomorphinans. In addition, we recently reported that an N-Et-substituted indolomorphinan possessed greater δ binding selectivity than either the N-Me or N-CPM analogues,[49] a finding consistent with the high selectivity found by Dondio in a related set of N-Et-substituted opioid ligands.[50] In contrast, the N-Et-substituted 4-phenolic ligands (**12**, **20**) display poor δ affinity and selectivity. These findings suggest that the SAR of the parent indolomorphinans does not generally apply to the 4-phenolic derivatives.

The poor activity of **13** in the MVD assay is at odds with its δ binding affinity. However, it has been noted that δ-selective opioid ligands with similar binding affinity in other series also display poor activity in MVD.[51,52] These results suggest that MVD may not be a reliable functional assay for δ-selective ligands with single-digit nanomolar affinity. A further complication of the MVD is the highly oxygenated assay conditions, possibly giving rise to para-aromatic oxidation[53] of **13**, and offers an alternative explanation for the poor activity of **13**. Thus, MVD was not considered a useful assay for the 4-phenolic ligands, and **13** was evaluated in the GTP-γ-S assays, which appears to be the functional assay of choice as **13** was shown to be a selective δ opioid antagonist (>56-fold μ/δ and μ/κ). Consistent with the binding assays, **13** possessed lower antagonist potency at all three sites compared to naltrindole. Unlike the binding assays, the reduction in antagonist potency was similar at all three receptors (ca. 350-fold), thereby resulting in a ligand of similar antagonist selectivity to naltrindole, but greatly reduced potency. Comparing naltrindole and **13**, it can be seen that the difference in δ antagonist potency (350-fold) is far greater than their difference in δ binding affinity (30-fold); thus there also appears to be some discrepancy between the binding and GTP-γ-S assays. Indeed, all three assays appear somewhat inconsistent: weak nonselective δ agonism in MVD, weak selective δ antagonism in GTP-γ-S, and highly selective δ binding

Table 3. Inhibition of Antagonists of GTP-γ-^{35}S Binding in Guinea Pig Caudate Stimulated by μ-, δ-, and κ-Selective Agonists

	K_i (nM) ± SD			selectivity ratio	
compound	μ^a	δ^b	κ^c	μ/δ	κ/δ
13	>1250	22.1 ± 2.1	>1250	>56	>56
1, naltrindole	3.20 ± 0.20	0.062 ± 0.006	8.85 ± 0.82	52	140

[a] Antagonism of DAMGO. [b] Antagonism of SNC80. [c] Antagonism of U69,593.

in displacement assays. Although the data from MVD cannot be relied upon due to the reasons given above, it is possible that **13** is actually a δ agonist but that the agonism cannot be detected in GTP-γ-S assays conducted with membranes. Indeed, a similar profile was reported by Childers for μ agonists in GTP-γ-S assays, where μ partial agonists behaved as μ antagonists in rat thalamic membranes.[54] However, both GTP-γ-S and binding assays agree that **13** is a δ-selective ligand with a selectivity equal to or greater than that of naltrindole, but with reduced δ activity, making **13** a useful new lead for the discovery of highly selective δ opioid ligands.

In conclusion, our approach to the design of highly selective δ opioid ligands by introducing groups known to be detrimental to μ affinity has led to the discovery of **13**, one of the most selective non-peptide δ opioid ligands yet described.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard on a Varian Gemini-300 spectrometer. Mass spectra (EI) were recorded on a VE Analytical 7070E mass spectrometer. Thin-layer chromatography (TLC) was performed on Analtech silica gel GHLF-0.25-mm plates. Column chromatography was performed with Fluka silica gel 60 (mesh 220−240) or neutral alumina (Brockmann 1, mesh 150). Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA, and the results were within ±0.4% of the theoretical values. All extracted solutions were dried over Na_2SO_4 and concentrated to dryness on a rotary evaporator under reduced pressure. With the exception of the preparation of dihydrothebainone, all reactions are unoptimized.

Dihydrothebainone (8).[38,55] BuLi (1.3 M, 2.8 mL, 3.6 mmol) was added to a solution of codeine (**5**) (470 mg, 1.6 mmol) in THF (20 mL) at −78 °C. After stirring at −78 °C for 1 h, the light-orange solution was warmed to room temperature to give a dark-red solution, which was stirred at room temperature for 20 min and then rapidly quenched with water (40 mL). The THF was removed, the organic components were extracted into $CHCl_3$ (3 × 30 mL), and the extracts were then washed with brine and dried. Removal of the solvent gave crude thebainone-A (450 mg). The crude thebainone-A was hydrogenated in AcOH (10 mL) with Pd/C (10%, 40 mg) at 30 psi for 4 h. After completion of the reaction (TLC), the mixture was diluted with water (20 mL), filtered through Celite, and basified (pH 9) with NH_4OH. The products were extracted into $CHCl_3$ (3 × 40 mL), and the extracts were washed with brine and dried. Removal of the solvent and purification as the hydrochloride salt from acetone gave **8**·HCl (415 mg, 78%): mp >250 °C. Anal. ($C_{18}H_{24}NO_3Cl·0.25H_2O$) C, H, N.[56]

17-Ethyl-17-nordihydrothebainone (**9**). Following the procedure described for **8**, compound **6**[36] (3.1 g, 10 mmol) was treated with BuLi (2.5 equiv) and hydrogenated to give the crude product. Column chromatography (SiO_2, EtOAc:MeOH:NH_3, 19:1:0.1) gave **9** (2.2 g, 71%): ^{1}H NMR ($CDCl_3$) δ 6.68 (d, 1H, J = 8.8 Hz, H-2), 6.59 (d, 1H, J = 8.8 Hz, H-1), 6.09 (s, 1H, 4-OH), 4.23 (dd, 1H, J = 14.2, 2.2 Hz, H-5), 3.83 (s, 3H, 3-OCH_3), 2.92 (d, 1H, J = 18.7 Hz, H-10b), 2.62 (m, 2H, H-18), 1.13 (t, 3H, J = 6.6 Hz, H-19); MS m/z (EI) 315 (M^+).

17-Cyclopropylmethyl-17-nordihydrothebainone (**10**). Following the procedure described for **8**, compound **7**[37] (3.3 g, 9.7 mmol) was treated with BuLi (2.5 equiv) and hydrogenated to give the crude product. Column chromatography (SiO_2, $CHCl_3$:MeOH, 19:1) gave **10** (2.5 g, 89%): ^{1}H NMR ($CDCl_3$) δ 6.68 (d, 1H, J = 8.8 Hz, H-2), 6.59 (d, 1H, J = 8.8 Hz, H-1), 6.12 (s, 1H, 4-OH), 4.23 (dd, 1H, J = 13.5, 2.2 Hz, H-5), 3.82 (s, 3H, 3-OCH_3), 2.94 (d, 1H, J = 18.5 Hz, H-10b), 0.92 (m, 1H, H-19), 0.60 (m, 2H, H-20 and H-21), 0.21 (m, 2H, H-20 and H-21); MS m/z (EI) 341 (M^+).

6,7-Didehydro-4-hydroxy-3-methoxy-17-methyl-6,7:2′,3′-indolomorphinan (**11**)**.** A solution of **8** (310 mg, 1.0 mmol), phenylhydrazine·HCl (160 mg, 1.1 mmol), and TsOH·H_2O (200 mg, 1.0 mmol) in EtOH (20 mL) was heated at reflux for 3 h. The cooled reaction mixture was diluted with water (20 mL) and the solution basified (pH 9) with NH_4OH. After removal of the EtOH, the products were extracted into $CHCl_3$ (3 × 30 mL) and the organic extracts were washed with brine, dried, and concentrated to give the crude product. Purification by column chromatography (Al_2O_3, EtOAc:MeOH, 95:5), followed by formation of the fumaric acid salt from MeOH, gave **11**·$C_4H_4O_4$ (220 mg, 44%): mp 270−272 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.74 (s, 1H, H-1′), 7.31 (m, 1H, indole ring), 7.23 (m, 1H, indole ring), 7.09 (m, 2H, indole ring), 6.58 (m, 2H, H-1 and H-2), 5.93 (s, 1H, 4-OH), 4.75 (d, 1H, J = 16.7 Hz, H-5), 3.78 (s, 3H, 3-OCH_3), 2.43 (s, 3H, H-18); MS m/z (EI) 374 (M^+). Anal. ($C_{26}H_{30}N_2O_6$) C, H, N.

6,7-Didehydro-17-ethyl-4-hydroxy-3-methoxymethyl-6,7:2′,3′-indolomorphinan (12). Following the procedure described for **11**, compound **9** (450 mg, 1.4 mmol) was treated with phenylhydrazine·HCl (1.1 equiv) and TsOH·H_2O (1 equiv) for 2 h. The crude product was purified as the hydrated oxalic acid salt from 2-PrOH/CH_2Cl_2 (280 mg, 51%): mp 172−173 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.73 (s, 1H, H-1′), 7.30 (m, 1H, indole ring), 7.23 (m, 1H, indole ring), 7.07 (m, 2H, indole ring), 6.58 (m, 2H, H-1 and H-2), 5.93 (s, 1H, 4-OH), 4.75 (d, 1H, J = 16.5 Hz, H-5), 3.78 (s, 3H, 3-OCH_3), 2.62 (m, 2H, H-18), 1.15 (t, 3H, J = 6.6 Hz, H-19); MS m/z (EI) 388 (M^+). Anal. ($C_{27}H_{30}N_2O_6·H_2O·0.25CH_2Cl_2$) C, H, N.

17-Cyclopropylmethyl-6,7-didehydro-4-hydroxy-3-methoxy-6,7:2′,3′-indolomorphinan (13). Following the procedure described for **11**, compound **10** (2.5 g, 7.3 mmol) was treated with phenylhydrazine·HCl (1.1 equiv) and TsOH·H_2O (1 equiv) for 2 h. The crude product was purified by column chromatography (SiO_2, $CHCl_3$:MeOH:NH_3, 19:1:0.1) and then converted to the hydrated (−)-malic acid salt from acetone (1.7 g, 42%): mp 210−211 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.74 (s, 1H, H-1′), 7.30 (m, 1H, indole ring), 7.23 (m, 1H, indole ring), 7.02 (m, 2H, indole ring), 6.58 (m, 2H, H-1 and H-2), 5.94 (s, 1H, 4-OH), 4.75 (d, 1H, J = 16.6 Hz, H-5), 3.75 (s, 3H, 3-OCH_3), 0.95 (m, 1H, H-19), 0.58 (m, 2H, H-20 and H-21), 0.18 (m, 2H, H-20 and H-21); MS m/z (EI) 414 (M^+). Anal. ($C_{31}H_{36}N_2O_7·0.33H_2O$) C, H, N.

14-Hydroxydihydrothebainone (**15**)**.**[55] Zinc dust (2.0 g, 31 mmol) was added in portions over 20 min to a solution of **14**·HCl (2.2 g, 6.3 mmol) in HCl (37%, 2 mL) and AcOH (20 mL) at reflux. After heating at reflux for a further 10 min, the reaction was cooled by the addition of ice/water (50 mL) and basified (pH 9) with NH_4OH, and the products were extracted into $CHCl_3$ (3 × 50 mL). The organic extracts were washed with brine (100 mL), dried, concentrated, and purified by column chromatography (SiO_2, EtOAc:MeOH:NH_3, 19:1:0.1) to give **15** (1.4 g, 71%): ^{1}H NMR ($CDCl_3$) δ 6.67 (d, 1H, J = 8.3 Hz, H-2), 6.58 (d, 1H, J = 8.3 Hz, H-1), 6.12 (s, 1H, 4-OH),

3.93 (dd, 1H, J = 14.2, 2.2 Hz, H-5), 3.62 (s, 3H, 3-OCH_3), 2.38 (s, 3H, H-18); MS m/z (EI) 317 (M^+).

6,7-Didehydro-4,14-dihydroxy-3-methoxy-17-methyl-6,7:2′,3′-indolomorphinan (16). Following the procedure described for **11**, compound **15** (700 mg, 2.2 mmol) was treated with phenylhydrazine·HCl (1.1 equiv) and TsOH·H_2O (1 equiv) for 2 h. The crude product was purified by column chromatography (SiO_2, $CHCl_3$:MeOH:NH_3, 19:1:0.1) and then converted to the fumaric acid salt from ^{i}PrOH/MeOH (250 mg, 22%): mp >270 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.75 (s, 1H, H-1′), 7.28 (m, 1H, indole ring), 7.22 (m, 1H, indole ring), 7.02 (m, 2H, indole ring), 6.58 (m, 2H, H-1 and H-2), 5.95 (s, 1H, 4-OH), 4.52 (d, 1H, J = 15.2 Hz, H-5), 3.73 (s, 3H, 3-OCH_3), 2.40 (s, 3H, H-18); MS m/z (EI) 390 (M^+). Anal. ($C_{28}H_{30}N_2O_7$·0.5MeOH) C, H, N.

14-Hydroxy-17-nordihydrothebainone (18). A mixture of noroxyoxycodone·HI (**17**)[41,42] (4.0 g, 9.3 mmol), NH_4Cl (5.0 g, 93 mmol), zinc dust (4.0 g, 62 mmol), and EtOH (95%, 60 mL) was heated at reflux for 2.5 h. After cooling, the mixture was filtered and the solids was washed with NH_4OH (8 mL). The combined filtrate and washings were concentrated, redissolved in a mixture of water (12 mL) and NH_4OH (8 mL), and extracted with $CHCl_3$ (25 mL, then 6 × 15 mL). The organic extracts were dried ($MgSO_4$), and the solvent was removed to give the crude product. Crystallization from ^{i}PrOH gave **18** (1.71 g, 61%): mp 203−205 °C dec; ^{1}H NMR ($CDCl_3$) δ 6.68 (d, 1H, J = 8.8 Hz, H-2), 6.57 (d, 1H, J = 8.8 Hz, H-1), 3.89 (d, 1H, J = 13.2 Hz, H-5), 3.82 (s, 3H, 3-OCH_3); MS m/z (EI) 303 (M^+). Anal. ($C_{17}H_{21}NO_4$·0.2H_2O) C, H, N.

6,7-Didehydro-4,14-dihydroxy-3-methoxy-6,7:2′,3′-indolomorphinan (19). Following the procedure described for **11**, compound **18** (1.35 g, 4.45 mmol) was treated with phenylhydrazine·HCl (1.1 equiv) and TsOH·H_2O (1 equiv) for 2 h. The crude product was purified as the hydrated hydrochloride salt from water (1.05 g, 50%): mp >250 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.80 (s, 1H, H-1′), 7.26 (m, 1H, indole ring), 7.22 (m, 1H, indole ring), 7.00 (m, 2H, indole ring), 6.59 (m, 2H, H-1 and H-2), 4.59 (d, 1H, J = 16.5 Hz, H-5), 3.77 (s, 3H, 3-OCH_3); MS m/z (EI) 376 (M^+). Anal. ($C_{23}H_{25}N_2O_3$·2.75H_2O) C, H, N.

6,7-Didehydro-17-ethyl-4,14-dihydroxy-3-methoxy-6,7:2′,3′-indolomorphinan (20). A mixture of iodoethane (0.07 mL, 0.88 mmol), the hydrochloride salt of **19** (700 mg, 1.5 mmol), $NaHCO_3$ (1 g, 11.9 mmol), and DMF (15 mL) was stirred at room temperature for 2 h. After quenching with NH_4OH (20 mL), the products were extracted into Et_2O (3 × 30 mL); the organic extracts were washed with brine (3 × 50 mL), dried, and concentrated to give the crude product. The product was purified by column chromatography (SiO_2, EtOAc), followed by formation of the hydrochloride salt from water (245 mg, 59%): mp 210−212 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.76 (s, 1H, H-1′), 7.26 (m, 1H, indole ring), 7.21 (m, 1H, indole ring), 7.02 (m, 2H, indole ring), 6.57 (m, 2H, H-1 and H-2), 5.96 (s, 1H, 4-OH), 4.50 (d, 1H, J = 15.4 Hz, H-5), 3.77 (s, 3H, 3-OCH_3), 2.58 (m, 2H, H-18), 1.13 (t, 3H, J = 6.6 Hz, H-19); MS m/z (EI) 404 (M^+). Anal. ($C_{25}H_{29}N_2O_3Cl$·2H_2O) C, H, N.

17-Cyclopropylmethyl-14-hydroxy-17-nordihydrothebainone (22).[55] Naltrexone 3-methyl ether·HCl (**21**)[43] (2.0 g, 5.1 mmol) was treated as **14** above. The crude product was purified by column chromatography (SiO_2, $CHCl_3$:MeOH, 19:1) to give **22** (1.4 g, 76%): ^{1}H NMR ($CDCl_3$) δ 6.67 (d, 1H, J = 8.3 Hz, H-2), 6.57 (d, 1H, J = 8.3 Hz, H-1), 6.13 (s, 1H, 4-OH), 3.94 (d, 1H, J = 12.9 Hz, H-5), 3.81 (s, 3H, 3-OCH_3), 0.83 (m, 1H, H-19), 0.55 (m, 2H, H-20 and H-21), 0.18 (m, 2H, H-20 and H-21); MS m/z (EI) 357 (M^+).

17-Cyclopropylmethyl-6,7-didehydro-4,14-dihydroxy-3-methoxy-6,7:2′,3′-indolomorphinan (23). Following the procedure described for **11**, compound **22** (1.4 g, 3.9 mmol) was treated with phenylhydrazine·HCl (1.1 equiv) and TsOH·H_2O (1 equiv) for 2 h. The crude product was purified as the (+)-tartaric acid salt from ^{i}PrOH (700 mg, 31%): mp 210 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.75 (s, 1H, H-1′), 7.28 (m, 1H, indole ring), 7.22 (m, 1H, indole ring), 6.98 (m, 2H, indole ring), 6.56 (m, 2H, H-1 and H-2), 5.96 (s, 1H, 4-OH), 4.50 (d, 1H, J = 15.6 Hz, H-5), 3.77 (s, 3H, 3-OCH_3), 0.92 (m, 1H, H-19), 0.59 (m, 2H, H-20 and H-21), 0.19 (m, 2H, H-20 and H-21); MS m/z (EI) 430 (M^+). Anal. ($C_{31}H_{36}N_3O_9$·0.5H_2O) C, H, N.

Biological Assays. 1. Receptor Binding Assays. μ Binding sites were labeled using [^{3}H]DAMGO (2.0 nM) as previously described[44] with several modifications. Rat membranes were prepared each day using a partially thawed−frozen rat brain which was polytroned in 10 mL/brain of ice-cold 10 mM Tris-HCl, pH 7.0. Membranes were then centrifuged twice at 30000g for 10 min each centrifugation. After the second centrifugation, the membranes were resuspended in 50 mL/brain of 25 °C 50 mM Tris-HCl, pH 7.4. Incubations proceeded for 2 h at 25 °C in 50 mM Tris-HCl, pH 7.4, along with a protease inhibitor cocktail. The nonspecific binding was determined using 20 μM levallorphan. δ Binding sites were labeled using [^{3}H]DADLE (2.0 nM) as previously described[45] with several modifications. Rat membranes were prepared each day using a partially thawed−frozen rat brain which was polytroned in 10 mL/brain of ice-cold 10 mM Tris-HCl, pH 7.0. Membranes were then centrifuged twice at 30000g for 10 min each centrifugation. After the second centrifugation, the membranes were resuspended in 50 mL/brain of 25 °C 50 mM Tris-HCl, pH 7.4. Incubations proceeded for 2 h at 25 °C in 50 mM Tris-HCl, pH 7.4, containing 100 mM choline chloride, 3 mM $MnCl_2$, 100 nM DAMGO to block μ binding sites, and a protease inhibitor cocktail. Nonspecific binding was determined using 20 μM levallorphan. κ 1 binding sites were labeled using [^{3}H]U69,593 (2.0 nM) as previously described[46] with several modifications. Guinea pig brain membranes were prepared each day using a partially thawed guinea pig brain which was polytroned in 10 mL/brain of ice-cold 10 mM Tris-HCl, pH 7.0. The membranes were then centrifuged twice at 30000g for 10 min each centrifugation. After the second centrifugation, the membranes were resuspended in 75 mL/brain of 25 °C 50 mM Tris-HCl, pH 7.4. Incubations proceeded for 2 h at 25 °C in 50 mM Tris-HCl, pH 7.4, containing 1 μg/mL captopril and a protease inhibitor cocktail. Nonspecific binding was determined using 1 μM U69,593. Each tritiated ligand was displaced by 10 concentrations of test drug, two times. All drug dilutions were done in 10 mM Tris-HCl, pH 7.4, containing 1 mg/mL bovine serum albumin. The IC_{50} and slope factor (N) were obtained by using the program MLAB. IC_{50} values were converted to K_i values according to the equation $K_i = IC_{50}/(1 + [L]/K_d)$.

2. GPI and MVD Bioassays.[47] Electrically induced smooth muscle contractions of mouse vas deferens and strips of guinea pig ileum longitudinal muscle myenteric plexus were used. Tissues came from male ICR mice weighing 25−40 g and male Hartley guinea pigs weighing 250−500 g. The tissues were tied to gold chain with suture silk, suspended in 20-mL baths containing 37 °C oxygenated (95% O_2, 5% CO_2) Krebs bicarbonate solution (magnesium free for the MVD), and allowed to equilibrate for 15 min. The tissues were then stretched to optimal length previously determined to be 1 g tension (0.5 g for MVD) and allowed to equilibrate for 15 min. The tissues were stimulated transmurally between platinum wire electrodes at 0.1 Hz, 0.4-ms pulses (2-ms pulses for MVD), and supramaximal voltage. An initial dose−response curve of DPDPE or PL-017 was constructed at the start of each assay to establish tissue effects, allowing each tissue to be used as its own control. Tissues not producing typical results were not used. Experimental compounds were added to the baths in 14−60-μL volumes. Succeeding doses of agonist were added cumulatively to the bath at 3-min intervals to produce a concentration−response curve. The tissues were then washed extensively with fresh buffer until the original contraction height was reestablished. Agonist effects of the compounds at 1 μM were measured as percent inhibition of contraction height 10 min after addition to the bath. Antagonist effects to DPDPE and PL-017 were assayed after incubation of the tissues with 1 μM concentration of the compound in the bath for 30 min. The tissues were then washed with fresh buffer for 30 min, and the agonist dose−response curve was repeated. Rightward shifts in the dose−response curves were calculated by dividing the antagonized dose−response curve IC_{50} value by the un-

antagonized IC_{50} value. IC_{50} values represent the mean of two to four tissues. IC_{50} estimates and their associated standard errors were determined by using a computerized nonlinear least-squares method.[57]

3. GTP-γ-^{35}S Functional Assays. Guinea pig caudate membranes (10 μg) were suspended in 300 μL of buffer containing 59 mM Tris (pH 7.7 at 25 °C), 100 mM NaCl, 5 μM $MgCl_2$, 1 mM EDTA, 1 mM DTT, 100 μM GDP, 0.1% BSA, 0.05−0.1 nM [^{35}S]GTP-γ-S, 500 nM or 10 μM agonists, and varying concentrations (at least 10 different concentrations) of antagonists. The reaction was initiated by the addition of membranes and terminated after 4 h by the addition of 3 mL of cold (4 °C) purified water (Milli-Q UV-Plus, Millipore) followed by rapid vacuum filtration through Whatman GF/B filters. The filters were then washed once with 5 mL of cold water. Bound radioactivity was counted by liquid scintillation spectroscopy using a Taurus (Micromedic) liquid scintillation counter at 40% efficiency. Nonspecific binding was determined in the presence of 10 μM GTP-γ-S. Assays were performed in triplicate and each experiment was performed at least three times. The K_i and slope factor were determined using the program MLAB on a total of 33−44 data points.

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