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

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Abstract

In previous studies we reported that addition of 7α-acylamino groups to *N*-phenylpropyl-4β-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 7α-amino (**5a**), 7α-alkylamino (**5b–e**), or 7α-dialkylamino (**5f–h**) group to **4** leads to opioid receptor ligands with varying degrees of agonist/antagonist activity. The 7α-amino and 7α-methylamino analogues were full agonists at the μ and δ receptors and antagonists at the κ receptor. The 7α-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 7α-acylamino group to the pure non-selective opioid receptor antagonist *N*-phenylpropyl-4β-methyl-5-(3-hydroxyphenyl)morphan (**4**) led to κ selective pure opioid receptor antagonist, the addition of a 7α-amino, 7α-alkylamino or 7α-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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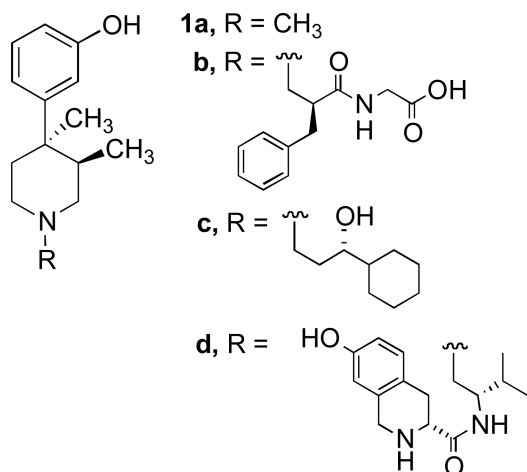[*]**Corresponding Author**. Phone: (919) 541-6679. Fax: (919) 541-8868. fic@rti.org.

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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 (1R,4S,5S,7R)-7-acylaminomorphans (**2**, see ref. 16, 17, and 18 for specific structures) were potent and selective kappa opioid receptor antagonists,[17,18] whereas certain (1S,4R,5R,7S)-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 (1R,4S,5S,7R)-7-aminomorphan (**5a**) and its enantiomer (1S,4R,5R,7S)-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**.
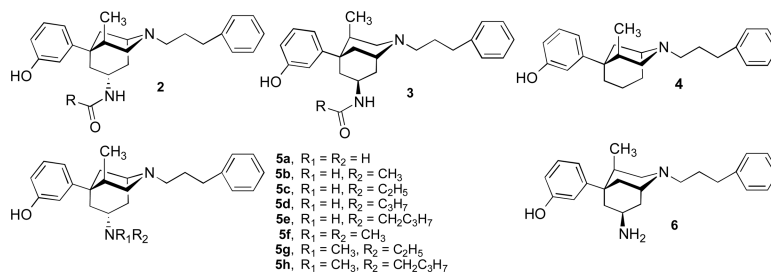
Chemistry

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-4β-methyl-5-phenylmorphan **8**, which was prepared by a route analogous to the one described previously (Scheme 2).[18] The ketone **8** was reduced under Clemenson 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 μM in the $[^{35}S]GTP\gamma S$ 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 $[^{35}S]GTP\gamma S$ 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.
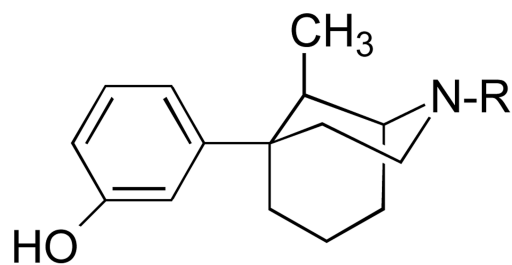
12a, R = CH$_3$
12b, R = C$_6$H$_5$(CH$_2$)$_2$
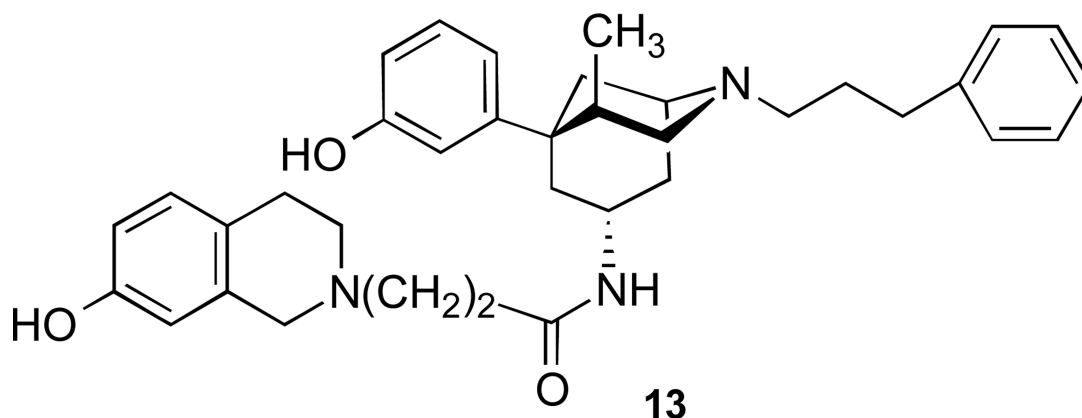
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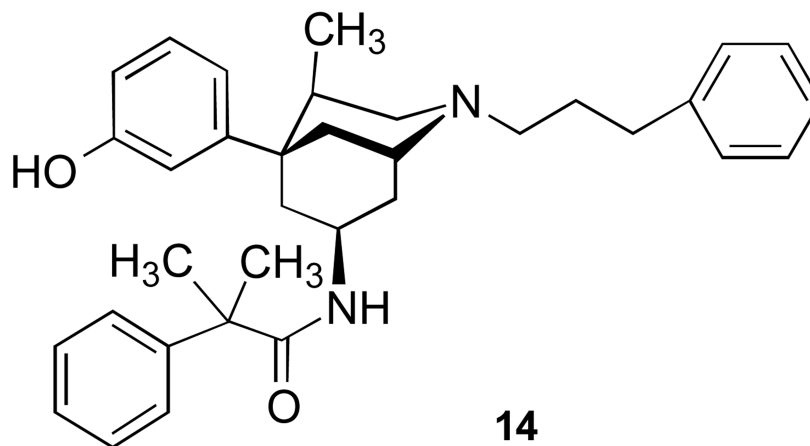
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Results and Discussion

In previous studies, we reported that *N*-methyl- and *N*-phenylethyl-9β-methyl-5-(3-hydroxyphenyl)morphans (**12a** and **12b**, respectively), which like *N*-phenylpropyl-4β-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 [^{35}S]GTPγS 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 7α-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 7α-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 7α-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} = 18nM, 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} = 293nM, 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 7α-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 7α-ethylmethylamino analogue **5g** resulted in a weak μ agonist/κ antagonist. Surprisingly, adding a methyl group to **5e** to give the 7α-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 [^{35}S]GTPγS 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 $[^{35}S]GTP\gamma S$ 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 MOR[25] and KOR.[26] However, although such calculations[27] 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-4β-methyl-5-(3-hydroxyphenyl)morphan (**4**) is converted into agonists or mixed agonists/antagonists by adding a 7α-amino (**5a**), 7α-alkylamino (**5b–e**), or 7α-dialkylamino **5f–h** group to **4**. The 7α-amino and 7α-methylamino analogues **5a** and **5b**, respectively, were full agonists at the μ and δ receptors and antagonists at the κ receptor. The 7α-ethylamino and 7α-propylamino analogues **5c** and **5d**, respectively, were either inactive or very weak agonists or antagonists at the δ and κ receptors. Somewhat surprising, the 7α-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 7α-dimethylamino and 7α-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 7α-acylamino group to the pure non-selective opioid receptor antagonist *N*-phenylpropyl-4β-methyl-5-(3-hydroxyphenyl)morphan (**4**) led to κ selective pure opioid receptor antagonist,[17] the addition of a 7α-amino, 7α-alkylamino or 7α-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 $[^{35}S]GTP\gamma S$ 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 F_{254} plates from EMD (Gibbstown, NJ). Chromatograms were visualized under UV light at 254 nM. ^{1}H 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 ^{1}H 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-4β-methyl-5-(3-(propan-2-yloxy)phenyl)morphan (**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: ^{1}H 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 (M + 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 °C. [α]$^{25}_D$ −15.7 (1.02, MeOH). Anal. ($C_{24}H_{32}ClNO$•0.25 H_2O) C, H, N.

5-(3-Hydroxyphenyl)-4-methyl-7-methylamino-2-(3-phenylprop-1-yl)-2-azabicyclo[3.3.1]nononane (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: ^{1}H 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 (M + H)$^+$ 379.5.

The free base **5b** was converted to **5b**•2HCl by adding 1M HCl in ether to solution of product in dichloromethane. [α]$^{25}_D$ −16.8 (0.88, MeOH). Anal. ($C_{25}H_{36}Cl_2N_2O$•2.5H_2O) C, H, N.

7-Ethylamino-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenlylprop-1-yl)-2-azabicyclo[3.3.1]nononane (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 (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 5c (55%) as a colorless oil: ^{1}H NMR ($CDCl_3$) 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); ^{13}C 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. $[\alpha]^{25}_D$ −10.0 (0.56, MeOH). Anal. ($C_{26}H_{38}Cl_2N_2O$•2.25H_2O) C, H, N.

5-(3-Hydroxyphenyl)-4-methyl-2-(3-phenylprop-1-yl)-7-propylamino-2-azabicyclo[3.3.1]nononane (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 (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 36 mg (68%) of 5d as a colorless oil: ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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. $[\alpha]^{25}_D$ −12.1 (0.98, MeOH). Anal. ($C_{27}H_{40}Cl_2N_2O$•1.0H_2O) C, H, N.

7-(N-Cyclopropylmethylamino)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylprop-1-yl)-2-azabicyclo[3.3.1]nononane (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 (Na_2SO_4), filtered, and evaporated to give a yellow residue. The residue was subjected to column

chromatography on silica gel using CMA80–CH$_2$Cl$_2$ (1:1) as the eluent to provide 48 mg (52%) of 5e as a colorless oil: ^{1}H NMR (CDCl$_3$) 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); ^{13}C NMR (CDCl$_3$) 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]$_D$ −11.2 (0.57, MeOH). Anal. (C$_{28}$H$_{40}$Cl$_2$N$_2$O•H$_2$O) C, H, N.

7-Dimethylamino-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylprop-1-yl)-2-azabicyclo[3.3.1]nononane (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 (Na$_2$SO$_4$), filtered, and evaporated to obtain a brown residue. The residue was subjected to column chromatography on silica gel using CMA80–CH$_2$Cl$_2$ (1:1) as the eluent to provide 52 mg (60%) of a colorless oil: ^{1}H NMR (CDCl$_3$) 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); ^{13}C NMR (CDCl$_3$) 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]$^{25}_D$ −10.9 (0.51, MeOH). Anal. (C$_{26}$H$_{38}$Cl$_2$N$_2$O•2.0 H$_2$O) C, H, N.

7-(*N*-Ethylmethylamino)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylprop-1-yl)-2 azabicyclo[3.3.1]nononane (5g) Dihydrochloride—

A solution of 7-ethylamino-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenlylprop-1-yl)-2-azabicyclo[3.3.1]nononane (**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 (Na$_2$SO$_4$), filtered, and evaporated to obtain a brown residue. The residue was subjected to column chromatography on silica gel using CMA80–CH$_2$Cl$_2$ (1:1) as the eluent to provide 27 mg (55%) of **5g** as a white solid: ^{1}H NMR (CDCl$_3$) 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); ^{13}C NMR (CDCl$_3$) 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]$^{25}_D$ −11.3 (0.73, MeOH). Anal. (C$_{27}$H$_{40}$Cl$_2$N$_2$O•1.75 H$_2$O) C, H, N.

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

A solution

of 7-(*N*-cyclopropylmethylamino)-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylprop-1-yl)-2-azabicyclo[3.3.1]nononane (**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 (Na_2SO_4), filtered, and evaporated to obtain a brown residue. The residue was subjected to column chromatography on silica gel using CMA80–CH_2Cl_2 (1:1) as the eluent to provide 36 mg (73%) of a colorless oil: ^{1}H NMR (CDCl$_3$) 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); ^{13}C NMR (CDCl$_3$) 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. $[\alpha]^{25}_D$ −9.1 (0.66, MeOH). Anal. (C$_{29}$H$_{42}$Cl$_2$N$_2$O•2.0 H$_2$O) C, H, N.

7-Formylamino-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenylprop-1-yl)-2-azabicyclo[3.3.1]nononane (7)—

To a cooled solution of formic acid (14 mg, 0.3 mmol) in CH_2Cl_2 (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-phenprop-1-yl)-2-azabicyclo[3.3.1]nononane [(*S*)-**5a**] (100 mg, 0.22 mmol) and diisopropylethylamine (552 mL, 3 mmol) in CH_2Cl_2 (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 Na_2CO_3 (15 mL), and the aqueous suspension was extracted with EtOAc (2×15 mL). The combined extracts were dried (Na_2SO_4), filtered, and evaporated to yield a colorless oil. The oil was subjected to flash chromatography on silica gel using CMA80–CH_2Cl_2 (1:1) as the eluent. Fractions containing product were pooled and evaporated to yield 68 mg (78%) of **7** as a clear oil: ^{1}H 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 Zn^0 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 (Na_2SO_4), filtered, and evaporated to obtain 550 mg (57%) of **9** after column chromatography using CH_2Cl_2–MeOH (100% to 90%): ^{1}H NMR (CDCl$_3$) 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); ^{13}C NMR (CDCl$_3$) 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 (Na_2SO_4), filtered, and evaporated to give 210 mg (86%) of **10** as a colorless oil after column chromatography using $CHCl_3$–CMA80 (100% to 20%): ^1H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 (Na_2SO_4), filtered, and evaporated to obtain a yellow residue. The residue was subjected to column chromatography on silica gel using CMA80–$CHCl_3$ (5% to 35%) as the eluent to provide 180 mg (60%) of **11** as a colorless oil: ^1H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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.

Acknowledgments

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

References

1. Zimmerman DM, Nickander R, Horng JS, Wong DT. New structural concepts for narcotic antagonists defined in a 4-phenylpiperidine series. Nature. 1978; 275:332–334. [PubMed: 692714]

2. Mitch CH, Leander JD, Mendelsohn LG, Shaw WN, Wong DT, Cantrell BE, Johnson BG, Reel JK, Snoddy JD, Takemori AE, Zimmerman DM. 3,4-Dimethyl-4-(3-hydroxyphenyl)piperidines: Opioid antagonists with potent anorectant activity. J. Med. Chem. 1993; 36:2842–2850. [PubMed: 8410999]

3. Thomas JB, Mascarella SW, Rothman RB, Partilla JS, Xu H, McCullough KB, Dersch CM, Cantrell BE, Zimmerman DM, Carroll FI. Investigation of the N-substituent conformation governing potency and mu receptor subtype-selectivity in (+)-(3R, 4R)-dimethyl-4-(3-hydroxyphenyl)piperidine opioid antagonists. J. Med. Chem. 1998; 41:1980–1990. [PubMed: 9599247]

4. Zimmerman DM, Gidda JS, Cantrell BE, Schoepp DD, Johnson BG, Leander JD. Discovery of a potent, peripherally selective trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine opioid antagonist for the treatment of gastrointestinal motility disorders. J. Med. Chem. 1994; 37:2262–2265. [PubMed: 8057274]

5. Zimmerman DM, Leander JD, Cantrell BE, Reel JK, Snoddy J, Mendelsohn LG, Johnson BG, Mitch CH. Structure-activity relationships of the trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine antagonists for μ and κ opioid receptors. J. Med. Chem. 1993; 36:2833–2841. [PubMed: 8410998]

6. Carroll FI. 2002 Medicinal Chemistry Division Award address: monoamine transporters and opioid receptors. Targets for addiction therapy. J. Med. Chem. 2003; 46:1775–1794. [PubMed: 12723940]

7. Casy AF, Dewar GH, Al-Deeb OAA. Stereochemical studies of the 4-alkyl-4-arylpiperidine class of opioid ligand. Magn. Reson. Chem. 1989; 27:964–972.

8. Delaney CP, Yasothan U, Kirkpatrick P. Alvimopan. Nat. Rev. Drug Discov. 2008; 7:727–728. [PubMed: 19172688]

9. Leslie JB. Alvimopan: a peripherally acting mu-opioid receptor antagonist. Drugs Today (Barc). 2007; 43:611–625. [PubMed: 17940638]

10. Statnick MA, Suter TM, Gackenheimer SL, Emmerson PJ, Quimby SJ, Gehlert DR, Wheeler WJ, Mitch CH. Na+-dependent high affinity binding of [3H]LY515300, a 3,4-dimethyl-4-(3-hydroxyphenyl)piperidine opioid receptor inverse agonist. Eur. J. Pharmacol. 2003; 482:139–150. [PubMed: 14660015]

11. Beardsley PM, Howard JL, Shelton KL, Carroll FI. Differential effects of the novel kappa opioid receptor antagonist, JDTic, on reinstatement of cocaine-seeking induced by footshock stressors vs cocaine primes and its antidepressant-like effects in rats. Psychopharmacology (Berl.). 2005; 183:118–126. [PubMed: 16184376]

12. Jackson KJ, Carroll FI, Negus SS, Damaj MI. Effect of the selective kappa-opioid receptor antagonist JDTic on nicotine antinociception, reward, and withdrawal in the mouse. Psychopharmacology (Berl.). 2010:285–294. [PubMed: 20232057]

13. Knoll AT, Meloni EG, Thomas JB, Carroll FI, Carlezon WA Jr. Anxiolytic-Like Effects of κ-Opioid Receptor Antagonists in Models of Unlearned and Learned Fear in Rats. J. Pharmacol. Exp. Ther. 2007; 323:838–845. [PubMed: 17823306]

14. Knoll AT, Muschamp JW, Sillivan SE, Ferguson D, Dietz DM, Meloni EG, Carroll FI, Nestler EJ, Konradi C, Carlezon WA. Kappa Opioid Receptor Signaling in the Basolateral Amygdala

Regulates Conditioned Fear and Anxiety in Rats. Biol. Psychiatry. 2011; 70:425–433. [PubMed: 21531393]

15. Nemeth CL, Paine TA, Rittiner JE, Beguin C, Carroll FI, Roth BL, Cohen BM, Carlezon WA Jr. Role of kappa-opioid receptors in the effects of salvinorin A and ketamine on attention in rats. Psychopharmacology (Berl.). 2010; 210:263–274. [PubMed: 20358363]

16. Thomas JB, Zheng X, Mascarella SW, Rothman Richard B, Dersch Christina M, Partilla John S, Flippen-Anderson Judith L, George Clifford F, Cantrell BE, Zimmerman Dennis M, Carroll FI. N-Substituted 9β-methyl-5-(3-hydroxyphenyl)morphans are opioid receptor pure antagonists. J. Med. Chem. 1998; 41:4143–4149. [PubMed: 9767649]

17. Carroll FI, Melvin MS, Nuckols MC, Mascarella SW, Navarro HA, Thomas JB. N-substituted 4β-methyl-5-(3-hydroxyphenyl)-7α-amidomorphans are potent, selective kappa opioid receptor antagonists. J. Med. Chem. 2006; 49:1781–1791. [PubMed: 16509593]

18. Thomas JB, Atkinson RN, Namdev N, Rothman RB, Gigstad KM, Fix SE, Mascarella SW, Burgess JP, Vinson NA, Xu H, Dersch CM, Cantrell BE, Zimmerman DM, Carroll FI. Discovery of an opioid kappa receptor selective pure antagonist from a library of N-substituted 4beta-methyl-5-(3-hydroxyphenyl)morphans. J. Med. Chem. 2002; 45:3524–3530. [PubMed: 12139463]

19. Carroll, FI. Design and Development of Pharmacotherapies for Substance Abuse.2006 Nathan B. Eddy Memorial Award Lecture; Proceedings of the 68th Annual Scientific Meeting of the College on Problems of Drug Dependence, National Institute on Drug Abuse; Bethesda, MD. 2007. p. 71-81.

20. Carroll FI, Zhang L, Mascarella SW, Navarro HA, Rothman RB, Cantrell BE, Zimmerman DM, Thomas JB. Discovery of the first N-substituted 4β-methyl-5-(3-hydroxyphenyl)morphan to possess highly potent and selective opioid delta receptor antagonist activity. J. Med. Chem. 2004; 47:281–284. [PubMed: 14711299]

21. Thomas JB, Zhang L, Navarro HA, Carroll FI. Highly potent and selective phenylmorphan-based inverse agonists of the opioid delta receptor. J. Med. Chem. 2006; 49:5597–5609. [PubMed: 16942033]

22. Carroll FI, Chaudhari S, Thomas JB, Mascarella SW, Gigstad KM, Deschamps J, Navarro HA. N-Substituted cis-4a-(3-hydroxyphenyl)-8a-methyloctahydroisoquinolines are opioid receptor pure antagonists. J. Med. Chem. 2005; 48:8182–8193. [PubMed: 16366600]

23. Roth BL, Baner K, Westkaemper R, Siebert D, Rice KC, Steinberg S, Ernsberger P, Rothman RB. Salvinorin A: a potent naturally occurring nonnitrogenous kappa opioid selective agonist. Proc. Natl. Acad. Sci U.S.A. 2002; 99:11934–11939. [PubMed: 12192085]

24. Besnard J, Ruda GF, Setola V, Abecassis K, Rodriguiz RM, Huang XP, Norval S, Sassano MF, Shin AI, Webster LA, Simeons FR, Stojanovski L, Prat A, Seidah NG, Constam DB, Bickerton GR, Read KD, Wetsel WC, Gilbert IH, Roth BL, Hopkins AL. Automated design of ligands to polypharmacological profiles. Nature. 2012; 492:215–220. [PubMed: 23235874]

25. Manglik A, Kruse AC, Kobilka TS, Thian FS, Mathiesen JM, Sunahara RK, Pardo L, Weis WI, Kobilka BK, Granier S. Crystal structure of the micro-opioid receptor bound to a morphinan antagonist. Nature. 2012; 485:321–326. [PubMed: 22437502]

26. Wu H, Wacker D, Mileni M, Katritch V, Han GW, Vardy E, Liu W, Thompson AA, Huang XP, Carroll FI, Mascarella SW, Westkaemper RB, Mosier PD, Roth BL, Cherezov V, Stevens RC. Structure of the human kappa-opioid receptor in complex with JDTic. Nature. 2012; 485:327–332. [PubMed: 22437504]

27. Surflex Dock, Sybyl-X, v. 2.1; Certara. 2013
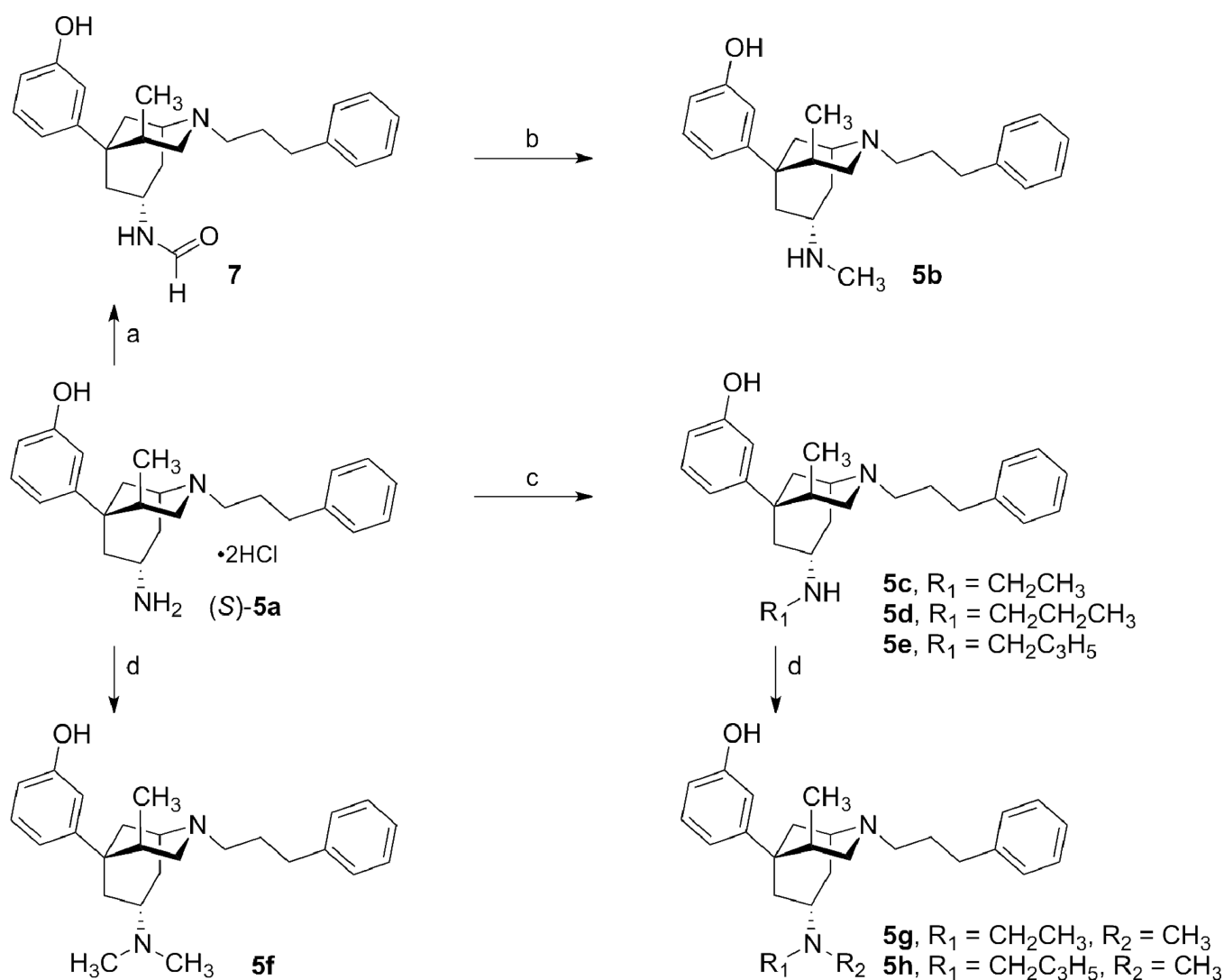
Scheme 1[a]
[a]Reagents: (a) Formic acid, PyBOP, DIPEA, CH_2Cl_2; (b) LAH, THF; (c) R_1CHO, $NaBH_3(CN)$, CF_3CH_2OH; (d) Paraformaldehyde, $NaBH_3(CN)$, CF_3CH_2OH
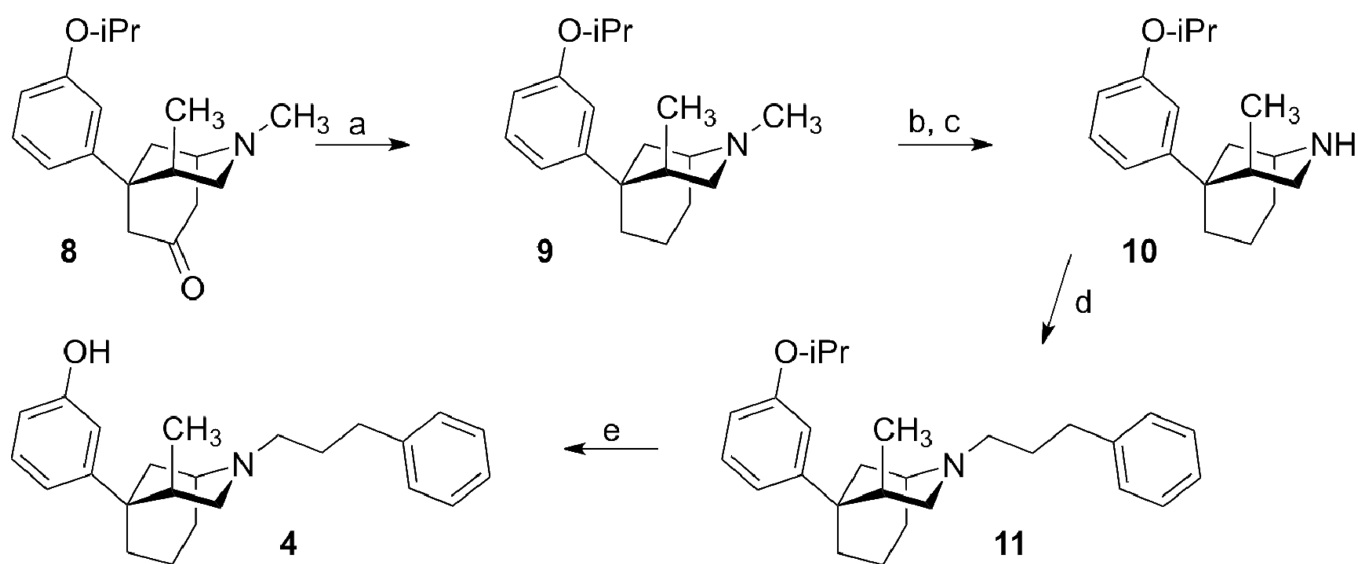
Scheme 2[a]

[a]Reagents: (a) Zn, HCl; (b) ACE-Cl, DCE, reflux; (c) MeOH, reflux; (d) 3-phenylpropionaldehyde, $NaBH_3(CN)$, CF_3CH_2OH; (e) BBr_3, CH_2Cl_2

Table 1

[35S]GTPγS Binding Results for **5a–h** in Cloned Human μ, δ, and κ Opioid Receptors[a]
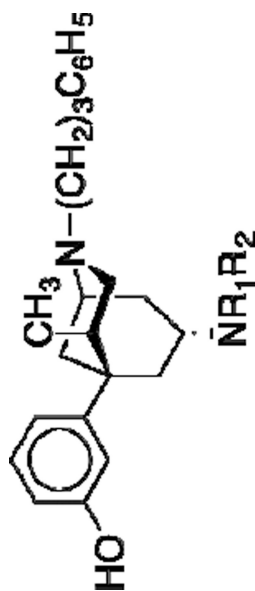
compd	R1	R2	Agonist[b]						Antagonist[b,c]		
			μ		δ		κ		μ, DAMGO	δ, DPDPE	κ, U50,488
			EC_{50} (nM)	E_{max} % DAMGO	EC_{50} (nM)	E_{max} % DPDPE	EC_{50} (nM)	E_{max} % U50,488	K_e (nM)	K_e (nM)	K_e (nM)
4	—	—	IA		IA		IA		1.9 ± 0.25	32.7 ± 8.9	12.9 ± 2.5
5a	H	H	19.5 ± 9	74 ± 12	7.5 ± 2	101 ± 4	IA		NT	NT	10.1 ± 3
6	H	H	20.6 ± 2	44 ± 5	IA		IA		NT	25.2 ± 8	21.7 ± 7
5b	H	CH_3	15 ± 2	105 ± 2	14.8 ± 0.03	101 ± 7.5	IA		NT	NT	43.8 ± 8
5c	H	C_2H_5	33 ± 1	14 ± 2	IA		IA		NT	230 ± 93	60.8 ± 19
5d	H	C_3H_7	18 ± 4	57 ± 11	IA		293 ± 129	20.7 ± 4	NT	69.4 ± 16	NT
5e	H	$CH_2C_3H_5$	130 ± 13	52 ± 2	IA		IA		NT	4.3 ± 0.4	31 ± 4
5f	CH_3	CH_3	6.5 ± 0.2	104 ± 7	38 ± 6	55 ± 2	IA		NT	NT	176 ± 50
5g	CH_3	C_2H_5	60 ± 17	94 ± 5	IA		IA		NT	IA	93 ± 29
5h	CH_3	$CH_2C_3H_5$	2.7 ± 0.8	109 ± 9	10.3 ± 3	24 ± 2	40 ± 16	38 ± 3	NT	NT	NT
13[d]			IA	—	IA	—	IA	—	52 ± 22	62 ± 20	0.09 ± 0.04
14[e]			IA	—	IA	—	IA	—	10.3 ± 3.7	0.10 ± 0.02	13.2 ± 2.6

[a] Data are from the mean ± SE from at least three experiments.

[b] IA = >5 μM.

[c] NT = not tested.

[d]Data taken from ref. 17.

[e]Data 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 1.13 ± 0.028	DOR^d 1.24 ± 0.14	KOR^e 3.26 ± 0.34
4	1.61 ± 0.216	160.5 ± 14.2	7.79 ± 0.69
5b	0.371 ± 0.046	36.2 ± 5.66	20.92 ± 2.60
5c	3.35 ± 0.47	264 ± 15.7	8.22 ± 1.78
5d	1.66 ± 0.12	73.8 ± 4.18	1.40 ± 0.20
5e	7.55 ± 1.18	43.2 ± 4.31	13.67 ± 1.74
5f	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

[a] The 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).

[b] The radioligand affinity (K_d) was determined by homologous competition binding using receptor specific radioligands.

[c] Radioligand used to determine MOR affinity is ^{3}H-DAMGO.

[d] Radioligand used to determine DOR affinity is ^{3}H-DADLE.

[e] Radioligand used to determine KOR affinity is ^{3}H-U-69593.