Rigid Phencyclidine Analogues. Binding to the Phencyclidine and σ_1 Receptors

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Three phencyclidine (PCP) analogues possessing a highly rigid carbocyclic structure and an attached piperidine ring which is free to rotate were synthesized. Each analogue has a specific fixed orientation of the ammonium center of the piperidinium ring to the centrum of the phenyl ring. The binding affinities of the rigid analogues 1-piperidino-7,8-benzobicyclo[4.2.0]octene (**14**), 1-piperidinobenzobicyclo[2.2.1]heptene (**16**), and 1-piperidinobenzobicyclo[2.2.2]octene (**13**) for the PCP receptor ([³H]TCP) and σ-receptor (NANM) were determined. The three analogues show low to no affinity for the PCP receptor but good affinity for the σ-receptor and can be considered σ-receptor selective ligands with PCP/σ ratios of 13, 293, and 368, respectively. The binding affinities for the σ-receptor are rationalized in terms of a model for the σ-pharmacophore.

Introduction

PCP (phencyclidine, 1-(1-phenylcyclohexyl)piperidine) (**1**) was originally introduced as a general anesthetic agent,[1−3] but it was subsequently withdrawn from use in humans because of severe psychomimetic side effects.[4−9] The focus of research on PCP has shifted from its use as an anesthetic toward potential applications as a neuropharmaceutical.[10,11] This effort has been spurred by the observation of anticonvulsant[12−14] and neuroprotective activity in rodents.[15] The search for noncompetitive NMDA antagonists has been substantially assisted by the development of a reliable binding assay,[16a] and to date a large number of PCP analogues have been synthesized and assayed as substrates for the PCP binding site.[16b−j] Among the noncompetitive NMDA antagonists, 1-[(2-thienyl)cyclohexyl]-piperidine (TCP),[17] (+)-*N*-allyl-*N*-normetazocine ((+)-NANM, (+)-SKF 10,047),[18] and MK-801[19−21] are prototypical.

Neuroprotection can be understood in terms of nerve cell death resulting from excessive stimulation caused by L-glutamate at excitatory synapses within the CNS.[22−29] Ischemia or reduced supply of oxygen (anoxia/hypoxia/ischemia) to the brain caused by birth asphyxia, traumatic head injury, stroke, or hypoglycemia results in unregulated calcium ion influx through a ligand-gated ion channel at a receptor which has *N*-methyl-D-aspartic acid (NMDA) as a specific ligand. This pathophysiology of neuron cell death has been termed excitotoxicity, and the calcium influx may result in osmolytic swelling, free radical production, and superoxide production, all of which contribute to neuron destruction.
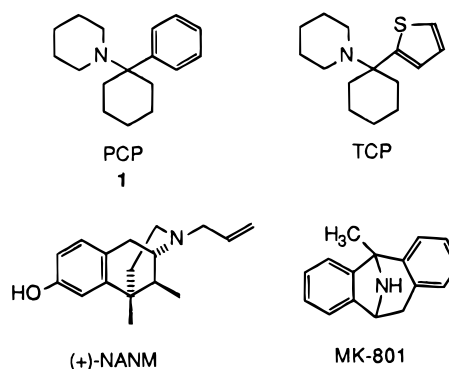
The NMDA subclass of glutamate receptors are composed of an ion channel which possesses multiple sites for agonist and antagonist binding. L-Glutamate is a fast excitatory neurotransmitter which acts upon ligand-gated ion channel receptors and is the endogenous ligand for the NMDA receptor.[30−34] NMDA (*N*-methyl-D-aspartate) is a synthetic compound. Figure 1 represents a schematic representation of the NMDA intracellular ion channel receptor.[35]

In Figure 1, L-glutamate is the endogenous ion channel agonist; glycine is a coagonist.[36] Within the ion channel, Mg²⁺ performs a regulatory function.[37] At rest, Mg²⁺ blocks the ion channel, and a negative intracellular membrane potential exists. The Mg²⁺ block is voltage dependent and is removed if the cell is partially depolarized.[38] Also within the ion channel, as shown in Figure 1, are the receptor sites for MK-801 and PCP.[39−42] This is the link to neuroprotection for both of these agents because they can counter the effects of excess L-glutamate excitotoxicity by blockade of the ion channel to ion influx.

The neuroprotective activity of both MK-801[23,24,43] and PCP[29] has been amply demonstrated.

Several PCP-like molecules cross react with the PCP receptor, the σ receptor, and the dopamine-D₂ receptors.[44] The high-affinity [³H]-*N*-allyl-*N*-normetazocine ((+)-SKF-10,047) binding site originally identified by
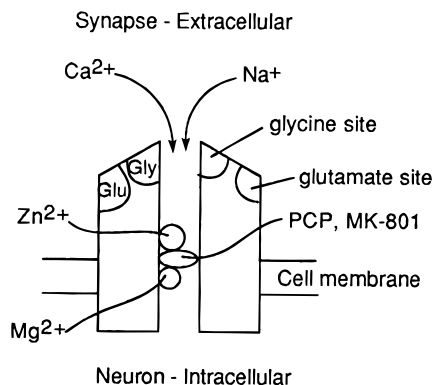
Synapse - Extracellular

Figure 1. Schematic NMDA receptor calcium ion channel complex.

Martin et al.[45] in 1976 as an opioid receptor type is now called the σ site.[46] PCP and (+)-SKF-10,047 bind to both PCP and σ receptors.[47] A distinction between the sites based upon ligand selectivity is revealed by the fact that [³H]-(+)-SKF-10,047 is displaced by neuroleptics such as haloperidol and perphenazine, while these compounds show no ability to displace PCP-like compounds.[48,49]

The physical nature of the σ receptor has not yet been fully defined, even though several classes of selective ligands have been identified. σ Receptors are widely found, occurring both in the nervous system and peripheral tissue such as liver, kidney, and intestine.[50] The range of σ receptor substrates is likewise broad, including progesterone[51] and inhibitors of cytochrome P-450.[52,53]

Numerous physiological and pharmacological roles have been suggested for σ receptors, although to date no drug has been developed based on the σ receptor.[54,55] The absence of an identified endogenous ligand does not add to the physical characterization of this receptor.[56]

The σ receptor is implicated in antiischemic and neuroprotective action.[57−61] Subtypes of σ recognition sites have been proposed based upon selectivity of binding of various ligands. The σ_1 site exhibits high affinity for (+)-benzomorphans such as (+)-pentazocine and (+)-N-allyl-N-normetazocine (SKF-10,047), and (−)-benzomorphans are σ_2 site ligands.[62] The pharmacophore for σ binding is multivariant. The distinction between the two sites is illustrated by the observation that N-phenylalkyl substitution of N-normetazocine significantly enhanced affinity for the σ site labeled with [³H]-(+)-3-PPP while affinity for PCP sites was decreased.[63] (+)-Pentazocine [(+)-N-(3,3-dimethylallyl)-N-normetazocine] bound with higher affinity than (+)-N-allyl-N-normetazocine to σ receptors.[63,64] The N-phenylpropyl-, -butyl-, and -pentyl-N-normetazocine derivatives also showed affinity for σ sites.

Some generalizations about structure−activity at the PCP and σ receptors can be made. PCP is a relatively flexible molecule which can undergo conformational ring inversion of the cyclohexyl and piperidinyl rings as well as rotation of the phenyl group about the carbon−carbon single bond (Scheme 1).

Under physiological conditions the protonated form can undergo a chair−chair conformational change for both the cyclohexyl and the piperidinyl rings, while the phenyl group can adopt two limiting rotational positions (Φ = ca. 0° or ca. 90°). The essential feature of this

Scheme 1
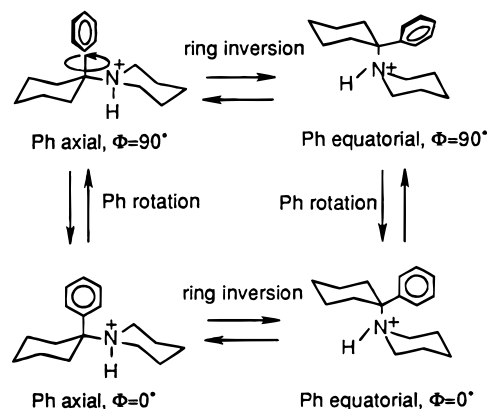
conformational analysis is that the rotational angle of $\Phi = 90°$ places the ammonium center near the centrum of the phenyl ring. The angle of $\Phi = 0°$ has the ammonium center in the plane of the phenyl ring. It has been concluded on the basis of ¹H NMR, ¹³C NMR, MM-2 calculations, and X-ray structure that the $\Phi = 90°$ angle[65] is the stable form of the active pharmacophore. This proposal has been tested experimentally in the cases of the rigid analogue aminohexahydrofluorene **2** which conforms to Φ = ca. 90°.[66]
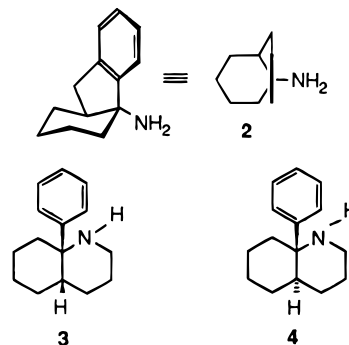

Also, the four enantiomers corresponding to cis- and trans-fused 8a-phenyldecahydroquinolines, **3** and **4**, were assayed for affinity for the PCP receptor with the conclusion that the anti N−H/C-phenyl arrangement is the preferred orientation for optimal binding.[67]

The structural requirements for σ binding have been indicated by the affinities of a series of molecules which possess the phenylpiperidino group. Thus, 2-(4-phenylpiperidino)ethyl 1-(4-nitrophenyl)cyclopentanecarboxylate hydrochloride (**5·HCl**) showed an affinity for the (+)-pentazocine binding site with a K_i of 50 pM, and this compound was inactive at the PCP, NMDA, and opioid receptors.[68]
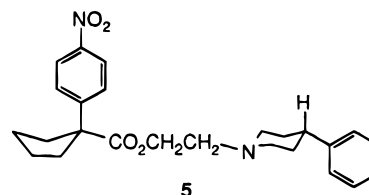
Other potent σ ligands were obtained by interposing methylene groups between the phenylcycloalkyl group and the nitrogen atom in the PCP framework as in **6**.[68]

6
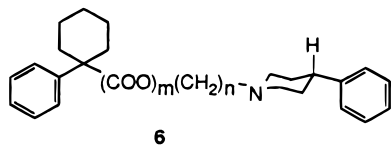
m=0, n=0: σ receptor IC$_{50}$=7.9 mM,
PCP IC$_{50}$=0.05 mM
m=0, n=1: σ receptor IC$_{50}$=0.1 mM,
PCP IC$_{50}$=1.8 mM
m=1, n=1: σ receptor IC$_{50}$= 0.026 mM,
PCP IC$_{50}$=34.890 mM

Activity at the σ site increases and affinity at the PCP receptor decreases by increasing the distance between the nitrogen atom and the phenyl ring, assuming the phenylcycloalkyl group occupies the first lipophilic site and not vice versa. The above results as well as molecular modeling studies support this view. According to this, "stretched" molecules rather than "globular" ones are better ligands for the σ site.[69] However, there are some potent σ ligands which seem to be more "globular" than "stretched", for example, benz[*f*]isoquinoline derivatives[70] and spiropiperidine analogues.[71]

An extremely potent σ ligand is **7**, and several variations upon this structure, such as **8**, exhibit K_i of 0.34 and 0.17 nM for displacement of 1-*n*-propyl-3-(3-hydroxyphenyl)piperidine.[72]

7

8
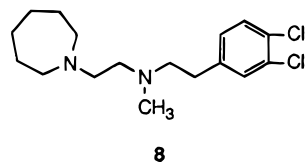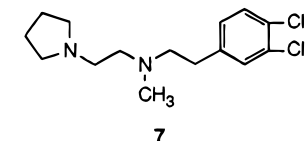
The σ binding site is thought to be composed of a primary lipophilic site, a nitrogen binding site, and a second lipophilic site. Caramiphen (**9**) binds with high affinity (26 nM) to the [^{3}H]-(+)-pentazocine site, and carbetapentane (**10**) binds with an IC$_{50}$ value of 32 nM. Neither inhibits PCP binding.[69]
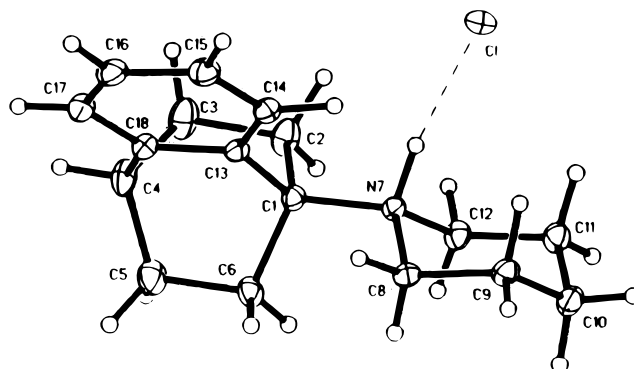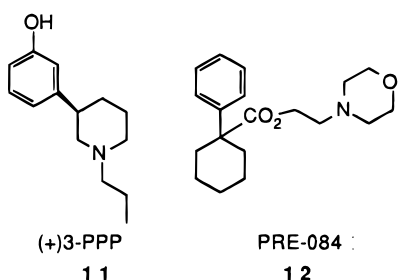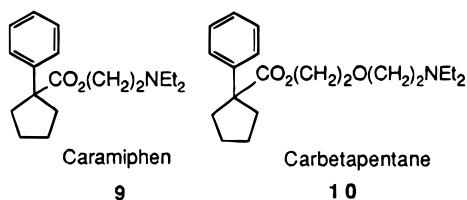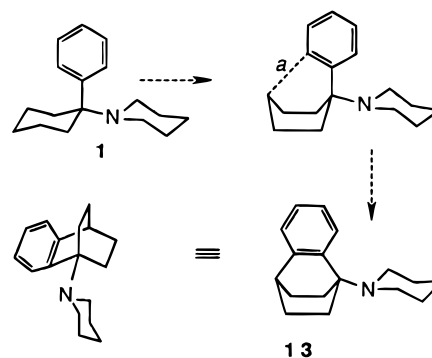

Caramiphen
9

Carbetapentane
10

(+)3-PPP
11

PRE-084
12

Figure 2. X-ray structure of compound **13**.

Scheme 2

13

(+)3-PPP (**11**) (IC$_{50}$ 13 nM in σ binding) and PRE−084 (**12**) (IC$_{50}$ 44 nM in σ binding and greater than 100 000 nM for PCP) are likewise selective σ ligands.[69] Again, these molecules follow the stretched rather than globular shape.

In the present study, rigid analogues of PCP were designed and synthesized in order to determine selectivity between the PCP and σ sites; the strategy of fixing the orientation of the ammonium center of PCP with respect to the centrum of the phenyl ring via carbon−carbon connection was pursued.

This was accomplished synthetically by tying down the rotating axial phenyl group into three limiting values for Φ. In the first case, $\Phi \approx 0°$, a C−C bond between the ortho position of the axial phenyl ring of PCP and C4 of the cyclohexyl ring of PCP (Scheme 2, bond *a*) yields the achiral 1-piperidinobenzobicyclo[2.2.2]-octene (**13**).

Because of the conformational rigidity of the bicyclo-[2.2.2]octene ring, the nitrogen atom of the piperidino ring occupies a position unambiguously in the plane of the aromatic ring. The X-ray structure shown in Figure 2 shows clearly this structural feature.

The second limiting structure for PCP is one in which the phenyl ring is twisted toward the nitrogen atom of the piperidine ring and this geometry is achieved by incorporation of a C−C bond between the ortho position of the axial phenyl ring of PCP and the C2 position of the cyclohexyl ring (Scheme 3, bond *b*), to yield the chiral 1-piperidino-7,8-benzobicyclo[4.2.0]octene (**14**) (Φ~60°).

Because of the conformational inflexibility of the cyclobutene ring, the nitrogen atom of the piperidine is above the plane of the benzenoid ring. This structure is similar to the aminohexahydrofluorene (**2**); however,

Scheme 3

14

Scheme 4

15 **16**
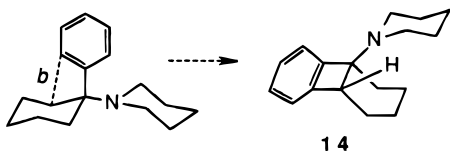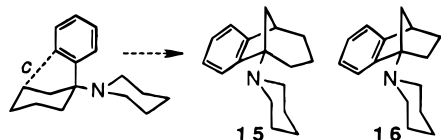
the annulated four-membered ring in **14** relative to the five-membered ring in **2** has the effect of moving the nitrogen atom closer to the centrum of the aromatic ring.

An intermediary fixed orientation rigid analogue (Scheme 4, bond *c*) is also conceivable, and this is achieved in **15** ($\Phi \approx 30°$). Compound **15** was not synthesized, but in fact the lower homologous benzobicyclo[2.2.1]norbornyl derivative **16** ($\Phi \approx 18°$) was. The reason for this choice is based on synthetic reasons. The sequence **26** → **27** → **28** → **29** (Scheme 7) benefits from the presence of a plane of symmetry in 4-phenylcyclohexanone **26**, which means **27**, **28**, and **29** are formed as unique regioisomers. An analogous sequence starting from 4-phenylcycloheptanone is complicated by the absence of a plane of symmetry perpendicular to both rings. Therefore, the Favorskii reaction yields two isomers. Subsequent reactions analogous to **27** → **28** → **29** would yield two isomeric phenylcyclohexanecarboxylic acids, only one of which could yield the desired intramolecular Friedel–Crafts product analogous to **28b** → **29**. Because of uncertainties in the Favorskii ring contraction as well as the feasibility of the subsequent reactions, we elected to synthesize the compound for which closely analogous procedures existed.

Chemistry

The synthesis of 1-piperidinobenzobicyclo[2.2.2]octene (**13**) proceeded from the Diels–Alder reaction between methyl 1,3-cyclohexadiene-1-carboxylate with benzyne via the sequences shown in Scheme 5.

The requisite diene **20** was prepared using a procedure of Grob et al.[73] via enamine formation upon crotonaldehyde (**17**) to yield 1-(*N*,*N*-diethylamino)-1,3-butadiene (**18**) and subsequent cycloaddition with methyl acrylate followed by loss of Et$_2$NH (**19** → **20**).[79] The Diels–Alder reaction between diene **20** and in situ formed benzyne afforded the adduct **21**. Catalytic hydrogenation upon the Diels–Alder adduct **21** yielded methyl 2,3-benzobicyclo[2.2.2]oct-2-ene-1-carboxylate **22a** which was hydrolyzed to yield 2,3-benzobicyclo[2.2.2]-oct-2-ene-1-carboxylic acid (**22b**), which in turn was converted to the amide **22c** via the acid chloride derived from the acid **22b** and subsequently to the amine **23** using a hypervalent iodine variation of the Hofmann amide rearrangement.[74] The resulting bridgehead amine **23** was converted to **13** using the method of Gabrielevitz et al.[75]

Analogue **14** was likewise produced by a [2 + 2] cycloaddition reaction between 1-piperidinocyclohexene

Scheme 5[a]

22a: R = OCH$_3$
22b: R = OH
22c: R = NH$_2$

23
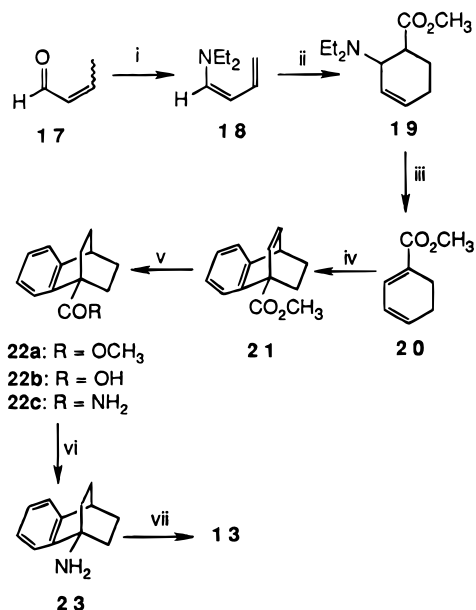
[a] (i) NHEt$_2$, KOH, C$_6$H$_6$; (ii) CH$_3$OOCCH=CH$_2$; (iii) HCl, C$_6$H$_6$, 160–170 °C; (iv) 1,2-C$_6$H$_4$NH$_2$(COOH), isoamyl nitrite, 70 °C; (v) (a) Pd–C, H$_2$, 30 psi, (b) KOH, H$_2$O, (c) PCl$_5$, CH$_2$Cl$_2$, −78 °C, (d) NH$_3$, −78 °C to rt; (vi) C$_6$H$_5$I(OH)OTs, CH$_3$CN reflux; (vii) Br(CH$_2$)$_5$Br, K$_2$CO$_3$, DMF reflux.

Scheme 6

24 **25** **14**

viii: nBuLi, Et$_2$O refl.
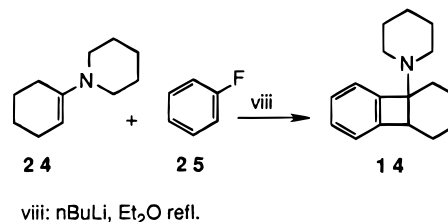
(**24**) and benzyne as shown in Scheme 6. The enamine **24** (prepared by reaction of piperidine with cyclohexanone) was added to fluorobenzene **25** in ether, and addition of butyllithium yielded the [2 + 2] cycloaddition product via the in situ generated benzyne.

The rigid analogue of intermediary rotational angle was synthesized as shown in Scheme 7. The starting point for the synthesis of 1-piperidinobenzobicyclo[2.2.1]-heptene (**16**) was the hypervalent iodine Favorskii ring contraction upon 4-phenylcyclohexanone (**26**). The trans-formed methyl 3-phenylcyclopentane-1-carboxylate (**27**) was carbomethoxylated to yield dimethyl 3-phenylcyclopentane-1,1-dicarboxylate (**28a**). Conversion to the free diacid **28b** followed by an intramolecular Friedel–Crafts reaction according to the procedure of Eaton et al.[76] yielded keto acid **29**. Hypervalent iodine iodinative decarboxylation[77] yielded the bridgehead iodo ketone **30**. Favorskii ring contraction yielded benzobicyclo[2.2.1]-heptene-1-carboxylic acid **31a**. The hypervalent iodine Hofmann rearrangement[74] upon the amide derived from the carboxylic acid **31b** yielded the bridgehead amine **32** which was converted to 1-piperidinobenzobicyclo-[2.2.1]heptene **16**.[78]

The X-ray structure of **13** is shown in Figure 2. The structures of **14** and **16** are established by ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectrometry.

Scheme 7[a]

28a: R = OCH$_3$
28b: R = OH

32: R = H
16: R$_2$ = -(CH$_2$)$_5$-

31a: R = OH
31b: R = NH$_2$
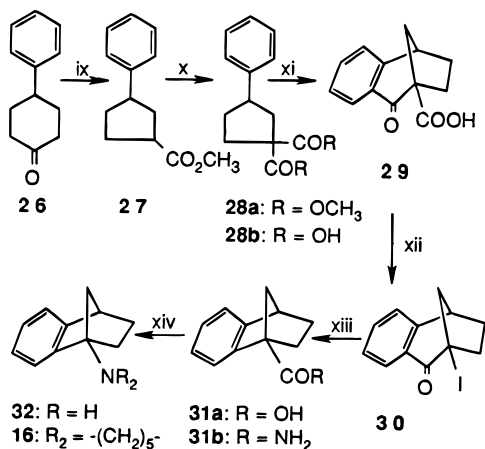
a (ix) KOH, C$_6$H$_5$I(OAc)$_2$, MeOH, −5 °C; (x) (a) LiN(iPr)$_2$, ClCOOCH$_3$, Et$_2$O, −78 °C, (b) KOH, MeOH, H$_2$O; (xi) P$_2$O$_5$, CH$_3$SO$_3$H; (xii) C$_6$H$_5$I(OAc)$_2$, I$_2$, AIBN, C$_6$H$_6$ reflux; (xiii) (a) NaOH, H$_2$O reflux, (b) PCl$_5$, Et$_2$O, (c) NH$_3$, CH$_2$Cl$_2$, −78 °C; (xiv) (a) C$_6$H$_5$I(OH)OTs, CH$_3$CN reflux, (b) K$_2$CO$_3$, Br(CH$_2$)$_5$Br, DMF reflux.

Table 1. Inhibition of [^{3}H]TCP and [^{3}H]NANM Binding[a]

| | IC$_{50}$, μM | | | |
compd	[^{3}H]TCP	[^{3}H]NANM	relative potency	PCP/σ ratio
PCP[b]	0.091 ± 0.005	0.53 ± 0.10	1	0.172
MK−801[b]	0.0053 ± 0.0003	1.7 ± 0.5	17.2	0.003
14	4.27 ± 0.02	0.330 ± 0.044	0.02	13
16	107 ± 7.1	0.365 ± 0.069	0.00085	293
13	117.5 ± 7.8	0.319 ± 0.058	0.00077	368

a Mean ± standard deviation of three experiments. *b* Literature data for PCP and MK-801 are included for comparison.[71]

Pharmacological Results and Discussion

The results of radioreceptors assays are presented in Table 1.

The general observation can be made that increased rigidity of the PCP analogues **13**, **14**, and **16** leads to significantly diminished affinity for the PCP site. Analogues **13** and **16** are essentially nonbinding while **14**, which has the Φ = 60° conformation, is a ligand, albeit about 50 times less active than PCP at the PCP binding site.

The relative order of affinity of the three rigid analogues of PCP agrees with the theoretical conclusions and experimental demonstration by Kozikowski et al.[67] that the Φ = ca. 90° orientation is the optimal for binding at the PCP site. Analogue **2**, which is structurally very similar to **14**, with the difference being an extra methylene group in **2** and an *N*-ethyl group rather than the piperidine group, shows either a 51% or 6% relative potency in PCP receptor binding depending upon the enantiomer.

(*R*)-**33**
51%

(*S*)-**33**
6%

Potency relative to PCP:
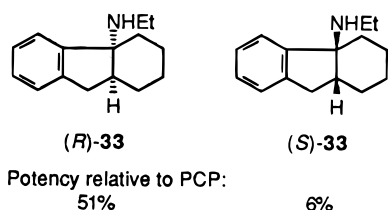
The relative potencies of these stereoisomers are considerably greater than **14**:PCP = 2%. Of course, **33**

exists in two enantiomeric forms; each individually is expected to have a different binding affinity, as the presence of the relatively bulky piperidino group versus the *N*-ethyl group accounts for part of the difference.

Inspection of the binding affinities for the three rigid analogues **13**, **14**, and **16** reveals that **13** and **16** are not ligands for the PCP receptor, and **14** shows a potency relative to PCP itself of about 2%. The fact that **14** corresponds to Φ = ca. 60°, which is closer to the optimal orientation, while **13** and **16** have Φ = ca. 0° and Φ = ca. 20−30°, respectively, which are closer to the less preferred geometry, agrees with the relative order of the binding: 117.5, 107, 4.27 μM. Comparison of (*R*)- and (*S*)-**33** with **14** is compromised by the fact that [NH$_2$Et]$^+$ is matched with the piperidine group.

Recently, Kozikowski and co-workers[67] have pointed out the importance of an anti relationship between the N−H bond of the protonated piperidino ring and the C−C bond joining the phenyl ring to the quaternary carbon atom in PCP as well as in the case of *cis*- and *trans*-fused 8a-phenyldecahydroquinolines for effective binding at the PCP receptor. For analogues **13**, **14**, and **16**, the energy difference between the anti orientation and conformations of angles less than 180° down to 60° are of less than 1 kcal/mol. Accordingly, this steric factor cannot account for the low potency of these compounds. One may conclude that the relatively high conformational flexibility of PCP allows for adaptation to an optimal fit at the receptor and, conversely, the rigidity of analogues such as **13**, **14**, and **16** prevents conformational relaxation into the correct conformation for optimal binding.

By contrast, rigid analogues **13**, **14**, and **16** bind to the σ receptor and are almost twice as potent as PCP and around 6 times as potent as MK-801. This shows the virtually inverse requirements for the two sites; MK-801 possesses an optimal orientation of the bridging ammonium center with respect to either of the two phenyl rings and each N−H bond of the protonated bridging NH$_2$$^+$ group has an anti relationship to the phenyl−bridgehead C−C bond. The three analogues fit approximately a pharmacophore model which has been proposed for the σ receptor.[68] Figure 3a shows the basic *N*-(phenylpropyl)-*N*-normetazocine structure, which consists of one lipophilic site constituted by the phenolic group and an ammonium center available as a hydrogen bonding site connected further to a second lipophilic site supplied by the N-substituent.

Analogues **13** and **16** fit this pharmacophore as indicated in parts b and c of Figure 3, respectively. For analogue **14** (Figure 3d), it is necessary to rotate the molecule to bring the ammonium center into position for hydrogen bonding. The site 2 lipophilic center is now constituted by the cyclohexyl ring. The alternative orientation, with the same spatial relationship as in Figure 3a−c, may also be considered, but this leads to somewhat weaker binding between lipophilic site 1 and the aromatic ring.

Conclusions

Systematic variation in the spatial orientation of the nitrogen center and aromatic ring in the synthesized rigid PCP analogues leads to sizable differences in binding constants to the PCP and NANM receptors.
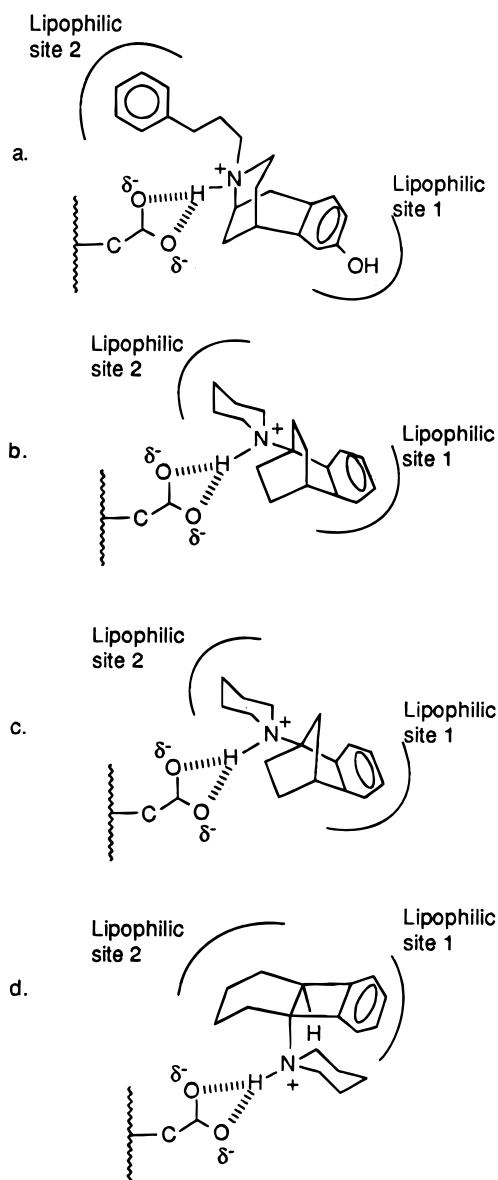
Figure 3. Hypothetical fitting of **13** (b), **16** (c), and **14** (d) into the pharmacophore model proposed for the σ-receptor in the case of *N*-(phenylpropyl)-*N*-normetazocine (a).

Because of the rigid carbocyclic structures of these molecules, models for selectivity in substrate–receptor binding were evaluated. These results may potentially serve as a basis for drug design in the neuropharmaceutical area.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. NMR spectra were recorded on one of the following instruments: Brucker WP-200 SY (200 MHz) NMR spectrometer, Brucker AM-400 (400 MHz) NMR spectrometer. IR spectra were recorded on IBM system 9000 FT-infrared spectrophotometer. Mass spectra (MS) were recorded on a HP5985a and MAT 90 system.

Reactions were monitored by analytical thin-layer chromatography using silica gel plates with UV light illumination, and 7% ethanolic phosphomolybdic acid/heat were used as developing agent. Merck silica gel (60 Å, 230–400 mesh) was used for flash chromatography.

All reactions were carried out under anhydrous conditions using freshly distilled dry solvent in an inert atmosphere (argon or nitrogen). Yields refer to isolated products that were found to be chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated.

Methyl 2-(*N,N*-Diethylamino)-3-cyclohexene-1-carboxylate (19). Crotonaldehyde (**17**) (7.0 g, 0.100 mol) was converted to 1-(*N,N*-diethylamino)-1,3-butadiene (**18**) (6 g, 48% yield) according to a literature procedure,[73] which was followed by reaction with methyl acrylate (6.4 g, 75 mmol) to give **19** (6.6 g, 65% yield), bp 118–120 °C/10 mmHg (lit.[79] bp 130–132 °C/12 mmHg).

Methyl 1,3-Cyclohexadiene-1-carboxylate (20). The compound **19** (6.6 g, 31 mmol) was converted to **20** (2.0 g, 44% yield) according to a literature procedure.[73] The product **20** had the following characteristic spectral data: ^{1}H NMR (CDCl$_3$) δ 7.00 (dd, 1H, CH=CH), 6.13 (m, 1H, CH=CH), 6.07 (m, 1H, CH=CH), 3.76 (s, 3H, CO$_2$CH$_3$), 2.45 (m, 2H, CH$_2$), 2.28 (m, 2H, CH$_2$); ^{13}C NMR (CDCl$_3$) δ 167.9 (C=O), 133.5, 133.2, 127.1, 123.9, 51.6, 22.8, 20.8; IR (neat) 2951, 2880, 2835, 1709, 1269, 1090 cm^{-1}.

Benzobicyclo[2.2.2]octene-1-carboxylic Acid (22b). A mixture of benzenediazonium-2-carboxylate (from 5.6 g of anthranilic acid and 10 mL of isoamyl nitrite) and methyl 1,3-cyclohexadiene-1-carboxylate (**20**) (3.3 g, 24 mmol) was heated at 70 °C for 15 h. After 200 mL of CH$_2$Cl$_2$ was added, the mixture was washed (saturated NaHCO$_3$, water) and dried (MgSO$_4$). The solvent was removed under reduced pressure. The residue was passed through a flash chromatography column with silica gel. Elution with hexane/ether (98:2, v/v) gave 3.0 g of a mixture of the methyl benzobicyclo[2.2.2]-octadiene-1-carboxylate (**21**) and methyl 1,3-cyclohexadiene-1-carboxylate (**20**).

The mixture was hydrogenated in MeOH under 30 psi in the presence of 10% palladium charcoal. The catalyst was removed by filtration. After removal of MeOH, the residue containing **22a** was dissolved in 5 mL of methanol, followed by addition of KOH (1.2 g, 21 mmol) in 10 mL of water. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with water, washed with ether, followed by acidification of the aqueous layer with 4 N HCl to pH = 1, and reextracted with 3 × 100 mL of ether. The combined ethereal extracts were washed with brine and dried (MgSO$_4$). After removal of the ether, the residue was recrystallized in hexane to give **22b** (2.04 g, 40%): ^{1}H NMR (CDCl$_3$) δ 7.31–7.23 (m, 5H, aromatic protons), 3.10 (m, 1H, bridgehead proton), 2.05 (m, 2H, CH$_2$), 1.87 (m, 4H, CH$_2$), 1.52 (m, 2H, CH$_2$); ^{13}C NMR (CDCl$_3$) δ 181.6 (C=O), 143.2, 140.4, 126.6, 126.1, 123.9, 122.2, 46.8, 34.5, 29.0, 26.0; IR (KBr) 3200–2500 (br, COOH), 1695 (C=O), 1605 (C=C), 700, 659 cm^{-1}; MS (CI) 203 (M + 1, 100), 157 (62), 129 (8).

Benzobicyclo[2.2.2]octene-1-carboxamide (22c). Benzobicyclo[2.2.2]octene-1-carboxylic acid (**22b**) (2.5 g, 11.8 mmol) was dissolved in dry CH$_2$Cl$_2$, and PCl$_5$ (2.5 g, 11.8 mmol) was added in several portions. The reaction mixture was stirred at room temperature for 16 h. The reaction solution was cooled to −78 °C, ammonia was bubbled into the solution until pH = 9, and the solution was allowed to warm to room temperature. Then, 50 mL of water was added, and the layers were separated. The organic layer was washed with brine and dried (MgSO$_4$). After removal of CH$_2$Cl$_2$, the crude product was recrystallized to give **22c** (1.8 g, 76% yield): mp 238–239 °C; ^{1}H NMR (methanol-*d*$_6$) δ 8.10 (d, br, 2H, CONH$_2$), 7.97 (m, 4H, aromatic protons), 3.80 (m, 1H, bridgehead proton), 2.60–2.40 (m, 6H, CH$_2$), 2.10 (m, 2H, CH$_2$); ^{13}C NMR (methanol-*d*$_6$) δ 178.2 (C=O), 146.1, 144.9, 128.6, 128.3, 126.2, 125.0, 48.7, 35.4, 31.2, 28.5; IR (KBr) 3404, 3192, 2934, 1657, 1116, 754, 698 cm^{-1}; MS (CI) 202 (M + 1, 100), 185, 157, 125, 111.

1-Aminobenzobicyclo[2.2.2]octene (23). A mixture of the amide **22c** (0.6 g, 3 mmol) and hydroxy(tosyloxy)iodobenzene (1.41 g, 3.6 mmol) in 20 mL of dry acetonitrile was refluxed for 20 h under nitrogen and then cooled to room temperature. After removal of the acetonitrile, 50 mL of 2 N HCl was added, and the solution was washed with ether. The aqueous solution was basified with saturated NaHCO$_3$ and extracted with ether. The combined ethereal extracts were

washed with water and dried (K_2CO_3). After removal of the ether, the product was purified by flash chromatography on silica gel (ether as eluent) and recrystallized from ether–hexane to give **23** (0.33 g, 64% yield): ^{1}H NMR (CDCl$_3$) δ 7.41 (d, 1H, aromatic proton), 7.27 (t, 1H, aromatic proton), 7.23 (t, 1H, aromatic proton), 7.17 (d, 1H, aromatic proton), 3.00 (m, 1H, bridgehead proton), 1.85 (m, 2H, CH$_2$), 1.78 (m, 2H, CH$_2$), 1.68 (br, 2H, NH$_2$), 1.52 (m, 2H, CH$_2$), 1.35 (m, 2H, CH$_2$); ^{13}C NMR (CDCl$_3$) δ 145.8, 142.9, 125.9, 123.2, 119.2, 52.3, 35.1, 34.2, 26.9; IR (KBr) 3400, 3350, 2943, 2864, 1643, 1608 cm^{-1}; MS (CI) 174 (M + 1, 100), 145, 130.

1-Piperidinobenzobicyclo[2.2.2]octene (13). A mixture of **23** (0.300 g, 1.73 mmol), anhydrous K$_2$CO$_3$ (0.382 g, 2.8 mmol), and 1,5-dibromopentane (0.40 g, 1.73 mmol) in 10 mL of dry DMF was refluxed for 45 min. Then 30 mL of water was added, and the basic material was converted to hydrochloride, shaken with benzene, separated, liberated with concentrated NH$_4$OH, and reextracted with CH$_2$Cl$_2$. After concentration, the residue was purified by flash chromatography on silica gel (ether:hexane, 1:5 v/v as eluent) and recrystallized from CH$_2$Cl$_2$–petroleum ether, to give 0.167 g of **13** (40% yield): mp 55–56 °C; ^{1}H NMR (CDCl$_3$) δ 7.45 (d, 1H, aromatic proton), 7.26 (t, 1H, aromatic proton), 7.15 (m, 2H, aromatic protons), 3.20 (t, 2H, CH$_2$N), 2.95 (m, 1H, bridgehead proton), 2.25 (t, 2H, CH$_2$N), 1.90–1.25 (m, 14H, rest CH$_2$ groups); ^{13}C NMR (CDCl$_3$) δ 144.5, 144.0, 125.4, 125.3, 123.3, 122.9, 60.1, 48.6, 33.8, 27.2, 27.1, 26.1, 25.4; IR (KBr) 3017, 2866, 1603, 1161, 787, 632 cm^{-1}; MS (CI) 242 (M + 1, 100). Anal. Calcd for C$_{17}$H$_{24}$ClN (**13** hydrochloride): C, 73.49; H, 8.71; N, 5.04. Found: C, 73.44; H, 8.68; N, 5.10.

1-Piperidino-7,8-benzobicyclo[4.2.0]octene (14). A solution of cyclohexanone (19.6 g, 0.200 mol) and piperidine (34 g, 0.400 mol) in 200 mL of benzene was heated to reflux, and heating was continued until 1 equiv of water was collected in a Dean–Stark trap. The solvent was removed from the reaction mixture, and the residue was distilled to provide the intermediate enamine **24**, 28 g (85% yield), bp 110 °C/10 mmHg (lit.[35]). To a refluxing solution of 1-piperidinocyclohexene **24** (7.8 g, 47 mmol) and fluorobenzene **25** (4.5 g, 47 mmol) in 200 mL of ether, under nitrogen, was added a solution of *n*-butyllithium (19 mL, 47 mmol, 2.5 M in hexane) in 200 mL of ether for over 90 min. After 20 h of reflux, 400 mL of dilute HCl was added, the layers were separated, and the aqueous portion was extracted with ether. Addition of excess NaOH to the aqueous portion, extraction with ether, and concentration gave the crude product. The crude product was purified by chromatography on silica gel (pentane–ether, 1:5, as eluent), yielding **14** (1 g, 45% yield): mp 43–44 °C; ^{1}H NMR (CDCl$_3$) δ 7.19–7.07 (m, 4H, aromatic protons), 3.58 (m, 1H), 2.74 (m, 2H, CH$_2$N), 2.62 (m, 2H, CH$_2$N), 2.11 (m, 1H), 1.97 (m, 1H), 1.82 (m, 2H), 1.61 (m, 5H), 1.43 (m, 5H), 1.22 (m, 1H), 1.10 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 149.0, 145.3, 127.4, 126.6, 122.4, 121.6, 69.5, 48.0, 45.1, 26.0, 25.5, 24.7, 24.5, 19.7, 18.4; IR (KBr) 3071, 2938, 2847, 1454, 754 cm^{-1}; MS (CI) 242 (M$^+$, 100). Anal. Calcd for C$_{17}$H$_{24}$ClN (**14** hydrochloride): C, 73.49; H, 8.71; N, 5.04. Found: C, 73.54; H, 8.70; N, 5.06.

Methyl 3-Phenylcyclopentane-1-carboxylate (27). 4-Phenylcyclohexanone (**26**) (50 g, 0.252 mol) was added to a solution of KOH (42 g, 0.758 mol) in 700 mL of MeOH at −5 °C, and the resulting solution was stirred at −5 °C for 15 min. (Diacetoxy)iodobenzene (184 g, 0.572 mol) was added in several portions at −5 °C in 10 min. After the addition was completed, the reaction mixture was stirred at −5 to 0 °C for 2 h. Then 1 L of water was added, and the aqueous solution was extracted with CH$_2$Cl$_2$ several times. The combined extracts were washed (brine) and dried (MgSO$_4$). After filtration and removal of the solvent under reduced pressure, the crude product was purified by flash chromatography on silica gel (hexane and hexane:ethyl acetate 9:1 as eluent) to give the ester **27** (20.6 g, 40% yield): mp 83–85 °C (lit.[78] mp 83–85 °C). Spectral properties were found to be in agreement with the literature data.[78]

Dimethyl 3-Phenylcyclopentane-1,1-dicarboxylate (28a). Compound **27** (10 g, 49 mmol) was converted to **28a**

by a literature procedure.[78] The crude product was purified by vacuum distillation, giving **28a** (10 g, 79% yield) as a colorless oil: bp 147–158 °C/0.6 mmHg (lit. 145–155 °C/0.5 mmHg). The ^{1}H NMR and IR data of the product agreed with the literature data.[78]

3-Phenylcyclopentane-1,1-dicarboxylic Acid (28b). The ester **28a** (10.0 g, 39 mmol) was hydrolyzed to **28b** by KOH in aqueous MeOH. The white solid product (7.5 g, 82% yield) melts with decomposition at 165–170 °C (lit.[76] 167–169 °C dec). The ^{1}H NMR and IR data of the acid agreed with the literature data.

9-Oxo-6,7,8,9-tetrahydro-5,8-methano-5H-benzocyclo-heptene-8-carboxylic Acid (29).[76] A mixture of P$_2$O$_5$ (46 g, 0.32 mol) and methanesulfonic acid (308 g, 3.21 mol) was stirred at room temperature for 2 h followed by addition of **28b** (7.5 g, 0.032 mol) and stirring for 4 h. Pouring the reaction mixture onto ice/water (1 L), followed by extraction with ether, gave keto acid **29** (6.7 g, 94% yield) as a light yellowish solid, mp 200–205 °C dec (lit. mp 204–206 °C). The spectral data were found to be in complete agreement with the literature data.

9-Oxo-6,7,8,9-tetrahydro-5,8-methano-5H-benzocyclo-heptene-8-Iodide (30). A mixture of 9-oxotetrahydro-5,8-methano-5H-benzocycloheptene-8-carboxylic acid (**29**) (1.5 g, 6.9 mmol), diacetoxyiodobenzene (4.48 g, 13.9 mmol), iodine (2.56 g, 10.4 mmol), and AIBN (0.113 g, 0.69 mmol) in 120 mL of dry benzene was refluxed for 24 h, cooled, and diluted with CH$_2$Cl$_2$ (100 mL). The reaction mixture was washed (saturated NaHCO$_3$, water, brine) and then dried (MgSO$_4$). After removal of the solvent, the residue was purified by flash chromatography on silica gel with 5:1 hexane:ether as the eluent, giving **30** (1.9 g, 92% yield) as a white solid, mp 47–48 °C; ^{1}H NMR (CDCl$_3$) δ 8.10 (d, 1H, Ph), 7.58 (t, 1H, Ph), 7.38 (t, 1H, Ph), 7.36 (d, 1H, Ph), 3.57 (m, 1H, bridgehead proton), 2.33–2.60 (m, 4H), 1.94 (m, 1H), 1.75 (m, 1H) ppm; ^{13}C NMR (CDCl$_3$) δ 193.0 (C=O), 149.9, 134.4, 128.9, 128.7, 127.2, 126.4, 69.8, 51.0, 43.4, 36.7, 32.4, 25.6 ppm; IR (KBr) 3065, 2945, 2870, 1689, 1597, 1456, 1346, 1285, 1196, 1157, 943 cm^{-1}; MS (CI) 300 (M + 1, 11.7), 299 (100), 171 (11.83), 143 (10.23).

Benzobicyclo[2.2.1]heptene-1-carboxylic Acid (31a). A mixture of the iodide (**30**) (1.11 g, 3.72 mmol) and 50 mL of 40% aqueous NaOH solution was refluxed for 48 h, cooled to room temperature, and diluted with 100 mL of water. The aqueous solution was washed with ether, acidified with concentrated HCl, and then extracted (CH$_2$Cl$_2$). The organic extracts were dried (MgSO$_4$) and concentrated. The crude product was purified by flash chromatography on silica gel with 5:1 hexane:ethyl acetate as the eluent, giving **31a** 0.350 g (50% yield): mp 89–91 °C (lit.[78] 90–91 °C); ^{1}H NMR (CDCl$_3$) δ 7.55 (m, 1H, Ph), 7.10–7.35 (m, 3H, Ph), 3.48 (m, 1H, bridgehead proton), 2.39 (m, 1H), 2.15 (m, 2H), 1.97 (d, 1H), 1.60 (m, 1H), 1.35 (m, 1H) ppm; ^{13}C NMR (CDCl$_3$) δ 180.9 (C=O), 147.1, 144.3, 126.5, 125.9, 120.8, 120.5, 57.9, 52.2, 43.5, 31.6, 28.4 ppm; IR (KBr) 3046, 2972, 2874, 2631, 1701, 1606, 1460, 1321, 1279, 1207, 1157, 941 cm^{-1}; MS (CI) 188 (M + 1, 69.5), 172 (52.9), 171 (9.44), 160 (100), 157 (15.3), 144 (30), 131 (47.7), 115 (93).

Benzobicyclo[2.2.1]heptene-1-carboxamide (31b). Benzobicyclo[2.2.1]heptene-1-carboxylic acid (**31a**) (0.350 g, 1.86 mmol) was dissolved in 25 mL of dry ether, and PCl$_5$ (0.427 g, 2.05 mmol) was added. The reaction mixture was stirred at room temperature overnight. After removal of the solvent, the residue was dissolved in 50 mL of dry CH$_2$Cl$_2$. The solution was added dropwise into a saturated ammonia/CH$_2$Cl$_2$ solution at −78 °C. The mixture was slowly warmed to room temperature with stirring and diluted with 100 mL of CH$_2$Cl$_2$. The organic solution was washed (water, saturated NaHCO$_3$) and then dried (MgSO$_4$). After removal of the solvent, the amide (**31b**) was obtained (0.318 g, 91% yield): mp 147.5–149 °C; ^{1}H NMR (CDCl$_3$) δ 7.35 (m, 1H, Ph), 7.10–7.20 (m, 3H, Ph), 6.58 (br, 1H, CONH), 5.87 (br, 1H, CONH), 3.44 (m, 1H, bridgehead proton), 2.26 (m, 1H), 2.07 (m, 1H), 1.96 (m, 1H), 1.89 (d, 1H), 1.45 (m, 1H), 1.28 (m, 1H) ppm; ^{13}C

NMR (CDCl$_3$) δ 175.9 (C=O), 145.8, 126.5, 126.1, 120.9, 119.9, 59.3, 52.8, 43.8, 30.1, 28.5 ppm; IR (KBr) 3370, 3194, 3046, 2945, 2868, 1657, 1622, 1458, 1300, 1262, 1206, 1126, 974 cm^{-1}; MS (CI) 188 (M + 1, 100), 170, 142, 114, 78.

1-Aminobenzobicyclo[2.2.1]heptene (32). A mixture of amide **31b** (0.318 g, 1.70 mmol) and hydroxy(tosyloxy)iodobenzene (0.800 g, 2.04 mmol) in 25 mL of acetonitrile was refluxed overnight. After removal of the solvent, the residue was dissolved in dilute HCl. The aqueous solution was washed with ether and then basified with concentrated NH$_4$OH and extracted (CH$_2$Cl$_2$). The combined extracts were washed with brine, dried (K$_2$CO$_3$), and concentrated to give **32** (0.250 g, 90% yield): ^{1}H NMR (CDCl$_3$) δ 7.35 (m, 1H, Ph), 7.10–7.20 (m, 3H, Ph), 3.25 (m, 1H, bridgehead proton), 2.62 (m, 1H), 2.52 (br, 2H, NH$_2$), 1.85 (m, 1H), 1.85 (m, 1H), 1.71 (m, 2H), 1.30 (m, 2H) ppm; ^{13}C NMR (CDCl$_3$) δ 149.0, 147.2, 125.8, 125.7, 120.6, 117.6, 66.8 (CNH$_2$), 57.4, 41.9, 33.9, 29.5 ppm; IR (neat) 3364, 3291, 3047, 3020, 2961, 2868, 1601, 1475, 1306, 1269, 1207, 1174, 968 cm^{-1}; MS *m/e* 160 (M + 1, 100), 143, 131, 83, 79.

1-Piperidinobenzobicyclo[2.2.1]heptene (16). A mixture containing the amine (**32**) (0.250 g, 1.57 mmol), 1,5-dibromopentane (0.361 g, 1.57 mmol), and anhydrous K$_2$CO$_3$ (0.350 g, 2.51 mmol) in 5 mL of DMF was kept at reflux for 45 min. Water was added, and the basic material was converted to the hydrochloride salt by addition of dilute HCl. The aqueous solution was washed with benzene, followed by liberation of the amine with concentrated NH$_4$OH and extraction with CH$_2$Cl$_2$. The combined extracts were dried (MgSO$_4$). After concentration, the residue was purified by flash chromatography on silica gel to yield **16** (0.08 g, 22%): mp 47–48 °C (the hydrochloride salt mp 233–235 °C); ^{1}H NMR (CDCl$_3$) δ 7.3–7.1 (m, 4H, Ph), 3.26 (m, 1H), 2.80 (t, 4H), 2.15 (m, 1H), 2.0 (m, 1H), 1.85 (d, 1H), 1.75–1.50 (m, 7H), 1.30 (m, 2H) ppm; ^{13}C NMR (CDCl$_3$) δ 147.7, 147.1, 125.6, 125.3, 121.0, 120.8, 77.0, 49.9, 47.3, 41.1, 29.0, 28.4, 26.7, 25.0 ppm; IR (neat) 3020, 2930, 2866, 2799, 1477, 1458, 1288, 750, 538 cm^{-1}; MS (CI) 228 (M + 1, 100), 227, 199, 143, 115. Anal. Calcd for C$_{16}$H$_{22}$-ClN (**16** hydrochloride): C, 72.85; H, 8.41; N, 5.31. Found: C, 72.81; H, 8.38; N, 5.36.

Biological Studies. Radioreceptor Assays. The binding assays involved displacement of [^{3}H]TCP or [^{3}H]NANM from tissue homogenate preparation of fresh whole rat brain minus cerebellum, as previously described by Jacobson et al.[16b] IC$_{50}$ values were calculated from inhibition curves. The inhibition constant (K_i) was determined by using the Cheng–Prusoff equation.[81] Experiments were performed in triplicate.

Supporting Information Available: Tables 2 and 3 containing bond lengths and bond angles for compound and an X-ray structure of **13** (3 pages). Ordering information is given on any current masthead page.

References

(1) Greifenstein, F. E.; Yoshitake, J.; De Vault, M.; Gajewski, J. E. A study of 1-arylcyclohexylamine for anesthesia. *Anesth. Analg.* **1958**, *37*, 283–284.

(2) Chen, G.; Ensor, C. R.; Russell, D.; Bohner, B. The pharmacology of 1-(1-phenylcyclohexyl)piperidine·HCl. *J. Pharmacol. Exp. Ther.* **1959**, *127*, 241–250.

(3) Chen, G.; Weston, J. K. The analgesic and anesthetic effects of 1-(1-phenylcyclohexyl)piperidine·HCl on the monkey. *Anesth. Analg.* **1960**, *39*, 132–137.

(4) Luby, E. D.; Cohen, B. D.; Rosenbaum, G.; Gottlieb, J. S.; Kelley, R. Study of a new schizophrenimimetic drug—Sernyl. *Arch. Neurol. Psychiatry* **1959**, *81*, 363–369.

(5) Luby, E. D.; Gottlieb, J. S.; Cohen, B. D.; Rosenbaum, G.; Domino, E. F. Model psychoses and schizophrenia. *Am. J. Psychiatry* **1962**, *119*, 61–67.

(6) Rainey, J. M.; Crowder, M. K. Prolonged psychosis attributed to phencyclidine: report of three cases. *Am. J. Psychiatry* **1975**, *132*, 1076–1078.

(7) Fauman, B.; Baker, F.; Coppleson, L. W.; Rosen, P.; Segal, M. B. Psychosis induced by phencyclidine. *J. Am. Coll. Emerg. Physicians* **1975**, *4*, 223–225.

(8) Luisada, P.; Brown, B. I. Clinical management of phencyclidine psychosis. *Clin. Toxicol.* **1976**, *9*, 539–545.

(9) Balster, R. L.; Chait, L. D. The behavioral pharmacology of phencyclidine. *Clin. Toxicol.* **1976, 9**, 513–528.

(10) (a) Johnson, K. M.; Jones, S. M. Neuropharmacology of phencyclidine: Basic mechanisms and therapeutic potential. *Annu. Rev. Pharmacol. Toxicol.* **1990**, *39*, 707–750. (b) Johnson, K. M. Neurochemistry and neurophysiology of phencyclidine. In *Psychopharmacology: Third Generation of Progress*; Meltzer, H. Y., Ed.; Raven: New York: 1987; pp 1581–1588.

(11) Contreras, P. C.; Monohan, J. B.; Lanthorn, T. H.; Pullan, L. M.; Di Maggio, D. A.; et al. Phencyclidine: physiological actions, interactions with excitatory amino acids and endogenous ligands. *Mol. Neurobiol.* **1987**, *1*, 191–211.

(12) Chen, G.; Bohner, B. Anticonvulsant properties of 1-(1-phenylcyclohexyl)piperidine·HCl and certain other drugs. *Proc. Soc. Exp. Biol. Med.* **1961**, *106*, 632–635.

(13) Leander, J. D.; Rathbun, R. C.; Zimmeman, D. M. Anticonvulsant effects of phencyclidine-like drugs: relation to *N*-methyl-D-aspartic acid antagonism. *Brain Res.* **1988**, *454*, 368–372.

(14) Sagratella, S.; Niglio, T.; Scotti de Carolis, A. An investigation on the mechanism of anticonvulsant action of ketamine and Phencyclidine on convulsions due to cortical application of penicillin in rabbits. *Pharmacol. Res. Commun.* **1989, 17**, 773–786.

(15) Hayes, B. A.; Balster, R. L. Anticonvulsant properties of phencyclidine-like drugs in mice. *Eur. J. Pharmacol.* **1985**, *117*, 121–125.

(16) (a) Contreras, P. C.; Rice, K. C.; Jacobson, A. E.; O'Donohue, T. L. Stereotyped behavior correlates better than ataxia with phencyclidine-receptor interactions. *Eur. J. Pharmacol.* **1986**, *121*, 9–18. (b) Jacobson, A. E.; Harrison, E. A., Jr.; Mattson, M. V.; Rafferty, M. F.; Rice, K. C.; Woods, J. H.; Winger, G.; Solomon, R. E.; Lessor, R. A.; Silverton, J. V. Enantiomeric and diastereomeric dioxadrols: Behavioral, biochemical and chemical determination of configuration necessary for phencyclidine-like properties. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 110–117. (c) Vincent, J. P.; Kartalowski, B.; Geneste, P.; Kamenka, J. M.; Lazdunski, M. Interaction of Phencyclidine ("Angel Dust") with a Specific Receptor in Rat Brain Membranes. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 4678–4682. (d) Zukin, S. R.; Zukin, R. S. Specific [^{3}H]-Phencyclidine Binding in Rat Central Nervous System. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 5372–5376. (e) Geneste, P.; Herrmenn, P.; Kamenka, J. M.; Pons, A. *Bull. Soc. Chim. Fr.* **1975**, 1619–1626 (in French). (f) Gabrielevitz, A.; Kloog, Y.; Kalir, A.; Balderman, D.; Sokolovsky, M. Interaction of phencyclidine and its new adamantyl derivatives with muscarinic receptors. *Life Sci.* **1980**, *26*, 89–95. (g) Thurkauf, A.; Hillary, P.; Mattson, M. V.; Jacobson, A. E.; Rice, K. C. The synthesis, pharmacological action, and receptor binding affinity of the enantiomeric 1-(1-phenyl-3-methylcyclohexyl)piperidines. *J. Med. Chem.* **1988**, *31*, 1625–1628. (h) Iorio, M. A.; Tomassini, L.; Mattson, M. V.; George, C.; Jacobson, A. E. Synthesis, stereochemistry and biological activity of the 1-(1-phenyl-2-methylcyclohexyl)piperidine and the 1-(1-phenyl-4-methylcyclohexyl)piperidines. Absolute configuration of the potent trans-(−)-1-(1-phenyl-2-methylcyclohexyl)piperidine. *J. Med. Chem.* **1991**, *34*, 2615–2623. (i) Itzhak, Y. [^{3}H]PCP-3-OH and (+)-[^{3}H]-SKF 10047 binding sites in rat brain membranes: evidence of multiplicity. *Eur. J. Pharmacol.* **1987**, *136*, 231–234. (j) de Costa, B. R.; Mattson, M. V.; George, C.; Linders, J. T. M. Synthesis, configuration, and activity of isomeric 2-phenyl-2-(*N*-piperidinyl)-bicyclo[3.1.0]hexanes at phencyclidine and σ binding sites. *J. Med. Chem.* **1992**, *35*, 4704–4712.

(17) Vignon, J.; Chicheportiche, R.; Chicheportiche, M.; Kamenka, J. M.; Geneste, P.; Lazdunski, M. [^{3}H]TCP: A new tool with high affinity for the PCP receptor in rat brain. *Brain Res.* **1983**, *280*, 194–197.

(18) Keats, A. S.; Telford, J. Narcotic antagonists as analgesics. In *Molecular Modification in Drug Design;* Gould, R. F., Ed.; Advances in Chemistry Series 45; American Chemical Society: Washington, DC, 1964; pp 170–176.

(19) Wong, E. H. F.; Kemp, J. A.; Priestly, T.; Knight, A. R.; Woodruff, G. N.; Iverson, L. L. The anticonvulsant MK-801 is a potent *N*-methyl-D-aspartate antagonist. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 7104–7108.

(20) Kemp, J. A.; Priestley, T.; Woodruff, G. N. MK-801, a novel, orally active anticonvulsant, is a potent, non-competitive *N*-methyl-D-aspartate receptor antagonist. *Br. J. Pharmacol. (Proc. Suppl.)* **1986**, *89*, 535P–537P.

(21) Woodruff, G. N.; Foster, A. C.; Gill, R.; Kemp, J. A.; Wong, E. H. F.; Iversen, L. L. The interaction between MK-801 and receptors for *N*-methyl-D-aspartate: functional consequences. *Neuropharmacology* **1987**, *26*, 903–909.

(22) Rothman, S. Synaptic release of excitatory amino acid neurotransmitter mediates anoxic neuronal death. *J. Neurosci.* **1984**, *4*, 1884−1891.

(23) Simon, R. P.; Swan, J. H.; Griffith, T.; Meldrum, B. S. Blockade of N-methyl-D-aspartate receptors may protect against ischemic damage in the brain. *Science* **1984**, *226*, 850−852.

(24) Wieloch, T. Hypoglycemia-induced neuronal damage prevented by an N-methyl-D-aspartate antagonist. *Science* **1985**, *230*, 681−683.

(25) Choi, D. W.; Koh, J.-Y.; Peters, S. Pharmacology of glutamate neurotoxicity in cortical cell culture: attenuation by NMDA antagonists. *J. Neurosci.* **1988**, *8*, 185−196.

(26) 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.

(27) Olney, J. W.; Price, M. T.; Fuller, T. A.; Labruyere, J.; Samson, L.; et al. The anti-excitotoxic effects of certain anesthetics, analgesics and sedative-hypnotics. *Neurosci. Lett.* **1986**, *68*, 29−34.

(28) Olney, J.; Price, M.; Salles, K. S.; Labruyere, J.; Frierdich, G. MK-801 powerfully protects against N-methyl-D-aspartate neurotoxicity. *Eur. J. Pharmacol.* **1987**, *141*, 357−361.

(29) Sauer, D.; Nuglish, J.; Rossberg, C.; Mennel, H.-D.; Beck, T.; et al. Phencyclidine reduces postischemic neuronal necrosis in rat hippocampus without changing blood flow. *Neurosci. Lett.* **1988**, *91*, 327−332.

(30) Watkins, J. C.; Evans, R. H. Excitatory amino acid transmitters. *Annu. Rev. Pharmacol. Toxicol.* **1981**, *21*, 165−204

(31) Monaghan, D. T.; Bridges, R. J.; Cotman, C. W. The excitatory amino acid receptors: Their classes, pharmacology, and distinct properties in the function of the central nervous system. *Annu. Rev. Pharmacol. Toxicol.* **1989**, *29*, 365−402.

(32) Carter, A. J. Glycine antagonists: Regulation of the NMDA receptor-channel complex by the strychnine-insensitive glycine site. *Drugs Future* **1992**, *17*, 595−613.

(33) Kemp, J. A.; Leeson, P. D. The glycine site of the NMDA receptor-five years on. *Trends Pharmacol. Sci.* **1993**, *14*, 20−25.

(34) Cotman, C. W.; Monaghan, D. T.; Ganong, A. H. Excitatory amino acid neurotransmission: NMDA receptors and Hebb-type synaptic plasticity. *Annu. Rev. Neurosci.* **1988**, *11*, 61−80.

(35) Sugihara, H.; Moriyoshi, K.; Ishii, T.; Masu, M.; Nakanishi, S. Structures and properties of seven isoforms of the NMDA receptor generated by alternative splicing. *Biochem. Biophys. Res. Commun.* **1992**, *185*, 826−832.

(36) Leeson, P. D.; Iversen, L. L. The glycine site on the NMDA receptor: Structure−activity relationships and therapeutic potential. *J. Med. Chem.* **1994**, *37*, 4053−4067.

(37) Mayer, M. L.; Westbrook, G. L.; Guthrie, P. B. Voltage-dependent block by Mg^{2+} of NMDA responses in spinal cord neurones. *Nature* **1984**, *309*, 261−263.

(38) Nowak, L.; Bregestovski, P.; Ascher, P.; Herbet, A.; Prochiantz, A. Magnesium gates L-glutamate activated channels in mouse central neurones. *Nature* **1984**, *307*, 462−465.

(39) Foster, A. C.; Wong, E. H. F. The novel anticonvulsant MK-801 binds to the activated state of the N-Methyl-D-asparate receptor in rat brain. *Br. J. Pharmacol.* **1987**, *91*, 403−409.

(40) Huettner, J. E.; Bean, B. P. Block of N-methyl-D-aspartate-activated current by the anticonvulsant MK-801: selective binding to open channels. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 1307−1311.

(41) Fagg, G. E. Phencycline and related drugs bind to the activated N-methyl-D-aspartate receptor channel complex in rat brain membranes. *Neurosci. Lett.* **1987**, *76*, 221−227.

(42) Johnson, K. M.; Snell, L. D.; Sacaan, A. I.; Jones, S. M. Pharmacological regulation of the phencylidine binding site associated with the NMDA receptor-operated ion channel. *Drug. Dev. Res.* **1989**, *17*, 281−297.

(43) (a) Thompson, W. J.; Anderson, P. S.; Britcher, S. F.; Lyle, T. A.; Thies, J. E.; Magill, C. A.; Varga, S. L.; Schwering, J. E.; Lyle, P. A.; Christy, M. E.; Evans, B. E.; Colton, C. D.; Holloway, M. K.; Springer, J. P.; Hershfield, J. M.; Ball, R. H.; Amato, J. S.; Larson, R. D.; Wong, E. H. F.; Kemp, J. A.; Tricklebank, M. D.; Singh, L.; Oles, R.; Priestly, T.; Marshall, G. R.; Knight, A. R.; Middlemiss, D. N.; Woodruff, G. N.; Iversen, L. L. Synthesis and pharmacological evaluation of a series of dibenzo[a,d]cycloalkenimines as N-methyl-D-aspartate antagonists. *J. Med. Chem.* **1990**, *33*, 789−808. (b) Gill, R.; Brazell, C.; Woodruff, G. N.; Kemp, J. A. The neuroprotective action of dizocilpine (MK-801) in the rat middle cerebral artery occlusion model of focal ischemia. *Br. J. Pharmacol.* **1991**, *103*, 2030−2036. (c) Hatfield, R. H.; Gill, R.; Brazell, C. The dose−response relationship and therapeutic window for dizocilpine (MK-801) in rat focal ischemia model. *Eur. J. Pharmacol.* **1992**, *216*, 1−7.

(44) (a) Carey, R. E.; Heath, R. G. The effects of phencyclidine on the uptake of ³H-catecholamines by rat striatal and hypothalamic synaptosomes. *Life Sci.* **1976**, *18*, 1105−1110. (b) Smith, R. C.; Meltzer, H. Y.; Arora, R. C.; Davis, J. M. Effects of phencyclidine on [³H] catecholamine and [³H]serotonin uptake in synaptosomal preparations from rat brain. *Biochem. Pharmacol.* **1977**, *26*, 1435−1439.

(45) Martin, W. R.; Eades, C. G.; Thompson, J. A.; Huppler, R. E.; Gilbert, P. E. The effects of morphine and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. *J. Pharmacol. Exp. Ther.* **1976**, *217*, 517−532.

(46) Quirion, R.; Chicheportiche, R.; Contreras, P.; Johnson, K. M.; Lodge, D.; et al. Classification and nomenclature of phencyclidine and sigma receptor sites. *Trends Neurosci.* **1987**, *10*, 444−446.

(47) Zukin, R. S.; Zukin, S. R. Demonstration of ³H-cyclazocine binding to multiple opiate receptor types. *Mol. Pharmacol.* **1981**, *20*, 246−254.

(48) Tam, S. W. (+)³H-SKF 10,047, (+)³H-ethylketocyclazocine, μ, κ, σ and phencyclidine binding sites in guinea pig brain membranes. *Eur. J. Pharmacol.* **1985**, *109*, 33−41.

(49) Su, T. P. Evidence for sigma opioid receptors: binding of ³H-SKF 10,047 to etrophine-inaccessible sites in guinea pig brain. *J. Pharmacol. Exp. Ther.* **1982**, *223*, 284−290.

(50) Maurice, T.; Lockhart, B. P. Neuroprotective and anti-amnesic potentials of sigma (σ) receptor ligands. *Prog. Neuro-Psychopharmacol. Biol. Psychiat.* **1997**, *21*, 69−102.

(51) Su, T. P.; London, E. D.; Jaffe, J. H. Steroid Binding at σ Receptors Suggests a Link Between Endocrine, Nervous, and Immune Systems. *Science* **1988**, *240*, 219−221.

(52) Ross, S. B. Proadifen-sensitive High Affinity Binding of ³H-Alaproclate to Liver Membranes. *Pharmacol. Toxicol.* **1987**, *61*, 282−287.

(53) Ross, S. B.; Gawell, L.; Hall, H. Stereoselective High-Affinity Binding of ³H-Alaproclate to Membranes from Rat Cerebral Cortex. *Pharmacol. Toxicol.* **1987**, *61*, 288−292.

(54) Ferris, R. M.; Tang, F. L. M.; Chang, K.-J.; Russell, A. Evidence that the Potential Antipsychotic Agent Rimcazole (BW 234U) Is a Specific, Competitive Antagonist of Sigma Sites in Brain. *Life Sci.* **1986**, *38*, 2329−2337.

(55) Taylor, D. P.; Dekleva, J. A Potential Antipsychotic Agent that Selectively Binds to Sigma Receptors. In: *Sigma and Phencyclidine-Like Compounds as Molecular Probes in Biology*; NPP Books: Ann Arbor, 1988; pp 345−355.

(56) Lehmann, J. Sigma Receptor, Schizophrenia and Cytochrome P-450. *Drug News Perspect.* **1991**, *4*, 208−210.

(57) Contreras, P. C.; Gray, N. M.; Ragan, D. M.; Lanthorn, T. H. BMY-14802 protects against ischemia-induced neuronal damage in the gerbil. *Life Sci.* **1992**, *51*, 1145−1149.

(58) Carter, C. J.; Lloyd, K. G.; Zivkovic, B.; Scatton, B. Ifenprodil and SL 82.0715 as cerebral antiischemic agents. III. Evidence for antagonistinc effects at the polyamine modulatory site within the N-methyl-D-aspartate receptor complex. *J. Pharmacol. Exp. Ther.* **1989**, *253*, 475−482.

(59) Prince, D. A.; Feeser, H. R. Dextromethorphan protects against cerebral infarction in rat model of hypoxia-ischemia. *Neurosci. Lett.* **1988**, *85*, 291−296.

(60) (a) Long, J. B.; Tidwell, R. E.; Tortella, F. C.; Rice, K. C.; de Costa, B. R. Selective sigma ligands protect against dynorphin A-induced spinal cord injury in rats. *Soc. Neurosci. Abs.* **1990**, *16*, 1122, abs 461.4. (b) Contreras, P. C.; Ragan, D. M.; Bremer, M. E.; Lanthorn, T. H.; Gray, N. M.; Iyengar, S.; Jacobson, A. E.; Rice, K. C.; de Costa, B. R. Evaluation of 450,488 H analogs for neuroprotective activity in the gerbil. *Brain Res.* **1991**, *546*, 79−82.

(61) Rao, T. S.; Cler, J.A.; Mick, S. J.; Ragan, D. M.; Lanthorn, T. H.; Contreras, P. C.; Iyengar, S.; Wood, P. L. Opipramol, a potent sigma ligand, is an anti-ischemic agent: Neurochemical evidence for an interaction with N-methyl-D-aspartate receptor complex *in vivo* by cerebral cGMP measurements. *Neuropharmacology* **1990**, *29*, 1199−1204.

(62) Quirion, R.; Bowen, W. D.; Itzhak, Y.; Junien, J. L.; Musacchio, J. M.; Rothman, R. B.; Su, T. P.; Tam, S. W.; Taylor, D. P. A proposal for the classification of sigma binding sites. *Trends Pharmacol. Sci.* **1992**, *13,* 85−86.

(63) Carroll, F. I.; Abraham, P.; Parham, K.; Bai, X.; Zhang, X.; Brine, G. A.; Mascarella, S. W.; Martin, B. R.; May, E. L.; Sauss, C.; DiPaolo, L.; Wallace, P.; Walker, J. M.; Bowen, W. D. Enantiomeric N- substituted N-normetazocines: A comparative study of affinities at σ, PCP, and μ opioid receptors. *J. Med. Chem.* **1992**, *35*, 2812−2818.

(64) Hudkins, R. L.; DeHaven-Hudkins, D. L. M_1 muscarinic antagonists interact with σ recognition sites. *Life Sci.* **1991**, *49*, 1229−1235.

(65) Eaton, T. A.; Houk, K. N.; Watkins, S. F.; Fronczek, F. R. Geometries and conformational Processes in Phencyclidine and a rigid adamantyl analogue: Variable-temperature NMR, X-ray crystallographic, and molecular mechanics studies. *J. Med. Chem.* **1983**, *26*, 479−486.

(66) (a) Kozikowski, A. P.; Pang, Y. P. Structural determinants of affinity for the phencyclidine binding site of the *N*-methyl-D-aspartate receptor complex: discovery of a rigid phencyclidine analogue of high binding affinity. *Mol. Pharmacol.* **1990**, *37*, 350−357. (b) Also see: Casalotti, S. O.; Kozikowski, A. P.; Fauq, A.; Tuckmantel, W.; Krueger, K. E. Design of an irreversible affinity ligand for the phencyclidine recognition site on the *N*-methyl-D-aspartate type glutamate receptors. *J. Pharmacol. Exp. Ther.* **1992**, *260*, 21−28.

(67) Chen, C.; Kozikowski, A. P.; Wood, P. L.; Reynolds, I. J.; Ball, R. G.; Pang, Y. P. Synthesis and biological activity of 8a-Phenyldecahydroquinolines as probes of PCP's binding conformation. A new PCP-like compound with increased in vivo potency. *J. Med. Chem.* **1992**, *35*, 1634−1638.

(68) Hudkins, R. L.; Mailman, R. B.; DeHaven-Hudkins, D. L. Novel (4-phenylpiperidinyl)- and (4-Phenylpiperazinyl)alkyl-spaced esters of 1-phenylcyclopentanecarboxylic acids as potent *σ*-selective compounds. *J. Med. Chem.* **1994**, *37*, 1964−1970.

(69) Su, T. P.; Wu, X.; Cone, E. J.; Kanhiya, S.; Tamara, M. G.; Dodge, A. L.; Parish, D. W. Sigma compounds derived from phencyclidine: Identification of PRE−084, a new, selective sigma ligand. *J. Pharmacol. Exp. Ther.* **1991**, *259*, 543−550.

(70) Russel, M. G. N.; Baker, R.; Billington, D. C.; Knight, A. K.; Middlemiss, D. N.; Noble, A. J. Benz[f]isoquinoline Analogues as High-Affinity *σ* Ligands. *J. Med. Chem.* **1992**, *35*, 2025−2033.

(71) Chambers, M. S.; Baker, R.; Billington, D. C.; Knight, A. K.; Middlemiss, D. N.; Wong, E. H. F. Spiropiperidines as High-Affinity, Selective *σ* Ligands. *J. Med. Chem.* **1992**, *35*, 2033−2039.

(72) de Costa, B. R.; Radesca, L.; Di Paolo, L.; Bowen, W. D. Synthesis, characterization, and biological evaluation of a novel class of *N*-(arylethyl)-N-alkyl-2-(1-pyrrolidinyl) ethylamines:

Structural requirements and binding affinity at the *σ* receptor. *J. Med. Chem.* **1992**, *35*, 38−47.

(73) Grob, C. A.; Ohta, M.; Renk, E.; Weiss, A. Synthese und Reaktionen 1-substituierter Bicyclo[2.2.2]octane. *Helv. Chim. Acta* **1958**, *41*, 1191−1197.

(74) Moriarty, R. M.; Khosrowshahi, J. S.; Awashti, A. K.; Penmasta, R. A convenient synthesis of 1-aminopolycycloalkanes and their tosylate salts. *Synth. Commun.* **1988**, *18*, 1179−1186.

(75) Gabrielevitz, A.; Kloog, Y.; Kallic, A.; Balderman, D.; Sokolowsky, M. Interaction of phencyclidine and its new adamantyl derivatives with muscarinic receptors. *Life Sci.* **1980**, *26*, 89−95.

(76) Eaton, P. E.; Carlson, G. R.; Lee, J. T. Phosphorus pentoxide − methanesulfonic acid. A convenient alternative to polyphosphoric acid. *J. Org. Chem.* **1973**, *38*, 4071−4073.

(77) Moriarty, R. M.; Tuladhar, S. M.; Penmasta, R.; Awashti, A. K. Unpublished results (UIC).

(78) Grunewald, G. L.; Ye, Q. Synthesis of benzobicyclo[3.2.1]octanes involving inversion of configuration via an N to O acetyl migration. *J. Org. Chem.* **1988**, *53*, 4021−4026.

(79) Hunig, S.; Kahanek, H. Diensynthesen mit 1-Diethylamino-butadien und thermische Spaltung der Addukte. *Chem. Ber.* **1957**, *90*, 238−245.

(80) Gray, N. M.; Cheng, B. K.; Mick, S. J.; Lair, C. M.; Contreras, P. C. Phencyclidine-like effects of tetrahydroisoquinolines and related compounds. *J. Med. Chem.* **1989**, *32*, 1242−1248.

(81) Cheng, Y.-C.; Prusoff, W. H. Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50% inhibition (IC_{50}) of an enzymatic reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108.