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

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Abstract

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 the lower potential energy relative to the axial conformation. Evaluation of compounds **6a–g** in the [³⁵S]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 selectively relative to the μ and δ receptors, respectively, possessed the best combination of κ potency and selectivity.

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, naloxone (**1a**) is approved for treating heroin overdose and to reverse respiratory depression caused by morphine.² Naltrexone (**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** lead to the discovery of the δ opioid receptor selective antagonist naltrindole (NTI, **2a**) and the κ opioid receptor antagonists, norbinaltorphimine (**3**, norBNI) 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 antagonist. Unlike other antagonists, including the oxymorphone class, antagonist activity was not

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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, **4b**), 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-4- β -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 7 α -amino-3-(1-piperidinyl)propionyl group gave **5b** which was a potent and selective kappa opioid receptor antagonist.^{19,20} While compounds **1–5** have proven highly useful in helping 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 [³⁵S]GTP- γ -S functional assay with several analogues showing preference for the κ opioid receptor.

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*-butyl lithium 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** and **6c**) 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** and **6c**.

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-butyl lithium 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**. 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 dimethylsulfoxide 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 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 **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 units of kcal/mol) and dihedral angle around the 4-4a bond. The lowest energy phenyl axial (4-4a dihedral $\approx \pm 60^\circ$ and phenyl equatorial (4-4a dihedral $\approx \pm 80^\circ$) 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-Ala²,MePhe⁴,Gly-ol⁵)enkephalin] (selective for μ opioid receptor), DPDPE [cyclo[D-Pen², D-Pen⁵]enkephalin] (selective for δ opioid receptor) and U69,593 {(5 α , 7 α , 8 β)-(-)-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 test compound. The K_e values were calculated using the formula: $K_e = [L]/[(A'/A)-1]$, where [L] is the concentration of antagonist and A' and A the agonist EC₅₀ value in the presence or absence of antagonist, respectively. The results, along with reference compounds JD₁Tic, norBNI, naltrexone, and **4c** are listed in Table 1.

Compounds **6a–g** were tested at 10 μ M for agonist activity at the μ , δ , and κ opioid receptors. Similar to reference compounds JD₁Tic, 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 to 41.7, 1.01 to 18.9, and 0.22 to 2.84 nM at the μ , δ , and κ receptors, respectively. Compounds **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. While 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 the N-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (**4**). The N-substituted *cis*-4a-(3-hydroxyphenyl)-8a-methyloctahydroisoquinolines (**6a–g**) presented in this study 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 compounds **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** (Figure 1 and Figure 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. Compound **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 compound **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 compounds **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 = CH₃), was reported to be an opioid agonist with twice the potency of morphine in the mouse-tail flick and writhing analgesic 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 compounds **6a–g** in the in vitro [³⁵S]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 a 10 μM concentration. 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 = CH₃). 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 compounds **6b** and **6c**). 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 antagonist operating via a 3-(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 other members of this family since it showed some preference for the κ receptor relative to the μ and δ receptors. The potency shift typical with larger N-substituents in this case serves to level the potency among the opioid receptors. It may be that the bridging ring in **6a** interacts with a lipophilic 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 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 compound **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 analog **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 like **27** and **28**, but lacking a 4 β or 9 β methyl group are antagonists if the N-substituent is larger than methyl (phenylethyl or phenylpropyl).²⁵ Even earlier work by Awaya and May²⁴ showed weak antagonism in 9 α -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 4 β methyl group in the **27** series and the 9 β 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 groups interaction with an excluded volume in the agonist domain, or perhaps may be acting as an “accessory 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** illustrates 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 4 β -methyl-5-(3-hydroxyphenyl)morphans series by attaching suitable address elements onto non-selective scaffolds.^{9,19} For example, we found that the addition of a 7 α -(2-piperidinylethylamido) group to the N-phenylpropyl-4 β -methyl-5-(3-hydroxyphenyl)morphans (**4a**) to give **4b** resulted in an enhanced potency and selectivity for the κ opioid receptor.¹⁹ In this study, the addition of a 6 α -(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 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, potency at the μ and δ receptor 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 6 α -[7-(1-phenyl-1-cyclopentyl)]amido group to **6d** to give **6f** did not result in 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 SAR suggest that they are related to the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine class of opioid antagonist. Addition of a 6-amido address group possessing an amino function to the core structure provides compounds with increased selectivity for the κ opioid receptor relative to the μ and δ opioid receptors that retain high κ potency. The most potent and κ selective analog 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 4 β -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

¹H NMR spectra were determined on a Bruker 300 spectrometer using tetramethylsilane as an internal standard. Mass spectral data was obtained using a Finnegan LCQ electrospray mass spectrometer in 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 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 Company 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). [³⁵S]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 compounds **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) *s*-BuLi (1.3M 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 Et₂O 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 Et₂O and ice-cold 1 N HCl. The aqueous layer was removed and stored in an ice bath, while 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 Et₂O. The aqueous layer was made basic with 50% NaOH to pH

10. The aqueous layer was extracted 3× with ice-cold Et₂O. The Et₂O extracts were dried (K₂CO₃), filtered, and the solvent removed at 0 °C. The resulting residue was dissolved in 40 mL of dry CH₃CN, and to this was added 3.91 g (0.027 mol) of NaI and 2.89 g (0.021 mol) of K₂CO₃. 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 dissolved in 100 mL of EtOH. To this mixture was added 3.35 g (0.089 mol) of NaBH₄ in one portion and the mixture 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 H₂O were added until the mixture was clear and basic. The volatiles were removed on a rota-evaporator, and the residue was extracted with CH₂Cl₂. The organic layer was dried over anhydrous Na₂SO₄. Removal of solvent on a rota-evaporator yielded crude product, which was purified by chromatography on alumina using 15% EtOAc-hexanes as the eluent, gave 2.1 g (76%) of desired product **9** as a colorless viscous oil: ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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** and 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 CH₂Cl₂. The organic extracts were dried (Na₂SO₄), 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 eq of 1 N HCl in dry Et₂O to give the hydrochloride salt: mp 291–293 °C; ¹H NMR (DMSO-d₆) 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); ¹³C NMR (DMSO-d₆) 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. (C₁₇H₂₆ClNO•0.75H₂O) C, H, N.

4a-(3-Methoxyphenyl)-8a-methyloctahydroisoquinoline (10)

To a solution of 430 mg (1.59 mmol) of **9** in anhydrous CH₂Cl₂ (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 NaHCO₃ solution, H₂O, the organic layer evaporated, and the resulting oil 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 NaHCO₃ solution. The mixture was extracted with 3:1, CH₂Cl₂-THF, and the combined organic extracts were washed once with H₂O. Removal of a solvent provided 0.36 g (89%) of crude **10** as a yellow oil: ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 190 mg (0.72 mmol) of **10** were mixed in CH₂Cl₂ (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 N₂ 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 190 mg (0.75 mmol) of **10** were mixed in CH_2Cl_2 (15 mL) and then treated with sodium triacetoxymethylborohydride 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** and 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 $\times$ 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 eq of 1 N HCl in dry Et_2O to give the hydrochloride salt as a white crystalline solid: mp 226–228 $^\circ\text{C}$; ^{13}C NMR ($\text{DMSO}-d_6$) 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. ($\text{C}_{24}\text{H}_{32}\text{ClNO}\cdot 0.5\text{H}_2\text{O}$) 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** and 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 $\times$ 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 eq of 1 N HCl in dry Et_2O to give the hydrochloride salt as a white crystalline solid: mp 262–264 $^\circ\text{C}$; ^1H 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. ($\text{C}_{25}\text{H}_{34}\text{ClNO}\cdot 0.5\text{H}_2\text{O}$) C, H, N.

Tetrahydro-2-(oxiranylethoxy)-2H-pyran (13).³⁰

To a chilled solution (0 $^\circ\text{C}$) of 3,4-dihydro-2H-pyran (117 g, 1.4 mol) in anhydrous Et_2O (600 mL) were added *p*-toluenesulfonic 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: ^1H NMR (CDCl_3) δ 5.80–5.89 (m, 1H, =CH-C), 5.02–5.06 (m overlapping, 2H, =CH₂), 4.59–4.60 (m, 1H, 2-H of THP), 3.77–3.83 (m, 2H, -CH₂O), 3.44–3.50 (m, 2H, CH₂O of THP), 2.33–2.38 (m, 2H, CH₂-CH=CH₂), 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), respectively; 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: ^1H 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 = 3Hz, 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 extracted with Et_2O -EtOAc (1:1, 3 $\times$ 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%): ^1H 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 triphenylphosphine (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 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 homogenous brownish black). After this time, MeOH (50 mL) was added dropwise and the mixture concentrated. The residue was partitioned

between cold Et₂O (500 mL) and cold 1 N NaOH (500 mL). The organic layer was further washed with H₂O (400 mL), dried over anhydrous K₂CO₃ and concentrated to afford semisolid material. The residue obtained was dissolved in a minimum amount of CHCl₃ and further diluted with hexane until precipitation of triphenylphosphine oxide was observed. 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: ¹H NMR (CDCl₃) 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) were stirred under a nitrogen atmosphere at ambient temperature for 1 h, poured into a mixture of ice (300 g) and 50% aqueous NaOH (50 mL) sufficient to make the solution strongly basic and the product extracted into cold Et₂O (400 mL). The ether layer was washed once with cold H₂O, dried over anhydrous K₂CO₃ 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 CH₃CN (200 mL) and heated at reflux over K₂CO₃ (12 g) for 3 h under a N₂ atmosphere. Upon cooling, the solution was filtered, concentrated and the residue taken up in dry MeOH (200 mL). The solution was cooled to 0 °C whereupon NaBH₄ (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 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 Et₂O-EtOAc (200 mL) and H₂O (200 mL). The aqueous phase was further extracted with a 1:1 mixture of Et₂O-EtOAc (2× 100 mL) and the combined organic layers were dried over anhydrous K₂CO₃-Na₂SO₄, 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%): ¹H-NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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-oxooctahydroisoquinoline (18)

Into a dry flask containing oxalyl chloride (3.45 mL, 6.9 mmol, 2.0 M solution in CH₂Cl₂) in CH₂Cl₂ (15 mL) cooled to –70 °C was added DMSO (0.83 mL, 11.7 mmol) in CH₂Cl₂ (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 compound **17** in CH₂Cl₂ was added over 30 min. After an additional 30 min at –70 °C, Et₃N (1.11 mL, 7.98 mmol) was added and the solution warmed to room temperature, washed with saturated aqueous NaHCO₃ (100 mL), dried over Na₂SO₄, concentrated and purified via flash chromatography (4% MeOH-CHCl₃) to afford 1.40 g (92%) of **18**: ¹H NMR (CDCl₃) δ 7.18 (t, J 13 = 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); ¹³C NMR (CDCl₃) 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-oxooctahydroisoquinolin Oxime (19)

N-Methyl-4a-(3-methoxyphenyl)-8a-methyl-6-oxooisoquinoline (**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 CH₂Cl₂-THF (4 × 50 mL). The combined organic layers were dried (Na₂SO₄), 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-methyloctahydroisoquinoline (20)

A slurry of oxime **19** (2.35 g, 0.077 mol) in anhydrous (CH₃)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, so 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 careful addition of H₂O (250 mL). The toluene layer was separated and the aqueous layer extracted with EtOAc (3 × 100 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (50% CMA-80 in CHCl₃) to afford 2.11 g (94%) of **20** as a colorless oil: ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 H₂O. The solution was cooled, washed with 1 N NaOH (3 × 50 mL) and H₂O. The organic layer was collected, dried (Na₂SO₄) and the solvent removed under reduced pressure yielding crude product. The crude product was purified by flash chromatography (30% EtOAc-hexanes on neutral Al₂O₃ Brockman activity II-III) to afford 2.22 g (90%) of **21** as a white solid: ¹H NMR (CDCl₃) 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, J₁ = J₂ = 15 Hz, J₃ = 6 Hz, 1H), 1.48–1.58 (m, 3H), 1.33–1.39 (m, 1H), 1.26 (s, 3H); ¹³C NMR (CDCl₃) 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 CH₂Cl₂ (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 NaHCO₃ solution and once with H₂O. The dried (Na₂SO₄) organic layer was evaporated and the resulting carbamate (foamy white solid, almost quantitative yield) was dissolved immediately in MeOH (100 mL) and the solution refluxed overnight. After cooling to room temperature, MeOH was removed under reduced pressure and the residue was treated

with saturated NaHCO₃ solution. This was extracted with 3:1, CH₂Cl₂-THF, and the combined organic extracts were washed once with H₂O and dried (Na₂SO₄). Removal of solvent under reduced pressure afforded 2.01 g (99%) of **22** as a white foamy solid: ¹H NMR (CDCl₃) 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, J₁ = 15 Hz, J₂ = 6 Hz, 2H), 1.31–1.48 (m, 3H), 1.24 (s, 3H); ¹³C NMR (CDCl₃) 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-methyloctahydro-isoquinoline Phthalimide (23)**

Hydrocinnamaldehyde (0.65 mL, 0.0049 mmol) and compound **22** (2.00 g, 0.0049 mol) were mixed in anhydrous CH₂Cl₂ (50 mL) and then treated with sodium triacetoxyborohydride (1.57 g, 0.0074 mol). The reaction mixture remains cloudy throughout the reaction. The mixture was stirred at room temperature under a N₂ atmosphere for 3 h. The reaction was monitored by TLC (20% EtOAc-hexanes; neutral Al₂O₃ Brockman activity II-III). After completion, the reaction mixture was quenched by adding saturated aqueous NaHCO₃, and the product was extracted with EtOAc (3 × 50 mL). The combined EtOAc extracts were dried (MgSO₄), 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 Al₂O₃ Brockman activity II-III) to afford 2.25 g (87%) of **23** as a white shiny solid. The sample used for X-ray analysis was recrystallized from a mixture of hexane and CH₂Cl₂: mp 136–138 °C; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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. (C₃₄H₃₈N₂O₃) 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 taken up in 3:1, CH₂Cl₂-THF (100 mL). The resulting white precipitate was separated by filtration and washed with cold CH₂Cl₂ (50 mL). The combined organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to yield crude product. The crude product was purified by flash chromatography (40% CMA-80 in CHCl₃) to afford 1.45 g (97%) of **24** as a colorless oil: ¹H NMR (CDCl₃) 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, J₁ = J₂ = 9 Hz, J₃ = 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); ¹³C NMR (CDCl₃) 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 compound **24** (105 mg, 0.267 mmol) dissolved in anhydrous THF (15 mL) was added 1-piperidinepropionic acid (63 mg, 0.40 mmol), Et₃N (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. Reaction progress was monitored by TLC (50% CMA-80 in CH₂Cl₂). The reaction mixture was diluted with EtOAc (25 mL) and washed with saturated aqueous NaHCO₃ (25 mL) followed by H₂O (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 (MgSO₄), and concentrated under reduced pressure to afford crude amide. The crude product was purified by flash chromatography (30% CMA-80 in CH₂Cl₂) to afford 121 mg (85%) of **25a** as a shiny white solid: ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 compound **25a** (90 mg, 0.169 mmol), dissolved in anhydrous CH₂Cl₂ (15 mL) and cooled to –78 °C, was added a 1.0 M solution in CH₂Cl₂ of BBr₃ (0.85 mL, 0.85 mmol) slowly. 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 NaHCO₃ and extracted with CH₂Cl₂ (2 × 25 mL). The combined organic layers were washed with 1 N NaOH (25 mL), dried (Na₂SO₄), filtered and concentrated in vacuo to afford crude product. The crude product was purified by flash chromatography (40% CMA-80 in CH₂Cl₂) to afford 75 mg (86%) of **6d** as a white solid: ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 eq of 1.0 M HCl in Et₂O. Removal of the solvent under reduced pressure afforded the dihydrochloride salt as a white solid which was recrystallized from a mixture of MeOH-Et₂O: mp 240–242 °C (fus.). Anal. (C₃₃H₄₉Cl₂N₃O₂•2.75H₂O) 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 compound **24** (80 mg, 0.203 mmol) dissolved in anhydrous THF (15 mL) 3-(3,4-dihydro-1H-isoquinolin-2-yl)-propionic acid hydrochloride (73 mg, 0.305 mmol), and Et₃N (0.142 mL, 1.01 mmol) was added, 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. Reaction progress was monitored by TLC (50% CMA-80 in CH₂Cl₂). The reaction mixture was diluted with EtOAc (25 mL) and washed with saturated aqueous NaHCO₃ (25 mL) followed by H₂O (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 (MgSO₄), and concentrated under reduced pressure to afford crude amide, **25b**. The crude product was purified by flash chromatography (30% CMA-80 in CH₂Cl₂) to afford 94 mg (80%) of **25b** as a shiny white solid: ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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

Compound **25b** (70 mg, 0.120 mmol) was dissolved in anhydrous CH₂Cl₂ (15 mL), cooled to −78 °C, and added to a 1.0 M solution of BBr₃ (0.60 mL, 0.60 mmol) in CH₂Cl₂ slowly. 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 NaHCO₃ and extracted with CH₂Cl₂ (2 × 25 mL). The combined organic layer was dried (Na₂SO₄), filtered and concentrated in vacuo to afford crude product. The crude product was purified by flash chromatography (30% CMA-80 in CH₂Cl₂) to afford 60 mg (88%) of **63** as a white solid: ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 eq of 1.0 M HCl in Et₂O. Removal of 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. (C₃₇H₄₉Cl₂N₃O₂•2H₂O) C, H, N.

1-Phenylcyclopentanecarboxylic Acid [4a-(3-Methoxyphenyl)-8a-methyl-2-(3-phenylpropyl)octahydroisoquinolin-6-yl]amide (25c)

To compound **24** (71 mg, 0.180 mmol) dissolved in anhydrous THF (15 mL) was added 1-phenyl-1-cyclopentanecarboxylic acid (51 mg, 0.27 mmol), Et₃N (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. Reaction progress was monitored by TLC (30% CMA-80 in CH₂Cl₂). The reaction mixture was diluted with EtOAc (25 mL) and washed with saturated aqueous NaHCO₃ (25 mL) followed by H₂O (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 (MgSO₄), and concentrated under reduced pressure to afford crude product. The crude product was purified by flash chromatography (25% CMA-80 in CH₂Cl₂) to afford 94 mg (92%) of **25c**: ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 CH₂Cl₂ (15 mL), cooled to −78 °C, and added to 1.0 M solution of BBr₃ (0.832 mL, 0.832 mmol) in CH₂Cl₂ slowly. 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 NaHCO₃ and extracted with CH₂Cl₂ (2 × 25 mL). The combined organic layer was dried (Na₂SO₄), filtered, and concentrated in vacuo to afford crude product. The crude product was purified by flash chromatography (30% CMA-80 in CH₂Cl₂) to afford 78 mg (86%) of **6f** as a white solid: ¹H NMR (CDCl₃) 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 ($\text{M} + \text{H}$) $^+$.

An analytical sample of the hydrochloride salt was prepared by dissolving the free base in MeOH and adding 3 eq of 1.0 M HCl in Et₂O. 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. ($\text{C}_{37}\text{H}_{47}\text{ClN}_3\text{O}_2 \cdot 0.75\text{H}_2\text{O}$) C, H, N.

Benzo[b]thiophene-2-carboxylic Acid [4a-(3-Methoxyphenyl)-8a-methyl-2-(3-phenylpropyl)octahydroisoquinolin-6-yl]amide (25d)

To compound **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), Et₃N (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 CH₂Cl₂). The reaction mixture was diluted with EtOAc (20 mL) and washed with saturated aqueous NaHCO₃ (20 mL) followed by H₂O (20 mL). The aqueous layers were back extracted with EtOAc (2 $\times$ 20 mL). The combined organic layers were washed with 1 N NaOH (25 mL), dried (MgSO₄), and concentrated under reduced pressure to afford crude product. The crude product was purified by flash chromatography (20% CMA-80 in CH₂Cl₂) 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 ($\text{M} + \text{H}$) $^+$.

Benzo[b]thiophene-2-carboxylic Acid 4a-(3-Hydroxyphenyl)-8a-methyl-2-(3-phenylpropyl)octahydroisoquinolin-6-yl]amide (6g) Hydrochloride

Compound **25d** (70 mg, 0.260 mmol) was dissolved in anhydrous CH₂Cl₂ (15 mL), cooled to –78 °C, and added to 1.0 M solution of BBr₃ (0.633 mL, 0.633 mmol) in CH₂Cl₂ slowly. 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 NaHCO₃, and extracted with CH₂Cl₂ (2 $\times$ 25 mL). The combined organic layer was dried (Na₂SO₄), filtered and concentrated in vacuo to afford crude product. The crude product was purified by flash chromatography (25% CMA-80 in CH₂Cl₂) to afford 60 mg (88%) of **6g** as a white solid: ^1H 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 ($\text{M} + \text{H}$) $^+$.

An analytical sample of the hydrochloride salt was prepared by dissolving the free base in MeOH and adding 3 eq of 1.0 M HCl in Et₂O. 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. ($\text{C}_{34}\text{H}_{39}\text{Cl}_2\text{N}_2\text{O}_2 \cdot 0.75\text{H}_2\text{O}$) C, H, N.

X-Ray Crystal Structure of 6a and 23

Single crystal X-ray diffraction data on compounds **6a** and **23** were collected at 293 and 233 K respectively using CuK α 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). 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 C-H distance set at 0.96 Å except for the amine (H3A) and hydroxyl (H3') hydrogens in compound **6a**. For these atoms, the coordinates were refined and the isotropic displacement parameter set to $1.2 \times$ 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 μ M in 1.4 mL polypropylene tubes (Marix Technologies, Hudson, NH) in 96-well format. The subtype selective agonists (D-Ala²,MePhe⁴,Gly-ol⁵)enkephalin (DAMGO, μ receptor), (D-Pen²,D-Pen⁵)enkephalin (DPDPE, δ receptor) or U69,593 (κ receptor) were run as positive controls as appropriate. The membranes were incubated with positive control or test compound, 0.1 nM [35 S]GTP- γ -S and 1 μ M GDP in 50 mM HEPES buffer (pH 7.4) at room temperature for one hour, after which bound radioligand was separated from free 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 μ M.

Determination of apparent affinity (K_e). 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 that for the determination of intrinsic activity except that the final GDP concentration was 10 μ M. The EC₅₀s were calculated from a three-parameter logistic curve fit to the data with Prism (version 3.0, GraphPad Software, Inc., San Diego, CA). The EC₅₀ 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. The A' was used only when it was at least 2-fold greater than A.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

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

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

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

Scheme 1.

Scheme 2.

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

Compd	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		

^aThe data represent the mean ± SE from at least three independent experiments. The final GDP assay concentration was 10 μM.

^bTaken from ref. 18.