Structural Determinants of Opioid Activity in the Orvinols and Related Structures: Ethers of Orvinol and Isoorvinol

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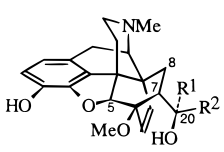
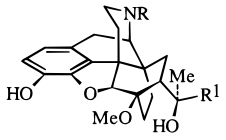
A series of ethers of orvinol and isoorvinol has been prepared and evaluated in opioid receptor binding and in vitro functional assays. The most striking finding was the very large difference in κ-opioid receptor activity between the diastereomeric ethyl ethers: 46-fold in binding, 150-fold in GPI, and 900-fold in the [^{35}S]GTPγS assay in favor of the (*R*)-diastereomer. Additionally in the (*R*)-series there was a 700-fold increase in κ-agonist potency in the [^{35}S]GTPγS assay when OEt was replaced by OBn. The data can be explained in a triple binding site model: an H-bonding site, a lipophilic site, and an inhibitory site with which the 20-Me group in the (*S*)-ethers may interact. It appears that κ-agonist binding of the orvinols avoids the inhibitory site in the intramolecular H-bonded conformation.

Introduction

The orvinols (**1**, **2**) are a series of opioids displaying a range of pharmacological profiles among which the potent agonists etorphine (**1a**)[1] and dihydroetorphine (**2a**),[2] the partial agonist buprenorphine (**2b**),[3] and the antagonist diprenorphine (**2d**)[1] have attracted particular attention. The importance of the C_7 side chain in conferring exceptional in vivo potency in the orvinols was early recognized,[4] but the roles played by the 20-OH and alkyl groups have not been clearly established. Bentley and Lewis[5] first proposed that the hydroxy group was involved in an H-bonding interaction to the receptor but later[1] suggested that its main function was to fix the conformation of the side chain by an intramolecular H-bond to the 6-methoxy group, allowing the major alkyl group in the more active 20(*R*)-diastereomer (e.g. **1a**) to more effectively partake in lipophilic interaction with the receptor. Others[6] have used this principle to further elaborate models of opioid receptor binding sites and to relate this to active conformations of the enkephalins[7] in which the aromatic ring of the phenylalanine component binds to the lipophilic site accessed by the alkyl or arylalkyl groups (R^2 in structure **1**) in the 20(*R*)-diastereomer of the orvinols. Rapoport and coworkers[8] cast doubts on the significance of the intramolecular H-bond in the active conformation of the (*R*)-orvinols by showing that in a related series without a 6-OMe group, the 20(*R*)-diastereomer retained superiority over the 20(*S*)-diastereomer. Hutchins and Rapoport[9] also showed that the OH group was not required for differential diastereomeric activity. They reported that the (*R*)-orvinan (**3a**) was 47 times more potent than the equivalent (*S*)-orvinan (**3b**) which matched the greater in vivo potency of etorphine (**1a**) over its (*S*)-diastereomer (**1b**).[1] The 20(*S*)-furanomorphide (**4b**), also formed in the synthesis of **4a,** was 9 times more potent than the (*R*)-isomer, and from this the authors concluded that the lipophilic site to which the alkyl group in the (*S*)-furanomorphide (**4b**), the (*R*)-orvinol (**1a**), and the (*R*)-orvinan (**3a**) binds was located below C_8.[9] They further hypothesized that in the (*R*)-orvinols the OH group, which in the proposed active conformation was pointing away from C_7, could potentiate binding to the receptor in an intermolecular H-bonding interaction with a suitably located H-bond acceptor in the active site. However all these hypotheses were formulated from data obtained from in vivo rodent antinociceptive assays in which several factors in addition to interaction with opioid receptors can have substantial influence. At that time no receptor binding or in vitro functional data were available.

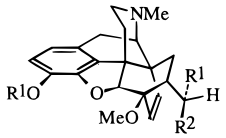


1
(a): R^1 = Me, R^2 = nPr [R]
(b): R^1 = nPr, R^2 = Me [S]

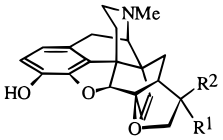


2
(a): R = Me, R^1 = nPr [R]
(b): R = CPM, R^1 = tBu [S]
(c): R = CPM, R^1 = nPr [R]
(d): R = CPM, R^1 = Me

CPM =



3
(a): R^1 = Me, R^2 = nBu [R]
(b): R^1 = nBu, R^2 = Me [S]



4
(a): R^1 = H, R^2 = nBu [R]
(b): R^1 = nBu, R^2 = H [S]

For some time we have been interested in comparing the activity of the orvinols and related structures in terms of affinity and efficacy for the individual types of opioid receptors (μ, κ, and δ). The present study involved the synthesis and evaluation of diastereomeric series of orvinol ethers (**5b**−**5d**) and isoorvinol ethers (**7b**−**7d**) in opioid receptor binding and in vitro functional assays.

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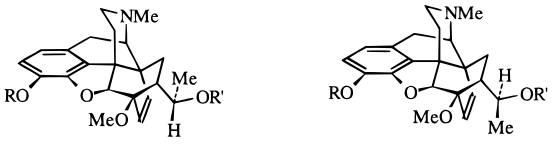


5: R = H **6**: R = Me [R] **7**: R = H **8**: R = Me [S]
(a): R' = H (b): R' = Me (c): R' = Et (d): R' = Bn

Synthesis

Thevinol (**6a**) and isothevinol (**8a**) were prepared by the literature methods.[10] They were converted with NaH to the alkoxides which were alkylated (MeI, EtI, BnBr) in refluxing THF in the presence of 18-crown-6. O-Demethylation of the resulting thevinol and isothevinol ethers (**6b**−**6d**, **8b**−**8d**) was performed using standard conditions of NaSPr in HMPA[16] to yield the target orvinol and isoorvinol ethers (**5b**−**5d**, **7b**−**7d**). The hydrochloride or oxalate salt of each compound was prepared prior to pharmacological testing.

Pharmacology

The ethers were evaluated in assays using cloned human opioid receptors transfected into Chinese hamster ovary (CHO) cells.[11] In the displacement binding assays (Table 1) in which the radioligands selective for individual types of opioid receptor were [^{3}H]DAMGO (μ), [^{3}H]Cl-DPDPE (δ), and [^{3}H]U69593 (κ), the ethers had generally high opioid receptor affinities with the exception of the (*S*)-methyl ether (**7b**) for κ- and δ-receptors. Affinity generally increased with the size of the ether group, and the affinity of the (*S*)-ethers (**7b**−**7d**) was generally lower than that of the equivalent (*R*)-ethers (**5b**−**5d**). This difference was relatively small for binding to μ-opioid receptors but was greater for δ- and κ-receptors. The biggest differences were between **5c** and **7c** (46-fold for κ) and between **5d** and **7d** (29-fold for δ).

The ethers were evaluated in the same cell line for the stimulation of [^{35}S]GTPγS binding (Table 2). These assays[11,12] allow the measurement of potency and efficacy as agonists for the individual types of opioid receptor. Efficacy is assessed in the same experiment against the standard selective agonists (as above in the binding assays) for μ-, κ-, and δ-receptors. The ethers generally displayed high-efficacy agonist activity for μ-, δ-, and κ-receptors. Only isoorvinol methyl ether (**7b**) for μ- and κ-receptors showed partial agonism. Potency in these assays generally followed affinity in the binding assay, i.e., OBn > OEt > OMe and (*R*) > (*S*). Differences of potency between diastereomers were small (2−3-fold) for μ but larger for κ and δ. The biggest differences were shown by the ethyl ethers (**5c** > **7c**) for κ-receptors and the benzyl ethers (**5d** > **7d**) for δ-receptors. The potency of orvinol ethyl ether (**5c**) as a κ-agonist in this assay was astonishingly 900 times greater than that of the (*S*)-diastereomer (**7c**). The extent of this difference is primarily attributable to the very low potency of **7c**. In the (*S*)-series replacing ethyl by benzyl resulted in a 700-fold increase in κ potency.

Data from the binding and GTPγS assays were obtained for the (*R*)- and (*S*)-orvinols etorphine (**1a**) and isoetorphine (**1b**). These ligands can be compared respectively with the (*R*)- and (*S*)-ethyl ethers (**5c**, **7c**) with the ^{n}Pr group equating to the OEt group and the 20-OH group in **1a** and **1d** taking the place of H in **5c** and **7c**. Etorphine and isoetorphine showed similar opioid receptor binding affinities (Table 1), but in GTPγS assays etorphine was 7−11-fold more potent than isoetorphine as a μ-, δ-, and κ-agonist and also significantly more efficacious as a μ- and δ-agonist. These differences in opioid receptor potency and efficacy would account for the 50-fold higher potency of etorphine over isoetorphine in rodent antinociceptive tests.[1]

Table 1. Opioid Receptor Binding Affinities of Orvinol and Isoorvinol Ethers, Etorphine, and Isoetorphine in Guinea Pig Brain Membranes or in Cloned Human Opioid Receptors Transfected onto CHO Cells

	K_i (nM)		
structure	[^{3}H]DAMGO (μ)	[^{3}H]Cl-DPDPE (δ)	[^{3}H]U69593 (κ)
5b[b]	1.6 ± 0.1	12.9 ± 0.8	3.9 ± 1.1
5c[a]	0.5 ± 0.15	2.7 ± 0.25	0.3 ± 0.1
5d[b]	0.64 ± 0.01	0.16 ± 0.01	0.84 ± 0.04
7b[b]	4.8 ± 0.4	77.5 ± 1.9	43.3 ± 2.5
7c[a]	1.0 ± 0.2	7.0 ± 0.7	13.9 ± 0.55
7d[b]	0.67 ± 0.07	4.6 ± 0.42	1.1 ± 0.08
etorphine, **1a**[a]	1.5 ± 0.35	0.7 ± 0.07	0.8 ± 0.2
isoetorphine, **1b**[a]	0.5 ± 0.05	1.1 ± 0.05	2.3 ± 0

[a] Affinities in guinea pig brain membranes. [b] Affinities in cloned human opioid receptors transfected onto CHO cells. Values are from two experiments each carried out in triplicate.

Further comparison of the ethyl ethers (**5c**, **7c**) and the orvinols (**1a**, **1b**) was undertaken in the guinea pig ileum (GPI) bioassay (Table 3). The (*R*)-ether **5c** showed a potent opioid agonist response that was reversed by nor-BNI (κ-antagonist) but not by CTAP (μ-antagonist). The (*S*)-diastereomer (**7c**) was 150-fold less potent, and the response was reversed by CTAP but not by nor-BNI. These data confirm the very large difference of κ-agonist effect between **5c** and **7c** shown in the GTPγS assay. Etorphine was a very high-potency agonist in GPI (10 times **5c**) with some antagonism by both nor-BNI and CTAP. Isoetorphine was 67-fold less potent than etorphine as an agonist in GPI but with μ selectivity.

Discussion

This investigation has confirmed that in the orvinols (e.g. **1**) and the related series of ethers (**5b**−**5d**, **7b**−**7d**) opioid activity is dependent on the configuration of C_{20} in favor of the (*R*)-diastereomers. However the profiles of affinity and efficacy of diastereomers at the individual opioid receptor types were different between the series. In the orvinol series, exemplified by etorphine (**1a**) and isoetorphine (**1b**), the agonist superiority of etorphine is attributable to moderately greater potency for all the receptor types and greater μ and δ efficacy. In contrast the (*R*)-ethyl ether (**5c**) in the functional assays was 150−900 times more potent as a κ-agonist than its diastereomer (**7c**) with much smaller differences in μ and δ effects. These results suggest that the *O*-alkyl groups in the ethers and the larger alkyl group in the orvinols do not bind to the κ-receptor in similar conformations. This would be the case if the OH group of the orvinols and the OR group in the ethers were involved in H-bonding interactions with an appropriately located κ-receptor H-bond donor group. Such an interaction with the 20β-OH group in the conformationally constrained orvinol analogues (**9a**, **9b**) was invoked to account for the substantially greater κ-agonist potency and efficacy of **9a** over **9b**, both in the [^{35}S]GTPγS assay and in vivo.[13] However the H-bond interaction cannot be the only involvement of the ether group in

Table 2. Activity of Orvinol and Isoorvinol Ethers, Etorphine, and Isoetorphine in Stimulating the Binding of [^{35}S]GTPγS in Cloned Human Opioid Receptors Transfected onto CHO Cells

	μ		δ		κ	
structure	EC_{50} (nM)	% stim[a]	EC_{50} (nM)	% stim[a]	EC_{50} (nM)	% stim[a]
5b	16.2 ± 9.2	77 ± 4.5	36.7 ± 10.4	113 ± 35	18.4 ± 0.5	83 ± 12.5
5c	4.85 ± 0.3	84 ± 4.8	23.6 ± 9.1	84 ± 10	0.61 ± 0.07	92 ± 6.3
5d	0.6 ± 0.2	106 ± 1.5	1.1 ± 0.15	91 ± 5.5	0.1 ± 0.02	99 ± 6
7b	34.9 ± 9.6	52 ± 10	160 ± 15	114 ± 26	161 ± 8.0	43 ± 2.5
7c	13.5 ± 7.4	86 ± 14	58.3 ± 4.5	45 ± 1.6	559 ± 179	78 ± 5.7
7d	1.8 ± 0.75	102 ± 0.5	19.4 ± 7.1	92 ± 0.5	0.8 ± 0.1	77 ± 18
etorphine, **1a**	0.66 ± 0.06	117 ± 24	1.5 ± 0.2	107 ± 2.0	2.0 ± 0.57	95 ± 16
isoetorphine, **1b**	7.3 ± 1.98	78 ± 6.8	12.7 ± 1.8	54 ± 10.8	13.9 ± 0.35	92 ± 6.4

[a] Percent (%) stimulation as measured against a selective agonist DAMGO (μ), Cl-DPDPE (δ), and U69593 (κ). Values are from two experiments each carried out in triplicate.

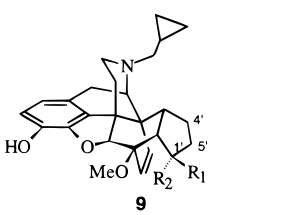
Table 3. Agonist Activity of Ethyl Ethers, Etorphine, and Isoetorphine in the GPI Assay

		K_e (nM)	
structure	IC_{50} (nM)	CTAP	nor-BNI
5c	0.51 ± 0.15	NR[a]	0.47 ± 0.06
7c	75.6 ± 17.2	94.5 ± 33	NR
1a	0.055 ± 0.016	186 ± 14.6	15.0 ± 2.0
1b	3.67 ± 0.76	10.7 ± 0.4	NR
DAMGO	8.25 ± 2.0	25.3 ± 2.5	NR
U69593	1.66 ± 0.63	NR	0.06 ± 0.017

[a] NR, no reversal. Values are from two experiments each carried out in triplicate.

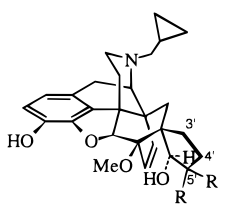
structures **5** and **7** in opioid receptor binding since in both the 20(*R*)- and 20(*S*)-series the benzyl ethers had higher affinity and efficacy than the methyl and ethyl ethers. This applied to all receptor types, but the κ effect from the functional data was particularly striking. In both (*R*)- and (*S*)-series the benzyl ether was 180 and 200 times more potent as a κ-agonist than the methyl ether and in the (*S*)-series was 700-fold more potent than the ethyl ether. This superiority of the (*S*) may be accounted for by the interaction of the phenyl group with a lipophilic site (Figure 1).

The proposed H-bonding interaction of the ethers with the κ-receptor would result in a conformation in which the benzyl group could access possible lipophilic sites in the spaces below C_8 or above C_7.[15] These sites which are occupied by cyclopentane rings in **9** and **10,** respectively, are compatible with κ-agonist activity. The space above C_7 is occupied by $C_{3'}$ and $C_{4'}$ in the spiro analogues (**10**) which have potent agonist activity.[14] However in this series there was a dramatic reduction in κ efficacy when methyl groups were introduced at $C_{5'}$ (**10b**).[14] This was attributed to one of the methyl groups occupying an inhibitory site and would also explain the lack of κ efficacy of buprenorphine (**2b**). The 20-Me group in the (*S*)-ethers could interact with this inhibitory site to account for the very low κ potency of the (*S*)-methyl and ethyl ethers (**7b**, **7c**) (Figure 1).



9

(a): R^1 = OH, R^2 = H [R]
(b): R^1 = H, R^2 = OH [S]



10

(a): R = H; (b): R = Me

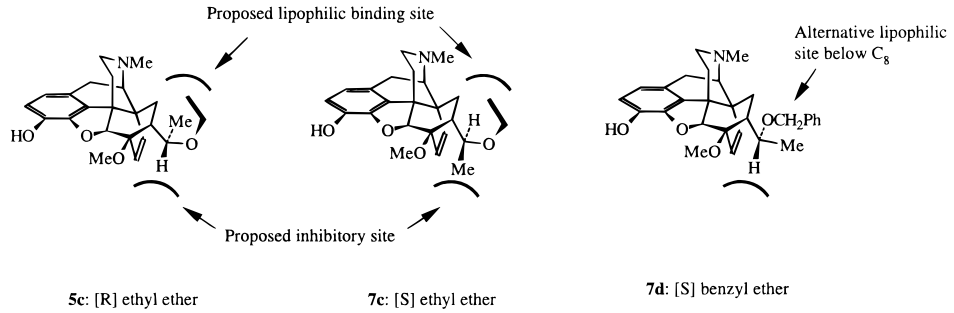
The lesser difference in κ-agonist potency between the diastereomeric orvinols (**1a**, **1b**) compared to the ethyl ethers (**5c**, **7c**) in the GTPγS assay was primarily due to the 40-fold higher potency of the (*S*)-orvinol (**1b**) over the (*S*)-ether (**7c**). The proposed active κ conformation of the orvinols with the H-bond to the receptor would place the 20-Me group of the (*R*)-diastereomer (**1a**) and the ^{n}Pr group in the (*S*)-diastereomer **1b** in the inhibitory site close to the C_6-OMe group. To avoid the inhibitory site the orvinols could adopt an alternative κ active conformation with 20-OH intramolecularly H-bonded to the C_6-OMe group. In the (*R*)-orvinol (**1a**) this would place the ^{n}Pr group in a position from which it could adopt a conformation equivalent to that of the cyclopentane ring in the spiro analogue (**10a**) which displayed extremely potent κ-agonist activity. Additionally the OH group in the spiro analogues and in this conformation for the (*R*)-orvinol (**1a**) is similarly placed. The equivalent conformation of the (*S*)-orvinol (**1b**) places the ^{n}Pr group in the space below C_8 which in the cyclopentano analogue (**9b**) was associated with substantial κ-agonist activity.[13]

In conclusion, the data presented for the series of ethers of orvinol and isoorvinol provide confirmation for the superior opioid activity of 20(*R*)-diastereomers over the 20(*S*)-equivalents in the orvinol and related series. However the enormous difference in κ-agonist potency in in vitro functional assays between the diastereomeric ethyl ethers was unexpected. A model of κ-agonist binding is proposed involving three sites: (i) an H-bonding site complementary to the 20β-OH group in the cyclopentano orvinol analogue (**9a**), (ii) a lipophilic site corresponding to the cyclopentane ring in the spiro orvinol analogue (**10a**), and (iii) an inhibitory site close to the C_6-OMe group occupied by the 20-Me group of the (*S*)-methyl and ethyl ethers in the H-bonded interaction with the receptor. To avoid the inhibitory site it appears that the κ-agonist binding of the orvinols features an intramolecular H-bond to the C_6-OMe group allowing interaction of the larger alkyl group in the (*R*)-diastereomers with the preferred lipophilic site.

Experimental Section

Chemistry. Infrared spectra were obtained on a Perkin-Elmer 881 spectrophotometer. The proton and carbon-13 NMR spectra were obtained on a JEOL JNM-GX 270 (67.5) spectrometer at 20 °C in $CDCl_3$ unless otherwise stated; *J* values are in Hz. Tetramethylsilane was used as the internal standard. Mass spectra were obtained on a Fisons Autosampler instrument with electron impact ionization (70 eV). Elemental analyses were obtained on a Perkin-Elmer 240C analyzer. All reagents were used as supplied by Aldrich.

Compounds for pharmacological analysis were converted into their oxalate salts by dissolving in EtOH and adding oxalic acid (1 equiv) in EtOH (**5b**, **5d**, **7b**, **7d**) or their hydrochloride salts (**5c**, **7c**) by dissolving in methanolic HCl.



5c: [R] ethyl ether **7c**: [S] ethyl ether **7d**: [S] benzyl ether

Figure 1. Proposed binding conformations of **5c**, **7c**, and **7d**.

General Procedure A. Potassium hydride (2 equiv) and 18-crown-6 (0.1 equiv) were added to a solution of thevinol (**5a**) or isothevinol (**7a**), in dry THF. The mixture was heated at gentle reflux for 1 h. The alkyl halide (MeI, EtI, BnBr; 5 equiv) was added and the mixture was stirred at reflux for 3 days. The reaction mixture was then cooled and quenched with ammonium chloride solution. The THF was removed in vacuo and the mixture extracted with ethyl acetate (×3). The organic extracts were washed with water and brine and dried ($MgSO_4$). Purification was by silica gel column chromatography eluting with EtOAc:petroleum ether (40−60), 4:1.

General Procedure B. Sodium 1-propanethiolate (5 equiv) was added to a stirred solution of the thevinol or isothevinol ether (**6b**−**6d**, **8b**−**8d**), respectively, in hexamethyl phosphoramide. After the effervescence had subsided the stirred mixture was heated at 110 °C for 3 h. After cooling, the reaction mixture was quenched with ammonium chloride solution and allowed to stir overnight. The mixture was then extracted with ethyl acetate (×3). The organic extracts were washed with water and brine (×6) and dried ($MgSO_4$). Purification was by silica gel column chromatography, eluting with 2% MeOH in CH_2Cl_2.

20(*R*)-Methoxy-7α-ethyl-6,14-endoethenotetrahydrothebaine (6b): procedure A; yield 16%; υ_{max} ($CHCl_3$) 1425, 1477, 1522, 1600, 2399, 2801 and 2935 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.90 (3H, d, J = 6.0, 20-CH_3), 1.25 (1H, dd, J = 13.2 and 7.2, 8α-H), 1.83 (1H, m, 15-C*H*H), 2.01 (1H, m, 15-CH*H*), 2.36 (3H, s, N−CH_3), 2.32−2.53 (4H, m, 7α-H, 10α-H and 16-CH_2), 2.73 (1H, dd, J = 12.9 and 9.3, 8β-H), 3.14−3.24 (2H, m, 9-H and 10β-H), 3.32 (3H, s, 19-OCH_3), 3.59 (3H, s, 6-OCH_3), 3.61 (1H, m, 19-H), 3.81 (3H, s, 3-OCH_3), 4.63 (1H, s, 5-H), 5.38 (1H, d, J = 8.7, 17-H), 5.70 (1H, d, J = 8.7, 18-H), 6.52 (1H, d, J = 8.1, 1-H) and (1H, d, J = 8.1, 2-H); δ_C (75 MHz; $CDCl_3$) 15.90 (20-C), 22.27 (10-C), 26.02 (8-C), 33.78 (15-C), 38.20 (7-C), 42.70, 43.50 (N−CH_3), 45.53 (16-C), 47.29, 52.43 (6-C), 56.06 (19-OCH_3), 56.49 (3-C), 60.03 (9-C), 76.15 (19-C), 80.32, 95.04 (5-C), 113.11 (2-C), 119.11 (1-C), 127.64 (18-C), 128.32, 134.44, 134.74 (17-C), 141.70 and 148.20; m/z 397 (M^+, 52%), 338 (35), 222 (38), 162 (33) and 59 (100).

20(*R*)-Ethoxy-7α-ethyl-6,14-endoethenotetrahydrothebaine (6c): procedure A; yield 20%; δ_H (300 MHz; $CDCl_3$) 0.90 (3H, d, J = 6.3, 20-CH_3), 1.18 (3H, t, J = 7.2, CH_2CH_3), 1.18 (1H, dd, J = 13.2 and 6.9, 8α-H), 1.84 (1H, m, 15 C*H*H), 2.02 (1H, m, 15-CH*H*), 2.37 (3H, s, N−CH_3), 2.33−2.54 (4H, m, 7α-H, 10α-H and 16-CH_2), 2.71 (1H, dd, J = 13.2 and 9.3, 8β-H), 3.15 (1H, d, J = 6.3, 9-H), 3.21 (1H, d, J = 18.6, 10β-H), 3.49 (2H, m, CH_2CH_3), 3.59 (3H, s, 6-OCH_3), 3.70 (1H, m, 19-H), 3.82 (3H, s, 3-OCH_3), 4.63 (1H, s, 5-H), 5.38 (1H, d, J = 8.7, 17-H), 5.77 (1H, d, J = 8.7, 18-H), 6.52 (1H, d, J = 8.1, 1-H) and 6.61 (1H, d, J = 8.1, 2-H); δ_C (75 MHz; $CDCl_3$) 15.92 (20-C), 16.85 (CH_2CH_3), 22.42 (10-C), 26.31 (8-C), 33.89 (15-C), 38.60 (7-C), 42.85, 43.67 (NCH_3), 45.73 (16-C), 47.42, 52.48 (6-C), 56.63 (3-C), 60.25 (9-C), 63.73 (CH_2CH_3), 74.37 (19-C), 80.55, 95.00 (5-C), 113.19 (2-C), 119.24 (1-C), 127.96 (17-C), 128.48, 134.62, 134.79 (18-C), 141.87 and 148.34; m/z 411 (M^+, 100%), 338 (90), 236 (71), 229 (39), 190 (29), 162 (41) and 73 (67).

20(*R*)-Benzyloxy-7α-ethyl-6,14-endoethenotetrahydrothebaine (6d): procedure A; yield 30%; υ_{max} ($CHCl_3$) 1210, 1427, 1476, 1526, 1601, 2400 and 3038 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.96 (3H, d, J = 6.2, 20-CH_3), 1.24 (1H, dd, J = 13.2 and 6.9, 8α-H), 1.83 (1H, m, 15-C*H*H), 2.01 (1H, m, 15-CH*H*), 2.36 (3H, s, NCH_3), 2.34−2.58 (4H, m, 7α-H, 10α-H and 16-CH_2), 2.77 (1H, dd, J = 13.2 and 9.3, 8β-H), 3.16 (1H, d, J = 6.6, 9-H), 3.21 (1H, d, J = 18.6, 10β-H), 3.49 (3H, s, 6-OCH_3), 3.81 (3H, s, 3-OCH_3), 4.53 (2H, s, CH_2Ph), 4.61 (1H, s, 5-H), 5.37 (1H, d, J = 8.7, 17-H), 5.68 (1H, d, J = 8.7, 18-H), 6.51 (1H, d, J = 8.1, 1-H), 6.61 (1H, d, J = 8.1, 2-H) and 7.26−7.35 (5H, m, Ar−H); δ_C (75 MHz; $CDCl_3$) 16.46 (20-C), 22.31 (10-C), 26.24 (8-C), 33.80 (15-C), 42.76, 43.54 (NCH_3), 45.59 (16-C), 47.31, 52.15 (6-C), 56.52 (3-C), 60.12 (9-C), 70.30 (CH_2Ph), 74.11 (19-C), 76.61, 80.40, 94.68 (5-C), 113.13 (2-C), 119.12 (1-C), 127.33 (18-C), 127.51, 127.88, 128.28, 128.37, 134.69 (17-C), 139.22, 141.76 and 148.25; m/z 473 (M^+, 94%), 338 (93), 298 (71), 254 (30), 229 (43), 162 (58) and 91 (100). Found M^+, 473.2576; $C_{30}H_{35}NO_4$ requires M, 473.2566.

20(*S*)-Methoxy-7α-ethyl-6,14-endoethenotetrahydrothebaine (8b): procedure A; yield 34%; υ_{max} ($CHCl_3$) 1224, 1425, 1476, 1523, 1601, 2398 and 3036 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 1.07 (3H, d, J = 6.3, 20-CH_3), 1.29 (1H, dd, J = 12.6 and 7.5, 8α-H), 1.74 (1H, m, 7α-H), 1.83 (1H, m, 15- C*H*H), 1.96 (1H, m, 15-CH*H*), 2.38 (3H, s, N−CH_3), 2.34−2.55 (3H, m, 10α-H and 16-CH_2), 2.72 (1H, dd, J = 12.6 and 9.6, 8β-H), 3.15−3.24 (2H, m, 9-H and 10β-H), 3.23 (3H, s, 19-OCH_3), 3.61 (3H, s, 6-OCH_3), 3.65 (1H, m, 19-H), 3.82 (3H, s, 3-OCH_3), 4.52 (1H, br s, 5-H), 5.37 (1H, d, J = 8.7, 17-H), 5.81 (1H, d, J = 8.7, 18-H), 6.51 (1H, d, J = 8.1, 1-H) and 6.62 (1H, d, J = 8.1, 2-H); δ_C (75 MHz; $CDCl_3$) 17.53 (20-C), 22.29 (10-C), 26.40 (8-C), 33.73 (15-C), 42.58, 43.62, 45.71, 47.04, 52.68, 56.60 (3-C), 60.17 (9-C), 73.91 (19-C), 80.40, 95.71 (5-C), 113.22 (2-C), 119.04 (1-C), 127.50 (18-C), 128.45, 133.00, 134.54 (17-C), 141.76 and 148.39; m/z 397 (M^+, 67%), 382 (9), 338 (59), 222 (70), 190 (42) and 50 (100).

20(*S*)-Ethoxy-7α-ethyl-6,14-endoethenotetrahydrothebaine (8c): procedure A; yield 23%; υ_{max} ($CHCl_3$) 1235, 1421, 1476, 1527, 1601, 2402, and 3028, cm^{-1}; δ_H (300 MHz; $CDCl_3$) 1.06 (3H, t, J = 6.9, CH_2CH_3), 1.04 (3H, d, J = 6.9, 20-CH_3), 1.35 (1H, dd, J = 12.3 and 6.9, 8α-H), 1.73 (1H, m, 7α-H), 1.83 (1H, m, 15-C*H*H), 1.97 (1H, m, 15-CH*H*), 2.39 (3H, s, N−CH_3), 2.34−2.55 (3H, m, 10α-H, 16-CH_2), 2.71 (1H, dd, J = 12.6 and 9.3, 8β-H), 3.18 (1H, d, J = 4.5, 9-H), 3.22 (1H, d, J = 15, 10β-H), 3.29−3.53 (2H, m, CH_2CH_3), 3.60 (3H, s, 6-OCH_3), 3.72 (1H, m, 19-H), 3.82 (3H, s, 3-OCH_3), 4.53 (1H, s, 5-H), 5.34 (1H, d, J = 8.9, 17-H), 5.77 (1H, d, J = 8.9, 18-H), 6.51 (1H, d, J = 7.8, 1-H) and 6.61 (1H, d, J = 7.8, 2-H); δ_C (75 MHz; $CDCl_3$) 15.61 (20-C), 18.78 (CH_2CH_3), 22.30 (10-C), 26.32 (8-C), 33.69 (15-C), 42.53 (7-C), 43.62 (N−CH_3), 45.71 (16-C), 47.01, 52.48 (6-C), 56.56 (3-C), 60.19 (9-C), 64.35 (CH_2CH_3), 71.86 (19-C), 80.46, 95.61 (5-C), 113.14 (2-C), 119.02 (1-C), 127.59 (18-C), 128.46, 132.87 (17-C), 134.62, 141.76 and 148.39; m/z 411 (M^+, 100%), 338 (81), 229 (61), 190 (55), 162 (46) and 72 (62).

20(*S*)-Benzyloxy-7α-ethyl-6,14-endoethenotetrahydrothebaine (8d): procedure A; yield 27%; δ_H (300 MHz; $CDCl_3$) 1.10 (3H, d, J = 6.6, 20 CH_3), 1.46 (1H, dd, J = 12.3 and 7.2), 1.80 (1H, m, 7α-H), 1.83 (1H, m, 15-CH*H*), 1.97 (1H, m, 15-C*H*H), 2.38 (3H, s, NCH_3), 2.35−2.55 (3H, m, 10α-H and 16-CH_2), 2.74 (1H, dd, J = 12.3 and 9.0, 8β-H), 3.18 (1H, d, J = 2.1, 9-H), 3.22 (1H, d, J = 13.5, 10β-H), 3.57 (3H, m, 6-OCH_3), 3.81 (3H, s, 3-OCH_3), 3.91 (1H, m, 19-H), 4.45 (2H, dd, J = 28.5 and 12.0, CH_2Ph), 4.54 (1H, br s, 5-H), 5.38 (1H,

d, J = 8.7, 17-H), 5.83 (1H, d, J = 8.7, 18-H), 6.51 (1H, d, J = 8.1, 1-H), 6.61 (1H, d, J = 8.1, 2-H) and 7.19−7.28 (5H, m, Ar−H); δ_C (75 MHz; $CDCl_3$) 14.19 (20-C), 18.47 (10-C), 22.30 (8-C), 26.16 (15-C), 33.71, 42.70 (7-C), 43.59 (NCH_3), 45.71 (16-C), 47.09, 52.57 (6-C), 56.54 (3-C), 60.19 (9-C), 70.73 (CH_2Ph), 71.58 (19-C), 80.37, 95.72 (5-C), 113.15 (2-C), 119.05 (1-C), 127.02 (18-C), 127.54, 127.66, 127.99, 128.44, 133.19 (17-C), 134.59, 139.37, 141.76 and 148.39; *m*/*z* 473 (M^+, 100%), 338 (83), 298 (64), 229 (36), 190 (39), 162 (38) and 91 (100). Found M^+, 473.2572; $C_{30}H_{35}NO_4$ requires M, 473.25566.

20(*R*)-Methoxy-7α-ethyl-6,14-endoethenotetrahydrooripavine (5b): procedure B; yield 65%; υ_{max} 1015, 1226, 1426, 1476, 1524, 1601, 2398 and 3026 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.90 (3H, d, J = 6.3, 20-CH_3), 1.13 (1H, dd, J = 13.2 and 6.9, 8α-H), 1.83 (1H, m, 15-C*H*H), 2.00 (1H, m, 15-CH*H*), 2.36 (3H, s, NCH_3), 2.32−2.54 (4H, m, 7α-H, 10α-H and 16-CH_2), 2.72 (1H, dd, J = 13.2 and 9.3, 8β-H), 3.19 (2H, m, 9-H and 10β-H), 3.32 (3H, s, 19-OCH_3), 3.58 (3H, s, 6-OCH_3), 3.61 (1H, m, 19-H), 4.63 (1H, br s, 5-H), 5.37 (1H, d, J = 8.4, 17-H), 5.66 (1H, d, J = 8.4, 18-H), 6.45 (1H, d, J = 7.8, 1-H) and 6.62 (1H, d, J = 7.8, 2-H); δ_C (75 MHz; $CDCl_3$) 15.96 (20-C), 22.40 (10-C), 26.13 (8-C), 33.70 (15-C), 36.86, 38.19, 42.82, 43.51, 45.62 (16-C), 47.58, 52.23, 56.07, 60.15, 76.25 (19-C), 80.47, 94.91 (5-C), 116.28 (2-C), 119.57 (1-C), 127.45 (18-C), 134.21, 134.90 (17-C), 137.89 and 146.91; *m*/*z* 383 (M^+, 100%), 324 (58), 222 (51), 215 (87), 162 (48) and 59 (75). Found M^+, 383.2090; $C_{23}H_{29}NO_4$ requires M, 383.2097. Anal. ($C_{23}H_{29}NO_4$·$(CO_2H)_2$·1.5H_2O) CHN.

20(*R*)-Ethoxy-7α-ethyl-6,14-endoethenotetrahydrooripavine (5c): procedure B; yield 64%; υ_{max} ($CHCl_3$) 1210, 1423, 1476, 1523, 1601, 2401 and 3028 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.91 (3H, d, J = 6.0, 20-CH_3), 1.17 (4H, m, CH_2CH_3 and 8α-H), 1.84 (1H, m, 15-C*H*H), 2.01 (1H, m, 15-CH*H*), 2.37 (3H, s, N−CH_3), 2.32−2.55 (4H, m, 7α-H, 10α-H and 16-CH_2), 2.63 (1H, d, J = 9.3, OH), 2.71 (1H, dd, J = 12.9 and 9.3, 8β-H), 3.16 (1H, d, J = 3.6, 9-H), 3.20 (1H, d, J = 15.6, 10β-H), 3.40−3.55 (2H, m, C$H_2$$CH_3$), 3.57 (3H, s, 6-$OCH_3$), 3.67 (1H, m, 19-H), 4.65 (1H, br s, 5-H), 5.36 (1H, d, J = 8.4, 17-H), 5.64 (1H, d, J = 8.4, 18-H), 6.47 (1H, d, J = 7.8, 1-H) and 6.60 (1H, d, m, J = 7.8, 2-H); δ_C (75 MHz; $CDCl_3$) 15.73 (CH_2CH_3), 16.71 (20-C), 22.36 (10-C), 26.23 (8-C), 33.58 (15-C), 38.29, 42.77 (7-C), 43.48 (N−CH_3), 45.60 (CH_2CH_3), 47.53, 52.02 (6-C), 60.10 (9-C), 63.59 (16-C), 74.21 (19-C), 80.51, 94.66 (5-C), 116.10 (2-C), 119.64 (1-C), 127.52 (18-C), 127.77, 134.24, 134.79 (17-C), 137.40 and 146.72; *m*/*z* 397 (M^+, 100%), 382 (12), 324 (72), 236 (52), 215 (93), 190 (36), 162 (49) and 73 (64). Anal. ($C_{24}H_{31}NO_4$·HCl·0.5H_2O) CHN.

20(*R*)-Benzyloxy-7α-ethyl-6,14-endoethenotetrahydrooripavine (5d): procedure B; yield 60%; υ_{max} ($CHCl_3$) 1193, 1422, 1476, 1518, 1528, 1601, 2400 and 3020 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.96 (3H, d, J = 6.3, 20-CH_3), 1.24 (1H, dd, J = 13.2 and 6.6, 8α-H), 1.83 (1H, m, 15-C*H*H), 2.01 (1H, m, 15-CH*H*), 2.36−2.55 (3H, s, NCH_3), 2.32 (4H, m, 7α-H, 10α-H and 16-CH_2), 2.77 (1H, dd, J = 13.2 and 9.3, 8β-H), 3.17 (1H, d, J = 6.0, 9-H), 3.20 (1H, d, J = 12.6, 10β-H), 3.44 (3H, s, 6-OCH_3), 3.78 (1H, m, 19-H), 4.52 (2H, s, CH_2Ph), 4.62 (1H, br s, 5-H), 5.36 (1H, d, J = 9.0, 17-H), 5.61 (1H, d, J = 9.0, 18-H), 6.47 (1H, d, J = 8.1, 1-H), 6.59 (1H, d, J = 8.1, 2-H) and 7.11−7.36 (5H, m, Ar−H); δ_H (75 MHz; $CDCl_3$) 16.52 (20-C), 22.35 (10-C), 26.21 (8-C), 33.52 (15-C), 38.28 (7-C), 42.77, 42.43 (NCH_3), 45.57 (16-C), 47.49, 51.67 (5-C), 60.07 (9-C), 70.24 (CH_2Ph), 73.94 (19-C), 80.47, 94.20 (5-C), 116.27 (2-C), 119.70 (1-C), 127.34 (18-C), 127.53, 127.69, 128.26, 134.19 (17-C), 134.70, 134.88, 137.45, 139.04 and 146.71; *m*/*z* 459 (M^+, 58%) 324 (36), 215 (42), 162 (250) and 91 (100). Found M^+, 459.2404; $C_{29}H_{33}NO_4$ requires M, 459.2410. Anal. ($C_{29}H_{33}NO_4$·$(CO_2H)_2$·0.5H_2O) CHN.

20(*S*)-Methoxy-7α-ethyl-6,14-endoethenotetrahydrooripavine (7b): procedure B; yield 53%; δ_H (300 MHz; $CDCl_3$) 1.05 (3H, d, J = 6.3, 20-CH_3), 1.28 (1H, dd, J = 12.3 and 7.2, 8α-H), 1.71−1.85 (2H, m, 15-C*H*H and 7α-H), 1.96 (1H, m, 15-CH*H*), 2.39 (3H, s, NCH_3), 2.33−2.55 (3H, m, 10α-H and 16-CH_2), 2.71 (1H, m, 8β-H), 3.16−3.25 (2H, m, 9-H and 10β-H), 3.22 (3H, s, 19-OCH_3), 3.59 (3H, s, 6-OCH_3), 3.63 (1H, m, 19-H), 4.52 (1H, br s, 5-H), 5.35 (1H, d, J = 8.7, 17-H), 5.77 (1H, d, J = 7.8, 18-H), 6.44 (1H, d, J = 8.1, 1-H) and 6.62 (1H, d, J = 8.1, 2-H); δ_C (75 MHz; $CDCl_3$) 17.42 (20-C), 22.36 (10-C), 26.38 (8-C), 33.59 (15-C), 36.86, 42.44, 42.63, 43.58, 45.76, 47.27, 52.52 (6-C), 56.53, 60.20 (9-C), 73.93 (19-C), 80.50, 95.52 (5-C), 116.17 (1-C), 119.39 (2-C), 127.35 (18-C), 133.09, 134.19 (17-C), 137.98 and 147.04; *m*/*z* 383 (M^+, 100%), 324 (61), 215 (86), 162 (38) and 59 (64). Found M^+, 383.2092; $C_{23}H_{29}NO_4$ requires M, 383.2097. Anal. ($C_{23}H_{29}NO_4$·$(CO_2H)_2$·H_2O) CHN.

20(*S*)-Ethoxy-7α-ethyl-6,14-endoethenotetrahydrooripavine (7c): procedure B; yield 59%; ν_{max} ($CHCl_3$) 1223, 1422, 1476, 1521, 1601, 2399, and 3034 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 1.05 (3H, d, J = 5.7, 20-CH_3), 1.05 (3H, t, J = 7.2, CH_2CH_3), 1.35 (1H, dd, J = 12.3 and 7.2, 8α-H), 1.74 (1H, m, 7α-H), 1.84 (1H, m, 15-C*H*H), 1.97, (1H, m, 15-CH*H*), 2.39 (3H, s, N−CH_3), 2.56−2.33 (3H, m, 10α-H and 16-CH_2), 2.64 (1H, d, J = 9.3, OH), 2.67 (1H, m, 8β-H), 3.18 (1H, d, J = 4.8, 9-H), 3.22 (1H, d, J = 7.2, 10β-H), 3.28−3.53 (2H, m, CH_2CH_3), 3.57 (3H, s, 6-OCH_3), 3.69 (1H, m, 19-H), 4.55 (1H, br s, 5-H), 5.32 (1H, d, J = 8.7, 17-H), 5.71 (1H, d, J = 8.7, 18-H), 6.47 (1H, d, J = 8.1, 1-H) and 6.59 (1H, d, J = 8.1, 2-H); δ_C (75 MHz; $CDCl_3$) 15.60 (CH_2CH_3), 18.64 (20-C), 22.40 (10-C), 26.31 (8-C), 33.52 (15-C), 42.19 (7-C), 42.61, 43.56 (N−CH_3), 45.74 (16-C), 47.29, 52.17 (6-C), 60.18 (9-H), 64.29 (CH_2CH_3), 71.91 (19-H), 80.59, 95.39 (5-C), 116.04 (2-C), 119.58 (1-C), 127.29 (18-C), 127.90, 132.98, 134.35 (17-C), 137.41 and 146.90; *m*/*z* 397 (M^+, 100%), 382 (12), 335 (38), 324 (74), 236 (58), 215 (99), 190 (54), 162 (48) and 73 (65). Anal. ($C_{24}H_{31}NO_4$·HCl·0.5H_2O) CHN.

20(*S*)-Benzyloxy-7α-ethyl-6,14-endoethenotetrahydrooripavine (7d): procedure B; yield 66%; υ_{max} 1222, 1421, 1476, 1520, 1601, 2398 and 3032 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 1.08 (3H, d, J = 6.3, 20-CH_3), 1.46 (1H, dd, J = 12.3 and 7.2, 8α-H), 1.75−1.86 (2H, m, 15-C*H*H and 7α-H), 1.97 (1H, m, 15-CH*H*), 2.39 (3H, s, NCH_3), 2.34−2.56 (3H, m, 10α-H and 16-CH_2), 2.73 (1H, dd, J = 12.3 and 9.3, 8β-H), 3.20 (2H, m, 10β-H and 9-H), 3.54 (3H, s, 6-OCH_3), 3.87 (1H, m, 19-H), 4.45 (2H, dd, J = 29.4 and 12.0, CH_2Ph), 4.55 (1H, br s, 5-H), 5.36 (1H, d, J = 8.7, 17-H), 5.77 (1H, d, J = 8.7, 18-H), 6.47 (1H, d, J = 8.1, 1-H), 6.59 (1H, d, J = 8.1, 2-H) and 7.20−7.27 (5H, m, Ar−H); δ_C (75 MHz; $CDCl_3$) 18.34 (20-C), 22.41 (10-C), 26.16 (8-C), 33.50 (15-C), 42.32 (7-C), 42.67, 43.53 (NCH_3), 45.73 (16-C), 47.36, 52.20 (6-C), 60.17 (9-C), 70.66 (CH_2Ph), 71.60 (19-C), 80.52, 95.33 (5-C), 116.14 (2-C), 119.62 (1-C), 127.05 (18-C), 127.40, 127.47, 127.83, 128.01, 133.28 (17-C), 134.30, 137.45, 139.29 and 146.90; *m*/*z* 459 (M^+, 71%), 324 (41), 298 (23), 215 (61), 190 (20), 162 (25) and 91 (100). Found M^+, 459.2397; $C_{29}H_{33}NO_4$ requires M, 459.2410. Anal. ($C_{29}H_{33}NO_4$·$(CO_2H)_2$·0.75H_2O) CHN.

Pharmacological Assays. Binding: Receptor binding studies were conducted on human opioid receptors transfected into Chinese hamster ovary (CHO) cells. The membrane was prepared in 50 mM Tris buffer at pH 7.7. Cells were harvested by scraping the plates with a rubber policeman and then centrifuged at 500*g* for 10 min. The cell pellet was suspended in Tris buffer, homogenized in a Polytron homogenizer, and centrifuged at 20000*g* for another 20 min and finally suspended in a small amount of buffer to determine protein content. Assays were conducted using [^{3}H]DAMGO, [^{3}H]Cl-DPDPE, and [^{3}H]U69,593 to bind to μ-, δ-, and κ-receptors, respectively. Cell membranes were incubated with the appropriate radioligand and unlabeled drug in a total volume of 200 μL in 96-well plates, usually for 1 h at 25 °C. After the incubation, samples are filtered through glass fiber filters using a Tomtec cell harvester. Filters were dried overnight before radioactivity levels were determined. Nonspecific binding was determined by using 1.0 μM of the unlabeled counterpart of each radioligand. K_i values were calculated using the Cheng−Prusoff transformation.

[^{35}S]GTPγS binding for functional activity: Membranes were prepared as above (but 20 mM HEPES, 10 mM $MgCl_2$ and 100 mM NaCl at pH 7.4 substituted for Tris buffer) and incubated with [^{35}S]GTPγS (50 pM), GDP (usually 10 μM), and the desired compound, in a total volume of 200 mL for 60 min at 25 °C. Samples are filtered over glass fiber filters and

counted as described for the binding assays. A dose−response curve with a prototypical full agonist (DAMGO, Cl-DPDPE, and U69593 for μ-, δ-, and κ-receptors, respectively) was conducted in each experiment to identify full and partial agonist compounds.

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