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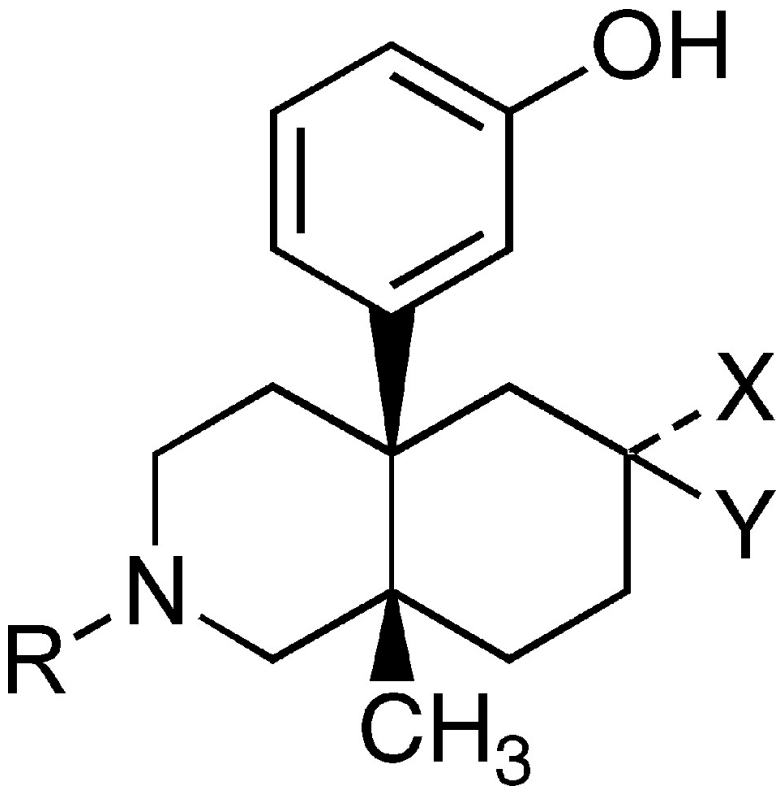

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N-Substituted *cis*-4a-(3-Hydroxyphenyl)-8a-methyloctahydroisoquinolines Are Opioid Receptor Pure Antagonists

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N-Substituted *cis*-4a-(3-hydroxyphenyl)-8a-methyloctahydroisoquinolines (**6a**−**g**) were designed and synthesized as conformationally constrained analogues of the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (**4**) class of opioid receptor pure antagonists. The methyloctahydroisoquinolines **6a**−**g** can exist in conformations where the 3-hydroxyphenyl substituent is either axial or equatorial, similar to the (3-hydroxyphenyl)piperidines **4**. The 3-hydroxyphenyl equatorial conformation is responsible for the antagonist activity observed in the (3-hydroxyphenyl)piperidine antagonists. Single-crystal X-ray analysis of **6a** shows that the 3-hydroxyphenyl equatorial conformation is favored in the solid state. Molecular modeling studies also suggest that the equatorial conformation has lower potential energy relative to that of the axial conformation. Evaluation of **6a**−**g** in the [^{35}S]GTP-γ-S in vitro functional assay showed that they were opioid receptor pure antagonists. *N*-[4a-(3-Hydroxyphenyl)-8a-methyl-2-(3-phenylpropyl)octahydroisoquinoline-6-yl]-3-(piperidin-1-yl)propionamide (**6d**) with a K_e of 0.27 nM at the κ opioid receptor with 154- and 46-fold selectivity relative to those of the μ and δ receptors, respectively, possessed the best combination of κ potency and selectivity.

Introduction

The opioid receptor system has been extensively studied, and thousands of compounds have been synthesized and evaluated by in vitro binding and functional assays as well as animal models.[1] An integral part of the effort to characterize the opioid receptor system has been the discovery of potent, pure antagonists. Naloxone (**1a**) and naltrexone (**1b**), both competitive antagonists at μ, δ, and κ opioid receptors,[1] have been extensively used as pharmacological tools to identify and characterize opioid systems. Additionally, **1a** is approved for treating heroin overdose and to reverse respiratory depression caused by morphine.[2] Compound **1b** is used to treat heroin and alcohol abuse.

Pioneering structure activity relationship (SAR) studies by Portoghese et al., based on the lead compound, **1b**, led to the discovery of the δ opioid receptor selective antagonist naltrindole (NTI, **2a**) and the κ opioid receptor antagonists, norbinaltorphimine (norBNI, **3**) and guanidinenaltrindole (GNTI, **2b**).[3−6] The N-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (**4**) are another interesting class of opioid receptor pure antagonists. Unlike activities of other antagonists, including that of the oxymorphone class, antagonist activity of **4** was not dependent on the structure of the N-substituent.[1] All reported N-substituted analogues, including the *N*-methyl analogue **4a**, were antagonists.[1,7−12] A few of the more interesting analogues include alvimopan (**4b**),[13−15] which has reached the NDA stage for GI motility disorder, (3*R*,4*R*)-1-[(*S*)-3-hydroxy-3-cyclohexylpropyl)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidine (LY255,582 (**4c**)),[16,17] 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-piperidinyl]methyl}-2-methylpropyl}-1,2,3,4-tetrahydro-3-isoquinoline-carboxamide (JDTic, **4d**), which we are developing to treat substance abuse (cocaine, heroin, nicotine, methamphetamine, and ethanol).[7−10,18] In other previous studies, we demonstrated that *N*-phenylpropyl-4β-methyl-5-(3-hydroxyphenyl)morphan (**5a**), which 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 an opioid receptor pure antagonist. The addition of a 7α-amino-3-(1-piperidinyl)propionyl group gave **5b**, which was a potent and selective κ opioid receptor antagonist.[19,20] Although **1**−**5** have proven highly useful in helping to characterize the pharmacological properties of the opioid system, much research remains to be done before the pharmacology of the opioid receptor system is fully understood. Structurally different chemotypes showing potent and selective opioid receptor antagonism will be particularly helpful.

As a continuation of our studies to develop new opioid receptor antagonists, we report in this paper that N-substituted *cis*-4a-(3-hydroxyphenyl)-8a-methyloctahydroisoquinolines (**6a**−**g**) are potent opioid antagonists in the [^{35}S]GTP-γ-S functional assay with several analogues showing preference for the κ opioid receptor.

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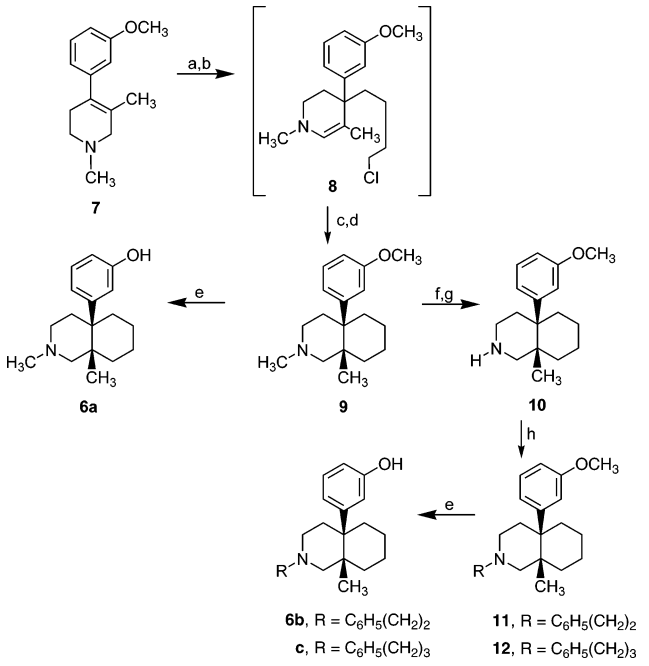
Scheme 1[a]



[a] Reagents: (a) *s*-C_4H_9Li, THF; (b) $Br(CH_2)_4Cl$, $(C_2H_5)_2O$; (c) NaI, CH_3CN; (d) $NaBH_4$, C_2H_5OH; (e) HBr, HOAc; (f) ACE-Cl, $(ClCH_2)_2$; (g) CH_3OH, reflux; (h) $NaBH(OAc)_3$, $C_6H_5CH_2CHO$ for **6b** or $C_6H_5(CH_2)_2CHO$ for **6c**.

Chemistry

N-Substituted *cis*-4a-(3-hydroxyphenyl)-8a-methyloctahydroisoquinolines (**6a**−**c**) were synthesized from tetrahydropyridine (**7**),[20] as outlined in Scheme 1. Deprotonation of **7** with *sec*-butyllithium in tetrahydrofuran at −78 °C provided the metalated enamine, which was added to an ethereal solution of 1-bromo-4-chlorobutane to give the endocyclic enamine **8**. Without isolation, this material was treated with sodium iodide in acetonitrile at reflux followed by reduction with sodium borohydride in ethanol to give the octahydroisoquinoline methyl ether **9**. O-Demethylation of **9** with refluxing 48% aqueous hydrogen bromide provided the desired **6a**. Single-crystal X-ray analysis of the hydrochloride salt of **6a** showed that the 4a-(3-hydroxyphenyl) group and the 8a-methyl group were cis to one another and that the 4a-(3-hydroxyphenyl) group was in the equatorial conformation relative to the piperidine ring (Figure 1).

The *N*-phenylethyl and *N*-phenylpropyl-*cis*-4a-(3-hydroxyphenyl)-8a-methyloctahydroisoquinolines (**6b**,**c**) were prepared starting with **9**. Treatment of **9** with 1-chloroethyl chloroformate (ACE-Cl) followed by refluxing the resulting product in methanol afforded the *N*-demethylated product **10**. Reductive amination of **10** with phenylacetaldehyde or hydrocinnamaldehyde using sodium triacetoxyborohydride as the reducing agent afforded the *N*-phenylethyl and *N*-phenylpropyl methyl ether intermediates **11** and **12**, respectively. Treatment of **11** and **12** with refluxing 48% aqueous hydrobromic acid in acetic acid provided the desired products **6b**,**c**.

The 6-amido *N*-phenylpropyl-*cis*-4a-(3-hydroxyphenyl)-8a-methyloctahydroisoquinoline analogues **6d**−**g** were synthesized as outlined in Scheme 2. Deprotonation of **7** with *sec*-butyllithium in tetrahydrofuran at −10 to 0 °C provided the metalated enamine, which was added to an ethereal solution of tetrahydro-(2-oxiranylethoxy)-2H-pyran (**13**) to provide the aminal **14**. The addition of bromine to a tetrahydrofuran solution of **14** and triphenylphosphine removed the tetrahydropyran protecting group and replaced the hydroxyl with a bromine to give **15** in a single step. Treatment of **15** with a mixture of acetic anhydride and trifluoroacetic acid afforded enamine intermediate **16**, which was cyclized by heating in acetonitrile containing potassium carbonate. Treatment of the product with sodium borohydride resulted in concomitant reduction of the enamine and hydrolysis of the acetate to give 6-hydroxyoctahydroisoquinoline (**17**). Swern (Moffatt−Swern) oxidation of **17** using oxalyl chloride and dimethyl sulfoxide in methylene chloride gave ketone **18**. Condensation of **18** with hydroxylamine hydrochloride in ethanol afforded oxime **19**, which yielded amine **20** on reduction using sodium and 2-propanol in refluxing toluene. Treatment of **20** with phthalic anhydride in toluene at reflux yielded the phthalimide **21**. N-Demethylation of **21** to give **22** was achieved with 1-chloroethyl chloroformate in 1,2-dichloroethane, followed by the hydrolysis of the resulting carbamate in refluxing methanol. Reductive alkylation of **22** with hydrocinnamaldehyde using sodium triacetoxyborohydride gave the *N*-phenylpropyl analogue **23**. Single-crystal X-ray analysis of **23** showed that the 4a-(3-hydroxyphenyl) group and the 8a methyl were cis to one another and that the 4a-(3-hydroxyphenyl) group was in the equatorial conformation relative to the piperidine ring (Figure 2). This is similar to the observation made for **6a**·HCl (Figure 1). In addition, the 6-phthalimide group is in an equatorial conformation and is trans to both the equatorial 4a-(3-hydroxyphenyl) and the axial 8a-methyl groups. Treating **23** with hydrazine in refluxing ethanol provided the *N*-phenylpropyl-6-amino compound, **24**. Coupling of **24** with the appropriately substituted carboxylic acid, using benzotriazol-1-yloxy-tris-(dimethylamino)phosphate (BOP, Castro's reagent) in tetrahydrofuran/triethylamine provided the desired methoxy-protected 6-amido compounds,

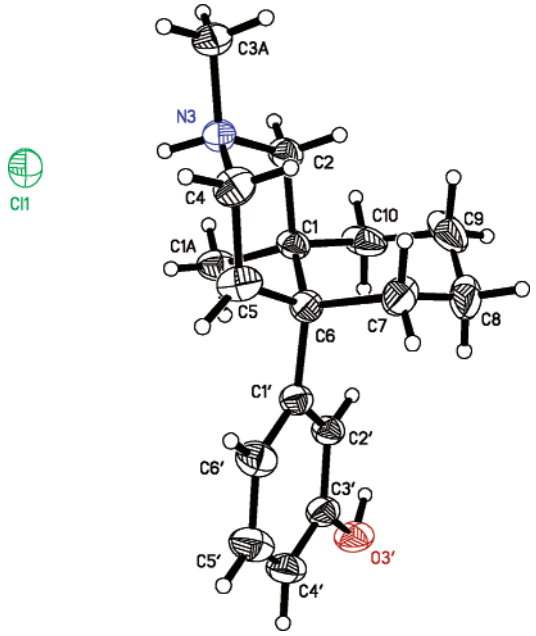
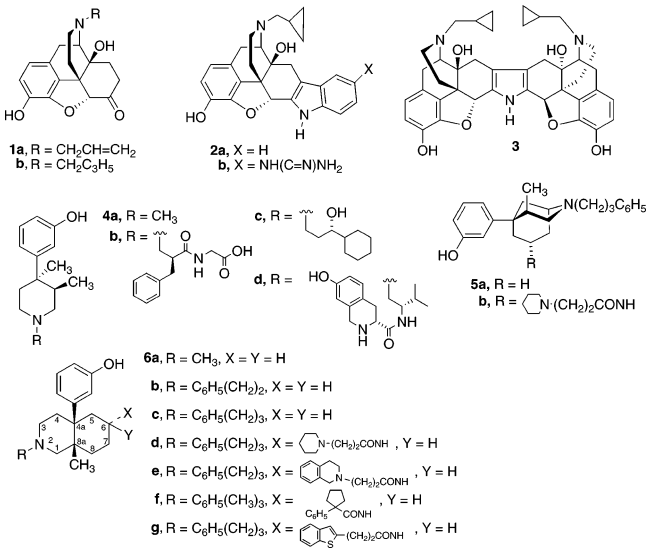


Figure 1. Structure of **6a** showing labeling of the nonhydrogen atoms. Displacement ellipsoids are at the 20% probability level.

25a−**d**. O-Demethylation of **25a**−**d** with borontribromide in methylene chloride at −78 °C provided final products **6d**−**g**.



Molecular Modeling

The phenyl axial vs phenyl equatorial preference relative to the piperidine ring of representative octahydroisoquinoline structures was modeled using Spartan '04 (version 1.0.1, Wavefunction, Inc.). Monte Carlo conformational searches were performed using the Spartan "Conformer Distribution" calculation option. Molecular mechanics energies based on the MMFF force field were used to guide the conformational search. The conformer distribution results were viewed in spreadsheet format with columns added for relative energy (energy of each conformer relative to the global energy minimum conformation expressed in kcal/mol) and dihedral angle around the **4**−**4a** bond. The lowest-energy phenyl axial (**4**−**4a** dihedral ≈ ±60°) and phenyl equatorial (**4**−**4a** dihedral ≈ ±180°) conformer of each structure modeled were identified by examination of the resulting molecular spreadsheet.

Biological Results

Measures of functional antagonism and selectivity of **6a**−**g** were obtained by monitoring the ability of test compounds to inhibit stimulated [^{35}S]GTP-γ-S binding produced by the selective agonists DAMGO [(D-Ala^2,-MePhe^4,Gly-ol^5)enkephalin] (selective for μ opioid receptor), DPDPE [cyclo[D-Pen^2,D-Pen^5]enkephalin] (selective for δ opioid receptor), and U69,593 {(5α,7α,8β)-(−)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-yl]benzeneacetamide} (agonist selective for κ opioid receptor) using cloned human opioid receptors expressed in CHO cells. Agonist dose-response curves were run in the presence or absence of a single concentration of the test compound. The K_es were calculated using the formula: K_e = [L]/[(A′/A) − 1)], where [L] is the concentration of antagonist and A′ and A are the agonist EC_{50} values in the presence or absence of antagonist, respectively. The results, along with reference compounds JDTic, norBNI, naltrexone, and **4c**, are listed in Table 1.

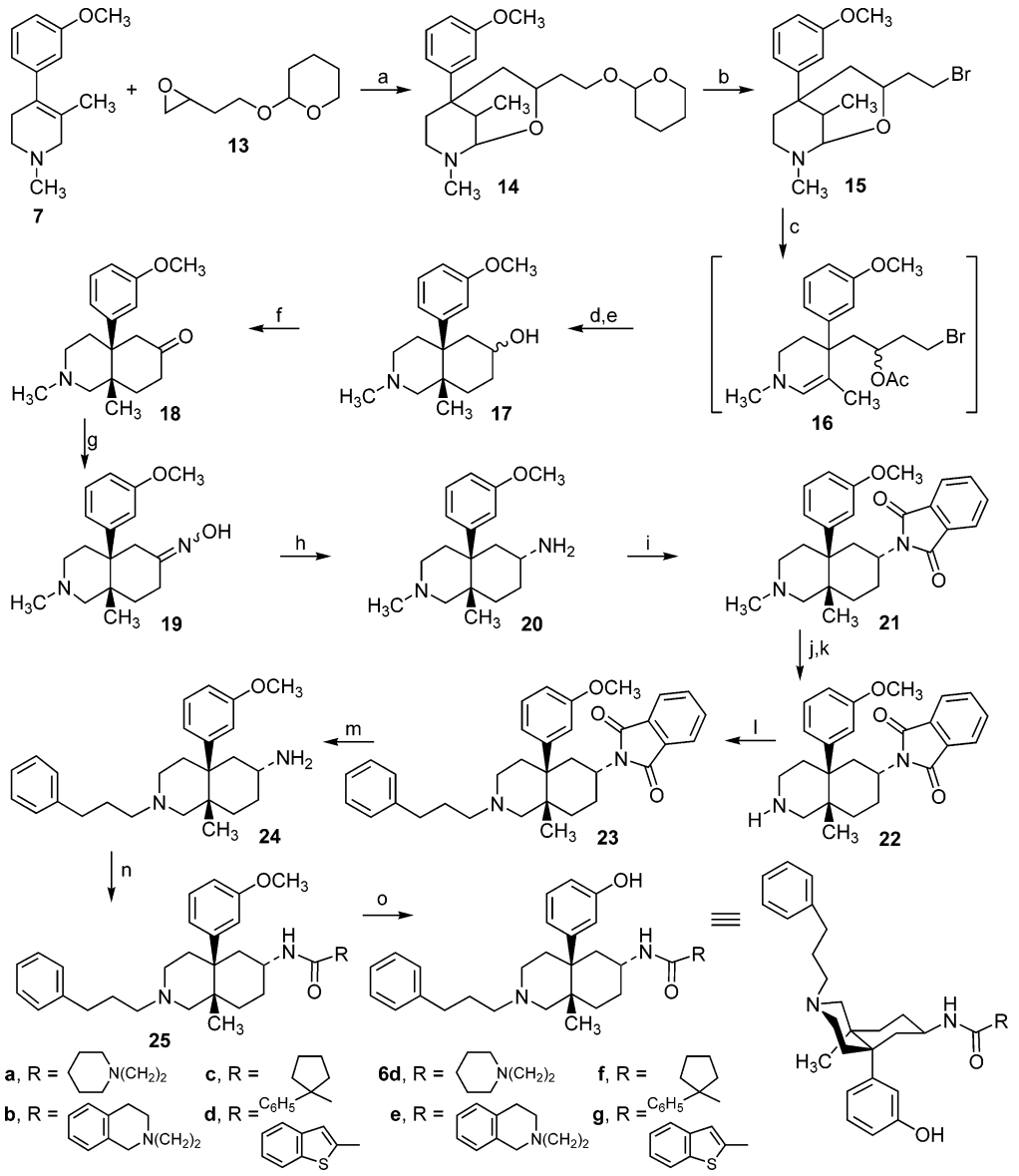
Compounds **6a**−**g** were tested at 10 μM for agonist activity at the μ, δ, and κ opioid receptors. Similar to reference compounds JDTic, norBNI, **4c**, and naltrexone, **6a**−**g** showed no agonist activity. In contrast, all compounds showed antagonist activity at all three receptors. Even the *N*-methyl analogue **6a** was an opioid receptor pure antagonist with K_e's of 99.4, 477, and 3.37 nM at the μ, δ, and κ receptors, respectively. The remaining analogues, which possess an *N*-phenylethyl (**6b**) or *N*-phenylpropyl group (**6c**−**g**) show K_e's of 0.8−41.7, 1.01−18.9, and 0.22−2.84 nM at the μ, δ, and κ receptors, respectively. Compound **6c** (K_e = 0.80), **6g** (K_e = 1.01), and **6e** (K_e = 0.22) are the most potent compounds at the μ, δ, and κ receptors, respectively. The most potent and selective κ opioid receptor compound of the group is **6d**, with a K_e of 0.27 nM at the κ receptor and 154- and 46-fold selectivities for the κ receptor versus the μ and δ receptors, respectively.

Discussion

Numerous SAR studies have shown that the antagonist activity of the N-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines is dependent on two factors: (1) the 3-methyl substituent and its trans relative relationship to the 4-methyl substituent and (2) an equatorial-oriented 3-hydroxyphenyl group. Although the 3-hydroxyphenyl ring in the 3,4-dimethyl-4-(3-hydroxyphenyl)piperidine analogues (**4**) can be in either an axial or equatorial position (Figure 3), X-ray and ^{1}H and ^{13}C NMR studies,[16,21,22] as well as molecular modeling studies,[12] suggest a preference for the 3-hydroxyphenyl equatorial conformation. It is believed that the antagonist activity results from the interaction with the opioid receptors in this conformation. One approach to gain additional information on this subject is to measure agonist/antagonist behavior using conformationally constrained analogues of **4**. The N-substituted *cis*-4a-(3-hydroxyphenyl)-8a-methyloctahydroisoquinolines (**6a**−**g**), where the C-4 and C-5 positions on the piperidine ring are connected through a four-carbon methylene linker, meet this requirement. The cis ring junction in **6a**−**g** allows the 4a-(3-hydroxyphenyl) group to exist in either the equatorial or axial conformation relative to the piperidine ring (Figure 3). However, single-crystal X-ray studies of **6a** and **23** (Figures 1 and 2) show that the equatorial position is the preferred conformation of the 3-hydroxyphenyl group in the solid state. In agreement with these X-ray crystallographic observations, molecular modeling calculations find that the equatorial position is the favored conformation for the 3-hydroxyphenyl group for both compounds. **6a** shows a small preference for the equatorial vs axial conformation (the global energy minimum for the equatorial conformation is 0.14 kcal/mol lower in calculated energy than the lowest-energy axial conformation). The corresponding global energy minimum conformation of **23** is also equatorial and is 6.74 kcal/mol lower in energy than the lowest-energy axial conformation (Figure 3). As a whole, these observations are consistent with the antagonist behavior found for **6a**−**g**.

The N-substituted *trans*-4a-(3-hydroxyphenyl)decahydroisoquinolines (**26**) are a class of compounds, similar to **6a**−**c**, that have a trans ring junction that locks the 4a-(3-hydroxyphenyl) group in an axial conformation.[23] The *N*-methyl compound, **26** (R = CH_3), was reported to be an opioid agonist with twice the potency of morphine in the mouse-tail flick and writhing analgesic

Scheme 2[a]



[a] Reagents and conditions: (a) *s*-BuLi, THF, −10 to 0 °C (1.5 h), 70%; (b) $(C_6H_5)_3P$, Br_2, THF, 0 °C to room temperature (12 h), 70%; (c) TFA, Ac_2O, room temperature (1 h); (d) K_2CO_3, CH_3CN, reflux (3 h); (e) $NaBH_4$, CH_3OH, 0 °C to room temperature (36 h), 70%; (f) oxalyl chloride, DMSO, −70 °C to room temperature (1 h), 92%; (g) $NH_2OH{\cdot}HCl$, absolute EtOH, reflux (5 h), 96%; (h) Na, $(CH_3)_2CHOH$, toluene, reflux (12 h), 94%; (i) phthalic anhydride, toluene, reflux (12 h), 90%; (j) ACE-Cl, 1,2-dichloroethane, reflux (5 h); (k) CH_3OH, reflux (12 h), 99%; (l) hydrocinnamaldehyde, $NaBH(OAc)_3$, 1,2-dichloroethane, room temperature, 87%; (m) N_2H_4 hydrate, EtOH, reflux (12 h), 97%; (n) appropriate acid, BOP reagent, TEA, THF, room temperature (2 h), ∼90%; (o) BBr_3, CH_2Cl_2, −78 °C to room temperature (1.5 h). [N.B.: All indicated configurations are relative stereochemistry.]

assays. Combining this information with the in vitro pharmacological results obtained for **6a**−**g** in this study clearly illustrates the importance of conformation to antagonist activity and provides additional support that these compounds are interacting with opioid receptors with the 4a-(3-hydroxyphenyl) group in the equatorial conformation. Table 1 lists data obtained from evaluating **6a**−**g** in the in vitro [^{35}S]GTP-γ-S functional assay. Details are presented in the Biological Results section. Note that none of the compounds showed opioid agonist activity when evaluated at 10 μM. In contrast, all compounds showed opioid antagonist activity at each opioid receptor. It is particularly interesting to note that the *N*-methyl analogue **6a** was a pure antagonist, distinctly different from **26** (R = CH_3). It was also found that the potency at the μ opioid receptor was increased when the *N*-methyl group was replaced with an *N*-phenylethyl and *N*-phenylpropyl group (see **6b**,**c**). This is in line with SAR of the related N-substituted *trans*-3,4,-dimethyl-(3-hydroxyphenyl) piperidines, such as **4c**. This trait appears to be general for antagonists operating via a 3-hydroxyphenyl equatorial conformation of the 4-(3-hydroxyphenyl)piperidine structure or substructure.

The compounds of this study clearly have opioid receptor properties that suggest they are related to the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine class of antagonists. However, the relative selectivity of **6a** for the opioid κ receptor is divergent from those of other members of this family because it showed some preference for the κ receptor relative to the μ and δ receptors. The potency shift typical with larger N-substituents in

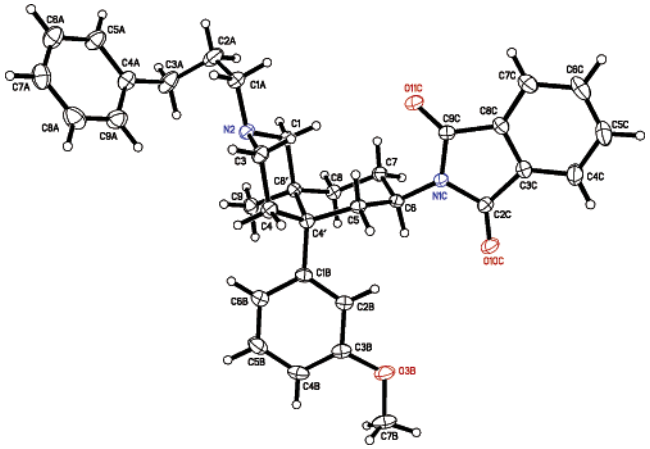


Figure 2. Structure of **23** showing labeling of the non-hydrogen atoms. Displacement ellipsoids are at the 30% probability level.

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

cmpd	μ, DAMGO K_e (nM)	δ, DPDPE K_e (nM)	κ, U69,593 K_e (nM)	μ/κ	δ/κ
6a	99.4 ± 28.3	477 ± 137	3.37 ± 0.47	29	141
6b	0.84 ± 0.22	18.9 ± 5.2	2.84 ± 0.97	0.3	7
6c	0.80 ± 0.10	12.4 ± 2.9	1.03 ± 0.14	0.8	12
6d	41.7 ± 7.8	12.3 ± 3.1	0.27 ± 0.08	154	46
6e	9.82 ± 3.7	4.56 ± 1.2	0.22 ± 0.02	45	21
6f	1.46 ± 0.15	6.46 ± 2.3	1.93 ± 0.48	0.8	3
6g	11.3 ± 2.0	1.01 ± 0.22	0.46 ± 0.13	25	2
JDTic[b], **4d**	3.41	79.3	0.01	341	7930
norBNI[b], **3**	19	4.4	0.04	475	110
Naltrexone, **1b**	3.35 ± 0.95	60.7 ± 10.6	4.63 ± 1.49		
LY255, 582, **4c**	0.10 ± 0.04	0.60 ± 0.11	0.29 ± 0.06		

[a] The data represent the mean ± SE from at least three independent experiments. The final GDP assay concentration was 10 μM. [b] Taken from ref 18.

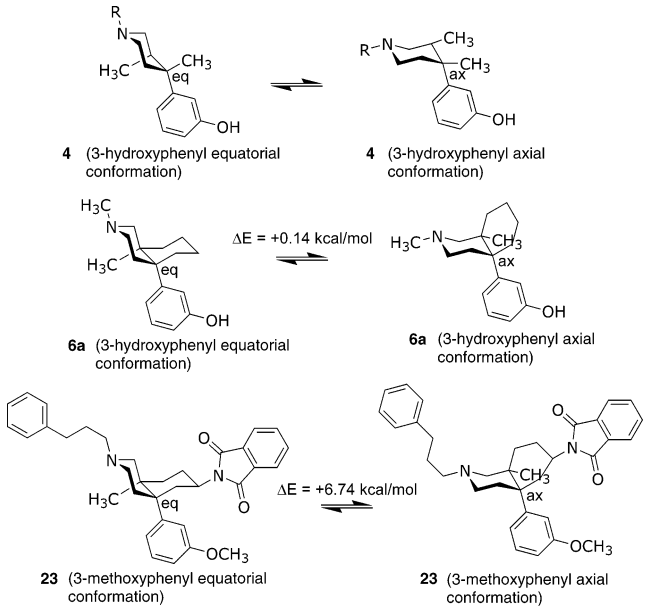


Figure 3. Conformational structures of **4**, **6a**, and **23**.

this case serves to level the potency among the opioid receptors. It may be that the bridging ring in **6a** interacts with a lipophillic site that is more pronounced in the κ opioid receptor. Such an interaction is consistent with our studies with κ-selective 5-(3-hydroxyphenyl)-morphans (**4a, 27,** and **28**), where we found that the

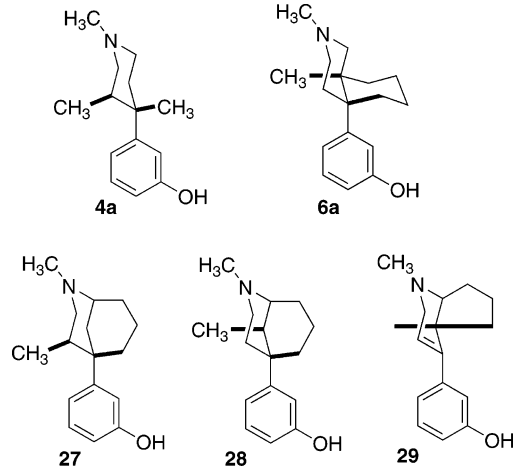
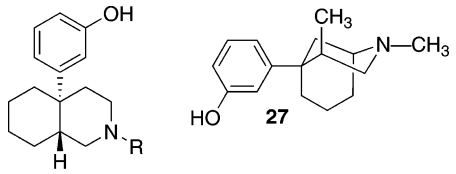


Figure 4. Comparison of structures of **4a, 6a**, **27**, **28**, and **29**. Bolded areas are key substructures for pure antagonist activity.

relative placement of the bridging ring and 4β-methyl group significantly impacted potency and selectivity for the κ receptor.[19,20]

Another important aspect of the present study is that it adds additional support to the role of the *trans*-3,4-dimethyl structure or substructure that is essential for the antagonist activity of the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (**4**) series (Figure 4). The 8a methyl and the 5-position methylene of the bridging ring fulfill this role in the isoquinoline compounds **6a**−**g**. Information as to the function of this and similar groups can be gleaned from the available literature. For **4a**, the *trans*-3,4-dimethyl is a requisite for potent, pure antagonist activity. This *N*-methyl derivative is a weak but pure antagonist lacking any agonist activity up to 10 μM.[11] Without the *trans*-3,4-dimethyl group, the compound is an agonist. The related *N*-methyl 5-(3-hydroxyphenyl)morphan antagonists **27** and **28** possess the *trans*-3,4-dimethyl-like substructure (Figure 4) as well as a 3-hydroxyphenyl conformation locked in place by a bridging ring.[19,20] Experimentally, both of these compounds lack agonist activity up to 10 μM and, importantly, are weak but pure antagonists. *N*-methyl 5-(3-hydroxyphenyl)morphan, lacking the 4β- or 9β-methyl groups present in **27** and **28**, respectively, is a potent morphine-like agonist.[24] In line with these observations, the *N*-methyl analogue **6a** in the present study was found to be a pure antagonist with potency for the μ receptor in the range observed for **27** and **28**.

Rice and Hashimoto have shown that 5-(3-hydroxyphenyl)morphans, such as **27** and **28** but lacking a 4β- or 9β-methyl group, are antagonists if the N-substituent is larger than a methyl (phenylethyl or phenylpropyl).[25] Even earlier work by Awaya and May[24] showed weak antagonism in 9α-methyl 5-(3-hydroxyphenyl)morphans and also in a similar series, the hexahydro-1H-1-pyridine (**29**) (Figure 4).[26] These findings, together with the data from the *N*-methyl derivatives **27** and **28**, indicate that the 3,4-dimethyl groups in the **4** series or the 4β-methyl group in the **27** series and the 9β-methyl group in **28** series all serve to block agonist activity irrespective of the N-substituent structure. This phenomenon may arise as a consequence of the methyl group's interaction with an excluded volume in the agonist domain or perhaps may be acting at an "acces-



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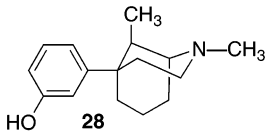

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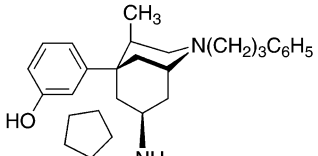

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sory site" to prevent a conformational change by the receptor or by some other mechanism.[27,28] Regardless of the mode of action, the data for **6a**−**g** illustrate in a novel series that the presence of this substructure coupled with the proper conformation confers pure antagonist activity in a reliable and predictable manner.

In recent reports, we have shown that opioid receptor subtype selectivity can be realized in the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine and the 4β-methyl-5-(3-hydroxyphenyl)morphan series by attaching suitable address elements onto nonselective scaffolds.[9,19] For example, we found that the addition of a 7α-(2-piperidinylethylamido) group to *N*-phenylpropyl-4β-methyl-5-(3-hydroxyphenyl)morphan (**4a**) to give **4b** resulted in an enhanced potency and selectivity for the κ opioid receptor.[19] In this study, the addition of a 6α-(2-piperidinylethylamido) group to **6c** provided **6d**, which showed a K_e of 0.27 nM at the κ receptor with 154- and 46-fold selectivity relative to those at the μ and δ receptors, respectively. Compound **6e** results from the addition of a 2-benzoisoquinolinylethylamido group to **6c**. This compound retains high potency for the κ receptor (K_e = 0.22 nM); however, the potency at the μ and δ receptors is also enhanced, resulting in only 45- and 21-fold selectivity, respectively. The 5-(3-hydroxyphenyl)morphan (**30**), which has a 7-(1-phenyl-1-cyclopentyl)amido side chain, is a potent and selective antagonist at the δ opioid receptor relative to the μ and κ receptors.[29] The addition of a 6α-[7-(1-phenyl-1-cyclopentyl)]amido group to **6d** to give **6f** did not result in an appreciable enhancement of δ opioid receptor potency. This difference in selectivity suggests that the side chains of these two series may be interacting differently with the δ receptor. Compound **6g**, which has a 6-(2-benzothiophenylethyl)amido group, possessed the highest potency for the δ receptor (K_e = 1.01 nM) but was not selective for the δ receptor.

In summary, the N-substituted *cis*-4a-(3-hydroxyphenyl)-8a-methyloctahydroisoquinolines, **6a**−**g**, represent a new chemotype whose SARs suggest that they are related to the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine class of opioid antagonist. The addition of a 6-amido address group possessing an amino function to the core structure provides compounds with an increased selectivity for the κ opioid receptor relative to those for the μ and δ opioid receptors that retain high κ potency. The most potent and κ-selective analogue identified in this study was *N*-[4a-(3-hydroxyphenyl)-8a-methyl-2-(3-phenylpropyl)octahydroisoquinolin-6-yl]-3-piperidin-1-yl]propionamide (**6d**). The similarities and differences in structural features between the 4β-methyl-5-(3-hydroxyphenyl)morphan and the octahydroisoquinoline classes have revealed new information regarding subtype selectivity in novel opioid receptor pharmacophores, which will be useful in the design of future κ- and δ-selective compounds.

Experimental Section

^{1}H NMR spectra were determined on a Bruker 300 spectrometer using tetramethylsilane as an internal standard. Mass spectral data were obtained using a Finnegan LCQ electrospray mass spectrometer in the positive ion mode at atmospheric pressure. Silica gel 60 (230−400 mesh) was used for column chromatography. All reactions were followed by thin-layer chromatography (TLC) using Whatman silica gel 60 TLC plates and were visualized by UV or by charring using 5% phosphomolybdic acid in ethanol. All solvents were reagent grade. Tetrahydrofuran and diethyl ether were dried over sodium benzophenone ketyl and distilled prior to use. Methylene chloride and chloroform were distilled from calcium hydride if used as reaction solvents. HCl in dry diethyl ether was purchased from Aldrich Chemical Co. and used while fresh before discoloration.

DAMGO, DPDPE, and U69,593 were obtained via the Research Technology Branch, NIDA, and were prepared by Multiple Peptide Systems (San Diego, CA). [^{35}S]GTP-γ-S was obtained from Perkin-Elmer Inc., (Boston, MA). GTP-γ-S and GDP were obtained from Sigma Chemical Company (St. Louis, MO). CMA-80 is a mixture of 80% chloroform, 18% methanol, and 2% concentrated ammonium hydroxide.

The nomenclature for **6a**−**g** follows IUPAC guidelines. All other compounds are named using typical opioid nomenclature.

***N*-Methyl-4a-(3-methoxyphenyl)-8a-methyloctahydroisoquinoline (9).** To a dry three-neck round-bottomed flask was charged 2.27 g (0.01 mol) of **7**[20] and 50 mL of dry THF. This was cooled to −78 °C, and to this was added 11.2 mL (14.6 mmol) of *s*-BuLi (1.3 M in cyclohexane) via syringe over 20 min. The flask was warmed to −20 °C and aged for 30 min. The flask was cooled to −78 °C and transferred by cannula into a mixture of 50 mL of dry Et_2O and 5.90 g (0.034 mol) of 1-bromo-4-chlorobutane at −50 °C over 20 min. This mixture was aged for 1 h and then quenched with ice-cold 1 N HCl. The contents of the flask were transferred to a separatory funnel with ice-cold Et_2O and ice-cold 1 N HCl. The aqueous layer was removed and stored in an ice bath, and the organic layer was twice extracted with ice-cold 1 N HCl. The combined aqueous layers were placed into a new separatory funnel and extracted twice with ice-cold Et_2O. The aqueous layer was made basic with 50% NaOH to pH 10. The aqueous layer was extracted 3× with ice-cold Et_2O. The Et_2O extracts were dried (K_2CO_3) and filtered, and the solvent was removed at 0 °C. The resulting residue was dissolved in 40 mL of dry CH_3CN, and to this was added 3.91 g (0.027 mol) of NaI and 2.89 g (0.021 mol) of K_2CO_3. The flask was attached to a reflux condenser and heated to reflux with stirring for 20 h. The reaction mixture was cooled to room temperature and filtered. The solvent was removed on a rota-evaporator, and the residue was dissolved in 100 mL of EtOH. To this mixture was added 3.35 g (0.089 mol) of $NaBH_4$ in one portion, and the mixture was allowed to stir overnight. On the following day, 1 N HCl was added to the mixture until no further evolution of hydrogen was observed. The mixture was stirred for 10 min, and then 50% NaOH and H_2O were added until the mixture was clear and basic. The volatiles were removed on a rota-evaporator, and the residue was extracted with CH_2Cl_2. The

organic layer was dried over anhydrous Na_2SO_4. The removal of the solvent on a rota-evaporator yielded crude product, which was purified by chromatography on alumina using 15% EtOAc−hexanes as the eluent and gave 2.1 g (76%) of the desired product **9** as a colorless viscous oil: ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 2H), 7.08 (s, 1H), 6.74 (br, 1H), 3.81 (s, 3H), 2.50 (m, 3H), 2.11 (s, 3H), 1.88 (m, 3H), 1.54 (br, 8H), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.1, 127.8, 121.6, 115.9, 109.7, 64.6, 54.7, 46.2, 41.6, 36.5, 35.3, 21.5, 21.2.

***N*-Methyl-4a-(3-hydroxyphenyl)-8a-methyloctahydroisoquinoline (6a) Hydrochloride.** To a 25-mL single-necked flask was added 180 mg (0.65 mmol) of **9**, 5 mL of glacial AcOH, and 5 mL of 48% HBr. This mixture was heated under reflux for 18 h and then cooled to room temperature. The pH was adjusted to 10 with cooling using 50% NaOH. This mixture was extracted 3× with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give 0.17 g (99%) of crude product as a white solid. Purification by chromatography on alumina using 15% EtOAc−hexanes gave 0.140 g (83%) of desired product as a crystalline, white solid.

This free base was dissolved in MeOH, and to this solution was added 3 equiv of 1 N HCl in dry Et_2O to give the hydrochloride salt: mp 291−293 °C; ^{1}H NMR (DMSO-d_6) δ 9.71 (br s, 1H), 9.18 (s, 1H), 7.09−6.73 (m, 3H), 6.51 (m, 1H), 3.90 (t, 1H), 3.38 (s, 3H), 2.57−2.49 (m, 4H), 2.28 (s, 1H), 1.61−1.29 (m, 6H), 1.02 (d, 2H), 0.91 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 156.9, 147.5, 128.7, 119.4, 116.3, 113.0, 59.8, 49.9, 43.3, 36.8, 36.6, 34.4, 32.5, 31.3, 24.7, 21.3, 20.5. Anal. ($C_{17}H_{26}ClNO\cdot 0.75H_2O$) C, H, N.

4a-(3-Methoxyphenyl)-8a-methyloctahydroisoquinoline (10). To a solution of 430 mg (1.59 mmol) of **9** in anhydrous CH_2Cl_2 (15 mL) at reflux was added 250 mg (1.75 mmol) of 1-chloroethyl chloroformate dropwise. The resulting solution was heated under reflux for 20 h and then cooled to room temperature. The mixture was washed with saturated $NaHCO_3$ solution and H_2O, the organic layer was evaporated, and the resulting oil was dissolved immediately in MeOH and heated under reflux overnight. After cooling to room temperature, the MeOH was removed under reduced pressure, and the residue was treated with saturated $NaHCO_3$ solution. The mixture was extracted with 3:1, CH_2Cl_2−THF, and the combined organic extracts were washed once with H_2O. The removal of the solvent provided 0.36 g (89%) of crude **10** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.98 (m, 3H), 6.76 (m, 1H), 3.80 (s, 3H), 3.06 (m, 2H), 2.45−1.43 (m, 13H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.0, 128.3, 122.2, 116.9, 110.0, 55.6, 55.5, 43.8, 43.5, 36.4, 35.3, 30.7, 24.4, 22.4, 21.9.

***N*-(2-Phenylethyl)-4a-(3-methoxyphenyl)-8a-methyloctahydroisoquinoline (11).** Phenylacetaldehyde (87 mg, 0.72 mmol) and **10** (190 mg, 0.72 mmol) were mixed in CH_2Cl_2 (15 mL) and then treated with sodium triacetoxyborohydride (230 mg, 1.08 mmol). The reaction mixture remained cloudy throughout the reaction. The mixture was stirred at room temperature under a N_2 atmosphere for 2 h. The reaction mixture was quenched by adding saturated $NaHCO_3$, and the product was extracted with EtOAc. The EtOAc extract was dried ($MgSO_4$), and the solvent was evaporated to give 0.25 g (95%) of a light-yellow oil. Purification by chromatography on alumina using 10% EtOAc−hexanes gave 0.23 g (89%) of desired product **11** as a colorless, clear viscous oil: ^{13}C NMR ($CDCl_3$) δ 158.9, 129.1, 128.6, 128.1, 126.2, 122.5, 117.1, 109.9, 63.2, 61.1, 55.5, 43.1, 37.4, 36.3, 34.0, 30.7, 22.4, 22.1.

***N*-(3-Phenylpropyl)-4a-(3-methoxyphenyl)-8a-methyloctahydroisoquinoline (12).** Hydrocinnamaldehyde (110 mg, 0.75 mmol) and **10** (190 mg, 0.75 mmol) were mixed in CH_2Cl_2 (15 mL) and then treated with sodium triacetoxyborohydride (240 mg, 1.12 mmol). The reaction mixture remained cloudy throughout the reaction. The mixture was stirred at room temperature under a N_2 atmosphere for 2.5 h. The reaction mixture was quenched by adding saturated $NaHCO_3$, and the product was extracted with EtOAc. The EtOAc extract was dried ($MgSO_4$), and the solvent was evaporated to give 0.28 g (99%) of **12** as a light-yellow viscous oil. Purification by chromatography on alumina using 5% EtOAc−hexanes gave 0.22 g (79%) of desired product **12** as a colorless, clear viscous oil, which was used without further purification to synthesize **6c**.

***N*-(2-Phenylethyl)-4a-(3-hydroxyphenyl)-8a-methyloctahydroisoquinoline (6b) Hydrochloride.** To a 25-mL single-necked flask was added 230 mg (0.64 mmol) of **11**, 5 mL of glacial AcOH, and 5 mL of 48% HBr. This mixture was heated under reflux for 18 h and then cooled to room temperature. The pH was adjusted to 10 with cooling using 50% NaOH. This mixture was extracted 3× with CH_2Cl_2. The resulting organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give 0.22 g (98%) of crude product as a white solid. Purification by chromatography on alumina using 20% EtOAc−hexanes gave 0.18 g (81%) of desired product **6b** as a crystalline, white solid.

The free base was dissolved in MeOH, and to this was added 3 equiv of 1 N HCl in dry Et_2O to give the hydrochloride salt as a crystalline, white solid: mp 226−228 °C; ^{13}C NMR (DMSO-d_6) δ 156.9, 147.5, 147.6, 129.0, 128.9, 128.7, 127.1, 119.4, 116.3, 113.0, 57.3, 48.7, 41.2, 36.6, 34.5, 32.4, 29.7, 24.8, 21.3, 20.6. Anal. ($C_{24}H_{32}ClNO\cdot 0.5H_2O$) C, H, N.

***N*-(3-Phenylpropyl)-4a-(3-hydroxyphenyl)-8a-methyloctahydroisoquinoline (6c) Hydrochloride.** To a 25-mL single-necked flask was added 220 mg (0.59 mmol) of **12**, 5 mL of glacial AcOH, and 5 mL of 48% HBr. This mixture was heated under reflux for 18 h and then cooled to room temperature. The pH was adjusted to 10 with cooling using 50% NaOH. This mixture was extracted 3× with CH_2Cl_2. The resulting organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give 0.21 g (98%) of crude product as a white solid. Purification by chromatography on alumina using 15% EtOAc−hexanes gave 0.16 g (76%) of desired product **6c** as a crystalline, white solid.

This free base was dissolved in MeOH, and to this was added 3 equiv of 1 N HCl in dry Et_2O to give the hydrochloride salt as a crystalline, white solid: mp 262−264 °C; ^{1}H NMR ($CDCl_3$) δ 9.66 (br s, 1H), 9.32 (s, 1H), 7.34−7.22 (m, 5H), 7.21−6.95 (m, 3H), 6.62 (d, 1H), 3.35 (m, 3H), 2.92 (m, 4H), 2.5 (m, 4H), 2.39−1.82 (m, 4H), 1.56 (m, 4H), 1.28 (d, J = 6 Hz, 1H), 1.13 (s, 3H). Anal. ($C_{25}H_{34}ClNO\cdot 0.5H_2O$) C, H, N.

Tetrahydro-2-(oxiranylethoxy)-2H-pyran (13).[30] To a chilled solution (0 °C) of 3,4-dihydro-2H-pyran (117 g, 1.4 mol) in anhydrous Et_2O (600 mL) were added *p*-toluensulfonic acid (0.5 g) and 3-buten-1-ol (25.0 g, 0.35 mol). The resulting mixture was stirred at room temperature for 5 h before quenching by the addition of concentrated NH_4OH (5 mL) and MeOH (50 mL). The solvent was evaporated in vacuo, and ether was added to the residue. The precipitated ammonium *p*-toluenesulfate was separated by filtration, the filtrate was concentrated, and the crude product was purified by flash column chromatography on silica gel (0−5% EtOAc−hexanes) to give 2-(3-butenyloxy) tetrahydropyran (49 g, 90%) as a colorless, viscous liquid: ^{1}H NMR ($CDCl_3$) δ 5.80−5.89 (m, 1H, =CH−C), 5.02−5.06 (m overlapping, 2H, =CH_2), 4.59−4.60 (m, 1H, 2-H of THP), 3.77−3.83 (m, 2H, −CH_2O), 3.44−3.50 (m, 2H, CH_2O of THP), 2.33−2.38 (m, 2H, CH_2−CH=CH_2), 1.51−1.71 (m, 6H, H's of THP).

Into a 500-mL flask containing 2-(3-butenyloxy) tetrahydropyran (49.0 g, 0.314 mol) in CH_2Cl_2 (500 mL) under a N_2 atmosphere and cooled to 0 °C was added freshly crystallized *m*-chloroperoxybenzoic acid (95 g, 0.55 mol). The mixture was maintained at 0 °C for a period of 24 h. The precipitated benzoic acid was removed via vacuum filtration. The filtrate was washed successively with 10% aqueous NaOH (500 mL) and saturated aqueous sodium sulfite (500 mL); the organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford tetrahydro-2-(oxiranylethoxy)-2H-pyran (**13**) as a pure, clear, colorless liquid (52 g, 95%), which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 4.62 (s, 1H), 3.86−3.92 (m, 2H), 3.52−3.55 (m, 2H), 3.08 (br, 1H), 2.78−2.81 (t, J = 3 Hz, 1H), 2.53−2.55 (t, J = 3 Hz, 1H), 1.53−1.88 (m, 8H).

5-(3-Methoxyphenyl)-8,9-dimethyl-3-[(tetrahydro-2H-pyran-2-yl)oxy]methyl-2-oxa-8-azabicyclo[3.3.1]nonane (14). Into a dry 1-L flask containing a solution of 1,3-dimethyl-4-(3-methoxyphenyl)-1,2,3,6-tetrahydropyridine (**7**) (24 g, 0.11 mol) in dry THF (600 mL) cooled in a salted ice bath was added 1.4 M *s*-BuLi in cyclohexane (85 mL, 119 mmol) dropwise under a N_2 atmosphere over a period of 0.5 h. The dark-red solution was further stirred at reduced temperature for an additional 15 min, whereupon the mixture was transferred by cannula into a second dry 2-L flask containing tetrahydro-2-(oxiranylethoxy)-2H-pyran (**13**) (20 g, 0.11 mol) in anhydrous Et_2O (150 mL) cooled to −10 °C. Upon complete addition of the metalated enamine to the epoxide, the resulting mixture was stirred for an additional 30 min at −5 °C. The reaction was quenched with a solution of 13 g of NaOH and 42 g of NaCl in 350 mL of H_2O at such a rate so as to maintain the solution temperature below 0 °C. The mixture was subsequently poured into 500 mL of H_2O, the layers were separated, and the aqueous layer was extracted with Et_2O−EtOAc (1:1, 3 × 200 mL). The combined organic layers were dried over anhydrous K_2CO_3, concentrated, and purified by flash column chromatography on silica gel (50% EtOAc−hexanes to 100% EtOAc gradient) to afford 5-(3-methoxyphenyl)-8,9-dimethyl-3-[(tetrahydro-2H-pyran-2-yl)oxy]methyl-2-oxa-8-azabicyclo-[3.3.1]nonane (**14**) as a mixture of diastereomers (30 g, 70%): ^{1}H NMR ($CDCl_3$) δ 7.22−7.28 (m, 1H), 6.71−6.97 (m, 3H), 4.59 (br m, 1H), 4.48 (br m, 1H), 4.19 (br m, 1H), 3.81−3.87 (m, 2H), 3.80 (s, 3H), 3.52 (br m, 2H), 2.62−2.64 (m, 3H), 2.37 (s, 3H), 2.45 (m, 1H), 1.51−1.82 (m, 2H), 0.69 (d, J = 6 Hz, 3H); LCMS (ESI): *m/z* 390.5 $[M + H]^+$.

3-(2-Bromoethyl)-5-(methoxyphenyl)-8,9-dimethyl-2-oxa-8-azabicyclo[3.3.1]nonane (15). In a dry 1-L flask containing 5-(3-methoxyphenyl)-8,9-dimethyl-3-[(tetrahydro-2H-pyran-2-yl)oxy]methyl-2-oxa-8-azabicyclo[3.3.1]nonane (**14**) (30 g, 0.076 mol) and triphenylphospine (31 g, 0.12 mol) dissolved in anhydrous THF (600 mL) under a N_2 atmosphere and cooled to 0 °C was added Br_2 (6.0 mL, 117 mmol) over a period of 30 min. During the course of addition, the solution, which was initially clear and yellowish, became a precipitous slurry. Upon complete addition, the mixture was stirred 30 min at reduced temperature and overnight at room temperature (reaction mixture becomes homogeneous brownish-black). After this time, MeOH (50 mL) was added dropwise, and the mixture was concentrated. The residue was partitioned between cold Et_2O (500 mL) and cold 1 N NaOH (500 mL). The organic layer was further washed with H_2O (400 mL), dried over anhydrous K_2CO_3, and concentrated to afford semisolid material. The residue obtained was dissolved in a minimum amount of $CHCl_3$ and further diluted with hexane until precipitation of triphenylphosphine oxide was observed. The removal of the precipitate followed by concentration of the filtrate and purification by flash chromatography (30% EtOAc−hexanes) afforded 20 g (70%) of 3-(2-bromoethyl)-5-(methoxyphenyl)-8,9-dimethyl-2-oxa-8-azabicyclo[3.3.1]nonane (**15**) as a mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 7.24−7.29 (m, 1H), 6.73−6.90 (m, 3H), 4.51−4.52 (m, 2H), 3.80 (s, 3H), 3.52−3.56 (m, 2H), 2.61−2.66 (m, 3H), 2.36 (s, 3H), 1.71−2.04 (m, 5H), 0.69 (d, J = 6 Hz, 3H); LCMS (APCI): *m/z* 370.3 $[M + H]^+$.

***N*-Methyl-4a-(3-methoxyphenyl)-8a-methyloctahydroisoquinoline-6-ol (17).** A solution of 3-(2-bromoethyl)-5-(methoxyphenyl)-8,9-dimethyl-2-oxa-8-azabicyclo[3.3.1]-nonane (**15**) (9.6 g, 0.026 mol), acetic anhydride (35 mL), and trifluoroacetic acid (35 mL) was stirred under a N_2 atmosphere at ambient temperature for 1 h and poured into a mixture of ice (300 g) and 50% aqueous NaOH (50 mL) sufficient to make the solution strongly basic, and the product was extracted into cold Et_2O (400 mL). The ether layer was washed once with cold H_2O, dried over anhydrous K_2CO_3, and concentrated at 0 °C to afford enamine **16** as a yellow viscous oil (10.8 g). The oil was immediately dissolved in molecular sieve-dried CH_3CN (200 mL) and heated at reflux over K_2CO_3 (12 g) for 3 h under a N_2 atmosphere. Upon cooling, the solution was filtered and concentrated, and the residue was taken up in dry MeOH (200 mL). The solution was cooled to 0 °C, whereupon $NaBH_4$ (11.9 g, 0.031 mol) was added over 30 min. The mixture was gradually warmed to room temperature and stirred for 36 h. The reaction was quenched with the addition of 4 N aqueous HCl (pH 1) and stirred for an additional 15 min. The solution was made basic (pH 14) through the addition of cold 50% aqueous NaOH. The resulting solution was concentrated and partitioned between a 1:1 mixture of Et_2O−EtOAc (200 mL) and H_2O (200 mL). The aqueous phase was further extracted with a 1:1 mixture of Et_2O−EtOAc (2 × 100 mL), and the combined organic layers were dried over anhydrous K_2CO_3−Na_2SO_4 and concentrated to afford the crude product (6.72 g). Purification via flash chromatography (35% EtOAc−hexanes gradient) using neutral alumina (activity II−III) afforded a diastereomeric mixture of *N*-methyl-4a-(3-methoxyphenyl)-8a-dimethyloctahydroisoquinoline-ols (**17**) (4.39 g, 58%): ^{1}H NMR ($CDCl_3$) δ 7.12−7.26 (m, 3H), 6.72−6.91 (m, 1H), 4.01 (m, 1H), 3.80 (s, 3H), 2.63−2.79 (m, 2H), 2.31 (s, 3H), 2.26−2.28 (m, 3H), 2.17−2.21 (m, 2H), 2.03−2.10 (m, 2H), 1.86 (m, 1H), 1.63−1.73 (m, 2H), 1.40 (m, 2H), 1.19 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.8, 149.3, 128.2, 121.3, 116.0, 109.8, 67.5, 64.9, 55.1, 52.6, 46.7, 43.9, 41.4, 36.2, 35.7, 35.1, 30.9, 25.3; LCMS (APCI): *m/z* 290.4 $[M + H]^+$.

***N*-Methyl-4a-(3-methoxyphenyl)-8a-methyl-6-oxo-octahydroisoquinoline (18).** Into a dry flask containing oxalyl chloride (3.45 mL, 6.9 mmol, 2.0 M solution in CH_2Cl_2) in CH_2Cl_2 (15 mL) cooled to −70 °C was added DMSO (0.83 mL, 11.7 mmol) in CH_2Cl_2 (10 mL) over 10 min. The solution was stirred for an additional 10 min at −70 °C, and 1.54 g, 5.32 mmol of **17** in CH_2Cl_2 was added over 30 min. After an additional 30 min at −70 °C, Et_3N (1.11 mL, 7.98 mmol) was added, and the solution was warmed to room temperature, washed with saturated aqueous $NaHCO_3$ (100 mL), dried over Na_2SO_4, concentrated, and purified via flash chromatography (4% MeOH−$CHCl_3$) to afford 1.40 g (92%) of **18**: ^{1}H NMR ($CDCl_3$) δ 7.18 (t, J = 3 Hz, 1H), 6.75−6.83 (m, 3H), 3.76 (s, 3H), 3.05 (d, J = 15 Hz, 1H), 2.73−2.94 (m, 2H), 2.35−2.63 (m, 6H), 2.33 (s, 3H), 1.77 (m, 1H), 1.27−1.32 (m, 2H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 213.3, 159.3, 147.1, 128.8, 121.1, 115.1, 111.7, 63.1, 55.4, 52.6, 47.3, 47.1, 45.7, 37.8, 36.4, 33.8, 32.9, 25.8; LCMS (ESI): *m/z* 288.6 $[M + H]^+$.

***N*-Methyl-4a-(3-methoxyphenyl)-8a-methyl-6-oxo-octahydroisoquinoline Oxime (19).** *N*-Methyl-4a-(3-methoxyphenyl)-8a-methyl-6-oxoisoquinoline (**18**) (1.41 g, 4.9 mmol) and hydroxylamine hydrochloride (1.70 g, 24.5 mmol) in EtOH (absolute, 100 mL) were heated to reflux for 5 h. The reaction mixture was allowed to cool to room temperature. Ethanol was removed under reduced pressure. The crude product was dissolved in aqueous 2 N NaOH solution (100 mL) and extracted with 3:1 CH_2Cl_2−THF (4 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (neutral alumina, Brockmann activity II−III) eluting with 9:1 EtOAc−hexanes to afford 1.43 g (96%) of **19** as a white solid (mixture of E/Z isomers): LCMS (ESI): *m/z* 303.5 $[M + H]^+$.

***N*-Methyl-6-amino-4a-(3-methoxyphenyl)-8a-methyl-octahydroisoquinoline (20).** A slurry of oxime **19** (2.35 g, 0.077 mol) in anhydrous $(CH_3)_2CHOH$ (100 mL) and anhydrous toluene (200 mL) was heated to reflux until the solution became clear. The heat was turned off, and Na (20 g, 0.87 mol) was added with care at such a rate as to maintain a steady reflux (make 30−40 pieces and store under hexane and add over 1.5 h). The first addition was kept small. (Note hydrogen evolution!) At the end, the reaction was slower; as a result, the heating mantle was turned back on to bring back to reflux. The reaction mixture was heated until all of the Na was consumed followed by cooling to 50 °C and quenching with the careful addition of H_2O (250 mL). The toluene layer was separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (50% CMA-80 in $CHCl_3$) to afford 2.11 g (94%) of **20** as a colorless

oil: ^{1}H NMR ($CDCl_3$) δ 7.14−7.44 (m, 3H), 6.71−6.74 (m, 1H), 3.80 (s, 3H), 3.05 (m, 1H), 2.77 (m, 1H), 2.64 (d, J = 12 Hz, 1H), 2.27−2.30 (m, 2H), 2.26 (s, 3H), 2.02−2.12 (m, 3H), 1.68−1.71 (m, 2H), 1.46−1.49 (m, 2H), 1.24 (m, 3H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.2, 150.2, 128.5, 121.8, 116.5, 110.0, 65.4, 55.5, 53.0, 47.1, 46.7, 43.8, 43.3, 36.6, 36.2, 32.2, 25.8; LCMS (APCI): *m/z* 289.4 $[M + H]^+$.

***N*-Methyl-6-amino-4a-(3-methoxyphenyl)-8a-methyloctahydroisoquinoline Phthalimide (21).** Amine **20** (1.70 g, 0.0058 mol) was dissolved in anhydrous toluene (100 mL) followed by the addition of phthalic anhydride (2.61 g, 0.018 mol), and the mixture was heated at reflux overnight using a Dean−Stark trap to collect H_2O. The solution was cooled and washed with 1 N NaOH (3 × 50 mL) and H_2O. The organic layer was collected and dried (Na_2SO_4), and the solvent was removed under reduced pressure yielding crude product. The crude product was purified by flash chromatography (30% EtOAc−hexanes on neutral Al_2O_3 Brockman activity II−III) to afford 2.22 g (90%) of **21** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.80−7.83 (m, 2H), 7.68−7.71 (m, 2H), 7.23−7.27 (m, 3H), 6.77−6.79 (m, 1H), 4.81 (m, 1H), 3.85 (s, 3H), 3.28 (t, J = 12 Hz, 1H), 3.01 (d, J = 12 Hz, 1H), 2.83−2.85 (m, 1H), 2.65−2.81 (m, 1H), 2.40−2.47 (m, 2H), 2.37 (s, 3H), 2.16−2.20 (m, 1H), 1.89 (ddd, $J_1 = J_2$ = 15 Hz, J_3 = 6 Hz, 1H), 1.48−1.58 (m, 3H), 1.33−1.39 (m, 1H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.8, 159.2, 148.4, 134.1, 132.4, 128.7, 123.3, 121.8, 116.0, 111.0, 64.8, 55.5, 52.9, 47.8, 47.2, 43.8, 36.7, 35.6, 34.1, 26.7, 24.3; LCMS (ESI): *m/z* 419.9 $[M + H]^+$.

6-Amino-4a-(3-methoxyphenyl)-8a-methyloctahydroisoquinoline Phthalimide (22). To a solution of **21** (2.09 g, 0.005 mol) in anhydrous CH_2Cl_2 (100 mL) at reflux was added 1-chloroethyl chloroformate (0.82 mL, 7.47 mmol) dropwise. The resulting solution was heated under reflux for 5 h and then cooled to room temperature. This was washed once with saturated $NaHCO_3$ solution and once with H_2O. The dried (Na_2SO_4) organic layer was evaporated, and the resulting carbamate (foamy, white solid, almost quantitative yield) was dissolved immediately in MeOH (100 mL), and the solution was refluxed overnight. After cooling to room temperature, MeOH was removed under reduced pressure, and the residue was treated with saturated $NaHCO_3$ solution. This was extracted with 3:1 CH_2Cl_2−THF, and the combined organic extracts were washed once with H_2O and dried (Na_2SO_4). The removal of solvent under reduced pressure afforded 2.01 g (99%) of **22** as a foamy, white solid: ^{1}H NMR ($CDCl_3$) δ 7.80−7.83 (m, 2H), 7.68−7.71 (m, 2H), 7.23−7.28 (m, 3H), 6.78−6.81 (m, 1H), 4.84 (m, 1H), 3.86 (s, 1H), 3.75−3.80 (m, 2H), 3.32 (t, J = 12 Hz, 1H), 3.03−3.15 (m, 2H), 2.90 (br s, 1H), 2.61−2.67 (m, 1H), 2.45 (d, J = 12 Hz, 1H), 2.27−2.31 (m, 1H), 1.83−1.93 (m, 2H), 1.64 (dd, J_1 = 15 Hz, J_2 = 6 Hz, 2H), 1.31−1.48 (m, 3H), 1.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 158.1, 147.0, 132.9, 131.1, 127.5, 122.1, 120.5, 114.7, 109.8, 67.0, 54.3, 53.2, 46.5, 43.5, 41.8, 35.2, 34.8, 33.9, 32.9, 29.4, 24.7, 24.1, 22.9; LCMS (APCI): *m/z* 405.2 $[M + H]^+$.

***N*-(3-Phenylpropyl)-6-amino-4a-(3-methoxyphenyl)-8a-methyloctahydroisoquinoline Phthalimide (23).** Hydrocinnamaldehyde (0.65 mL, 0.0049 mmol) and **22** (2.00 g, 0.0049 mol) were mixed in anhydrous CH_2Cl_2 (50 mL) and then treated with sodium triacetoxyborohydride (1.57 g, 0.0074 mol). The reaction mixture remained cloudy throughout the reaction. The mixture was stirred at room temperature under a N_2 atmosphere for 3 h. The reaction was monitored by TLC (20% EtOAc−hexanes; neutral Al_2O_3 Brockman activity II−III). After completion, the reaction mixture was quenched by adding saturated aqueous $NaHCO_3$, and the product was extracted with EtOAc (3 × 50 mL). The combined EtOAc extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure to give crude product. The crude product was purified by flash chromatography (10% EtOAc−hexanes on neutral Al_2O_3 Brockman activity II−III) to afford 2.25 g (87%) of **23** as a shiny, white solid. The sample used for X-ray analysis was recrystallized from a mixture of hexane and CH_2Cl_2: mp 136−138 °C; ^{1}H NMR ($CDCl_3$) δ 7.79−7.82 (m, 2H), 7.68−7.71 (m, 2H), 7.18−7.32 (m, 8H), 6.76−6.81 (m, 1H), 4.81 (m, 1H), 3.85 (s, 3H), 3.31 (t, J = 12 Hz, 1H), 2.94 (d, J = 12 Hz, 1H), 2.80 (d, J = 9 Hz, 1H), 2.67−2.73 (m, 3H), 2.34−2.53 (m, 4H), 2.25 (d, J = 12 Hz, 1H), 1.78−1.94 (m, 3H), 1.51−1.62 (m, 2H), 1.49 (d, J = 12 Hz, 1H), 1.31−1.37 (m, 1H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.4, 160.9, 150.3, 144.5, 135.7, 134.0, 130.4, 130.3, 130.2, 127.6, 124.9, 123.5, 117.6, 112.6, 90.0, 63.6, 59.9, 57.2, 52.9, 49.5, 46.2, 38.6, 38.5, 37.3, 35.7, 35.6, 31.0, 28.3, 25.9. LCMS (ESI): *m/z* 523.7 $[M + H]^+$. Anal. ($C_{34}H_{38}N_2O_3$) C, H, N.

***N*-(3-Phenylpropyl)-6-amino-4a-(3-methoxyphenyl)-8a-methyloctahydroisoquinoline (24).** Compound **23** (2.00 g, 0.0038 mol) and hydrazine hydrate (1.02 mL, 21.0 mmol) were dissolved in EtOH (100 mL) and heated at reflux overnight. The filtrate was cooled, and the white precipitate was filtered and washed with cold EtOH. The solution was concentrated under reduced pressure, and the crude material was taken up in 3:1 CH_2Cl_2−THF (100 mL). The resulting white precipitate was separated by filtration and washed with cold CH_2Cl_2 (50 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to yield crude product. The crude product was purified by flash chromatography (40% CMA-80 in $CHCl_3$) to afford 1.45 g (97%) of **24** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.14−7.30 (m, 8H), 6.70−6.74 (m, 1H), 3.86 (s, 3H), 3.05 (m, 1H), 2.77−2.79 (br m, 1H), 2.65 (ddd, $J_1 = J_2$ = 9 Hz, J_3 = 3 Hz, 2H), 2.58 (d, J = 12 Hz, 1H), 2.26−2.36 (m, 4H), 2.04−2.12 (m, 3H), 1.68−1.81 (m, 4H), 1.44−1.50 (m, 4H), 1.32 (m, 1H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.2, 150.3, 142.9, 128.9, 128.6, 128.5, 126.0, 121.8, 116.5, 110.0, 62.6, 58.2, 55.5, 51.3, 46.9, 44.5, 43.2, 36.7, 36.3, 34.0, 32.1, 29.2, 25.8; LCMS (APCI): *m/z* 393.8 $[M + H]^+$.

***N*-[4a-(3-Methoxyphenyl)-8a-methyl-2-(3-phenylpropyl)octahydroisoquinolin-6-yl]-3-(piperidin-1-yl)propionamide (25a).** To **24** (105 mg, 0.267 mmol) dissolved in anhydrous THF (15 mL) was added 1-piperidinepropionic acid (63 mg, 0.40 mmol), Et_3N (0.17 mL, 1.33 mmol), and BOP reagent (140 mg, 0.32 mmol), and the reaction mixture was allowed to stir at room temperature for 1.5 h. The reaction progress was monitored by TLC (50% CMA-80 in CH_2Cl_2). The reaction mixture was diluted with EtOAc (25 mL) and washed with saturated aqueous $NaHCO_3$ (25 mL) followed by H_2O (25 mL). The aqueous layers were back extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with 1 N NaOH (25 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford crude amide. The crude product was purified by flash chromatography (30% CMA-80 in CH_2Cl_2) to afford 121 mg (85%) of **25a** as a shiny, white solid: ^{1}H NMR ($CDCl_3$) δ 8.77 (d, J = 6 Hz, 1H), 7.15−7.30 (m, 8H), 6.72−6.75 (m, 1H), 4.24 (m, 1H), 3.82 (s, 3H), 2.76 (br, 1H), 2.65−2.68 (m, 2H), 2.42−2.56 (m, 3H), 2.32−2.37 (m, 6H), 2.07−2.30 (m, 7H), 1.62−1.83 (m, 5H), 1.59−1.61 (m, 4H), 1.48−1.59 (m, 4H), 1.25−1.27 (br, 1H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.2, 159.2, 148.8, 142.8, 128.8, 128.7, 128.6, 126.0, 122.2, 116.2, 110.9, 62.4, 58.4, 55.6, 54.9, 54.0, 51.4, 45.5, 44.1, 38.1, 37.0, 36.8, 35.5, 34.0, 32.5, 29.2, 28.4, 26.9, 26.7, 24.6; LCMS (ESI): *m/z* 532.8 $[M + H]^+$.

***N*-[4a-(3-Hydroxyphenyl)-8a-methyl-2-(3-phenylpropyl)octahydroisoquinolin-6-yl]-3-(piperidin-1-yl)propionamide (6d) Dihydrochloride.** To **25a** (90 mg, 0.169 mmol), dissolved in anhydrous CH_2Cl_2 (15 mL) and cooled to −78 °C, was slowly added a 1.0 M solution in CH_2Cl_2 of BBr_3 (0.85 mL, 0.85 mmol). The reaction mixture was allowed to stir at −78 °C for 30 min and at room temperature for 2 h. The reaction mixture was cooled to 0 °C, quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with 1 N NaOH (25 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to afford crude product. The crude product was purified by flash chromatography (40% CMA-80 in CH_2Cl_2) to afford 75 mg (86%) of **6d** as a white solid: ^{1}H NMR ($CDCl_3$) δ 8.73 (d, J = 6 Hz, 1H), 7.09−7.31 (m, 8H), 6.68−6.72 (m, 1H), 4.30 (m, 1H), 2.78−2.85 (br, 1H), 2.59−2.69 (m, 4H), 2.50−2.55 (br, 4H), 2.36−2.42 (m, 4H), 2.20−2.27 (m, 3H), 2.05 (m, 2H), 1.78−1.85 (m, 5H), 1.62−1.65 (m, 4H), 1.43−1.50 (m, 4H), 1.21−1.25 (m, 2H), 1.19 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.8, 155.7,

148.2, 142.4, 128.5, 128.2, 125.7, 121.1, 116.5, 112.8, 61.8, 58.0, 54.3, 53.5, 50.9, 45.4, 43.6, 37.4, 36.6, 36.3, 35.0, 33.6, 31.9, 28.6, 27.9, 26.6, 25.9, 24.0; LCMS (ESI): *m/z* 518.9 $[M + H]^+$.

An analytical sample of the dihydrochloride salt was prepared by dissolving the free base in MeOH and adding 6 equiv of 1.0 M HCl in Et_2O. The removal of the solvent under reduced pressure afforded the dihydrochloride salt as a white solid, which was recrystallized from a mixture of MeOH−Et_2O: mp 240−242 °C (fus.). Anal. ($C_{33}H_{49}Cl_2N_3O_2 \cdot 2.75H_2O$) C, H, N.

3-(3,4-Dihydro-1H-isoquinolin-2-yl)-*N*-[4a-(3-methoxyphenyl)-8a-methyl-2-(3-phenylpropyl)octahydroisoquinolin-6-yl]propionamide (25b). To **24** (80 mg, 0.203 mmol), dissolved in anhydrous THF (15 mL) were added 3-(3,4-dihydro-1H-isoquinolin-2-yl)-propioinic acid hydrochloride (73 mg, 0.305 mmol) and Et_3N (0.142 mL, 1.01 mmol), and the reaction mixture was stirred at room temperature for 15 min. After this time, BOP reagent (99 mg, 0.22 mmol) was added, and the reaction mixture was allowed to stir at room temperature for 1.5 h. The reaction progress was monitored by TLC (50% CMA-80 in CH_2Cl_2). The reaction mixture was diluted with EtOAc (25 mL) and washed with saturated aqueous $NaHCO_3$ (25 mL) followed by H_2O (25 mL). The aqueous layers were back extracted with EtOAc (2 × 20 mL). The combined organic layer was washed with 1 N NaOH (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford crude amide, **25b**. The crude product was purified by flash chromatography (30% CMA-80 in CH_2Cl_2) to afford 94 mg (80%) of **25b** as a shiny, white solid: ^1H NMR ($CDCl_3$) δ 8.29 (d, J = 6 Hz, 1H), 7.03−7.31 (m, 12H), 6.70−6.73 m, 1H), 4.23 (m, 1H), 3.80 (s, 1H), 3.68 (s, 2H), 2.94 (t, J = 6 Hz, 2H), 2.77−2.82 (m, 4H), 2.62−2.67 (m, 3H), 2.42 (t, J = 6 Hz, 2H), 2.25−2.35 (m, 2H), 1.74−1.87 (m, 7H), 1.19−1.34 (m, 3H), 1.14 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.9, 159.2, 148.8, 142.8, 134.4, 134.1, 129.1, 128.9, 128.7, 128.6, 127.4, 126.9, 126.8, 126.3, 126.1, 122.1, 116.2, 110.8, 62.1, 58.2, 55.6, 54.1, 51.1, 50.5, 45.6, 44.0, 37.9, 36.8, 36.7, 35.3, 34.0, 33.0, 29.7, 29.2, 28.3, 26.8; LCMS (ESI): *m/z* 580.9 $[M + H]^+$.

3-(3,4-Dihydro-1H-isoquinolin-2-yl)-*N*-[4a-(3-hydroxyphenyl)-8a-methyl-2-(3-phenylpropyl)octahydroisoquinolin-6-yl]propionamide (6e) Dihydrochloride. 25b (70 mg, 0.120 mmol) was dissolved in anhydrous CH_2Cl_2 (15 mL), cooled to −78 °C, and added slowly to a 1.0 M solution of BBr_3 (0.60 mL, 0.60 mmol) in CH_2Cl_2. The reaction mixture was allowed to stir at −78 °C for 30 min and at room temperature for 1.5 h. The reaction mixture was cooled to 0 °C, quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to afford crude product. The crude product was purified by flash chromatography (30% CMA-80 in CH_2Cl_2) to afford 60 mg (88%) of **6e** as a white solid: ^1H NMR ($CDCl_3$) δ 8.55 (d, J = 6 Hz, 1H), 7.05−7.31 (m, 12H), 6.66−6.69 (m, 1H), 4.28 (m, 1H), 3.68 (s, 2H), 2.94 (t, J = 6 Hz, 2H), 2.78−2.83 (m, 4H), 2.61−2.66 (3H), 2.45 (t, J = 6 Hz, 2H), 2.23−2.34 (m, 3H), 2.02−2.13 (m, 2H), 1.69−1.80 (m, 8H), 1.251.32 (m, 3H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.2, 156.0, 148.6, 142.8, 134.3, 134.1, 129.1, 128.9, 126.6, 126.9, 126.3, 126.1, 121.1, 116.8, 113.2, 62.1, 58.2, 55.6, 54.0, 51.0, 50.4, 45.7, 43.9, 37.7, 36.8, 36.6, 35.2, 34.0, 32.8, 29.6, 29.1, 28.2, 27.0; LCMS (ESI): *m/z* 566.5 $[M + H]^+$.

An analytical sample of the dihydrochloride salt was prepared by dissolving the free base in MeOH and adding 6 equiv of 1.0 M HCl in Et_2O. The removal of the solvent under reduced pressure afforded the dihydrochloride salt as a white solid, which was recrystallized from a mixture of MeOH−EtOAc: mp 178−180 °C (fus.). Anal. ($C_{37}H_{49}Cl_2N_3O_2 \cdot 2H_2O$) C, H, N.

1-Phenylcyclopentanecarboxylic Acid [4a-(3-Methoxyphenyl)-8a-methyl-2-(3-phenylpropyl)octahydroisoquinolin-6-yl]amide (25c). To **24** (71 mg, 0.180 mmol) dissolved in anhydrous THF (15 mL) was added 1-phenyl-1-cyclopentanecarboxylic acid (51 mg, 0.27 mmol), Et_3N (0.126 mL, 0.904 mmol), and BOP reagent (88 mg, 0.20 mmol), and the reaction mixture was allowed to stir at room temperature for 2 h. The reaction progress was monitored by TLC (30% CMA-80 in CH_2Cl_2). The reaction mixture was diluted with EtOAc (25 mL) and washed with saturated aqueous $NaHCO_3$ (25 mL) followed by H_2O (25 mL). The aqueous layers were back extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with 1 N NaOH (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford crude product. The crude product was purified by flash chromatography (25% CMA-80 in CH_2Cl_2) to afford 94 mg (92%) of **25c**: ^1H NMR ($CDCl_3$) δ 7.17−7.36 (m, 13H), 6.71−6.73 (m, 1H), 4.92 (d, J = 6 Hz, 1H), 4.19 (m, 1H), 3.79 (s, 3H), 2.74 (br, 1H), 2.62−2.64 (m, 2H), 2.33−2.45 (m, 5H), 2.10−2.31 (m, 2H), 1.98−2.09 (m, 3H), 1.61−1.84 (m, 10H), 1.46 (d, J = 12 Hz, 1H), 1.20−1.33 (m, 2H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 176.1, 159.2, 148.9, 144.8, 142.8, 129.0, 128.9, 128.7, 128.6, 127.2, 127.1, 126.0, 121.9, 116.3, 110.7, 62.2, 59.6, 58.2, 55.5, 51.2, 46.2, 44.2, 37.8, 37.4, 37.2, 36.9, 36.6, 35.6, 33.9, 29.2, 28.1, 26.6, 24.4; LCMS (ESI): *m/z* 565.6 $[M + H]^+$.

1-Phenylcyclopentanecarboxylic Acid [4a-(3-Hydroxyphenyl)-8a-methyl-2-(3-phenylpropyl)octahydroisoquinolin-6-yl]amide (6f) Hydrochloride. Compound **25c** (94 mg, 0.166 mmol) was dissolved in anhydrous CH_2Cl_2 (15 mL), cooled to −78 °C, and added slowly to a 1.0 M solution of BBr_3 (0.832 mL, 0.832 mmol) in CH_2Cl_2. The reaction mixture was allowed to stir at −78 °C for 30 min and at room temperature for 1.5 h. The reaction mixture was cooled to 0 °C, quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to afford crude product. The crude product was purified by flash chromatography (30% CMA-80 in CH_2Cl_2) to afford 78 mg (86%) of **6f** as a white solid: ^1H NMR ($CDCl_3$) δ 7.09−7.34 (m, 14 H), 6.68−6.70 (br, 1H), 5.06 (d, J = 9 Hz, 1H), 4.26 (m, 1H), 2.71 (br, 1H), 2.61−2.64 (m, 2H), 2.35−2.45 (m, 5H), 2.00−2.10 (m, 5H), 1.63−1.98 (m, 10H), 1.41 (d, J = 12 Hz, 1H), 1.18−1.23 (m, 2H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 176.7, 156.2, 148.5, 144.5, 142.7, 129.1, 128.9, 128.7, 128.6, 127.3, 127.2, 126.0, 121.3, 116.8, 113.3, 62.1, 59.6, 58.2, 51.1, 46.4, 44.0, 37.5, 37.4, 37.3, 36.9, 36.6, 35.4, 33.9, 29.0, 28.0, 26.8, 24.4; LCMS (APCI): *m/z* 551.2 $[M + H]^+$.

An analytical sample of the hydrochloride salt was prepared by dissolving the free base in MeOH and adding 3 equiv of 1.0 M HCl in Et_2O. The removal of the solvent under reduced pressure afforded the hydrochloride salt as a white solid, which was recrystallized from a MeOH−EtOAc combination: mp 194−195 °C (fus.). Anal. ($C_{37}H_{47}ClN_3O_2 \cdot 0.75H_2O$) C, H, N.

Benzo[*b*]thiophene-2-carboxylic Acid [4a-(3-Methoxyphenyl)-8a-methyl-2-(3-phenylpropyl)octahydroisoquinolin-6-yl]amide (25d). To **24** (52 mg, 0.132 mmol) dissolved in anhydrous THF (10 mL) was added benzo[*b*]thiophene-2-carboxylic acid (35 mg, 0.198 mmol), Et_3N (0.092 mL, 0.662 mmol), and BOP reagent (64 mg, 0.145 mmol), and the reaction mixture was allowed to stir at room temperature for 1.5 h. The reaction was monitored by TLC (30% CMA-80 in CH_2Cl_2). The reaction mixture was diluted with EtOAc (20 mL) and washed with saturated aqueous $NaHCO_3$ (20 mL) followed by H_2O (20 mL). The aqueous layers were back extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with 1 N NaOH (25 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford crude product. The crude product was purified by flash chromatography (20% CMA-80 in CH_2Cl_2) to afford 70 mg (96%) of **25d**: ^1H NMR ($CDCl_3$) δ 7.74−7.81 (m, 3H), 7.36−7.40 (m, 2H), 7.18−7.31 (m, 7H), 6.74−6.75 (m, 1H), 6.12 (d, J = 9 Hz, 1H), 4.47 (m, 1H), 3.81 (s, 3H), 2.76−2.79 (br, 1H), 2.59−2.67 (m, 3H), 2.36−2.39 (m, 2H), 2.15−2.29 (m, 4H), 1.89−1.94 (m, 3H), 1.60−1.81 (m, 4H), 1.53 (d, J = 12 Hz, 1H), 1.26−1.32 (m 1H), 1.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.9, 159.3, 148.7, 142.8, 141.2, 139.5, 139.2, 128.9, 128.8, 128.7, 126.6, 126.1, 125.3, 125.2, 123.1, 122.0, 116.4, 110.8, 62.3, 58.3, 55.6, 51.2, 47.1, 44.4, 38.1, 37.0, 36.8, 35.6, 34.0, 29.2, 28.3, 26.7; LCMS (ESI): *m/z* 553.9 $[M + H]^+$.

Benzo[*b*]thiophene-2-carboxylic Acid [4a-(3-Hydroxyphenyl)-8a-methyl-2-(3-phenylpropyl)octahydroisoquin-

olin-6-yl]amide (6 g) Hydrochloride. Compound **25d** (70 mg, 0.260 mmol) was dissolved in anhydrous CH_2Cl_2 (15 mL), cooled to −78 °C, and slowly added to a 1.0 M solution of BBr_3 (0.633 mL, 0.633 mmol) in CH_2Cl_2. The reaction mixture was allowed to stir at −78 °C for 30 min and at room temperature for 1.5 h. The reaction was cooled to 0 °C, quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to afford crude product. The crude product was purified by flash chromatography (25% CMA-80 in CH_2Cl_2) to afford 60 mg (88%) of **6g** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.77−7.81 (m, 3H), 7.37−7.41 (m, 2H), 7.25−7.27 (m, 3H), 7.12−7.19 (m, 5H), 6.73−6.76 (m, 1H), 6.27 (d, J = 12 Hz, 1H), 4.48 (m, 1H), 2.74 (m, 1H), 2.58−2.65 (m, 3H), 2.36−2.38 (m, 2H), 2.15−2.26 (m, 4H), 1.78−1.86 (m, 5H), 1.56−1.70 (m, 1H), 1.47 (d, J = 12 Hz, 1H), 1.21−1.23 (m, 2H), 1.19 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.0, 155.8, 148.2, 142.4, 140.9, 139.2, 138.6, 128.6, 128.4, 126.4, 125.8, 125.3, 125.1, 125.0, 122.8, 121.3, 116.5, 113.2, 61.9, 58.0, 50.8, 47.0, 43.9, 37.5, 36.7, 36.4, 35.2, 33.6, 28.7, 27.9, 26.4; LCMS (APCI): m/z 539.3 $[M + H]^+$.

An analytical sample of the hydrochloride salt was prepared by dissolving the free base in MeOH and adding 3 equiv of 1.0 M HCl in Et_2O. The removal of solvent under reduced pressure afforded the hydrochloride salt as a white solid, which was recrystallized from a mixture of MeOH−EtOAc: mp 206−208 °C (fus.). Anal. ($C_{34}H_{39}Cl_2N_2O_2S\cdot0.75H_2O$) C, H, N.

X-ray Crystal Structure of 6a and 23. Single-crystal X-ray diffraction data on **6a** and **23** were collected at 293 and 233 K, respectively, using Cu Kα radiation and a Bruker SMART 6000 CCD area detector. Corrections were applied for Lorentz, polarization, and absorption effects. Data were 96.0% complete to 66.91° θ (**6a**) and 94.7% complete to 67.84° θ (**23**). The structures were solved by direct methods and refined by full-matrix least squares on F^2 values using the programs found in the SHELXTL suite (Bruker, SHELXTL v6.10, 2000, Bruker AXS Inc., Madison, WI). The parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms on carbons were included using a riding model [coordinate shifts of C applied to H atoms] with the C−H distance set at 0.96 Å except for the amine (H3A) and hydroxyl (H3′) hydrogens in **6a**. For these atoms, the coordinates were refined, and the isotropic displacement parameter was set to 1.2× the isotropic displacement parameter of the parent atom.

Pharmacological Methods. Determination of Intrinsic Activity. Test compounds were assayed for their ability to stimulate [^{35}S]GTP-γ-S binding in CHO cell membrane homogenates expressing either the human μ, κ, or δ opioid receptor. The compounds were assayed in triplicate at 1 and 10 μM in 1.4-mL polypropylene tubes (Marix Tecnologies, Hudson, NH) in a 96-well format. The subtype selective agonists DAMGO (μ receptor), DPDPE (δ receptor), or U69,593 (κ receptor) were run as positive controls as appropriate. The membranes were incubated with a positive control or the test compound, 0.1 nM [^{35}S]GTP- γ-S and 1 μM GDP in 50 mM HEPES buffer (pH 7.4) at room temperature for 1 h, after which bound radioligand was separated from free radioligand via rapid vacuum filtration over GF-B filters with a Brandel Scientific (Gaithersburg, MD) 96-well harvester. Bound radioactivity was determined using a TopCount 12-detector instrument (Packard Instruments) using standard scintillation counting techniques. The data were normalized to samples containing vehicle (basal binding). Dose-response curves were run on any compound stimulating basal more than 50% at 10 μM.

Determination of K_es. The ability of a single concentration of test compound to shift the agonist dose-response curve to the right was used to determine its K_e. Assay conditions were identical to those for the determination of intrinsic activity except that the final GDP concentration was 10 μM. The EC_{50}'s were calculated from a three-parameter logistic curve fit to the data with Prism (version 3.0, GraphPad Software, Inc., San Diego, CA). The EC_{50} values for Agonist (A) and agonist + test compound (A′) were used to calculate the test compound K_e from the formula: $K_e = [L]/(DR - 1)$, where [L] equals the concentration of test compound in the assay and DR equals the dose ratio or A′/A. A′ was used only when it was at least 2-fold greater than A.

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Supporting Information Available: Crystal data, structural refinement analysis, atomic coordinates, bond lengths, bond angles, anisotropic displacement parameters, hydrogen coordinates, and isotropic displacement parameters of **6a**·HCl and **23**. Elemental analysis data for **6a**−**g** and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Aldrich, J. V. Narcotic Analgesics. In *Burger's Medicinal Chemistry and Drug Discovery*, 6th ed.; Abraham, D. J., Ed.; John Wiley & Sons: New York, 2003; Vol. 6, Chapter 7.
(2) Kreek, M. J.; LaForge, K. S.; Butelman, E. Pharmacotherapy of addictions. *Nat. Rev. Drug Discovery* **2002**, *1*, 710−726.
(3) Jones, R. M.; Hjorth, S. A.; Schwartz, T. W.; Portoghese, P. S. Mutational Evidence for a Common κ Antagonist Binding Pocket in the Wild-Type κ and Mutant μ[K303E] Opioid Receptors. *J. Med. Chem.* **1998**, *41*, 4911−4914.
(4) Jones, R. M.; Portoghese, P. S. 5′-Guanidinonaltrindole, a highly selective and potent κ-opioid receptor antagonist. *Eur. J. Pharmacol.* **2000**, *396*, 49−52.
(5) Portoghese, P. S.; Lipkowski, A. W.; Takemori, A. E. Binaltorphimine and nor-binaltorphimine, potent and selective κ-opioid receptor antagonists. *Life Sci.* **1987**, *40*, 1287−1292.
(6) Stevens, W. C., Jr.; Jones, R. M.; Subramanian, G.; Metzger, T. G.; Ferguson, D. M.; Portoghese, P. S. Potent and Selective Indolomorphinan Antagonists of the Kappa-Opioid Receptor. *J. Med. Chem.* **2000**, *43*, 2759−2769.
(7) Thomas, J. B.; Mascarella, S. W.; Rothman, R. B.; Partilla, J. S.; Xu, H.; McCullough, K. B.; Dersch, C. M.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. Investigation of the N-Substituent Conformation Governing Potency and μ Receptor Subtype-Selectivity in (+)-(3*R*,4*R*)-Dimethyl-4-(3-hydroxyphenyl)piperidine Opioid Antagonists. *J. Med. Chem.* **1998**, *41*, 1980−1990.
(8) Thomas, J. B.; Fall, M. J.; Cooper, J. B.; Rothman, R. B.; Mascarella, S. W.; Xu, H.; Partilla, J. S.; Dersch, C. M.; McCullough, K. B.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. Identification of an Opioid κ Receptor Subtype-Selective N-Substituent for (+)-(3*R*,4*R*)-dimethyl-4-(3-hydroxyphenyl)-piperidine. *J. Med. Chem.* **1998**, *41*, 5188−5197.
(9) Thomas, J. B.; Atkinson, R. N.; Vinson, N. A.; Catanzaro, J. L.; Perretta, C. L.; Fix, S. E.; Mascarella, S. W.; Rothman, R. B.; Xu, H.; Dersch, C. M.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. Identification of (3*R*)-7-Hydroxy-*N*-((1*S*)-1-[[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-2-methylpropyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide as a Novel Potent and Selective Opioid κ Receptor Antagonist. *J. Med. Chem.* **2003**, *46*, 3127−3137.
(10) Thomas, J. B.; Atkinson, R. N.; Rothman, R. B.; Fix, S. E.; Mascarella, S. W.; Vinson, N. A.; Xu, H.; Dersch, C. M.; Lu, Y.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. Identification of the First *trans*-(3*R*, 4*R*)-Dimethyl-4-(3-hydroxyphenyl)piperidine Derivative to Possess Highly Potent and Selective Opioid κ Receptor Antagonist Activity. *J. Med. Chem.* **2001**, *44*, 2687−2690.
(11) Zimmerman, D. M.; Nickander, R.; Horng, J. S.; Wong, D. T. New structural concepts for narcotic antagonists defined in a 4-phenylpiperidine series. *Nature* **1978**, *275*, 332−334.
(12) Zimmerman, D. M.; Leander, J. D.; Cantrell, B. E.; Reel, J. K.; Snoddy, J.; Mendelsohn, L. G.; Johnson, B. G.; Mitch, C. H. 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.
(13) Zimmerman, D. M.; Gidda, J. S.; Cantrell, B. E.; Schoepp, D. D.; Johnson, B. G.; Leander, J. D. 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.
(14) Schmidt, W. K. Alvimopan (ADL 8−2698) Is a Novel Peripheral Opioid Antagonist. *Am. J. Surg.* **2001**, *182*, 27S−38S.

(15) Leone, N.; Wentz, L. News Release from Adolor Corporation—FDA Accepts Entereg(TM) (alvimopan) New Drug Application (NDA) for Review. http://phx.corporate-ir.net/phoenix.zhtml?c=120919&p=irol-newsArticle&t=Regular&id=611171& (2004).
(16) Mitch, C. H.; Leander, J. D.; Mendelsohn, L. G.; Shaw, W. N.; Wong, D. T.; Cantrell, B. E.; Johnson, B. G.; Reel, J. K.; Snoddy, J. D.; Takemori, A. E.; Zimmerman, D. M. 3,4-Dimethyl-4-(3-hydroxyphenyl)piperidines: Opioid Antagonists with Potent Anorectant Activity. *J. Med. Chem.* **1993**, *36*, 2842−2850.
(17) Statnick, M. A.; Suter, T. M.; Gackenheimer, S. L.; Emmerson, P. J.; Quimby, S. J.; Gehlert, D. R.; Wheeler, W. J.; Mitch, C. H. Na^+-dependent high affinity binding of [^{3}H]LY515300, a 3,4-dimethyl-4-(3-hydroxyphenyl)piperidine opioid receptor inverse agonist. *Eur. J. Pharmacol.* **2003**, *482*, 139−50.
(18) Carroll, F. I.; Thomas, J. B.; Dykstra, L. A.; Granger, A. L.; Allen, R. M.; Howard, J. L.; Pollard, G. T.; Aceto, M. D.; Harris, L. S. Pharmacological properties of JDTic: a novel κ-opioid receptor antagonist. *Eur. J. Pharmacol.* **2004**, *501*, 111−119.
(19) Thomas, J. B.; Atkinson, R. N.; Namdev, N.; Rothman, R. B.; Gigstad, K. M.; Fix, S. E.; Mascarella, S. W.; Burgess, J. P.; Vinson, N. A.; Xu, H.; Dersch, C. M.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. Discovery of an Opioid κ Receptor Selective Pure Antagonist from a Library of N-Substituted 4β-Methyl-5-(3-hydroxyphenyl)morphans. *J. Med. Chem.* **2002**, *45*, 3524−3530.
(20) Thomas, J. B.; Zheng, X.; Mascarella, S. W.; Rothman, R. B.; Dersch, C. M.; Partilla, J. S.; Flippen-Anderson, J. L.; George, C. F.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. N-Substituted 9β-Methyl-5-(3-hydroxyphenyl)morphans Are Opioid Receptor Pure Antagonists. *J. Med. Chem.* **1998**, *41*, 4143−4149.
(21) Casy, A. F.; Dewar, G. H.; Al-Deeb, O. A. A. Stereochemical influences upon the opioid ligand activities of 4-alkyl-4-arylpiperidine derivatives. *Chirality* **1989**, *1*, 202−208.
(22) Casy, A. F.; Dewar, G. H.; Al-Deeb, O. A. A. Stereochemical studies of the 4-alkyl-4-arylpiperidine class of opioid ligand. *Magn. Reson. Chem.* **1989**, *27*, 964−972.
(23) Zimmerman, D. M.; Cantrell, B. E.; Swartzendruber, J. K.; Jones, N. D.; Mendelsohn, L. G.; Leander, J. D.; Nickander, R. C. Synthesis and Analgesic Properties Of N-Substituted *trans*-4a-Aryldecahydroisoquinolines. *J. Med. Chem.* **1988**, *31*, 555−560.
(24) Awaya, H.; May, E. L.; Aceto, M. D.; Merz, H.; Rogers, M. E.; Harris, L. S. Racemic and Optically Active 2,9-Dimethyl-5-(*m*-hydroxyphenyl)morphans and Pharmacological Comparison with the 9-Demethyl Homologues. *J. Med. Chem.* **1984**, *27*, 536−539.
(25) Hashimoto, A.; Jacobson, A. E.; Rothman, R. B.; Dersch, C.; George, C. F.; Flippen-Anderson, J. L.; Rice, K. Probes for Narcotic Receptor Mediated Phenomena. Part 28: New Opioid Antagonists from Enantiomeric Analogues for 5-(3-Hydroxyphenyl)-*N*-phenylethylmorphan. *Bioorg. Med. Chem.* **2002**, *10*, 3319−3329.
(26) Awaya, H.; May, E. L.; Aceto, M. D.; Harris, L. S.; Silverton, J. V.; Rice, K. C.; Mattson, M. V.; Jacobson, A. E. Hexahydro-1*H*-1-pyrindines from Acid Rearrangement of 9-Alkylidene-5-(*m*-methoxyphenyl)-2-methylmorphans. A New Structural Type of Narcotic Antagonists. *J. Med. Chem.* **1987**, *30*, 947−950.
(27) Portoghese, P. S.; Takemori, A. E. Different Receptor Sites Mediate Opioid Agonism and Antagonism. *J. Med. Chem.* **1983**, *26*, 1341−1343.
(28) Nogrady, T. *Medicinal Chemistry: A Biochemical Approach*; Oxford University Press: New York, 1985; p 68.
(29) Carroll, F. I.; Zhang, L.; Mascarella, S. W.; Navarro, H. A.; Rothman, R. B.; Cantrell, B. E.; Zimmerman, D. M.; Thomas, J. B. Discovery of the First N-Substituted 4β-Methyl-5-(3-hydroxyphenyl)morphan to Possess Highly Potent and Selective Opioid δ Receptor Antagonist Activity. *J. Med. Chem.* **2004**, *47*, 281−284.
(30) CAUTION: See Meyers, A. I.; Schwartzman, S.; Olson, G. L.; Cheung, H.-C. *Tetrahedron Lett.* **1976**, 2417.

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