# Novel 1-Phenylpiperazine and 4-Phenylpiperidine Derivatives as High-Affinity σ Ligands

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σ receptors may represent an exciting new approach for the development of novel psychotherapeutic agents. Unfortunately, many of the commonly used σ ligands lack selectivity (e.g., many bind at phencyclidine or dopamine receptors) or suffer from other serious drawbacks. Recently, we described a series of 2-phenylaminoethanes that bind at σ receptors with high affinity and selectivity. Because there is evidence that 1-phenylpiperazines can structurally mimic the 2-phenylaminoethane moiety, we prepared a series of 1-phenylpiperazines and related analogues and incorporated structural features already shown to enhance the σ binding of the 2-phenylaminoethanes. Several of these derivatives bind at σ receptors with high affinity ($K_i$ = 1–10 nM) and lack appreciable affinity for phencyclidine and dopamine receptors. In as much as certain of these agents structurally resemble the high-affinity, but nonselective, σ ligand haloperidol, and because they bind with 10 times the affinity of haloperidol, we have apparently identified what appears to be the primary σ pharmacophore of that agent.

σ receptors represent an exciting new area of research that is attracting attention for their possible involvement in various psychiatric disorders.[1,2] Certain classical neuroleptics, such as the butyrophenones and the phenothiazines,[3,4] and a variety of nonclassical neuroleptics[4,5] have been demonstrated to bind at σ receptors. Members of several classes of antidepressants, such as the tricyclic antidepressants,[6] monoamine oxidase inhibitors,[6,7] and serotonin uptake inhibitors,[8] also bind at σ sites. At this time, however, it is unclear whether these agents produce any of their therapeutic effects via a σ mechanism. σ ligands may also have indirect effects; for example, they may modulate *N*-methyl-D-aspartate function[9] and glutamate release,[10] perhaps via interaction at polyamine recognition sites,[11] and dopaminergic function.[12] σ receptors have also been implicated in certain physiological functions such as colonic motility,[13] intestinal ion transport,[14] synthesis of the pineal hormone melatonin,[15] and possibly in motor activity[16] and dystonic disorders.[17] Much of the present uncertainty regarding a precise role for σ receptors stems from a lack of high-affinity σ-selective ligands.

Several different types of agents have been demonstrated to bind at putative σ receptors, and the most commonly employed include σ-opiates such as *N*-allylnormetazocine (NANM, SKF 10,047) and cyclazocine (1, R = $CH_2CH{=}CH_2$ and $CH_2$-c-$C_3H_5$, respectively), the guanidine derivative 1,3-di-*o*-tolylguanidine (DTG; 2), the 3-phenylpiperidine (+)-3-(3-hydroxyphenyl)-*N*-(1-propyl)piperidine [(+)-3-PPP; 3], and certain butyrophenone neuroleptics such as haloperidol (4). Unfortunately, many of these agents suffer from serious drawbacks that limit their utility as tools to investigate σ pharmacology. The σ opiates 1 possess only modest affinity for σ sites and, in addition, bind with high affinity at phencyclidine (PCP) sites.[1,3] DTG (2) has been shown to produce PCP-like stimulus effects in rats.[18] 3-PPP (3) and many of its analogues possess considerable dopaminergic character.[19] Although haloperiodol is reported to be one of the highest affinity σ agents, it lacks selectivity and binds at D2 dopamine receptors with an affinity comparable to its affinity for σ sites.[2] Other butyrophenone neuroleptics, such as the arylpiperazine azaperone (5),[3] also bind at σ sites but these agents typically bind with even higher affinity at dopamine receptors. Recently, a new group of σ ligands, diaminocyclohexane derivatives, has been shown to bind with much greater selectivity.[20]

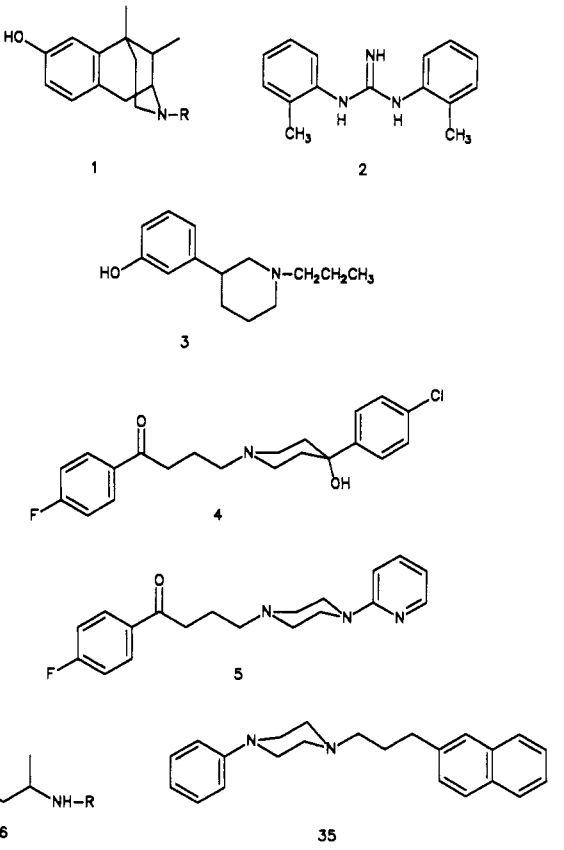


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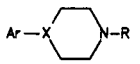
**Table I.** $\sigma$ Receptor Affinities of Some Simple Piperazine Derivatives




| no. | Ar | X | R | $\sigma$ $K_i$, nM[a] |
|---|---|---|---|---|
| 7 | phenyl | N | H | 11440 (380) |
| 8 | benzoyl | N | H | 11360 (1750) |
| 9 | 3-Cl-phenyl | N | H | 6150 (430) |
| 10 | 3-$CF_3$-phenyl | N | H | 1340 (340) |
| 11 | 4-Cl-phenyl | N | H | 1150 (150) |
| 12 | 2-OMe-phenyl | N | H | 11200 (1560) |
| 13 | 4-OMe-phenyl | N | H | 5850 (240) |
| 14 | 1-naphthyl | N | H | 2720 (450) |
| 15 | 2-naphthyl | N | H | 550 (90) |
| 16 | 2-pyrimidinyl | N | H | >10000 |
| 17 | benzyl | N | H | 10480 (1150) |
| 18 | 2-OMe-phenyl | COH | H | 14280 (4660) |
| 19 | phenyl | CH | H | 1980 (14) |
| 20 | phenyl | N | $CH_2CH_2CH_3$ | 74 (4) |

[a] $K_i$ value followed by ±SEM in parentheses. $K_i$ values represent duplicate or triplicate determinations.

We have recently demonstrated that *N*-(3-phenylpropyl)-1-phenyl-2-aminopropane (PPAP; **6**, R = $CH_2CH_2CH_2C_6H_5$) binds at $\sigma$ sites with high affinity ($K_i \approx 20$ nM and about 20 times the affinity of the $\sigma$-opiate NANM) and selectivity,[21,22] and have proposed that amine-substituted 2-phenylaminoethane constitutes the primary pharmacophore of the $\sigma$ opiates.[22] This moiety is also present in the 3-phenylpiperidines, such as 3-PPP (**3**), and may constitute a common pharmacophore. In the course of our investigations on other neurotransmitter systems, we have previously shown that 4-phenylpiperazines occasionally serve as biological mimics of the phenylaminoethane moiety;[23] therefore, the possibility exists that appropriately substituted 1-phenylpiperazines might mimic $\sigma$-related phenylaminoethanes and also bind at $\sigma$ sites in a manner similar to that of **6**. Some encouragement for this concept was derived from subsequent reports that piperazine derivatives such as azaperone (**5**)[3] and BMY 14802 ($\alpha$-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazinebutanol)[24] bind with modest affinity at $\sigma$ receptors. Our investigation began with an evaluation of several simple 1-phenylpiperazine derivatives in order to (i) obtain their $\sigma$ affinity ($K_i$ values), (ii) formulate structure–affinity relationships, and (iii) determine how various substituents influence binding. Many of these compounds (i.e., those shown in Table I) were already on hand from previous studies and offered a convenient starting point. Once these studies were accomplished, terminal amine substituents we had previously shown to be important for binding in the **6** series[21] were incorporated into the simple phenylpiperazine derivatives.

## Chemistry

Most of the target compounds were readily prepared in two or three steps (Table II). For the most part, the syntheses involved acylation of a phenylpiperazine or phenylpiperidine with the appropriate acyl halide followed by reduction of the resulting amide with a $BH_3$–$Me_2S$ mixture (method A), $LiAlH_4$ (method B), or $AlH_3$ (method C). In several instances, a phenylpiperidine was reductively alkylated by treatment with 3-phenylpropionaldehyde under conditions of catalytic hydrogenation (method D). Other methods of preparation included formation of a piperidine ring by aminoalkylation of an $\alpha$-methylstyrene using a method developed by Schmidle and Mansfield[25,26] (method E), and acylation of a pre-


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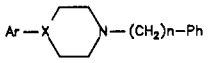
**Table II.** Physicochemical and $\sigma$ Binding Properties of Piperidine and Piperazine Analogues




| no. | Ar | X | n | prep[a] | | | mp, °C | formula[b] | $\sigma$ $K_i$, nM[c] |
|---|---|---|---|---|---|---|---|---|---|
| 21 | 3-Cl-phenyl | N | 2 | A | 40 | B | 197–198 | $C_{18}H_{21}N_2 \cdot HCl$[d] | 10.5 (2.6) |
| 22 | 3-$CF_3$-phenyl | N | 2 | A | 30 | B | 200 dec | $C_{19}H_{21}F_3N_2 \cdot HCl$[e] | 7.5 (1.4) |
| 23 | phenyl | N | 3 | B | 50 | P | 178–180 | $C_{19}H_{24}N_2 \cdot HCl$[f] | 6.7 (0.7) |
| 24 | 3-Cl-phenyl | N | 3 | A | 67 | B | 168–169 | $C_{19}H_{23}ClN_2 \cdot HCl$[d] | 19.2 (1.0) |
| 25 | 4-Cl-phenyl | N | 3 | C | 40 | E | 196–197 | $C_{19}H_{23}ClN_2 \cdot HCl$[g] | 2.9 (0.2) |
| 26 | phenyl | N | 4 | B | 45 | E | 208–210 | $C_{20}H_{26}N_2 \cdot 2HCl$[b,h] | 2.6 (0.2) |
| 27 | 3-$CF_3$-phenyl | N | 4 | B | 62 | E | 148–149 | $C_{21}H_{25}F_3N_2 \cdot HCl$[j] | 5.4 (1.2) |
| 28 | phenyl | CH | 3 | D | 58 | E | 217–218[i] | | 1.1 (0.2) |
| 29 | phenyl | CH | 4 | B | 28 | E | 223–225 | $C_{21}H_{27}N \cdot HCl$[j] | 0.8 (0.1) |
| 30 | phenyl | CH | 5 | B | 46 | E | 188–189 | $C_{22}H_{29}N \cdot HCl$[k] | 0.9 (0.1) |
| 31 | phenyl | COH | 3 | D | 90 | E | 207–209 | $C_{20}H_{25}NO \cdot HCl$ | 3.0 (0.3) |
| 32 | 4-Cl-phenyl | C= | 4 | E | 35 | E | 162–164 | $C_{25}H_{28}ClNO_4$[l] | 4.1 (2.0) |
| 33 | 2-naphthyl | N | 3 | B | 61 | E | 213–214 | $C_{23}H_{26}N_2 \cdot HCl$ | 2.8 (0.1) |
| 34 | benzoyl | N | 4 | F | 50 | E | 217–218 | $C_{21}H_{26}N_2O \cdot HCl$ | 125 (17) |
| 35 | | | | | | | | | 4.0 (1.4) |
| 4 | (haloperidol) | | | | | | | | 10.4 (3.8) |

[a] Preparation = prep. First column is method (see Experimental Section), second is % yield, and third is recrystallization solvent: A = absolute EtOH, B = 2-butanone, E = absolute EtOH/anhydrous $Et_2O$, P = 2-propanol. [b] Empirical formula; all compounds analyzed within 0.4% of theory for C, H, and N. Compound **26** has been previously reported, but due to confusion about the salt (i.e., mono- or dihydrochloride), it was submitted for Cl analysis. [c] $K_i$ value is followed by ±SEM. Each $K_i$ value represents two to nine determinations. [d] Crystallized with 1 mol of $H_2O$. [e] Crystallized with 0.5 mol of $H_2O$. [f] Crystallized with 1.25 mol of $H_2O$. [g] Compound **25**, though mentioned in the literature (ref 29), has not been previously characterized. [h] Crystallized with 5 mol of $H_2O$; lit.[30] mp 205 °C. [i] Lit.[31] mp 214–216 °C. [j] Crystallized with 0.2 mol of $H_2O$. [k] Crystallized with 0.1 mol of $H_2O$. [l] Compound **32** represents a hydrogen maleate salt.

formed 1-(arylalkyl)piperazine (method F).

## Results and Discussion

To initiate this investigation, we first examined the binding affinities of several simple 1-phenylpiperazines. 1-Phenylpiperazine (**7**) itself binds at $\sigma$ receptors with low affinity ($K_i$ = 11 440 nM; Table I) and with approximately 5 times the affinity of the parent 1-phenyl-2-aminopropane (**6**, R = H; $K_i$ = 46 400 nM).[21] Realizing that 1-phenyl-2-aminopropane is a primary amine, that 1-phenylpiperazine is a secondary amine, and that simple N-methylation of 1-phenyl-2-aminopropane to the secondary amine **6** (R = $CH_3$; $K_i$ = 8320 nM) enhances affinity by about 5-fold,[21] there is good agreement between the affinities of the parent structures for the two series of compounds. 1-Benzoylpiperazine (**8**) binds with an affinity ($K_i$ = 11 360 nM; Table I) comparable to that of 1-phenylpiperazine (**7**). Next, we examined a small series of 1-phenylpiperazine derivatives (already on hand as a result of other investigations) in order to determine whether or not aromatic substitution would have any significant affect on affinity. It is fairly evident from the results presented in Table I that most aromatic substituents have little effect. With the exception of the incorporation of a 4-chloro group (i.e., **11**; $K_i$ = 1150 nM) or a 3-trifluoromethyl group (i.e., **10**; $K_i$ = 1340 nM), none of the other substituted simple piperazines (i.e., **9**–**13**) displayed more than twice the affinity of the parent compound. Replacement of the phenyl portion of **7** with a 2-naphthyl group resulted in a 20-fold enhanced affinity (**15**; $K_i$ = 550 nM), whereas replacement by 1-naphthyl (i.e., **14**) had less of an effect. Replacement of the piperazine 1-position nitrogen atom with a C(OH) group appears to have no effect on affinity (i.e., comparing **12** with **18**), whereas replacement by a methylene group (comparing 4-phenylpiperidine (**19**; $K_i$ = 1980 nM) with 1-phenylpiperazine (**7**) resulted in about a 6-fold increase in affinity.

N-Alkylation of the 1-phenyl-2-aminopropanes results in dramatic enhancement of $\sigma$ affinity.[21,22] Likewise, N-alkylation enhances the affinity of 1-phenylpiperazine. For example, incorporation of an *n*-propyl group, as in 1-phenyl-4-*n*-propylpiperazine (**20**; $K_i$ = 74 nM), results in increased affinity. Paralleling the approximately 1700-fold increase observed upon going from 1-phenyl-2-aminopropane (**6**, R = H) to PPAP (**6**, R = $CH_2CH_2CH_2C_6H_5$), incorporation of an *N*-(3-phenylpropyl) group (i.e., **23**; $K_i$ = 6.7 nM) also enhances the $\sigma$ affinity of 1-phenylpiperazine by 1700-fold. On the basis of the data shown in Table II, the 3- and 4-chloro derivatives of **23** were prepared and examined; the 3-chloro derivative **24** binds with approximately one-third the affinity of the parent compound **23**, whereas the 4-chloro derivative **25** binds with about twice the affinity of **23**. Shortening the side chain from three to two methylene units (i.e., **21** and **22**) results in little change in affinity, as does lengthening the chain from three to four methylene units (i.e., **26** and **27**).

The finding that the piperidine derivative **19** (Table I) binds with a several-fold greater affinity than the corresponding 1-phenylpiperazine (**7**) prompted the examination of several additional compounds. The tetrahydropyridyl analogue **32** binds with high affinity ($K_i$ = 4.1 nM). Replacement of the N1 piperazine nitrogen atom of **23** ($K_i$ = 6.7 nM) with a C(OH) group (i.e., **31**; $K_i$ = 3.0 nM) doubles affinity. However, replacement of that same nitrogen atom by a CH group (**28**; $K_i$ = 1.1 nM) results in a 6-fold increase in affinity. This increase parallels the increase observed when comparing **7** and **19**. Extending the side chain of **28** from three to either four (**29**; $K_i$ = 0.8 nM) or five (**30**; $K_i$ = 0.9 nM) methylene units has relatively little additional effect. It should be noted, however, that as with the 1-phenyl-2-aminopropane and 1-phenylpiperazine series, the affinity of the *N*-(3-phenylpropyl) analogue **28** is 1700-fold higher than that of the parent 4-phenylpiperidine (**19**).

Because increased lipophilicity of the terminal amine substituent seems to enhance the affinity of 1-phenylpiperazines, we evaluated the *N*-(2-naphthylpropyl) ana-

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logue of **23** (i.e., **35**; $K_i$ = 4.0 nM); however, this compound was found to bind with an affinity similar to that of **23** ($K_i$ = 6.7 nM). 1-Benzoylpiperazine (**8**) binds at $\sigma$ receptors with low affinity ($K_i$ > 11 360 nM). Nevertheless, because 1-phenylpiperazine also binds with low affinity, we prepared the *N*-(4-phenylbutyl) derivative of **8** (**34**; $K_i$ = 125 nM), which binds with only 100 times the affinity of the parent piperazine **8** and about one-fiftieth the affinity of **26**. It would appear that incorporation of the *N*-(phenylalkyl) group has different effects on the affinity of 1-benzoylpiperazine relative to 1-phenylpiperazine and 4-phenylpiperidine, suggesting that the former may bind in a manner that differs somewhat from that of the latter two.

While our studies were in progress, Largent and coworkers suggested that 3- and 4-phenylpiperidines constitute important pharmacophores at $\sigma$ binding sites.[3] Although considerable work has been done on 3-phenylpiperidine derivatives,[19,27] relatively little has been published on 4-phenylpiperidines. The results of the present study would tend to support the concept that 4-phenylpiperidines are important pharmacophores. Nevertheless, early reports led to molecular modeling studies involving certain phenylpiperidines and related compounds[28] that have resulted in hypotheses concerning a requirement for (or, at least, the importance of) electronegative substituents in the aromatic ring. For the most part, however, analogues lacking these electronegative substituents were not included in those studies. The results of the present investigation (as well as results of studies on analogues of **6**)[22] would suggest that although these electronegative substituents may be involved in binding, their role is minimal. For example, introduction of a 3-chloro group or a 4-chloro group enhances the affinity of 1-phenylpiperazine (**7**) by 2-fold and 10-fold, respectively. However, for the *N*-(3-phenylpropyl) derivatives, incorporation of a 3-chloro group (i.e., **24**) reduces affinity by 3-fold, whereas incorporation of the 4-chloro group (i.e., **25**) increases affinity by only 2-fold. These aromatic substituents seem to have a less pronounced effect on the N-substituted derivatives than on their N-unsubstituted parent. Likewise, replacing the phenyl group of 1-phenylpiperazine (**7**) with a 2-naphthyl group increases affinity by 20-fold, whereas the naphthyl analogue **33** possesses only twice the affinity of its phenyl counterpart **23**. The above results indicate that either (a) the simple phenylpiperazines are binding in a manner that is different from that of their N-substituted analogues, (b) the phenylpiperazines are behaving in a manner different from those compounds previously examined, or (c) the N substituent has a much more pronounced effect that overshadows the smaller effect of the aromatic substituents.

**Table III.** Binding Profiles for Selected Examples

| no. | $IC_{50}$, nM[a] D1 | D2 | PCP |
|---|---|---|---|
| **26** | 2820 (±450) | 45 (±10) | >10000 |
| **28** | >10000 | 335 (±40) | >10000 |
| **29** | >10000 | 165 (±40) | >10000 |
| **30** | >10000 | 210 (±45) | >10000 |
| **31** | >10000 | 1250 (±60) | >10000 |
| **35** | 3000 (±40) | 160 (±30) | >10000 |
| **4** (halo) | 337 (±95) | 5.5 (±1.5) | ND |

[a] $IC_{50}$ values are followed by ±SEM. Values represent duplicate or triplicate determinations except for haloperidol where $n$ = 3–5. ND = not determined. Using radioligand binding assay techniques identical to those reported in the previous article in this series,[22] compounds **31** and **35** were additionally examined at $\beta$-adrenergic, muscarinic, quasqualate, and kainate binding sites and were found, in duplicate determinations, to bind with low affinity ($IC_{50}$ > 10 000 nM).

One of the highest affinity $\sigma$ ligands and one involved in many of the molecular modeling studies is the piperidine derivative haloperidol (**4**). Although it has been assumed that certain structural features found in this molecule may be consequential to binding, the actual role of these substituents has not been specifically examined. It was not our intention to examine the structure–affinity relationships of haloperidol analogues; however, the results of the present study suggest that the previously published models may be in need of revision. For example, compound **29** may be viewed as an unadorned analogue of haloperidol that lacks (a) the aromatic fluoro group, (b) the carbonyl oxygen, (c) the benzylic hydroxyl group, and (d) the aromatic chloro group; and yet, **29** ($K_i$ = 0.8 nM) binds with more than 10 times the affinity of haloperidol ($K_i$ = 10.4 nM). Indeed, **29** is one of the highest affinity $\sigma$ ligands reported to date. Due to the structural similarity between **29** and haloperidol (**4**), it must be concluded that certain of the substituents in haloperidol actually detract from binding. A full understanding of the contribution of the other substituents awaits a detailed structure–affinity relationship investigation. Nevertheless, due to the higher affinity of **29** relative to haloperidol (**4**), it would appear that an N-substituted 4-phenylpiperidine is not only important for binding at $\sigma$ receptors[3] but that it actually constitutes the primary $\sigma$ pharmacophore of haloperidol (present investigation). Furthermore, because **28** and **30** also bind with 10 times the affinity of **4**, the four-carbon chain separating the phenyl group from the piperidine ring is not an absolute requirement for binding. Future molecular modeling studies will need to take these factors into account.

Because various $\sigma$ ligands bind at dopamine D1 and D2 receptors and at PCP binding sites (see introduction), six representative high-affinity compounds were selected for further evaluation (Table III). None of the compounds bind at PCP sites and all of the compounds bind at D1 and D2 sites with affinities significantly lower than that of haloperidol (**4**). Comparing the piperazine derivative **26** with its corresponding piperidine **29**, it is clear that the piperidine analogue binds with a lower affinity at D1 and D2 dopamine receptors. Compounds **28–30** are piperidine derivatives that vary only with regard to their chain lengths; apparently, alteration of this chain length from three to five methylene groups has little effect on binding at dopamine receptors or PCP sites (Table III). Nevertheless, these compounds bind at $\sigma$ receptors with greater than a 150-fold (D2 dopamine) to 10 000-fold (D1 dopamine and PCP) selectivity. The benzylic hydroxy analogue **31** binds with a profile similar to that of its corresponding piperidine derivative **28** except that it possesses

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a 4-fold lower affinity for D2 dopamine receptors. IC50 values for haloperidol binding at D1 and D2 receptors are provided for purpose of comparison (Table III).

## Summary

Previous investigators have demonstrated that piperazine and piperidine derivatives bind at $\sigma$ receptors and have suggested that 4-phenylpiperidines may constitute an important structural moiety for interaction at these sites. We have shown in the present study that 1-phenylpiperazine, 4-phenylpiperidine, and simple aromatic-substituted derivatives thereof bind at $\sigma$ receptors with rather low affinity (Table I), but that modification of the terminal amine substituent so as to mimic the terminal amine substituents of **6** can enhance affinity by more than 10000-fold. The 4-phenylpiperidine derivatives bind at $\sigma$ receptors with about 6 times the affinity of the corresponding 1-phenylpiperazines, and benzylic hydroxylation, although tolerated, does not enhance $\sigma$ affinity. Finally, removal of all the electronegative substituents of haloperidol results in a 10-fold increase in affinity; these findings provide information on a possible pharmacophore for haloperidol-type compounds and question the significance of previously published $\sigma$ binding models that suggest that the presence of such electronegative substituents is important for binding.

## Experimental Section

**Chemistry.** Proton magnetic resonance spectra were obtained with a JEOL FX90Q spectrometer with tetramethylsilane as an internal standard. Spectral data are consistent with assigned structures. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab and values are within 0.4% of theory. Experimental details below illustrate one of the methods (A–F) described in Table II.

**1-[3-(Trifluoromethyl)phenyl]-4-(2-phenylethyl)-piperazine Hydrochloride (22). Method A.** Phenylacetyl chloride (0.7 g, 4.3 mmol) in a 8 mL of dry THF was added in a dropwise manner to a stirred solution of freshly distilled 1-[3-(trifluoromethyl)phenyl]piperazine (1.0 g, 4.3 mmol) and $Et_3N$ (0.4 g, 4.3 mmol) in dry THF at 0 °C. The reaction mixture was allowed to warm to room temperature with continued stirring (2 h). The solid was removed by filtration, and the filtrate was evaporated under reduced pressure to afford a clear oil. An $Et_2O$ (100 mL) solution of the oil was washed with 5% HOAc (2 × 100 mL) and dried ($MgSO_4$), and the solvents were removed at reduced pressure to afford a clear oil that solidified on standing to give 1.1 g (73%) of the amide: mp 75–77 °C. A solution of the amide (0.57 g, 1.6 mmol) in dry THF (25 mL) was added in a dropwise manner to a stirred solution of $BH_3$–$Me_2S$ complex (15 mL of a 2.0 M solution in THF; 30 mmol) in 20 mL of THF. The reaction mixture was allowed to stir at room temperature under an $N_2$ atmosphere for 48 h and was then quenched by the addition of 25 mL of a saturated solution of HCl gas in MeOH and evaporated to a white residue. The residue was dissolved in MeOH (50 mL) and again evaporated to dryness. Concentrated HCl (10 mL) was added, and the solvent was evaporated to yield a white residue. Recrystallization from 2-butanone afforded 0.18 g (30%) of **22**: mp 200 °C dec.

**1-Phenyl-4-(3-phenylpropyl)piperazine Hydrochloride (23). Method B.** Hydrocinnamoyl chloride (1.5 mL, 0.01 mol) in THF (10 mL) was added dropwise to a stirred solution of 1-phenylpiperazine (1.5 mL, 0.01 mol) and $Et_3N$ (1.4 mL, 0.01 mol) in THF (40 mL). The reaction mixture was allowed to stir for 2 h and set aside overnight. The mixture was filtered and the solid material was washed with THF (ca. 30 mL). The combined filtrate and washings were evaporated under reduced pressure, and the oily residue was dissolved in $Et_2O$ (40 mL), washed with $H_2O$ (2 × 20 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give a pale yellow oil of the amide intermediate in 70% yield. A solution of the amide (2.0 g, 7 mmol) in anhydrous $Et_2O$ (30 mL) was added dropwise at 0 °C to a stirred suspension of $LiAlH_4$ (1.0 g, 25 mmol) in anhydrous $Et_2O$ (30 mL). After complete addition, the reaction mixture was heated at reflux with stirring overnight and cooled to 0 °C, and excess $LiAlH_4$ was decomposed by addition of few drops of 30% NaOH. The reaction mixture was filtered and the solid material was washed with $Et_2O$ (ca. 30 mL). The combined filtrate and washings were washed with $H_2O$ (30 mL), dried ($MgSO_4$), and saturated with HCl gas to give a white solid hydrochloride salt; recrystallization from 2-propanol gave a 50% yield of compound **23**: mp 178–180 °C.

**1-(4-Chlorophenyl)-4-(3-phenylpropyl)piperazine Hydrochloride (25). Method C.** Hydrocinnamoyl chloride (1.0 mL, 6.5 mmol) in THF (10 mL) was added dropwise to a stirred solution of 1-(4-chlorophenyl)piperazine dihydrochloride (1.7 g, 6.5 mmol) and $NEt_3$ (2.8 mL, 20 mmol) in THF (40 mL). The reaction mixture was allowed to stir overnight and filtered, and the solid material was washed with THF (ca. 30 mL). The combined filtrate and washings were evaporated under reduced pressure, and the oily residue was dissolved in $Et_2O$ (40 mL), washed with $H_2O$ (2 × 20 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give a solid product (mp 112–113 °C) of the amide intermediate. A solution of $AlH_3$ in anhydrous $Et_2O$ was prepared by addition of $LiAlH_4$ (2.5 g, 66 mmol) to a stirred solution of $AlCl_3$ (2.9 g, 22 mmol) in anhydrous $Et_2O$ (50 mL). Immediately thereafter, a solution of the above amide (0.73 g, 22 mmol) in a mixture of anhydrous $Et_2O$ (25 mL) and dry THF (5 mL) was added dropwise with stirring. The reaction mixture was allowed to stir overnight at room temperature and then heated gently at reflux for 3 h. The reaction flask was cooled in an ice bath, and excess hydride was decomposed by addition of wet THF (5 mL) and 2% NaOH solution (5 mL). The residual oil was dissolved in $Et_2O$ (50 mL), washed with $H_2O$ (2 × 30 mL), dried ($MgSO_4$), and saturated with HCl gas. The hydrochloride salt was collected by filtration, dried, and recrystallized from an absolute EtOH–$Et_2O$ mixture to afford 0.28 g (40%) of **25** as white crystals: mp 196–197 °C.

**4-Hydroxy-4-phenyl-1-(3-phenylpropyl)piperidine Hydrochloride (31). Method D.** A mixture of 4-hydroxy-4-phenylpiperidine (0.35 g, 2 mmol) and hydrocinnamaldehyde (0.27 g, 2 mmol) in 95% EtOH (20 mL) was hydrogenated at 45 psi in the presence of 10% Pd/C (100 mg) for 2 h. The suspension was filtered, the filtrate was evaporated under reduced pressure to an oily residue, and an ethereal solution of the oil was treated with HCl gas-saturated $Et_2O$ until precipitation ceased. The crude product was collected by filtration and recrystallized from an absolute EtOH–anhydrous $Et_2O$ mixture to yield 0.59 g (90%) of **31** as white crystals: mp 207–209 °C.

**4-(4-Chlorophenyl)-1-(4-phenylbutyl)-1,2,5,6-tetrahydropyridine Hydrogen Maleate (32). Method E.** Orthophosphoric acid (85% 0.43 g) was slowly added to solution of glacial HOAc (1.9 g) and $Ac_2O$ (0.4 g); after the exothermic reaction ceased, paraformaldehyde (0.36 g), 4-chloro-$\alpha$-methylstyrene (0.62 g, 4 mmol), and 4-phenylbutylamine (0.6 g, 4 mmol) were added. The reaction mixture was allowed to stir at 100–115 °C for 4 h and was then set aside for 2 days. Water (10 mL) was added; the mixture was made basic by the addition of solid $Na_2CO_3$ and extracted with hexanes (3 × 10 mL). The solution was dried (anhydrous $K_2CO_3$), and the solvent was evaporated. The crude residue was recrystallized from MeOH to give about 0.4 g of the free base (mp 87–90 °C). A solution of the free base in anhydrous $Et_2O$ was treated with a saturated ethereal solution of maleic acid (0.5 g/20 mL), and the crude salt was collected and recrystallized from absolute EtOH–anhydrous $Et_2O$ to give 0.6 g (35%) of **32** as fine crystals: mp 162–164 °C.

**1-Benzoyl-4-(4-phenylbutyl)piperazine Hydrochloride (34). Method F.** A solution of *N*-(4-phenylbutyl)piperazine (**36**) (1.0 g, 4.6 mmol) in $CHCl_3$ (20 mL) was added to a solution of benzoyl chloride (0.7 g, 5 mmol) in $CHCl_3$ (20 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature overnight, the solvent was removed by evaporation under reduced pressure, and the yellow solid residue was recrystallized from an absolute EtOH–anhydrous $Et_2O$ mixture to afford 0.83 g (50%) of **34**: mp 217–218 °C.

**1-Phenyl-4-[3-(2-naphthyl)propyl]piperazine Dihydrochloride (35).** Ethyl chloroformate (0.35 g, 3 mmol) was added dropwise at 0 °C to stirred solution of 3-(2-naphthyl)propionic acid (0.6 g, 3 mmol) and $NEt_3$ (0.3 g, 3 mmol) in $CH_2Cl_2$ (30 mL).

The reaction mixture was allowed to stir at 0 °C for 30 min, whereupon a solution of 1-phenylpiperazine (0.5 g, 3 mmol) in $CH_2Cl_2$ (10 mL) was added in dropwise manner. After complete addition, the reaction mixture was allowed to stir at room temperature for 4 h, washed with water (2 × 10 mL), and dried ($MgSO_4$). The solvent was removed by evaporation under reduced pressure to give a white solid residue; recrystallization from 95% EtOH gave 0.7 g (66%) of the amide as white crystals (mp 101 °C). A solution of the amide (0.68 g, 2 mmol) in dry THF (30 mL) was added dropwise at 0 °C to stirred suspension of $LiAlH_4$ (0.5 g, 12 mmol) in dry THF (30 mL). After complete addition, the stirred reaction mixture was heated at reflux overnight. The mixture was cooled to 0 °C and the excess $LiAlH_4$ was decomposed by addition of $H_2O$ containing a few drops of 30% NaOH. The reaction mixture was filtered and the solid material was washed with THF (ca. 20 mL). The combined filtrate and washings were evaporated under reduced pressure; an $Et_2O$ (40 mL) solution of the oily residue was washed with $H_2O$ (20 mL), dried ($MgSO_4$), and saturated with HCl gas to give a white solid hydrochloride salt. Recrystallization from absolute EtOH gave 0.48 g (66%) of **35** as white crystals: mp 190–192 °C. Anal. ($C_{23}H_{26}N_2 \cdot 2HCl$) Cl.

***N*-(4-Phenylbutyl)piperazine (36).** Ethyl chloroformate (4.32 g, 0.04 mol) was added dropwise, at 0 °C, to a stirred solution of 4-phenylbutyric acid (4.56 g, 0.04 mol) and $NEt_3$ (4.0 g, 0.04 mol) in $CH_2Cl_2$ (40 mL); stirring was allowed to continue for 30 min at 0–5 °C, whereupon a solution of 1-piperazinecarboxaldehyde (4.56 g, 0.04 mol) in $CH_2Cl_2$ (20 mL) was added. The reaction mixture was allowed to stir at room temperature for 4 h and set aside overnight. The mixture was washed with $H_2O$ (2 × 20 mL) and the organic portion was dried ($MgSO_4$) and evaporated in vacuo to dryness. The residual oil (5.8 g, 80%) was used in the next step without further purification. The *N*-formyl derivative (5.7 g, 22 mmol) was dissolved in a concentrated HCl–methanol solution (1:9, 200 mL). The resulting mixture was stirred at room temperature for 18 h, and the solvent was then removed by evaporation under reduced pressure. The solid residue was suspended in absolute EtOH (200 mL), heated under reflux for 15 min, and filtered while hot. After cooling to room temperature, the alcoholic solution was diluted with anhydrous $Et_2O$ and allowed to stand at −15 °C overnight. The white precipitated product was collected by filtration and air-dried to give 2.3 g (40%) of 1-(4-phenylbutyryl)piperazine hydrochloride (mp 185–188 °C). The free base of the amide (2 g, 8.6 mmol) was dissolved in dry THF (40 mL) and added in dropwise manner, at 0 °C, to a stirred suspension of $LiAlH_4$ (2.0 g, 52 mmol) in dry THF (40 mL). After complete addition, the reaction mixture was heated at reflux overnight and then cooled to 0 °C. Excess $LiAlH_4$ was decomposed by addition of $H_2O$ (2 mL) and 30% NaOH (5 drops). The inorganic material was removed by filtration and washed with THF (ca. 30 mL). The combined filtrates and washings were evaporated in vacuo to dryness. The residual oil was dissolved in $Et_2O$ (40 mL), washed with $H_2O$ (20 mL), and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, 1.4 g (71%) of a clear oil corresponding to 1-(4-phenylbutyl)piperazine was obtained. (A sample of the HCl salt was prepared for identification: mp 242–245 °C after recrystallization from EtOH–$Et_2O$.) The free base was used without further purification in the preparation of **34**.

**Radioligand Binding Studies. Guinea Pig/[$^3$H]DTG.** Sigma receptor binding assays, using [$^3$H]DTG (di-*o*-tolylguanidine) as radioligand and guinea pig brain membranes as source of receptor, were performed exactly as described in our previous study.[22] Briefly, guinea pig brain membranes (P2 microsomal fraction) were prepared from frozen guinea pig brains (Taconic) to a final protein concentration of 3 mg/mL and stored at −70 °C. For the assay, the membranes were thawed and diluted 1:3 with 50 mM Tris-HCl (pH 7.4), and 0.4 mL was combined with 50 μL of [$^3$H]DTG (1–2 nM final concentration) and 50 μL of unlabeled competing drug or buffer. The mixtures were incubated for 90 min at room temperature and incubation was terminated by rapid filtration under vacuum through Whatman GF/B or Schleicher & Schuell no. 32 glass fiber filters using a Brandel 48-well cell harvester. The filters were washed three times with 5 mL of cold Tris-HCl buffer, and each filter was suspended in 5 mL of Cytoscint (ICN Biomedicals); radioactivity was measured by liquid scintillation spectrometry at a counting efficiency of 50%. Nonspecific binding was measured in the presence of 10 μM haloperidol. Data represent the mean and SEM of at least three competition curves (unless otherwise stated). IC50 values, determined by analyzing displacement curves using nonlinear least-squares regression analysis, were converted to $K_i$ values using the Cheng–Prusoff equation.[32]

**Other Assays.** Dopamine D1 ([$^3$H]SCH-23390), dopamine D2 ([$^3$H]domperidone), and PCP ([$^3$H]MK-801) receptor assays were also performed as described in the previous manuscript in this series.[22] Dopamine binding assays used washed membranes prepared from frozen rat striata resuspended in a buffer containing 50 mM Tris-HCl, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$ (pH 7.4 at 37 °C). PCP binding assays were performed with rat brain membranes using [$^3$H]MK-801 (97 Ci/mmol).

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