Is a Nitrogen Atom an Important Pharmacophoric Element in Sigma Ligand Binding?

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Abstract—A lingering question in σ receptor ligand development is whether a nitrogen atom serves as an important pharmacophoric element in binding affinity. To address this question, we have synthesized several phenylalkylpiperidines and phenylalkylpiperazines and demonstrated that removal of the N atom from a typical phenylalkylpiperidine led to little or no binding to σ receptors. In addition, where two N atoms occur in a compound, such as with phenylalkylpiperazines, the N atom on the longer alkyl chain appears to be more important. Thus, based on this study, the N atom is an important pharmacophoric element in the binding of phenylalkylpiperidines and phenylalkylpiperazines to σ receptors.

Although the initial excitement about sigma ligands has subsided somewhat, they continue to attract attention because of the involvement of sigma receptors in several physiological functions. 1–8 For example, several recent publications support the hypothesis that sigma ligands may serve as atypical antipsychotic agents with minimal extrapyramidal action. 9 In addition, sigma receptors appear to modulate K+ channels, 10 and may serve as targets for drug design against certain tumor cells. 11 Unlike most neurotransmitter receptors, however, sigma receptors seemingly accommodate a very wide variety of structural classes. 1,2 This situation has made it difficult to obtain a unifying common pharmacophore model for each of the known receptor subtypes. Although several sigma receptor subtypes might remain to be identified, the presence of a nitrogen atom appears to be a common pharmacophoric element for most sigma ligands. Unfortunately, the role of the nitrogen atom as a required pharmacophoric element is clouded by the finding that steroid molecules lacking a basic nitrogen atom bind to sigma receptors with moderate affinity, and may effect several physiological actions through sigma receptors. 12–17

In our work, 18–25 on developing structure–affinity relationship models for sigma receptor ligands, we have used the N atom as a primary pharmacophore element for alignment purposes. 18,19 On a number of such occasions, however, we were faced with the decision of selecting one nitrogen atom, among several, as the primary pharmacophoric element. We have previously shown that modifications around the nitrogen atom in phenylalkylamines and phenylpiperidines often led to changes in ligand binding affinity. 20,24,25 Therefore, we have sought a better understanding of the role and contributions of the nitrogen atom in sigma ligand binding because it might lead to the design and synthesis of new and more selective agents for sigma receptors. Thus, the primary purpose of this study was to evaluate the contributions of the N atom to sigma receptor binding using phenylpiperazines, phenylpiperidines and phenylalkylamines as the scaffold. It was also of interest to determine if the resulting modifications lead to more potent and selective σ ligands; consequently, both σ-1 and σ-2 receptor binding data were obtained on most of the compounds.

Chemistry

Standard synthetic methods were used to obtain most of the compounds examined in this investigation. Compound 1 was available commercially from Aldrich Chemicals. Both 3 and 4 were obtained by direct N-alkylation of 1 and 2, respectively. Using the appropriate phenylalkyl...
bromides generated from commercially available phenyl-alkanols, compounds 5-9 were similarly synthesized. The preparation of compound 10 (Scheme 1) required the use of the Wittig reaction. Thus, triphenylphosphine was alkylated with 5-phenylpentyl bromide to obtain the phosphonium bromide, which was subsequently reacted with sulfanyl carbanion generated from DMSO and sodium hydride. The resulting carbanion was reacted with N-methyl-4-piperidinone to form the corresponding olefin, which was catalytically reduced using palladium/carbon to yield the desired compound. Compound 11 was resynthesized using a published procedure. To synthesize compound 12 (Scheme 2), the key intermediate, 4-cyclohexylbutanal, was obtained by oxidation of 4-cyclohexylbutanol under Collins’ conditions. The aldehyde was added to a mixture of 4-nitrobenzyltriphenylphosphonium bromide and methyl sulfinyl carbanion, generated from dimethylsulfoxide and sodium hydride, to yield the required nitrophenyl olefin. Hydrogenation under Parr conditions and in the presence of palladium and carbon yielded the desired compound.

Compound 13 was obtained by nitration of 11 to form N-[5-(4-nitrophenyl)pentyl]piperidine and by the subsequent hydrogenation using 10% palladium on carbon. Compound 14 was obtained by the direct reduction of the commercially available natural product, piperine, followed by lithium aluminum hydride reduction of the resulting amide. Finally, compound 16 was obtained by direct methylation of 7.


Scheme 2. Synthesis of compound 12.


Results and Discussion

Radioligand binding data are shown in Table 1. 1-Benzylpiperazine (1) and 1-benzyloxydiazepam (2) do not bind to σ receptors (i.e., \( K_i > 10,000 \) nM). Alkylation of the terminal N atom with a Ph-(CH\(_2\))\(_n\)-X (where X = halide) in each of these compounds, results in a dramatic increase in the \( K_i \) for the 1 binding affinity of the resulting products. However, while there is at least a 50,000-fold increase from 1 to 3 (\( K_i = 0.2 \) nM), there is a much smaller increase from 2 to 4 (\( K_i = 125 \) nM).

At least two possible hypotheses can be expounded for the significant difference in the binding affinities. A basic nitrogen atom is required at N(a) and the introduction of an amide N at that position therefore results in a lack of binding affinity. By implication, N(a) must be very important for binding to σ-1 receptors. A second hypothesis for the difference in binding affinity can be attributed to the change in the position of the phenyl-A ring brought about by the carbonyl group or by intolerance of the carbonyl oxygen itself. To further explore these issues, we synthesized compound 5 in which N(a) is replaced by CH and in order to evaluate the importance of N(a) to binding. Compound 5 binds with a \( K_i \) of 0.8 nM; only a 4-fold difference with 3. Inserting an additional methylene group in phenylalkyl derivatives 3 and 5 yielded similar results (i.e., 6, \( K_i = 0.4 \) nM, and 7, \( K_i = 0.6 \) nM, respectively). These results suggest that N(a) is not essential for high affinity binding to σ-1 receptors. Interestingly, previous work in our laboratories has demonstrated that the phenyl-A ring plays essentially no role in the binding of phenylalkylamines or phenylpiperidines at sigma receptors. Thus, removal of the

### Table 1. Sigma receptor ligand binding data

<table>
<thead>
<tr>
<th>Compound</th>
<th>Binding constants, ( K_i ) (nM)</th>
<th>( K_i ) (nM)</th>
<th>( K_i ) (nM)</th>
<th>Ratio of ( K_i ) (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>&gt;10,000</td>
<td>NT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>&gt;10,000</td>
<td>NT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.2 (0.1)</td>
<td>3.1 (0.6)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.4 (0.2)</td>
<td>NT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.6 (0.2)</td>
<td>2.8 (0.8)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1.4 (0.4)</td>
<td>79 (13)</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>0.07 (0.02)</td>
<td>7 (2)</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1.3 (0.3)</td>
<td>97 (18)</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>0.48</td>
<td>50 (12)</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>&gt;36,000</td>
<td>54,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>38 (8)</td>
<td>830 (132)</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>0.86 (0.24)</td>
<td>554 (180)</td>
<td>644</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>0.32 (0.10)</td>
<td>63 (12)</td>
<td>197</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>2.7 (0.9)</td>
<td>NT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( ^a \)Previously reported as non-selective sigma receptor ligand; see ref 22.
\( ^b \)Previously reported in ref 20.
\( ^c \)SEM in parenthesis.
\( ^d \)NT = was not determined.
phenyl A ring from 6 and 7 led to compounds 8 ($K_i=1.4 \text{ nM}$) and 9 ($K_i=0.07 \text{ nM}$) with affinities consistent with our previous findings.

So far, the replacement of N(a) with CH in the piperazines series appears to have no serious bearing on the binding of these compounds to $\sigma-1$ receptors. The question then arises as to what role N(b) plays in the binding of the piperazines. We reasoned that if N(a) does not contribute significantly to binding at $\sigma-1$ receptors, and if a nitrogen atom is required, N(b) must be the essential N atom required for binding affinity. We therefore synthesized compound 10 in an attempt to answer this question. Compound 10 ($K_i=1.3 \text{ nM}$) binds as well as 8 although its binding affinity is 20-fold lower than that of 9. We can deduce from these results that compounds in which N(a) is present bind to $\sigma-1$ receptors in essentially the same way notwithstanding the presence of other nitrogen atoms such as N(b). Furthermore, although N(b) provides a more effective binding to sigma receptors, the presence of other N atoms leads to additional interactions which somehow detracts from maximum binding. This observation is consistent with our previous suggestion that phenylalkylamines, phenylalkylpiperidines and phenylalkylpiperazines may utilize reverse modes of binding to $\sigma-1$ receptors$^{26}$ (see Fig. 1 below).

Compound 9 displays the highest affinity of the compounds examined. It is important, then, to examine the role the N atom plays in the binding of such compounds. We have previously reported that N-α-phenylpentylpiperidine (11), a demethylated analogue of 9, binds with high affinity at $\sigma-1$ receptors ($K_i=0.48 \text{ nM}$). In order to evaluate the necessity of the nitrogen atom for sigma binding, we wished to replace it with a methine group. However, this would likely result in a water-insoluble compound. To overcome this problem, we needed to attach a watersolubilizing group elsewhere in the molecule. We selected the para position of the phenyl ring based on previous results indicating that substitution at this position might be tolerated and affinity may not be significantly affected at $\sigma-1$ receptors.$^{25}$ We explored aromatic substitution to further evaluate this concept and found that aromatic substitution is tolerated and can, depending upon the substituents incorporated (e.g. 14 and 15), actually enhance affinity and/or selectivity; this will be further discussed below. One of the compounds prepared and examined was the amino-substituted derivative 12 ($K_i>36,000 \text{ nM}$); compound 13 ($K_i=38 \text{ nM}$) was used as the positive control. Since compound 13 binds with moderate affinity, it can be concluded that replacement of the piperidine nitrogen atom with CH reduces affinity by at least a 1000-fold and, hence, a nitrogen atom is an essential pharmacophoric element in the binding of these and related ligands to $\sigma-1$ receptors. An alternative, but less satisfying, explanation is that compound 12 binds in an entirely different manner to result in low affinity.

In the course of exploring aromatic substitution, as described above, we prepared several aryl substituted compounds including 14 and 15. The purpose of these studies was to determine the influence of aryl substituents on $\sigma-1$ binding and subsequently to determine if such substitutions detract from binding. Compounds 14 ($K_i=0.86 \text{ nM}$) and 15 ($K_i=0.32 \text{ nM}$) were both found to bind with high affinity. Comparing compounds 11 ($K_i=0.48 \text{ nM}$) and 15 ($K_i=0.32 \text{ nM}$) also supports the suggestion that aromatic substitution has little influence on $\sigma-1$ binding. Interestingly, compound 14 displayed the highest $\sigma-2/\sigma-1$ selectivity among the ligands evaluated in this study (14: $\sigma-1 K_i=0.86 \text{ nM}; \sigma-2 K_i=554 \text{ nM}$, for a ratio of 664).

Having established the importance of the N(b) atom for maximum binding, it was also of interest to examine the nature of the nitrogen atom as it binds the sigma receptors. In this regard, we wanted to know if a lone pair of electrons on the nitrogen was needed for binding or if protonation of the nitrogen occurs on binding. A very simple way to do this is to introduce a permanent positive charge on the nitrogen such as occurs in quaternization. We therefore prepared and examined the N-methylated analogue of compound 7 (i.e. compound 16). Compound 16 binds with a $K_i=2.7 \text{ nM}$; implying that the lone pair of electrons on these compounds probably becomes protonated at $\sigma-1$ receptors and that a protonated N atom may be required for $\sigma-1$ receptor binding.

The binding affinities of several of the present compounds were also examined at $\sigma-2$ receptors (Table 1). All of the compounds investigated displayed (4- to >600-fold) lower affinity at $\sigma-2$ than at $\sigma-1$ receptors. Comparing compounds 12 and 13, it would appear that N(b) might also be an important feature for $\sigma-2$ binding. It also seems that

**Figure 1.** Proposed receptor features important for $\sigma-1$ binding$^{18,20}$ and the modes of binding of phenylpiperazines (4 modes) and phenylpiperidines (2 modes).
aqueous portion was reextracted with Et₂O (30 mL) and aqueous ammonia solution (15 mL). The aqueous portion was re-extracted with Et₂O (30 mL) and the combined organic portions were pooled, washed with H₂O (20 mL) and dried (MgSO₄). Solvent was removed under reduced pressure and the residue (335 mg, 19%) was converted to the hydrochloride salt using ethereal HCl: mp 163–165 °C. 1H NMR (300 MHz, DMSO-d₆) δ 7.42–7.10 (10 H, m), 3.76 (2H, t), 3.50 (2H, d, br), 3.28 (2H, m), 2.62 (4H, m), 2.20 (1H, br), 1.88–1.32 (m); 13C NMR (75 MHz, DMSO-d₆) δ 23.43, 26.36, 28.84 (2C), 30.65, 35.54, 36.62, 41.95, 52.92 (2C), 57.52, 125.85, 126.36, 128.36 (4C), 128.49, (2C), 128.98 (2C), 139.12, 141.80. Anal. C₂₂H₃₂N₂Cl₂.0.2H₂O, C, H, N.

1-Methyl-4-(5-phenylpentyl)piperazine dihydrobromide (8). A stirred mixture of 1-methylpiperazine (0.3 g, 3.0 mmol), 5-phenylpentyl bromide (0.7 g, 3.1 mmol), K₂CO₃ (0.9 g, 6.2 mmol) and KI (100 mg) in 1,2-dimethoxyethane (DME) (8 mL) was heated under reflux for 5 h and allowed to cool to room temperature. The mixture was partitioned between Et₂O (30 mL) and 10% NaOH solution (15 mL). The aqueous portion was reextracted with Et₂O (30 mL) and the combined organic portions were pooled, washed with H₂O (20 mL) and dried (MgSO₄). A saturated hydrogen bromide solution in anhydrous Et₂O was added to obtain a salt, which was recrystallized from MeOH (0.51 g, 43%): mp 239 °C (Dec.). 1H NMR (300 MHz, DMSO-d₆) δ 7.22 (2H, d, J = 9 Hz), 7.17 (1H, d, J = 7 Hz), 7.15 (2H, dd, J = 9, 7 Hz), 7.30 (4H, s, br), 3.39 (4H, s, br), 3.18 (2H, s, br), 2.88 (3H, s), 2.54 (2H, t, J = 7 Hz), 1.68 (2H, m), 1.56 (2H, m), 1.27 (2H, m); 13C NMR (75 MHz, DMSO-d₆) δ 25.67, 30.58, 35.04, 38.96, 84.11, 125.94, 128.51, 141.87. Anal. C₁₉H₂₉N₂Br₂, C, H, N.

4-Methyl-1-(5-phenylpentyl)piperidine hydrogen oxalate (9). Method A was used. Product (1.2 g, 75%), mp 138–139 °C. Recrystallization solvent: MeOH/Et₂O. 1H NMR (300 MHz, DMSO-d₆) δ 7.23 (2H, d, J = 9 Hz), 7.15 (2H, dd, J = 9, 7 Hz), 7.12 (1H, d, J = 7 Hz), 3.62 (2H, d, J = 15 Hz), 2.92 (2H, dd, J = 15, 9 Hz), 2.55 (2H, t, J = 7 Hz), 1.65 (11H, m), 1.29 (3H, d, J = 6 Hz); 13C NMR (75 MHz, DMSO-d₆) δ 20.82, 23.38, 26.06, 29.14, 30.48, 30.84, 35.31, 53.09, 57.29, 125.64, 128.16, 141.63, 163.08. Anal. C₁₉H₂₅NO₄, C, H, N.

N-Methyl-4-(phenylpiperidin-1-yl)pyridine hydrogen oxalate (10). A mixture of triphenylphosphine (3.8 g, 14.5 mmol) and 5-phenylpentyl bromide (3.1 g, 13.6 mmol) in dry benzene (20 mL) was allowed to reflux overnight (~24 h). After cooling to room temperature, anhydrous Et₂O was added, the solid was filtered and washed with several portions of anhydrous Et₂O and dried under reduced pressure at 50 °C overnight (6.1 g, 91%); mp 143–145 °C. A solution of methyl sulfinyl carbunation was obtained by stirring a mixture of dried DMSO (10 mL) and powdered

**Conclusion**

In this study, it has been demonstrated that at least one N atom in phenylpiperidines and phenylpiperazines is important for binding at sigma receptors. In the case of the piperazines, the N atom attached to the longer chain, N(b), is more important than N(a). Furthermore, several modes of binding are available to each molecule at the binding site and therefore reversed modes of binding are possible as well. Thus, we have now extended our previously reported sigma ligand model to include the various modes of binding for phenylpiperidines and phenylpiperazines at the σ-1 receptors (Fig. 1). If the N atom is important in σ binding, how can we explain the binding of non-basic steroids to sigma receptors? At this point, it can only be speculated that steroids probably bind in a different manner at the σ receptors from the phenylalkylamines, such as the ones discussed in this manuscript.

**Experimental**

**Syntheses**

Proton and carbon magnetic resonance spectra were obtained on QE 300 (300 MHz/75 MHz) spectrometers with tetramethylsilane as internal standard. The unit of all J values shown in the experiments is Hz, and all spectra are consistent with the assigned structures. Melt- ing points were determined on a Thomas Hoover apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab and determined values are within 0.4% of calculated values. No attempt was made to optimize yields in any of the synthesis presented.

1-Benzyl-4-(5-phenylpentyl)piperazine (6) hydrochloride (method A). A stirred mixture of 1-benzylpiperazine (0.4 g, 2.3 mmol), 5-phenylpentyl bromide (0.5 g, 2.2 mmol), K₂CO₃ (0.6 g, 4.3 mmol), and KI (50 mg) in 1,2-dimethoxyethane (DME) (8 mL) was heated under reflux overnight (20 h) and allowed to cool to room temperature. The mixture was partitioned between Et₂O (30 mL) and aqueous ammonia solution (15 mL). The aqueous portion was reextracted with Et₂O (30 mL) and the combined organic portions were pooled, washed with H₂O (20 mL) and dried (MgSO₄). Solvent was removed under reduced pressure and the residue chromatographed over silica gel using 50% EtOAc/hexane to yield a yellowish oil, which was converted to the hydrochloride salt using ethereal HCl: mp 163–165 °C. 1H NMR (300 MHz, DMSO-d₆) δ 7.42–7.10 (10 H, m), 3.76 (2H, t), 3.50 (2H, d, br), 3.28 (2H, m), 2.62 (4H, m), 2.20 (1H, br), 1.88–1.32 (m); 13C NMR (75 MHz, DMSO-d₆) δ 23.43, 26.36, 28.84 (2C), 30.65, 35.54, 36.62, 41.95, 52.92 (2C), 57.52, 125.85, 126.36, 128.36 (4C), 128.49, (2C), 128.98 (2C), 139.12, 141.80. Anal. C₂₂H₃₂N₂Cl₂.0.2H₂O, C, H, N.

4-Benzyl-1-(5-phenylpentyl)piperidine hydrochloride (7). A stirred mixture of 4-benzylpiperidine (1.0 g, 5.7 mmol), 5-phenylpentyl bromide (1.95 g, 8.6 mmol), K₂CO₃ (1.57 g, 11.4 mmol), and KI (100 mg) in 1,2-dimethoxyethane (DME) (10 mL) was heated under reflux over the weekend (60 h) and allowed to cool to room temperature. The mixture was partitioned between Et₂O (30 mL) and aqueous ammonia solution (15 mL). The aqueous portion was re-extracted with Et₂O (30 mL) and the combined organic portions were pooled, washed with H₂O (20 mL) and dried (MgSO₄). Solvent was removed under reduced pressure and the residue (335 mg, 19%) was converted to the hydrochloride salt using ethereal HCl: mp 163–165 °C. 1H NMR (300 MHz, DMSO-d₆) δ 7.42–7.10 (10 H, m), 3.76 (2H, t), 3.50 (2H, d, br), 3.28 (2H, m), 2.62 (4H, m), 2.20 (1H, br), 1.88–1.32 (m); 13C NMR (75 MHz, DMSO-d₆) δ 23.43, 26.36, 28.84 (2C), 30.65, 35.54, 36.62, 41.95, 52.92 (2C), 57.52, 125.85, 126.36, 128.36 (4C), 128.49, (2C), 128.98 (2C), 139.12, 141.80. Anal. C₂₂H₃₂N₂Cl₂.0.2H₂O, C, H, N.
sodium hydride (0.2 g) under N2 and heating at \(\sim 50^\circ\)C for 15 min. The resulting solution was cooled to 0°C and a solution of 5-phenylpentyltriphenylphosphonium bromide (3 g, 6.1 mmol) in dry DMSO (10 mL) was added in a dropwise manner over 5 min. After 15 min of stirring at room temperature, a solution of 1-methyl-4-piperidone (0.6 g, 5.3 mmol) in dry DMSO (10 mL) was added in a dropwise manner over \(\sim 5\) min. The resulting reddish yellow solution was allowed to stir at room temperature for \(\sim 20\) h and then poured into H2O (80 mL) and extracted with Et2O (3 \(\times 50\) mL). The pooled Et2O solution was washed with H2O (2 \(\times 50\) mL) and dried (MgSO4). Solvent was removed under reduced pressure and the residue was recrystallized from abs EtOH (0.31 g, 17%). 1H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 7.19 (5H, m), 5.25 (1H, t, \(J = 9\) Hz), 3.01 (4H, s, br), 2.65 (3H, s), 2.54 (2H, t, \(J = 6\) Hz), 2.32 (4H, m), 1.95 (2H, dt, \(J = 9, 9\) Hz), 1.51 (2H, m), 1.29 (2H, m). 13C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 25.01, 26.89, 29.12, 31.33, 32.67, 35.38. 25.141, 42.28, 54.25. A solution of this product (0.25 g, 0.74 mmol) in abs EtOH (40 mL) was hydrogenated under Parr conditions (psi 50) for 3 h in the presence of Pd/C (10%) (0.1 g) catalyst. The mixture was filtered, the solvent was removed under reduced pressure and the residue was recrystallized from MeOH/anhydrous Et2O/EtOAc (0.19 g, 77%). mp 142–144°C. 1H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 7.18 (5H, m), 5.25 (1H, t, \(J = 9\) Hz), 3.01 (4H, s, br), 2.65 (3H, s), 2.51 (2H, t, \(J = 6\) Hz), 2.32 (4H, m), 1.95 (2H, dt, \(J = 9, 9\) Hz), 1.51 (2H, m), 1.27 (2H, m). 13C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 25.01, 26.85, 29.21, 30.87, 32.23, 35.38, 42.28, 54.16, 54.82, 125.73, 126.03, 128.83, 130.54, 142.56, 165.20.

A solution of this product (0.25 g, 0.74 mmol) in abs EtOH (40 mL) was hydrogenated under Parr conditions (psi 50) for 3 h in the presence of Pd/C (10%) (0.1 g) catalyst. The mixture was filtered, the solvent was removed under reduced pressure and the residue was recrystallized from MeOH/anhydrous Et2O/EtOAc (0.19 g, 77%). mp 142–144°C. 1H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 7.19 (5H, m), 5.25 (1H, t, \(J = 9\) Hz), 3.01 (4H, s, br), 2.65 (3H, s), 2.51 (2H, t, \(J = 6\) Hz), 2.32 (4H, m), 1.95 (2H, dt, \(J = 9, 9\) Hz), 1.51 (2H, m), 1.27 (2H, m). 13C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 25.01, 26.85, 29.21, 30.87, 32.23, 35.38, 42.28, 54.16, 54.82, 125.73, 126.03, 128.83, 130.54, 142.56, 165.20.

1-(5-Phenylpentyl)piperidine (11). A stirred mixture of piperidine (1.1 g, 13 mmol), 5-phenylpentyl bromide (3.1 g, 14 mmol) KI (20 mg) and K2CO3 (2 g, 15 mmol) in 1,2-dimethoxyethane (DME) (10 mL) was heated under reflux for 12 h and allowed to cool to room temperature. The mixture was partitioned between Et2O (30 mL) and 10% NaOH solution (15 mL). The aqueous portion was reextracted with Et2O (30 mL) and the combined organic portions were pooled, washed with H2O (20 mL) and dried (MgSO4). The oxalate salt was prepared and recrystallized from MeOH (3.1 g, 74%), mp 159–161°C. 1H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 6.87 (2H, d, \(J = 6\) Hz), 2.37 (2H, t, \(J = 6\) Hz), 1.61 (6H, m), 1.43 (2H, m), 1.13 (9H, m), 0.87 (2H, m). 13C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 26.19, 29.12, 31.33, 32.67, 35.33, 35.52, 42.87, 53.49, 125.99, 128.63, 142.65, 165.27. Anal. C19H29NO4. C, H, N.

N-[5-(4-aminophenyl)pentyl]piperidine dihydrogen oxalate (13). An ice-cold solution of compound 11 (0.5 g, 1.6 mmol), concd H2SO4 (2 mL) and glacial AcOH (3 mL) were mixed, and a mixture of concd H2SO4 (1 mL) and fuming HNO3 (1 mL) was added in a dropwise manner to maintain the temperature at \(\sim 0^\circ\)C. Stirring was continued at room temperature for 0.5 h. Thereafter, the mixture was poured onto ice (50 g), basified by the addition of solid NaOH and extracted with Et2O (2 \(\times 50\) mL). The pooled organic portion was dried (MgSO4) and the oxalate salt was prepared and recrystallized from MeOH (205 mg, 37%), mp 159–161°C. The resulting compound (0.38 g) in MeOH (50 mL) was hydrogenated at a pressure of 50 psi in a Parr bottle containing 10% Pd/C (0.2 g) until sufficient H2 was taken up (24 h). The catalyst was removed by filtration, the solvent was removed under reduced pressure and the oxalate salt was prepared. Recrystallization was achieved from Abs EtOH/ EtOAc (0.24 g, 51%), mp 99–103°C. 1H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 6.87 (2H, d, \(J = 12\) Hz), 6.18 (2H, d, \(J = 12\) Hz), 2.37 (2H, t, \(J = 12\) Hz), 1.72 (2H, d, \(J = 15\) Hz), 1.50 (2H, m), 1.23 (9H, m). 13C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 26.19, 29.12, 31.33, 32.67, 35.33, 35.52, 42.87, 53.49, 125.99, 128.63, 142.65, 165.27. Anal. C19H29NO4. C, H, N.

1-[1-(3,4-Methylenedioxyphenyl)-2,4-pentadienyl]piperidine hydrochloride (14). A solution of pipeline (1 g, 3.5 mmol) in Et2O (50 mL) was added to a stirred suspension of LiAlH4 (0.93 g, 7 equiv) in Et2O (100 mL) and the mixture allowed to reflux under an atmosphere of N2 for 24 h. The reaction was quenched by the addition of drops of H2O (20 mL) and stirring was continued for an additional 0.5 h. The ethereal portion was decanted and 10% NaOH (60 mL) was added to the residue. The

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resulting mixture was then filtered and the filtrate extracted with Et2O (2×50 mL). The total combined organic phases was washed with H2O (20 mL), dried (MgSO4) and ethereal HCl was added to obtain a precipitate of the salt. The precipitate was recrystallized from EtOAc/MeOH to give yellow crystals, mp 174–176°C. 1H NMR (300 MHz, CDCl3) δ 12.10 (1H, s, br), 6.92 (1H, d, J = 1.5 Hz), 6.82 (1H, d, J = 1.5 Hz), 6.78 (1H, s), 6.65 (1H, dd, J = 11, 16 Hz), 6.54 (1H, d, J = 16 Hz), 6.48 (1H, dd, J = 16, 12 Hz), 6.03 (1H, dt, J = 16, 8 Hz), 5.98 (2H, s), 3.65 (2H, dd, J = 4, 12 Hz), 3.51 (2H, d, J = 12 Hz), 2.63 (2H, dt, J = 12, 4 Hz), 2.25 (2H, m), 1.89 (2H, m), 1.42 (2H, m); 13C NMR (300 MHz, CDCl3) δ 21.91, 22.41, 52.26, 59.13, 101.05, 105.42, 108.26, 118.80, 121.76, 124.65, 130.54, 135.46, 139.99, 147.79, 149.00. Anal. C17H22NO2Cl.0.15H2O, C, H, N.

1-[5-(3,4-Methylenedioxyphenyl)-pentyllpiperidinum hydro-
gen oxalate (15). A mixture of piperine (1.0 g, 3.5 mmol), 10% Pd/C (0.24 g) and MeOH (50 mL) was hydrogenated at 50 psi for 2 h. The mixture was filtered, and solvent was removed in vacuo to afford an amide; IR \( \gamma = 1651 \text{ cm}^{-1} \). Without further purification, the amide was dissolved in Et2O (50 mL) and added dropwise onto a suspension of LiAlH4 (0.6 g, 0.01 mol) in Et2O (50 mL). The mixture was allowed to reflux for 4 h after which it was cooled in ice and quenched by the addition of H2O (3 mL), 10% NaOH (3 mL) and H2O (10 mL). The resulting mixture was allowed to stir for additional 0.5 h, the organic phase was decanted, and the aqueous phase was extracted with Et2O (2×50 mL). The organic phases were pooled, dried (MgSO4) and a saturated solution of oxalic acid was added to precipitate the salt.

The salt was recrystallized from EtOAc/MeOH to give yellow crystals, mp 174–180°C. 1H NMR (300 MHz, CDCl3) δ 6.72 (1H, d), 6.63 (1H, s), 6.58 (1H, d), 5.91 (2H, s), 3.62 (2H, d), 2.95 (2H, m), 2.60 (2H, m), 2.50 (2H, t), 2.08–1.66 (7H, m), 1.58 (2H, m), 1.45–1.22 (3H, m); 13C NMR (75 MHz, CDCl3) δ 21.88, 22.51 (2C), 23.29, 25.90, 30.72, 35.01, 53.16 (2C), 57.17, 100.53, 107.93, 108.55, 120.88, 135.46, 163.08. Anal. C16H25NO5O2 C, H, N.

4-Benzyl-1-(5-phenylpentyl)-1-methylpiperidinum chloride (16). A mixture of compound 7 (270 mg, 0.84 mmol) methyl iodide (1.5 mL) and acetonitrile (1 mL) was heated for 22 h, charged with additional methyl iodide (1.5 mL) and heated for 5 more hours. The solvent was removed, the residue was reconstituted in EtOAc/MeOH and allowed to crystallize in the refrigerator (261 mg, 65%), mp 144–145°C. 1H NMR (300 MHz, DMSO-d6) δ 7.25 (5H, m), 7.16 (5H, m), 3.62 (6H, m), 3.18 (3H, s), 2.67 (2H, d, J = 8 Hz), 2.50 (2H, t, J = 7 Hz), 2.09 (2H, m), 1.73 (7H, m); 13C NMR (75 MHz, DMSO-d6) δ 22.11, 25.88, 26.07, 30.87, 34.59, 35.58, 41.50, 45.23, 60.83, 67.70, 125.83, 126.50, 128.38, 128.47, 128.56, 129.12, 138.43, 141.92. Anal. C24H34NI0.75H2O, C, H, N.

Binding studies

The σ1 radioligand-binding assay was carried out as previously reported27 using (+)-[3H]pentazocine as the radioligand. Approximately 100 μg of guinea pig brain membranes and (-)[3H]pentazocine (3–4 nM final concentration) in a final volume of 500 μL of 50 mM Tris–HCl buffer (pH 8.0). For the standard equilibrium essay, the mixtures were incubated for 4 h at 37°C, the reactions quenched with 4 mL of ice-cold incubation buffer, and the mixtures rapidly filtered over Whatman GF/B or Schleicher & Schuell no. 32 glass fiber filters followed by three 4 mL rinses with additional ice-cold buffer. The radioactivity on the filters was determined by scintillation spectrometry at an efficiency of about 50%. Nonspecific binding was determined in the presence of 10 μM haloperidol. IC50 values were determined from competitive curves using nonlinear least-squares regression analysis and converted to Ki values with the Cheng–Prusoff transformation. Each Ki value was determined from three to five separate determinations.

The σ-2 selective binding assay27 was performed using about 2 nM [3H]DTG as the radioligand in the presence of 200 nM (+)pentazocine to block the σ-1 sites, with 400 μg of guinea pig brain membranes in a total volume of 500 μL of 50 mM TRIS-HCl, 7.4. Nonspecific binding was determined in the presence 10 μM haloperidol. For the standard equilibrium assay the mixtures were incubated for 30 min at room temperature, filtered and the radioactivity determined as described for σ-1.

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References and Notes


