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Effect of the 3- and 4-Methyl Groups on the Opioid Receptor Properties of N-Substituted *trans*-3,4-Dimethyl-4-(3-hydroxyphenyl)piperidines

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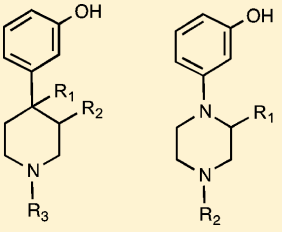
Supporting Information

ABSTRACT: N-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (**2a,b**) are opioid receptor antagonists where the antagonist properties are not due to the type of N-substituent. In order to gain a better understanding of the contribution that the 3- and 4-methyl groups make to the pure antagonist properties of **2a,b**, we synthesized analogues of **2a,b** that lacked the 4-methyl (**5a,b**), 3-methyl (**6a,b**), and both the 3- and 4-methyl group (**7a,b**) and compared their opioid receptor properties. We found that (1) all *N*-methyl and *N*-phenylpropyl substituted compounds were nonselective opioid antagonists (2) all *N*-phenylpropyl analogues were more potent than their *N*-methyl counterparts, and (3) compounds **2a,b** which have both a 3- and 4-methyl substituent, were more potent antagonists than analogues **5a,b**, **6a,b**, and **7a,b**. We also found that the removal of 3-methyl substituent of *N*-methyl and *N*-phenylpropyl 3-methyl-4-(3-hydroxyphenyl)piperazines (**8a,b**) gives (**4a,b**), which are opioid antagonists.



INTRODUCTION

In many classes of opioid compounds, small changes in structure modify the extent to which the opioid ligand exhibits agonist and/or antagonist properties.[1,2] In the morphine family and in fused-ring opioids such as the 4,5-epoxymorphinon-3-one,[3] morphinan,[4] benzomorphan,[5] and isoquinoline[6] series, N-substituent variation modulates relative agonist/antagonist potency. The *N*-methyl analogues are almost always pure agonist, while the *N*-allyl and *N*-cyclopropylmethyl analogues usually have antagonist properties. For example, naloxone (**1a**) and naltrexone (**1b**) are pure opioid receptor antagonists (Chart 1).[1] In contrast to these polycyclic structures, pure opioid receptor antagonist properties of N-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (**2**) (Chart 1) discovered by Zimmerman and co-workers[7,8] were a consequence of substitution at the 3-position on the piperidine ring rather than substitution at the nitrogen. A number of subsequent SAR studies have shown that all N-substituted analogues of **2**, including the *N*-methyl (**2a**) analogue, are pure opioid receptor antagonists.[7−9] The N-substituent on **2** apparently only affects the antagonist potency and opioid receptor selectivity.[9−14] In other SAR studies, Zimmerman reported that replacing the 4-methyl group with a larger substituent led to compounds with both opioid receptor agonist and antagonist properties. For example, *N*-methyl-*trans*-3-methyl-4-propyl-4-(3-hydroxylphenyl)piperidine (**3**) (Chart 1) showed both agonist and antagonist effects.[8] In contrast to numerous studies on the opioid antagonist properties of the N-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines **2**,[7−14] the opioid receptor properties of N-substituted 4-(3-hydroxyphenyl)piperidines lacking a 4-methyl and/or a 3-methyl group on the piperidine ring have received little, if any, study. We recently reported that the *N*-methyl- and *N*-phenylpropyl-(*S*)-(3)-methyl-4-(3-hydroxyphenyl)piperazines **4a** and **4b** (Chart 1), respectively, which do not have a 4-methyl substituent, were nonselective, potent, pure opioid antagonists.[15] These results suggested that *N*-methyl- and *N*-phenylpropyl-3-methyl-4-(3-hydroxyphenyl)piperidines **5a** and **5b** could also be pure opioid receptor antagonists (Chart 1). In order to gain a better understanding of the contributions that 3- and 4-methyl groups make to the pure antagonist properties of 4-(3-hydroxyphenyl)piperidine and the 3-methyl group to the antagonist properties of 4-(3-hydroxyphenyl)piperazine compounds, we synthesized **2a,b**, **4a,b**, **5a,b**, **6a,b**, **7a,b**, and **8a,b** (Chart 1) and compared their opioid receptor properties as determined by the in vitro [^{35}S]GTPγS functional assay. We found that (1) with the exception of **6a**, all compounds studied were nonselective pure opioid antagonists at the μ, κ, and δ receptors or inactive, and even compound **6a** was only a very weak agonist at the δ receptor and an antagonist at the μ and κ receptors; (2) similar to **2b**, all *N*-phenylpropyl analogues were more potent antagonists than their *N*-methyl counterparts; and (3) analogues **2a,b**, which have both a 3- and a 4-methyl substituent, were more potent antagonists than analogues that lacked a 3-, 4-, or both methyl substituents.

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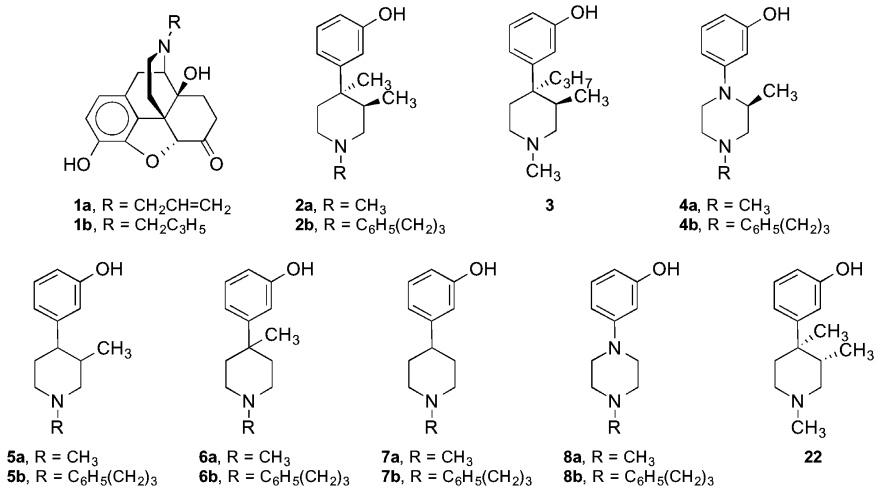
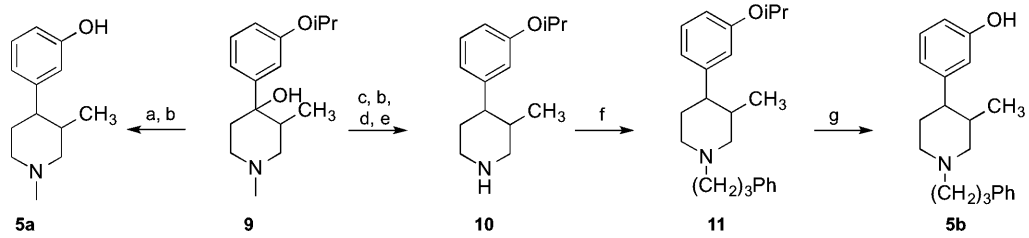
Chart 1. Structures of Compounds 1a,b, 2a,b, 3, 4a,b, 5a,b, 6a,b, 7a,b, 8a,b, and 22

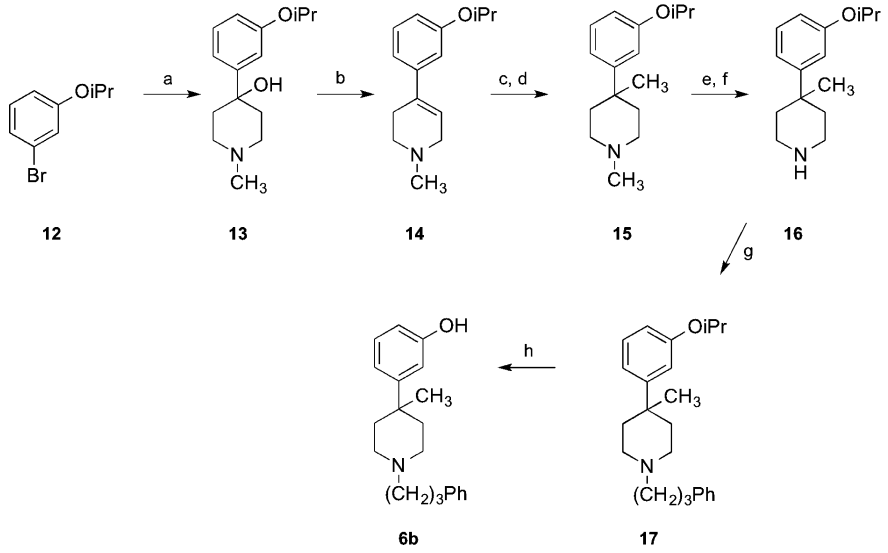


Scheme 1[a]



[a]Reagents and conditions: (a) HCl/AcOH; (b) Pd/C, H_2; (c) TsOH, tol; (d) ACE-Cl; (e) EtOH, reflux; (f) $Ph(CH_2)_2CHO$, $NaBH(OAc)_3$; (g) BCl_3.

Scheme 2[a]



[a]Reagents and conditions: (a) *n*-BuLi, *N*-methyl-4-piperidinone; (b) TsOH, tol; (c) *n*-BuLi, Me_2SO_4; (d) $NaBH_4$, MeOH; (e) ACE-Cl; (f) MeOH, reflux; (g) $Ph(CH_2)_2CHO$, $NaCNBH_3$; (h) BCl_3.

CHEMISTRY

Compounds **5a** and **5b** were prepared from a common intermediate (**9**)[16] (Scheme 1). Following deprotection and dehydration with refluxing hydrochloric acid in glacial acetic acid, the intermediate from **9** was reduced via catalytic hydrogenation to afford **5a** as a mixture of geometric isomers. Careful chromatography and trituration of the resulting oil afforded a solid that proved to be the pure cis-isomer as determined by ^{1}H NMR spectral analysis. In order to prepare the secondary amine **10**, the dehydrated, hydrogenated intermediate from **9** was treated with 1-chloroethyl chloroformate (ACE-Cl) in refluxing chloroform and then refluxed in ethanol to decompose the intermediate chloroethyl carbamate. Reductive amination of **10** with 3-phenylpropanal

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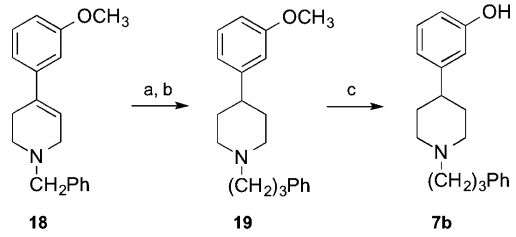
afforded **11**, which was deprotected with boron trichloride to afford **5b** as a mixture of isomers. The major, cis-isomer (as determined by ^{1}H NMR spectral analysis), selectively crystallized as the tosylate salt from isopropanol and diethyl ether.

Compound **6b** was prepared according to Scheme 2. The aryllithium reagent prepared from 3-bromoisopropoxybenzene (**12**)[16] was added to *N*-methyl-4-piperidinone. The resulting alcohol **13** was dehydrated with *p*-toluenesulfonic acid in refluxing toluene to afford the tetrahydropyridine **14**. Deprotonation with *n*-butyllithium gave the blood-red anion which was quenched with dimethylsulfate. The resulting enamine was reduced with sodium borohydride to afford **15**. As with the preparation of **5b**, reaction with ACE-Cl was followed by refluxing **5b** in methanol to afford the secondary amine **16**. Reductive amination of **16** with 3-phenylpropanal afforded **17**, which was treated with boron trichloride in methylene chloride to yield **6b**.

The preparation of **7b** is shown in Scheme 3. Catalytic hydrogenation of the readily available intermediate **18**[17]

Scheme 3[a]

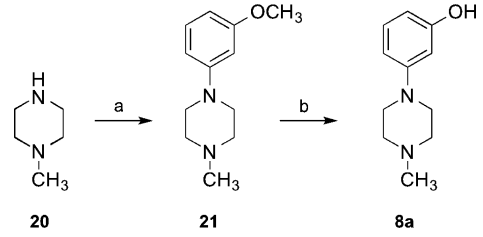


[a]Reagents: (a) H_2, $Pd(OH)_2/C$; (b) $Ph(CH_2)_2CHO$, $NaBH_3CN$; (c) BBr_3, CH_2Cl_2.

reduced both the olefin and cleaved the *N*-benzyl group, affording an intermediate of acceptable purity for reductive amination with 3-phenylpropanal to give **19**. Intermediate **19** was deprotected with boron tribromide in methylene chloride to afford **7b**.

As shown in Scheme 4, the N-arylation[15] of *N*-methylpiperazine **20** with 3-bromoanisole afforded **21**. Deprotection with boron tribromide gave compound **8a**.

Scheme 4[a]



[a]Reagents and conditions: (a) 3-bromoanisole, $Pd(t\text{-}Bu_3P)_2$, tol; (b) BBr_3, CH_2Cl_2.

BIOLOGY

All compounds were initially screened for intrinsic and antagonist activity at 10 μM in the [^{35}S]GTPγS binding assay at the human μ, κ, and δ opioid receptors overexpressed in CHO cells. Compounds identified as agonists were evaluated in opioid receptor-appropriate assay using eight different concentrations selected to provide clear indication of the upper and lower asymptotes of the concentration–response curve. 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) 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]GTPγS binding produced by the selective agonist DAMGO (μ), DPDPE (δ), or U69,593 (κ). Agonist concentration–response curves were run in the presence or absence of a single concentration of test compound. At least two different concentrations of test compound were used in these experiments, and these had to cause a minimum 4-fold shift in the agonist EC_{50} before a K_e was calculated. 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.

RESULTS AND DISCUSSION

The N-substituted 3,4-dimethyl-4-(3-hydroxyphenyl)-piperidines (**2**) are a class of pure opioid antagonists discovered by Zimmerman and co-workers.[7−9] In 1978, Zimmerman reported that the addition of a *trans*-3-methyl group to the opioid agonist 1,4-dimethyl-4-(3-hydroxyphenyl)piperidine (**6a**) gave *trans*-*N*-methyl-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine (**2a**), which was a pure opioid antagonist. The discovery of the structurally unique, pure antagonist **2a** was highly interesting, since prior to this discovery, all pure opioid antagonists were *N*-allyl or *N*-cyclopropylmethyl analogues of opioid agonists such as naloxone (**1a**) and naltrexone (**1b**).[3]

Resolution of the N-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (**2**) showed that both the (3*R*,4*R*)- and (3*S*,4*S*)-isomers were pure opioid antagonists with the (3*R*,4*R*)-isomer being a more potent antagonist than the (3*S*,4*S*)-isomer.[9] However, even small alterations of the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine structure imparted opioid agonist activity to the molecule in animal antinociceptive tests. For example, *cis*-*N*-methyl-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (**22**) (Chart 1) has mixed agonist–antagonist properties. In addition, when the 4-methyl group of **2a** was replaced with a 4-propyl group, the resulting *trans*-*N*-methyl-3-methyl-4-propyl-4-(3-hydroxypiperidine) (**3**) was a mixed agonist–antagonist.[8] To our knowledge no systematic study using the same assay has been conducted on the N-substituted 3,4-dimethyl-4-(3-hydroxyphenyl)piperidine class of opioid ligands having the 3-methyl-, 4-methyl-, or both methyl substituents removed to determine the effect that the contribution of the 3- and 4-methyl substituents of the piperidine ring has on antagonist properties at each of the opioid receptors.

In this study, we compared the opioid receptor properties of **4a**,**b** and **5a**,**b** which have only a 3-methyl group, **6a**,**b** which have only a 4-methyl group, and **7a**,**b** and **8a**,**b** which have neither methyl group to those of **2a**,**b** which have both the 3- and 4-methyl groups present. Each compound was tested for its opioid receptor agonist and antagonist properties using the [^{35}S]GTPγS binding assay to gain information about the contribution of the 3- and 4-methyl substituents on the piperidine ring of **2a**,**b** to the pure opioid antagonist properties of these compounds. Zimmerman and co-workers reported that **2a** had an AD_{50} of 0.74 mg/kg as an antagonist of morphine-induced antinociception at the μ receptor and an AD_{50} of >5.0 mg/kg of κ agonist U50,488-induced antinociception in the

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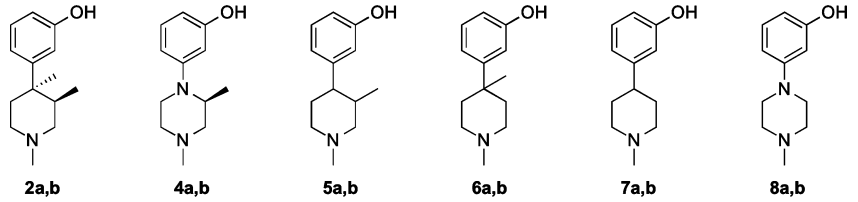
Table 1. Inhibition of Agonist-Stimulated [^{35}S]GTPγS Binding in Cloned Human μ, δ, and κ Opioid Receptors[a]



		K_e (nM)		
compd	R	μ, DAMGO	δ, DPDPE	κ, U69,593
2a	CH_3	29.3 ± 3.4[b]	681 ± 241[b]	134 ± 27.1
2b	$C_6H_5(CH_2)_3$	0.1 ± 0.02[b]	0.9 ± 0.32[b]	0.88 ± 0.17
4a	CH_3	508 ± 26	IA[d]	194 ± 32
4b	$C_6H_5(CH_2)_3$	0.88 ± 0.03	13.4 ± 4.2	4.09 ± 0.79
5a	CH_3	1248 ± 423	IA[d]	1307 ± 447
5b	$C_6H_5(CH_2)_3$	11.9 ± 2	46 ± 18	16.5 ± 5
6a	CH_3	974 ± 230	agonist[c]	477 ± 150
6b	$C_6H_5(CH_2)_3$	5.5 ± 0.59	178 ± 47	21.3 ± 9.0
7a	CH_3	IA[d]	IA[d]	2700 ± 1300
7b	$C_6H_5(CH_2)_3$	75.6 ± 21	418 ± 120	5.8 ± 2.0
8a	CH_3	4300 ± 1700	1600 ± 480	IA[d]
8b	$C_6H_5(CH_2)_3$	8.47 ± 1.42	34.3 ± 5.8	36.8 ± 16.8

[a]With the exception of **6a**, all compounds had no agonist activity at 10 μM. [b]Data taken from ref 15 [c]Compound **6a** had ED_{50} = 8300 ± 2500 nM with E_{max} = 64% ± 5% of DPDPE max. [d]Compounds that at 10 μM caused less than a 4× shift in the agonist EC_{50} were considered inactive (IA). The data represent the mean ± SE from at least three independent experiments.

mouse writhing test.[9] Zimmerman and co-workers had previously reported that **2a** did not have any opioid receptor agonist activity in the mouse writhing test and the rat tail heat analgesic test.[7,8] We found that **2a** had K_e values of 29.3, 681, and 134 nM at the μ, δ, and κ opioid receptors, respectively, with no opioid agonist efficacy at 10 μM at all three opioid receptors in a [^{35}S]GTPγS assay. In a follow-up study to the report by McElvain and Clemens[18] that **6a** was a morphine-like opioid agonist, Zimmerman and co-workers reported that **6a** had ED_{50} = 3.4 mg/kg in the mouse writhing test.[7] We found that **6a** was a weak agonist at the δ opioid receptor with ED_{50} = 8300 nM and E_{max} = 64% and was an antagonist at the μ and κ receptor with K_e values of 974 and 477 nM, respectively. In our study, we even found that the *N*-methyl analogue **7a**, which does not have a 3- or 4-methyl, was still a pure but weak opioid antagonist with K_e value of 2700 nM at the κ receptor, was inactive at the μ and δ receptors, and had no agonist activity at 10 μM at all three receptors.

Zimmerman and co-workers reported that changing the *N*-methyl group in **2a** to the *N*-phenylpropyl group present in **2b** resulted in a much more potent antagonist. Compound **2b** had an AD_{50} value of 0.28 mg/kg for μ antagonism of morphine-induced antinociception in the mouse writhing test compared to 0.74 mg/kg for **2a** in the test.[9] Similar to **2a**,**b**, we also found that changing the *N*-methyl group in **5a**, **6a**, and **7a** to give the *N*-phenylpropyl analogues **5b**, **6b**, and **7b** resulted in greatly increased antagonist potency, particularly at the μ and κ receptors with no agonist efficacy in the [^{35}S]GTPγS binding assay for all three compounds. Compound **5b** had K_e values of 11.9 and 16.5 nM at the μ and κ receptors, respectively, and was 105- and 79-fold more potent than **5a** as an antagonist at the μ and κ receptors (Table 1). Compound **6b** with K_e values of 5.5 and 21.3 nM at the μ and κ receptors, respectively, was 177 and 22 times more potent than **6a** as an antagonist at the μ and κ receptors. Unlike **6a**, which is an agonist at the δ receptor, **6b** is an antagonist at the δ receptor with K_e = 178 nM (Table 1). Compound **7a** is a weak antagonist at the κ receptor and has no antagonist properties at the μ and δ receptors. In contrast to the lack of antagonist properties of **7a** at the μ and δ receptors, **7b** is a weak antagonist at the μ and δ receptors with K_e values of 75.6 and 418 nM. Surprisingly, **7b**, with K_e = 5.8 nM at the κ receptor, showed 13- and 72-fold selectivity for the κ relative to the μ and δ opioid receptors, respectively.

In a previous study, we reported that both the *N*-methyl- and *N*-phenylpropyl-3-methylpiperazine analogues **4a** and **4b** were potent, pure opioid receptor antagonists.[15] The *N*-methyl compound **4a** has K_e values of 508 and 194 at the μ and κ receptors, respectively, and no antagonism at the δ receptor, whereas the *N*-phenylpropyl **4b** has K_e values of 0.88, 13.4, and 4.09 nM at the μ, δ, and κ receptors, respectively (Table 1). In this study, we found that *N*-methyl- and *N*-phenylpropyl-4-(3-hydroxyphenyl)piperidines (**8a**,**b**), which like **7a**,**b** do not have a 3- or 4-methyl substituent, were pure opioid antagonists. Compound **8b**, with K_e values of 8.47, 34.3, and 36.8 nM at the μ, δ, and κ opioid receptors, was 507- and 47-fold more potent at the μ and δ opioid receptors than **8a**. Compounds **4a**,**b** and **8a**,**b** had no opioid agonist efficacy at 10 μM.

Previous ^{1}H NMR and single crystal X-ray structural studies have suggested an equatorial orientation for the 4-(3-hydroxyphenyl) group in the N-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (**2**) class of opioid antagonists.[19,20] The pure opioid receptor antagonists' activity of this class of compounds has been attributed to the compounds having the 4-(3-hydroxyphenyl) group in the equatorial orientation. The fact that compounds **5a**,**b**, **6a**,**b**, **7a**,**b**, and **8a**,**b** are all opioid receptor antagonists suggests that the 4-(3-hydroxyphenyl) group in each of these compounds is in an orientation similar to that found in the N-substituted 3,4-dimethyl-4-(3-hydroxyphenyl)piperidine class of opioid antagonists.

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In summary, a study of the in vitro functional opioid agonist−antagonist properties of the N-substituted 4-(3-hydroxyphenyl)piperidines **2a,b**, **5a,b**, **6a,b**, and **7a,b** revealed that all these N-substituted 4-(3-hydroxyphenyl)piperidines were opioid receptor antagonists at the μ and κ receptors. In addition, all compounds with the exception of the 1,4-dimethyl-4-(3-hydroxyphenyl)piperidine (**6a**) were also antagonists at the δ opioid receptor. The very low δ opioid receptor efficacy of ED_{50} = 8300 nM and antagonist properties at the μ and κ receptors suggest that the analgesic activity seen in the animal studies reported by McElvain and Clemens[18] and Zimmerman and co-workers[7] for **6a** might be due to the interaction with a target other than the opioid receptors or metabolism to an active metabolite. These studies show that neither the 3-methyl nor 4-methyl substituents on the piperidine rings of **2a,b** are required to obtain potent μ and κ opioid receptor antagonists.

The study of the in vitro functional efficacy properties of the *N*-methyl- and *N*-phenylpropyl-4-(3-hydroxyphenyl)-piperazines (**8a** and **8b**, respectively) revealed that both compounds were opioid receptor antagonists at the μ, δ, and κ receptors. Thus, the 3-methyl substituent present in **4a** and **4b** is not needed to obtain pure opioid antagonists in the N-substituted 4-(3- hydroxyphenyl)piperazine class of compounds.

Even though the 3- and 4-methyl substituents of **2a,b** are not required for obtaining pure opioid receptor antagonism, the presence of these two methyl substituents does increase the potency as an opioid receptor antagonist relative to the potency of **5a,b**, **6a,b**, and **7a,b**. However, compounds **5a,b**, **6a,b**, and **7a,b**, particularly **6a,b** and **7a,b** which are not chiral, are much simpler to synthesize than **2a,b**. Compounds **4a,b**, which have a 3-methyl substituent on the piperazine ring, are also more potent than **8a,b** which lack a 3-methyl substituent. Since modification of the N-substituent in **2** led to alvimopam, a drug on the market for the treatment of GI motility disorders; JDTic, a potent and selective κ opioid receptor antagonist that is active in several animal models of CNS disorder; and LY255582, which was developed to treat obesity; it will be interesting to see if additional structural modifications of **5a,b**, **6a,b**, and **7a,b** as well as **4a,b** and **8a,b** will lead to new opioid receptor antagonists with potential for drug development.

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. 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 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 NH_4OH−aq (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 were determined relative to an internal tetramethylsilane standard (0.00 ppm). Chemical shift values for ^{13}C were 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-[(3*R*,4*R*)-1,3,4-Trimethylpiperidin-4-yl]phenol (2a) and 3-[(3*R*,4*R*)-3,4-Dimethyl-1-(3-phenylpropyl)piperidin-4-yl]phenol (2b). Compounds **2a** and **2b** were prepared according to a literature method.[9]

3-[(2*S*)-2,4-Dimethylpiperazin-1-yl]phenol (4a) and 3-[(2*S*)-2-Methyl-4-(3-phenylpropyl)piperazin-1-yl]phenol (4b). Compounds **4a** and **4b** were synthesized as previously reported.[15]

3-(1,3-Dimethylpiperidin-4-yl)phenol (5a) Hydrobromide. A solution of racemic 1,3-dimethyl-4-[3-(propan-2-yloxy)phenyl]-4-piperidinol (**9**)[16] (4.20 g, 15.9 mmol) was dissolved and refluxed in 12 N HCl (5 mL) and AcOH (10 mL) for 24 h. The solution was concentrated to dryness and then dissolved in dilute NH_4OH, extracted with EtOAc, dried (Na_2SO_4), and concentrated to afford an oil (3.23 g). A portion of the resulting oil (1.62 g) in EtOH (100 mL) with 20% $Pd(OH)_2$ on carbon (0.15 g) was shaken under 50 psi of H_2 for 12 h. The solution was filtered through Celite, concentrated to a residue, and subjected to chromatography on silica gel using a gradient up to 50% CMA80 in CH_2Cl_2. The resulting oil was triturated to a solid with CH_2Cl_2 and a trace of MeOH, filtered, and washed with cold Et_2O to afford **5a** (1.24 g, 76% over two steps), which proved to be the pure cis-isomer by NMR analysis. The solid was dissolved and then concentrated from MeOH and 48% HBr to afford the hydrobromide salt: mp 245−247 °C; ^{1}H NMR (DMSO-d_6) δ 9.32 (s, 1H), 8.99 (bs, 1H), 7.12 (t, 1H, J = 7.8 Hz), 6.67−6.55 (m, 3H), 3.54, 3.21 (m, 3H), 3.12−2.85 (m, 2H), 2.79 (d, 3H, J = 4.4 Hz), 2.37−2.31 (m, 2H), 1.94−1.76 (m, 1H), 0.76 (d, 3H, J = 7.4 Hz); ^{13}C NMR (DMSO-d_6) δ 157.3, 143.6, 129.2, 117.6, 113.9, 113.3, 59.2, 54.2, 43.4, 40.3, 32.6, 21.5, 11.3; MS (ESI) m/z 206.2 $(M + H)^+$. Anal. ($C_{13}H_{20}BrNO$) C, H, N.

3-[3-Methyl-1-(3-phenylpropyl)piperidin-4-yl]phenol (5b) Tosylate. A solution of **11** (246 mg, 0.70 mmol) in CH_2Cl_2 (7 mL) in a salt water−ice bath was treated with BCl_3 (7 mL, 1 M in CH_2Cl_2). After 30 min, the solution was washed with saturated $NaHCO_3$ (5 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica gel using EtOAc and then 20% CH_3OH in $CHCl_3$ to obtain 174 mg (80%) of **5b** as a colorless oil that proved to be a mixture of the cis and trans geometric isomers (4:1). The tosylate salt of the major, cis isomer crystallized from *i*-PrOH/Et_2O had mp 123−125 °C. ^{1}H NMR (CD_3OD) δ 7.71 (d, 2H, J = 8.1 Hz), 7.33−7.16 (m, 7H), 7.13 (t, 1H, J = 7.8 Hz), 6.69−6.59 (m, 3H), 3.62 (d, 1H, J = 12.0 Hz), 3.49 (d, 1H, J = 12.5 Hz), 3.32−3.21 (m, 1H), 3.18−2.97 (m, 4H), 2.70 (t, 2H, J = 7.5 Hz), 2.44−1.96 (m, 4H), 2.35 (s, 3H), 1.89 (d, 1H, J = 14 Hz), 0.82 (d, 3H, J = 7.4 Hz); ^{13}C NMR (CD_3OD) δ 158.7, 144.6, 141.7, 141.5, 130.5, 129.9, 129.7, 129.5, 127.5, 127.0, 119.3, 115.1, 114.7, 98.2, 59.8, 58.4, 54.8, 42.7, 34.7, 33.6, 26.8, 23.2, 21.3, 11.7. Anal. ($C_{28}H_{35}NO_4S$) C, H, N.

3-(1,4-Dimethylpiperidin-4-yl)phenol (6a) Hydrochloride. Compound **6a** was synthesized as described by McElvain and Clemens.[18] ^{1}H NMR ($CDCl_3$) δ 7.15 (t, 1H, J = 7.9 Hz), 6.81 (d, 1H, J = 8.0 Hz), 6.76 (t, 1H, J = 1.7 Hz), 6.62 (dd, 1H, J = 7.9, 1.9 Hz), 2.67−2.43 (m, 4H), 2.31 (s, 3H), 2.21−2.08 (m, 2H), 1.86−1.73 (m, 2H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.1, 129.5, 117.1, 113.4, 113.2, 52.1, 45.7, 36.3, 35.5; MS (ESI) m/z 206.1 $(M + H)^+$. The free base was converted to **6a**·HCl as white needles from methanol/ether: mp 187−189 °C. Anal. ($C_{13}H_{20}ClNO·0.25H_2O$) C, H, N.

3-[4-Methyl-1-(3-phenylpropyl)piperidin-4-yl]phenol (6b) Hydrochloride. A solution of **17** (98 mg, 0.45 mmol) in CH_2Cl_2 (5 mL) was treated with BCl_3 (5 mL, 1 M in CH_2Cl_2) at −78 °C. When the mixture was warmed to room temperature, the reaction was quenched with aqueous piperazine and the mixture was refluxed for 30 min. The cooled solution was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried (Na_2SO_4), and concentrated. The residue was subjected to chromatography on silica gel using a gradient of CMA80 in CH_2Cl_2 to afford **6b** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.27−7.08 (m, 6H), 6.83 (d, 1H, J = 7.9 Hz), 6.76−6.73 (m, 1H), 6.59 (dd, 1H, J = 7.9, 2.0 Hz), 5.87 (bs, 1H), 2.41−2.33 (m, 2H), 2.61−2.18 (m, 6H), 2.17−2.05 (m, 2H), 1.90−1.69 (m, 4H), 1.17 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.5, 141.9, 129.4, 128.5, 128.3,

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125.8, 117.6, 113.5, 113.1, 58.4, 50.2, 36.6, 36.1, 33.9, 28.2; MS (ESI) m/z 310.6 $(M + H)^+$. The free base was converted to 32.5 mg (32%) of **6b**·HCl as a pale yellow powder from methanol/ether: mp 47−51 °C (fusion). Anal. ($C_{21}H_{28}ClNO·1.25H_2O$) C, H, N.

3-(1-Methylpiperidin-4-yl)phenol (7a) Hydrochloride. Compound **7a** was synthesized as described by McElvain and Clemens.[18] ^{1}H HMR ($CDCl_3$) δ 7.12 (t, 1H, J = 7.8 Hz), 6.63−6.66 (m, 2H), 6.58 (s, 1H), 3.02 (d, 2H, J = 11.7 Hz), 2.39−2.30 (m, 1H), 2.32 (s, 3H), 2.08 (t, 2H, J = 12.0 Hz), 1.73 (q, 2H, J = 13.1 Hz), 1.60 (d, 2H, J = 12.7 Hz); ^{13}C NMR ($CDCl_3$) δ 157.6, 147.7, 129.7, 119.1, 114.2, 113.2, 56.3, 46.2, 42.2, 32.9; MS (ESI) m/z 192.1 $(M + H)^+$. Concentration from HCl in CH_3OH gave **7a**·HCl: mp 203−206 °C. Anal. ($C_{12}H_{18}ClN_2O$) C, H, N.

3-[1-(3-Phenylpropyl)piperidin-4-yl]phenol (7b) Hydrochloride. A solution of **19** (1.0 g, 3.2 mmol) in CH_2Cl_2 (20 mL) at −78 °C was treated with BBr_3 (1 M in CH_2Cl_2, 6.78 mL). After warming to room temperature and being stirred for 2 h, the mixture was again cooled to −78 °C, treated with MeOH (20 mL), and then allowed to warm to room temperature. The solution was evaporated, the residue dissolved in MeOH (20 mL), then evaporated. The residue was purified by chromatography on silica gel using CMA80/CH_2Cl_2 (1:1) to afford 0.51 g (54%) of **7b** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.36−7.17 (m, 5H), 7.12 (t, 1H, J = 7.7 Hz), 6.77−6.60 (m, 3H), 3.66 (d, 2H, J = 12.1 Hz), 3.21−3.01 (m, 4H), 2.89−2.78 (m, 1H), 2.74 (t, 2H, J = 7.54 Hz), 2.18−1.87 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 159.8, 146.4, 141.5, 130.8, 129.7, 129.5, 127.5, 118.7, 114.9, 114.6, 57.9, 54.4, 40.8, 33.6, 31.9, 26.9; ESI MS $(M + H)^+$ 296.0. The hydrochloride salt prepared by adding HCl (1 M in Et_2O) to a solution of the free base in Et_2O gave **7b**·HCl: mp 206−207 °C. Anal. ($C_{20}H_{26}ClNO$) C, H, N.

3-(4-Methylpiperazin-1-yl)phenol (8a) Dihydrochloride. A solution of **21** in CH_2Cl_2 (10 mL) was treated with BBr_3 (15 mL, 1 M in CH_2Cl_2) at −78 °C. After warming to room temperature, the mixture was concentrated to a residue, dissolved in aqueous piperazine (10 mL), then refluxed for 1 h. The cooled solution was extracted with EtOAc (3 × 25 mL). The combined organics were washed with water, dried (Na_2SO_4), and concentrated. The residue was dissolved in CH_3OH, acidified with HCl (1 M in Et_2O), and concentrated to yield 489 mg (54%) of **8a**·HCl: ^{1}H NMR ($CDCl_3$) δ 11.4 (bs, 1H), 8.83 (bs, 2H), 7.04 (t, 1H, J = 8.1 Hz), 6.50−6.41 (m, 2H), 6.35 (d, 1H, J = 8.1 Hz), 3.72 (d, 2H, J = 8.8 Hz), 3.45 (d, 2H, J = 6.4 Hz), 3.14 (d, 4H, J = 8.6 Hz), 2.78 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.3, 150.5, 129.8, 107.8, 107.1, 103.4, 51.8, 45.6, 41.8; MS (ESI) m/z 193.2 $(M + H)^+$. Mp 216−220 °C (fusion). Anal. ($C_{11}H_{18}Cl_2N_2O·0.5H_2O$) C, H, N.

3-[4-(3-Phenylpropyl)piperazin-1-yl]phenol (8b). Compound **8b** was previously synthesized and reported.[15]

3-Methyl-4-[3-(propan-2-yloxy)phenyl]piperidine (10) Hydrochloride. A solution of racemic **9** was dehydrated according to literature procedure.[16] A sample of this material (5.01 g, 20.4 mmol) in MeOH (60 mL) with 10% Pd on carbon (0.50 g) was shaken under 50 psi of H_2 for 48 h. The suspension was filtered through Celite and concentrated to provide a residue which was carried forward without further purification. The residue was dissolved in $CHCl_3$ (200 mL), combined with 1-chloroethyl chloroformate (25.1 g, 0.176 mmol) and $NaHCO_3$ (14.0 g, 167 mmol), and refluxed 72 h, with additions of ACE-Cl (7.8 g, 55 mmol after 12 h; 3.9 g, 27 mmol after 18 h). The mixture was concentrated and then dissolved in a minimum of EtOH at reflux. Upon cooling of the mixture, 0.92 g of **10**·HCl (17% over two steps) was collected by filtration. ^{1}H NMR (CD_3OD) δ 7.23 (t, 1H, J = 7.9 Hz), 6.83−6.70 (m, 3H), 4.59 (septet, 1H, J = 6.0 Hz), 3.56−3.25 (m, 3H), 3.25−3.02 (m, 2H), 2.44−2.29 (m, 1H), 2.26 (m, 1H), 1.96−1.84 (m, 1H), 1.30 (d, 6H, J = 6.0 Hz), 0.84 (d, 3H, J = 7.3 Hz); ^{13}C NMR (CD_3OD) δ 129.1, 119.0, 115.0, 113.43, 69.5, 49.7, 44.3, 41.6, 32.2, 21.0, 20.9, 10.1.

3-Methyl-1-(3-phenylpropyl)-4-[3-(propan-2-yloxy)phenyl]-piperidine (11). A solution of **10**·HCl (343 mg, 1.27 mmol) in 1,2-dichloroethane (4.5 mL) was treated with NEt_3 (362 μL, 2.6 mmol), 3-phenylpropanal (190 μL, 1.1 mmol), and $NaBH(OAc)_3$ (393 mg, 1.85 mmol). After being stirred for 2 h, the mixture was poured into saturated $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica gel with 0−40% EtOAc in hexanes to yield 246 mg (55%) of **11** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.34−7.13 (m, 6H), 6.80−6.67 (m, 3H), 4.54 (septet, 1H, J = 6.0 Hz,), 3.07−2.93 (m, 1H), 2.90−2.57 (m, 4 H), 2.45−1.95 (m, 6H), 1.91−1.72 (m, 2H), 1.69−1.56 (m, 1H), 1.33 (d, 6H, J = 6.0 Hz), 0.83 (d, 3H, J = 7.0 Hz).

1-Methyl-4-[3-(propan-2-yloxy)phenyl]piperidin-4-ol (13). A solution of *n*-BuLi (8.7 mL, 2.5 M in hexanes, 22 mmol) was added dropwise to 1-bromo-3-(1-methylethoxy)benezene (**12**)[16] (5.25 g, 24.4 mmol) in THF (14 mL) at −78 °C. After 1 h, *N*-methyl-4-piperdinone (2.49 g, 22.0 mmol) was added dropwise at −78 °C. The mixture was allowed to warm to room temperature overnight and then was chilled to 0 °C and added to 6 M HCl (8 mL) and concentrated. The aqueous emulsion was extracted with hexane. The organic layer was discarded. The aqueous layer was adjusted to pH 13−14 with 2 M NH_4OH and extracted with hexane. The combined hexane layers were dried (Na_2SO_4) and concentrated to afford 2.29 g (42%) of **13**. ^{1}H NMR ($CDCl_3$) δ 7.25 (t, 1H, J = 7.9 Hz), 7.09−7.02 (m, 2H), 6.81−6.76 (m, 1H), 4.56 (septet, 1H, J = 6.0 Hz), 2.79−2.70 (m, 2H), 2.51−2.38 (m, 2H), 2.35 (s, 3H), 2.17 (td, 2H, J = 12.8, 4.2 Hz), 1.80−1.70 (m, 2H), 1.33 (d, 6H, J = 6.0 Hz).

1-Methyl-4-[3-(propan-2-yloxy)phenyl]-1,2,3,6-tetrahydropyridine (14). A toluene (15 mL) solution of **13** (2.29 g, 9.2 mmol) was refluxed with TsOH·H_2O (3.50 g, 18.4 mmol) for 3 h. The cooled solution was extracted with water, and the toluene layer was discarded. The aqueous layer was adjusted to pH 13−14 with 2 M NaOH and then extracted with hexane. The combined hexane layers were washed with 2 M NaOH, dried (Na_2SO_4), and concentrated to afford 1.67 g (79%) of **14**. ^{1}H NMR ($CDCl_3$) δ 7.25−7.15 (m, 1H), 6.96 (d, 1H, J = 8.0 Hz), 6.91 (s, 1H), 6.77 (dd, 1H, J = 8.1, 2.4 Hz), 6.05 (m, 1H), 4.55 (septet, 1H, J = 6.1 Hz), 3.13−3.08 (m, 2H), 2.69−2.63 (m, 2H), 2.61−2.53 (m, 2H), 2.40 (s, 3H), 1.33 (d, 6H, J = 6.0 Hz).

4-Dimethyl-4-[3-(propan-2-yloxy)phenyl]piperidine (15). A solution of *n*-BuLi (4.5 mL, 2.5 M in hexanes, 11.3 mmol) was added dropwise to a solution of **14** (1.67 g, 7.22 mmol) in THF (17.5 mL) maintained between −10 and −20 °C. After 15 min, the solution was cooled to −50 °C and dimethyl sulfate (0.77 mL, 8.1 mmol) was slowly and cautiously added. The mixture was stirred an additional 30 min. Then 2 M NH_4OH (10 mL) was added. The resulting mixture was extracted with hexane. The hexane layer was washed with water, dried (Na_2SO_4), and concentrated to a residue. The residue was dissolved in CH_3OH (20 mL), cooled in an ice bath, and treated with $NaBH_4$ (0.42 g, 11 mmol). The mixture was stirred for 3 h at room temperature and then was quenched with the addition of acetone and saturated $NaHCO_3$. The concentrated residue was dissolved in water and EtOAc. The aqueous layer was extracted again with EtOAc before the combined organic layer was washed with water and then concentrated to afford 1.45 g (81%) of **15**. ^{1}H NMR ($CDCl_3$) δ 7.22 (t, 1H, J = 8.0 Hz), 6.91 (d, 1H, J = 7.8 Hz), 6.88 (s, 1H), 6.72 (dd, 1H, J = 8.0, 2.2 Hz), 4.54 (septet, 1H, J = 6.0 Hz), 2.54−2.33 (m, 4H), 2.56 (s, 3H), 2.20−2.08 (m, 2H), 1.81−1.70 (m, 2H), 1.34 (d, 6H, J = 6.1 Hz), 1.21 (s, 3H).

4-Methyl-4-[3-(propan-2-yloxy)phenyl]piperidine (16). A sample of **15** (1.44 g, 5.8 mmol) was concentrated thrice from toluene and then dissolved in 1,2-dichloroethane (8.7 mL). A freshly distilled aliquot of 1-chloroethyl chloroformate (1.81 mL, 17.4 mmol) was added under an inert atmosphere, and the resulting black solution was refluxed overnight. The concentrated residue was then dissolved in CH_3OH and refluxed for 1 h. The concentrated residue was dissolved in 2 M NaOH and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), concentrated, and subjected to chromatography on silica gel using a gradient of CMA80 in DCM to afford 677 mg (50%) of **16**. ^{1}H NMR ($CDCl_3$) δ 7.23 (t, 1H, J = 8.0 Hz), 6.94−6.86 (m, 2H), 6.72 (dd, 1H, J = 8.1, 2.3 Hz), 4.55 (septet, 1H, J = 6.0 Hz), 2.97−2.77 (m, 4H), 2.09−1.97(m, 2H), 1.74−1.59 (m, 2H), 1.34 (d, 6H, J = 6.1 Hz), 1.24 (s, 3H).

4-Methyl-1-(3-phenylpropyl)-4-[3-(propan-2-yloxy)phenyl]-piperidine (17). A solution of **16** (105 mg, 0.45 mmol) and 3-phenylpropanal (78 mg, 0.54 mmol) in trifluoroethanol (3 mL) was

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stirred for 15 min at room temperature before $NaCNBH_3$ (60 mg, 0.9 mmol) was added. After 18 h, the solution was concentrated. The residue was taken up in dilute NH_4OH and extracted with CH_2Cl_2. The concentrated organic layer was subjected to chromatography on silica gel using a gradient of CMA80 in CH_2Cl_2 to afford 98 mg (62%) of **17**. ^1H NMR ($CDCl_3$) δ 7.30−7.13 (m, 6H), 6.91 (s, 1H), 6.90−6.86 (m, 1H), 6.71 (dd, 1H, J = 8.1, 2.0 Hz), 4.53 (septet, 1H, J = 6.1 Hz), 2.66−2.06 (m, 10H), 1.88−1.70 (m, 4H), 1.33 (d, 6H, J = 6.1 Hz), 1.20 (s, 3H).

4-(3-Methoxyphenyl)-1-(3-phenylpropyl)piperidine (19). A solution of 1-benzyl-4-(3-methoxyphenyl)-1,2,5,6-tetrahydropyridine (**18**)[17] (1.14 g, 4.1 mmol) in EtOH (25 mL) with 20% $Pd(OH)_2$ on carbon (0.50 g) was shaken under 40 psi of H_2 for 18 h. The suspension was filtered through Celite, and the resulting solution was treated with 3-phenylpropanal (550 mg, 4.1 mmol). After the mixture was stirred for 30 min, $NaBH_3CN$ (0.75 g, 12 mmol) was added. After 18 h, the mixture was evaporated and the residue treated with saturated $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 25 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated to obtain a yellow residue. The residue was purified by chromatography on silica gel with CMA80/CH_2Cl_2 (1:1) to afford 1.10 g (87%) of **19** as a colorless oil. ^1H NMR ($CDCl_3$) δ 7.28−7.14 (m, 6H), 6.79 (m, 3H), 3.79 (s, 3H), 3.07 (d, 2H, J = 15 Hz), 2.65 (t, 2H), 2.48 (m, 1H), 2.40 (t, 2H), 2.01 (m, 2H), 1.81 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 159.8, 148.3, 142.4, 129.3, 128.4, 128.3, 125.8, 119.3, 112.7, 111.3, 58.6, 55.2, 54.4, 42.9, 33.9, 33.4, 28.9; ESI MS $(M + H)^+$ 310.5.

1-(3-Methoxyphenyl)-4-methylpiperazine (21). A solution of 1-methylpiperazine (**20**) (500 mg, 5 mmol), 3-bromoanisole (0.94 mL, 7.5 mmol), and KO-*t*-Bu (842 mg, 7.5 mmol) in toluene (20 mL) was degassed with nitrogen before $Pd(t\text{-}Bu_3P)_2$ (13 mg, 0.025 mmol) was added. The mixture was refluxed overnight. Chromatography on silica using a gradient of CMA80 in DCM afforded 687 mg (66%) of **21**.

■ 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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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

[^{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; ACE-Cl, 1-chloroethyl chloroformate

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