

A critical structural determinant of opioid receptor interaction with phenolic 5-phenylmorphans

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Abstract—The opioid receptor binding affinities of *N*-methyl- and *N*-phenethyl-5-phenylmorphans with a *meta*-hydroxy substituent [3-(2-methyl-2-azabicyclo[3.3.1]non-5-yl)-phenol (**1a**), and 3-(2-phenethyl-2-azabicyclo[3.3.1]non-5-yl)-phenol (**1b**)] were compared with the affinities of four new ligands bearing an *ortho*- or *para*-hydroxyl substituent (2-(2-methyl-2-azabicyclo[3.3.1]non-5-yl)-phenol (**2a**) and 2-(2-phenethyl-2-azabicyclo[3.3.1]non-5-yl)-phenol (**2b**), 4-(2-methyl-2-azabicyclo[3.3.1]non-5-yl)-phenol (**3a**), and 4-(2-phenethyl-2-azabicyclo[3.3.1]non-5-yl)-phenol (**3b**)) that were synthesized from 2-bromoanisole or the known 2-methyl-5-phenyl-2-azabicyclo[3.3.1]nonane (**13**), respectively. The data indicated that either the electronic state of the phenolic ring is critical for the ligand's interaction with an opioid receptor, or that there must be a specific distance and angle for a hydrogen bond between the phenolic moiety and an amino acid in the binding domain that cannot be altered.

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1. Introduction

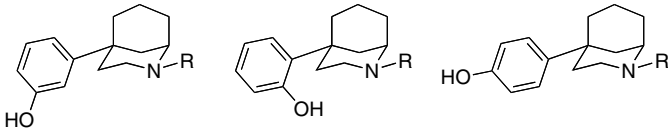
The 5-phenylmorphans class of analgesics was examined in the 1950's by May and co-workers as part of their attempt to dissociate the undesirable effects of morphine from its analgesic action through molecular simplification.^{1–3} An initial compound that they prepared in the 5-phenylmorphans series, (±)-5-*m*-hydroxyphenyl-*N*-methylmorphans ((±)-3-(2-methyl-2-azabicyclo[3.3.1]non-5-yl)-phenol, **1a**, Table 1) was found to be as potent as compounds in the epoxymorphinan (e.g., morphine), morphinan (e.g., levorphanol), and 6,7-benzomorphans (e.g., metazocine) classes of antinociceptives,⁴ yet it had only an azabicyclo ring structure with an attached, freely rotating, phenolic ring. We recently reported that the levorotatory enantiomer of the *N*-phenethyl analogue of *m*-hydroxy-5-phenylmorphans ((-)-3-(2-phenethyl-2-azabicyclo[3.3.1]non-5-yl)-phenol, **1b**, Table 1)

had opioid antagonist activity,^{5,6} and that finding answered the question of whether pure opioid antagonists could be obtained in the 5-phenylmorphans series when the phenolic ring was not sterically hindered.⁷ It is well known that a phenolic hydroxyl moiety positioned *meta* to the quaternary carbon atom in the epoxymorphinan, morphinan, and 6,7-benzomorphans series of rigid cyclic opioids, greatly enhances the antinociceptive activity of the compound,^{8–11} and, no doubt, the interaction of these compounds with the opioid receptor. The hydroxy group on the aromatic ring in the 5-phenylmorphans was originally placed in the *meta*-position presumably because it appeared to have a close structural resemblance to the known antinociceptive compounds. However, in all of the structurally rigid analogues of morphine (epoxymorphinans, etc.), the phenolic ring is axially oriented to the piperidine ring. In the 5-phenylmorphans series, the phenolic ring is equatorially oriented to the piperidine ring, and can rotate. Steric hindrance to that rotation⁷ appears to increase the affinity of the *N*-phenethyl-5-phenylmorphans opioid antagonists to the opioid receptor, but steric hindrance does not appear to be essential for either agonist or antagonist effects.⁶ The difference in the orientation of

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Table 1. Binding affinity of 5-phenylmorphans to opioid receptors

			
	1a: R = CH ₃ 1b: R = CH ₂ CH ₂ C ₆ H ₅	2a: R = CH ₃ 2b: R = CH ₂ CH ₂ C ₆ H ₅	3a: R = CH ₃ 3b: R = CH ₂ CH ₂ C ₆ H ₅
Compd	K _i (nM ± SD)		
	[³ H]DAMGO (μ) ^a	[³ H]DADLE (δ) ^b	[³ H]U69,593 (κ) ^c
2a	>7200	>8400	>6300
2b	840 ± 120	>8400	>6300
3a	2060 ± 230	>8400	>6300
3b	310 ± 30	2940 ± 360	1600 ± 280
1a	43 ± 4	610 ± 60	925 ± 110
1b	30 ± 3	290 ± 30	240 ± 18

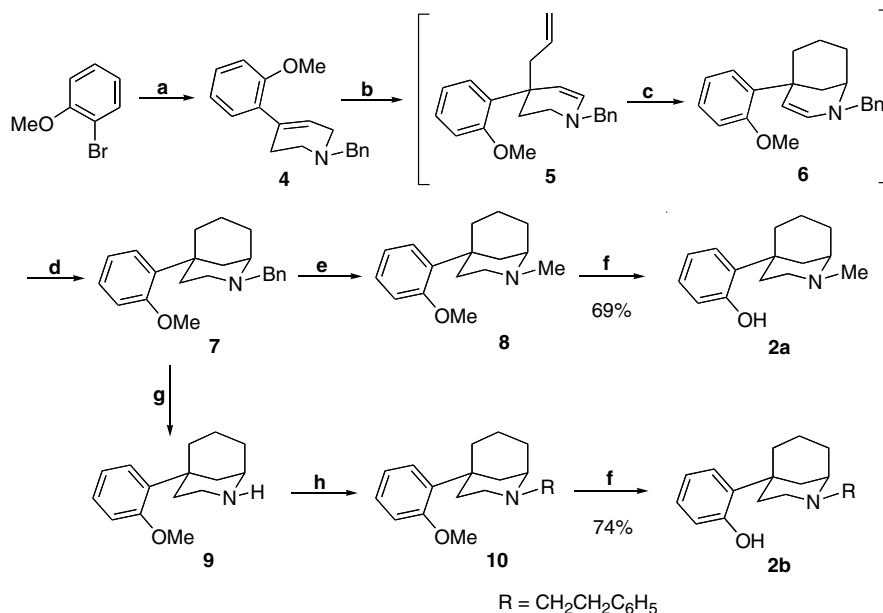
^a [³H]DAMGO (D-Ala², MePhe⁴Gly-ol⁵)enkephalin, agonist selective for μ-opioid receptor.^b [³H]DADLE (D-Ala², D-Leu⁵)enkephalin, agonist selective for δ-opioid receptor.^c [³H]U69,593 (*trans*-3,4-dichloro-*N*-methyl[2-(1-pyrrolidinyl)cyclohexyl]benzene acetamide), agonist selective for κ-opioid receptor.

the phenolic ring between rigid cyclic opioids and the 5-phenylmorphans makes it difficult to predict whether the *meta* position of the hydroxyl moiety is optimal for receptor binding in the 5-phenylmorphans. Certainly, the *N*-substituents that are able to induce agonist and antagonist behavior in the various aforementioned classes of structurally rigid opioids, are known not to do so in the 5-phenylmorphans. Thus, for example, a change of the *N*-methyl or *N*-pentyl moiety in these structurally rigid opioids to an *N*-allyl or *N*-cyclopropylmethyl group has been frequently used to convert a potent, high affinity agonist, to a potent, high affinity opioid antagonist. Such a change does not confer antagonist activity to the 5-phenylmorphans.¹² We decided to attempt to determine whether a specific spatial position of the phenolic hydroxyl group in the 5-phenylmorphans is essential to its interaction with opioid receptors. This could, indirectly, provide information about the interaction of these ligands with the amino acids in the transmembrane helices in the opioid receptor, since there is likely to be only a modest difference in three-dimensional space between a phenolic hydroxyl positioned on either side of the *meta*-hydroxyl group and the amino acid in the opioid receptor with which it interacts. An inability to interact with the hydroxyl group in a slightly different area might indicate that there is little conformational mobility in the binding site. However, it is also possible that the electronic charges induced in the aromatic ring through resonance with an *ortho*- or *para*-phenolic moiety, in contrast to the *meta*-oriented hydroxyl group, might have a considerable effect on interaction with the appropriate opioid receptor's amino acids. It would, therefore, be of interest to examine the affinity of these ligands in order to discern whether the position of a phenolic hydroxyl on the aromatic ring is as critical for receptor interaction in the 5-phenylmorphans, where the aromatic ring can freely rotate, as it is in the rigid cyclic opioids. We have, thus, synthesized the alternative phenolic compounds, 2-(2-methyl-2-azabicyclo[3.3.1]non-5-yl)-phenol (**2a**), 2-(2-

phenethyl-2-azabicyclo[3.3.1]non-5-yl)-phenol (**2b**), 4-(2-methyl-2-azabicyclo[3.3.1]non-5-yl)-phenol (**3a**), and 4-(2-phenethyl-2-azabicyclo[3.3.1]non-5-yl)-phenol (**3b**), the *ortho*- and *para*-phenolic hydroxyl compounds in an *N*-methyl- and *N*-phenethyl-5-phenylmorphans, and determined their binding affinity with μ-, δ-, and κ-opioid receptors. The 3-(2-methyl-2-azabicyclo[3.3.1]non-5-yl)-phenol (**1a**), and 3-(2-phenethyl-2-azabicyclo[3.3.1]non-5-yl)-phenol (**1b**) were resynthesized for comparison.

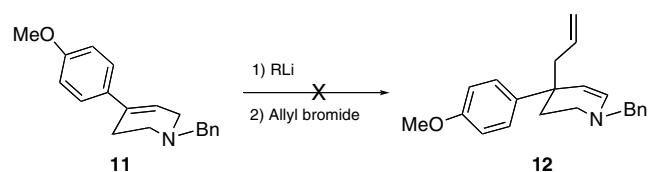
2. Chemistry

The synthesis of the *ortho*-hydroxy phenylmorphans (**2a** and **2b**) was achieved as shown in Scheme 1. Lithiation of 2-bromoanisole by *n*-BuLi^{13,14} followed by its addition to 1-benzyl-4-piperidone gave a hydroxypiperidine intermediate that, without purification, was dehydrated to tetrahydropyridine **4** in good yield (71% over two steps). The metalated enamine resulting from lithiation of **4** was reacted with allyl bromide to give endocyclic enamine **5**, which upon treatment with a 1:1 mixture of HCO₂H and H₃PO₄ at room temperature for 88 h gave an intermediate enamine **6**. This enamine was immediately reduced with NaBH₄ to 2-benzyl-5-(2-methoxyphenyl)-2-azabicyclo[3.3.1]nonane (**7**). Hydrogenation of **7** in the presence of formaldehyde resulted in hydrogenolysis of the *N*-benzyl substituent followed by reductive methylation to give the *ortho*-methoxy substituted 5-phenylmorphans **8**, from **6**, in 66% yield over three steps. Demethylation of **8** gave the desired *ortho*-phenolic compound **2a** (2-(2-methyl-2-azabicyclo[3.3.1]non-5-yl)-phenol). Its *N*-phenethyl analogue **2b** (2-(2-phenethyl-2-azabicyclo[3.3.1]non-5-yl)-phenol), was obtained through catalytic debenzoylation of **7**, and acylation of **9** with phenylacetyl chloride and reduction of the resulting compound amide, to give the intermediate **10**. *O*-Demethylation of **10** gave **2b**, as shown in Scheme 1.



Scheme 1. Reagents and conditions: (a) i. THF, -78°C , $n\text{-BuLi}$, then 1-benzyl-4-piperidone, to rt; ii. toluene, $p\text{-toluenesulfonic acid monohydrate}$, reflux, 71% over two steps; (b) THF, -50°C , $sec\text{-BuLi}$, then allyl bromide, to 0°C ; (c) $\text{H}_3\text{PO}_4\text{--HCO}_2\text{H}$ (1:1), rt; (d) MeOH, 0°C , NaBH_4 , then rt, 66% over three steps; (e) MeOH, 10% Pd-C, 37% HCHO in H_2O , cat. AcOH, H_2 , 60°C , 85%; (f) AcOH, 48% HBr , reflux; (g) MeOH, 10% Pd-C, cat. AcOH, 60°C , 92%; (h) (i) CH_2Cl_2 , phenylacetyl chloride, DMAP, 0°C ; (ii) THF, LiAlH_4 , 0°C , 92% over two steps.

The synthesis of **2a** and **2b** involved the lithiation of a phenyl ring system bearing oxygen functionality at the *ortho*-position. This was not applicable to the synthesis of the *para*-hydroxy 5-phenylmorphans **3**. When lithiation followed by allylation was attempted with tetrahydropyridine **11**, only starting material was recovered, not compound **12**, as shown in Scheme 2. It is possible that the benzylic anion (see A in Fig. 1) resulting from lithiation of **11** was destabilized by a partial negative charge that is generated through the contribution of the electron-donating methoxy group at the *para*-position as



Scheme 2. Attempted allylation.

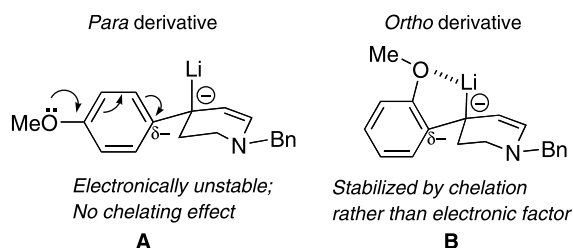
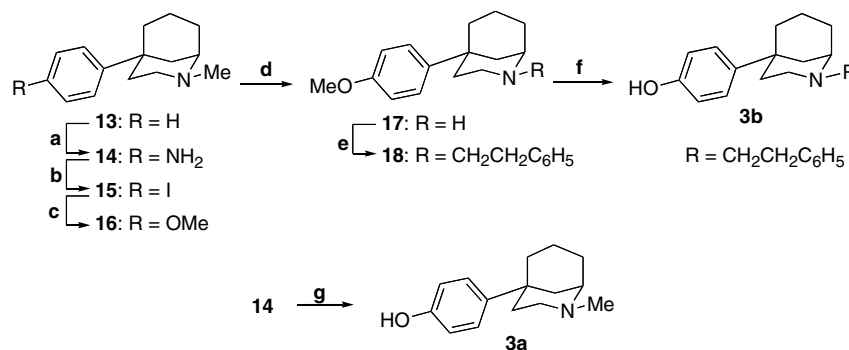


Figure 1. Possible stabilization of benzylic anion resulting from lithiation.

shown in Figure 1. Although this electronic effect is also hypothesized in the lithiation of tetrahydropyridine **4** (see B in Fig. 1), the destabilization of benzylic anion by an electron-donating methoxy group at the *ortho*-position was probably relieved by intramolecular chelation between the *ortho*-methoxy group and lithium.

This unexpected problem in the lithiation of **11** forced an alternative approach to functionalization of the *para*-position, using 5-phenylmorphans **13** (Scheme 3). The nonoxygenated compound **13**¹⁵ was prepared according to the literature.¹⁴ Nitration of **13** followed by reduction gave the anilino phenylmorphans **14**. The by-product obtained from nitration was removed by column chromatography. Compound **14** was converted to iodophenylmorphans **15** by a Sandmeyer reaction in the presence of 37% HCl , NaNO_2 , and KI ,¹⁶ and **15** was used for incorporation of the necessary oxygen functionality. Using the protocol of Buchwald and co-workers,^{17,18} *para*-methoxy-5-phenylmorphans **16** (5-(4-methoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonane) was successfully obtained from a copper-catalyzed coupling reaction of **15** and dry MeOH in the presence of a trace amount of CuI , 1,10-phenanthroline, and Cs_2CO_3 in 89% yield. *para*-Methoxy-5-phenylmorphans **16** was, then, *N*-demethylated using 2,2,2-trichloroethylformate^{19–21} and K_2CO_3 followed by reductive cleavage by Zn powder to give 5-phenylmorphans **17** in reasonable yield (61% over two steps). Acylation and reduction of **17**, followed by demethylation, gave **3b** (4-(2-phenethyl-2-azabicyclo[3.3.1]non-5-yl)-phenol) as shown in Scheme 3. The *N*-methyl analogue, **3a** (4-(2-methyl-2-azabicyclo[3.3.1]non-5-yl)-phenol) was directly obtained from **14** via a Sandmeyer reaction.



Scheme 3. Reagents and conditions: (a) i. 70% HNO₃, 40 °C; ii. ethanol, 10% Pd-C, cat. AcOH, 60 °C, 83% over two steps; (b) concd HCl, NaNO₂, then KI, 54%; (c) abs. MeOH, CuI (10 mol%), 1,10-phenanthroline (20 mol%), Cs₂CO₃, sealed tube, 80 °C, 89%; (d) i. abs. toluene, 2,2,2-trichloroethylformate, K₂CO₃, reflux; ii. 75% AcOH, Zn powder, rt, 61% over two steps; (e) i. CH₂Cl₂, phenylacetyl chloride, DMAP, 0 °C; ii. abs. THF, LiAlH₄, 0 °C, 83% over two steps; (f) AcOH, 48% HBr, reflux, quantitative; (g) 35% H₂SO₄, NaNO₂, H₂O, urea, then Cu(NO₃)₂, Cu₂O, 58%.

3. Results and discussion

As seen in Table 1, modification of the position of the *meta*-hydroxyl group results in an almost complete loss in affinity for any opioid receptor, in both the *N*-methyl and in the *N*-phenethyl series. Obviously, there is a critical need for a specific phenolic position. Thus, unlike the *N*-substituted analogues in the rigid cyclic series of opioids mentioned above, the *meta*-hydroxy compounds in the 5-phenylmorphans series obey the same rules as in the rigid cyclic opioids. It is possible that the amino acids with which these phenolic hydroxyls interact in the binding pocket of the transmembrane helices of the opioid receptors cannot hydrogen-bond with a phenolic hydroxyl moiety unless the exact distance and angular relationship of the *meta*-hydroxyl exists, as opposed to the *ortho*- or *para*-analogue. This inability of the receptor to interact with the *ortho*- or *para*-oriented ligand implies that there is insufficient conformational mobility in the helical area, even though ligands have been noted to be able to modify the conformation of related G-protein coupled receptors, heretofore.^{22,23} However, as mentioned above, it is well known that *ortho*- and *para*-oriented substituents on an aromatic ring effect the electronic nature of that ring differently than a *meta*-oriented substituent. In an SAR study of rigid cyclic opioids, the calculated electronic charge at a relatively few specific atoms in the molecule were noted to have the strongest influence on biological activity. One of those atoms was located at the C3 position in the aromatic ring (the position at which a *meta*-oriented hydroxyl group is attached).²⁴ Thus, the lack of receptor interaction with the newly synthesized ligands could rationally be ascribed to an electronic effect weakening the attraction of the receptor's amino acids for the aromatic ring, with a subsequent loss of binding energy. Future study of this electronic influence could provide information that could increase our understanding of the effect of ligands on the opioid receptor.

4. Experimental

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Proton nuclear magnetic resonance (¹H NMR) spectra were recorded in CDCl₃ (unless otherwise noted) with tetramethylsilane (TMS) as the internal standard on a Varian Gemini-300 spectrometer. Mass spectra (MS) were recorded on a VG 7070E spectrometer or a Finnigan 4600 spectrometer in the chemical ionization mode (MS, CI-NH₃) and a JEOL SX102a mass spectrometer in the FAB mode with xenon gas. Direct electron impact (DEI) was also obtained on the JEOL SX102a mass spectrometer. Thin layer chromatography (TLC) was performed on Analtech silica gel GHLF 0.25 mm plates. Flash column chromatography was performed with Fluka silica gel 60 (mesh 220–240). Medium pressure column chromatography (using silica gel) was carried out at 30 psi with an RT Scientific Co. (Manchester, NH) High Pressure Chromatography System. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA, and the results were within ±0.4% of the theoretical values. All extracted solutions were dried over sodium sulfate (Na₂SO₄) and concentrated to dryness on a rotary evaporator under reduced pressure.

4.1. 1-Benzyl-4-(2-methoxyphenyl)-1,2,3,6-tetrahydropyridine (4)

n-BuLi (1.6 M) in hexanes (74.3 mL, 118.9 mmol) was added dropwise to a solution of 2-bromoanisole (23.6 g, 118.9 mmol) in THF (150 mL) at –70 °C and stirred for 1 h. A solution of 1-benzyl-4-piperidinone (15.0 g, 79.3 mmol) in THF (100 mL) was added dropwise to the reaction mixture, which was slowly allowed to warm to room temperature and stirred overnight. After recooling to 0 °C, the reaction was quenched by addition of 2 N HCl solution. The aqueous layer was extracted with ethyl acetate (3 × 200 mL), basified with NH₄OH, and re-extracted with ethyl acetate (3 × 200 mL). The combined organic solution was washed with water and brine, dried over sodium sulfate, filtered, and concentrated to give a crude amino alcohol (23.1 g), which, without purification, was dehydrated to **4** in the next reaction. A mixture of the crude amino alcohol (23.1 g, 77.8 mmol) and *p*-toluenesulfonic acid monohydrate (20.7 g, 108.9 mmol) in toluene (600 mL) was refluxed for 18 h with a Dean-Stark trap to remove water. After removal of toluene,

the residual material was diluted with ethyl acetate and NH_4OH . The aqueous layer was extracted with ethyl acetate (3×200 mL), washed with water and brine, dried over sodium sulfate, and concentrated to dryness. Column chromatography of the crude material with 10% ethyl acetate in hexanes gave **4** (15.6 g, 71% over two steps) as a colorless oil. The HCl salt was prepared; mp 184–185 °C; ^1H NMR (free base) δ 7.41–7.15 (m, 7H), 6.93–6.84 (m, 2H), 5.79–5.76 (m, 1H), 3.80 (s, 3H), 3.65 (s, 2H), 3.17–3.16 (m, 2H), 2.70–2.66 (m, 2H), 2.57–2.53 (m, 2H); MS m/z 279 ($\text{M}+\text{H}^+$); HRMS (FAB) calcd for $\text{C}_{19}\text{H}_{21}\text{NO}$ ($\text{M}+\text{H}^+$)⁺ 279.1623, found 279.1622. Anal. Calcd for $\text{C}_{19}\text{H}_{22}\text{ClNO}$: C, 72.25; H, 7.02; N, 4.43. Found: C, 72.04; H, 7.12; N, 4.36.

4.2. 2-Benzyl-5-(2-methoxyphenyl)-2-azabicyclo[3.3.1]-nonane (**7**)

sec-BuLi (1.4 M) in cyclohexane (1.41 mL, 1.98 mmol) was added dropwise to a solution of **4** (542 mg, 1.94 mmol) in THF (15 mL) at –50 °C and the mixture was allowed to warm to –20 °C over 1 h. After cooling to –50 °C, allyl bromide (171 μL , 1.98 mmol) was added, and the mixture was allowed to warm slowly to 0 °C over 2 h. The reaction was quenched by addition of water, diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate, filtered, and concentrated to give a crude endocyclic enamine **5**, which was used directly for the next reaction. The crude **5** was diluted with HCO_2H – H_3PO_4 (5 mL:5 mL) and stirred at room temperature for 88 h. The reaction mixture was poured into ice water, treated with 40% NaOH solution (to pH ~8) and extracted with ethyl acetate (3×50 mL). The organic layer washed with water and brine, dried over sodium sulfate, and concentrated to provide crude enamine **6**. At 0 °C, NaBH_4 (147 mg, 3.88 mmol) was added to a solution of **6** in MeOH (10 mL). The mixture was allowed to warm to room temperature and stirred for 1.5 h. After removal of MeOH, the residue was diluted with water, neutralized with 2 N HCl solution (pH ~8), extracted with ethyl acetate (3×20 mL), washed with water and brine, dried over sodium sulfate, and concentrated to dryness. Column chromatography of the crude material with 3% acetone in hexanes afforded **7** (413 mg, 66% over three steps) as a colorless solid; mp 99–100 °C (recrystallized from hexanes); ^1H NMR (free base) δ 7.39–7.14 (m, 7H), 6.93–6.86 (m, 2H), 3.81 (s, 3H), 3.71 (q, $J = 13$ and 6 Hz, 2H), 3.11 (br s, 1H), 2.96–2.88 (m, 1H), 2.75–2.67 (m, 1H), 2.57–2.45 (m, 2H), 2.20–2.16 (m, 1H), 2.06–1.97 (m, 3H), 1.86–1.70 (m, 3H), 1.64–1.56 (m, 1H); MS m/z 322 ($\text{M}+\text{H}^+$); HRMS (FAB) calcd for $\text{C}_{22}\text{H}_{27}\text{NO}$ ($\text{M}+\text{H}^+$)⁺ 321.2093, found 321.2102. Anal. Calcd for $\text{C}_{22}\text{H}_{27}\text{NO}$: C, 82.20; H, 8.47; N, 4.36. Found: C, 82.03; H, 8.52; N, 4.35.

4.3. 5-(2-Methoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]-nonane (**8**)

A mixture of **7** (598 mg, 1.86 mmol), 10% Pd–C (100 mg), AcOH (10 drops), and 37% formaldehyde in H_2O (154 μL , 1.9 mmol), in MeOH (25 mL) was heated

at 60 °C for 2 h in a hydrogen atmosphere while vigorously stirring. It was cooled to room temperature and the mixture basified with NH_4OH (pH ~8) and stirred for 10 min, filtered through a pad of Celite, washed with MeOH, and the solvent was evaporated in vacuo. Column chromatography of the crude material with CH_2Cl_2 –MeOH– NH_4OH (91:9:1) gave *N*-methylated **8** (390 mg, 85%) as a pale yellow oil; **8**·HCl: mp 196 °C (dec); ^1H NMR (free base) δ 7.21–7.15 (m, 2H), 6.94–6.87 (m, 2H), 3.83 (s, 3H), 3.10–3.05 (m, 1H), 3.02–2.92 (m, 1H), 2.79–2.71 (m, 1H), 2.65–2.57 (m, 1H), 2.54–2.47 (m, 1H), 2.45 (s, 3H), 2.17–2.05 (m, 2H), 1.97–1.73 (m, 3H), 1.64–1.55 (m, 3H), 1.52–1.31 (m, 2H); MS m/z 245 ($\text{M}+\text{H}^+$); HRMS (FAB) calcd for $\text{C}_{16}\text{H}_{23}\text{NO}$ ($\text{M}+\text{H}^+$)⁺ 245.1780, found 245.1763; Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{ClNO} \cdot 0.1\text{H}_2\text{O}$: C, 67.76; H, 8.60; N, 4.94. Found: C, 67.77; H, 8.60; N, 4.89.

4.4. 2-(2-Methyl-2-azabicyclo[3.3.1]non-5-yl)-phenol (**2a**)

A 48% HBr solution (0.7 mL) was added to a solution of **8** (37.6 mg, 0.153 mmol) in AcOH (0.7 mL), and the mixture was refluxed for 21 h, cooled to 0 °C, diluted with water, and basified with 40% NaOH solution (pH ~10).

The mixture was extracted with ethyl acetate– CHCl_3 –MeOH (8:1:1, 3×10 mL), and the organic solution was washed with water and brine, dried over sodium sulfate, and concentrated to give crude **2a**. Column chromatography of crude **2a** with CHCl_3 –MeOH– NH_4OH (80:20:1) provided **2a** (24.4 mg, 69%) as a pale-yellow oil; **2a**·HCl: mp 232–233 °C; ^1H NMR (free base) δ 7.17 (dd, $J = 8$ and 2 Hz, 1H), 7.05 (dt, $J = 8$ and 2 Hz, 1H), 6.85 (dt, $J = 8$ and 2 Hz, 1H), 6.67 (dd, $J = 8$ and 2 Hz, 1H), 3.14–3.09 (m, 1H), 3.03 (dt, $J = 12$ and 5 Hz, 1H), 2.86–2.79 (m, 1H), 2.52–2.42 (m, 2H), 2.49 (s, 3H), 2.17–2.04 (m, 2H), 1.97–1.87 (m, 2H), 1.70–1.57 (m, 2H), 1.48–1.36 (m, 2H); MS m/z 232 ($\text{M}+\text{H}^+$); HRMS (FAB) calcd for $\text{C}_{15}\text{H}_{22}\text{NO}$ ($\text{M}+\text{H}^+$)⁺ 232.1701, found 232.1706. Anal. Calcd for $\text{C}_{15}\text{H}_{22}\text{ClNO} \cdot 0.25\text{H}_2\text{O}$: C, 66.16; H, 8.33; N, 5.14. Found: C, 66.25; H, 8.25; N, 5.04.

4.5. 5-(2-Methoxyphenyl)-2-azabicyclo[3.3.1]nonane (**9**)

A mixture of **7** (586 mg, 1.82 mmol), 10% Pd–C (100 mg), and AcOH (10 drops) in MeOH (30 mL) was heated at 60 °C for 2.5 h in a hydrogen atmosphere. After cooling to room temperature, it was basified with NH_4OH (pH ~10), filtered through a pad of Celite, washed with MeOH, and concentrated to provide the crude product. Column chromatography of crude product with H_2Cl_2 –MeOH– NH_4OH (91:9:1) afforded **9** (390 mg, 85%) as a pale yellow oil; **9**·HCl: mp 181–182 °C; ^1H NMR (free base) δ 7.22–7.16 (m, 2H), 6.95–6.87 (m, 2H), 3.83 (s, 3H), 3.47–3.45 (m, 1H), 3.37–3.28 (ddd, $J = 14$, 10, and 5 Hz, 1H), 2.97 (dt, $J = 13$ and 6 Hz, 1H), 2.50–2.41 (m, 2H), 2.16–2.20 (m, 3H), 1.82–1.59 (m, 4H), 1.53–1.42 (m, 1H); MS (DEI) m/z 231 (M^+); HRMS (DEI) calcd for $\text{C}_{15}\text{H}_{21}\text{NO}$ (M^+)⁺ 231.1623, found 231.1626; Anal. Calcd for $\text{C}_{15}\text{H}_{22}\text{ClNO}$:

C, 67.28; H, 8.28; N, 5.23. Found: C, 67.07; H, 8.36; N, 5.15.

4.6. 5-(2-Methoxyphenyl)-2-phenethyl-2-azabicyclo[3.3.1]nonane (10)

Phenylacetyl chloride (22 μ L, 0.163 mmol) was added to a mixture of **9** (31.5 mg, 0.136 mmol) and DMAP (25.0 mg, 0.204 mmol) in CH_2Cl_2 (1 mL) at 0 °C, and stirred for 1 h. The mixture was diluted with 10% MeOH in ethyl acetate (20 mL), washed with water and brine, dried over sodium sulfate, filtered, and concentrated to give a crude amide, which was reduced without purification. LiAlH_4 (1 M) in THF (148 μ L, 0.148 mmol) was added dropwise to a solution of the crude amide (ca. 0.136 mmol) in THF (1.2 mL) at 0 °C, and stirred for 2 h. The reaction was quenched by addition of saturated NH_4Cl solution and the mixture was filtered through a pad of Celite and washed with ethyl acetate. The organic solution was washed with water and brine, dried over sodium sulfate, filtered, and concentrated to give the crude product. Column chromatography of crude material with 15% ethyl acetate in hexanes provided **10** (38.0 mg, 92% over two steps) as a pale-yellow oil; **10**·HCl: mp 244–246 °C; ^1H NMR (free base) δ 7.32–7.16 (m, 7H), 6.94–6.87 (m, 2H), 3.83 (s, 3H), 3.25 (br s, 1H), 2.96–2.75 (m, 4H), 2.64–2.56 (m, 1H), 2.53–2.47 (m, 1H), 2.21–2.17 (m, 1H), 2.02–1.76 (m, 4H), 1.62–1.53 (m, 1H), 1.49–1.22 (m, 4H); MS m/z 336 ($\text{M}+\text{H}$) $^+$; HRMS (FAB) calcd for $\text{C}_{23}\text{H}_{29}\text{NO}$ ($\text{M}+\text{H}$) $^+$ 335.2249, found 335.2258; Anal. Calcd for $\text{C}_{23}\text{H}_{30}\text{ClNO}$: C, 74.27; H, 8.13; N, 3.77. Found: C, 74.07; H, 8.17; N, 3.77.

4.7. 2-(2-Phenethyl-2-azabicyclo[3.3.1]non-5-yl)-phenol (2b)

According to the procedure described for the conversion of **8** into **2a**, **10** (174 mg, 0.519 mmol) was converted to **2b** (123.6 mg, 74%) as a pale-yellow oil; **2b**·HCl: mp 264–265 °C; ^1H NMR (free base) 7.31–7.15 (m, 6H), 7.04 (dt, J = 8 and 2 Hz, 1H), 6.85 (dt, J = 8 and 1 Hz, 1H), 6.67 (dd, J = 8 and 2 Hz, 1H), 3.28 (br s, 1H), 2.99–2.94 (m, 2H), 2.87–2.78 (m, 4H), 2.65–2.52 (m, 2H), 2.28 (br d, J = 12 Hz, 1H), 2.08–1.87 (m, 5H), 1.67–1.45 (m, 2H); MS m/z 322 ($\text{M}+\text{H}$) $^+$; HRMS (FAB) calcd for $\text{C}_{22}\text{H}_{28}\text{NO}$ ($\text{M}+\text{H}$) $^+$ 322.2171, found 322.2182. Anal. Calcd for $\text{C}_{22}\text{H}_{28}\text{ClNO}\cdot 1.25\text{H}_2\text{O}$: C, 69.46; H, 8.08; N, 3.68. Found: C, 69.42; H, 7.99; N, 3.74.

4.8. 4-(2-Methyl-2-azabicyclo[3.3.1]non-5-yl)-phenylamine (14)

2-Methyl-5-phenyl-2-azabicyclo[3.3.1]nonane (**13**) 14 (1.61 g, 7.55 mmol) was dissolved in 70% HNO_3 (5 mL) and heated at 40 °C for 24 h. After cooling to 0 °C, the reaction was diluted with water, basified with saturated NaOH solution, and extracted with ethyl acetate– CHCl_3 –MeOH (8:1:1, 3×100 mL). The organic solution was washed with water and brine, dried over sodium sulfate, filtered through a pad of silica gel, and con-

centrated to give the crude nitrated product. It was reduced without purification. A mixture of nitrated product, 10% Pd–C (300 mg), and AcOH (12 drops) in EtOH (80 mL) was heated at 60 °C for 1.5 h in a hydrogen atmosphere. After cooling to room temperature, the reaction was basified with NH_4OH (pH $\sim$ 8) and stirred for 10 min. The mixture was filtered through a pad of Celite, and concentrated to give **14** as a crude product. It was purified by column chromatography using CHCl_3 –MeOH– NH_4OH (91:9:1) to give phenylamine **14** (1.436 g, 83% over two steps) as a brownish oil; ^1H NMR (free base) δ 7.14 (br d, J = 9 Hz, 2H), 6.65 (br d, J = 8 Hz, 2H), 3.56 (br s, 2H), 3.10–3.00 (m, 2H), 2.87–2.81 (m, 1H), 2.47 (s, 3H), 2.21–1.82 (m, 2H), 1.71–1.57 (m, 2H), 1.43–1.32 (m, 1H); MS m/z 231 ($\text{M}+\text{H}$) $^+$; HRMS (FAB) calcd for $\text{C}_{15}\text{H}_{22}\text{N}_2$ ($\text{M}+\text{H}$) $^+$ 230.1783, found 230.1777.

4.9. 5-(4-Iodophenyl)-2-methyl-2-azabicyclo[3.3.1]nonane (15)

A solution of NaNO_2 (177 mg, 2.56 mmol) in water (1 mL) was added dropwise to a mixture of **14** (536 mg, 2.33 mmol) and concentrated HCl (1.1 mL) at 0 °C, and the mixture was stirred for 10 min. This was added to an aqueous KI solution (3.862 g, in 4.5 mL of water), and the mixture was allowed to stand overnight. It was then diluted with 10% MeOH in CH_2Cl_2 (100 mL), washed with water, 10% NaOH solution, a saturated sodium bisulfite solution, and brine, dried over sodium sulfate, filtered, and concentrated to give a crude product. Column chromatography of the crude product with CHCl_3 –MeOH– NH_4OH (91:9:1) gave **15** (426 mg, 54%) as a brownish oil; **15**·HCl: mp 244 °C; ^1H NMR (free base) δ 7.65 (br d, J = 9 Hz, 2H), 7.08 (br d, J = 9 Hz, 2H), 3.59 (br s, 1H), 3.36 (br d, J = 8 Hz, 2H), 2.77 (s, 3H), 2.39–2.27 (m, 2H), 2.17–2.09 (m, 2H), 2.04–1.82 (m, 3H), 1.80–1.66 (m, 3H); MS m/z 342 ($\text{M}+\text{H}$) $^+$; HRMS (FAB) calcd for $\text{C}_{15}\text{H}_{20}\text{IN}$ ($\text{M}+\text{H}$) $^+$ 342.0719, found 342.0720.

4.10. 5-(4-Methoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonane (16)

A mixture of **15** (51.0 mg, 0.149 mmol), CuI (2.8 mg, 0.015 mmol), 1,10-phenanthroline (5.4 mg, 0.03 mmol), and Cs_2CO_3 (68.2 mg, 0.21 mmol) in absolute MeOH (0.7 mL) was placed in a sealed tube and heated at 110 °C for 22 h. After cooling, the mixture was filtered through a pad of silica gel and concentrated to give the crude **16**. Column chromatography with CHCl_3 –MeOH– NH_4OH (91:9:1) provided **16** (32.7 mg, 89%) as a yellow oil; **16**·HCl: mp 228–229 °C; ^1H NMR (free base) δ 7.27 (br d, J = 9 Hz, 2H), 6.86 (br d, J = 9 Hz, 2H), 3.79 (s, 3H), 3.17–3.07 (m, 2H), 2.93 (ddd, J = 12, 7, and 2 Hz, 1H), 2.52 (s, 3H), 2.25–2.21 (m, 2H), 2.11–1.87 (m, 6H), 1.76–1.58 (m, 2H); MS m/z 246 ($\text{M}+\text{H}$) $^+$; HRMS (FAB) calcd for $\text{C}_{16}\text{H}_{24}\text{NO}$ ($\text{M}+\text{H}$) $^+$ 246.1858, found 249.1849. Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{ClNO}\cdot 0.25\text{H}_2\text{O}$: C, 67.12; H, 8.62; N, 4.89. Found: C, 67.11; H, 8.58; N, 4.94.

4.11. 5-(4-Methoxyphenyl)-2-azabicyclo[3.3.1]nonane (17)

A mixture of **16** (259 mg, 1.06 mmol), K_2CO_3 (219 mg, 1.58 mmol), and 2,2,2-trichloroethyl chloroformate (2 mL) in dry toluene (4 mL) was heated at 110 °C for 17 h. After being filtered through a pad of Celite, the organic layer was evaporated, and the residual material used for the next reaction without purification. Zn powder (207 mg, 3.17 mmol) in 75% AcOH (4 mL) was added, and the mixture was vigorously stirred at room temperature for 15 h. After filtration, it was diluted with a mixture of ethyl acetate and 10% MeOH in $CHCl_3$, basified with NH_4OH (pH ~10), washed with water and brine, dried over sodium sulfate, filtered, and concentrated to give crude **17**. Column chromatography of the crude product with $CHCl_3$ –MeOH– NH_4OH (85:15:1) gave **17** (148.2 mg, 61% over two steps) as a pale-yellow oil; **17**·HCl: mp 258 °C (dec); 1H NMR (free base) δ 7.26 (br d, $J = 9$ Hz, 2H), 6.87 (br d, $J = 9$ Hz, 2H), 3.79 (s, 3H), 3.55 (dt, $J = 13$ and 5 Hz, 1H), 3.38 (br s, 1H), 2.99 (ddd, $J = 13$, 7, and 2 Hz, 1H), 2.23–1.55 (m, 10H); MS m/z 232 ($M+H$)⁺; HRMS (FAB) calcd for $C_{15}H_{22}NO$ ($M+H$)⁺ 232.1701, found 232.1699. Anal. Calcd for $C_{15}H_{22}ClNO \cdot 0.1H_2O$: C, 66.83; H, 8.30; N, 5.20. Found: C, 66.79; H, 8.24; N, 5.18.

4.12. 5-(4-Methoxyphenyl)-2-phenethyl-2-azabicyclo[3.3.1]nonane (18)

According to the procedure described in the conversion of **9** into **10**, **17** (123.3 mg, 0.53 mmol) was converted to **18** (148.9 mg, 83% over two steps) as a colorless oil; **18**·HCl: mp 255–256 °C; 1H NMR (free base) δ 7.32–7.20 (m, 7H), 6.88–6.85 (m, 2H), 3.80 (s, 3H), 3.24–3.22 (m, 1H), 3.07–2.97 (m, 2H), 2.86–2.75 (m, 4H), 2.15–1.87 (m, 6H), 1.70–1.58 (m, 3H), 1.44–1.32 (m, 1H); MS m/z 336 ($M+H$)⁺; HRMS (FAB) calcd for $C_{23}H_{30}NO$ ($M+H$)⁺ 336.2327, found 336.2340. Anal. Calcd for $C_{23}H_{30}ClNO \cdot 0.1H_2O$: C, 73.91; H, 8.14; N, 3.75. Found: C, 73.92; H, 8.10; N, 3.77.

4.13. 4-(2-Phenethyl-2-azabicyclo[3.3.1]non-5-yl)-phenol (3b)

According to the procedure described in the conversion of **8** into **2a**, **18** (85.5 mg, 0.25 mmol) was converted to **3b** (81.9 mg, quantitative) as a pale yellow oil; **3b**·HCl: mp 245 °C (dec); 1H NMR (free base) δ 7.32–7.20 (m, 7H), 6.78 (dd, $J = 9$ and 1 Hz, 2H), 3.24 (br s, 1H), 3.07–3.01 (m, 2H), 2.86–2.78 (m, 4H), 2.17–1.87 (m, 8H), 1.71–1.59 (m, 3H); MS m/z 322 ($M+H$)⁺; HRMS (FAB) calcd for $C_{22}H_{28}NO$ ($M+H$)⁺ 322.2171, found 322.2161. Anal. Calcd for $C_{22}H_{28}ClNO \cdot 1.5H_2O$: C, 68.64; H, 8.12; N, 3.64. Found: C, 68.78; H, 8.02; N, 3.58.

4.14. 4-(2-Methyl-2-azabicyclo[3.3.1]non-5-yl)-phenol (3a)

An aqueous $NaNO_2$ solution (32.6 mg in 0.3 mL of water) was added dropwise to a solution of **14** (81.8 mg,

0.36 mmol) in 35% H_2SO_4 (1 mL) at 0 °C and stirred for 5 min. Urea was added to the reaction until KI–starch indicator paper did not show an immediate dark purple color. $Cu(NO_3)_2 \cdot 2.5H_2O$ (1.28 g, in 11.9 mL of water) and Cu_2O (50.8 mg) were added to this mixture, and it was vigorously stirred at room temperature for 30 min. The reaction was basified with NH_4OH (pH ~10), extracted three times with ethyl acetate– $CHCl_3$ –MeOH (8:1:1). The organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated to give a crude product. Column chromatography of crude material with $CHCl_3$ –MeOH– NH_4OH (91:9:1) gave **3a** (47.5 mg, 58%) as a yellow oil; **3a**·HCl: mp 245–246 °C; 1H NMR (HCl salt) (CD_3OD) δ 7.20 (br d, $J = 9$ and 2 Hz, 2H), 6.78 (br d, $J = 9$ Hz, 2H), 3.76 (br s, 1H), 3.65 (dt, $J = 13$ and 5 Hz, 1H), 3.43 (dd, $J = 13$ and 7 Hz, 1H), 3.37–3.36 (m, 1H), 2.95 (s, 3H), 2.37–2.26 (m, 3H), 2.21–1.71 (m, 4H); MS m/z 232 ($M+H$)⁺; HRMS (FAB) calcd for $C_{15}H_{22}NO$ ($M+H$)⁺ 232.1701, found 232.1711. Anal. Calcd for $C_{15}H_{22}ClNO$: C, 67.28; H, 8.28; N, 5.23. Found: C, 66.89; H, 8.34; N, 5.30.

4.15. Opioid binding assays

Opioid binding assays proceeded according to published procedures.^{25–27} Mu receptors were labeled with [3H]DAMGO (D -Ala², MePhe⁴Gly-ol⁵)enkephalin, 2 nM). Rat membranes for mu and delta receptor binding assays were prepared each day using a partially thawed frozen rat brain that was homogenized with a polytron in 10 mL/brain of ice-cold 10 mM Tris–HCl, pH 7.0. Membranes were then centrifuged twice at 30,000g for 10 min and resuspended with ice-cold buffer following each centrifugation. After the second centrifugation, the membranes were resuspended in 50 mM Tris–HCl, pH 7.4 (60 mL/brain), at 25 °C. Incubations proceeded for 2 h at 25 °C in 50 mM Tris–HCl, pH 7.4, along with a protease inhibitor cocktail (PIC). The nonspecific binding was determined using 20 μ M of levallorphan. Delta binding sites were labeled using [3H]DADLE (D -Ala², D -Leu⁵)enkephalin, 2 nM) and rat brain membranes. Rat membranes were prepared each day as described above. After the second centrifugation, the membranes were resuspended in 50 mM Tris–HCl, pH 7.4 (50 mL/brain), at 25 °C. Incubations proceeded for 2 h at 25 °C in 50 mM Tris–HCl, pH 7.4, containing 100 mM choline chloride, 3 mM $MnCl_2$, 100 nM DAMGO to block binding to mu sites, and PIC. Nonspecific binding was determined using 20 μ M levallorphan. Kappa binding sites were labeled using [3H]U69,593 (*trans*-3,4-dichloro-*N*-methyl[2-(1-pyrrolidiny)cyclohexyl]benzene acetamide, 2 nM). Guinea pig brain membranes were prepared each day using partially thawed guinea pig brain that was homogenized with a polytron in 15 mL/brain of ice-cold 10 mM Tris–HCl, pH 7.0. The membranes were then centrifuged twice at 30,000g for 10 min and resuspended with ice-cold buffer following each centrifugation. After the second centrifugation, the membranes were resuspended in 50 mM Tris–HCl, pH 7.4 (85 mL/brain), at 25 °C. Incubations proceeded for 2 h at 25 °C in 50 mM Tris–HCl, pH 7.4, containing 1 μ g/mL of captopril and PIC. Nonspecific

binding was determined using 1 μ M U69,593. Each radioligand was displaced by 8–10 concentrations of test drug. Compounds were prepared as 1 mM solution with 10 mM Tris buffer (pH 7.4) containing 10% DMSO before drug dilution. All drug dilutions were done in 10 mM Tris–HCl, pH 7.4, containing 1 mg/mL bovine serum albumin. All washes were done with ice-cold 10 mM Tris–HCl, pH 7.4. The data of two separate experiments (opioid binding assays) were pooled; the IC_{50} and slope factor (N) were obtained by using the nonlinear least-squares curve-fitting program MLAB-PC (Civilized Software, Bethesda, MD). K_i values were calculated according to the equation $K_i = IC_{50}/(1 + [L]/K_d)$.

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