Potent and Selective Indolomorphinan Antagonists of the Kappa-Opioid Receptor

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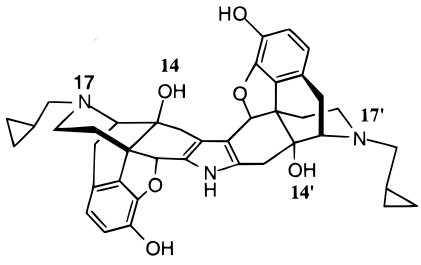
The indole moiety in the delta-opioid antagonist, naltrindole (**2**, NTI), was employed as a scaffold to hold an "address" for interaction with the kappa-opioid receptor. The attachment of the address to the 5′-position of the indole moiety was based on superposition of NTI upon the kappa antagonist, norbinaltorphimine (**1**, norBNI). A variety of cationic groups were employed as a kappa address in an effort to investigate its interaction with the anionic address subsite, Glu297, on the kappa receptor. Some of the groups that were employed for this purpose were amines, amidines, guanidines, and quaternary ammonium. Members of the series were found to have a varying degree of kappa antagonist potency and kappa selectivity when tested in smooth muscle preparations. The 5′-guanidine derivative **12a** (GNTI) was the most potent member of the series and had the highest kappa selectivity ratio. GNTI was 2 times more potent and 6−10-fold more selective than norBNI (**1**). In general, the order of potency in the series was: guanidines > amidines ∼ quaternary ammonium > amines. The kappa antagonist potency appeared to be a function of a combination of the pK_a and distance constraint of the cationic substituent of the ligand. Receptor binding studies were qualitatively in agreement with the pharmacological data. Molecular modeling studies on **12a** suggested that the protonated N-17 and guanidinium groups of GNTI are associated with Asp138 (TM3) and Glu297 (TM6), respectively, while the phenolic hydroxyl may be involved in donor−acceptor interactions with the imidazole ring of His291. It was concluded that the basis for the high kappa selectivity of GNTI is related both to association with the nonconserved Glu297 residue and to unfavorable interactions with an equivalent position in mu- and delta-opioid receptors.

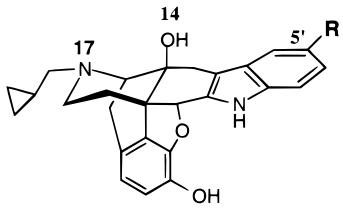
Introduction

The OP_2 receptor, commonly known as the kappa-opioid receptor, is one of three major opioid receptor types that are found in the central nervous system and in the periphery.[1] The precise roles of kappa receptors have not yet been established, but it appears that the kappa-selective endogenous opioid peptides (e.g., dynorphin A) function both as neuro- and immunomodulators. A number of nonpeptide kappa agonists have been developed as potential analgesics, and some of these ligands have found wide use as pharmacological tools in opioid research.[2] Norbinaltorphimine (**1**, norBNI) is the only antagonist currently available that is highly selective for kappa receptors.[3]

The structure−activity relationship of norBNI (**1**) has been extensively investigated.[4] As a bivalent ligand, norBNI contains two naltrexone-derived pharmacophores. It has been demonstrated that only one of these pharmacophores is required for kappa antagonist activity and that the basic group (N-17′) in the second pharmacophore acts as an "address" to confer selectivity.[4b] In this regard, it has been suggested that the decahydroisoquinoline moiety within the second pharmacophore of the receptor-bound ligand acts as a scaffold to rigidly hold an address which is directed to an acidic residue within the kappa receptor. Site-directed mutagenesis of the kappa receptor has revealed the acidic residue to be Glu297, which is located at the top of the transmembrane spanning helix 6 (TM6).[5] Homology modeling suggests that the corresponding residue is a tryptophan within the OP_1 (delta-opioid)



1 Norbinaltorphimine (norBNI)



2 R = -H, Naltrindole (NTI)
3 R = -CH_2NH(C=NH)-alkyl

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receptor and a lysine within the OP_3 (mu-opioid) receptor (Trp284 and Lys303, respectively).[6]

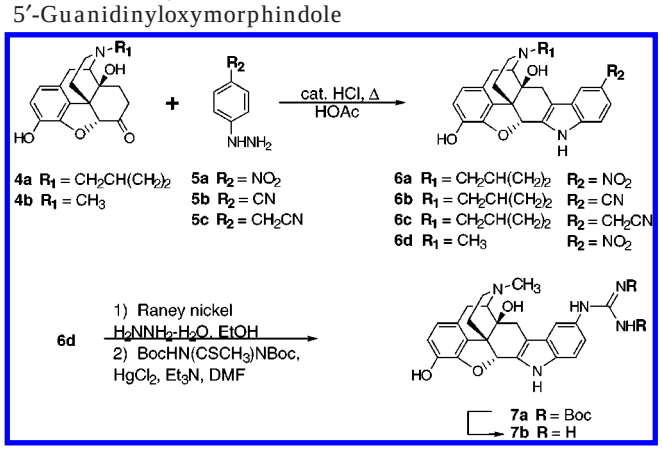
In light of the structural requirements for the kappa antagonist activity of norBNI and the importance of a rigid scaffold for orienting the address, we have investigated an alternative scaffold that was hoped to function in a similar fashion. Superposition of the conserved structural motif of the delta-opioid antagonist naltrindole (**2**, NTI) upon that of norBNI led to the design of 5′-alkylamidine-substituted NTI analogues **3** that proved to be potent and selective kappa-opioid antagonists.[7] In the present report we describe the use of the indole moiety of NTI as a scaffold to project a variety of protonated or cationic groups toward the putative address subsite, Glu297, of the kappa receptor.[8] By exploiting this scaffold and differences between the nonconserved residues at an equivalent location in different types of opioid receptors, we describe herein a new series of potent and highly selective kappa-opioid antagonists.

Chemistry

To vary the distance of functional groups attached to the 5′-position of NTI, suitable synthetic precursors were needed. We prepared the 5′-amino-NTI[9] and 5′-substituted nitriles as intermediates to provide access to both amines and amidines. These choices allowed positioning of the address at different distances from the NTI scaffold. Thus, intermediates **6a**−**c** (Scheme 1) were prepared by Fischer indole cyclization[10] of naltrexone (**4a**) and commercially available 4-nitrophenylhydrazine (**5a**),[9] the previously reported 4-cyanophenylhydrazine (**5b**),[11] or 4-(cyanomethyl)phenylhydrazine (**5c**).[12] Consistent with previous observations of the Fischer indole synthesis, stronger electron-withdrawing groups on arylhydrazines required more forcing conditions and reduced the isolated yield of indole intermediates **6a**−**c**.[10]

Oxymorphone **4b** was also condensed with **5a** to afford 5′-nitrooxymorphindole (**6d**). Oxymorphindole **6d** was reduced to the corresponding amine using Raney nickel and hydrazine hydrate,[13] and the resulting amine was condensed with 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea in a mercury-assisted reaction to afford the di-Boc-guanidine **7a** in 86% yield for the two steps. The Boc groups were removed under acidic conditions to afford the 5′-guanidinyloxymorphindole (**7b**).

Scheme 1. Synthesis of 5′-NTI Derivatives and 5′-Guanidinyloxymorphindole



The nitriles **6b**,**c** were converted to thioamides **8a,b** by treatment with H_2S in the presence of diisopropylethylamine (Scheme 2). The respective thioamides were then alkylated with iodomethane, and the resulting *S*-methyl thioimidates were immediately treated with ammonia to afford the amidines **9a**,**b**. Reduction of **6a**, with Raney nickel and hydrazine hydrate cleanly afforded **10a**.[9] Nitriles **6b,c** were also reduced to the corresponding amines **10b**[7],**c** using Raney nickel as a catalyst.[7,14]

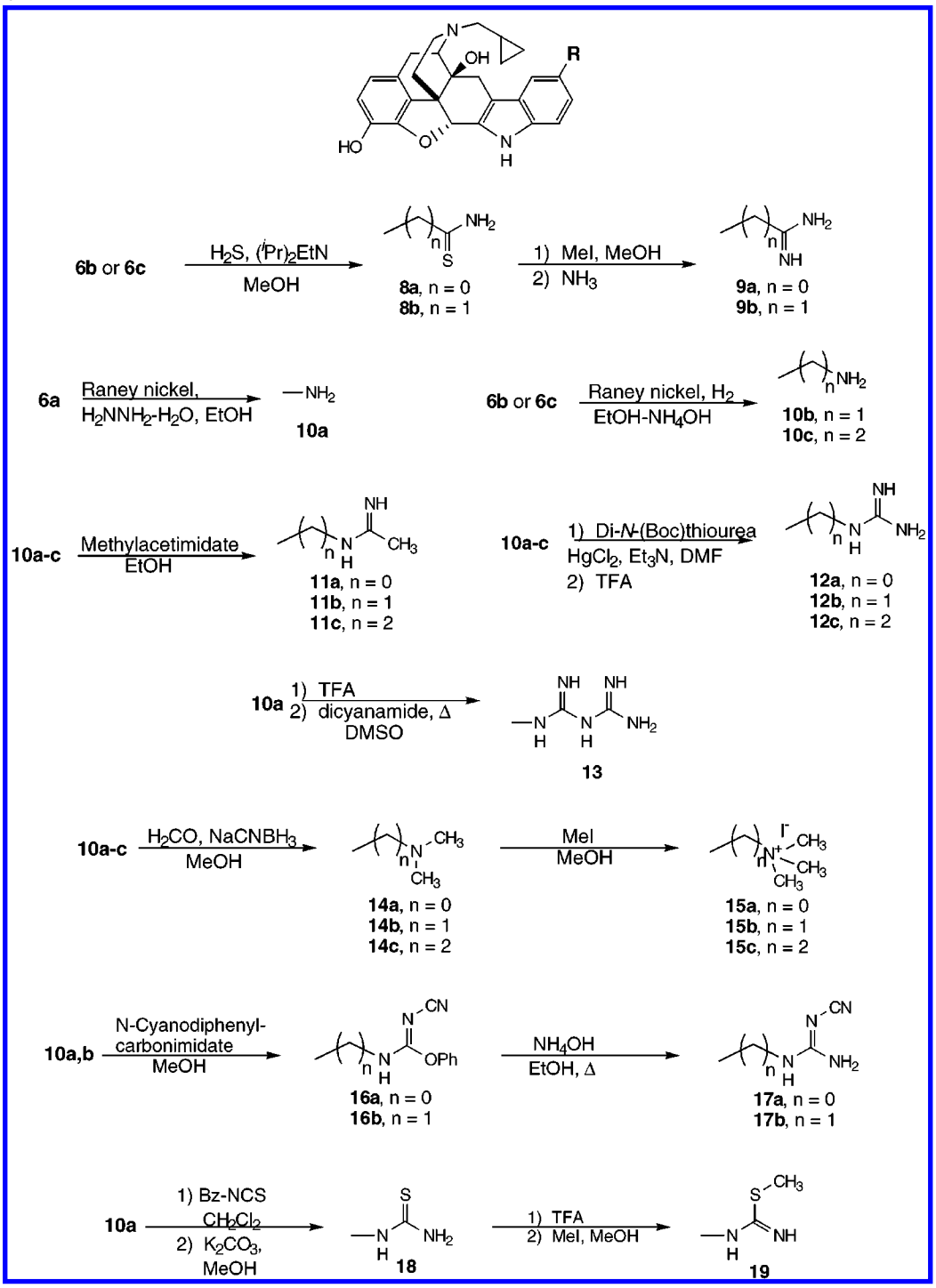
Inconsistent results with the Pinner synthesis[15] led us to modify the standard synthesis of methyl acetimidate. Treating a solution of acetonitrile in toluene with 4 N HCl-dioxane, followed by addition of methanol, led to the rapid formation of methyl acetimidate. We found that this procedure was not general, as most other imidate hydrochlorides failed to precipitate from toluene efficiently. Synthesis of acetamidines from the amines **10a**−**c** was optimized using a large excess of methyl acetimidate such that the desired amidines **11a**−**c** could be obtained in yields as high as 86%.

The guanidines **12a**−**c** were obtained via the mercury-assisted condensation of amines **10a**−**c** with bis(*tert*-butoxycarbonyl)thiourea.[16] Condensation of the TFA salt of **10a** and dicyanamide in DMSO at 100−110 °C yielded the biguanidine **13**.[17] The amines **10a**−**c** were also reductively alkylated using formaldehyde and sodium cyanoborohydride to afford the dimethylamino compounds **14a**−**c**. Each of these was further alkylated with iodomethane to afford the quaternary ammonium salts **15a**−**c**. The cyanoguanidines **17a,b** were prepared by reacting amines **10a,b** with *N*-cyanodiphenylcarbonimidate followed by treatment of the respective intermediates **16a**,**b** with ammonia. Treating 5′-amino-NTI (**10a**) with benzoyl isothiocyanate yielded the *N*-benzoylthiourea **18** after basic deprotection. The TFA salt of this compound was then alkylated with iodomethane to afford the *S*-methylpseudothiourea **19**. Having synthesized this series of 5′-substituted NTI derivatives, we then evaluated the relevant pharmacology.

Biological Testing

All target compounds were tested against the electrically stimulated guinea pig ileal longitudinal muscle (GPI) and mouse vas deferens (MVD) preparations as previously described.[18] With the exception of three compounds (**11c**, **12a**, and **15c**) that were tested at 20 nM in the GPI preparation, all compounds were tested at 100 nM after incubation for 15 min (Table 1). Morphine (M), ethylketazocine (EK), and [D-Ala^2,D-Leu^5]-enkephalin[19] (DADLE) were employed as mu-, kappa-, and delta-selective agonists, respectively. M and EK were used in the GPI preparation, and DADLE was used in the MVD preparation. A minimum of three replicate determinations were carried out for the active compounds, while some of the inactive compounds were tested only twice against MVD and are reported without error margins. The antagonist potency is expressed as the IC_{50} ratio, which is the IC_{50} concentration of the agonist in the presence of antagonist divided by the control IC_{50} of the agonist in the same preparation. Antagonism is expressed as K_e values derived from the relationship: $K_e = [\text{antagonist}]/(1 - IC_{50}\ \text{ratio})$.

Scheme 2. Synthesis of Functionalized NTI Derivatives



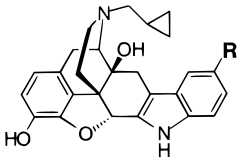
The most potent antagonist, GNTI (**12a**), exhibited 2-fold greater potency over norBNI (**1**). The selectivity ratios, kappa/mu and kappa/delta, were approximately 6- and 10-fold greater than those of norBNI. The importance of the protonated guanidine group of **12a**, for conferring potent kappa antagonism, becomes apparent when **12a** is compared to the nonbasic cyanoguanidine **17a** or the isoelectronic thiourea **18**. Some of the more potent antagonists were the amidine **9a**, the guanidines **12a,b**, and the biguanidine **13**. These ligands also possessed greater kappa/delta selectivity ratios when compared to norBNI (**1**).

Receptor binding assays were performed on the more potent analogues using HEK-293 cells, transiently transfected with plasmids encoding rat kappa-, rat mu-, or mouse delta-opioid receptors and were determined in triplicate using [^{3}H]diprenorphine (Table 2). Norbinaltorphimine (**1**), amidine **9b**, GNTI (**12a**), and biguanidine **13** were among the more selective and higher affinity members of the series. It is noteworthy that the oxymorphone-derived analogue **7b** possessed 16-fold less affinity for kappa receptors than GNTI (**12a**) but substantially greater kappa selectivity due to its exceptionally low affinity for mu and delta receptors.

Molecular Modeling

To better understand how the indole scaffold of NTI (**2**) might present certain functional groups to the

Table 1. Opioid Antagonist Activity of 5′-Substituted NTI Derivatives in the MVD and GPI Preparations



		kappa[a]		mu[b]		delta[c]		K_e selectivity ratio[d]	
compd	R	IC_{50} ratio[e]	K_e[f] (nM)	IC_{50} ratio	K_e (nM)	IC_{50} ratio	K_e (nM)	mu/kappa	delta/kappa
1, norBNI		49.8 ± 7.8[g]	0.4	2.6 ± 0.6[g]	13	10.4 ± 2.9	11	31	33
7b		6.8 ± 1.8	17	1.1	*h*	1.7	*h*	6.3[i]	4.1[i]
9a	$-(C{=}NH)NH_2$	142 ± 43	0.7	7.4 ± 0.2	16	0.3	*h*	22	142[i]
9b	$-CH_2(C{=}NH)NH_2$	46.7 ± 12	2.2	2.1 ± 0.6	*h*	1.8	*h*	22[i]	26[i]
10a	$-NH_2$	4.0 ± 2.0	*h*	2.8 ± 0.2	57	10.3 ± 4.2	*h*	1.5[i]	0.4[i]
10b	$-CH_2NH_2$	3.9 ± 0.2	34	2.6 ± 0.5	61	6.4 ± 1.1	18	1.8	0.5
10c	$-CH_2CH_2NH_2$	48.1 ± 3.9	2.1	3.2 ± 1.3	*h*	2.3	*h*	15[i]	21[i]
11a	$-NH(C{=}NH)CH_3$	99.4 ± 15	1.0	7.5 ± 1.3	16	1.9 ± 0.6	*h*	15	52[i]
11b	$-CH_2NH(C{=}NH)CH_3$	17.3 ± 4.3	6.1	12.4 ± 2.7	8.8	0.88	*h*	1.4	17.3[i]
11c	$-CH_2CH_2NH(C{=}NH)CH_3$	72.1 ± 18[g]	0.3	14.1 ± 2.7	7.6	6.4 ± 1.1	18	27	65
12a; GNTI	$-NH(C{=}NH)NH_2$	139 ± 33[g]	0.2	4.4 ± 0.7	30	1.9 ± 0.5	*h*	193	366[i,j]
12b	$-CH_2NH(C{=}NH)NH_2$	172 ± 20	0.6	10.3 ± 2.4	11	0.88	*h*	19	172[i]
12c	$-CH_2CH_2NH(C{=}NH)NH_2$	59.8 ± 14	1.7	9.1 ± 0.4	12	30.1 ± 9.5	3.4	7.3	2.0
13	$-NH(C{=}NH)NH(C{=}NH)NH_2$	512 ± 89	0.2	7.9 ± 2.3	14	0.41	*h*	74	512[i]
14a	$-N(CH_3)_2$	15.8 ± 1.6	6.8	3.8 ± 0.8	36	2.4 ± 0.7	*h*	5.3	6.6[i]
14b	$-CH_2N(CH_3)_2$	125 ± 29	0.8	11.2 ± 0.5	9.8	1.4	*h*	12	87[i]
14c	$-CH_2CH_2N(CH_3)_2$	32.0 ± 8.9	3.2	2.4 ± 0.5	*h*	1.8	*h*	13[i]	18[i]
15a	$-N^+(CH_3)_3I^-$	33.3 ± 6.8	3.1	2.7 ± 0.3	*h*	3.6 ± 1.2	*h*	13[i]	9.1[i]
15b	$-CH_2N^+(CH_3)_3I^-$	154 ± 39	0.7	25.8 ± 5.9	4.0	0.79	*h*	6.2	154[i]
15c	$-CH_2CH_2N^+(CH_3)_3I^-$	48.0 ± 10[g]	0.4	18.5 ± 5.6	5.7	2.5 ± 0.5	*h*	13	96[i,j]
17a	$-NH(C{=}N{-}CN)NH_2$	33.0 ± 7.6	3.1	7.2 ± 1.7	16	12.0 ± 3.0	9.1	5.1	2.9
17b	$-CH_2NH(C{=}N{-}CN)NH_2$	35.4 ± 9.4	2.9	6.7 ± 1.7	18	17.9 ± 4.2	5.9	6.2	2.0
18	$-NH(C{=}S)NH_2$	14.9 ± 5.5	7.2	3.6 ± 0.7	38	1.3	*h*	5.3	12[i]
19	$-NH(C{=}NH)SCH_3$	43.6 ± 19.5[g]	0.5	7.4 ± 1.8	16	1.9	*h*	33	115[i,j]

[a] Ethylketazocine in the GPI. [b] Morphine in the GPI. [c] [D-Ala^2,D-Leu^5]enkephalin in the MVD. [d] Ratio of K_e values unless otherwise specified. [e] The ratio of the IC_{50} of an agonist in the presence of an antagonist divided by the control IC_{50}. Values are expressed as mean ± SEM when the number of experiments was 3 or more or the mean only when the number of experiments was 2. [f] K_e = [antagonist]/(IC_{50} ratio − 1). All antagonists were tested at a concentration of 100 nM unless otherwise noted. [g] Tested at 20 nM. [h] Not calculated because the IC_{50} ratio is not significantly different from unity ($p > 0.05$). [i] Expressed as kappa/mu or kappa/delta ratios of IC_{50} ratios because one or more of the IC_{50} ratio values were not significantly different from unity ($p > 0.05$). If the IC_{50} ratio was less than unity, 1.0 was used in the calculations. [j] The selectivity ratio was calculated by using the presented data and extrapolating the kappa IC_{50} ratio for the antagonist at 100 nM.

Table 2. Receptor Binding Affinity of 5′-Substituted NTI Derivatives[a]

	K_i (nM)			selectivity ratio	
compd	kappa	mu	delta	mu/kappa	delta/kappa
1, norBNI	0.244 ± 0.064	49.7± 6.6	41.5 ± 13	204	170
7b	2.83 ± 0.52	876 ± 150	>10000	310	>3533
9a	0.529 ± 0.16	65.7 ± 13	112 ± 11	124	212
9b	0.214 ± 0.044	40.8 ± 9.6	33.0 ± 11	191	154
12a	0.180 ± 0.052	22.5 ± 3.9	46.2 ± 5.1	125	257
12b	0.745 ± 0.12	66.0 ± 14	30.8 ± 4.9	89	41
12c	0.507 ± 0.13	33.4 ± 4.7	10.7 ± 3.0	66	21
13	0.226 ± 0.033	21.5 ± 3.3	108 ± 22	95	478
14b	0.823 ± 0.17	36.0 ± 11	15.7 ± 8.6	44	19
15b	0.354 ± 0.14	12.8 ± 1.5	78.4 ± 14	36	221
17a	4.46 ± 1.76	89.8 ± 17	9.46 ± 2.6	20	2

[a] Receptor binding assays were performed on HEK-293 cells transiently transfected with plasmids encoding the corresponding rat kappa-, rat mu-, or mouse delta-opioid receptor and were measured in triplicate using [^{3}H]diprenorphine.

receptor, molecular modeling studies were performed. The pyrrolomorphinan component of the most strongly bound member of the series, GNTI (**12a**), was modeled from the X-ray coordinates of norBNI.[20] To probe the conformational preferences of solvated GNTI, a 2-ns molecular dynamics simulation was performed in the presence of explicit TIP3P[21] water molecules using the AMBER 4.1[22] suite of programs. The most favored solution conformation of **12a** was reminimized in vacuo by stripping off the solvent molecules. This structure was subsequently used to dock **12a** into the transmembrane (TM) domain of the model-built kappa-opioid receptor[23] using the automated docking procedure implemented in the DOCK 3.5 program package.[24] The identified docking orientations revealed an ion pair between the protonated N-17 of the ligand (**12a**) and the carboxylate group of Asp138 (TM3) to associate the receptor−ligand complex. The importance of this interactions has been demonstrated by an Asp138Asn point mutation for the kappa receptor. [25]

A 1-ns molecular dynamics simulation of the receptor−**12a** bound complex revealed GNTI to reside in a cavity lined by residues in TM3, -5, -6, and -7 (Figure 1). The *N*-cyclopropylmethyl group of **12a** was aligned between the TM3 and -7 interhelical region, while the tyramine moiety occupied the larger pocket and is surrounded by aromatic residues such as Tyr139, Phe231, Phe235, Trp287, and His291 from TM3, -5, and -6. The indole ring and the 5′-guanidine substituent projected toward the extracellular region of the kappa-opioid receptor. It is noteworthy that the imidazole ring of His291 was proximal to the phenolic hydroxy group of GNTI, as it has been reported that this group is essential for potent kappa-opioid receptor antagonist activity.[4a]

The protonated N-17 nitrogen of the antagonist pharmacophore appeared to form a salt bridge with the

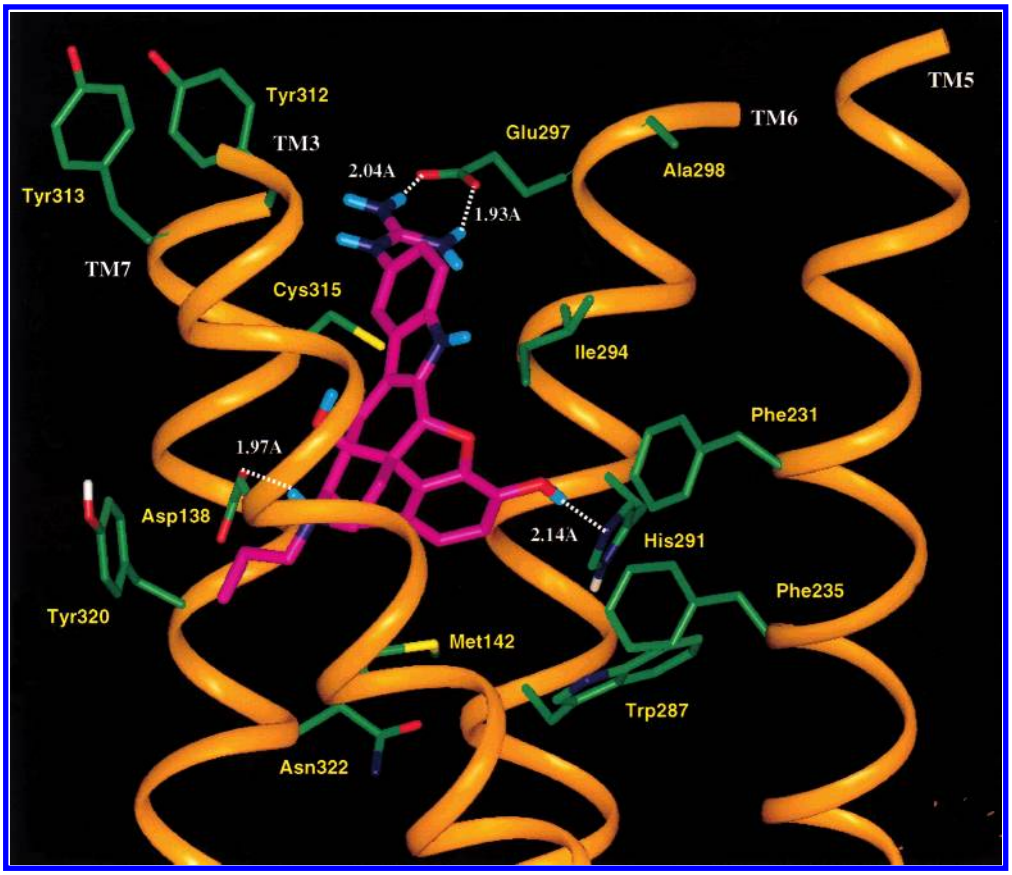


Figure 1. View of kappa receptor-bound GNTI (**12a**) resulting from MD simulations. Selected residues within 5 Å of GNTI are displayed, and TM1, -2, and -4 are omitted for clarity.

carboxylate oxygens of the conserved Asp138 in TM3 with an average distance of 2.3 Å. GNTI (**12a**) also showed a close association between the protons of the 5′-guanidine moiety and the carboxylate group of Glu297 located at the top of TM6 (average distance: 2.3−2.7 Å). The guanidinium moiety of **12a** was found to orient in an orthogonal relationship relative to the indole ring, and this presents the cationic group in an optimized position for interaction with Glu297. Apart from the specific point interactions described above, GNTI appeared to be surrounded by a network of hydrophobic residues: Val134, Met142, Ile194, Leu224, Ile294, Leu295, and Ile316.

Discussion and Conclusions

In the present study, the rigid indole moiety of the delta-opioid receptor antagonist, naltrindole (**2**), has been used as a scaffold to direct a 5′-substituted cationic group (a "kappa address") to a nonconserved acidic residue on the kappa-opioid receptor. This is analogous to the interaction of the N-17′ protonated amine group of the prototypical kappa-opioid receptor antagonist, norbinaltorphimine (norBNI, **1**), with Glu297 at the top of TM6.[5]

Ligands with high kappa antagonist potency contained guanidinium, amidinium, or quaternary ammonium cationic substituents. The generally high pK_a values (in the range of 11−16) of the guanidinium and amidinium congeners, and the fact that trimethylammonium-substituted compounds are totally ionized, strongly support the notion that a cationic group at the 5′-position is required for potent kappa antagonist activity.

The importance of a positively charged address in contributing to kappa antagonist potency is exemplified by comparing the kappa antagonist potency of the 5′-guanidine compound **12a** (GNTI) with its closely related *N*-cyano derivative **17a** or the isoelectronic thiourea **18**. The finding (Table 1) that GNTI (**12a)** was approximately 15-fold more potent than the nonbasic cyanoguanidine **17a** highlights the contribution of a positively charged group at the 5′-position of the indole scaffold. In this connection, it is noteworthy that there is a distance-dependent potency of the guanidine group between GNTI (**12a**) and its less potent homologues **12b,c**, presumably as a consequence of the more favorable interaction of GNTI with Glu297. However, no difference in the kappa antagonist potency was observed for the corresponding less potent cyanoguanidine homologues **17a**,**b**. The absence of a potency change is consistent with a mode of interaction of the uncharged cyanoguanidine group with the kappa receptor that is different from that of the cationic guanidinium substituent. The finding that other homologous members of the series containing highly basic or quaternary ammonium substituents also exhibited differential kappa antagonist potency is consistent with this idea. This suggests that the charged substituents are engaged in ionic bonding with Glu297, while the neutral cyanoguanidine substituent is involved in some other type of interaction.

Modeling of GNTI (**12a**) docked to the kappa-opioid receptor has revealed a good fit for the positioning of its two basic groups next to acidic residues that are within the cavity formed by the bundle of TM helices. This is consistent with the docking of norBNI (**2**) to the kappa receptor, given the similar intramolecular distances between the two basic groups of these ligands.[23] Accordingly, the protonated 17-amino group in the antagonist pharmacophore of **12a** is located next to the conserved Asp138 (TM3), and the orthogonally oriented 5′-guanidinium substituent is aligned with the nonconserved Glu297 (Figure 1). The planar geometry of the guanidinium group would tend to enhance affinity through stabilization afforded by hydrogen bonding with the carboxylate anion of Glu297.

In addition to the interaction of Asp138 and Glu297 with the basic groups of GNTI, molecular modeling uncovered a third key residue, His291, which might contribute to kappa antagonist activity. Given the proximity of the phenolic hydroxy group of GNTI to His291, it is possible that it may act as a hydrogen-bonding donor with the imidazole group. Such an interaction, while consistent with the known requirement of a 3-hydroxy group for potent kappa antagonist activity, awaits verification through site-directed mutagenesis of His291.[4a]

The importance of the 17-cyclopropylmethyl group for conferring antagonist activity to GNTI (**12a**) was examined by preparing the 17-methyl analogue **7b**, given that similar modification of norBNI was reported to obliterate activity.[4a] The finding that **7b** is a feeble kappa antagonist suggests that effective electrostatic interaction of Asp138 and Glu297 with the two cationic groups of GNTI depends on the presence of a cyclopropylmethyl group. This may conceivably be a reflection of different binding modes promoted by the N-17 substituent.

The selectivity of ligands in the present series is a function of the affinity for kappa receptors and the degree of exclusion at mu and delta receptors. Given that the nonconserved Glu297 is primarily responsible for conferring high affinity to ligands such as GNTI (**12a**), residues at equivalent positions in the mu (Lys303) and delta (Trp284) receptors would tend to hinder binding through electrostatic repulsion in the former or steric hindrance in the latter. Moreover, since the interactions of members of the series at the subsite position equivalent to Glu297 in mu and delta receptors are nonspecific, the antagonist potencies of ligands at these receptors exhibit relatively smaller differences. Consequently, ligands with higher kappa antagonist potency in this series generally possess higher selectivity.

Experimental Section

General. Materials. Naltrexone and oxymorphone were obtained from Mallinckrodt. All reactions were carried out under an inert atmosphere of nitrogen. Pyridine and triethylamine were distilled from KOH, while dichloromethane and acetonitrile were distilled from calcium hydride prior to use. Diethyl ether, benzene, and tetrahydrofuran were distilled from benzophenone ketyl and were used similarly. Dry dimethylformamide was obtained by storing reagent grade material over 4 Å sieves for at least 24 h. Dry methanol or ethanol was prepared by distillation from magnesium methylate or ethylate, respectively. Toluene was distilled from sodium. All other chemicals were reagent grade and used without further purification. Thin-layer chromatography was performed on analytical Uniplate silica gel GF plates (250 μm by 2.5 × 20 cm) purchased from Analtech. Chromatographic elution solvent systems are reported as vol:vol ratios. All ^{1}H and ^{13}C NMR spectra were recorded on a Varian 300-MHz or a GE 300-MHz spectrometer. Infrared (IR) spectra were recorded on a Perkin-Elmer PE-281 spectrophotometer or a Nicolet 5DXC FT-IR spectrometer as potassium bromide (KBr) disks. Mass spectra were obtained on a Finnigan 4000 or VG707EHF spectrometer by the Chemistry Mass Spectrometry Laboratory at the Department of Chemistry, University of Minnesota. Elemental analyses were performed by M-H-W Laboratories in Phoenix, AZ, or Galbraith Laboratories, Inc., Knoxville, TN, and are within ±0.4% of theoretical values. Melting points were determined in open capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. Optical rotations were recorded on a Rudolph Research Autopol III polarimeter at a wavelength of 589 nm. HPLC was performed with Beckman model 110A pumps, a Beckman analytical optical unit (fixed wavelength UV), and a Hewlett-Packard HP3390A integrating recorder. Purifications were performed with a Ranin Dynamax Macro HPLC column (C18, 5 μm, 1 × 28 cm) or an Alltech Altima C18 column (10 μm, 250 × 22 mm). All recorded spectra are for the free base unless otherwise stated. Most principals were purified by silica gel flash chromatography (dichloromethane−methanol−ammonium hydroxide), then by silica gel preparative TLC (dichloromethane−methanol−ammonium hydroxide), and finally by reverse-phase HPLC (acetonitrile−water−0.1% TFA), to afford the tested compounds as trifluoroacetic acid salts. The experimental procedures used to synthesize molecules in this series that are not described herein are provided in the Supporting Information.

Receptor Binding. HEK-293 cells were grown in DMEM media (Gibco, BRL) containing 10% iron-supplemented bovine calf serum (Hyclone) and 1% penicillin/streptomycin (Gibco, BRL). Cells were seeded at 16% 24 h prior to transfection. Fresh media was added 2 h prior to transfection. Rat kappa-, rat mu-, or mouse delta-opioid receptor cDNA was subcloned into pcDNA3 (Invitrogen). Cells were transfected with plasmid DNA (20 μg/100 mm plate) of each of the three types using a modified calcium phosphate precipitation method.[26] Medium was changed 5 h after transfection. Transfected cells were harvested 48−72 h after tranfection. Cells were washed three times with 25 mM HEPES buffer (pH 7.4) and were resuspended with 8−12 mL of 25 mM HEPES/100 mm plate. Binding assays were performed using 100 pM [^{3}H]diprenorphine (NIDA Drug Supply Program) and were performed in triplicate. Nonselective binding was determined using 1 μM naltrexone. Assays were incubated at room temperature for 90 min and were terminated by filtration through a Whatman GF/B filter that had been presoaked in 0.25% poly(ethylenimine) immediately prior to filtration. Filters were washed three times with 4 mL of ice-cold 25 mM HEPES buffer, and scintillation counting was performed with a Beckman 3801 LS scintillation counter. Protein concentrations were determined by the method of Bradford.[27]

Methyl Acetimidate Hydrochloride.[14] To 70 mL of dry toluene were added 1.65 mL (31.6 mmol, 1.03 equiv) of acetonitrile, 9.5 mL of 4.0 N HCl in dioxane (37.9 mmol, 1.2 equiv), and 1.25 mL of methanol (30.8 mmol). The resulting solution was stirred under nitrogen at room temperature for 1.5 h during which time it became a suspension. Product was filtered from the reaction, and the filtrate was allowed to continue stirring under nitrogen. After an additional 48 h a second crop of product was recovered. Each was recovered as a colorless powder slightly contaminated with ammonium chloride: total yield 1.32 g (38%); mp 92−93 °C (colorless prisms from dichloromethane−hexanes); ^{1}H NMR (DMSO-d_6) δ 4.02 (s, 3H, $-OCH_3$), 2.33 (s, 3H, $-CH_3$); ^{13}C NMR (DMSO-d_6) δ 169.87, 26.76, 23.00; MS (LRCI) m/z 74 $(M + H)^+$.

17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5′-nitro-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (6a). A slurry of naltrexone hydrochloride **(4a)** (15.0 g, 39.7 mmol) and 6.8

g (44.4 mmol, 1.1 equiv) of 4-nitrophenylhydrazine **(5a)** in 90 mL of acetic acid was heated at 95−99 °C, and 90 mL of concentrated HCl was added. The mixture was stirred at 100−110 °C for 7 days. The reaction was then cooled, diluted with 200 mL of water, and neutralized with solid $NaHCO_3$. The suspension was extracted with 1 L of ethyl acetate which was then combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel flash chromatography (5 × 52 cm, 94.5:5:0.5 dichloromethane−ethanol−NH_4OH). Product was recovered as a hard, yellow-brown solid: yield 7.78 g (43%). The product was further purified by dissolving the material in a minimal amount of dichloromethane and precipitating impurities by the addition of ether. The filtrate was then acidified by the addition of HCl gas, and the salt was recovered as a yellow powder: silica gel TLC R_f 0.57 (89:10:1 dichloromethane−methanol−NH_4OH); ^{1}H NMR (HCl salt, 300 MHz, DMSO-d_6) δ 12.31 (s, 1H), 9.5 (br s, 1H), 9.1 (br s, 1H), 8.25 (s, 1H), 7.84 (d, J = 9 Hz, 1H), 7.45 (d, J = 9 Hz, 1H), 6.74 (d, J = 8 Hz, 1H), 6.58 (d, J = 8 Hz, 1H), 5.70 (s, 1H), 4.20 (d, J = 5 Hz, 1H), 3.8 (br s, 1H), 3.42 (d, J = 19 Hz, 1H), 2.9−3.3 (m, 5H), 2.63 (m, 2H), 2.52 (m, 1H), 1.73 (d, J = 7 Hz, 1H), 1.09 (m, 1H), 0.66 (m, 1H), 0.58 (m, 1H), 0.48 (m, 1H), 0.39 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 144.07, 141.87, 141.28, 141.14, 134.61, 129.96, 126.55, 122.50, 121.26, 120.38, 119.11, 118.47, 116.71, 113.05, 112.35, 83.47, 73.11, 63.14, 61.91, 57.90, 47.26, 29.67, 29.08, 26.57, 6.89, 6.33, 0.77; HRMS (FAB) m/z 460.1847 $(M + H)^+$, $C_{26}H_{28}N_3O_3$ requires 460.1872.

5′-Cyano-17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (6b). A slurry of naltrexone hydrochloride **(4a)** (2.70 g, 7.15 mmol) and 1.34 g (7.87 mmol, 1.1 equiv) of hydrazine **5b** in 40 mL of acetic acid was heated at 95−99 °C, and 20 drops of concentrated HCl was added. The mixture was stirred at 95−99 °C for 24 h under nitrogen, then product was filtered off and washed with ether. Nitrile **6b** was obtained as a gray powder: yield 2.09 g (62%). The filtrate was made basic by the addition of 2 M KOH and was extracted with dichloromethane (4 × 100 mL). The dichloromethane was dried ($MgSO_4$), concentrated in vacuo, and purified by silica gel flash chromatography (4 × 30 cm, gradient between 95:5 dichloromethane−methanol and 89:10:1 dichloromethane−methanol−NH_4OH). Product was recovered as a light yellow solid: yield 425 mg (14%); silica gel TLC R_f 0.24 (95:5 dichloromethane−methanol); ^{1}H NMR (DMSO-d_6) δ 11.83 (s, 1H), 9.0 (br s, 1H), 7.90 (d, J = 1 Hz, 1H), 7.47 (dd, J = 0.5, 8.5 Hz), 7.40 (dd, J = 1.5, 8.5 Hz, 1H), 6.52 (d, J = 8 Hz, 1H), 6.48 (d, J = 8 Hz, 1H), 5.53 (s, 1H), 3.29 (d, J = 6.5 Hz, 1H), 3.06 (d, J = 19 Hz, 1H), 2.65−2.8 (m, 3H), 2.39 (d, J = 6.5 Hz, 2H), 2.31 (dt, J = 4.5, 12.5 Hz, 1H), 2.13 (dt, J = 1, 10.5 Hz, 1H), 1.89 (s, 1H), 1.58 (br d, J = 9 Hz), 0.7−0.9 (m, 1H), 0.49 (m, 2H), 0.14 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 143.36, 140.32, 138.91, 132.99, 131.12, 126.53, 125.05, 124.75, 121.21, 119.01, 117.46, 113.04, 111.62, 110.00, 100.91, 83.65, 72.54, 61.95, 59.02, 47.82, 31.40, 28.96, 23.14, 21.60, 9.58, 4.37, 3.91.

6,7-Didehydro-4,5α-epoxy-17-methyl-5′-nitro-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (6d). A slurry of oxymorphone hydrochloride **(4b)** (3.0 g, 8.88 mmol) and 1.75 g (9.23 mmol, 1 equiv) of 4-nitrophenylhydrazine hydrochloride **(5a)** in 25 mL of acetic acid was stirred at room temperature for 1 h then was heated at 70−75 °C for 3 h. The reaction was then cooled and concentrated in vacuo. The resulting solid was treated with 100 mL of ethyl acetate and 100 mL of a saturated $NaHCO_3$ solution. The aqueous phase was separated and washed with ethyl acetate (2 × 100 mL). The organic portions were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel flash chromatography (5 × 52 cm, 94.5:5:0.5 dichloromethane−methanol−NH_4OH). The product **6d** was recovered as a hard, yellow-brown solid: yield 1.18 g (32%); silica gel TLC R_f 0.50 (89:10:1 dichloromethane−methanol−NH_4OH); ^{1}H NMR (DMSO-d_6) δ 11.98 (s, 1H), 8.98 (s, 1H), 8.33 (d, J = 2 Hz, 1H), 7.94 (dd, J = 2, 9 Hz, 1H), 7.44 (d, J = 9 Hz, 1H), 6.49 (s, 2H), 5.50 (s, 1H), 4.73 (s, 1H), 3.12 (d, J = 19 Hz, 1H), 2.95 (d, J = 6 Hz, 1H), 2.76 (d, J = 16 Hz, 1H), 2.67 (dd, J = 6, 19 Hz, 1H), 2.4−2.5 (m, 3H), 2.32 (s, 3H), 2.12 (dt, J = 6, 11.5 Hz, 1H), 1.53 (d, J = 11 Hz, 1H); HRMS (FAB) m/z 420.1542 $(M + H)^+$, $C_{23}H_{22}N_3O_5$ requires 420.1559.

5′-N^1-[N^2,N^3-Bis(*tert*-butoxycarbonyl)guanidinyl]-6,7-didehydro-4,5α-epoxy-17-methyl-3,14-dihydroxyindolo-[2′,3′:6,7]morphinan (7a). Raney nickel (ca. 1 g) was added to a solution of 5′-nitrooxymorphindole **(6d)** (1.12 g, 2.67 mmol) in 50 mL of ethanol, then 2.0 mL of hydrazine hydrate was added. The suspension was stirred under nitrogen at room temperature for 1 h then was filtered of catalyst and concentrated in vacuo. After drying under high vacuum, the crude amine was treated with 776 mg (2.67 mmol, 1.0 equiv) of 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea, 408.8 mg (1.51 mmol, 0.56 equiv) of mercuric chloride, 10.0 mL of DMF, and 375 μL (2.69 mmol, 1.0 equiv) of triethylamine. The reaction was stirred under nitrogen at room temperature for 20 h then was concentrated in vacuo. The residue was purified by silica gel flash chromatography (3 × 27 cm, 94.5:5:0.5 dichloromethane−methanol−NH_4OH) providing the product **7a** as a cream-colored solid: yield 1.45 g (86%); silica gel TLC R_f 0.30 (94.5:5:0.5 dichloromethane−methanol−NH_4OH); ^{1}H NMR (DMSO-d_6) δ 11.50 (s, 1H), 11.18 (s, 1H), 9.86 (s, 1H), 8.91 (s, 1H), 7.91 (s, 1H), 7.37 (d, J = 1.5 Hz, 1H), 7.25 (d, J = 8.5 Hz, 1H), 7.13 (dd, J = 1.5, 8.5 Hz, 1H), 6.47 (s, 2H), 5.45 (s, 1H), 4.67 (s, 1H), 3.11 (d, J = 18 Hz, 1H), 2.93 (d, J = 6 Hz, 1H), 2.69 (s, 3H), 2.60 (d, J = 15 Hz, 1H), 2.2−2.4 (m, 3H), 2.1−2.2 (m, 1H), 1.4−1.5 (m, 10H), 1.31 (br s, 9H); HRMS (FAB) m/z 632.3109 $(M + H)^+$, $C_{23}H_{22}N_3O_5$ requires 632.3084.

6,7-Didehydro-4,5α-epoxy-5′-guanidinyl-17-methyl-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (7b). A solution containing 223.5 mg (354 μmol) of **7a** in 2.0 mL of trifluoroacetic acid was stirred under nitrogen at room temperature for 18 h. The solution was concentrated under a stream of nitrogen, and the residue was evaporated from dichloromethane twice. After drying under high vacuum the residue was purified by silica gel preparative TLC (2 × 1.0 mm, 78:20:2 dichloromethane−methanol−NH_4OH) affording the product as a colorless solid: yield 136.3 mg (89.3%); silica gel TLC R_f 0.46 (78:20:2 dichloromethane−methanol−NH_4OH); ^{1}H NMR (DMSO-d_6) δ 11.51 (s, 1H), 9.85 (s, 1H), 9.29 (s, 1H), 7.37 (d, J = 8.7 Hz, 1H), 7.32 (br s, 3H), 7.20 (s, 1H), 6.91 (dd, J = 2, 9 Hz, 1H), 6.58 (d, J = 8.7 Hz, 1H), 6.54 (d, J = 8.7 Hz, 1H), 6.25 (br s, 1H), 5.65 (s, 1H), 3.72 (br s, 1H), 3.44 (m, 1H), 3.3−3.4 (m, 1H), 3.0−3.2 (m, 2H), 2.85 (m, 1H), 2.82 (s, 3H), 2.4−2.7 (m, 2H), 1.75 (d, J = 11.5 Hz, 1H); HRMS (FAB) m/z 432.2038 $(M + H)^+$, $C_{23}H_{22}N_3O_5$ requires 432.2036. Anal. ($C_{24}H_{25}N_5O_2$·2TFA·2H_2O) C, H, N.

17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5′-(thioamido)methyl-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (8b). Diisopropylethylamine (5 mL) was added to a solution of nitrile **6c** (1.00 g, 2.20 mmol) in 10 mL of methanol. The resulting solution was stirred and cooled to −78 °C under nitrogen, and H_2S was condensed into the vessel (ca. 3 mL). The vessel was sealed and was allowed to warm to room temperature where it remained for 7 days. The vessel was then cooled to −78 °C, was opened, and was allowed to warm to room temperature under a steady stream of nitrogen. The solution was then concentrated in vacuo and was purified by silica gel flash chromatography (3 × 27 cm, 95:5:0.5 dichloromethane−methanol−ammonium hydroxide). The product was recovered as a colorless solid: yield 925.3 mg (86.1%); silica gel TLC R_f 0. (89:10:1 dichloromethane−methanol−ammonium hydroxide); ^{1}H NMR (DMSO-d_6) δ 11.11 (s, 1H), 9.35 (br s, 1H), 9.10 (br s, 1H), 8.91 (s, 1H), 7.29 (s, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.05 (dd, J = 1.5, 8.4 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 6.45 (d, J = 8.4 Hz, 1H), 5.47 (s, 1H), 4.7 (br s, 1H), 3.79 (s, 2H), 3.25 (d, J = 6 Hz, 1H), 3.03 (d, J = 11 Hz, 1H), 2.6−2.8 (m, 3H), 2.3−2.5 (m, 3H), 2.2 (m, 1H), 1.58 (d, J = 9 Hz, 1H), 0.9 (m, 1H), 0.49 (m, 2H), 0.13 (m, 2H); ^{13}C NMR (methanol-d_4) δ 208.71, 143.33, 139.64, 136.64, 130.79, 130.22, 126.90, 126.45, 124.73, 123.13, 118.80, 118.64, 116.96, 111.24, 109.98, 94.96, 84.68, 73.13, 62.18, 58.95, 51.61, 43.48, 31.31, 28.53, 22.81, 8.82, 3.35, 2.93; HRMS (FAB) m/z 488.1987 $(M + H)^+$, $C_{28}H_{30}N_3O_3S$ requires 488.2008.

5′-Amidinomethyl-17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (9b). Trifluoroacetic acid (170 μL, 2.21 mmol, 1.2 equiv) was added to a solution of thioamide **8b** (910.1 mg, 1.87 mmol) in 10 mL of methanol followed by the addition of 200 μL (3.21 mmol, 1.7 equiv) of iodomethane. The reaction was sealed under nitrogen and was allowed to stir at room temperature for 23 h. The reaction was then cooled to −78 °C, and ammonia (c.a. 1 mL) was condensed into the flask. The vessel was sealed and was allowed to stir at room temperature for 2 days. To drive the reaction more toward completion the vessel was heated at 75−85 °C for 24 h. The solution was then concentrated in vacuo and was purified by silica gel flash chromatography (3 × 30 cm, 6:3:1 dichloromethane−methanol−ammonium hydroxide). After drying, crude product was recovered as a yellow-brown solid: yield 958.6 mg (100+%); silica gel TLC R_f 0.61 (78:20:2 dichloromethane−methanol−ammonium hydroxide); ^{1}H NMR (methanol-d_4) δ 7.54 (s, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.10 (dd, J = 1.2, 8.4 Hz, 1H), 6.74 (d, J = 8 Hz, 1H), 6.69 (d, J = 8 Hz, 1H), 5.70 (s, 1H), 4.25 (s, 1H), 3.85 (s, 2H), 3.34 (m, 2H), 3.20 (dd, J = 7, 13 Hz, 1H), 3.08 (m, 2H), 2.95 (dd, J = 7.5, 13 Hz, 1H), 2.65 (m, 3H), 1.72 (d, J = 9 Hz, 1H), 1.12 (m, 1H), 0.81 (m, 1H), 0.73 (m, 1H), 0.53 (m, 2H); ^{13}C NMR (methanol-d_4) δ 171.00, 143.36, 140.45, 137.00, 130.18, 128.99, 126.98, 123.19, 123.05, 121.50, 119.62, 119.39, 118.09, 111.99, 108.51, 83.68, 72.50, 62.06, 57.47, 46.65, 46.14, 38.23, 29.17, 28.43, 5.76, 5.16, 2.32; HRMS (FAB) m/z 471.2433 $(M + H)^+$, $C_{28}H_{31}N_4O_3$ requires 471.2396. Anal. ($C_{28}H_{30}N_4O_3$·2TFA·2H_2O) C, H, N.

5′-Amino-17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (10a).[8] To a solution containing 7.4 g (16.1 mmol) of **6a** in 100 mL of ethanol was added about 1−2 g of wet Raney nickel, under nitrogen, with the rigorous exclusion of oxygen. Hydrazine hydrate, 6 mL (124 mmol, 7.7 equiv), was added dropwise over 10 min. The reaction was stirred under nitrogen for 2 h then was filtered of catalyst with added methanol. The filtrate was concentrated in vacuo and was purified by silica gel flash chromatography (4 × 29 cm, 94.5:5:0.5 dichloromethane−methanol−NH_4OH). Product was recovered as a faintly tan solid: yield 4.74 g (69%); silica gel TLC R_f 0.42 (89:10:1 dichloromethane−methanol−NH_4OH); ^{1}H NMR (DMSO-d_6) δ 10.59 (s, 1H), 8.93 (br s, 1H), 7.01 (d, J = 9 Hz, 1H), 6.44−6.56 (m, 4H), 5.43 (s, 1H), 4.72 (br s, 1H), 4.42 (br s, 1H), 3.45 (d, J = 5.5 Hz, 1H), 3.03 (d, J = 19 Hz, 1H), 2.6−2.8 (m, 2H), 2.54 (d, J = 15 Hz, 1H), 2.3−2.5 (m, 4H), 2.1−2.3 (m, 2H), 1.55 (d, J = 11.5 Hz, 1H), 0.86 (m, 1H), 0.48 (m, 2H), 0.12 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 144.25, 141.86, 140.89, 132.23, 131.75, 130.55, 128.16, 125.36, 119.22, 117.93, 113.84, 112.58, 109.66, 102.66, 85.39, 73.29, 62.99, 59.79, 48.33, 44.39, 32.29, 29.94, 10.35, 4.88, 4.75; HRMS (FAB) m/z 430.2127 $(M + H)^+$, $C_{26}H_{28}N_3O_3$ requires 430.2131. Anal. ($C_{26}H_{27}N_3O_3$·2TFA·2H_2O) C, H, N.

5′-Aminomethyl-17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (10b).[7] To a solution of nitrile **6b**·HCl·H_2O (2.00 g, 1.27 mmol) in 27 mL of ethanol and 3 mL of NH_4OH was added about 500 mg of wet Raney nickel. The suspension was hydrogenated at 70−75 psi for 3 days, then an additional 300 mg of catalyst was added. Hydrogenation was continued another 2 days, then the reaction was quickly filtered of catalyst and concentrated in vacuo. The residue was purified by silica gel flash chromatography (3 × 27 cm, 78:20:2 dichloromethane−methanol−NH_4OH) affording the product as a slightly pink solid: yield 1.09 g (63%); silica gel TLC R_f 0.37 (78:20:2 dichloromethane−methanol−NH_4OH); ^{1}H NMR (DMSO-d_6) δ 11.02 (s, 1H), 7.25 (s, 1H), 7.21 (d, J = 8.5 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 8 Hz, 1H), 7.44 (d, J = 8 Hz, 1H), 5.47 (s, 1H), 4−5 (3 br s), 3.70 (s, 2H), 3.23 (d, J = 6 Hz, 1H), 3.02 (d, J = 9 Hz, 1H), 2.6−2.8 (m, 3H), 2.2−2.5 (m, 4H), 2.11 (dt, J = 3, 12 Hz, 1H), 1.55 (br d, J = 11.5 Hz, 1H), 0.86 (m, 1H), 0.47 (m, 2H), 0.11 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 140.99, 136.86, 134.90, 132.11, 130.99, 127.25, 125.28, 123.04, 119.29, 117.95, 117.69, 112.06, 110.95, 85.10, 73.27, 62.92, 59.76, 48.42, 47.18, 44.34, 32.23, 29.88, 23.81, 10.36, 4.85, 4.68. Anal. ($C_{27}H_{29}N_3O_3$·2TFA·2H_2O) C, H, N.

5′-[(N^2-Acetamidino)methyl]-17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-3,14-dihydroxyindolo[2′,3′:6,7]-morphinan (11b). Ethanol (5 mL) was added to 250.8 mg (565 μmol) of **10b**[7] and 250.8 mg (2.29 mmol, 4.0 equiv) of methyl acetimidate hydrochloride. The mixture was brought to reflux where it remained for 1 h, and the solution was then concentrated in vacuo. The residue was purified by silica gel flash chromatography (3 × 23 cm, 78:20:2 dichloromethane−methanol−NH_4OH). Product was recovered as a faintly yellow solid: yield 236.1 mg (86%); silica gel TLC R_f 0.22 (78:20:2 dichloromethane−methanol−ammonium hydroxide); ^{1}H NMR (DMSO-d_6) δ 11.40 (s, 1H), 9.99 (br t, 1H), 9.30 (s, 1H), 9.0 (br s, 1H), 7.35 (s, 1H), 7.32 (d, J = 8 Hz, 1H), 7.09 (d, J = 8 Hz, 1H), 6.63 (d, J = 8 Hz, 1H), 6.53 (d, J = 8 Hz, 1H), 5.65 (s, 1H), 4.46 (s, 2H), 4.14 (br s, 1H), 2.8−3.1 (m, 4H), 2.6 (m, 2H), 2.4−2.5 (m, 3H), 2.13 (s, 3H), 1.74 (d, J = 10 Hz, 1H), 1.1 (m, 1H), 0.65 (m, 1H), 0.6 (m, 1H), 0.45 (m, 1H), 0.4 (m, 1H); ^{13}C NMR (methanol-d_4) δ 164.70, 144.01, 140.91, 137.82, 130.99, 130.20, 127.38, 125.23, 123.19, 119.76, 119.01, 118.34, 112.38, 109.68, 84.66, 73.25, 62.81, 58.57, 47.62, 45.77, 29.94, 29.42, 24.00, 18.16, 7.29, 5.04, 3.07; HRMS (FAB) m/z 485.2541 $(M + H)^+$, $C_{29}H_{33}N_4O_3$ requires 485.2553. Anal. ($C_{29}H_{32}N_4O_3$·2TFA·2H_2O) C, H, N.

17-Cyclopropylmethyl-6,7-didehydro-4,5-α-epoxy-5′-guanidinyl-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (12a). Amine **10a**[8] (646 mg, 1.5 mmol) was dissolved in 3.0 mL of anhydrous DMF (3.0 mL) and was cooled to 0 °C on an ice bath under nitrogen. Bis-Boc-thiourea (275 mg, 1.65 mmol, 1.1 equiv) and triethylamine (461 μL, 2.2 equiv) were added sequentially, and the reaction mixture was stirred for 10 min at 0 °C. Mercury(II) chloride (449 mg, 1.1 equiv) was added in one portion, and rapid stirring was mantained for 20 min. The ice bath was removed, and the reaction mixture was allowed to attain room temperature over 1 h. The mixture was filtered through a Celite pad to remove mercuric sulfide, and the cake was subsequently washed repeatedly with methanol. The filtrate was concentrated under reduced pressure to afford a brown oil which was purified by silica gel flash chromatography (80:10:1 chloroform−methanol−NH_4OH) affording the bis-Boc-guanidine as a colorless solid: yield 781 mg (76%); silica gel TLC R_f 0.29 (89:10:1 dichloromethane−methanol−NH_4OH); ^{1}H NMR ($CDCl_3$) δ 10.14 (bs, 1H), 9.42 (bs, 1H), 7.35 (d, J = 1.7 Hz, 1H), 7.18 (d, 1H), 7.08 (d, J = 8.7 Hz, 1H), 6.54 (d, J = 8.2 Hz, 1H), 6.47 (d, J = 8.2 Hz, 1H), 5.56 (s, 1H), 3.38−2.38 (m, 9H), 1.72 (m, 1H), 1.45 (s, 9H), 1.38 (s, 9H), 0.93−0.89 (m, 1H), 0.54−0.52 (m, 2H), 0.14−0.12 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 163.68, 154.41, 153.36, 143.16, 139.51, 139.48, 135.41, 135.34, 131.46, 130.67, 130.30, 127.97, 126.61, 124.60, 119.37, 118.79, 117.32, 117.21, 113.81, 111.44, 110.98, 109.99, 84.96, 83.45, 79.45, 72.80, 62.38, 59.46, 50.36, 49.73, 47.88, 43.60, 31.35, 28.69, 28.08, 23.12, 9.33, 3.91, 3.84; HRMS (FAB) m/z 672.3408 $(M + H)^+$, $C_{37}H_{46}N_5O_7$ requires 672.3397.

The bis-Boc-guanidine (200 mg, 0.29 mmol) was dissolved in 250 μL of anhydrous dichloromethane and was cooled to 0 °C under nitrogen. This solution was stirred rapidly for 15 min, then TFA (230 μL, 10 equiv) was added dropwise over a 10-min period. Rapid stirring was maintained for a further 48 h at ambient temperature. Volatile components were removed under reduced pressure affording an oil that was washed with diethyl ether. This produced a colorless precipitate that was isolated by vacuum filtration: yield 177 mg (82.3%); $[\alpha]^{20}_D$ −2.45° (c 1.0, methanol); silica gel TLC R_f 0.29 (78:20:2 dichloromethane−methanol−NH_4OH); ^{1}H NMR (TFA salt, methanol-d_4) δ 7.44 (d, J = 8.5 Hz, 1H), 7.34 (d, J = 2.0 Hz, 1H), 7.00 (dd, J = 8.6, 2.0 Hz, 1H), 6.67 (d, J = 8.2 Hz, 1H), 6.64 (d, J = 8.2 Hz, 1H), 5.72 (s, 1H), 4.21 (d, J = 6.0 Hz, 1H), 3.42−3.29 (m, 3H), 3.20−3.15 (m, 1H), 3.03−2.86 (m, 3H), 2.80−2.68 (m, 2H), 1.95−1.91 (m, 1H), 1.29−1.11 (m, 1H), 0.90−0.74 (m, 2H), 0.59−0.50 (m, 2H); ^{13}C NMR (TFA salt, methanol-d_4) δ 158.74 (q, $^2J_{C-F}$ = 40.72 Hz), 158.04, 144.06, 141.37, 137.45, 131.75, 129.54, 127.76, 126.19, 121.88, 121.44, 119.87, 118.60, 117.26, 114.74 (q, $^1J_{C-F}$ = 285.34 Hz), 113.37,

109.33, 105.01, 84.12, 72.83, 62.86, 58.13, 46.78, 29.42, 28.98, 28.95, 24.22, 6.09, 5.45, 2.58; HRMS (FAB) *m/z* 472.2326 (M + H)$^+$, $C_{27}H_{30}N_5O_3$ requires 472.2349. Anal. ($C_{27}H_{29}N_5O_3$·2TFA·2H_2O) C, H, N.

17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5′-guanidinylmethyl-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (12b). The aminomethyl-NTI derivative **10b**[7] (200 mg, 0.451 mmol) was dissolved in 4.0 mL of anhydrous DMF and was cooled to 0 °C in an ice bath. Bis-Boc-thiourea (137 mg, 0.496 mmol, 1.1 equiv) and triethylamine (138 μL, 2.2 equiv) were added sequentially, then the reaction was stirred for 10 min at 0 °C. Mercury(II) chloride (135 mg, 1.1 equiv) was added in one portion, and rapid stirring was maintained for 20 min, after which the ice bath was removed and the reaction mixture was allowed to attain room temperature. After 1 h the mixture was filtered through a Celite pad under vacuum to remove mercuric sulfide, and the cake was subsequently washed repeatedly with methanol. Removal of all volatile components under reduced pressure produced a brown oil which was subjected to flash column chromatography (elution system 80:1 chloroform−methanol) to afford the bis-Boc-guanidine as a colorless solid: yield 229 mg (69%); ^{1}H NMR (methanol-d_4) δ 7.51 (s, 1H), 7.40 (d, *J* = 8.34 Hz, 1H), 7.18 (dd, *J* = 8.4, 1.4 Hz, 1H), 6.64 (s, 2H, H1), 5.68 (s, 1H), 4.12 (s, 2H), 4.03 (bs, 1H), 3.38−2.38 (m, 9H), 1.72 (m, 1H), 1.45 (s, 9H), 1.38 (s, 9H), 0.93−0.89 (m, 1H), 0.54−0.52 (m, 2H), 0.14−0.12 (m, 2H).

The bis-Boc-guanidine (150 mg, 0.22 mmol) was dissolved in 10 mL of anhydrous dichloromethane and was cooled to 0 °C. This solution was stirred rapidly for 15 min, then 2 mL of trifluoroacetic acid was added dropwise over a 10-min period. Rapid stirring was maintained for a further 48 h at ambient temperature. Volatile components were then removed under reduced pressure, and the resultant oil was washed with diethyl ether. This produced a precipitate that was isolated by vacuum filtration to afford **12b** as a colorless solid: yield 151 mg (91%); IR KBr disk (cm^{-1}) 3374.05, 1679.11, 1504.93, 1462.58, 1431.85, 1328.01, 1202.20, 1135.29, 1060.20, 1029.46, 1011.47, 929.80, 911.89, 868.08, 837.96, 800.38, 721.89, 597.48; ^{1}H NMR (methanol-d_4) δ 7.38 (m, 2H), 7.11 (dd, *J* = 8.60, 1.46 Hz, 1H), 6.67 (m, 2H), 5.72 (s, 1H), 4.41 (s, 2H), 4.21 (d, *J* = 6.0 Hz, 1H), 3.42−3.29 (m, 3H), 3.20−3.15 (m, 1H), 3.03−2.86 (m, 3H), 2.80−2.68 (m, 2H), 1.95−1.91 (m, 1H), 1.29−1.11 (m, 1H), 0.90−0.74 (m, 2H), 0.59−0.50 (m, 2H); HRMS (FAB) *m/z* 486.2507 (M + H)$^+$, $C_{28}H_{32}N_5O_3$ requires 486.2505. Anal. ($C_{28}H_{31}N_5O_3$·2TFA·2H_2O) C, H, N.

5′-*N*-Biguanidino-17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (13). Trifluoroacetic acid, 99 μL (1.28 mmol, 2.2 equiv), was added to a solution containing 250 mg (582 μmol) of **10a**[8] in 5 mL of methanol. The solution was concentrated in vacuo then was dried under high vacuum. Dicyandiamide (90 mg, 1.07 mmol, 1.8 equiv) was added to the flask, and the solids were dissolved in 500 μL of dry DMSO. The solution was heated at 100−110 °C for 3 days then was concentrated in vacuo. One-half of the reaction mixture was purified by silica gel flash chromatography (2 × 26 cm, 6:3:1 dichloromethane−methanol−ammonium hydroxide) affording the crude product as a colorless solid: yield 117.8 mg (39.4%). The residue was further purified by silica gel preparative TLC (1.0 mm, 6:3:1 dichloromethane−methanol−ammonium hydroxide): silica gel TLC R_f 0. (6:3:1 dichloromethane−methanol−ammonium hydroxide); ^{1}H NMR (TFA salt in methanol-d_4) δ 7.32 (m, 2H), 7.04 (dd, *J* = 2, 9 Hz, 1H), 6.69 (m, 2H), 5.66 (s, 1H), 4.12 (br s, 1H), 3.29 (m, 2H), 3.13 (dd, *J* = 7, 13 Hz, 1H), 2.8−3.0 (m, 3H), 2.5−2.7 (m, 3H), 1.70 (d, *J* = 8 Hz, 1H), 1.07 (m, 1H), 0.81 (m, 1H), 0.72 (m, 1H), 0.47 (m, 2H); ^{13}C NMR (TFA salt in methanol-d_4) δ 176.94, 165.32, 160.34, 143.42, 140.64, 130.56, 129.03, 126.75, 122.89, 121.12, 118.04, 114.93, 108.56, 95.17, 83.68, 72.33, 62.21, 57.55, 41.57, 28.82, 25.91, 23.45, 21.50, 5.58, 4.87, 2.09; HRMS (FAB) *m/z* 514.2576 (M + H)$^+$, $C_{28}H_{32}N_7O_3$ requires 514.2567. Anal. ($C_{28}H_{31}N_7O_3$·3TFA·2H_2O) C, H, N.

5′-(Dimethylamino)methyl-17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (14b). To a solution of **10b**[7] (124.7 mg, 281 μmol) in 1.25 mL of methanol was added 20.0 μL of formaldehyde (267 μmol, 0.95 equiv); the resulting imine precipitated from solution. Addition of 32.2 μL of acetic acid (511 μmol, 1.82 equiv) effected dissolution, and 420 μL of a 1 M sodium cyanoborohydride solution (1.5 equiv) was added. The reaction was stirred under nitrogen for 24 h, then an additional 420 μL of sodium cyanoborohydride was added followed by 20.0 μL of formaldehyde. After 1 h the reaction was then concentrated in vacuo and was purified by silica gel flash chromatography (2 × 25 cm, 89:10:1 dichloromethane−methanol−NH_4OH) to afford the product as a colorless solid: yield 110.2 mg (83%); mp 180−185 °C dec (colorless crystals from ether−methanol); silica gel TLC R_f 0.57 (78:20:2 dichloromethane−methanol−NH_4OH); ^{1}H NMR (DMSO-d_6) δ 11.07 (s, 1H), 8.8−9.1 (br s, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.19 (s, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 6.49 (d, *J* = 8.0 Hz, 1H), 6.44 (d, *J* = 8.0 Hz, 1H), 5.47 (s, 1H), 4.4−4.8 (br s, 1H), 3.37 (s, 2H), 3.23 (d, *J* = 5.5 Hz), 3.02 (d, *J* = 18 Hz), 2.6−2.8 (m, 3H), 2.2−2.5 (m, 4H), 2.1−2.2 (m, 1H), 2.07 (s, 6H), 1.55 (d, *J* = 11.5 Hz, 1H), 0.85 (m, 1H), 0.46 (m, 2H), 0.11 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 144.14, 140.94, 137.17, 132.10, 131.05, 129.63, 127.14, 125.32, 124.44, 119.70, 119.32, 117.93, 112.07, 110.95, 85.07, 73.27, 65.16, 62.91, 59.74, 49.71, 48.40, 45.87, 44.37, 32.20, 29.85, 23.79, 10.31, 4.85, 4.68; HRMS (FAB) *m/z* 472.2599 (M + H)$^+$, $C_{29}H_{34}N_3O_3$ requires 472.2600. Anal. ($C_{29}H_{33}N_3O_3$) C, H, N.

5′-(Trimethylammonium)methyl-17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-3,14-dihydroxyindolo[2′,3′:6,7]-morphinan Iodide (15b). Iodomethane (15 mL, 241 μmol, 1.1 equiv) was added to a solution containing 101.3 mg (215 μmol) of **14b** in 2.0 mL of methanol. The reaction was stirred in the dark under nitrogen for 16 h and then was filtered of product with added methanol. The filtered salt was recovered as a colorless solid: yield 65.6 mg (50%); mp 245 °C dec (colorless needles from methanol); silica gel TLC R_f 0.24 (6:3:1 dichloromethane−methanol−NH_4OH); ^{1}H NMR (DMSO-d_6) δ 11.44 (s, 1H), 8.94 (br s, 1H), 7.50 (s, 1H), 7.39 (d, *J* = 8 Hz, 1H), 7.17 (dd, *J* = 1.5, 8 Hz, 1H), 6.46 (s, 2H, H1), 5.49 (s, 1H), 4.75 (br s, 1H), 4.47 (s, 2H), 3.32 (s, 9H), 3.27 (m, 1H), 3.00 (d, *J* = 15 Hz, 1H), 2.6−3.0 (m, 3H), 2.2−2.5 (m, 4H), 2.1−2.2 (m, 1H), 1.57 (d, *J* = 11 Hz, 1H), 0.85 (m, 1H), 0.48 (m, 2H), 0.12 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 144.09, 140.09, 138.49, 132.39, 131.98, 127.38, 124.62, 119.55, 119.19, 117.98, 112.74, 111.62, 105.01, 84.68, 73.20, 62.94, 59.63, 52.50, 52.45, 48.42, 30.95, 5.95, 5.78; HRMS (FAB) *m/z* 486.2750 (M$^+$), $C_{30}H_{36}N_3O_3$ requires 486.2757. Anal. ($C_{30}H_{36}IN_3O_3$) C, H, N.

5′-[*N*-(*N*′-Cyano)guanidinylmethyl]-17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-3,14-dihydroxyindolo-[2′,3′:6,7]morphinan (17b). Amine **10b**[7] (100 mg, 225 μmol) was dissolved in 5 mL of methyl alcohol. *N*-Cyanodiphenylcarbonimidate (54 mg, 227 μmol, 1 equiv) was added, and the solution was heated at 60 °C for 24 h under nitrogen. The reaction was then cooled to room temperature, and all volatiles were removed in vacuo. The resultant brown oil was subjected to silica gel flash column chromatography to afford the *O*-phenylisourea **16b** as a colorless solid: yield 105 mg (79%); HRMS (FAB) *m/z* 588.2602 (M + H)$^+$, $C_{35}H_{34}N_5O_4$ requires 588.2611.

The *O*-phenylisourea **16b** (100 mg, 0.17 mmol) was dissolved in 10 mL of 3:1 NH_4OH−ethanol. The reaction vessel was sealed, and the contents were stirred vigorously at reflux for 90 h. Volatile components from the reaction mixture were removed in vacuo, and residue was purified by silica gel flash chromatography (98:1:1 ethyl acetate−methanol−NH_4OH) affording the product as a colorless solid: yield 61.6 mg (71%); mp >250 °C dec (colorless crystals from ether−methanol); IR KBr disk ν (cm^{-1}) 3328.9 (bs), 3221.4 (bs), 2926.3 (bs), 2180.7 (s, CN), 1633.9 (s), 1567.2 (s), 1560 (s), 1490 (m), 1459 (m), 1385.6 (w), 1352.2 (w), 1154.2 (w), 1115.1 (m); ^{1}H NMR (methanol-d_4) δ 7.32 (s, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 6.56 (s, 2H), 5.59 (s, 1H), 3.49 (m, 1H), 3.30 (s, 2H), 3.20 (d, *J* = 19 Hz, 1H), 2.7−3.0 (m, 3H), 2.3−2.7 (m, 5H), 1.75 (d, *J* = 10 Hz, 1H), 0.96 (m, 1H), 0.60 (m, 2H), 0.23 (m, 2H); HRMS (FAB) *m/z* 511.2420 (M + H)$^+$, $C_{29}H_{31}N_6O_3$ requires 511.2458. Anal. ($C_{29}H_{30}N_6O_3$) C, H, N.

17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5′-thiourea-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (18). Benzoyl isothiocyanate (400 μL, 3.02 mmol, 1.1 equiv) was added to a suspension of **10a**[8] (1.207 g, 2.81 mmol) in 25 mL of dry dichloromethane at 0−3 °C. The reaction was allowed to warm to ambient temperature, and after 3 h the resulting solution was concentrated in vacuo and the residue was purified by silica gel flash chromatography (3 × 27 cm, 95:5: 0.5 dichloromethane−methanol−ammonium hydroxide) affording the *N*-benzoylthiourea as a light tan solid: yield 1.40 g (84%); silica gel TLC R_f 0.40 (95:5:0.5 dichloromethane−methanol−ammonium hydroxide); ^{1}H NMR (DMSO-d_6) δ 12.63 (s, 1H), 11.45 (br s, 1H), 11.33 (s, 1H), 9.03 (br s, 1H), 7.95 (d, J = 8 Hz, 2H), 7.79 (s, 1H), 7.60 (t, J = 7 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.35 (d, J = 8.4 Hz, 1H), 7.22 (d, J = 9 Hz, 1H), 6.55 (d, J = 8 Hz, 1H), 6.49 (d, J = 8 Hz, 1H), 5.52 (s, 1H), 3.5 (br s, 1H), 3.34 (s, 1H), 3.06 (d, J = 19 Hz, 1H), 2.6−2.8 (m, 3H), 2.25−2.6 (m, 4H), 2.17 (m, 1H), 1.58 (d, J = 11 Hz, 1H), 0.86 (m, 1H), 0.48 (m, 2H), 0.14 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 179.93, 169.48, 144.16, 141.06, 136.03, 134.17, 133.30, 132.16, 131.80, 130.55, 129.78, 129.73, 129.54, 126.96, 125.05, 120.61, 119.56, 118.16, 115.39, 112.53, 111.34, 84.74, 73.29, 62.71, 59.56, 48.32, 31.87, 29.81, 23.89, 9.94, 5.09, 4.57; HRMS (FAB) m/z 593.2216 (M + H)$^+$, $C_{34}H_{33}N_4O_4S$ requires 593.2209.

Anhydrous K_2CO_3 (2.38 g) was added to a solution of the *N*-benzoylthiourea (1.31 g, 2.21 mmol) in 25 mL of methanol. The resulting suspension was stirred at room temperature for 16 h then was filtered of solids with added methanol. The filtrate was concentrated in vacuo and was purified by silica gel flash chromatography (3 × 23 cm, 89:10:1 dichloromethane−methanol−ammonium hydroxide) affording the product **18** as a colorless solid: yield 1.093 g (100%); silica gel TLC R_f 0.59 (89:10:1 dichloromethane−methanol−ammonium hydroxide); ^{1}H NMR (DMSO-d_6) δ 1.20 (s, 1H), 9.51 (s, 1H), 8.96 (br s, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.23 (s, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.51 (d, J = 8 Hz, 1H), 6.46 (d, J = 8 Hz, 1H), 5.50 (s, 1H), 4.8 (br s, 1H), 4.11 (m, 1H), 3.0−3.4 (m, 3H), 2.6−2.8 (m, 3H), 2.2−2.5 (m, 4H), 2.1−2.2 (m, 1H), 1.57 (d, J = 11 Hz, 1H), 0.87 (m, 1H), 0.49 (m, 2H), 0.14 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 181.90, 144.16, 140.96, 135.96, 131.97, 130.86, 127.35, 125.43, 121.03, 119.48, 118.03, 115.81, 112.78, 111.32, 84.87, 73.22, 62.71, 59.61, 32.10, 29.81, 23.84, 10.17, 5.06, 4.58; HRMS (FAB) m/z 489.1929 (M + H)$^+$, $C_{27}H_{29}N_4O_3S$ requires 489.1898. Anal. ($C_{27}H_{28}N_4O_3S$·1TFA·2H_2O) C, H, N.

17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5′-*N*²-(*S*-methylpseudothiourea)-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (19). Thiourea **17** (456.5 mg, 934 μmol) was dissolved in 10 mL of methanol and was cooled to 0−3 °C in an ice bath. TFA (500 μL) was added, and the solution was then concentrated in vacuo. The TFA salt of **18** was then dissolved in 10 mL of methanol, then 200 μL of iodomethane was added. The resulting solution was heated to reflux where it remained for 5.5 h. The solution was then concentrated and dried affording the crude thiouronium salt **19**. The salt was purified by silica gel flash chromatography (2 × 27 cm, 89:10:1 dichloromethane−methanol−ammonium hydroxide) affording the product as a colorless solid: yield 420.8 mg (89.6%); silica gel TLC R_f 0.45 (89:10:1 dichloromethane−methanol−ammonium hydroxide); ^{1}H NMR (DMSO-d_6) δ 10.88 (s, 1H), 9 (br s, 1H), 7.15 (d, J = 8.5 Hz, 1H), 6.72 (br s, 1H), 6.54 (d, J = 8 Hz, 1H), 6.47 (d, J = 8 Hz, 1H), 6.43 (d, J = 8 Hz, 1H), 6.0 (br s, 1H), 5.44 (s, 1H), 4.72 (s, 1H), 3.31 (s, 1H), 3.23 (d, J = 6 Hz, 1H), 3.02 (d, J = 19 Hz, 1H), 2.5−2.8 (m, 2H), 2.2−2.5 (m, 8H), 2.11 (t, J = 9 Hz, 1H), 1.54 (d, J = 11 Hz, 1H), 0.85 (m, 1H), 0.46 (m, 2H), 0.12 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 162.41, 150.80, 148.24, 147.46, 141.01, 140.86, 138.80, 137.61, 137.46, 134.44, 132.00, 125.90, 125.69, 124.51, 119.26, 117.57, 117.36, 91.82, 79.82, 69.49, 66.38, 54.96, 51.03, 38.81, 36.45, 30.42, 20.62, 16.90, 11.52, 11.29; HRMS (FAB) m/z 503.2110 (M + H)$^+$, $C_{28}H_{31}N_4O_3S$ requires 503.2117. Anal. ($C_{28}H_{30}N_4O_3S$·2TFA·2H_2O) C, H, N.

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Supporting Information Available: Further experimental details and elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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