Probes for Narcotic Receptor-Mediated Phenomena. 20. Alteration of Opioid Receptor Subtype Selectivity of the 5-(3-Hydroxyphenyl)morphans by Application of the Message–Address Concept: Preparation of δ-Opioid Receptor Ligands

Craig M. Bertha, Judith L. Flippen-Anderson,§ Richard B. Rothman,† Frank Porreca,‡ Peg Davis,‡ Heng Xu,† Karen Becketts,† Xian-Yuan Cha,† and Kenner C. Rice*

Laboratory of Medicinal Chemistry, Building 8, Room B1-23, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892, Laboratory for the Structure of Matter, Naval Research Laboratory, Code 6030, Washington, D.C. 20375, Clinical Psychopharmacology Section, National Institute on Drug Abuse, Addiction Research Center, Baltimore, Maryland 21224, and Department of Pharmacology, University of Arizona Health Science Center, 1501 North Campbell Avenue, Tucson, Arizona 85724

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Derivatives of racemic and optically active 5-(3-hydroxyphenyl)-2-methylmorphan (5-(3-hydroxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonane, **1**) were synthesized containing additional aromatic moieties, as an application of the message–address concept targeted at producing δ-opioid receptor selective ligands. *In vitro* radioreceptor binding studies in rat brain revealed that both of the parent enantiomers, (−)- and (+)-**1**, had a high affinity for the μ-opioid receptor (21 nM), a slight affinity for κ_1-opioid receptors (~800–900 nM), and less than 1000 nM affinity for the δ-opioid receptor (μ/δ IC_{50} ratio of <0.02 for both). A derivative of (−)-**1** containing an indole moiety fused at the C6–C7 position of the phenylmorphan nucleus, (−)-**11**, displayed a >180-fold increase in affinity for the δ-opioid receptor with an IC_{50} value of 6 nM. The parent compound (−)-**1** had only 26% agonist activity at 30 μM in the mouse vas deferens (δ) bioassay, whereas compound (−)-**11** had an IC_{50} of 393 nM in this preparation, indicating the importance of the indole moiety in imparting δ-opioid agonist activity to the phenylmorphan (−)-**11**. A structure–activity relationship (SAR) study of *N*-alkyl derivatives of the racemic nor **11** indicated similarities between the interaction of various derivatives with the μ- and δ- but not the κ_1-opioid receptor. As studies on the molecular basis of the interaction of opioid ligands with their respective receptors continue to gain momentum, the SAR data described herein for the synthetic phenylmorphans will prove useful for further studies.

The opioid receptors (μ, δ, and κ) and their subtypes are involved in the control of various aspects of the perception of pain, pleasure, and mood as well as regulation of immune function, and the development of selective opioid receptor ligands offers the potential for improving clinical treatments involving these systems. Recent studies indicate that compounds that act at the δ receptor have broad clinical potential. For example, naltrindole, a δ receptor selective antagonist, has been shown to block reinforcing properties of cocaine, potentially leading to treatment and prevention of cocaine abuse.[1] Other studies suggest that δ receptor antagonists might be of use for treatment of alcohol abuse[2] and as immunosuppressants for organ transplantation.[3] Various δ_2 receptor agonists can selectively modulate μ receptor-mediated antinociception but not tolerance, possibly leading to improvements in the treatment of pain.[4] Furthermore, the blockade of δ receptors has been shown to prevent the development of morphine tolerance and dependence in mice.[5] This finding may have implications for the treatment of patients requiring chronic narcotic therapy and suggests the potential useful properties of compounds that are δ antagonist/μ agonists. Recent studies suggest that analgesics that selectively act through δ receptors might not cause the unwanted side effects associated with standard μ receptor analgesics, namely, respiratory depression, physical dependence, and gastrointestinal effects.[6] Specific ligands also have the potential to be used as tools for research in the study of the opioid receptor system and can, in turn, be the lead compounds for the preparation of affinity ligands[7] and imaging agents.[8] These compounds can be used for the characterization and visualization of receptor subtypes in living animals and, therefore, can act as novel agents for the diagnosis of central nervous system (CNS) disorders as well as agents for monitoring drug therapy involving the opioid receptor system. At the present there exist very few selective nonpetidic ligands, either agonists or antagonists, for the δ-opioid receptor. Antagonists include naltrindole and related derivatives,[9] and a selective δ agonist, SNC80, has recently been reported.[10] These facts, taken with the above clinical findings, indicate the importance of developing new highly selective opioid receptor ligands, especially compounds acting at the δ receptor or perhaps interacting with both the δ and μ receptors simultaneously.

Design Rationale

One approach to developing opioid compounds with specificity for a particular receptor involves the modification of known potent opioid compounds. Two classes of nonpeptidic rigid opioid compounds can be distinguished by the spatial relationship between the phenolic

* Corresponding author.
† National Institute on Drug Abuse.
‡ University of Arizona.
§ Naval Research Laboratory.
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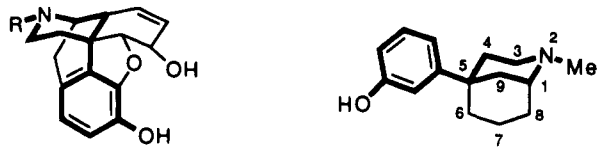


4,5-epoxymorphinans
R = Me, morphine

(-)-1, 2-methyl-5-(3-hydroxyphenyl) morphan

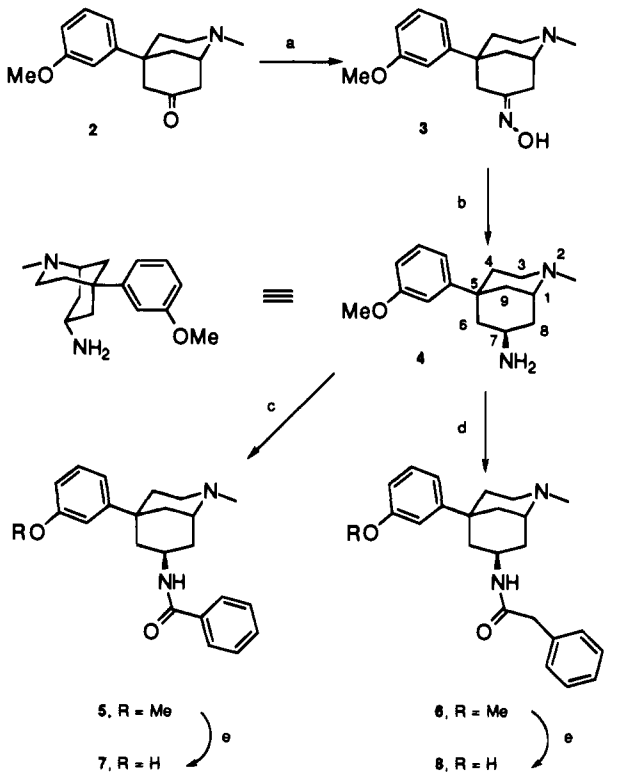
Figure 1. Orientation of the phenolic moiety relative to the piperidine ring in classical 4,5-epoxymorphinans (axial) as compared with the 2-methyl-5-phenylmorphans (equatorial).

moiety and the piperidine ring containing a basic amino group. The 4,5-epoxymorphinans (e.g., morphine) have the phenolic group in an axial orientation relative to a piperidine ring containing the basic nitrogen. In contrast, the 5-(3-hydroxyphenyl)-2-methylmorphans possess a phenolic moiety in an equatorial orientation relative to the piperidine containing the basic amino group (see Figure 1).

May and Murphy[11] first reported the synthesis of 2-methyl-5-phenylmorphan, and the compound was almost as potent an analgesic as meperidine. With a *m*-hydroxyl function on the phenyl ring, the activity was increased 8-fold and this racemate was as potent as morphine (sc).[12] Optical resolution of this racemate interestingly gave two active compounds. Whereas (+)-**1** was an agonist with 4 times the potency of morphine, (−)-**1** was a morphine-like agonist and had moderate antagonist properties as well.[13] This is in sharp contrast to the 4,5-epoxymorphinans, where the unnatural (+) isomers are devoid of any analgesic activity.[14] *In vitro* binding assays revealed that both the (+) and the (−) isomers had a high affinity for the μ-opioid receptor, slight affinity for the κ-opioid receptor, and virtually no affinity for the δ-opioid receptor.[15] Furthermore, replacement of the *N*-methyl substituent with moieties known to confer narcotic antagonist activity in the 4,5-epoxymorphinans, such as propyl, allyl, and cyclopropylmethyl, did not produce compounds with antagonist properties.[16] Because of the distinct differences between the phenyl-equatorial 5-(3-hydroxyphenyl)morphans and the 4,5-epoxymorphinans in structure, activities of optical isomers, and structure−activity relationships (SAR) of "antagonist" groups, the chemical modification of this class of compounds to improve or alter selectivity at opioid receptors was of great interest.

Portoghese et al. applied the message−address concept of Schwyzer[17] by the addition of a phenyl moiety via an indole group to the opioid antagonist naltrexone, producing naltrindole, a highly selective δ receptor opioid antagonist.[18] It was proposed that the classical phenyl-axial opiates (e.g., morphine and derivatives) would mimic the Tyr portion of the endogenous opioid peptides and that the introduced phenyl moiety of naltrindole would mimic the Phe[4].[19] However, these and further SAR studies which focus on the message−address concept do not enable us to predict *a priori* what changes in subtype selectivity or agonist−antagonist properties might result from the introduction of an additional aromatic group into the nonclassical phenyl-equatorial 5-(3-hydroxyphenyl)morphan opioid compounds. Because of the ease with which it could be obtained, we chose 5-(3-methoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-7-one (**2**)[20] (see Scheme 1) as our starting material with the hope that the opioid binding

Scheme 1[a]



[a] Reagents and conditions: (a) NH_2OH·HCl, ethanol, reflux, 1 h; (b) Na in 2-propanol; (c) PhCOCl, Schotten−Baumann; (d) $PhCH_2COCl$, Schotten−Baumann; (e) BBr_3, $CHCl_3$.

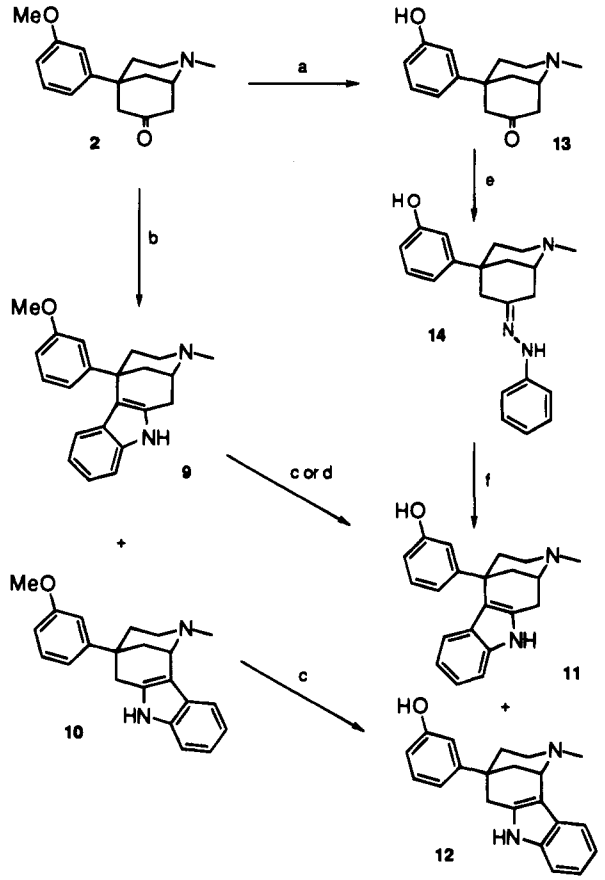
selectivity could be modified by the addition of phenyl-containing substituents in a specific conformational space within these ligands. We now report on these efforts toward the development of new nonpeptidic δ-opioid receptor ligands.

Chemical Synthesis

Compounds **7** and **8** were synthesized from **2**[20] (see Scheme 1) by the formation of the oxime **3** (96%) which was subsequently reduced by Na in 2-propanol stereoselectively forming the primary amine **4** (92%). The amine was reacted under Schotten−Baumann conditions with benzoyl chloride or phenylacetyl chloride producing **5** (93%) and **6** (97%), respectively. Both **5** and **6** were demethylated with boron tribromide in chloroform forming compounds **7** (57%) and **8** (54%).[21] The relative configuration of compounds **4**−**8** for C1, C5, and C7 (phenylmorphan numbering) was determined to be *R**, *S**, and *R**, respectively, by single-crystal X-ray analysis of compound **5**, *vide infra*.

Compounds **11** and **12** were also prepared from **2** (see Scheme 2). The indole derivatives **9** (73%) and **10** (5%) were the major and minor isomers of the reaction of phenylhydrazine with **2** using Fischer indole synthesis conditions, and the assignment of the isomers was based on single-crystal X-ray analyses of compounds **9** and **10**, *vide infra*. Demethylation of **9** was accomplished using 48% HBr or boron tribromide producing **11** in 67% and 69% yields, respectively. Demethylation of **10** with boron tribromide gave **12** in 44% yield. Alternatively, larger quantities of **12** could be obtained by demethylation of **2** with boron tribromide or 48% HBr to give the phenolic **13**[22] (82% and 94%, respectively) with subsequent production of the 7-phenylhydrazone **14**

Scheme 2[a]

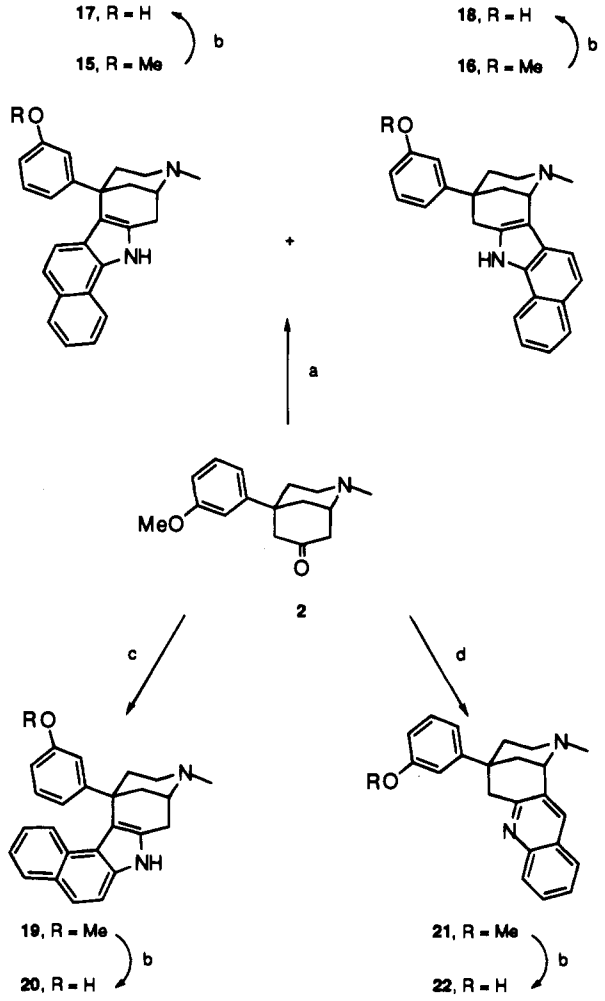


[a] Reagents and conditions: (a) 48% HBr, reflux, 1.5 h; (b) phenylhydrazine·HCl, glacial acetic acid, reflux, 19 h; (c) BBr_3, $CHCl_3$; (d) 48% HBr, acetic acid, reflux, 2 h, room temperature, overnight; (e) phenylhydrazine·HCl, ethanol, reflux; (f) neat polyphosphoric acid, 80–90 °C.

(82%) which could be cyclized utilizing neat polyphosphoric acid at 80–90 °C giving both **11** (20%) and **12** (19%). Compound **11** could also be formed directly from **13** by reaction with phenylhydrazine in HCl(g)-saturated ethanol (72%).

Compounds **17** and **18** were prepared (see Scheme 3) by reaction of **2** with 1-naphthylhydrazine in HCl(g)-saturated ethanol forming a mixture of **15** (54%) and **16** (23%). The assignment of the benzindole regioisomers was accomplished by comparison of the proton NMR spectra to those of compounds **9** and **10**, whose structural assignments were confirmed by single-crystal X-ray analyses. Proton NMR spectra for **9** and **15** have similar characteristics: the C1 proton (see Scheme 1 for numbering) of **9** resonates at δ 3.40 (m, 1H) and that of **15** appears at δ 3.45 (m, 1H), whereas the C8 protons of **9** appear as a doublet and a double-doublet with geminal coupling, δ 3.11 (d, 1H, J = 17.6 Hz), 2.82 (dd, 1H, J = 5.3, 17.5 Hz), compared to those of **15**, δ 3.24 (d, 1H, J = 17.6 Hz), 2.91 (dd, 1H, J = 5.4, 17.3 Hz). The C1 (phenylmorphan numbering) proton of **10** appears at δ 4.36 (t, 1H, J = 3.1 Hz), and that of **16** resonates at δ 4.42 (t, 1H, J = 3.3 Hz). Furthermore the C6 protons of **10** appear as a close pair of doublets with geminal coupling: δ 3.09 (d, 1H, J = 17.3 Hz), 3.02 (d, 1H, J = 17.4 Hz), whereas those of **16** resonate at δ 3.15 (d, 1H, J = 17.2 Hz), 3.08 (d, 1H, J = 17.5 Hz). After chromatographic separation the two isomers, **15** and **16** were demethylated with boron tribromide to

Scheme 3[a]

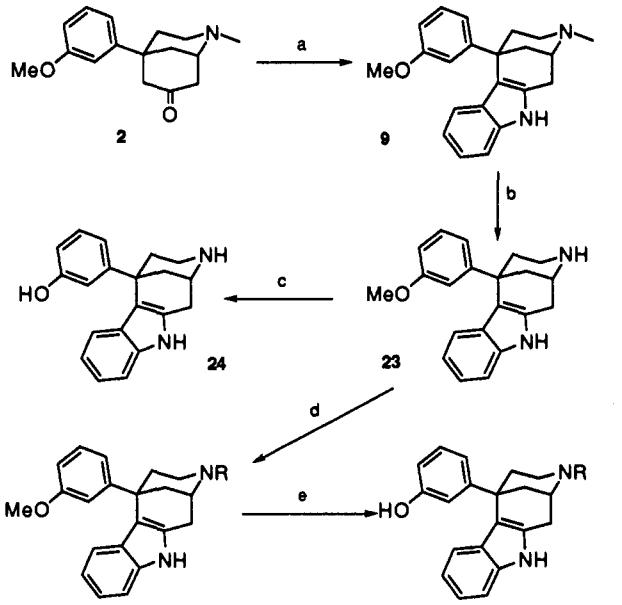


[a] Reagents and conditions: (a) 1-naphthylhydrazine·HCl, HCl(g)-saturated EtOH, reflux; (b) BBr_3, $CHCl_3$; (c) 2-naphthylhydrazine·HCl, HCl(g)-saturated EtOH, reflux; (d) 2-aminobenzaldehyde, KOH, methanol, reflux.

form **17** (51%) and **18** (57%). Compound **20** was prepared by reaction of **2** with 2-naphthylhydrazine in HCl(g)-saturated ethanol which gave **19** (67%) which was subsequently demethylated with boron tribromide yielding **20** (86%). The reaction of **2** with 2-naphthylhydrazine gave one major isomer (four possible), and the assignment of the regioisomer **19** was based on similarities of the proton NMR spectrum with those of **9** and **15**: the C1 proton resonates at δ 3.40 (m, 1H), and the C8 protons appear as a doublet and a double-doublet, δ 3.17 (d, 1H, J = 17.0 Hz), 2.90 (dd, 1H, J = 5.2, 17.2 Hz). The assignment of the attachment of C6 of the phenylmorphan with the C1 of the 2-naphthylhydrazine as opposed to the C3 was based on the appearance of the methyl protons of the methoxyphenyl of **19** as two distinct singlets, δ 3.93, 3.31 (2 s, 3H), due to a restricted rotation of the methoxyphenyl imposed by the terminal phenyl of the benzindole. Quinoline **21** was prepared by reaction of **2** with 2-aminobenzaldehyde under Friedländer[23] conditions forming **21** (86%), and this was then demethylated with boron tribromide giving **22** (82%). The C7–C8 attachment of the quinoline in compounds **21** and **22** was determined by a single-crystal X-ray analysis of compound **22**, *vide infra*.

The syntheses of various *N*-alkyl derivatives of nor-**11** are described in Scheme 4. Compound **2** was reacted

Scheme 4[a]



25 R = Et	**35** R = Et
26 R = *n*-Pr	**36** R = *n*-Pr
27 R = *n*-Bu	**37** R = *n*-Bu
28 R = *n*-pentyl	**38** R = *n*-pentyl
29 R = *n*-hexyl	**39** R = *n*-hexyl
30 R = *n*-heptyl	**40** R = *n*-heptyl
31 R = benzyl	**41** R = benzyl
32 R = cyclopropylmethyl	**42** R = cyclopropylmethyl
33 R = allyl	**43** R = allyl
34 R = phenylethyl	**44** R = phenylethyl

[a] Reagents and conditions: (a) phenylhydrazine·HCl, HCl(g)-saturated EtOH, reflux; (b) (1) 1-chloroethyl chloroformate, 1,2-dichloroethane, K_2CO_3, reflux, (2) MeOH, HCl(g) reflux; (c) AcOH, 48% HBr, reflux; (d) (1) Schotten–Baumann acylation, (2) $LiAlH_4$, THF except for R = allyl where (d) allyl bromide, ethanol, room temperature; (e) BBr_3, $CHCl_3$.

with phenylhydrazine forming **9** (method B, 82%) which was then *N*-demethylated with 1-chloroethyl chloroformate[24] yielding **23** (84%). Compound **23** was *O*-demethylated with 48% HBr in refluxing acetic acid providing **24** (75%). Compound **23** could be alkylated by reaction with various acid chlorides under Schotten–Baumann conditions followed by $LiAlH_4$ reduction of the resultant amides providing the amines **25**–**34** (81–95%) with the exception of **33** which was prepared by reaction of **23** with allyl bromide (53%) with recovery of 28% of **23**. Compounds **25**–**34** were demethylated with boron tribromide yielding compounds **35**–**44**, respectively (75–99%).

The enantiomers of **11** were synthesized from the resolved enantiomers of **13**[22] by reaction with phenylhydrazine using Fischer indole synthesis conditions. The enantiomers of **44** were also synthesized from the resolved isomers of **13**. The compounds (+)- and (−)-**13** were methylated with diazomethane to form (+)- and (−)-**2**. The remaining synthetic steps for the preparation of (+)- and (−)-**44** were analogous to the preparation of racemic **44** from racemic **2**. The absolute configurations of (+)- and (−)-**11** as well as (+)- and (−)-**44** were known from the previously reported determination of the absolute configurations of (+)- and (−)-**13**.[22]

X-ray Crystallography of 5, 9, 10, and 22. The results of the X-ray studies are illustrated in Figure 2, and a summary of crystal data and refinement parameters is shown in Table 5. Compound **5** crystallized as a hydrobromide salt with one molecule of water and one molecule of ethanol in the asymmetric unit. Compound **9** crystallized as a monohydrated salt with methanesulfonic acid, whereas **10** and **22** were crystallized as their free bases with no included solvent. There were two independent molecules in the asymmetric unit of **22**, both of which had the same conformation. The saturated six-membered rings showed normal chair conformations in all four compounds, and bond lengths and angles were unremarkable. Several important features were established by the X-ray studies. The relative configuration of the amino attached to C7 of **5** was determined to be R^* with respect to C1 (R^*) and C5 (S^*). The indole moieties of **9** and **10** were determined to be fused to the C6–C7 and C7–C8 positions (phenylmorphan numbering), respectively. Furthermore, compound **22** had the quinoline moiety fused to the C7–C8 position of the phenylmorphan nucleus.

Results and Discussion

Biological Data. In order to determine if the modified 5-(3-hydroxyphenyl)morphans had an increased affinity for δ-opioid receptors relative to the parent compounds, *in vitro* binding assays were determined for μ and δ receptors in rat brain and κ_1 receptors in guinea pig brain (see Table 1). Both of the parent enantiomers, (−)- and (+)-**1**, had high affinity for the μ-opioid receptor of 21 nM, a slight affinity for κ_1-opioid receptors (819 and 911 nM, respectively), and less than 1000 nM affinity for the δ-opioid receptor (μ/δ IC_{50} ratio of <0.02 for both), in agreement with previous reports.[15] Incorporation of a (phenylcarbonyl)amino moiety at the C7 position resulted in compound **7**, which had an 8-fold decrease in μ affinity and a >2-fold increase in affinity for the δ receptor with an IC_{50} for δ of 488 nM (μ/δ IC_{50} ratio of 0.32) relative to the parent compounds (−)- and (+)-**1**. An extra methylene between the additional phenyl group and the parent nucleus gave **8**, which had a 6-fold decrease in μ affinity and a >4-fold increase in affinity for the δ receptor (IC_{50} for δ 227 nM, μ/δ IC_{50} ratio of 0.52) compared to either parent compound (−)- or (+)-**1**. Both **7** and **8** had a decreased affinity for κ_1 receptors relative to the parent compounds. Encouraged by these results with the additional, rotationally unrestricted phenyl moieties of **7** and **8**, it seemed prudent to prepare compounds with conformationally restricted supplemental phenyl-containing groups.

The first two rigid analogs prepared were the indole isomers **11** and **12** (see Scheme 2). Interestingly, the introduction of the 7-phenylhydrazone of compound **14** increased the μ and κ_1 binding affinity about 2- and 3-fold, respectively, and increased the δ receptor binding affinity by >9-fold over the binding affinities of the parent compound (−)- or (+)-**1**. The C7–C8 indole moiety of racemic **12** decreased the binding affinity to μ receptors by 2-fold and did not enhance the affinity for δ or κ_1 receptors. In sharp contrast, the addition of the indole group to the C6–C7 position produced **11**, which had about the same binding affinity for the μ receptor and a slightly decreased affinity for κ_1 receptors relative to the parent compounds. However, compound **11** had a δ receptor affinity >140 times that of either parent compound with an IC_{50} of 7.1 nM and a μ/δ IC_{50} ratio of 4.20.

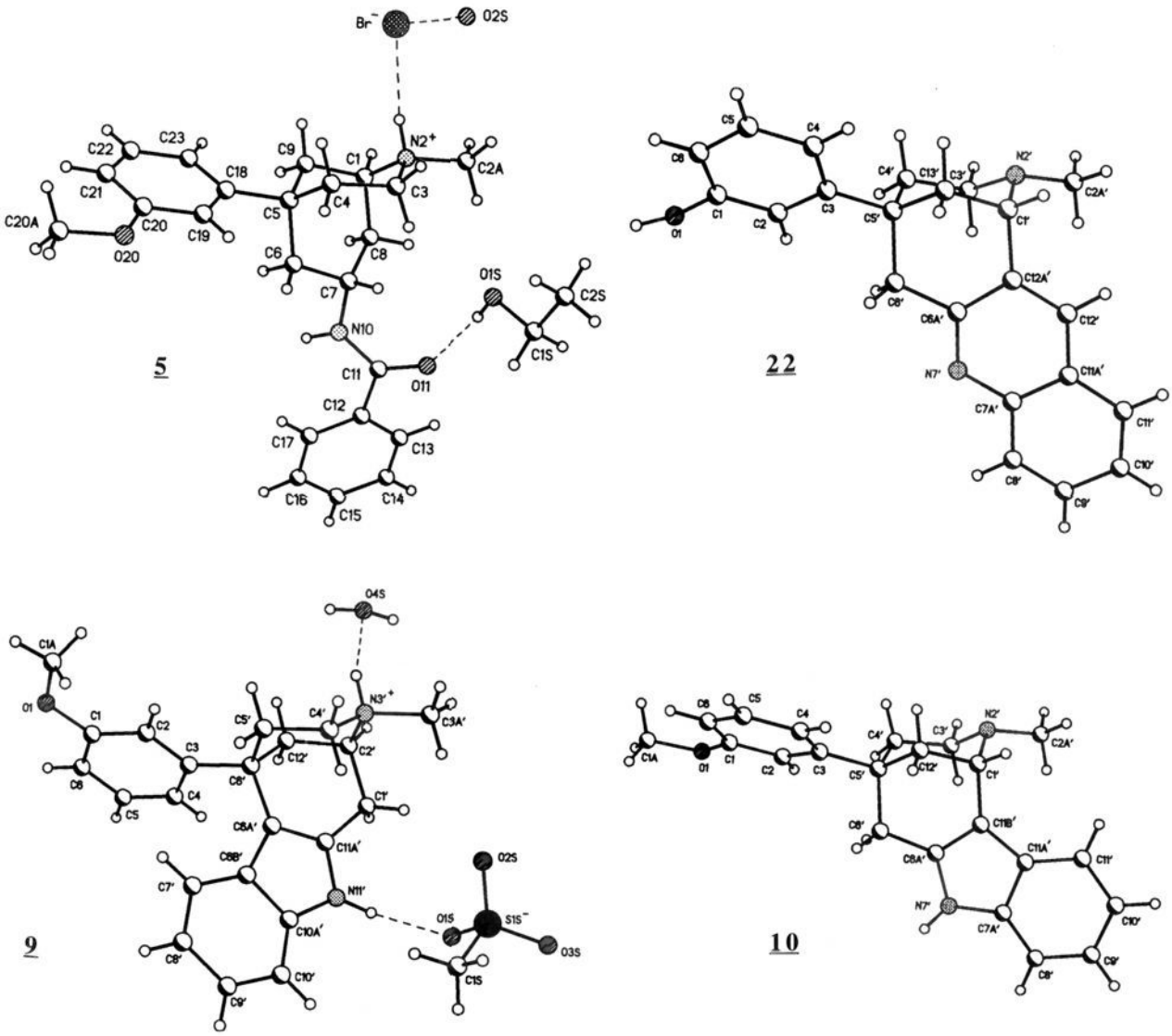


Figure 2. Results of the X-ray studies on **5, 9, 10**, and **22**. The figure is drawn using the experimentally determined coordinates. Anions and solvent molecules are also shown as is hydrogen bonding within the asymmetric unit of **5** and **9**.

Several other rigid variations included compounds shown in Scheme 3, **17**, **18**, **20**, and **22**. Whereas compound **18** had low affinity and selectivity for the δ receptor with an IC_{50} of 1052 nM and a μ/δ IC_{50} ratio of 0.35, compound **20** had weak affinity for the μ, δ, and κ_1 receptors. Compound **20** is structurally related to the potent μ/δ ligand **11** with an additional benzene ring fused at the C4−C5 position of the indole. The additional ring might inhibit binding simply due to a steric interaction; however, reduction in binding affinity might also be due to the limited rotational freedom of the phenolic moiety imposed by the added benzene ring. *In vitro* binding data also revealed that the quinoline moiety of **22** increased the affinity for μ, δ, and κ_1 receptors 19-, >4-, and 4-fold, respectively, relative to the unsubstituted 5-(3-hydroxyphenyl)-2-methylmorphans, producing a compound with the highest binding affinity for the μ-opioid receptor of those tested (IC_{50} of 1.1 nM). Compound **17**, which is a relative of the δ receptor selective **11** differing only by the fusion of a benzene ring at the C6−C7 of the indole group, had the best selectivity for the δ receptor with an IC_{50} of 12.6 nM and a μ/δ IC_{50} ratio of 16.5. The increased selectivity of **17** for δ over **11** results almost exclusively from an 8 fold decrease in affinity for the μ receptor.

Both compounds **11** and **17** displayed *in vitro* selectivity for the δ receptor. Due to the superior water solubility of compound **11** versus **17**, a study of various *N*-alkyl and -aralkyl derivatives of **11** was undertaken possibly to enhance the δ-opioid receptor selectivity (see Scheme 4). The amine substituent was varied from H to *N*-heptyl, and the rank order binding affinities for μ and δ receptors from rat brain were seen to be basically the same. All were somewhat more potent at δ receptors relative to μ receptors (see Figure 3). This may indicate that the compounds are interacting in a similar manner with these two receptor subtypes. Recent studies on the cloned opioid receptors have shown that the rat brain μ-opioid receptor shows 58% and 57% identity (66% and 68% similarity) with the amino acid sequences of the mouse δ- and κ-opioid receptors.[25] None of the compounds in this series have appreciable binding affinity for the κ_1-opioid receptor. That the binding selectivity of these compounds differs widely for the μ- and δ-opioid receptor relative to the κ_1 receptor

Table 1. Inhibition of Radioligand Binding to Rat Brain μ and δ Receptors and Guinea Pig Brain κ_1 Receptors

compd	IC_{50} (nM±SD) [^{3}H]DAMGO (μ)[37]	[^{3}H]DADLE (δ)[38]	[^{3}H]U69,593 (κ_1)[39]	μ/δ
(−)-1	20.8 ± 1.7	>1000	818.6 ± 96.2	<0.02
(+)-1	21.4 ± 2.4	>1000	910.5 ± 50.6	<0.02
7[a]	158.1 ± 15.0	487.8 ± 29.3	5563 ± 415	0.32
8[a]	119.1 ± 14.3	227.1 ± 37.2	2216 ± 268	0.52
13[a]	21.2 ± 1.8	720 ± 58	2025.7 ± 172.9	0.03
(−)-**13**	33.5 ± 3.4	273.4 ± 64.6	981.5 ± 93.9	0.12
(+)-**13**	136.8 ± 20.0	1136 ± 255	5071 ± 739	0.12
14	8.7 ± 0.9	111.3 ± 7.4	240.5 ± 23.6	0.08
11[a]	29.8 ± 3.9	7.1 ± 0.9	>1000	4.20
12[a]	43.9 ± 4.0	>1000	798.3 ± 86.4	<0.04
17	208.2 ± 39.8	12.6 ± 2.2	>1000	16.5
18	366.3 ± 16.9	1052 ± 60	>1000	0.35
20	>1000	>10000	>1000	
22	1.1 ± 0.1	229 ± 17	197 ± 40	4.8×10^{-3}
24	357 ± 47	69.5 ± 7.5	>10000	5.14
35[a]	1261 ± 91	233.3 ± 26.3	>1000	5.40
36[a]	299.6 ± 20.8	40.5 ± 4.5	>1000	7.40
37[a]	72.4 ± 10.8	18.0 ± 0.7	>1000	4.02
38	23.5 ± 3.7	6.9 ± 0.5	993 ± 84	3.41
39	70.6 ± 4.5	34.0 ± 5.5	>1000	2.08
40	66.6 ± 7.2	46.7 ± 5.2	>1000	1.43
41	508.2 ± 53.9	184 ± 41	90.0 ± 6.0	2.76
42[a]	180.2 ± 16.9	84.1 ± 4.3	934 ± 100	2.14
43[a]	361 ± 65	140.1 ± 10.0	2160 ± 143	2.58
44	50.6 ± 4.6	5.7 ± 0.7	>1000	8.88
(−)-11	14.2 ± 1.0	5.6 ± 1.5	ND	2.54
(+)-11	21.4 ± 1.4	660.1 ± 160.2	ND	0.03
(−)-**44**	25.0 ± 2.0	6.2 ± 0.6	>1000	4.03
(+)-**44**	89.2 ± 19.5	>1000	>1000	<0.09
morphine[b]	1.94 ± 0.31	684 ± 83	ND	
DADLE[b]	ND	1.71 ± 0.23	ND	
(−)-etorphine[b]	0.14 ± 0.03	7.37 ± 0.52	1.82 ± 0.33	

[a] *O*-Methyl derivatives had IC_{50} values (μ, δ, and κ_1) >1000 nM. [b] See Xu, H.; Kim, C.-H.; Zhu, Y. C.; Weber, R. J.; Jacobson, A. E.; Rice, K. C.; Rothman, R. B. *Neuropharmacology* **1991**, *30*, 455–462.

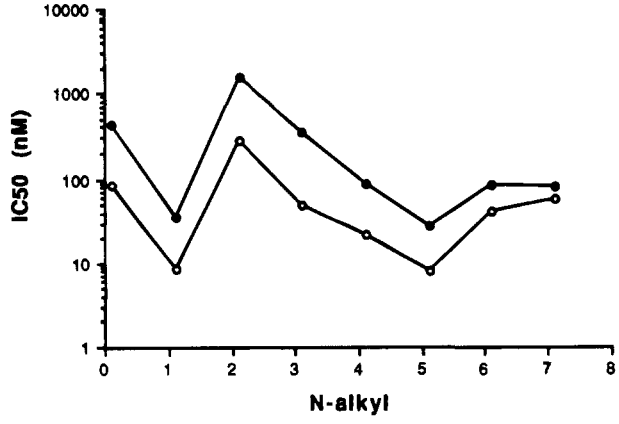


Figure 3. Comparison of potencies (IC_{50}, nM) of *N*-(H through heptyl)-*N*-nor-11 in opioid receptor assays using rat brain membranes. Radioligands were [^{3}H]DAMGO for μ-opioid receptor (●) and [^{3}H]DADLE for δ-opioid receptors (○).

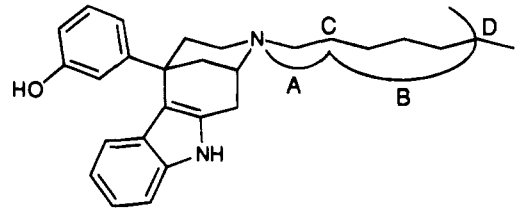


Figure 4. Rationalization of the effect of *N*-alkyl substituents on the binding affinity (IC_{50} values) of derivatives of 11 for both μ and δ receptors. A and B are hydrophobic sites, and C and D are areas of unfavorable steric interaction.

may prove useful for computer-assisted molecular modeling of these receptors.[26]

It is interesting that the affinity of the *N*-ethyl derivative for both the μ and δ receptors is much lower than that of all the other straight-chain alkyl derivatives. Presumably the binding affinities for the μ and δ receptors is not solely governed by steric factors alone, as both the *N*-methyl and pentyl derivatives (**11** and **38**, respectively) have equal affinity for the μ and δ receptors. It seems reasonable that a favorable counteracting hydrophobic interaction favors the increasingly longer hydrophobic *N*-alkyl substituent which allows the *N*-pentyl compound **38** to have comparable binding affinities to both μ and δ receptors as does the *N*-methyl derivative **11** (see Figure 4). One plausible scenario that would explain the *in vitro* binding data would involve the existence of two hydrophobic sites, A and B, in both μ and δ receptors. The *N*-methyl moiety of **11** would fit favorably in site A, but the larger *N*-ethyl group of **35** could have an unfavorable steric interaction at site C. The incorporation of larger *N*-alkyl chains up to *N*-pentyl (**38**) would increasingly favor binding due to an interaction with a second hydrophobic site, B, thereby overriding the unfavorable steric interaction at site C. Due to a limit in the size of site B, further increases in *N*-alkyl chain length greater than *N*-pentyl would produce compounds with a second unfavorable steric interaction at site D, again decreasing the binding affinity for the μ and δ receptors. The μ/δ IC_{50} ratio varies in a narrow range from 1.43 for *N*-heptyl to 7.40 for *N*-propyl with the two highest affinity compounds for both μ and δ receptors being **11** (*N*-methyl) and **38** (*N*-pentyl) with μ/δ IC_{50} ratios of 4.20 and 3.41, respectively. *N*-Benzyl, *N*-cyclopropylmethyl, and *N*-allyl substituents provided compounds with moderate affinity for both the μ and δ receptors with μ/δ IC_{50} ratios of 2.76,

Table 2. Agonist Activity of Selected Compounds in the Mouse Vas Deferens (MVD) and Guinea Pig Ileum (GPI) Bioassays (Data are presented as mean ± SEM)

	IC_{50} ± SEM (nM)		
compd	GPI (μ receptors)	MVD (δ receptors)	GPI (μ)/ MVD (δ)
(−)-1	639 ± 93	26% at 30 μM	
(+)-1	169 ± 28	557 ± 134	0.3
11	2073 ± 556	347 ± 30	6
(+)-11	1939 ± 473	1388 ± 719	1.4
(−)-11	2345 ± 64	393 ± 67	6
DPDPE[a]	7300 ± 1700	4.1 ± 0.5	1800
DADLE	28.8 ± 8.8	447 ± 133	9.3

[a] See ref 28.

2.14, and 2.58, respectively. The *N*-phenylethyl compound **44** had high affinity for the δ receptor with an IC_{50} of 5.7 nM and a μ/δ IC_{50} ratio of 8.88, a 2-fold enhancement of the δ receptor selectivity relative to the *N*-methyl compound **11**. It seemed apparent that variation of the amine substituents in the racemic series would not provide compounds with greatly enhanced μ/δ IC_{50} ratios relative to the prototypical ligand **11**.

Thus far, all *in vitro* binding studies were performed on racemic compounds. It has been well established that drug enantiomers can display vastly dissimilar pharmacological effects,[27] and therefore it was important to test some of the enantiomeric pairs of the more δ receptor selective compounds in the racemic series. Also, the possibility existed that either of the separated enantiomers might display an increased selectivity for the δ-opioid receptor relative to the racemates. Considering affinity, δ selectivity, and solubility characteristics, we chose to prepare the optical isomers of **11** and **44**. *In vitro* binding assays revealed that for both compounds the (+) isomers had high affinity for the μ receptor and low affinity for the δ receptor. On the other hand, the (−) isomers of **11** and **44** had high affinity for both the μ and δ receptors with μ/δ IC_{50} ratios of 2.54 and 4.03, respectively. Relative to the parent phenylmorphan with the analogous stereochemistry (compound (−)-**1**), compounds (−)-**11** and (−)-**44** have >180- and >160-fold increased affinity for the δ opioid receptor with IC_{50} values of 5.6 and 6.2 nM, respectively.

The opioid activity (Table 2) of the parent phenylmorphans (−)- and (+)-**1**, the δ receptor selective **11**, and its separate enantiomers was next evaluated in the isolated mouse vas deferens (MVD) and the guinea pig ileum (GPI) bioassays.[28] These bioassays revealed that the parent phenylmorphan (+)-**1** had good agonist activity in the GPI bioassay (μ) and moderate agonist activity in the MVD bioassay (δ), with a GPI/MVD ratio of 0.3. The bioassays for (−)-**1** revealed moderate agonist activity in the GPI preparation (μ) and practically no agonist activity in the MVD preparation (δ), consistent with the observed antagonist properties *in vivo*.[29] The bioassay data for **11**, (+)-**11**, and (−)-**11** mirrored the results of the binding assays for the μ and δ receptors. Compound (+)-**11** had a GPI/MVD ratio of 1.4, whereas (−)-**11** had a ratio of 6. *In vitro* binding data for (−)-**11** had indicated high affinity for the μ and δ receptors; however, the low efficacy of (−)-**11** in both the GPI and MVD bioassays did not bear this out. The corresponding parent phenylmorphan of compound (−)-**11** is compound (−)-**1**. Interestingly, whereas (−)-**1** only had 26% agonist activity at 30 μM in the MVD (δ) bioassay, compound (−)-**11** had an IC_{50} of 393 nM in this preparation, indicating the importance of the indole moiety fused to the C6−C7 position of the phenylmorphan nucleus in imparting agonist activity to the compound in this bioassay.

Conclusion

We have applied the message−address concept, as interpreted by Portoghese et al.,[19] to the phenyl-equatorial 5-(3-hydroxyphenyl)morphans and have produced derivatives with greatly enhanced *in vitro* binding affinity for δ-opioid receptors. A wide variety of compounds were prepared which possessed additional aromatic moieties attached in both conformationally restricted and unrestricted fashion. It was found that an indole moiety fused at the C6−C7 position of the parent compound (−)-**1** produced a compound with >180-fold enhancement of affinity for δ opioid receptors. Furthermore, the MVD (δ) bioassay revealed that one of these compounds, (−)-**11**, had agonist properties that were substantially enhanced relative to the parent phenylmorphan (−)-**1**. While these derivatives have a substantially greater affinity than the parent compounds for the δ-opioid receptor, affinity for the μ-opioid receptor remains unchanged. Structure−activity relationships for the *N*-alkyl derivatives related to **11** revealed that these derivatives may be interacting analogously with both μ and δ receptors but not with κ_1 receptors. Recently the cDNAs of μ, δ, and κ receptors have been cloned,[30] and the amino acid sequences are known. As studies proceed to determine the molecular basis for the interaction of opioid ligands with their respective receptors, as well as the molecular basis for the message−address concept, SAR data, as described for these 5-(3-hydroxyphenyl)morphan derivatives, will be of great importance.

Experimental Section

General Instrumentation and Methods. Proton NMR spectra were recorded for the free bases of all compounds in $CDCl_3$ (unless otherwise specified) on a Varian Gemini-300 spectrometer, and the data are reported in the following format: chemical shift (all relative to Me_4Si), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet, ap = apparent), integration, coupling constants, and exchangeability after D_2O addition. Electron impact (EI) mass spectra were recorded on a VG Micromass 7070F spectrometer, chemical ionization (CI) mass spectra were recorded on a Finnigan 4600, and FAB mass spectra were recorded on a JEOL XS-102 double-focusing mass spectrometer. UV spectra were recorded on a Hewlett-Packard 8450A UV/vis spectrophotometer, and IR spectra were recorded on a Bio-Rad FTS-45 spectrophotometer. Polarimetric measurements were taken using a Perkin-Elmer 241MC polarimeter. Thin layer chromatography (TLC) was performed on Analtech silica gel GHLF 0.25-mm plates. Preparative TLC was performed on Analtech silica gel GF 2.00-mm plates. Radial disk chromatography was performed on 4.00-mm Merck silica gel 60 GF_{254} (mean particle size = 15 μm) disks. Column chromatography was performed with Fluka silica gel 60 (mesh 220−440). Elemental microanalyses were performed by Atlantic Microlab, Inc. Melting points were recorded on a Thomas-Hoover capillary apparatus or a Mel-Temp II apparatus (>260 °C) and are uncorrected. The yields reported are not optimized. Compounds 11 and 12 were named following Chemical Abstract rules by Chemical Abstract Services, Columbus, OH.

5-(3-Methoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-7-one Oxime (3). A mixture of **2**[31] (2.20 g, 8.47 mmol) and hydroxylamine hydrochloride (3.12 g, 44.9 mmol) in absolute

ethanol (50.0 mL) was heated to reflux, but before this point was reached, a white solid precipitated. This mixture was held at reflux for 40 min and allowed to cool. The solvent was evaporated from the mixture, the solid residue was taken up in 1 M NH_4OH (150 mL), and this was extracted with chloroform (2 × 150 mL). The extracts were dried (K_2CO_3) and evaporated, and the resulting oil was triturated with ether. The resulting white crystalline solid was filtered and air-dried, yield 2.23 g (96%) mp 131–133 °C. A salt with HCl was prepared by dissolving 0.18 g in warm 2-propanol and acidifying with 37% HCl. The white crystalline solid was filtered and dried, yield 0.20 g. An analytical sample was prepared by recrystallization from 2-propanol: mp 247–249 °C; ^1H NMR δ 7.93 (br, 1H, ex w/D_2O), 7.28 (t, 1H, J = 8.0 Hz), 6.99 (m, 1H), 6.94 (m, 1H), 6.78 (dd, 1H, J = 2.2, 8.1 Hz), 3.81 (s, 3H), 3.60 (d, ~0.5 H, J = 16.6 Hz), 3.02 (d, ~0.5H, J = 16.1 Hz), 3.30 (br m, 1H), 2.57–2.88 (m, 2H), 2.46, 2.44 (2 s, 3H), 2.33 (m, 1H), 1.90–2.16 (m, 5H), 1.70 (dd, 1H, J = 4.4, 16.6 Hz); MS (CI–NH_3) m/z 275 (MH^+). Anal. ($C_{16}H_{22}N_2O_2$·HCl) C, H, N.

(1*R,5*S**,7*R**)-7-Amino-5-(3-methoxyphenyl)-2-methyl-2-azabi-cyclo[3.3.1]nonane Fumarate (4).** A mixture of Na (49 g, 2.1 mol) and toluene was heated to reflux, and after the Na melted a solution of **3** (4.27 g, 15.6 mmol) in warm 2-propanol (500 mL) was slowly added via an addition funnel. After the addition was complete, another portion of 2-propanol (500 mL) was added. After all of the Na was dissolved, the solution was allowed to cool to 50 °C and diluted with H_2O (2.5 L). The toluene layer was separated, and the aqueous layer was extracted with chloroform (4 × 500 mL). The toluene and chloroform layers were combined, dried (K_2CO_3), and evaporated yielding an oil. This was dissolved in chloroform (100 mL), and this solution was washed with half-saturated brine (100 mL). The aqueous layer was back-extracted with chloroform (3 × 50 mL), and all of the chloroform layers were combined and dried (Na_2SO_4/K_2CO_3). Evaporation gave an oil which was dissolved in ethanol, and the insoluble material was removed by filtration through a Celite pad. The filtrate was warmed, and a warm solution of fumaric acid (1.81 g) in ethanol (35 mL) was added. The resultant slightly off-white crystals were filtered, rinsed with ethanol (30 mL), and dried in a vacuum oven at 45 °C: yield 5.71 g (92%); mp 192–194 °C; ^1H NMR δ 7.19 (t, 1H, J = 8.0 Hz), 6.88 (td, 1H, J = 1.3, 7.9 Hz), 6.84 (t, 1H, J = 2.2 Hz), 6.68 (m, 1H), 3.74 (s, 3H), 3.44 (septet, 1H, J = 5.9 Hz), 3.09 (quintet, 1H, J = 3.2 Hz), 2.80 (ddd, 1H, J = 1.9, 7.3, 12.2 Hz), 2.69 (dt, 1H, J = 5.1, 12.1 Hz), 2.39 (m, 1H), 2.37 (s, 3H), 2.23 (m, 1H), 1.68–2.03 (m, 4H), 1.30 (br, 2H, ex w/D_2O), 1.20 (m, 1H), 1.00 (m, 1H); MS (CI–NH_3) m/z 261 (MH^+). Anal. ($C_{16}H_{24}N_2O$·$C_4H_4O_4$·1.25H_2O) C, H, N.

(1*R,5*S**,7*R**)-5-(3-Methoxyphenyl)-2-methyl-7-[(phenylcarbonyl)amino]-2-azabicyclo[3.3.1]nonane Hydrobromide (5).** The following materials were stirred at ambient temperature under Schotten–Baumann conditions for 2 h: **4** (1.00 g, 2.51 mmol), 10% NaOH (30 mL), chloroform (30 mL), and benzoyl chloride (0.42 mL, 3.6 mmol). The chloroform layer was separated, and the aqueous layer was extracted with chloroform (30 mL). The chloroform extracts were combined, dried (K_2CO_3), and evaporated. The resultant oil was dissolved in 2-propanol (8 mL) and made acidic with 48% HBr. The off-white crystals were filtered and rinsed with 2-propanol (8 mL) and excess petroleum ether, yield 1.08 g (93%), mp 181-183 °C. An analytical sample was prepared by recrystallization of a small portion from ethanol yielding colorless needles that had no sharp melting point: ^1H NMR δ 7.72 (d, 2H, J = 7.1 Hz), 7.43 (m, 3H), 7.25 (t, 1H, J = 7.9 Hz), 6.94 (d, 1H, J = 7.9 Hz), 6.90 (m, 1H), 6.75 (dd, 1H, J = 2.8, 8.1 Hz), 5.78 (d, 1H, J = 7.9 Hz, ex w/ D_2O), 4.89 (m, 1H), 3.80 (s, 3H), 3.24 (m, 1H), 2.89 (m, 2H), 2.66 (m, 1H), 2.54 (m, 1H), 2.50 (s, 3H), 2.15 (m, 2H), 1.93 (m, 2H), 1.38 (m, 1H), 1.21 (dt, 1H, J = 3.7, 13.0 Hz); MS (CI–NH_3) m/z 365 (MH^+). Anal. ($C_{23}H_{28}N_2O_2$·HBr·H_2O) C, H, N.

(1*R,5*S**,7*R**)-5-(3-Methoxyphenyl)-2-methyl-7-[[(phenylmethyl)carbonyl]amino]-2-azabicyclo[3.3.1]nonane Hydrobromide (6).** **6** was prepared from **4** and phenylacetyl chloride analogous to the preparation of **5**, yield 1.12 g (97%), mp 256–258 °C dec. An analytical sample was prepared by recrystallization of 300 mg from ethanol yielding 258 mg of crystals: mp 256–258 °C dec; ^1H NMR δ 7.28 (m, 6H), 6.89 (d, 1H, J = 7.7 Hz), 6.84 (t, 1H, J = 2.0 Hz), 6.74 (dd, 1H, J = 2.6, 8.2 Hz), 4.95 (d, 1H, J = 8.0 Hz, ex w/D_2O), 4.66 (m, 1H), 3.79 (s, 3H), 3.52 (s, 2H), 3.14 (quintet, 1H, J = 3.2 Hz), 2.90 (m, 2H), 2.46 (m, 1H), 2.44 (s, 3H), 2.35 (dd, 1H, J = 4.4, 13.2 Hz), 2.08 (m, 2H), 1.86 (m, 2H), 1.09 (m, 1H), 0.93 (dt, 1H, J = 3.7, 13.0 Hz); MS (CI–NH_3) m/z 379 (MH^+). Anal. ($C_{24}H_{30}N_2O_2$·HBr) C, H, N.

(1*R,5*S**,7*R**)-5-(3-Hydroxyphenyl)-2-methyl-7-[(phenylcarbonyl)amino]-2-azabicyclo[3.3.1]nonane Hydrobromide (7).** A solution of boron tribromide (1.3 mL, 13.8 mmol) in pentene-stabilized (ps) chloroform (20 mL) was slowly added to a solution of free based **5** (0.84 g, 2.3 mmol) in chloroform (15 mL) at −20 °C with vigorous stirring. The addition was slow enough to maintain the reaction temperature below −10 °C. After 45 min the reaction solution was allowed to warm to ambient temperature. The reaction mixture was poured into a stirring mixture of 28% NH_4OH (5 mL) and ice (25 g). This mixture was stirred in an ice bath for 30 min. The white solid was filtered, dried, dissolved in hot methanol, and made acidic with 48% HBr. The solution was allowed to cool and evaporated, and the residue was dissolved in hot water (100 mL). The insoluble material was filtered, and upon cooling, slightly off-white crystals formed. These were filtered, rinsed with water, and dried in a vacuum oven at 50 °C: yield 565 mg (57%); mp >300 °C; ^1H NMR δ 7.73 (m, 2H), 7.45 (m, 3H), 7.15 (t, 1H, 7.8 Hz), 6.83 (d, 1H, J = 7.8 Hz), 6.76 (t, 1H, J = 2.3 Hz), 6.66 (dd, 1H, J = 2.5, 8.1 Hz), 5.87 (d, 1H, J = 7.9 Hz, ex w/D_2O), 4.86 (ap octet, 1H), 3.22 (m, 1H), 2.92 (m, 2H), 2.63 (dd, 1H, J = 5.6, 13.3 Hz), 2.49 (m, 1H), 2.48 (s, 3H), 2.13 (br d, 1H, J = 11.7 Hz), 2.02 (br d, 1H, J = 12.8 Hz), 1.87 (m, 2H), 1.34 (m, 1H), 1.21 (m, 1H); MS (EI) m/z 350 (M^+). Anal. ($C_{22}H_{26}N_2O_2$·HBr) C, H, N.

(1*R,5*S**,7*R**)-5-(3-Hydroxyphenyl)-2-methyl-7-[[(phenylmethyl)carbonyl)amino]-2-azabicyclo[3.3.1]-nonane Hydrobromide (8).** 8 was prepared from the free base of **6** analogous to the preparation of **7**, yield 541.4 mg (54%), mp 266–268 °C. An analytical sample was prepared by dissolving 100 mg of the compound in hot methanol, allowing the solution to cool, and then placing this in a closed container with ether: yield 83 mg; mp 268–270 °C; ^1H NMR δ 7.31 (m, 3H), 7.21 (m, 2H), 7.14 (t, 1H, J = 7.9 Hz), 6.79 (d, 1H, J = 7.9 Hz), 6.73 (m, 1H), 6.65 (dd, 1H, J = 2.5, 8.1 Hz), 5.01 (d, 1H, J = 8.1 Hz, ex w/D_2O), 4.64 (m, 1H), 3.53 (s, 2H), 3.14 (m, 1H), 2.86 (m, 2H), 2.45 (m, 1H), 2.43 (s, 3H), 2.32 (dd, 1H, J = 5.3, 12.8 Hz), 2.04 (m, 2H), 1.83 (m, 2H), 1.08 (m, 1H), 0.94 (m, 1H); MS (EI) m/z 364 (M^+). Anal. ($C_{23}H_{28}N_2O_2$·HBr) C, H, N.

1,2,3,4,5,11-Hexahydro-6-(3-methoxyphenyl)-3-methyl-2,6-methano-6*H*-azocino[4,5-*b*]indole Methanesulfonate (9; Method A) and 1,2,3,4,6,7-Hexahydro-5-(3-methoxyphenyl)-2-methyl-1,5-methano-5*H*-azocino[4,3-*b*]indole (10). A solution of **2**·HBr (1.005 g, 2.954 mmol) and phenylhydrazine hydrochloride (648 mg, 4.48 mmol) in glacial acetic acid (15.0 mL) was heated to reflux under argon for 19 h. The glacial acetic acid was evaporated, and the red residue was shaken with a mixture of chloroform (100 mL) and 1 M NH_4OH (100 mL) saturated with NaCl. The chloroform extract was dried (Na_2SO_4) and evaporated, and the resulting orange foam was dissolved in 2-propanol (6 mL) and brought to pH 3 with methanesulfonic acid. A few drops of water were also added. The off-white crystalline solid was filtered and rinsed with cold 2-propanol (4 mL) and then with petroleum ether (bp 30–60 °C, 5 mL) yielding 960.1 mg (73%) of **9**, mp 152–153 °C dec. An analytical sample was prepared by recrystallization from 2-propanol (two times): ^1H NMR δ 7.83 (br, 1H, ex w/D_2O), 7.25 (m, 2H), 7.00 (m, 3H), 6.81 (dd, 1H, J = 3.1, 8.2 Hz), 6.75 (m, 1H), 6.39 (d, 1H, J = 8.1 Hz), 3.77 (s, 3H), 3.40 (m, 1H), 3.11 (d, 1H, J = 17.6 Hz), 2.82 (dd, 1H, J = 5.3, 17.5 Hz), 2.66 (ddd, 1H, J = 2.0, 4.5, 11.6 Hz), 2.48 (dt, 1H, J = 4.4, 12.1 Hz), 2.44 (s, 3H), 2.17 (m, 3H), 1.93 (qd, 1H, J = 2.5, 12.1 Hz); IR (KBr) 3403.3, 3052.9, 2931.8, 2834.5, 1607.0, 1583.8, 1484.6, 1459.2, 1432.8, 1376.9, 1339.8, 1285.5, 1269.9,

1165.2, 1151.2, 1054.7, 1018.9, 805.3, 780.7, 742.8, 707.7 cm^{-1}; MS (EI) m/z 332 (M^+), 275 ($M^+ - C_3H_7N$); MS m/z (CI–NH_3) m/z 333 (MH^+); UV (MeOH) λ_{max} 225, 274, 280, 290 nm. Anal. ($C_{22}H_{24}N_2O \cdot CH_4SO_3 \cdot H_2O$) C, H, N.

The filtrate was evaporated and free based with chloroform (30 mL) and 1 M NH_4OH (30 mL) saturated with NaCl. The chloroform extract was dried (Na_2SO_4) and evaporated and the resultant oil dissolved in acetonitrile (4 mL). A tan crystalline solid (**10**) was filtered and rinsed with cold acetonitrile, 47.9 mg (5%), mp 183–185 °C. An analytical sample was prepared by recrystallization from acetonitrile: mp 185-186 °C; ^1H NMR δ 7.92 (br, 1H, ex w/D_2O), 7.57 (m, 1H), 7.30 (m, 2H), 7.12 (m, 2H), 7.01 (d, 1H, J = 7.8 Hz), 6.97 (t, 1H, J = 2.1 Hz), 6.78 (dd, 1H, J = 2.2, 8.0 Hz), 4.36 (t, 1H, J = 3.1 Hz), 3.82 (s, 3H), 3.09 (d, 1H, J = 17.3 Hz), 3.02 (d, 1H, J = 17.4 Hz), 2.57 (td, 1H, J = 3.6, 11.3 Hz), 2.50 (dd, 1H, J = 3.3, 12.1 Hz) 2.32 (s, 3H), 2.2–2.3 (m, 2H), 2.00 (ap dd, 2H, J = 3.7, 9.2 Hz); IR (KBr) 3407.6, 3133.1, 3054.1, 3030.4, 2933.6, 2838.8, 1607.1, 1581.8, 1492.3, 1460.7, 1451.2, 1425.7, 1373.2, 1331.9, 1310.6, 1292.2, 1172.5, 1055.0, 1043.5, 1006.9, 803.4, 781.3, 744.2, 704.0 cm^{-1}; MS (EI) m/z 332 (M^+), 275 ($M^+ - C_3H_7N$); MS (CI–NH_3) m/z 333 (MH^+); UV (MeOH) λ_{max} 220, 273, 280, 287 nm. Anal. ($C_{22}H_{24}N_2O$) C, H, N.

Method B for Preparation of 9. 1,2,3,4,5,11-Hexahydro-6-(3-methoxyphenyl)-3-methyl-2,6-methano-6*H*-azocino[4,5-*b*]indole Methanesulfonate. A solution of **2**·HBr (10.02 g, 29.45 mmol) and phenylhydrazine hydrochloride (6.39 g, 44.2 mmol) in HCl(g)-saturated ethanol (150 mL) and ethanol (50 mL) was heated to reflux under argon for 16 h. The solvent was evaporated, and the red residue was partitioned between a mixture of chloroform (400 mL) and 1 M NH_4OH (250 mL). The chloroform extract was dried (Na_2SO_4) and evaporated, and the resulting orange foam was dissolved in 2-propanol (50 mL) and brought to pH 4 with methanesulfonic acid. Water (25 drops) was also added. The light yellow crystalline solid was filtered and rinsed with cold 2-propanol and then with excess petroleum ether (bp 30–60 °C). This solid was partitioned between chloroform (250 mL) and 1 M NH_4OH (200 mL). The chloroform layer was separated, dried (Na_2SO_4), and evaporated to give an oil. This was triturated with ether/petroleum ether (25 mL:25 mL), and **9** was filtered and dried: yield 7.99 g (82%); mp 170–172 °C; ^1H NMR matched that of **9** from method A above.

3-(1,2,3,4,5,11-Hexahydro-3-methyl-2,6-methano-6*H*-azocino[4,5-*b*]indol-6-yl)phenol Methanesulfonate (11). Method A. Compound **9** (0.67 g, 1.5 mmol) was shaken thoroughly in a separatory funnel with 1 M NH_4OH (35 mL), saturated with NaCl, and chloroform (50 mL). The chloroform layer was removed, dried (Na_2SO_4), and evaporated. The resultant off-white foam was dried overnight on a high-vacuum line. A solution of this foam in ethanol-free chloroform (13 mL) was added over a period of 2 min to a well-stirred solution of 0.80 mL (8.5 mmol) of BBr_3 in 20.0 mL of ethanol-free chloroform (20 mL) maintained at room temperature and under an atmosphere of argon. Stirring was continued for 15 min after the addition, and then this mixture was poured into a stirring mixture of 5 mL of 28% NH_4OH and 15 g of ice. The biphasic mixture was stirred for 30 min at 0 °C. A small amount of solid was filtered from the mixture, and the chloroform layer was evaporated. The resulting residue and the filtered solid were combined and triturated with methanol/water (1:1) with a few drops of 28% NH_4OH. The resulting off-white solid was filtered and air-dried, yield 0.39 g. A portion, 0.20 g, of this was dissolved in hot methanol (8 mL), and the solution was brought to pH 3 with methanesulfonic acid. The first and second crops of 11 weighed 0.22 g (69% from **9**). An analytical sample was prepared by recrystallization from methanol (7 mL): mp >300 °C; ^1H NMR (DMSO-d_6) δ 10.76 (br s, 1H, ex w/D_2O), 9.12 (br s, 1H, ex w/D_2O), 7.21 (d, 1H, J = 8.1 Hz), 7.12 (t, 1H, J = 7.9 Hz), 6.85 (ap t, 2H, J = 7.6 Hz), 6.77 (s, 1H), 6.63 (dd, 1H, J = 2.6, 7.9 Hz), 6.58 (t, 1H, J = 7.3 Hz), 6.18 (d, 1H, J = 7.9 Hz), 3.27 (m, 1H), 3.02 (d, 1H, J = 17.7 Hz), 2.74 (d, 1H, J = 5.3, 17.7 Hz), 2.52 (m, 1H), 2.31 (s, 3H), 2.24 (dd, 1H, J = 4.4, 11.8 Hz), 2.08 (td, 1H, J = 2.7, 12.0 Hz), 1.94 (dt, 1H, J = 2.8, 11.6), 1.85 (dd, 1H, J = 3.4, 12.0 Hz), 1.72 (d, 1H, J = 10.0 Hz); MS (CI–NH_3) 319 m/z (MH^+). Anal. ($C_{21}H_{22}N_2O \cdot CH_4SO_3$) C, H, N.

Method B. Compound **9** (283.0 mg, 0.6336 mmol) was dissolved in glacial acetic acid (3 mL), and then 48% HBr (2 mL) was added and the solution heated to reflux under an argon atmosphere. The solution became dark in color after 10 min, was maintained at reflux for 2 h, and then left to stir at room temperature overnight. The solution was evaporated to dryness, and the residue was triturated with water (5 mL) and 28% NH_4OH (5 mL). The off-white solid was filtered, rinsed with water (30 mL), and dissolved in hot methanol (10 mL), and the solution was made acidic with methanesulfonic acid. The white crystalline solid was filtered, rinsed with 2-propanol (3 mL) and petroleum ether (3 mL), and dried: yield 175.9 mg (67%); mp >300 °C; ^1H NMR of the free base was superimposable with that of 11 obtained by method A.

Method C. A solution of compound **13**[22] (1.00 g, 4.08 mmol) and phenylhydrazine hydrochloride (1.18 g, 8.16 mmol) in HCl-saturated ethanol (70 mL) was heated to reflux under an argon atmosphere for 24 h. The solvent was evaporated, the residue was triturated with 1 M NH_4OH (100 mL), and the pink solid was filtered and rinsed with water (25 mL). The solid was dried in a vacuum oven overnight. The solid was dissolved in hot methanol (65 mL) and made acidic with $MeSO_3H$. The off-white crystalline solid was filtered and rinsed with 2-propanol and petroleum ether, yield 1.22 g (72%) of 11. A portion of this salt (500 mg) was free based by dissolving it in hot methanol/water (20 mL/10 mL) and adjusting the pH to 9 with 28% NH_4OH. The white crystalline material was filtered and rinsed with water. After drying the weight was 370 mg: mp 222–224 °C; ^1H NMR of the free base was superimposable with that of 11 obtained by method B.

3-(1,2,3,4,6,7-Hexahydro-2-methyl-1,5-methano-5*H*-azocino[4,3-*b*]indol-5-yl)phenol (12) from 10. A solution of **10** (125 mg, 0.376 mmol) in 1.0 mL of ethanol-free chloroform was added over a period of 2 min to a well-stirred solution of 0.18 mL (1.90 mmol) of BBr_3 in 6.0 mL of ethanol-free chloroform. The reaction mixture was maintained at room temperature and under an atmosphere of argon for 15 min. The reaction was quenched by adding a mixture of 1.0 mL of 28% NH_4OH and 3.5 g of ice, and this two-phase mixture was vigorously stirred for 30 min at 0 °C. The resulting pink solid was filtered and rinsed with cold chloroform (2 mL) and cold water (6 mL). The solid was dissolved in methanol and purified by preparative TLC (chloroform/methanol/28% NH_4OH, 90/10/0.5, R_f = 0.21). The free base of **12** weighed 52 mg (44%), and it had a ^1H NMR that matched that of **12** prepared from **14**.

5-(3-Hydroxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-7-one Phenylhydrazone (14). A solution of the free base of **13** (549.8 mg, 2.088 mmol) and phenylhydrazine hydrochloride (498.5 mg, 3.447 mmol) in absolute ethanol (40.0 mL) was heated at reflux under argon for 1.3 h. The reaction solution was evaporated, and the residue was triturated with 10 mL of 15% Na_2CO_3 and 10 mL of methanol. The off-white solid was filtered and rinsed with 15 mL of water: yield 652.0 mg (82%); mp 194–195 °C dec; MS (CI–NH_3) m/z 336. Anal. ($C_{21}H_{25}N_3O \cdot H_2O$) C, H, N.

3-(1,2,3,4,5,11-Hexahydro-3-methyl-2,6-methano-6*H*-azocino[4,5-*b*]indol-6-yl)phenol Methanesulfonate (11) and 3-(1,2,3,4,6,7-Hexahydro-2-methyl-1,5-methano-5*H*-azocino[4,3-*b*]indol-5-yl)phenol Hydroiodide (12) from 14. Approximately 8 mL of polyphosphoric acid was placed in a 100-mL beaker and heated with a silicon oil bath to 80–90 °C. Compound **14** (478.5 mg, 1.426 mmol) was added, and the mixture was stirred for 10 min at which point ethanol (4.0 mL) was slowly added and heating was continued for another 15 min. The thick green solution was poured into a stirring mixture of 35 mL of 28% NH_4OH and 85 g of ice. The milky solution was adjusted to pH 9.0–9.5 with 37% HCl, and this was extracted with chloroform (5 × 50 mL). The aqueous layer was saturated with NaCl and extracted once more with chloroform (50 mL). The extracts were combined, dried (K_2CO_3), and evaporated yielding a sticky residue. This was dissolved in methanol (3 mL) and made acidic with methanesulfonic acid. A seed crystal of 11 was added. The white crystalline 11 was filtered and rinsed with 2-propanol (2 mL)

and petroleum ether (3 mL): yield 116.8 mg (20%); ^{1}H NMR of the free base was identical to that of 11 prepared by demethylation of **9**. The filtrate was evaporated, and the residue was triturated with 5 mL of 1 M NH_4OH. A pink solid was filtered and rinsed with 5 mL of water. After air-drying the solid was dissolved in 5 mL of methanol and the solution made acidic with 57% HI. The crystalline **12** was filtered and rinsed with methanol, yield 123.6 mg (19%). An analytical sample was prepared by recrystallization from water: yield 103 mg; mp >260 °C; ^{1}H NMR (DMSO-d_6) δ 10.9 (br s, 1H, ex w/D_2O), 9.3 (s, 1H, ex w/D_2O), 7.50 (m, 1H), 7.28 (dd, 1H, J = 2.1, 7.2 Hz), 7.16 (t, 1H, J = 8.0 Hz), 6.98 (m, 2H), 6.88 (d, 1H, J = 8.6 Hz), 6.82 (t, 1H, J = 2.0 Hz), 6.63 (dd, 1H, J = 2.3, 7.9 Hz), 4.20 (m, 1H), 3.08 (d, 1H, J = 17.6 Hz), 2.82 (d, 1H, J = 17.2 Hz), 2.40 (m, 1H), 2.27 (dd, 1H, J = 3.2, 12.0 Hz), 2.13 (s, 3H), 2.07 (m, 1H), 1.99 (m, 2H), 1.71 (dt, 1H, J = 5.1, 13.5 Hz); MS (FAB) m/z 319 (MH^+). Anal. ($C_{21}H_{22}N_2O$·HI) C, H, N.

(−)-(2*S*,6*R*)-3-(1,2,3,4,5,11-Hexahydro-3-methyl-2,6-methano-6*H*-azocino[4,5-*b*]indol-6-yl)phenol Methanesulfonate ((−)-11). A solution of (+)-**13**[22] (>99% ee) (422.4 mg, 1.722 mmol) and phenylhydrazine hydrochloride (0.50 g, 3.46 mmol) in HCl(g)-saturated ethanol (35 mL) was heated to reflux under an argon atmosphere for 24 h. The orange reaction solution was evaporated on a rotary evaporator and the residue was triturated with 50 mL of 1 M NH_4OH. A pink solid was filtered and washed with water (25 mL). The solid was dried in a vacuum oven and dissolved in hot methanol (55 mL), and the solution was boiled down to a volume of 40 mL. The hot solution was made acidic with methanesulfonic acid and allowed to cool. The off-white crystalline solid was filtered and rinsed with methanol (5 mL), yield 469.3 mg (66%). The product was further purified by dissolving it in hot methanol (70 mL) and then concentrating the solution to about 40 mL and allowing it to cool. The recrystallized yield was 436.6 mg: $[\alpha]^{22}_D$ (salt in DMSO, c = 1.04) = −81.4°; $[\alpha]^{22}_D$ (free base in DMSO, c = 0.43) = −115.5°; ^{1}H NMR matched that of 11. Anal. ($C_{21}H_{22}N_2O·CH_4SO_3$) C, H, N.

(+)-(2*R*,6*S*)-3-(1,2,3,4,5,11-Hexahydro-3-methyl-2,6-methano-6*H*-azocino[4,5-*b*]indol-6-yl)phenol Methanesulfonate ((+)-11). The procedure was identical to that for the preparation of (−)-11 starting with 429.4 mg of (−)-**13**[22] (>99% ee). The yield of (+)-11 was 465.2 mg (64%), and the recrystallized yield was 434.8 mg: $[\alpha]^{22}_D$ (salt in DMSO, c = 0.95) = +78.2°; $[\alpha]^{22}_D$ (free base in DMSO, c = 0.99) = +110.5°; ^{1}H NMR matched that of 11. Anal. ($C_{21}H_{22}N_2O·CH_4SO_3$) C, H, N.

1,2,3,4,5,13-Hexahydro-6-(3-methoxyphenyl)-3-methyl-2,6-methano-6*H*-azocino[4,5-*b*]-6,7-benzindole Hydrochloride (15) and 1,2,3,4,6,7-Hexahydro-5-(3-methoxyphenyl)-2-methyl-1,5-methano-5H-azocino[4,3-*b*]-6,7-benzindole (16). A mixture of **2**·HBr (1.00 g, 2.94 mmol) and 1-naphthylhydrazine dihydrochloride[19] (2.05 g, 8.87 mmol) in glacial acetic acid (75 mL) was heated to reflux for 39 h under an atmosphere of argon. The solvent was evaporated from the reaction mixture, the residue was taken up in 1 M NH_4OH (100 mL)/saturated brine (50 mL), and this was extracted with chloroform (3 × 100 mL). The chloroform extracts were combined, dried (Na_2SO_4), and evaporated onto silica gel (12 g). This was loaded on a silica gel column (200 g), and the column was eluted with chloroform/methanol/28% NH_4OH (95:5:0.5). The minor product (R_f = 0.60 with chloroform/methanol/28% NH_4OH (90:10:0.5)) was purified by another 30-g silica gel column with the same eluting solvent. The appropriate fractions yielded a residue that upon trituration with petroleum ether gave **16** as a tan solid, 257 mg (23%), that was used directly for the next step; ^{1}H NMR δ 8.91 (br s, 1H, ex w/D_2O), 8.00 (d, 1H, J = 8.2 Hz), 7.90 (d, 1H, 7.9 Hz), 7.63 (d, 1H, J = 8.7 Hz), 7.50 (m, 2H), 7.39 (t, 1H, J = 7.3 Hz), 7.28 (t, 1H, J = 7.9 Hz), 6.98 (m, 2H), 6.79 (dd, 1H, J = 2.5, 8.2 Hz), 4.42 (t, 1H, J = 3.3 Hz), 3.82 (s, 3H), 3.15 (d, 1H, J = 17.2 Hz), 3.08 (d, 1H, J = 17.5 Hz), 2.56 (m, 2H), 2.33 (s, 3H), 2.26 (m, 2H), 2.02 (m, 2H); MS (CI−NH_3) m/z 383 (MH^+); HRMS (FAB) calcd for $C_{26}H_{27}N_2O$ (MH^+) 383.2117, found 383.2132. The major product **15** from the first column (R_f = 0.43 with chloroform/methanol/28% NH_4OH (90:10:0.5)) was obtained as a foam from the appropriate fractions and dissolved in hot 2-propanol (10 mL), and the solution was made acidic with 37% HCl (0.30 mL). The slightly pink crystalline solid was filtered, rinsed with 2-propanol and petroleum ether, and dried, yield 675 mg (54%). An analytical sample was prepared by free-basing 140 mg of the salt and reforming an HCl salt: yield 123 mg; mp 250−252 °C; ^{1}H NMR δ 8.63 (br s, 1H, ex w/D_2O), 7.95 (d, 1H, J = 8.2 Hz), 7.79 (d, 1H, J = 8.1 Hz), 7.47 (t, 1H, J = 7.3 Hz), 7.33 (t, 1H, J = 7.7 Hz), 7.26 (m, 1H), 7.16 (d, 1H, J = 8.7 Hz), 7.06 (br s, 2H), 6.83 (dd, 1H, J = 2.5, 8.2 Hz), 6.51 (d, 1H, J = 8.7 Hz), 3.76 (s, 3H), 3.45 (m, 1H), 3.24 (d, 1H, J = 17.6 Hz), 2.91 (dd, 1H, J = 5.4, 17.3 Hz), 2.68 (m, 1H), 2.53 (dt, 1H, J = 4.4, 7.6 Hz), 2.47 (s, 3H), 2.24 (m, 3H), 1.94 (dd, 1H, J = 2.2, 12.0 Hz); MS (CI−NH_3) m/z 383 (MH^+). Anal. ($C_{26}H_{26}N_2O$·HCl·0.25H_2O) C, H, N.

1,2,3,4,5,13-Hexahydro-6-(3-methoxyphenyl)-3-methyl-2,6-methano-6*H*-azocino[4,5-*b*]-4,5-benzindole Hydrobromide (19). A mixture of **2**·HBr (1.00 g, 2.94 mmol) and 2-naphthylhydrazine dihydrochloride[19] (1.37 g, 5.93 mmol) in glacial acetic acid (75 mL) was heated to reflux under an atmosphere of argon for 14 h. The solvent was evaporated, and the residue was taken up in 1 M NH_4OH (100 mL)/saturated brine (50 mL). This was extracted with chloroform (3 × 100 mL); the extracts were combined, dried (Na_2SO_4), and evaporated onto silica gel (10 g). This was loaded as a chloroform slurry onto a silica gel column (150 g) packed in chloroform, and the eluting solvent was chloroform/methanol/28% NH_4OH (95:5:0.5). The fractions containing the major compound (R_f = 0.24 in eluting solvent) were combined and evaporated yielding a light yellow foam. This was dissolved in hot 2-propanol (13 mL) and made acidic with 48% HBr. The salt was filtered and rinsed with 2-propanol and petroleum ether: yield 915 mg (67%); mp 288−290 °C; ^{1}H NMR δ 8.30 (br s, 1H, ex w/D_2O), 7.75 (dd, 1H, J = 2.2, 7.8 Hz), 7.44 (m, 3H), 7.17 (m, 2H), 6.93 (ap q, 2H), 6.74 (m, 2H), 3.93, 3.31 (2 s, 3H), 3.40 (m, 1H), 3.17 (d, 1H, J = 17.0 Hz), 2.90 (dd, 1H, J = 5.2, 17.2 Hz), 2.74 (m, 2H), 2.45 (s, 3H), 2.17 (m, 4H); MS (CI−NH_3) m/z 383 (MH^+). Anal. ($C_{26}H_{26}N_2O$·HBr·0.25H_2O) C, H, N.

1,2,3,4,5,6-Hexahydro-5-(3-methoxyphenyl)-2-methyl-1,5-methano-2-azocino[4,3-*b*]quinoline Dihydrobromide (21). A solution of **2**·HBr (912 mg, 2.68 mmol), 87% KOH (1.17 g, 18.1 mmol), and 2-aminobenzaldehyde (969 mg, 8.00 mmol) was heated to reflux in methanol (75 mL) under an atmosphere of argon for 53 h. The reaction mixture was evaporated to dryness, and the residue was taken up in 1 M NH_4OH (125 mL)/saturated brine (25 mL) and extracted with chloroform (5 × 50 mL). The extracts were combined, dried (Na_2SO_4), and evaporated onto silica gel (4.5 g). This was loaded as a slurry in chloroform onto an 80-g silica gel column packed in chloroform. The column was eluted with chloroform/methanol (100:1), and the fractions containing the major product (R_f = 0.28 in chloroform/methanol (100:1)) were collected and evaporated yielding a light yellow foam. The foam was dissolved in hot 2-propanol (10 mL), and 48% HBr (0.90 mL) was added. The crystalline salt was filtered, rinsed with 2-propanol and petroleum ether, and air-dried: yield 1.209 g (86%); mp >240 °C dec; ^{1}H NMR δ 8.02 (d, 1H, J = 8.5 Hz), 7.83 (m, 2H), 7.70 (t, 1H, J = 8.0 Hz), 7.51 (t, 1H, J = 7.5 Hz), 7.31 (t, 1H, J = 8.1 Hz), 7.08 (d, 1H, J = 7.8 Hz), 7.03 (t, 1H, J = 2.0 Hz), 6.80 (dd, 1H, J = 2.5, 8.1 Hz), 4.09 (ap t, 1H, J = 3.2 Hz), 3.83 (s, 3H), 3.61 (d, 1H, J = 18.6 Hz), 3.34 (d, 1H, J = 18.7 Hz), 2.66 (br d, 1H, J = 12.6 Hz), 2.56 (td, 1H, J = 2.8, 12.6 Hz), 2.31 (td, 1H, J = 2.8, 12.6 Hz), 2.23 (s, 3H), 2.03 (m, 3H); MS (CI−NH_3) m/z 345 (MH^+). Anal. ($C_{23}H_{24}N_2O$·2HBr·H_2O) C, H, Br, N.

General Procedure for the Preparation of 17, 18, 20, and 22. The appropriate free-base precursor was dissolved in ps chloroform (30 mL/mmol) and cooled to <−50 °C with a dry ice/acetone bath, and a solution of 6−8 equiv of BBr_3 in ps chloroform (1−2 mL/mmol) was added over a period of 2−3 min. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. The mixture was poured into a mixture of 1.5−2.5 mL of 28% NH_4OH and 9−15 g of ice resulting in pH 9. The biphasic mixture was stirred at 0 °C for 30 min, and any solid was filtered using a sintered-glass funnel. The chloroform layer of the filtrate was sepa-

rated, and the aqueous layer was extracted with chloroform (25 mL). The chloroform layers were combined, dried (Na_2SO_4), and evaporated. The crude free bases from filtration and extraction were combined and purified as described below.

3-(1,2,3,4,5,13-Hexahydro-3-methyl-2,6-methano-6*H*-azocino[4,5-*b*]-6,7-benzindol-6-yl)phenol (17) from 15. The crude free base was dissolved in a minimum amount of hot methanol, and hot water was added until the solution was slightly turbid. A small amount of hot methanol was added to remove the turbidity. The tan crystalline solid was filtered out and air-dried. The yield was 127 mg (51%), mp 201–203 °C dec. An analytical sample was prepared by recrystallization from methanol/water (3:1, 20 mL): yield 93 mg; mp >190 °C dec; ^{1}H NMR (MeOH-d_4) δ 8.13 (d, 1H, J = 8.1 Hz), 7.71 (d, 1H, J = 8.2 Hz), 7.41 (t, 1H, J = 7.9 Hz), 7.26 (t, 1H, J = 7.2 Hz), 7.16 (t, 1H, J = 7.9 Hz), 7.04 (d, 1H, J = 8.7 Hz), 6.96 (br d, 1H, J = 7.3 Hz), 6.90 (br s, 1H), 6.70 (dd, 1H, J = 2.5, 8.0 Hz), 6.45 (d, 1H, J = 8.8 Hz), 3.45 (m, 1H), 3.30 (d, 1H, J = 17.6 Hz), 3.00 (dd, 1H, J = 5.3, 17.8 Hz), 2.70 (m, 1H), 2.51 (m, 1H), 2.48 (s, 3H), 2.25 (m, 2H), 2.06 (dd, 1H, J = 3.4, 12.6 Hz), 1.91 (dd, 1H, J = 2.2, 12.5 Hz); MS (CI–NH_3) m/z 369 (MH^+). Anal. ($C_{25}H_{24}N_2O$·0.5H_2O) C, H, N.

3-(1,2,3,4,6,7-Hexahydro-2-methyl-1,5-methano-5*H*-azocino[4,3-*b*]-6,7-benzindol-5-yl)phenol Hydrochloride (18) from 16. The crude free base was dissolved in methanol (5 mL), and this solution was evaporated onto silica gel (1.5 g). This was loaded as a slurry in chloroform onto a silica gel (30 g) column packed in chloroform. The column was eluted with chloroform/methanol/28% NH_4OH (90:10:0.5). The fractions containing the major compound (R_f = 0.20 in the eluting solvent) were collected, combined, and evaporated. The residue was dissolved in hot 2-propanol (2 mL), and the insoluble material was filtered out. The filtrate was made acidic with 37% HCl, and the mixture was heated to obtain a solution. The pink crystalline solid was filtered and rinsed with 2-propanol (2 mL) and excess petroleum ether: yield 90 mg (57%); mp >270 °C dec; ^{1}H NMR δ 8.68 (br s, 1H, ex w/D_2O), 7.97 (d, 1H, J = 8.2 Hz), 7.92 (d, 1H, J = 8.0 Hz), 7.67 (d, 1H, J = 8.8 Hz), 7.52 (m, 2H), 7.40 (t, 1H, J = 7.2 Hz), 7.24 (t, 1H, J = 8.0 Hz), 6.99 (d, 1H, J = 7.8 Hz), 6.94 (s, 1H), 6.72 (dd, 1H, J ~ 2 Hz, J = 7.8 Hz), 4.44 (br s, 1H), 3.15 (s, 2H), 2.57 (m, 2H), 2.35 (s, 3H), 2.28 (m, 2H), 2.02 (ap d, 2H, J = 5.2 Hz); MS (CI–NH_3) m/z 369 (MH^+). Anal. ($C_{25}H_{24}N_2O$·HCl·0.25H_2O) C, H, N.

3-(1,2,3,4,5,13-Hexahydro-3-methyl-2,6-methano-6*H*-azocino[4,5-*b*]-4,5-benzindol-6-yl)phenol Perchlorate (20) from 19. The crude free base was dissolved in methanol, and the solvent was evaporated. The residue was dissolved in hot acetonitrile (15 mL), and the free base crystallized out and was dried, yield 170 mg (86%). A portion (165 mg) of this was dissolved in hot 2-propanol (3 mL), and the solution was filtered. This solution was made acidic with 61% perchloric acid. The slightly pink solid crystallized out after scratching the flask: yield 115 mg (47%); mp 279–281 °C dec; ^{1}H NMR δ 8.30 (br, 1H, ex w/D_2O), 7.75 (br d, 1H, J = 7.8 Hz), 6.59–7.54 (m, 9H), 3.31 (br s, 1H), 3.12 (ap dd, 1H, J = 7.9, 17.5 Hz), 2.86 (m, 1H), 2.68 (m, 2H), 2.36 (s, 3H), 2.10 (m, 4H); MS (CI–NH_3) m/z 369 (MH^+). Anal. ($C_{25}H_{24}N_2O$·$HClO_4$) C, H, N.

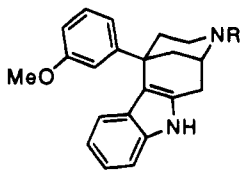
3-(1,2,3,4,5,6-Hexahydro-2-methyl-1,5-methano-2-azocino[4,3-*b*]quinolin-5-yl)phenol (22) from 21. The crude free base was dissolved in 0.3 M HCl (35 mL). Chloroform (50 mL) was added, and the pH was adjusted to 9 with 28% NH_4OH. The chloroform layer was separated, and the aqueous layer was extracted with chloroform (25 mL). The extracts were combined, dried (Na_2SO_4), and evaporated. The resulting yellow oil was triturated with acetonitrile (15 mL) yielding an off-white crystalline solid: 259 mg (82%); mp 219–221 °C; ^{1}H NMR δ 8.4 (br, 1H, ex w/D_2O), 8.08 (d, 1H, J = 8.5 Hz), 7.84 (ap t, 2H, J = 3.9 Hz), 7.70 (m, 1H), 7.52 (t, 1H, J = 7.5 Hz), 7.19 (t, 1H, J = 7.9 Hz), 6.96 (m, 2H), 6.72 (dd, 1H), 4.07 (t, 1H, J = 3.2 Hz), 3.54 (d, 1H, J = 18.7 Hz), 3.29 (d, 1H, J = 19.0 Hz), 2.55 (m, 2H), 2.28 (td, 1H, J = 2.7, 12.6 Hz), 2.23 (s, 3H), 2.02 (m, 3H); MS (CI–NH_3) m/z 331 (MH^+). Anal. ($C_{22}H_{22}N_2O$) C, H, N.

1,2,3,4,5,11-Hexahydro-6-(3-methoxyphenyl)-2,6-methano-6*H*-azocino[4,5-*b*]indole Hydrochloride (23). The free base of compound **9** (3.89 g, 11.7 mmol) was placed in a dry three-neck 500-mL round-bottom flask fitted with a condenser and argon inlet. Then K_2CO_3(s) (86 g) was added followed by 1,2-dichloroethane (350 mL). Through a rubber septum 1-chloroethyl chloroformate (5.5 mL, 54.7 mmol) was added, and this solution was heated to reflux under an argon atmosphere for 17 h. The reaction mixture was filtered to remove the solid material, and the filtrate was evaporated on a rotary evaporator yielding a yellow foam. This was dissolved in methanol and made acidic with HCl(g)-saturated methanol (25 mL). This solution was heated to reflux for 2.25 h. The solution was evaporated to dryness, and hot acetone (100 mL) was added. The first crop of crystals was filtered and weighed 2.37 g. The filtrate was evaporated to dryness, and the residue was suspended in 1 M NH_4OH (50 mL) and saturated aqueous NaCl (50 mL). This solution was extracted with chloroform (5 × 50 mL); these extracts were combined, dried (Na_2SO_4), and evaporated. The residue was dissolved in methanol (80 mL), and HCl(g)-saturated methanol (20 mL) was added. This solution was heated to reflux for 2 h under argon, cooled, and evaporated to dryness. The residue was triturated with acetone, and a second crop of the salt crystallized and was filtered, rinsed with acetone and petroleum ether, and air-dried, yield 1.08 g. The filtrate was evaporated, free based with 1 M NH_4OH, and extracted with chloroform (3 × 25 mL). The extracts were dried (Na_2SO_4), and the chloroform was evaporated to a low volume. The filtrate was purified by radial disk chromatography eluting with chloroform/methanol/28% NH_4OH (75:25:0.5). The appropriate fractions were collected, combined, and evaporated yielding an off-white foam. The first two crops of the hydrochloride salt of the product were free based with 1 M NH_4OH (100 mL) and chloroform (2 × 75 mL). The chloroform extracts were dried (Na_2SO_4) and evaporated, and the residue was added to that obtained from the radial chromatography. The resultant foam was triturated with ether and the compound filtered, yield 3.15 g (84%), mp 187–189 °C. An analytical sample of the HCl salt was prepared by dissolving a small portion of the free base in methanol, acidifying with HCl(g)-saturated methanol, and evaporating. The residue was dissolved in acetone and the compound crystallized and was filtered: mp 207–210 °C; ^{1}H NMR δ 7.90 (br s, 1H, ex w/D_2O), 7.26 (m, 2H), 7.01 (m, 3H), 6.82 (dd, 1H, J = 2.9, 8.1 Hz), 6.75 (t, 1H, J = 7.8 Hz), 6.37 (d, 1H, J = 7.9 Hz), 3.77 (s, 3H), 3.66 (m, 1H), 3.34 (dd, 1H, J = 5.7, 17.4 Hz), 2.90 (ddd, 1H, J = 2.0, 4.8, 12.8 Hz), 2.81 (d, 1H, J = 17.2 Hz), 2.65 (dt, 1H, J = 3.2, 12.4 Hz), 2.27 (dt, 1H, J = 4.6, 12.1 Hz), 2.17 (td, 1H, J = 2.6, 12.5 Hz), 1.95 (m, 2H); MS (CI–NH_3) m/z 319 (MH^+). Anal. ($C_{21}H_{22}N_2O$·HCl·C_3H_6O) C, H, N.

3-(1,2,3,4,5,11-Hexahydro-2,6-methano-6*H*-azocino-[4,5-*b*]indol-6-yl)phenol Hydrobromide (24). A mixture of **23** (202.6 mg, 0.6363 mmol), 48% HBr (2.0 mL), and glacial acetic acid (2.0 mL) was heated to reflux for 2 h. The reaction mixture was cooled, and the solid was filtered via a sintered-glass funnel. This solid was partially dissolved in methanol and made basic with 28% NH_4OH. The mixture was triturated and then evaporated. The residue was triturated with 0.5 M NH_4OH, and the solid was filtered and dried overnight in a vacuum oven. The solid was dissolved in warm methanol/acetic acid (1:1, 15 mL) and then filtered to remove any insoluble impurities. The filtrate was made acidic with 48% HBr, and this solution was evaporated. The residue was triturated with 2-propanol and the product filtered, yield 184 mg (75%). An analytical sample was prepared by recrystallizing 129 mg from water (10 mL): yield 72 mg, mp; >300 °C; ^{1}H NMR δ 10.86 (s, 1H, ex w/D_2O), 9.16 (br s, 1H, ex w/D_2O), 7.25 (d, 1H, J = 8.0 Hz), 7.16 (t, 1H, J = 7.9 Hz), 6.88 (t, 1H, J = 7.5 Hz), 6.83 (br d, 1H, J = 7.4 Hz), 6.76 (br s, 1H), 6.67 (dd, 1H, J = 2.4, 8.0 Hz), 6.60 (t, 1H, J = 7.4 Hz), 6.18 (d, 1H, J = 7.9 Hz), 3.63 (m, 1H), 3.27 (dd, 1H, J = 5.6, 17.8 Hz), 2.84 (ap d, 2H, J = 17.5 Hz), 2.41 (dt, 1H, J = 2.8, 12.3 Hz), 2.19 (dt, 1H, J = 3.9, 12.2 Hz), 2.06 (d, 1H, J = 12.3 Hz), 1.86 (dd, 1H, J = 3.6, 12.4 Hz), 1.76 (d, 1H, J = 11.7 Hz); MS (FAB) m/z 305 (MH^+). Anal. ($C_{20}H_{20}N_2O$·HBr) C, H, N.

3-Allyl-1,2,3,4,5,11-hexahydro-6-(3-methoxyphenyl)-

Table 3. Chemical Properties and Purification Methods for Compounds **25**–**32** and **34**[a]



compd	R	yield (%)	method[c]	mp (°C)	formula[b]
25	Et	83	A	181.5–182.5	$C_{23}H_{26}N_2O$
26	*n*-Pr	87	B	271–273	$C_{24}H_{28}N_2O$·HBr
27	*n*-Bu	87	C, B	274–276	$C_{25}H_{30}N_2O$·HBr·0.25H_2O
28	*n*-pentyl	82	B	263–265	$C_{26}H_{32}N_2O$·HBr
29	*n*-hexyl	87	D	261–263	$C_{27}H_{34}N_2O$·HCl
30	*n*-heptyl	81	B	249–251	$C_{28}H_{36}N_2O$·HBr
31	benzyl	95	E	180–182	$C_{28}H_{28}N_2O$
32	cyclopropylmethyl	89	B	282–284	$C_{25}H_{28}N_2O$·HBr
		86	F	118–121	$C_{25}H_{28}N_2O$·C_3H_8O
34	phenylethyl	84	C, D	262–263	$C_{29}H_{30}N_2O$·HCl·0.33H_2O

[a] All compounds exhibited proton NMR and mass spectra consistent with the representative compound **9**. [b] All compounds exhibited satisfactory (±0.4%) elemental analyses for C, H, N. [c] Method A, recrystallize from acetonitrile/water (1:1); B, crystallize HBr salt from 2-propanol; C, purify by passing through a silica gel pad with chloroform/methanol/28% NH_4OH (95:5:0.5); D, crystallize HCl salt from 2-propanol; E, trituration with petroleum ether; F, crystallize from 2-propanol.

2,6-methano-6*H*-azocino[4,5-*b*]indole (33). A solution of **23** (1.00 g, 3.14 mmol) and allyl bromide (0.33 mL, 3.81 mmol) in absolute ethanol (60 mL) was stirred at room temperature for 95 h. The reaction solution was evaporated to dryness, and the residue was taken up in 1 M NH_4OH (40 mL) and saturated NaCl (20 mL). This was extracted with chloroform (4 × 25 mL), and the extracts were combined, dried (Na_2SO_4), and were evaporated. The residue was purified by radial disk chromatography eluting with chloroform/methanol/28% NH_4OH (95:5:0.5). The appropriate fractions were combined and evaporated giving an off-white foam that was thoroughly dried on a high-vacuum line, yield 601.8 mg (53%). Unreacted **23** was recovered from the disk by elution with methanol. The solvent was evaporated from the combined fractions, and the yellow residue was triturated with ether yielding an off-white solid that weighed 283 mg (28%). A ^1H NMR of this solid matched that of the spectrum of an authentic sample. A portion, 100 mg, of the allylated product was recrystallized by dissolving it in acetonitrile (3 mL) and adding water (3 mL): yield 74 mg; mp 148.5–149.5 °C; ^1H NMR δ 7.82 (br s, 1H, ex w/D_2O), 7.25 (t, 2H, J = 8.8 Hz), 7.00 (m, 3H), 6.81 (dd, 1H, J = 2.9, 8.2 Hz), 6.75 (t, 1H, J = 7.6 Hz), 6.38 (d, 1H, J = 7.9 Hz), 5.92 (m, 1H), 5.22 (dd, 1H, J = 1.6, 17.1 Hz), 5.15 (d, 1H, J = 9.9 Hz), 3.76 (s, 3H), 3.51 (m, 1H), 3.20 (m, 2H), 3.04 (d, 1H, J = 17.6 Hz), 2.79 (dd, 1H, J = 5.2, 17.6 Hz), 2.70 (m, 1H), 2.47 (dt, 1H, J = 4.5, 12.1 Hz), 2.18 (td, 1H, J = 2.7, 12.5 Hz), 2.10 (dt, 2H, J = 3.2, 11.8 Hz), 1.91 (qd, 1H, J = 2.4, 12.2 Hz); MS (CI–NH_3) m/z 359 (MH^+). Anal. ($C_{24}H_{26}N_2O$) C, H, N.

General Procedure for Preparation of 25–32 and 34. To a mixture of **23** (0.50 g, 1.6 mmol) in chloroform (15 mL) and 10% NaOH (15 mL) was added the appropriate acid chloride (2 equiv), and the mixture was stirred vigorously for 1–2 h. The chloroform layer was separated, and the aqueous layer was extracted with chloroform (15 mL). The two chloroform layers were combined, dried (Na_2SO_4), and evaporated. A solution of 1.0 M $LiAlH_4$ in THF (20 mL) was added, and the solution was stirred under an argon atmosphere for 1 h. The reaction was quenched[32] carefully with water (0.75 mL), 15% NaOH (0.75 mL), and water (2.25 mL) with vigorous stirring. The thick mixture was diluted with tetrahydrofuran (15 mL), and the solid material was filtered from the mixture. The filtrate was evaporated to dryness, and the residue was partitioned between 1 M NH_4OH (25 mL) and chloroform (2 × 25 mL). The chloroform extracts were combined, dried (Na_2SO_4), and evaporated. The residue was purified by crystallization or the formation of an appropriate salt. Properties and methods of purification for compounds **25**–**32** and **34** are presented in Table 3.

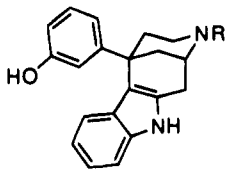
General Procedure for the Preparation of 35–44. The appropriate-free base precursor (0.8–0.9 mmol) was dissolved in ps chloroform (13 mL) and cooled to <−50 °C with a dry ice/acetone bath, and a solution of 5 equiv of BBr_3 in ps chloroform (7 mL) was added over a period of 5 min. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. The mixture was poured into a stirring mixture of 2 mL of 28% NH_4OH and 7–9 g of ice. The biphasic mixture was stirred at 0 °C for 30 min, and any solid was filtered using a sintered-glass funnel. The chloroform layer of the filtrate was separated, and the aqueous layer was extracted with chloroform (20 mL). The chloroform layers were combined, dried (Na_2SO_4), and evaporated. The resulting residue and the filtered solid were dissolved in a minimum amount of hot methanol, any insoluble material was filtered, and the filtrate was made acidic with HCl(g)-saturated ethanol. Evaporation yielded the crude HCl salt. Properties of salts of compounds **35**–**44** and methods of purification are presented in Table 4.

(+)-(1*S*,5*S*)-5-(3-Methoxyphenyl)-2-methyl-2-azabicyclo-[3.3.1]nonan-7-one Hydrobromide ((+)-2·HBr). A solution of (+)-**13**[22] (>99% ee) (1.50 g, 6.11 mmol) in methanol (25 mL) was treated with excess diazomethane in ether.[33] After standing for 48 h the excess diazomethane was destroyed by adding acetic acid, and the solution was evaporated. The residue was taken up in 1 M NH_4OH (250 mL) and extracted with chloroform (4 × 100 mL). This solution was evaporated onto silica gel (3.5 g) and run on a 75-g silica gel column with chloroform/methanol/28% NH_4OH (98:2:0.2). The fractions containing the product (R_f = 0.42 with chloroform/methanol/28% NH_4OH (95:5:0.5)) were evaporated, and the resulting oil was dissolved in hot 2-propanol. This solution was made acidic with 48% HBr. The resulting crystalline salt was filtered and rinsed with 2-propanol: yield 1.42 g (68%); mp 176–177 °C; $[\alpha]^{22}_D$ (salt in H_2O, c = 0.81) = +12.1°; $[\alpha]^{22}_D$ (free base in chloroform, c = 0.69) = +7.5°; ^1H NMR of the free base matched that of **2**. Anal. ($C_{16}H_{21}NO_2$·HBr) C, H, N.

(−)-(1*R*,5*R*)-5-(3-Methoxyphenyl)-2-methyl-2-azabicyclo-[3.3.1]nonan-7-one Hydrobromide ((−)-2·HBr). The procedure was analogous to that for (+)-**2**·HBr starting with (−)-**13**[22] (>99% ee): yield 64%; mp 176–177 °C. $[\alpha]^{22}_D$ (salt in H_2O, c = 1.33) = −12.0°; $[\alpha]^{22}_D$ (free base in chloroform, c = 0.46) = −7.2°; ^1H NMR of the free base matched that of **2**. Anal. ($C_{16}H_{21}NO_2$·HBr) C, H, N.

(−)-(1*S*,5*R*)-3-[1,2,3,4,5,11-Hexahydro-3-(2-phenylethyl)-2,6-methano-6*H*-azocino[4,5-*b*]indol-6-yl]phenol ((−)-44). (−)-**44** was prepared from (+)-**2**·HBr analogous to the procedure for the preparation of **44** from **2**·HBr except that the crude product was purified by column chromatography on a 30-g silica gel column packed in chloroform. The column was eluted with chloroform/methanol/28% NH_4OH (95:5:0.5). The free

Table 4. Chemical Properties and Purification Methods for Compounds **35–44**[a]



compd	R	yield (%)	method[c]	mp (°C)	formula[b]
35	Et	99	A	314–316 dec	$C_{22}H_{24}N_2O{\cdot}HCl$
36	*n*-Pr	90	B	>300 dec	$C_{23}H_{26}N_2O{\cdot}HCl{\cdot}0.25H_2O$
37	*n*-Bu	92	B	304–306 dc	$C_{24}H_{28}N_2O{\cdot}HCl{\cdot}H_2O$
38	*n*-pentyl	88	A	295–297 dc	$C_{25}H_{30}N_2O{\cdot}HCl$
39	*n*-hexyl	98	A	288–291 dec	$C_{26}H_{32}N_2O{\cdot}HCl$
40	*n*-heptyl	75	C	282–284 dec	$C_{27}H_{34}N_2O{\cdot}HCl$
41	*n*-benzyl	90	B	308–310 dec	$C_{27}H_{26}N_2O{\cdot}HCl$
42	cyclopropylmethyl	97	B	304–307 dec	$C_{24}H_{26}N_2O{\cdot}HCl{\cdot}0.5H_2O$
43	allyl	83	A	294–297 dec	$C_{23}H_{24}N_2O{\cdot}HCl$
44	phenylethyl	82	D	297–299 dec	$C_{28}H_{28}N_2O{\cdot}HCl{\cdot}0.5H_2O$

[a] All compounds exhibited proton NMR and mass spectra consistent with the representative compound 11. [b] All compounds exhibited satisfactory (±0.4%) elemental analyses for C, H, N. [c] Method A, triturate with 2-propanol, free base with ethyl acetate/1 M NH_4OH, prepare HCl salt, and recrystallize from acetonitrile/water (1:1); B, triturate with 2-propanol and recrystallize from acetonitrile/water (1:1); C, triturate with 2-propanol, free base with ethyl acetate/1 M NH_4OH, prepare HCl salt, and recrystallize from methanol/water (2:1); D, recrystallize from ethanol/water (1:1), free base with ethyl acetate/1 M NH_4OH, prepare HCl salt, and recrystallize from acetonitrile/water (1:1).

Table 5. Summary of Crystal Data and Refinement Parameters

compound	**5**	**9**	**10**	**22**
empirical formula	$C_{23}H_{29}N_2O_2{}^+Br^-C_2H_6O{\cdot}H_2O$	$C_{23}H_{25}N_2O^+CH_3SO_3^-{\cdot}H_2O$	$C_{22}H_{24}N_2O$	$C_{22}H_{22}N_2O$
crystal habit	colorless rod	colorless plate	colorless plate	colorless plate
crystal system	orthorhombic	monoclinic	orthorhombic	triclinic
space group	*Pbcn*	$P2_1/c$	*Fdd2*	$P\bar{1}$
a, Å	20.661(3)	7.499(1)	21.056(3)	11.017(2)
b, Å	18.448(3)	8.241(1)	51.56(2)	13.115(3)
c, Å	13.172(2)	36.341(5)	6.603(1)	13.129(3)
α, deg	90	90	90	85.09(3)
β, deg	90	94.99(1)	90	75.13(3)
γ, deg	90	90	90	70.46(3)
V, Å	5021(1)	2237.3(5)	7169(3)	1727.9(6)
Z	8	4	16	4
formula weight/*F*(000)	509.5/2144	446.5/952	332.4/2848	330.4/704
ϱ(calcd), g cm^{-3}	1.348	1.376	1.236	1.270
radiation, wavelength, (Å)	Cu Kα, 1.54178	Cu Kα, 1.54178	Cu Kα, 1.54178	Cu Kα, 1.54178
temp, K	243	293	293	293
crystal dim, mm	0.12 × 0.14 × 0.43	0.08 × 0.30 × 0.38	0.06 × 0.40 × 0.44	0.06 x 0.16 x 0.80
μ, absorp coef, mm^{-1}	2.49	1.60	0.59	0.61
2*θ* max, deg	112	112	112	112
data collected	3405	3279	2061	4934
independent data (R_{int})	3278 (0.023)	2904 (0.016)	1287 (0.015)	4495 (0.016)
observed data ($I > 2\sigma I$)	2546	2201	1189	2493
absorption correction	face indexed	face indexed	none	none
max/min transmission	0.730/0.446	0.831/0.610		
parameters refined	283	290	230	458
R-factors observed data, R_1[a], R_w2[b]	0.062, 0.144	0.059, 0.129	0.036, 0.090	0.089, 0.195
R-factors all data	0.082, 0.168	0.083, 0.150	0.040, 0.093	0.159, 0.234
goodness of fit[c] all data	1.14	1.15	1.05	1.121
fourier differences, e Å^{-3}	0.63, −0.37	0.38, −0.28	0.12, −0.14	0.26, −0.23

[a] $\Sigma||\Delta|/\Sigma|F_o||$. [b] $[\Sigma(w\Delta^2)/\Sigma)(wF_o^2)]^{1/2}$. [c] $[\Sigma w(\Delta^2)/(N_o - N_p)]^{1/2}$.

base was recrystallized from methanol yielding colorless needles: mp 229–231 °C;^{1}H NMR was identical to that of **44**; $[\alpha]^{22}_D$ (DMSO, c = 0.52) = −135.5°. Anal. ($C_{28}H_{28}N_2O{\cdot}^2/_3CH_4O$) C, H, N.

(+)-(1*R*,5*S*)-3-[1,2,3,4,5,11-Hexahydro-3-(2-phenylethyl)-2,6-methano-6*H*-azocino[4,5-*b*]indol-6-yl]phenol ((+)-44). (+)-**44** was prepared from (−)-**2**·HBr analogous to the procedure for the preparation of (−)-**44**: mp 229–231 °C;^{1}H NMR was identical to that of **44**; $[\alpha]^{22}_D$ (DMSO, c = 0.49) = +133.1°. Anal. ($C_{28}H_{28}N_2O{\cdot}^2/_3CH_4O$) C, H, N.

Single-Crystal X-ray Analyses of 5, 9, 10, and 22. Crystals of **5** (as HBr salt) were grown from ethanol. Crystals of compound **9** (as a $MeSO_3H$ salt) were grown from 2-propanol. Crystals of **10** and **22** were grown from acetonitrile. Data for all four compounds were collected on a computer-controlled automatic diffractometer, Siemens R3m/V, and corrected for Lorentz and polarization effects. Data for **5** and **9** were also corrected for absorption effects. The structures were solved by direct methods with the aid of the program SHELXTL[34] and refined by full-matrix least squares on F^2 values using the program SHELXLS-93.[35] The parameters refined included the coordinates and anisotropic thermal parameters for all non-hydrogen atoms. For the most part, hydrogen atoms were included using a riding model in which the coordinate shifts of their covalently bonded atoms were applied to the attached hydrogens with C–H = 0.96 Å, N–H = 0.91 Å, and O–H = 0.82 Å. H angles were idealized and U_{iso}(H) set at fixed ratios of U_{iso} values of bonded atoms. For **9**, **10**, and **22**, coordinates were refined for H atoms bonded to nitrogen and oxygen. Additional experimental and structural analysis details are given in Table 5, and tables of crystal

coordinates, bond distances, bond angles, and hydrogen bonds are available as supplementary material.[36]

Biological Assays. [^{3}H]DAMGO, [^{3}H]DADLE, and [^{3}H]-U69,593 Radioligand Binding Assays. μ binding sites were labeled using [^{3}H]DAMGO (1–3 nM) and rat brain membranes as previously described.[37] Briefly, incubations proceeded for 4 h at 25 °C in 50 mM Tris-HCl, pH 7.4, along with a protease inhibitor cocktail (PIC). The nonspecific binding was determined using 20 μM levallorphan. δ binding sites were labeled using [^{3}H]DADLE (1.7–2.5 nM) and rat brain membranes as previously described.[38] Incubations proceeded for 3–4 h at 25 °C in 10 mM Tris-HCl, pH 7.4, containing 100 mM choline chloride, 3 mM $MnCl_2$, and 100 nM DAMGO to block binding to μ sites and PIC. Nonspecific binding was determined using 20 μM levallorphan. κ_1 binding sites were labeled using [^{3}H]-U69,593 (1.2–2.3 nM) and guinea pig brain membranes depleted of μ and δ binding sites by pretreatment with irreversible ligands BIT and FIT as previously described,[39] except that the incubation temperature was at 25 °C. Incubations proceeded for 4–6 h at 25 °C in 50 mM Tris-HCl, pH 7.4, containing PIC and 1 μg/mL captopril. Nonspecific binding was determined using 1 μM U69,593.

Each ^{3}H ligand was displaced by 8–10 concentrations of test drug, two times. All drug dilutions were done in 10 mM Tris-HCl, pH 7.4, containing 1 mg/mL bovine serum albumin. Compounds **39**, **41**, and **44** were prepared as 1 mM solutions with 10 mM Tris buffer (pH 7.4) containing 10% DMSO and 8% Emulphor EL-620 before drug dilution. Compounds **17**, (−)-**44**, and (+)-**44** were prepared as 1 mM solutions with 10 mM Tris buffer (pH 7.4) containing 10% DMSO and 5% Emulphor EL-620 before drug dilution. The IC_{50} and slope factor (n) were obtained by using the program MLAB.

GPI and MVD Bioassays. Electrically induced smooth muscle contraction of mouse vas deferens and strips of guinea pig ileum longitudinal muscle myenteric plexus were used as a bioassay.[40] Tissues came from male ICR mice weighing 25–40 g and male Hartley guinea pigs weighing 250–500 g. The tissues were tied to gold chain with suture silk, suspended in 20-mL baths containing 37 °C oxygenated (95% O_2, 5% CO_2) Krebs bicarbonate solution (magnesium free for the MVD), and allowed to equilibrate for 15 min. The tissues were then stretched to optimal length previously determined to be 1 g tension (0.5 g for MVD) and allowed to equilibrate for 15 min. The tissues were stimulated transmurally between platinum wire electrodes at 0.1 Hz, 0.4-ms pulses (2-ms pulses for MVD), and supramaximal voltage. Drugs were added to the baths in 14–60 μM volumes. The agonists remained in contact with the tissue until maximum inhibition was reached before the addition of the next cumulative dose. Percent inhibition was calculated by using the average contraction height for 1 min preceding the addition of the agonist divided by the contraction height at maximal inhibition after exposure to the dose of agonist. IC_{50} values represent the mean of two to four tissues. IC_{50} estimates and their associated standard errors were determined by using a computerized nonlinear least squares method.[41]

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Supplementary Material Available: Tables of crystallographic data for **5**, **9**, **10**, and **22** including bond lengths, bond angles, and atomic coordinates (20 pages). Ordering information is given on any current masthead page.

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