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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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(5) Supporting Information

ABSTRACT: In previous studies we reported that addition of 7α -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 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 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 nonselective 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.

-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 structure–activity</sup> relationship (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, (3R,4R)-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 (3R)-7-hydroxy-N-{(1S)-1-{[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidine]methyl}-2-methylpropyl}-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide (1d, 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 refs 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 refs 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-4 β -methyl-5-(3-hydroxyphenyl)morphan (4), which, like **2** and **3**, can be viewed as a *trans*-3,4dimethyl-4-(3-hydroxyphenyl)piperidine with the 4-(3-hydroxyphenyl) group locked in an equatorial piperidine chair

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conformation, was a nonselective 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 Nformylaminomorphan 7. Reduction of the 7-formylaminomorphan 7 with lithium aluminum hydride (LAH) in tetrahydrofuran afforded 5b. Reductive amination of 5a with 1.1 equiv 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-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 μ M in the [³⁵S]GTP γ S



^{*a*}Reagents: (a) Formic acid, PyBOP, DIPEA, CH₂Cl₂; (b) LAH, THF, (c) R₁CHO, NaBH₃(CN), CF₃CH₂OH; (d) paraformaldehyde, NaBH₃(CN), CF₃CH₂OH.

Scheme 1^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 γ S Binding Results for 5a-h in Cloned Human μ , δ , and κ Opioid Receptors^{*a*}



			agonist ^b						antagonist ^{<i>b,c</i>}		
				и	δ	;	ĸ	:	μ , DAMGO	δ , DPDPE	к, U50,488
compd	R_1	R_2	EC ₅₀ (nM)	E _{max} % DAMGO	EC ₅₀ (nM)	E _{max} % DPDPE	EC ₅₀ (nM)	E _{max} % U50,488	$K_{\rm e}$ (nM)	$K_{\rm e}$ (nM)	$K_{\rm e}$ (nM)
4			IA		IA		IA		1.9 ± 0.25	32.7 ± 8.9	12.9 ± 2.5
5a	Н	Н	19.5 ± 9	74 ± 12	7.5 ± 2	101 ± 4	IA		NT	NT	10.1 ± 3
6	Н	Н	20.6 ± 2	44 ± 5	IA		IA		NT	25.2 ± 8	21.7 ± 7
5b	Н	CH ₃	15 ± 2	105 ± 2	14.8 ± 0.03	101 ± 7.5	IA		NT	NT	43.8 ± 8
5c	Н	C_2H_5	33 ± 1	14 ± 2	IA		IA		NT	230 ± 93	60.8 ± 19
5d	Н	C_3H_7	18 ± 4	57 ± 11	IA		293 ± 129	20.7 ± 4	NT	69.4 ± 16	NT
5e	Н	CH ₂ C ₃ H 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 ₂ C ₃ H 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
^{<i>a</i>} Data a	re from	the mean -	± SE from at	least three ex	periments. ^b IA	$A > 5 \mu M.$ ^c N	JT = not teste	d. ^{<i>d</i>} Data tak	en from ref 1	7. ^e Data taken	from ref 21.

binding assay at the human μ , κ , and δ opioid receptors overexpressed 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 EC₅₀ 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, respec-

tively, as the radioligands using previously reported methods. 23,24 The results are listed in Table 2.

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 nonselective opioid receptor pure antagonists.^{6,16} Thus, it was not surprising that 4 was also a nonselective 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 (1R,4S,5S,7R) [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

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

	K_{i}^{a} (nM)						
compound	MOR ^c	DOR^d	KOR ^e				
$K_{\rm d}^{\ b}$	1.13 ± 0.028	1.24 ± 0.14	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 (refs 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 ³H-DAMGO. ^{*d*}Radioligand used to determine DOR affinity is ³H-DADLE. ^{*e*}Radioligand used to determine KOR affinity is ³H-U-69593.



578- and 689-fold selectivity relative to the *μ* and *δ* receptors (Table 1).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 1).^{20,21} Compound **14** was also an inverse agonist with an IC₅₀ = 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 EC₅₀ at μ was 19.5 nM ($E_{max} = 74\%$), and the EC₅₀ 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 IC₅₀ = 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 to determine what effect 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 7α -methylamino analogue 5b resulted in an increase in μ efficacy (105% compared to 74% for **5a**) with ED₅₀ and $E_{\rm max}$ 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 (EC₅₀ = 33 nM and $E_{\text{max}} = 14\%$) and complete loss of agonist activity at the δ receptor. The compound was also a weak opioid antagonist $(K_{\rm e} = 230 \text{ and } 60.8 \text{ nM} \text{ at } \delta \text{ and } \kappa \text{ receptors, respectively}).$ Similar to 5c, 5d was an agonist at the μ receptor (EC₅₀ = 18nM, $E_{\text{max}} = 57\%$). 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 (EC₅₀ = 293 nM, E_{max} = 20.7%). Adding a cyclopropylmethyl group to 5a gave 5e, which was a weak agonist at the μ receptor (EC₅₀ = 130 nM, $E_{\text{max}} = 52\%$), 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 (EC₅₀ = 6.5 nM, E_{max} = 104%) with weaker δ agonist potency and efficacy (EC₅₀ = 38 nM, $E_{\text{max}} = 55\%$) and a weak κ antagonist ($K_{\text{e}} = 176$ 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 7 α -methylcyclopropylmethyl analogue 5h resulted in the most potent μ agonist in the series (EC₅₀ = 2.7 nM, E_{max} = 109%) with somewhat weaker agonist efficacy at the δ (EC₅₀ = 10.3 nM, $E_{\text{max}} = 24\%$) and κ (EC₅₀ = 40 nM, $E_{\text{max}} = 38\%$) 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 $[{}^{35}S]GTP\gamma S$ 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 EC₅₀ = 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 nonselective 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 7α -amino (5a), 7α -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 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 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-(3hydroxyphenyl)morphan class of opioid receptor ligands. Whereas the addition of a 7α -acylamino group to the pure nonselective opioid receptor antagonist N-phenylpropyl-4βmethyl-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 led to opioid ligands that are largely μ or δ agonist with mixed agonist/ antagonist properties. For the most part the [35S]GTPγS 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 SECTION

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. Airsensitive 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 CHCl₃-MeOH-aq NH₄OH (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; ¹³C 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 ¹³C 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-[(1R,4S,5S)-4-Methyl-2-(3-phenylpropyl)-2-azabicyclo-[3.3.1]non-5-yl]phenol(4) Hydrochloride. To a solution of Nphenylpropyl-4 β -methyl-5-(3-(propan-2-yloxy)phenyl)morphan (11) (100 mg, 0.26 mmol) in dichloromethane (10 mL) at -78 °C, boron tribromide (0.51 mL, 0.51 mmol) (1 M solution in CH₂Cl₂) was added dropwise. 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 was redissolved in MeOH (10 mL) and stirred for 10 min. The residue resulting from evaporation of the methanol was treated with saturated NaHCO₃ aqueous solution (15 mL) and extracted with ethyl acetate $(3 \times 15 \text{ mL})$. The combined organic layers were dried (Na₂SO₄), filtered, and evaporated to obtain 11, which was subjected to column chromatography on silica gel using CMA80-CH₂Cl₂ (1:1) as the eluent to provide 60 mg (66%) of 4 as a colorless oil: ¹H NMR (CDCl₃) 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 (CDCl₃) 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 1 M HCl in ether to ethereal solution of product. MP 152–155 °C. $[\alpha]_{D}^{25}$ –15.7 (1.02, MeOH). Anal. (C₂₄H₃₂ClNO·0.25 H₂O) 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 was stirred for 10 min; then 20 mL 5% Na2CO3 solution was added slowly, and the resulting solution was stirred for additional 10 min. The suspension was filtered and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 \times 10 mL), and the combined organic layers were dried (Na₂SO₄), filtered, and evaporated to obtain a vellow residue. The residue was subjected to column chromatography on silica gel using CMA80-CH₂Cl₂ (1:1) as the eluent to provide 32 mg (56%) of **5b** as a colorless oil: ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 1 M HCl in ether to solution of product in dichloromethane. $[\alpha]^{25}_{D}$ –16.8 (0.88, MeOH). Anal. ($C_{25}H_{36}Cl_2N_2O$ ·2.5H₂O) 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), triethylamine (140 mL, 1.0 mmol) was added, and the mixture was stirred for 30 min at room temperature. Acetaldehyde (22 mg, 0.5 mmol) was added to the reaction mixture, and stirring was 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 \times 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); 13 C NMR (DMSO) δ 157.6, 148.3, 140.5, 129.6, 128.4, 128.2,

The free base **5c** was converted to **5c**·2HCl by adding 1 M HCl in ether to solution of **5c** in dichloromethane. $[\alpha]^{25}_{D}$ -10.0 (0.56, MeOH). Anal. (C₂₆H₁₈Cl₂N₂O·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), triethylamine (35 mL, 0.25 mmol) was added, and the mixture was stirred for 30 min at room temperature. Propionaldehyde (8 mg, 0.14 mmol) was added to the reaction mixture and stirring was 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-CH $_2$ Cl $_2$ (1:1) as the eluent to provide 36 mg (68%) of 5d as a colorless oil: ¹H NMR $(CDCl_3) \delta 7.31-7.07 (m, 6H), 6.60 (m, 3H), 3.39 (b, 2H), 3.15 (s, 3.15)$ 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 (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 1 M HCl in ether to solution of product in ether. $[\alpha]^{25}_{D}$ –12.1 (0.98, MeOH). Anal. (C₂₇H₄₀Cl₂N₂O·1.0H₂O) C, H, N.

7-(N-Cyclopropylmethylamino)-5-(3-hydroxyphenyl)-4methyl-2-(3-phenylprop-1-yl)-2-azabicyclo[3.3.1]nonane (5e) Dihydrochloride. To a solution of (-)-5-(3-hydroxyphenyl)-4methyl-2-(3-phenylpropyl)-2-azabicyclo-[3.3.1]nonan-7-amine [(S)-5a] hydrochloride (100 mg, 0.22 mmol) in trifluoroethanol (5 mL), triethylamine (70 mL, 0.5 mmol) was added, 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 \times 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- CH_2Cl_2 (1:1) as the eluent to provide 48 mg (52%) of 5e as a colorless oil: ¹H NMR (CDCl₃) & 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 1 M HCl in ether to solution of **5e** in ether. $[\alpha]_D$ –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)-**Sa**] hydrochloride (100 mg, 0.22 mmol) in trifluoroethanol (5 mL), triethylamine (140 mL, 1.0 mmol) was added, and the reaction mixture was 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 1 M HCl in ether to ethereal solution of product. $[\alpha]_{D}^{25}$ –10.9 (0.51, MeOH). Anal. (C₂₆H₃₈Cl₂N₂O·2.0H₂O) 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-phenlylprop-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 was stirred for 10 min at room temperature. At this point sodium cyanoborohydride (15 mg, 0.24 mmol) was added, and the reaction mixture was 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 \times 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–CH $_2\text{Cl}_2$ (1:1) as the eluent to provide 27 mg (55%) of 5g as a white solid: ¹H NMR $(CDCl_3) \delta 7.27 - 7.15 (m, 6H), 6.63 (m, 3H), 3.55 (b, 1H), 3.20 (s, 1H))$ 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); 3 C 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 1 M HCl in ether to solution of product in ether. $[\alpha]_{D}^{25} -11.3$ (0.73, MeOH). Anal. (C₂₇H₄₀Cl₂N₂O·1.75H₂O) 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 was 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-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); 13 C 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 **Sh** was converted to **Sh**·2HCl salt by adding 1 M HCl in ether to solution of product in ether. $[\alpha]^{25}_{D}$ –9.1 (0.66, MeOH). Anal. (C₂₉H₄₂Cl₂N₂O·2.0 H₂O) C, H, N.

7-Formylamino-5-(3-hydroxyphenyl)-4-methyl-2-(3-phenyl-prop-1-yl)-2-azabicyclo[3.3.1]nonane (7). To a cooled solution of formic acid (14 mg, 0.3 mmol) in CH_2Cl_2 (5 mL), PyBOP (130 mg, 0.30 mmol) was added. 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]nonane [(S)-Sa] (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 and then evaporated to yield a yellow residue. The residue was suspended in 5%

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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-2yloxy)phenyl]-2-azabicyclo[3.3.1]nonan-7-one (8)¹⁸ (1.01 g, 3.35 mmol) in diethylether (100 mL) (2 M 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 (Na_2SO_4) , 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); 13 C 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 and cooled to room temperature, and the solvent was evaporated in vacuo to provide a yellow residue. The residue was dissolved in methanol (10 mL), and the mixture was refluxed overnight. TLC analysis showed complete conversion. The solvent was removed by evaporation, and the residue was dissolved in water (10 mL) and basified using 50% sodium hydroxide solution to pH 12. The product was extracted using ether (3 \times 15 mL), and the combined ethereal layers were 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); 13 C 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-4 β -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 was stirred overnight. The reaction mixture was evaporated, and the residue was treated with saturated sodium bicarbonate (10 mL) and then extracted with ether $(3 \times 15 \text{ mL})$. 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 (5-35%) as the eluent to provide 180 mg (60%) of 11 as a colorless oil: ${}^{1}\text{H}$ 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); 13 C 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.

ASSOCIATED CONTENT

S Supporting Information

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

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS USED

GPCRs, G-protein-coupled receptors; cDNAs, cDNA; SAR, structure activity relationship; [³⁵S]GTPγS, sulfur-35 guanosine-5'-O-(3-thio)triphosphate; DAMGO, [D-Ala²,MePhe⁴,Glyol⁵]enkephalin; DPDPE, [D-Pen²,D-Pen⁵]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-1yloxy-tris(dimethylamino)phosphonium hexafluorophosphate; DIPEA, diisopropylethylamine; PYBOP, benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate; ACE-Cl, 1chloroethylchloroformate

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