Synthesis and Biological Evaluation of Conformationally Restricted 2-(1-Pyrrolidinyl)-*N*-[2-(3,4-dichlorophenyl)ethyl]-*N*-methylethylenediamines as σ Receptor Ligands. 1. Pyrrolidine, Piperidine, Homopiperidine, and Tetrahydroisoquinoline Classes

Brian R. de Costa,* Celia Dominguez, Xiao-shu He, Wanda Williams, Lilian Radesca,† and Wayne Bowen

Laboratory of Medicinal Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20892

Received May 26, 1992

The synthesis and σ receptor affinity of a series of conformationally restricted derivatives of 2-(1-pyrrolidinyl)-*N*-[2-(3,4-dichlorophenyl)ethyl]-*N*-methylethylenediamine (1) is described. The pyrrolidinyl (or *N,N*-dialkyl), ethylenediamine, *N*-alkyl, and phenylethyl portions of this σ receptor pharmacophore were restricted by its incorporation into 1,2-cyclohexanediamine-, pyrrolidine-, piperidine-, homopiperidine-, and tetrahydroisoquinoline-containing ligands. The σ receptor binding affinities of these compounds were determined using [^{3}H](+)-pentazocine in guinea pig brain homogenates. The synthesis of all but one class was achieved by acylation and alane reduction of the appropriate diamine precursors whose synthesis is also reported. σ receptor affinities ranged from 1.34 nM for 6,7-dichloro-2-[2-(1-pyrrolidinyl)ethyl]tetrahydroisoquinoline (12) to 455 nM for (1*R*,2*R*)-*trans*-*N*-[2-(3,4-dichlorophenyl)ethyl]-*N*-methyl-2-(1-pyrrolidinyl)cyclohexylamine [(−)-4]. In this displacement assay, (+)-pentazocine exhibited a K_i of 3.1 nM while DTG and haloperidol showed K_i values of 27.7 and 3.7 nM, respectively. The conformationally free parent compound 1 exhibited a K_i value of 2.1 nM. Comparison of both the σ receptor affinities and nitrogen atom geometry of the compounds revealed that a gauche relation of the nitrogen atoms of *cis*-1,2-cyclohexanediamines is not imperative for high affinity as we had previously thought. It is highly likely that nitrogen lone pair orientations and steric factors on the aliphatic portions of these ligands play a major role in the σ receptor binding of this pharmacophore.

Introduction

σ receptors are a unique class of high-affinity, saturable, stereospecific central nervous system (CNS) receptors that at the time of their identification were confused with opioid receptors[1] and later with phencyclidine (PCP) receptors.[2] However, with the development of specific, high-affinity ligands from diverse chemical classes, the role of this receptor has become clearer.[3] σ receptors have been the focus of intense study during the past decade (for a review, see ref 3). These studies have implicated σ receptors in numerous pharmacological and biochemical effects which include negative modulation of cholinergic agonist stimulated phosphoinositide turnover (second messenger systems),[4] dystonia induced by antipsychotic drugs,[5] certain motor disorders,[6] and effect on serotonin and electrically induced smooth muscle contraction.[7] Because most antipsychotic drugs exhibit very high affinity for the σ receptor,[3] it has also been implicated in certain psychoses[8]

† Present address: DuPont-Merck Pharmaceutical Co., Chambersworks Process Facility (S1), Deep Water, New Jersey 08023-0999.

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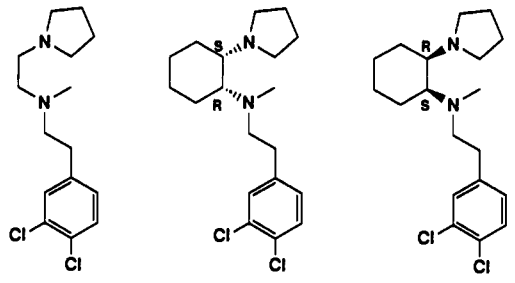
Chart I



1 (+)-2 (-)-2

as well as the behavioral effects of cocaine.[9] σ receptor ligands have been suggested as a treatment modality for certain movement disorders as well as psychotic behavior.[3] The more recent identification of neuroprotective activity among a number of structurally dissimilar σ receptor ligands has suggested a role of this receptor in neuroprotective mechanisms.[10] This is further supported by the recent finding of an association of σ receptors with a divalent cation channel analogous to the NMDA/glutamate calcium channel.[11] σ receptors have recently been classified into two subtypes based upon the differential biochemical and pharmacological properties of structurally diverse ligands.[3b]

The abundance of σ receptors in peripheral tissues such as liver and spleen[12] as well as on components of the immune system[13] suggests that these receptors may have an important role outside of the CNS. One of our major goals in this area is to identify novel compounds from diverse structural classes with high affinity and selectivity for the σ receptor. On the basis of a rational approach, we recently identified the substituted ethylenediamine (1) (Chart I) to be a highly potent and specific ligand for σ receptors when tested for its ability to displace [^{3}H]-(+)-3-PPP.[14] Compound 1 (K_i = 0.34 nM) proved to be among the most potent and selective compounds ever tested by us. This compound was derived from previously reported *cis*-1,2-cyclohexanediamine σ ligands (+)-2 (K_i = 6.0 nM, [^{3}H](+)-3-PPP) and (-)-2 (K_i = 1.3 nM, [^{3}H]-(+)-3-PPP)[15] by removal of the cyclohexyl ring and associated stereochemical constraints. The high affinity of 1 was surprising considering the apparent importance of the cis geometry[16] of (+)- and (-)-2 for high σ receptor affinity.

Since their initial identification, ethylenediamines such as 1 and *cis*-1,2-cyclohexanediamines such as (+)- and (-)-2 have proved to be valuable tools for investigating σ receptor biochemistry and pharmacology.[17]

From our structure–activity relationship (SAR) work with 1,[14] we have identified 1 or a simplified analogue 3[14] in which the pyrrolidine ring is replaced by *N*,*N*-dimethylamino to be the σ receptor active pharmacophore of (+)- and (-)-2 and related *cis*-cyclohexanediamines.

Conformational restriction of flexible drugs has proved invaluable in medicinal chemistry in determining drug–receptor steric requirements, the identification of new structures with greater efficacy and selectivity as well as completely new pharmacological profiles. For example, the synthesis of 9-azabicyclo[4.2.1]nona[2,3-*c*]pyridine,[18] the first bridged analog of nornicotine, was found to possess 16 times the receptor binding affinity and 3 times the toxicological activity of nornicotine. The adamantyl analog of the drug of abuse phencyclidine (PCP) was found not to bind to PCP receptors but instead showed potent antagonist activity at muscarinic receptors.[19] However, bridging of the 2-position of the phenyl ring of PCP to the 2-position of the cyclohexyl ring via a methylene group gave 1,2,3,4,4a,9a-hexahydro-*N*-methyl-4a*H*-fluorenamine which proved to be significantly more potent and selective than PCP both in vivo and in vitro.[20] Conformational restriction of *N*-(3-phenyl-*n*-propyl)-1-phenyl-2-aminopropane resulted in N-substituted 2-aminotetralins as a new class of σ receptor ligands.[21]

In this study we wished to investigate the effect of conformational restriction of pharmacophore 1 (or 3) by

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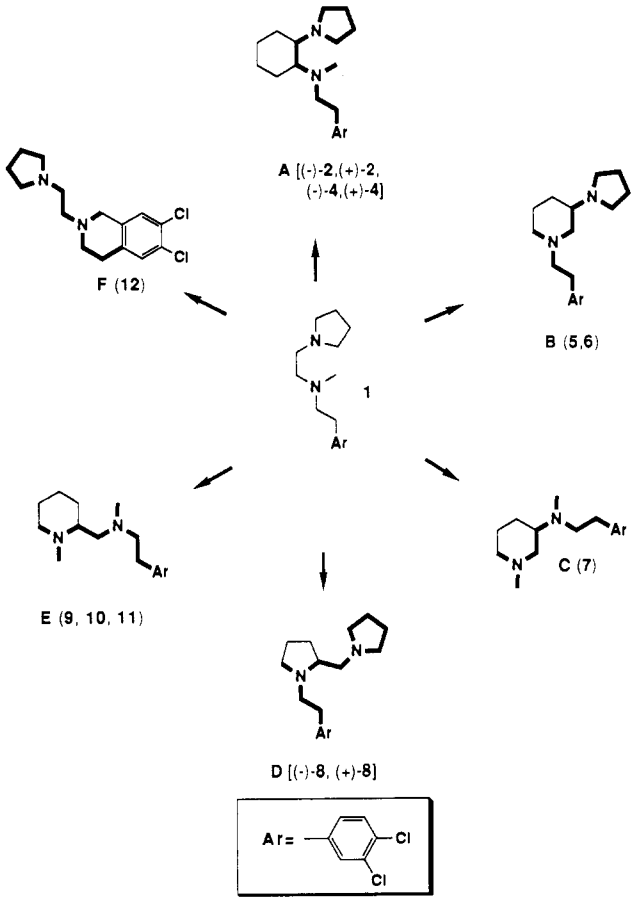
Chart II



incorporating it into a variety of simple semirigid systems (Chart II)[22] allowing restriction either separately or together of the *N,N*-dialkyl (or pyrrolidinyl), ethylenediamine, *N*-alkyl, and phenylethyl portions of the molecule. This approach has the potential to provide as yet undiscovered high-affinity σ ligands and to furnish information on receptor topography/bound conformation of 1 and/or 3. A computer-assisted molecular modeling study of the interaction of 1, 3, and restrained analogs with the σ receptor will be the subject of a future study.[23]

We report the synthesis and [^{3}H](+)-pentazocine displacement constants (guinea pig brain) of the compound classes A–F (Chart II). Parent (unrestricted) ligand 1 and *cis*- and *trans*-1,2-cyclohexanediamines (class A) (Chart II and Table I) which were previously reported by us for displacement of [^{3}H](+)-3-PPP binding[14,16] are tested here against [^{3}H](+)-pentazocine for internal comparison. Pyrrolidine, piperidine, homopiperidine and tetrahydroisoquinoline classes B–F (Chart II and Table II) constituted the remainder of the compounds. In trans diamines (+)-4 and (−)-4, the nitrogen atoms are oriented gauche and in 5, 6, and 7, the amine nitrogen atoms are constrained in the transoid (antiperiplanar) configuration which in the 1,2-cyclohexanediamine series proved to be deleterious toward σ receptor affinity with this particular pharmacophore. Proline derived enantiomers (*R*)-(+)-8 and (*S*)-(−)-8 (Table II) served to examine conformational restriction of the *N*-[(3,4-dichlorophenyl)ethyl]-*N*-alkylamino group and also to examine σ receptor enantioselectivity within this class of compounds. 1-Methyl-2-[(methylamino)methyl]piperidine 9 and 1-ethyl-2-[(alkylamino)methyl]pyrrolidines 10 and 11 (Table II) were synthesized in order to investigate the effect of partial restriction of the *N,N*-dialkylamino substituent. Isoquinoline 12 (class F) allowed examination of the effect of restriction of the (3,4-dichlorophenyl)ethyl substituent on σ binding. Compound 12 differs from previously reported isoquinoline-type σ ligands[24] in that it incorporates a second basic nitrogen atom.

(22) An extension of this work will be presented in part 2 of this paper.
(23) Linders, J. T. M.; et al., in preparation, 1992.

Chemistry

The stereoisomers (+)- and (−)-2, (+)- and (−)-4 (class A in Chart II) were synthesized previously and are described in earlier publications.[15,16]

For improved clarity, "Ar" in Schemes I–IV and Tables I and II refers to 3,4-dichlorophenyl. 3-(1-Pyrrolidinyl)-piperidine 5 (Table II) was obtained starting with 3-hydroxypiperidine (Scheme I). Carbamate 13 was transformed in high yield to azide 15 via methanesulfonate ester 14. Catalytic reduction of 15 provided amine 16 (62%) which was converted to pyrrolidine 17 (quantitative) by treatment with 1,4-dibromobutane/K_2CO_3 in DMF at 55 °C. Quantitative removal (CF_3COOH) of the BOC protecting group, coupling with 3,4-dichlorophenylacetic acid, and AlH_3 reduction afforded 5. Treatment of 16 with boiling ethyl formate (Scheme I) followed by $LiAlH_4$ reduction provided diamine 21, which was readily transformed to 7. Compound 6 (Table II) was synthesized via N,N-dialkylation with butane 1,4-dibromide of commercially available (Aldrich) 3-aminocaprolactam (Scheme II).

(*R*)-(+)- and (*S*)-(−)-8 (Table II) were synthesized as shown in Scheme III. (−)-8 based on the configuration of natural proline was readily obtained from commercially available (Aldrich) (*S*)-(+)-2-[(1-pyrrolidinyl)methyl]pyrrolidine [(*S*)-(+)-26]. (*R*)-(+)-8 based on the configuration of unnatural proline was obtained starting with commercially available (Bachem, CA) (*R*)-Boc-proline. Coupling with pyrrolidine in the presence of hydroxybenzotriazole (HOBT)[25] and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride afforded (+)-27, which was N-deprotected (CF_3COOH) and reduced to diamine (*R*)-(−)-26. The enantiomeric purity of (*R*)-(−)-26 and (*R*)-(+)-26 was found to be >98% by formation of the corresponding ureas by reaction of these amines with optically pure (*S*)-(+)-α-methylbenzyl isocyanate in dry $CHCl_3$ and examination by ^{1}H-NMR spectroscopy as described previously.[26]

2-(Aminomethyl)piperidine 9 (Table II) was synthesized (Scheme III) starting with (±)-pipecolinic acid. In a one-pot reaction, treatment of intermediate amino alcohol 31 with $MeSO_2Cl$ followed by an excess of $MeNH_2$ gas afforded crude 32, which was transformed to 9.

Starting with commercially available 1-ethyl-2-(aminomethyl)pyrrolidine (Aldrich), pyrrolidine 11 (Scheme III) was obtained via the sequence of N-formylation

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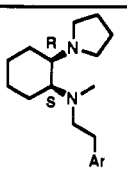
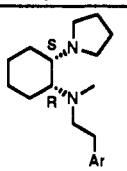
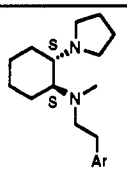
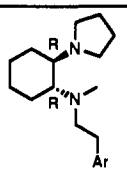
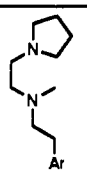
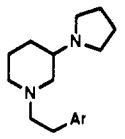
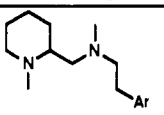
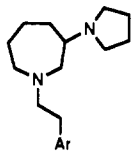
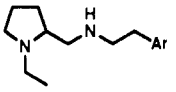
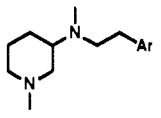
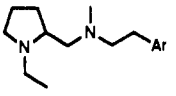
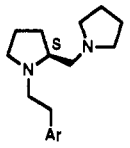
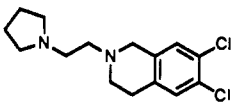
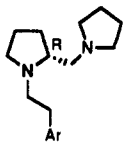
Table I. Affinities of 1,2-Cyclohexanediamines (Class A) and Ethylenediamine 1 at the σ Receptor[a,b]

					
	(−)-2	(+)-2	(+)-4	(−)-4	1
K_i ([^{3}H](+)-Pent), (nM) ± SEM	7.78 ± 0.95	18.68 ± 0.11	427 ± 74	455 ± 111	2.1 ± 0.81

[a] Ar = 3,4-dichlorophenyl. [b] Sigma binding affinities were determined by incubating [^{3}H](+)-pentazocine in the presence of 12 concentrations of test ligand in one of three concentration ranges: 0.0005–100, 0.005–1000, or 0.05–10 000 nM. All assay conditions were as described in Methods. Values are the average of two to three experiments ± SEM, each carried out in duplicate. The CDATA iterative curve fitting program (EMG Software, Inc., Baltimore, MD) was used to determine IC_{50} values. The Cheng–Prussoff equation[32] was then used to convert IC_{50} values to apparent K_i values. The following K_d value (as determined in independent experiments) was employed to calculate K_i: [^{3}H](+)-pentazocine (guinea pig brain), K_d = 4.8 nM.

Table II. σ Receptor Affinities of Amino-Substituted Pyrrolidine, Piperidine, Homopiperidine, and Tetrahydroisoquinolines (Classes B–F) and Standard Ligands[a,b]

compound	K_i([^{3}H](+)-Pent), nM ± SEM	compound	K_i([^{3}H](+)-Pent), nM ± SEM
 5	3.56 ± 1.56	 9	3.69 ± 0.85
 6	2.67 ± 0.37	 10	16.05 ± 3.62
 7	2.30 ± 0.13	 11	1.48 ± 0.37
 (−)-8	1.75 ± 0.43	 12	1.34 ± 0.30
 (+)-8	4.34 ± 0.08	(+)-pentazocine 1,3-di-*o*-tolylguanidine haloperidol	3.1 ± 0.3 27.7 ± 4.3 3.7 ± 0.6

[a] Ar = 3,4-dichlorophenyl. [b] Sigma binding affinities were determined by incubating [^{3}H](+)-pentazocine in the presence of 12 concentrations of test ligand in one of three concentration ranges: 0.0005–100, 0.005–1000, or 0.05–10 000 nM. All assay conditions were as described in Methods. Values are the average of two to three experiments ± SEM, each carried out in duplicate. The CDATA iterative curve fitting program (EMF Software, Inc., Baltimore, MD) was used to determine IC_{50} values. The Cheng–Prussoff equation[32] was then used to convert IC_{50} values to apparent K_i values. The following K_d value (as determined in independent experiments) was employed to calculate K_i: [^{3}H](+)-pentazocine (guinea pig brain), K_d = 4.8 nM.

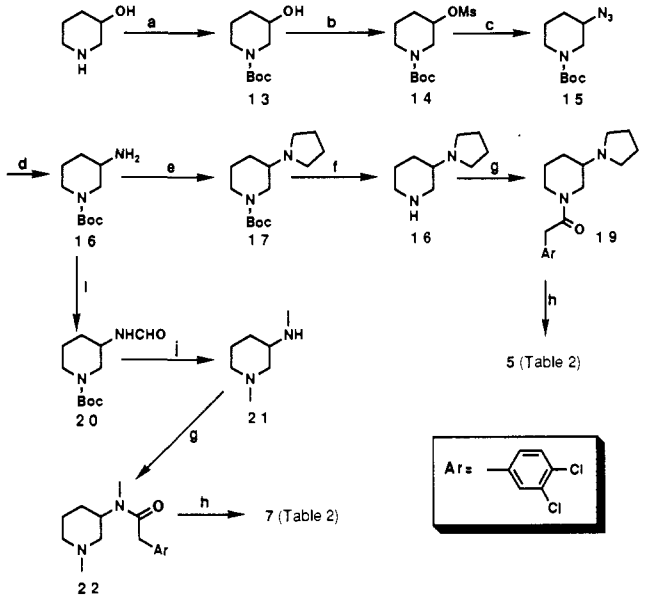
followed by reduction. Pyrrolidine **10** was similarly obtained.

Ethylenediamine **37**[14] was utilized as a precursor for tetrahydroisoquinoline **12** (Table II) (Scheme IV). Thus, treatment of a solution of **37** in CF_3SO_3H with HCHO and NaCl (as a source of chloride ions for chloromethylation) during 11 h at 20 °C in a one-pot reaction afforded **12** (31%) as the major product. The ^{1}H-NMR spectrum of **12** exhibited two uncoupled singlets at 7.10 and 7.18 ppm, suggesting a para orientation as shown in Table II.

Results and Discussion

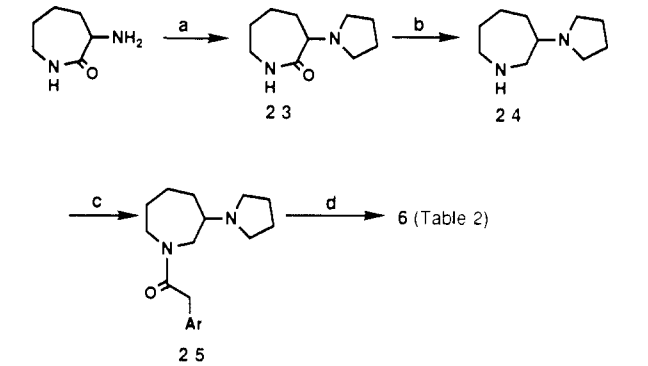
We synthesized and tested a series of conformationally restricted 2-(1-pyrrolidinyl)-*N*-[2-(3,4-dichlorophenyl)-ethyl]-*N*-methylethylenediamines in order to discover new and possibly more potent (than 1) σ receptor ligands containing this pharmacophore as well as to gain information about the probable receptor bound conformation of pharmacophore 1. We successfully approached this problem of conformational restriction by incorporating

Scheme I. Synthesis of 3-Aminopiperidine Type σ Receptor Ligands (Classes B and C)[a]



[a] (a) $(Boc)_2O$, aq $NaHCO_3$, rt; (b) $MeSO_3Cl$, THF, Et_3N; (c) NaN_3, DMF, 70 °C; (d) H_2, 10% Pd/C, MeOH/AcOH (1:1); (e) 1,4-dibromobutane, K_2CO_3, DMF, 55 °C; (f) CF_3COOH, rt; (g) 3,4-dichlorophenylacetic acid, DCC, CH_2Cl_2, rt; (h) AlH_3, THF, rt; (i) EtOCHO, reflux; (j) $LiAlH_4$, THF, reflux.

Scheme II. Synthesis of 3-Aminohomopiperidine σ Ligand (Class B)[a]

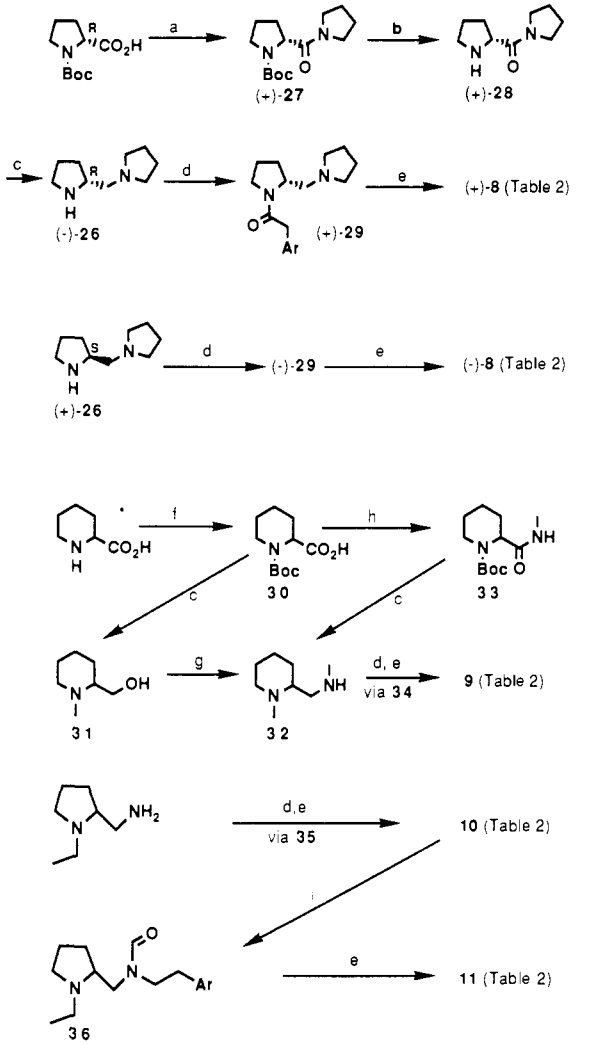


[a] (a) 1,4-dibromobutane, K_2CO_3, DMF, 55 °C; (b) $LiAlH_4$, THF, reflux; (c) 3,4-dichlorophenylacetic acid, DCC, CH_2Cl_2, rt; (d) AlH_3, THF, rt; Ar = 3,4-dichlorophenyl.

this pharmacophore into pyrrolidine, piperidine, homopiperidine, and tetrahydroisoquinolines.

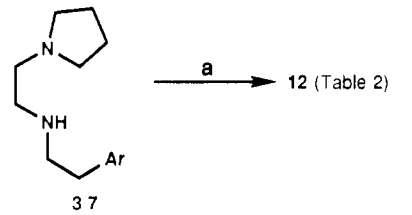
The results, shown in Tables I (previously reported compounds) and II, with [^{3}H](+)-pentazocine as the radioligand reveal a spectrum of σ receptor affinities ranging from 1.34 nM for **12** to 455 nM for (−)-**4**. Examination of the σ receptor affinities of the 1,2-cyclohexanediamines (Table I) indicates the cis diastereoisomers (+)- and (−)-**2** to be significantly more potent than the trans diastereoisomers [(+)- and (−)-**4**] with greatest preference for the *cis*-(1*S*,2*R*)-(−)-**2** isomer. These results are in agreement with those obtained previously using (+)-3-PPP as the radioligand,[16] suggesting that [^{3}H]-(+)-3-PPP, [^{3}H](+)-pentazocine and the compounds in Tables I and II are binding to the same population of σ receptors in these assays. This also supports our previous observation that both (+)-pentazocine and (+)-3-PPP label the σ_1-subtype in guinea pig brain.[27] However, the conformationally flexible **1** and selected compounds from Tables I and II (unpublished) displaced [^{3}H](+)-pentazocine with higher K_i values than those obtained using [^{3}H](+)-3-PPP,[14] suggesting either differential in-teraction with σ-1 and σ-2 subtypes or complex interaction with σ receptors.

Scheme III. Synthesis of 2-(Aminomethyl)pyrrolidines and Piperidines (Classes D and E)[a]



[a] (a) 1-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, HOBT, pyrrolidine, CH_2Cl_2, rt; (b) CF_3COOH, rt; (c) $LiAlH_4$, THF, reflux; (d) 3,4-dichlorophenylacetic acid, DCC, CH_2Cl_2, rt; (e) AlH_3, THF, rt; (f) $(Boc)_2O$, aq $NaHCO_3$, rt; (g) (i) $MeSO_2Cl$, (ii) $MeNH_2$ (gas) (excess); (h) (i) isobutyl chloroformate, Et_3N, $CHCl_3$, −10 °C, (ii) $MeNH_2$ (gas); (i) EtOCHO, reflux; Ar = 3,4-dichlorophenyl.

Scheme IV. Synthesis of 2-[2-(1-Pyrrolidinyl)ethyl]-tetrahydroisoquinoline σ Ligand **12** (Class F)[a]



[a] (a) CF_3SO_3H, HCHO, NaCl, rt, sealed tube; Ar = 3,4-dichlorophenyl.

Examination of the σ receptor affinities of the conformationally restricted ethylenediamines (Tables I and II) and comparison with the geometry of their nitrogen atoms indicates that a cisoid nitrogen geometry is not imperative for high affinity as we had previously believed[16] from binding results obtained with enantiomeric *cis*- and *trans*-cyclohexanediamines (see Table I). This is exemplified

by the high affinity of compounds 5, 6, and 7 all containing nitrogen atoms disposed antiperiplanar. This contrasts to the considerably lower affinities of *trans*-1,2-cyclohexanediamines (Table I) containing gauche oriented nitrogen atoms. This suggests that more complex factors than simple geometry of the nitrogen atoms are responsible for high affinity at the σ receptor. Nitrogen lone pair orientations and steric factors on the aliphatic portions of the ligands almost certainly play a significant role in the binding of this pharmacophore (1). Of significance also may be the fact that both the nitrogen lone pair of electrons in (+)- and (−)-4 are free to rotate whereas in 5, 6, and 7, one of these lone pairs of electrons is fixed in space.

Compound 11 was synthesized to investigate the effect of opening up of the pyrrolidinyl ring of 1 and at the same time partially restricting the ethylenediamine group. The net effect was an increase in binding affinity compared with 1 (Table II). The 11-fold lowered affinity of the desmethyl analog 10 compared with 11 is an indication that a small amount of lipophilic bulk (i.e. methyl) on this nitrogen atom is important for optimal binding affinity as we have observed previously in the flexible ethylenediamines[14] and 1,2-cyclohexanediamines.[16]

Isoquinoline 12 allows conformational freedom of the ethylenediamine portion of the pharmacophore but constrains the 3,4-dichlorophenyl and *N*-methyl nitrogen. In this compound, very high σ receptor affinity was observed as for 1.

Enantiomeric ligands 2 and 8 revealed a 2.4-fold preference for (1*S*,2*R*)-(−)-2 and a 2.5-fold preference for (*S*)-(−)-8 for displacement of [^{3}H](+)-pentazocine compared with their respective enantiomers (+)-2 and (+)-8. These enantioselectivity ratios are comparable to those typically observed among different classes of σ ligands.[3a]

In summary, the binding data reveals a considerable degree of conformational freedom of 1 and suggests that the σ receptor is not subject to rigid steric constraints with this pharmacophore.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Specific rotation determinations at the sodium D line were obtained in a 1-dM cell using a Perkin-Elmer 241-MC polarimeter. Elemental analyses were performed at Atlantic Microlabs, Atlanta, GA; where molecular formulae are indicated followed by the symbols of the elements, elemental analyses were determined to be within ±0.4% of the theoretical values. Chemical-ionization mass spectra (CIMS) were obtained using a Finnigan 1015 mass spectrometer. Electron-ionization mass spectra (EIMS) and high-resolution mass measurements (HRMS) were obtained using a VG-Micro Mass 7070F mass spectrometer. ^{1}H-NMR spectra were measured from $CDCl_3$ solutions using a Varian XL-300 spectrometer. Thin-layer chromatography (TLC) was performed on 250 μM Analtech GHLF silica gel plates. TLC system A corresponds to $CHCl_3$–MeOH–concentrated aqueous NH_3 (90:9:1). TLC system B corresponds to $CHCl_3$/MeOH/concentrated aqueous NH_3 (80:18:2). TLC system C corresponds to EtOAc/hexanes (1:2). No attempt was made to optimize the yields. For purposes of clarity, enantiomeric compounds are indicated with prefixes indicating absolute configuration and/or the direction of rotation whereas racemic compounds are shown without prefixes.

1-(*tert*-Butoxycarbonyl)-3-hydroxypiperidine (13). To a stirred solution of 3-hydroxypiperidine (25.0 g, 247 mmol) and $NaHCO_3$ (62.3 g, 742 mmol, 3 equiv) in water (500 mL) was added di-*tert*-butyl dicarbonate (64.7 g, 296 mmol, 1.2 equiv), and the solution was stirred for 48 h at room temperature (rt). The aqueous mixture was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extract was back-washed with water (50 mL) and dried by filtration through Na_2SO_4. Evaporation of the solvent afforded the desired product as a colorless oil. Distillation under high vacuum (140 °C/1.2 mmHg) afforded 13 as an oil which crystallized on standing (45.5 g, 92%): mp 70–72 °C; ^{1}H NMR ($CDCl_3$) δ 3.73 (d, J = 10 Hz, 2H), 3.52 (m, 1H), 3.12 (m, 2H), 1.88 (m, 1H), 1.76 (m, 1H), 1.19–1.66 (complex m, 2H), 1.46 (s, 9H); CIMS (MH^+ calcd for $C_{10}H_{19}NO_3$) 202, found (MH^+) 202. Anal. Calcd for $C_{10}H_{19}NO_3$: C, H, N.

1-(*tert*-Butoxycarbonyl)-3-[(methylsulfonyl)oxy]piperidine (14). To a stirred solution of 13 (44.3 g, 220 mmol) and Et_3N (61.4 mL, 440 mmol, 2 equiv) in THF (250 mL) was added dropwise at rt (maintained by cooling from an ice bath) methanesulfonyl chloride (27.77 g, 242 mmol, 1.1 equiv). The reaction mixture was stirred for 1 h at rt when TLC (solvent system C) indicated completion. The precipitated Et_3N·HCl was removed by filtration and the filter cake was washed with 50 mL of THF. The combined filtrate and washings were evaporated in vacuo to give the crude product as a yellow oil. This was dissolved in EtOAc/hexanes (1:2) and passed through a pad of silica gel eluting with ethyl acetate/hexanes (1:3). Evaporation of the filtrate afforded the product as a pale yellow oil (59.1 g, 96%) which crystallized on standing. Recrystallization from EtOAc/hexane (1:10) afforded an analytically pure sample: mp 69–70 °C; ^{1}H NMR ($CDCl_3$) δ 4.72 (m, 1H), 3.63 (m, 2H), 3.46 (m, 1H), 3.32 (m, 1H), 3.05 (s, 3H), 1.75–2.06 (complex m, 4H), 1.46 (s, 9H); CIMS (MH^+ calcd for $C_{11}H_{21}NO_5S$) 280, found (MH^+) 280. Anal. Calcd for $C_{11}H_{21}NO_5S$: C, H, N.

3-Azido-1-(*tert*-butoxycarbonyl)piperidine (15). A mixture of 14 (57.1 g, 205 mmol) and NaN_3 (39.9 g, 614 mmol, 3.0 equiv) in DMF (200 mL) was heated and stirred at 70 °C for 48 h when TLC (solvent system C) indicated the reaction to be complete. The reaction mixture was cooled to rt and poured into cold water (200 mL). The aqueous mixture was extracted with Et_2O (500 mL), and the organic extract was back-washed with water (2 × 100 mL) and dried (Na_2SO_4) and the solvent was evaporated in vacuo to afford 15 (45.5 g, 98%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.66–3.80 (m, 1H), 3.57 (m, 1H), 3.46 (m, J_{app} = 4.0 Hz, 1H), 3.12 (m, 2H), 1.90–2.05 (m, 2H), 1.69–1.83 (m, 2H), 1.47 (s, 9H). No attempt was made to further purify or characterize this compound.

3-Amino-1-(*tert*-butoxycarbonyl)piperidine (16). A solution of 15 (37.1 g, 164 mmol) in a mixture of MeOH (100 mL) and acetic acid (25 mL) was added 10% Pd–C (3.7 g), and the reaction mixture was hydrogenated (50 psi) for 24 h at rt in a Parr apparatus. Analysis of the reaction by TLC (solvent system A) and IR (to look for presence or absence of N_3 str peak at 2100 cm^{-1}) indicated the reaction to be complete. The solution was filtered through Celite to remove catalyst, and the filtrate was evaporated in vacuo to give the crude product as an oily residue. The residue was dissolved in 500 mL of 10% aqueous acetic acid and the solution was extracted with Et_2O (3 × 200 mL). The combined ethereal extract was discarded and the aqueous solution was basified by addition of excess concentrated aqueous NH_3 solution. The basified mixture was extracted with Et_2O (3 × 200 mL) and the combined organic extract was dried (Na_2SO_4) and evaporated to give 16 (22.8 g, 69%) as a pale yellow oil. 16·hemifumarate (2-propanol): mp 197–198 °C; ^{1}H NMR ($CDCl_3$) δ 3.93 (br s, 1H), 3.82 (dm, J_{gem} = 13 Hz, 1H), 2.70–2.87 (complex m, 2H), 2.56 (m, 1H), 1.93 (dm, J_{gem} = 13 Hz, 1H), 1.68 (m, 1H), 1.46 (s, 9H), 1.29–1.41 (complex m, 3H), 1.24 (m, 1H); CIMS (MH^+ calcd for $C_{10}H_{20}N_2O_2$) 201, found (MH^+) 201. Anal. Calcd for $C_{10}H_{20}N_2O_2 \cdot 0.5C_4H_4O_4$: C, H, N.

1-(*tert*-Butoxycarbonyl)-3-(1-pyrrolidinyl)piperidine (17). To a stirred solution of the base obtained from 16·fumarate (3.00 g, 9.49 mmol) in DMF (25 mL) was added butane 1,4-dibromide (2.25 g, 10.4 mmol, 1.1 equiv), and the solution was stirred at 55 °C for 48 h under a N_2 atmosphere. Anhydrous K_2CO_3 (1.44 g, 10.4 mmol, 1.1 equiv) was added, and stirring and heating (55 °C) were continued for a further 24 h. The reaction mixture was cooled and poured into 10% K_2CO_3 (120 mL), and the aqueous mixture was extracted with Et_2O (2 × 150 mL). The combined organic extract was extracted with 10% citric acid (200 mL). The

(27) Hellewell, S. B.; Bowen, W. D. A sigma-like binding site in rat pheochromocytoma (PC12) cells: Decreased affinity for (+)-benzomorphans and lower molecular weight suggest a different sigma receptor from that in guinea pig brain. *Brain Res.* **1990**, *527*, 244–253.

citric acid extract was washed with a further 2 × 150 mL of Et_2O and the combined organic layer was discarded. The aqueous extract was basified by the addition of excess aqueous NH_3 and then extracted with CH_2Cl_2 (3 × 100 mL). The combined CH_2Cl_2 extract was dried (Na_2CO_3) and the solvent evaporated in vacuo to afford **17** (2.41 g, quantitative) as a colorless oil. **17**·fumarate (EtOAc): mp 136–138 °C; ^1H NMR ($CDCl_3$) δ 3.94 (br d, J_{gem} = 13 Hz, 1H), 2.48–2.80 (complex m, 6H), 2.06 (m, 2H), 1.60–1.84 (complex m, 6H), 1.46 (s, 9H), 1.30–1.50 (m, 2H); CIMS (MH^+ calcd for $C_{14}H_{26}N_2O_2$) 255, found (MH^+) 255; Anal. Calcd for $C_{18}H_{30}N_2O_6 \cdot 0.125H_2O$: C, H, N.

3-(1-Pyrrolidinyl)piperidine (18). **17**·fumarate (2.00 g, 5.40 mmol) was suspended in $CHCl_3$ (20 mL), and the solution was treated with CF_3COOH (25 mL). TLC (solvent system A) indicated the reaction to be complete after 10 min at rt. The solvent was evaporated in vacuo, and the residue was dissolved in cold (5 °C) 50% aqueous NaOH (100 mL) and extracted with $CHCl_3$ (2 × 100 mL). The combined organic layer was dried (Na_2SO_4), and the solvent was evaporated in vacuo to give **18** (0.80 g, quantitative) as a colorless oil. **18**·HBr (2-propanol): mp 217–218 °C; ^1H NMR ($CDCl_3$) δ 3.22 (dm, J_{gem} = 11 Hz, 1H), 2.94 (dm, J_{gem} = 12 Hz, 1H), 2.48–2.62 (complex m, 6H), 1.98–2.11 (complex m, 2H), 1.65–1.82 (complex m, 6H), 1.30–1.54 (complex m, 2H); CIMS (calcd for $C_9H_{18}N_2$) 155, found (MH^+) 155. Anal. Calcd for $C_9H_{20}Br_2N_2$: C, H, N.

3-(1-Pyrrolidinyl)-1-[(3,4-dichlorophenyl)acetyl]piperidine (19).[28] To a stirred solution of 3,4-dichlorophenylacetic acid (2.0 g, 9.75 mmol, 1.5 equiv) in CH_2Cl_2 (50 mL) was added a solution of DCC (2.68 g, 13.0 mmol, 2 equiv in CH_2Cl_2 (50 mL). The mixture was stirred at rt for 10 min during which time a white precipitate formed. To this was added **18** base (1.0 g, 6.5 mmol). The reaction mixture was stirred for 10 min at rt or until TLC (solvent system A) indicated reaction to be complete. The precipitated dicyclohexylurea (DCU) was removed by filtration and washed with a little (10 mL) ether. The combined filtrate and washings were diluted to 200 mL with ether and extracted with 10% aqueous citric acid (100 mL). The organic layer was discarded, and the aqueous citric acid layer was washed with ether (3 × 50 mL) and basified with excess concentrated aqueous NH_3 solution. The basified solution was extracted with CH_2Cl_2 (2 × 100 mL), the combined organic extract was back-washed with water (50 mL) and dried (Na_2SO_4), and the solvent was evaporated in vacuo to give **19** (2.2 g, quantitative) as an oil. Crystallization of the oxalate salt from 2-propanol gave **19**·oxalate: mp 134–135 °C; ^1H NMR ($CDCl_3$) δ 7.40 (43%), 7.37 (57%) (d, J = 8.2 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H), 7.11 (dm, J = 8.2 Hz, 1H), 4.50 (dm, J = 13 Hz, 1H), 3.60–4.0 (m, 1H), 3.68 (s, 2H), 2.73–3.10 (complex m, 2H), 2.62 (m, 2H), 2.50 (m, 2H), 2.04 (m, 2H), 1.65–1.95 (complex m, 5H), 1.43 (m, 2H); CIMS (MH^+ calcd for $C_{16}H_{22}Cl_2N_2O$) 341, found (MH^+) 341. Anal. Calcd for $C_{19}H_{24}Cl_2N_2O_5$: C, H, N.

3-(1-Pyrrolidinyl)-1-[2-(3,4-dichlorophenyl)ethyl]piperidine (5). A solution of **19** (1.1 g, 3.23 mmol) in dry THF (20 mL) was added dropwise at rt to a stirred solution of AlH_3 in THF[29] (24.4 mL of a 0.66 M solution, 16.1 mmol, 5 equiv). The reaction mixture was stirred for 20 min at rt and then poured into 15% aqueous NaOH (100 mL) and extracted with $CHCl_3$ (300 mL). The organic layer was dried (Na_2SO_4) and the solvent was evaporated in vacuo to give the crude product as a colorless oil. **5**·HBr (0.96 g, 61%) (EtOH): mp 279–280 °C; ^1H NMR ($CDCl_3$) δ 7.33 (d, J = 8.3 Hz, 1H), 7.29 (d, J = 1.8 Hz, 1H), 7.03 (dd, J = 1.8, 8.3 Hz, 1H), 3.08 (m, 1H), 2.84 (m, 1H), 2.76 (m, 2H), 2.51–2.66 (complex m, 6H), 2.25 (m, 1H), 2.00 (t, J = 10 Hz, 2H), 1.50–1.83 (complex m, 7H), 1.26 (m, 1H); CIMS (MH^+ calcd for $C_{17}H_{24}Cl_2N_2$) 327, found (MH^+) 327. Anal. Calcd for $C_{17}H_{26}Br_2Cl_2N_2$: C, H, N.

1-(*tert*-Butoxycarbonyl)-3-formamidopiperidine (20). **16** (10.1 g, 50.5 mmol) was dissolved in ethyl formate (50 mL), and the solution was refluxed overnight when TLC (solvent system A) showed the reaction to be complete. The solvent was evaporated in vacuo and the residue was dried under high vacuum to give the product **20** (11.5 g, quantitative) as a colorless oil: ^1H NMR ($CDCl_3$) δ 8.16 (s, 1H), 6.03 (20%), 5.77 (80%) (br s, 1H), 4.06 (m, 1H), 3.22–3.58 (complex m, 4H), 1.20–1.89 (complex m, 4H), 1.46 (s, 9H); CIMS (MH^+ calcd for $C_{11}H_{20}N_2O_3$) 229, found (MH^+) 229; HRMS (M^+ calcd for $C_{11}H_{20}N_2O_3$) 228.1474, found (M^+) 228.1469.

3-(Methylamino)-1-methylpiperidine (21). A solution of **20** (10.8 g, 47.4 mmol) in THF (20 mL) was added dropwise at rt to a stirred solution of $LiAlH_4$ in THF (153 mL of a 1.0 M solution, 153 mmol, 3.2 equiv). The solution was stirred overnight at rt when TLC (solvent system B) indicated incomplete reduction. However, reduction was found to be complete after boiling under reflux for 4 h. The solution was stirred, cooled to 0 °C (ice bath), and treated dropwise with water (5.8 mL), 15% aqueous NaOH (5.8 mL), and finally water (17.4 mL). The mixture was stirred for 1 h and then filtered. Aqueous HCl was added (to pH = 1) and the solvent was evaporated in vacuo to give **21**·hydrochloride (8.28 g, 87%) as an oil which failed to crystallize. However, the bisfumarate salt crystallized from MeOH: mp 184–186 °C; ^1H NMR ($CDCl_3$) δ 2.82 (m, 1H), 2.48–2.68 (complex m, 2H), 2.43 (s, 3H), 2.26 (s, 3H), 1.98 (m, 1H), 1.82 (m, 2H), 1.65–1.76 (m, 1H), 1.36–1.65 (complex m, 2H); CIMS (MH^+ calcd for $C_7H_{16}N_2$) 129, found (MH^+) 129. Anal. Calcd for $C_{15}H_{24}N_2O_8$: C, H, N.

3-[*N*-[(3,4-Dichlorophenyl)acetyl]-*N*-methylamino]-1-methylpiperidine (22). **21** (3.00 g, 23.4 mmol) and 3,4-dichlorophenylacetic acid (7.21 g, 35.2 mmol, 1.5 eq) were coupled using DCC (9.67 g, 46.9 mmol, 2 equiv) as described above for **19** to give **22** (5.4 g, 73%) as a crystalline solid. Recrystallization from EtOAc/isooctane (1:4) afforded a pure sample: mp 99–100 °C; ^1H NMR ($CDCl_3$) δ 7.38 (60%), 7.37 (40%) (d, J = 7.8 Hz, 1H), 7.34 (d, J = 1.9 Hz, 1H), 7.12 (60%), 7.09 (40%), (dd, J = 1.9, 7.8 Hz, 1H), 4.58 (40%), 3.82 (60%) (m, 1H), 3.71 (60%), 3.64 (40%), (s, 2H), 2.88 (40%), 2.84 (60%) (s, 3H), 2.66–2.86 (m, 2H), 2.27 (60%), 2.26 (40%) (s, 3H), 1.33–2.08 (complex m, 6H); CIMS (MH^+ calcd for $C_{15}H_{20}Cl_2N_2O$) 315, found (MH^+) 315. Anal. Calcd for $C_{15}H_{20}Cl_2N_2O$: C, H, N.

3-[*N*-[2-(3,4-Dichlorophenyl)ethyl]-*N*-methylamino]-1-methylpiperidine (7). **22** (2.09 g, 6.63 mmol) was reduced with AlH_3 in THF as described for **5** to give **7** (2.0 g, quantitative) as a colorless oil. **7**·fumarate (2-propanol): mp 166–167 °C; ^1H NMR ($CDCl_3$) δ 7.34 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 4.1 Hz, 1H), 7.03 (dd, J = 4.1, 8.1 Hz, 1H), 2.89 (dm, J_{gem} = 11 Hz, 1H), 2.53–2.81 (complex m, 6H), 2.35 (s, 3H), 2.27 (s, 3H), 1.65–1.86 (complex m, 4H), 1.58 (m, 1H), 1.18 (m, 1H); CIMS (MH^+ calcd for $C_{15}H_{22}Cl_2N_2$) 301, found (MH^+) 301. Anal. Calcd for $C_{23}H_{30}Cl_2N_2O_8$: C, H, N.

3-(1-Pyrrolidinyl)caprolactam (23). A mixture of D,L-α-aminocaprolactam (5.0 g, 39.0 mmol), 1,4-dibromobutane (8.42 g, 39.0 mmol, 1 equiv), and K_2CO_3 (5.39 g, 39 mmol, 1.0 equiv) was reacted in DMF (40 mL) as described above for **17** to give **23** (4.58 g, 64%) as a colorless oil. **23**·fumarate (2-propanol): mp 215 °C dec; ^1H NMR ($CDCl_3$) δ 5.72 (br s, 1H, NH), 3.73 (m, 1H), 2.96–3.10 (m, 2H), 2.68 (m, 2H), 2.53 (m, 2H), 1.46–2.05 (complex m, 10H); CIMS (MH^+ calcd for $C_{10}H_{18}N_2O$) 183, found (MH^+) 183; HRMS (M^+ calcd for $C_{10}H_{18}N_2O$) 182.1419, found (M^+) 182.1413. This salt (bisfumarate) failed to yield a satisfactory elemental analysis due to extensive solvation.

3-(1-Pyrrolidinyl)homopiperidine (24). **23** (4.58 g, 25.2 mmol) was reduced with $LiAlH_4$ (50.4 mL of a 1.0 M solution in THF, 50.4 mmol, 2 equiv) as described above for **21** to give **24** (3.82 g, 90%) as a pale yellow oil. **24**·fumarate (2-propanol): mp 155–156 °C; ^1H NMR ($CDCl_3$) δ 2.93 (d, J = 5 Hz, 2H), 2.85 (m, 2H), 2.56 (m, 4H), 2.31 (m, 1H), 1.59–1.87 (complex m, 9H), 1.50 (m, 1H); CIMS (MH^+ calcd for $C_{10}H_{20}N_2$) 169, found (MH^+) 169; HRMS (M^+ calcd for $C_{10}H_{20}N_2$ 168.1626, found (M^+) 168.1630. Anal. Calcd for $C_{18}H_{28}N_2O_8 \cdot 0.5H_2O$: C, 52.80; H, 7.14; N, 6.84. Found: C, 52.47; H, 6.64; N, 6.11.

1-[(3,4-Dichlorophenyl)acetyl]-3-(1-pyrrolidinyl)homopiperidine (25). **24** (0.80 g, 4.76 mmol) was coupled with 3,4-dichlorophenylacetic acid (1.05 g, 5.12 mmol, 1.1 equiv) in the presence of DCC (1.3 g, 6.30 mmol, 1.2 equiv) as described for **19** to give **25** in quantitative yield as a yellow oil. **25**·fumarate (2-propanol) (1.66 g, 74%): mp 156–158 °C; ^1H NMR ($CDCl_3$) δ 7.39 (d, J = 8.3 Hz, 1H), 7.36 (d, J = 2.0 Hz, 1H), 7.12 (40%), 7.10 (60%) (dd, J = 2.0, 8.3 Hz, 1H), 4.32 (40%) (d, J_{gem} = 13 Hz, J = 3.7 Hz, 1H), 3.54–3.87 (complex m, 5H), 3.30 (m, 2H),

(28) This compound was recently reported by G. Giardina, in the Abstracts of The Twelvth Advanced Course in Medicinal Chemistry, University of Urbino (Università Degli Studi Di Urbino), 1992, pp 21–63.

2.94 (m, 1H), 2.36–2.84 (complex m, 4H), 1.18–1.96 (complex m, 9H); CIMS (MH^+ calcd for $C_{18}H_{24}Cl_2N_2O$) 355, found (MH^+) 355. Anal. Calcd for $C_{23}H_{28}Cl_2N_2O_5 \cdot 0.75H_2O$: C, H, N.

1-[2-(3,4-Dichlorophenyl)ethyl]-3-(1-pyrrolidinyl)homopiperidine (6). **25** (0.90 g, 2.64 mmol) was reduced with AlH_3 in THF as described for **5** to give **6** (0.85 g, 98% yield). **6**·oxalate (2-propanol): mp 161–163 °C; ^1H NMR ($CDCl_3$) δ 7.33 (d, J = 8.2 Hz, 1H), 7.31 (d, J = 2.0 Hz, 1H), 7.03 (dd, J = 2.0, 8.2 Hz, 1H), 2.86 (dd, J_{gem} = 13 Hz, J = 3.9 Hz, 1H), 2.53–2.78 (complex m, 11H), 2.42 (m, 1H), 1.93 (m, 1H), 1.59–1.81 (complex m, 7H), 1.54 (m, 2H); CIMS (MH^+ calcd for $C_{18}H_{26}Cl_2N_2$) 341, found (MH^+) 341. Anal. Calcd for $C_{22}H_{30}Cl_2N_2O_8 \cdot 0.5H_2O$: C, H, N.

(*R*)-(+)-1-[*N*-(*tert*-Butoxycarbonyl)prolinamido]pyrrolidine [(*R*)-(+)-27]. To a stirred solution of *N*-Boc-D-proline (9.8 g, 45.6 mmol) in dry CH_2Cl_2 (50 mL) was added a solution of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (10.49 g, 54.7 mmol, 1.2 equiv) in CH_2Cl_2 (50 mL) followed by hydroxybenzotriazole (HOBT) (7.39 g, 54.7 mmol, 1.2 equiv). The solution was allowed to stir for 20 min at rt. Pyrrolidine (6.48 g, 91.1 mmol, 2.0 equiv) was added dropwise, and the mixture was stirred overnight at rt. The solvent was evaporated and the residue was taken up in EtOAc (300 mL), extracted with 5% aqueous citric acid (2 × 100 mL) and saturated aqueous $NaHCO_3$ (200 mL), and dried (Na_2SO_4). Evaporation of the solvent in vacuo afforded (+)-**27** as a clear colorless oil (8.6 g, 70%) (1 spot on TLC solvent system A) which crystallized from EtOAc/isooctane (1:4): mp 83–84 °C; $[\alpha]_D$ = +33.9° (*c* 1.88, MeOH); ^1H NMR ($CDCl_3$) δ 4.48 (50%), 4.35 (50%) (m, 1H), 3.30–3.78 (complex m, 6H), 1.72–2.24 (complex m, 8H), 1.46 (50%), 1.40 (50%) (s, 9H); CIMS (MH^+ calcd for $C_{14}H_{24}N_2O_3$) 269, found (MH^+) 269. Anal. Calcd for $C_{14}H_{24}N_2O_3$: C, H, N.

(*R*)-(+)-1-Prolinamidopyrrolidine [(R)-(+)-28]. (+)-**27** (5.0 g, 18.7 mmol) in CH_2Cl_2 (40 mL) was treated with CF_3COOH (20 mL), and the solution was stirred at rt for 50 min after which time TLC (solvent system A) indicated the reaction to be complete. The solvent was evaporated in vacuo, and the residue was taken up in saturated K_2CO_3 (30 mL) and extracted with $CHCl_3$ (3 × 150 mL). The combined organic layer was filtered through Na_2SO_4, and the solvent was evaporated in vacuo to give (*R*)-(+)-**28** (3.1 g, quantitative) as a colorless oil which failed to crystallize as many different salts: ^1H NMR ($CDCl_3$) δ 3.75 (dd, J = 6.4, 8.1 Hz, 1H), 3.34–3.58 (complex m, 4H), 3.19 (m, 1H), 2.82 (m, 1H), 2.52 (br s, 1H, NH), 2.09 (m, 1H), 1.59–2.03 (complex m, 7H); CIMS (MH^+ calcd for $C_9H_{18}N_2O$) 169, found (MH^+) 169; HRMS (M^+ calcd for $C_9H_{18}N_2O$) 168.1263, found (M^+) 168.1257.

(*R*)-(−)-1-(2-Pyrrolidinylmethyl)pyrrolidine [(R)-(−)-26]. (*R*)-(+)-**28** (3.00 g, 17.8 mmol) was reduced with $LiAlH_4$ (54 mL of a 1 M solution in THF, 54 mmol, 3.0 equiv) as described for **21** to give (*R*)-(−)-**26** (2.50 g, 91%) as a colorless oil. (*R*)-(−)-**26**·fumarate (2-propanol): mp 130–132 °C; $[\alpha]_D$ = −19.5° (*c* 1.37, MeOH); ^1H NMR ($CDCl_3$) δ 3.21 (quintet, J = 6.7 Hz, 1H), 2.98 (m, 1H), 2.85 (m, 1H), 2.42–2.63 (complex m, 5H), 2.35 (dd, J_{gem} = 12 Hz, J = 5.3 Hz, 1H), 1.88 (m, 1H), 1.53–1.80 (complex m, 6H), 1.24–1.41 (m, 1H); CIMS (MH^+ calcd for $C_9H_{18}N_2$) 155, found (MH^+) 155. Anal. Calcd for $C_{17}H_{28}N_2O_8$: C, H, N.

(*R*)-(+)-1-[(3,4-Dichlorophenyl)acetyl]-2-(1-pyrrolidinylmethyl)pyrrolidine [(R)-(+)-29]. R-(−)-**26** (3.1 g, 20.1 mmol) and 3,4-dichlorophenylacetic acid (6.19 g, 30.2 mmol, 1.5 equiv) were coupled in the presence of DCC as described above for **19** to give (*R*)-(+)-**29** (2.2 g, 35%) as a colorless oil. (*R*)-(+)-**29**·fumarate (EtOAc): mp 136–137 °C dec; $[\alpha]_D$ = +23.9° (*c* 1.48, MeOH); ^1H NMR ($CDCl_3$) δ 7.35–7.41 (m, 2H), 7.13 (30%), 7.11 (70%) (dd, J = 2.0, 8.1 Hz, 1H), 4.27 (70%), 3.98 (30%) (m, 1H), 3.72 (30%) (d, J = 6.3 Hz, 1H), 3.57 (70%) (s, 2H), 3.34–3.61 (complex m, 2H), 2.38–2.70 (complex m, 6H), 1.68–2.11 (complex m, 8H); CIMS (MH^+ calcd for $C_{17}H_{22}Cl_2N_2O$) 341, found (MH^+) 341. Anal. Calcd for $C_{21}H_{26}Cl_2N_2O_5$: C, H, N.

(*R*)-(+)-1-[2-(3,4-Dichlorophenyl)ethyl]-2-(1-pyrrolidinylmethyl)pyrrolidine [(*R*)-(+)-8]. (*R*)-(+)-**29** (base obtained from 2.00 g (4.38 mmol) of fumarate salt by partitioning with 5% aqueous NaOH/$CHCl_3$) was reduced with AlH_3 as described above for **5** to give (*R*)-(+)-**8** (1.24 g, 87%) as a colorless oil. (*R*)-(+)-**8**·HBr (EtOH): mp 255–256 °C; $[\alpha]_D$ = +31.3° (*c* 0.85, MeOH); ^1H NMR ($CDCl_3$) δ 7.34 (d, J = 8.3 Hz, 1H), 7.31 (d, J = 2.0 Hz, 1H), 7.05 (dd, J = 2.0, 8.3 Hz, 1H), 3.18 (m, 1H), 3.09 (m, 1H), 2.75 (m, 2H), 2.33–2.62 (complex m, 8H), 2.22 (q, J = 8.6 Hz, 1H), 1.56–2.05 (complex m, 8H); CIMS (MH^+ calcd for $C_{17}H_{24}Cl_2N_2$) 327, found (MH^+) 327. Anal. Calcd for $C_{17}H_{26}Br_2Cl_2N_2$: C, H, N.

(*S*)-(−)-1-[(3,4-Dichlorophenyl)acetyl]-2-(1-pyrrolidinylmethyl)pyrrolidine [(*S*)-(−)-29]. Commercially available (*S*)-(+)-1-(2-Pyrrolidinylmethyl)pyrrolidine (96%, Aldrich) [(+)-**26**] (4.43 g, 28.8 mmol) and 3,4-dichlorophenylacetic acid (8.85 g, 43.2 mmol, 1.5 equiv) were coupled in the presence of DCC (11.88 g, 57.6 mmol, 2 equiv) as described for **19** to give (*S*)-(−)-**29** (9.1 g, 93%) as a colorless oil. (*S*)-(−)-**29**·fumarate (EtOAc): mp 138–139 °C; $[\alpha]_D$ = −24.9° (*c* 1.75, MeOH); ^1H NMR ($CDCl_3$) identical to its enantiomer (*R*)-(+)-**29** above; CIMS (MH^+ calcd for $C_{17}H_{22}Cl_2N_2O$) 341, found (MH^+) 341. Anal. Calcd for $C_{21}H_{26}Cl_2N_2O_5$: C, H, N.

(*S*)-(−)-1-[2-(3,4-Dichlorophenyl)ethyl]-2-(1-pyrrolidinylmethyl)pyrrolidine [(*S*)-(−)-8]. (*S*)-(−)-**29** (5.9 g, 17.3 mmol) was reduced with AlH_3 in THF as described above for **5** to give (*S*)-(−)-**8** as a colorless oil (5.09 g, 90%). (−)-**8**·HBr (EtOH): mp 255–256 °C; $[\alpha]_D$ = −29.7° (*c* 2.94, MeOH); ^1H NMR ($CDCl_3$) identical to its enantiomer above; CIMS (MH^+ calcd for $C_{17}H_{24}Cl_2N_2$) 327, found (MH^+) 327. Anal. Calcd for $C_{17}H_{26}Br_2Cl_2N_2$: C, H, N.

1-(*tert*-Butoxycarbonyl)-2-piperidinecarboxylic Acid (30). A mixture of pipecolinic acid (48.43 g, 375 mmol), di-*tert*-butyl dicarbonate (98.2 g, 450 mmol, 1.2 equiv) and $NaHCO_3$ (126 g, 1500 mmol, 4.0 equiv) in water (1000 mL) was stirred overnight at rt. Crushed ice (200 g) was added to the reaction mixture which was then treated dropwise with a solution of 120 mL of 12 M HCl made up to 500 mL with water. The pH was adjusted to ca. 3.5 by addition of a further amount of HCl. The solution was extracted with EtOAc (2 × 500 mL), and the combined organic extract was back-washed with water (2 × 500 mL) and evaporated in vacuo to give **30** (48.7 g, 57%) as a beige crystalline solid: mp 123–124 °C; ^1H NMR ($CDCl_3$) δ 4.93 (58%), 4.78 (42%) (m, 1H), 3.96 (m, 1H), 2.96 (m, 1H), 2.22 (m, 1H), 1.68 (complex m, 3H), 1.23–1.50 (m, 2H), 1.46 (s, 9H); CIMS (MH^+ calcd for $C_{11}H_{19}NO_4$) 230, found (MH^+) 230. Anal. Calcd for $C_{11}H_{19}NO_4$: C, H, N.

1-Methyl-2-piperidinemethanol (31). **30** (23.2 g, 101 mmol) was reduced with a 1.0 M solution of $LiAlH_4$ in THF (405 mL, 405 mmol, 4 equiv) as described above for **21** to give **31** (13.1 g, quantitative) as a colorless oil. **31**·fumarate (2-propanol): mp 118–120 °C; ^1H NMR ($CDCl_3$) δ 3.85 (dd, J_{gem} = 11 Hz, J = 3.9 Hz, 1H), 3.39 (dd, J_{gem} = 11 Hz, J = 2.2 Hz, 1H), 2.89 (m, 1H), 2.30 (s, 3H), 2.15 (m, 1H), 1.97 (m, 1H), 1.76 (m, 1H), 1.42–1.68 (complex m, 4H), 1.28 (m, 1H); CIMS (MH^+ calcd for $C_7H_{16}NO$) 130, found (MH^+) 130. Anal. ($C_{11}H_{19}NO_5$) C, H, N.

1-Methyl-2-[(methylamino)methyl]piperidine (32). Method A. To a stirred solution of $MeSO_2Cl$ (7.81 g, 68.2 mmol, 1.1 equiv) in hydrocarbon stabilized $CHCl_3$ (100 mL) was added, dropwise at rt, a solution of **31** (8.00 g, 62 mmol) in $CHCl_3$ (25 mL). The reaction mixture was stirred at rt until complete by TLC (solvent system B), and the solvent was evaporated in vacuo. The residue was dissolved in water (100 mL) and added dropwise to a stirred solution of $MeNH_2$ in water (420 mL of a 40% solution). The reaction mixture was stirred overnight at rt, cooled (ice), and then treated with NaOH (120 g). The basified solution was extracted with $CHCl_3$ (2 × 200 mL), and the combined organic extract was evaporated in vacuo to give **32** (8.8 g, quantitative). The oxalate salt crystallized from MeOH: mp 177.5–178 °C; ^1H NMR ($CDCl_3$) δ 2.84 (m, 1H), 2.66 (d, J = 4.4 Hz, 2H), 2.44 (s, 3H), 2.26 (s, 3H), 2.09 (m, 1H), 1.96 (m, 1H), 1.39–1.79 (m, 4H), 1.26 (m, 2H); CIMS (MH^+ calcd for $C_8H_{18}N_2$) 143, found (MH^+) 143. Anal. Calcd for $C_{12}H_{22}N_2O_8$: C, H, N.

Method B. A solution of *N*-*t*-Boc-*N'*-methylpipecolinamide (**33**) (1.0 g, 4.1 mmol) in THF (10 mL) was added dropwise to a 1 M solution of AlH_3 in THF (21 mL, 21 mmol, 5 equiv) at room temperature as described above for **5** to give **32** identical to that described above in method A. **32**·oxalate (MeOH) (0.68 g, 71%): mp 177.5–178 °C; ^1H NMR ($CDCl_3$) identical to that of material obtained via method A above.

1-(*tert*-Butoxycarbonyl)-*N*-methylpipecolinamide (33). *N*-*t*-Boc-pipecolinic acid (**30**) (3 g, 13.1 mmol) was dissolved in $CHCl_3$ (30 mL), and Et_3N (1.9 mL) was added. The solution was cooled down to −10 °C (ice–salt bath), and isobutyl chloroformate

(1.8 g, 13.1 mmol, 1 equiv) was added. The reaction was stirred at −10 °C for 30–45 min, and then $MeNH_2$ (gas) was bubbled through the reaction mixture for 2 h. The organic layer was washed with brine (3 × 100 mL), ice-cooled 10% citric acid solution (2 × 70 mL), saturated $NaHCO_3$ (1 × 50 mL), and finally brine (2 × 50 mL). The solvent was removed to give analytically pure **33** as a colorless crystalline solid (5.1 g, quantitative yield): mp 83–83.5 °C; ^1H NMR ($CDCl_3$) δ 6.07 (br s, 1H, NH), 4.73 (m, 1H), 4.04 (m, 2H), 2.84 (50%), 2.82 (50%) (s, 3H, NHMe), 2.67–2.85 (m, 1H, CH_2N), 2.33 (m, 1H, CH_2N), 1.25–1.75 (complex m, 4H), 1.48 (s, 9H); CIMS (MH^+ calcd for $C_{12}H_{22}N_2O_3$) 243, found (MH^+) 243. Anal. Calcd for $C_{12}H_{22}N_2O_3$: C, H, N.

2-[[*N*-[(3,4-Dichlorophenyl)acetyl]-*N*-methylamino]methyl]-1-methylpiperidine (34). The base obtained from **32**·oxalate (3.5 g, 15.1 mmol) and 3,4-dichlorophenylacetic acid (4.64 g, 22.6 mmol, 1.5 equiv) was coupled in CH_2Cl_2 in the presence of DCC (6.22 g, 30.2 mmol, 2 equiv) as described above for **19** to give **34** (3.1 g, 62%) as a colorless oil which failed to form any crystalline salts: ^1H NMR ($CDCl_3$) δ 7.33–7.41 (m, 2H), 7.10 (dd, J = 2.1, 8.2 Hz, 1H), 3.86 (dd, J_{gem} = 13 Hz, J = 4.4 Hz, 1H), 3.67 (dd, J_{gem} = 13 Hz, J = 2.7 Hz, 1H), 3.65 (s, 2H), 3.11–3.29 (m, 1H), 3.05 (63%), 2.96 (37%) (s, 3H), 2.84 (m, 1H), 2.33 (63%), 2.31 (37%) (s, 3H), 2.07–2.34 (m, 2H), 1.15–1.84 (complex m, 5H); CIMS (MH^+ calcd for $C_{16}H_{22}Cl_2N_2O$) 329, found (MH^+) 329; HRMS (M^+ calcd for $C_{16}H_{22}Cl_2N_2O$) 328.1109, found (M^+) 328.1117.

2-[[*N*-[2-(3,4-Dichlorophenyl)ethyl]-*N*-methylamino]methyl]-1-methylpiperidine (9). **34** (2.00 g, 6.08 mmol) was reduced with 1.0 M AlH_3 in THF (30 mL, 30 mmol, 5 equiv) as described for **5** above to give **9** (1.91 g, quantitative) as a colorless oil. This product failed to form any crystalline salts even after rigorous purification of the base. The crude reaction product was further purified by column chromatography eluting with $CHCl_3$/MeOH/concentrated aqueous NH_3 (solvent system A) prior to submission for biological testing. **9**: ^1H NMR ($CDCl_3$) δ 7.33 (d, J = 8.1 Hz, 1H), 7.30 (d, J = 2.0 Hz, 1H), 7.03 (dd, J = 2.0, 8.1 Hz, 1H), 2.82 (m, 1H), 2.69 (d, J = 7.5 Hz, 2H), 2.49–2.66 (m, 3H), 2.28 (s, 3H), 2.25 (s, 3H), 2.16–2.25 (m, 1H), 2.08 (m, 1H), 1.94 (m, 1H), 1.64–1.81 (m, 2H), 1.49–1.81 (m, 2H), 1.09–1.30 (m, 2H); CIMS (MH^+ calcd for $C_{16}H_{24}Cl_2N_2$) 315, found (MH^+) 315; HRMS (M^+ calcd for $C_{16}H_{24}Cl_2N_2$) 314.1316, found (M^+) 314.1332.

2-[[(3,4-Dichlorophenyl)acetamido]methyl]-1-ethylpyrrolidine (35). 2-(Aminomethyl)-1-ethylpyrrolidine (Aldrich) (3.2 g, 25 mmol) and 3,4-dichlorophenylacetic acid (7.7 g, 37.6 mmol, 1.5 equiv) were coupled in CH_2Cl_2 in the presence of DCC (10.6 g, 51 mmol, 2 equiv) as described above for **19** to give **35** (7.6 g, 97%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.41 (d, J = 8.2 Hz, 1H), 7.39 (d, J = 2.0 Hz, 1H), 7.13 (dd, J = 2.0, 8.2 Hz, 1H), 6.13 (br s, 1H), 3.51 (s, 2H), 3.37 (m, 1H), 3.07 (m, 2H), 2.65 (m, 1H), 2.53 (m, 1H), 2.04–2.21 (m, 2H, CH_2CH_3), 1.81 (m, 1H), 1.67 (m, 1H), 1.35–1.60 (complex m, 2H), 0.99 (t, J = 7.2 Hz, 3H); CIMS (MH^+ calcd for $C_{15}H_{20}Cl_2N_2O$) 315, found (MH^+) 315. Anal. Calcd for $C_{15}H_{20}Cl_2N_2O$: C, H, N.

2-[[*N*-[(3,4-Dichlorophenyl)ethyl]amino]methyl]-1-ethylpyrrolidine (10). **35** (base) (6.39 g, 20.3 mmol) was reduced with a 1.0 M solution of AlH_3 in THF (60 mL, 60 mmol, 3 equiv) as described above for **5** to give crude **10** as a colorless oil (6.1 g, quantitative). **10**·oxalate (6.5 g, 80%) crystallized from 2-propanol/MeOH (1:1): mp 181–182 °C dec; ^1H NMR ($CDCl_3$) δ 7.35 (d, J = 8.1 Hz, 1H), 7.31 (d, J = 1.8 Hz, 1H), 7.05 (dd, J = 1.8, 8.1 Hz, 1H), 3.14 (m, 1H), 2.80–2.91 (m, 2H), 2.67–2.80 (complex m, 4H), 2.58 (m, 1H), 2.48 (m, 1H), 2.24 (m, 1H), 2.15 (q, J = 8.6 Hz, 1H), 1.89 (m, 1H), 1.73 (m, 2H), 1.60 (m, 2H), 1.07 (t, J = 8.6 Hz, 3H); CIMS (MH^+ calcd for $C_{15}H_{22}Cl_2N_2$) 301, found (MH^+) 301. Anal. Calcd for $C_{17}H_{24}Cl_2N_2O_4 \cdot 0.5H_2O$: C, H, N.

2-[[*N*-[2-(3,4-Dichlorophenyl)ethyl]formamido]methyl]-1-ethylpyrrolidine (36). A solution of **10** (1.2 g, 3.99 mmol) in EtOCHO (50 mL) containing 6 drops of formic acid was boiled under reflux overnight when TLC (solvent system A) indicated the reaction to be complete. The solvent was evaporated in vacuo, and the residue was partitioned between excess dilute aqueous NH_3 (50 mL) and $CHCl_3$ (50 mL). The $CHCl_3$ layer was separated, dried (Na_2SO_4), and evaporated in vacuo to give the product as an oil (1.31 g, quantitative). Two rotamers were visible on TLC (solvent system A): ^1H NMR for major 80% rotamer ($CDCl_3$) δ 8.39 (s, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.28 (d, J = 2.0 Hz, 1H), 7.00 (dd, J = 2.0, 8.2 Hz, 1H), 3.95 (dd, J_{gem} = 13 Hz, J = 4.7 Hz, 1H), 3.28–3.86 (complex m, 6H), 2.77–2.98 (complex m, 4H), 2.15 (m, 1H), 1.84–2.09 (complex m, 3H), 1.37 (t, J = 7.2 Hz, 3H); CIMS (MH^+ calcd for $C_{16}H_{22}Cl_2N_2O$) 329, found (MH^+) 329. No attempt was made to further purify this material.

2-[[*N*-[2-(3,4-Dichlorophenyl)ethyl]-*N*-methylamino]methyl]-1-ethylpyrrolidine (11). **36** (0.82 g, 2.49 mmol) was reduced with a 1.0 M solution of AlH_3 in THF (10 mL, 10 mmol, 4 equiv) as described above for **5** to give crude **11** as a colorless oil. **11**·oxalate (1.18 g, 96%) crystallized from 2-propanol: mp 172–173 °C; ^1H NMR ($CDCl_3$) δ 7.33 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 2.0 Hz, 1H), 7.03 (dd, J = 2.0, 8.1 Hz, 1H), 3.17 (m, 1H), 2.92 (m, 1H), 2.32–2.76 (complex m, 8H), 2.28 (s, 3H), 2.20 (m, 1H), 2.11 (q, J = 8.1 Hz, 1H), 1.84–1.98 (m, 1H), 1.51–1.83 (m, 2H), 1.09 (t, J = 8.1 Hz, 3H); CIMS (MH^+ calcd for $C_{16}H_{24}Cl_2N_2$) 315, found (MH^+) 315. Anal. Calcd for $C_{20}H_{28}Cl_2N_2O_8$: C, H, N.

2-[2-(1-Pyrrolidinyl)ethyl]-6,7-dichloro-1,2,3,4-tetrahydroisoquinoline (12). **37** (base) (see ref 14 for preparation) (1.00 g, 3.48 mmol) was dissolved in trifluoromethanesulfonic acid (10 mL), and to the stirred solution was added (at −78 °C) NaCl (1 g) followed by 37% aqueous HCHO (1 mL) and the reaction mixture was sealed in a thick-walled glass tube using a Teflon cap. The reaction mixture was stirred for 11 h at rt and then poured into 10% aqueous Na_2CO_3 (200 mL) and extracted with $CHCl_3$ (200 mL). The organic extract was dried (Na_2SO_4), and the solvent was evaporated in vacuo to give the crude product as an oil. This was dissolved in a 1:1 mixture of EtOH/MeOH (10 mL) and treated with 47% aqueous HBr to pH 1.5. Crystallization was induced by scratching with a glass rod to give **12**·HBr (0.50 g, 31%) as a colorless crystalline solid: mp 280–283 °C dec; ^1H NMR ($CDCl_3$) δ 7.18 (s, 1H), 7.10 (s, 1H), 3.61 (s, 2H), 2.84 (m, 2H), 2.75 (m, 2H), 2.71 (s, 4H), 2.58 (m, 4H), 1.79 (m, 4H); CIMS (MH^+ calcd for $C_{15}H_{20}Cl_2N_2$) 299, found (MH^+) 299. Anal. Calcd for $C_{15}H_{22}Br_2Cl_2N_2$: C, H, N.

Biological Materials and Methods. Membrane Preparation. σ receptor binding assays were performed using the crude synaptosomal (P_2) membrane fraction of guinea pig brain.

Crude P_2 membrane fractions were prepared from frozen (−80 °C) guinea pig brains (PeI-Freeze, Rogers, AK), minus cerebella. After removal of cerebella, brains were allowed to thaw slowly on ice and placed in ice-cold 10 mM Tris-HCl, pH 7.4 containing 320 mM sucrose (Tris–sucrose buffer). Brains were then homogenized in a Potter-Elvehjem homogenizer by 10 strokes of a motor driven Teflon pestle in a volume of 10 mL/gm tissue wet weight. The homogenate was centrifuged at 1000*g* for 10 min at 4 °C, and the supernatants were saved. The pellets were resuspended by vortexing in 2 mL/g ice-cold Tris–sucrose and centrifuged again at 1000*g* for 10 min. The combined 1000*g* supernatant was centrifuged at 31000*g* for 15 min at 4 °C. The pellets were resuspended by vortexing in 3 mL/gm of 10 mM Tris-HCl, pH 7.4, and the suspension was allowed to incubate at 25 °C for 15 min. Following centrifugation at 31000*g* for 15 min, the pellets were resuspended by gentle Potter-Elvehjem homogenization to a final volume of 1.53 mL/gm in 10 mM Tris-HCl pH 7.4. Aliquots were stored at −80 °C until use. Protein concentration was determined by the method of Lowry et al.[30] using bovine serum albumin (BSA) as standard.

σ Receptor Binding Assays. σ receptors were labeled using [^3H](+)-pentazocine (specific activity = 51.7 Ci/mmol) prepared as previously described.[31] Briefly, guinea pig brain membranes were incubated with 3 nM [^3H](+)-pentazocine using 500 μg of membrane protein in a volume of 500 μL of 50 mM Tris-HCl, pH 8.0. Incubations were carried out for 120 min at 25 °C. Nonspecific binding was carried out in the presence of 10 μM unlabeled (+)-pentazocine. Assays were terminated by dilution with 5 mL of ice-cold 10 mM Tris-HCl, pH 8.0, and vacuum

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filtration through glass fiber filters (Scleicher and Schuell, Keene, NH). The filters were pretreated with polyethyleneimine as described previously.[31]

Chemicals. All scintillation counting was performed with a Packard Model 4450 scintillation spectrometer using Ecoscint cocktail (National Diagnostics, Manville, NJ) after overnight extraction of the counts from the filters. All filtration was carried out using a Brandel Cell Harvester (Gaithersburg, MD). Polyethylenimine and Tris were purchased from Sigma Chemicals (St. Louis, MO). [^{3}H](+)-Pentazocine (51.7 Ci/mmol) and unlabeled pentazocine were synthesized as described previously by us.[31]

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