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Probes for narcotic receptor mediated phenomena. Part 42: Synthesis and in vitro pharmacological characterization of the *N*-methyl and *N*-phenethyl analogues of the racemic *ortho*-c and *para*-c oxide-bridged phenylmorphans

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ABSTRACT

A new synthesis of *N*-methyl and *N*-phenethyl substituted *ortho*-c and *para*-c oxide-bridged phenylmorphans, using *N*-benzyl- rather than *N*-methyl-substituted intermediates, was used and the pharmacological properties of these compounds were determined. The *N*-phenethyl substituted *ortho*-c oxide-bridged phenylmorphan(*rac*-(3*R*,6a*S*,11a*S*)-2-phenethyl-2,3,4,5,6,11a-hexahydro-1*H*-3,6a-methanobenzofuro-[2,3-*c*]azocin-10-ol (**12**)) was found to have the highest μ-opioid receptor affinity (K_i = 1.1 nM) of all of the a- through f-oxide-bridged phenylmorphans. Functional data ([^{35}S]GTP-γ-S) showed that the racemate **12** was more than three times more potent than naloxone as an μ-opioid antagonist.

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1. Introduction

The syntheses of the 12 racemic *ortho*-a and *para*-a through -f oxide-bridged phenylmorphans (Fig. 1) have been published.[1–10] These compounds were prepared to examine the possibility that spatial characteristics, that is, interatomic distances and shape,[11,12] might be related to their ability to interact with particular opioid receptors and function as agonists or antagonists. Several of the structurally rigid a–f compounds have been found to have good affinity for opioid receptors, and most of those display opioid antagonist activity. Thus far, only one compound, the (−)-enantiomer of the *N*-phenethyl substituted *para*-e isomer,[7] has been found to have morphine-like agonist activity in vivo. The (+)-enantiomer of the *N*-phenethyl substituted *ortho*-b isomer was found to be a weak and non-selective antagonist,[3] and the (−)-enantiomer of the *N*-phenethyl substituted *para*-f isomer was found to be four times more potent than naloxone in the [^{35}S]GTPγS assay.[7] The *ortho*-d and *para*-d isomers were found to have little affinity for any opioid receptor (K_i > 200 nM)[3] and the *ortho*-a and *para*-a isomers are in the process of being evaluated. An insufficient quantity of the *N*-methyl-substituted *ortho*-c and *para*-c isomers was initially prepared[4] to allow pharmacological evaluation, and the *N*-phenethyl analogues were not synthesized formerly. We now report the

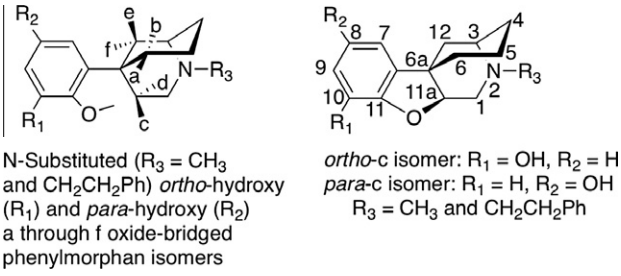

Figure 1. Structures of N-substituted *ortho*-a and *para*-a through -f oxide-bridged phenylmorphans and the *ortho*-c and *para*-c oxide-bridged phenylmorphan isomers.

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synthesis of the racemic *N*-methyl and *N*-phenethyl analogues of the *ortho*-c and *para*-c isomers (Fig. 1) in sufficient quantities to permit determination of their binding affinity and efficacy.

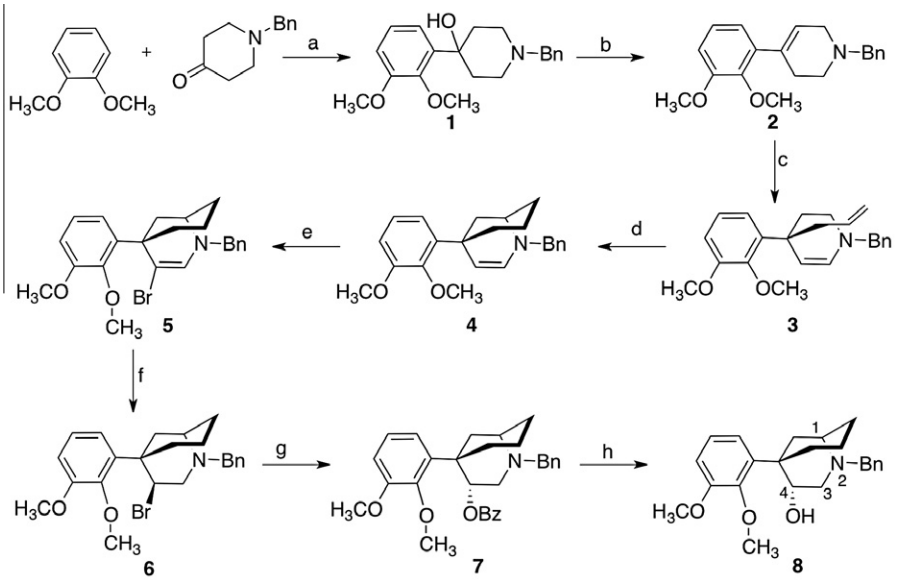
2. Chemistry

The *ortho*-c and *para*-c compounds were initially synthesized using an *N*-methyl substituent in a lengthy and low yielding route.[4] Since we sought higher yielding reactions and, as well, needed a different *N*-substituent in our final product (the *N*-phenethyl), we decided to modify the synthetic sequence of Tadic et al.[4] by utilizing an *N*-benzyl substituent. For the initial reactions (for compounds **2** through **9**), the *N*-benzyl compounds were prepared in better overall yields than the corresponding *N*-methyl analogs. The syntheses of *rac*-*N*-methyl (**13**) and *N*-phenethyl (**12**) -*ortho*-c compounds were accomplished in 11 and 12 steps, respectively, as shown in Schemes 1 and 2.

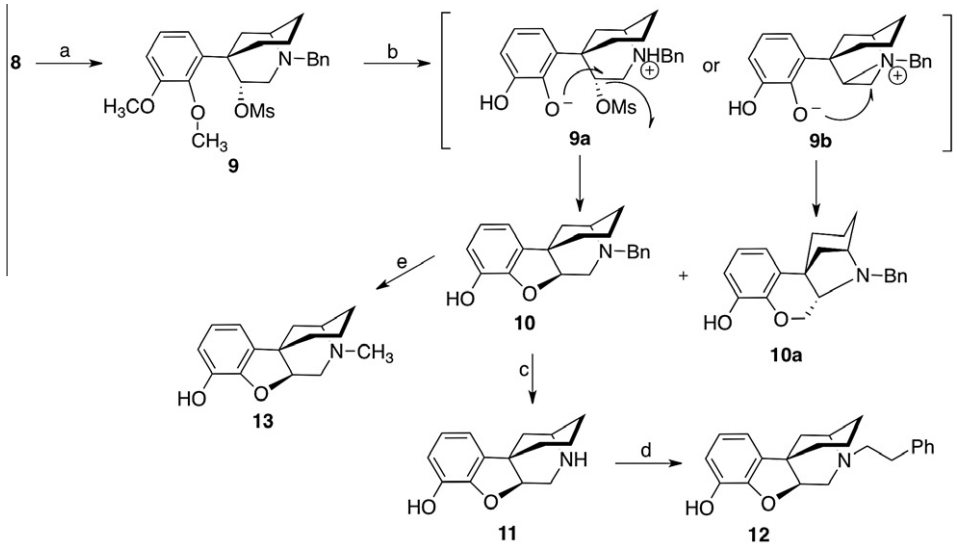
1-Benzyl-4-(2,3-dimethoxyphenyl)piperidin-4-ol (**1**) was prepared from commercially available materials (Scheme 1), and a 65% yield was obtained after purification by column chromatography. The crude alcohol **1** was sufficiently pure for use in the next reaction in which water was eliminated from the molecule under acidic conditions to form the 1,2,3,6-tetrahydropyridine **2** in 67% yield.

Phenylmorphan **4** was prepared using an extension of prior methodology[13] by alkylation of **2** with allyl bromide to give **3** that was cyclized to enamine **4** with a mixture of formic and phosphoric acids. The 5-phenylmorphan **4** had the structural requirements necessary to go forward to the essential intermediate, mesylate **9**. Crude **4** was brominated at C4 of the 5-phenylmorphan with *N*-bromoacetamide, and the ensuing bromide **5** was reduced with sodium cyanoborohydride to give the saturated bromo compound **6**, in 73% yield from **5**, and 60% yield over the three steps from crude **3**. In order to obtain the correct oxide-bridged phenylmorphan, the c-isomer, inversion of the configuration at C4 in **6** was required. This was accomplished by displacement of the bromine at C4 with potassium benzoate in DMF at 80 °C presumably via an SN2 mechanism, to give the benzoate **7** in 68% yield. The 2-azabicyclo[3.3.1]nonan-4-ol (**8**) was obtained by methanolysis of the ester under alkaline conditions in 66% yield. The essential mesylate intermediate **9** was obtained in 59% yield from **8**, with the correct configuration at C4 to allow cyclization to the *ortho*-c oxide-bridged phenylmorphan **10**. This was accomplished using boron tribromide in cold chloroform to cleave the aromatic ether moieties to the bisphenolic compound followed by base-catalyzed ring closure of **9** to the desired product **10** in 27% yield in a larger scale run, over two steps from **8**. Competing formation of aziridinium ion intermediate **9b** (Scheme 2) led to the undesired five-membered ring compound **10a**, possibly via an initial attack of the unpaired electrons on nitrogen on the C4-mesylate to displace the mesylate moiety and form the aziridinium ring.[5] The structure of the intermediate **10** was confirmed as the *ortho*-c isomer (Scheme 2) by X-ray crystallographic analysis of **10**·HCl. (Fig. 2).

Compound **10** was used as the starting material for conversion to *N*-methyl- and *N*-phenethyl-substituted *para*-hydroxy compounds **19** and **22**, respectively (Scheme 3).[4] To accomplish this, both the phenolic hydroxyl group in **10** and the N-substituent had to be removed. To remove the phenolic hydroxy group a tetrazoyl ether **14** was prepared by reaction of **10** with phenylchlorotetrazole in DMF at room temperature.[14] Column chromatography gave the pure compound, in 89% yield. Both the tetrazoyloxy moiety and the *N*-benzyl group were concomitantly cleaved by reduction with 10% Pd/C and hydrogen in acidic solution, in 45% yield after chromatography, to give the intermediate **15** that could be used to prepare the desired N-substituted *para*-c oxide-bridged phenylmorphans; the oxide-bridge was undisturbed during this series of reactions. N-Methylation was carried out in 82% yield after chromatography using formaldehyde in an atmosphere of hydrogen at room temperature to give **16**. Aromatic nitration in the *para*-position (*para* oriented to the oxide-bridge) to give **17** was achieved using sodium nitrite in trifluoroacetic acid in 39% yield. It was sufficiently pure for use in the preparation of the *para*-amino compound **18**. Hydrogenation of **17** using 10% Pd/C in acidic solution gave the desired amino compound **18**, in 68% yield, which was converted to the desired phenol **19** by sequential diazotization with sodium nitrite in 30% sulfuric acid followed by treatment with $Cu(NO_3)_2$ and Cu_2O. The *N*-methyl substituted *para*-c oxide-bridged phenylmorphan **19** was purified through recrystallization of its hydrochloride salt. The phenol was protected by conversion to the acetate **20**, in 98% yield, using acetic



Scheme 1. Synthesis of phenylmorphan alcohol **8**: Reagents and conditions: (a) *n*-BuLi, Et_2O, 0 °C, 65%; (b) *p*-TSA, toluene, 67%; (c) *sec*-BuLi, allyl bromide, THF, 68%; (d) 88% HCOOH + 85% H_3PO_4, 20 °C, 4 days; (e) NBA, THF, −78 °C, 30 min; (f) $NaCNBH_3$, 20 °C, 30 min; (g) anhydrous potassium benzoate, DMF, 80 °C, 16 h; (h) NaOMe, MeOH, 40 °C, 3 h.



Scheme 2. Synthesis of *rac*-*N*-methyl and *N*-phenethyl-*ortho*-c compounds (2-methyl- and 2-phenethyl-2,3,4,5,6,11a-hexahydro-1*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-10-ol). Reagents and conditions: (a) methanesulfonyl anhydride, triethylamine, $NaHCO_3$, 60%; (b) BBr_3, $CHCl_3$, −2 °C, 1 h, 14% (27% **10** in larger scale run; (c) 10% Pd/C, H_2, EtOH, 60 °C, 6 h, 78%; (d) (2-bromoethyl)benzene, $NaHCO_3$, DMF, 80–90 °C, 4 h, 71%; (e) 10% Pd/C, H_2, MeOH, 60 °C, 12 h, then 37% HCHO, H_2, room temperature, 4 h.

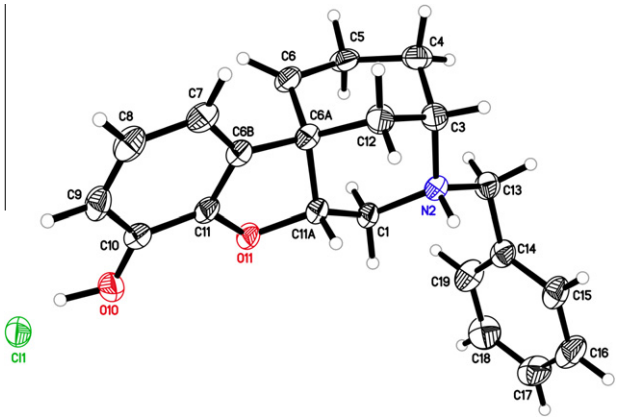


Figure 2. X-ray crystal structure of the HCl salt of *rac*-(3*R*,6a*S*,11a*S*)-2-benzyl-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocine-10-ol (**10**). Displacement ellipsoids are shown at the 50% level.

anhydride at 60 °C for 1 h. The crude phenolic secondary amine **21** was obtained, in 30% yield after chromatography, through oxidation of the tertiary amine **20** by cupric acetate in an acetonitrile–water mixture with ammonium thiosulfate. It was sufficiently pure for reaction with (2-bromoethyl)benzene in DMF to give the desired *N*-phenethyl derivative of the *para*-c oxide-bridged phenylmorphan **22**, in 67% yield after chromatography.

In an alternate synthesis (Scheme 4) of the *N*-methyl substituted compound, the conversion of the *N*-benzyl compound **8** to its *N*-methyl analogue **23**, was accomplished in 68% yield. The analogue **23** was converted[4] to the mesylate **24** quantitatively. The mesylate **24**, the *N*-methyl analog of **9**, was not isolated. Compound **25** was ring-closed to **13**, the *N*-methyl analogue of **10**, in 70% yield (47% over three steps from **8**).[4] Much less of **26** (in Scheme 4), comparable to **10a** in Scheme 2, was formed, presumably because with the *N*-methyl substituted compound, much more so than with the *N*-benzyl substituent, the SN2 pathway was favored over formation of the aziridinium ion. The mechanism by which the different N-substituents influenced the reaction is uncertain.

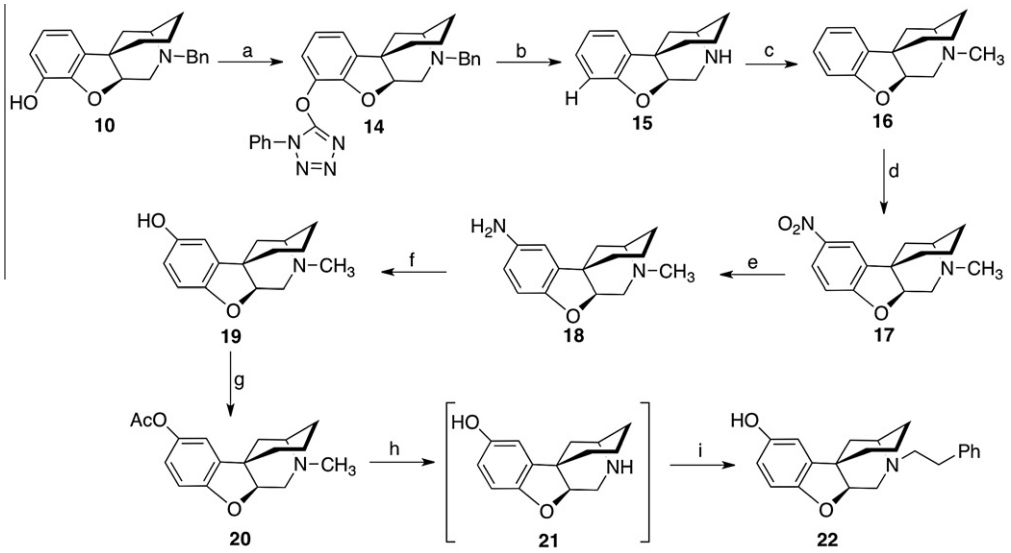
Even if the removal of an *N*-methyl substituent in an oxide-bridged phenylmorphan to form the secondary amine proceeds in only moderate[7,15] yields (64–77%), and the necessity of an extra step that is needed to prepare the *N*-phenethyl-substituted compound from the *N*-methyl analogue is considered, the route to compound **13** in Scheme 2 using the alternate method in Scheme 4 appears preferable.

3. Results and discussion

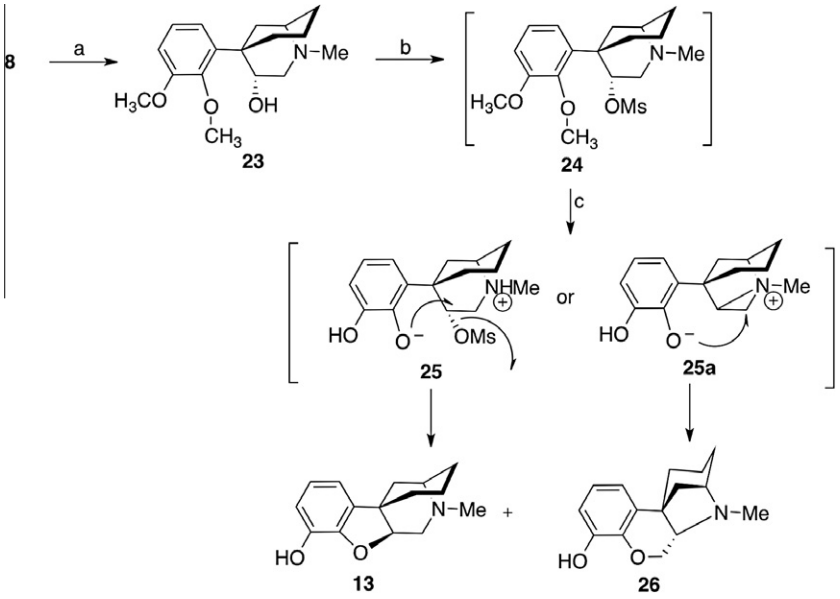
As can be seen in Table 1, there is a considerable difference between the binding affinities of the *N*-methyl and the *N*-phenethyl-substituted compounds. The *N*-phenethyl-substituted *ortho*-c isomer **12** was found to have the highest affinity (K_i = 1.1 nM, two to three times the affinity of morphine) of all of the a- through f-oxide bridged phenylmorphans. It was fairly selective for the μ-receptor, having about 50 fold less affinity for κ-receptors and about 1200-fold less affinity for δ-receptors. The *para*-hydroxy analogue had 60-fold less affinity for μ-receptors than the comparable *N*-phenethyl *ortho*-hydroxy compound, and it did not have appreciable affinity for δ- or κ-receptors. The *N*-methyl analogues of these compounds had little affinity for any opioid receptor (Table 1).

It is apparent that the position of the phenolic hydroxyl is of great importance to the affinity of the molecule, and that the *N*-phenethyl substituent is necessary for effective interaction with the μ-receptor. The shape of the *ortho*-c compound, the interatomic distance between heteroatoms, the tertiary amine and the phenolic oxygen, are all apparently necessary for high affinity interaction with μ-receptors. This interaction with the μ-opioid receptor resulted in opioid antagonist activity, as determined by [^{35}S]-GTP-γ-S assays (Table 2).

The *N*-phenethyl *ortho*-c phenylmorphan **12** was more than three times as potent as naloxone as a μ-opioid antagonist (Table 2), and had κ-opioid antagonist activity as well (one tenth the potency of norBNI). We expect that one of the enantiomers of this compound will have subnanomolar affinity and close to the optimal shape and the required heteroatom spatial positioning needed by oxide-bridged phenylmorphans for high potency and selectivity as an μ-opioid antagonist. Future work will be focused on obtaining a sufficient amount of these enantiomers for pharmacological analyses, and the synthesis will be based on the *N*-benzyl route modified by the alternative procedure noted in Scheme 4.



Scheme 3. Synthesis of *rac*-*N*-methyl and *N*-phenethyl-*para*-c compounds (2-methyl- and 2-phenethyl-2,3,4,5,6,11a-hexahydro-1*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-8-ol. Reagents and conditions: (a) 5-phenylchlorotetrazole, K_2CO_3, DMF, 32 h, 89%; (b) 10% Pd/C, glacial acetic acid, H_2, 30–50 psi, 72 h, 45%; (c) 10% Pd/C, 37% HCHO, MeOH, H_2, 4 h, 82%; (d) $NaNO_2$, trifluoroacetic acid, 5 °C, 2 h, 39%; (e) 10% Pd/C, MeOH, 37% HCl, H_2, 1.5 h, 68%; (f) 30% H_2SO_4, 0 °C, $NaNO_2$, 2 h, then $Cu(NO_3)_2$, Cu_2O, 0 °C, 1 h, 67%; (g) Ac_2O, 60 °C, 2 h, 98%; (h)[14] CH_3CN/H_2O (5:1), $Cu(OAc)_2$, $(NH_4)_2S_2O_8$, 12 h, aqueous 10% $Na_2S_2O_3$; (i) (2-bromoethyl)benzene, $NaHCO_3$, DMF, 80–90 °C, 2 h, 67%.



Scheme 4. Alternative higher yielding route to **13**. Reagents and conditions: (a) 10% Pd/C, ammonium formate, reflux 2 h, then 88% formic acid, 37% formaldehyde, reflux 3 h, 68%; (b) methanesulfonyl anhydride, triethylamine, $NaHCO_3$, 99%; (c) BBr_3, $CHCl_3$, −0 °C, 5 h, 70%, (47% from **8** to **13**).

4. Experimental

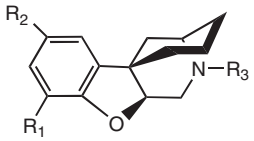
4.1. General

Melting points were determined on a Buchi B-545 instrument and are uncorrected. Proton and carbon nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard on a Varian Gemini-300 spectrometer and on a Bruker AVANCE-500. Mass spectra (HRMS) were recorded on a VG 7070E spectrometer or a JEOL SX102a mass spectrometer. Thin layer chromatography (TLC) analyses were carried out on Analtech silica gel GHLF 0.25 mm plates using various gradients of $CHCl_2$/MeOH containing 1% NH_4OH or gradients of EtOAc/*n*-hexane. Visualization was accomplished under UV light or by staining in an iodine chamber. Flash column chromatography was performed with Fluka Silica Gel 60 (mesh 220–400). Atlantic Microlabs, Inc., Norcross, GA performed elemental analyses, and the results were within ±0.4% of the theoretical values.

4.1.1. 1-Benzyl-4-(2,3-dimethoxyphenyl)piperidin-4-ol (1)

Following the general procedure of Burke et al.,[5] a solution of 1,2-dimethoxybenzene (36.4 g, 0.26 mol) in anhydrous Et_2O (225 mL) was cooled in an ice bath and stirred under argon while a 2.5 M solution of *n*-BuLi (80 mL, 0.20 mol) was added over a period of 30 min. The ice bath was removed, and the solution was stirred at room temperature for 19 h. The resulting white suspension was cooled to 0 °C, and a solution of 1-benzyl-4-piperidinone

Table 1
[^{3}H] Binding data for *ortho*-c and *para*-c oxide-bridged phenylmorphans



Compd	R_1	R_2	R_3	μ[a]	δ[b]	κ[c]
13	OH	H	Me	619 ± 26	>5200	>40,000
19	H	OH	Me	1500 ± 90	>5200	1080 ± 53
22	H	OH	PhEt	67 ± 6	1250 ± 147	1230 ± 78
12	OH	H	PhEt	1.1 ± 0.1	1230 ± 111	51 ± 3
Morphine				2.6 ± 0.01		

Opiate receptor binding assays were performed using CHO hMOR, CHO hDOR and CHO hKOR cells, respectively; $N = 3$.
[a] [^{3}H]-DAMGO.
[b] [^{3}H]-DADLE.
[c] [^{3}H]-U69,593.

Table 2
Functional data ([^{35}S]GTP-γ-S)[a] for *N*-phenethyl *ortho*-c oxide-bridged phenylmorphan (**12**)

Compd	μ-Antagonism K_e (nM)	κ-Antagonism K_e (nM)
12	0.71 ± 0.09	1.79 ± 0.51
Naloxone	2.3 ± 0.3	11 ± 2
norBNI	17 ± 3	0.11 ± 0.02

[a] K_e determinations were conducted as described in Methods in the section 'Data analysis and statistics'. Each parameter value is ±SD ($n = 3$–4).

(38.2 g, 0.20 mol) in Et_2O (38 mL) was added slowly over 20 min. The solid dissolved, giving a cloudy yellow solution that was washed with aqueous $NaHCO_3$ and filtered to remove a white solid. The organic phase was washed with H_2O and brine, dried over Na_2SO_4, and evaporated to give the crude alcohol **1**. Column chromatography using hexane and EtOAc (5:1) gave **1** (55.6 g, 65.4%) as a yellow oil. An HCl salt was prepared and recrystallized from MeOH. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24–7.38 (m, 5H), 7.01 (t, J = 8.1 Hz, 1H), 6.90 (dd, J = 8.1, 1.5 Hz, 1H), 6.85 (dd, J = 8.1, 1.5 Hz, 1H), 4.24 (s, 1H), 3.95 (s, 3H), 3.85 (s, 3H), 3.58 (s, 2H), 2.76 (d, J = 11.1, 2H), 2.59 (td, J = 11.7, 2.4 Hz), 2.13 (td, J = 12.6, 4.2 Hz), 1.90 (d, J = 13.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.64, 147.23, 140.37, 138.61, 129.24, 128.13, 126.87, 123.78, 117.70, 111.71, 71.49, 63.25, 61.07, 55.75, 49.16, 37.29; HRMS calcd for $C_{20}H_{26}NO_3$ [M+H]$^+$: 328.1913; found: 328.1909. Anal. Calcd for $C_{20}H_{25}NO_3$·HCl·0.2H_2O: C, 65.37; H, 7.24; N, 3.81. Found: C, 65.18; H, 7.26; N, 3.96.

4.1.2. 1-Benzyl-4-(2,3-dimethoxyphenyl)-1,2,3,6-tetrahydropyridine (2)

The mixture of the crude alcohol **1** (40 g, 0.122 mol) and *p*-toluensulfonic acid monohydrate (30 g, 0.158 mol) in toluene (650 mL) was refluxed for 18 h with a Dean-Stark trap to remove H_2O. After removal of toluene, the residual material was diluted with EtOAc and saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc. The combined organic phase was washed with H_2O and brine, dried over Na_2SO_4 and concentrated to dryness. Column chromatography of the crude material with hexane and EtOAc (5:1) gave **2** (25.37 g, 67.2%) as a light yellow oil. The HCl salt was prepared and recrystallized from MeOH. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24–7.40 (m, 5H), 6.98 (t, J = 8.1 Hz, 1H), 6.80 (td, J = 8.1, 1.5 Hz, 2H), 5.79 (m, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 3.64 (s, 2H), 3.16 (dd, J = 6, 2.7 Hz, 2H), 2.68 (t, J = 6.6 Hz, 2H), 2.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.79, 146.57, 138.26, 137.06, 134.77, 129.24, 128.22, 127.04, 124.24, 123.76, 121.41, 111.09, 62.74, 60.63, 55.84, 53.24, 50.03, 29.67; HRMS calcd for $C_{20}H_{24}NO_2$ [M+H]$^+$: 310.1807; found: 310.1803. Anal. Calcd for $C_{20}H_{23}NO_2$·HCl: C, 69.45; H, 6.99; N, 4.05. Found: C, 69.29; H, 7.04; N, 4.16.

4.1.3. (*R**)-4-Allyl-1-benzyl-4-(2,3-dimethoxyphenyl)-1,2,3,4-tetrahydropyridine (3)

sec-BuLi (1.4 M) in cyclohexane (62 mL, 0.086 mol) was added dropwise to a solution of **2** (26 g, 0.084 mol) in THF (500 mL) at −50 °C, allyl bromide (7.44 mL, 0.086 mol) was added, and the mixture was allowed to warm slowly to room temperature and stirred overnight. The reaction was quenched by addition of H_2O, diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated to give a crude enamine **3**. Column chromatography of the crude material with hexane and EtOAc (5:1) gave **3** (19.9 g, 67.8%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20–7.32 (m, 5H), 6.99 (dd, J = 8.1, 2.1 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.80 (dd, J = 7.5, 2.1 Hz, 1H), 6.13 (d, J = 8.1 Hz, 1H), 5.51 (m, 1H), 4.94 (m, 2H), 4.62 (dd, J = 8.1, 1.8 Hz, 1H), 3.97 (dd, J = 19.5, 15 Hz, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.91 (dd, J = 13.8, 6 Hz, 1H), 2.76 (td, J = 11.4, 3.9 Hz, 1H), 2.56 (dd, J = 12, 2.7 Hz, 1H), 2.45(m, 2H), 1.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.08, 147.32, 140.79, 138.73, 136.09, 135.12, 128.26, 127.92, 126.99, 124.04, 122.27, 116.39, 110.71, 103.09, 60.08, 58.92, 55.68, 45.12, 44.02, 40.89, 33.98.

4.1.4. (1*R**,5*R**)-2-Benzyl-5-(2,3-dimethoxyphenyl)-2-azabicyclo[3.3.1]non-3-ene (4)

Crude **3** (20.6 g, 0.059 mol) was dissolved in a mixture of 152 mL of 88% HCOOH and 152 mL of 85% H_3PO_4 at 0 °C. The mixture was stirred for 4 days at room temperature. The reaction mixture was diluted with 400 mL of H_2O, cooled in ice, and treated with 40% NaOH solution (to pH ~8) and extracted with EtOAc (5 × 40 mL). The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated to give crude enamine **4** as a dark-brown oil (22 g).

4.1.5. (1*R**,5*S**)-2-Benzyl-4-bromo-5-(2,3-dimethoxyphenyl)-2-azabicyclo[3.3.1]non-3-ene (5)

The crude **4** (20 g, 0.057 mol) was dissolved in 200 mL of dry THF, cooled to −78 °C, and *N*-bromoacetamide (8.76 g, 0.063 mol) solution in THF (40 mL) was slowly added. After stirring for 30 min at −78 °C, the mixture was allowed to warm up slowly to room temperature and stirred at room temperature for 20 min. The solvents were evaporated, and the oily residue was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer was washed with H_2O and brine, and dried over Na_2SO_4. Evaporation of solvent gave crude **5** (24 g).

4.1.6. (1*R**,4*S**,5*S**)-2-Benzyl-4-bromo-5-(2,3-dimethoxyphenyl)-2-azabicyclo[3.3.1]nonane (6)

Addition of 37% HCl (17.5 mL) to a suspension of crude **5** (21 g, 0.049 mol) in MeOH (250 mL) gave a dark brown solution to which was added $NaCNBH_3$ (3.74 g, 0.060 mol). The resulting milky mixture was stirred 30 min at room temperature and them diluted with saturated aqueous $NaHCO_3$ (100 mL). After removal of MeOH, the residue was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was washed with H_2O and brine, and dried over Na_2SO_4. Evaporation of solvent gave **6** as a crude oil. Column chromatography of the crude material with hexane and EtOAc (10:1) gave **6** (15.4 g, 73.5%; 60% from crude **3**) as a white solid. The HCl salt was prepared and recrystallized from MeOH. Mp (free base) 125.9–126.2 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.22–7.39 (m, 5H), 6.95–7.03 (m, 2H), 6.87 (dd, J = 7.2, 2.4 Hz, 1H), 5.34 (dd, J = 11.1, 6.9 Hz, 1H), 3.95 (s, 3H), 3.86 (s, 3H), 3.77 (dd, J = 24.6, 13.5 Hz, 2H), 3.45 (t, J = 11.4 Hz, 1H), 3.18 (dd, J = 12, 6.6 Hz, 1H),

3.00 (br s, 1H), 2.85 (d, J = 12.6 Hz, 1H), 2.57 (m, 1H), 1.81–2.17 (m, 5H), 1.50 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.32, 148.48, 140.10, 139.28, 128.51, 128.25, 126.91, 122.69, 120.19, 111.34, 60.51, 58.81, 58.19, 56.89, 55.75, 51.73, 41.21, 37.94, 32.52, 24.45, 22.00; HRMS calcd for $C_{23}H_{29}BrNO_2$ $[M+H]^+$: 430.1382; found: 430.1375. Anal. Calcd for $C_{23}H_{28}BrNO_2 \cdot HCl \cdot 0.2H_2O$: C, 58.72; H, 6.30; N, 2.98. Found: C, 58.65; H, 6.31; N, 3.06.

4.1.7. (1*R**,4*R**,5*S**)-2-Benzyl-5-(2,3-dimethoxyphenyl)-2-azabicyclo[3.3.1]nonan-4-yl benzoate (7)

The bromo compound **6** (1 g, 2.32 mmol) was dissolved in DMF (20 mL) and anhydrous potassium benzoate (1.115 g, 6.96 mmol) was added while stirring. The suspension was gradually heated under argon in an oil bath to 80 °C (30 min), and maintained at that temperature for 16 h. It was cooled to room temperature and diluted with H_2O. The aqueous phase was extracted with Et_2O. The combined organic extracts were washed with H_2O dried over Na_2SO_4, and the solvent removed in vacuo. Column chromatography of the crude material with hexane and EtOAc (5:1) gave the ester **7** (1.58 g, 68.1%). The HCl salt was prepared and recrystallized from MeOH. Mp (HCl salt) 98.1–99.2 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.64 (d, J = 7.5 Hz, 2H), 7.43(d, J = 7.5 Hz, 2H), 7.20–7.31 (m, 6H), 6.96 (m, 2H), 6.83 (dd, J = 6.9, 2.7 Hz, 1H), 4.64 (m, 2H), 4.15 (d, J = 13.8 Hz, 1H), 3.98 (t, J = 6.3 Hz, 1H), 3.89 (s, 3H), 3.88 (m, 1H), 3.84 (s, 3H), 3.11 (t, J = 5.1 Hz, 1H), 2.69 (m, 1H), 1.94–2.22 (m, 3H), 1.45–1.79 (m, 3H), 1.25 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.61, 153.33, 148.43, 141.40, 138.14, 132.53, 130.21, 129.48, 128.37, 128.04, 126.59, 123.20, 119.94, 111.13, 69.98, 65.88, 62.21, 60.63, 60.10, 55.79, 49.33, 41.46, 31.91, 31.34, 20.41; HRMS calcd for $C_{30}H_{34}NO_4$ $[M+H]^+$: 472.2488; found: 472.2493. Anal. Calcd for $C_{30}H_{33}NO_4 \cdot HCl \cdot 1.1H_2O$: C, 68.26; H, 6.91; N, 2.65. Found: C, 68.06; H, 6.82; N, 2.65.

4.1.8. (1*R**,4*R**,5*S**)-2-Benzyl-5-(2,3-dimethoxyphenyl)-2-azabicyclo[3.3.1]nonan-4-ol (8)

0.5 M NaOMe in MeOH (29 mL, 14.64 mmol) was slowly added to a vigorously stirred solution of the ester **7** (3.45 g, 7.32 mmol) in MeOH (40 mL). The reaction mixture was stirred for 3 h at 40 °C. After removal of MeOH, the oily residue was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The combined organic phase was washed with H_2O and brine, dried over Na_2SO_4 and evaporated to dryness. Column chromatography of the crude material with hexane and EtOAc (3:1) gave **8** (1.78 g, 66%) as a white solid. Mp (free base) 154.8–155.2 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23–7.41 (m, 5H), 6.98 (t, J = 7.8 Hz, 1H), 6.84 (dd, J = 8.4, 1.5 Hz, 1H), 6.79 (dd, J = 8.4, 1.5 Hz, 1H), 3.96 (m, 3H), 3.89 (s, 3H), 3.85 (s, 3H), 3.76 (d, J = 13.8 Hz, 1H), 3.36 (t, J = 6.3 Hz, 1H), 3.11 (t, J = 4.5 Hz, 1H), 2.44 (m, 1H), 1.88–2.12 (m, 4H), 1.49–1.67 (m, 2H), 1.29 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.35, 148.02, 140.76, 139.03, 128.30, 128.27, 126.87, 123.43, 119.55, 111.18, 73.67, 62.63, 61.45, 60.70, 59.16, 55.76, 50.05, 41.73, 31.70, 31.64, 19.70; HRMS calcd for $C_{23}H_{30}NO_3$ $[M+H]^+$: 368.2226; found: 368.2219. Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.36; H, 7.75; N, 3.86.

4.1.9. (1*R**,4*R**,5*S**)-2-Benzyl-5-(2,3-dimethoxyphenyl)-2-azabicyclo[3.3.1]nonan-4-yl methanesulfonate (9)

Methanesulfonyl anhydride (777.6 mg, 4.33 mmol) was added to a solution of **8** (795.8 g, 2.16 mmol) in $CHCl_3$ (20 mL) and triethylamine (0.8 mL, 5.4 mmol). The colorless solution was stirred under argon at room temperature for 2 h, and the reaction was quenched with a saturated solution of $NaHCO_3$. The aqueous phase was extracted with $CHCl_3$. The combined organic solutions were washed with H_2O, dried over Na_2SO_4 and evaporated to dryness to give mesylate **9** (1.29 mg, 59.7%). The HCl salt was prepared and recrystallized from MeOH. Mp (**9**·HCl) 149.2–149.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20–7.42 (m, 5H), 7.00 (t, J = 7.8 Hz, 1H), 6.84–6.89 (m, 2H), 4.60 (dd, J = 9.9, 7.8 Hz, 1H), 4.51 (dd, J = 9.6, 3.9 Hz, 1H), 4.09 (d, J = 14.4 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.83 (m, 2H), 3.10 (t, J = 5.4 Hz, 1H), 2.80 (s, 3H), 2.58 (m, 1H), 1.99 (m, 3H), 1.66–1.75 (m, 2H), 1.49 (m, 1H), 1.25 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.36, 141.13, 137.29, 128.15, 128.12, 126.69, 123.28, 119.51, 111.39, 71.54, 70.09, 62.48, 60.66, 60.53, 59.88, 55.77, 49.65, 41.36, 37.06, 31.69, 31.12, 20.62; HRMS calcd for $C_{24}H_{32}NO_5S$ $[M+H]^+$: 446.2001; found 446.2000. Anal. Calcd for $C_{24}H_{31}NO_5S \cdot HCl \cdot 0.4H_2O$: C, 58.92; H, 6.76; N, 2.86. Found: C, 58.71; H, 6.76; N, 2.86.

4.1.10. (3*R**,6a*S**,11a*S**)-2-Benzyl-2,3,4,5,6,11a-hexahydro-1*H*-3,6a-methanobenzofuro[2,3-c]azocin-10-ol (10)

4.1.10.1. (6a*S**,8*S**,11a*R**)-7-Benzyl-6a,7,8,9,10,11-hexahydro-6*H*-8,11a-methanochromeno[3,4-b]azepin-4-ol (10a).

Small scale: A solution of mesylate **9** (655.5 mg, 1.47 mmol) in $CHCl_3$ (10 mL) was added dropwise to a vigorously stirred solution of BBr_3 (1.4 mL, 14.7 mmol) in $CHCl_3$ (10 mL) that was cooled to −2 °C. The mixture was stirred for 1 h at 0–5 °C, and quenched with a mixture of concentrated NH_4OH (20 mL) and crushed ice (1.5 g). The mixture was then brought to room temperature, and the organic phase was separated. The aqueous layer was saturated with NaCl, extracted with $CHCl_3$ and MeOH (3:1). The aqueous solution was re-extracted with $CHCl_3$ and MeOH (3:1). The combined organic phase was dried over Na_2SO_4 and evaporated to dryness to give **10a** (90.1 mg) and **10** (23.3 mg, 4.9%). The hydrochloride salt of **10** was prepared by adding HCl in ether to the tertiary amine **10** in ether; the salt that formed was recrystallized from methanol.

Larger scale, modified conditions for **10**: A solution of **9** (2.8 g, 6.28 mmol) in $CHCl_3$ (65 mL) was added dropwise to a vigorously stirred solution of BBr_3 (6.1 mL, 16 g, 64 mmol) in $CHCl_3$ (210 mL) at −2 °C under argon. The temperature was maintained at 0 to–5 °C for 1 h and the reaction was quenched with a mixture of concentrated NH_4OH (200 mL) and ice (150 g). The reaction was brought to room temperature and the organic phase was separated. The aqueous phase was saturated with NaCl and extracted with $CHCl_3$ (3×). The combined organic extracts were washed with a little H_2O, dried over Na_2SO_4 and the solvent was removed. Silica gel chromatography using a linear gradient of hexanes to 25% EtOAc in hexanes provided **10** (0.56 g, 27% in two steps from **8**). Other runs gave yields from 14% to 22% yields (over two steps). **10**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24–7.38 (m, 5H), 6.77 (m, 2H), 6.66 (dd, J = 6.9, 1.5 Hz, 1H), 4.29 (dd, J = 11.7, 5.7 Hz, 1H), 3.94 (d, J = 13.8 Hz, 1H), 3.88 (d, J = 13.8 Hz, 1H), 3.40 (dd, J = 11.7, 10.2 Hz, 1H), 3.23 (dd, J = 9.9, 5.4 Hz, 1H), 3.14 (m, 1H), 2.27 (d, J = 14.7 Hz, 1H), 2.11 (dd, J = 12, 2.1 Hz, 1H), 1.38–2.04 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.90, 140.86, 139.61, 139.38, 128.48, 128.29, 127.00, 122.02, 114.89, 113.69, 89.62, 58.68, 52.71, 50.87, 44.65, 36.65, 31.83, 26.59, 21.73; HRMS calcd for $C_{21}H_{24}NO_2$ $[M+H]^+$: 322.1807; found 322.1813. Anal. Calcd for $C_{21}H_{23}NO_2 \cdot HCl \cdot 0.9H_2O$: C, 67.42; H, 6.95; N, 3.74. Found: C, 67.45; H, 6.85; N, 3.75.

Compound **10a**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25–7.38 (m, 5H), 6.69–6.76(m, 2H), 6.65–6.54(m, 1H), 4.29 (dd, J = 12, 9.6 Hz, 1H), 3.96 (dd, J = 9.6, 4.8 Hz, 1H), 3.79 (dd, J = 28.5, 13.2 Hz, 2H), 3.35 (t, J = 5.4 Hz, 1H), 3.04 (dd, J = 12, 5.4 Hz, 1H), 2.11–2.21 (m, 1H), 1.94–2.01 (m, 1H), 1.79–1.89 (m, 2H), 1.45–1.64 (m, 3H), 1.23–1.33 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.29, 140.40, 139.50, 132.43, 128.55, 128.22, 127.06, 119.93, 115.57, 112.88, 69.76, 66.96, 63.33, 61.78, 44.06, 38.44, 35.62, 32.28, 18.52; HRMS calcd for $C_{21}H_{24}NO_2$ $[M+H]^+$: 322.1807; found 322.1805.

4.1.11. (3*R**,6a*S**,11a*S**)-2,3,4,5,6,11a-Hexahydro-1*H*-3,6a-methanobenzofuro[2,3-c]azocin-10-ol (11)

A mixture of **10** (20 mg, 0.06 mmol) and 10% Pd/C (15 mg) in EtOH (2 mL) was heated at 60 °C for 6 h in an hydrogen atmosphere. After cooling to room temperature, it was basified with NH_4OH (pH ~9), filtered through a pad of Celite, washed with MeOH, and concentrated to provide the crude product. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH/NH_4OH, 90:10:1) to give **11** (10.98 mg, 78.3%); ^1H NMR ($CDCl_3$, 300 MHz): δ 6.78–6.82 (m, 2H), 6.67 (dd, J = 6.6, 1.2 Hz, 1H), 4.23 (dd, J = 12.0, 5.0 Hz, 1H), 3.83 (t, J = 11.1 Hz, 1H), 3.57 (br s, 2H), 1.53–2.25 (m, 8H).

4.1.12. (3*R**,6a*S**,11a*S**)-2-Phenethyl-2,3,4,5,6,11a-hexahydro-1*H*-3,6a-methanobenzofuro[2,3-c]azocin-10-ol (12)

A mixture of **11** (40 mg, 0.17 mmol), $NaHCO_3$ (15.98 mg, 0.19 mmol) and (2-bromoethyl) benzene (25.74 μL, 0.19 mmol) in DMF (3 mL) was heated at 80–90 °C for 4 h under argon. After cooling to room temperature, the mixture was diluted with Et_2O, and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. Column chromatography of the crude material with hexane and EtOAc (5:1) gave **12** (40.3 mg, 70.6%). The HCl salt was prepared and recrystallized from MeOH. Mp (HCl salt) 258.6–259.4 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.22–7.31 (m, 5H), 6.74–6.82 (m, 2H), 6.66 (d, J = 7.5 Hz, 1H), 4.29 (dd, J = 11.5, 5.5 Hz, 1H), 3.43 (m, 2H), 3.23 (br s, 1H), 2.83–2.98 (m, 4H), 2.23 (d, J = 12 Hz, 1H), 2.13 (d, J = 12.0 Hz, 1H), 1.99 (d, J = 12.0 Hz, 1H), 1.45–1.79 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.97, 140.94, 140.31, 139.50, 128.74, 128.35, 126.07, 122.09, 115.17, 113.72, 89.39, 56.53, 52.80, 51.21, 44.59, 36.70, 34.89, 31.70, 26.48, 21.71; HRMS calcd for $C_{22}H_{26}NO_2$ $[M+H]^+$: 336.1964; found 336.1969. Anal. Calcd for $C_{22}H_{25}NO_2$·HCl: C, 71.05; H, 7.05; N, 3.77. Found: C, 70.89; H, 6.96; N, 3.77.

4.1.13. (3*R**,6a*S**,11a*S**)-2-Methyl-2,3,4,5,6,11a-hexahydro-1*H*-3,6a-methanobenzofuro[2,3-c]azocin-10-ol (13)

A mixture of **10** (20 mg, 0.06 mL) and 10% Pd/C (5 mg) in MeOH (2 mL) was heated at 60 °C for 12 h in a hydrogen atmosphere. 37% HCHO (6 μL, 0.07 mmol) was added to the mixture and it was stirred at room temperature for 4 h in a hydrogen atmosphere. The mixture was filtered through a pad of Celite, washed with MeOH, and solvent removed in vacuo to provide the crude product. Column chromatography of the crude material with CH_2Cl_2/MeOH/NH_4OH (95:5:1) gave **13** (11.03 mg, 72.5%). The HCl salt was prepared and recrystallized from MeOH. Mp (HCl salt) 218.7–219.3 °C (dec); ^1H NMR ($CDCl_3$, 300 MHz): δ 6.70–6.81 (m, 2H), 6.63 (dd, J = 6.0, 1.2 Hz, 1H), 4.29 (dd, J = 11.1, 6.0 Hz, 1H), 3.36 (m, 2H), 3.11 (br s, 1H), 2.59 (s, 3H), 2.24 (m, 1H), 2.12 (dd, J = 12.3, 1.8 Hz, 1H), 2.02 (m, 1H), 0.83–1.79 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.49, 139.51, 137.06, 122.17, 115.63, 113.54, 88.85, 54.47, 53.10, 42.02, 36.46, 31.58, 29.69, 25.71, 21.42; HRMS calcd for $C_{15}H_{20}NO_2$ $[M+H]^+$: 246.1494; found 246.1494. Anal. Calcd for $C_{15}H_{19}NO_2$·HCl·0.3H_2O: C, 62.73; H, 7.23; N, 4.88. Found: C, 62.81; H, 7.20; N, 4.81.

4.1.14. (3*R**,6a*S**,11a*S**)-2-Benzyl-10-((1-phenyl-1*H*-tetrazol-5-yl)oxy)-2,3,4,5,6,11a-hexahydro-1*H*-3,6a-methanobenzofuro[2,3-*c*]azocine (14)

A mixture of the *ortho*-c oxide-bridged phenylmorphan **10** (33 mg, 0.1 mmol) and K_2CO_3 (27.64 mg, 0.2 mmol) in DMF (1 mL) was stirred under argon at room temperature. 5-Phenylchlorotetrazole (21.67 mg, 0.12 mmol) was added and the stirring continued for 32 h after starting material could no longer be discerned on TLC. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic phase was dried over Na_2SO_4 and solvent was removed. Column chromatography of the crude material with hexane and EtOAc (5:1) gave **14** (41.43 mg, 88.9%); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.82 (m, 2H), 7.45–7.57 (m, 3H), 7.23–7.35 (m, 5H), 7.20 (dd, J = 7.8 Hz, 0.9 Hz, 1H), 7.04 (dd, J = 7.2, 0.9 Hz, 1H), 6.96 (dd, J = 8.4, 7.5 Hz, 1H), 4.36 (dd, J = 11.4, 5.4 Hz, 1H), 3.94 (d, J = 13.8 Hz, 1H), 3.78 (d, J = 13.8 Hz, 1H), 3.35 (t, J = 10.2 Hz, 1H), 3.17 (m, 2H), 2.27 (d, J = 12.9 Hz, 1H), 2.14 (dd, J = 12.3, 2.1 Hz, 1H), 1.46–2.05 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.33, 142.02, 139.40, 137.88, 133.20, 129.64, 129.24, 128.41, 128.30, 127.01, 122.17, 121.98, 120.18, 119.70, 90.05, 58.67, 52.85, 50.57, 44.59, 36.51, 32.03, 26.56, 21.69; HRMS calcd for $C_{28}H_{28}N_5O_2$ $[M+H]^+$: 466.2243; found 466.2252. Anal. Calcd for $C_{28}H_{27}N_5O_2$·0.3H_2O: C, 71.41; H, 5.91; N, 14.87. Found: C, 71.32; H, 5.94; N, 14.92.

4.1.15. (3*R**,6a*S**,11a*S**)-2,3,4,5,6,11a-Hexahydro-1*H*-3,6a-methanobenzofuro[2,3-*c*]azocine (15)

10% Pd/C catalyst (138.6 mg) was added to a solution of the phenyltetrazole ether **14** (111.7 mg, 0.24 mmol) in glacial HOAc (3 mL). The reaction mixture was hydrogenated at room temperature at 30 psi for 24 h. The hydrogenation was continued for an additional 48 h at 50 psi until starting material could no longer be observed on TLC. The reaction mixture was filtered and the catalyst was washed with HOAc and H_2O. Ice was added to maintain the temperature at 5 °C while the combined acidic solution was carefully neutralized with NH_4OH. The basic aqueous solution was extracted with $CHCl_3$ and then with $CHCl_3$/MeOH (3:1). The combined organic material was washed with H_2O and the washings were back extracted with $CHCl_3$. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed. Column chromatography (hexane/EtOAc, 5:1) gave **15** (23.6 mg, 45%); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.06–7.17 (m, 2H), 6.88–6.93 (m, 2H), 4.12 (dd, J = 12.9, 6.3 Hz, 1H), 3.76 (t, J = 12 Hz, 1H), 3.40 (m, 2H), 2.22 (d, J = 12.3 Hz, 1H), 1.45–2.08 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.72, 138.42, 127.85, 121.68, 121.27, 110.75, 89.31, 47.98, 45.69, 44.01, 38.24, 32.81, 32.16, 21.66; HRMS calcd for $C_{14}H_{18}NO$ $[M+H]^+$: 216.1388; found 216.1390.

4.1.16. (3*R**,6a*S**,11a*S**)-2-Methyl-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-c]azocine (16)

A mixture of **15** (10 mg, 0.05 mL), 10% Pd/C (3 mg), and 37% HCHO (3 μL, 0.04 mmol) in MeOH (2 mL) was stirred at room temperature for 4 h in a hydrogen atmosphere. The mixture was filtered through a pad of Celite, washed with MeOH, and concentrated to provide the crude product. Column chromatography with CH_2Cl_2/MeOH/NH_4OH (95:5:1) gave **16** (9.4 mg, 82%) as a white solid. Mp (free base) 59.1–59.3 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.08–7.15(m, 2H), 6.88–6.92 (m, 2H), 4.26 (dd, J = 11.5, 5.5 Hz, 1H), 3.40 (t, J = 10 Hz, 1H), 3.27 (dd, J = 9.5, 5.5, 1H), 3.09 (br s, 1H), 2.59 (s, 3H), 2.28 (d, J = 13 Hz, 1H), 2.16 (d, J = 12 Hz, 1H), 2.00 (d, J = 12 Hz, 1H), 1.72–1.79 (m, 2H), 1.58–1.64 (m, 1H), 1.40–1.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.34, 138.33, 127.68, 121.71, 121.17, 110.76, 88.44, 54.34, 53.24, 43.60, 42.21, 36.61, 32.01, 25.91, 21.60; HRMS calcd for $C_{15}H_{20}NO$ $[M+H]^+$: 230.1545; found 230.1545. Anal. Calcd for $C_{15}H_{19}NO$·0.1H_2O: C, 77.95; H, 8.37; N, 6.06. Found: C, 78.14; H, 8.46; N, 6.33.

4.1.17. (3*R**,6a*S**,11a*S**)-2-Methyl-8-nitro-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-c]azocine (17)

$NaNO_2$ (360 mg, 5.22 mmol) was slowly added to a solution of **16** (200 mg, 0.87 mmol) in trifluoroacetic acid (4 mL), cooled to 5 °C in an ice bath, and the mixture was stirred for 2 h under argon, until the starting material was no longer detectable on TLC. The mixture was diluted with ice water and carefully basified with NH_4OH. The aqueous solution was extracted with $CHCl_3$/MeOH (3:1). The combined organic phase was washed with H_2O, dried over Na_2SO_4 and the solvent was removed to give **17** (93.2 mg,

39%); ^{1}H NMR ($CDCl_3$ 500 MHz): δ 8.13 (d, J = 8.5 Hz, 1H), 7.98 (br s, 1H), 6.94 (d, J = 8.5 Hz, 1H), 4.40 (dd, J = 11.0, 5.0 Hz, 1H), 3.44 (t, J = 10 Hz, 1H), 3.29 (dd, J = 9.0, 5.0 Hz, 1H), 3.12 (br s, 1H), 2.60 (s, 3H), 2.29(m, 1H), 2.21 (d, J = 10 Hz, 1H), 2.03 (d, J = 10 Hz, 1H), 1.65–1.80 (m, 3H), 1.45–1.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.83, 142.40, 139.58, 125.30, 118.23, 110.73, 90.10, 54.11, 52.77, 43.68, 42.15, 36.25, 32.18, 25.64, 21.49; HRMS calcd for $C_{15}H_{19}N_2O_3$ $[M+H]^+$: 275.1396; found 275.1387.

4.1.18. (3*R**,6a*S**,11a*S**)-8-Amino-2-methyl-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-c]azocine (18)

The nitrophenyl compound **17** (70 mg, 0.255 mmol) was dissolved in MeOH (10 mL) containing 0.18 mL of concentrated hydrochloric acid. Pd/C catalyst (55 mg) was added and the solution was hydrogenated at room temperature for 1.5 h, when the starting material was no longer detectable on TLC. The mixture was filtered and the catalyst was washed with MeOH. The combined filtrate was concentrated in vacuo, H_2O was added, and the aqueous solution was extracted with $CHCl_3$. The combined organic phase was dried over Na_2SO_4 and the solvent removed to afford the amine **18** (42.4 mg, 68%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.70 (d, J = 8 Hz, 1H), 6.46–6.48 (m, 2H), 4.20 (dd, J = 11.5, 4.0 Hz, 1H), 3.44 (br s, 2H), 3.36 (t, J = 10.5 Hz, 1H), 3.24 (m, 1H), 3.07 (br s, 1H), 2,58 (s, 3H), 2.27 (m, 1H), 2.09 (d, J = 11.5 Hz, 1H), 1.97 (m, 1H), 1.58–1.77 (m, 3H), 1.41–1.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.31, 140.52, 139.26, 114.02, 110.83, 109.73, 88.28, 54.38, 53.33, 43.85, 42.21, 36.55, 31.77, 25.89, 21.57; HRMS calcd for $C_{15}H_{21}N_2O$ $[M+H]^+$: 245.1654; found 245.1641.

4.1.19. (3*R**,6a*S**,11a*S**)-2-Methyl-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-c]azocine-8-ol (19)

The amine **18** (30 mg, 0.12 mmol) was cooled in an ice-salt bath and dissolved in 30% H_2SO_4 (15 mL). Ice (6 g) was added to the solution, followed by a solution of $NaNO_2$ (10.2 mg, 0.14 mmol) in H_2O (3 mL). The mixture was stirred for 2 h under argon, maintaining the temperature at 0 °C. This mixture was added over 15 min to a cooled aqueous mixture of $Cu(NO_3)_2{\cdot}2.5\ H_2O$ (720 mg, 3.09 mmol) and Cu_2O (24 mg, 0.17 mmol). The stirring was continued for 1 h at 0 °C, and the reaction mixture was poured into an aqueous solution of 10% KOH (60 mL) and ice. The pH was adjusted to 9 by the addition of a saturated solution of NH_4Cl and the aqueous solution was extracted with $CHCl_3$/MeOH (3:1) to give **19** (20 mg, 67%). An HCl salt was prepared and recrystallized from acetone. Mp (HCl salt) 202.9–203.7 °C (dec); ^{1}H NMR (CD_3OD, 300 MHz): δ 6.50–6.66 (m, 3H), 4.10 (dd, J = 11.7, 5.4 Hz, 1H), 3.37 (dd, J = 12, 10.5 Hz, 1H), 3.17 (dd, J = 10.5, 5.4 Hz, 1H), 3.06 (br s, 1H), 2.56 (s, 3H), 2.29 (d, J = 14.4 Hz, 1H), 2.19 (dd, J = 12.6, 2.4 Hz, 1H), 1.44–1.94 (m, 6H); ^{13}C NMR (CD_3OD, 75 MHz): δ 153.84, 153.27, 140.49, 114.77, 111.75, 110.39, 89.42, 56.16, 54.46, 45.24, 42.44, 37.23, 32.82, 26.73, 22.59; HRMS calcd for $C_{15}H_{20}NO_2$ $[M+H]^+$: 246.1494; found 246.1487. Anal. Calcd for $C_{15}H_{19}NO_2{\cdot}HCl{\cdot}0.1H_2O$: C, 63.53; H, 7.18; N, 4.94. Found: C, 63.20; H, 7.18; N, 4.97.

4.1.20. (3*R**,6a*S**,11a*S**)-2-Methyl-2,3,4,5,6,11a-hexahydro-1*H*-3,6a-methanobenzofuro[2,3-c]azocin-8-yl acetate (20)

The phenol **19** (70 mg, 0.28 mmol) in acetic anhydride (2 mL) was heated at 60 °C for 1 h under argon. After cooling to room temperature, it was diluted with CH_2Cl_2, washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. Column chromatography of the crude material with hexane and EtOAc (5:1) gave **20** (80 mg, 98%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.81–6.86 (m, 3H), 4.30 (dd, J = 11.5, 5.5 Hz, 1H), 3.39 (t, J = 11.5 Hz, 1H), 3.26 (dd, J = 10.0, 5.5 Hz, 1H), 3.09 (br s, 1H), 2.58 (s, 3H), 2.27 (br s, 4H), 2.11 (d, J = 12.5, 1H), 2.01 (d, J = 10.5 Hz, 1H), 1.75–1.79 (m, 2H), 1.60–1.63 (m, 1H), 1.42–1.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.93, 156.87, 144.73, 139.27, 120.35, 115.47, 110.88, 88.81, 54.27, 53.12, 44.01, 42.14, 36.38, 31.93, 25.82, 21.52, 21.08; HRMS calcd for $C_{17}H_{22}NO_3$ $[M+H]^+$: 288.1600; found 288.1590. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.92; H, 7.51; N, 4.68.

4.1.21. (3*R**,6a*S**,11a*S**)-2,3,4,5,6,11a-Hexahydro-1*H*-3,6a-methanobenzofuro[2,3-c]azocin-8-ol (21)

The tertiary amine **20** (54.6 mg, 0.19 mmol) was dissolved in CH_3CN/H_2O (5:1). $Cu(OAc)_2$ (69 mg, 0.38 mmol) and $(NH_4)_2S_2O_8$ (176.97 mg, 0.76 mmol) were added to the solution.[14] The mixture was stirred overnight at room temperature and the reaction was quenched with aqueous 10% $Na_2S_2O_3$. The reaction mixture was basified to pH ~9 with concentrated aqueous NH_4OH, extracted with a $CHCl_3$/MeOH (3:1) mixture. The aqueous solution was then re-extracted with $CHCl_3$/MeOH (3:1). The organic solution was dried over Na_2SO_4, filtered, and the solvent removed in vacuo. Column chromatography with CH_2Cl_2/MeOH/NH_4OH (90:10:1) gave crude **21** (13.5 mg, 30.5%). The crude product **21** was not purified but used directly in the next step.

4.1.22. (3*R**,6a*S**,11a*S**)-2-Phenethyl-2,3,4,5,6,11a-hexahydro-1*H*-3,6a-methanobenzofuro[2,3-c]azocin-8-ol (22)

A mixture of **21** (12 mg, 0.052 mmol), $NaHCO_3$ (4.8 mg, 0.057 mmol) and (2-bromoethyl)benzene (7.7 μL, 0.057 mmol) in DMF (3 mL) was heated at 80–90 °C for 4 h under argon. After cooling to room temperature, it was diluted with Et_2O and washed with H_2O and brine. The solvent was dried over Na_2SO_4, filtered, and removed in vacuo. Column chromatography of the crude material with hexane/EtOAc (5:1) gave **12** (11.7 mg, 67.3%). The HCl salt was prepared and recrystallized from MeOH. Mp (HCl salt) 252.1–254.5 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.19–7.30 (m, 5H), 6.74 (d, J = 8.5 Hz, 1H), 6.56–6.59 (m, 2H), 4.24 (dd, J = 11.5, 5.5 Hz, 1H), 3.40 (m, 2H), 3.21 (br s, 1H), 2.81–2.97 (m, 4H), 2.22 (d, J = 12 Hz, 1H), 2.09 (d, J = 11.0 Hz, 1H), 1.97 (d, J = 11.0 Hz, 1H), 1.42–1.82 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.29, 150.15, 140.33, 139.71, 128.74, 128.36, 126.07, 113.72, 110.81, 109.60, 88.61, 56.55, 52.95, 51.29, 44.37, 36.51, 34.92, 31.84, 26.56, 21.75; HRMS calcd for $C_{22}H_{26}NO_2$ $[M+H]^+$: 336.1964; found 336.1968. Anal. Calcd for $C_{22}H_{25}NO_2{\cdot}HCl$: C, 71.05; H, 7.05; N, 3.77. Found: C, 70.79; H, 7.04; N, 3.80.

4.1.23. ((1*R**,4*R**,5*S**)-5-(2,3-dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-4-ol (23). Alternative route to (3*R**,6a*S**,11a*S**)-2-methyl-2,3,4,5,6,11a-hexahydro-1*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-10-ol (13)

To a solution of **8** (3.67 g, 10 mmol) in MeOH (300 mL) was added 10% Pd/C (2 g) and the mixture was heated to boiling. To this was added a solution of ammonium formate (2.9 g, 46 mmol) in H_2O (3 mL) and the mixture was stirred and refluxed for 2 h, at which time 88% formic acid (1 mL) and 37% formaldehyde (2 mL) were added. After stirring at reflux temperature for another 3 h the mixture was filtered and washed with MeOH. The solvents were removed in vacuo and the residual material dissolved in H_2O, basified with 28% NH_4OH and extracted with $CHCl_3$ (2×). The combined extracts were washed with H_2O and dried over Na_2SO_4. The solvent was removed in vacuo to give **23** as an orange crystalline solid. Recrystallization from 2-propanol gave **23** (1.85 g) as fine white crystals, mp 163–165 °C (lit.[4] 163–164 °C). An additional 0.11 g was obtained from the mother liquor (68% total yield). Compound **24** was prepared[4] similarly to **9** and the crude **24** was used to prepare **13** as a crystalline free base (46–50% yield from **8**), mp 192–193 °C (lit.[4] 195–196 °C).

4.1.24. Opioid binding assays

As described,[16] the recombinant CHO cells (hMOR-CHO, hDOR-CHO and hKOR-CHO) were produced by stable transfection with the respective human opioid receptor cDNA, and provided by Dr. Larry Toll (SRI International, CA). The cells were grown on plastic flasks in DMEM (90%) (hDOR-CHO and hKOR-CHO) or DMEM/ F-12 (45%/45%) medium (hMOR-CHO) containing 10% FetalClone II (HyClone) and Geneticin (G-418: 0.10–0.2 mg/mL) (Invitrogen) under 95% air/5% CO_2 at 37° C. Cell monolayers were harvested and frozen in −80 °C. The hKOR-CHO, hMOR-CHO and hDOR-CHO cells are used for opioid binding experiments. For the [^{35}S]-GTP-γ-S binding experiments, we use hKOR-CHO and hMOR-CHO cells for assaying KOR and MOR receptor function. Currently, we use the NG108–15 neuroblastoma × glioma cell for the DOR [^{35}S]-GTP-γ-S binding assay, and obtain an excellent signal-to-noise ratio. In summary, we use the hDOR-CHO cells for DOR binding assays, and the NG108–15 cells for the DOR [^{35}S]-GTP-γ-S binding assay.

We currently use [^{3}H][D-Ala^2-MePhe^4,Gly-ol^5]enkephalin ([^{3}H]DAMGO, SA = 44–48 Ci/mmol) to label MOR, [^{3}H][D-Ala^2, D-Leu^5]enkephalin ([^{3}H]DADLE, SA = 40–50 Ci/mmol) to label DOR and [^{3}H](−)-U69,593 (SA = 50 Ci/mmol) to label KOR binding sites. On the day of the assay, cell pellets were thawed on ice for 15 minutes then homogenized with a polytron in 10 mL/pellet of ice-cold 10 mM Tris–HCl, pH 7.4. Membranes were then centrifuged at 30,000*g* for 10 min, resuspended in 10 mL/pellet ice-cold 10 mM Tris–HCl, pH 7.4 and again centrifuged 30,000*g* for 10 min. Membranes were then resuspended in 25 °C 50 mM Tris–HCl, pH 7.4 (~100 mL/pellet hMOR-CHO, 50 mL/pellet hDOR-CHO and 120 mL/pellet hKOR-CHO). All assays took place in 50 mM Tris–HCl, pH 7.4, with a protease inhibitor cocktail [bacitracin (100 μg/mL), bestatin (10 μg/mL), leupeptin (4 μg/mL) and chymostatin (2 μg/mL)], in a final assay volume of 1.0 mL. All drug dilution curves were made up with buffer containing 1 mg/mL BSA. Nonspecific binding was determined using 20 μM levallorphan ([^{3}H]DAMGO and [^{3}H]DADLE) and 1 μM (−)-U69,593 (for [^{3}H]U69,593 binding). [^{3}H]Radioligands were used at ~2 nM concentrations. Triplicate samples were filtered with Brandel Cell Harvesters (Biomedical Research & Development Inc., Gaithersburg, MD), over Whatman GF/B filters, after a 2 h incubation at 25 °C. The filters were punched into 24-well plates to which was added 0.6 mL of LSC-cocktail (Cytoscint). Samples were counted, after an overnight extraction, in a Trilux liquid scintillation counter at 44% efficiency. Opioid binding assays had ~30 μg protein per assay tube. Inhibition curves were generated by displacing a single concentration of radioligand by 10 concentrations of drug.

4.1.25. [^{35}S]GTP-γ-S binding assays

The [^{35}S]-GTP-γ-S assays were conducted as described elsewhere.[16] 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. [^{35}S]GTP-γ-S binding was determined as described previously. Briefly, 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.

4.1.26. Data analysis and statistics

These methods are described elsewhere.[16] For opioid binding experiments, the pooled data of three experiments (typically 30 data points) are fit to the two-parameter logistic equation for the best-fit estimates of the IC_{50} and N values: Y = 100/(1 + ([INHIBITOR]/IC50)^N), where 'Y' is the percent of control value. K_i values for test drugs are calculated according to the standard equation: $K_i = IC_{50}/(1+[radioligand]/K_d)$. For the [^{3}H]radioligands, the following K_d values (nM ± SD, $n = 3$) were used in the Ki calculation: [^{3}H]DAMGO (0.93 ± 0.04), [^{3}H]DADLE (1.9 ± 0.3) and [^{3}H](−)-U69,593 (11 ± 0.6). The corresponding Bmax values were (fmol/mg protein ± SD, $n = 3$): [^{3}H]DAMGO (1912 ± 68), [^{3}H]DADLE (3655 ± 391) and [^{3}H](−)-U69,593 (3320 ± 364).

For the [^{35}S]GTP-γ-S binding experiments, the percent stimulation of [^{35}S]GTP-γ-S binding was calculated according to the following formula: $(S - B)/B \times 100$, where B is the basal level of [^{35}S]GTP-γ-S binding and S is the stimulated level of [^{35}S]GTP-γ-S binding. Agonist dose-response curves (ten points/curve) are generated, and the data of several experiments, 3 or more, are pooled. The EC_{50} values (the concentration that produces fifty percent maximal stimulation of [^{35}S]GTP-γ-S binding) and E_{max} are determined using either the program MLAB-PC (Civilized Software, Bethesda, MD), KaleidaGraph (Version 3.6.4, Synergy Software, Reading, PA) or Prism 4.0 (GraphPad Software, Inc, San Diego, CA). In most cases, the percent stimulation of the test compound is reported as a percent of the maximal stimulation of 1000 nM DAMGO, 500 nM SNC80 or 500 nM (−)-U50,488 in the appropriate cell type. For determination of K_e values using the 'shift' experimental design, agonist (DAMGO, (−)-U50,488 or SNC80) dose–response curves are generated, using the appropriate cell type, in the absence and presence (ten points/curve) of a test compound. The data of several experiments, 3 or more, are pooled, and the K_e values are calculated according to the equation: [Test Drug]/($EC_{50\text{-}2}/EC_{50\text{-}1} - 1$), where $EC_{50\text{-}2}$ is the EC_{50} value in the presence of the test drug and $EC_{50\text{-}1}$ is the value in the absence of the test drug.

4.1.27. X-ray crystal structure of 10

Single-crystal X-ray diffraction data on **10** (HCl salt of *rac*-(3*R*,6a*S*,11a*S*)-2-benzyl-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocine-10-ol) were collected at 173 K using MoKα radiation ($\lambda = 0.71073$ Å) and a Bruker APEX 2 CCD area detector. The samples were prepared for data collection by coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was mounted on a MicroMesh mount (MiTeGen, Inc.) and transferred immediately to the diffractometer. The $0.233 \times 0.161 \times 0.063$ mm^3 crystal of **10** was triclinic in space group $P\bar{1}$ with unit cell dimensions $a = 7.783(3)$ Å, $b = 10.028(4)$ Å, $c = 12.657(5)$ Å, $\alpha = 103.490(5)$, $\beta = 107.365(5)$, and $\gamma = 93.687(6)$. Data were 98% complete to 26.38° θ (approximately 0.80 Å) with an average redundancy of 2.07. The asymmetric unit contains a single molecule. Corrections were applied for Lorentz, polarization, and absorption effects. All 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).

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. Atomic coordinates for **10** have been deposited with the Cambridge Crystallographic Data Centre (deposition number 806,302). 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.2011.04.028.

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