Naphthylisopropylamine and *N*-benzylamphetamine derivatives as monoamine oxidase inhibitors

Marcelo Vilches-Herrera [a], Juan Miranda-Sepúlveda [b], Marco Rebolledo-Fuentes [a,c], Angélica Fierro [c,d], Susan Lühr [a], Patricio Iturriaga-Vasquez [a,c], Bruce K. Cassels [a,c], Miguel Reyes-Parada [b,c,*]

[a] *Department of Chemistry, Faculty of Sciences, University of Chile, Casilla 653, Santiago, Chile*
[b] *School of Medicine, Faculty of Medical Sciences, University of Santiago de Chile, Alameda 3363, Santiago, Chile*
[c] *Millennium Institute for Cell Dynamics and Biotechnology, Beauchef 861, Santiago, Chile*
[d] *Faculty of Chemistry and Biology, University of Santiago de Chile, Alameda 3363, Santiago, Chile*

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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 MAOI-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 π 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,[9] *N,N*′-bis[2-oxo-2*H*-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**),[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-aminopropane (**2a**), and 1-(6-methoxy- (**2b**), ethoxy- (**2c**), propoxy- (**2d**), butoxy-(**2e**), benzyloxy- (**2f**), and methylthio- (**2g**) 2-naphthyl)-2-amino-propanes, the N-benzyl derivatives of **2b** and **2e** (**2h** and **2i**, respectively) (Table 1), 1-(4-methoxy- (**3b**), ethoxy- (**3c**), propoxy- (**3d**), butoxy- (**3e**), benzyloxy- (**3f**) and methylthio- (**3g**) phenyl)-2-aminopropanes (Table 2), and the N-benzyl- (**4a**), N-4-hydroxyben-zyl- (**4b**), N-4-methoxybenzyl- (**4c**), N-4-butoxybenzyl- (**4d**), and N-4-benzyloxybenzyl- (**4e**) derivatives of **3g** (Table 3) were synthesized following published methodology (see Section 4).
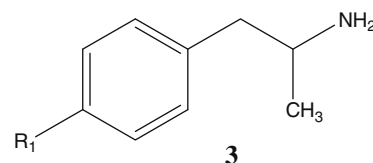
2.2. Biochemistry and molecular docking

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,[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
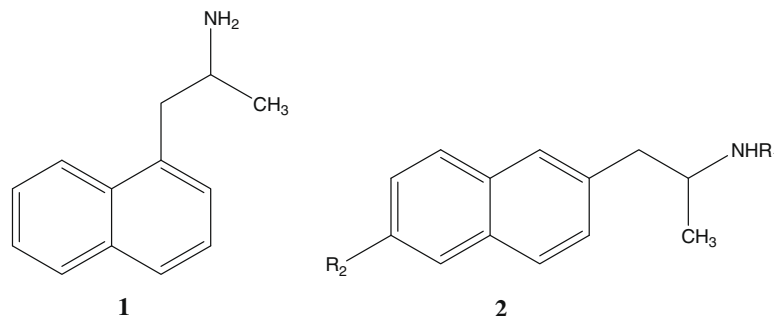
Table 2
Amphetamine derivatives

Compound	R_1	K_i [a] (μM)	
		MAO-A	MAO-B
3a	H	12.2 ± 2.72	NE
3b	CH_3O	0.25 ± 0.04	NE
3c	CH_3CH_2O	0.22 ± 0.02	>100
3d	$CH_3CH_2CH_2O$	0.13 ± 0.02	>100
3e	$CH_3CH_2CH_2CH_2O$	0.32 ± 0.04	>100
3f	$PhCH_2O$	3.42 ± 0.17	0.71 ± 0.11
3g	CH_3S	0.25 ± 0.02	NE

[a] Calculated from IC$_{50}$ values using the Cheng–Prusoff equation; K_m (5-HT, MAO-A) = 100 μM, K_m (DMAPEA, MAO-B) = 5 μM. NE: no effect at 100 μM.

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 π system from a phenyl (amphetamine; **3a**) to a naphthyl ring (**1 and 2a**) induced an increase of the inhibitory potency. According to Vallejos et al.,[14] this finding could be expected on the basis of the higher HOMO energy of naphthalene as compared with benzene,[19,20] as well as the negative charge-descriptor coefficients of both. Indeed, AM1 semiempirical 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.
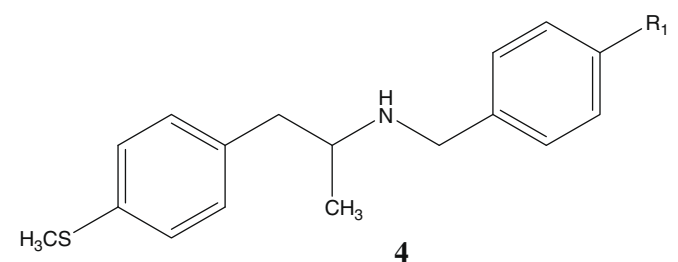
Table 1
Naphthylisopropylamine derivatives

Compound	R_1	R_2	K_i[a] (μM)	
			MAO-A	MAO-B
1	—	—	5.63 ± 0.21	>100
2a	H	H	0.42 ± 0.04	>100
2b	H	CH_3O	0.18 ± 0.05	16.3 ± 7.78
2c	H	CH_3CH_2O	0.45 ± 0.09	13.6 ± 3.33
2d	H	$CH_3CH_2CH_2O$	0.68 ± 0.11	13.5 ± 0.038
2e	H	$CH_3CH_2CH_2CH_2O$	1.53 ± 0.07	ND
2f	H	$PhCH_2O$	3.78 ± 0.21	2.56 ± 0.35
2g	H	CH_3S	0.50 ± 0.04	ND
2h	$PhCH_2$	CH_3O	6.93 ± 0.83	24.7 ± 1.21
2i	$PhCH_2$	$CH_3CH_2CH_2CH_2O$	14.5 ± 0.50	22.2 ± 5.83

[a] Calculated from IC$_{50}$ values using the Cheng–Prusoff equation; K_m (5-HT, MAO-A) = 100 μM, K_m (DMAPEA, MAO-B) = 5 μM. ND: not determined.

Table 3
N-Benzyl-4-methylthioamphetamine derivatives

Compound	R$_1$	K_i ^{a} (µM)	
		MAO-A	MAO-B
4a	H	>100	>100
4b	OH	>100	>100
4c	OCH$_3$	>100	NE
4d	OCH$_2$CH$_2$CH$_2$CH$_3$	90 ± 2.12	NE
4e	OCH$_2$Ph	>100	NE

^{a} Calculated from IC$_{50}$ values using the Cheng–Prusoff equation; K_m (5-HT, MAO-A) = 100 µM, K_m (DMAPEA, MAO-B) = 5 µM. NE: no effect at 100 µM.
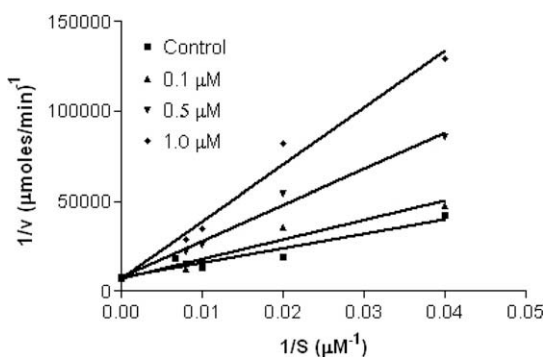

Figure 1. Lineweaver–Burk plot for the inhibition of rat MAO-A by **2b**.
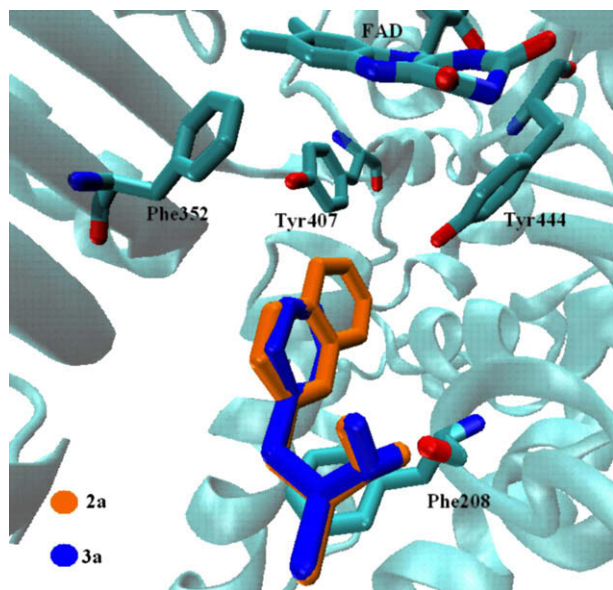

Figure 2. Superimposed structures of compounds **2a** (orange) and **3a** (blue), docked into the active site of MAO-A. For the sake of clarity, some residues are not shown.

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 MAOI-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, Phe177 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 anti-addictive 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,[12] alkylthio[13,15] and alkylamino[11] 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 naphthyl-isopropylamine 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 alkoxyl chain attached to C6 of the naphthyl moiety is lengthened, a decrease of the inhibitory activity is observed (compounds
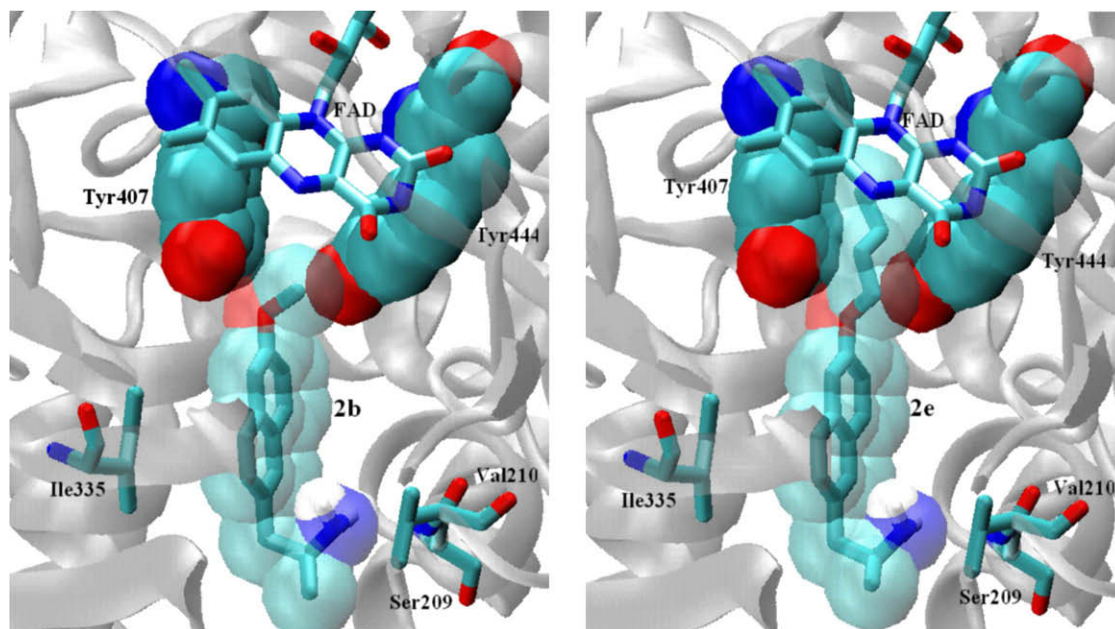
Figure 3. Comparison of the binding modes of compounds **2b** (left panel) and **2e** (right panel), which exemplifies the appearance of a steric repulsion and the lack of a hydrogen bond when trying to accommodate substituents longer than methoxyl between Tyr407 and Tyr444.

2c–2e). 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.
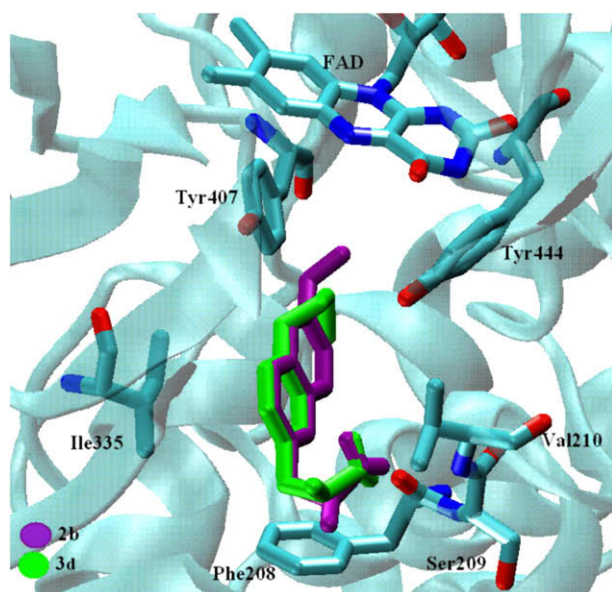

Figure 4. Superimposed structures of compounds **2b** (purple) and **3d** (green), docked into the active site of MAO-A. Some residues are not shown.

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 MAOI-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

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 methods,[24,31–33] which involved the condensation of appropriately substituted aromatic aldehydes with nitroethane, the subsequent reduction of the corresponding nitrostyrenes with LiAlH$_4$ and the final preparation of the amine hydrochloride. The 6-substituted-2-naphthaldehydes were obtained by Grignard reaction of O-alkylated derivatives of 6-bromo-2-naphthol,[34] which, in turn, was prepared by selective debromination of 1,6-dibromo-2-naphthol with tin.[35] 2-Bromo-6-methythionaphthalene was obtained via 2-O-(6-bromonaphthyl)-dimethylthiocarbamate,[36] and subsequent Newman–Kwart rearrangement to afford 2-S-(6-bromonaphthyl)-dimethylthiocarbamate,[37,38] followed by hydrolysis and S-methylation. An alternative, higher-yielding route to 6-methylthio-2-naphthaldehyde involved substitution of the aromatic bromine atom by a cyano group using CuCN,[39] followed by reduction with DIBAH,[40] and hydrolysis of the resulting imine. All N-benzyl derivatives (**4a–4e**, **2h** and **2i**) were obtained by reductive amination with NaBH$_3$CN of the corresponding arylisopropylamine in the presence of the appropriately substituted benzaldehyde. Melting points are uncorrected and were determined with a Reichert Galen III hot plate microscope. ^{1}H NMR spectra were recorded using Bruker AMX 400 and AMX 300 spectrometers at 400 or 300 MHz, respectively. Chemical shifts are reported relative to TMS ($\delta = 0.00$) or HDO ($\delta = 4.79$) and coupling constants (J) are given in Hertz. The elemental analyses for C, H, N, O and S were performed on a CE Instruments (model EA 1108) analyzer.

4.1.1. Preparation of 6-bromo-2-naphthol

To a solution of 2-naphthol (140 mmol) in acetic acid (60 ml) was added Br$_2$ (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). ^{1}H NMR (CDCl$_3$) 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-bromonaphthalenes

To a stirred solution of 6-bromo-2-naphthol (1 mmol) in CH$_3$CN (100 ml), K$_2$CO$_3$ (3 mmol) and the appropriate alkyl 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 H$_2$O (2 × 100 ml). The organic layer was dried over Na$_2$SO$_4$ and concentrated. The product crystallized after adding methanol.

4.1.2.1. 2-Bromo-6-methoxynaphthalene. Yield 81%, mp 102.5–104.0 °C. ^{1}H NMR (CDCl$_3$) 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, $J_1 = 8.6$ Hz, $J_2 = 1.9$ Hz, ArH), 7.14 (dd, 1H, $J_1 = 9.1$ Hz, $J_2 = 2.4$ Hz, ArH), 7.08 (d, 1H, $J = 2.1$ Hz, ArH), 3.89 (s, 3H, OCH$_3$).

4.1.2.2. 2-Bromo-6-ethoxynaphthalene. Yield 67%, mp 72.9–76.3 °C. ^{1}H NMR (CDCl$_3$) 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, $J_1 = 9.1$ Hz, $J_2 = 2.3$ Hz, ArH), 7.09 (s, 1H, ArH), 4.14 (q, 2H, $J = 7.1$ Hz, CH$_3$CH$_2$O), 1.48 (t, 3H, $J = 6.8$ Hz, CH$_3$CH$_2$O).

4.1.2.3. 2-Bromo-6-propoxynaphthalene. Yield 80%, mp 64.7–65.1 °C. ^{1}H NMR (CDCl$_3$) δ 7.95 (s, 1H, ArH), 7.68 (d, 1H, $J = 8.9$ Hz, ArH), 7.62 (d, 1H, $J = 8.6$ Hz, ArH), 7.53 (dd, 1H, $J_1 = 8.9$ Hz, $J_2 = 2.1$ Hz, ArH), 7.21 (dd, 1H, $J_1 = 8.8$ Hz, $J_2 = 2.5$ Hz, ArH), 7.13 (d, 1H, $J = 2.3$ Hz, ArH), 4.07 (t, 2H, $J = 6.6$ Hz, CH$_3$CH$_2$CH$_2$O), 1.92 (m, 2H, CH$_3$CH$_2$CH$_2$O), 1.13 (t, 3H, $J = 7.6$ Hz, CH$_3$CH$_2$CH$_2$O).

4.1.2.4. 2-Bromo-6-butoxynaphthalene. Yield 54% mp 54.0–55.3 °C. ^{1}H NMR (CDCl$_3$) 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, $J_1 = 8.8$ Hz, $J_2 = 1.8$ Hz, ArH), 7.15 (dd, 1H, $J_1 = 9.1$ Hz, $J_2 = 2.5$ Hz, ArH), 7.08 (d, 1H, $J = 2.3$ Hz, ArH), 4.06 (t, 2H, $J = 6.6$ Hz, CH$_3$CH$_2$CH$_2$CH$_2$O), 1.83 (m, 2H, CH$_3$CH$_2$CH$_2$CH$_2$O), 1.53 (m, 2H, CH$_3$CH$_2$CH$_2$CH$_2$O), 1.00 (t, 3H, $J = 7.7$ Hz, CH$_3$CH$_2$CH$_2$CH$_2$O).

4.1.2.5. 6-Benzyloxy-2-bromonaphthalene. Yield 50%, mp 89.5–94.8 °C. ^{1}H NMR (CDCl$_3$) 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, ArCH$_2$O).

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 I$_2$ crystal in dry THF (100 ml) and refluxed under N$_2$ 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 Na$_2$SO$_4$ 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). ^{1}H NMR (CDCl$_3$) δ 10.07 (s,1H, CHO), 8.23 (s, 1H, ArH), 7.90 (dd, 1H, $J_1 = 8.5$ Hz, $J_2 = 1.2$ Hz, ArH), 7.87 (d, 1H, $J = 8.8$ Hz, ArH), 7.78 (d, 1H, $J = 8.5$ Hz, ArH), 7.21 (dd, 1H,

J_1 = 8.8 Hz, J_2 = 2.8 Hz, ArH), 7.16 (d, 1H, J = 2.1 Hz, ArH), 3.94 (s, 3H, OCH$_3$).

4.1.3.2. 6-Ethoxy-2-naphthaldehyde.
Yield 21%, mp 67.3–68.1 °C (yellow crystals). ^{1}H NMR (CDCl$_3$) δ 10.07 (s, 1H, CHO), 8.22 (s, 1H, ArH), 7.89 (dd, 1H, J_1 = 8.8 Hz, J_2 = 1.8 Hz, ArH), 7.87 (d, 1H, J = 9.3 Hz, ArH), 7.76 (d, 1H, J = 8.3 Hz, ArH), 7.21 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.6 Hz, ArH), 7.14 (d, 1H, J = 2.3 Hz, ArH), 4.17 (q, J = 7.1 Hz, CH$_3$CH$_2$O), 1.48 (t, 3H, J = 6.8 Hz, CH$_3$CH$_2$O).

4.1.3.3. 6-Propoxy-2-naphthaldehyde.
Yield 25%, mp 43.0–44.5 °C (yellow crystals). ^{1}H NMR (CDCl$_3$) δ 10.08 (s, 1H, CHO), 8.24 (s, 1H, ArH), 7.91 (d, 1H, J = 7.4, ArH), 7.88 (d, 1H, J = 9.0 Hz, ArH), 7.77 (d, 1H, J = 8.6 Hz, ArH), 7.23 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.4 Hz, ArH), 7.16 (d, 1H, J = 1.8 Hz, ArH), 4.07 (t, 2H, J = 6.4 Hz, CH$_3$CH$_2$CH$_2$O), 1.89 (m, 2H, CH$_3$CH$_2$CH$_2$O), 1.09 (t, 3H, J = 7.4 Hz, CH$_3$CH$_2$CH$_2$O).

4.1.3.4. 6-Butoxy-2-naphthaldehyde.
Yield 43%, mp 31.5–33.0 °C (yellow crystals). ^{1}H NMR (CDCl$_3$) δ 10.09 (s, 1H, CHO), 8.24 (s, 1H, ArH), 7.91 (dd, 1H, J_1 = 9.0 Hz, J_2 = 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, J_1 = 8.9 Hz, J_2 = 2.5 Hz, ArH), 7.16 (d, 1H, J = 2.4 Hz, ArH), 4.12 (t, 2H, J = 6.4 Hz, CH$_3$CH$_2$CH$_2$ CH$_2$O), 1.86 (m, 2H, CH$_3$CH$_2$ CH$_2$CH$_2$O), 1.55 (m, 2H, CH$_3$CH$_2$CH$_2$CH$_2$O), 1.01 (t, 3H, J = 7.3 Hz, CH$_3$CH$_2$CH$_2$CH$_2$O).

4.1.3.5. 6-Benzyloxy-2-naphthaldehyde.
Yield 15%, mp 94.5–97.8 °C (yellow crystals). ^{1}H NMR (CDCl$_3$) δ 10.08 (s, 1H, CHO), 8.24 (s, 1H, ArH), 7.89 (dd, 2H, J_1 = 8.3 Hz, J_2 = 2.5 Hz, ArH), 7.78 (d, 1H, J = 9.0 Hz, ArH), 7.47 (d, 2H, J = 7.3 Hz, ArCH$_2$), 7.42 (d, 1H, J = 7.4 Hz, ArCH$_2$), 7.40 (d, 1H, J = 7.5 Hz, ArCH$_2$), 7.35 (d, 1H, J =7.4 Hz, ArCH$_2$), 7.30 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.2 Hz, ArH), 7.25 (d, 1H, J = 2.0 Hz, ArH), 5.20 (s, 2H, ArCH$_2$O).

4.1.4. General procedure for the preparation of naphthylnitropropenes
The appropriate naphthaldehyde (1 mmol), nitroethane (10 mmol) and cyclohexylamine (5 mmol) were dissolved in acetic acid (50 ml). This reaction mixture was kept at 100 °C for 24 h, after which the solvent was evaporated. Boiling methanol (30 ml) was added to the product obtained, and after cooling to 4 °C, the corresponding nitrostyrenes crystallized.

4.1.4.1. 1-(1-Naphthyl)-2-nitropropene.
Yield 80%, mp 59.8–60.5 °C (yellow crystals). ^{1}H NMR (CDCl$_3$) δ 8.68 (s, 1H, ArCH), 7.96 (m, 3H, ArH), 7.62 (m, 3H, ArH), 7.07 (d, 1H, J = 7.1 Hz, ArH), 2.41 (s, 3H, CH$_3$CNO$_2$).

4.1.4.2. 1-(2-Naphthyl)-2-nitropropene.
Yield 75%, mp 81.0–83.5 °C (yellow crystals). ^{1}H NMR (CDCl$_3$) δ 8.30 (s, 1H, ArCH), 7.94 (m, 4H, ArH), 7.59 (m, 3H, ArH), 2.59 (s, 3H, CH$_3$CNO$_2$).

4.1.4.3. 2-(6-Methoxynaphthyl)-1-nitropropene.
Yield 77%, mp 87.5–88.3 °C (yellow crystals). ^{1}H NMR (CDCl$_3$) δ 8.21 (s, 1H, ArCH), 7.84 (s, 1H, ArH), 7.77 (d, 1H, J = 3.8 Hz, ArH), 7.75 (d, 1H, J = 4.0 Hz, ArH), 7.48 (dd, 1H, J_1 = 8.6 Hz, J_2 = 1.3 Hz, ArH), 7.19 (dd, 1H, J_1 = 9.1 Hz, J_2 = 2.2 Hz, ArH), 7.13 (d, 1H$_g$, J = 2.3 Hz, ArH), 3.93 (s, 3H, OCH$_3$), 2.53 (s, 3H, CH$_3$CNO$_2$).

4.1.4.4. 2-(6-Ethoxynaphthyl)-1-nitropropene.
Yield 69%, mp 108.0–109.8 °C (yellow crystals). ^{1}H NMR (CDCl$_3$) δ 8.21 (s, 1H, ArCH), 7.84 (s, 1H, ArH), 7.77 (d, 1H, J = 3.5 Hz, ArH), 7.74 (d, 1H, J = 3.03 Hz, ArH), 7.47 (d, 1H, J = 8.6 Hz, ArH), 7.19 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.2 Hz, ArH), 7.12 (d, 1H, J = 1.8 Hz, ArH), 4.16 (q, 2H, J = 6.8 Hz, CH$_3$CH$_2$O), 2.53 (s, 3H, CH$_3$CNO$_2$), 1.48 (t, 3H, J = 6.8 Hz, CH$_3$CH$_2$O).

4.1.4.5. 1-Nitro-2-(6-propoxynaphthyl)-propene.
Yield 76%, mp 70.0–71.3 °C (yellow crystals). ^{1}H NMR (CDCl$_3$) δ 8.22 (s, 1H, ArCH), 7.84 (s, 1H, ArH), 7.76 (d, 1H, J = 3.5 Hz, ArH), 7.74 (d, 1H, J = 3.0 Hz, ArH), 7.47 (d, 1H, J = 8.6 Hz, ArH), 7.19 (dd, 1H, J_1 = 8.9 Hz, J_2 = 2.0 Hz, ArH), 7.12 (s, 1H, ArH), 4.05 (t, 2H, J = 6.3 Hz, CH$_2$CH$_2$CH$_2$O), 2.54 (s, 3H, CH$_3$CNO$_2$), 1.88 (m, 2H, CH$_2$CH$_2$CH$_2$O), 1.08 (t, 3H, J = 7.3 Hz, CH$_3$CH$_2$CH$_2$O).

4.1.4.6. 2-(6-Butoxynaphthyl)-1-nitropropene.
Yield 70%, mp 50.8–51.8 °C (yellow crystals). ^{1}H NMR (CDCl$_3$) δ 8.21 (s, 1H, ArCH), 7.83 (s, 1H, ArH), 7.75 (d, 2H, J = 8.3 Hz, ArH), 7.47 (dd, 1H, J_1 = 8.6 Hz, J_2 = 1.3 Hz, ArH), 7.18 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.3 Hz, ArH), 7.13 (d, 1H, J = 2.0 Hz, ArH), 4.09 (t, 2H, J = 6.6 Hz, CH$_3$CH$_2$CH$_2$CH$_2$O), 2.53 (s, 3H, CH$_3$CNO$_2$), 1.83 (m, 2H, CH$_3$CH$_2$CH$_2$CH$_2$O), 1.53 (m, 2H, CH$_3$CH$_2$CH$_2$CH$_2$O), 1.00 (t, 3H, J = 7.3 Hz, CH$_3$CH$_2$CH$_2$CH$_2$O).

4.1.4.7. 2-(6-Benzyloxynaphthyl)-1-nitropropene.
Yield 76% mp 151.0–153.3 °C (yellow crystals). ^{1}H NMR (CDCl$_3$) δ 8.22 (s, 1H, ArCH), 7.85 (s, 1H, ArH), 7.77 (m, 2H, ArH), 7.48 (d, 3H, J = 8.1 Hz, ArCH$_2$), 7.40 (m, 2H, ArH), 7.35 (d, 1H, J = 7.1 Hz, ArH), 7.27 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.3 Hz, ArH), 7.22 (d, 1H, J = 1.8 Hz, ArH), 5.19 (s, 2H, ArCH$_2$O), 2.53 (s, 3H, CH$_3$CNO$_2$).

4.1.5. General procedure for the preparation of naphthylisopropylamine hydrochlorides (1 and 2a–2f)
LiAlH$_4$ (10 mmol) was carefully suspended in dry THF (60 ml) with good stirring. Then, the corresponding nitrostyrene (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 MgSO$_4$ 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.

4.1.5.1. 1-(1-Naphthyl)-2-aminopropane hydrochloride (1).
Yield 11%, mp 215.0–218.5 °C. ^{1}H NMR (D$_2$O) δ 7.98 (d, 1H, J = 8.1 Hz, ArH), 7.89 (d, 1H, J = 8.1 Hz, ArH), 7.81 (d, 1H, J = 8.1 Hz, ArH), 7.52 (m, 2H, ArH), 7.42 (t, 1H, J = 7.58 Hz, ArH), 7.36 (d, 1H, J = 7.07 Hz, ArH), 3.68 (m, 1H, ArCH$_2$CH(CH$_3$)NH$_3$$^+$), 3.29 (m, 2H, ArCH$_2$), 1.24 (d, 3H, J = 6.6 Hz, ArCH$_2$CH(CH$_3$)NH$_3$$^+$). Anal. Calcd for C$_{13}H_{16}$ClN: C, 70.42; H, 7.27; N, 6.32. Found: C, 66.91; H, 8.27; N, 6.35.

4.1.5.2. 1-(2-Naphthyl)-2-aminopropane hydrochloride (2a).
Yield 40%, mp 205.0–207.0 °C (lit.[28] 205.2–205.5 °C). ^{1}H NMR (D$_2$O) δ 7.82 (t, 3H, ArH), 7.69 (s, 1H, ArH), 7.46 (m, 2H, ArH), 7.33 (d, 1H, J = 8.1 Hz, ArH), 3.62 (m, 1H, ArCH$_2$CH(CH$_3$)NH$_3$$^+$), 2.98 (d, 2H, J = 7.1 Hz, ArCH$_2$), 1.22 (d, 3H, J = 6.6 Hz, ArCH$_2$CH(CH$_3$)NH$_3$$^+$). Elemental analysis of this compound was reported previously.[28]

4.1.5.3. (6-Methoxy-2-naphthyl)-2-aminopropane hydrochloride (2b).
Yield 47%, mp 237.8–238.2 °C. ^{1}H NMR (D$_2$O) δ 7.69 (d, 2H, J = 7.6 Hz, ArH), 7.58 (s, 1H, ArH), 7.27 (d, 1H, J = 8.3 Hz, ArH), 7.20 (s, 1H, ArH), 7.08 (dd, 1H, J_1 = 9.1 Hz, J_2 = 1.5 Hz, ArH), 3.80 (s, 3H, OCH$_3$), 3.57 (m, 1H, ArCH$_2$CH(CH$_3$)NH$_3$$^+$), 2.93 (d, 2H, J = 7.3 Hz, ArCH$_2$), 1.20 (d, 3H, J = 6.6 Hz, ArCH$_2$CH(CH$_3$)NH$_3$$^+$). Anal. Calcd for C$_{14}H_{18}$ClNO: C, 66.79; H, 7.21; N, 5.56. Found: C, 65.01; H, 7.80; N, 5.40.

4.1.5.4. (6-Ethoxy-2-naphthyl)-2-aminopropane hydrochloride (2c).
Yield 30%, mp 252.9–254.5 °C. ^{1}H NMR (D$_2$O) δ 7.63 (d, 2H, J = 8.9 Hz, ArH), 7.52 (s, 1H, ArH), 7.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.3 Hz, ArH), 7.15 (d, 1H, J = 2.3 Hz, ArH), 7.01 (dd, 1H, J_1 = 8.9 Hz, J_2 = 2.3 Hz, ArH), 4.01 (q, 2H, J = 6.8 Hz, OCH_2CH$_3$), 3.48 (m, 1H, ArCH$_2$CH(CH$_3$)NH$_3^+$), 2.85 (d, 2H, J = 7.1 Hz, ArCH_2), 1.23 (t, 3H, J = 7.1 Hz, OCH$_2$CH_3), 1.11 (d, 3H, J = 6.8 Hz, ArCH$_2$CH(CH_3)NH$_3^+$). Anal. Calcd for C$_{15}$H$_{20}$ClNO: C, 67.79; H, 7.58; N, 5.27. Found: C, 66.81; H, 8.39; N, 5.14.

4.1.5.5. (6-Propoxy-2-naphthyl)-2-aminopropane hydrochloride (2d).
Yield 68%, mp 232.6–236.6 °C. ^{1}H NMR (DMSO-d_6) δ 7.72 (d, 2H, J = 8.6 Hz, ArH), 7.60 (s, 1H, ArH), 7.29 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz, ArH), 7.23 (d, 1H, J = 2.5 Hz, ArH), 7.10 (dd, 1H, J_1 = 9.1 Hz, J_2 = 2.5 Hz, ArH), 3.97 (t, 2H, J = 6.6 Hz, CH$_3$CH$_2$CH_2O), 3.40 (m,1H, ArCH$_2$CH(CH$_3$)NH$_3^+$), 3.05 (dd, 1H, J_1 = 5.3 Hz, J_2 = 13.4 Hz, ArCH_2), 2.74 (dd, 1H, J_1 = 8.8 Hz, J_2 = 13.4 Hz, ArCH_2), 1.74 (m, 2H, CH$_3$CH_2CH$_2$O), 1.08 (d, 3H, J = 6.6 Hz, ArCH$_2$CH(CH_3)NH$_3^+$), 0.96 (t, 3H, J = 7.3 Hz, CH_3CH$_2$CH$_2$O). Anal. Calcd for C$_{16}$H$_{22}$ClNO: C, 68.68; H, 7.93; N, 5.01. Found: C, 68.37; H, 9.31; N, 5.08.

4.1.5.6. (6-Butoxy-2-naphthyl)-2-aminopropane hydrochloride (2e).
Yield 14%, mp 234.5–237.0 °C. ^{1}H NMR (DMSO-d_6) δ 7.71 (d, 2H, J = 7.8 Hz, ArH), 7.60 (s, 1H, ArH), 7.29 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz, ArH), 7.24 (d, 1H, J = 2.3 Hz, ArH), 7.09 (dd, 1H, J_1 = 8.9 Hz, J_2 = 2.5 Hz, ArH), 4.01 (t, 2H, J = 6.6 Hz, CH$_3$CH$_2$CH$_2$CH_2O), 3.42 (m, 1H, ArCH$_2$CH(CH$_3$)NH$_3^+$), 3.07 (dd, 1H, J_1 = 5.3 Hz, J_2 = 13.4 Hz, ArCH), 2.73 (dd, 1H, J_1 = 8.8 Hz, J_2 = 13.4 Hz, ArCH), 1.70 (m, 2H, CH$_3$CH$_2$CH_2CH$_2$O), 1.42 (m, 2H, CH$_3$CH_2CH$_2$CH$_2$O), 1.08 (d, 3H, J = 6.6 Hz, ArCH$_2$CH(CH_3)NH$_3^+$), 0.90 (t, 3H, J = 7.3 Hz, CH_3CH$_2$CH$_2$CH$_2$O). Anal. Calcd for C$_{17}$H$_{24}$ClNO: C, 69.49; H, 8.23; N, 4.77. Found: C, 69.51; H, 9.88; N, 4.87.

4.1.5.7. (6-Benzyloxy-2-naphthyl)-2-aminopropane hydrochloride (2f).
Yield 33%, mp 236.2–238.2 °C. ^{1}H NMR (DMSO-d_6) δ 7.77 (d, 2H, J = 8.3 Hz, ArH), 7.66 (s, 1H, ArH), 7.49 (d, 2H, J = 7.7 Hz, ArH), 7.40 (m, 3H, ArCH$_2$), 7.35 (d, 2H, J = 8.4 Hz, ArCH$_2$), 7.22 (dd, 1H, J_1 = 8.9 Hz, J_2 = 2.5 Hz, ArH), 5.20 (s, 2H, ArCH_2O), 3.45 (m, 1H, ArCH$_2$CH(CH$_3$)NH$_3^+$), 3.09 (dd, 1H, J_1 = 5.5 Hz, J_2 = 13.4 Hz, ArCH_2), 2.78 (dd, 1H, J_1 = 8.8 Hz, J_2 = 13.4 Hz, ArCH_2), 1.12 (d, 3H, J = 6.4 Hz, ArCH$_2$CH(CH_3)NH$_3^+$). Anal. Calcd for C$_{20}$H$_{22}$ClNO: C, 73.27; H, 6.76; N, 4.27. Found: C, 72.95; H, 7.51; N, 4.34.

4.1.6. Preparation of 6-O-(2-bromonaphthyl)-dimethylthiocarbamate
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 Na$_2$SO$_4$ 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). ^{1}H NMR (CDCl$_3$) 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, J_1 = 8.8 Hz, J_2 = 2.0 Hz, ArH), 7.48 (d, 1H, J = 2.02 Hz, ArH), 7.29 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.3 Hz, ArH), 3.49 (s, 3H, NCH_3), 3.41 (s, 3H, NCH_3).

4.1.7. Preparation of 6-S-(2-bromonaphthyl)-dimethylthiocarbamate
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 in methanol the product was obtained as yellow crystals. Yield 50%, mp 111.3–113.5 °C. ^{1}H NMR (CDCl$_3$) 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(CH$_3$)$_2$).

4.1.8. Preparation of 6-bromo-2-mercaptonaphthalene
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 MgSO$_4$, 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). ^{1}H NMR (CDCl$_3$) 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 Hz, 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). ^{1}H NMR (CDCl$_3$) 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, J_1 = 8.6 Hz, J_2 = 1.5 Hz, ArH), 2.62 (s, 3H, SCH_3).

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 NH$_3$, extracted with DCM, dried with Na$_2$SO$_4$, filtered and the solvent evaporated under reduced pressure. The product crystallized after adding methanol. Yield 32%, mp 98.8–100.3 °C (white crystals). ^{1}H RMN (CDCl$_3$) δ 8.19 (s, 1H, ArH), 7.81 (t, 2H, J = 9.1 Hz, ArH), 7.63 (dd, 1H, J_1 = 8.6 Hz, J_2 = 1.5 Hz, ArH), 7.60 (s, 1H, ArH), 7.50 (dd, 1H, J_1 = 9.1 Hz, J_2 = 2.0 Hz, ArH), 2.52 (s, 3H, SCH_3).

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 H$_2$SO$_4$ were added giving a gelatinous product, which was filtered over Celite. The solvent 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-nitropropene
This compound was prepared following the same general procedure used for the synthesis of naphthyl-nitropropenes (step 4.1.4.). Yield 42%, mp 99.6–101.6 °C (yellow crystals). ^{1}H NMR (CDCl$_3$) 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, J_1 = 8.6 Hz, J_2 = 1.5 Hz, ArH), 7.46 (dd, 1H, J_1 = 8.6 Hz, J_2 = 2.0 Hz, ArH), 2.65 (s, 3H, CH_3CNO$_2$), 2.59 (s, 3H, SCH_3).

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). ^{1}H NMR (DMSO-d_6) δ 7.81 (m, 2H, ArH), 7.71 (s, 2H, ArH), 7.40 (d, 2H, J = 8.6 Hz, ArH), 3.52 (m, 1H, ArCH$_2$-

C*H*(CH$_3$)NH$_3$$^+$), 3.14 (dd, 1H, *J*$_1$ = = 5.6 Hz, *J*$_2$ = 13.1 Hz, ArC*H*), 2.83 (dd, 1H, *J*$_1$ = 8.6 Hz, *J*$_2$ = 13.1 Hz, ArC*H*), 2.58 (s, 3H, SC*H*$_3$), 1.15 (d, 3H, *J* = 6.1 Hz, ArCH$_2$CH(C*H*$_3$)NH$_2$). Anal. Calcd for C$_{14}$H$_{18}$ClNS: C, 62.79; H, 6.77; N, 5.23; 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 NaBH$_3$CN (1.6 mmol) 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, EtOAc). In all cases the product was obtained as an oil, which was dissolved in a minimal volume (3 ml) 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*-Benzyl-(6-methoxy-2-naphthyl)-2-aminopropane hydrochloride (2h).
Yield 25%, mp 251.0–218.0 °C. ^{1}H NMR (CDCl$_3$), 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, OCH$_3$), 3.87 (d, 1H, *J* = 13.1 Hz, NHC*H*Ar), 3.76 (d, 1H, *J* = 13.1 Hz, NHC*H*Ar), 3.05 (m, 1H, ArCH$_2$C*H*(CH$_3$)NH$_3$$^+$), 2.91 (dd, 1H, *J*$_1$ = 7.1 Hz, *J*$_2$ = 13.6 Hz, ArC*H*), 2.77 (dd, 1H, *J*$_1$ = 6.6 Hz, *J*$_2$ = 13.4 Hz, ArC*H*), 1.14 (d, 3H, *J* = 6.1 Hz, ArCH$_2$CH(C*H*$_3$)NH$_3$$^+$). Anal. Calcd for C$_{21}H_{24}$ClNO: 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. ^{1}H NMR (D$_2$O) δ 7.72 (s,1H, ArH), 7.71 (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*$_1$ = 9.1 Hz, *J*$_2$ = 2.5 Hz, ArH), 4.20 (m, 2H, NHC*H*$_2$Ar), 4.02 (t, 2H, *J* = 6.6 Hz, CH$_3$CH$_2$CH$_2$C*H*$_2$O), 3.40 (d, 2H, *J* = 13.4 Hz, ArC*H*$_2$), 2.75 (m, 1H, ArCH$_2$C*H*(CH$_3$)NH$_3$$^+$), 1.70 (m, 2H, CH$_3CH_2$C*H*$_2CH_2$O), 1.42 (m, 2H, CH$_3$C*H*$_2CH_2CH_2$O), 1.15 (d, 3H, *J* = 6.3 Hz, ArCH$_2$CH(C*H*$_3$)NH$_3$$^+$), 0.90 (t, 3H, *J* = 7.3 Hz, C*H*$_3$CH$_2$CH$_2$CH$_2$O). Anal. Calcd for C$_{24}$H$_{30}$ClNO: 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, ^{1}H NMR (CDCl$_3$) δ 10.03 (s, 2H, NH$_2$$^+$), 7.65 (d, 2H, *J* = 7.0 Hz, ArH), 7.45–7.25 (m, 3H, ArH), 7.15 (d, 2H, *J* = 8.3 Hz, ArH), 7.01 (d, 2H, *J* = 8.3 Hz, ArH), 4.10 (d, 1H, *J* = 3.5 Hz, NH$_2$$^+$C*H*$_2$Ar), 4.02 (d, 1H, *J* = 3.6 Hz, NH$_2$$^+$C*H*$_2$Ar), 3.41 (dd, 2H, *J*$_1$ = 13.1, *J*$_2$ = 3.6 Hz, ArC*H*$_2$CH(CH$_3$)NH$_2$$^+CH_2$Ar), 3.45 (dd, 2H, *J* = 3.6 Hz, NH$_2$$^+$C*H*$_2$Ar), 3.13 (m, 1H, ArCH$_2$C*H*(CH$_3$)NH$_2$$^+CH_2$Ar), 2.77 (dd, 1H, *J* = 12.9 Hz, NH$_2$$^+$C*H*$_2$Ar), 2.45 (s, 3H, C*H*$_3$S), 1.31 (d, 3H, *J* = 6.4 Hz, CH(C*H*$_3$)NH$_2$$^+$). Anal. Calcd for C$_{17}H_{22}$ClNS: 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, ^{1}H NMR (CDCl$_3$/DMSO-*d*$_6$) δ 9.63 (s, 2H, NH$_2$$^+$), 9.36 (s, 1H, ArOH), 7.45 (d, 2H, *J* = 8.5 Hz, ArH), 7.18 (d, 2H, *J* = 8.2 Hz ArH), 7.12 (d, 2H, *J* = 8.2 Hz, ArH), 6.87 (d, 2H, *J* = 8.4 Hz, ArH), 4.04 (m, 2H, NH$_2$$^+$C*H*$_2$Ar), 3.38 (dd, 1H, *J*$_1$ = 12.8, *J*$_2$ = 3.6 Hz, ArC*H*$_2$CH(CH$_3$)NH$_2$$^+CH_2$Ar), 3.26 (m, 1H, ArCH$_2$C*H*(CH$_3$)NH$_2$$^+H_2$$^+CH_2$Ar), 2.78 (dd, 1H, *J* = 12.9 Hz, ArC*H*$_2$CH(CH$_3$)NH$_2$$^+CH_2$Ar), 2.47 (s, 3H, C*H*$_3$S), 1.29 (d, 3H, *J* = 6.4 Hz, CH(C*H*$_3$)NH$_2$$^+$). Anal. Calcd for C$_{17}H_{22}$ClNOS: 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.

4.1.14.5. *N*-4-Methoxybenzyl-(4-methylthioamphetamine) hydrochloride (4c).
Yield 86%, mp 172.7–173.2 °C, ^{1}H NMR (CDCl$_3$) δ 9.85 (s, 2H, NH$_2$$^+$), 7.55 (d, 2H, *J* = 8.5 Hz, ArH), 7.15 (d, 2H, *J* = 8.3 Hz ArH), 7.05 (d, 2H, *J* = 8.2 Hz, ArH), 6.88 (d, 2H, *J* = 8.7 Hz, ArH), 4.03 (m, 2H, ArC*H*$_2$NH$_2$$^+$), 3.65 (s, 3H, CH$_3$OAr), 3.38 (dd, 2H, *J*$_1$ = 13.0, *J*$_2$ = 3.4 Hz, ArC*H*$_2$CH(CH$_3$)NH$_2$$^+CH_2$Ar), 3.13 (m, 1H, ArCH$_2$C*H*(CH$_3$)NH$_2CH_2$Ar), 2.72 (dd, 1H, *J* = 12.8 Hz, ArC*H*$_2$CH(CH$_3$)NH$_2$$^+CH_2$Ar), 2.45 (s, 3H, C*H*$_3$S), 1.29 (d, 3H, *J* = 6.3 Hz, CH(C*H*$_3$)NH$_2$). Anal. Calcd for C$_{18}$H$_{24}$ClNOS: C, 63.98; H, 7.16; N, 4.15; S, 9.49. Found: C, 60.39; H, 8.05; N, 4.04; S, 11.66.

4.1.14.6. *N*-4-Butoxybenzyl-(4-methylthioamphetamine) hydrochloride (4d).
Yield 80%, mp 184.8–189.2 °C, ^{1}H NMR (CDCl$_3$) δ 9.89 (s, 2H, NH$_2$$^+$), 7.55 (d, 2H, *J* = 8.6 Hz, ArH), 7.15 (d, 2H, *J* = 8.2 Hz, ArH), 7.05 (d, 2H, *J* = 8.2 Hz, ArH), 6.85 (d, 2H, *J* = 8.5 Hz, ArH), 4.01 (1H, d, *J* = 13.2 Hz, ArC*H*$_2$NH$_2$$^+$), 3.92 (1H, d, *J* = 13.2 Hz, ArC*H*$_2$NH$_2$$^+$), 3.75 (t, 2H, *J* = 6.5 Hz, ArOC*H*$_2$(CH$_2$)$_2$CH$_3$), 3.40 (dd, 1H, *J*$_1$ = 13.0, *J*$_2$ = 3.4 Hz, NH$_2$$^+$C*H*$_2$Ar), 3.16 (m, 1H, ArCH$_2$C*H*(CH$_3$)NH$_2$$^+CH_2$Ar), 2.76 (dd, 1H, *J* = 13.0 Hz, NH$_2$C*H*$_2$Ar), 2.47 (s, 3H, C*H*$_3$S), 1.69 (qui, 2H, *J* = 6.5 Hz, ArOCH$_2$C*H*$_2$CH$_2$CH$_3$) 1.43 (sex, 2H, *J* = 7.5 Hz, ArOCH$_2$CH$_2$C*H*$_2$CH$_3$) 1.31 (d, 3H, *J* = 6.4 Hz, CH(C*H*$_3$)NH$_2$$^+$), 0.96 (t, 3H, *J* = 7.5 Hz, ArOCH$_2$CH$_2$CH$_2$C*H*$_3$). Anal. Calcd for C$_{21}$H$_{30}$ClNOS: C, 66.38; H, 7.96; N, 3.69; S, 8.44. Found: C, 65.92; H, 8.44; N, 3.82; S, 11.54.

4.1.14.7. *N*-4-Benzyloxybenzyl-(4-methylthioamphetamine) hydrochloride (4e).
Yield 95%, mp 188.0–189.1 °C, ^{1}H NMR (CDCl$_3$) δ 8.95 (s, 2H, NH$_2$$^+$), 7.42 (d, 2H, *J* = 8.5 Hz, ArH), 7.38 (dd, 2H, *J* = 6.8 Hz, ArH), 7.34 (dddd, 2H, *J* = 7.2 Hz, ArH), 7.26 (dddd, 1H, *J* = 7.1 Hz, ArH), 7.16 (d, 2H, *J* = 8.6 Hz, ArH), 7.10 (d, 2H, *J* = 8.3 Hz, ArH), 7.01 (d, 2H, *J* = 8.8 Hz, ArH), 5.08 (s, 2H, ArC*H*$_2$O), 4.10 (1H, d, *J*$_{app}$ = 13.3 Hz, ArC*H*$_2$ NH$_2$$^+$), 4.05 (1H, d, *J*$_{app}$ = 13.3 Hz, ArC*H*$_2$ NH$_2$$^+$), 3.19 (dd, 1H, *J*$_1$ = 13.0, *J*$_2$ = 3.7 Hz, ArC*H*$_2$CH(CH$_3$)NH$_2$$^+CH_2$Ar), 2.54 (dd, 1H, *J* = 13.1 Hz, ArC*H*$_2$CH(CH$_3$)NH$_2$$^+CH_2$Ar), 2.39 (s, 3H, C*H*$_3$S), 1.25 (d, 3H, *J* = 6.0 Hz, CH(C*H*$_3$)NH$_2$$^+$). Anal. Calcd for C$_{24}H_{28}$ClNOS: C, 69.63; H, 6.82; N, 3.38; S, 7.75. Found: C, 69.62; H, 6.93; N, 3.50; S, 10.69.

4.2. Biochemistry

The effects of the compounds on MAO-A or MAO-B activities were studied following previously reported methodologies,[12,24] using a crude rat brain mitochondrial suspension as a source of enzyme. Serotonin (100 μM) and 4-dimethylaminophenethylamine (5 μM) were used as selective substrates for MAO-A and -B, respectively, and these compounds and their metabolites were detected by HPLC with electrochemical detection as described previously.[12,24] IC$_{50}$ values (mean ± SD from at least two independent experiments, each in triplicate) were determined using GRAPH PAD PRISM software, from plots of inhibition percentages (calculated in relation to a sample of the enzyme treated under the same conditions without inhibitors) versus −log inhibitor concentration. K_i were determined from the IC$_{50}$ values using the Cheng–Prusoff equation: $K_i = $ IC$_{50}/(1 + [S]/K_m)$,[41] K_m (5-HT, MAO-A) = 100 μM, K_m (DMAPEA, MAO-B) = 5 μM. A kinetic study was carried out on **2b** to ascertain the type of inhibition, using four substrate concentrations (25, 50, 100, and 125 μM), and three inhibitor concentrations (0.1, 0.5, and 1.0 μM), incubating for five different times. Each experiment was performed in duplicate.

4.3. Molecular simulation

The crystallographic data of rat MAO-A (PDB: 1O5 W) were used for all calculations. The AUTODOCK 3.05 suite[42] was then used to perform the docking simulations and conditions were as previously reported.[15,27] Briefly, the hydrogen atoms of the protein and

the FAD molecule were built using Insight II,[43] and the structures were relaxed following a minimization protocol using Discover_3 and the ESFF force field. The grid maps were calculated using the autogrid3 option and were centered on the putative ligand-binding site. The volumes chosen for the grid maps were made up of $40 \times 40 \times 40$ points, with a grid-point spacing of 0.375 Å. The partial charges of different compounds were corrected using RESP methodology.[44] 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.

Acknowledgments

References and notes

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