Synthesis and Evaluation of Conformationally Restricted *N*-[2-(3,4-Dichlorophenyl)ethyl]-*N*-methyl-2-(1-pyrrolidinyl)ethylamines at σ Receptors. 2. Piperazines, Bicyclic Amines, Bridged Bicyclic Amines, and Miscellaneous Compounds

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As a continuation of our earlier study (*J. Med. Chem.* **1992**, *35*, 4334-4343) we conformationally restricted the σ-receptor ligand 2-(1-pyrrolidinyl)-*N*-[2-(3,4-dichlorophenyl)ethyl]-*N*-methylethylamine (1) by incorporating it into a series of homologous piperazines **3-9** and homopiperazines **10** and **11**, diazabicyclononanes and decanes, bridgehead bicyclooctanes and nonanes as well as other miscellaneous compounds. σ-Receptor binding affinities were obtained using [^{3}H](+)-pentazocine in guinea pig brain membrane σ_1 sites. The studies suggest that the nitrogen lone pair orientation found in the piperazines affords the strongest binding interaction. Other nitrogen lone pair orientations or compounds representing unlikely staggered conformations of **1** [as in 4-[2-(3,4-dichlorophenyl)ethyl]-1,4-diazabicyclo[3.2.2]nonane (**16**)] show very weak σ interaction. Comparison of the binding data of different N-substituted homologues of **1** with those of the 1-[2-(3,4-dichlorophenyl)ethyl]-4-alkylpiperazines suggests that the two nitrogen atoms of **1** are working in opposition to one another in terms of their sensitivity to steric bulk. The high binding affinity of the 1,4-diazabicyclo[4.3.0]nonanes **12** suggests that these may approximate the methyl and pyrrolidine ring conformations found in **1** when it is bound to the σ receptor. Compound **12** exhibited a 4-fold enantioselectivity favoring (+)-**12**. The synthesis of 6,7-dichloro-2-[[2-(1-pyrrolidinyl)ethyl]amino]tetralin (**19**) and its desmethyl derivative **20** permitted constraint of the 3,4-dichlorophenyl and *N*-methyl moieties of **1** into a gauche orientation. The binding data suggests that this conformation in **1** favors strong binding interaction at σ-receptors. σ-Receptor K_i's ranged from 0.55 nM for 1-[2-(3,4-dichlorophenyl)ethyl]-4-*n*-butylpiperazine (**7**) to 654 nM for **16**. Overall comparison of the results indicate that **1** is subject to considerable conformational freedom and suggests that the σ receptor is not subject to rigid stereochemical restraints with **1**. These results add to our earlier study where we restrained **1** using simple monocyclic heterocycles.

Introduction

Investigation of the biological and functional role of the σ receptor is a relatively new and interesting area (for a review, see ref 1) that is now gaining momentum with the development of highly specific σ-receptor probes.[1] Several classes of centrally active agents including neuroleptics such as butryophenones, phenothiazines, and the tricyclic antidepressants,[2] certain (+)-benzomorphan opiates,[3] disubstituted guanidines,[4] and 3-phenylpiperidines (dopamine autoreceptor agonists)[2,5] bind with high affinity to this site. The binding of neuroleptics and monoamine oxidase inhibitors[6] to σ receptors suggests their involvement in some of the therapeutic effects of these compounds. σ receptors have been implicated in biochemical and physiological effects that include motor disorders,[7] synthesis of pineal hormone,[8] inhibition of carbachol stimulated P_i turnover,[9] and colonic motility.[10] σ receptors may also be coupled to the polyamine binding site of the *N*-methyl-D-aspartate (NMDA) receptor.[11] This interaction with the polyamine site may account for at least some of the neuroprotective effects of different classes of σ ligands.[12] A major obstacle to further understanding the σ receptor has been the paucity of selective ligands. We have therefore been actively involved in the development of σ ligands with high selectivity and biological efficacy (review ref 1) as well as the identification of σ-receptor antagonists. Additionally, the development of novel σ ligands has provided the tools for demonstrating heterogeneity of this receptor. At least two subtypes, designated σ_1 and σ_2 have been established.[1a,b] These subtypes may account for the differential biological activities of σ ligands.

Along these lines, we recently identified the substituted ethylene diamine **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.[13] Compound **1** (K_i = 0.34 nM) proved to be among the most potent and selective compounds ever tested by us. Compound **2** has recently been shown to be a selective σ-receptor antagonist in several functional assays (unpublished).

Our structure-activity studies with **1** and **2** have allowed us to identify them as σ-receptor active substructures of the previously reported[13] 1,2-*cis*-cyclohexanediamines. Examination of *cis*- and *trans*-cyclohexanediamines (class A in Chart II),[14] revealed the cis diastereoisomers to be significantly more potent at σ receptors than the corre-

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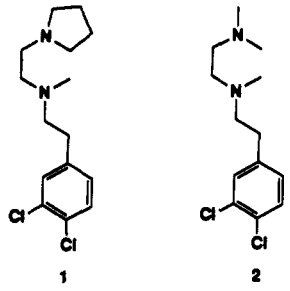
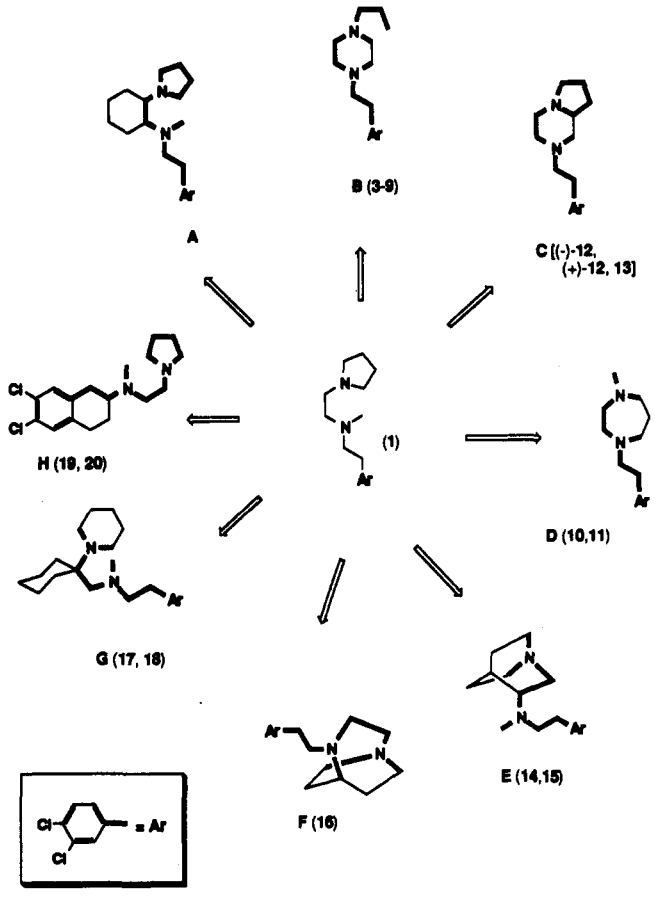
Chart I



1 2

Chart II

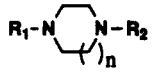


sponding trans diastereoisomers suggesting that a gauche orientation (dihedral angle ca. 60°) between the C–N bonds of 1 is necessary for high affinity at σ receptors. To further investigate the steric requirements of 1 at σ receptors, we conformationally restricted it using monocyclic heterocycles.[15] This study (part I of this paper[15]) showed that the nitrogen lone pair orientations and steric factors about the aliphatic portion of the molecule play a role in the binding of 1.

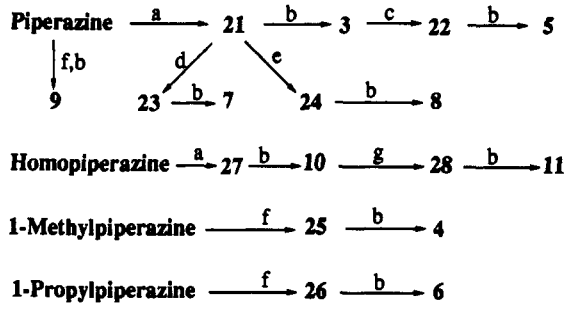
In this paper, we examine the effect of incorporating 1 into piperazines, 2-aminotetralines, and rigid bicyclic/bridgehead ring systems (classes B–H in Chart II). The geminal 1-(aminomethyl)cyclohexylamine (class G) was studied to investigate the steric requirements of 1, while the amino tetralins (class H) allowed conformational restriction of the 3,4-dichlorophenyl and NMe group in a gauche orientation. The binding affinity of the parent (unrestricted) ligand 1 against [^{3}H](+)-pentazocine was previously determined to be 2.1 nM.[15]

Piperazines (B) 3–9 and homopiperazines (D) 10 and 11 (Table I) permitted restriction of the nitrogen atoms of 1 in a gauche orientation with trans antiperiplanar lone

Scheme I. Synthesis of Piperazine and Homopiperazine Classes B and D[a]



Compd	n	R_1	R_2
piperazine	1	H	H
1-methylpiperazine	1	Me	H
1-propylpiperazine	1	n-Pr	H
homopiperazine	2	H	H
3	1	H	$Ar(CH_2)_2$
4	1	Me	$Ar(CH_2)_2$
5	1	Et	$Ar(CH_2)_2$
6	1	n-Pr	$Ar(CH_2)_2$
7	1	n-Bu	$Ar(CH_2)_2$
8	1	n-Pent	$Ar(CH_2)_2$
9	1	$Ar(CH_2)_2$	$Ar(CH_2)_2$
10	2	H	$Ar(CH_2)_2$
11	2	Me	$Ar(CH_2)_2$
21	1	H	$ArCH_2CO$
22	1	MeCO	$Ar(CH_2)_2$
23	1	n-PrCO	$ArCH_2CO$
24	1	n-BuCO	$ArCH_2CO$
25	1	Me	$ArCH_2CO$
26	1	n-Pr	$ArCH_2CO$
27	2	H	$ArCH_2CO$
28	2	HCHO	$Ar(CH_2)_2$



[a] (a) (3,4-Dichlorophenyl)acetic acid, DCC, CH_2Cl_2, excess piperazine; (b) AlH_3, THF, rt; (c) Ac_2O, aqueous $NaHCO_3$, $CHCl_3$; (d) n-C_3H_7COCl, aqueous $NaHCO_3$, $CHCl_3$; (e) n-C_4H_9COCl, aqueous $NaHCO_3$, $CHCl_3$; (f) (3,4-dichlorophenyl)acetic acid, DCC, CH_2Cl_2; (g) $CCl_3CH(OH)_2$, toluene, 90 °C. "Ar" = 3,4-dichlorophenyl.

pairs of electrons. In the *cis*-1,2-cyclohexanediamines and ethylenediamines we observed[13,14] that increasing the size of the *N*-alkyl substituent caused a reduction in σ-binding affinity. This is opposite to the effect observed with typical σ ligands such as (+)-opiate, octahydrobenzo[*f*]quinolines (OHBQ's), and 3-phenylpiperidines[1a,2] where extension of the *N*-alkyl side chain resulted in improvements in σ-binding activity. The effect of *N*-alkyl substitution on the binding of piperazines and homopiperazines (Table I) was investigated for this same reason.

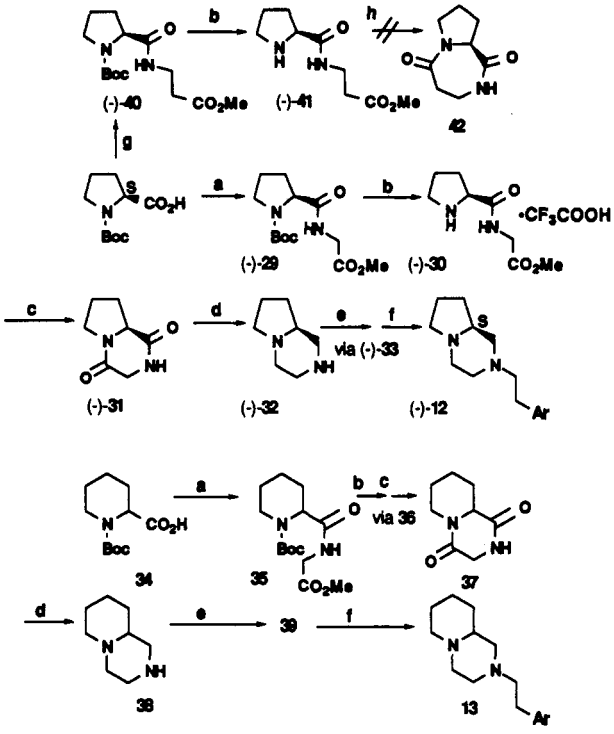
Class C, the 1,4-diazabicyclo[4.3.0]nonanes and 1,4-diazabicyclo[4.4.0]decanes (Table II) immobilize the ethylene, dialkylamine (pyrrolidine), and *N*-methyl moieties.

The 3-aminoquinuclidines (class E) and 1,4-diazabicyclo-[3.2.2]nonane (class F) (Table III) completely immobilize one or both of the nitrogen lone pairs of electrons and do not allow a trans antiperiplanar arrangement of lone pair of electrons as in the piperazines.

Chemistry

Compound 3 (Table I) (class B in Chart II) was obtained by the sequence of monoacylation of commercial piperazine with 3,4-dichlorophenylacetic acid followed by AlH_3[13,17] reduction (Scheme I). The sequence of acylation of 3 with acetic anhydride in aqueous $NaHCO_3$ (98%) followed by

Scheme II. Synthesis of Enantiomeric 1,4-Diazabicyclo[4.3.0]nonanes [(+)- and (−)-12] and 1,4-Diazabicyclo[4.4.0]decane (13) (Class C)[a]



[a] (a) 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, HOBT, glycine methyl ester hydrochloride, Et_3N, rt; (b) CF_3COOH, rt; (c) MeOH, Et_3N, reflux; (d) $LiAlH_4$, THF, reflux; (e) (3,4-dichlorophenyl)acetic acid, DCC, CH_2Cl_2, rt; (f) AlH_3, THF, rt; (g) 1-[3-(dimethylamino)propyl)]-3-ethylcarbodiimide hydrochloride, HOBT, β-alanine methyl ester hydrochloride, Et_3N, rt; (h) toluene, reflux 72 h or MeOH, reflux, 7 days. "Ar" = 3,4-dichlorophenyl.

AlH_3 reduction afforded **5** (Table I and Scheme I). Piperazines **4** and **6–9** (Scheme I) were similarly obtained. Compound **10** (Table I) was obtained similarly (Scheme I) starting with homopiperazine. The sequence of N-formylation of **10** with $CCl_3CH(OH)_2$ in refluxing $CHCl_3$ gave **28** (quantitative) which on AlH_3 reduction was transformed to **11** (78%). In all of the amide reductions in this paper, as in our previous studies, AlH_3[13,17] was employed in place of $LiAlH_4$ since the latter reagent resulted in extensive halogen reduction. BH_3 was also found to be unsuitable since it formed stable boron complexes.

(+)- and (−)-**12** of defined absolute configuration and the racemic homologue **13** (Table II) were synthesized as in Scheme II. Coupling of *t*-Boc-(*S*)-proline with glycine methyl ester in the presence of HOBT[18] and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride afforded (−)-**29** as a crystalline solid (58%). N-Deprotection with CF_3COOH followed by evaporation of the solvent in vacuo gave (−)-**30**·CF_3COOH salt in quantitative yield. Neutralization of this salt by partitioning with aqueous $NaHCO_3/CHCl_3$ or treatment with excess Et_3N gave (−)-**30** base which on standing at room temperature spontaneously cyclized to diketopiperazine (−)-**31**. This cyclization was found to proceed well in MeOH at room temperature and was accelerated on refluxing to give (−)-**31** in 65% yield. The homologous amino ester (−)-**41** (Scheme II), however, under the same conditions failed to cyclize to **42**, suggesting that the ring closure of (−)-**30** is sensitive to internal geometry. $LiAlH_4$ reduction of (−)-**31** gave (−)-**32** which was subsequently transformed to the target compound (−)-**12**. The enantiomer (+)-**12** and homologue **13** were prepared in the same way as (−)-**12** (Scheme II).

3-Aminoquinuclidines (**14** and **15**) (class E, Table III) were synthesized starting from commercially available (Aldrich) 3-aminoquinuclidine (Scheme III). 1,4-Diazabicyclo[3.2.2]nonane **16** (Table III) was synthesized starting from 3-quinuclidone (Aldrich) (Scheme III). Formation of the corresponding oxime **45**[19] (80%) followed by treatment of this with CF_3COOH provided the Beckman rearrangement product **46** in 94% yield. The sequence of AlH_3 reduction to bicyclic amine **47** (75%) followed by DCC coupling with 3,4-dichlorophenylacetic acid and AlH_3 reduction furnished **16**.

Class G, the 1-(aminomethyl)cyclohexylamines were synthesized starting from 1-(1-piperidinyl)cyclohexylnitrile (**49**)[20] (Scheme III). Careful AlH_3 reduction of this compound at ambient temperature resulted in a 1:5 mixture of 1-cyclohexylpiperidine (**50**) and 1-[1-(aminomethyl)cyclohexyl]piperidine (**51**). The mixture was readily separated via crystallization of the corresponding fumarate salt from MeOH. **51** was readily transformed to **17**. The sequence of N-formylation of **17** with refluxing EtOCHO in the presence of formic acid followed by AlH_3 reduction in THF at ambient temperature yielded **18**.

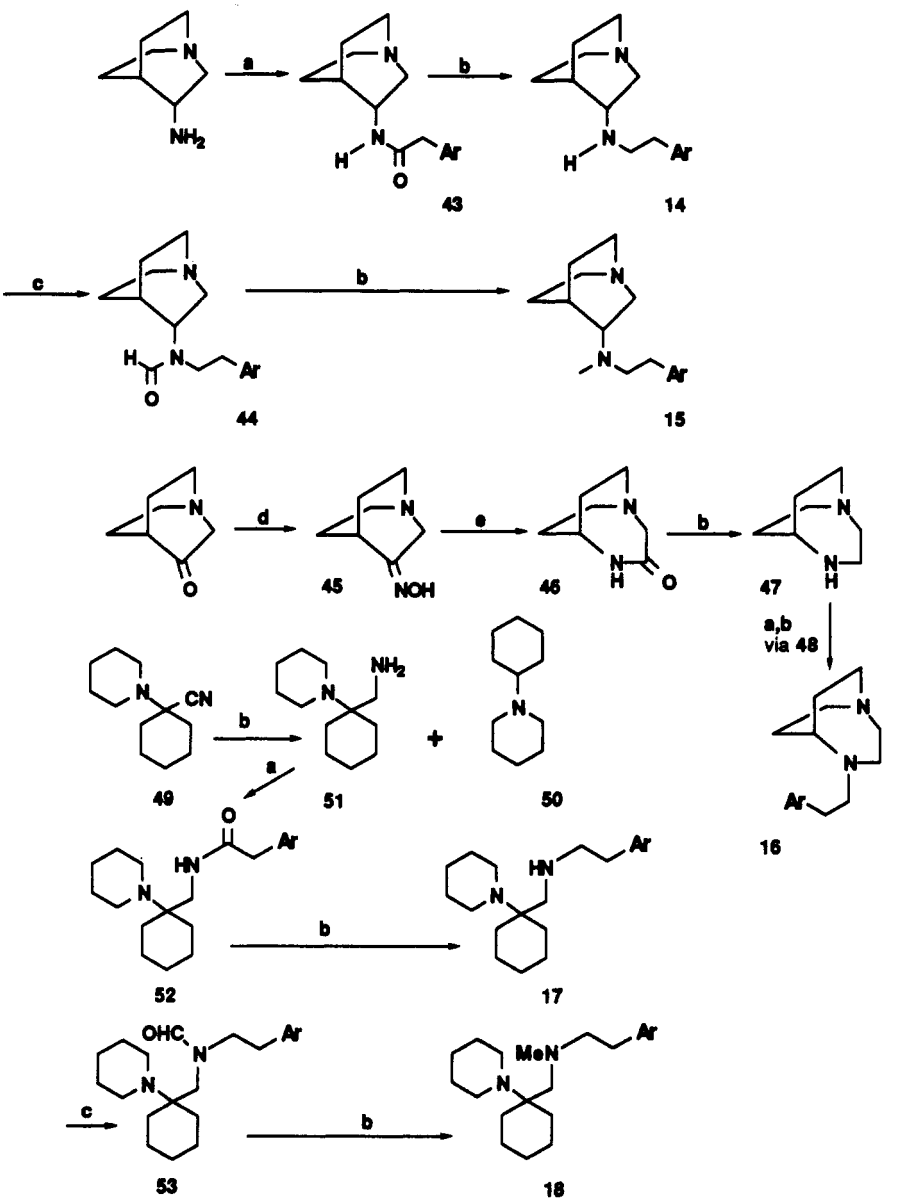
2-Aminotetralins **19** and **20** (class H) were synthesized (Scheme IV) starting from 6,7-dichloro-2-tetralone (**54**).[21] Reductive amination of **54** with 1-(2-aminoethyl)pyrrolidine and $NaCNBH_3$ in the presence of CH_3COOH gave **19** in 55% yield. This was readily transformed to its *N*-methyl derivative **20**. The characterization of most of the compounds reported herein is summarized in Table IV. The remaining compounds are described in the Experimental Methods.

Results and Discussion

In a continuation of our studies[15] on the conformational restriction of the flexible σ ligand, 2-(1-pyrrolidinyl)-*N*-[2-(3,4-dichlorophenyl)ethyl]-*N*-methylethylamine (**1**), we have probed new conformations through the use of rigid bicyclic and bridged bicyclic amines, piperazines, and other compounds (Tables I–III). In the piperazine series (Table I), increasing the size of the nitrogen substituent from methyl to pentyl resulted in an increase in affinity with optimal binding (lowest K_i) occurring at butyl. The symmetrical bis(arylethyl)piperazine **9** showed a similar binding affinity to the pentyl derivative **8**, suggesting that these groups have similar steric requirements at the receptor. The propyl derivative **6**[16] displayed a 2-fold improvement in binding over **1** (of which it is a structural isomer). Since substitution of **1** from methyl through to butyl has been found to reduce binding affinity at σ receptors,[13] it appears that the two nitrogen atoms of **1** have opposing steric requirements.

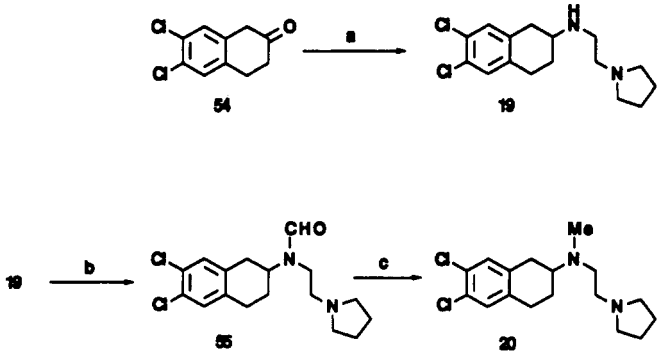
Complete removal of the piperazine alkyl substituent as in **3** resulted in a 216-fold reduction in binding affinity (compared with the *N*-butyl derivative **7**), suggesting that alkyl substituents on this nitrogen are necessary for strong binding interaction. Expansion of the piperazine ring as in homopiperazine derivatives **10** and **11** resulted in a 19-fold reduction in binding affinity (comparing **11** with **4**). Distortion of the nitrogen atom lone electron pairs from the antiperiplanar arrangement found in the piperazines may account for loss of binding activity of the homopip-

Scheme III. Synthesis of Bridgehead Bicyclooctane and Bicyclononane Classes E and F and Miscellaneous Compounds (G)[a]



[a] (a) (3,4-Dichlorophenyl)acetic acid, DCC, CH_2Cl_2, rt; (b) AlH_3, THF, rt; (c) HCOOEt, HCOOH, reflux; (d) $HONH_2$·HCl, NaOAc, EtOH, rt; (e) CF_3COOH. "Ar" = 3,4-dichlorophenyl.

Scheme IV. Synthesis of 2-Aminotetralin-type σ Ligands (Class H)[a]



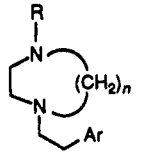
[a] (a) 2-(1-pyrrolidinyl)ethylamine, $NaCNBH_3$, CH_3COOH; (b) EtOCHO, HCOOH, reflux; (c) AlH_3, THF, rt.

erazines. It is notable that in the piperazines, removal of the *N*-methyl group (see **3** and **4**) resulted in a 13-fold lowering of affinity, whereas the same change in the homopiperazines failed to have any effect.

The effect of immobilization of the pyrrolidinyl, *N*-methyl, and NC–CN bond rotation of **1** was investigated through synthesis of the enantiomers of **12** (Table II). The data suggest that these enantiomers may represent σ-receptor-bound conformations of **1** with preference for the conformation represented by the more active enantiomer (+)-**12**. The relatively low (4-fold) enantioselectivity ratio of these compounds compares with those of other σ ligands related to **1**.[13,14] Racemic homologue **13** showed an increase in affinity (compared with **12**) similar to that observed with increasing the steric bulk on the piperazine (Table I) and ethylenediamine[13] nitrogen atom distal to the aromatic ring.

In the bridgehead bicyclic diamines **14–16** (Table III), considerably reduced binding was observed compared with the nonbridgehead bicyclic amines (Table II) and piperazines (Table I). The lone pair orientations of **1** represented by **14–16** are far removed from the arrangement

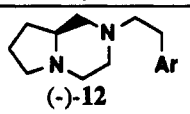
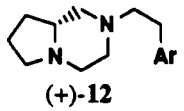
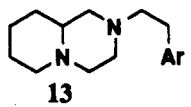
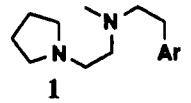
Table I. σ-Receptor Affinities of Piperazine and Homopiperazine (Classes B and D) and Standard (Reference) Ligands[a]



compd	R	n	K_i ([³H](+)-Pent) (nM ± SEM)
3	H	2	119 ● 22
4	Me	2	9.2 ● 1.3
5	Et	2	1.6 ± 0.1
6	nPr	2	1.2 ± 0.1
7	nBu	2	0.55 ± 0.12
8	nPent	2	1.7 ± 0.3
9	2-(3,4-dichlorophenyl)ethyl	2	1.7 ● 0.3
10	H	3	154 ± 10
11	Me	3	174 ± 23
(+)-pentazocine			3.1 ± 0.3[b]
1,3-di-o-tolylguanidine			28 ± 4.3[b]
haloperidol			3.7 ± 0.6[b]

[a] Sigma binding affinities were determined by incubating [³H](+)-pentazocine in the presence of 12 concentrations of test ligand in one of three concentration ranges: 0.0005–100 nM, 0.005–1000 nM, or 0.05–10000 nM. All assay conditions were as described in the Experimental Methods. Values are the average of 2–3 experiments ± SEM, each carried out in duplicate. The GraphPAD (San Diego, CA) iterative curve fitting program was used to determine IC_{50} values. The Cheng–Prussof equation[30] 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: [³H](+)-pentazocine (guinea pig brain), K_d = 4.8 nM. In all cases, "Ar" = 3,4-dichlorophenyl. [b] Previously reported data.[15]

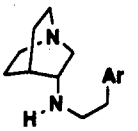
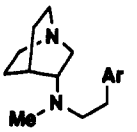
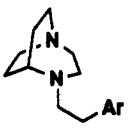
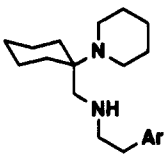
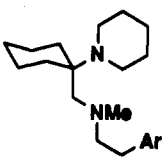
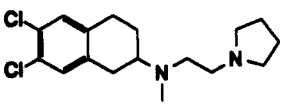
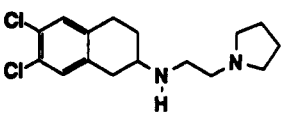
Table II. Affinities of Enantiomeric 1,4-Diazabicyclo[4.3.0]nonane (12) and 1,4-Diazabicyclo[4.4.0]decane (13) Classes at the σ Receptor[a]

compd	K_i ([³H](+)-Pent) (nM ± SEM)
 (-)-12	5.4 ± 0.7
 (+)-12	1.4 ± 0.2
 13	0.98 ± 0.06
 1	2.1 ± 0.8[b]

[a] Sigma binding affinities were determined by incubating [³H](+)-pentazocine in the presence of 12 concentrations of test ligand in one of three concentration ranges: 0.0005–100 nM, 0.005–1000 nM, or 0.05–10000 nM. All assay conditions were as described in the Experimental Methods. Values are the average of 2–3 experiments ± SEM, each carried out in duplicate. The GraphPAD (San Diego, CA) iterative curve fitting program was used to determine IC_{50} values. The Cheng–Prussoff equation[30] 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: [³H](+)-pentazocine (guinea pig brain), K_d = 4.8 nM. In all cases, "Ar" = 3,4-dichlorophenyl. [b] Previously reported data.[15]

found in the piperazines. Compound 16, for example, has nitrogen lone pairs of electrons oriented at roughly 90° to each other; it also represents a very unlikely staggered conformation of 1.

Table III. σ-Binding Affinities of Bridgehead Bicyclooctanes and Nonanes (Classes E and F) and Miscellaneous Compounds (Classes G and H)[a]

compd		K_i ([³H](+)-Pent) (nM ± SEM)
	14	607 ± 62
	15	80 ± 11
	16	654 ± 68
	17	16.3 ± 1.5
	18	78 ± 1.0
	19	1.3 ± 0.2
	20	3.9 ± 0.5

[a] Sigma binding affinities were determined by incubating [³H](+)-pentazocine in the presence of 12 concentrations of test ligand in one of three concentration ranges: 0.0005–100 nM, 0.005–1000 nM, or 0.05–10000 nM. All assay conditions were as described in the Experimental Methods. Values are the average of 2–3 experiments ± SEM, each carried out in duplicate. The GraphPAD (San Diego, CA) iterative curve fitting program was used to determine IC_{50} values. The Cheng–Prussoff equation[30] 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: [³H](+)-pentazocine (guinea pig brain), K_d = 4.8 nM. In all cases, "Ar" = 3,4-dichlorophenyl.

In 1,[13] to the nitrogen atom proximal to the aromatic ring and 15 and 19 (Table III), addition of a methyl group improved the σ-binding affinity. However, the opposite effect was observed with the spiro compounds 17 and 18 (Table III) as well as the *cis*-cyclohexanediamines.[14] The varying effects of *N*-methyl addition to the phenylethylamine nitrogen atoms of these compounds suggests that this atom may have subtle differences in its interaction at the σ-binding site from one structural class of compounds to the next.

We previously observed a boundary condition to σ binding in the *N*-butyl derivative of 1.[13] It is possible that the 37-fold reduction (with respect to 1) in the binding affinity of 18 is due to steric interference resulting from a similar boundary condition.

The high σ-binding affinity of aminotetralins **19** and **20** suggests that a gauche orientation between the aromatic group and the phenylethylamine N atom of **1** may be tolerated for binding.

Conclusion

By incorporation of flexible σ ligand **1** in a variety of rigid bicyclic amines, bridgehead bicyclic amines, piperazines, and other ring systems we have been able to probe its interaction at σ receptors. The data suggest that antiperiplanar N lone pairs afford the best binding affinity. Other N lone pair orientations or compounds representing staggered conformations of **1** (as in **16**) show very weak σ interaction. The reduction in binding affinity with respect to **1** of the spiro derivative **18** indicates that it is subject to certain steric limitations to binding.

The results with the *N*-alkylpiperazines (Table I) and *N*-alkyl derivatives of **1**[13] suggest that the two nitrogen atoms of **1** work in opposition to each other. The high binding affinity of the diazabicyclononanes **12** indicates that these may approximate the methyl and pyrrolidine ring conformations found in σ-receptor bound **1**.

Overall comparison of the results indicates that **1** is subject to considerable conformational freedom and suggests that the σ_1 receptor does not require rigid stereochemical and steric constraints. Studies of σ_2 receptor requirements are underway.

Experimental 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 (Pel-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/g 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/g 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/g in 10 mM Tris·HCl pH 7.4. Aliquots were stored at −80 °C until used. Protein concentration was determined by the method of Lowry et al.[22] using bovine serum albumin (BSA) as standard.

σ-Receptor Binding Assays. σ_1 receptors were labeled using [^{3}H]-(+)-pentazocine (specific activity = 51.7 Ci/mmol). Briefly, guinea pig brain membranes were incubated with 3 nM [^{3}H]-(+)-pentazocine using 500 μg of membrane protein in 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 filtration through glass fiber filters (Schleicher and Schuell, Keene, NH). The filters were pretreated with polyethyleneimine as described previously.[23]

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). Polyethyleneimine 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.[23]

General Synthetic Methods. 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 C, H, and N, elemental analyses were determined to be within ±0.4% of the theoretical values for these elements unless indicated otherwise. 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 obtained from $CDCl_3$ solutions using a Varian XL-300 spectrometer. ^{1}H NMR spectra of compounds reported as salts were taken from the free bases forms. Thin-layer chromatography (TLC) was performed on 250 μm Analtech GHLF silica gel plates. TLC solvent system A corresponds to $CHCl_3$–MeOH–concentrated aqueous NH_3 (90:9:1). TLC solvent system B corresponds to EtOAc–hexanes (1:2). TLC solvent system C corresponds to $CHCl_3$–MeOH–concentrated aqueous NH_3 (80:18:2). TLC solvent system D corresponds to $CHCl_3$–MeOH–concentrated aqueous NH_3 (95:4.5:0.5). For the purposes of clarity, enantiomeric compounds are prefixed with the sign of rotation and/or absolute configuration whereas racemic compounds are not prefixed. The chemical characterization of compounds **3–55** prepared according to methods A–H is shown in Table IV and the Experimental Methods. The ^{1}H NMR resonances[31] of all the compounds in Table IV are in accordance with their structures. All crystalline compounds reported under the general methods A–H (below) and in Table IV were crystallized from ca. 1:10 ratio of compound or salt/solvent.

General Methods A-H. 1-[2-(3,4-Dichlorophenyl)ethyl]-piperazine (3). Method A. The fumarate salt of **21**[16] (2.00 g, 5.14 mmol) was converted to the free base by partitioning between 10% aqueous NaOH (50 mL) and $CHCl_3$ (50 mL). The base was azeotropically dried by evaporation (3 × 20 mL) with toluene. The **21** (base) was dissolved in dry THF (20 mL) and added dropwise during 5 min to a freshly prepared solution of AlH_3[13,17] in THF (27.5 mL of a 1.0 M solution, 27.5 mmol). TLC (solvent system A) indicated the reaction to be complete after 20 min at room temperature (rt). The reaction mixture was carefully poured into 15% aqueous NaOH (100 mL), and the solution was extracted with $CHCl_3$ (200 mL). The organic layer was dried by filtration through a short column of Na_2SO_4, and the solvent was evaporated in vacuo to give **3** as a colorless oil. This was dissolved in MeOH (30 mL), and the solution was heated to boiling and the heat source was removed. The hot solution was treated with 48% aqueous HBr to pH 3 (wetted colorpHast pH paper, EM Science, Gibbstown, NJ). Crystallization occurred on cooling of the solution to rt. The crystals were filtered and twice washed with a little cold (0 °C) MeOH and Et_2O and dried in vacuo at 60 °C. Yield of **3**·HBr (1.70 g, 79%): mp 284–285 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.34 (d, J = 8.3 Hz, 1 H), 7.30 (d, J = 2.0 Hz, 1 H), 7.04 (dd, J = 2.0, 8.3 Hz, 1 H), 2.91 (m, 4 H), 2.76 (distorted t, J = 7.9 Hz, 2 H), 2.54 (distorted t, J = 7.9 Hz, 2 H), 2.43–2.53 (m, 4 H); CIMS MH^+ ($C_{12}H_{16}Cl_2N_2$) requires 259, found 259. Anal. ($C_{12}H_{18}Br_2Cl_2N_2 \cdot 2H_2O$): C, H, N.

1-(Acetyl)-4-[2-(3,4-dichlorophenyl)ethyl]piperazine (22). Method B. To a rapidly stirred solution of **3**·HBr (1.00 g, 2.38 mmol) in a mixture of saturated aqueous $NaHCO_3$ (50 mL) and $CHCl_3$ (50 mL) was added a solution of acetic anhydride (0.29 g, 2.84 mmol) (or other appropriate acid chloride or anhydride) in $CHCl_3$ (5 mL). The reaction mixture was stirred for 10 min at rt when TLC (solvent system A) indicated the reaction to be complete. The $CHCl_3$ layer was separated, and the aqueous layer was washed with a further 50 mL of $CHCl_3$. The combined organic layer was dried (Na_2SO_4) and evaporated in vacuo to give **22** (0.70 g, 98%) as a colorless oil. **22**·oxalate (2-propanol): mp 174–175 °C; ^{1}H NMR ($CDCl_3$) δ 7.35 (d, J = 8.3 Hz, 1 H), 7.30 (d, J = 2.0 Hz, 1 H), 7.04 (dd, J = 2.0, 8.3 Hz, 1 H), 3.64 (m, 2 H), 3.48 (m, 2 H), 2.76 (t, J = 8.3 Hz, 2 H), 2.59 (t, J = 8.3 Hz, 2 H), 2.48

Table IV. Characterization of Compounds Prepared According to Methods A–H in Experimental Methods

compd (salt)	mp (°C) (solvent)	method	starting material	% yield[b]	MS	anal.[c]
4·HBr[a]	281–282 dec (EtOH)	A	25	75	MH^+ ($C_{13}H_{18}Cl_2N_2$)	$C_{13}H_{20}Br_2Cl_2N_2$
5·HBr[a]	286–287 dec (EtOH)	A	22	81	MH^+ ($C_{14}H_{20}Cl_2N_2$)	$C_{14}H_{22}Br_2Cl_2N_2$
6·HBr[d]	290–292 dec (MeOH)	A	26	76		
7·HBr[a]	279–280 dec (EtOH)	A	23	75	MH^+ ($C_{16}H_{24}Cl_2N_2$)	$C_{16}H_{26}Br_2Cl_2N_2$
8·HBr[a]	271–273 dec (EtOH)	A	24	56	MH^+ ($C_{17}H_{26}Cl_2N_2$)	$C_{17}H_{28}Br_2Cl_2N_2$
10·oxalate[a]	197–198 dec (EtOH)	A	27	81	MH^+ ($C_{13}H_{18}Cl_2N_2$)	$C_{17}H_{22}Cl_2N_2O_8$
11·oxalate[a]	202–203 dec (MeOH)	A	28	78	MH^+ ($C_{14}H_{20}Cl_2N_2$)	$C_{18}H_{24}Cl_2N_2O_8$
(*S*)-(−)-12·HBr[a,e]	261.5–262.5 dec (EtOH)	A	(*S*)-(−)-33	68	MH^+ ($C_{15}H_{20}Cl_2N_2$)	$C_{15}H_{22}Br_2Cl_2N_2$
(*R*)-(+)-12·HBr[a,f]	263–265 dec (EtOH)	A	(*R*)-(+)-33	48	MH^+ ($C_{15}H_{20}Cl_2N_2$)	$C_{15}H_{22}Br_2Cl_2N_2$
13·HBr[a]	272–273 dec (EtOH)	A	39	69	MH^+ ($C_{16}H_{22}Cl_2N_2$)	$C_{16}H_{24}Br_2Cl_2N_2$
14·fumarate[a]	154–156 (2-PrOH)	A	43	63	MH^+ ($C_{15}H_{20}Cl_2N_2$)	$C_{23}H_{28}Cl_2N_2O_8$
15·fumarate[a]	184–185 (2-PrOH)	A	44	70	MH^+ ($C_{16}H_{22}Cl_2N_2$)	$C_{24}H_{30}Cl_2N_2O_8$
16·fumarate[a]	167–168 (2-PrOH)	A	48	48	MH^+ ($C_{15}H_{20}Cl_2N_2$)	$C_{21}H_{26}Cl_2N_2O_8$[g]
17·oxalate[a]	185–187 (MeOH/2-PrOH)	A	52	100	MH^+ ($C_{20}H_{30}Cl_2N_2$)	$C_{24}H_{34}Cl_2N_2O_4$
18·HBr[a]	214–215 (MeOH)	A	53	59	MH^+ ($C_{21}H_{32}Cl_2N_2$)	$C_{21}H_{34}Br_2Cl_2N_2$
20·HBr[a]	183–185 (EtOH)	A	55	61	MH^+ ($C_{17}H_{24}Cl_2N_2$)	$C_{17}H_{26}Br_2Cl_2N_2·H_2O$
23[a]	99–100 (EtOAc)	B[h]	21	59	MH^+ ($C_{16}H_{20}Cl_2N_2O_2$)	$C_{16}H_{20}Cl_2N_2O_2$
24[a]	109–113 (2-PrOH)	B[i]	21	53	M^+ ($C_{17}H_{22}Cl_2N_2O_2$)	*j*
26[k]	54–55 (isooctane)	C	1-propylpiperazine	100		
27·fumarate[a]	179–180 (MeOH)	C	homopiperazine	50	MH^+ ($C_{13}H_{16}Cl_2N_2O$)	$C_{17}H_{20}Cl_2N_2O_5$
(*R*)-(+)-29[l]	70–71 (1:3 EtOAc/isooctane)	D	*N*-tBOC-D-proline	35	MH^+ ($C_{13}H_{22}N_2O_5$)	$C_{13}H_{22}N_2O_5$
(*R*)-(+)-30·oxalate[m]	119–120 (2-PrOH)	E	(*R*)-(+)-29	100	MH^+ ($C_8H_{14}N_2O_3$)	$C_{10}H_{16}N_2O_7$
(*R*)-(+)-31[o,n]	205–208 (2-PrOH)	F	(*R*)-(+)-30	63	MH^+ ($C_7H_{10}N_2O_2$)	$C_7H_{10}N_2O_2$
(*R*)-(+)-32·HBr[n,p]	234–236 (MeOH)	G	(*R*)-(+)-31	67	MH^+ ($C_7H_{14}N_2$)	$C_7H_{16}Br_2N_2$
(*R*)-(+)-33[a,q]	101–102 (2-PrOH)	C	(*R*)-(+)-32	94	MH^+ ($C_{15}H_{18}Cl_2N_2O$)	$C_{15}H_{18}Cl_2N_2O$
(*S*)-(−)-33[a,r]	102.5–103.5 (2-PrOH)	C	(*S*)-(−)-32	77	MH^+ ($C_{15}H_{18}Cl_2N_2O$)	$C_{15}H_{18}Cl_2N_2O$
35[a]	118.5–119.5 (1:3 EtOAc/isooctane)	D	N-tBOC-pipecolinic acid	45	MH^+ ($C_{14}H_{24}N_2O_5$)	$C_{14}H_{24}N_2O_5$
36·fumarate[a]	116–118 (EtOAc)	E	35	100	MH^+ ($C_9H_{16}N_2O_3$)	$C_{13}H_{20}N_2O_7·0.5H_2O$[s]
37[a,t]	159–160 (2-PrOH)	F	36	55	MH^+ ($C_8H_{12}N_2O_2$)	$C_8H_{12}N_2O_2$
38·oxalate[a,u]	178–179 dec (MeOH)	G	37	95	MH^+ ($C_8H_{16}N_2$)	$C_{12}H_{20}N_2O_8$
39[a]	119–120 (2-PrOH)	C	38	100	MH^+ ($C_{16}H_{20}Cl_2N_2O$)	$C_{16}H_{20}Cl_2N_2O$
(*S*)-(−)-40[a,v]	71–72 (1:3 EtOAc/isooctane)	D[w]	N-tBOC-L-proline	63	MH^+ ($C_{14}H_{24}N_2O_5$)	$C_{14}H_{24}N_2O_5$
(*S*)-(−)-41·oxalate[a,x]	139–141 (2-PrOH)	E	(*S*)-(−)-40	97	MH^+ ($C_9H_{16}N_2O_3$)	$C_{11}H_{18}N_2O_7$
43[a]	148–149 (EtOAc/isooctane)	B	3-aminoquinuclidine dihydrochloride	100	MH^+ ($C_{15}H_{18}Cl_2N_2O$)	$C_{15}H_{18}Cl_2N_2O$
47·HCl[a,y]	250 dec (EtOH)	A	46	75	MH^+ ($C_7H_{14}N_2$)	$C_7H_{16}Cl_2N_2·0.33H_2O$
48·oxalate[a]	180–182 (2-PrOH)	C	47	34	MH^+ ($C_{15}H_{18}Cl_2N_2O$)	$C_{17}H_{20}Cl_2N_2O_5$
51·fumarate[a,z]	168.5–169.5 (2-PrOH)	A[aa]	1-(1-piperidinyl)-cyclohexylnitrile[bb]	68	MH^+ ($C_{12}H_{24}N_2$)	$C_{12}H_{24}N_2·0.5C_4H_4O_4$
52[a]	121–121.5 (2-PrOH)	C	51	57	MH^+ ($C_{20}H_{28}Cl_2N_2O$)	$C_{20}H_{28}Cl_2N_2O$
53[a]	oil	H	17	85	MH^+ ($C_{21}H_{31}Cl_2N_2O$)	*cc*
55·HBr[a]	226–228 (MeOH)	H	19	80	MH^+ ($C_{17}H_{22}Cl_2N_2O$)	$C_{17}H_{23}BrCl_2N_2O$

[a] The ^1H NMR spectral data for the free base or neutral forms of this compound is shown in ref 31. [b] No attempt was made to optimize the yield. [c] Where molecular formulae are given, the elemental composition for the elements C, H, and N was found to be within ±0.4%. [d] Obtained by AlH_3 reduction of **26** as described previously[16] [lit.[16] mp 290–292 °C dec]. [e] $[\alpha]_D = -6.8°$ ($c = 1.32$, MeOH). [f] $[\alpha]_D = +5.7°$ ($c = 1.09$, MeOH). [g] >0.4% for carbon due to solvation. [h] Method B using propionyl chloride as the acylating reagent. [i] Method B using butyryl chloride as the acylating reagent. [j] This compound failed to yield a satisfactory elemental analysis due to solvation; HRMS M^+ ($C_{17}H_{22}Cl_2N_2O_2$) requires 356.1058, found 356.1045. [k] This compound was obtained as previously described[16] (lit.[16] mp 54–55 °C). [l] $[\alpha]_D = +91°$ ($c = 1.21$, $CHCl_3$). [m] $[\alpha]_D = +39°$ ($c = 0.49$, MeOH). [n] This compound is described in ref 24. [o] $[\alpha]_D = +190°$ ($c = 1.59$, H_2O). [p] $[\alpha]_D = +5.0°$ ($c = 1.57$, H_2O). [q] $[\alpha]_D = +12.7°$ ($c = 1.05$, $CHCl_3$). [r] $[\alpha]_D = -12.0°$ ($c = 1.14$, $CHCl_3$). [s] >0.4% for H and N due to solvation. [t] This compound is described in ref 25. [u] This is described in ref 26. [v] $[\alpha]_D = -87°$ ($c = 1.17$, $CHCl_3$). [w] Method D using β-alanine methyl ester hydrochloride. [z] $[\alpha]_D = -39.3°$ ($c = 1.13$, MeOH); attempts to cyclize free base of **41** by refluxing it for several days in MeOH or overnight in toluene resulted in unchanged starting material. [y] This compound is described in ref 28. [z] This compound is described in ref 29. [aa] Analysis of the crude reaction product by GC revealed a 1:4 mixture of the desired **51** and 1-cyclohexylpiperidine (**50**). [bb] This compound was synthesized as previously described.[20] [cc] HRMS (M^+ calcd for $C_{21}H_{31}Cl_2N_2O$) 397.1813, found 397.1830.

(m, 4 H), 2.09 (s, 3 H); CIMS MH^+ (calcd for $C_{14}H_{18}Cl_2N_2O$) requires 301, found 301. Anal. ($C_{16}H_{20}Cl_2N_2O_5$): C, H, N.

1-(3,4-Dichlorophenylacetyl)-4-methylpiperazine (25). Method C. To a stirred solution of 3,4-dichlorophenylacetic acid (8.1 g, 39.5 mmol) in CH_2Cl_2 (100 mL) was added a solution of DCC (10.86 g, 52.6 mmol) in CH_2Cl_2 (100 mL), and the mixture was stirred for 10 min at rt. To the precipitated complex was added 1-methylpiperazine (3.96 g, 39.5 mmol), and stirring was continued until TLC (solvent system A) indicated the reaction to be complete. The precipitated DCU was removed by filtration, and the filter cake was washed with Et_2O (50 mL). The filtrate was diluted with enough Et_2O to render the organic layer less dense than the aqueous layer, and the organic extract was then extracted with 10% aqueous citric acid (200 mL) and discarded. The aqueous layer was washed with Et_2O (2 × 200 mL), and the combined washings were discarded. The aqueous layer was basified by addition of excess concentrated aqueous NH_3 solution and extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layer was washed with water, dried (Na_2SO_4), and evaporated to give **25** (11.3 g, quantitative) as a crystalline solid. Recrystallization from isooctane afforded **25**: mp 91–92 °C; ^1H NMR ($CDCl_3$) δ 7.40 (d, $J = 8.1$ Hz, 1 H), 7.35 (d, $J = 1.8$ Hz, 1 H), 7.09 (dd, $J = 1.8$, 8.1 Hz, 1 H), 3.66 (s, 2 H), 3.62–3.70 (m, 2 H), 3.46 (m, 2 H), 2.37 (m, 2 H), 2.27–2.33 (complex m, 2 H), 2.28 (s, 3 H); CIMS MH^+ ($C_{13}H_{16}Cl_2N_2O$) requires 287, found 287. Anal. ($C_{13}H_{16}Cl_2N_2O$): C, H, N.

1,4-Bis[2-(3,4-dichlorophenylethyl)]piperazine (9). To a stirred mixture of piperazine (1.05 g, 12.2 mmol), $CHCl_3$ (100 mL), and saturated aqueous $NaHCO_3$ (100 mL) was added dropwise at rt a solution of (3,4-dichlorophenyl)acetyl chloride (5.45 g, 24.4 mmol, 2 equiv) in $CHCl_3$ (50 mL). As the reaction proceeded, a white creamy suspension formed. After 20 min at rt, the reaction was found to be complete by TLC (solvent system A). The reaction mixture was filtered and the filter cake was washed with cold distilled water and oven dried overnight in vacuo to yield 5.20 g (91%) of diamide: mp 282–283 °C; ^1H NMR (DMSO-d_6) δ 7.55 (d, $J = 8.3$ Hz, 2 H), 7.48 (d, $J = 1.9$ Hz, 2 H), 7.20 (dd, $J = 1.9$, 8.3 Hz, 2 H), 3.77 (br s, 4 H, CH_2CON), 3.41–

3.54 (m, 8 H); CIMS MH+ ($C_{20}H_{18}Cl_4N_2O_2$) requires 459, found 459. Anal. ($C_{20}H_{18}Cl_4N_2O_2$·0.5H_2O): C, H, N.

To a stirred solution of AlH_3[13,17] (53 mL of a 0.66 M solution in THF, 35 mmol, 8.2 equiv) was added, portionwise, diamide from above (2.00 g, 4.3 mmol). The reaction mixture was quenched and the product isolated as described above for **3** to give **9**·HCl (MeOH) (1.64 g, 75%): mp 300–301 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.34 (d, J = 8.2 Hz, 2 H), 7.30 (d, J = 2.0 Hz, 2 H), 7.04 (dd, J = 2.0, 8.2 Hz, 2 H), 2.72–2.80 (m, 4 H), 2.50–2.62 (complex m, 12 H); CIMS MH+ ($C_{20}H_{22}Cl_4N_2$) requires 431, found 431. Anal. ($C_{20}H_{24}Cl_6N_2$): C, H, N.

1-[2-(3,4-Dichlorophenyl)ethyl]-4-formylhomopiperazine (28). **10**·oxalate (1.98 g, 4.37 mmol) was converted to **10** by partitioning between 1.0 M aqueous KOH (50 mL) and $CHCl_3$ (2 × 50 mL). The base was dried under high vacuum and dissolved in toluene (30 mL). To the solution was added chloral hydrate (0.80 g, 4.83 mmol), and the solution was heated at 90 °C for 90 min when TLC (solvent system A) indicated the reaction to be complete. The solvent was evaporated in vacuo to give **28** (1.32 g, quantitative). **28**·fumarate crystallized from EtOAc: mp 122–123 °C; ^{1}H NMR ($CDCl_3$) δ 8.09 (s, 1 H, C*H*O), 7.34 (d, J = 8.3 Hz, 1 H), 7.29 (m, 1 H), 7.02 (dd, J = 2.0, 8.3 Hz, 1 H), 3.54 (m, 2 H), 3.46 (m, 2 H), 2.66–2.82 (complex m, 8 H), 1.86 (m, 2 H); CIMS MH+ ($C_{14}H_{18}Cl_2N_2O$) requires 301, found 301. Anal. ($C_{18}H_{22}Cl_2N_2O_5$): C, H, N.

(*S*)-(−)-N-(*tert*-Butoxycarbonyl)prolylglycine Methyl Ester [(*S*)-(−)-29]. Method D. To a stirred mixture of Boc-L-proline (5.0 g, 23 mmol), glycine methyl ester hydrochloride (2.92 g, 23 mmol, 1.0 equiv) (or other amino acid methyl ester hydrochloride, e.g. β-alanine methyl ester hydrochloride), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (5.34 g, 27.9 mmol, 1.2 equiv) and HOBT monohydrate (3.77 g, 27.9 mmol, 1.2 equiv) was added Et_3N (6.5 mL, 46.6 mmol, 2.0 equiv), and the reaction mixture was stirred for 24 h at rt when TLC (solvent system B) indicated the reaction to be complete. The solvent was evaporated in vacuo, and the residue was taken up in EtOAc (200 mL) and washed successively with water (200 mL), 5% aqueous citric acid (4 × 60 mL), and 10% aqueous K_2CO_3 (2 × 100 mL), and the solvent was evaporated in vacuo to give the product as a colorless crystalline solid (3.89 g, 58%): mp 70–71 °C (EtOAc/isooctane 1:3); $[\alpha]_D$ = −89° (*c* 1.09, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.54 (br s, 1 H, CONH), 4.05 (m, 2 H), 3.75 (s, 3 H), 3.46 (m, 2 H), 2.06–2.44 (m, 2 H), 1.91 (m, 3 H), 1.47 (s, 9 H, *tBu*); CIMS MH+ ($C_{13}H_{22}N_2O_5$) requires 287, found 287. Anal. ($C_{13}H_{22}N_2O_5$): C, H, N.

(*S*)-(−)-Prolylglycine Methyl Ester [(*S*)-(−)-30]. Method E. (S)-(−)-**29** (2.6 g, 9.09 mmol) was dissolved in CF_3COOH (10 mL), and the solution was stirred at rt for 1 h when TLC (solvent system A) indicated the reaction to be complete. The reaction solvent was evaporated in vacuo to give (*S*)-(−)-**30**·CF_3COOH (2.73 g, quantitative) as a colorless oil. Attempts to convert this material to free (*S*)-(−)-**30** resulted in rapid cyclization to (*S*)-(−)-**31**. However, if conditions were maintained sufficiently cold (4 °C) and the base was isolated by partitioning between cold saturated K_2CO_3 solution and $CHCl_3$, then the product was sufficiently stable for analysis by ^{1}H NMR spectroscopy and CIMS. For purposes of further characterization, (*S*)-(−)-**30**·oxalate was crystallized from 2-propanol: mp 119–120 °C; $[\alpha]_D$ = −42° (*c* 1.1, MeOH); ^{1}H NMR ($CDCl_3$) δ 8.09 (br s, 1 H, CONH), 4.04 (d, J = 5.9 Hz, 2 H), 3.78 (dd, J = 5.1, 9.0 Hz, 1 H), 3.75 (s, 3 H), 2.90–3.08 (m, 2 H), 2.07–2.21 (m, 1 H), 1.89–2.01 (m, 1 H), 1.61–1.83 (m, 2 H), 1.63 (br s, 1 H, NH); CIMS MH+ ($C_8H_{14}N_2O_3$) requires 187, found 187. Anal. ($C_{10}H_{16}N_2O_7$): C, H, N. This intermediate was found to be stable as the oxalate salt.

(*S*)-(−)-1,4-Diazabicyclo[4.3.0]nonane-2,5-dione [(*S*)-(−)-31]. Method F. (*S*)-(−)-**30**·CF_3COOH (2.73 g, 9.09 mmol) (from 2.60 g, 9.09 mmol of (*S*)-(−)-**29** above) was dissolved in MeOH (50 mL) and treated with Et_3N (5.0 mL, 36 mmol, 4 equiv). The reaction mixture was boiled under reflux overnight or until complete by TLC (solvent system A). The solvent was evaporated in vacuo, and the oily residue was dissolved in hot 2-propanol (20 mL). Crystallization occurred spontaneously on cooling to rt to give (*S*)-(−)-**31** (0.91 g, 65%): mp 211–213 °C (lit.[24] mp 213–214 °C); $[\alpha]_D$ = −191° (*c* 1.71, H_2O); ^{1}H NMR ($CDCl_3$) δ 6.41 (br s, 1 H, NH), 4.10 (d, J_{gem} = 16 Hz, 2 H), 3.89 (dd, J_{gem} = 17 Hz, J = 4.4 Hz, 1 H), 3.51–3.71 (complex m, 2 H), 2.39 (m, 1 H), 1.82–2.17 (complex m, 3 H); CIMS MH+ ($C_7H_{10}N_2O_2$) requires 155, found 155. Anal. ($C_7H_{10}N_2O_2$): C, H, N.

(*S*)-(−)-1,4-Diazabicyclo[4.3.0]nonane [(*S*)-(−)-32]. Method G. (*S*)-(−)-**31** (0.91 g, 5.91 mmol) was added portionwise at ambient temperature to a stirred solution of $LiAlH_4$ in THF (24 mL of a 1.0 M solution, 24 mmol). The reaction mixture was boiled under reflux for 10 min when TLC (solvent system C) indicated the reaction to be complete. The solution was cooled to 0 °C and then treated dropwise with water (0.9 mL), 15% aqueous NaOH (0.9 mL), and finally water (2.7 mL). The mixture was stirred for 1 h and filtered. The filter cake was washed with a little cold THF (10 mL), and the combined filtrates and washings were evaporated in vacuo to give (*S*)-(−)-**32** as a colorless oil, bp 55 °C (5 mm). [lit.[24] bp 61–63 °C (8 mm)]. Treatment of a solution of the base in EtOH/2-propanol (1:1) with 48% HBr gave (*S*)-(−)-**32**·HBr (1.04 g, 61%) as colorless crystals: mp 234–236 °C; $[\alpha]_D$ = −4.45° (*c* 2.92, H_2O); ^{1}H NMR ($CDCl_3$) δ 2.92–3.16 (complex m, 4H), 2.84 (m, 1 H), 2.48 (m, 1 H), 2.06–2.18 (m, 2 H), 1.64–1.90 (complex m, 4 H), 1.24–1.45 (m, 1 H); CIMS MH+ ($C_7H_{14}N_2$) requires 127, found 127. Anal. ($C_7H_{16}Br_2N_2$): C, H, N.

3-[*N*-[2-(3,4-Dichlorophenyl)ethyl]formamido]quinuclidine (44). Method H. The free amine from **14**·fumarate (2.0 g, 3.77 mmol) (by partitioning with NH_3/$CHCl_3$) was dissolved in EtOCHO (50 mL) containing HCOOH (5 drops), boiled under reflux, and the solvent was evaporated in vacuo. The residue was dissolved in $CHCl_3$ (50 mL) washed with saturated $NaHCO_3$ (50 mL) and water (50 mL), and the solvent was evaporated in vacuo to give **44** as a colorless oil. This was purified by column chromatography on silica gel eluting with solvent system D to give pure **44** (1.23 g, quantitative) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 8.36 (s, 1 H, CHO), 7.38 (d, J = 8.2 Hz, 1 H), 7.32 (d, J = 2.1 Hz, 1 H), 7.08 (dd, J = 2.1, 8.2 Hz, 1 H), 3.61 (m, 2 H), 3.39 (m, 2 H), 3.15 (m, 2 H), 2.68–3.00 (complex m, 6 H), 1.46–1.96 (complex m, 4 H); CIMS MH+ ($C_{16}H_{20}Cl_2N_2O$) requires 327, found 327; HRMS (M+ calcd for $C_{16}H_{20}Cl_2N_2O$) 326.0953, found 326.0941.

3-Quinuclidone Oxime (45).[27a] To a stirred solution of 3-quinuclidone hydrochloride (75 g, 0.464 mol) and NH_2OH·HCl (38.7 g, 0.577 mol, 1.2 equiv) in EtOH (1000 mL) was added NaOAc·3H_2O (189.4 g, 1.39 mol, 3.0 equiv), and the reaction mixture was stirred overnight at rt when TLC (solvent system A) indicated complete reaction. The solvent was evaporated in vacuo, and the residue was dissolved in water (800 mL). K_2CO_3 was added to pH = 10 when a copious suspension of **45** (base) formed. The aqueous mixture was filtered, and the filter cake was washed (3×) with cold water and oven dried in vacuo to give 65.0 g (quantitative) of **45** as a colorless solid.[19] Crystallization from EtOH (300 mL) afforded **45** (52.0 g, 80%): mp 117–119 °C; ^{1}H NMR ($CDCl_3$) δ 8.93 (br s, 1 H, NOH), 3.66 (s, 2 H), 2.92 (m, 4 H), 2.59 (t, J = 0, 3.2 Hz, 1 H), 1.81 (m, 4 H); CIMS MH+ ($C_7H_{12}N_2O_2$) requires 141, found 141. Anal. ($C_7H_{12}N_2O_2$): C, H, N.

1,4-Diazabicyclo[3.2.2]nonan-3-one (46). **45** (10 g, 71.4 mmol) in a 250-mL round-bottom flask was treated with CF_3COOH (30 mL) with stirring. The solution became hot followed by an increase in viscosity as it cooled to rt. TLC (solvent system A) indicated the reaction to be 95% complete after 10 min at rt. After 1h, the reaction was complete. The reaction mixture was poured into a solution of K_2CO_3 (67 g) in water (200 mL) and extracted with $CHCl_3$ (4 × 200 mL). The combined organic extract was dried (Na_2SO_4), and the solvent was evaporated in vacuo to give **46**[27] (9.4 g, 94%) as a white crystalline solid. Recrystallization from hot 2-propanol (80 mL) afforded **46**[27] (7.90 g, 79%): mp 218–219 °C; ^{1}H NMR ($CDCl_3$) δ 8.40 (br s, 1 H, CONH), 3.66 (s, 2 H), 2.78–3.03 (m, 4 H), 2.59 (m, 1 H), 1.81 (m, 4 H); CIMS MH+ ($C_7H_{12}N_2O$) requires 141; found 141. Anal. ($C_7H_{12}N_2O$): C, H, N.

6,7-Dichloro-2-[[2-(1-pyrrolidinyl)ethyl]amino]tetralin (19). 6,7-Dichloro-2-tetralone[21] (820 mg, 3.8 mmol) was dissolved in 15 mL of absolute ethanol and added to a solution of 1-(2-aminoethyl)pyrrolidine (2.30 g, 20 mmol) in 25 mL of absolute ethanol containing glacial acetic acid (1.5 mL). The solution was stirred for 15 min at rt. $NaBH_3CN$ (960 mg, 15 mmol) was added in one portion, and the mixture was stirred for 48 h at room temperature under Ar. The mixture was evaporated under

reduced pressure, and the residue was dissolved in 1 M HCl (25 mL) and washed with diethyl ether (2 × 10 mL). The aqueous layer was basified with concentrated aqueous NH_3 and extracted with $CHCl_3$ (3 × 15 mL). The combined $CHCl_3$ extracts were washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was dissolved in 15 mL of ethanol and acidified with 48% HBr. The crystalline material (1.10 g) was collected and dissolved in 15 mL of boiling MeOH. After the solution was cooled to room temperature, pure **19**·HBr (1.00 g, 55% based on tetralone **54**) was obtained as a colorless microcrystals: mp >260 °C; ^{1}H NMR ($CDCl_3$) δ 7.16 (s, 1 H, ArH), 7.15 (s, 1 H, ArH), 2.98 (d, J = 4.4 Hz, 1 H), 2.81 (m, 2 H), 2.62 (t, J = 6.2 Hz, 2 H), 2.51 (m, 4 H), 2.05 (m, 2 H), 1.75 (m, 4 H); CIMS MH^+ ($C_{16}H_{22}Cl_2N_2$) requires 313, found 313. Anal. ($C_{16}H_{24}Br_2Cl_2N_2$): C, H, N.

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(31) The ^{1}H-NMR data of the compounds in Table IV taken from $CDCl_3$ solutions is as follows: **4** δ 7.34 (d, J = 8.4 Hz, 1 H), 7.30 (d, J = 2.0 Hz, 1 H), 7.04 (dd, J = 2.0, 8.4 Hz, 1 H), 2.75 (m, 2 H), 2.56 (m, 2 H), 2.35–2.69 (m, 8 H), 2.30 (s, 3 H); **5** δ 7.34 (d, J = 8.3 Hz, 1 H), 7.30 (d, J = 1.8 Hz, 1 H), 7.04 (dd, J = 1.8, 8.3 Hz, 1 H), 2.76 (m, 2 H), 2.40–2.63 (complex m, 10 H), 2.43 (q, J = 7.2 Hz, 2 H), 1.09 (t, J = 7.2 Hz, 3 H); **7** δ 7.34 (d, J = 8.2 Hz, 1H), 7.30 (d, J = 2.0 Hz, 1 H), 7.03 (dd, J = 2.0, 8.2 Hz, 1 H), 2.76 (t, J = 7.8 Hz, 2H), 2.40–2.64 (complex m, 10 H), 2.34 (t, J = 7.7 Hz, 2 H), 1.48 (m, 2 H), 1.31 (m, 2 H), 0.92 (t, J = 7.3 Hz, 3 H); **8** δ 7.34 (d, J = 8.2 Hz, 1 H), 7.30 (d, J = 1.9 Hz, 1 H), 7.04 (dd, J = 1.9, 8.2 Hz, 1 H), 2.76 (t, J = 7.9 Hz, 2 H), 2.40–2.66 (complex m, 10 H), 2.33 (t, J = 7.8 Hz, 2 H), 1.50 (m, 2 H), 1.20–1.38 (m, 4 H), 0.90 (t, J = 6.9 Hz, 3 H); **10** δ 7.34 (d, J = 8.3 Hz, 1 H), 7.30 (d, J = 2.0 Hz, 1 H), 7.03 (dd, J = 2.0, 8.3 Hz, 1 H), 2.93 (m, 4 H), 2.74 (m, 8 H), 1.78 (quintet, J_{app} = 6.0 Hz, 2 H); **11** δ 7.33 (d, J = 8.3 Hz, 1 H), 7.30 (d, J = 2.2 Hz, 1 H), 7.03 (dd, J = 2.2, 8.3 Hz, 1 H), 2.68–2.82 (complex m, 8 H), 2.64 (m, 4 H), 2.36 (s, 3 H, N*Me*), 1.82 (m, 2H); *S*-(–)-**12** δ 7.34 (d, J = 8.3 Hz, 1H), 7.30 (d, J = 2.0 Hz, 1 H), 7.04 (dd, J = 2.0, 8.3 Hz, 1 H), 3.00–3.12 (complex m, 3 H), 2.89 (dm, J = 7.8 Hz, 1 H), 2.73–2.81 (m, 2 H), 2.58–2.67 (m, 2 H), 2.30 (d, J = 7.6 Hz, 2 H), 2.00–2.22 (complex m, 2 H), 1.68–1.98 (complex m, 4 H), 1.42 (m, 1 H); **13** δ 7.34 (d, J = 8.3 Hz, 1 H), 7.30 (d, J = 2.0 Hz, 1 H), 7.04 (dd, J = 2.0, 8.3 Hz, 1 H), 2.81–2.91 (m, 2 H), 2.75 (m, 3 H), 2.54 (m, 2 H), 2.31 (d, J = 8.3 Hz, 2 H), 1.86–2.11 (complex m, 3 H), 1.48–1.82 (complex m, 5 H), 1.16–1.39 (m, 2 H); **14** δ 7.36 (d, J = 8.3 Hz, 1 H), 7.32 (d, J = 2.0 Hz, 1 H), 7.06 (dd, J = 2.0, 8.3 Hz, 1 H), 3.11 (ddd, J = 2.0, 8.8, 13 Hz, 1 H), 2.65–2.90 (complex m, 9 H), 2.35 (dm, J = 14 Hz, 1 H), 1.58–1.82 (complex m, 4 H), 1.46 (m, 1 H), 1.32 (m, 1 H); **15** δ 7.34 (d, J = 8.3 Hz, 1 H), 7.30 (d, J = 1.9 Hz, 1 H), 7.02 (dd, J = 1.9, 8.3 Hz, 1 H), 2.95 (ddd, J = 2.0, 8.4, 13 Hz, 1 H), 2.61–2.85 complex m, 6 H), 2.46–2.61 (complex m, 3 H), 2.25 (s, 3 H), 2.16 (m, 1 H), 1.93 (m, 1 H), 1.60–1.84 (complex m, 2 H), 1.43 (m, 1 H), 1.27 (m, 1 H); **16** δ 7.36 (d, J = 8.3 Hz, 1 H), 7.32 (d, J = 2.0 Hz, 1 H), 7.05 (dd, J = 2.0, 8.3 Hz, 1H), 3.11 (m, 1 H), 2.65–2.91 (complex m, 8 H), 2.36 (dm, J = 14 Hz, 1 H), 1.19–1.84 (complex m, 7 H); **17** δ 7.35 (d, J = 8.2 Hz, 1 H), 7.34 (d, J = 1.7 Hz, 1 H), 7.08 (dd, J = 1.7, 8.2 Hz, 1 H), 2.80 (m, 4 H), 2.60 (br s, 2 H), 2.46 (m, 4 H), 1.50–1.67 (complex m, 6 H), 1.21–1.50 (complex m, 11 H); **18** δ 7.32 (d, J = 8.1 Hz, 1 H), 7.29 (d, J = 2.0 Hz, 1 H), 7.02 (dd, J = 2.0, 8.1 Hz, 1 H), 2.63–2.71 (m, 2 H), 2.56–2.63 (m, 2 H), 2.49 (m, 4 H), 2.30 (s, 3 H), 2.25 (br s, 2 H), 1.04–1.69 (complex m, 16 H); **20** δ 7.16 (s, 1 H, Ar*H*), 7.15 (s, 1 H, Ar*H*), 2.36 (s, 3 H, NCH_3), 1.78 (m, 4 H), 1.61 (m, 2 H), 2.03 (m, 2 H), 2.50–2.90 (complex m, 11 H); **23** δ 7.41 (d, J = 8.3 Hz, 1 H), 7.35 (dd, J = 1.8 Hz, 1 H), 7.09 (dd, J = 1.8, 8.3 Hz, 1 H), 3.69 (s, 2 H), 3.33–3.68 (complex m, 8 H), 2.31 (t, J = 7.4 Hz, 2 H), 1.67 (quintet, J_{app} = 7.6 Hz, 2 H), 0.97 (t, J = 7.3 Hz, 3 H); **24** δ 7.41 (d, J = 8.3 Hz, 1 H), 7.35 (d, J = 1.6 Hz, 1 H), 7.09 (d, J = 8.3 Hz, 1 H), 3.69 (s, 2 H), 3.30–3.70 (complex m, 8 H), 2.34 (t, J = 8.0 Hz, 2 H), 1.45–1.80 (complex m, 4 H), 0.93 (t, J = 7.3 Hz, 3 H); **27** δ 7.35–7.42 (complex m, 2 H), 7.12 (dm, J = 8.0 Hz, 1 H), 3.68 (55% rotamer), 3.67 (45% rotamer) (s, 2 H), 3.64 (m, 2 H), 3.56 (55% rotamer) (t, J = 6.3 Hz), 3.50 (45% rotamer) (t, J = 5.4 Hz) (2 H), 2.95 (55% rotamer) (t, J = 5.4 Hz), 2.90 (45% rotamer) (t, J = 5.4 Hz) (2 H), 2.85 (t, J = 5.8 Hz, 2H), 1.80 (quintet, J = 5.7 Hz, 2H); (*S*)-(–)-**33** δ 7.39 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.09 (d, J = 2.0, 7.9 Hz, 1H), 4.67 (dd, J_{gem} = 39 Hz, J = 13 Hz, 1H), 3.81 (dd, J_{gem} = 44, J = 13 Hz, 1H), 3.68 (d, J = 3.8 Hz, 2H), 2.73–3.28 (complex m, 3H), 1.93–2.48 (complex m, 3H), 1.64–1.93 (complex m, 4H), 1.32–1.48 (m, 1H); **35** δ 6.60 (br s, 1H, CON*H*), 4.81 (m, 1H), 3.82–4.35 (complex m, 4H), 3.76 (s, 3H, OMe), 2.89 (m, 1H), 2.32 (m, 1H), 1.33–1.72 (complex m, 4H), 1.49 (s, 9H, *tert*-Bu); **36** δ 7.29 (br s, 1H, N*H*CO), 4.05 (d, J = 5.6 Hz, 2H), 3.76 (s, 3H, $COOCH_3$), 3.26, (m, 1H), 3.06 (dm, J_{gem} = 12 Hz, 1H), 2.70 (m, 1H), 1.97 (m, 1H), 1.80 (m, 1H), 1.33–1.67 (complex m, 5H); **37** δ 6.11 (br s, 1H, NH), 4.70 (dm, J_{gem} = 13 Hz, 1H), 4.05 (br s, 2H), 3.85 (dm, J_{gem} = 11 Hz, 1H), 2.53 (m, 1H), 2.36 (m, 1H), 2.02 (m, 1H), 1.74 (m, 1H), 1.40–1.68 (complex m, 3H); **38** δ 2.94 (m, 2H), 2.75–2.84 (m, 2H), 2.72 (dm, J = 11 Hz, 1H), 2.50 (dd, J = 10, 12 Hz, 1H), 2.00–2.20 (complex m, 2H), 1.71–1.89 (complex m, 2H), 1.54–1.69 (complex m, 3H), 1.49 (m, 1H), 1.11–1.38 (complex m, 2H); **39** δ 7.39 (d, J = 8.3 Hz, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.09 (d, J = 8.3 Hz, 1H), 4.48 (m, 1H), 3.66 (br s, 2H), 3.64 (m, 1H), 3.29 and 2.87 (m, 1H), 2.64–2.85 (complex m, 2H), 2.41 and 2.09 (m, 1H), 1.93–2.06 (complex m, 2H), 1.40–1.87 (complex m, 5H), 1.12–1.36 (complex m, 2H); *S*-(–)-**40** δ 4.23 (br s, 1 H, N*H*), 3.69 (s, 3H), 3.30–3.65 (complex m, 4 H), 2.54 (t, J = 6.1 Hz, 2 H), 2.02–2.40 (complex m, 2 H), 1.79–1.92 (m, 3 H), 1.45 (s, 9H, *t*-Bu); *S*-(–)-**41** δ 7.97 (br s, 1H, CON*H*), 3.71 (m, 1H), 3.70 (s, 3H), 3.51 (dt, J = 6.3, 6.3 Hz, 2H), 2.95–3.05 (m, 1H), 2.83–2.93 (m, 1H), 2.54 (t, J = 6.3 Hz, 2H), 2.05–2.19 (m, 1H), 1.83–1.95 (m, 1H), 1.76 (br s, 1H, N*H*), 1.62–1.76 (m, 2H); **43** δ 7.43 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 2.0 Hz, 1H), 7.13 (dd, J = 2.0, 8.3 Hz, 1H), 5.60 (br s, 1H, CON*H*), 3.94 (m, 1H, C*H*NHCO), 3.51 (s, 2H), 3.32 (m, 1H), 2.80 (m, 4H), 2.40 (dm, J = 14 Hz, 1H), 1.81–1.92 (complex m, 2H), 1.58–1.69 (m, 1H), 1.37–1.55 (m, 2H); **47** δ 3.02–3.25 (m, 1H), 2.66–3.02 (complex m, 3H), 2.59 (m, 1H), 2.43 (m, 1H), 2.25–2.40 (m, 1H), 1.87 (m, 1H), 1.04–1.77 (complex m, 6H); **48** δ 7.43 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 2.1 Hz, 1H), 7.13 (dd, J = 2.1, 8.3 Hz, 1H), 5.52 (br s, 1H), 3.94 (m, 1H), 3.51 (s, 2H), 3.32 (m, 1H), 2.67–2.91 (m, 4H), 2.37 (ddd, J = 2.0, 4.9, 14 Hz, 1H), 1.88 (q, J_{app} = 3.1 Hz, 1H), 1.59–1.68 (m, 2H), 1.45 (m, 2H); **51** δ 2.68 (s, 2H), 2.57 (t, J = 5.0 Hz, 4H), 1.22–1.69 (complex m, 18 H); **52** δ 7.45 (d, J = 8.1 Hz, 1H), 7.38 (d, J = 1.5 Hz, 1H), 7.12 (dd, J = 1.5, 8.1 Hz, 1H), 3.54 (s, 2H), 3.27 (d, J = 4.2 Hz, 2H), 2.35 (m, 4H), 1.50–1.67 (complex m, 4H), 1.00–1.48 (complex m, 12 H); **53** (major 80% rotamer) δ 8.22 (s, 1H, C*H*O), 7.42 (d, J = 8.2 Hz, 1H), 7.32 (d, J = 2.0 Hz, 1H), 7.00 (dd, J = 2.0, 8.2 Hz, 1H), 3.40–4.20 (complex m, 10 H), 3.25 (m, 2 H), 2.87 (t, J = 6.9 Hz, 2 H), 2.60 (m, 1 H), 1.20–2.05 (complex m, 12 H); **55** δ 8.21 (60%) and 8.16 (40%) (s, 1 H, C*H*O), 7.20–7.14 (m, 2 H, Ar*H*), 4.32 (40%) and 3.70 (60%) (m, 1 H), 3.60 (m, 1 H), 3.36 (t, 1 H), 2.90 (complex m, 4 H), 2.66 (q, 2 H), 2.55 (m, 4 H), 2.00 (m, 4 H), 1.78 (m, 4 H).