Published in final edited form as:

Eur J Med Chem. 2013 September ; 67: . doi:10.1016/j.ejmech.2013.06.030.

Probes for narcotic receptor mediated phenomena. 48. C7- and C8-Substituted 5-phenylmorphans opioids from diastereoselective alkylation

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Abstract

The exploration of the effect of substituents at C7 and C8 of the 5-phenylmorphans on their affinity for opioid receptors was enabled by our recently introduced “one pot” diastereoselective synthesis that provided C7-oxo, hydroxy and alkyl substituents, C8-alkyl substituted 5-phenylmorphans, and compounds that had a new cyclohexane ring that includes the C7 and C8 carbon atoms of the 5-phenylmorphans. The affinity of the 5-phenylmorphans for opioid receptors is increased by a C8-methyl substituent, compared with its C7 analogue. The affinity of the newly synthesized compounds is generally for the μ -opioid receptor, rather than the δ - or κ -receptors. Addition of a new cyclohexane ring to the C7 and C8 positions on the cyclohexane ring of the 5-phenylmorphans enhances μ -receptor affinity, bringing the K_i to the subnanomolar level. Unexpectedly, the *N*-methyl substituted compounds generally had higher affinity than comparable *N*-phenethyl-substituted relatives. The configurations of two compounds were determined by single-crystal X-ray crystallographic analyses.

Keywords

C7- and C8-substituted 5-phenylmorphans; opioid receptor affinity; “one-pot” diastereoselective synthesis

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Appendix. Supplementary material: Supplementary data associated with this article can be found, in the online version, at

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1. Introduction

We have examined the effects of substituents in various positions on the cyclohexane ring of the 5-phenylmorphane structure[1] because we have found that some substituents in specific positions in that structure can have a remarkable effect on opioid receptor affinity and efficacy. For example, the (-)-C9*S*-OH enantiomer **1** was found to have subnanomolar affinity for the μ -opioid receptor as well as moderate affinity for the δ -receptor, and it was considerably more potent than morphine as an analgesic.[2].

Other C9-analogs also had high affinity for the μ -receptor.[2] With the hope of finding additional compounds that had affinity for both μ - and δ -opioid receptors, we thought that it would be of interest to examine the effects of substituents in the C7- and C8 positions of the 5-phenylmorphane nucleus; the C8 position is comparable to the C9 position in its spatial distance from the nitrogen atom. Since compounds with both μ - and δ -opioid receptor affinity have been said to have enhanced properties or fewer side-effects than those that act at only μ -receptors[3-8]_ENREF_3_ENREF_3_ENREF_4 we thought it would be of interest to determine whether compounds with substituents at C8 act similarly to compounds with substituents at C9, or whether compounds with substituents a further distance from that nitrogen atom, at, say, C7, would improve receptor affinity and efficacy. We needed, then, a synthetic path to the C8 and C7 substituted 5-phenylmorphans, and we discovered one. We have previously reported this “one pot” diastereoselective synthesis that provided C7-oxo, hydroxy and alkyl substituents, as well as C8-alkyl substituted 5-phenylmorphans, as well as compounds that had a new cyclohexane ring that includes the C7 and C8 carbon atoms of the 5-phenylmorphane.[9] The use of this synthetic pathway has allowed us to prepare *N*-derivatives other than the *N*-methyl and *N*-benzyl compounds that were noted in our initial paper. We now report on compounds that have been synthesized and evaluated in opioid receptor binding assays.

2. Results and Discussion

2.1. Chemistry

The C-7 and C-8 substituted 5-phenylmorphans were synthesized in a 3-step procedure based on highly distereoselective acid-catalyzed ene-imine cyclization that has been previously reported by our group.[9] The reported cyclization protocol always gave C7-*trans* and C8-*cis* isomers (relative to the piperidine ring) as a single product without any minor isomers. Thus, the cyclohexane annulated compound **7d** and **8d** also were formed as a single product with the same stereochemistry. As we noted previously, [9] a possible mechanism that explained the obtained data suggested 6-membered *Re*-face C-C bond formation and an intramolecular hydride shift as key aspects of the highly diastereoselective cyclization that gave *trans* selectivity at C7 and *cis* selectivity at C8.

Alkylation of the known tetrahydropyridine **2** with a substituted allyl bromide generated a quaternary carbon center. Acid-catalyzed ene-imine cyclization of the alkylated intermediate **3**, followed by in-situ reduction of resulting cyclized imine **4**, gave the desired *N*-benzyl-5-phenylmorphans **5a-d**[9] in good yields (Scheme 1). The *N*-Bn compounds **5a-d** were converted into their secondary amines **6** by Pd/C catalyzed hydrogenolysis (Scheme 2). The amines were alkylated to their *N*-methyl relatives by reductive alkylation with formalin and Pd/C, or *N*-alkylated with phenethyl bromide to obtain the *N*-phenethyl derivatives. Finally, the OMe group was deprotected to yield the desired phenolic products **7** and **8**.

The relative stereochemistry between the piperidine ring and the C7-methyl and C7-hydroxyl substituent in the cyclohexane ring was determined by X-ray crystallographic analyses (Fig. 1).[9] With a C7- δ -methyl substituent the relative stereochemistry of the C7

moiety in racemic **7b** and the piperidine ring, as shown in Fig. 1, was *trans* (C1*R**, C5*S** and C7*S**), and with the C7 -hydroxyl it was *cis* (C1*S**, C5*R**, and C7*S**). For the synthesis of 7-oxo and hydroxy derivatives, *N*-benzyl-7-oxo-5-phenylmorphane **9** was prepared by the reported procedure.[10] Debenzylation of **9**, then *N*-alkylation followed by *O*-demethylation gave the desired C7-oxo compound **10c**. The C7-hydroxy derivatives **11a-b** were obtained by NaBH₄ reduction, followed by *O*-demethylation (Scheme 3). Unlike the C7-methyl or phenyl substituted compounds (**7b-c**, **8b-c**) that were *trans*-oriented relative to the piperidine ring, reduction of C7-oxo compounds (**10a-b**) gave C7 -(*cis*)-hydroxy derivatives **11a-b** (Fig. 1). The configuration of compound **11a**, prepared from the enantiopure ketone **10a** by optical resolution using a chiral acid, was determined by X-ray crystallography. The absolute configuration of the compound **11a** was found to be C1*S*, C5*R*, and C7*S*.

2.2. Opioid Receptor Affinity

As noted in Table 1, with the exception of one pair of compounds, the 7 -OH compounds **11a** and **11b**, the *N*-methyl substituted derivatives were found to have greater affinity for the μ -opioid receptor than their *N*-phenethyl-substituted relatives. This is very unusual among the 5-phenylmorphans where compounds with an *N*-phenethyl substituent almost invariably have higher affinity than the *N*-methyl relative for the μ -receptor.[1] The higher affinity of the *N*-phenethyl analogues also holds in the pyridin-6-ol series of compounds introduced by Hutchison et al.[11], and with oxide-bridged phenylmorphans.[12-14].

The C8-methyl compounds were found to have higher μ -opioid affinity than the comparable C7-methyl compounds in both the *N*-methyl and the *N*-phenethyl-substituted phenylmorphans. (**7a** vs **7b**, and **8a** vs **8b**). An oxygen atom in the C7 position (**11a** and **11b**) and the C7-ketone (**10c**) in the cyclohexane ring of these phenylmorphans reduced affinity to the μ -receptor, unlike the hydroxyl group at C9 which greatly increased affinity. [2] The *N*-phenethyl compounds with a C8-methyl (**8a**, K_i = 2.2 nM) or a compound with an additional cyclohexane ring at the C7-C8 position (**8d**, K_i = 4 nM) had greater, or nearly equivalent affinity, for the μ -receptor as morphine (Table 1).

A substituent at C8 appears to confer higher affinity for opioid receptors than that same substituent at C7. The C7-methyl isomers **7b** and **8b** had less affinity for all of the opioid receptors than the C8-methyl compounds **7a** and **8a**. Most surprising was the affinity of **7d**, the *N*-methyl relative of **8d**; it was found to have subnanomolar affinity for the μ -receptor (K_i = 0.9 nM). The observed ca. 4-fold difference in affinity of the *N*-methyl-substituted **7d** and the *N*-phenethyl-substituted **8d**, though not extreme, is very unusual in the 5-phenylmorphane series. The additional cyclohexane ring has apparently caused a substantial change in the ability of *N*-methyl substituted phenylmorphane-type compounds to bind to the μ -receptor. None of the compounds in Table 1 had appreciable affinity for δ -opioid receptors, and only **8c**, the C7-phenyl compound in the *N*-phenethyl series, had good affinity for δ -receptors (K_i = 4 nM).

3. Conclusions

We have found that, in general, the affinity of the 5-phenylmorphans for opioid receptors is increased by a C8-methyl substituent, compared with its C7 analogue. The affinity is mostly for the μ -opioid receptor, rather than δ - or κ -receptors, and an additional cyclohexane ring added to the C7 and C8 positions on the azabicyclo ring system (3-(2-methyl-7,8-cyclohexyl-2-azabicyclo[3.3.1]nonan-5-yl)phenol, **7d**) considerably enhances μ -receptor affinity, lowering the K_i to the subnanomolar level. Further, when a substituent other than an hydroxyl group appears at either C7 or C8 in the 5-phenylmorphans, the *N*-methyl substituted isomer was found to have higher μ -affinity than its *N*-phenethyl relative.

4. Experimental Section

4.1. Materials and methods

Compounds **2**,^[9] **5a-d**,^[9] and **9**^[10] were prepared as previously described. *n*-BuLi was titrated and THF was dried over molecular sieves before use. Other chemicals and solvents were used directly without further purification. Chemicals were purchased from Sigma-Aldrich Inc. or Alfa Aesar. Melting points were determined on a Buchi B-545 instrument and are uncorrected. Thin layer chromatography (TLC) analyses were carried out on Analtech silica gel GHLF 0.25 mm plates using various concentrations of CHCl₃/MeOH containing 1% NH₄OH or 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) using CHCl₃: MeOH: NH₄OH (90: 9: 1). Proton and carbon nuclear magnetic resonance (¹H- and ¹³C-NMR) spectra were recorded in CDCl₃ with CHCl₃ (δ 7.24), as an internal standard, on a Varian Gemini-300 spectrometer and a Bruker DMX500 wide-bore spectrometer ((proton frequency 500.13 MHz) running XWINNMR v3.1, carbon 125.757) with the values given in ppm and *J*(Hz) assignments of ¹H resonance coupling. Mass spectra (HRMS) were recorded on a VG 7070E spectrometer or a JEOL SX102a mass spectrometer. IR spectra were recorded on a Beckman IR 4230 spectrometer. Atlantic Microlabs, Inc., Norcross, GA, or Micro-Analysis, Inc., Wilmington, DE, performed elemental analyses, and the results were within ±0.4% of the theoretical values.

4.2. Preparation of compounds

4.2.1 General procedure of debenzylation—To a reaction flask, an *N*-Bn compound, Pd/C (10 wt %), AcOH (0.1 mL), and MeOH (5 mL/1 mmol of *N*-Bn) were added. After the vessel was evacuated and refilled with hydrogen gas 3 times, the reaction mixture was stirred at 60 °C under a balloon pressure of hydrogen gas. After 6 h, the mixture was filtered through celite pad to remove the catalyst, and the solvent was evaporated. The residue was dissolved in CH₂Cl₂ (100 mL) and it was washed with 2 N NaOH. The aqueous layer was extracted twice with CH₂Cl₂ (100 mL each). The combined organics were washed with brine, dried over Na₂SO₄, filtered, and evaporated. The crude product was purified by column chromatography.

4.2.2. 5-(3-Methoxyphenyl)-8-methyl-2-azabicyclo[3.3.1]nonane (6a)—Using the general procedure, the *N*-Bn compound **5a** (1.0 g, 3.0 mmol) was converted into secondary amine **6a** (0.76 g, > 99 %). ¹H NMR (500 MHz, CDCl₃): δ 7.26-7.23 (t, *J* = 8.0 Hz, 1H), 6.96-6.91 (m, 2H), 6.74-6.73 (dd, *J* = 1.5, 8.0 Hz, 1H), 3.80 (s, 3H), 3.43-3.37 (dt, *J* = 5.0, 12.5 Hz, 1H), 3.02 (br s, 1H), 2.95-2.91 (m, 2H), 2.16-1.99 (m, 3H), 1.88-1.65 (m, 6H), 1.07-1.06 (d, *J* = 5.0 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 159.6, 154.0, 129.1, 117.3, 111.4, 110.2, 55.2, 52.5, 42.4, 39.8, 38.5, 38.1, 35.9, 35.3, 31.5, 19.3; IR cm⁻¹ (neat): 2926.8, 1607.4, 1582.2, 1486.3, 1453.1, 1430.9, 1291.9, 1268.0, 1049.1; HRMS calcd for C₁₆H₂₄NO (M+H)⁺: 246.1858, found: 246.1866.

4.2.3. 5-(3-Methoxyphenyl)-7-methyl-2-azabicyclo[3.3.1]nonane (6b)—Using the general procedure, *N*-Bn compound **5b** (1.0 g, 3.0 mmol) was converted into secondary amine **6b** (0.75 g, > 99 %). ¹H NMR (500 MHz, CDCl₃): δ 7.35-7.24 (m, 1H), 6.95-6.88 (m, 2H), 6.75-6.74 (d, *J* = 6.0 Hz, 1H), 3.81 (s, 3H), 3.55-3.46 (m, 2H), 3.05-3.02 (d, *J* = 7.5 Hz, 2H), 2.95-2.90 (m, 1H), 2.51-2.40 (m, 1H), 2.15-2.00 (m, 4H), 1.84-1.79 (m, 2H), 1.32-1.17 (m, 2H), 0.90-0.89 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 159.6, 153.8, 129.3, 117.2, 111.4, 110.4, 55.4, 48.6, 48.5, 48.3, 42.5, 41.1, 37.7, 36.3, 28.6, 24.6; IR cm⁻¹ (neat): 2950, 2920, 2867, 2836, 1606, 1582, 1485, 1456, 1430, 1285, 1256, 1169, 1050; HRMS calcd for C₁₆H₂₄NO: 246.1858 (M+H)⁺, found: 246.1859.

4.2.4. 5-(3-Methoxyphenyl)-7-phenyl-2-azabicyclo[3.3.1]nonane (6c)—Using the general procedure, *N*-Bn compound **5c** (1.5 g, 3.77 mmol) was converted into secondary amine **6c** (1.2 g, > 99 %). ¹H NMR (500 MHz, CDCl₃): δ 7.25–7.14 (m, 6H), 6.94–6.86 (m, 3H), 6.72–6.68 (m, 1H), 3.82 (br s, 1H), 3.73 (s, 3H), 3.69–3.58 (m, 1H), 3.29–3.25 (m, 1H), 2.44–2.42 (d, *J* = 11.0 Hz, 1H), 2.35–2.29 (t, *J* = 15.0 Hz, 2H), 2.20–2.19 (d, *J* = 8.5 Hz, 2H), 2.01–1.95 (m, 2H), 1.87–1.47 (m, 2H); ¹³C NMR (126 MHz, CDCl₃): δ 159.6, 151.9, 145.9, 129.4, 128.5, 126.9, 126.4, 116.9, 111.2, 110.8, 55.1, 53.5, 51.4, 48.3, 47.1, 41.1, 39.1, 36.7, 35.6; IR cm^{−1} (neat): 3327.0, 3057.7, 3025.7, 2914.1, 2843.7, 1599.7, 1581.1, 1491.8, 1451.8, 1255.4, 1160.8, 1050.8, 1032.5; HRMS calcd for C₂₁H₂₆NO: 308.2014 (M+H)⁺, found: 308.2015.

4.2.5. 5-(3-Methoxyphenyl)-7,8-cyclohexyl-2-azabicyclo[3.3.1]nonane (6d)—Using the general procedure, *N*-Bn compound **5d** (0.9 g, 2.4 mmol) was converted into secondary amine **6d** (0.63 g, 93 %). ¹H NMR (500 MHz, CDCl₃): δ 7.37 (br s, 1H), 7.10–7.07 (t, *J* = 8.0 Hz, 1H), 6.77–6.72 (m, 2H), 6.59–6.57 (d, *J* = 8.0 Hz, 1H), 3.63 (s, 3H), 3.37–3.31 (dt, *J* = 5.5, 12.5 Hz, 1H), 3.30 (br s, 1H), 3.07–3.03 (dd, *J* = 7.5, 12.0 Hz, 1H), 2.24–2.21 (d, *J* = 12.5 Hz, 1H), 1.97–1.71 (m, 7H), 1.58–1.48 (m, 3H), 1.22–1.11 (m, 4H), 0.71–0.65 (m, 1H); ¹³C NMR (126 MHz, CDCl₃): δ 159.3, 151.9, 129.0, 116.8, 111.0, 110.3, 54.9, 52.5, 46.6, 45.6, 40.8, 38.4, 37.2, 35.5, 35.3, 35.2, 29.9, 26.6, 26.2; IR cm^{−1} (neat): 2921.7, 2848.3, 1601.1, 1581.8, 1485.9, 1446.1, 1429.8, 1253.4, 1168.6, 1046.6; HRMS calcd for C₁₉H₂₈NO: 286.2171 (M+H)⁺, found: 286.2170.

4.2.6. 5-(3-Methoxyphenyl)-2-azabicyclo[3.3.1]nonan-7-one (9a)—Using the general procedure, *N*-Bn compound **9** (4 g, 0.012 mol) was converted into secondary amine **9a** (3.0 g, > 99 %, pale yellow oil). ¹H NMR (500 MHz, CDCl₃): δ 7.24–7.20 (t, *J* = 8.5 Hz, 1H), 6.88–6.87 (d, *J* = 1.0 Hz, 1H), 6.82 (s, 1H), 6.73–6.71 (d, *J* = 8.0 Hz, 1H), 3.74 (s, 3H), 3.71–3.70 (m, 1H), 2.89–2.87 (d, *J* = 7.5 Hz, 2H), 2.77–2.74 (d, *J* = 17.0 Hz, 1H), 2.54 (m, 2H), 2.43–2.40 (d, *J* = 16.5 Hz, 1H), 2.31–2.09 (m, 2H), 1.85–1.73 (m, 2H); ¹³C NMR (126 MHz, CDCl₃): δ 210.3, 159.7, 150.3, 129.6, 116.8, 111.2, 111.0, 55.2, 53.2, 49.4, 47.4, 39.2, 39.1, 38.9, 37.4.

4.3. General procedure of *N*-methylation

To a reaction flask, amine (1.1 g, 4.5 mmol), Pd/C (0.11 g, 10 wt %), AcOH (0.05 mL), formalin (37 % in water, 0.34 mL, 4.5 mmol), and MeOH (20 mL) were added. After the vessel was evacuated 3 × using H₂ gas, the reaction mixture was stirred at room temperature under a balloon pressure of H₂ gas. After 3 h, the mixture was filtered through a celite pad to remove the catalyst, and the solvent was evaporated. The residue was dissolved in CH₂Cl₂ (20 mL) and it was washed with 2 N NaOH. The aqueous layer was extracted with CH₂Cl₂ (20 mL × 2). The combined organics were washed with brine, dried over Na₂SO₄, filtered, and evaporated. The crude product was purified by column chromatography.

4.4. General procedure of *N*-phenethylation

Amine (1.4 g, 5.7 mmol), K₂CO₃ (2.4 g, 17.1 mmol), KI (0.23 g, 1.4 mmol), and phenethyl bromide (1.2 mL, 8.6 mmol) were dissolved in anhyd acetonitrile (50 mL), and the resulting mixture was refluxed overnight. After additional phenethyl bromide (0.4 mL, 2.8 mmol) was added, the mixture was refluxed for another 4 h. The reaction was cooled to room temperature and filtered through a celite pad, and then the solvent was evaporated. The crude product was purified by column chromatography.

4.5. General procedure of O-demethylation

The methoxy compound was dissolved in 48 % HBr (4 mL per 1 mmol of methoxy compound), and the resulting mixture was refluxed for 2.5 h. After the reaction was completed, the solution was cooled to -78°C , and then concd NH_4OH was slowly added to pH 9. The product was extracted with CH_2Cl_2 (20 mL $\times$ 3). The combined organics were washed with brine, dried over Na_2SO_4 , filtered, and evaporated. The crude product was purified by column chromatography.

4.5.1. 3-(2-Methyl-8-methyl-2-azabicyclo[3.3.1]nonan-5-yl)phenol (7a)—Using the general procedures, secondary amine **6a** (0.35 g, 1.43 mmol) was *N*-methylated (0.34 g, 92 %). ^1H NMR (500 MHz, CDCl_3): δ 7.24–7.21 (t, J = 8.0 Hz, 1H), 6.91–6.86 (m, 2H), 6.72–6.70 (dd, J = 2.0, 8.0 Hz, 1H), 3.79 (s, 3H), 2.86–2.82 (m, 1H), 2.66–2.58 (m, 2H), 2.46 (m, 3H), 2.36–2.32 (m, 1H), 2.07–1.80 (m, 4H), 1.49–1.43 (m, 4H), 1.00–0.99 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3): δ 159.6, 155.4, 129.2, 117.7, 111.7, 110.1, 60.7, 55.3, 49.5, 47.3, 40.7, 37.6, 36.6, 34.5, 34.3, 28.1, 19.4; IR cm^{-1} (neat): 2929.4, 2867.7, 2785.6, 1608.0, 1582.0, 1484.3, 1451.2, 1290.7, 1264.1, 1047.5; HRMS calcd for $\text{C}_{17}\text{H}_{26}\text{NO}$: 260.2014 ($\text{M}+\text{H}$) $^+$, found: 260.2000.

The compound in this *N*-methyl compound (0.20 g, 0.77 mmol) was then *O*-demethylated to give **7a** using the general procedure (0.20 g, > 99 %). ^1H NMR (500 MHz, CDCl_3): δ 7.16–7.13 (t, J = 8.0 Hz, 1H), 6.85–6.83 (d, J = 8.0 Hz, 1H), 6.76–6.75 (d, J = 4.0 Hz, 1H), 6.63–6.61 (d, J = 8.0 Hz, 1H), 3.02–2.97 (m, 1H), 2.77 (br s, 1H), 2.68–2.63 (m, 1H), 2.51 (m, 3H), 2.33–2.29 (m, 1H), 1.99–1.81 (m, 4H), 1.58–1.50 (m, 4H), 1.07–1.06 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3): δ 156.3, 155.0, 129.4, 117.0, 113.0, 112.8, 60.6, 49.7, 46.6, 40.2, 37.6, 36.1, 35.3, 34.4, 29.1, 19.8; IR cm^{-1} (neat): 3049.9, 2929.4, 2868.7, 1598.6, 1583.2, 1450.4, 1273.4, 1166.3; HRMS calcd for $\text{C}_{16}\text{H}_{24}\text{NO}$: 246.1858 ($\text{M}+\text{H}$) $^+$, found: 246.1855. Compound **7a** was converted into its HBr salt and crystallized from EtOH/EtOAc (0.20 g); mp 200.4–201.8 $^{\circ}\text{C}$. Anal. Calcd. for $\text{C}_{16}\text{H}_{24}\text{NOBr}$: C, 58.90; H, 7.41; N, 4.29. Found: C, 58.62; H, 7.20; N, 4.21.

4.5.2. 3-(2-Phenethyl-8-methyl-2-azabicyclo[3.3.1]nonan-5-yl)phenol (8a)

Using the general procedure, secondary amine **6a** (0.25 g, 1.02 mmol) was converted into the *N*-phenethyl compound (0.22 g, 62 %). ^1H NMR (500 MHz, CDCl_3): δ 7.27–7.16 (m, 6H), 6.91–6.90 (d, J = 7.5 Hz, 1H), 6.87 (s, 1H), 6.71–6.69 (d, J = 8.0 Hz, 1H), 3.77 (s, 3H), 3.02–2.98 (m, 1H), 2.86–2.69 (m, 6H), 2.32–2.29 (dd, J = 4.0, 15.0 Hz, 1H), 2.04–1.78 (m, 4H), 1.51–1.44 (m, 4H), 0.93–0.92 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3): δ 159.6, 155.4, 141.1, 129.2, 129.0, 128.4, 125.9, 117.7, 111.8, 110.1, 61.3, 59.3, 55.3, 46.3, 40.6, 37.6, 36.6, 35.3, 34.8, 34.7, 28.4, 19.4; IR cm^{-1} (neat): 3026.4, 2929.7, 2865.4, 1606.8, 1582.4, 1485.3, 1453.7, 1291.2, 1265.4, 1050.5; HRMS calcd for $\text{C}_{24}\text{H}_{32}\text{NO}$: 350.2484 ($\text{M}+\text{H}$) $^+$, found: 350.2491.

The compound (0.15 g, 0.43 mmol) was *O*-demethylated using the general procedure to give **8a** (0.15 g, > 99 %). ^1H NMR (500 MHz, CDCl_3): δ 7.26–7.11 (m, 6H), 6.84–6.79 (m, 2H), 6.66–6.60 (m, 2H), 3.04–3.00 (m, 1H), 2.88–2.72 (m, 6H), 2.28–2.25 (d, J = 13.0 Hz, 1H), 1.96–1.79 (m, 4H), 1.50–1.46 (m, 4H), 0.98–0.97 (d, J = 6.0 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3): δ 156.1, 155.2, 140.9, 129.5, 129.0, 128.5, 126.1, 117.2, 113.1, 112.9, 60.9, 59.1, 46.8, 40.3, 37.6, 36.3, 35.7, 34.8, 34.4, 29.0, 19.7; IR cm^{-1} (neat): 2929.6, 1584.9, 1453.1, 1364.3, 1453.1, 1364.3, 1272.6, 1163.9; HRMS calcd for $\text{C}_{23}\text{H}_{30}\text{NO}$: 336.2327 ($\text{M}+\text{H}$) $^+$; found: 336.2317. Compound **8a** was converted into its HBr salt and crystallized from EtOH/EtOAc (0.14 g); mp 258.0–259.6 $^{\circ}\text{C}$. Anal. Calcd. for $\text{C}_{23}\text{H}_{30}\text{NOBr} + 0.25 \text{H}_2\text{O}$: C, 65.67; H, 7.31; N, 3.33. Found: C, 65.65; H, 7.10; N, 3.33.

4.5.3. 3-(2-Methyl-7-methyl-2-azabicyclo[3.3.1]nonan-5-yl)phenol (7b)—Using the general procedure, secondary amine **6b** (0.30 g, 1.22 mmol) was converted into the *N*-methyl derivative (0.195 g, 61 %). ¹H NMR (500 MHz, CDCl₃): δ 7.30-7.27 (t, *J* = 8.0 Hz, 1H), 7.00-6.99 (d, *J* = 7.5 Hz, 1H), 6.96 (s, 1H), 6.78-6.77 (d, *J* = 7.5 Hz, 1H), 3.84 (s, 3H), 3.14 (br s, 1H), 3.07-3.01 (dt, *J* = 12.5, 4.5 Hz, 1H), 2.92-2.89 (dd, *J* = 11.5, 7.5, 1H), 2.51 (s, 3H), 2.30-2.21 (m, 5H), 2.03-1.96 (m, 1H), 1.89-1.87 (d, *J* = 12.0 Hz, 1H), 1.24-1.19 (t, *J* = 13.5, 1H), 1.03-0.98 (t, *J* = 13.5 Hz, 1H), 0.91-0.89 (d, *J* = 5.5 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 159.6, 153.4, 129.2, 117.3, 111.4, 110.4, 55.2, 54.9, 51.2, 47.8, 43.2, 39.2, 37.2, 35.7, 33.4, 28.8, 24.6; IR cm⁻¹ (neat): 2950, 2923, 2837, 1608, 1583, 1486, 1456, 1431, 1379, 1291, 1258, 1171, 1053; HRMS calcd for C₁₇H₂₆NO: 260.2014 (M+H)⁺, found: 260.2014.

The compound (0.16 g, 0.62 mmol) was *O*-demethylated to yield **7b** (0.15 g, > 99 %). ¹H NMR (500 MHz, CDCl₃): δ 10.17 (br s, 1H), 7.13-7.10 (t, *J* = 8.0 Hz, 1H), 6.79-6.77 (d, *J* = 8.0 Hz, 1H), 6.74 (s, 1H), 6.61-6.59 (d, *J* = 9.5 Hz, 1H), 3.16 (br s, 1H), 3.04-2.90 (m, 2H), 2.46 (s, 3H), 2.25-2.15 (m, 3H), 2.07-1.94 (m, 3H), 1.80-1.77 (d, *J* = 12.5 Hz, 1H), 1.18-1.13 (t, *J* = 13.0 Hz, 1H), 1.01-0.97 (t, *J* = 12.0 Hz, 1H), 0.85-0.84 (d, *J* = 5.5 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 157.4, 152.7, 129.3, 115.8, 113.5, 112.8, 54.9, 51.1, 47.8, 42.6, 38.2, 36.4, 35.3, 33.2, 28.7, 24.8; IR cm⁻¹ (neat): 3047.7, 2949.2, 2922.5, 2866.3, 1597.7, 1581.9, 1482.0, 1448.0, 1378.8, 1366.3, 1278.0, 1246.2, 1186.1, 1137.0; HRMS calcd for C₁₆H₂₄NO: 246.1858 (M+H)⁺, found: 246.1862. The title compound **7b** was converted into its HBr salt and crystallized from EtOH/EtOAc (0.17 g); mp 213.5-214.7 °C. Anal. Calcd. for C₁₆H₂₄NOBr: C, 58.90; H, 7.41; N, 4.29. Found: C, 58.71; H, 7.57; N, 4.16. The relative configuration of **7b** was determined by X-ray crystallography (Fig. 1, C1 = *R*, C5 = *S*, and C7 = *S*).

4.5.4. 3-(2-Phenethyl-7-methyl-2-azabicyclo[3.3.1]nonan-5-yl)phenol (8b)—

Using the general procedure, secondary amine **6b** (0.25 g, 1.02 mmol) was converted into the *N*-phenethyl derivative (0.18 g, 50 %). ¹H NMR (500 MHz, CDCl₃): δ 7.26-7.19 (m, 6H), 6.94-6.92 (d, *J* = 8.0 Hz, 1H), 6.89 (s, 1H), 6.71-6.69 (d, *J* = 7.5 Hz, 1H), 3.76 (s, 3H), 3.21 (br s, 1H), 3.10-2.93 (m, 2H), 2.80-2.72 (m, 4H), 2.21-2.00 (m, 5H), 1.96-1.90 (m, 1H), 1.81-1.79 (d, *J* = 12.5 Hz, 1H), 1.16-1.11 (t, *J* = 12.5 Hz, 1H), 0.95-0.90 (t, *J* = 13.0 Hz, 1H), 0.83-0.81 (d, *J* = 5.5 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 159.6, 153.7, 140.9, 129.2, 128.9, 128.4, 126.1, 117.3, 111.5, 110.4, 58.1, 55.2, 53.0, 49.7, 48.0, 39.0, 37.3, 36.3, 35.8, 34.7, 28.8, 24.7; IR cm⁻¹ (neat): 3026.1, 2948.7, 2923.9, 1607.0, 1582.6, 1485.7, 1455.2, 1431.4, 1291.3, 1258.5, 1170.7, 1052.6; HRMS calcd for C₂₄H₃₂NO: 350.2484 (M+H)⁺, found: 350.2488.

The compound (0.15 g, 0.43 mmol) was *O*-demethylated to yield **8b** (0.14 g, 97 %). ¹H NMR (500 MHz, CDCl₃ w/0.1 mL of CD₃OD): δ 7.24-7.14 (m, 6H), 6.86-6.85 (m, 2H), 6.69-6.68 (d, *J* = 8.0 Hz, 1H), 4.78 (br s, 1H), 3.28 (br s, 1H), 3.20-2.99 (m, 2H), 2.83-2.77 (m, 4H), 2.23-2.09 (m, 5H), 1.96-1.85 (m, 2H), 1.21-1.15 (t, *J* = 13.0 Hz, 1H), 1.03-0.97 (t, *J* = 12.5 Hz, 1H), 0.87-0.85 (d, *J* = 5.5 Hz, 3H); ¹³C NMR δ (126 MHz, CDCl₃ w/0.1 mL of CD₃OD): δ 156.6, 152.9, 139.9, 129.1, 128.5, 128.3, 126.0, 115.9, 112.6, 111.8, 57.6, 52.7, 52.6, 49.2, 48.8, 38.2, 36.5, 35.6, 33.7, 33.6, 28.6; IR cm⁻¹ (neat): 3026.4, 2948.5, 2923.9, 2865.7, 1738.6, 1598.9, 1583.0, 1496.0, 1482.6, 1454.3, 1366.1, 1276.0, 1229.9, 1217.1; HRMS calcd for C₂₃H₃₀NO: 336.2327 (M+H)⁺, found: 336.2339. The title compound **18d** was converted into its HBr salt and crystallized from EtOH/EtOAc (0.16 g); mp 232.0-233.2 °C. Anal. Calcd. for C₂₃H₃₀NOBr + 0.5 M H₂O: C, 64.98; H, 7.40; N, 3.29. Found: C, 64.83; H, 7.40; N, 3.26.

4.5.5. 3-(2-Methyl-7-phenyl-2-azabicyclo[3.3.1]nonan-5-yl)phenol (7c)—Using the general procedure, secondary amine **6c** (0.25 g, 0.81 mmol) was converted into the *N*-

methyl derivative (0.25 g, 96 %). ^1H NMR (500 MHz, CDCl_3): δ 7.26-7.13 (m, 6H), 6.95-6.91 (m, 2H), 6.71-6.69 (d, J = 5.5, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 3.47-3.42 (m, 1H), 3.18-3.10 (m, 2H), 2.95-2.89 (m, 1H), 2.48 (s, 3H), 2.41-2.38 (m, 1H), 2.28-2.15 (m, 3H), 2.00-1.97 (m, 2H), 1.70-1.64 (dt, J = 1.5, 13.5 Hz, 1H), 1.53-1.47 (dt, J = 3.0, 13.5 Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3): δ 159.6, 153.1, 147.2, 129.3, 126.3, 117.3, 111.5, 110.5, 55.2, 54.8, 51.4, 47.0, 43.3, 40.2, 38.7, 37.2, 35.8, 32.6; IR cm^{-1} (neat): 3059.5, 3026.1, 2924.6, 2844.4, 1599.5, 1581.8, 1486.4, 1431.3, 1288.7, 1248.1, 1165.1, 1050.9, 1027.9; HRMS calcd for $\text{C}_{22}\text{H}_{28}\text{NO}$: 322.2171 ($\text{M}+\text{H}$) $^+$, found: 322.2170.

The compound (0.25 g, 0.77 mmol) was *O*-demethylated to yield **7c** (0.23 g, 97 %). ^1H NMR (500 MHz, CDCl_3): δ 9.50 (br s, 1H), 7.26-7.06 (m, 6H), 6.77-6.74 (m, 2H), 6.59-6.57 (d, J = 9.5 Hz, 1H), 3.43-3.37 (m, 1H), 3.23 (br s, 1H), 3.15-3.09 (dt, J = 5.0, 12.0 Hz, 1H), 2.97-2.93 (m, 1H), 2.46 (s, 3H), 2.40-2.37 (d, J = 12.0 Hz, 1H), 2.25-2.20 (t, J = 7.5 Hz, 2H), 2.07-1.91 (m, 3H), 1.67-1.61 (t, J = 13.0 Hz, 1H), 1.54-1.48 (dt, J = 3.0, 13.0 Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3): δ 157.3, 152.5, 146.9, 129.5, 128.6, 126.9, 126.4, 116.1, 113.6, 112.7, 54.7, 51.3, 46.8, 42.8, 40.2, 38.1, 36.5, 35.5, 32.1; IR cm^{-1} (neat): 3060.4, 3027.3, 2934.6, 1598.0, 1582.1, 1492.4, 1451.8, 1376.6, 1279.4, 1245.5; HRMS 308.2011 ($\text{M}+\text{H}^+$); 308.2014 calcd for $\text{C}_{21}\text{H}_{26}\text{NO}$. HRMS calcd for $\text{C}_{21}\text{H}_{26}\text{NO}$: 308.2014 ($\text{M}+\text{H}$) $^+$, found 308.2011. The title compound **7c** was converted into its HBr salt and crystallized from MeOH/EtOAc (0.18 g); mp 268.8-270.1 $^\circ\text{C}$. Anal. Calcd. for $\text{C}_{21}\text{H}_{26}\text{NOBr} + 0.3 \text{ M H}_2\text{O}$: C, 64.10; H, 7.07; N, 3.56. Found: C, 63.84; H, 6.73; N, 3.54.

4.5.6. 3-(2-Phenethyl-7-phenyl-2-azabicyclo[3.3.1]nonan-5-yl)phenol (**8c**)—

Using the general procedure, secondary amine **6c** (0.25 g, 0.81 mmol) was converted into its *N*-phenethyl derivative (0.19 g, 57 %). ^1H NMR (500 MHz, CDCl_3): δ 7.35-7.15 (m, 11H), 6.94-6.89 (m, 2H), 6.73-6.71 (dd, J = 8.0, 2.0 Hz, 1H), 3.76 (s, 3H), 3.53-3.44 (m, 2H), 3.22-3.20 (m, 2H), 2.95 (s, 2H), 2.43-2.27 (m, 4H), 2.21-1.92 (m, 4H), 1.73-1.57 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3): δ 159.7, 152.5, 146.5, 139.6, 136.2, 129.4, 129.1, 128.8, 128.4, 127.0, 126.4, 118.3, 117.2, 111.5, 112.2, 110.8, 57.7, 55.3, 53.5, 49.6, 40.0, 37.3, 36.4, 36.2, 35.9, 33.5; IR cm^{-1} (neat): 3059.3, 3025.4, 2927.6, 2833.0, 1600.8, 1581.5, 1492.7, 1452.6, 1289.3, 1243.6, 1165.9, 1048.8, 1030.2; HRMS calcd for $\text{C}_{29}\text{H}_{34}\text{NO}$: 412.2640 ($\text{M}+\text{H}$) $^+$, found 412.2632.

The compound (0.20 g, 0.49 mmol) was *O*-demethylated to yield **8c** (0.15 g, 79 %). ^1H NMR (500 MHz, CDCl_3): δ 7.27-7.09 (m, 11H), 6.83-6.79 (m, 2H), 6.64-6.63 (dd, J = 7.5, 1.5 Hz, 1H), 3.43-3.41 (m, 2H), 3.14-3.12 (m, 2H), 2.88-2.84 (m, 3H), 2.37-2.21 (m, 3H), 2.14-1.88 (m, 4H), 1.68-1.50 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3): δ 156.6, 152.9, 146.9, 140.1, 136.2, 129.6, 129.4, 129.0, 127.4, 127.0, 126.5, 116.7, 113.6, 112.7, 57.9, 52.9, 50.0, 46.9, 40.2, 38.0, 36.8, 36.1, 33.9, 33.0; IR cm^{-1} (neat): 3059.7, 3026.1, 2927.7, 2848.7, 1599.0, 1582.9, 1493.0, 1452.0, 1365.5, 1276.0, 1232.3, 1177.1; HRMS calcd for $\text{C}_{28}\text{H}_{32}\text{NO}$: 398.2484 ($\text{M}+\text{H}$) $^+$, found 398.2488. The title compound **8c** was converted into its HBr salt and crystallized from EtOAc/Et₂O (0.10 g); mp 155.6-157.1 $^\circ\text{C}$. Anal. Calcd. for $\text{C}_{28}\text{H}_{32}\text{NOBr} + 1.2 \text{ M H}_2\text{O}$: C, 67.29; H, 6.94; N, 2.80. Found: C, 66.95; H, 6.58; N, 2.76.

4.5.7. 3-(2-Methyldecahydro-1,5-methanobenzo[c]azocin-5(2*H*)-yl)phenol (**7d**)

—Using the general procedure, secondary amine **6d** (0.22 g, 0.77 mmol) was converted into its *N*-methyl derivative (0.23 g, > 99 %). ^1H NMR (500 MHz, CDCl_3): δ 7.15-7.11 (t, J = 8.0 Hz, 1H), 6.77-6.71 (m, 2H), 6.63-6.62 (d, J = 6.0 Hz, 1H), 3.68 (s, 3H), 3.32-3.28 (m, 1H), 3.15 (br s, 1H), 2.92-2.87 (m, 1H), 2.68 (s, 3H), 2.46-2.44 (d, J = 13.5 Hz, 1H), 2.19-2.13 (m, 1H), 2.04-2.00 (m, 2H), 1.88-1.56 (m, 8H), 1.36-1.09 (m, 3H), 0.82-0.75 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3): δ 159.6, 152.1, 129.4, 117.0, 111.3, 110.6, 62.7, 55.2, 49.5, 47.4, 47.3, 45.2, 35.7, 34.8, 34.6, 34.1, 30.0, 27.1, 26.8, 25.8; IR cm^{-1} (neat): 2925.3,

2851.4, 1601.4, 1582.5, 1486.0, 1448.2, 1256.1, 1050.4; HRMS calcd for $C_{20}H_{30}NO$: 300.2327 ($M+H$)⁺, found 300.2319.

The compound (0.18 g, 0.60 mmol) was *O*-demethylated to yield **7d** (0.17 g, > 99 %). ¹H NMR (500 MHz, $CDCl_3$): δ 8.00 (br s, 1H), 7.10-7.06 (t, J = 8.5 Hz, 1H), 6.75 (s, 2H), 6.63-6.61 (d, J = 7.5 Hz, 1H), 3.02-2.97 (m, 1H), 2.76 (br s, 1H), 2.67-2.62 (m, 1H), 2.48 (m, 3H), 2.26-2.23 (d, J = 14.5 Hz, 1H), 1.99-1.81 (m, 3H), 1.78-1.73 (m, 2H), 1.64-1.50 (m, 5H), 1.28-1.02 (m, 4H), 0.82-0.75 (m, 1H); ¹³C NMR (126 MHz, $CDCl_3$): δ 156.9, 154.2, 129.3, 116.3, 113.3, 112.9, 60.8, 49.5, 48.1, 46.3, 45.8, 36.9, 36.3, 35.8, 35.3, 35.1, 31.1, 27.6, 26.6; IR cm^{-1} (neat): 3044.3, 2920.2, 2849.1, 1597.4, 1583.2, 1446.1, 1273.1, 1246.2; HRMS 286.2171 ($M+H$)⁺; 286.2171 calcd for $C_{19}H_{28}NO$. HRMS calcd for $C_{19}H_{28}NO$: 286.2171 ($M+H$)⁺, found 286.2171. Compound **7d** was converted into its HBr salt and crystallized from EtOH (0.14 g); mp 223.8-225.3 °C. Anal. Calcd. for $C_{16}H_{24}NOBr + 0.5 M H_2O$: C, 60.83; H, 7.79; N, 3.73. Found: C, 60.85; H, 8.02; N, 3.48.

4.5.8. 3-(2-Phenethyldecahydro-1,5-methanobenzo[c]azocin-5(2*H*)-yl)phenol

(8d)—Using the general procedure, secondary amine **6d** (0.22 g, 1.02 mmol) was converted into its *N*-phenethyl derivative (0.29 g, 97 %). ¹H NMR (500 MHz, $CDCl_3$): δ 7.37-7.26 (m, 6H), 7.01-6.99 (d, J = 7.5 Hz, 1H), 6.97 (s, 1H), 3.86 (s, 3H), 3.08-3.04 (m, 1H), 2.94-2.80 (m, 7H), 2.42-2.39 (m, 1H), 2.21-2.06 (m, 2H), 1.99-1.56 (m, 7H), 1.45-1.18 (m, 4H), 1.01-0.97 (t, J = 10.5 Hz, 2H); ¹³C NMR (126 MHz, $CDCl_3$): δ 159.6, 155.4, 141.1, 129.0, 128.3, 125.9, 117.6, 111.7, 110.0, 61.4, 59.4, 55.2, 49.9, 49.8, 48.9, 48.7, 46.1, 37.4, 35.8, 34.8, 34.4, 30.4, 27.2, 26.6; IR cm^{-1} (neat): 3026.3, 2970.6, 2920.7, 2848.5, 1602.1, 1581.8, 1485.3, 1450.3, 1366.0, 1230.0, 1216.9, 1051.2; HRMS calcd for $C_{27}H_{36}NO$: 390.2797 ($M+H$)⁺, found 390.2797.

The compound (0.20 g, 0.51 mmol) was *O*-demethylated to yield **8d** (0.18 g, 94 %). ¹H NMR (500 MHz, $CDCl_3$): δ 7.30-7.13 (m, 6H), 6.85-6.84 (m, 2H), 6.70-6.68 (d, J = 9.0 Hz, 1H), 3.05-3.01 (m, 1H), 2.90-2.81 (m, 5H), 2.31-2.28 (d, J = 14.5 Hz, 1H), 2.08-1.89 (m, 3H), 1.83-1.52 (m, 6H), 1.44-1.38 (m, 1H), 1.31-1.12 (m, 4H), 1.02-0.97 (t, J = 11.0 Hz, 1H), 0.88-0.83 (m, 1H); ¹³C NMR (126 MHz, $CDCl_3$): δ 156.3, 155.0, 140.8, 129.4, 129.1, 129.0, 128.6, 128.5, 126.1, 116.9, 113.0, 112.8, 61.0, 59.3, 49.9, 48.5, 46.7, 36.9, 36.3, 36.2, 35.7, 35.3, 35.0, 34.2, 30.8, 26.5; IR cm^{-1} (neat): 3456.5, 3026.5, 297.7, 2923.3, 2850.6, 1597.6, 1584.4, 1447.0, 1365.9, 1229.3, 1217.1, 1119.0; HRMS 376.2649 ($M+H$)⁺; 376.2640 calcd for $C_{26}H_{34}NO$. HRMS calcd for $C_{26}H_{34}NO$: 376.2640 ($M+H$)⁺, found 376.2649. Compound **8d** was converted into its HBr salt and crystallized from EtOH/EtOAc (0.14 g); mp 150.2-153.6 °C. Anal. Calcd. for $C_{23}H_{30}NOBr + 0.5 M H_2O$: C, 67.13; H, 7.58; N, 3.01. Found: C, 67.04; H, 7.63; N, 2.82.

4.5.9. 5-(3-Methoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-7-one (10a)—To a reaction flask, NBn compound **9** (4 g, 0.012 mol), Pd/C (0.4 g, 10 wt %), AcOH (1 mL), and MeOH (100 mL) were added. After the vessel was evacuated using H_2 gas 3 ×, the reaction mixture was stirred at 60 °C under balloon pressure of H_2 gas. After 6 h, the mixture was filtered through a celite pad to remove the catalyst, and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (100 mL) and was washed with 2 N NaOH; the aqueous layer was extracted with CH_2Cl_2 (100 mL × 2). The combined organics were washed with brine, dried over Na_2SO_4 , filtered, and evaporated. The crude product was purified by column chromatography to give the secondary amine as a pale yellow oil (3.0 g, > 99 %). ¹H NMR (500 MHz, $CDCl_3$): δ 7.24-7.20 (t, J = 8.5 Hz, 1H), 6.88-6.87 (d, J = 1.0 Hz, 1H), 6.82 (s, 1H), 6.73-6.71 (d, J = 8.0 Hz, 1H), 3.74 (s, 3H), 3.71-3.70 (m, 1H), 2.89-2.87 (d, J = 7.5 Hz, 2H), 2.77-2.74 (d, J = 17.0 Hz, 1H), 2.54 (m, 2H), 2.43-2.40 (d, J = 16.5 Hz, 1H), 2.31-2.09 (m, 2H), 1.85-1.73 (m, 2H); ¹³C NMR (126 MHz, $CDCl_3$): δ 210.3, 159.7, 150.3, 129.6, 116.8, 111.2, 111.0, 55.2, 53.2, 49.4, 47.4, 39.2, 39.1, 38.9, 37.4.

The secondary amine (1.1 g, 4.5 mmol) was methylated using Pd/C (0.11 g, 10 wt %), AcOH (0.05 mL), formalin (37 % in water, 0.34 mL, 4.5 mmol), and MeOH (20 mL) to give 0.69 g (59 %) of **10a** as a colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 7.28-7.24 (t, *J* = 8.0 Hz, 1H), 6.92-6.91 (d, *J* = 7.5 Hz, 1H), 6.87 (s, 1H), 6.77-6.75 (dd, *J* = 8.0, 2.0 Hz, 1H), 3.78 (s, 3H), 3.45 (br s, 1H), 2.94-2.90 (dd, *J* = 2.0, 17.0 Hz, 1H), 2.78-2.68 (m, 2H), 2.46-2.43 (m, 2H), 2.39 (s, 3H), 2.34-2.31 (m, 1H), 2.20-2.13 (m, 2H), 1.96-1.86 (m, 2H); ¹³C NMR (126 MHz, CDCl₃): δ 210.5, 159.9, 150.2, 129.8, 117.1, 111.4, 111.3, 56.1, 55.4, 53.3, 47.6, 42.8, 38.8, 38.3, 38.0.

4.6. 5-(3-Methoxyphenyl)-2-phenethyl-2-azabicyclo[3.3.1]nonan-7-one (**10b**)—

The secondary amine (1.4 g, 5.7 mmol), obtained by *N*-debenzylation of **9**, was converted to its *N*-phenethyl derivative **10b** by the general procedure (1.3 g, 67 %, colorless oil). ¹H NMR (500 MHz, CDCl₃): δ 7.31-7.21 (m, 6H), 6.96-6.95 (d, *J* = 8.0 Hz, 1H), 6.91 (s, 1H), 6.80-6.79 (d, *J* = 8.0 Hz, 1H), 3.82 (s, 3H), 3.61 (br s, 1H), 2.93-2.70 (m, 7H), 2.49-2.34 (m, 3H), 2.30-2.14 (m, 2H), 2.05-1.89 (m, 2H); ¹³C NMR (126 MHz, CDCl₃): δ 210.5, 159.9, 150.2, 140.3, 129.7, 128.9, 128.5, 126.3, 117.1, 111.4, 111.2, 57.1, 55.4, 54.7, 53.4, 45.7, 39.3, 38.2, 37.8, 34.7; IR cm⁻¹ (neat): 2930, 2811, 1694, 1597, 1494, 1462, 1358, 1251, 1278, 1045; HRMS calcd for C₂₃H₂₈NO₂: 350.2120 (M+H)⁺, found 350.2115.

4.6.1. 5-(3-Hydroxyphenyl)-2-phenethyl-2-azabicyclo[3.3.1]nonan-7-one (**10c**)—

Using the general procedure for *O*-demethylation, compound **10c** was obtained as a pale yellow oil (69 mg, 72 %). ¹H NMR (500 MHz, CDCl₃): δ 7.28-7.14 (m, 6H), 6.85-6.83 (d, *J* = 7.5 Hz, 1H), 6.80 (s, 1H), 6.70-6.69 (d, *J* = 8.0 Hz, 1H), 3.64 (br s, 3H), 2.95-2.72 (m, 7H), 2.46-2.34 (m, 3H), 2.22-2.14 (m, 2H), 2.00-1.94 (dt, *J* = 13.0, 4.5 Hz, 1H), 1.88-1.86 (d, *J* = 18.0 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃): δ 211.2, 156.7, 150.0, 139.8, 129.9, 128.8, 128.6, 126.4, 116.5, 114.0, 112.5, 57.0, 54.6, 53.3, 45.9, 39.2, 39.1, 37.7, 37.4, 34.2; IR cm⁻¹ (neat): 3054, 2944, 2816, 1699, 1600, 1495, 1446, 1265, 1180, 1122; HRMS calcd for C₂₂H₂₆NO₂: 336.1964 (M+H)⁺, found 336.1923. Anal. Calcd. for C₂₂H₂₅NO₂: C, 78.83; H, 7.52; N, 4.18. Found: C, 78.57; H, 7.54; N, 4.00. Compound **10c** was converted into its HBr salt and crystallized from EtOH/EtOAc (64 mg), mp (HBr salt): 244.0 ~ 244.3 °C.

4.6.2 5-(3-Hydroxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-7-ol (11a**)**—To a stirred solution of the enantiopure ketone **10a** (15 mg, 0.044 mmol) in MeOH (3 mL) was added NaBH₄ (12.2 mg, 0.32 mmol) portionwise at 0 °C. The resulting mixture was warmed up to room temperature and stirred for 12 h. The reaction was quenched with H₂O and the product was extracted with CH₂Cl₂ (20 mL × 3). The combined organics were washed with brine, dried over Na₂SO₄, filtered, and evaporated. The crude product was purified by preparative TLC. ¹H NMR (500 MHz, CDCl₃): δ 7.30-7.28 (t, *J* = 7.5 Hz, 1H), 6.92-6.90 (d, *J* = 7.0 Hz, 1H), 6.86 (s, 1H), 6.77-6.75 (dd, *J* = 2.0, 8.0 Hz, 1H), 4.15-4.13 (t, *J* = 4.0 Hz, 1H), 3.84 (s, 3H), 3.12 (br s, 1H), 2.73-2.61 (m, 3H), 2.42 (s, 3H), 2.38-2.35 (d, *J* = 12.5 Hz, 1H), 2.27-2.25 (d, *J* = 14.0 Hz, 1H), 2.09-2.06 (d, *J* = 14.5 Hz, 1H), 1.96-1.92 (dt, *J* = 13.5, 4.0 Hz, 1H), 1.81-1.77 (dd, *J* = 10.0, 14.0 Hz, 1H), 1.72-1.69 (d, *J* = 13.0 Hz, 1H), 1.61-1.56 (dt, *J* = 3.5, 14.0 Hz, 1H).

Compound **11a** was obtained as a colorless oil using the general procedure for *O*-demethylation (12 mg, 80 % over two steps). ¹H NMR (500 MHz, CDCl₃ w/one drop of CD₃OD): δ 7.12-7.09 (t, *J* = 8.0 Hz, 1H), 6.72(s, 2H), 6.62-6.61 (d, *J* = 7.5 Hz, 1H), 4.03-4.01 (t, *J* = 5.5 Hz, 1H), 3.10 (br s, 1H), 2.67- 2.61 (m, 2H), 2.30 (s, 3H), 2.23-2.19 (m, 1H), 2.08-1.94 (m, 2H), 1.87-1.80 (m, 3H), 1.70-1.60 (m, 2H); ¹³C NMR (126 MHz, CDCl₃ w/one drop of CD₃OD): δ 156.9, 154.6, 129.5, 115.9, 112.9, 112.0, 67.0, 55.4, 46.9, 46.2, 43.1, 38.0, 34.2, 33.2, 32.0; IR cm⁻¹ (neat): 3246, 2938, 1585, 1480, 1449, 1374, 1279, 1194, 1063, 1048; HRMS calcd for C₁₅H₂₂NO₂: 248.1651 (M+H)⁺, found 248.1655. Compound **11a** was converted into its HBr salt and crystallized in EtOAc with few drops of

MeOH. The absolute configuration of **11a** was determined by X-ray crystallography (Fig 1, C1 = *S*, C5 = *R*, and C7 = *S*). Anal. Calcd. for C₁₅H₂₂NO₂Br: C, 54.89; H, 6.76; N, 4.27. Found: C, 54.66; H, 6.78; N, 4.08.

4.6.3. 5-(3-Hydroxyphenyl)-2-phenethyl-2-azabicyclo[3.3.1]nonan-7-ol (**11b**)—

To a stirred solution of the ketone **10b** (0.17 g, 0.49 mmol) in MeOH (5 mL) was added NaBH₄ (1.8 g, 49 mmol) portionwise at 0 °C. The resulting mixture was warmed up to room temperature and stirred for 12 h. The reaction was quenched with water and the product was extracted with CH₂Cl₂ (5 mL × 3). The combined organics were washed with brine, dried over Na₂SO₄, filtered, and evaporated. The crude product was purified by column chromatography to give a colorless oil (0.13 g, 76 %). ¹H NMR (500 MHz, CDCl₃): δ 7.29-7.24 (m, 6H), 6.92-6.90 (d, *J* = 7.5 Hz, 1H), 6.88 (s, 1H), 6.78-6.76 (dd, *J* = 8.0, 1.5 Hz, 1H), 4.13 (br s, 1H), 3.83 (s, 3H), 3.27 (br s, 1H), 2.85-2.70 (m, 7H), 2.43-2.40 (dd, *J* = 12.5, 2.0 Hz, 1H), 2.31-2.29 (d, *J* = 14.0 Hz, 1H), 2.09-2.06 (m, 1H), 1.99-1.96 (m, 1H), 1.76-1.69 (m, 2H), 1.60-1.55 (dt, *J* = 3.5, 14.0 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃): δ 159.7, 155.4, 139.9, 129.5, 128.7, 128.6, 126.3, 117.1, 111.2, 110.3, 68.0, 59.0, 55.2, 55.0, 47.9, 45.0, 37.5, 35.5, 34.5, 34.3, 32.8; IR cm⁻¹ (neat): 3362, 3026, 2935, 2832, 1602, 1582, 1486, 1453, 1430, 1370, 1292, 1259, 1159, 1132, 1051; HRMS calcd for C₂₃H₃₀NO₂: 352.2277 (M+H)⁺, found 352.2236.

Compound **11b** was obtained as a pale brown solid using the general procedure for *O*-demethylation (70 mg, 66 %). ¹H NMR (500 MHz, CDCl₃): δ 7.38-7.21 (m, 6H), 7.21 (s, 1H), 6.80-6.77 (m, 2H), 4.27 (br s, 1H), 3.35 (br s, 1H), 2.96-2.75 (m, 7H), 2.54-2.52 (d, 12.0 Hz, 1H), 2.43-2.41 (d, *J* = 13.5 Hz, 1H), 2.19-2.16 (d, *J* = 14.5 Hz, 1H), 2.08-2.06 (d, *J* = 11.5 Hz, 1H), 1.82-1.73 (m, 2H), 1.64-1.61 (d, *J* = 4.0 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃): δ 157.4, 155.0, 139.7, 129.6, 128.8, 128.7, 126.5, 115.0, 113.5, 112.5, 68.3, 59.0, 55.3, 48.2, 45.1, 37.5, 35.5, 34.4, 34.1, 32.5; IR cm⁻¹ (neat): 3245, 3026, 2929, 1600, 1585, 1496, 1453, 1370, 1277, 1131; HRMS calcd for C₂₂H₂₈NO₂: 338.2120 (M+H)⁺, found 338.2111. Compound **11b** was converted into its HBr salt and crystallized from EtOAc (64 mg), mp 227.4-229.2 °C. Anal. Calcd. for C₂₂H₂₈NO₂Br: C, 63.20; H, 6.75; N, 3.35. Found: C, 62.86; H, 6.70; N, 3.26.

4.7. Pharmacology

4.7.1. Cell culture and membrane preparation for binding assays—As noted previously,[1, 15, 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 were provided by Dr. Larry Toll (SRI International, CA). The cells were grown on plastic flasks in DMEM (100%) (hDOR-CHO and hKOR-CHO) or DMEM/F-12 (50%/50%) medium (hMOR-CHO) containing 10% FBS, and G-418 (0.10-0.2 mg/mL) under 95% air/5% CO₂ at 37 °C. Cell monolayers were harvested and frozen at -80 °C.

4.7.2 Opioid binding assays—We used [³H][D-Ala²-MePhe⁴,Gly-ol⁵]enkephalin ([³H]DAMGO, SA=44-48 Ci/mmol) to label MOR, [³H][D-Ala²,D-Leu⁵]enkephalin ([³H]DADLE, SA=40-50 Ci/mmol) to label DOR and [³H](−)-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 min 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 minutes, resuspended in 10 mL/pellet ice-cold 10mM 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 μ M levallorphan ($[^3\text{H}]\text{DAMGO}$ and $[^3\text{H}]\text{DADLE}$) and 1 μ M (-)-U69,593 (for $[^3\text{H}]\text{U69,593}$ binding). $[^3\text{H}]\text{Radioligands}$ 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 $^{\circ}\text{C}$. The filters were punched into 24-well plates to which was added 0.6 mL of LSC-cocktail (Cytosint). Samples were counted, after an overnight extraction, in a Trilux liquid scintillation counter at 44% efficiency. Opioid binding assays had ~ 30 μ g protein per assay tube. Inhibition curves were generated by displacing a single concentration of radioligand by 10 concentrations of drug. 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: $Y = 100 / (1 + ([\text{INHIBITOR}] / \text{IC}_{50})^N)$, where “Y” is the percent of control value. K_i values for test drugs are calculated according to the standard equation: $K_i = \text{IC}_{50} / (1 + [\text{radioligand}] / K_d)$. For the $[^3\text{H}]\text{radioligands}$, the following K_d values ($\text{nM} \pm \text{SD}$, $n=3$) were used in the K_i calculation: $[^3\text{H}]\text{DAMGO}$ (0.93 ± 0.04), $[^3\text{H}]\text{DADLE}$ (1.9 ± 0.3) and $[^3\text{H}](-)\text{-U69,593}$ (11 ± 0.6). The corresponding B_{max} values were ($\text{fmol/mg protein} \pm \text{SD}$, $n=3$): $[^3\text{H}]\text{DAMGO}$ (1912 ± 68), $[^3\text{H}]\text{DADLE}$ (3655 ± 391) and $[^3\text{H}](-)\text{-U69,593}$ (3320 ± 364).

4.8. X-ray crystal data on compounds **11a** and **7b**

Single-crystal X-ray diffraction data on compounds **11a** and **7b** were collected using MoK radiation and a Bruker APEX-2 CCD area detector. Crystals were prepared for data collection by coating with high viscosity microscope oil. The oil-coated crystal was mounted on a micro-mesh mount (Mitegen, Inc.) and transferred to the diffractometer. The structures were solved by direct methods and refined by full-matrix least squares on F^2 values using the programs found in the SHELXTL suite (Bruker, SHELXTL v6.10, 2000, Bruker AXS Inc., Madison, WI). Corrections were applied for Lorentz, polarization, and absorption effects. Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms on carbons were included using a riding model [coordinate shifts of C applied to H atoms] with C-H distance set at 0.96 $\text{\AA}$. Complete.

Atomic coordinates for **11a** and **7b** have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers CCDC 933697, and CCDC 933698, respectively). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.8.1. Compound 11a—A $0.288 \times 0.209 \times 0.062$ mm^3 crystal was prepared for data collection and a data set collected at 296 $^{\circ}\text{K}$. The crystal was monoclinic in space group $P 2_1$, with unit cell dimensions $a = 8.0575(6)$, $b = 6.1223(5)$, $c = 15.2147(14)$ $\text{\AA}$, and $\beta = 102.892(3)^{\circ}$. Data was 99.3% complete to 25.00° (~ 0.83 $\text{\AA}$) with an average redundancy of 3.97. The final anisotropic full matrix least-squares refinement on F^2 with 181 variables converged at $R1 = 6.29\%$, for the observed data and $wR2 = 18.85\%$ for all data.

4.8.2. Compound 7b—A $0.258 \times 0.184 \times 0.058$ mm^3 crystal was prepared for data collection and a data set collected at 100 $^{\circ}\text{K}$. The crystal was orthorhombic in space group $P b c a$, with unit cell dimensions $a = 19.330(2)$, $b = 8.4573(9)$, and $c = 19.3738(19)$ $\text{\AA}$. Data was 99.5% complete to 25.00° (~ 0.83 $\text{\AA}$) with an average redundancy of 8.30. The final anisotropic full matrix least-squares refinement on F^2 with 183 variables converged at $R1 = 5.00\%$, for the observed data and $wR2 = 16.25\%$ for all data.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The work of the Drug Design and Synthesis Section, CBRB, NIDA, & NIAAA, was supported by the NIH Intramural Research Programs of the National Institute on Drug Abuse (NIDA) and the National Institute of Alcohol Abuse and Alcoholism. The Clinical Psychopharmacology Section, CBRB, NIDA, was supported by the NIH Intramural Research Program of the National Institute on Drug Abuse (NIDA). We also thank Dr. Klaus Gawrisch and Dr. Walter Teague (Laboratory of Membrane Biochemistry and Biophysics, NIAAA, for NMR spectral data. The authors also express their thanks to Noel Whittaker, Mass Spectrometry Facility, NIDDK, for mass spectral data. The X-ray crystallographic work was supported by NIDA through an Interagency Agreement #Y1-DA1101 with the Naval Research Laboratory (NRL).

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Highlights

>The addition of a second cyclohexane ring to 5-phenylmorphans induced subnanomolar affinity, predominantly at m-opioid receptors. >Compounds with a substituent at C8 have higher affinity for the μ -receptor than those with substituents at C7 in the cyclohexane ring of the 5-phenylmorphans. >A formerly discovered “one pot” diastereoselective synthesis provided the C7- and C8-substituted compounds that have been difficult to access. >The diastereoselective synthesis resulted in the formation of a chiral crystal of 11a; its absolute configuration was determined through X-ray crystallographic analysis.

Figure 1. X-ray crystallographic structure of HBr salt of 7b (C7a-Me) and 11a (C7b-OH)

Scheme 1.
General scheme

Scheme 2. N-Derivatization followed by O-demethylation

Scheme 3. Synthesis of 7-oxo and 7-hydroxy compounds

Table 1

Binding affinity of tested compounds at opioid receptors

Compound	Ki (nM)					
	R1	R2	R	μ^a	b	c
7a	Me	H	Me	1.49 $\pm$ 0.06	139 $\pm$ 23	39 $\pm$ 1.3
8a	Me	H	Phenethyl	2.23 $\pm$ 0.15	126 $\pm$ 18	54 $\pm$ 1.3
7b	H	Me	Me	4.92 $\pm$ 0.37	721 $\pm$ 45	302 $\pm$ 13
8b	H	Me	Phenethyl	7.2 $\pm$ 0.4	260 $\pm$ 28	91 $\pm$ 10
7c	H	Phenyl	Me	23 $\pm$ 1.3	583 $\pm$ 30	136 $\pm$ 4
8c	H	Phenyl	Phenethyl	52 $\pm$ 2.5	318 $\pm$ 16	4.05 $\pm$ 0.20
7d	R1,R2	= cHex	Me	0.90 $\pm$ 0.04	116 $\pm$ 2.87 ^d	22 $\pm$ 0.87
8d	R1,R2	= cHex	Phenethyl	4.0 $\pm$ 0.13	103 $\pm$ 3.02	82 $\pm$ 3.35
10c	H	Oxo	Phenethyl	40 $\pm$ 2.8	3,540 $\pm$ 273	198 $\pm$ 19
11a	H	-OH	Me	22 $\pm$ 2.4	1,961 $\pm$ 220	1,229 $\pm$ 126
11b	H	-OH	Phenethyl	10.4 $\pm$ 1.8	876 $\pm$ 87	135 $\pm$ 13
Morphine				2.6 $\pm$ 0.01	605 $\pm$ 36	299 $\pm$ 49

Compound	K _i (nM)					
	R1	R2	R	μ ^a	<i>b</i>	<i>c</i>
DAMGO				1.2 ± 0.1	1500 ± 170	-
U69,593				2370 ± 94	12540 ± 1075	3.5 ± 0.3

Opiate receptor binding assays were performed using CHO hMOR, CHO hDOR and CHO hKOR cells. Except where noted, the data of three experiments were pooled (N=30 data points) and fit to the two-parameter logistic equation for the best-fit estimates ($\pm$ SD) of the IC₅₀, the value of which was then used to calculate the K_i value, as described in section 5.7.2.

^a [³H]-DAMGO.

^b [³H]-DADLE.

^c [³H]-U69,593.

^d Exploratory assay.