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MAO inhibition by arylisopropylamines: the effect of oxygen substituents at the β-position

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Abstract—Twenty-nine arylisopropylamines, substituted at the β-position of their side chain by an oxo, hydroxy, or methoxy group, were evaluated in vitro as MAO-A and MAO-B inhibitors. The oxo derivatives ('cathinones') were in general less active as MAO-A inhibitors than the corresponding arylisopropylamines, but exhibited an interesting MAO-B inhibiting activity, which was absent in the hydroxy, methoxy, and β-unsubstituted analogues. These results suggest that selective affinity for the two MAO isoforms in this family of compounds is modulated not only by the aryl substitution pattern but also by the side-chain substituents on the aryl-alkylamine scaffold.
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1. Introduction

Structure–activity relationship studies on monoamine oxidase (MAO) inhibitors have been reported for various families of compounds.[1–5] A common goal of these studies has been to understand how drug–receptor interactions modulate affinity and selectivity for the two pharmacologically important A and B isoforms of MAO. The recent elucidation of the MAO-B structure[6,7] has made possible a much more detailed understanding of these interactions and opened up new possibilities for the design of more selective and potent inhibitors.

Because of their structural simplicity, phenylalkylamines constitute a family of MAO inhibitors that may be used advantageously as a model for the study of the enzyme receptor site. Two decades ago several 4-aminophenethylamine derivatives were shown to selectively inhibit the MAO-A isoform,[8] and it was later suggested that structural variations on the aromatic ring of this model compound might lead to more potent inhibitors.[9] An evaluation of a large collection of ring-substituted phenylisopropylamines showed that the presence of an alkoxy or thioalkoxy group at the 4-position tended to increase the in vitro activity of these MAO-A inhibitors.[10] Quite recently, a QSAR study on both sets of compounds indicated the requirement of an electron-rich ring for charge-transfer interactions of the inhibitor with residues present in the active site.[11]

Structural variations on the side chain of these compounds are known to alter their MAO inhibitory activity. 3-Phenylpropylamine binds 75-fold more tightly to MAO-A than phenethylamine. While the latter is a substrate, 4-phenylbutylamine is a good competitive inhibitor of that isoform.[12] Thus, side chain variations could prove of value not only because they might increase the activity of these MAO-A inhibitors, but also because they could alter the selectivity of these compounds. In this connection it may be pointed out that benzylamine is a typical MAO-B substrate. The selective MAO-A inhibitor moclobemide (**1**, a substituted morpholine) and selective MAO-B inhibitors like the primary amines lazabemide (**2**) or *N*-(2-aminoethyl)-*p*-chlorobenzamide (**3**) may be regarded as

Keywords: Monoamine oxidase inhibition; β-Substituted phenylisopropylamines; Cathinones; Norephedrines; β-Methoxyphenylisopropylamines.
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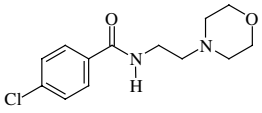
phenylalkylamine isosteres with an oxo substituent at the β-position of the side chain. We are unaware of any systematic study published on the MAO inhibitory activity of α- or β-substituted phenylalkylamines. In this paper we describe the preparation and in vitro evaluation as MAO inhibitors of 29 ring-substituted phenylisopropylamines, with a side-chain β-oxo, -hydroxy, or -methoxy substituent.



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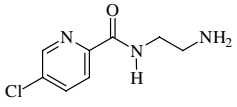

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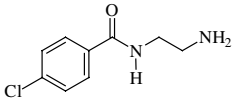

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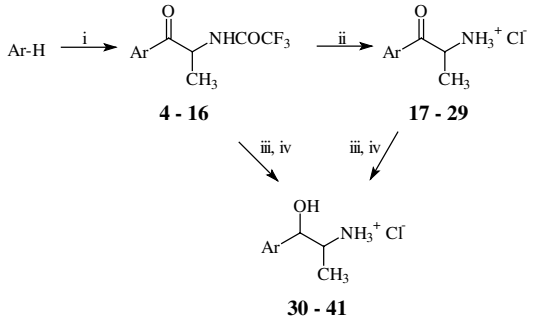
2. Results

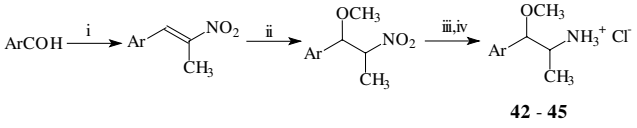
The racemic 2-amino-1-arylpropanones (**17**–**29**) were obtained in the form of the corresponding hydrochlorides, following the same two-step procedure described previously for the enantiomerically pure cathinone derivatives.[13] Reduction of these racemic cathinones, or of the intermediate trifluoroacetamides, by $NaBH_4$ led to the corresponding 2-amino-1-aryl-1-propanols, isolated as the hydrochloride salts (**30**–**41**).



i) N-trifluoroacetamidoalanylchloride / $AlCl_3$; ii) HCl / *i*-PrOH ; iii) $NaBH_4$; iv) HCl

The ^1H NMR spectra of the β-hydroxy derivatives (**30**–**41**) exhibited only one set of signals. This suggested that the isolated products consisted of only one pair of enantiomers and that the reduction of the racemic cathinones by $NaBH_4$ was a highly enantioselective process. Following a previous analysis for the identification of diastereomeric 1-aryl-1-methoxy-2-aminopropanes,[14] and based on the rather small coupling constants (ca. 4 Hz) between the α and β side-chain protons observed in the NMR spectra of these substances, we assigned the *erythro* configurations (*R*,*S*/*S*,*R* pair) to the isolated β-hydroxy compounds (**30**–**41**), which may therefore be described as norephedrine derivatives.

The hydrochloride salts of the 2-amino-1-methoxy-1-arylpropanes (**42**–**45**) were prepared by the synthetic sequence shown below, which started from the corresponding benzaldehydes.



42 - 45

i) $EtNO_2$ / $BuNH_2$; ii) MeONa ; iii) $LiAlH_4$; iv) HCl

Conversion into the corresponding nitrostyrenes, followed by Michael addition of methoxide anion, and reduction of the obtained addition product, formed diastereomeric mixtures of these derivatives.

In contrast with the norephedrines, the β-methoxy derivatives (**42**–**45**) exhibited pairs of signals with similar intensities in their ^1H NMR spectra, an indication that the products consisted of diastereomeric mixtures of two racemic pairs. All three series of compounds were evaluated as MAO-A and MAO-B inhibitors.

Table 1 lists the MAO inhibitory activities of all the racemic cathinones, for both MAO isoforms.

For the sake of comparison, in vitro inhibition data for some analogous phenylisopropylamines with no side-chain β-substituent are included in Table 1.[10]

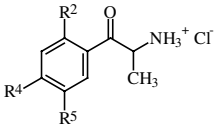
Table 2 lists the activities of the pairs of enantiomerically pure cathinones prepared, as described previously,[13] from (*R*)- and (*S*)-alanine.

The activities of the norephedrines and of the β-methoxy derivatives are given in Tables 3 and 4, respectively.

3. Discussion

Our data shed light on the effects of different ring substituents at the 4-position and of the side-chain β-substituents on the MAO inhibitory activities of the prepared compounds. As noted previously for phenylisopropylamines,[10] small thioalkyl ring substituents at the 4-position lead to more effective MAO-A inhibitors than the corresponding alkoxy substituents. Thus, racemic 4-methoxycathinone (**19**) showed a higher IC_{50} value than its thiomethyl analogue (**24**) (77 and 46 μM, respectively), and the same is true for the ethoxy (**20**) and thioethyl (**25**) pair (37 and 15 μM, respectively) (Table 1). In the norephedrine series (Table 3), the 4-methoxy derivative (**32**) only had a slightly higher IC_{50} value than the 4-thiomethyl analogue (**36**) (9.8 and 7.3 μM, respectively), but again the 4-ethoxy derivative

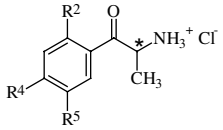
Table 1. MAO inhibitory activities of racemic cathinones (**17**–**29**) and some analogous phenylisopropylamines (PIA), IC_{50}, μM[a]



Compound number	$R^2 = R^5$	R^4	Cathinones		PIA[b]	
			MAO-A	MAO-B	MAO-A	MAO-B
17	H	H	Inactive	>100	11	Inactive
18	H	CH_3	>100	>100	NT[c]	NT
19	H	OCH_3	77.0	Inactive	0.3	Inactive
20	H	OCH_2CH_3	37.0	>100	0.2	>100
21	H	$O(CH_2)_2CH_3$	7.2	8.9	NT	NT
22	H	$O(CH_2)_3CH_3$	14.4	6.0	NT	NT
23	H	$OCH_2CH(CH_3)_2$	13.6	6.2	NT	NT
24	H	SCH_3	45.5	>100	0.2	Inactive
25	H	SCH_2CH_3	15.1	>100	0.1	29
26	H	$S(CH_2)_2CH_3$	12.4	100	NT	NT
27	H	$S(CH_2)_3CH_3$	11.6	23.3	NT	NT
28	H	$SCH_2CH(CH_3)_2$	17.1	9.5	NT	NT
29	OCH_3	H	100	Inactive	>100	Inactive

[a] Compounds described as inactive were completely devoid of activity at 100 μM; compounds giving less than 50% inhibition at this concentration are reported with $IC_{50} > 100$ μM.
[b] Data from Ref. 10.
[c] NT: not tested.

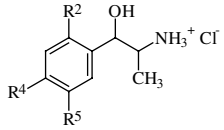
Table 2. MAO inhibitory activities of enantiomerically pure cathinones,[13] IC_{50} (μM)[a]



$R^2 = R^5$	R^4	Configuration	MAO-A	MAO-B
H	CH_3	(*S*)	>100	100
H	OCH_3	(*S*)	>100	>100
H	SCH_3	(*S*)	44.5	>100
H	SCH_3	(*R*)	38.9	NT[b]
H	SC_2H_5	(*S*)	12.9	>100
H	SC_2H_5	(*R*)	38.0	NT
H	OC_4H_9	(*S*)	29.5	5.6
H	OC_4H_9	(*R*)	6.8	6.4

[a] Compounds giving less than 50% inhibition at the threshold concentration of 100 μM are reported with $IC_{50} > 100$ μM.
[b] Not tested.

Table 3. MAO inhibitory activities of norephedrines (**30**–**41**), IC_{50} (μM)[a]

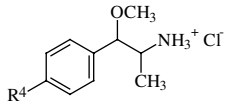


Compound number	$R^2 = R^5$	R^4	MAO-A	MAO-B
30	H	H	>100	Inactive
31	H	CH_3	12.0	Inactive
32	H	OCH_3	9.8	Inactive
33	H	OCH_2CH_3	7.0	Inactive
34	H	$O(CH_2)_2CH_3$	2.8	100
35	H	$O(CH_2)_3CH_3$	4.7	65
36	H	SCH_3	7.3	Inactive
37	H	SCH_2CH_3	1.9	>100
38	H	$S(CH_2)_2CH_3$	1.7	>100
39	H	$S(CH_2)_3CH_3$	1.6	>100
40	H	$SCH_2CH(CH_3)_2$	3.7	>100
41	OCH_3	H	Inactive	Inactive

[a] Compounds described as inactive were completely devoid of activity at a 100 μM; compounds giving less than 50% inhibition at this concentration are reported with $IC_{50} > 100$ μM.

(**33**) was clearly less active than the 4-thioethyl analogue (**37**) (7.0 and 1.9 μM, respectively). Interestingly, 4-methylnorephedrine was only slightly less active versus MAO-A than its 4-methoxy counterpart, suggesting that a heteroatom connecting the alkyl chain to the ring may not play any essential role in the inhibition of this isoform of the enzyme. In the β-methoxy series (Table 4), the 4-methoxy derivative (**44**) (78 μM) was also less active than the 4-thiomethyl analogue (**45**) (51 μM). The length of the alkyl chain on the *para*-substituent is also clearly important. The inhibitory activity is maximal for C_3–C_4 chains, in both the thioalkyl and the alkoxy series, and seems to fall off with branching of the alkyl group. This is illustrated by the series of 4-alkoxycathinones of Table 1, where the IC_{50} values vary in the order OMe (77) > OEt (37) > OPr (7.2) < OBu^n (14.1) ~ OBu^i (13.6) and the corresponding 4-alkylthio compounds: SMe (46) > SEt (15.1) > SPr (12.4) ~ SBu^n (11.6) < SBu^i (17.1). A similar trend is observed for the norephedrines (Table 3), with the 4-alkoxy derivatives: OMe (9.8) > OEt (7.0) > OPr (2.8) < OBu^n (4.7); and more clearly with the 4-thioalkyl analogues: SMe (7.3) > SEt (1.9) > SPr (1.7) ~ SBu^n (1.6) < SBu^i (3.7).

Table 4. MAO inhibitory activities of β–methoxyarylisopropylamines (**42**–**45**), IC_{50} (μM)[a]



Compound number	R^4	MAO-A	MAO-B
42	H	>100	>100
43	CH_3	>100	>100
44	OCH_3	77.5	>100
45	SCH_3	50.6	>100

[a] Compounds giving less than 50% inhibition at the threshold concentration of 100 μM are reported with $IC_{50} > 100$ μM.

The data of Table 2 show that the MAO inhibitory activities are not very different for pairs of enantiomeric cathinones. As the values obtained for the racemic compounds (Table 1) are presumably averages of unequal contributions from each enantiomer, we may assume that they do not differ greatly from the IC_{50} values of the individual isomers. If this is also true for the β-hydroxy- and β-methoxyarylisopropylamines, we can safely compare the effects of the different β-substituents on the MAO inhibitory activity of these series using our data for the racemic cathinones and norephedrines and the diastereomeric mixtures of β-methoxy compounds.

In our series, the introduction of an oxo, hydroxy or methoxy substituent at the β-position of the side chain decreases the inhibitory activity of arylisopropylamines vis-à-vis MAO-A. In particular, the data of Table 1 show that the presence of a side-chain β-oxo group increases the IC_{50} values of arylisopropylamines as MAO-A inhibitors by at least two orders of magnitude. This might be due to a reduction of the electron-donating ability of the aromatic ring by the carbonyl group, thus rendering charge-transfer interactions with amino acid residues in the enzyme active site more difficult.[11] This interpretation seems to find support in the observation that the reduction of the carbonyl group to a β-hydroxy substituent, which no longer withdraws charge from the ring, increases the inhibitory activity several fold, as can be seen in Table 3. However, the MAO-A inhibitory activities of the 4-methoxy- and 4-thiomethylcathinones (IC_{50} values 77 and 46 μM, respectively) are practically identical to those of the β-methoxy analogues (78 and 51 μM, respectively). This casts some doubt on the above interpretation, since the β-methoxy, like the β-hydroxy group, is not expected to withdraw charge from the ring. Although the deactivating effect of a β-oxo group due to its electron-withdrawing ability cannot be ruled out in this analysis, there seems to be an additional specific effect, which may be held responsible for the reduced MAO-A inhibitory activity of these cathinones. One possibility is that the coplanarity of the ring and the carbonyl group is an unfavorable feature. As reduction of the carbonyl group to hydroxyl in these compounds increased their MAO-A inhibitory activity, this might indicate that the more flexible side chain allows a better fit to the enzyme active site. It could also mean that MAO-A tolerates a hydrogen-bond-acceptor β substituent less than a hydrogen-bond-donating group, or none at all. Finally, increased steric hindrance by the β-methoxy group could be a factor contributing to the relatively low potency of the β-methoxylated compounds.

An interesting result of the present study is the inhibition of MAO-B by several substituted cathinones (Table 1). The inescapable comparison with the selective MAO-B inhibitors lazabemide (**2**) and *N*-(2-aminoethyl)-*p*-chlorobenzamide (**3**), points to a special role of this group in modulating the affinity of these compounds for both MAO isoforms. Nevertheless, the fact that the closely related moclobemide (**1**) is a selective MAO-A inhibitor, and the high degree of similarity predicted for the active sites of MAO-A and MAO-B,[6,15] indicate that the structural basis of selectivity for one or the other isoform may be much more subtle.

The recently elucidated X-ray crystal structure of MAO-B in its pargyline-inhibited form revealed the existence of two domains in the enzyme, an entrance and a substrate cavity.[6] A small, compact inhibitor molecule like isatin only occupies the substrate cavity, whereas longer molecules like 1,4-diphenyl-2-butene and the chlorobenzamide **3** occupy both the entrance and the substrate cavity.[7] By analogy with **3**, it would seem that our cathinone and norephedrine inhibitors may span the two cavities of MAO-B when the *para*-substituent is at least as long as a propoxy group, enhancing the affinity of these compounds for the enzyme via hydrophobic interactions with residues such as Leu 167, Leu 164, Ile 316, and Pro 104. We might thus explain the low micromolar IC_{50} values of the 4-*n*-propoxy (**21**), -*n*-butoxy (**22**), and -*i*-butoxy (**23**) cathinones, although not the much weaker MAO-B inhibitory activity of the corresponding norephedrines. It is intriguing, however, that of the alkylthio cathinone counterparts, **26** should be rather inactive and only **28** should have a potency approaching that of **21**. On the contrary, the MAO-A inhibitory potencies of the alkoxy and alkylthio compounds follow almost perfectly smooth sequences. The greater potency of the compounds with methyl- (**24**) or ethylthio substituents (**25**) as compared to their methoxy (**19**) and ethoxy (**20**) counterparts might be related to the somewhat larger size of the sulfur-containing groups. With larger *para*-substituents, a practically constant IC_{50} of 12–14 μM is reached, which seems to fall off somewhat for 4-*i*-butylthiocathinone (**28**).

The hydrophilic region of the binding cavity is filled with ordered water molecules that hydrogen bond with the inhibitor, the flavin ring and the active site amino acid residues.[7] Although no data are available for 4-propoxy- or -butoxy phenylisopropylamines, our results suggest that a side-chain β-oxo group may increase the affinity of these inhibitor molecules for MAO-B relative to MAO-A. It is noteworthy that the replacement of the oxo by a hydroxyl group led to a several-fold improvement in activity of these compounds as MAO-A inhibitors, and to a significant decrease in their activity as MAO-B inhibitors (Table 3). This suggests a highly specific interaction of the β-oxo substituent with the

substrate cavity of the MAO-B isoform, possibly by bonding specifically with some hydrogen-bond-donor fragment in the cavity.

The basicity of the carbonyl group, like that of the amides **1**–**3**, is enhanced by conjugation with a heteroatom. In our case, the cathinones **17**–**29** may be regarded as vinylogous esters and thioesters, a view which is supported by the bond lengths of some of their trifluoroacetamides, determined by X-ray diffraction.[13] Therefore, the keto group of the cathinones seems to be a good hydrogen-bond acceptor candidate.

In order to verify this suggestion, we performed dynamics simulations of a MAO-B/inhibitor complex, docking 4-butoxycathinone (**22**), one of the best MAO-B inhibitors of the series, into the enzyme active site. The results are shown in Figure 1. As can be seen in this figure, the inhibitor side chain fits into the space defined by Tyr 398, Tyr 435, and the FAD cofactor, and its β-oxo group accepts a hydrogen bond from the phenolic OH group of Tyr 435, in agreement with our hypothesis.

In conclusion, the presence in arylisopropylamines of a β-oxo, -hydroxy, or -methoxy side-chain substituent reduces the activity of these compounds as MAO-A inhibitors. This is especially true of the aminopropanones, or cathinones, that are at least two orders of magnitude less active than the corresponding β-unsubstituted arylisopropylamines. However, unlike the parent arylisopropylamines or their β-hydroxy or β-methoxy derivatives, some cathinones inhibit MAO-B at low micromolar IC_{50} values that suggest them as possible leads for the development of more selective, reversible MAO-B inhibitors, which are currently lacking in the therapeutic arsenal.

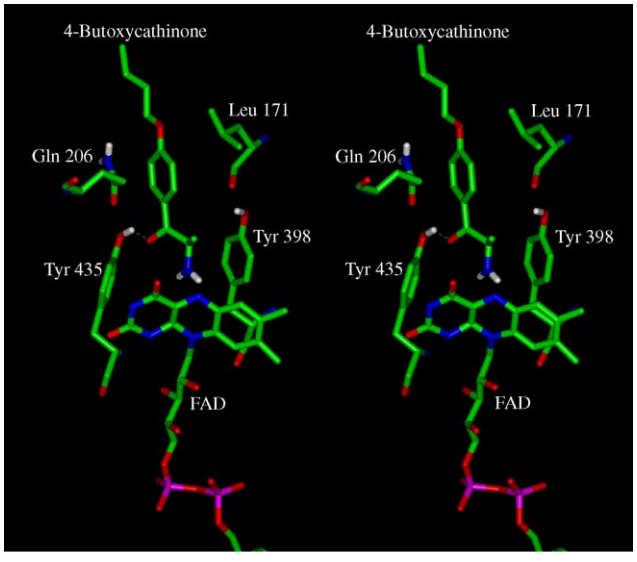


Figure 1. Stereoview of 4-butoxycathinone (**22**) in the active site of MAO-B, showing its interactions with the FAD cofactor and with aminoacid residues.

4. Experimental

Melting points were obtained in capillaries with an Electrothermal apparatus and were not corrected. NMR spectra were recorded with Bruker AMX 300 and Bruker Avance 400 spectrometers, employing tetramethylsilane as an internal standard. Chemical shifts are reported relative to TMS ($\delta = 0.00$). Optical rotations were measured with a Perkin–Elmer 241 polarimeter.

(*R*,*S*)-*N*-Trifluoroacetylalanine was prepared from (*R*,*S*)-alanine (Aldrich), ethyl trifluoroacetate, and 1,1,3,3-tetramethylguanidine in 95% yield, following the procedure described previously for the preparation of its enantiomers.[13] The product had a melting point of 120–121 °C, lit.[16] 120–121 °C.

4.1. General procedure for the preparation of (*R*,*S*)-2-trifluoroacetamido-1-aryl-1-propanones (4–16)

The racemic (*R*,*S*)-2-trifluoroacetamido-1-aryl-1-propanones were prepared by a Friedel–Crafts acylation of the corresponding arenes with (*R*,*S*)-*N*-trifluoroacetylalanyl chloride, obtained in situ by reaction of (*R*,*S*)-*N*-trifluoroacetylalanine and oxalyl chloride, following our previously reported procedure.[13] In this way, the following propanones were prepared.

4.1.1. (*R*,*S*)-2-Trifluoroacetamido-1-phenyl-1-propanone (4). Yield 48%, mp 74–76 °C, lit.[17] 76–77.5 °C. ^{1}H NMR ($CDCl_3$) 1.53 (d, 3H, $J = 7.3$ Hz, CH_3CH), 5.54 (m, 1H, CHCH$_3$), 7.54 (d, 2H, $J = 7.3$ Hz, ArH-3,5), 7.62–7.69 (m, 2H, NH, ArH-4), 7.99 (d, 2H, $J = 8.0$ Hz, ArH-2,6). ^{13}C NMR ($CDCl_3$) 19.3 (*C*H$_3$CH), 50.8 (*C*HCH$_3$), 115.8 (q, *C*F$_3$CO), 128.8 (ArC-4), 129.2 (ArC-3,5), 133.0 (ArC-1), 134.6 (ArC-2,6), 156.6 (q, CF$_3$*C*O), 197.0 (ArCOCH).

4.1.2. (*R*,*S*)-2-Trifluoroacetamido-1-(4-methylphenyl)-1-propanone (5). Yield 43%, mp 55–57 °C. ^{1}H NMR ($CDCl_3$) 1.52 (d, 3H, $J = 7.1$ Hz, CH_3CH), 2.45 (s, 3H, CH_3Ar), 5.46–5.56 (m, 1H, CHCH$_3$), 7.34 (d, 2H, $J = 8.0$ Hz, ArH-3,5), 7.67 (s, 1H, NH), 7.89 (d, 2H, $J = 8.3$ Hz, ArH-2,6). ^{13}C NMR ($CDCl_3$) 19.9 (*C*H$_3$CH), 22.2 (*C*H$_3$Ar), 51.1 (*C*HCH$_3$), 116.1 (q, *C*F$_3$CO), 129.4 (ArC-3,5), 130.2 (ArC-2,6), 130.8 (ArC-1), 146.2 (ArC-4), 156.9 (q, CF$_3$*C*O), 196.9 (Ar*C*OCH). HRMS m/z 259.0816, calculated for $C_{12}H_{12}F_3NO_2$, 259.0820.

4.1.3. (*R*,*S*)-2-Trifluoroacetamido-1-(4-methoxyphenyl)-1-propanone (6). Yield 66%, mp 93–95 °C. ^{1}H NMR ($CDCl_3$) 1.52 (d, 3H, $J = 6.9$ Hz, CH_3CH), 3.91 (s, 3H, CH_3O), 5.44–5.53 (m, 1H, CHCH$_3$), 7.00 (d, 2H, $J = 9.0$ Hz, ArH-3,5), 7.70 (d, 1H, $J = 3.7$ Hz, NH), 7.98 (d, 2H, $J = 9.0$ Hz, ArH-2,6). ^{13}C NMR ($CDCl_3$) 20.0 (*C*H$_3$CH), 50.7 (*C*H$_3$O), 56.1 (*C*HCH$_3$), 114.8 (ArC-3,5), 115.8 (q, *C*F$_3$CO), 126.1 (ArC-1), 131.6 (ArC-2,6), 156.5 (q, CF$_3$*C*O), 165.1 (ArC-4), 195.7

(Ar*C*OCH). HRMS *m/z* 275.0772, calculated for $C_{12}H_{12}F_3NO_3$, 275.0769.

4.1.4. (*R*,*S*)-2-Trifluoroacetamido-1-(4-ethoxyphenyl)-1-propanone (7). Yield 51%, mp 93–94 °C. ^{1}H NMR ($CDCl_3$) 1.46 (t, 3H, $J = 7.0$ Hz, CH_3CH$_2$O), 1.52 (d, 3H, $J = 7.0$ Hz, CH_3CH), 4.13 (q, 2H, $J = 7.0$ Hz, CH$_3$CH_2O), 5.48 (m, 1H, C*H*CH$_3$), 6.98 (d, 2H, $J = 8.9$ Hz, ArH-3,5), 7.68 (br s, 1H, N*H*), 7.96 (d, 2H, $J = 8.9$ Hz, ArH-2,6). ^{13}C NMR ($CDCl_3$) 14.6 (*C*H$_3$CH), 19.6 (*C*H$_3$CH$_2$O), 50.6 (*C*HCH$_3$), 64.0 (CH$_3$*C*H$_2$O), 115.8 (q, *C*F$_3$CO), 114.7 (ArC-3,5), 125.5 (ArC-1), 131.2 (ArC-2,6), 156.5 (q, CF$_3$*C*O), 164.1 (ArC-4), 195.3 (Ar*C*OCH). HRMS *m/z* 289.0924, calculated for $C_{13}H_{14}F_3NO_3$, 289.0926.

4.1.5. (*R*,*S*)-2-Trifluoroacetamido-1-(4-propoxyphenyl)-1-propanone (8). Yield 50%, mp 63–65 °C. ^{1}H NMR ($CDCl_3$) 1.06 (t, 3H, $J = 7.3$ Hz, CH_3CH$_2$CH$_2$O), 1.52 (d, 3H, $J = 7.3$ Hz, CHCH_3), 1.85 (m, 2H, CH$_3$CH_2CH$_2$O), 4.01 (t, 2H, $J = 6.7$ Hz, CH$_3$CH$_2$-CH_2O), 5.47 (m, 1H, C*H*CH$_3$), 6.98 (d, 2H, $J = 8.5$ Hz, ArH-3,5), 7.65 (s, 1H, N*H*), 7.95 (d, 2H, $J = 9.1$ Hz, ArH-2,6). ^{13}C NMR ($CDCl_3$) 10.4 (*C*H$_3$CH$_2$CH$_2$O), 19.6 (CH*C*H$_3$), 22.4 (CH$_3$*C*H$_2$CH$_2$O), 50.4 (*C*HCH$_3$), 70.0 (CH$_3$CH$_2$*C*H$_2$O), 117.5 (q, CO*C*F$_3$), 114.8 (ArC-3,5), 125.5 (ArC-1), 131.3 (ArC-2,6), 156.0 (q, *C*OCF$_3$), 164.3 (ArC-4), 195.3 (Ar*C*OCH). HRMS *m/z* 303.1079, calculated for $C_{14}H_{16}F_3NO_3$, 303.1082.

4.1.6. (*R*,*S*)-2-Trifluoroacetamido-1-(4-butoxyphenyl)-1-propanone (9). Yield 39%, mp 51–52 °C. ^{1}H NMR ($CDCl_3$) 0.92 (t, 3H, $J = 7.4$ Hz, CH_3CH$_2$CH$_2$CH$_2$O), 1.39–1.47 (m, 5H, CHCH_3 and CH$_3$CH_2CH$_2$CH$_2$O), 1.70–1.77 (m, 2H, CH$_3$CH$_2$CH_2CH$_2$O), 3.98 (t, 2H, $J = 6.6$ Hz, CH$_3$CH$_2$CH$_2$CH_2O), 5.41 (m, 1H, C*H*CH$_3$), 6.91 (d, 2H, $J = 8.9$ Hz, ArH-3,5), 7.58 (s, 1H, N*H*), 7.88 (d, 2H, $J = 8.9$ Hz, ArH-2,6). ^{13}C NMR ($CDCl_3$) 14.0 (*C*H$_3$CH$_2$CH$_2$CH$_2$O), 19.4 (CH*C*H$_3$), 19.9 (CH$_3$-*C*H$_2$CH$_2$CH$_2$O), 31.3 (CH$_3$CH$_2$*C*H$_2$CH$_2$O), 50.7 (*C*HCH$_3$), 68.4 (CH$_3$CH$_2$CH$_2$*C*H$_2$O), 116.1 (q, CO*C*F$_3$), 115.1 (ArC-3,5), 125.7 (ArC-1), 131.5 (ArC-2,6), 156.8 (q, *C*OCF$_3$), 164.6 (ArC-4), 195.5 (Ar-*C*OCH). HRMS *m/z* 317.1222, calculated for $C_{15}H_{18}F_3NO_3$, 317.1239.

4.1.7. (*R*,*S*)-2-Trifluoroacetamido-1-(4-isobutoxyphenyl)-1-propanone (10). Yield 53%, mp 75–77 °C. ^{1}H NMR ($CDCl_3$) 1.03 (d, 6H, $J = 6.6$ Hz, (CH_3)$_2$CHCH$_2$O), 1.49 (d, 3H, $J = 7.2$ Hz, CHCH_3), 2.06–2.14 (m, 1H, (CH$_3$)$_2$C*H*CH$_2$O), 3.79 (d, 2H, $J = 6.4$ Hz, (CH$_3$)$_2$-CHCH_2O), 5.40–5.49 (m, 1H, C*H*CH$_3$), 6.96 (d, 2H, $J = 8.9$ Hz, ArH-3,5), 7.62 (s, 1H, N*H*), 7.93 (d, 2H, $J = 9.0$ Hz, ArH-2,6). ^{13}C NMR ($CDCl_3$) 19.1 ((*C*H$_3$)$_2$-CHCH$_2$O), 19.7 (CH*C*H$_3$), 28.2 ((CH$_3$)$_2$*C*HCH$_2$O), 50.4 (*C*HCH$_3$), 74.8 ((CH$_3$)$_2$CH*C*H$_2$O), 115.8 (q, CO*C*F$_3$), 114.8 (ArC-3,5), 125.5 (ArC-1), 131.2 (ArC-2,6), 156.4 (q, *C*OCF$_3$), 164.5 (ArC-4), 195.3 (Ar*C*OCH). HRMS *m/z* 317.1237, calculated for $C_{15}H_{18}F_3NO_3$, 317.1239.

4.1.8. (*R*,*S*)-2-Trifluoroacetamido-1-(4-methylthiophenyl)-1-propanone (11). Yield 40%, mp 91–93 °C. ^{1}H NMR ($CDCl_3$) 1.52 (d, 3H, $J = 7.1$ Hz, CH_3CH), 2.55 (s, 3H, CH_3S), 5.44–5.51 (m, 1H, C*H*CH$_3$), 7.32 (d, 2H, $J = 8.2$ Hz, ArH-3,5), 7.65 (s, 1H, N*H*), 7.89 (d, 2H, $J = 8.8$ Hz, ArH-2,6). ^{13}C NMR ($CDCl_3$, 75 MHz) 14.6 (*C*H$_3$CH), 19.5 (*C*H$_3$S), 50.6 (*C*HCH$_3$), 116.9 (q, *C*F$_3$CO), 125.1 (ArC-3,5), 128.8 (ArC-1), 129.2 (ArC-2,6), 148.4 (ArC-4), 156.5 (q, CF$_3$*C*O), 195.8 (Ar-*C*OCH). HRMS *m/z* 291.0542, calculated for $C_{12}H_{12}F_3NO_2S$, 291.0541.

4.1.9. (*R*,*S*)-2-Trifluoroacetamido-1-(4-ethylthiophenyl)-1-propanone (12). Yield 27%, mp 86–88 °C. ^{1}H NMR ($CDCl_3$) 1.40 (t, 3H, $J = 7.7$ Hz, CH_3CH$_2$S), 1.52 (d, 3H, $J = 7.1$ Hz, CH_3CH), 3.05 (q, 2H, $J = 7.7$ Hz, CH$_3$CH_2S), 5.5 (quintet, 1H, $J = 7.1$ Hz, CH$_3$C*H*), 7.33 (d, 2H, $J = 8.8$ Hz, ArH-3,5), 7.63 (s, 1H, N*H*), 7.87 (d, 2H, $J = 8.2$ Hz, Ar-2,6). ^{13}C NMR ($CDCl_3$) 13.8 (*C*H$_3$CH), 19.5 (*C*H$_3$CH$_2$S), 25.8 (CH$_3$*C*H$_2$S), 50.6 (*C*HCH$_3$), 115.7 (q, *C*F$_3$CO), 126.1 (ArC-3,5), 129.0 (ArC-1), 129.2 (ArC-2,6), 147.4 (ArC-4), 156.5 (q, CF$_3$*C*O), 195.8 (Ar*C*OCH). HRMS *m/z* 305.0701, calculated for $C_{13}H_{14}F_3NO_2S$, 305.0697.

4.1.10. (*R*,*S*)-2-Trifluoroacetamido-1-(4-propylthiophenyl)-1-propanone (13). Yield 35%, mp 79–80 °C. ^{1}H NMR ($CDCl_3$) 1.06 (t, 3H, $J = 7.4$ Hz, CH_3CH$_2$CH$_2$S), 1.49 (d, 3H, $J = 7.0$ Hz, CHCH_3), 1.68–1.80 (m, 2H, CH$_3$CH_2CH$_2$S), 2.98 (t, 2H, $J = 7.4$ Hz, CH$_3$CH$_2$-CH_2S), 5.40–5.49 (m, 1H, C*H*CH$_3$), 7.32 (d, 2H, $J = 8.9$ Hz, ArH-3,5), 7.57 (s, 1H, N*H*), 7.84 (d, 2H, $J = 8.9$ Hz, ArH-2,6). ^{13}C NMR ($CDCl_3$) 13.5 (CH*C*H$_3$), 19.5 (*C*H$_3$CH$_2$CH$_2$S), 22.1 (CH$_3$*C*H$_2$CH$_2$S), 33.7 (CH$_3$CH$_2$*C*H$_2$S), 50.6 (*C*HCH$_3$), 115.8 (q, CO*C*F$_3$), 126.3 (ArC-3,5), 129.1 (ArC-1), 129.2 (ArC-2,6), 147.7 (ArC-4), 156.5 (q, *C*OCF$_3$), 195.8 (Ar*C*OCH). HRMS *m/z* 319.0857, calculated for $C_{14}H_{16}O_2F_3NS$, 319.0854.

4.1.11. (*R*,*S*)-2-Trifluoroacetamido-1-(4-butylthiophenyl)-1-propanone (14). Yield 26%, mp 76–78 °C. ^{1}H NMR ($CDCl_3$) 0.94 (t, 3H, $J = 7.4$ Hz, CH_3CH$_2$CH$_2$CH$_2$S), 1.42–1.54 (m, 5H, CHCH_3 and CH$_3$CH_2CH$_2$CH$_2$S), 1.64–1.74 (m, 2H, CH$_3$CH$_2$CH_2CH$_2$S), 3.00 (t, 2H, $J = 7.4$ Hz, CH$_3$CH$_2$CH$_2$CH_2S), 5.40–5.49 (m, 1H, C*H*CH$_3$), 7.31 (d, 2H, $J = 8.7$ Hz, ArH-3,5), 7.58 (s, 1H, N*H*), 7.84 (d, 2H, $J = 8.9$ Hz, ArH-2,6). ^{13}C NMR ($CDCl_3$) 13.6 (CH*C*H$_3$), 19.5 (*C*H$_3$CH$_2$CH$_2$CH$_2$S), 19.9 (CH$_3$*C*H$_2$CH$_2$CH$_2$S), 30.7 (CH$_3$CH$_2$*C*H$_2$CH$_2$S), 31.4 (CH$_3$CH$_2$CH$_2$*C*H$_2$S), 50.6 (*C*HCH$_3$), 115.7 (q, CO*C*F$_3$), 126.2 (ArC-3,5), 129.1 (ArC-1), 129.2 (ArC-2,6), 147.7 (ArC-4), 155.4 (q, *C*OCF$_3$), 195.8 (Ar*C*OCH). HRMS *m/z* 333.1012, calculated for $C_{15}H_{18}O_2F_3NS$, 333.1010.

4.1.12. (*R*,*S*)-2-Trifluoroacetamido-1-(4-isobutylthiophenyl)-1-propanone (15). Yield 14%, mp 74–75 °C. ^{1}H NMR ($CDCl_3$) 1.05 (d, 6H, $J = 6.8$ Hz, (CH_3)$_2$CHCH$_2$S), 1.49 (d, 3H, $J = 7.2$ Hz, CHCH_3), 1.87–2.00 (m, 1H, (CH$_3$)$_2$C*H*CH$_2$S), 2.87 (d, 2H, $J = 7.0$ Hz, (CH$_3$)$_2$CH-

CH_2S), 5.40–5.49 (m, 1H, $J = 7.0$ Hz, $CHCH_3$), 7.31 (d, 2H, $J = 8.7$ Hz, ArH-3,5), 7.59 (s, 1H, N*H*), 7.83 (d, 2H, $J = 8.7$ Hz, ArH-2,6). ^{13}C NMR ($CDCl_3$) 19.5 ($(CH_3)_2CHCH_2S$), 22.1 ($CHCH_3$), 28.1 ($(CH_3)_2CH$-CH_2S), 40.6 ($(CH_3)_2CHCH_2S$), 50.6 ($CHCH_3$), 115.8 (q, $COCF_3$), 126.3 (ArC-3,5), 129.09 (ArC-1), 129.14 (ArC-2,6), 148.0 (ArC-4), 156.5 (q, $COCF_3$), 195.8 (Ar*C*OCH). HRMS m/z 333.1001, calculated for $C_{15}H_{18}O_2F_3NS$, 333.1010.

4.1.13. (*R*,*S*)-2-Trifluoroacetamido-1-(2,5-dimethoxyphenyl)-1-propanone (16). Yield 77%, mp 121–123 °C. ^{1}H NMR ($CDCl_3$) 1.45 (d, 3H, $J = 7.0$ Hz, CH_3CH), 3.82 (s, 3H, 5-OCH_3), 3.95 (s, 3H, 2-OCH_3), 5.59–5.69 (m, 1H, CH_3CH), 6.98 (d, 1H, $J = 8.8$ Hz, ArH-3), 7.15 (dd, 1H, $J_o = 9.1$, $J_m = 3.5$ Hz, ArH-4), 7.38 (d, 1H, $J_m = 3.5$ Hz, ArH-6), 7.70 (s, 1H, N*H*). ^{13}C NMR ($CDCl_3$) 18.0 (CH_3CH), 55.0 ($CHCH_3$), 55.8 (CH_3O-5), 56.2 (CH_3O-2), 113.2 (ArC-3), 114.7 (ArC-4), 115.8 (q, CF_3CO), 122.2 (ArC-6), 123.5 (ArC-5), 153.4 (ArC-2), 153.7 (ArC-1), 156.4 (q, CF_3CO), 197.7 (Ar*C*OCH). HRMS m/z 305.0874, calculated for $C_{13}H_{14}F_3NO_4$, 305.0875.

4.2. General procedure for the preparation of (*R*,*S*)-2-amino-1-aryl-1-propanone hydrochlorides (17–29)

The acid hydrolysis of the trifluoroacetamidopropanones (**4**–**16**) in 2-propanol, following a previously described procedure,[13] gave the corresponding racemic cathinone derivatives (**17**–**29**). In this way the following compounds were prepared.

4.2.1. (*R*,*S*)-2-Amino-1-phenyl-1-propanone hydrochloride (17). Yield 93%, mp 183–184 °C, lit.[17] mp 184–185 °C. ^{1}H NMR (DMSO-d_6) 1.44 (d, 3H, $J = 7.2$ Hz, $CHCH_3$), 5.13 (q, 1H, $J = 7.2$ Hz, $CHCH_3$), 7.60 (m, 2H, ArH-3,5), 7.74 (m, 1H, ArH-4), 8.06 (d, 2H, $J = 8.4$ Hz, ArH-2,6), 8.95 (s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 19.0 ($CHCH_3$), 52.7 ($CHCH_3$), 130.6 (ArC-3,5), 130.9 (ArC-2,6), 134.7 (ArC-4), 136.4 (ArC-1), 198.5 (Ar*C*OCH).

4.2.2. (*R*,*S*)-2-Amino-1-(4-methylphenyl)-1-propanone hydrochloride (18). Yield 55%, mp 198–200 °C, lit.[18] mp 217 °C. ^{1}H NMR (D_2O) 1.48 (d, 3H, $J = 7.3$ Hz, $CHCH_3$), 2.32 (s, 3H, CH_3Ar), 5.05 (q, 1H, $J = 7.3$ Hz, $CHCH_3$), 7.34 (d, 2H, $J = 8.4$ Hz, ArH-3,5), 7.80 (d, 2H, $J = 8.3$ Hz, ArH-2,6). ^{13}C NMR (D_2O) 19.7 ($CHCH_3$), 23.9 (CH_3Ar), 54.7 ($CHCH_3$), 131.9 (ArC-3,5), 132.5 (ArC-1), 132.8 (ArC-2,6), 150.0 (ArC-4), 200.5 (Ar*C*OCH).

4.2.3. (*R*,*S*)-2-Amino-1-(4-methoxyphenyl)-1-propanone hydrochloride (19). Yield 96%, mp 201–202 °C, lit.[19] mp 226 °C. ^{1}H NMR (DMSO-d_6) 1.46 (d, 3H, $J = 7.1$ Hz, $CHCH_3$), 3.91 (s, 3H, CH_3O), 5.09 (br m, 1H, $CHCH_3$), 7.15 (d, 2H, $J = 8.9$ Hz, ArH-3,5), 8.08 (d, 2H, $J = 8.9$ Hz, ArH-2,6), 8.50 (br s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 17.8 ($CHCH_3$), 50.8 ($CHCH_3$), 56.1 (CH_3O), 114.8 (ArC-3,5), 125.9 (ArC-1), 131.6 (ArC-2,6), 164.5 (ArC-4), 195.2 (Ar*C*OCH).

4.2.4. (*R*,*S*)-2-Amino-1-(4-ethoxyphenyl)-1-propanone hydrochloride (20). Yield 70%, mp 211–212 °C, ^{1}H NMR ($CDCl_3$) 1.39 (t, 3H, $J = 6.9$ Hz, CH_3CH_2O), 1.46 (d, 3H, $J = 7.1$ Hz, CH_3CH), 4.19 (q, 2H, $J = 7.0$ Hz, CH_3CH_2O), 5.08 (m, 1H, $CHCH_3$), 7.12 (d, 2H, $J = 8.9$ Hz, ArH-3,5), 8.07 (d, 2H, $J = 8.9$ Hz, ArH-2,6), 8.57 (br s, 3H, NH_3). ^{13}C NMR ($CDCl_3$) 12.2 (CH_3CH), 15.3 (CH_3CH_2O), 48.2 ($CHCH_3$), 61.7 (CH_3CH_2O), 112.6 (ArC-3,5), 123.3 (ArC-1), 129.1 (ArC-2,6), 161.3 (ArC-4), 192.6 (Ar*C*OCH). HRMS m/z 193.1104, calculated for $C_{11}H_{15}O_2N$ $(M-HCl)^+$, 193.1103.

4.2.5. (*R*,*S*)-2-Amino-1-(4-propoxyphenyl)-1-propanone hydrochloride (21). Yield 75%, mp 210–211 °C. ^{1}H NMR (DMSO-d_6) 0.99 (t, 3H, $J = 7.3$ Hz, CH_3-CH_2CH_2O), 1.43 (d, 3H, $J = 6.8$ Hz, $CHCH_3$), 1.70–1.82 (m, 2H, $CH_3CH_2CH_2O$), 4.06 (t, 2H, $J = 6.6$ Hz, $CH_3CH_2CH_2O$), 5.05 (m, 1H, $CHCH_3$), 7.10 (d, 2H, $J = 8.8$ Hz, ArH-3,5), 8.04 (d, 2H, $J = 9.3$ Hz, ArH-2,6), 8.53 (br s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 10.8 ($CHCH_3$), 17.9 ($CH_3CH_2CH_2O$), 22.3 ($CH_3CH_2CH_2O$), 50.8 ($CHCH_3$), 70.0 ($CH_3CH_2CH_2O$), 115.3 (ArC-3,5), 125.9 (ArC-1), 131.8 (ArC-2,6), 164.0 (ArC-4), 195.3 (Ar*C*OCH). HRMS m/z 207.1258, calculated for $C_{12}H_{17}O_2N$ $(M-HCl)^+$, 207.1259.

4.2.6. (*R*,*S*)-2-Amino-1-(4-butoxyphenyl)-1-propanone hydrochloride (22). Yield 67%, mp 206–208 °C. ^{1}H NMR (DMSO-d_6) 0.92 (t, 3H, $J = 7.1$ Hz, CH_3CH_2-CH_2CH_2O), 1.39–1.43 (m, 5H, $CHCH_3$, CH_3CH_2-CH_2CH_2O), 1.66–1.75 (m, 2H, $CH_3CH_2CH_2CH_2O$), 4.08 (t, 2H, $J = 6.5$ Hz, $CH_3CH_2CH_2CH_2O$), 5.02 (m, 1H, $CHCH_3$), 7.07 (d, 2H, $J = 8.7$ Hz, ArH-3,5), 8.01 (d, 2H, $J = 8.7$ Hz, ArH-2,6), 8,51 (s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 14.1 ($CHCH_3$), 17.9 (CH_3CH_2-CH_2CH_2O), 19.1 ($CH_3CH_2CH_2CH_2O$), 31.0 (CH_3CH_2-CH_2CH_2O), 50.8 ($CHCH_3$), 68.3 ($CH_3CH_2CH_2CH_2O$), 115.3 (ArC-3,5), 125.9 (ArC-1), 131.7 (ArC-2,6), 164.1 (ArC-4), 195.2 (Ar*C*OCH). HRMS m/z 221.1416, calculated for $C_{13}H_{19}O_2N$ $(M-HCl)^+$, 221.1416.

4.2.7. (*R*,*S*)-2-Amino-1-(4-isobutoxyphenyl)-1-propanone hydrochloride (23). Yield 64%, mp 202–203 °C. ^{1}H NMR (DMSO-d_6) 0.99 (d, 6H, $J = 6.6$ Hz, $(CH_3)_2CHCH_2O$), 1.43 (d, 3H, $J = 7.1$ Hz, $CHCH_3$), 1.99–2.09 (m, 1H, $(CH_3)_2CHCH_2O$), 3.87 (d, 2H, $J = 6.6$ Hz, $(CH_3)_2$-$CHCH_2O$), 5.04 (q, 1H, $J = 7.1$ Hz, $CHCH_3$), 7.10 (d, 2H, $J = 9.0$ Hz, ArH-3,5), 8.03 (d, 2H, $J = 9.0$ Hz, ArH-2,6), 8.58 (s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 17.3 ($CHCH_3$), 18.8 ($(CH_3)_2CHCH_2O$), 27.5 ($(CH_3)_2$-$CHCH_2O$), 50.3 ($CHCH_3$), 74.1 ($(CH_3)_2CHCH_2O$), 114.8 (ArC-3,5), 125.4 (ArC-1), 131.2 (ArC-2,6), 163.6 (ArC-4), 194.7 (Ar*C*OCH). HRMS m/z 221.1411, calculated for $C_{13}H_{19}O_2N$ $(M-HCl)^+$, 221.1416.

4.2.8. (*R*,*S*)-2-Amino-1-(4-methylthiophenyl)-1-propanone hydrochloride (24). Yield 53%, mp 201–202 °C. ^{1}H NMR (DMSO-d_6) 1.43 (d, 3H, $J = 7.1$ Hz, CHCH_3), 2.56 (s, 3H, CH_3S), 5.07 (q, 1H, $J = 7.0$ Hz, CHCH$_3$), 7.42 (d, 2H, $J = 8.4$ Hz, ArH-3,5), 7.98 (d, 2H, $J = 8.4$ Hz, ArH-2,6), 8.58 (br s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 14.1 (CH*C*H$_3$), 17.5 (*C*H$_3$S), 50.8 (*C*HCH$_3$), 125.4 (ArC-3,5), 129.1 (ArC-1), 129.5 (ArC-2,6), 147.7 (ArC-4), 195.7 (Ar*C*OCH). HRMS *m*/*z* 195.0711, calculated for $C_{10}H_{13}OSN$ (M−HCl)$^+$, 195.0718.

4.2.9. (*R*,*S*)-2-Amino-1-(4-ethylthiophenyl)-1-propanone hydrochloride (25). Yield 62%, mp 200–201 °C. ^{1}H NMR (DMSO-d_6) 1.30 (t, 3H, $J = 7.3$ Hz, CH_3CH$_2$S), 1.43 (d, 3H, $J = 7.1$ Hz, CHCH_3), 3.12 (q, 2H, $J = 7.3$ Hz, CH$_3$CH_2S), 5.07 (d, 1H, $J = 5.2$ Hz, CHCH$_3$), 7.44 (d, 2H, $J = 8.5$ Hz, ArH-3,5), 7.98 (d, 2H, $J = 8.5$ Hz, ArH-2,6), 8.52 (br s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 14.6 (CH*C*H$_3$), 18.1 (*C*H$_3$CH$_2$S), 25.5 (CH$_3$*C*H$_2$S), 51.4 (*C*HCH$_3$), 126.8 (ArC-3,5), 129.9 (ArC-1), 130.2 (ArC-2,6), 147.0 (ArC-4), 196.3 (Ar*C*OCH). HRMS *m*/*z* 209.0869, calculated for $C_{11}H_{15}OSN$ (M−HCl)$^+$, 209.0874.

4.2.10. (*R*,*S*)-2-Amino-1-(4-propylthiophenyl)-1-propanone hydrochloride (26). Yield 60%, mp 190–191 °C. ^{1}H NMR (DMSO-d_6) 1.00 (t, 3H, $J = 7.3$ Hz, CH_3CH$_2$-CH$_2$S), 1.42 (d, 3H, $J = 7.2$ Hz, CHCH_3), 1.61–1.70 (m, 2H, CH$_3$CH_2CH$_2$S), 3.07 (t, 2H, $J = 7.4$ Hz, CH$_3$-CH$_2$CH_2S), 5.06 (q, 1H, $J = 7.2$ Hz, CHCH$_3$), 7.44 (d, 2H, $J = 8.8$ Hz, ArH-3,5), 7.96 (d, 2H, $J = 8.6$ Hz, ArH-2,6), 8.55 (br s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 13.2 (CH*C*H$_3$), 17.2 (*C*H$_3$CH$_2$CH$_2$S), 21.6 (CH$_3$*C*H$_2$CH$_2$S), 32.4 (CH$_3$CH$_2$*C*H$_2$S), 50.5 (*C*HCH$_3$), 126.0 (ArC-3,5), 129.0 (ArC-1), 129.3 (ArC-2,6), 146.3 (ArC-4), 195.4 (Ar*C*OCH). HRMS *m*/*z* 223.1027, calculated for $C_{12}H_{17}OSN$ (M−HCl)$^+$, 223.1031.

4.2.11. (*R*,*S*)-2-Amino-1-(4-butylthiophenyl)-1-propanone hydrochloride (27). Yield 25%, mp 189–190 °C. ^{1}H NMR (DMSO-d_6) 0.89 (t, 3H, $J = 7.4$ Hz, CH_3CH$_2$CH$_2$-CH$_2$S), 1.38–1.47 (m, 5H, CHCH_3, CH$_3$CH_2CH$_2$CH$_2$S), 1.57–1.64 (m, 2H, CH$_3$CH$_2$CH_2CH$_2$O), 3.08 (t, 2H, $J = 7.4$ Hz, CH$_3$CH$_2$CH$_2$CH_2S), 5.05 (q, 1H, $J = 7.0$ Hz, CHCH$_3$), 7.43 (d, 2H, $J = 8.6$ Hz, ArH-3,5), 7.96 (d, 2H, $J = 8.8$ Hz, ArH-2,6), 8.55 (s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 13.5 (CH*C*H$_3$), 17.2 (*C*H$_3$CH$_2$CH$_2$CH$_2$S), 21.4 (CH$_3$*C*H$_2$CH$_2$CH$_2$S), 30.2 (CH$_3$CH$_2$*C*H$_2$CH$_2$S), 30.3 (CH$_3$CH$_2$CH$_2$*C*H$_2$S), 50.6 (*C*HCH$_3$), 126.0 (ArC-3,5), 129.0 (ArC-1), 129.3 (ArC-2,6), 146.3 (ArC-4), 195.4 (Ar*C*OCH). HRMS *m*/*z* 237.1187, calculated for $C_{13}H_{19}OSN$ (M−HCl)$^+$, 237.1187.

4.2.12. (*R*,*S*)-2-Amino-1-(4-isobutylthiophenyl)-1-propanone hydrochloride (28). Yield 67%, mp 190–191 °C. ^{1}H NMR (DMSO-d_6) 1.01 (d, 6H, $J = 6.8$ Hz, (CH_3)$_2$-CHCH$_2$S), 1.42 (d, 3H, $J = 7.2$ Hz, CHCH_3), 1.81–1.91 (m, 1H, (CH$_3$)$_2$CHCH$_2$S), 2.98 (d, 2H, $J = 6.7$ Hz, (CH$_3$)$_2$CHCH_2S), 5.05 (q, 1H, $J = 7.2$ Hz, CHCH$_3$), 7.44 (d, 2H, $J = 8.6$ Hz, ArH-3,5), 7.95 (d, 2H, $J = 8.6$ Hz, ArH-2,6), 8.52 (s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 17.7 (CH*C*H$_3$), 22.2 ((*C*H$_3$)$_2$CHCH$_2$S), 28.1 ((CH$_3$)$_2$CH*C*H$_2$S), 51.1 (*C*HCH$_3$), 126.6 (ArC-3,5), 129.5 (ArC-1), 129.8 (ArC-2,6), 147.0 (ArC-4), 195.9 (Ar*C*OCH). Analysis found: C, 56.74; H, 7.15; N, 5.15, calculated for $C_{13}H_{20}ClOSN$: C, 57.02; H, 7.36; N, 5.12.

4.2.13. (*R*,*S*)-2-Amino-1-(2,5-dimethoxyphenyl)-1-propanone hydrochloride (29). Yield 75%, mp 176–177°C, lit.[20] mp 176 °C. ^{1}H NMR (DMSO-d_6) 1.36 (d, 3H, $J = 7.1$ Hz, CH_3CH), 3.74 (s, 3H, 5-OCH_3), 3.88 (s, 3H, 2-OCH_3), 4.80 (br s, 1H, CH$_3$CH), 7.18–7.27 (m, 3H, ArH-3,4,6), 8.54 (br s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 16.4 (*C*H$_3$CH), 55.2 (*C*HCH$_3$), 56.5 (*C*H$_3$O-5), 57.3 (*C*H$_3$O-2), 114.9 (ArC-3), 115.3 (ArC-4), 122.5 (ArC-6), 124.1 (ArC-5), 153.7 (ArC-2), 154.0 (ArC-1), 197.1 (Ar*C*OCH).

4.3. General procedures for the preparation of 2-amino-1-aryl-1-propanol hydrochlorides (30–41)

4.3.1. Method (a). To a solution of the racemic 2-trifluoroacetamido-1-aryl-1-propanone (0.7 mmol) in ethanol (8 mL) was added with stirring $NaBH_4$ (0.17 g, 4.5 mmol) and the mixture was stirred at 25 °C for 48 h. The solvent was evaporated under reduced pressure, water (15 mL) was added, and the aqueous suspension was extracted with dichloromethane (2×15 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated. The residual amine was dissolved in dry ether (10 mL) and the hydrochloride precipitated with gaseous HCl.

4.3.2. Method (b). The racemic 2-amino-1-aryl-1-propanone hydrochloride was reduced with $NaBH_4$, according to method (a). The mixture was stirred at 25 °C for 18 h and the hydrochloride was obtained after the same work-up. In this way, the following compounds (**30**–**41**) were prepared.

4.3.3. 2-Amino-1-(phenyl)-1-propanol hydrochloride (30). Prepared by method (a), yield 65%, mp 172–175 °C lit.[21] 174–176 °C. ^{1}H NMR (DMSO-d_6) 0.95 (d, 3H, $J = 6.4$ Hz, CH_3CH), 3.36 (m, 1H, CHCH$_3$), 5.00 (dd, 1H, $J = 3.5$, $J' = 4.1$ Hz, CHOH), 6.03 (d, 1H, $J = 4.1$ Hz, CHOH), 7.25–7.32 (m, 1H, ArH-4), 7.37 (m, 4H, ArH-2,6,3,5), 8.22 (s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 11.8 (*C*H$_3$CH), 52.3 (*C*HCH$_3$), 71.7 (*C*HOH), 126.4 (ArC-3,5), 127.8 (ArC-4), 128.6 (ArC-2,6), 141.7 (ArC-1).

4.3.4. 2-Amino-1-(4-methylphenyl)-1-propanol hydrochloride (31). Prepared by method (a), yield 60%, mp 193–195 °C. lit.[22] 205 °C. ^{1}H NMR (DMSO-d_6) 0.94 (d, 3H, $J = 6.8$ Hz, CH_3CH), 2.29 (s, 3H, CH_3Ar), 3.32 (m, 1H, CHCH$_3$), 4.94 (dd, 1H, $J = 3.5$, $J' = 4.1$ Hz, CHOH),

5.95 (d, 1H, $J = 4.1$ Hz, CHO*H*), 7.17 (d, 2H, $J = 7.6$ Hz, ArH-3,5), 7.25 (d, 2H, $J = 8.2$ Hz, ArH-2,6), 8.19 (s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 11.9 (*C*H$_3$CH), 21.2 (*C*H$_3$-Ar), 52.4 (*C*HCH$_3$), 71.6 (*C*HOH), 126.3 (ArC-3,5), 129.2 (ArC-2,6), 136.8 (ArC-1), 138.7 (ArC-4).

4.3.5. 2-Amino-1-(4-methoxyphenyl)-1-propanol hydrochloride (32). Prepared by method (a), yield 82%, mp 198–199 °C. lit.[19] mp 216.5 °C. ^{1}H NMR (DMSO-d_6) 0.97 (d, 3H, $J = 7.0$ Hz, CH_3CH), 3.30 (dd, 1H, $J = 7.0$ and 2.9 Hz, C*H*CH$_3$), 3.75 (s, 3H, CH_3O), 4.93 (d, 1H, $J = 2.3$ Hz, C*H*OH), 5.94 (s, 1H, CHO*H*), 6.93 (d, 2H, $J = 8.8$ Hz, ArH-3,5), 7.28 (d, 2H, $J = 8.8$ Hz, ArH-2,6), 8.20 (s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 11.8 (*C*H$_3$CH), 52.2 (*C*HCH$_3$), 55.3 (*C*H$_3$O), 71.3 (*C*HOH), 113.8 (ArC-3,5), 127.4 (ArC-2,6), 133.3 (ArC-1), 158.7 (ArC-4).

4.3.6. 2-Amino-1-(4-ethoxyphenyl)-1-propanol hydrochloride (33). Prepared by method (a), yield 50%, mp 175–177 °C. ^{1}H NMR (DMSO-d_6) 0.95 (d, 3H, $J = 6.8$ Hz, CH_3CH), 1.32 (t, 3H, $J = 6.8$ Hz, CH_3CH$_2$O), 3.30 (d, 1H, $J = 6.4$ Hz, C*H*CH$_3$), 4.01 (q, 2H, $J = 6.8$ Hz, CH$_3$CH_2O), 4.91 (s, 1H, C*H*OH), 5.96 (d, 1H, $J = 3.9$ Hz, CHO*H*), 6.91 (d, 2H, $J = 8.3$ Hz, ArH-3,5), 7.26 (d, 2H, $J = 8.3$ Hz, ArH-2,6), 8.17 (s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 12.0 (*C*H$_3$CH), 15.2 (*C*H$_3$CH$_2$O), 52.4 (*C*HCH$_3$), 63.4 (CH$_3$*C*H$_2$O), 71.5 (*C*HOH), 114.5 (ArC-3,5), 127.6 (ArC-2,6), 133.4 (ArC-1), 158.2 (ArC-4). HRMS m/z 195.1264, calculated for $C_{11}H_{17}O_2N$ (M−HCl)$^+$, 195.1259.

4.3.7. 2-Amino-1-(4-propoxyphenyl)-1-propanol hydrochloride (34). Prepared by method (a), yield 72%, mp 108–115 °C. ^{1}H NMR (DMSO-d_6) 0.95–1.00 (m, 6H, CH_3CH, CH_3CH$_2$CH$_2$O), 1.66–1.78 (m, 2H, CH$_3$CH_2CH$_2$O), 3.31 (s, 1H, C*H*CH$_3$), 3.91 (t, 2H, $J = 6.4$ Hz, CH$_3$CH$_2$CH_2O), 4.91 (d, 1H, $J = 2.5$ Hz, C*H*OH), 5.94 (s, 1H, CHO*H*), 6.92 (d, 2H, $J = 8.8$ Hz, ArH-3,5), 7.26 (d, 2H, $J = 8.3$ Hz, ArH-2,6), 8.16 (s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 10.9 (*C*H$_3$CH$_2$CH$_2$O), 12.0 (*C*H$_3$CH), 22.5 (CH$_3$*C*H$_2$CH$_2$O), 52.4 (*C*HCH$_3$), 69.4 (CH$_3$CH$_2$*C*H$_2$O), 71.5 (*C*HOH), 114.5 (ArC-3,5), 127.6 (ArC-2,6), 133.4 (ArC-1), 158.4 (ArC-4). HRMS m/z 209.1413, calculated for $C_{12}H_{19}O_2N$ (M−HCl)$^+$, 209.1416.

4.3.8. 2-Amino-1-(4-butoxyphenyl)-1-propanol hydrochloride (35). Prepared by method (b), yield 74%, mp 165–170 °C. ^{1}H NMR (DMSO-d_6) 0.91–0.97 (m, 6H, CHCH_3, CH_3CH$_2$CH$_2$CH$_2$O), 1.39–1.49 (m, 2H, CH$_3$CH_2CH$_2$CH$_2$O), 1.65–1.75 (m, 2H, CH$_3$CH$_2$CH_2-CH$_2$O), 3.29–3.31 (m, 1H, C*H*CH$_3$), 3.95 (t, 2H, $J = 6.5$ Hz, CH$_3$CH$_2$CH$_2$CH_2O), 4.88 (dd, 1H, $J = 3.4$, $J' = 4.1$ Hz, C*H*OH), 5.92 (d, 1H, $J = 4.2$ Hz, CHO*H*), 6.92 (d, 2H, $J = 8.8$ Hz, ArH-3,5), 7.26 (d, 2H, $J = 8.6$ Hz, ArH-2,6), 8.09 (s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 13.0 (*C*H$_3$CH$_2$CH$_2$CH$_2$O), 15.1 (CH*C*H$_3$), 20.2 (CH$_3$*C*H$_2$CH$_2$CH$_2$O), 32.2 (CH$_3$CH$_2$*C*H$_2$CH$_2$O), 53.3 (*C*HCH$_3$), 68.5 (CH$_3$CH$_2$CH$_2$*C*H$_2$O), 72.4 (*C*HOH), 115.5 (ArC-3,5), 128.6 (ArC-2,6), 134.3 (ArC-1), 159.4 (ArC-4). HRMS m/z 223.1579, calculated for $C_{13}H_{21}O_2N$ (M−HCl)$^+$, 223.1572.

4.3.9. 2-Amino-1-(4-methylthiophenyl)-1-propanol hydrochloride (36). Prepared by method (a), yield 50%, mp 183–185°C. ^{1}H NMR (DMSO-d_6) 0.94 (d, 3H, $J = 6.8$ Hz, CH_3CH), 2.46 (s, 3H, CH_3S), 3.32 (br s, 1H, C*H*CH$_3$), 4.94 (br s, 1H, C*H*OH), 6.05 (d, 1H, $J = 3.7$ Hz, CHO*H*), 7.23–7.31 (m, 4H, ArH-2,3,5,6), 8.22 (s, 3H, NH$_3$). ^{13}C NMR (DMSO-d_6) 11.9 (*C*H$_3$CH), 15.1 (*C*H$_3$S) 52.23 (*C*HCH$_3$), 71.4 (*C*HOH), 126.1 (ArC-3,5), 127.1 (ArC-2,6), 137.4 (ArC-1), 138.3 (ArC-4). HRMS m/z 197.0877, calculated for $C_{10}H_{15}OSN$ (M−HCl)$^+$, 197.0874.

4.3.10. 2-Amino-1-(4-ethylthiophenyl)-1-propanol hydrochloride (37). Prepared by method (a), yield 41%, mp 203–205 °C. ^{1}H NMR (DMSO-d_6) 0.94 (d, 3H, $J = 6.8$ Hz, CH_3CH), 1.22 (t, 3H, $J = 7.3$ Hz, CH_3CH$_2$), 2.97 (q, 2H, $J = 7.3$ Hz, SCH_2CH$_3$), 3.34 (m, 1H, C*H*CH$_3$), 4.94 (m, 1H, C*H*OH), 6.06 (s, 1H, CHO*H*), 7.30 (s, 4H, ArH-2,3,5,6), 8.20 (s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 11.9 (*C*H$_3$CH), 14.6 (*C*H$_3$CH$_2$S), 26.5 (CH$_3$*C*H$_2$S), 52.2 (*C*HCH$_3$), 71.4 (*C*HOH), 127.1 (ArC-3,5), 128.2 (ArC-2,6), 135.5 (ArC-1), 139.0 (ArC-4). HRMS m/z 211.1030, calculated for $C_{11}H_{17}OSN$ (M−HCl)$^+$, 211.1031.

4.3.11. 2-Amino-1-(4-propylthiophenyl)-1-propanol hydrochloride (38). Prepared by method (b), yield 99%, mp 150–155 °C. ^{1}H NMR (DMSO-d_6) 0.94–1.99 (m, 6H, CH_3CH, CH_3CH$_2$CH$_2$S), 1.54–1.63 (m, 2H, CH$_3$CH_2-CH$_2$S), 2.94 (t, 2H, $J = 7.1$ Hz, CH$_3$CH$_2$CH_2S), 4.92 (dd, 1H, $J = 3.7$, $J' = 4.2$ Hz, C*H*OH), 6.03 (d, 1H, $J = 4.2$ Hz, CHO*H*), 7.31 (s, 4H, ArH-2,3,5,6), 8.13 (s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 11.5 (*C*H$_3$CH), 13.1 (*C*H$_3$CH$_2$CH$_2$S), 21.9 (CH$_3$*C*H$_2$CH$_2$S), 34.0 (CH$_3$-CH$_2$*C*H$_2$S), 51.7 (*C*HCH$_3$), 71.0 (*C*HOH), 126.7 (ArC-3,5), 127.8 (ArC-2,6), 135.3 (ArC-1), 138.5 (ArC-4). HRMS m/z 225.1193, calculated for $C_{12}H_{19}OSN$ (M−HCl)$^+$, 225.1187.

4.3.12. 2-Amino-1-(4-butylthiophenyl)-1-propanol hydrochloride (39). Prepared by method (b), yield 50%, mp 138–143 °C. ^{1}H NMR (DMSO-d_6) 0.88 (t, 3H, $J = 7.3$ Hz, CH_3CH$_2$CH$_2$CH$_2$S), 0.95 (d, 3H, $J = 6.8$ Hz, CHCH_3), 1.36–1.45 (m, 2H, CH$_3$CH_2CH$_2$-CH$_2$S), 1.52–1.59 (m, 2H, CH$_3$CH$_2$CH_2CH$_2$S), 2.95 (t, 2H, $J = 7.2$ Hz, CH$_3$CH$_2$CH$_2$CH_2S), 4.93 (dd, 1H, $J = 4.0$, $J' = 4.3$ Hz, C*H*OH), 6.02 (d, 1H, $J = 4.4$ Hz, CHO*H*), 7.31 (s, 4H, ArH-2,3,5,6), 8.15 (s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 11.5 (*C*H$_3$CH$_2$CH$_2$CH$_2$S), 13.4 (CH*C*H$_3$), 21.2 (CH$_3$*C*H$_2$CH$_2$CH$_2$S), 30.6 (CH$_3$CH$_2$-*C*H$_2$CH$_2$S), 31.7 (CH$_3$CH$_2$CH$_2$*C*H$_2$S), 51.7 (*C*HCH$_3$), 71.0 (*C*HOH), 126.7 (ArC-3,5), 127.7 (ArC-2,6), 135.4

(ArC-1), 138.5 (ArC-4). HRMS m/z 239.1338, calculated for $C_{13}H_{21}OSN$ $(M-HCl)^+$, 239.1344.

4.3.13. 2-Amino-1-(4-isobutylthiophenyl)-1-propanol hydrochloride (40). Prepared by method (b), yield 80%, mp 120–125 °C. ^1H NMR (DMSO-d_6) 0.94–0.99 (m, 9H, $(CH_3)_2CHCH_2S$, $CHCH_3$), 1.73–1.83 (m, 1H, $(CH_3)_2CHCH_2S$), 2.85 (d, 2H, $J = 6.8$ Hz, $(CH_3)_2CHCH_2S$), 4.94 (dd, $J = 3.7$, $J' = 4.0$ Hz, 1H, CHOH), 6.02 (d, 1H, $J = 4.2$ Hz, CHOH), 7.31 (s, 4H, ArH-2,3,5,6), 8.19 (s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 11.4 ($CHCH_3$), 21.6 ($(CH_3)_2CHCH_2S$), 27.7 ($(CH_3)_2CHCH_2S$), 40.9 ($(CH_3)_2CHCH_2S$), 51.7 ($CHCH_3$), 71.0 (CHOH), 126.6 (ArC-3,5), 127.7 (ArC-2,6), 135.6 (ArC-1), 138.5 (ArC-4). HMRS m/z 239.1346, calculated for $C_{13}H_{21}OSN$ $(M-HCl)^+$, 239.1344.

4.3.14. 2-Amino-1-(2,5-dimethoxyphenyl)-1-propanol hydrochloride (41). Prepared by method (a), yield 56%, mp 200–202 °C. lit.[20] 174 °C, lit.[23] 215 °C. ^1H NMR (DMSO-d_6) 0.91 (d, 3H, $J = 7.0$ Hz, CH_3CH), 3.39–3.40 (m, 1H, $CHCH_3$), 3.71 (s, 3H, 2-CH_3O), 3.75 (s, 3H, 5-CH_3O), 5.13 (d, 1H, $J = 2.3$ Hz, CHOH), 6.83 (dd, 1H, $J_o = 8.5$, $J_m = 2.9$ Hz, ArH-4), 6.93 (d, 1H, $J_o = 8.8$ Hz, ArH-3), 7.01 (d, 1H, $J_m = 2.9$ Hz, ArH-6), 8.18 (s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 12.1 (CH_3CH), 49.8 ($CHCH_3$), 55.8 (CH_3O-2), 56.3 (CH_3O-5), 67.0 (CHOH), 112.1, 113.0, and 113.8 (ArC-3,4,6), 130.6 (ArC-1), 149.9 (ArC-5), 153.6 (ArC-2).

4.4. General procedure for the preparation of 2-amino-1-aryl-1-methoxypropane hydrochlorides (42–45)

These compounds were obtained by Michael addition of sodium methoxide to previously prepared nitrostyrenes, followed by reduction of the resulting 1-aryl-1-methoxy-2-nitropropanes with $LiAlH_4$. This route had been previously employed, with full characterization of the intermediate styrenes and methoxyethanes, for the preparation of 1-aryl-1-methoxy-2-nitroethanes.[24]

A solution of the appropriate benzaldehyde (20 mmol), butylamine (2 mL, 20 mmol), and nitroethane (2.9 mL, 40 mmol) in glacial acetic acid (10 mL) was refluxed for 1 h. The dark red solution was cooled and poured into ice-water to precipitate the crude nitrostyrene, which was recrystallized in methanol, or purified by column chromatography (silica gel, CH_2Cl_2 as eluent). The dry nitrostyrene thus obtained (2 mmol) was dissolved in dry benzene (10 mL) and to this cooled (0 °C) solution was then added 3 M CH_3ONa in methanol (2.5 mL). After stirring for 1 h, glacial acetic acid (3 mL) was added, followed by water (20 mL). The aqueous solution was extracted with dichloromethane (2×30 mL), the organic phases were combined, dried over anhydrous Na_2SO_4 and concentrated to give the crude 1-aryl-1-methoxy-2-nitropropane, which was purified by column chromatography (silica gel, dichloromethane as eluent). The obtained product was redissolved in dry THF (10 mL) and the resulting solution was added dropwise to a stirred and cooled (0 °C) suspension of $LiAlH_4$ (0.62 g, 16.5 mmol) in dry THF (10 mL). The mixture was refluxed for 2 h. It was then cooled and quenched with 2-propanol and subsequently with 1 M NaOH. The precipitated hydroxides were filtered, and washed with CH_2Cl_2. The filtrate, which consisted of a two-phase system, was made acid with 1 M HCl (20 mL) and the organic extracts were discarded. The aqueous phase was then basified with 2 M NaOH, and this solution was extracted with dichloromethane. The organic extracts were dried over anhydrous Na_2SO_4 and concentrated to give the crude 2-amino-1-aryl-1-methoxypropane. This was redissolved in dry ether (10 mL) and the corresponding hydrochlorides were precipitated by passing gaseous HCl through this solution. The diastereomeric mixture of 2-amino-1-aryl-1-methoxypropane hydrochlorides was then filtered and dried. In this way the following compounds (**42–45**) were prepared.

4.4.1. 2-Amino-1-phenyl-1-methoxypropane hydrochloride (42). Yield 40%, based on the corresponding benzaldehyde, mp 195–197 °C, lit.[25] 186–188 °C. Diastereomeric mixture, according to the NMR spectra, which showed double signals, with equal intensities, for the aliphatic side-chain protons. ^1H NMR (DMSO-d_6) 0.94 (d, 3H, $J = 6.7$ Hz, $CHCH_3$), 0.98 (d, 3H, $J = 6.9$ Hz, $CHCH_3$), 3.12 (s, 3H, CH_3OCH), 3.27 (s, 3H, CH_3OCH), 3.30–3.34 (m, 2H, $CHCH_3$), 4.20 (d, 1H, $J = 9.3$ Hz, $CHOCH_3$), 4.68 (d, 1H, $J = 3.1$ Hz, $CHOCH_3$), 7.30–7.44 (m, 10H, ArH-2,3,4,5,6), 8.35 (s, 6H, NH_3).

4.4.2. 2-Amino-1-(4-methylphenyl)-1-methoxypropane hydrochloride (43). Yield 47%, based on the corresponding benzaldehyde, mp 230–231 °C. Diastereomeric mixture, according to the NMR spectra, which showed double signals, with equal intensities, for the aliphatic side-chain protons. ^1H NMR (DMSO-d_6) 0.93 (d, 3H, $J = 6.7$ Hz, $CHCH_3$), 0.98 (d, 3H, $J = 6.7$ Hz, $CHCH_3$), 2.32 (s, 6H, CH_3Ar), 3.11 (s, 3H, CH_3OCH), 3.25 (s, 3H, CH_3OCH), 3.3 (br s, 2H, $CHCH_3$), 4.13 (d, 1H, $J = 9.4$ Hz, $CHOCH_3$), 4.60 (d, 1H, $J = 3.1$ Hz, $CHOCH_3$), 7.24 (s, 8H, ArH-2,3,5,6), 8.27 (s, 6H, NH_3). HRMS m/z 179.1307, calculated for $C_{11}H_{17}ON$ $(M-HCl)^+$, 179.1310.

The diastereomeric mixture (**43**) was recrystallized from ethanol to give one product, which exhibited a ^1H NMR spectrum without doubling of the signals. Based on the observed coupling constants, this racemic mixture was assigned the *threo* *S,S* and *RR*) configuration.[14] ^1H NMR (DMSO-d_6) 0.91 (d, 3H, $J = 6.7$ Hz, $CHCH_3$), 2.48 (s, 3H, CH_3Ar), 3.10 (s, 3H, CH_3OCH), 3.32 (br s, 2H, $CHCH_3$), 4.08 (d, 1H, $J = 9.2$ Hz, $CHOCH_3$), 7.25 (s, 4H, ArH-2,3,5,6), 8.17 (s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) 15.4 ($CHCH_3$), 21.1 (CH_3Ar), 51.4 ($CHCH_3$), 56.3 (CH_3OCH), 84.6 ($CHOCH_3$), 128.0 (ArC-3,5), 129.7 (ArC-2,6), 134.4 (ArC-1), 138.5 (ArC-4).

4.4.3. 2-Amino-1-(4-methoxyphenyl)-1-methoxypropane hydrochloride (44). Yield 43%, based on the corresponding benzaldehyde, mp 195–197 °C, lit.[14] corresponding to the *threo* configuration, 178–180 °C. Diastereomeric mixture, according to the NMR spectrum, which showed double signals, with equal intensities, for the aliphatic side-chain protons. ^{1}H NMR (DMSO-d_6) 0.93 (d, 3H, $J = 6.6$ Hz, CHCH_3), 1.00 (d, 3H, $J = 6.7$ Hz, CHCH_3), 3.10 (s, 3H, CH_3OCH), 3.23 (s, 3H, CH_3OCH), 3.26–3.33 (m, 2H, CHCH$_3$), 3.76 (s, 3H, CH_3OAr), 3.77 (s, 3H, CH_3OAr), 4.12 (d, 1H, $J = 9.3$ Hz, CHOCH$_3$), 4.57 (d, 1H, $J = 3.4$ Hz, CHOCH$_3$), 6.98 (d, 4H, $J = 8.2$ Hz, ArH-3,5), 7.22–7.27 (m, 4H, ArH-2,6), 8.28 (br s, 6H, NH_3).

4.4.4. 2-Amino-1-(4-methylthiophenyl)-1-propane hydrochloride (45). Yield 21%, based on the corresponding benzaldehyde, mp 135–140 °C. Diastereomeric mixture, according to the NMR spectrum, which showed double signals, with equal intensities, for the aliphatic side-chain protons. ^{1}H NMR (DMSO-d_6) 0.94 (d, 3H, $J = 6.6$ Hz, CHCH_3), 1.00 (d, 3H, $J = 6.7$ Hz, CHCH_3), 2.49 (s, 6H, CH_3SAr), 3.12 (s, 3H, CH_3OCH), 3.25 (s, 3H, CH_3OCH), 3.28–3.34 (m, 2H, CHCH$_3$), 4.14 (d, 1H, $J = 9.4$ Hz, CHOCH$_3$), 4.59 (d, 1H, $J = 3.2$ Hz, CHOCH$_3$), 7.24–7.32 (m, 8H, ArH-2,3,5,6), 8.26 (br s, 6H, NH_3). HRMS m/z 211.1029, calculated for $C_{11}H_{17}OSN$ $(M-HCl)^+$, 211.1031.

4.5. Evaluation of the MAOI activity of all prepared compounds

The MAOI activity of all the compounds described here was assessed in vitro following a previously reported protocol.[10] Rat brain mitochondrial suspensions were employed as a source of crude MAO. The activities of both isoforms in the absence or presence of different concentrations of the inhibitor were assessed in triplicate by HPLC (Merck-Hitachi L-7110 pump with a Macrosphere KP300 C18 5 μm column and a Labchrom L-3500A amperometric detector). Serotonin (5-HT) and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) were used as standards for measuring MAO-A inhibition. 4-Dimethylaminophenethylamine (4-DMAPEA), a sensitive, specific MAO-B substrate,[26] and its oxidation product 4-dimethylaminophenylacetic acid (4-DMAPAA) were employed for evaluations of MAO-B inhibition.

4.6. Molecular simulation

The crystallographic data of MAO-B (PDB: 1OJA) were used for all calculations. The hydrogen atoms of the protein and the FAD molecule were built using Insight II,[27] and then were relaxed following a minimization protocol using Discover_3,[27] and the CVFF force field. The calculations were performed using a distance-dependent dielectric constant of 80.

The Autodock 3.02 program[28] was then used to perform a docking simulation of the MAO-B/FAD/4-butoxycathinone complex. The protein and the cathinone ligand were assigned partial charges using the CVFF force field. All water molecules were removed. Atomic solvation parameters and fragmental volumes were assigned to the protein atoms using the Addsol program. The grid maps were calculated using the autogrid3 option and were centered on the putative ligand-binding site. The volume chosen for the grid maps was made up of $60\times60\times60$ points, with a grid-point spacing of 0.375 Å. The Autotors option was used to define the rotating bonds in the cathinone. In the Lamarckian genetic algorithm (LGA) dockings, an initial population of random individuals with a population size of 50 individuals, a maximum number of 1.5×10^6 energy evaluations, a maximum number of generations of 27,000, a mutation rate of 0.02, and a cross-over rate of 0.80 were employed. Proportional selection was used, where the average worst energy was calculated over a window of the previous 10 generations. In the LGA dockings, the pseudo-Solis and Wets local search method was used, with a maximum of 300 iterations per local search. The probability of performing a local search on an individual in the population was 0.06. The docked cathinone complexes were built using the lowest free-energy binding positions.

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