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4 β -Methyl-5-(3-hydroxyphenyl)morphan Opioid Agonist and Partial Agonist Derived from a 4 β -Methyl-5-(3-hydroxyphenyl)morphan Pure Antagonist

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Abstract

In previous studies we reported that addition of 7 α -acylamino groups to *N*-phenylpropyl-4 β -methyl-5-(3-hydroxyphenyl)morphan (**4**) led to compounds that were pure opioid receptor antagonists. In contrast to these findings we report in this study that addition of a 7 α -amino (**5a**), 7 α -alkylamino (**5b–e**), or 7 α -dialkylamino (**5f–h**) group to **4** leads to opioid receptor ligands with varying degrees of agonist/antagonist activity. The 7 α -amino and 7 α -methylamino analogues were full agonists at the μ and δ receptors and antagonists at the κ receptor. The 7 α -cyclopropylmethylamino analogue **5h** was a full agonist at the μ receptor with weaker agonist activity at the δ and κ receptors. Whereas the addition of a 7 α -acylamino group to the pure non-selective opioid receptor antagonist *N*-phenylpropyl-4 β -methyl-5-(3-hydroxyphenyl)morphan (**4**) led to κ selective pure opioid receptor antagonist, the addition of a 7 α -amino, 7 α -alkylamino or 7 α -dialkylamino group to **4** leads to opioid ligands that are largely μ or δ agonist with mixed agonist/antagonist properties.

N-Substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (**1**) are a structurally unique class of opioid receptor antagonists.¹ All *N*-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (**1**) including the *N*-methyl analogue **1a** are opioid receptor pure antagonists at all three opioid receptor subtypes.^{1–6} Numerous SAR studies showed that the antagonist activity of this class of antagonists resulted from the 3-methyl substituent on the piperidine ring and its *trans* relative relationship to the 4-methyl substituent and the equatorially-oriented 3-hydroxyphenyl group at the 4-position.^{2,4,7} A few of the more interesting analogues include alvimopam (**1b**),^{8,9} which is a drug on the market for GI motility disorder, (3*R*,4*R*)-1-[(*S*)-3-hydroxy-3-cyclohexylpropyl]-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidine (**1c**, LY255,582),^{2,10} which was developed to treat obesity, and (3*R*)-7-hydroxy-*N*-{(1*S*)-1-[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidine]methyl}-2-methylpropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide (**1d**,

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ASSOCIATED CONTENT

Supporting Information

Elemental analysis data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JDTic), which has shown activity in animal models of cocaine relapse,¹¹ nicotine withdrawal,¹² depression,¹¹ anxiety,^{13,14} and schizophrenia.¹⁵

In previous studies we showed that certain *N*-substituted (1*R*,4*S*,5*S*,7*R*)-7-acylaminomorphans (**2**, see ref. 16, 17, and 18 for specific structures) were potent and selective kappa opioid receptor antagonists,^{17,18} whereas certain (1*S*,4*R*,5*R*,7*S*)-7-acylaminomorphans (**3**, see ref. 19, 20, and 21 for specific structures) were potent and selective delta opioid receptor antagonists.^{19–21} In the present study, we report, as expected, that *N*-phenylpropyl-4β-methyl-5-(3-hydroxyphenyl)morphan (**4**), which, like **2** and **3**, can be viewed as a *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine with the 4-(3-hydroxyphenyl) group locked in an equatorial piperidine chair conformation, was a non-selective opioid receptor pure antagonist. In this study we report the surprising results that (1*R*,4*S*,5*S*,7*R*)-7-aminomorphan (**5a**) and its enantiomer (1*S*,4*R*,5*R*,7*S*)-7-aminomorphan (**6**) are opioid receptor partial agonists and report the effects on the opioid receptor profile of adding alkyl substituents to **5a** to give **5b–h**.

Chemistry

7-Aminomorphans **5a** and **6** were synthesized as previously reported.^{20,21} Scheme 1 outlines the procedures used to synthesize the 7-alkyl- and 7-dialkylaminomorphans **5b–e** and **5f–h**, respectively. 7α-Aminomorphan [**5a**] was coupled with formic acid using benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PYBOP) in methylene chloride containing diisopropylethylamine (DIPEA) to give the *N*-formylaminomorphan **7**. Reduction of the 7-formylaminomorphan **7** with lithium aluminum hydride (LAH) in tetrahydrofuran afforded **5b**. Reductive amination of **5a** with 1.1 equivalents of acetaldehyde, propionaldehyde, or cyclopropanecarboxaldehyde using sodium cyanoborohydride in 2,2,2-trifluoroethanol yielded 7-alkylaminomorphans **5c**, **5d**, and **5e**, respectively. Reductive

amination of **5a**, **5d**, and **5e** with excess paraformaldehyde using sodium cyanoborohydride provided 7-dialkylaminomorphans **5f**, **5g**, and **5h**, respectively.

Compound **4** was synthesized starting with *N*-alkyl-4 β -methyl-5-phenylmorphane **8**, which was prepared by a route analogous to the one described previously (Scheme 2).¹⁸ The ketone **8** was reduced under Clemmensen reduction conditions to provide **9**. *N*-Demethylation of **9** was achieved in 86% yield using 1-chloroethyl chloroformate (ACE-Cl) in refluxing dichloroethane followed by treatment with refluxing methanol to provide **10** (Scheme 2). Reductive amination of **10** with phenylpropionaldehyde provided **11** in 60% yield. Treatment of **11** with boron tribromide in methylene chloride yielded **4**.

Biology

Test compounds **4**, **5a–h**, and **6** were initially screened for intrinsic and antagonist activity at 10 μ M in the [³⁵S]GTP γ S binding assay at the human μ , κ , and δ opioid receptors over-expressed in CHO cells (Table 1).²² Compounds identified as agonists were evaluated in receptor-appropriate assay using eight different concentrations selected to provide clear indication of the upper and lower asymptotes of the concentration-response curve (Table 1). The $E_{\max}$ and EC_{50} were calculated, and the $E_{\max}$ was reported as a percentage of the $E_{\max}$ of the agonist standard (DAMGO, μ ; DPDPE, δ ; and U50,488, κ) run on the same assay plate. Measures of functional antagonism and selectivity were obtained by measuring the ability of test compounds to inhibit stimulated [³⁵S]GTP γ S binding produced by the selective agonists DAMGO (μ), DPDPE (δ), or U69,593 (κ).²² Agonist dose response curves were run in the presence or absence of a single concentration of test compound. The K_e values were calculated using the formula $K_e = [L]/DR - 1$, where $[L]$ is the concentration of test compound, and DR is the ratio of agonist EC_{50} value in the presence or absence of test compound.

Compounds **4**, **5b–f**, and **5h** were also evaluated for inhibition of binding to the human MOR, DOR, and KOR using [³H]DAMGO, [³H]DADLE, and [³H]U69,593, respectively, as the radioligands using previously reported methods.^{23,24} The results are listed in Table 2.

12a, R = CH₃

12b, R = C₆H₅(CH₂)₂

13

14

Results and Discussion

In previous studies, we reported that *N*-methyl- and *N*-phenylethyl-9 β -methyl-5-(3-hydroxyphenyl)morphans (**12a** and **12b**, respectively), which like *N*-phenylpropyl-4 β -methyl-5-(3-hydroxyphenyl)morphan (**4**), can be viewed as a *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine with the 4-(3-hydroxyphenyl) group locked in an equatorial piperidine chair conformation, were both non-selective opioid receptor pure antagonists.^{6,16} Thus, it was not surprising that **4** was also a non-selective opioid receptor pure antagonist with K_e values of 1.9, 32.7, and 12.9 nM at the μ , δ , and κ receptors, respectively.

The 7-aminomorphans (1*R*,4*S*,5*S*,7*R*) [**5a**] and its enantiomer (**6**) were synthesized in previously reported studies as intermediates for the synthesis of the 7-acylaminomorphans **2** and **3**, respectively. Acylation of **5a** with a number of acids having an amino function in the acyl group led to several potent and selective κ opioid receptor pure antagonists.¹⁷ For example, compound **13** had K_e values of 0.09 nM at the κ receptor with 578- and 689-fold selectivity relative to the μ and δ receptors (Table).¹⁷ Acylation of **6** with 2-methyl-2-phenylpropionic acid gave **14**, which had K_e values of 10.3, 0.1, and 13.2 nM at the μ , δ , and κ receptors, respectively, and, thus, was selective for the δ opioid receptors (Table).^{20,21} Compound **14** was also an inverse agonist with an IC_{50} = 0.4 nM (% of basal binding = 64%).^{20,21}

Since (*S*)-**5a** and **6** were intermediates used only for the synthesis of the 7-acylaminomorphans selective pure kappa opioid receptor antagonists (**2**)¹⁷ and the selective pure δ opioid receptor antagonist (**3**),^{20,21} respectively, we only determined their inhibition of radioligand binding at the μ , δ , and κ receptors. The [³⁵S]GTP γ S binding properties for these two compounds were not determined in our previous studies. Surprisingly, in this study we found that **5a**, which results from adding a 7 α -amino group to the pure opioid antagonist **4**, was a potent agonist at both the μ and δ opioid receptors and a potent antagonist at the κ opioid receptor. The EC_{50} at μ was 19.5 nM (E_{max} = 74%), and the EC_{50} at δ was 7.5 nM (E_{max} = 101%). The K_e value for **5a** at the κ receptor was 10.1 nM. The epimeric **6** was a somewhat weaker agonist at μ with an IC_{50} = 20.6 nM (E_{max} = 44%) and an antagonist at δ and κ with K_e values of 25.2 and 21.7 nM, respectively. Since **5a** was a relatively potent agonist at the μ and δ receptors, we designed and synthesized a series of mono- and dialkyl analogues of **5a** to see if it was possible to develop an even more potent μ/δ agonist. The series of compounds was also designed so that the effects of adding mono- and dialkyl groups to the 7 α -amino of **5a** would have on the agonist/antagonist activities and their subtype selectivities. The addition of a methyl group to **5a** to give the 7 α -methylamino analogue **5b** resulted in an increase in μ efficacy (105% compared to 74% for **5a**) with ED_{50} and E_{max} values at the δ receptor similar to those of **5a**, and an antagonist K_e value of 43.8 nM at the κ receptor compared to 10.1 nM for **5a**. Increasing the size of **5b** by one methylene group to give the *N*-ethylamino analogue **5c** resulted in a reduction of agonist activity at the μ receptor (EC_{50} = 33 nM and E_{max} = 14%) and complete loss of agonist activity at the δ receptor. The compound was also a weak opioid antagonist (K_e = 230 and 60.8 nM at δ and κ receptors, respectively). Similar to **5c**, **5d** was an agonist at the μ receptor (EC_{50} = 18 nM, E_{max} = 57%). The *N*-propylamino analogue had no agonist activity at the δ receptor and was a weak antagonist at the δ receptors (K_e = 69.4 nM). In contrast to **5c**, **5d** was a weak agonist at κ receptor (EC_{50} = 293 nM, E_{max} = 20.7%). Adding a cyclopropylmethyl group to **5a** gave **5e** which was a weak agonist at the μ receptor (EC_{50} = 130 nM, E_{max} = 52%), potent antagonist at the δ receptor (K_e = 4.3 nM), and a moderate antagonist at the κ receptor (K_e = 31 nM). The addition of a methyl group to **5b** to give the 7 α -dimethylamino analogue **5f** resulted in a potent μ agonist (EC_{50} = 6.5 nM, E_{max} = 104%) with weaker δ agonist potency and efficacy (EC_{50} = 38 nM, E_{max} = 55%) and a weak κ antagonist (K_e = 176 nM). Addition of an ethyl substituent to **5b** to give the 7 α -ethylmethylamino analogue **5g** resulted in a weak μ agonist/ κ antagonist. Surprisingly, adding a methyl group to **5e** to give the 7 α -methylcyclopropylmethyl analogue **5h** resulted in the most potent μ agonist in the series (EC_{50} = 2.7 nM, E_{max} = 109%) with somewhat weaker agonist efficacy at the δ (EC_{50} = 10.3 nM, E_{max} = 24%) and κ (EC_{50} = 40 nM, E_{max} = 38%) receptors.

The inhibition of radioligand binding K_i values for **4**, **5b–f**, and **5h** for the most part paralleled the EC_{50} and K_e values obtained in the [³⁵S]GTP γ S binding assays. For example compound **4** had higher affinity for the MOR and KOR receptor than the DOR receptor. In

the case of the MOR receptor, compounds **5b**, **5f**, and **5h** had the highest affinities at MOR and **5e** had the lowest affinity. Compounds **5c** and **5d** had intermediate K_i values at MOR. It is interesting to note that compounds **5b**, **5f**, and **5h** all had higher affinity for MOR than DAMGO. All of the compounds tested had weaker affinities for the DOR than at the MOR. Compounds **5f** and **5h** had the highest affinities for the DOR. Compounds **5b** and **5e** did not parallel the [^{35} S]GTP γ S binding at DOR very well. Compound **5b** had an EC_{50} = 14.8 at DOR and a K_i = 36.2 nM. Compound **5e** had a K_e = 4.3 nM and a K_i = 43.2 nM at DOR. With the exception of **5d** all of the compounds tested had lower affinity for the KOR than for the MOR. However, **5h** has a K_i value of 0.43 and 0.92 nM at the MOR and KOR, respectively. This is not too surprising since **5h** had an EC_{50} = 40 nM at the KOR.

In an effort to visualize the structural basis for the unexpected μ -opioid agonist activity of **5h**, docking calculations were performed using the recently reported X-ray crystallographic structures of the MOR²⁵ and KOR.²⁶ However, although such calculations²⁷ examining the interaction of a variety of agonists and antagonists docked to the KOR have provided reasonable docking poses; thus far, consistent results have not been obtained for the MOR.

In summary, the non-selective opioid receptor pure antagonist *N*-phenylpropyl-4 β -methyl-5-(3-hydroxyphenyl)morphan (**4**) is converted into agonists or mixed agonists/antagonists by adding a 7 α -amino (**5a**), 7 α -alkylamino (**5b–e**), or 7 α -dialkylamino **5f–h** group to **4**. The 7 α -amino and 7 α -methylamino analogues **5a** and **5b**, respectively, were full agonists at the μ and δ receptors and antagonists at the κ receptor. The 7 α -ethylamino and 7 α -propylamino analogues **5c** and **5d**, respectively, were either inactive or very weak agonists or antagonists at the δ and κ receptors. Somewhat surprising, the 7 α -cyclopropylamino analogue **5e** was also a weak agonist but a potent antagonist at the δ receptor and a somewhat weaker antagonist at the κ receptor. Even more surprising was the fact that the 7 α -dimethylamino and 7 α -cyclopropylmethylamino analogues **5f** and **5h** were potent, full agonists at the μ receptor. It is particularly interesting to note that acylation of the partial agonist **5a** leads to potent and selective κ opioid receptor pure antagonists (see **13** in the table) whereas alkylation of **5a** leads to compounds with varying degrees of agonist efficacy. Results from these studies provide unexpected structure activity information on the *N*-substituted 4-(3-hydroxyphenyl)morphan class of opioid receptor ligands. Whereas the addition of a 7 α -acylamino group to the pure non-selective opioid receptor antagonist *N*-phenylpropyl-4 β -methyl-5-(3-hydroxyphenyl)morphan (**4**) led to κ selective pure opioid receptor antagonist,¹⁷ the addition of a 7 α -amino, 7 α -alkylamino or 7 α -dialkylamino group to **4** leads to opioid ligands that are largely μ or δ agonist with mixed agonist/antagonist properties. For the most part the [^{35} S]GTP γ S binding data and inhibition of binding data paralleled each other. Since **5h** is a potent μ and δ agonist, this compound may have potential for development as an analgesic. In addition, since **5a** has an opioid profile somewhat similar to buprenorphine, this compound or further modification of this lead structure could lead to a compound to treat opioid addiction.

Experimental

General Procedures

All solvents were dried prior to use according to known procedures; all reagents were obtained from commercial sources or were synthesized from literature procedures, and were used without further purification unless otherwise noted. Air-sensitive reactions were performed under slight positive pressure of nitrogen. Room temperature is assumed to be between 20 and 25 °C. Evaporation of solvents was accomplished under reduced pressure (water aspirator, 12 mmHg), at less than 40 °C, unless otherwise noted. Melting points were taken on a Mel-Temp apparatus and are uncorrected. Chromatography solvent systems are

expressed in v:v ratios or as %v. CMA80 refers to a solution of CHCl_3 –MeOH–aq NH_4OH (80:18:2). Thin layer chromatography was performed on aluminum oxide IB-F plated from J. T. Baker (Phillipsburg, NJ) or silica gel 60 F₂₅₄ plates from EMD (Gibbstown, NJ). Chromatograms were visualized under UV light at 254 nm. ^1H NMR spectra were obtained at 300 MHz on a Bruker DPX300 spectrometer; ^{13}C NMR spectra were obtained at 75 MHz on a Bruker DPX300 spectrometer. Chemical shift values for ^1H determined relative to an internal tetramethylsilane standard (0.00 ppm); chemical shift values for ^{13}C determined relative to solvent (CDCl_3 = 77.23 ppm). Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. Purity of compounds (>95%) was established by elemental analysis.

3-[(1*R*,4*S*,5*S*)-4-Methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-5-yl]phenol(4) Hydrochloride—

To a solution of *N*-phenylpropyl-4 β -methyl-5-(3-(propan-2-yloxy)phenyl)morphane (**11**) (100 mg, 0.26 mmol) in dichloromethane (10 mL) at -78°C was added boron tribromide (0.51 mL, 0.51 mmol) (1M solution in CH_2Cl_2) drop wise. The reaction mixture was stirred at -78°C for 30 min, treated with MeOH (10 mL), warmed to rt, and stirred for 10 min. The methanol was removed by evaporation and the residue redissolved in MeOH (10 mL), and stirred for 10 min. The residue resulting from evaporation of the methanol was treated with saturated NaHCO_3 aqueous solution (15 mL) and extracted with ethyl acetate (3×15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to obtain **11**, which was subjected to column chromatography on silica gel using CMA80– CH_2Cl_2 (1:1) as the eluent to provide 60 mg (66%) of **4** as a colorless oil: ^1H NMR (CDCl_3) δ 7.21–7.10 (m, 6H), 6.67 (m, 2H), 3.26 (d, 1H), 3.14 (b, 1H), 2.66 (m, 5H), 2.35 (d, 1H), 2.12 (m, 3H), 1.83 (m, 3H), 1.69–1.55 (m, 3H), 1.37 (m, 1H), 0.72 (d, 3H); ^{13}C NMR (CDCl_3) δ 158.4, 153.6, 143.4, 130.1, 129.5, 129.4, 126.9, 117.5, 113.4, 113.2, 57.4, 55.8, 54.3, 41.1, 39.3, 34.6, 33.3, 29.8, 25.2, 23.9, 19.3; ESI MS ($\text{M} + \text{H}$)⁺ 351.3

The free base **4** was converted to **4**•HCl salt by adding 1M HCl in ether to ethereal solution of product. MP 152–155 $^\circ\text{C}$. $[\alpha]_{\text{D}}^{25} -15.7$ (1.02, MeOH). Anal. ($\text{C}_{24}\text{H}_{32}\text{ClNO} \cdot 0.25 \text{H}_2\text{O}$) C, H, N.

5-(3-Hydroxyphenyl)-4-methyl-7-methylamino-2-(3-phenylprop-1-yl)-2-azabicyclo[3.3.1]nonane (5b) Dihydrochloride—

To a suspension of LAH (57 mg, 1.5 mmol) in THF (5 mL) in a 10-mL microwave tube was added a solution of **7** (58 mg, 0.15 mmol) in THF (1 mL) slowly. The reaction mixture was heated in the microwave at 110°C for 10 min. At this point TLC analysis showed complete conversion of the starting material. The reaction mixture was diluted with ethyl acetate (10 mL) and the solution stirred for 10 min, then 20 mL 5% Na_2CO_3 solution was added slowly, and the resulting solution stirred for additional 10 min. The suspension was filtered and the organic layer separated. The aqueous layer was extracted with ethyl acetate (3×10 mL) and the combined organic layers dried (Na_2SO_4), filtered, and evaporated to obtain a yellow residue. The residue was subjected to column chromatography on silica gel using CMA80– CH_2Cl_2 (1:1) as the eluent to provide 32 mg (56%) of **5b** as a colorless oil: ^1H NMR (CDCl_3) δ 7.29–7.10 (m, 6H), 6.63–6.71 (m, 3H), 3.30 (m, 1H), 3.17 (b, 1H), 2.85 (dd, 1H), 2.65 (m, 4H), 2.52–2.29 (m, 8H), 2.08 (m, 1H), 1.78 (quint, 2H), 1.56 (d, 1H), 1.20 (t, 1H), 1.01 (t, 1H), 0.72 (d, 3H); ^{13}C NMR (CDCl_3) δ 157.21, 151.55, 142.59, 129.45, 128.70, 128.47, 125.88, 116.57, 113.20, 55.91, 54.68, 54.53, 53.54, 46.62, 40.19, 37.97, 33.61, 32.80, 31.25, 29.90, 29.35, 18.75; ESI MS ($\text{M} + \text{H}$)⁺ 379.5.

The free base **5b** was converted to **5b**•2HCl by adding 1M HCl in ether to solution of product in dichloromethane. $[\alpha]_{\text{D}}^{25} -16.8$ (0.88, MeOH). Anal. ($\text{C}_{25}\text{H}_{36}\text{Cl}_2\text{N}_2\text{O} \cdot 2.5\text{H}_2\text{O}$) C, H, N.

7-Ethylamino-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylprop-1-yl)-2-azabicyclo[3.3.1]nonane (5c) Dihydrochloride—To a solution of (–)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]nonan-7-amine [(S)-**5a**] hydrochloride (200 mg, 0.44 mmol) in trifluoroethanol (5 mL) was added triethylamine (140 mL, 1.0 mmol) and the mixture stirred for 30 min at room temperature. Acetaldehyde (22 mg, 0.5 mmol) was added to the reaction mixture and stirring continued for 10 min at which point sodium cyanoborohydride (64 mg, 1.0 mmol) was added. TLC analysis showed complete conversion of the starting material after 1 h. The reaction mixture was evaporated, treated with saturated sodium bicarbonate (5 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried (Na₂SO₄), filtered, and evaporated to obtain a yellow residue. The residue was subjected to column chromatography on silica gel using CMA80–CH₂Cl₂ (1:1) as the eluent to provide **5c** (55%) as a colorless oil: ¹H NMR (CDCl₃) δ 7.31–7.10 (m, 6H), 6.62 (m, 3H), 3.33 (b, 1H), 3.18 (s, 1H), 2.87 (dd, 1H), 2.69–2.55 (m, 5H), 2.48 (t, 2H), 2.14 (m, 6H), 2.07 (m, 1H), 1.79 (quint, 2H), 1.49 (m, 2H), 1.25 (m, 2H), 1.07 (t, 3H); 0.68 (d, 3H); ¹³C NMR (DMSO) δ 157.6, 148.3, 140.5, 129.6, 128.4, 128.2, 126.1, 111.7, 54.1, 53.7, 53.4, 50.4, 45.5, 38.0, 35.1, 32.2, 28.5, 24.9, 24.8, 17.4, 11.3, 8.5; ESI MS (M + H)⁺ 393.8.

The free base **5c** was converted to **5c**•2HCl by adding 1M HCl in ether to solution of **5c** in dichloromethane. [α]_D²⁵ –10.0 (0.56, MeOH). Anal. (C₂₆H₃₈Cl₂N₂O•2.25H₂O) C, H, N.

5-(3-Hydroxyphenyl)-4-methyl-2-(3-phenylprop-1-yl)-7-propylamino-2-azabicyclo[3.3.1]nonane (5d) Dihydrochloride—To a solution of (–)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]nonan-7-amine [(S)-**5a**] hydrochloride (50 mg, 0.11 mmol) in trifluoroethanol (2 mL) was added triethylamine (35 mL, 0.25 mmol) and the mixture stirred for 30 min at room temperature. Propionaldehyde (8 mg, 0.14 mmol) was added to the reaction mixture and stirring continued for 10 min. At this point sodium cyanoborohydride (16 mg, 0.25 mmol) was added. TLC analysis showed complete conversion of the starting material after 1 h. The reaction mixture was evaporated, treated with saturated sodium bicarbonate (5 mL), and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried (Na₂SO₄), filtered, and evaporated to obtain a yellow residue. The residue was subjected to column chromatography on silica gel using CMA80–CH₂Cl₂ (1:1) as the eluent to provide 36 mg (68%) of **5d** as a colorless oil: ¹H NMR (CDCl₃) δ 7.31–7.07 (m, 6H), 6.60 (m, 3H), 3.39 (b, 2H), 3.15 (s, 1H), 2.84 (dd, 1H), 2.72–2.55 (m, 5H), 2.48 (t, 2H), 2.32 (m, 3H), 2.04 (b, 1H), 1.79 (quint, 2H), 1.51 (m, 3H), 1.25 (t, 1H), 1.08 (t, 1H); 0.90 (t, 3H), 0.67 (d, 2H); ¹³C NMR (CDCl₃) δ 156.8, 151.8, 142.6, 129.4, 128.7, 128.4, 125.8, 117.2, 113.7, 113.1, 56.0, 54.4, 53.7, 53.1, 48.7, 47.2, 40.2, 37.9, 33.6, 32.8, 32.1, 29.3, 23.0, 18.6, 11.9; ESI MS (M + H)⁺ 407.7

The free base **5d** was converted to **5d**•2HCl by adding 1M HCl in ether to solution of product in ether. [α]_D²⁵ –12.1 (0.98, MeOH). Anal. (C₂₇H₄₀Cl₂N₂O•1.0H₂O) C, H, N.

7-(N-Cyclopropylmethylamino)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylprop-1-yl)-2-azabicyclo[3.3.1]nonane (5e) Dihydrochloride—To a solution of (–)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]nonan-7-amine [(S)-**5a**] hydrochloride (100 mg, 0.22 mmol) in trifluoroethanol (5 mL) was added triethylamine (70 mL, 0.5 mmol) and the mixture stirred for 30 min at room temperature. Cyclopropanecarboxaldehyde (18 mg, 0.25 mmol) was added to the reaction mixture, and stirring continued for 10 min when sodium cyanoborohydride (32 mg, 1.0 mmol) was added. TLC analysis showed complete conversion of the starting material after 1 h. The reaction mixture was evaporated, treated with saturated sodium bicarbonate (5 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried (Na₂SO₄), filtered, and evaporated to give a yellow residue. The residue was subjected to column

chromatography on silica gel using CMA80–CH₂Cl₂ (1:1) as the eluent to provide 48 mg (52%) of **5e** as a colorless oil: ¹H NMR (CDCl₃) δ 7.20–7.00 (m, 6H), 6.60 (m, 3H), 4.37 (b, 2H), 3.45 (b, 1H), 3.16 (s, 1H), 2.83 (dd, 1H), 2.64 (m, 3H), 2.49 (m, 4H), 2.33 (m, 3H), 2.06 (b, 1H), 1.79 (quint, 2H), 1.58 (d, 2H), 1.08 (t, 1H); 0.96 (m, 1H), 0.76 (d, 3H), 0.48 (d, 2H), 0.13 (d, 2H); ¹³C NMR (CDCl₃) δ 156.7, 151.6, 142.5, 129.2, 128.5, 128.3, 125.7, 116.7, 113.1, 112.7, 55.8, 54.4, 53.3, 52.6, 51.7, 47.1, 40.1, 37.8, 33.4, 32.7, 31.8, 29.2, 18.6, 15.5, 10.8, 3.7, 3.6; ESI MS (M + H)⁺ 419.7.

The free base **5e** was converted to **5e**•2HCl salt by adding 1M HCl in ether to solution of **5e** in ether. [α]_D²⁵ –11.2 (0.57, MeOH). Anal. (C₂₈H₄₀Cl₂N₂O•H₂O) C, H, N.

7-Dimethylamino-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylprop-1-yl)-2-azabicyclo[3.3.1]nonane (5f) Dihydrochloride—To a solution of (–)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]nonan-7-amine [(S)-**5a**] hydrochloride (100 mg, 0.22 mmol) in trifluoroethanol (5 mL) was added triethylamine (140 mL, 1.0 mmol) and the reaction mixture stirred for 30 min. Paraformaldehyde was added to the reaction mixture and stirred for 10 min at room temperature. At this point sodium cyanoborohydride (32 mg, 0.5 mmol) was added. The suspension was stirred overnight then evaporated under reduce pressure, treated with saturated sodium bicarbonate (5 mL), and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried (Na₂SO₄), filtered, and evaporated to obtain a brown residue. The residue was subjected to column chromatography on silica gel using CMA80–CH₂Cl₂ (1:1) as the eluent to provide 52 mg (60%) of a colorless oil: ¹H NMR (CDCl₃) δ 7.32–7.05 (m, 6H), 6.63 (m, 3H), 3.20 (b, 1H), 3.12 (vb, 1H), 2.83 (dd, 1H), 2.65 (t, 3H), 2.49 (t, 2H), 2.34 (m, 9H), 2.05 (m, 1H), 1.79 (quint, 2H), 1.49 (m, 2H), 1.25 (m, 2H), 0.68 (d, 3H); ¹³C NMR (CDCl₃) δ 156.5, 151.6, 142.4, 129.3, 128.5, 128.3, 125.7, 116.9, 113.3 (broad, 2C), 60.1, 55.6, 54.4, 53.6, 43.2, 41.4, 40.1, 38.0, 33.4, 32.1, 29.2, 27.2, 18.5; ESI MS (M + H)⁺ 393.7;

The free base **5f** was converted to **5f**•2HCl salt by adding 1M HCl in ether to ethereal solution of product. [α]_D²⁵ –10.9 (0.51, MeOH). Anal. (C₂₆H₃₈Cl₂N₂O•2.0 H₂O) C, H, N.

7-(N-Ethylmethylamino)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylprop-1-yl)-2-azabicyclo[3.3.1]nonane (5g) Dihydrochloride—A solution of 7-ethylamino-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylprop-1-yl)-2-azabicyclo[3.3.1]nonane (**5c**) (47 mg, 0.12 mmol) in trifluoroethanol (3 mL) was treated with paraformaldehyde and the reaction mixture stirred for 10 min at room temperature. At this point sodium cyanoborohydride (15 mg, 0.24 mmol) was added and the reaction mixture stirred for 1 h. At this point TLC analysis showed complete conversion of the starting material. The reaction mixture was evaporated, treated with saturated sodium bicarbonate (5 mL), and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried (Na₂SO₄), filtered, and evaporated to obtain a brown residue. The residue was subjected to column chromatography on silica gel using CMA80–CH₂Cl₂ (1:1) as the eluent to provide 27 mg (55%) of **5g** as a white solid: ¹H NMR (CDCl₃) δ 7.27–7.15 (m, 6H), 6.63 (m, 3H), 3.55 (b, 1H), 3.20 (s, 1H), 2.82 (dd, 1H), 2.64 (m, 5H), 2.51 (t, 2H), 2.30 (m, 6H), 1.79 (quint, 2H), 1.50 (m, 2H), 1.26 (t, 1H), 1.11 (t, 3H), 0.69 (d, 3H); ¹³C NMR (CDCl₃) δ 156.8, 151.3, 142.3, 129.3, 128.5, 128.3, 125.7, 116.6, 113.9, 113.3, 57.7, 55.8, 54.5, 53.5, 50.7, 47.3, 42.4, 40.1, 37.9, 36.5, 33.4, 32.1, 29.1, 18.5, 10.9. ESI MS (M + H)⁺ 407.6.

The free base **5g** was converted to **5g**•2HCl salt by adding 1M HCl in ether to solution of product in ether. [α]_D²⁵ –11.3 (0.73, MeOH). Anal. (C₂₇H₄₀Cl₂N₂O•1.75 H₂O) C, H, N.

7-(N-Cyclopropylmethylmethylamino)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylprop-1-yl)-2-azabicyclo[3.3.1]nonane (5h) Dihydrochloride—A solution

of 7-(*N*-cyclopropylmethylamino)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylprop-1-yl)-2-azabicyclo[3.3.1]nonane (**5e**) (48 mg, 0.11 mmol) in trifluoroethanol (3 mL) was treated with paraformaldehyde and the reaction mixture stirred for 10 min at room temperature. At this point sodium cyanoborohydride (15 mg, 0.22 mmol) was added. TLC analysis showed complete conversion of the starting material after 1 h. The reaction mixture was evaporated, treated with saturated sodium bicarbonate (5 mL), and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried (Na₂SO₄), filtered, and evaporated to obtain a brown residue. The residue was subjected to column chromatography on silica gel using CMA80–CH₂Cl₂ (1:1) as the eluent to provide 36 mg (73%) of a colorless oil: ¹H NMR (CDCl₃) δ 7.30–7.11 (m, 6H), 6.74 (m, 3H), 5.15 (b, 1H), 3.78 (m, 1H), 3.26 (s, 1H), 2.78 (dd, 1H), 2.64 (m, 5H), 2.49 (m, 5H), 2.36 (d, 2H), 2.24 (d, 1H), 1.81 (quint, 2H), 1.55 (m, 2H), 1.35 (t, 1H), 1.26 (s, 1H), 0.94 (m, 1H), 0.71–0.65 (m, 5H), 0.25 (d, 2H); ¹³C NMR (CDCl₃) δ 156.6, 150.6, 142.1, 129.4, 128.5, 128.3, 125.8, 116.8, 113.7, 112.9, 58.8, 58.2, 55.6, 54.5, 53.5, 41.3, 40.2, 37.7, 36.7, 33.3, 31.9, 28.9, 26.4, 18.5, 7.2, 4.6, 4.4; ESI MS (M + H)⁺ 433.6.

The free base **5h** was converted to **5h**•2HCl salt by adding 1M HCl in ether to solution of product in ether. [α]_D²⁵ –9.1 (0.66, MeOH). Anal. (C₂₉H₄₂Cl₂N₂O•2.0 H₂O) C, H, N.

7-Formylamino-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylprop-1-yl)-2-azabicyclo[3.3.1]nonane (7)—To a cooled solution of formic acid (14 mg, 0.3 mmol) in CH₂Cl₂ (5 mL) was added PyBOP (130 mg, 0.30 mmol). To this solution was added a mixture of 7-amino-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylprop-1-yl)-2-azabicyclo[3.3.1]nonane [(*S*)-**5a**] (100 mg, 0.22 mmol) and diisopropylethylamine (552 mL, 3 mmol) in CH₂Cl₂ (5 mL). The combined solution was stirred at room temperature for 2 h then evaporated to yield a yellow residue. The residue was suspended in 5% aqueous Na₂CO₃ (15 mL), and the aqueous suspension was extracted with EtOAc (2 × 15 mL). The combined extracts were dried (Na₂SO₄), filtered, and evaporated to yield a colorless oil. The oil was subjected to flash chromatography on silica gel using CMA80–CH₂Cl₂ (1:1) as the eluent. Fractions containing product were pooled and evaporated to yield 68 mg (78%) of **7** as a clear oil: ¹H NMR (MeOD) δ 7.96 (s, 1H), 7.23 (m, 6H), 6.69 (m, 3H), 4.66 (m, 1H), 3.42 (b, 1H), 3.20 (m, 1H), 2.94 (m, 1H), 2.69 (m, 5H), 2.38 (m, 4H), 1.89 (m, 3H), 1.35 (m, 3H), 0.75 (d, 3H); ESI MS (M + H)⁺ 393.7.

2,4-Dimethyl-5-[3-(propan-2-yloxy)phenyl]-2-azabicyclo[3.3.1]nonane (9)—To a suspension of 2,4-dimethyl-5-[3-(propan-2-yloxy)phenyl]-2-azabicyclo[3.3.1]nonan-7-one (**8**)¹⁸ (1.01 g, 3.35 mmol) in diethylether (100 mL) (2M HCl) at 0 °C was added Zn dust (14.2 g, 218 mmol) portion-wise over a 30-min period. HCl gas was bubbled through the reaction solution until all the Zn⁰ had reacted. The reaction mixture was poured into a mixture of water (500 mL) and chloroform (250 mL). The pH of the aqueous layer was adjusted to 13 with 50% sodium hydroxide solution, and the insoluble white material was removed by filtration through a celite pad. The filtrate was placed in a separatory funnel and the chloroform layer was separated, dried (Na₂SO₄), filtered, and evaporated to obtain 550 mg (57%) of **9** after column chromatography using CH₂Cl₂–MeOH (100% to 90%): ¹H NMR (CDCl₃) δ 7.12 (t, 1H), 6.80 (m, 2H), 6.74 (d, 1H), 4.56 (septet, 1H), 3.33 (dd, 1H), 3.07 (m, 1H), 2.63 (d, 1H), 2.45 (s, 3H), 2.40 (m, 1H), 2.19 (m, 2H), 1.95 (m, 1H), 1.70 (m, 3H), 1.35 (d, 6H), 0.77 (d, 3H); ¹³C NMR (CDCl₃) δ 18.9, 22.1, 23.2, 23.8, 32.9, 37.9, 38.3, 39.8, 43.1, 54.3, 58.1, 69.8, 112.2, 113.8, 117.3, 128.9, 152.7, 157.9; ESI MS (M + H)⁺ 288.8

4-Methyl-5-[3-(propan-2-yloxy)phenyl]-2-azabicyclo[3.3.1]nonane (10)—To a solution of 2,4-dimethyl-5-[3-(propan-2-yloxy)phenyl]-2-azabicyclo[3.3.1]nonane (**9**) (260

mg, 0.9 mmol) in dry dichloroethane was added 1-chloroethyl chloroformate (1.29 g, 9.0 mmol). The reaction mixture was refluxed overnight, cooled to room temperature and the solvent evaporated in vacuo to provide a yellow residue. The residue was dissolved in methanol (10 mL) and the mixture refluxed overnight. TLC analysis showed complete conversion. The solvent was removed by evaporation and the residue dissolved in water (10 mL) and basified using 50% sodium hydroxide solution to pH 12. The product was extracted using ether (3 × 15 mL) and the combined ethereal layers dried (Na₂SO₄), filtered, and evaporated to give 210 mg (86%) of **10** as a colorless oil after column chromatography using CHCl₃–CMA80 (100% to 20%): ¹H NMR (CDCl₃) δ 7.12 (t, 1H), 6.66 (m, 3H), 4.46 (septet, 1H), 3.69 (dd, 1H), 3.24 (br, 1H), 2.56 (m, 2H), 2.01 (m, 4H), 1.83 (m, 1H), 1.63 (m, 4H), 1.24 (d, 6H), 0.56 (d, 3H); ¹³C NMR (CDCl₃) δ 157.9, 153.1, 129.0, 117.4, 113.6, 112.2, 69.7, 49.1, 47.8, 39.8, 38.5, 37.9, 32.1, 31.5, 22.8, 22.1, 17.2.

N-Phenylpropyl-4β-methyl-5-(3-(propan-2-yloxy)phenyl)morphan (11)—To a solution of 4-methyl-5-[3-(propan-2-yloxy)phenyl]-2-azabicyclo[3.3.1]nonane (**10**) (210 mg, 0.77 mmol) in 2,2,2-trifluoroethanol (7 mL) was added 3-phenylpropionaldehyde (114 mg, 0.85 mmol). The reaction mixture was stirred for 30 min at room temperature. At this point sodium borohydride (58 mg, 1.54 mmol) was added and the reaction mixture stirred overnight. The reaction mixture was evaporated and the residue treated with saturated sodium bicarbonate (10 mL) and then extracted with ether (3 × 15 mL). The organic layer was dried (Na₂SO₄), filtered, and evaporated to obtain a yellow residue. The residue was subjected to column chromatography on silica gel using CMA80–CHCl₃ (5% to 35%) as the eluent to provide 180 mg (60%) of **11** as a colorless oil: ¹H NMR (CDCl₃) δ 7.20 (m, 6H), 6.70 (m, 2H), 6.63 (d, 1H), 4.46 (septet, 1H), 3.59 (t, 1H), 3.11 (dd, 1H), 2.98 (m, 1H), 2.58 (m, 3H), 2.98 (t, 2H), 2.30 (d, 1H), 2.01 (m, 3H), 1.84 (m, 2H), 1.55 (m, 3H), 1.24 (d, 6H), 0.65 (d, 3H); ¹³C NMR (CDCl₃) δ 157.9, 153.1, 142.7, 128.9, 128.6, 128.2, 125.9, 117.6, 113.8, 112.2, 69.8, 55.6, 54.5, 53.1, 39.9, 38.6, 34.3, 33.5, 32.9, 32.1, 29.5, 24.7, 23.2, 22.2, 22.2, 18.8.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS USED

GPCRs	G-protein-coupled receptors
cDNAs	complementary deoxyribonucleic acid
SAR	structure activity relationship
[³⁵ S]GTPγS	sulfur-35 guanosine-5'-O-(3-thio)triphosphate
DAMGO	[D-Ala ² ,MePhe ⁴ ,Gly-ol ⁵]enkephalin
DPDPE	[D-Pen ² ,D-Pen ⁵]enkephalin
U69,593	(5α,7α,8β)-(-)-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-yl]benzeneacetamide
CHO	Chinese hamster ovary
GDP	guanosine diphosphate

BOP	benzotriazole-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
DIPEA	diisopropylethylamine
PYBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate; benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
ACE-Cl	1-chloroethylchloroformate

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Scheme 1^a

^aReagents: (a) Formic acid, PyBOP, DIPEA, CH_2Cl_2 ; (b) LAH, THF; (c) R_1CHO , $\text{NaBH}_3(\text{CN})$, $\text{CF}_3\text{CH}_2\text{OH}$; (d) Paraformaldehyde, $\text{NaBH}_3(\text{CN})$, $\text{CF}_3\text{CH}_2\text{OH}$

Scheme 2^a

^aReagents: (a) Zn, HCl; (b) ACE-Cl, DCE, reflux; (c) MeOH, reflux; (d) 3-phenylpropionaldehyde, NaBH₃(CN), CF₃CH₂OH; (e) BBr₃, CH₂Cl₂

Table 1

[³⁵S]GTP-γS Binding Results for **5a–h** in Cloned Human μ, δ, and κ Opioid Receptors^a

compd	R ₁	R ₂	Agonist ^b				Antagonist ^{b,c}			
			μ	δ	κ		μ, DAMGO	δ, DPDPE	κ, U50,488	
			EC ₅₀ (nM)	EC ₅₀ (nM)	EC ₅₀ (nM)	E _{max} % DAMGO	E _{max} % DPDPE	E _{max} % U50,488	K _e (nM)	K _e (nM)
4	—	—	IA	IA	IA	74 ± 12	101 ± 4	—	1.9 ± 0.25	12.9 ± 2.5
5a	H	H	19.5 ± 9	7.5 ± 2	IA	44 ± 5	101 ± 4	—	NT	10.1 ± 3
6	H	H	20.6 ± 2	IA	IA	—	—	—	NT	21.7 ± 7
5b	H	CH ₃	15 ± 2	14.8 ± 0.03	IA	105 ± 2	101 ± 7.5	—	NT	43.8 ± 8
5c	H	C ₂ H ₅	33 ± 1	IA	IA	14 ± 2	—	—	NT	60.8 ± 19
5d	H	C ₃ H ₇	18 ± 4	IA	IA	57 ± 11	—	20.7 ± 4	NT	NT
5e	H	CH ₂ C ₃ H ₅	130 ± 13	IA	IA	52 ± 2	—	—	NT	31 ± 4
5f	CH ₃	CH ₃	6.5 ± 0.2	38 ± 6	IA	104 ± 7	55 ± 2	—	NT	176 ± 50
5g	CH ₃	C ₂ H ₅	60 ± 17	IA	IA	94 ± 5	—	—	NT	93 ± 29
5h	CH ₃	CH ₂ C ₃ H ₅	2.7 ± 0.8	10.3 ± 3	IA	109 ± 9	24 ± 2	38 ± 3	NT	NT
13^d			IA	IA	IA	—	—	—	52 ± 22	0.09 ± 0.04
14^e			IA	IA	IA	—	—	—	10.3 ± 3.7	13.2 ± 2.6

^aData are from the mean ± SE from at least three experiments.

^bIA = >5 μM.

^cNT = not tested.

^dData taken from ref. 17.

^eData taken from ref. 21.

Table 2 Binding Affinities (K_i) for **4** and **5b–f** and **5h**. at MOR, KOR and DOR

Compound	K_i^a (nM)		
K_d^b	MOR ^c	DOR ^d	KOR ^e
4	1.13 ± 0.028	1.24 ± 0.14	3.26 ± 0.34
5b	1.61 ± 0.216	160.5 ± 14.2	7.79 ± 0.69
5c	0.371 ± 0.046	36.2 ± 5.66	20.92 ± 2.60
5d	3.35 ± 0.47	264 ± 15.7	8.22 ± 1.78
5e	1.66 ± 0.12	73.8 ± 4.18	1.40 ± 0.20
5f	7.55 ± 1.18	43.2 ± 4.31	13.67 ± 1.74
5g	0.28 ± 0.018	18.4 ± 3.12	9.9 ± 1.80
5h	0.43 ± 0.034	9.04 ± 0.80	0.92 ± 0.096

^aThe MOR, DOR and KOR binding affinities for the synthesized compounds were measured at the Psychoactive Drug Screening Program (PDSP), University of North Carolina at Chapel Hill using competition radioligand binding assays as previously described (ref. 23 and 24).

^bThe radioligand affinity (K_d) was determined by homologous competition binding using receptor specific radioligands.

^cRadioligand used to determine MOR affinity is ³H-DAMGO.

^dRadioligand used to determine DOR affinity is ³H-DADLE.

^eRadioligand used to determine KOR affinity is ³H-U-69593.