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Probes for narcotic receptor mediated phenomena. 43. Synthesis of the *ortho*-a and *para*-a, and improved synthesis and optical resolution of the *ortho*-b and *para*-b oxide-bridged phenylmorphans: Compounds with moderate to low opioid-receptor affinity

Feng Li [a,†], John E. Folk [a,✠], Kejun Cheng [a], Muneaki Kurimura [a,‡], Jason A. Deck [a,§], Jeffrey R. Deschamps [b,c], Richard B. Rothman [d], Christina M. Dersch [d], Arthur E. Jacobson [a], Kenner C. Rice [a,*]

[a] *Drug Design and Synthesis Section, Chemical Biology Research Branch, National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Department of Health and Human Services, 5625 Fishers Lane, Room 4N03, Bethesda, MD 20892-9415, USA*
[b] *Center for Biomolecular Science and Engineering, Naval Research Laboratory, Washington DC 20375, USA*
[c] *Center for Molecular Modeling, Division of Computational Bioscience, CIT, National Institutes of Health, DHHS, Bethesda, MD 20892, USA*
[d] *Clinical Psychopharmacology Section, Chemical Biology Research Branch, National Institute on Drug Abuse, Addiction Research Center, National Institutes of Health, Department of Health and Human Services, Baltimore, MD 21224, USA*

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ABSTRACT

N-Phenethyl-substituted *ortho*-a and *para*-a oxide-bridged phenylmorphans have been obtained through an improved synthesis and their binding affinity examined at the various opioid receptors. Although the *N*-phenethyl substituent showed much greater affinity for μ- and κ-opioid receptors than their *N*-methyl relatives (e.g., K_i = 167 nM and 171 nM at μ- and κ-receptors vs >2800 and 7500 nM for the *N*-methyl *ortho*-a oxide-bridged phenylmorphan), the a-isomers were not examined further because of their relatively low affinity. The *N*-phenethyl substituted *ortho*-b and *para*-b oxide-bridged phenylmorphans were also synthesized and their enantiomers were obtained using supercritical fluid chromatography. Of the four enantiomers, only the (+)-*ortho*-b isomer had moderate affinity for μ- and κ-receptors (K_i = 49 and 42 nM, respectively, and it was found to also have moderate μ- and κ-opioid antagonist activity in the [^{35}S]GTP-γ-S assay (K_e = 31 and 26 nM).

1. Introduction

We have synthesized the structurally rigid oxide-bridged phenylmorphans in order to gain further insight into the receptor-active conformation of the various opioid receptor subtypes, and have been correlating this information with their agonist, antagonist, or inverse-agonist activity. The synthesis of the racemic *ortho*-a and *ortho*-b, and *para*-a and *para*-b, *N*-methyl substituted oxide-bridged phenylmorphans (*rac*-(4*R*,6a*R*,11b*R*)-2,3,4,5,6,6a-hexahydro-3-methyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocin-8-ol and 10-ol and *rac*-(4*R*,6a*S*,11b*R*)-2,3,4,5,6,6a-hexahydro-3-methyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-8-ol and 10-ol, Figure 1)[1–4] was previously accomplished and provided four of the twelve possible racemic *ortho*- and *para*-hydroxyphenyl substituted a through f oxide-bridged phenylmorphans (Fig. 1). The a-isomers were among the earliest compounds prepared[2,3] and, at that time, we did not realize that an *N*-methyl substituted compound was unlikely to interact well with opioid receptors. An insufficient amount of the compound was initially prepared and this did not allow us to pursue conversion to other N-substituents. The b-isomers were prepared last[4] because of the difficulty of synthesizing the strained 5,6-*trans*-fused ring junction that must be formed to obtain them. We have now obtained the *N*-phenethyl-substituted *ortho*-a and *para*-a-isomers, have improved the synthesis of the *N*-phenethyl substituted *ortho* and *para*-b-isomers, optically resolved the b-isomers, and examined the binding affinities as well as the efficacies of the compounds with higher affinity. An *N*-phenethyl substituent usually, but not always,[5] increases the affinity of benzomorphan or phenylmorphan-like compounds for opioid receptors,[4,6] as well as their activity as either agonists or antagonists.[4] We have previously reported that the

* Corresponding author. Tel.: +1 301 496 1856; fax: +1 301 402 0589.
E-mail addresses: kr21f@nih.gov, ricek@bdg8.niddk.nih.gov (K.C. Rice).
† Current address: Department of Pharmacology, Toxicology and Therapeutics, University of Kansas Medical Center, Kansas City, KS 66160, USA.
‡ Current address: Qs' Research Institute, Otsuka Pharmaceutical Co., Ltd, 463-10 Kagasuno Kawauchi-cho, Tokushima 771-0192, Japan.
§ Current address: Division of Food Contact Notifications, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition, US Food and Drug Administration, 5100 Paint Branch Parkway, College Park, MD 20740, USA.
✠ Deceased 12/27/10.

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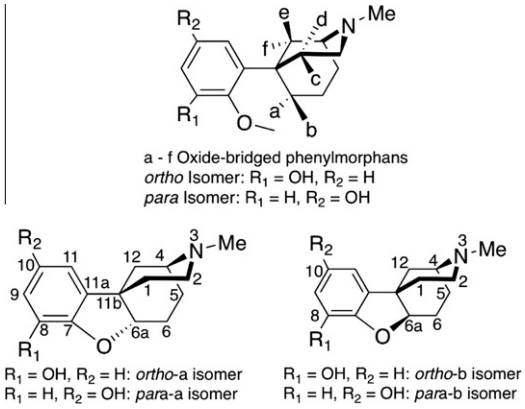


Figure 1. General structure of the a through f oxide-bridged phenylmorphans, and the structures of the *ortho*- and *para*-a and *ortho*- and *para*-b oxide-bridged phenylmorphans.

racemic *N*-phenethyl substituted *ortho*-b isomer exhibited moderate affinity for κ-opioid receptors (K_i = 26 nM),[4] and less affinity for μ-opioid receptors. Since it is theoretically possible for one enantiomer to retain all of the κ-opioid receptor affinity and the other the μ-affinity, we examined the enantiomers of both the *ortho*-b and *para*-b isomers to see if there was enhanced receptor-selectivity.

Oxide-bridged phenylmorphans are structurally rigid molecules and those that interact with opioid receptors probably do so by presenting a specific spatial pattern in the binding pocket of the receptor. The receptor binding pocket is likely to allow only a limited number of orientations for these molecules and the structural rigidity of the oxide-bridged phenylmorphans severely restricts that number. The oxide-bridged phenylmorphans cannot change their conformation to enable or facilitate receptor interaction. In our work on the synthesis of all of the a through f-racemates[1–4,7–13] we began with the view that if an oxide-bridged phenylmorphan had high affinity for an opioid receptor and acted as an opioid agonist or antagonist we would separate the enantiomers, determine absolute configuration through X-ray crystallographic structure analysis and, via quantum chemical studies,[13] examine the spatial characteristics of a molecule needed for their activity. In order to explore the effects of the *ortho*-a and *para*-a compounds on opioid receptors, the two racemic *N*-methyl analogs were re-synthesized and a new N-substituent, the *N*-phenethyl, was introduced and evaluated in both. Similarly, to examine the enantiomeric b-isomers, we resynthesized the racemate, improving its synthesis, and separated the enantiomers using supercritical fluid chromatography.[14]

2. Chemistry

The synthesis of the racemic *N*-methyl substituted *ortho*-a and *para*-a isomers was carried out essentially as previously reported.[2,3] The spectral properties of intermediates were found to be similar to those in the literature and those of the *N*-methyl substituted *ortho*-a and *para*-a isomers were identical to the previously prepared compounds.[2,3] To prepare the *N*-phenethyl analogs, *rac*-(4*R*,6a*R*,11b*R*)-3-methyl-2,3,4,5,6,6a-hexahydro-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocin-8-ol (**1**) was heated in acetic anhydride to give acetate (**2**, Scheme 1). The acetate was reacted with ethylchloroformate under basic conditions to give the ethylcarbamate (**3**), and the secondary amine **4** was obtained from **3** by refluxing in H_2SO_4 overnight. Reaction with phenethylbromide in DMF under basic conditions gave the desired *ortho*-a compound, *rac*-(4*R*,6a*R*,11b*R*)-2,3,4,5,6,6a-hexahydro-3-phenethyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocin-8-ol (**5**). A similar series of reactions in the *para*-a series (Scheme 1) gave *rac*-(4*R*,6a*R*,11b*R*)-2,3,4,5,6,6a-hexahydro-3-phenethyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocin-10-ol (**10**).

The synthesis of the racemic *ortho* and *para*-b series essentially followed the reported route[4] except for the modification of a few procedures to improve the yield. *rac*-(1*R*,5*R*,6*S*)-5-(2-Fluoro-5-nitrophenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-6-ol (**13**) was originally prepared from *rac*-(1*R*,5*R*,6*S*)-(5-(2-fluorophenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-6-ol (**11**) in 62% yield on a 0.8 mmol scale without isolation of the intermediate acetate (**12**).[4] However, when the reaction was carried out on a larger scale (~25 mmol) needed for optical resolution, the yields were lower (<50%). TLC indicated that all of the starting material had been used and a significant amount of a lower R_f compound was obtained. This procedure was modified to provide **13** in two steps (Scheme 2). Using the path shown in Scheme 2, compound **11**, prepared in eight steps from *rac*-(*S*)-2-(2-(dimethylamino)ethyl)-2-(2-fluorophenyl)cyclohexanone,[11] was acetylated using Ac_2O and AcOH and nitrated with fuming nitric acid to give *rac*-(1*R*,5*S*,6*R*)-5-(2-fluorophenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-6-yl acetate (**12**) in 92–96% yields over several runs. The acetyl moiety was removed with 2 N HCl to give the azabicyclo[3.3.1]nonan-6-ol (**13**) in 93–96% yields.

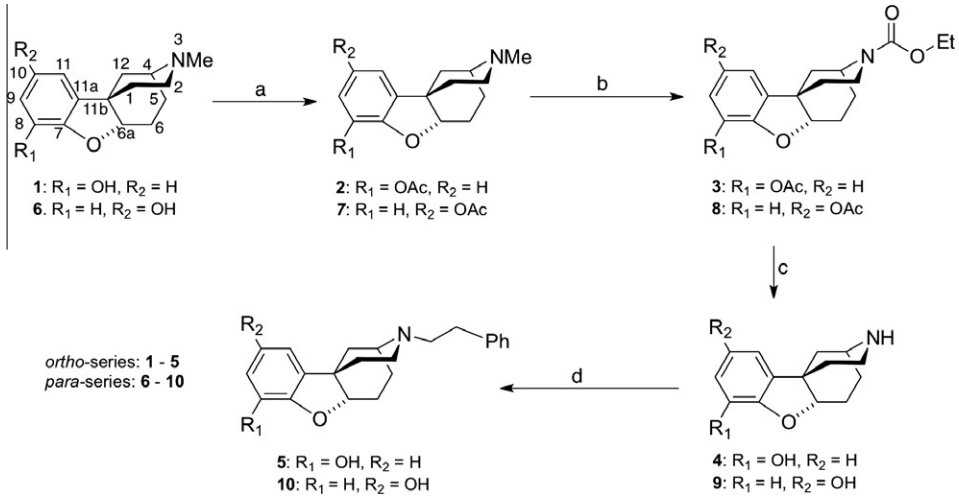
Conversion to the desired *N*-phenethyl substituent required an N-demethylation step. In the reported route,[4] **14** was converted to **15** using 1-chloroethyl chlorformate (56% yield and 17% recovery of starting material). Similarly, 1-chloroethyl chlorformate was used to *N*-demethylate **17** to **18** in 52% yield with a 42% recovery of starting material after chromatography. To improve the procedure, the *N*-methyl compound **14** was first reacted with BrCN in acetonitrile, then refluxed in glacial acetic acid and 2 N HCl to give **15** quantitatively (Scheme 2). Compound **15** was used to obtain the *N*-phenethyl substituted *para*-b compound **16** in three additional steps.[4] The BrCN procedure was also used to convert **17** to **18** in 95% yield (Scheme 2), and **18** was used to obtain the *N*-phenethyl substituted *ortho*-b compound **19** in three further well-known steps.[4]

The racemic compounds **16** and **19** (Scheme 3) were optically resolved by supercritical fluid chromatography[14] to give the (+)- and (−)-enantiomers of the *N*-phenethyl substituted *para*-b racemate (**16a** and **16b**, respectively) and the (+)- and (−)-enantiomers of the *N*-phenethyl substituted *ortho*-b racemate (**19a** and **19b**, respectively). X-ray crystallographic analysis determined the stereochemistry of **16b**, and **19b** the levo enantiomers ((4*S*,6a*R*,11b*S*)-2,3,4,5,6,6a-hexahydro-3-phenethyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-10-ol and ((4*S*,6a*R*,11b*S*)-2,3,4,5,6,6a-hexahydro-3-phenethyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-8-ol, respectively (Fig. 2)).

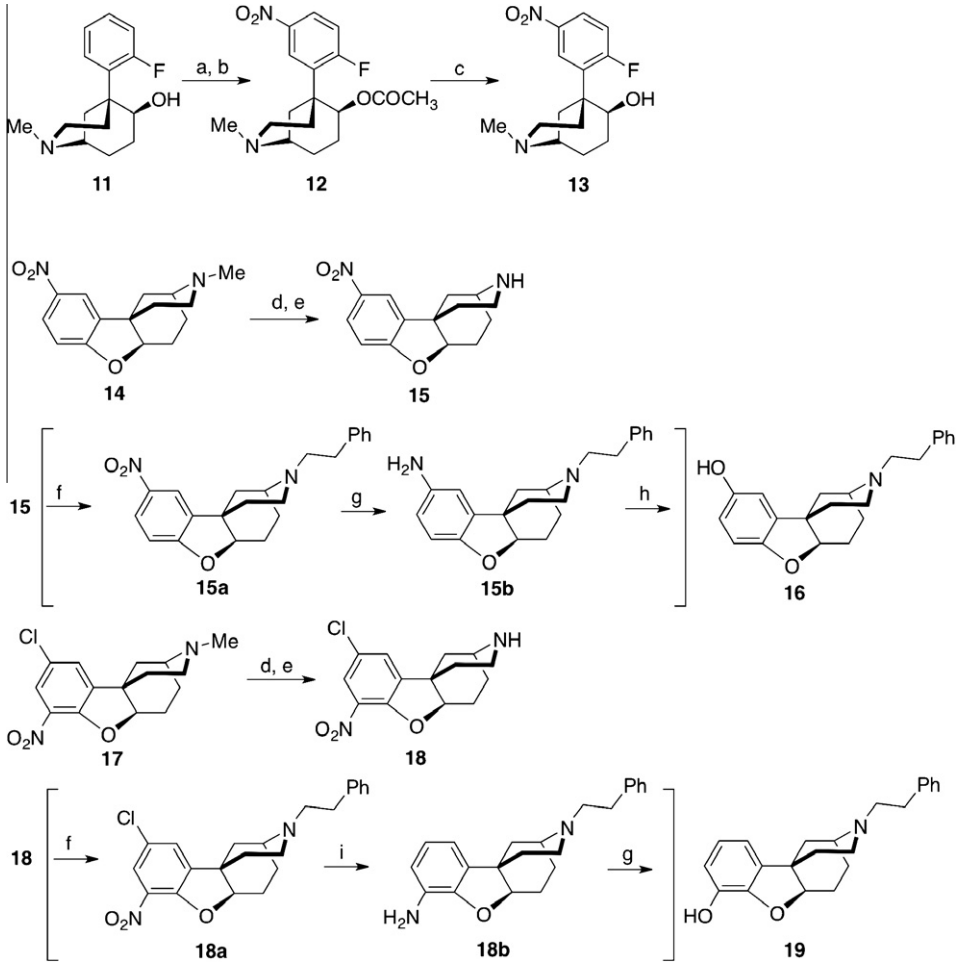
3. Results and discussion

The racemic *N*-methyl analogs in the *ortho*- and *para*-a oxide-bridged phenylmorphan series (**1** and **6**, respectively) did not have much affinity at any of the opioid receptors ($K_{i>2800}$ nM at μ, Table 1). The racemic *N*-phenethyl-substituted *ortho*-a analog **5** (Table 1) had the same low affinity at both μ- and κ-receptors (K_i = 170 nM), and the *N*-phenethyl-substituted *para*-a analog **10** had higher affinity for κ-receptors (K_i = ~100 nM) than for μ-receptors (K_i = ~500 nM). The *N*-phenethyl-substituted *ortho*-a and *para*-a isomers were weak or moderately potent κ-antagonists (K_e = 163 and 46 nM, respectively), and weak μ-antagonists (Table 2, K_e = 274, and 123 nM, respectively, Table 2). Although the *N*-phenethyl analogs had markedly higher affinity than the comparable *N*-methyl compounds (Table 1), the racemic a-isomers did not have sufficient affinity at any opioid receptor to warrant separation of their enantiomers or further pharmacological evaluation.

Interestingly, the *N*-phenethyl substituted chiral *ortho*-b enantiomer **19b** lost the racemate's selectivity for κ-opioid receptors

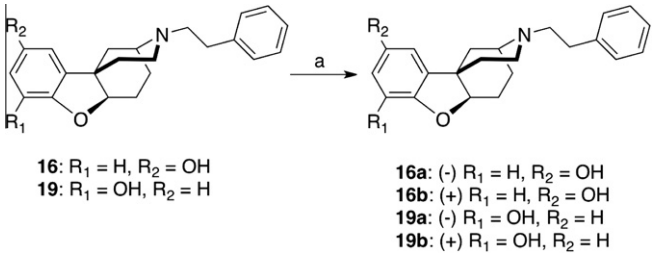


Scheme 1. Synthesis of racemic *N*-phenethyl *ortho*- and *para*-a isomers. Reagents and conditions: (a) Ac_2O, 60 °C, 1 h, 92–94%; (b) EtOCOCl, K_2CO_3, $ClCH_2CH_2Cl$, overnight, 92–93%; (c) H_2SO_4, overnight, 80–81%; (d) phenethyl bromide, DMF, 90 °C, 3 h, 68–70%.



Scheme 2. Improved steps in synthesis of *ortho* and *para*-b isomers. Reagents and conditions: (a) Ac_2O, AcOH, 90 °C; (b) fuming HNO_3, 92–96% from **11**; (c) 2 N HCl, reflux 3 h, 5 N NaOH, 93–96%; (d) BrCN, K_2CO_3, acetonitrile, reflux 2H; (e) HCl, AcOH, reflux 18 h; (f) $Ph(CH_2)_2Br$, NaI, CH_3CN, reflux; (g) 10% Pd-C, EtOH; (h) $NaNO_2$, $Cu(NO_3)_2{\cdot}2.5H_2O$, Cu_2O, 35% H_2SO_4; (i) 10% Pd-C, HCO_2NH_4, EtOH. For experimental procedures used to prepare **15a**, **15b**, **18a**, and **18b**, see Kurimura et al.[4]

(Table 1). Kurimura et al.,[4] reported that the *N*-phenethyl substituted *ortho*-b racemate was seven-fold selective for κ over μ-receptors. This chiral *ortho*-b enantiomer **19b** had considerably higher affinity at μ-receptors than the racemate (K_i = 49 nM (Table 1) vs 190 nM[4] for the racemate) and about the same, or perhaps a little less affinity than the racemate at κ-receptors (K_i = 42 nM (Table 1) vs 26 nM[4] for the racemate). The enantiomer **19b** was found to be both a moderately potent κ- and μ-antagonist (K_e = 31 and 26 nM, respectively, Table 2) in the [^{35}S]GTP-γ-S assay.



Scheme 3. Optical resolution of the *N*-phenethyl substituted *ortho*- and *para*-b racemates. (a) Supercritical fluid chromatography, CO_2–MeOH/2-propanol (1:1) with 1% propan-2-amine.

The opioid receptor affinity and the agonist and antagonist activity of the rigid *N*-phenethyl substituted *ortho*- and *para*-a through -f oxide-bridged phenylmorphans is likely to be related to their specific 3-dimensional molecular shape and the different interatomic distances between their heteroatoms, and their aromatic ring, with sets of amino acids in a receptor binding pocket. In our work with the phenylmorphans, we have found that only the (−)-*para*-e isomer had morphine-like agonist activity in vivo.[13] The (−)-*ortho*-f isomer was four times as potent as naloxone as a μ-antagonist,[13] and the *rac ortho*-c isomer had much higher affinity for the μ-receptor than the (−)-*ortho*-f isomer, and was a very potent μ-antagonist.[16] The (+)-*ortho*-b isomer was a considerably weaker antagonist (Table 2). Future research on the oxide-bridged phenylmorphans will focus on the optical resolution of the *rac ortho*-c isomer, as well as the use of different N-substituents that could provide further data for our probe of the opioid receptor from the viewpoint of the ligand.

4. Experimental section

4.1. Chemistry

All melting points were determined on a Thomas–Hoover melting-point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR, 300 or 500 MHz) and carbon nuclear magnetic resonance (^{13}C NMR, 75 or 125 MHz) spectra were recorded on a Varian Gemini-300 or a Bruker DMX500 wide-bore spectrometer ((proton frequency 500.13 MHz) running XWINNMR v3.1, carbon 125.757) in $CDCl_3$ (unless otherwise noted) with the values given in ppm (TMS as internal standard) and *J* (Hz) assignments of ^{1}H resonance coupling. The high resolution electrospray ionization (ESI) mass spectra were obtained on a Waters LCT Premier time-of-flight (TOF) mass spectrometer. Thin-layer chromatography (TLC) was performed on 0.25 mm Analtech GHLF silica gel. Flash column chromatography was performed with Bodman silica gel LC 60 A. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA, or Micro-Analytics, Inc, Wilmington, DE. Optical resolution of **16** and **19** was carried out by Avery Discovery Services, Worcester, MA, using supercritical fluid chromatography.

4.1.1. *rac*-(4*R*,6a*R*,11b*R*)-3-Methyl-2,3,4,5,6,6a-hexahydro-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-8-acetate (2)

A mixture of acetic anhydride (1.0 mL) and the phenol **1** (60 mg, 0.25 mmol) was heated at 80 °C for 1 h. After removal of the solvent, the residue was diluted with $CHCl_3$ (15 mL) and washed with NH_4OH, dried over $MgSO_4$. The solvent was evaporated to provide **2** (66 mg, 92%) as a light yellow oil. This was used directly in the next step. HRMS $[M+H]^+$ calcd for $C_{17}H_{22}NO_3$: 288.1600. Found: 288.1602

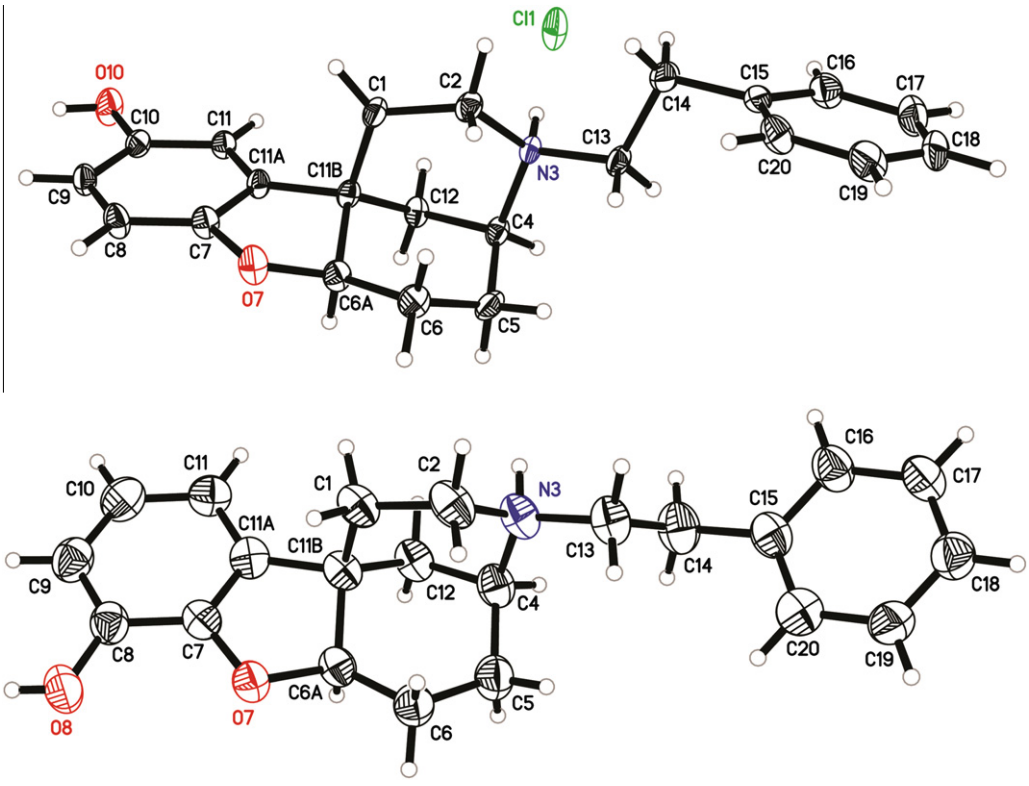
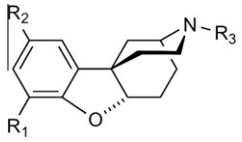


Figure 2. X-ray crystallographic structures of (−)-(4*S*,6a*R*,11b*S*)-2,3,4,5,6,6a-hexahydro-3-phenethyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-10-ol hydrochloride (top) and -8-ol hydrobromide (bottom) (*N*-phenethyl *para*-b isomer, **16b**, and *N*-phenethyl *ortho*-b isomer **19a**).

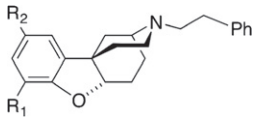
Table 1
[^{3}H] opioid receptor binding data[a] for *ortho*-a and *para*-a isomers **1**, **5**, **6**, and **10** and for *ortho*-b and *para*-b enantiomers **16a**, **16b**, **19a**, and **19b**



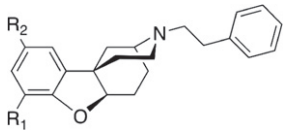
Compd	R_1	R_2	R_3	K_i (nM)		
				μ	δ	κ
rac **1**	OH	H	Me	>2800	>4900	7500 ± 1029
rac **5**	OH	H	PhEt	167 ± 14	>4900	171 ± 14
rac **6**	H	OH	Me	>2800	>4900	>8600
rac **10**	H	OH	PhEt	486 ± 39	>4900	98 ± 5
16a: (+)-4*R*,6a*S*,11b*R*	H	OH	PhEt	250 ± 28	>5,000	199 ± 10
16b: (−)-4*S*,6a*R*,11b*S*	H	OH	PhEt	352 ± 28	>5,000	102 ± 3
19a: (−)-4*S*,6a*R*,11b*S*	OH	H	PhEt	384 ± 38	>5,000	367 ± 19
19b: (+)-4*R*,6a*S*,11b*R*	OH	H	PhEt	49 ± 3	>5,000	42 ± 1.8
Morphine				2.55 ± 0.01		

[a] Assays were conducted[15] using CHO cells, which were stably transfected and express the μ-, δ- or κ-opiate receptors, respectively. All results $n = 3$.

Table 2
Functional data ([^{35}S]GTP-γ-S) for *N*-phenethyl-substituted *ortho*-a and *para*-a racemates **5** and **10** and for *ortho*-b and *para*-b enantiomers **16a**, **16b**, **19a**, and **19b**



ortho-a and *para*-a racemates



ortho-b and *para*-b enantiomers

Compd	R_1	R_2	K_e (nM)[a]	
			μ-Antagonism	κ-Antagonism
rac **5**	OH	H	274 ± 49	163 ± 29
rac **10**	H	OH	23 ± 10	46 ± 9
16a: (+)-4*R*,6a*S*,11b*R*	H	OH	47 ± 9	100 ± 3
16b: (−)-4*S*,6a*R*,11b*S*	H	OH	227 ± 33	103 ± 17
19a: (−)-4*S*,6a*R*,11b*S*	OH	H	328 ± 67	761 ± 191
19b: (+)-4*R*,6a*S*,11b*R*	OH	H	31 ± 6	22 ± 6
Naloxone			2.3 ± 0.3	—
norBNI			—	0.11 ± 0.02

[a] [^{35}S]GTP-γ-S binding was performed using CHO hMOR cells which express the human μ-opiate receptor, and were conducted as described in Section 4.2.1. All values $n = 3$.

4.1.2. *rac*-(4*R*,6a*R*,11b*R*)-3-Ethylcarboxylate-2,3,4,5,6,6a-hexahydro-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-8-acetate (3)

To a solution of **2** (66 mg, 0.23 mmol) in $ClCH_2CH_2Cl$ (3.0 mL) were added K_2CO_3 (159 mg, 1.15 mmol) followed by ethylchloroformate (124 mg, 1.15 mmol). The reaction mixture was refluxed overnight. After filtration and removal of the solvent, the residue was diluted with H_2O, extracted with $CHCl_3$ (3 × 15 mL), and the organic layer dried over $MgSO_4$. The solvent was removed in vacuo to afford carbamate **3** (73 mg, 92%) as light yellow oil. It was used directly in the next step without further purification. HRMS $[M+H]^+$ calcd for $C_{19}H_{24}NO_5$: 346.1654. Found: 346.1662.

4.1.3. *rac*-(4*R*,6a*R*,11b*R*)-2,3,4,5,6,6a-Hexahydro-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocin-8-ol (4)

H_2SO_4 (3.0 mL, 40% w/w) was added to compound **3** (73 mg, 0.21 mmol) and the mixture was heated to reflux and stirred overnight. After cooling to 0 °C, the reaction mixture was made basic with aqueous NaOH (pH 8). The basicity was raised to pH 9 with NH_4OH and the mixture was extracted with $CHCl_3$/MeOH (10:1). The organic solution was dried over $MgSO_4$ and the solvent was removed in vacuo to give the secondary amine **4** (38 mg, 80%) as a white powder that was used directly for the next step without further purification.

4.1.4. *rac*-(4*R*,6a*R*,11b*R*)-2,3,4,5,6,6a-Hexahydro-3-phenethyl-1*H*-4,11b-methanobenzofuro [3,2-*d*]azocin-8-ol (5)

The secondary amine **4** (32 mg, 0.14 mmol) was dissolved in DMF (1.0 mL), followed by the addition of $NaHCO_3$ (13 mg, 0.154 mmol) and (2-bromoethyl)benzene (29 mg, 0.154 mmol). The reaction mixture was stirred at 90 °C for 3 h. After removal of the solvent in vacuo, the residue was diluted with $CHCl_3$ (10 mL), and the organic material was washed with H_2O (2 × 4 mL). The organic phase was dried over $MgSO_4$, evaporated and the resulting residue was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH 40:1) to afford compound **5** (32 mg, 70%) as a white powder, mp 82–83 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56–1.73 (m, 4H), 1.78–1.89 (m, 2H), 2.11–2.24 (m, 2H), 2.50 (td, J = 12.9 Hz, 3.3 Hz, 1H), 2.58–2.73 (m, 2H), 2.79–2.89 (m, 3H), 3.34 (br, 1H), 4.58 (t, J = 6.6 Hz, 1H), 6.64–6.79 (m, 3H), 7.18–7.33 (m, 5H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 16.1, 29.9, 34.5, 35.2, 36.6, 43.4, 44.2, 50.7, 56.9, 87.9, 115.0, 115.2, 121.5, 126.4, 128.7, 128.9, 140.4, 145.8, 146.0; HRMS $[M+H]^+$ calcd for $C_{22}H_{26}NO_2$: 336.1964. Found: 336.1957. Anal. Calcd for $C_{22}H_{25}NO_2 \cdot 0.85CHCl_3$: C, 62.81, H, 5.96, N, 3.21. Found: C, 62.84, H, 5.89, N, 3.28.

4.1.5. *rac*-(4*R*,6a*R*,11b*R*)-3-Methyl-2,3,4,5,6,6a-hexahydro-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-10-acetate (7)

Acetic anhydride (1.0 mL) and the phenol **6** (64 mg, 0.26 mmol) were heated at 80 °C for 1 h. After removal of the solvent, the residue was diluted with $CHCl_3$ (16 mL) and the organic solution was washed with NH_4OH and dried over $MgSO_4$. The solvent was evaporated to give **7** (70 mg, 94%) as a light yellow oil. This was used directly in the next step. HRMS $[M+H]^+$ calcd for $C_{17}H_{22}NO_3$: 288.1600. Found: 288.1500.

4.1.6. *rac*-(4*R*,6a*R*,11b*R*)-3-Carboxylate-2,3,4,5,6,6a-hexahydro-1*H*-4,11b-methanobenzofuro [3,2-*d*]azocine-10-acetate (8)

To a solution of **7** (70 mg, 0.24 mmol) in $ClCH_2CH_2Cl$ (3.0 mL) were added K_2CO_3 (168 mg, 1.21 mmol) followed by ethylchloroformate (131 mg, 1.21 mmol). The reaction mixture was refluxed overnight. After filtration and removal of solvent, the residue was diluted with H_2O, extracted with $CHCl_3$ (3 × 16 mL) and dried over $MgSO_4$. The solvent was evaporated to afford carbamate **8** (77 mg, 93%) as light yellow powder. It was used directly in the next step without further purification. HRMS $[M+H]^+$ calcd for $C_{19}H_{24}NO_5$: 346.1654. Found: 346.1638.

4.1.7. *rac*-(4*R*,6a*R*,11b*R*)-2,3,4,5,6,6a-Hexahydro-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocin-10-ol (9)

H_2SO_4 (3.0 mL, 40% w/w) was added to compound **8** (77 mg, 0.22 mmol) and the mixture was heated to reflux and stirred overnight. After cooling down to 0 °C, the reaction mixture was made basic with aq NaOH (pH 8). The basicity was raised to pH 9 using NH_4OH and the mixture was extracted with $CHCl_3$/MeOH (10:1). The organic solution was dried over $MgSO_4$ and

the solvent was evaporated in vacuo to give the secondary amine **9** (41 mg, 81%) as a white powder that was used directly in the next step without further purification.

4.1.8. *rac*-(4*R*,6a*R*,11b*R*)-2,3,4,5,6,6a-Hexahydro-3-phenylethyl-1*H*-4,11b-methanobenzofuro [3,2-*d*]azocin-10-ol (10)

The secondary amine **9** (40 mg, 0.18 mmol) was dissolved in DMF (1.0 mL), followed by addition $NaHCO_3$ (13 mg, 0.19 mmol) and (2-bromoethyl)benzene (36 mg, 0.193 mmol). The reaction mixture was stirred at 90 °C for 3 h. After removal of the solvent in vacuo, the residue was diluted with $CHCl_3$ (10 mL) and the organic material was washed with H_2O (2 × 4 mL). The organic phase was dried over $MgSO_4$ and the resulting residue was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH 40:1) to give compound **10** (40 mg, 68%) as off-white powder, mp 76–77 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.66–1.87 (m, 6H), 2.10–2.26 (m, 3H), 2.54 (t, J = 12.6 Hz, 1H), 2.69 (m, 2H), 2.84–2.93 (m, 2H), 3.39 (br, 1H), 4.84 (t, J = 8.5 Hz, 1H), 6.61–6.63 (m, 3H), 7.25–7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7, 24.6, 24.7, 25.0, 29.9, 32.3,42.1, 44.9, 52.0, 56.0, 85.9, 109.8, 111.0, 115.6, 127.1, 128.9, 192.0, 129.2, 129.5, 151.9, 152.02. HRMS $[M+H]^+$ calcd for $C_{22}H_{26}NO_2$: 336.1964; found, 336.1962. Anal. Calcd for $C_{22}H_{25}NO_2$ .0.85 $CHCl_3$: C, 62.81; H, 5.96; N, 3.21. Found: C, 62.73; H, 5.90; N, 3.22.

4.1.9. *rac*-(1*R*,5*S*,6*R*)-5-(2-Fluoro-5-nitrophenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-6-yl acetate (12)

A mixture of *rac*-(1*R*,5*R*,6*S*)-(5-(2-fluorophenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-6-ol[4] (**11**, 5.5 g, 22 mmol) and Ac_2O (3.96 mL, 42 mmol) in 14 mL of AcOH was stirred at 90 °C for 18 h. The AcOH was removed under reduced pressure and fuming HNO_3 (13 mL) was added slowly at −5 °C with stirring. The mixture was allowed to warm to room temperature over 1 h. A second portion of fuming HNO_3 (15 mL) was then added. After stirring for 2 h at room temperature, the mixture was cooled (−5 to −10 °C) and carefully basified with 5 N NaOH (ca. 100 mL), maintaining the temperature between 0 and −5 °C. The product was extracted with CH_2Cl_2 (2×) and the combined extracts were washed with H_2O and brine and dried ($MgSO_4$). Removal of solvent gave **12** (7.09 g, 96%) as light yellow crystals. A sample was recrystallized from EtOAc, mp 138.5–139 °C. ^1H NMR (500 MHz; $CDCl_3$) δ 8.21 (dd, J = 6.9, 2.7 Hz, 1H), 8.10 (td, J = 6.1, 2.7 Hz, 1H), 7.12 (dd, J = 11.8, 9.0 Hz, 1H), 5.36 (dd, J = 10.2, 7.6 Hz, 1H), 3.04 (td, J = 12.1, 4.8 Hz, 1H), 3.00–2.90 (m, 2H), 2.71–2.64 (m, 1H), 2.54–2.42 (m, 4H), 2.33–2.25 (m, 1H), 2.13–2.03 (m, 2H), 1.98 (d, J = 13.0 Hz, 1H), 1.89–1.77 (m, 4H), 1.61–1.51 (m, 1H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 170.2, 166.6, 164.5, 144.1, 144.1, 135.3, 135.2, 124.9, 124.8, 124.6, 124.5, 118.0, 117.8, 75.5, 75.5, 52.9, 50.6, 43.1, 39.7, 39.6, 37.9, 37.9, 37.8, 30.0, 28.7, 23.6, 21.0.

HRMS $[M+H]^+$ calcd for $C_{17}H_{22}N_2O_4F$: 337.1564. Found: 337.1560. Anal. Calcd for $C_{17}H_{22}N_2O_4F$: C, 60.70, H, 6.29; N, 8.33. Found: C, 60.89; H, 6.32; N, 8.32.

4.1.10. *rac*-(1*R*,5*R*,6*S*)-5-(2-Fluoro-5-nitrophenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-6-ol (13)

The acetate **12** (7 g, 20 mmol) in 2 N HCl (140 mL) was refluxed for 3 h. The mixture was cooled, basified with 5 N NaOH (ca. 70 mL), extracted with CH_2Cl_2 (2×), and the combined extracts were washed with H_2O and brine and dried ($MgSO_4$). The solvent was removed to give **13** (5.95 g, 96%), identical with the known compound.[4]

4.1.11. *rac*-(4*R*,6a*S*,11b*R*)-2,3,4,5,6,6a-Hexahydro-10-nitro-3-*N*-phenethyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine (15)

To a mixture of *rac*-(4*R*,6a*S*,11b*R*)-2,3,4,5,6,6a-hexahydro-3-methyl-10-nitro-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine[4] (**14**, 5.26 g, 19.2 mmol) and K_2CO_3 (2.16 g, 15.6 mmol) in 125 mL of acetonitrile was added with stirring a solution of cyanogen bromide (2.44 g, 23.0 mmol) in 5 mL of acetonitrile, and the mixture was refluxed for 2 h. After cooling, the solids were removed by filtration and the solvent evaporated. To the residue was added a mixture of 30 mL of glacial HOAc and 120 mL of 2 N HCl, and the mixture was refluxed for 18 h. After cooling, the mixture was basified with 5 N NaOH and extracted with $CHCl_3$ (3×). The combined extracts were washed with a small volume of H_2O, dried ($MgSO_4$) and the solvent removed to give **15** (5 g, quantitative) as a light yellow powder sufficiently pure for the next reaction.

4.1.12. *rac*-(4*R*,6a*S*,11b*R*)-10-Chloro-2,3,4,5,6,6a-hexahydro-8-nitro-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine (18)

The secondary amine **18** was prepared from *rac*-(4*R*,6a*S*,11b*R*)-10-chloro-2,3,4,5,6,6a-hexahydro-3-methyl-8-nitro-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine[4] (**17**) using the procedure for the preparation of compound **15** from **14**, to give a yellow solid (95%) sufficiently pure for the next reaction.

4.1.13. Optical resolution of *rac*-(4*R*,6a*S*,11b*R*)-2,3,4,5,6,6a-hexahydro-3-phenethyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-10-ol (16)

The racemic *N*-phenethyl substituted *para*-b (**16**, 366 mg) and *ortho*-b (**19**, 295 mg) isomers were resolved using supercritical fluid chromatography.[14] Resolution of the racemic *para*-b isomer **16** was conducted on a preparative scale using a 3x25 cm (S,S)-Whelk-01 column (Regis Technologies, Morton Grove, IL) using 65% liquid CO_2 (solvent) and 35% isopropanol with 0.1% isopropylamine (co-solvent) isocratically at 80 mL/min. The sample was applied in MeOH/CH_2Cl_2 (1:1) and retention times were 0.8 and 2.5 min for the *para*-b enantiomers **16a** and **16b** with recoveries of 170 mg and 168 mg, respectively, and estimated ee values of 98% for both.

4.1.13.1. *rac*-(4*R*,6a*S*,11b*R*)-2,3,4,5,6,6a-Hexahydro-3-phenethyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-10-ol (16a).

Compound **16a** (base): $[\alpha]_D^{23}$ +52.1 (c 0.87, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, J = 7.5 Hz, 2H), 7.23–7.17 (m, 3H), 6.72 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 2.4 Hz, 1H), 6.62 (dd, J = 8.4, 2.4 Hz, 1H), 4.09 (dd, J = 11.6, 6.6 Hz, 1H), 3.15 (s, 1H), 2.93–2.87 (m, 1H), 2.86–2.68 (m, 5H), 2.51 (d, J = 12.4 Hz, 1H), 2.35 (dd, J = 14.8, 1.7 Hz, 1H), 2.26–2.16 (m, 1H), 1.87–1.77 (m, 2H), 1.74–1.65 (m, 1H), 1.53–1.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 150.6, 140.4, 138.7, 128.9, 128.6, 126.3, 114.9, 110.9, 110.4, 91.7, 58.1, 52.8, 49.4, 44.0, 38.1, 34.5, 31.8, 27.6, 22.6; HRMS $[M+H]^+$ calcd for $C_{22}H_{26}NO_2$: 336.1964. Found: 336.1955.

4.1.13.2. *rac*-(4*S*,6a*R*,11b*S*)-2,3,4,5,6,6a-Hexahydro-3-phenethyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-10-ol (16b). Compound 16b (base): $[\alpha]_D^{23}$ −55.7 (c 0.94, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, J = 7.4 Hz, 2H), 7.25–7.16 (m, 3H), 6.72 (d, J = 8.4 Hz, 1H), 6.67 (s, 1H), 6.61 (d, J = 8.7 Hz, 1H), 4.09 (dd, J = 11.9, 6.3 Hz, 1H), 3.13 (s, 1H), 2.94–2.88 (m, 1H), 2.86–2.66 (m, 5H), 2.49 (d, J = 12.2 Hz, 1H), 2.35 (d, J = 14.1 Hz, 1H), 2.27–2.16 (m, 2H), 1.87–1.77 (m, 2H), 1.75–1.65 (m, 1H), 1.52–1.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 150.6, 140.4, 138.7, 128.9, 128.6, 126.3, 114.9, 110.9, 110.4, 91.7, 58.1, 52.8, 49.4, 44.0, 38.1, 34.5, 31.8, 27.6, 22.6; HRMS $[M+H]^+$ calcd for $C_{22}H_{26}NO_2$: 336.1964. Found: 336.1955.

Enantiomers **16a** and **16b** were converted to their HBr salts in 2-propanol-H_2O. Compound **16a**·HBr: $[\alpha]_D^{23}$ +57.2 (c 0.51, MeOH:-H_2O, 1:1); mp 276–280 °C. Anal. Calcd for $C_{22}H_{26}BrNO_2$: C, 63.46, H, 6.29, N, 3.36. Found: C, 63.16, H, 6.28, N, 3.32. Compound **16b**·HBr: $[\alpha]_D^{23}$ -55.8 (c 0.51, MeOH:H_2O, 1:1); mp 276–278 °C. Anal.

Calcd for $C_{22}H_{26}BrNO_2$: C, 63.46, H, 6.29, N, 3.36. Found: C, 63.36, H, 6.36, N, 3.33.

4.1.14. Optical resolution of *rac*-(4*R*,6a*S*,11b*R*)-2,3,4,5,6,6a-hexahydro-3-phenethyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-8-ol (19)

Optical resolution of the racemic *ortho*-b isomer **19** was achieved in the same manner as with **16**, above. The sample was applied in 2-propanol and retention times were 2.6 and 3.1 min for *ortho*-b fractions 1 and 2 (**19a** and **19b**, respectively) with recoveries of 121 and 126 mg and estimated ee values of 99.9% and 98.5%, respectively.

4.1.14.1. *rac*-(4*R*,6a*S*,11b*R*)-2,3,4,5,6,6a-Hexahydro-3-phenethyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-8-ol (19a).

Compound **19a** (base): $[\alpha]_D^{23}$ −64.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.5 Hz, 2H), 7.22–7.17 (m, 3H), 6.80 (t, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 6.68 (d, *J* = 7.2 Hz, 1H), 5.60 (br s, 1H), 4.15 (dd, *J* = 12.6, 5.7 Hz, 1H), 3.11 (s, 1H), 2.99–2.93 (m, 1H), 2.85 (td, *J* = 11.7, 5.9 Hz, 1H), 2.81–2.68 (m, 4H), 2.46 (d, *J* = 12.4 Hz, 1H), 2.38–2.32 (m, 1H), 2.32–2.18 (m, 2H), 1.87–1.73 (m, 3H), 1.51–1.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.0, 141.0, 140.6, 138.9, 128.9, 128.5, 126.2, 122.2, 115.3, 114.0, 92.6, 58.2, 53.0, 49.3, 44.3, 38.3, 34.7, 31.9, 27.5, 23.0; HRMS $[M+H]^+$ calcd for $C_{22}H_{26}NO_2$: 336.1964. Found: 336.1967.

4.1.14.2. *rac*-(4*S*,6a*R*,11b*S*)-2,3,4,5,6,6a-Hexahydro-3-phenethyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-8-ol (19b).

Compound 19b (base): $[\alpha]_D^{23}$ +63.4 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.4 Hz, 2H), 7.22–7.17 (m, 3H) 6.80 (t, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 7.2 Hz, 1H), 5.78, (br s, 1H), 4.15 (dd, *J* = 12.6, 5.7 Hz, 1H), 3.11 (s, 1H), 2.96 (dd, *J* = 10.9, 8.2 Hz, 1H), 2.85 (td, *J* = 11.7, 5.9 Hz, 1H), 2.81–2.68 (m, 4H), 2.47 (d, *J* = 12.2 Hz, 1H), 2.39–2.32 (m, 1H), 2.32–2.17 (m, 2H), 1.87–1.73 (m, 3H), 1.52–1.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.1, 141.0, 140.5, 138.8, 128.9, 128.5, 126.2, 122.2, 115.3, 114.0, 92.6, 58.2, 53.0, 49.3, 44.3, 38.2, 34.7, 31.8, 27.5, 22.9; HRMS $[M+H]^+$ calcd for $C_{22}H_{26}NO_2$: 336.1964. Found: 336.1960.

Enantiomers **19a** and **19b** was converted to their HBr salts in 2-propanol. Compound **19a**·HBr: $[\alpha]_D^{23}$ -53.3 (*c* 0.59, MeOH/H_2O, 1:1); mp 298–300 °C. Anal. Calcd for $C_{22}H_{26}BrNO_2$: C, 63.46, H, 6.29, N, 3.36. Found: C, 63.57, H, 6.20, N, 3.32. Compound **19b**·HBr: $[\alpha]_D^{23}$ +52.6 (*c* 0.53, MeOH:H_2O, 1:1); mp 298–300 °C. Anal. Calcd for $C_{22}H_{26}BrNO_2$: C, 63.46, H, 6.29, N, 3.36. Found: C, 63.51, H, 6.23, N, 3.32.

4.2. Binding and Efficacy assays. Cell culture and membrane pre paration

As noted previously,[15] the recombinant CHO cells (hMOR–CHO, hDOR–CHO and hKOR–CHO) were produced by stable transfection with the respective human opioid receptor cDNA, and were provided by Dr. Larry Toll (SRI International, CA). The cells were grown on plastic flasks in DMEM (100%) (hDOR–CHO and hKOR–CHO) or DMEM/F-12 (50%/50%) medium (hMOR-CHO) containing 10% FBS, and G-418 (0.10–0.2 mg/mL) under 95% air/5% CO_2 at 37 °C. Cell monolayers were harvested and frozen at −80 °C.

4.2.1. [^{35}S]GTP-γ-S binding assays

The assays were conducted with minor modifications of published methods.[17] In this description, buffer 'A' is 50 mM Tris–HCl, pH 7.4, containing 100 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA and buffer 'B' is buffer A plus 1.67 mM DTT and 0.15% BSA. On the day of the assay, cells were thawed on ice for 15 min and homogenized using a polytron in 50 mM Tris–HCl, pH 7.4, containing 4 μg/mL leupeptin, 2 μg/mL chymostatin, 10 μg/mL bestatin and 100 μg/mL bacitracin. The homogenate was centrifuged at 30,000×*g* for 10 min at 4 °C, and the supernatant discarded. The membrane pellets were resuspended in buffer B and used for [^{35}S]GTP-γ-S binding assays. Test tubes received the following additions: 50 μL buffer A plus 0.1% BSA, 50 μL GDP in buffer A/0.1% BSA (final concentration = 40 μM), 50 μL drug in buffer A/0.1% BSA, 50 μL [^{35}S]-GTP-γ-S in buffer A/0.1% BSA (final concentration = 50 pM), and 300 μL of cell membranes (50 μg of protein) in buffer B. The final concentrations of reagents in the [^{35}S]GTP-γ-S binding assays were: 50 mM Tris–HCl, pH 7.4, containing 100 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA, 1 mM DTT, 40 μM GDP and 0.1% BSA. Incubations proceeded for 3 h at 25 °C. Nonspecific binding was determined using GTP-γ-S (40 μM). Bound and free [^{35}S]GTP-γ-S were separated by vacuum filtration (Brandel) through GF/B filters. The filters were punched into 24-well plates to which was added 0.6 mL LSC-cocktail (Cytoscint). Samples were counted, after an overnight extraction, in a Trilux liquid scintillation counter at 27% efficiency.

4.3. X-ray crystal data on compounds 16b and 19a

Single-crystal X-ray diffraction data on compounds **16b** and **19a** were collected using MuKα radiation and a Bruker Platinum 135 CCD area detector. Crystals were prepared for data collection by coating with high viscosity microscope oil. The oil-coated crystal was mounted on a micro-mesh mount (Mitergen, Inc.) and transferred to the diffractometer. The structures were solved by direct methods and refined by full-matrix least squares on F^2 values using the programs found in the SHELXTL suite (Bruker, SHELXTL v6.10, 2000, Bruker AXS Inc., Madison, WI). Corrections were applied for Lorentz, polarization, and absorption effects. Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms on carbons were included using a riding model [coordinate shifts of C applied to H atoms] with C–H distance set at 0.96 Å. Complete information on data collection and refinement is available in the Supplementary data.

For compound **16b** a 0.643 × 0.104 × 0.026 mm^3 crystal was prepared for data collection and a data set collected at room temperature. The crystal was orthorhombic in space group $P\,2_12_12_1$, with unit cell dimensions a = 7.4195(2), b = 12.5090(3), and c = 20.7761(5) Å. Data was 98.5% complete to 68.26° θ with an average redundancy of 4.98. The final anisotropic full matrix least-squares refinement on F^2 with 235 variables converged at R_1 = 4.56%, for the observed data and wR_2 = 13.56% for all data.

For compound **19a** a 0.364 × 0.085 × 0.042 mm^3 crystal was prepared for data collection and a data set collected at room temperature. The crystal was monoclinic in space group $P\,2_1$, with unit cell dimensions a = 9.1613(3), b = 11.7449(4), c = 18.4218(6) Å, and b = 90.721°. Data was 91.2% complete to 68.04° θ with an average redundancy of 3.09. The final anisotropic full matrix least-squares refinement on F^2 with 476 variables converged at R_1 = 4.99%, for the observed data and wR_2 = 14.94% for all data.

Atomic coordinates for **16b** and **19a** have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers 816329 and 816330, respectively). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.05.035.

References and notes

1. Burke, T. R., Jr.; Jacobson, A. E.; Rice, K. C.; Weissman, B. A.; Silverton, J. V. In *Problems of Drug Dependence 1983*; Harris, L. S., Ed.; National Institute on Drug Abuse Research Monograph 49; DHHS ((ADM) 84–1316): Washington DC, 1984; Vol. 49, p 109.
2. Burke, T. R., Jr.; Jacobson, A. E.; Rice, K. C.; Silverton, J. V. *J. Org. Chem.* **1984**, *49*, 1051.
3. Yamada, K.; Flippen-Anderson, J. L.; Jacobson, A. E.; Rice, K. C. *Synth. Stuttg.* **2002**, 2359.
4. Kurimura, M.; Liu, H.; Sulima, A.; Przybyl, A. K.; Ohshima, E.; Kodato, S.; Deschamps, J. R.; Dersch, C.; Rothman, R. B.; Lee, Y. S.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2008**, *51*, 7866.
5. May, E. L. *J. Org. Chem.* **1956**, *21*, 899.
6. Zhang, Y.; Lee, Y. S.; Rothman, R. B.; Dersch, C. M.; Deschamps, J. R.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2009**, *52*, 7570.
7. Burke, T. R., Jr.; Jacobson, A. E.; Rice, K. C.; Silverton, J. V. *J. Org. Chem.* **1984**, *49*, 2508.
8. Linders, J. T.; Burke, T. R.; Jacobson, A. E.; Rice, K. C. In *Problems of Drug Dependence, 1990*; Harris, L. S., Ed.; National Institute on Drug Abuse Research Monograph 105: Washington, DC, 1991, p 388.
9. Kodato, S.; Linders, J. T. M.; Gu, X.-H.; Yamada, K.; Flippen-Anderson, J. L.; Deschamps, J. R.; Jacobson, A. E.; Rice, K. C. *Org. Biomol. Chem.* **2004**, *2*, 330.
10. Tadic, D.; Linders, J. T. M.; Flippen-Anderson, J. L.; Jacobson, A. E.; Rice, K. C. *Tetrahedron* **2003**, *59*, 4603.
11. Hashimoto, A.; Przybyl, A. K.; Linders, J. T. M.; Kodato, S.; Tian, X. R.; Deschamps, J. R.; George, C.; Flippen-Anderson, J. L.; Jacobson, A. E.; Rice, K. C. *J. Org. Chem.* **2004**, *69*, 5322.
12. Zezula, J.; Jacobson, A. E.; Rice, K. C. *Heterocycles* **2007**, *71*, 881.
13. Zezula, J.; Singer, L. B.; Przybyl, A. K.; Hashimoto, A.; Dersch, C. M.; Rothman, R. B.; Deschamps, J.; Lee, Y. S.; Jacobson, A. E.; Rice, K. C. *Org. Biomol. Chem.* **2008**, *6*, 2868.
14. White, C.; Burnett, J. *J. Chromatogr. A* **2005**, *1074*, 175.
15. Fontana, G.; Savona, G.; Rodriguez, B.; Dersch, C. M.; Rothman, R. B.; Prisinzano, T. E. *Tetrahedron* **2008**, *64*, 10041.
16. Kim, J.-H.; Deschamps, J. R.; Rothman, R. B.; Dersch, C. M.; Folk, J. E.; Cheng, K.; Jacobson, A. E.; Rice, K. C. *Bioorg. Med. Chem.* **2011**. doi:10.1016/j.bmc.2011.04.028.
17. Xu, H.; Hashimoto, A.; Rice, K. C.; Jacobson, A. E.; Thomas, J. B.; Carroll, F. I.; Lai, J.; Rothman, R. B. *Synapse* **2001**, *39*, 64.