cis-Cyclopropylamines as mechanism-based inhibitors of Monoamine Oxidases.

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Running title

cis-Cyclopropylamines inactivate monoamine oxidases

Abstract *(232 words)*

Cyclopropylamines, inhibitors of monoamine oxidases (MAO) and lysine-specific demethylase (LSD1), provide a useful structural scaffold for the design of mechanism-based inhibitors for the therapy of depression and cancer. For new compounds with the less common *cis* relationship and with an alkoxy substituent at the 2-position of the cyclopropyl ring, the apparent affinity from docking revealed little difference between the enantiomers. Using the racemate, kinetic parameters for the reversible and irreversible inhibition of MAO were determined. No inhibition of LSD1 was observed. The reversible inhibition of MAO A gave high IC_{50} values for most compounds but sub-micromolar values with MAO B. After pre-incubation with the enzyme, the inhibition was irreversible in both MAO A and MAO B and the activity was not restored by dilution. Spectral changes during inactivation of MAO A showed bleaching at 456 nm and an increase at 400 nm, consistent with flavin modification. These derivatives are MAO B-selective mechanism-based inhibitors without inhibition of LSD1. The best inhibitor was *cis*-N-benzyl-2-methoxycyclopropylamine, with an IC_{50} of 5 nM for MAO B and 170 nM for MAO A after 30 min preincubation. This *cis*-cyclopropylamine is over 20-fold more effective than tranylcypromine so could be studied as a lead for selective inhibitors of MAO B that do not inhibit LSD1.

Abbreviations

MAO, monoamine oxidase; TCP, tranylcypromine; LSD1, histone demethylase (also known as KDM1A)

Introduction

Interest in cyclopropylamine chemistry was revived when tranylcypromine (TCP; *trans*-2-phenylcyclopropan-1-amine) was identified as an irreversible inhibitor of LSD1, one of the key demethylase enzymes in epigenetic gene regulation [1, 2]. TCP is a mechanism-based inactivator of monoamine oxidases (MAO) and has been used in the treatment of depression for decades [3-5]. TCP inactivates MAO B by forming the C4a adduct with the flavin cofactor whereas LSD1 forms the N5 adduct [5, 6]. These adducts are formed after the oxidation of tranylcypromine by the enzyme, and each may arise via a C4a-N5 cyclic structure [6-8]. A new series of 1-substituted cyclopropylamine derivatives with improved affinity for LSD1 formed different adducts depending on the derivative, at C4a, N5, or bridging both, probably via a radical mechanism [9]. The inactivation is irreversible so new protein synthesis is required for the restoration of activity in the cell.

The potential usefulness of cyclopropylamine inhibitors of MAO and LSD1 for the therapy of depression [10-12] and cancer [4, 13-17], and the need for selective inhibition of the targets has prompted the synthesis and evaluation of new inhibitors such as *trans* 1-substituted derivatives [9]. For the MAO enzymes, more derivatives of *trans*-isomers have been studied, but *cis*-2-phenylcyclopropylamine is only slightly less effective than the *trans*-isomer [18-20]. Enantiomeric selectivity is also a concern. On MAO B, the 1*R*,2*S*-(-)-TCP was 20-fold more effective as a competitive inhibitor, but *cis*-2-phenylcyclopropylamine showed no enantiomeric selectivity [4, 5, 21]. LSD1 showed no enantiomeric selectivity for TCP [5, 22], but the two enantiomers of a 1-substituted cyclopropylamine gave different adducts [9].

Here we report the inhibition of the two forms of MAO by selected *cis*-isomers of primary and secondary cyclopropylamines with an alkoxy group at the 2-position of the cyclopropyl ring replacing the more common phenyl substitution [23]. The *trans*-compound TCP, already well-established as a drug before the full impact of two forms of MAO was appreciated [21, 24, 25], is

included as a reference compound. We show that *cis*-cyclopropylamine, like TCP, forms a covalent adduct with the flavin in MAO A and MAO B. Docking studies, performed to explore enantiomer binding in MAO A and MAO B, also revealed occupancy of the imidazoline (I2) site [26-28] in the entrance cavity of MAO B.

TABLE 1 HERE

Results

No inhibition of LSD1

The *cis*-cyclopropylamine compounds, synthesised as before [23], were tested against LSD1 for which TCP is an established lead. In the LSD1 enzyme assay, the compounds were inactive at the maximum tested concentration of 25 μM.

Molecular modelling with MAO to explore enantiomeric selectivity

Reversible binding can be predicted by docking, so this was used to guide the selection of previously synthesised compounds [23] used in this study and then to explore whether the enantiomers might bind differently to MAO A and MAO B (Table 1). Molecular modelling [29] was performed to determine binding energies and estimated K_i values for the *cis*-cyclopropylamines with MAO A and MAO B (**Supplementary Table S1**). Theoretical K_i values for both enantiomers of all seven compounds were obtained by docking the compounds into MAO A (2Z5X) and MAO B (2V5Z) using Autodock [30] (as shown in **Table 1**) and Vina [31]. Both programmes gave concordant values for the binding energies with essentially no difference between the (1*R*,2*S*) and (1*S*,2*R*) enantiomers (**Supplemental Table S1**). The aromatic group improves binding energy, and the para-methyl group makes compounds **3** and **6** better than **4** in this theoretical ranking. The para-chloro compound **7** gives values similar to the para-methyl one.

Based on the lack of enantiomeric differences, racemic *cis*-cyclopropylamines were used for the experimental work.

Reversible binding: Experimental IC_{50} values

For MAO A and B, the reversible interaction was measured as IC50. Under the conditions of the assay used here, the IC50 values with MAO A are proportional to Ki and reflect the initial reversible binding of the inhibitor to MAO A [32]. For MAO B, the IC50 is influenced by the oxidative half-reaction as well as the reductive half reaction because the rates of reduction and reoxidation of the flavin in the steady state are similar. In practice, the affinity of the inhibitor for the reduced form of MAO B becomes significant, so that the experimental IC50 is influenced by more factors than is the true Ki for binding to a single (oxidised) form of MAO B [32]. The reversible inhibition of MAO A by these *cis*-cyclopropylamine compounds is very poor as indicated by the high IC_{50} values for all compounds except **4** (**Table 1**). In contrast, the IC_{50} values are around micromolar for compounds **1, 2, 4, and 5** with MAO B (Table 1), demonstrating that the selectivity of reversible binding for MAO B is as good as (for **3, 6, 7),** or better than the standard drug, TCP (for **1, 2, 4, 5**).

The Ki values obtained from docking calculations should predict at least qualitatively the experimental values for reversible binding for MAO A in these assays that were carefully designed to reflect the initial reversible binding to the active site. With the exception of compound **4**, the calculated K_i values for MAO A from Autodock shown in Table 1 agree with the order of potency observed in the experimental IC_{50} values. In contrast, for MAO B compounds **3**, **6** and **7** give poor experimental IC_{50} values, compared to the predicted affinity (Table 1), presumably for the kinetic reasons explained above. In general, the output from Autodock predicted a selectivity for MAO B over MAO A much smaller than found experimentally.

TABLE 2 HERE

IC_{50} values for irreversible binding

All compounds showed a time-dependent increase in inhibition (decreased IC_{50}) due to irreversible inactivation, as demonstrated by the lack of restoration of activity after dilution. **Table 2** gives the IC_{50} values after a 30 min preincubation of the inhibitor with the enzyme.

The selectivity ratios calculated from the 30 min IC_{50} values indicate that **6** and **7** act equally on MAO A and B. The other compounds (**1-5**) are better inactivators of MAO B than of MAO A and, thus, are more selective than TCP (**Table 2**). The most effective inactivator is *N*-benzyl-2-methoxycyclopropylamine (**4**) with an IC_{50} of 5 nM against MAO B, 15–fold more potent than TCP and 10-fold more selective for MAO B. Comparing the selectivity at 0 and 30 min, compounds **1**, **2**, **5**, **6** and **7** do not change, but compound **3** is more selective at 30 min whereas **4** has a lower selectivity for MAO B at 30 min. Compounds that give unchanged, more, and less selectivity (**1**, **3**, **4**, **6**) were studied in detail to investigate whether the rate constant for inactivation (k_{inact}) could account for the differences.

TABLE 3 HERE

Kinetic parameters for inactivation of MAO A and MAO B by *cis*-cyclopropylamines

After pre-incubation with the enzyme, the inhibition by all four selected compounds (**1**, **3**, **4**, **6**) was irreversible and the activity was not restored by dilution into excess substrate. The kinetic parameters for the mechanism-based irreversible inactivation of MAO A, termed K_I and k_{inact} [33], were determined from the time course of inactivation and are presented in **Table 3**. The MAO A irreversible K_I values are all poor, with the exception of **4** (**Table 3**). The K_I values for MAO B indicate much more discrimination of the structural variations in the compounds: **4** (0.07 μM) < **1** (0.9 μM) < **3** (5 μM) < **6** (17 μM), presumably as a result of its narrower substrate cavity [34].

For MAO A, 2-methoxy-2-methylcyclopropylamine (**1**) gives the fastest rate of inactivation (k_{inact} = 0.17 min^{-1}), perhaps because its small size facilitates the correct orientation for its oxidation. Compounds **3**, **4**, and **6** all inactivate MAO A at slower rates. Both 4 and 1 inactivate MAO A without generation of detectable H_2O_2. For MAO B, **1** gives the slowest inactivation (k_{inact} = 0.016 min^{-1}), whereas **4** gives the fastest (k_{inact} = 0.104 min^{-1}), but both generate H_2O_2 during the preincubation with MAO B, indicating less tight coupling between oxidation and adduct formation.

The specificity constants (k_{inact}/K_I) provide a comparison of the efficiency of inactivation by each compound, and from them, the selectivity for MAO B compared to MAO A is calculated as a ratio (last column of **Table 3**). The specificity constants for inactivation show that all compounds inactivate MAO B more efficiently than MAO A. Compared to TCP, compound **4** more effectively inactivates MAO A (4 times better) and MAO B (> 20 times better). Compound **4** is also 5 times more selective for MAO B. The rate of inactivation (k_{inact}) by compound **4** is considerably lower than that by TCP (15-fold in MAO A and > 2-fold in MAO B) but the low K_I values for **4**, particularly for MAO B (65 nM) offset the lower rates.

FIGURE 1 HERE

Characterization of the adduct formed between MAO A and 4

Covalent adducts with the N5 group of the FAD moiety of MAO, such as formed after inactivation by clorgyline or deprenyl, are characterised by a distinctive change in the spectrum of MAO that differs from that seen for the C4a adduct [35-38]. The spectral changes that occur during adduct formation with *cis*-cyclopropylamines **4** were studied (**Fig. 1**). The MAO A flavin absorbance at 456 nm was bleached indicating at least partial reduction of the flavin (**Fig. 1A**). The absorbance at 400 nm increased but this increase lagged behind the rapid flavin reduction as seen in the time

course (**Fig. 1B**) and in the difference spectra in **Fig. 1C**. This suggests a slower chemical step for adduct formation after the reduction of the flavin.

The spectral change during inactivation of MAO A by compound **4** has some similarity to that for N5 modification by clorgyline, but it has a less intense absorbance increase at 400 nm rather than the large 415 nm increase seen for N5 propargyl adducts with MAO A. However, the flavin remains reduced after denaturation with urea, suggesting that it is a stable adduct, unlike the labile adducts for *trans*-cyclopropylamines assumed to be at C4a [39] where reoxidation of the flavin is obvious after urea denaturation.

FIGURE 2 HERE

Small *cis*-cyclopropylamines can occupy multiple positions in the active sites

With the exception of **4**, all the cis-cyclopropylamines are poor inactivators of MAO compared to TCP. Molecular modelling was used to compare how these small molecules interacted with the active sites of the two enzymes. **Multiple poses were found for each compound at various locations in the active site and with varying orientations, as illustrated for selected enantiomers in Fig. 2.** Interestingly, in MAO B, poses with energy minima for the smallest compound **1** are found in the entrance cavity, in mid-cavity, and near the flavin. The latter location (as shown in **Fig. 2, top**) near the N5 of the flavin is required in order to inactivate MAO B. The amino acids surrounding the (1*R*,2*S*)- enantiomer of compound **1** near the flavin are shown in **Fig. 3** (**left**). The entrance cavity pose (**Fig. 3, right**) was found in only two of the ten Autodock runs for (1*R*,2*S*)-**1** and gave an energy of -3.74 kcal mol^{-1}, and in only one run for (1*S*,2*R*)-**1** with an energy of -4.33 kcal mol^{-1}. This entrance cavity location (**Fig. 3**) is similar to that of 2-BFI bound in the imidazoline I_2 site of MAO B that has been characterised in binding studies and demonstrated by crystallography [26, 27]. However, unlike the I_2 ligands that have nM affinity, the predicted K_i for binding of compound **1** at this location is in the micromolar range.

The low probability of binding close to the flavin may also explain the low rate of inactivation (**Table 3**: k_{inact} is 0.016 min^{-1} for **1** with MAO B compared to 0.263 min^{-1} for TCP). The introduction of a benzyl substituent at the nitrogen improves the affinity for MAO A but not for MAO B, and increases the rate of inactivation (0.016 min^{-1} for **1** to 0.104 min^{-1} for **4**) for MAO B but not for MAO A (**Table 3**).

FIGURE 3 HERE

Discussion

The inhibition of MAOs by cyclopropylamines is well established, and is exemplified by the clinical drug tranylcypromine (TCP). In TCP, the cyclopropylamine bears a *trans* relationship. The phenyl substituent is considered to facilitate ring opening of the cyclopropyl ring by stabilizing radical-type intermediates [41]. This has led to considerable interest in *trans*-substituted tranylcypromine analogues as MAO inhibitors as well as inhibitors of the recently identified epigenetic enzyme LSD1. Here, we have investigated novel cyclopropylamines with the less common *cis* relationship. Furthermore, our compounds do not contain a phenyl ring as cyclopropane substituent but instead have an intervening alkoxy group. These new cyclopropylamine derivatives were found to be inactive against LSD1 at concentrations of 25 μM. For MAO, although the initial binding is micromolar, these *cis*-cyclopropylamines inhibit MAO A and MAO B irreversibly at submicromolar levels, making them selective for MAO without an effect on LSD1. The best inhibition was observed with MAO B. Compound **4** is >20 times more effective than TCP, so this di-substituted cyclopropylamine (secondary amine) could be studied as a lead for selective inhibitors of MAO B that do not inhibit LSD1.

Both the primary (**1**, **2**) and the secondary (**3**-**7**) amines can inactivate both MAO isoenzymes, confirming that *cis*-cyclopropylamines interact with MAO to form reactive products that can form a covalent bond to the flavin. The spectrum with MAO A during inactivation and the stability of the

adduct formed during unfolding suggest that the modification by *N*-benzyl-2-methoxycyclo-propylamine **4** may be at the N5 of the flavin. Although the crystal structure of MAO B after TCP inactivation shows C4a modification, the structure of LSD1 shows that TCP modifies the N5 of the flavin [5]. Recent crystal structures have revealed that some 1-substituted cyclopropylamines formed different adducts with LSD1 at C4a, N5, or bridging both, probably via a radical mechanism [9]. Others have also reported formation of a cyclic N5 and C4a adduct [6-8, 13, 22, 42, 43], so perhaps both are possible even if only one form crystallizes. The spectrum of the adduct is not definitively that of an N5 adduct such as formed with clorgyline or deprenyl [35, 44], so only the stability [39] favours that interpretation for this *cis*-cyclopropylamine. This work does not address the structure of the adduct nor the mechanism of adduct formation but the lack of H_2O_2 production during inactivation of MAO A means that a radical mechanism proposed by others must be considered [9, 45].

Conclusion

cis-*N*-Benzyl-2-methoxycyclopropylamine **(4)** is a new irreversible MAOI with IC_{50} 5 nM for MAO B, 170 nM for MAO A, and no activity on LSD1.

Experimental procedures

Compounds

The *cis*-isomers of primary and secondary cyclopropylamines with an alkoxy group at the 2-position of the cyclopropyl ring replacing the more common phenyl substitution were synthesized as previously described [23].

Enzyme activity

Initial activity for membrane-bound MAO (Sigma-Aldrich, UK) was determined from the production of hydrogen peroxide, coupled to a dye *via* horseradish peroxidase producing the fluorescent resorufin [46-48]. For the reversible inhibition, IC_{50} values were determined from the rates with varied inhibitor concentrations in the presence of 2.5 x K_M substrate concentration with the enzyme added last. Under the conditions used, the K_M for tyramine with MAO A was 0.4 mM and for MAO B was 0.16 mM. The rates were analysed in Graphpad PRISM v4.

The IC_{50} values for the irreversible inactivation of MAO A and MAO B were determined from the activity (assayed as above) remaining after 30 min of incubation of the enzyme and inhibitor. Inactivation parameters (K_I and k_{inact}) were determined as in [33, 38]. Data are expressed as value ± standard deviation (SD) obtained by fitting the data (at least 20 points) to the appropriate three-parameter equation using GraphPad PRISM 4. At least two separate determinations were made for each value reported.

Molecular Docking

Molecular models of the *cis*-cyclopropylamine inhibitors were built and optimised using ArgusLab 4.0.1 on an Intel i7 HP Laptop, operating Windows 8 Home Premium. MAO A (PDB code: 2Z5X) and MAO B (PDB code: 2V5Z) protein structures were minimised using Accelrys 6.0 adopting a CHARMM force field and simulated annealing. All .pdbqt, .gpf ,and .dpf files where created using AutoDock tools software, adopting a Lamarckian genetic algorithm and converted to .glg and .dlg files using the AutoGrid4 and AutoDock4 coding sequences, respectively. Docking was achieved using AutoDock4 and Vina coding scripts. All comparisons were carried out using PyMOL.

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Author Contributions

RRR, AG, SM, and TM planned the experiments; TM, KY, MTB, and RRR performed the experiments; TM, RRR, KY, SM and AG analyzed the data; ES, NDK, and SM contributed essential reagents; RRR wrote the paper with the assistance of all authors.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. Binding energy and predicted K_i values for both enantiomers of the *cis*-cyclopropylamines with MAO A and MAO B

Table 1. Experimental IC_{50} values and predicted K_i values for reversible inhibition of MAO by *cis*-cyclopropylamines

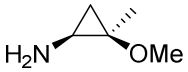
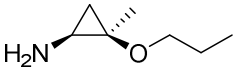
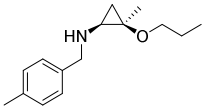
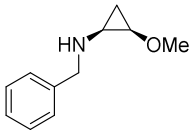
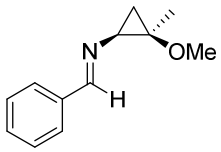
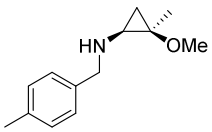
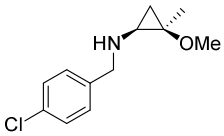
Compound		Experimental (racemic) IC_{50} (μM)		Selectivity $\frac{IC_{50}\ MAOA}{IC_{50}MAOB}$	Autodock (1*S*,2*R*) K_i (μM)	
		MAO A	MAO B		MAO A	MAO B
1		>300	3.70	>81	2010	674
2		>300	0.78	>385	691	445
3		52.4	24.5	2.1	4.65	2.88
4		21.1	0.17	124	89.0	48.8
5		>400	4.61	>87	61.7	14.4
6		115	64.0	1.8	17.4	7.81
7		71.3	33.4	2.1	16.0	6.37
Tranylcypromine		23.6	4.02	5.9	91.0	105

Table 2. Irreversible inhibition of MAO after 30 min.

Compound (racemic)	**IC_{50} (μM)***		**$\frac{IC_{50}\ MAOA}{IC_{50}MAOB}$**
	MAO A	**MAO B**	**Selectivity**
1	6.12 ±0.03	0.084 ±0.05	73
2	21.6 ± 0.5	0.029 ±0.002	745
3	10.8 ±5.0	0.104 ±0.017	104
4	0.175 ±0.068	0.00470 ± 0.00005	37
5	3.00 ±0.30	0.120 ± 0.004	25
6	2.55 ±0.22	3.03 ±0.20	0.8
7	1.75 ±0.20	1.49 ±0.22	1.1
Tranylcypromine	0.237 ±0.061	0.0735 ±0.0049	3.2
Clorgyline	0.00039	0.013	0.03
Deprenyl	0.635	0.00029	2190

* IC_{50} values ±sd from the three-parameter fit to at least 20 experimental values.

Table 3. Parameters for inactivation by TCP and by 2-substituted *cis*-analog

	MAO A			MAO B			Selectivity for MAO B
Compound	K_I (μM)	k_{inact} (min^{-1})	k_{inact}/K_I (min. mM^{-1})	K_I (μM)	k_{inact} (min^{-1})	k_{inact}/K_I (min. mM^{-1})	MAO B k_{inact}/K_I / MAO A k_{inact}/K_I
1	58.9 ±7.4	0.167 ±0.010	2.84	0.90 ±0.18	0.016 ±0.001	18	6.33
3	30.4 ±9.5	0.028 ±0.003	0.92	4.5 ±0.6	0.037 ±0.002	8.22	8.93
4	0.123 ±0.051	0.052 ±0.012	440	0.065 ±0.012	0.104 ±0.005	1600	3.64
6	16.6 ±3.2	0.030 ±0.003	1.81	17.5 ±5.6	0.058 ±0.007	3.31	1.83
TCP	7.7 ±1.0	0.776 ±0.034	101	3.8 ±0.6	0.263 ±0.005	69	0.68

Figure Legends

Fig. 1. MAO A inactivation by 4: spectral change during adduct formation.

The original spectra (left) and the time course (middle) show rapid reduction of MAO A (18 μM) flavin by compound **4** (20 μM). Adduct formation at 400 nm proceeds more slowly than reduction of the flavin at 456 nm as shown in the time course (middle) and the difference spectra (right, where the spectrum for MAO A alone has been subtracted from the MAO A+**4** mixture). The incubation shown resulted in about 90% inactivation; a second addition of compound **4** was required for complete inactivation.

Fig. 2. Docking poses for cis-cyclopropylamines in the active sites of MAO A and MAO B.

Left: MAO A (PDB code 2Z5X); Right: MAO B (PDB code 2V5Z). Docking simulations were carried out using AutoDock4 (carbons in green) and Vina (carbons in white); visualisation was carried out using PyMOL. Compound **1** with MAO A (top, left) was 1*R*,2*S*, whereas for all the others, the enantiomer was 1*S*,2*R*. Optimum poses were defined by the steric position necessary for interaction between the flavin N5 and the inhibitor

Fig. 3. Amino acids surrounding (1*R*,2*S*)-1 either near the flavin or in the imidazoline I_2 site of MAO B.

Docking of compound **1** (carbons in green) to MAO B (2V5Z) was carried out using AutoDock (10 runs). Various poses were found: **A -** bound near the flavin (yellow); **B -** in 2 of 10 poses, near the I_2 site within the entrance cavity. Hydrogen bonding interactions are shown as green dashes.

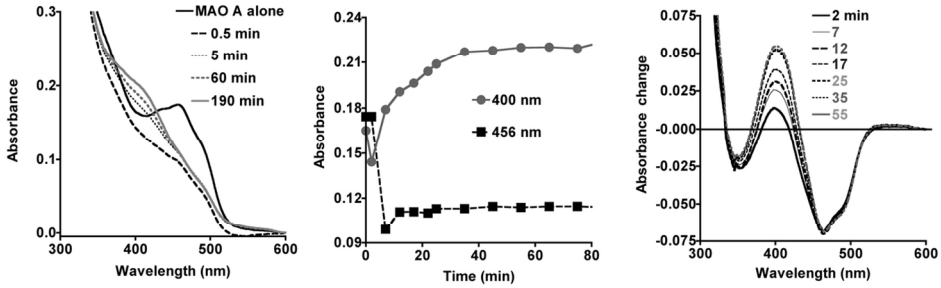


Fig. 1. MAO A inactivation by 4: spectral change during adduct formation.
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60x20mm (600 x 600 DPI)

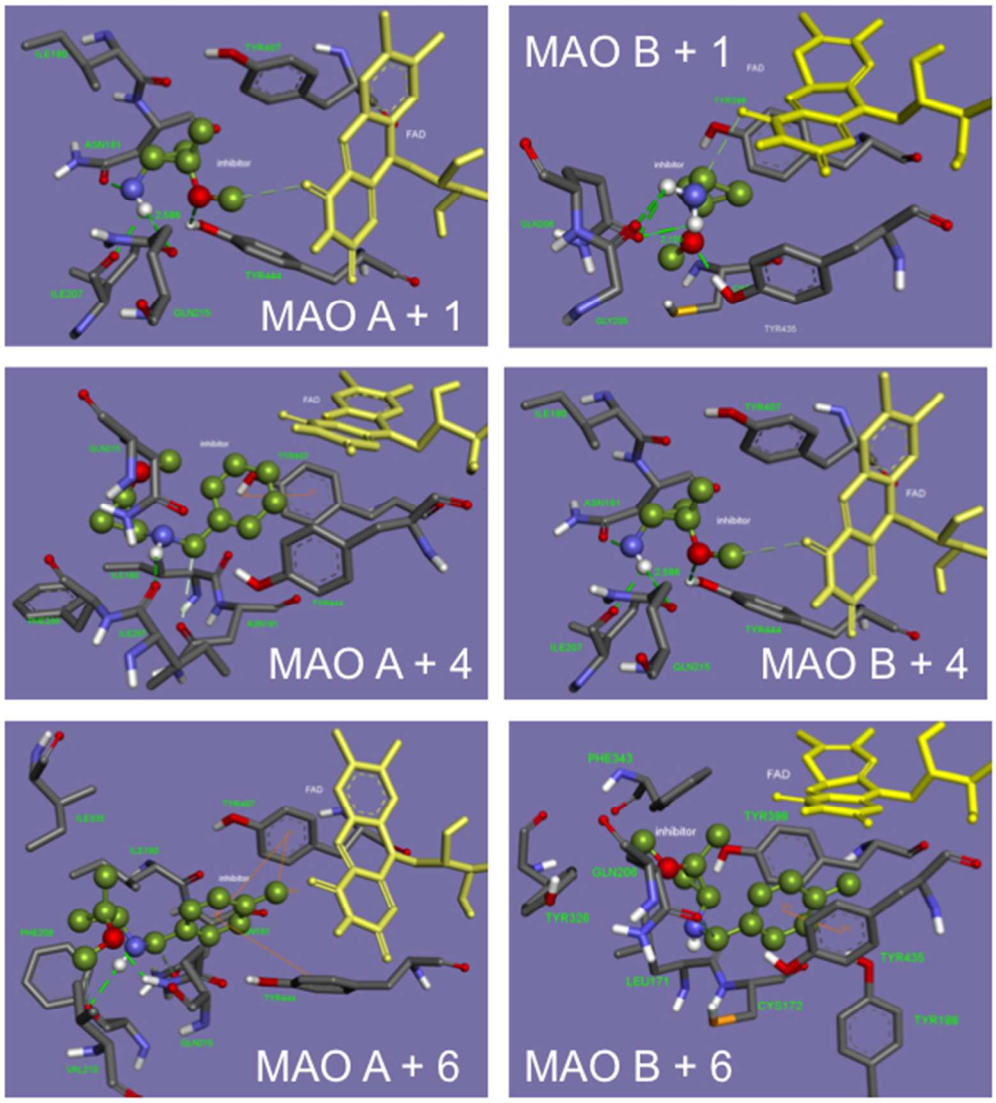

Fig. 2. Docking poses for <cis>-cyclopropylamines in the active sites of MAO A and MAO B. Left: MAO A (PDB code 2Z5X); Right: MAO B (PDB code 2V5Z). Docking simulations were carried out using AutoDock4 (carbons in green) and Vina (carbons in white); visualisation was carried out using PyMOL. Compound 1 with MAO A (top, left) was 1R,2S, whereas for all the others, the enantiomer was 1S,2R. Optimum poses were defined by the steric position necessary for interaction between the flavin N5 and the inhibitor.

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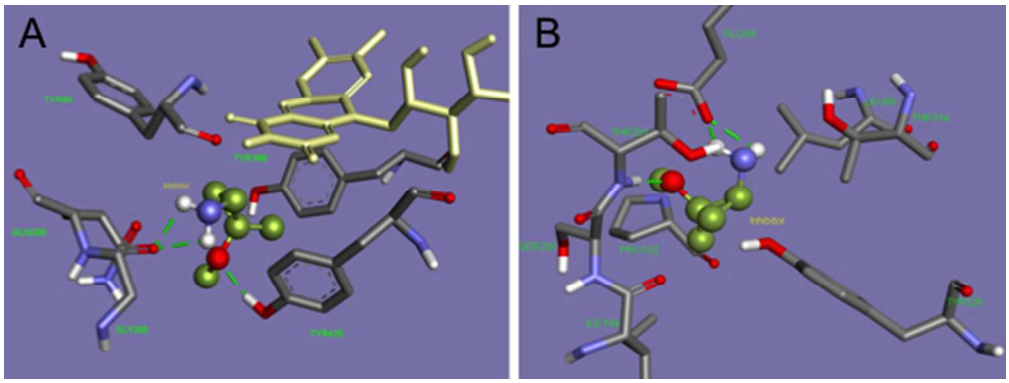

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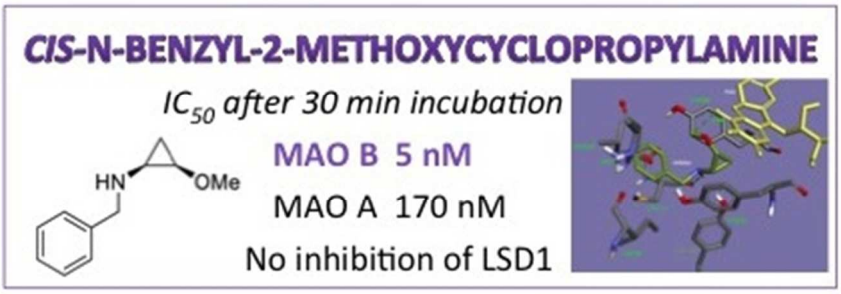

Graphical Abstract
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Supporting information

cis-Cyclopropylamines as mechanism-based inhibitors of Monoamine Oxidases.

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Supplementary Table S1 footnote

*Docking simulations (10 runs) used a 70x70x70 point grid centered on the N5 of the flavin. Final molecular conformations (poses) with the same energy were grouped into clusters. Predicted K_i values are for the highest populated cluster.

Supplementary Table S1. Binding energy and predicted K_i * (See Table 1 for structures of compounds)

			AutoDock				Vina
Enzyme	Enantiomer	Compound	Clusters	Poses in top Cluster	Affinity (kcal mol^{-1})	Predicted K_i (μM)	Affinity (kcal mol^{-1})
MAO A	(1*R*,2*S*)	**1**	2	4	-3.64	2000	-4.2
		2	4	2	-4.28	729.0	-4.8
		3	2	6	-6.24	19.61	-7.3
		4	2	6	-5.46	95.29	-6.4
		5	2	7	-5.74	58.13	-6.6
		6	2	9	-6.41	19.60	-7.3
		7	1	10	-6.61	13.28	-7.1
	(1*S*,2*R*)	**1**	2	9	-3.64	2010	-4.2
		2	3	2	-4.30	691.3	-5.0
		3	1	10	-7.18	4.65	-7.2
		4	3	1	-5.53	88.97	-6.5
		5	1	10	-5.72	61.73	-6.5
		6	3	8	-6.19	17.41	-7.3
		7	3	2	-6.47	16.02	-6.8
MAO B	(1*R*,2*S*)	**1**	2	8	-3.82	1500	-4.2
		2	5	3	-4.55	446.7	-5.5
		3	2	8	-7.32	2.79	-8.0
		4	2	9	-5.52	87.37	-6.9
		5	1	10	-6.69	12.23	-6.7
		6	4	7	-6.88	9.01	-7.5
		7	2	6	-6.73	7.79	-7.3
	(1*S*,2*R*)	**1**	2	1	-4.33	674.2	-4.4
		2	2	1	-4.57	445.3	-5.6
		3	3	6	-7.55	2.88	-7.4
		4	3	8	-5.85	48.81	-6.9
		5	1	10	-6.43	14.39	-7.1
		6	3	1	-6.97	7.81	-7.5
		7	2	7	-7.09	6.37	-7.3