Naphthylisopropylamine and N-benzylamphetamine derivatives as monoamine oxidase inhibitors

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ABSTRACT

A series of naphthylisopropylamine and N-benzyl-4-methylthioamphetamine derivatives were evaluated as monoamine oxidase inhibitors. Their potencies were compared with those of a series of amphetamine derivatives, to test if the increase of electron richness of the aromatic ring and overall size of the molecule might improve their potency as enzyme inhibitors. Molecular dockings were performed to gain insight regarding the binding mode of these inhibitors and rationalize their different potencies. In the case of naphthylisopropylamine derivatives, the increased electron-donating capacity and size of the aromatic moiety resulting from replacement of the phenyl ring of amphetamine derivatives by a naphthalene system resulted in more potent compounds. In the other case, extension of the arylisopropylamine molecule by N-benzylation of the amino group led to a decrease in potency as monoamine oxidase inhibitors.

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1. Introduction

The two isoforms of monoamine oxidase (MAO, E.C. 1.4.3.4), namely MAO-A and MAO-B, are targets for a series of therapeutically valuable drugs. Thus, selective MAO-A inhibitors (MAOI-A) are used as antidepressants while selective MAO-B are used in the treatment of Parkinson’s disease.1,2

The availability of high resolution crystal structures of both MAO isoforms,3–6 and the concomitant use of molecular simulation approaches are leading to a better understanding of the main binding interactions of several inhibitors at the enzymes’ active sites, and have facilitated the interpretation of their structure–activity relationships (SARs).7–10

Many phenylisopropylamine derivatives, often referred to in the literature as ‘substituted amphetamines’, have been shown by us and others to be potent and selective MAOI-A.11–13 In a previous QSAR study based on quantum-chemical calculations at the AM1 level of theory,14 we reported that electron-rich aromatic rings and higher HOMO energies correlated with an increased activity of substituted amphetamines as MAOI-A. In that work, this effect was interpreted as suggesting that these characteristics would favor charge-transfer interactions with the isoalloxazine ring of the enzyme’s cofactor. Nevertheless, our current knowledge of the MAO structures and with regard to the putative binding modes of this class of compounds,15 indicates that increased MAOI activity might be better rationalized as a consequence of stronger n-type interactions with aromatic and non-aromatic residues present in the active site of the protein.16 In this regard, it seemed interesting to test the effect of replacing the phenyl ring of the amphetamine derivatives by a naphthalene moiety, as a way of increasing the electron richness and HOMO energy and therefore their inhibitory activity.

Structural and molecular simulation data on MAO-A, on the other hand, suggest that the substrate/inhibitor binding site (both in human and rat MAO-A) could accommodate larger molecules than substituted phenylisopropylamines.4–6 Thus, recent studies have shown that molecules such as 4-phenyl-2-thiazolylhydrazone,16 N,N′-bis[2-oxo-2H-1-benzopyran]-3-carboxamide,17 or 4-[(4-bromo-N-imidazolyl)-aryloxazolidinone derivatives,18 fit into this binding site and are potent (although not necessarily selective) inhibitors of MAO-A activity. Therefore, replacement of a phenyl by a naphthyl group could improve the inhibitory potency of these compounds not only because of the greater ability of the latter family to interact with aromatic residues in the enzyme’s active site but also as a consequence of the increased size of the ligand.
In addition, based on the putative binding mode of the potent and selective inhibitor 4-methylthioamphetamine (3g),\textsuperscript{15} we decided to explore if the inhibitory activity of the parent molecule might increase by virtue of the introduction of bulky, substituted benzyl groups on the amine function of this compound. In order to test these hypotheses, the present study describes the synthesis, MAO inhibitory properties and molecular docking results for a series of naphthylisopropylamine and N-benzyl-4-methylthioamphetamine derivatives.

2. Results and discussion

2.1. Chemistry

Racemic 1-(1-) (1) and 1-(2-naphthyl)-2-aminopropene (2a), and 1-(6-methoxy- (2b), ethoxy- (2c), propoxy- (2d), butoxy- (2e), benzoyloxy- (2f), and methylthio- (2g) 2-naphthyl)-2-aminopropanes, the N-benzyl derivatives of 2b and 2e (2h and 2i, respectively) (Table 1), 1-(4-methoxy- (3b), ethoxy- (3c), propoxy- (3d), butoxy- (3e), benzoyloxy- (3f) and methylthio- (3g) phenyl)-2-aminopropanes (Table 2), and the N-benzyl- (4a), N-4-hydroxybenzyl- (4b), N-4-methoxybenzyl- (4c), N-4-butoxybenzyl- (4d), and N-4-benzoxylbenzyl- (4e) derivatives of 3g (Table 3) were synthesized following published methodology (see Section 4).

2.2. Biochemistry and molecular docking

Tables 1–3 summarize the effects of the aforementioned compounds, plus amphetamine (3a), upon rat MAO-A and MAO-B.

Competitive inhibition of MAO-A was shown previously for several phenylisopropylamine analogues,\textsuperscript{15} and has now been demonstrated for 6-methoxynaphthylisopropylamine (2b) (Fig. 1). This type of inhibition was assumed in the remaining cases studied here.

Similarly to that seen in previous studies with amphetamine derivatives, most of the naphthylisopropylamine analogues shown in Table 1 exhibited selective MAO-A inhibitory properties with $K_i$ values in the low micromolar or submicromolar range. In agreement with one of our hypotheses, in the case of the ring-unsubstituted compounds the extension of the naphthalene as compared with benzene,\textsuperscript{19,20} as well as the negative charge-descriptor coefficients of both. Indeed, AM1 semipirical calculations performed for amphetamine (3a) and 2-naphthylisopropylamine (2a) resulted in HOMO energy values of $-9.31$ eV and $-8.69$ eV, respectively. These results further support the notion that charge-transfer interactions might be important contributors to the affinity of these types of compounds at the MAO-A active site. As discussed below, however, steric factors also appear to play a crucial role in determining MAO inhibitory potency.

\begin{table}[ht]
\centering
\caption{Naphthylisopropylamine derivatives}
\begin{tabular}{ccc}
\hline
\textbf{Compound} & \textbf{R$_1$} & \textbf{R$_2$} & \textbf{K$_i$ (mM)} \\
\hline
1 & -- & -- & 5.63 ± 0.21 \\
2a & H & H & 0.42 ± 0.04 \\
2b & H & CH$_3$O & 0.18 ± 0.05 \\
2c & H & CH$_3$CH$_2$O & 0.45 ± 0.09 \\
2d & H & CH$_3$CH$_2$CH$_2$O & 0.68 ± 0.11 \\
2e & H & CH$_3$CH$_2$CH$_2$CH$_2$O & 1.53 ± 0.07 \\
2f & H & PhCH$_2$O & 3.78 ± 0.21 \\
2g & H & CH$_3$S & 0.50 ± 0.04 \\
2h & PhCH$_3$ & CH$_3$O & 6.93 ± 0.83 \\
2i & PhCH$_3$ & CH$_3$CH$_2$CH$_2$CH$_2$O & 14.5 ± 0.50 \\
\hline
\end{tabular}
\footnotetext{\textsuperscript{a} Calculated from IC$_{50}$ values using the Cheng–Prusoff equation; $K_{in}$ (5-HT, MAO-A) = 100 $\mu$M, $K_{in}$ (DMAPEA, MAO-B) = 5 $\mu$M. ND: not determined.}
\end{table}

\begin{table}[ht]
\centering
\caption{Amphetamine derivatives}
\begin{tabular}{ccc}
\hline
\textbf{Compound} & \textbf{R$_1$} & \textbf{R$_2$} & \textbf{K$_i$ (mM)} \\
\hline
3a & H & 12.2 ± 2.72 & NE \\
3b & CH$_3$O & 0.25 ± 0.04 & NE \\
3c & CH$_3$CH$_2$O & 0.22 ± 0.02 & >100 \\
3d & CH$_3$CH$_2$CH$_2$O & 0.13 ± 0.02 & >100 \\
3e & CH$_3$CH$_2$CH$_2$CH$_2$O & 0.32 ± 0.04 & >100 \\
3f & PhCH$_3$O & 3.42 ± 0.17 & 0.71 ± 0.11 \\
3g & CH$_3$S & 0.25 ± 0.02 & NE \\
\hline
\end{tabular}
\footnotetext{\textsuperscript{a} Calculated from IC$_{50}$ values using the Cheng–Prusoff equation; $K_{in}$ (5-HT, MAO-A) = 100 $\mu$M, $K_{in}$ (DMAPEA, MAO-B) = 5 $\mu$M. NE: no effect at 100 $\mu$M.}
\end{table}
Although the substances synthesized by us are racemic mixtures, in a few instances it has been shown that (S)-arylisopropylamines are the eutomers for MAO inhibition,21–24 and therefore our docking experiments were performed with the (S) isomers. As shown in Figure 2, docking experiments revealed that compound 2a as well as 3a exhibit binding modes where their aromatic rings are oriented in such a way as to establish π–π interactions with the aromatic groups of Phe208, Tyr69 and Phe352, whereas the amino group points away from the flavin ring forming a hydrogen bond with the carbonyl group of Phe208. It should be noted that in both cases (and also for the remaining naphthylisopropylamines) a majority of the AUTODOCK runs showed the lowest docking energies associated with this orientation. The relevance of the aforementioned aromatic residues, particularly Phe208, to the establishment of molecular interactions with aromatic rings present in structurally diverse MAO-A has been highlighted in previous QSAR and molecular modeling studies.9,17,25,26

As discussed in previous reports,15,27 this binding mode provides a rationale for the inhibitory activity of these classes of compounds, since they would block the access of substrates to the active site while avoiding their own deamination by locating the amino group far from the influence of the flavin ring. Nevertheless, not only does the electron richness of the aromatic ring increase by extending the aromatic π system, but also its size. The analysis of the aromatic environment surrounding the binding poses of 2a and 3a into the active site of MAO-A, shows that Tyr444, Tyr407, and the isoalloxazine ring of FAD are located in the close vicinity (less than 6 Å) of ring B (distal to the aminopropyl moiety) of the naphthyl derivative, while these residues are approximately 2 Å further from the phenyl group of 3a, which coincides with ring A (i.e., the one linked to the alkylamino chain) of compound 2a (Fig. 2). Furthermore, the second aromatic ring of 2a establishes an additional interaction with Gln215, at a distance of 3.4 Å. Thus, the 30-fold difference in potency between 2a and 3a could be ascribed to an increased probability of establishing dispersive short length interactions common to both compounds and also to a greater number of interactions.

Interestingly, 1 and 2a which showed a difference of more than an order of magnitude in their potency as MAOI-A, differed only slightly in their binding poses (RMSD 0.5 Å, data not shown). Even though energy parameters obtained with the docking program correlated well with the experimental data, further studies are necessary to interpret the differential activity of these two positional isomers.

It is worth pointing out that compound 2a, previously referred to as PAL-287,28 has been shown to suppress cocaine self-administration in rhesus monkeys.28,29 This effect has been attributed to the dopamine and serotonin releasing properties of the drug. Considering the well documented overlap between depression and addiction,30 and the potent effect of the drug upon MAO-A demonstrated here, it is enticing to suggest that at least part of the antidepressant properties of PAL-287 might be related to its MAOI-A activity.

Data from previous SAR studies with amphetamine derivatives had shown that para-alkoxy,2 alkylthio13,15 and alkylamino11 substituents increase the activity of the parent compound versus MAO-A, and that this increase was maximal with alkyl substituents containing 2–3 carbon atoms and decreases with longer chains (Refs. 11–15 and compounds 3a–3e, Table 2). Therefore, we explored the effect of a similar substitution pattern in the naphthylisopropylamine derivatives. As shown in Table 1, compound 2b, which has a methoxyl group at position 6 of the aromatic ring, was twice as potent as its unsubstituted analogue, and slightly more active than p-methoxyamphetamine (3b). However, when the alkyl chain attached to C6 of the naphthyl moiety is lengthened, a decrease of the inhibitory activity is observed (compounds

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**Table 3**

<table>
<thead>
<tr>
<th>Compound</th>
<th>R₁</th>
<th>Kᵢ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAO-A</td>
<td>MAO-B</td>
</tr>
<tr>
<td>4a</td>
<td>H</td>
<td>100</td>
</tr>
<tr>
<td>4b</td>
<td>OH</td>
<td>100</td>
</tr>
<tr>
<td>4c</td>
<td>OCH₃</td>
<td>100</td>
</tr>
<tr>
<td>4d</td>
<td>OCH₂CH₂CH₂CH₃</td>
<td>90 ± 2.12</td>
</tr>
<tr>
<td>4e</td>
<td>OCH₂Ph</td>
<td>100</td>
</tr>
</tbody>
</table>

*Calculated from IC₅₀ values using the Cheng-Prusoff equation; Kₐ (5-HT, MAO-A) = 100 µM, Kᵢ (DMAPEA, MAO-B) = 5 µM. NE: no effect at 100 µM.*

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**Figure 1.** Lineweaver–Burk plot for the inhibition of rat MAO-A by 2b.

**Figure 2.** Superimposed structures of compounds 2a (orange) and 3a (blue), docked into the active site of MAO-A. For the sake of clarity, some residues are not shown.
The docking poses of 2b–2e suggest the appearance of a steric repulsion when trying to accommodate substituents longer than methoxyl between Tyr407 and Tyr444 (Fig. 3). It should be pointed out that, lacking such steric repulsion, a hydrogen bond involving the hydroxyl group of Tyr407 and the ether oxygen atom further stabilizes the interaction of 2a with the enzyme.

Indeed, compounds 2b and 3d, which were the most potent of their corresponding series, occupied virtually the same region of the MAO-A active site (Fig. 4), giving a clear indication about the optimal length of the ligand required to attain maximal inhibitory activity. In fact, the maximal hydrogen–hydrogen distances in the most favorable binding conformations of 2b and 3d are 10.5 and 10.3 Å, respectively.

Unexpectedly, when the oxygen atom of compound 2b was replaced by a sulfur atom to give compound 2g, this produced a decrease in potency versus MAO-A. In previous studies with several 4-substituted amphetamine derivatives such an isosteric replacement always resulted in improved inhibitory activities.12,13 Again, the greater length of the S–C bond as compared with the O–C bond (about 1.8 vs 1.4 Å) might be enough to exceed the optimal size of the ligand, thus explaining the lower activity of compound 2g.

Previous studies had shown that 4-substituted amphetamine derivatives generally show little or no activity versus MAO-B.12,13 Interestingly, compound 3f, which was the least potent MAO-I-A of the phenylisopropylamine series with the exception of amphetamine itself (Table 2), showed a considerable effect upon MAO-B, a behavior that was similar to that exhibited by the corresponding naphthylisopropylamine analogue (2f, Table 1), indicating that the benzyloxy group is an attractive substituent to modulate the selectivity of this type of drugs.

None of the N-benzyl-4-methylthioamphetamine derivatives studied (compounds 4a–4e, Table 3) showed significant effects upon MAO activities. A similar, though lesser decrease in potency regarding the parent compound was also observed in the case of the two N-benzyl-naphthylisopropylamine derivatives (2h and 2i, Table 1). Although for amphetamine derivatives it has been reported that the presence of relatively small alkyl substituents on the amino group leads to a decrease of MAO-A inhibitory activity;12,24 there were no data about the influence of the introduction of aromatic substituents that might establish additional interactions with protein residues. The present results indicate that, in line with previous data, N-benzyl substitution also produces a decrease in potency of either amphetamine or naphthylisopropylamine derivatives. This lack of activity could indicate that either the ligand does not reach the active site or that, once there, it is unable to establish attractive interactions with certain amino acid residues. In agreement with our experimental results, the docking data showed that high interaction energies (positive values in most cases) were obtained for all binding poses of the ligands at the MAO-A active site. Besides providing a possible explanation for the lack of inhibitory activity of this kind of compounds, these theoretical results give further support to the predictive value of

![Figure 3](image-url) Comparison of the binding modes of compounds 2b (left panel) and 2e (right panel), which exemplifies the appearance of a steric repulsion and the lack of a hydrogen bond when trying to accommodate substituents longer than methoxyl between Tyr407 and Tyr444.

![Figure 4](image-url) Superimposed structures of compounds 2b (purple) and 3d (green), docked into the active site of MAO-A. Some residues are not shown.
molecular simulation when analyzing their interactions with MAOs.

3. Conclusions

Two hypotheses, based on the published MAO crystal structures, considering modifications of the amphetamine scaffold, were evaluated. In one case, an increased electron-donating capacity and size of the aromatic moiety by replacing the phenyl ring of amphetamine (3a) by naphthalene (1 and 2a), resulted in more potent compounds. Nevertheless, this effect can be offset by the introduction of substituents at C6 of the naphthalene ring leading to molecules that exceed an optimal length. Aside from specific considerations for the naphthylisopropylamine series, the replacement of a phenyl by a naphthyl ring provides heretofore unused positions on the aromatic moiety, which can be exploited for drug design. In the other case, extension of the arylisopropylamine molecule by N-benzylation of the amino group led to a decrease in potency as MAOI.

Finally, further studies are desirable to assess the possible role of MAO-A inhibition in the antiaddictive properties of PAL-287 and, presumably, its analogues.

4. Experimental

4.1. Chemistry

All reagents and solvents were commercially available and were used without further purification. Amphetamine sulfate (3a) was purchased from Sigma (St. Louis, MO). The naphthylisopropylamines (1, 2a–2g) and amphetamines (3b–3g) were synthesized following standard published methods24,31–33 which involved the condensation of appropriately substituted aromatic aldehydes with nitroethane, the subsequent reduction of the corresponding nitrostyrenes with LiAlH4 and the final preparation of the amine via Grignard reaction of O-alkylated derivatives of 6-bromo-2-naphthol (140 mmol) in acetic acid (60 ml). The reaction mixture was added Br2 (14 ml) in acetic acid (14 ml). The reaction mixture was refluxed for 3 h during which three portions of Sn (2 × 0.03 mol and 0.12 mol) were added. Then, the mixture was cooled to 50 °C, and the Sn salts formed were filtered and discarded. The remaining solution was poured into cold water (400 ml) where the product precipitated as a pink powder. Yield 64%, mp 124.5–127.5 °C (lit.35 123–127 °C). 1H NMR (CDCl3) δ 7.92 (s, H, ArH), 7.67 (d, 1H, J = 9.6 Hz, ArH), 7.56 (d, 1H, J = 8.8 Hz, ArH), 7.49 (d, 1H, J = 8.9 Hz, ArH), 7.12 (s, 2H, ArH), 5.03 (s, 1H, OH).

4.1.2. General procedure for the preparation of 6-alkoxy-2-bromo-naphthalenes

To a stirred solution of 6-bromo-2-naphthol (1 mmol) in CH2CN (100 ml), K2CO3 (3 mmol) and the appropriate alkyll halide (2 mmol) were added. The reaction mixture was refluxed and stirred for 24 h and then the solvent was removed by rotary evaporation. The product (a white solid) was extracted with EtOAc and 25% NaOH (2 × 100 ml) and then with H2O (2 × 100 ml). The organic layer was dried over Na2SO4 and concentrated. The product crystallized after adding methanol.

4.1.2.1. 2-Bromo-6-methoxy-naphthalene. Yield 81%, mp 102.5–104.0 °C. 1H NMR (CDCl3) δ 7.89 (s, 1H, ArH), 7.62 (d, 1H, J = 9.1 Hz, ArH), 7.58 (d, 1H, J = 8.8 Hz, ArH), 7.47 (dd, 1H, J1 = 8.6 Hz, J2 = 1.9 Hz, ArH), 7.14 (dd, 1H, J1 = 9.1 Hz, J2 = 2.4 Hz, ArH), 7.08 (d, 1H, J = 2.1 Hz, ArH), 3.89 (s, 3H, OCH3).

4.1.2.2. 2-Bromo-6-ethoxynaphthalene. Yield 67%, mp 72.9–76.3 °C. 1H NMR (CDCl3) δ 7.91 (s, 1H, ArH), 7.64 (d, 1H, J = 9.1 Hz, ArH), 7.58 (d, 1H, J = 8.8 Hz, ArH), 7.49 (d, 1H, J = 8.6 Hz, ArH), 7.16 (dd, 1H, J1 = 9.1 Hz, J2 = 2.3 Hz, ArH), 7.09 (s, 1H, ArH), 4.14 (q, 2H, J = 7.1 Hz, CH2CH2O), 1.48 (t, 3H, J = 6.8 Hz, CH3CH2O).

4.1.2.3. 2-Bromo-6-propoxynaphthalene. Yield 80%, mp 64.7–65.1 °C. 1H NMR (CDCl3) δ 7.95 (s, 1H, ArH), 7.68 (d, 1H, J = 8.9 Hz, ArH), 7.59 (d, 1H, J = 8.6 Hz, ArH), 7.53 (dd, 1H, J1 = 8.9 Hz, J2 = 2.1 Hz, ArH), 7.21 (dd, 1H, J1 = 8.8 Hz, J2 = 2.5 Hz, ArH), 7.13 (d, 1H, J = 2.3 Hz, ArH), 4.07 (t, 2H, J = 6.6 Hz, CH2CH2CH2O), 1.92 (m, 2H, CH2CH2CH2O), 1.13 (t, 3H, J = 7.6 Hz, CH3CH2CH2O).

4.1.2.4. 2-Bromo-6-butoxynaphthalene. Yield 54%, mp 54.0–55.3 °C. 1H NMR (CDCl3) δ 7.90 (s, 1H, ArH), 7.63 (d, 1H, J = 8.8 Hz, ArH), 7.58 (d, 1H, J = 8.6 Hz, ArH), 7.48 (dd, 1H, J1 = 8.8 Hz, J2 = 1.8 Hz, ArH), 7.15 (d, 1H, J1 = 9.1 Hz, J2 = 2.5 Hz, ArH), 7.08 (d, 1H, J = 2.3 Hz, ArH), 4.06 (t, 2H, J = 6.6 Hz, CH2CH2CH2CH2O), 1.83 (m, 2H, CH2CH2CH2CH2O), 1.53 (m, 2H, CH2CH2CH2CH2O), 1.00 (t, 3H, J = 7.7 Hz, CH3CH2CH2CH2O).

4.1.2.5. 6-Benzyl-2-bromonaphthalene. Yield 50%, mp 89.5–94.8 °C. 1H NMR (CDCl3) δ 7.97 (s, 1H, ArH), 7.71 (d, 1H, J = 9.1 Hz, ArH), 7.64 (d, 1H, J = 8.6 Hz, ArH), 7.53 (m, 3H, ArH), 7.46 (m, 2H, ArH), 7.40 (d, 1H, J = 7.6 Hz, ArH), 7.28 (d, 1H, J = 2.5 Hz, ArH), 7.23 (d, 1H, J = 2.5 Hz, ArH), 5.22 (s, 2H, ArCH2).

4.1.3. General procedure for the preparation of 6-alkoxy-2-naphthaldehydes

The appropriate 6-alkoxy-2-bromonaphthalene (1 mmol) dissolved in dry tetrahydrofuran (THF: 50 ml), was added dropwise to a mixture of 1.2 g of Mg and an I2 crystal in dry THF (100 ml) and refluxed under N2 for 4 h. After cooling to 0 °C, DMF (1.2 mmol) was added, and the mixture was left at room temperature for 24 h. After evaporating the solvent, acetic acid (10%, 60 ml) was added and the mixture was extracted with DCM. The organic layer was dried over Na2SO4 and concentrated. The product crystallized after adding methanol.

4.1.3.1. 6-Methoxy-2-naphthaldehyde. Yield 40%, mp 77.0–80.8 °C (yellow crystals). 1H NMR (CDCl3) δ 10.07 (s, 1H, CHO), 8.23 (s, 1H, ArH), 7.90 (dd, 1H, J1 = 8.5 Hz, J2 = 1.2 Hz, ArH), 7.07 (d, 1H, J = 8.8 Hz, ArH), 7.78 (d, 1H, J = 8.5 Hz, ArH), 7.21 (dd, 1H, J = 8.5 Hz, ArH), 7.12 (s, 1H, OH).
\[ J_1 = 8.8 \text{ Hz}, J_2 = 2.8 \text{ Hz}, \text{ArH} \], 7.16 (d, 1H, J = 2.1 Hz, ArH), 3.94 (s, 3H, CH3O).}{1.3.2. 6-Ethoxy-2-naphthaldehyde. Yield 21\%, mp 67.3–68.1 °C (yellow crystals).}{1H NMR (CDCl3) \( \delta \) 10.07 (s, 1H, CHO), 8.22 (s, 1H, ArH), 7.89 (dd, 1H, J = 8.8 Hz, J2 = 1.8 Hz, ArH), 8.77 (d, 1H, J = 9.3 Hz, ArH), 7.76 (d, 1H, J = 8.3 Hz, ArH), 7.21 (dd, 1H, J1 = 8.8 Hz, J2 = 2.6 Hz, ArH), 7.14 (d, 1H, J = 2.3 Hz, ArH), 4.17 (q, J = 7.1 Hz, CH2CH2O), 1.48 (t, 3H, J = 6.8 Hz, CH3CH2O).}{1.3.3. 6-Propoxy-2-naphthaldehyde. Yield 25\%, mp 43.0–44.5 °C (yellow crystals).}{1H NMR (CDCl3) \( \delta \) 10.08 (s, 1H, CHO), 8.24 (s, 1H, ArH), 7.91 (d, 1H, J = 7.4 Hz, ArH), 7.88 (d, 1H, J = 9.0 Hz, ArH), 7.77 (d, 1H, J = 8.6 Hz, ArH), 7.23 (dd, 1H, J1 = 9.0 Hz, J2 = 2.4 Hz, ArH), 7.16 (d, 1H, J = 1.8 Hz, ArH), 3.97 (t, 2H, J = 6.4 Hz, CH2CH2CH2O), 1.89 (m, 2H, CH2CH2CH2O), 1.09 (t, 3H, J = 7.4 Hz, CH3CH2O).}{1.3.4. 6-Butoxy-2-naphthaldehyde. Yield 43\%, mp 31.5–33.0 °C (yellow crystals).}{1H NMR (CDCl3) \( \delta \) 10.09 (s, 1H, CHO), 8.24 (s, 1H, ArH), 7.91 (d, 1H, J = 9.0 Hz, J2 = 1.6 Hz, ArH), 7.89 (d, 1H, J = 9.4 Hz, ArH), 7.78 (d, 1H, J = 8.6 Hz, ArH), 7.23 (dd, 1H, J1 = 8.9 Hz, J2 = 2.5 Hz, ArH), 7.16 (d, 1H, J = 2.4 Hz, ArH), 4.12 (t, 2H, J = 6.4 Hz, CH2CH2CH2O), 1.86 (m, 2H, CH2CH2CH2O), 1.55 (m, 2H, CH2CH2CH2O), 1.01 (t, 3H, J = 7.3 Hz, CH3CH2CH2O).}{1.4. General procedure for the preparation of naphthylhydroxyarylamine hydrochlorides (1 and 2a–2f)\}: LiAlH4 (10 mmol) was carefully suspended in dry THF (60 ml) with good stirring. Then, the corresponding nitrosoarene (1 mmol) dissolved in THF (30 ml) was added dropwise. The reaction mixture was refluxed and stirred for 3 days. After cooling to room temperature, excess hydride was destroyed by careful dropwise addition of water and then NaOH (15\%; 3:1 in relation to the hydride). The mixture was filtered to remove the insoluble salts, dried with MgSO4 and the solvent evaporated under reduced pressure. In all cases the amine was obtained as an oil that was purified by distillation using a Kugelrohr device. The product was taken up into a minimal quantity (3 ml) of 2-propanol and converted to the hydrochloride by adding concentrated HCl (4–5 drops). The solution was diluted with anhydrous ether, which resulted in the formation of white crystals.
4.1.5.4. (6-Ethoxy-2-naphthyl)-2-aminopropane hydrochloride (2c). Yield 30%, mp 252.9–254.5 °C. 1H NMR (D2O) δ 7.63 (d, 2H, J = 8.9 Hz, ArH), 7.52 (s, 1H, ArH), 7.20 (dd, 1H, J1 = 8.3 Hz, J2 = 1.3 Hz, ArH), 7.15 (d, 1H, J = 2.3 Hz, ArH), 7.01 (dd, 1H, J1 = 8.9 Hz, J2 = 2.3 Hz, ArH), 4.01 (q, 2H, J = 6.8 Hz, OCH2CH3), 3.48 (m, 1H, ArCH2CH(CH3)NH2+). 2.85 (d, 2H, J = 7.1 Hz, ArCH2), 1.23 (t, 3H, J = 7.1 Hz, OCH2CH3 ). 1.11 (d, 3H, J = 6.8 Hz, ArCH2CH(CH3)NH2+). Anal. Calcd for C15H20ClNO: C, 67.79; H, 7.58; N, 5.27. Found: C, 68.05; H, 7.23; N, 5.14.

4.1.5.5. (6-Propoxy-2-naphthyl)-2-aminopropane hydrochloride (2f). Yield 14%, mp 234.5–237.0 °C. 1H NMR (CDCl3) δ 7.63 (d, 2H, J = 8.6 Hz, ArH), 7.60 (s, 1H, ArH), 7.29 (dd, 1H, J1 = 8.9 Hz, J2 = 2.5 Hz, ArH), 7.09 (dd, 1H, J1 = 5.3 Hz, J2 = 13.4 Hz, ArH), 7.14 (m, 2H, CH2CH2CH2O), 1.08 (d, 3H, J = 6.6 Hz, ArCH2CH(CH3)NH2+). 0.96 (t, 3H, J = 7.3 Hz, CH2CH2CH2O). Anal. Calcd for C17H22ClNO: C, 73.27; H, 6.76; N, 4.27. Found: C, 73.05; H, 6.74; N, 4.27.

4.1.6. Preparation of 6-O-(2-bromonaphthyl)-dimethylcarbamate
The previously prepared 6-bromo-2-naphthol (1 mmol) was dissolved in DMF (100 ml) with good stirring at −10 °C, and then NaH (1.5 mmol) was carefully added. Then, dimethylthiocarbamoyl chloride (1.5 mmol) dissolved in DMF (50 ml) was added, and this reaction mixture was kept at 80–90 °C for 48 h. After cooling to room temperature, KOH (15%, 200 ml) was added and the mixture extracted with DCM. The organic layer was dried with Na2SO4 and after filtering, removal of the solvent in vacuo gave the product, which was recrystallized from methanol. Yield 54%, mp 128.3–129.5 °C (white crystals). 1H NMR (CDCl3) δ 8.02 (s, 1H, ArH), 7.77 (d, 1H, J = 8.9 Hz, ArH), 7.68 (d, 1H, J = 8.9 Hz, ArH), 7.56 (dd, 1H, J1 = 8.8 Hz, J2 = 2.0 Hz, ArH), 7.48 (d, 1H, J = 2.02, ArH), 7.29 (dd, 1H, J1 = 8.8 Hz, J2 = 2.3 Hz, ArH), 3.49 (s, 3H, NCH3). 2.85 (d, 2H, J = 7.1 Hz, ArCH2). 1.23 (t, 3H, J = 7.1 Hz, OCH2CH3). 1.11 (d, 3H, J = 6.8 Hz, ArCH2CH(CH3)NH2+). Anal. Calcd for C17H18Br2ClNO: C, 52.63; H, 5.01; N, 3.42. Found: C, 53.05; H, 5.19; N, 3.41.

4.1.7. Preparation of 6-S-(2-bromonaphthyl)-dimethylcarbamate
The compound prepared in the previous step was melted and kept at 220 °C for 6 h and the product was purified by column chromatography on Silica Gel 60, eluting with DCM. After recrystallization from methanol the product was obtained as yellow crystals. Yield 50%, mp 111.3–113.5 °C. 1H NMR (CDCl3) δ 8.00 (d, 2H, J = 9.4 Hz, ArH), 7.76 (d, 1H, J = 8.6 Hz, ArH), 7.69 (d, 1H, J = 8.6 Hz, ArH), 7.57 (d, 2H, J = 8.6 Hz, ArH), 3.09 (s, 6H, N(CH3)2).

4.1.8. Preparation of 6-bromo-2-mercaptoponaphthalene
A mixture of the compound prepared in the previous step (1 mmol) in methanol (50 ml) and KOH (10 mmol) was refluxed for 24 h. After cooling to room temperature, the mixture was made acid with concentrated HCl, extracted with DCM, dried with MgSO4, and filtered; and the solvent evaporated under reduced pressure. Finally the product was recrystallized from methanol. Yield 63%, mp 158.3–163.5 °C (white crystals). 1H NMR (CDCl3) δ 7.93 (s, 1H, ArH), 7.70 (s, 1H, ArH), 7.63 (d, 1H, J = 8.6 Hz, ArH), 7.55 (d, 2H, J = 4.0, ArH), 7.35 (d, 1H, J = 8.6, ArH).

4.1.9. Preparation of 2-bromo-6-methylthionaphthalene
This compound was prepared following the same general procedure used for the synthesis of 2-bromo-6-alkoxynaphthalenes (step 4.1.2.). Yield 86%, mp 87.6–88.9 °C (white crystals). 1H NMR (CDCl3) δ 7.97 (s, 1H, ArH), 7.68 (d, 1H, J = 9.1 Hz, ArH), 7.64 (d, 1H, J = 9.1 Hz, ArH), 7.57 (d, 2H, J = 8.6 Hz, ArH), 7.43 (dd, 1H, J1 = 8.6 Hz, J2 = 1.5 Hz, ArH), 2.62 (s, 3H, SCH3).

4.1.10. Preparation of 2-cyano-6-methylthionaphthalene
To a solution of the compound prepared in the previous step (1 mmol) in DMF (70 ml), CuCN (1.5 mmol) was added and the mixture was refluxed for 48 h. After cooling to room temperature, the reaction mixture was poured into ice/water, made basic with Na2CO3, extracted with DCM, dried with Na2SO4 and filtered; and the solvent evaporated under reduced pressure. The product crystallized after adding methanol. Yield 72%, mp 108.8–110.3 °C (white crystals). 1H NMR (CDCl3) δ 8.19 (s, 1H, ArH), 7.81 (t, 2H, J = 9.1 Hz, ArH), 7.63 (dd, 1H, J1 = 8.6 Hz, J2 = 1.5 Hz, ArH), 7.60 (s, 1H, ArH), 7.50 (dd, 1H, J1 = 9.1 Hz, J2 = 2.0 Hz, ArH), 2.52 (s, 3H, SCH3).

4.1.11. Preparation of 6-methylthio-2-naphthaldehyde
To a solution of the compound prepared in the previous step (1 mmol) in THF (50 ml), 5 ml of DIBAH (1 M in THF) were added, and the reaction mixture was kept at room temperature for 4 h. Then, methanol and water made acid with drops of H2SO4 were added giving a gelatinous product, which was filtered over Celite. The product was evaporated under reduced pressure and the product crystallized after adding methanol (yield 58.2%). The final product was recognized by TLC, developing with 2,4-dinitrophenylhydrazine, and used in the subsequent steps without further purification.

4.1.12. Preparation of 1-(6-methylthio-2-naphthyl)-2-nitropropane
This compound was prepared following the same general procedure used for the synthesis of naphthyl-nitropropanes (step 4.1.4.). Yield 42%, mp 99.6–101.6 °C (yellow crystals). 1H NMR (CDCl3) δ 8.27 (s, 1H, ArCH), 7.91 (s, 1H, ArH), 7.82 (m, 2H, ArH), 7.62 (s, 1H, ArH), 7.56 (dd, 1H, J1 = 8.6 Hz, J2 = 1.5 Hz, ArH), 7.46 (dd, 1H, J1 = 8.6 Hz, J2 = 2.0 Hz, ArH), 2.65 (s, 3H, CH3CN=O2), 2.59 (s, 3H, SCH3).

4.1.13. Preparation of (6-methylthio-2-naphthyl) isopropylamine hydrochloride (2g)
This compound was prepared following the same general procedure used for the synthesis of the other naphthylisopropylamine hydrochlorides (step 4.1.5.). Yield 47%, mp 216–219 °C (yellow crystals). 1H NMR (DMSO-d6) δ 7.81 (m, 2H, ArH), 7.71 (s, 2H, ArH), 7.40 (d, 2H, J = 8.6 Hz, ArH), 3.52 (m, 1H, ArCH2...
3.14 (dd, 1H, J = 5.6 Hz, J = 13.1 Hz, ArCH), 2.83 (dd, 1H, J = 8.6 Hz, J = 13.1 Hz, ArCH), 2.58 (s, 3H, SCH), 1.15 (d, 3H, J = 6.1 Hz, ArCH₂CH₂CH₂(NH)₂). Anal. Calc. for C₁₅H₂₀ClN₃O₂: C, 62.67; H, 7.23; N, 5.25; S, 11.97. Found: C, 61.03; H, 7.62; N, 5.15; S, 13.17.

4.1.14. General procedure for the preparation of N-benzyl derivatives (2h and 2i and 4a–4e)

To a well-stirred solution of the appropriate amine (compounds 2b, 2e or 3g: 1 mmol) as a free base in methanol (50 ml), was added dropwise the corresponding benzaldehyde (1 mmol), stirring at room temperature for 24 h. To this mixture was added Na₂B₄O₇·11H₂O solution (1.5 mL) and stirring was continued for additional 20 min. NaOH 40% (3 mL) was added to terminate the reaction. After removing the solvent under vacuum the product was purified by preparative TLC (Silica Gel 60, ElOAc). In all the cases the product was obtained as an oil, which was dissolved in a minimal volume of 2-propanol and converted to the hydrochloride by adding concentrated HCl (1–3 drops). The solution was diluted with anhydrous ether, which resulted in the formation of white crystals.

4.1.14.1. N-Benzy1-(6-methoxy-2-naphthyl)-2-aminopropane hydrochloride (2h). Yield 25%, mp 215.0–218.0°C. ¹H NMR (CDCl₃) δ 7.65 (d, 2H), J = 8.3 Hz, ArH), 7.51 (s, 1H, ArH), 7.22 (m, 6H, ArH), 7.12 (d, 2H, J = 9.6 Hz, ArH), 3.90 (s, 3H, OCH₃). 3.87 (d, 1H, J = 13.1 Hz, NHCH₂Ar), 3.76 (d, 1H, J = 13.1 Hz, NHCH₂Ar), 3.05 (m, 1H, ArCH₂CH₂CH₂(NH)₂⁺), 2.91 (dd, 1H, J = 7.1 Hz, J = 13.6 Hz, ArCH), 2.77 (dd, 1H, J = 6.6 Hz, J = 13.4 Hz, ArCH), 1.44 (3H, J = 6.1 Hz, ArCH₂CH₂CH₂(NH)₂⁺). Anal. Calc. for C₂₃H₂₆ClN₂O: C, 73.78; H, 7.08; N, 4.10. Found: C, 72.33; H, 7.36; N, 4.25.

4.1.14.2. N-Benzyl-(6-butoxy-2-naphthyl)-2-aminopropane hydrochloride (2i). Yield 18% mp 210.0–214.0°C. ¹H NMR (D₂O) δ 7.72 (s, 1H, ArH), 7.17 (d, 1H, J = 1.8 Hz, ArH), 7.61 (s, 1H, ArH), 7.57 (d, 2H, J = 6.6 Hz, ArH), 7.40 (m, 3H, ArH), 7.27 (d, 1H, J = 8.6 Hz, ArH), 7.24 (d, 1H, J = 2.0 Hz, ArH), 7.09 (dd, 1H, J = 9.1 Hz, J = 2.5 Hz, ArH), 4.20 (m, 2H, NH₂CH₂Ar), 4.02 (t, 2H, J = 6.6 Hz, CH₂CH₂CH₂CH₂O), 3.40 (d, 2H, J = 13.4 Hz, ArCH₂), 2.75 (m, 1H, ArCH₂CH₂CH₂(NH)₂⁺), 1.70 (m, 2H, CH₂CH₂CH₂CH₂O), 1.42 (m, 2H, CH₂CH₂CH₂CH₂O), 1.15 (d, 3H, J = 6.3 Hz, ArCH₂CH₂CH₂(NH)₂⁺). 0.90 (t, 3H, J = 7.3 Hz, CH₂CH₂CH₂CH₂O). Anal. Calc. for C₂₆H₃₃ClN₂O: C, 75.08; H, 7.88; N, 3.65. Found: C, 74.59; H, 9.18; N, 3.81.

4.1.14.3. N-Benzyl-(4-methylthioamphetamine) hydrochloride (4a). Yield 90%, mp 184.0–185.3°C. ¹H NMR (CDCl₃) δ 10.03 (3H, J = 9.1 Hz, ArH), 7.65 (d, 2H, J = 7.0 Hz, ArH), 7.45–7.25 (m, 3H, ArH), 7.15 (d, 2H, J = 8.3 Hz, ArH), 7.01 (d, 2H, J = 8.3 Hz, ArH), 4.10 (d, 1H, J = 3.6 Hz, NH₂CH₂Ar), 4.02 (d, 1H, J = 3.6 Hz, NH₂CH₂Ar), 3.41 (dd, 2H, J = 13.1 Hz, J = 3.6 Hz, ArCH₂CH₂CH₂(NH)₂⁺), 3.45 (dd, 2H, J = 3.6 Hz, NH₂CH₂Ar), 3.13 (m, 1H, ArCH₂CH₂CH₂(NH)₂⁺), 2.77 (dd, 1H, J = 12.9 Hz, NH₂CH₂Ar), 2.45 (s, 3H, CH₃S), 1.31 (d, 3H, J = 6.4 Hz, CH₂CH₂(NH)₂⁺). Anal. Calc. for C₁₅H₁₇N₂O: C, 66.32; H, 7.20; N, 4.55; S, 10.41. Found: C, 66.41; H, 7.58; N, 4.74; S, 12.76.

4.1.14.4. N-4-Hydroxybenzyl-(4-methylthioamphetamine) hydrochloride (4b). Yield 94%, mp 198.3–199.5°C. ¹H NMR (CDCl₃/ DMSO-d₆) δ 9.63 (s, 3H, NH₂), 9.36 (s, 1H, ArH), 7.45 (d, 2H, J = 8.5 Hz, ArH), 7.18 (d, 2H, J = 8.2 Hz, ArH), 7.12 (d, 2H, J = 8.2 Hz, ArH), 6.87 (d, 2H, J = 8.4 Hz, ArH), 4.04 (m, 2H, NH₂CH₂Ar), 3.38 (dd, 1H, J = 12.8 Hz, J = 3.6 Hz, ArCH₂CH₂(NH)₂⁺), 3.26 (m, 1H, ArCH₂CH₂(NH)₂⁺), H⁺CH₂Ar), 2.78 (dd, 1H, J = 12.9 Hz, ArCH₂CH₂(NH)₂⁺), 2.47 (s, 3H, CH₃S), 1.29 (d, 3H, J = 6.4 Hz, CH₂CH₂(NH)₂⁺). Anal. Calc. for C₁₅H₁₇N₂O: C, 63.04; H, 6.85; N, 4.32; S, 9.90. Found: C, 61.27; H, 7.72; N, 4.30; S, 12.07.
the FAD molecule were built using Insight II, and the structures were relaxed following a minimization protocol using Discover, and the ESFF force field. The grid maps were calculated using the autogrid option and were centered on the putative ligand-binding site. The volumes chosen for the grid maps were made up of 40 x 40 x 40 points, with a grid-point spacing of 0.375 Å. The partial charges of different compounds were corrected using RESP methodology. The dielectric constant was adjusted to 2 in the grid parameter file (gpf) of the Autodock suite. The docked compound complexes were built using the lowest docked-energy binding positions. Although both enantiomers of compounds were studied, in all cases the results obtained for the (S)-isomers were used for the analysis.

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References and notes