Articles

Synthesis and Pharmacological Evaluation of Hexahydrofluorenamines as Noncompetitive Antagonists at the *N*-Methyl-D-aspartate Receptor[1]

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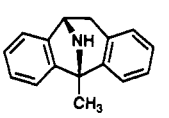
The noncompetitive (PCP) site of the *N*-methyl-D-aspartate (NMDA) receptor complex has been implicated in a number of pathologies, including the etiology of ischemic stroke. Recent testing has shown that *cis*-1,2,3,4,9,9a-hexahydro-*N*-methyl-4a*H*-fluoren-4a-amine (1), a rigid analog of PCP, is a potent antagonist at this site (IC_{50} = 30 nM for displacement of [^{3}H]TCP). On the basis of this finding, a number of derivatives encompassing variations in stereochemistry, amine substitution and position, aromatic and aliphatic ring substitution, and heteroatom ring substitution have been prepared to explore the structure–activity relationships around this ring system. All compounds were evaluated for their PCP receptor affinity; potent compounds were also tested in vitro (cultured neurons) and in vivo (prevention of NMDA-induced lethality in mice). The present hexahydrofluorenamines demonstrated a wide range of potencies, with optimal affinity concentrated in analogs containing a heteroatom (sulfur) in the B ring (IC_{50} of 11 nM versus [^{3}H]TCP for **16b**), methyl substitution on the amine, and *R* stereochemistry at the 4a position. No significant improvement in affinity was seen with aromatic ring substitution. Aliphatic ring substitution, large amine substituents, and alterations in the position of amine substitution on the ring system resulted in a loss of potency. To explore the effect of simultaneous hydrogen bonding with a putative receptor atom from two directions, the 2-hydroxymethyl derivatives were prepared. This substitution resulted in a loss in receptor binding affinity. Molecular modeling, X-ray, and NMR studies have been used to determine an optimal conformation of the hexahydrofluoreneamines at the receptor site.

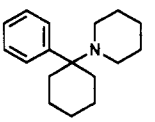
Introduction

The excitatory amino acids aspartate and glutamate are major neurotransmitters within the mammalian central nervous system.[2-5] There are at least three subtypes of glutamate receptors, most often characterized by the prototypical agonists *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainic acid (KA).[6] Of these subtypes, the NMDA receptor has received the most attention because of its possible involvement in a variety of neuropathologies.[7]

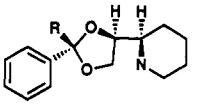
There are several sites that modulate the activity of the NMDA receptor complex,[8] including a noncompetitive NMDA site. Noncompetitive antagonists such as PCP,[9,10] dexoxadrol,[11,12] etoxadrol,[11,12] and MK801 (dizocilpine)[13-16] are believed to manifest their effects through the blockade of the cation channel associated with the NMDA receptor.[17] In agreement with theories postulating an excitotoxic effect resulting from excessive stimulation of the NMDA receptor by glutamate and aspartate, noncompetitive antagonists such as dizocilpine have proven efficacious in preventing neuronal degeneration, both in vitro (degeneration of cultured neurons resulting from hypoxic conditions)[18,19] and in vivo (reduced infarct due to carotid artery occlusion).[20,21]



DIZOCILPINE (MK-801)



PHENCYCLIDINE (PCP)



DEXOXADROL R = Ph
ETOXADROL R = Et

In the early 1960s, *N*-methylhexahydrofluorenamine (1) was identified as a potent cataleptic agent in pigeons[22] with activity similar to that described for PCP. Binding studies (Table I) now demonstrate that 1 is a potent noncompetitive antagonist at the PCP site of the NMDA receptor.[23,24] With the objective of developing the structure–activity relationships surrounding this lead, several series of related tricyclic derivatives have been prepared. Specifically, variations in amine substitution and position, aromatic ring substitution, alterations in the nature and size of the B and C rings, and enantiomeric resolution have been explored (Figure 1). In addition, a series of hydroxyamino- and diamino-substituted analogues have been synthesized to test whether binding affinity could be improved by a simultaneous interaction of two hydrogen bonding groups with a putative receptor atom. In this

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Table I. Summary of Results for Hexahydrofluorenamines

compd no.[a]	Ar	X	Y	Z	n	R	prepn	log P: shake flask[b]	log P: HPLC correlation[54]	[^{3}H]TCP binding IC_{50}[c] (nM)	glutamate-stimulated calcium influx IC_{50}[c] (μM)	NMDA lethality ED_{50}[d] (mg/kg)
dizocilpine								2.1		2.92 ± 0.42 (N = 5)	0.054 ± 0.009 (N = 7)	0.22
PCP								3.63		36.5 ± 10 (N = 4)	0.20 ± 0.03 (N = 4)	0.55
etoxadrol										107		
1 (racemic)	Ph	CH_2	H	NHMe	2	H	Scheme I	0.54		30 (N = 2)	0.1	0.58
1a (+)	Ph	CH_2	H	NHMe	2	H	Scheme I	0.33	3.37	9.9 (N = 4)	0.12	0.10
1b (−)	Ph	CH_2	H	NHMe	2	H	Scheme I	0.43	3.38	107 (N = 3)	2.55	3–10
2 (+)	Ph	CH_2	H	NH_2	2	H	Scheme I			13.4	0.51	0.61
3 (+)	Ph	CH_2	H	NHEt	2	H	ref 33			55.2	0.061	0.20
12a	Ph	CH_2	H	NHBn	1	H	Scheme II			(4%)[e] (N = 2)		
12b	Ph	CH_2	H	NHBn	3	H	Scheme II			(6%)[e] (N = 3)		
12d	[2,3]-thienyl	CH_2	H	NHBn	2	H	Scheme II			(10%)[e] (N = 2)		
12g	6-OMe Ph	CH_2	H	NHBn	2	H	Scheme II			492		
13a	Ph	CH_2	H	NHMe	1	H	Scheme II			350		
13b	Ph	CH_2	H	NHMe	3	H	Scheme II	0.66	3.77	113 (N = 2)	1.2	
13c	Ph	CH_2	H	NHMe	2	4-Me	Scheme II		3.44	79	0.39	0.8
13d	[2,3]-thienyl	CH_2	H	NHMe	2	H	Scheme II			66		1.1
13e	Ph	CH_2	H	NHMe	2	2-Me	Scheme II			95		
13f	7-OMe Ph	CH_2	H	NHMe	2	H	Scheme II	0.21	3.51	(11%)[e]		
13g	6-OMe Ph	CH_2	H	NHMe	2	H	Scheme II	0.65	3.54	22	0.16	0.51
13h	6-OH Ph	CH_2	H	NHMe	2	H	Scheme II			16.5	0.14	0.99
14a	Ph	CH_2	H	NH_2	1	H	Scheme II	−0.28	2.58	(5%)[e] (N = 2)		
14b	Ph	CH_2	H	NH_2	3	H	Scheme II			304 (N = 2)		
14c	Ph	CH_2	H	NH_2	2	4-Me	Scheme II			159		
15c	Ph	CH_2	H	NHEt	2	4-Me	Scheme II		3.80	323 (N = 2)		
16a	Ph	O	H	NHEt	2	H	ref 32			141	1.8	1.5
16b	Ph	S	H	NHMe	2	H	ref 38			11.3 (N = 2)	0.21	0.41
20	Ph	CH_2	NHMe	H	2[f]	H	Scheme III	0.04	3.28	(0%)[e] (N = 2)		
24a	Ph	CH_2	NH_2	H	2	H	Scheme III	0.30	2.94	(0%)[e] (N = 2)		
24b	Ph	CH_2	NHMe	H	2	H	Scheme III	0.62	3.43	(0%)[e] (N = 2)		
25a	Ph	CH_2	CH_2NH_2	H	2	H	Scheme III			(1%)[e]		
25b	Ph	CH_2	CH_2NHMe	H	2	H	Scheme III			(0%)[e] (N = 2)		
32a	Ph	C=CH_2	H	NH_2	2	H	Scheme IV			(4%)[e] (N = 2)		
32b	Ph	C=CH_2	H	NHMe	2	H	Scheme IV	0.76	3.79	528		
40a	Ph	CH_2	H	NHMe	2	2-CH_2NHCH_3	Scheme V	−2.65	2.48	(0%)[e]		
40b	Ph	CH_2	H	NHMe	2	2-CH_2NH_2	Scheme V	−1.42	1.84	765 (N = 2)		
45a	Ph	CH_2	H	NH_2	2	2-CH_2OH	Scheme VI	0.86	0.93	253 (N = 3)		
45b[g]	Ph	CH_2	H	NHMe	2	2-CH_2OH	Scheme VI	0.17	1.41	3935 (N = 2)		

[a] All compounds are racemic unless the enantiomer is specified. [b] log P values were measured using a standard shake flask method at pH 7.4. [c] N = 1 unless otherwise indicated. [d] N = 10 animals. [e] Percent inhibition at 10^{-7} M. [f] 2,3 double bond present. [g] Tested as the hydroiodide salt.

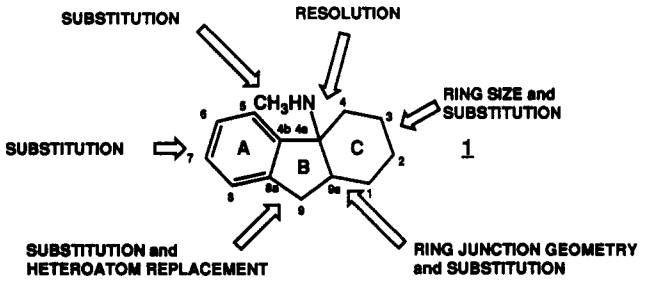


Figure 1. Summary of chemical modifications made to the hexahydrofluorenamine ring system.

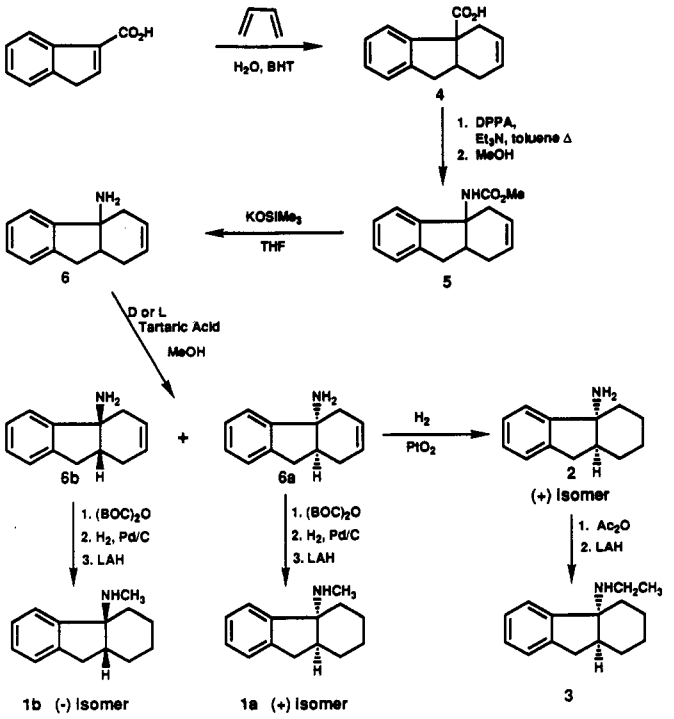
paper, we report the synthesis, PCP receptor affinity, in vitro and in vivo evaluation, and SAR of these novel hexahydrofluorenamine derivatives. Molecular modeling, X-ray, and NMR studies are also described to support a hypothesis for an optimal conformation of these compounds at the receptor site.

Chemistry

Compound 1 and its primary amine congener 2 were prepared previously as described by Godefroi and co-workers.[25] Kozikowski and co-workers have recently repeated this synthesis and have also reported the resolution of 2 into its enantiomers.[23,26] We have reexamined Godefroi's original chemistry and have shortened the route and improved yields at almost every step, as shown in Scheme I. The initial Diels–Alder reaction utilizing indene-3-carboxylic acid and butadiene had been run previously without solvent[25] or in toluene.[23] These preparations yielded the desired fluorenecarboxylic acid 4 accompanied by large amounts of polymeric byproducts. When water was substituted as the solvent,[27] yields of the Diels–Alder adduct were significantly improved. The acid 4 underwent a smooth Curtius rearrangement to the carbamate 5 following sequential treatment with diphenyl phosphorazidate and methanol. The carbamate was then efficiently hydrolyzed directly and in high yield to the primary amine 6 using potassium trimethylsilanolate in refluxing tetrahydrofuran. Potassium trimethylsilanolate had been previously used to hydrolyze esters to their carboxylate salts,[28] but this is the first example of its use for the hydrolysis of carbamates. The parent amine 6 was resolved with tartaric acid[23] to yield enantiomers 6a and 6b. The (+)-enantiomer 6a was subsequently converted to the primary amine 2 and ethylamine 3 as described previously.[23] The methyl amines 1a and 1b were synthesized from 6a and 6b, respectively, by conversion to the carbamates followed by reduction. Enantiomeric purity was assessed by HPLC according to the method of Sedman.[29] The Diels–Alder route shown in Scheme I was amenable for the synthesis of analogues containing either 5- or 6-membered B rings. Attempts to make 7-membered B rings by this route failed under a variety of Diels–Alder conditions, including high pressure.

The alternate chemistry of Godefroi[25] was also modified to produce a number of analogs of 1 bearing modifications in the carbocyclic skeleton (Scheme II). An appropriately substituted *o*-bromobenzyl bromide, or 2-(chloromethyl)-3-bromothiophene (7), was used to alkylate an enamine 8. The alkylated product was then hydrolyzed to produce the ketones **9a–g**. Conversion to the imines was affected in high yields with either benzylamine to produce **10a–d,g** or methylamine to produce **11d–g**. The imines were treated with butyllithium to form the tricyclic amines **12a–d,g** and **13d–g**. Attempts to make larger B rings with this procedure proved unsuccessful due to an inability to compete with proton transfer. The benzylamines **12a–c** were subsequently converted to the primary amines **14a–c** under hydrogenolysis conditions. The amine **14c** was converted to the acetamide and reduced with lithium aluminum hydride to produce the ethyl amine **15c**. Conversion of the primary amines **14a–c** to the *tert*-butyl carbamates followed by reduction yielded the methylamines **13a–c**. The synthesis of the furan derivative **16a** has been published previously[25] using the same methodology shown in Scheme II. The tetrahydrothiophene analog **16b** was synthesized previously using Diels–Alder chemistry.[30]

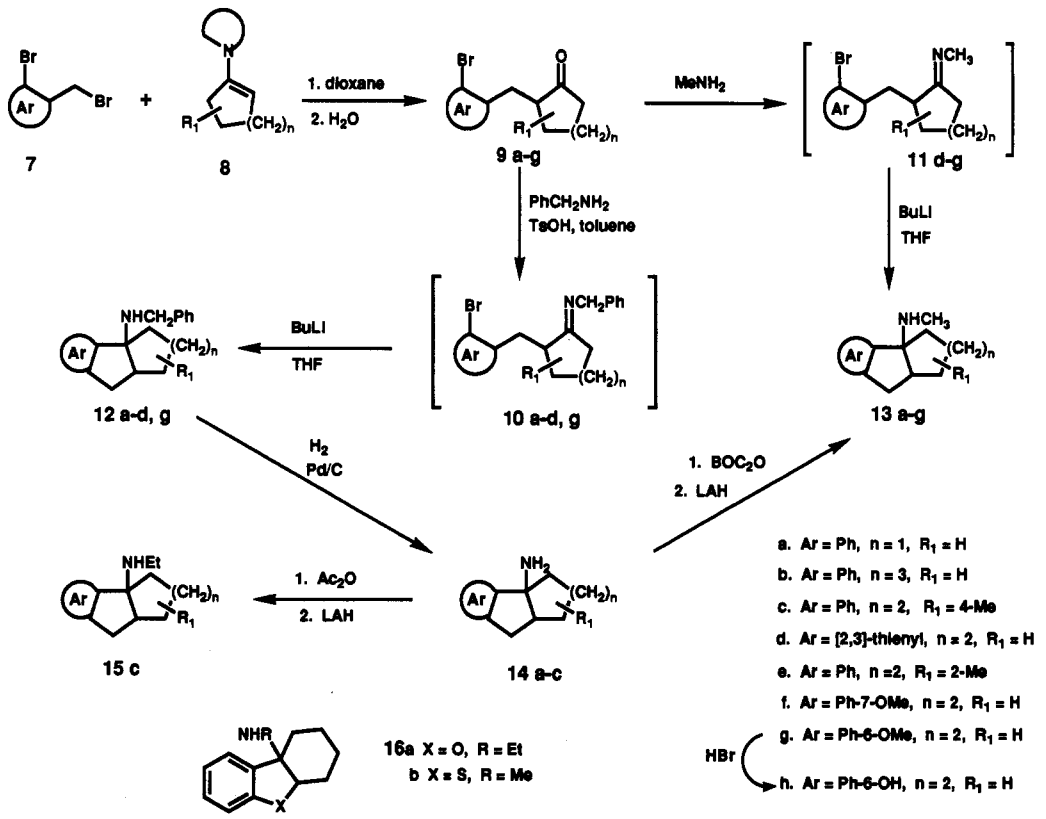
Scheme I



Two lines of evidence suggested that the iminium ring closure proceeded to form exclusively the cis ring-fused product. Extensive NMR experiments were performed on the methyl carbamate of **14b**. Proton assignments were derived from COSY and NOESY experiments. A DEPT experiment was used to unambiguously assign the lone methine carbon; its attached proton was then identified from a HETCOR experiment. The carbamate NH was assigned by exchange with deuterated water. A strong NOE between the NH and the methine proton was observed in the NOESY spectrum, consistent with a cis geometry at the ring fusion site. An X-ray crystal structure of the 4-methyl derivative **13c** (vide infra) also demonstrated a cis ring fusion between the B and C rings, as shown in Figure 3.

The synthesis of derivatives containing the amine at the alternative bridgehead position is shown in Scheme III. The tricyclic ester 17 was prepared as described previously.[31] The ester was hydrolyzed in good yield to the acid 18, rearranged to the carbamate 19, and then converted to the unsaturated methylamine 20. The saturated derivatives were prepared by the catalytic hydrogenation of 17 to produce the ester 21. Conversion of the ester to the acid 22 and rearrangement to the methyl carbamate 23 proceeded using previously described meth-

Scheme II



odology. The carbamate **23** was then hydrolyzed to the primary amine **24a** or reduced to the methylamine **24b**. The one-carbon homologated amines **25a** and **25b** were produced by conversion of the acid **22** to the amides followed by reduction with lithium aluminum hydride.

Derivatives with an exocyclic olefin at the 9-position were synthesized as shown in Scheme IV. The ester **26** underwent a Diels–Alder reaction with butadiene to produce the tricyclic ester **27** which was hydrogenated to produce **28**. In the key step, benzylic oxidation with chromium trioxide[32] produced the ketone **29** in moderate yields. Tebbe reagent[33] was used to make the exocyclic olefin **30** in 75% yield after Wittig chemistry failed. The ester was then converted to the primary amine **32a** and methylamine **32b**.

Diamine derivatives of **1** were synthesized as shown in Scheme V. The methyl ester **33** underwent a regioselective 4 + 2 cycloaddition with 1-methoxy-3-[(trimethylsilyl)-oxy]-1,3-butadiene followed by acidic hydrolysis to produce the unsaturated ketone **34** as a single isomer. The double bond was hydrogenated to form the saturated ketone **35**, which was subsequently treated with diethyl cyanophosphonate and lithium cyanide, followed by samarium iodide, to yield a 3:1 cis/trans mixture of the epimeric nitriles **36** and **37**, respectively. The nitriles were separated by silica gel chromatography, and the cis nitrile **36** was converted to the carbamate **38**. NOESY NMR experiments were used to establish the cis stereochemistry of compound **38**. When the nitrile **38** was subjected to hydrogenolysis with Raney nickel followed by treatment with methyl chloroformate, the biscarbamate **39** was obtained. The carbamate **39** was then reduced with lithium aluminum hydride to yield diamine **40a**. Alternatively, when **38** was reduced with Raney nickel/hydrogen followed by lithium aluminum hydride, the diamine **40b** was produced.

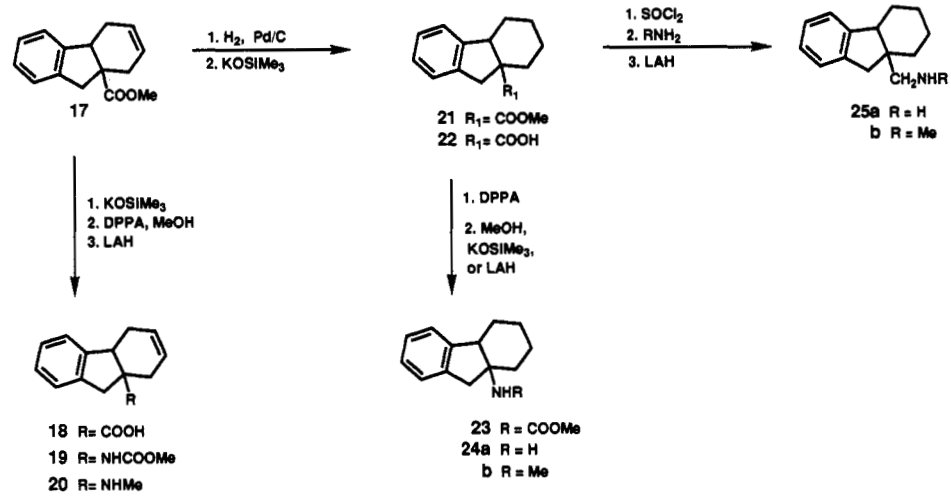
The analogous amino alcohols were synthesized as shown in Scheme VI. The alcohol **41** was protected as the benzyl ether and then treated with hydrochloric acid to yield the ketone **42**. Attempted alkylation of **42** using the enamine chemistry described previously was unsuccessful. Compound **43** was obtained by alkylating the lithium diisopropylamide-derived enolate of **42** with 2-bromobenzyl bromide. The alkylated ketone **43** was subsequently treated with benzylamine followed by *tert*-butyllithium to produce the tricyclic benzylamine **44**. Hydrogenolysis with palladium on carbon surprisingly yielded the primary amine with the benzyl ether still present. The alcohol **45a** was then produced as a mixture of isomers after additional treatment with trimethylsilyl iodide.[34] The ketone **43** could be alternatively treated with methylamine and t-butyl lithium to produce the methyl amine **46**. Debenzylation with trimethylsilyl iodide afforded the amino alcohol **45b** as the hydroiodide salt following silica gel chromatography.

Biological Testing

All compounds were evaluated for their affinity at the PCP site of the NMDA receptor by their ability to displace [^{3}H]-1-(1-thienylcyclohexyl)piperidine ([^{3}H]TCP)[35] in rat brain homogenates (Table I). For the higher affinity ligands (in general, IC_{50} vs [^{3}H]TCP of <150 nM), potency as noncompetitive NMDA antagonists was determined in vitro using a glutamate-stimulated calcium influx assay (GSCI).[36] Cultures of fetal rat brain neurons were exposed to a 30-min 100 μM L-glutamate stimulus in the presence or absence of test agents. A trace of $^{45}Ca^{2+}$ in the test medium was used as a means for measuring calcium influx. In vivo activity was assessed by prevention of NMDA-induced lethality in mice (Table I).

The present hexahydrofluorenamines demonstrated a wide range of potency for the noncompetitive receptor.

Scheme III



Scheme IV

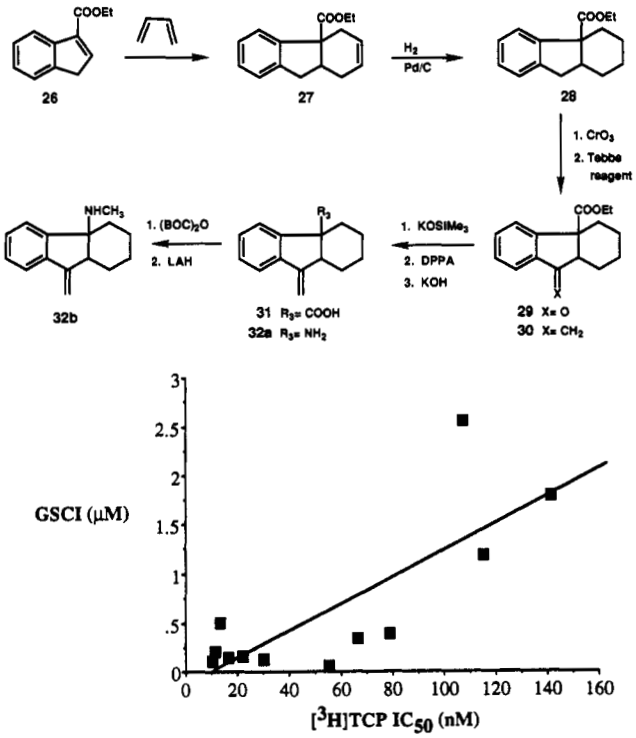


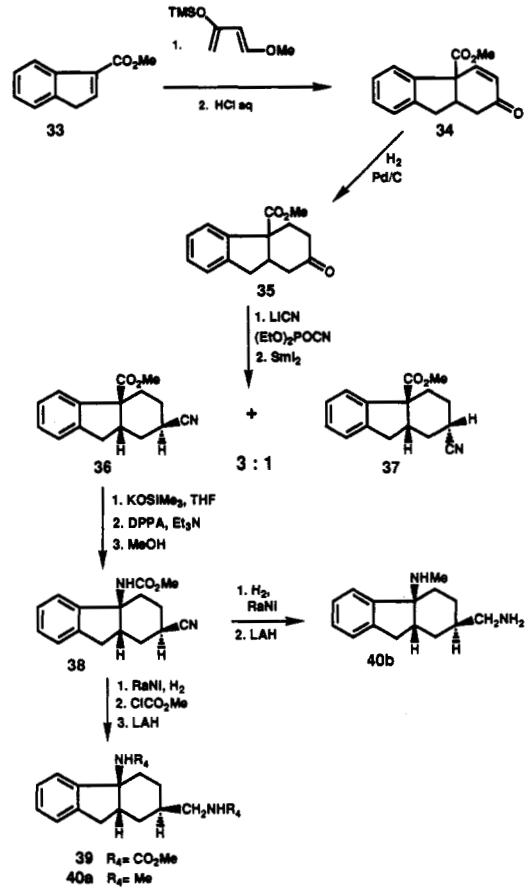
Figure 2. Correlation of [^{3}H]TCP binding affinity with glutamate-stimulated calcium influx (Table I, GSCI). The relevant equation is as follows: GSCI (μM) = 0.014(±0.003) [^{3}H]TCP IC_{50} (nM) − 0.10 (n = 13, r^2 = 0.67, F = 22, s = 0.47).

Receptor binding affinity was significantly correlated with inhibition of glutamate-stimulated calcium influx (GSCI) (Figure 2). Perhaps most illustrative of this point was the enantiomeric pair **1a** and **1b**. The (+)-enantiomer had a higher receptor affinity than the (−)-enantiomer (9.9 nM versus 107 nM), a difference that was also reflected in the GSCI assay (0.12 μM versus 2.55 μM). [^{3}H]TCP receptor binding was also correlated with activity in the in vivo NMDA lethality assay (Table I).

X-ray Analysis

The solid-state conformation of **13c** was determined via X-ray crystallography (see Experimental Section) for comparison with the conformation used in the modeling study. The crystal structure of **13c** contains a cis ring fusion between the B and C rings, and the C (cyclohexyl) ring is in a chair conformation (Figure 3). The methyl and the methylamino substituents are disposed cis to each other, pointing to the same side of the molecule (Figure 3, away from the viewer). The *R,S* relative configuration at positions 4a and 9a, respectively, is consistent with the recently reported structure for the more active enantiomer of the primary amine **2**.[23]

Scheme V



Molecular Modeling Studies

To rationalize the structure–activity relationships and to understand the conformational preferences of these flexible systems, key reference compounds and selected analogs from Table I were analyzed using molecular modeling techniques,[37] as part of a larger modeling study

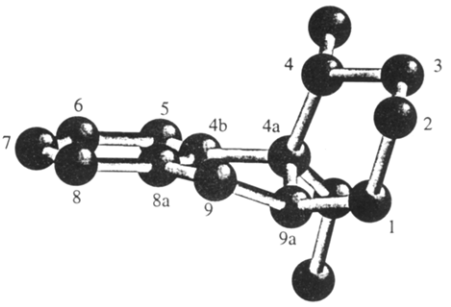


Figure 3. X-ray crystal structure of **13c**.

on noncompetitive NMDA antagonists (Figure 4; see the Experimental Section for details).[38-41] The modeled version of **13c** was designated $\mathbf{13c}_{model}$. For comparison with the modeled version, the crystal structure of **13c** was input, minimized, and designated $\mathbf{13c}_{xray}$.

In Figure 5 is shown a comparison between $\mathbf{13c}_{model}$ (red) and $\mathbf{13c}_{xray}$ (green). Similarities include the cis ring fusion, chair conformation of the cyclohexyl ring, cis arrangement of the methyl and methylamino substituents, and *RS* stereochemical configuration of the ring fusion atoms. The major difference is the pucker of the 5-membered "B" ring, with $\mathbf{13c}_{model}$ puckered up and $\mathbf{13c}_{xray}$ down. As a result of this down pucker in the crystal structure, the cyclohexyl C ring is now projected down toward the receptor interaction atom [N] location, where it would be expected to project steric hindrance (Figure 5).

Both MAXIMIN[42] and AM-1[43] were employed to investigate the energy differences between the two B ring puckered versions of **13c**. Using MAXIMIN (no electrostatic term used), a significant energy difference of 7.6 kcal/mol was found between $\mathbf{13c}_{model}$ and $\mathbf{13c}_{xray}$, with $\mathbf{13c}_{xray}$ being more stable. Roughly the same difference (6.8 kcal) in calculated heats of formation resulted when AM-1 was used with full geometry optimization. Such differences are likely to hamper interconversion of the two forms; gas-phase calculations predict that the "down-puckered" X-ray version is more stable.

To investigate whether the energy difference was due primarily to steric interactions of the C-ring methyl substituent, this group was removed from both versions and the minimizations were repeated on **1a**. The results show much smaller energy differences between the two forms, 1.7 kcal/mol and 3.8 kcal using MAXIMIN and AM-1 (full geometry optimization), respectively, with the "down puckered", X-ray version continuing to be more stable. These reduced energy differences relative to the methyl-substituted **13c** would not be expected to prevent interconversion of the two forms. Thus, a hydrogen bond interaction between a receptor atom and the basic amine within the unsubstituted analog **1a**, which would contribute roughly 4 kcal/mol in energy stabilization, could be expected to drive the structure into the "up puckered" B ring conformation, overcoming the 2–4 kcal/mol difference in energy of the two forms. The 7–8 kcal/mol difference in energy calculated for **13c** would be expected to hinder this conformational change. Indeed, the NMR analysis (vide infra) of the closely related unsubstituted compound **3** showed that the "up puckered" version predominates in solution.

Therefore, the reduced potency observed for **13c** relative to **1a** may not be due to volume intolerance of the methyl group itself, but rather a conformational change (downward pucker) induced in the ring system. This would result in a steric impact on the receptor site, as shown in Figure 5, when **13c** is fit to the pharmacophore model.

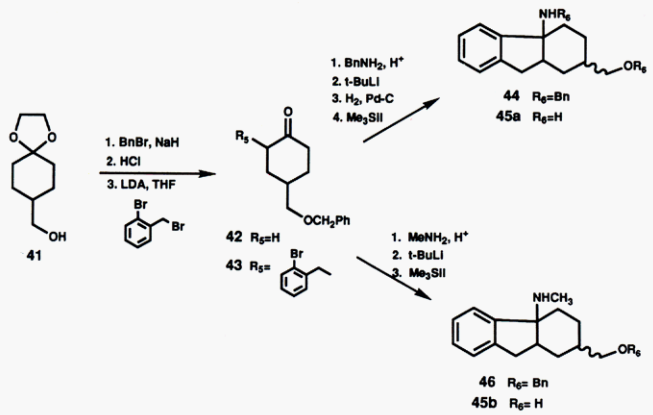
NMR Studies

To further investigate and compare the preferred solution conformations of **1a** and **13c**, several of the targeted compounds were investigated by NMR spectroscopy. In comparing the ^{1}H NMR spectra of **3** and **13c**, it was readily apparent that there were large differences in the appearance of the proton NMR spectra. In particular, compound **3**, which lacks a methyl group at the 4-position on the C ring, exhibited spectra with sharp lines, while **13c**, which contains a 4-methyl group, displayed spectra with broad lines. These results are consistent with a single low-energy conformation of the hexahydrofluorenamine ring system existing when there is no methyl group present on the aliphatic six-membered ring. Addition of the 4-methyl group cis to the amine disrupts the single low-energy state and is manifested in the proton NMR spectra as exchange broadening.

To further understand the conformational preferences of the hexahydrofluorenamines, the solution conformation of **3** was determined by a detailed analysis of the vicinal proton coupling constants. The crucial region of the molecule that determines the 5-member ring pucker, and thereby how well the conformation fits that of **1a** from the molecular modeling study, is centered around carbon 9a and includes the protons H9, H9′, H9a, H1, and H1′. Because H9 and H9′ are only coupled to each other and to H9a, one-dimensional decoupling experiments allowed close initial estimates of $^2J_{H9,H9'}$, $^3J_{H9,H9a}$, and $^3J_{H9'H9a}$. These data were input into the LAOCOON[44] spectral simulation program along with the experimental multiplet frequencies for proton 1. The program was allowed to iterate until the simulated spectrum had an acceptable fit. A comparison of a region of the simulated and experimental spectrum is shown in Figure 6. A general Karplus relationship was applied to the four vicinal coupling constants to extract the corresponding dihedral angles. The calculated vicinal coupling constants and the corresponding dihedral angles from the LAOCOON calculations are shown in Table II. Because of the constraints of the fused ring system and the availability of two vicinal coupling constants for each bond, a single solution was obtained in which the B ring was puckered "up" at C9a and the amine substituent was directed away (Figure 7). The solution structure of **3** is thus very unlike the crystal structure of **13c** and is consistent with the previously described conformation for **1a** used in the modeling studies.[23]

Consistent with the modeling study, the NMR spectra further suggest that the C ring of **3** adopts a chair conformation in which the amine and the C9 are close to equatorial. In this conformation, a bulky group attached to C4 cis to the amine (such as the methyl group in **13c**) may be forced to be axial. However, from the modeling analysis, this would result in a steric impact on the putative receptor interaction atom. Thus, two or more higher energy conformations with different B or C ring puckers may exist in equilibrium, thereby causing the broadening observed in the proton NMR spectrum of **13c**. It is probable that the bioactive conformation suggested from the modeling studies exists transiently in solution and that this conformation may be adopted by **13c** upon binding to the receptor, at some cost in internal energy.

Scheme VI



Structure–Activity Relationships

Amine Configuration, Substitution, and Position. In agreement with previous studies[23] in which the enantiomers of the primary amine **2** were examined, the (+)-**1a** isomer (absolute configuration 4a*R*) has greater affinity in [^{3}H]TCP binding than the (−)-**1b** isomer (absolute configuration 4a*S*). In general, optimal potency was observed with *N*-methyl substitution (Table I, compounds **1a,b** and **13a–c**). *N*-Benzyl substitution (**12a,b,d,g**) markedly reduced affinity while NH_2 and NHEt analogs (**15c** and **16b**) had comparable affinity. This suggests a steric intolerance in this region of the receptor for large N-substituents and supports an optimal substitution pattern such that methylamine > primary amine ≈ ethylamine ≫ benzylamine. Placement of the amino functionality at the alternate bridgehead position (**20**, **24a**, and **24b**) resulted in a complete loss of receptor affinity. Although such compounds can be fit to previously described pharmacophore models[12,45–47] of the PCP site within the NMDA receptor complex, the angle at which a hydrogen bond is made between the amine and the putative receptor atom is altered, falling in a region described[47] as being detrimental to receptor affinity. Addition of a methylene spacer between the amine and

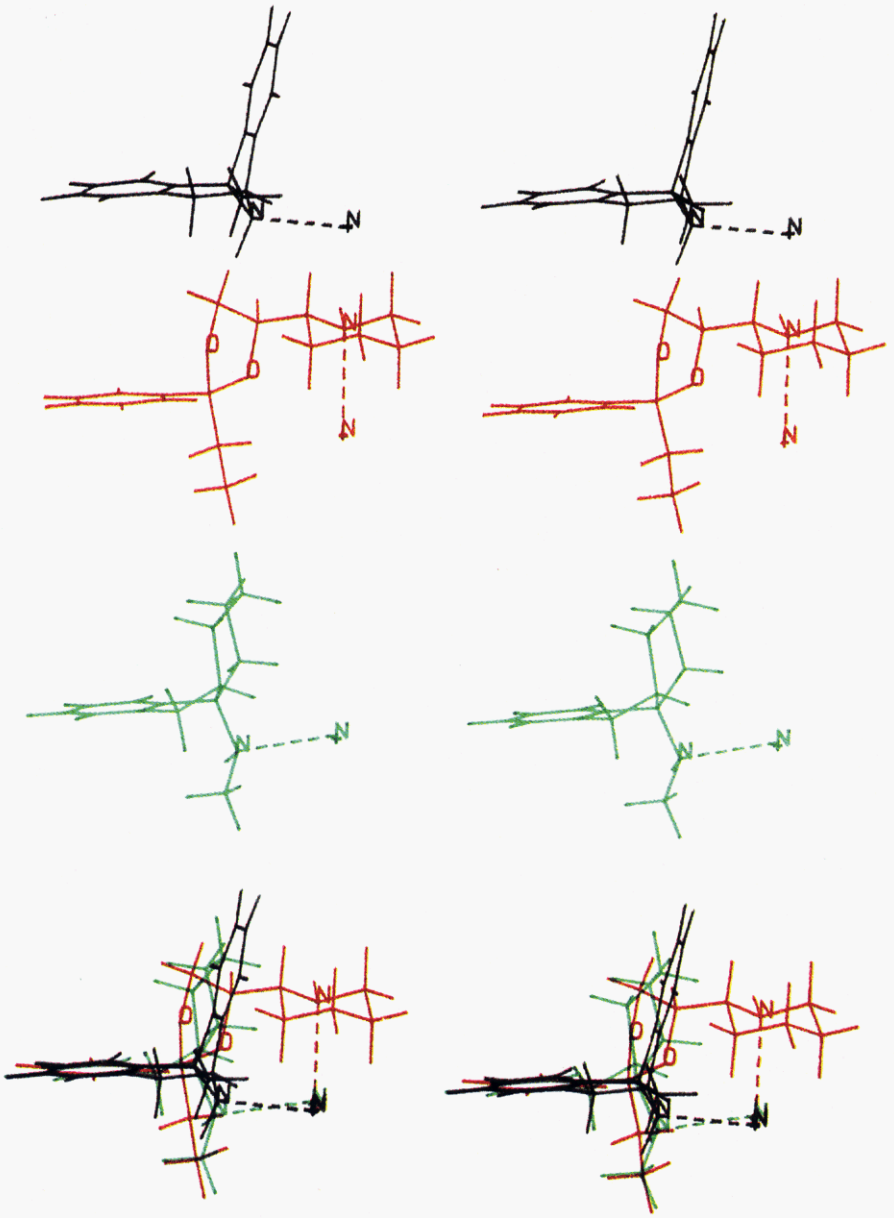


Figure 4. Stereoviews of the fit conformations of dizocilpine (black), etoxadrol (red), **1a** (green), and their superposition after fitting (bottom). A putative receptor site (N) atom used in the fitting process has been included.

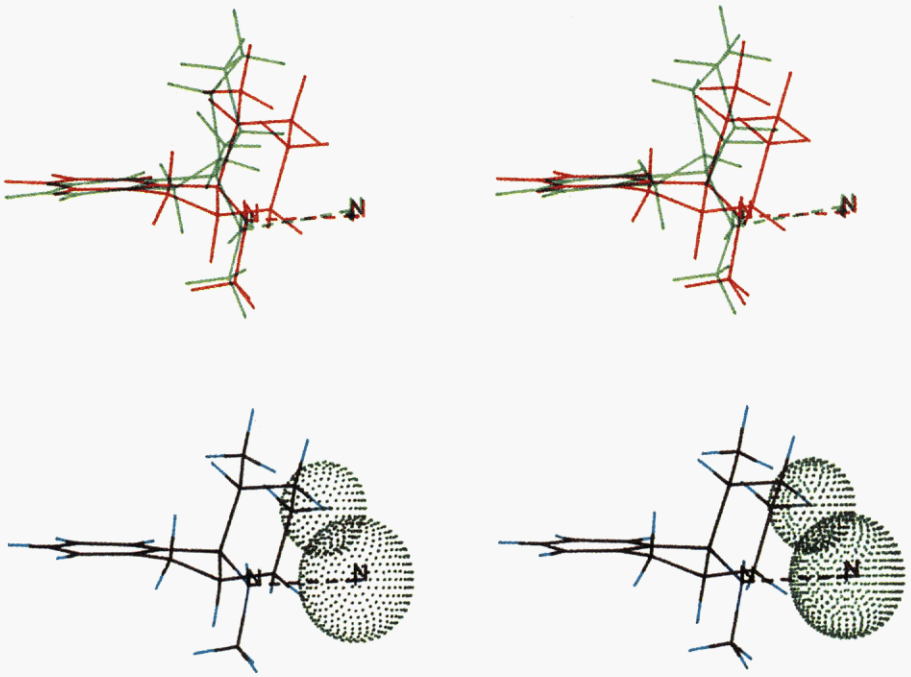


Figure 5. (Top) stereoview of the modeled (green) and X-ray (red) versions of **13c** (**13c**$_{model}$ and **13c**$_{xray}$, respectively). See the Experimental Section for details. (Bottom) **13c**$_{xray}$, color coded by atom type, with the putitive receptor site (N) atom used in the fitting process included. A steric contact between one of the cyclohexyl ring hydrogens and the receptor site atom is illustrated by the interpenetration of van der Waals dot surfaces.

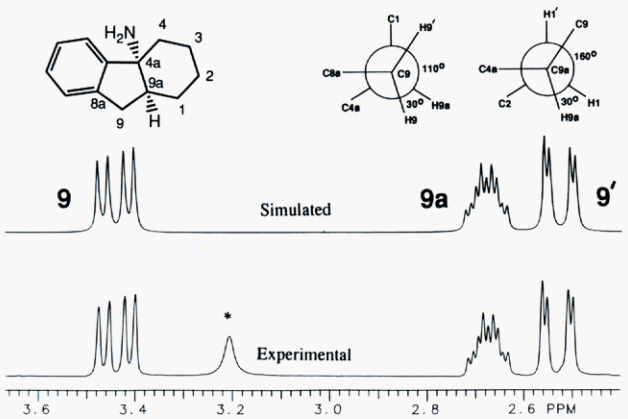


Figure 6. Comparison of the simulated and observed ^{1}H NMR spectra of **3**.

Table II. Coupling Constants and the Derived Dihedral Angles for H9a, H1, H1′, H9, and H9′ in **3**

proton pair	coupling constant (Hz)	dihedral angle
H9, H9′	16.1	
H9, H9a	6.3	30
H9′, H9a	3.0	110
H1′, H9a	9.4	160
H1, H9a	6.3	30
H1, H1′	16.0	

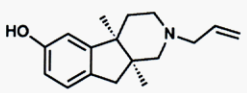
the ring system (**25a** and **25b**) did not restore binding affinity to these analogs.

Aromatic Substitution. 6-Methoxy and hydroxy substitution (**13g** and **13h**) provided a slight improvement in receptor binding affinity. This is in contrast to the SAR exhibited by phencyclidine analogs, where *m*-methoxy and hydroxyphenyl substitution improved binding affinity more than 5-fold over the unsubstituted parent.[48] Substitution of a methoxy group at the 7-position (**13f**) drastically reduced affinity at the NMDA receptor. Replacement of the benzo ring by thiophene also reduced potency somewhat (Table I, compare **13d** with **1**).

B and C Ring Modifications. Methylene substitution at the benzylic position of the B ring (**32a** and **32b**) resulted in a large reduction in binding affinity. Replacement of the benzylic methylene in the B-ring of **2** with heteroatoms resulted in compounds with equivalent (O-containing analog **16a**) or slightly improved (S-containing analog **16b**) affinity when compared to the racemic parent **1**.

Fluorenamine derivatives with a methyl group in the 2- or 4-position of the C ring retained significant binding when the amino group was methyl substituted (**13c** and **13e**). It was not clear why the analogous primary amine **14c** did not show similar binding affinity. Contraction of the cyclohexyl C ring to cyclopentyl (**13a**) or expansion to cycloheptyl (**13b**) reduced affinity, supporting an ideal ring size of six carbons for high affinity. The cyclopentyl ring may be inadequately filling the "upper lipophilic cleft" in the PCP pharmacophore,[45] while the cycloheptyl analog may be consuming receptor-excluded volume. The marked reduction in affinity of the C ring cyclopentyl, NH_2 analog **14a** may also be due to its low log P (Table I).

Comparison of the noncompetitive antagonist etoxadrol to other active compounds by overlapping the aromatic rings suggests that the nitrogen atom of etoxadrol approaches the NMDA noncompetitive receptor from the top face of the receptor binding site (Figures 4 and 8).[46] Additional evidence for receptor interaction from this direction comes from the relatively rigid hexahydroindeno-[1,2-*c*]pyridine **47**,[49] a compound reported to have an IC_{50}



47

of 62 nM versus [^{3}H]PCP (Figure 8). These unusual fits in the binding site model suggested that compounds might be designed to take advantage of this receptor's apparent ability to bind the heteroatom of ligands from more than

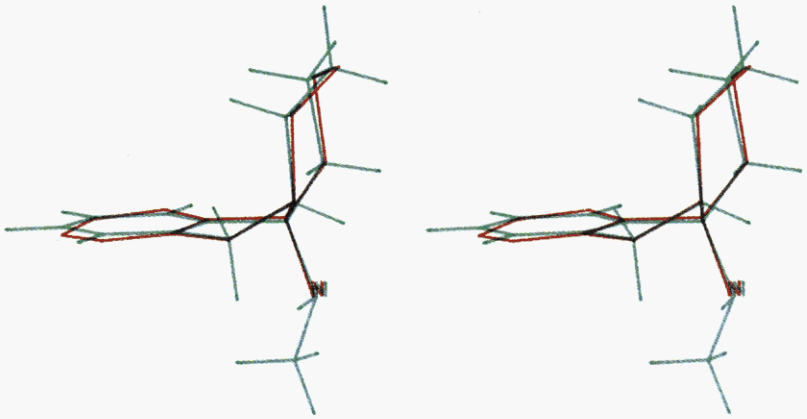


Figure 7. Comparison of the NMR-derived conformation of **3** (red, without hydrogens) and the modeled version of **1c** (green, with hydrogens added).

one direction. It was envisioned that an additional amino or hydroxyl group could hydrogen bond to the putative receptor atom from an analogous direction to that of the basic amine on etoxadrol while maintaining the interaction present in PCP. Molecular modeling studies suggested that 2-substitution of the C ring by $-CH_2X$ groups in the S configuration, where X was a hydrogen bonding group such as OH or NH_2, would present a group in the proper orientation for hydrogen bonding to the putative receptor atom, similar to what has been reported for etoxadrol[12] (Figure 8). In addition, the high receptor affinity retained by the 2-Me analog **13e** in the present hexahydrofluorenamine series suggested that there was steric tolerance in this region of the receptor.

The resulting 2-substituted analogs (**40a,b** and **45a,b**) all displayed reduced affinity relative to the parent **1** (or **2**). This may be due to a number of factors. Aside from increased entropy due to the introduction of a flexible 2-substituent, the reduced log *P* exhibited by **40a** and **40b** at pH 7.4 (Table I), due to protonation of the amine side chain, may be adversely affecting binding. All 2-substituted analogs were tested as a mixture of four stereoisomers (racemic at the 2 and 4a positions); resolution would certainly result in an increase in affinity. The debenzylation of the *O*-benzyl ester for **45b** involved the use of trimethylsilyl iodide, and the resulting HI salt was quite tightly complexed (see the Experimental Section). This HI complex may be adversely affecting the binding of this analog.

Conclusions

Consistent with literature reports that describe a tight SAR for other classes of noncompetitive NMDA antagonists, the present series of hexahydrofluorenamines demonstrated a wide range of affinities with fairly subtle changes in substitution pattern. In line with previous studies,[23] the (+)-enantiomer **1a** was approximately 10-fold more potent than the (−)-isomer **1b**. There appears to be a size-limiting pocket near the basic amine that tolerates up to a benzyl group. Interestingly, heteroatom substitution in the central "B" ring was tolerated, with slightly decreased and increased affinities observed with oxygen and sulfur insertion, respectively (**16a** and **16b**). Similar to the PCP SAR, improved potency was seen with 6-hydroxy substitution (**13h**), while 7-substitution abolished activity (**13f**). These positions correspond to the meta and para positions, respectively, of PCP when the

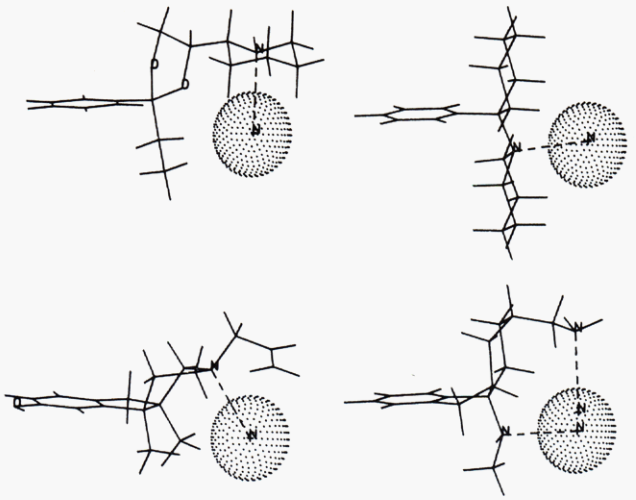


Figure 8. The noncompetitive antagonists etoxadrol (top left), PCP (top right), the hexahydroindeno[1,2-*c*]pyridine **47** (bottom left), and **40b** (bottom right), as viewed edge-on to the common phenyl rings. A hypothetical receptor atom has been added (a nitrogen surrounded by dots), 2.8 Å distant from the basic amines, along the lone pair direction (dotted lines) indicating a hydrogen bonding interaction in common to these antagonists.

two structures are superimposed (Figures 4 and 8). However, the magnitude of the potency increase resulting from *m*-OH substitution was less than that reported for PCP. Reduced lipophilicity may be playing a role in reducing the affinity of **13h** (expected log *P* of 0–0.4 based on the measured values for the unsubstituted parent **1** and the methoxy-substituted **13g**; see Table I).

Consistent with the strict structural requirements reported to be present at this receptor, certain alterations in the directionality of hydrogen bonding between the basic amine and a putative receptor atom (see **20**, **24**, and **25**; Table I) markedly reduced affinity. Analogues containing C-ring substituents designed to interact with a receptor site from two directions were generally less potent. However, a number of other mitigating factors were also present in these analogs. The reduced affinity observed for **40a** and **b** was likely due to their low log *P* values. Very tight complexation of iodine by **45b** is likely preventing this compound from tight receptor binding. Compound **45a**, tested as a mixture of four isomers, nonetheless retains significant affinity for the receptor site (253 nM). It remains to test this theory by the preparation of additional analogs and/or the separation of isomers in the case of **45**.

As mentioned previously, log *P* also appears to play a role in determining affinity to the PCP site, a relationship

that has been observed previously[50] for PCP analogs. In the present series, compounds with a measured log P of <0.3 (shake flask) or <2.6 (HPLC correlation method) are less potent (IC_{50} > 100 nM versus [^{3}H]TCP), regardless of how they fit the pharmacophore model. Relative affinity is governed by other factors for more lipophilic analogs. Thus, the hexahydrofluorenamines reported herein represent novel ligands for the PCP site and have proven useful in the generation and refinement of a pharmacophore model of this receptor. Details of this model will appear in future publications.

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Nicolet MX-1 FT spectrometer, and ^{1}H NMR spectra were recorded on an IBM W-P100SY NMR spectrometer (100 MHz), a Varian XL200 NMR spectrometer (200 MHz), or a Varian XL300 NMR spectrometer (300 MHz) equipped with a 5-mm broadband switchable probe. IR and NMR spectra are not reported, but all spectra were consistent with the proposed structures. The mass spectra were obtained on a Finnigan 4500 mass spectrometer or a VG Analytical 7070E/HF mass spectrometer. Where analyses are indicated by the symbols of the elements, the results are within 0.4% of the theoretical values; values outside the limits are indicated. TLC was carried out with 0.25-mm silica gel F254 (E. Merck) glass plates. Some intermediate products were used directly without further purification or characterization.

(±)-*cis*-1,4,9,9a-Tetrahydro-4a*H*-fluorene-4a-carboxylic Acid (4). A 2-L stainless steel stirred pressure reactor was charged with indene-3-carboxylic acid (160 g, 1 mol), water (500 mL), and 2,6-di-*tert*-butyl-4-methylphenol (2 g). The reactor was sealed, and butadiene (500 g) was added under nitrogen pressure of 500 psi. The mixture was heated at 100 °C for 63 h. The reactor was cooled and vented overnight to remove excess butadiene. Water was separated from the resulting gum, and the organics were extracted into hot methanol. The methanol solution was decanted from a gummy polymer layer and treated with Darco G60 and Celite and filtered to give a final volume of 6 L. The methanolic layer was concentrated under reduced pressure, and the resulting solid was recrystallized from 90% aqueous methanol (2 L) and dried under vacuum to give the title compound (166 g, 78%) as a white solid, mp 120–121 °C. Anal. ($C_{14}H_{14}O_2$) C, H.

Methyl (±)-*cis*-(1,4,9,9a-Tetrahydro-4a*H*-fluoren-4a-yl)-carbamate (5). To a mixture of compound 4 (90 g, 0.421 mol) in toluene (1.5 L) was added triethylamine (46.76 g, 0.463 mol). After the solids were dissolved, a solution of diphenylphosphoryl azide (127.2 g, 0.463 mol) in toluene (300 mL) was added. An additional 300 mL of toluene was added, and the reaction allowed to stir at room temperature for 0.5 h. The mixture was slowly heated to 92 °C and stirred overnight. The solution was concentrated under reduced pressure, and the isocyanate was purified via flash chromatography eluting with toluene to yield 55.3 g of an oil. The oil was dissolved in MeOH (500 mL), DMAP (50 mg) was added, and the mixture was heated to reflux overnight. The reaction was concentrated under reduced pressure and the residue taken up in diethyl ether (600 mL). The organics were washed twice with 1 N HCl (75 mL) and then a saturated NaCl solution. The organics were dried ($MgSO_4$) and concentrated to give the title compound (60.75 g, 59%) as an oil. The compound was used without further purification.

(±)-*cis*-1,4,9,9a-Tetrahydro-4a*H*-fluoren-4a-amine (6). To a solution of the carbamate 5 (60.75 g, 0.25 mol) in THF (500 mL) was added potassium trimethylsilanolate (64.0 g, 0.50 mol). The mixture was heated to reflux overnight. The reaction mixture was poured onto 1 N HCl and washed twice with diethyl ether (200 mL). The aqueous layer was made basic (pH = 14) with solid NaOH and extracted with diethyl ether (900 mL). The organics extracts were washed twice with saturated NaCl (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give the title compound (34.8 g, 75%).

(+)-(4a*R*-*cis*)-1,4,9,9a-Tetrahydro-4a*H*-fluoren-4a-amine (6a) and (−)-(4a*S*-*cis*)-1,4,9,9a-Tetrahydro-4a*H*-fluoren-4a-amine (6b). The enantiomers of 6 were separated utilizing a modified procedure as described by Kozikowski.[23] Compound 6 (8.15 g, 43.5 mmol) could be separated to compound **6a** (1.84 g, 23%), $[\alpha]_D$ = +82° (c = 0.95, $CHCl_3$, 23 °C), and compound **6b** (1.99 g, 24%), $[\alpha]_D$ = −87° (c = 1.03, $CHCl_3$, 23 °C). After three recrystallizations from methanol the enantiomeric purity was determined by HPLC on a 4.6-mm × 25-cm Beckman Ultrasphere C18 5-μm column at 215 nm. The mobile phase used was 60:40 0.02 M $NH_4H_2PO_4$–tetrahydrofuran. Analysis of the 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC) derivatives[29] of **6a** and **6b** demonstrated that both enantiomers had enantiomeric purity greater than 98.5%.

(+)-(4a*S*-*cis*)-1,2,3,4,9,9a-Hexahydro-*N*-methyl-4a*H*-fluoren-4a-amine, Monohydrochloride (1a). To a solution of compound **6a** (1.64 g, 8.85 mmol) in CH_2Cl_2 (25 mL) was added triethylamine (1.35 mL, 9.7 mmol). The solution was cooled to 0 °C, and ethyl chloroformate (0.92 mL, 9.6 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched by the addition of a saturated $NaHCO_3$ (20 mL) solution. The organic phase was separated, dried ($MgSO_4$), concentrated under reduced pressure, and purified via silica gel chromatography using 2:9 ethyl acetate/heptane to give an oil (0.99 g, 44%). A mixture of the oil (0.9 g, 3.5 mmol) and 5% Pd/C (0.1 g) in EtOH (75 mL) was stirred under a H_2 atmosphere (50 psi) for 3 h. The solution was filtered through Celite and the resulting organic filtrate concentrated under reduced pressure to give the title compound (0.83 g, 91%) as a colorless oil. The material was used without any further purification. To a slurry of $LiAlH_4$ (0.35 g, 9.24 mmol) in THF (10 mL) was added a solution of the oil (0.80 g, 3.08 mmol) in THF (10 mL). The mixture stirred for 18 h at room temperature followed by addition of $Na_2SO_4 \cdot 10H_2O$. The precipitate was filtered and washed with diethyl ether. The filtrate was dried ($MgSO_4$) and then concentrated under reduced pressure. The amine was converted to the hydrochloride salt by treatment with HCl in 2-propanol to give the title compound (0.49 g, 58%) as a white solid: mp 195–196 °C ($C_{14}H_{19}N \cdot HCl$) C, H, N, Cl; rotation $[\alpha]_D$ = +35° (c = 1.0, $CHCl_3$, 23 °C).

(−)-(4a*S*-*cis*)-1,2,3,4,9,9a-Hexahydro-*N*-methyl-4a*H*-fluoren-4a-amine, Monohydrochloride (1b). In a manner similar to that described for the preparation of **1a**, compound **6b** (1.79 g, 9.55 mmol) was converted to the title compound (0.47 g, 58%) as a white solid: mp 195–196 °C ($C_{14}H_{19}N \cdot HCl$) C, H, N, Cl; rotation $[\alpha]_D$ = −31° (c = 0.97, $CHCl_3$, 23 °C).

Method A. General procedure for the preparation of compounds **9a–g** (Scheme II). To a solution of the enamine in dioxane (0.5 M solution) was added the alkyl halide. The reaction mixture was heated to reflux and stirred for 8 h. Water was added, and the mixture was heated for 2 h. The organic phase was taken up in diethyl ether, washed with brine, dried ($MgSO_4$), and then concentrated to give the alkylated ketones **9a–g**.

Method B. General procedure for the preparation of compounds **12a–d,g** (Scheme II). A reaction flask fitted with a Dean-Stark trap was charged with the ketone, benzylamine, *p*-toluenesulfonic acid, and toluene. The reaction mixture was heated to reflux for 12 h, cooled to room temperature, filtered, and concentrated in vacuo. The residue was dried in vacuo (0.5 mmHg) at 75 °C. The residue was taken up in dry THF and cooled to −78 °C followed by addition of the butyllithium. The mixture was stirred at −78 °C for 1 h and warmed to room temperature. The reaction was quenched by the addition of a saturated ammonium chloride solution and the product taken up in diethyl ether. The organic phase was dried ($MgSO_4$) and concentrated to give the desired benzylamines **12a–d,g**.

Method C. General procedure for the preparation of compounds **13d–g** (Scheme II). A sealed reaction flask was charged with the ketone, methylamine, 4-Å molecular sieves, and toluene. The mixture was heated to 50 °C for 15 h. The sieves were removed by filtration and washed with toluene, and the organics were concentrated under reduced pressure. The residue was taken up in dry THF and cooled to −78 °C followed by addition of the butyllithium. The mixture was allowed to stir at −78 °C for 1 h and then warmed to room temperature. The reaction was quenched by addition of a saturated NH_4Cl solution and the

product taken up in diethyl ether. The organic extracts were dried ($MgSO_4$) and then concentrated to give the desired *N*-methylamines, **13d–g**.

2-[(2-Bromophenyl)methyl]cyclopentanone (9a). The title compound was prepared with the following reagents using method A: 1-pyrrolidinyl-1-cyclopentene (15.1 g, 0.11 mol), 2-bromobenzyl bromide (30.0 g, 0.12 mol), and dioxane (100 mL). The crude mixture was purified via bulb to bulb distillation under vacuum to yield compound **9** as a clear oil (12.5 g, 45%). Anal. ($C_{12}H_{13}BrO$) C (calcd, 56.94; found, 56.37), H, Br (calcd, 31.57; found, 32.89).

(±)-*cis*-2,3,8,8a-Tetrahydro-*N*-(phenylmethyl)cyclopent[*a*]inden-3a(1*H*)-amine, Monohydrochloride (12a). The title compound was prepared with the following reagents using method B: compound **9a** (8.0 g, 32 mmol), benzylamine (4.5 g, 38 mmol), *p*-toluenesulfonic acid (75 mg), toluene (200 mL), *n*-BuLi (2.2 M in hexane, 14.3 mL, 31.5 mmol), and THF (150 mL). The free base of the amine was purified via column chromatography to give a yellow oil (3.49 g, 43%). A sample was converted to the title compound using HCl in 2-propanol to obtain a white solid, mp 266–268 °C. Anal. ($C_{19}H_{21}N$·HCl) C, H, N, Cl.

(±)-*cis*-2,3,8,8a-Tetrahydrocyclopent[*a*]inden-3a(1*H*)-amine, Monohydrochloride (14a). A mixture of compound **12a** (2.67 g, 10 mmol), 20% Pd/C (0.5 g) in THF (50 mL), and MeOH (50 mL) was stirred under a H_2 atmosphere (50 psi) for 15 min. Filtration of the mixture through a pad of Celite and concentration gave the title compound as a white solid (1.5 g, 71%), mp 270–271 °C. Anal. ($C_{12}H_{15}N$·HCl·0.013H_2O) C, H, N, H_2O.

(±)-*cis*-2,3,8,8a-Tetrahydro-*N*-methylcyclopent[*a*]inden-3a(1*H*)-amine, Monohydrochloride (13a). In a manner similar to that described for compound **1a** the free base of **14a** (0.23 g, 1.3 mmol) was treated with di-*tert*-butyl dicarbonate (0.46 g, 2.6 mmol). The product was reduced with $LiAlH_4$ (0.53 g, 14 mmol) to give the title compound as a white solid (0.16 g, 51%), mp 202–203 °C. Anal. ($C_{13}H_{17}N$·HCl) C (calcd, 69.79; found, 69.31), H, N.

2-[(2-Bromophenyl)methyl]cycloheptanone (9b). The title compound was prepared with the following reagents using method A: 1-morpholino-1-cycloheptene (10.0 g, 0.055 mol), dioxane (50 mL), and 2-bromobenzyl bromide (15.0 g, 0.06 mol). The crude mixture was purified via bulb to bulb distillation under vacuum to yield the title compound as a clear oil (8.5 g, 55%) that was a semisolid at 23 °C. Anal. ($C_{14}H_{17}BrO$) C (calcd, 59.80; found, 59.20), H, Br (calcd, 28.41; found, 28.99).

(±)-*cis*-6,7,8,9,9a,10-Hexahydro-*N*-(phenylmethyl)benz[*a*]azulen-4b(5*H*)-amine, Monohydrochloride (12b). The title compound was prepared with the following reagents using method B: compound **9b** (8.75 g, 0.031 mol), benzylamine (4.32 g, 0.04 mol), toluene (100 mL), and *p*-toluenesulfonic acid (100 mg). The imine **10b** was isolated as a yellow oil (11.4 g, 99%) and was used without additional purification. An aliquot of this material (8.94 g, 0.025 mol) was converted to the final product. With *t*-BuLi (1.7 M in pentane, 14.7 mL, 0.025 mol) and THF (100 mL). The crude product was purified via column chromatography with petroleum ether followed by ethyl acetate/petroleum ether (1:9) to give a yellow oil (4.8 g, 66%). The compound was dissolved in anhydrous diethyl ether and treated with HCl in 2-propanol to afford the title compound as a white solid, mp 192–194 °C. Anal. ($C_{21}H_{25}N$·HCl·0.03H_2O) C (calcd, 76.79 found, 76.16), H, N, Cl, H_2O.

(±)-*cis*-6,7,8,9,9a,10-Hexahydrobenz[*a*]azulen-4b(5*H*)-amine, Monohydrochloride (14b). A mixture of compound **12b** (5.59 g, 0.019 mol), 20% Pd/C (0.5 g) in THF (50 mL), and MeOH (50 mL) was stirred under a H_2 atmosphere (50 psi) for 18 min. Filtration of the mixture through a pad of Celite and concentration gave an oil. The oil was converted to the hydrochloride salt using HCl in 2-propanol. The solid was recrystallized with 2-propanol/diethyl ether to afford the title compound (2.5 g, 54%) as a white solid, mp 224–226 °C. Anal. ($C_{14}H_{19}N$·HCl) C, H, N, Cl.

(±)-*cis*-6,7,8,9,9a,10-Hexahydro-*N*-methylbenz[*a*]azulen-4b(5*H*)-amine, Monohydrochloride (13b). To a solution of the free base **14b** (0.48 g, 2.4 mmol) in CH_2Cl_2 (20 mL) was added di-*tert*-butyl dicarbonate (0.62 g, 3.6 mmol). The reaction was refluxed for 20 h, additional carbonate (180 mg) was added, and the reaction was refluxed another 4 h. The reaction was cooled, and the CH_2Cl_2 solution was washed with 5% sodium bicarbonate. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated. The residue was purified via column chromatography using petroleum ether followed by 20:80 ethyl acetate/petroleum ether. The carbamate was isolated as a clear oil (0.65 g, 90%). To a slurry of $LiAlH_4$ (0.91 g, 24 mmol) in diethyl ether (10 mL) was added a solution of the carbamate (0.72 g, 2.4 mmol) in diethyl ether (5 mL) over a 5-min period. The reaction was stirred at 25 °C for 3 days. The reaction was quenched by addition of water (0.9 mL), followed by NaOH (12.5% aqueous solution, 0.8 mL), followed by water (2.0 mL). The aluminum salts were slurried in additional diethyl ether and filtered. The combined ether solutions were dried ($MgSO_4$), filtered, and concentrated in vacuo. The oily residue was dissolved in diethyl ether and treated with HCl in 2-propanol to afford the title compound as a white solid (0.47 g, 78%), mp 207–208 °C. Anal. ($C_{15}H_{21}N$·HCl) C, H, N, Cl.

2-[(2-Bromophenyl)methyl]-4-methylcyclohexanone (9c). The title compound was prepared with the following reagents using method A: 6-methyl-1-pyrrolidinyl-1-cyclohexene (12.47 g, 75.4 mmol), 2-bromobenzyl bromide (17 g, 67.9 mmol), and dioxane (100 mL). The crude material was purified via MPLC using petroleum ether followed by 10:90 CH_2Cl_2/petroleum ether as the solvent system to afford the title compound (15.67 g, 74%) as a light yellow oil. The compound was used without further purification.

(±)-(4α,4aα,9aα)-1,2,3,4,9,9a-Hexahydro-4-methyl-*N*-(phenylmethyl)-4a*H*-fluoren-4a-amine (12c). The title compound was prepared with the following reagents using method B: compound **9c** (4.91 g, 17.5 mmol), benzylamine (2.4 g, 22.7 mmol), *p*-toluenesulfonic acid (50 mg), toluene (100 mL), THF (75 mL), and *t*-BuLi (1.7 M, 15.4 mL, 26.25 mmol). The crude material was purified via MPLC using CH_2Cl_2 as the eluant to give the title compound (3.91 g, 60%). The compound was used without further purification.

(±)-(4α,4aα,9aα)-1,2,3,4,9,9a-Hexahydro-4-methyl-4a*H*-fluoren-4a-amine, Monohydrochloride (14c). A mixture of compound **12c** (6.54 g, 22.3 mmol), 20% Pd/C (0.5 g) in THF (50 mL), and MeOH (50 mL) was stirred under a H_2 atmosphere (50 psi) for 15 min. The mixture was filtered through a pad of Celite and concentrated under reduced pressure. Purification via MPLC using 1:99 MeOH/CH_2Cl_2 followed by 5:95 MeOH/CH_2Cl_2 gave the amine (2.9 g, 64%). The free base (1.0 g) was treated with HCl in 2-propanol to afford the title compound (1.03 g, 87%) as a white solid, mp 270 °C. Anal. ($C_{14}H_{19}N$·HCl) C, H, N, Cl.

(±)-(4α,4aα,9aα)-1,2,3,4,9,9a-Hexahydro-*N*,4-dimethyl-4a*H*-fluoren-4a-amine, Monohydrochloride (13c). To a solution of the free base of compound **14c** (0.77 g, 3.82 mmol) in CH_2Cl_2 (10 mL) was added di-*tert*-butyl dicarbonate. The mixture was heated to reflux for 24 h. The organics were concentrated under reduced pressure and then purified via MPLC using 10:90 CH_2Cl_2/petroleum ether followed by 50:50 CH_2Cl_2/petroleum ether to afford the carbamate (0.96 g, 83%). The carbamate was dissolved in diethyl ether (5 mL) and added to a solution of $LiAlH_4$ (1.17 g, 30.85 mmol) in diethyl ether (50 mL). After being stirred for 24 h the solution was poured onto a saturated potassium sodium tartrate solution. After being stirred for 2 h the mixture was extracted with ethyl acetate (500 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The amine was purified via MPLC using CH_2Cl_2 followed by 5:95 MeOH/CH_2Cl_2 to afford the free base of **13c** (620 mg, 93%). A solution of 0.49 g of this material in diethyl ether was treated with HCl in 2-propanol to give the title compound (0.47 g, 87%), mp 241 °C. Anal. ($C_{15}H_{21}N$·HCl) C, H, N, Cl.

(±)-(4α,4aα,9aα)-*N*-Ethyl-1,2,3,4,9,9a-hexahydro-4-methyl-4a*H*-fluoren-4a-amine, Monohydrochloride (15c). To a solution of the amine **14c** (1.1 g, 5.46 mmol) in CH_2Cl_2 (15 mL), NEt_3 (1.66 g, 16.4 mmol), and DMF (0.5 mL) was added acetic anhydride (0.61 g, 6.0 mmol). Using the reaction conditions and purifications for compound **13c** the title compound (0.59 g, 41% overall from **14c**) was obtained as a white solid, mp 204 °C. Anal. ($C_{16}H_{23}N$·HCl) C, H, N, Cl.

2-[(3-Bromo-2-thienyl)methyl]cyclohexanone (9d). The title compound was prepared with the following reagents using

method A: 1-pyrrolidinyl-1-cyclohexene (21.4 g, 0.14 mol) and 2-(chloromethyl)-3-bromothiophene (30.0 g, 0.14 mol). The crude product was purified via column chromatography using 9:1 heptane/ethyl acetate followed by bulb to bulb distillation giving the title compound (22.98 g, 60%) as a yellow oil. The compound was used without further purification. Anal. ($C_{11}H_{13}BrOS$) C (Calcd, 45.98; found, 47.78), H, Br (calcd, 27.84; found, 30.62).

(±)-*cis*-4,5,6,7,7a,8-Hexahydro-*N*-(phenylmethyl)-3b*H*-indeno[2,1-*b*]thiophen-3b-amine, Monohydrochloride (12d). The title compound was prepared with the following reagents using method B: compound **9d** (5.0 g, 18.3 mmol), benzylamine (2.16 g, 20.1 mmol), toluene (100 mL), *p*-toluenesulfonic acid (50 mg), THF (55 mL), and *n*-BuLi (1.55 M, 12 mL, 18.6 mmol). The crude product was purified via silica gel chromatography using 100:10:1 heptane/ethyl acetate/NEt_3 to give a yellow oil. The product was converted to the salt with HCl in 2-propanol to give the title compound (0.65 g, 15%) as a white solid, mp 179–81 °C. Anal. ($C_{18}H_{21}NS$·HCl) C, H, N, S, Cl.

(±)-*cis*-4,5,6,7,7a,8-Hexahydro-*N*-methyl-3b*H*-indeno[2,1-*b*]thiophen-3b-amine, Monohydrochloride (13d). The title compound was prepared with the following reagents using method C: compound **9d** (5.05 g, 18.5 mmol), methylamine (25 mL), 4-Å molecular sieves (15 g), toluene (100 mL), THF (20 mL), and *n*-BuLi (1.6 M, 10.7 mL, 17.1 mmol). The crude product was purified by column chromatography using 1:9:90 NH_4OH/MeOH/$CHCl_3$ to give the free base (2.8 g, 73%) as a yellow oil. The amine was converted to the title compound using HCl in diethyl ether and recrystallized from MeOH/diethyl ether to give a white solid (1.4 g), mp 196 °C. Anal. ($C_{12}H_{17}NS$·HCl) C, H, N.

2-[(2-Bromophenyl)methyl]-4-methylcyclohexanone (9e). To a solution of freshly prepared LDA (0.245 mol) in THF (250 mL) at 0 °C was added a solution of 4-methylcyclohexanone (25 g, 0.223 mmol) in THF (100 mL). After the solution was stirred for 45 min a solution of 2-bromobenzyl bromide (50 g, 200 mmol) in THF (50 mL) was added and the mixture stired for 18 h. The reaction was quenched by the addition of water, extracted with diethyl ether (4 L), dried ($MgSO_4$), concentrated under reduced pressure, and then purified by MPLC using petroleum ether increasing to 10:90 CH_2Cl_2/petroleum ether to give the title compound (48.71 g, 78%). The material was used without further purification. Anal. ($C_{14}H_{17}OBr$) C (calcd, 59.8; found, 60.87), H.

(±)-1,2,3,4,9,9a-Hexahydro-*N*,2-dimethyl-4a*H*-fluoren-4a-amine, Monohydrochloride (13e). The title compound was prepared with the following reagents using method B: compound **9e** (39 g, 0.14 mol), benzene (200 mL), and *p*-toluenesulfonic acid (100 mg). Methylamine gas was passed into the refluxing solution until the formation of water had stopped. The reaction was continued as described in method B using *n*-BuLi (1 M, 33.6 mL, 0.336 mol) and diethyl ether (300 mL). The compound was treated with HCl in 2-propanol and recrystallized from MeOH/diethyl ether to give the title compound (4.5 g, 13%) as a white solid, mp 233–4 °C. Anal. ($C_{15}H_{21}N$·HCl) C, H, N, Cl.

2-[(2-Bromo-5-methoxyphenyl)methyl]cyclohexanone (9f). The title compound was prepared with the following reagents using method A: 1-pyrrolidinyl-1-cyclohexene (10.09 g, 68 mmol), 2-bromo-5-methoxybenzyl bromide (18.68 g, 68 mmol), and dioxane (150 mL). The crude product was purified by column chromatography using 10:90 ethyl acetate/heptane to give the title compound (7.5 g, 37%) as an oil. Anal. ($C_{14}H_{17}BrO_2$) C (calc, 56.58, found, 57.22), H, Br. The compound was used without further purification.

(±)-*cis*-1,2,3,4,9,9a-Hexahydro-7-methoxy-*N*-methyl-4a*H*-fluoren-4a-amine, Monohydrochloride (13f). The title compound was prepared with the following reagents using method C: compound **9f** (7.0 g, 23.6 mmol), methylamine (10 g), molecular sieves (15 g), toluene (100 mL), THF (30 mL), and *n*-BuLi (1.6 M, 14.8 mL, 23.7 mmol). The crude product was purified via column chromatography using 90:9:1 $CHCl_3$/MeOH/NH_4OH to give the free base (4.83 g, 89%) as a yellow oil. The compound was converted to the HCl salt using HCl in diethyl ether to give the title compound (3.7 g, 68%), mp 156–57 °C. Anal. ($C_{15}H_{21}NO$·0.95HCl·0.18H_2O) C, H, N, Cl.

2-[(2-Bromo-4-methoxyphenyl)methyl]cyclohexanone (9g). The title compound was prepared with the following reagents using method A: 1-pyrrolidinyl-1-cyclohexene (44.49 g, 0.29 mol) and 2-bromo-4-methoxybenzyl chloride (69.26 g, 0.29 mol). The compound was purified by fractional distillation (bp 153 °C, 1 mmHg) to give the title compound (14.5 g, 17%). Anal. ($C_{14}H_{17}BrO_2$) C, H, Br (Calcd, 26.91; found, 27.76).

(±)-*cis*-1,2,3,4,9,9a-Hexahydro-6-methoxy-*N*-(phenylmethyl)-4a*H*-fluoren-4a-amine, Monohydrochloride (12g). The title compound was prepared with the following reagents using method B: compound **9g** (2.0 g, 6.7 mmol), benzylamine (0.79 g, 7.4 mmol), *p*-toluenesulfonic acid (50 mg), and *n*-BuLi (1.6 M, 3.2 mL, 2.7 mmol). The crude product was purified by column chromatography using 10:90 MeOH/CH_2Cl_2 to obtain the free base (350 mg, 17%) as a yellow oil. The product was converted to the hydrochloride salt with HCl in diethyl ether to give the title compound (170 mg, 43%), mp 171 °C. Anal. ($C_{21}H_{25}NO$·HCl) C, H, N, Cl.

(±)-*cis*-1,2,3,4,9,9a-Hexahydro-6-methoxy-*N*-methyl-4a*H*-fluoren-4a-amine, Monohydrochloride (13g). The title compound was prepared with the following reagents using method C: compound **9g** (5.05 g, 17.2 mmol), methylamine (25 mL), 4-Å molecular sieves (15 g), toluene (100 mL), *n*-BuLi (1.6 M, 10.7 mL, 6.68 mmol), and THF (50 mL). The crude product was purified by column chromatography using 89:19:1 MeOH/CH_2Cl_2/NH_4OH to give 2.8 g of a yellow oil. The product was converted to the hydrochloride salt with HCl in diethyl ether to give the title compound as a white solid (2.6 g, 56%), mp 196 °C. Anal. ($C_{21}H_{25}NO$·HCl) C, H, N, Cl.

(±)-*cis*-2,3,4,4a,9,9a-Hexahydro-4a-(methylamino)-1*H*-fluoren-6-ol (13h). A solution of the amine **13g** (500 mg, 1.9 mmol) and 48% HBr (50 mL) was heated to reflux for 15 min. After cooling, the solution was poured onto dilute NH_4OH and extracted with ethyl acetate (125 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting solid was washed with 3 mL of hot MeOH followed by diethyl ether to give the title compound (180 mg, 49%) as a white solid: mp 182–183 °C. Anal. ($C_{14}H_{19}NO$·0.18MeOH) C, H, N.

(±)-*cis*-4b,5,8,9-Tetrahydro-8a*H*-fluorene-8a-carboxylic Acid (18). Compound 17[31] (4.0 g, 0.175 mol) was converted to the title compound by the method described for compound **22** to give the acid (3.6 g, 96%). An analytically pure sample was obtained by recrystallization from hot MeOH/water, mp 155–157 °C. Anal. ($C_{14}H_{14}O_2$) C, H.

Methyl (±)-*cis*-(4b,5,8,9-Tetrahydro-8a*H*-fluoren-8a-yl)-carbamate (19). Compound 18 (0.5 g, 2.34 mmol) was converted to compound **19** by the method described for compound **23** to afford the title compound (0.40 g, 70%) as an oil. The compound was used without further purification.

(±)-*cis*-4b,5,8,9-Tetrahydro-*N*-methyl-8a*H*-fluoren-8a-amine, Monohydrochloride (20). Compound **19** (0.40 g, 1.65 mmol) was converted to compound **20** by the method described for compound **13c** to give the title compound (110 mg, 28%), mp 163–164 °C. Anal. ($C_{14}H_{17}N$·HCl) C, H, N, Cl.

Methyl (±)-*cis*-4b,5,6,7,8,9-Hexahydro-8a*H*-fluorene-8a-carboxylate (21). A mixture of compound 17[31] (7.06 g, 0.031 mol) and 10% Pd/C (1.0 g) in EtOH (100 mL) was stirred under a H_2 atmosphere (51 psi) at 25 °C for 15 min. The solution was filtered through Celite and then concentrated under reduced pressure. Purification via column chromatography using 9:1 heptane/ethyl acetate followed by recrystallization from hexanes gave the title compound (5.9 g, 84%) as white needles, mp 56 °C. Anal. ($C_{15}H_{17}O_2$) C, H.

(±)-*cis*-4b,5,6,7,8,9-Hexahydro-8a*H*-fluorene-8a-carboxylic Acid (22). To a solution of compound **21** (3.4 g, 15 mmol) in THF (50 mL) was added potassium trimethylsilanolate (3.8 g, 30 mmol). The mixture was heated to reflux and stirred for 2.5 h. The solid that formed during the reaction was collected by suction filtration and dissolved in 1 N HCl (100 mL). The aqueous phase was extracted with diethyl ether (150 mL), dried ($MgSO_4$), and then concentrated under reduced pressure. The compound solidified upon standing to give the title compound (2.88 g, 90%) as a white solid, mp 144 °C. Anal. ($C_{14}H_{16}O_2$) C, H (calcd, 7.41; found 6.83). The compound was used without further purification.

Methyl (±)-*cis*-(4b,5,6,7,8,9-Hexahydro-8a*H*-fluoren-8a-yl)carbamate (23). A three-neck flask was charged with compound **22** (0.5 g, 2.3 mmol), NEt_3 (0.26 g, 2.57 mmol), and benzene (10 mL), followed by addition of diphenyl phospho-

razidate (0.64 g, 2.3 mmol). The mixture was heated to reflux for 18 h followed by addition of MeOH (20 mL). After being heated for an additional 18 h the solution was concentrated to dryness. The crude product was purified using a 4-mm chromatatron plate by eluting with 9:1 heptane/ethyl acetate to obtain the title compound (0.3 g, 53%) as a yellow oil. The compound was used without further purification.

(±)-*cis*-4b,5,6,7,8,9-Hexahydro-8a*H*-fluoren-8a-amine, Monohydrochloride (24a). To a solution of compound **23** (0.56 g, 2.8 mmol) in THF (20 mL) was added potassium trimethylsilanolate (1.5 g, 10.2 mmol). The mixture was heated to reflux for 48 h. The reaction was cooled and concentrated under reduced pressure. The residue was dissolved in water and the product extracted into diethyl ether (75 mL). The amine was extracted with 1 N HCl. The aqueous layer made basic with solid NaOH, and the amine was extracted back into diethyl ether (75 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The amine was converted to the HCl salt by treatment with HCl in diethyl ether to give the title compound (0.35 g, 67%) as a white solid: mp >250 °C. Anal. ($C_{13}H_{17}N$·HCl·0.29H_2O) C, H, N, Cl.

(±)-*cis*-4b,5,6,7,8,9-Hexahydro-*N*-methyl-8a*H*-fluoren-8a-amine, Monohydrochloride (24b). To a slurry of $LiAlH_4$ (0.47 g, 12 mmol) in diethyl ether (10 mL) was added a solution of compound **23** (0.30 g, 1.22 mmol) in diethyl ether (10 mL). The mixture stirred for 18 h at room temperature followed by addition of Na_2SO_4·10H_2O. The precipitate was filtered and washed with ether. The filtrate was dried ($MgSO_4$) and then concentrated under reduced pressure. The amine was converted to the salt by treatment with HCl in 2-propanol to give the title compound (0.11 g, 38%) as a white solid, mp 205–207 °C. Anal. ($C_{14}H_{19}N$·0.95HCl·0.34H_2O) C, H, N, Cl.

(±)-*cis*-4b,5,6,7,8,9-Hexahydro-8a*H*-fluorene-8a-methanamine, Monohydrochloride (25a). A solution of compound **22** (0.5 g, 2.3 mmol) in thionyl chloride (15 mL) was heated to reflux for 2.5 h. The reaction was concentrated under reduced pressure, the residue was taken up in benzene (10 mL) and cooled to 0 °C, and then ammonia gas was bubbled through the mixture for 1 h. The solution was concentrated to dryness under reduced pressure and the residue dissolved in dry THF (15 mL) and added to a slurry of $LiAlH_4$ (0.9 g, 24 mmol) in THF (15 mL) at 0 °C. After the mixture was stirred for 18 h the reaction was quenched by the addition of solid Na_2SO_4·10H_2O. The precipitate was filtered and washed with ether. The organic extracts were dried over $MgSO_4$ and then concentrated under reduced pressure. The amine was converted to the hydrochloride salt by treatment with HCl in 2-propanol to give the title compound (0.13 g, 23%) as a white solid, mp 200–210 °C dec. Anal. ($C_{14}H_{19}N$·HCl·0.25H_2O) C, H, N, Cl.

(±)-*cis*-4b,5,6,7,8,9-Hexahydro-*N*-methyl-8a*H*-fluorene-8a-methanamine, Monohydrochloride (25b). A solution of compound **22** (0.5 g, 2.3 mmol) in thionyl chloride (15 mL) was heated to reflux for 2.5 h. The reaction was concentrated under reduced pressure, the residue was taken up in benzene (10 mL) and cooled to 0 °C, and then methylamine gas bubbled through the mixture for 2 h. The solution was concentrated to dryness under reduced pressure, dissolved in dry THF (15 mL), and added to a slurry of $LiAlH_4$ (1.0 g, 26.4 mmol) in THF (15 mL) at 0 °C. The reaction was worked up and converted to the HCl salt as described for compound **24a** to give the title compound (0.4 g, 80%) as a white solid, mp 244–250 °C. Anal. ($C_{15}H_{21}N$·HCl) C, H, N, Cl.

Ethyl (±)-*cis*-1,4,9,9a-Tetrahydro-4a*H*-fluorene-4a-carboxylate (27). A 2-L stainless steel stirred pressure reactor was charged with ethyl 1*H*-indene-3-carboxylate (**26**) (22.18 g, 118 mmol), toluene (50 mL), and 2,6-di-*tert*-butyl-4-methylphenol (250 mg). The reactor was sealed, and butadiene (50 g, 0.92 mol) was added under nitrogen pressure of 500 psi. The mixture was heated to 180 °C for 20 h. The reactor was cooled and vented. The toluene solution was decanted from the gummy polymer layer and concentrated under reduced pressure. The residue was purified by bulb to bulb distillation under vacuum at 205 °C to give the desired material (10.8 g) as a crude oil. Analytically pure material could be obtained by column chromatography using 1:25 ethyl acetate/heptane to give the title compound (10.5 g, 37%) as a pale yellow oil. The compound was used without further purification.

Ethyl (±)-*cis*-1,2,3,4,9,9a-Hexahydro-4a*H*-fluorene-4a-carboxylate (28). A mixture of compound **27** (10.31 g, 43 mmol) and 5% Pd/C (0.5 g) in EtOH (100 mL) was stirred under a H_2 atmosphere (50 psi) for 3 h. The solution was filtered through Celite, and the resulting filtrate concentrated under reduced pressure to give the title compound (9.9 g, 94%) as a colorless oil. The material was used without any further purification.

Ethyl (±)-*cis*-1,2,3,4,9,9a-Hexahydro-9-oxo-4a*H*-fluorene-4a-carboxylate (29). A solution of compound **28** (5 g, 20.5 mmol) in acetic acid (500 mL) at 17–20 °C was treated dropwise with chromium trioxide solution (85 mL, 10.5 g in 95:5 acetic acid/water). After being stirred for 3 h, the reaction mixture was poured into water (3 L) and extracted with diethyl ether (3 × 1 L). The organic extracts were washed with water (500 mL) followed by saturated sodium bicarbonate until the wash was pH 8. The organic phase was dried ($MgSO_4$) and evaporated to give a pale green oil (4.7 g), which was purified by silica gel chromatography (9:1 heptane/ethyl acetate as eluant) to give recovered starting material (1.5 g) and compound **29** (2.4 g, 45%) as a clear oil. The compound was used without further purification.

Ethyl (±)-*cis*-1,2,3,4,9,9a-Hexahydro-9-methylene-4a*H*-fluorene-4a-carboxylate (30). Tebbe reagent[33] (1.7 g, 5.85 mmol) was stirred in anhydrous THF (20 mL) and cooled to −78 °C. A solution of compound **29** (1.0 g, 3.9 mmol) in THF (10 mL) was added. After 3 h an additional 1-g portion of Tebbe reagent was added and the reaction was warmed to room temperature. After being stirred for 18 h the reaction mixture was cooled to −78 °C and quenched by dropwise treatment with 15% NaOH (3.8 mL) solution. The reaction mixture was warmed to room temperature and extracted with diethyl ether (3 × 50 mL). The organic extracts were dried ($MgSO_4$), filtered, and concentrated to give an orange oil (1.9 g). The oil was purified by silica gel chromatography (loaded with $CHCl_3$/heptane and eluted with 30:1 heptane/ethyl acetate) to give the title compound as a clear oil (0.75 g, 75%). The compound was used without further purification.

(±)-*cis*-1,2,3,4,9,9a-Hexahydro-9-methylene-4a*H*-fluorene-4a-carboxylic Acid (31). A solution of compound **30** (0.84 g, 3.3 mmol) in THF (15 mL) was treated with potassium trimethylsilanolate (0.9 g, 7 mmol) and sonicated in a sealed tube for 16 h. After evaporation, the residue was dissolved in water and washed with diethyl ether (2 × 50 mL). The aqueous solution was acidified with 1 N HCl and extracted with diethyl ether (2 × 75 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated to give the title compound as a white solid (0.75 g, 100%). The compound was used without further purification.

(±)-*cis*-1,2,3,4,9,9a-Hexahydro-9-methylene-4a*H*-fluorene-4a-amine, Monohydrochloride (32a). A solution of the acid **31** (0.75 g, 3.29 mmol) and NEt_3 (0.8 mL) in anhydrous toluene (25 mL) under a nitrogen atmosphere was treated with diphenyl phosphorazidate (1 g, 3.6 mmol) and heated at reflux for 30 min. After cooling, the reaction mixture was washed consecutively with water and saturated NaCl solution. The organic phase was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by silica gel chromatography to give the isocyanate as a yellow oil: IR 2250 cm^{-1}; MS (EI) 225, 183. A mixture of the isocyanate in benzene (15 mL) and 50% KOH (8 mL) was stirred for 15 h. After the phases were separated, the benzene layer was washed with water. The combined aqueous layers were acidified to pH 1 with 2 N HCl, washed with diethyl ether, and then basified to pH 10 with 1 N NaOH. The aqueous layer was extracted with diethyl ether (2 × 50 mL) and the organic layer dried ($MgSO_4$), filtered, and evaporated to give the free amine as a colorless film (0.48 g, 73%). The free amine (0.19 g, 0.95 mmol) was dissolved in diethyl ether and treated dropwise with an HCl in 2-propanol solution. The solvent was removed and the residue redissolved in diethyl ether and hexanes. Evaporation gave the title compound as a white solid (194 mg, 87%), mp 150 °C dec. Anal. ($C_{14}H_{17}N$·HCl) C, H, N, (calcd, 5.94; found, 5.35), Cl.

(±)-*cis*-1,2,3,4,9,9a-Hexahydro-*N*-methyl-9-methylene-4a*H*-fluoren-4a-amine, Monohydrochloride (32b). The amine **32a** (0.29 g, 1.44 mmol) and di-*tert*-butyl dicarbonate (0.63 g, 2.88 mmol) in CH_2Cl_2 (20 mL) were heated at reflux for 16 h. The solvent was evaporated and the residue purified by silica gel chromatography using 20:1 hexane/ethyl acetate as eluant to

give the BOC-amine as a colorless oil (0.39 g, 90% yield). A suspension of $LiAlH_4$ in diethyl ether (10 mL) was cooled in an ice bath, and the BOC-amine in diethyl ether (5 mL) was added via a dropping funnel. After 2 h, the reaction was quenched by consecutive treatment with water (0.5 mL), 12.5% NaOH (0.4 mL), and water (1 mL). The precipitate was removed by filtration and washed with diethyl ether. The filtrate was dried (Na_2SO_4) and evaporated to give a colorless oil (0.29 g). The amine was converted to the salt with HCl in 2-propanol. Successive dissolution and evaporation from diethyl ether, diethyl ether/benzene, and diethyl ether/hexane gave the title compound as a white solid (0.32 g, 99%), mp 212–14 °C. Anal. ($C_{15}H_{19}N$·HCl) C, H, N, Cl (calcd, 14.19; found, 13.37).

Methyl (±)-*cis*-1,2,9,9a-Tetrahydro-2-oxo-4a*H*-fluorene-4a-carboxylate (34). A mixture of compound **33** (61.4 g, 0.35 mol) and 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene (40.5 g, 0.235 mol) was heated to 130 °C for 72 h. The mixture was taken up in THF (500 mL) with 5% aqueous HCl (50 mL) added and the mixture stirred for 18 h. The mixture was concentrated to approximately 100 mL under reduced pressure, extracted with diethyl ether (2 L), washed with water, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by MPLC using CH_2Cl_2 followed by 5:95 MeOH/CH_2Cl_2 to give the title compound (33.59 g, 59%) as a colorless thick oil: MS (EI) *m/e* 242 (M^+). Anal. ($C_{15}H_{14}O_3$) C, H.

Methyl (±)-*cis*-1,2,3,4,9,9a-Hexahydro-2-oxo-4a*H*-fluorene-4a-carboxylate (35). A solution of compound **34** (24.6 g, 0.102 mol) in pyridine (100 mL) and 10% Pd/C (1.0 g) was stirred under a H_2 atmosphere (50 psi) for 15 min. The mixture was filtered through a pad of Celite and concentrated under reduced pressure and the crude product purified via MPLC using CH_2Cl_2 followed by 2:98 MeOH/CH_2Cl_2 to give the title compound (19.3 g, 78%) as a light yellow oil. The compound was used without further purification.

Methyl (±)-(2α,4aα,9aα)-2-Cyano-1,2,3,4,9,9a-hexahydro-4a*H*-fluorene-4a-carboxylate (36). To a solution of compound **35** (5.0 g, 20.5 mmol) in dry THF (30 mL) was added diethyl cyanophosphonate (4.0 g, 24.6 mmol) followed by addition of LiCN (0.81 g, 24.6 mmol). The mixture was stirred for 24 h. Water (20 mL) was added, and the organics were taken up in ethyl acetate (150 mL). The organics were dried ($MgSO_4$), concentrated under reduced pressure, and taken up in dry THF (20 mL) and *t*-BuOH (2.0 mL). To a separate flask of samarium metal (6.2 g, 41 mmol) in dry THF (40 mL) was added diiodoethane (7.7 g, 27.3 mmol) in dry THF (10 mL). After the solution was stirred for 1 h at room temperature a solution of the cyano phosphate solution was added to the SmI_2 solution over 5 min and the stirring continued for an additional 1 h. The reaction was quenched by the addition of aqueous 10% HCl solution (20 mL). The reaction mixture was extracted with diethyl ether (1 L), dried ($MgSO_4$), filtered, concentrated, and then purified by MPLC using a 5:95 ethyl acetate/petroleum ether solvent system to afford **37** (1.11 g) and **36** (2.67 g) (73% combined yield). Anal. ($C_{16}H_{17}NO_2$) C, H, N.

Methyl (±)-(2α,4aα,9aα)-(2-Cyano-1,2,3,4,9,9a-hexahydro-4a*H*-fluoren-4a-yl)carbamate (38). The ester **36** (3.73 g, 14.61 mmol) was converted to the acid following the procedure as described for the preparation of compound **22**. The crude material (3.6 g) was used without any further purification. To a solution of the crude acid (3.89 g, 16.1 mmol) in benzene (40 mL) was added NEt_3 (1.8 g, 17.7 mmol) followed by diphenyl phosphorazidate (4.44 g, 16.1 mmol). The mixture was heated to reflux for 4 h. MeOH (40 mL) was added and the mixture heated to reflux for 24 h. The reaction mixture was concentrated to dryness and the residue purified via MPLC using 20:80 ethyl acetate/petroleum ether followed by 30:70 ethyl acetate/petroleum ether to afford the title compound (3.3 g, 76%) as a white solid. Anal. ($C_{16}H_{18}N_2O_2$) C, H, N.

(±)-(2α,4aα,9aα)-2,3,4,4a,9,9a-Hexahydro-4a-(methylamino)-1*H*-fluorene-2-methanamine, Dihydrochloride (40b). To a solution of compound **38** (2.32 g, 8.6 mmol) in methanolic ammonia (100 mL) was added RaNi (3 g) under a H_2 atmosphere and the mixture stirred for 16 h. The RaNi was removed by filtration, and the organics were concentrated under reduced pressure. The residue was purified via MPLC using 10:90 MeOH/CH_2Cl_2 to afford the reduced nitrile (1.99 g, 85%). A solution of the amine carbamate (0.26 g, 0.95 mmol) in diethyl ether (5 mL) was added to a solution of $LiAlH_4$ (0.4 g, 10.5 mmol) in diethyl ether (40 mL). The mixture was heated to reflux for 5 h, cooled, and slowly poured onto a saturated solution of potassium sodium tartrate (50 mL). The resulting solution was extracted with diethyl ether, dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was taken up in diethyl ether and treated with HCl in diethyl ether to afford the title compound (110 mg, 38%) as a white solid, mp 161–165 °C. Anal. ($C_{15}H_{22}N_2$·2HCl) C, H, N, Cl.

Methyl (±)-(2α,4aα,9aα)-[[2,3,4,4a,9,9a-Hexahydro-4a-[(methoxycarbonyl)amino]-1*H*-fluoren-2-yl]methyl]carbamate (39). A solution of compound **38** (0.84 g, 3.1 mmol) was reduced as described for compound **40b**. The crude product was dissolved in CH_2Cl_2 (15 mL) followed by addition of NEt_3 (0.38 g, 3.73 mmol) and methyl chloroformate (0.35 g, 3.73 mmol). The mixture was stirred for 24 h at room temperature. The organics were concentrated under reduced pressure and the residue purified via MPLC using CH_2Cl_2 followed by 5:95 MeOH/CH_2Cl_2 to afford the title compound (0.94 g, 91%) as a colorless oil. The compound was used without further purification.

(±)-(2α,4aα,9aα)-2,3,4,4a,9,9a-Hexahydro-*N*-methyl-4a-(methylamino)-1*H*-fluorene-2-methanamine, Dihydrochloride (40a). A solution of compound **39** (0.7 g, 2.1 mmol) was reduced with $LiAlH_4$ (0.4 g, 10.5 mmol) as described for compound **38**. The free base in diethyl ether (50 mL) was treated with HCl in 2-propanol to afford the title compound (0.25 g, 37%) containing 1 equiv of 2-propanol, mp 140 °C. Anal. ($C_{16}H_{24}N_2$·2HCl·C_3H_8O) C, H, N, Cl.

4-[(Phenylmethoxy)methyl]cyclohexanone (42). To a solution of NaH (2.5 g, 105 mmol) in dry THF (150 mL) was added a solution of the compound **41**[51] (15 g, 87.1 mmol) in dry THF (25 mL). The mixture was stirred for 30 min at room temperature followed by addition of benzyl bromide (11.4 mL, 95.8 mmol). The reaction was stirred at room temperature for 4 days and poured onto water. The resulting mixture was extracted with diethyl ether (2 L), dried ($MgSO_4$), filtered, concentrated, and purified by column chromatography using 2:98 MeOH/CH_2Cl_2 to obtain the *O*-benzyl ether–ketal (19.43 g, 85%) as a colorless oil. To a solution of the ketal (11.79 g, 45 mmol) in THF (300 mL) was added 50 mL of a 2% aqueous HCl solution. The mixture was stirred for 72 h at room temperature. The reaction mixture was extracted with diethyl ether (500 mL) and washed with a saturated NaCl solution. The organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the title compound (9.47 g, 97%) as a colorless oil. The compound was used without further purification.

2-[(2-Bromophenyl)methyl]-4-[(phenylmethoxy)methyl]-cyclohexanone (43). To a solution of freshly prepared LDA (125 mmol) in dry THF (150 mL) at 0 °C was added a solution of compound **42** (22.65 g, 103.8 mmol) in dry THF (50 mL). After the solution was stirred for 45 min a solution of 2-bromobenzyl bromide (28.5 g, 114 mmol) was added as a solution in THF (30 mL). The reaction was stirred at 0 °C for 3 h, warmed to room temperature, and stirred for 18 h. The reaction was quenched by the addition of a saturated NH_4Cl solution (100 mL), extracted with diethyl ether (3 L), dried ($MgSO_4$), concentrated under reduced pressure, and purified via MPLC using CH_2Cl_2 followed by 1:99 MeOH/CH_2Cl_2 to afford the title compound (18.7 g, 47%) as a colorless oil. Anal. ($C_{21}H_{23}O_2Br$) C, H.

(±)-1,2,3,4,9,9a-Hexahydro-2-[(phenylmethoxy)methyl]-*N*-(phenylmethyl)-4a*H*-fluoren-4a-amine (44). The title compound was prepared with the following reagents using method B: compound **43** (1.73 g, 4.47 mmol), benzylamine (0.62 g, 5.8 mmol), *p*-toluenesulfonic acid (20 mg), *t*-BuLi (1.7 M in pentane, 4.0 mL, 6.7 mmol), and THF (20 mL). The crude product was purified by MPLC using CH_2Cl_2 followed by 5:95 MeOH/CH_2Cl_2 as the solvent system to afford the title compound (0.37 g, 21%) as a colorless oil. The compound was used without further purification.

(±)-4a-Amino-2,3,4,4a,9,9a-hexahydro-1*H*-fluorene-2-methanol, Monohydrochloride (45a). A mixture of compound **44** (0.71 g, 1.8 mmol) and 5% Pd/C (0.1 g) in MeOH (25 mL) was stirred under a H_2 atmosphere (50 psi) for 6 h. The reaction mixture was concentrated under reduced pressure and filtered through a silica gel plug using a 5:95 MeOH/CH_2Cl_2 solution.

The filtrate was concentrated, the residue was taken up in CH_2Cl_2 (5 mL), and trimethylsilyl iodide (0.74 mL, 5.2 mmol) was added. The mixture was stirred for 3 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with a saturated sodium bicarbonate solution, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was taken up in diethyl ether (20 mL), and 10 drops of a saturated HCl in 2-propanol solution was added. The white precipitate was collected and dried under vacuum to afford the title compound (180 mg, 68%) as a white solid, mp 259 °C. Anal. ($C_{14}H_{19}NO\cdot HCl\cdot 0.48H_2O$) C, H, N, Cl.

(±)-2,3,4,9,9a-Hexahydro-*N*-methyl-2-[(phenylmethoxy)-methyl]-4a*H*-fluoren-4a-amine (46). The title compound was prepared with the following reagents using method C: compound **43** (3.0 g, 7.7 mmol), methylamine (25 g), 4-Å molecular sieves (15 g), toluene (100 mL), THF (25 mL), and *n*-BuLi (1.6 M, 5.8 mL, 9.3 mmol). The crude product was purified by MPLC using CH_2Cl_2 followed by 5:95 MeOH/CH_2Cl_2 as the solvent system to afford the title compound (0.4 g, 16%) as a colorless oil. The compound was used without further purification.

(±)-2,3,4,4a,9,9a-Hexahydro-4a-(methylamino)-1*H*-fluorene-2-methanol, Monohydroiodide (45b). Compound **46** (0.44 g, 1.3 mmol) was taken up in CH_2Cl_2 (25 mL), and trimethylsilyl iodide (1.0 mL, 7.0 mmol) was added. The mixture was stirred for 6 h at room temperature. The reaction mixture was treated with saturated sodium bicarbonate solution (10 mL) and extracted with ethyl acetate (500 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The compound was purified via MPLC using 10:90 MeOH/CH_2Cl_2 followed by 20:80 MeOH/CH_2Cl_2 and was isolated from the column as the hydroiodide salt. The solution was concentrated and the residue triturated with diethyl ether to give the title compound (161 mg, 56% yield) as a white solid, mp 70 °C. Anal. ($C_{15}H_{21}NO\cdot HI$) C, H, N.

Biological Methods. [^{3}H]TCP Binding Assay. Assays were carried out as described previously[35] using the modifications described below.

Preparation of Membranes. Male Long–Evans rats (180–200 g) were sacrificed by decapitation and the whole brain homogenized in 20 vol of ice-cold 50 mM Tris–HCl, pH 7.7, with a Brinkman Polytron setting 5.5 for 25–30 s. The suspension was centrifuged at 48000*g* for 10 m, 4 °C. The supernatant was discarded, and the pellet resuspended and washed two more times as before. The final pellet was suspended in 5 mM Tris–HCl buffer, pH 8.0, at a concentration of 15 mg original wet weight/mL and stored on ice until used on the same day. NOTE: We have frozen whole brains at −80 °C for up to a month with no loss in binding.

Binding Assay. Triplicate incubations were carried out in 12 × 75 polystyrene tubes containing 15 mg of brain membranes, test agents and 2 nM [^{3}H]TCP (New England Nuclear; specific activity, 46.9 Ci/mmole) in 2 mL of 5 mM Tris–HCl, pH 8.0, at 25 °C for 30 min. Bound [^{3}H]TCP was separated by vacuum filtration through glass fiber (Whatman GF/B) filters, which had been soaked 1–3 h in 0.05% polyethylenimine, using a Brandell cell harvester. The filters were washed three times with 5 mL of ice-cold 5 mM Tris–HCl, pH 7.7. Filters were placed in scintillation vials and covered with about 250 μL of ethanol before the addition of Beckman Ready Protein scintillation cocktail and allowed to stand 1 h or longer before counting by scintillation spectrophotometry at 45% efficiency. Nonspecific binding was defined as the binding in the presence of (+)-*N*-allylnormetazocine (100 μM) from NIDA and was typically 15% of total. NOTE: Binding can also be run in 20 mM HEPES, pH 7.4.

Glutamate-Induced ^{45}Ca Uptake. Sterile, 96-well tissue culture plates (Costar) were incubated for 3 h at rt with 100 μg/mL of 30–70 K poly-L-lysine hydrobromide (Sigma). Wells were washed three times with Dulbecco's Modified Eagle's/Ham F-12 nutrient mixture (Sigma) (DME/F12) medium and were allowed to dry overnight. Cortical hemispheres were sectioned from Sprague Dawley fetal rat brains in their 18th day of embryonic development. Tissues were incubated for 20 min in magnesium- and calcium-free HBSS containing 2.5 g/L of Trypsin (Sigma), washed three times with HBSS, and then triturated into a single cell suspension. This procedure has historically yielded >92% cell viability using Trypan Blue dye exclusion staining. Cells were adjusted to a final concentration of one fetal brain/20 mL by suspending them in supplemented DME/F12 growth medium containing 10% horse and 6% fetal calf serums, 16.1 mg/L of putrescine, 5 mg/L of bovine insulin and human transferrin, and 5 μg/L of sodium selenite (all Sigma). A 100-μL lot of this suspension was pipetted into individual wells of previously prepared 96-well plates, which were subsequently incubated in a humidified, 3% CO_2, 37 °C chamber. Glial cell division was halted after 4 days of incubation by adding 100 μL/well of 10% horse DME/F12 containing 30 and 70 μg/mL of 5-fluoro-2-deoxyuridine and uridine, respectively. Two days later, 100 μL of growth medium was removed from each well and replaced with an equal volume of fresh 10% horse DME/F12. Subsequent feedings were performed in an identical manner when deemed necessary.

Experiments were conducted 14–17 days post isolation using magnesium-free HBSS, containing 1.8 mM Ca^{2+} and 1 μCi/mL of $^{45}Ca^{2+}$ (ICN). Prior to glutamate exposure, growth medium was removed and replaced with 50 μL/well of HBSS. Thirty min thereafter, an additional 50 μL of HBSS, containing appropriate concentrations of test compound and 200 μM/L of glutamate (Sigma), was added to each well. Following 30 min of additional exposure, cells were rinsed three times with saline, lysed with distilled water, aliquot with scintillation cocktail, and counted for radioactive emissions.

NMDA-Induced Seizures and Lethality in Mice. CF-1 mice (20–30 grams) received a bolus IV injection of test compound 5 min prior to a bolus IV injection of 25 mg/kg of *N*-methyl-D-aspartate (NMDA) (Sigma). Seizures occur immediately following NMDA injection in unprotected animals, which subsequently expire within approximately 1 min. An inverted screen was used to monitor ataxia, and was performed 4 min following test compound injection. Survival (n = 10) was recorded 30 min following NMDA injection.

Molecular Modeling. As part of a larger modeling study involving a diverse set of noncompetitive NMDA antagonists,[38–41] the structures of dizocilpine, etoxadrol (2*S*,4*S*,6*S* isomer), the hexahydroindeno[1,2-*c*]pyridine **47**, and PCP depicted in Figures 4 and 8 were constructed using SYBYL[52] from available fragments within the program and placed in conformations consistent with previous studies.[12,45–47] Consistent with previous reports[23,26] and NMR data (vide infra), the ring structures of **1a**, **13c**, and **40b** were built as the cis *RS* stereoisomer. The central "B" ring (Figure 4) was puckered "up" (Figure 5), and the cyclohexyl "C" ring was placed in a chair conformation. This orientation allowed the fluorenamines to closely mimic the spatial occupation of PCP in its putative receptor bound conformation, and to project the lipophilic C ring into an area of space occupied by the cyclohexyl ring of PCP and dioxolane ring of etoxadrol when the phenyl rings in common to these antagonists were superimposed.

The methyl group on the cyclohexane ring of **13c** was added in the equatorial position, trans to the $NHCH_3$ substituent. Two considerations guided the placement of the methyl group in this position. First, the PCP SAR[45] demonstrated that a cis arrangement of the phenyl and a 2-methylcyclohexyl (which results in a trans disposition of the basic amine in the piperidine ring of PCP and the methyl group) was preferred for high affinity. This corresponds to a trans orientation of the $NHCH_3$ and CH_3 groups in **13c**. Second, an axial methyl group would project steric bulk toward the receptor interaction atom, severely hindering the crucial hydrogen bonding interaction, resulting in a far less potent compound than the IC_{50} = 79 nM that is observed for **13c**. The CH_2NH_2 substituent on the C ring of **40b** was added in the *R* configuration (cis to the $NHCH_3$), and the torsion angles were adjusted so as to place the terminal amine in a similar area of space as the basic amine in etoxadrol. Each structure was minimized using MAXIMIN,[42] aggregating the phenyl ring carbons and specifying an 0.001 kcal/mol energy change between successive iterations as the convergence criteria.

To each of the minimized versions were added hypothetical receptor atom(s) (tetrahedral nitrogens) 2.8 Å from the basic amines lying along the lone pair direction. A 2-Å-long tensor perpendicular to the plane of the phenyl rings, piercing through their centroid, was also added. Etoxadrol, PCP, **1a**, **13c**, **40b**, and **47** were then fit to each other, as well as to other antagonists,[38] using the endpoints of this tensor, and the hypothetical receptor

atom(s), to give the overlays depicted in Figures 4 and 8. In the case of **40b**, both receptor atoms were used in the fit. The minimized, fit version of **13c** was designated $\mathbf{13c}_{model}$.

The crystal structure of **13c** was read into SYBYL using the CRYSIN command, minimized using MAXIMIN using the same defaults and options as were used for the other antagonists and least-squares fit to the fit version of **1a** above. This minimized, fit version of the Xray structure was designated $\mathbf{13c}_{xray}$. A comparison of $\mathbf{13c}_{xray}$ and $\mathbf{13c}_{model}$ is shown in Figure 2.

X-ray Crystallographic Analysis of 13c. Crystals of **13c** belonging to the monoclinic space group $P21/C$ were obtained by evaporation of a solution in ethanol; formula $C_{15}H_{21}N{\cdot}HCl$; formula weight 251.80; crystal size, $0.20 \times 0.20 \times 0.20$ mm^3; cell dimensions, $a = 7.3976(2)$ Å, $b = 13.8838(6)$ Å, $c = 13.7612(4)$ Å, $\beta = 94.078(3)°$, $V = 1409.79(8)$ Å^3. A total of 1876 reflections were observed. Lattice constants and intensity data were measured by using graphite-monochromatic Cu Kα on an Enraf-Nonius CAD-4 automatic diffractometer. The NRCCAD programs were used for centering, indexing, and data collection. The unit-cell dimensions were obtained by least-squares fit of 24 well-centered reflections in the range $60° \leq 2\theta \leq 100°$. During data collection, the intensities of two standard reflections were monitored every 100 reflections. No decay was observed.

The structure was solved by direct methods and refined by full-matrix least-squares methods using the NRCVAX programs.[53] No absorption correction was applied. Hydrogen positions were located in a difference Fourier map. The final refinement included anisotropic thermal parameters for nonhydrogen atoms and only positional parameters for the hydrogen atoms. An isotropic extinction coefficient (0.34) was included in the refinement to account for secondary extinction effects.

NMR Experiments. NMR spectra were recorded on a Varian XL300 equipped with a Molorola 68000-based host computer operating at 300 MHz for proton and 75 MHz for carbon observation. Nuclear Overhauser difference spectra were obtained by subtracting a spectrum acquired with application with a selective decoupler pulse on an individual peak, from a similarly acquired spectrum with the decoupler set off resonance. A minimum decoupler power level was applied during the 5-s relaxation time to provide nearly complete saturation of the desired resonance. One- and two-dimensional experiments including correlated spectroscopy (COSY), nuclear Overhauser spectroscopy (NOESY), heteronuclear correlated spectroscopy (HETCOR), and distortionless enhancement by polarization transfer (DEPT) were conducted using pulse sequences provided by Varian Associates. Typically, two-dimensional experiments were acquired using 256 blocks of 1024 complex data points with a recycle time of 1 s between pulses. NMR spectral simulations were calculated with the auxiliary program LAOCOON 5 supplied with the NMR1 program.[44]

Preparation of Methyl (±)-*cis*-(6,7,8,9,9a,10-Hexahydrobenz[a]azulen-4b-yl)carbamate for NMR Experiments. A solution of the free base of amine **14b** (0.2 g, 0.84 mmol), NEt_3 (0.358 g, 3.6 mmol), and methyl chloroformate (0.27 g, 2.76 mmol) in CH_2Cl_2 (20 mL) was stirred at 5 °C for 3 h and then at room temperature for 18 h. The reaction was poured onto water and the product extracted into CH_2Cl_2, dried ($MgSO_4$), and then concentrated under reduced pressure. The crude product was purified via medium-pressure column chromatography (MPLC) using petroleum ether with increasing amounts of ethyl acetate up to 18:82 to give the title compound (60 mg, 27%) as an oil.

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Supplementary Material Available: Physical data for compounds prepared (11 pages); calculated and observed structure factors (14 pages). Ordering information is given on any current masthead page.

References

(1) Presented in part at the 201st American Chemical Society Meeting, Atlanta, GA, 1991; Abstr. 201 MEDI 17, 18, and 25.
(2) Cotman, C. W.; Foster, A.; Lanthorn, T. An overview of glutamate as a neurotransmitter. *Adv. Biochem. Psychopharmacol.* **1981**, *27*, 1–27.
(3) Foster, A. C.; Fagg, G. E. Acidic amino acid binding sites in mammalian neuronal membranes: their characteristics and relationship to synaptic receptors. *Brain Res. Rev.* **1984**, *7*, 103–64.
(4) Watkins, J. C.; Evans, R. H. Excitatory amino acid transmitters. *Annu. Rev. Pharmacol. Toxicol.* **1981**, *21*, 165–204.
(5) Monaghan, D. T.; Cotman, C. W. Distribution of *N*-Methyl-D-aspartate-sensitive L-[^{3}H]Glutamate-binding Sites in Rat Brain. *J. Neurosci.* **1985**, *5*, 2909–19.
(6) Cotman, C. W.; Iversen, L. L. Excitatory amino acids in the brain—focus on NMDA receptors. *Trends Neurosci.* **1987**, *10*, 263–65.
(7) Johnson, G. Recent Advances in Excitatory Amino Acid Research. *Annu. Rep. Med. Chem.* **1989**, *24*, 41–50.
(8) Wong, E. H. F.; Kemp, J. A. Sites for antagonism on the *N*-methyl-D-aspartate receptor channel complex. *Ann. Rev. Pharmacol. Toxicol.* **1991**, *31*, 401–25.
(9) Lehmann, J.; Loo, P.; McPherson, S.; ffrench-Mullen, J. M. H.; Steel, D.; Braunwalder, A.; Williams, M.; Wood, P. L. In *Excitatory Amino Acid Transmission*; Hicks, T. P., Lodge, D., H., Eds.; Liss: New York, 1987; p 91.
(10) Wroblewski, J. T.; Nicoletti, F.; Fadda, E. E. Phencyclidine is a negative allosteric modulator of signal transduction at two subclasses of excitatory amino acid receptors. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 5068–72.
(11) Jacobson, A. E.; Harrison, E. A., Jr.; Mattson, M. V.; Rafferty, M. F.; Rice, K. C.; Wood, J. H.; Winger, G.; Solomon, R. E.; Lessor, R. A.; Silverton, J. V. Enantiomeric and Diastereomeric Dioxadrols: Behavioral, Biochemical and Chemical Determination of the Configuration Necessary for Phencyclidine-Like Properties. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 110–17.
(12) Thurkauf, A.; Zenk, P. C.; Balster, R. L.; May, E. L.; George, C.; Carroll, F. I.; Mascarella, S. W.; Rice, K. C.; Jacobson, A. E.; Mattson, M. V. Synthesis, Absolute Configuration, and Molecular Modeling Study of Etoxadrol, a Potent Phencyclidine-like Agonist. *J. Med. Chem.* **1988**, *31*, 2257–63.
(13) Loo, P. A.; Braunwalder, A. F.; Williams, M.; Sills, M. A. The novel anticonvulsant MK-801 interacts with central phencyclidine recognition sites in rat brain. *Eur. J. Pharmacol.* **1987**, *135*, 261–63.
(14) Sircar, R.; Rappaport, M.; Nichtenhauser, R.; Zukin, S. R. The novel anticonvulsant MK-801: a potent and specific ligand of the brain phencyclidine/δ-receptor. *Brain Res.* **1987**, *435*, 235–40.
(15) Wong, E. H. F.; Kemp, J. A.; Priestley, T.; Knight, A. R.; Woodruf, G. N.; Iversen, L. L. The anticonvulsant MK-801 is a potent *N*-methyl-D-aspartate antagonist. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 7104–08.
(16) Wong, E. H. F.; Knight, A. R.; Woodruff, G. N. [^{3}H]MK-801 labels a site on the *N*-methyl-D-aspartate receptor channel complex in rat brain membranes. *J. Neurochem.* **1988**, *50*, 274–81.
(17) MacDonald, J. F.; Nowak, L. M. Mechanisms of blockade of excitatory amino acid receptor channels. *Trends Pharmacol. Sci.* **1990**, *11*, 167–72.
(18) Olney, J.; Price, M.; Salles, K. S.; Labruyere, J.; Frierdich, G. MK-801 powerfully protects against *N*-methyl aspartate neurotoxicity. *Eur. J. Pharmacol.* **1987**, *141*, 357–61.
(19) Rondouin, G.; Drian, M.-J.; Chicheportiche, R.; Kamenka, J.-M.; Privat, A. Non-competitive antagonists of *N*-methyl-D-aspartate receptors protect cortical and hippocampal cell cultures against glutamate neurotoxicity. *Neurosci. Lett.* **1988**, *91*, 199–203.
(20) McDonald, J. W.; Silverstein, F. S.; Johnston, M. W. MK-801 protects the neonatal brain from hypoxic-ischemic damage. *Eur. J. Pharmacol.* **1987**, *140*, 359–61.
(21) Gill, R.; Foster, A. C.; Woodruff, G. N. Systemic administration of MK-801 protects against ischemia-induced hippocampal neurodegeneration in the gerbil. *J. Neurosci.* **1987**, *7*, 3343–9.
(22) Chen, G. Evaluation of phencyclidine-type cataleptic activity. *Arch. Int. Pharmacodyn. Ther.* **1965**, *157*, 193–201.
(23) Kozikowski, A. P.; Pang, Y.-P. Synthesis and chemical resolution of a novel class of rigid 1-(1-phenylcyclohexyl)piperidine (PCP) analogues. *Synlett* **1990**, 58–63.
(24) Bigge, C. F.; Hays, S. J.; Johnson, G.; Novak, P. M.; Ortwine, D. F. Polycyclic Amines Useful as Cerebrovascular Agents. U. S. Patent 5,071,853, 1991.
(25) Godefroi, E. F.; Simanyi, L. H. t-Carbinamines derived from partially hydrogenated fluorenes and dibenzofuranes. *J. Org. Chem.* **1963**, *28*, 1112–19.
(26) Pang, Y.-P.; Kozikowski, A. P. Synthesis of methoxy and hydroxy analogues of 1,2,3,4,4a,9a-hexahydro-4a-fluorenamine: rigid phencyclidine analogues as probes of phencyclidine binding site topography. *J. Org. Chem.* **1991**, *56*, 4499–508.
(27) Blokzijl, W.; Blandamer, M. J.; Engberts, J. B. F. N. Diels–Alder reactions in aqueous solutions. Enforced hydrophobic interactions between diene and dienophile. *J. Am. Chem. Soc.* **1991**, *113*, 4241–6.
(28) Laganis, E. D.; Chanard, B. L. Metal Silanolates: Organic Soluble Equivalents for O^{-2}. *Tetrahedron Lett.* **1984**, *25*, 5831–4.
(29) Sedman, A. J.; Gal, J. Resolution of the enantiomers of propanol and other β-adrenergic antagonists by high performance liquid chromatography. *J. Chromatogr.* **1983**, *278*, 199–203.
(30) Godefroi, E. F.: U. S. Patent 3,111,527, 1963, *Chem. Abstr. 60*, 2895g.

(31) Abelman, M. M.; Oh, T.; Overman, L. E. Intramolecular alkene arylations for rapid assembly of polycyclic systems containing quaternary centers. A new synthesis of spirooxindoles and other fused and bridged ring systems. *J. Org. Chem.* **1987**, *52*, 4130–3.
(32) Burnham, J. W.; Duncan, W. P.; Eisenbraun, E. J. Effects of alkyl substituents in the chromic acid oxidation of tetralins. *J. Org. Chem.* **1974**, *39*, 1416–20.
(33) Clawson, L.; Buchwald, S. L.; Gruber, R. H. The methylenation of enolizable ketones and esters using organotitanium chemistry. *Tetrahedron Lett.* **1984**, *25*, 5733–6.
(34) This sequence produced an approximate 1:1 ratio of isomers as evidenced by proton NMR.
(35) Largent, B. L.; Gunlach, A. L.; Snyder, S. H. Pharmacological and autoradiographic discrimination of sigma and phencyclidine receptor binding sites in brain with (+)-[^{3}H]-3-[3-hydroxyphenyl]-*N*-(1-propyl)piperidine and [^{3}H]-1-[1-(2-thienyl)cyclohexyl]piperidine. *J. Pharmacol. Exp. Ther.* **1986**, *238*, 739–48.
(36) Marcoux, F. W.; Goodrich, J. E.; Probert, A. W.; Dominick, M. A. *Sigma and Phencyclidine-like compounds as molecular probes in biology*; Domino, E. F., Kamenka, J. M., Eds.; NPP Books: Ann Arbor, MI, 1988; pp 735–46.
(37) Marshall, G. R.; Barry, C. D.; Bosshard, H. E.; Dammkoehler, R. A.; Dunn, D. A. The Comformational Parameter in Drug Design: The Active Analog Approach. *Computer-Assisted Drug Design*; Olson, E. C., Christofferson, R. E., Eds.; ACS symposium Series 112; American Chemical Society: Washington, D.C., 1979; pp 205–226.
(38) The modeling study involved the superposition of a diverse set of PCP ligands (*m*-OH PCP, MK-801, SKF10047, etoxadrol, PD33353, and PD134365) to generate an initial model, followed by refinement with the addition of selected MK-801, PCP, PD33352, and PD134365 analogs. Preliminary reports of the modeling have appeared;[39-41] a full paper on this work is in preparation.
(39) Humblet, C.; Ortwine, D. F. Molecular modeling of noncompetitive NMDA antagonists. Development of a predictive pharmacophore model and its use in the design of novel analogs. 201st American Chemical Society Meeting, Atlanta, GA, 1991; Abstr. 201, MEDI 24.
(40) Bigge, C. F.; Johnson, G.; Hays, S. J.; Malone, T. C.; Ortwine, D. F.; Boxer, P. A.; Marcoux, F. W.; Coughenour, L. L. Development of Polycyclic Amines as Potent Noncompetitive NMDA Antagonists. In *Multiple Sigma and PCP Receptor Ligands: Mechanisms for Neuromodulation and Neuroprotection*; Kamenka, J. M., Domino, E. F., Eds.; NPP Books: Ann Arbor, MI, 1992; pp 1–22.
(41) Malone, T. C.; Ortwine, D. F.; Johnson, G.; Probert, A. W., Jr. Synthesis and Biological Activity of Conformationally Constrained 4a-Phenanthreneamine Derivatives As Noncompetitive NMDA Antagonists. *Bioorg. Med. Chem. Lett.*, in press.
(42) Labanowski, J.; Motoc, I.; Naylor, C. B.; Mayer, D.; Dammkoehler, R. A. Three-dimensional quantitative structure-activity relationships. 2. Conformational mimicry and topographical similarity of flexible molecules. *Quant. Struct.-Act. Relat.* **1986**, *5*, 138–52.
(43) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. AM1: A new general purpose quantum mechanical molecular model. *J. Am. Chem. Soc.* **1985**, *107*, 3902–9.
(44) LAOCOON 5, New Methods Research, Inc., Syracuse, NY.
(45) Manallack, D. T.; Wong, M. G.; Costa, M.; Andrews, P. R.; Beart, P. M. Receptor site topographies for phencyclidine-like and sigma drugs: Predictions from quantitative conformational, electrostatic and radioreceptor analyses. *Mol. Pharmacol.* **1988**, *34*, 863–79.
(46) Carroll, F. I.; Brine, G. A.; Mascarella, S. W. Phencyclidine (PCP) and phencyclidine-like compounds: a molecular graphics-molecular mechanics study. *NIDA Res. Monogr.* **1988**, *90*, 122–28.
(47) Leeson, P. D.; Carling, R. W.; James, K.; Smith, J. D.; Moore, K. W.; Wong, E. H. F.; Baker, R. Role of hydrogen bonding in ligand interaction with the N-methyl-D-aspartate receptor ion channel. *J. Med. Chem.* **1990**, *33*, 1296–1305.
(48) Kalir, A. Structure Activity Relationships for Phencyclidine Derivatives. In *PCP (Phencyclidine): Current and Historical Perspectives*; Domino, E. F., Ed.; NPP Books: Ann Arbor, MI, 1981; pp 31–46.
(49) Cantrell, B. E.; Leander, J. D.; Mendelsohn, L. G.; Schoepp, D. D.; Hermann, R. B.; Zimmerman, D. M. The Search For a PCP Antagonist: The Discovery Of Potent PCP-Like Activity in Hexahydroindeno(2,1-c)Pyridine Series of Compounds. In *Sigma and Phencyclidine-Like Compounds as Molecular Probes in Biology*; Domino, E. F., Kamenka, J.-M., Eds.; NPP Books: Ann Arbor, MI, 1988.
(50) Inami, Y.; Tomita, T.; Terada, Y. Quantitative structure–activity relationship analysis of phencyclidine derivatives. *Chem. Pharm. Bull.* **1991**, *39*, 1426.
(51) Berkowitz, W. F.; Amarasekara, A. S.; Perumattam, J. J. A photochemical approach to the taxanes. *J. Org. Chem.* **1987**, *52*, 1119–24.
(52) Version 5.3.2 of SYBYL (Tripos Associates, 1699 S. Hanley Road, St. Louis, MO 63144), operating on a VAX 6430, was used for all calculations.
(53) Gabe, E. J.; Lee, F. L.; LePage, Y. *Data collection, structure determination, proteins and data bases*; Sheldrick, G. M., Kruger, C., Goddard, R., Eds.; Clarendon Press: Oxford, 1985; pp 167–74.
(54) Haky, J. E.; Young, A. M. Evaluation of a Simple HPLC Correlation Method for the Estimation of the Octanol–Water Partition Coefficients of Organic Compounds. *Liq. Chrom.* **1984**, *7*, 675–689.