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Fluorinated phenylcyclopropylamines. Part 4: Effects of aryl substituents and stereochemistry on the inhibition of monoamine oxidases by 1-aryl-2-fluoro-cyclopropylamines

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Abstract—A series of *para*-ring-substituted (*E*)- and (*Z*)-1-aryl-2-fluorocyclopropylamines were examined as inhibitors of recombinant human liver monoamine oxidase A (MAO A) and B (MAO B). Unlike the parent 1-phenylcyclopropylamine, which is a selective inhibitor of MAO B, both (*E*)- and (*Z*)-diastereomers of derivatives having fluorine at the 2-position of the cyclopropane ring were potent and selective irreversible inhibitors of MAO A. Both electron releasing groups (Me, OMe) and electron attracting groups (Cl, F) substituted in the *para*-position caused a modest increase in activity. Geminal difluoro-substitution caused a loss of potency of 100-fold compared to either (*E*)- or (*Z*)-monofluorinated analogue. Surprisingly, (1*S*,2*R*)-2-fluoro-1-phenylcyclopropylamine and the (1*R*,2*S*)-enantiomer were essential equally potent as inhibitors of MAO A and MAO B. None of the tested 1-aryl-2-fluorocyclopropylamines exhibited significant inhibition of tyramine oxidase.

1. Introduction

The enzymatic oxidation of amines to aldehydes is a critical biochemical process in all organisms, including mammals, plants, and both prokaryotic and eukaryotic microorganisms. They have been classified into two groups, copper- (EC: 1.4.3.6) and flavin- (EC: 1.4.3.4) containing amine oxidases.[1] Copper-containing amine oxidases (CAO) require copper and an organic co-factor, for example, 2,4,5-trihydroxyphenylalanine quinone, for activity and are strongly inhibited by semicarbazide.[2] The flavin-containing monoamine oxidases exist in two forms, MAO A and MAO B that are characterized by different substrate and inhibitor selectivities. MAO A and B are composed of 527 and 520 amino acids, respectively, and have a 70% amino acid identity.[3] Each isozyme has a flavin co-factor covalently linked to a cysteine residue in the active center.

Recognition of the importance of monoamine oxidases as targets for drug intervention for treatment of a variety of conditions has produced an enormous interest in development of inhibitors of these enzymes. Of particular importance in this approach is the development of potent inhibitors selective for specific classes (e.g., CAO vs MAO) and/or subclasses (e.g., MAO A vs MAO B) of amine oxidase. Examples of inhibitors investigated in this research include 1- and 2-phenylcyclopropylamines, among the most extensively studied MAO inhibitors[4] and fluorinated allylamines.[5] In the latter example, the presence of fluorine was critical to activity. In our own research in this area, we have prepared two series of fluorinated inhibitors, 1-aryl-2-fluorocyclopropylamines (**1**) and 2-aryl-2-fluorocyclopropylamines (**2**), compounds that incorporate two structural units present separately in previously synthesized active MAO inhibitors.[6] We initially examined these as inhibitors of CAO and have reported that certain of the 2-aryl-2-fluorocyclopropylamines, but not 1-phenyl-2-fluorocyclopropylamine, are potent and selective inhibitors of CAO.[6,7] Whereas the 2-aryl-2-fluorocyclopropylamines were less active as inhibitors of MAO than CAO, preliminary data revealed that

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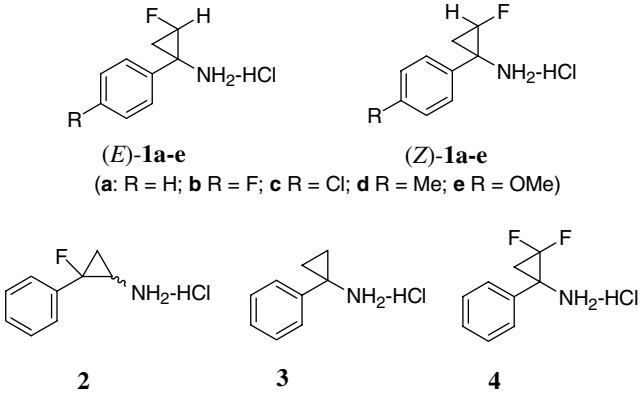
(*E*)-2-fluoro-1-phenylcyclopropylamine ((*E*)-**1a**) displayed a dramatic reversal of MAO A versus MAO B selectivity.[8] Thus, the parent 1-phenylcyclopropylamine (**3**) is selective for MAO B. In marked contrast, (*E*)-**1a** had lower activity at this isozyme, but had dramatically increased activity at MAO A. We have now extended our studies to include an examination of the diastereoselectivity, enantioselectivity and aromatic ring substituent effects on potency and selectivity of inhibition of MAO A and MAO B. In this report we describe the syntheses of (*E*)- and (*Z*)-*para*-aromatic ring-substituted 1-aryl-2-fluorocyclopropylamines ((*E*)- and (*Z*)-**1a**–**e**).

In addition, we report the preparation and purification of the individual enantiomers of (*E*)-2-fluoro-1-phenylcyclopropylamine ((1*R*,2*S*)-**1a** and (1*S*,2*R*)-**1a**) and assignment of absolute configuration by X-ray analysis. The effects of stereochemistry and ring substitution on inhibition of recombinant MAO A and MAO B were measured and these results are discussed. In addition, inhibition of tyramine oxidase by 1-aryl-2-fluoro-cyclopropylamines was investigated.



2. Results

2.1. Chemistry

(*E*)-2-Fluoro-1-phenylcyclopropylamine (**1a**) was previously prepared[6] from ethyl (*E*)-3-fluoro-2-phenylacrylate, synthesized by the procedure reported by McDonald et al.[5] A key step in the synthesis is cycloaddition of diazomethane followed by photochemical extrusion of nitrogen. The latter step occurs with a modest loss of stereo integrity to produce mainly (*E*)-2-fluorocyclopropyl ester ((*E*)-**5**) along with lesser amounts of (*Z*)-**5** (Scheme 1). The formation of both isomers allows both (*E*)- and (*Z*)-1-aryl-2-fluorocylopropylamines to be synthesized from the common starting (*E*)-2-aryl-3-fluoro esters. The mixture of diastereomeric cyclopropyl esters **5** was converted to the hydrazides **6**. Curtius rearrangement of the derived carbonyl azides **7**, as reported for the synthesis of (*E*)-**1a**,[6] gave the *t*-butylcarbamates **8** (Scheme 1). The (*E*)- and (*Z*)-carbamates were separated by chromatography and hydrolyzed to give (*E*)- and (*Z*)-**1a**–**e** as single diastereomers.

The (*E*/*Z*) configurations of cyclopropylamines ((*E*)- and (*Z*)-**1a**) were assigned by analysis of their NOESY spectra in DMSO-d_6 (Fig. 1). Thus, NOE is observed between the phenyl proton and the proton of C*H*F in the NOESY spectra of amine (*Z*)-**1a**, while no NOE is observed between phenyl proton and the proton of C*H*F in the corresponding spectra of amine (*E*)-**1a**. Subsequent X-ray analysis of one of the diastereomeric enantiopure amides confirmed its stereochemical assignment as (1*R*,2*S*)-**1a** (see below).

The synthetic route to 2,2-difluoro-1-phenylcyclopropylamine (**4**) was based on similar chemistry from ethyl 3,3-difluoro-2-phenylacrylate, prepared as reported by McDonald et al.[5]

In order to prepare the individual enantiomers of (*E*)-**1a**, the racemic compound was converted to the diastereomeric *N*-(2-fluoro-1-phenylcyclopropyl)-(2*R*)-2-hydroxy-2-phenyl-acetamides (**10a**,**b**) (Scheme 2). The diastereomers were separated chromatographically and hydrolyzed to give (1*R*,2*S*)-**1a** and (1*S*,2*R*)-**1a** as hydrochloride salts (Scheme 2). The lower R_f diastereomer **10b** was crystallized from ethyl acetate/*n*-hexane to give a crystal suitable for X-ray analysis. This was shown to be the (1*R*,2*S*)-isomer (Fig. 2).

2.2. Enzyme inhibition results

Stock solutions of the human liver mitochondrial outer membrane MAO A and B, expressed in the methylotrophic yeast *Pichia pastoris,* were used for enzyme assays. The activities of MAO A and MAO B in the

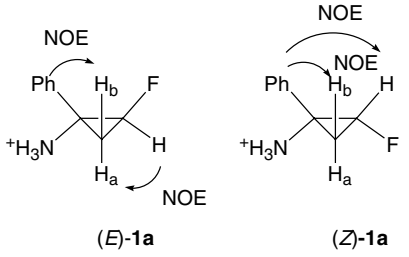


Figure 1. The NOEs observed in the NOESY spectrum of (*E*)-**1a** and (*Z*)-**1a** (DMSO-d_6, 300 MHz).

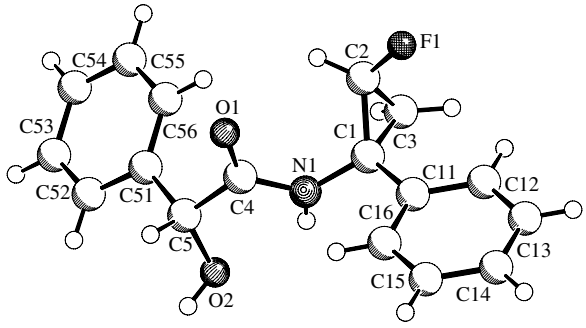
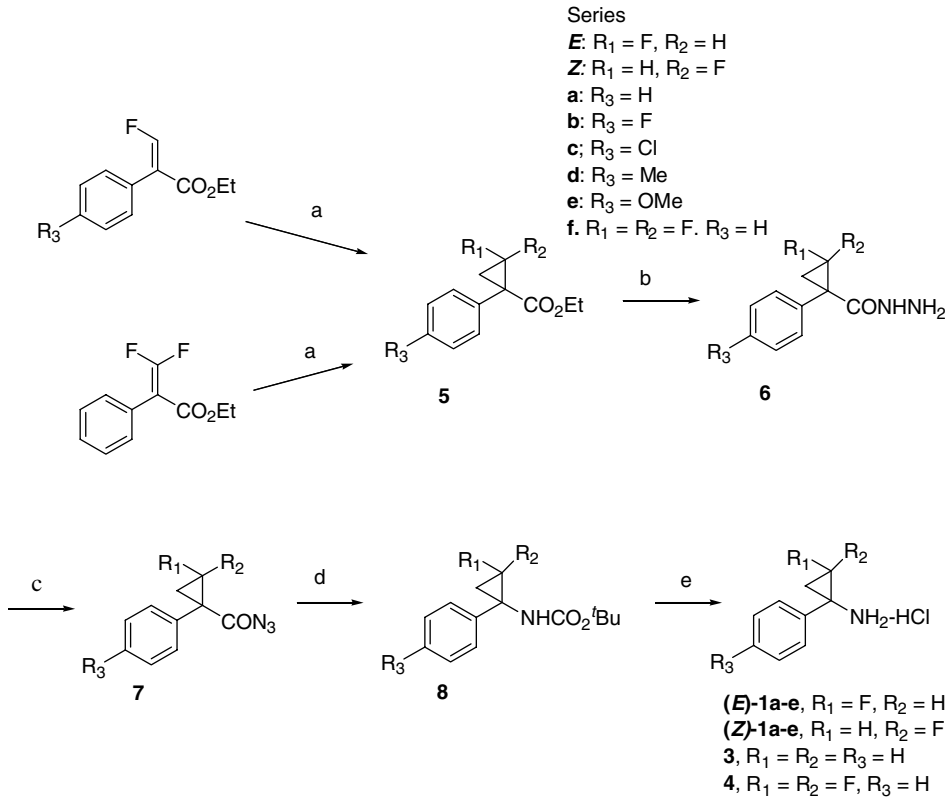


Figure 2. X-ray structure of *N*-[(1*R*,2*S*)-2-fluoro-1-phenylcyclopropyl]-(2*R*)-2-hydroxy-2-phenyl-acetamide (**10b**).



Scheme 1. Reagents and conditions: (a) (i) CH_2N_2; (ii) hν, ether; (b) hydrazine, rt; (c) HCl, $NaNO_2$, ether, rt; (d) *t*-BuOH, reflux; (e) 2 N HCl, ether.

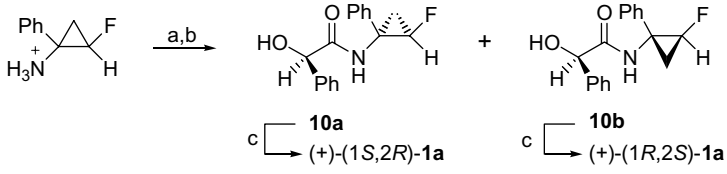
presence of inhibitors were monitored spectrometrically at 25 °C using 1 mM kynuramine hydrobromide and 1 mM benzylamine, respectively, as substrates. The inhibition assay was carried out in the presence of 6% of dimethylsulfoxide (DMSO) to improve the solubility of inhibitors used in this study. MAO A and B retained 87% and 86% of the original activities, respectively, after the addition of DMSO to the assay mixture. The relative activity was calculated based on the standard assay system containing 6% DMSO but not containing inhibitor.

2.2.1. Inhibition of MAO B. Figure 3 shows the inhibition curve of (*E*)-**1a**–**e** for MAO B. As shown in Figure 3A, an increase of the relative activity was observed at higher inhibitor concentration. For this reason, IC_{50} values could not be estimated from these data. To investigate this complication, control experiments were carried out. The absorbance increase at 250 nm was also observed in the reaction mixture when both benzylamine and MAO B were omitted. Therefore, the control data were subtracted from the data of complete system to give the curves shown in Figure 3B. The IC_{50} values were mathematically calculated by using Figure 3B data and are summarized in Table 1.

Figure 4 shows the inhibition curve of (*Z*)-isomers and difluoro-compound **4** for MAO B. In the control experiment, for (*Z*)-**1c**, (*Z*)-**1e** and the difluoro-compound **4**, no increase of absorbance at 250 nm was observed in control experiments as above. However, an increase of the absorbance was seen with (*Z*)-**1a**, (*Z*)-**1b**, and (*Z*)-**1d**, so inhibition curves were corrected by subtraction of the control data as shown in Figure 4B, and the IC_{50} values were calculated from these results.

We have no clear explanation for this increase in absorption at 250 nm in the absence of benzylamine and MAO B, a phenomenon more pronounced for the (*E*)-isomers. This may reflect relative stabilities of the (*E*)- and (*Z*)-isomers under the assay conditions.

As can be seen from the data in Table 1, all cyclopropane ring-fluorinated derivatives **1** were relatively weak inhibitors of MAO B. The (*Z*)-isomers were from 2-fold



Scheme 2. Reagents and conditions: (a) (*R*)-*O*-acetylmandelic acid, DCC, DMAP, DCM, 0 °C to rt, 74%; (b) 1% triethylamine (1.1 equiv) in methanol, rt, **10a** (38%, dr = 94:6), **10b** (36%; dr = 93:7); (c) 2 N HCl (aq), reflux, (+)-**1a** (80%), (−)-**1a** 68%.

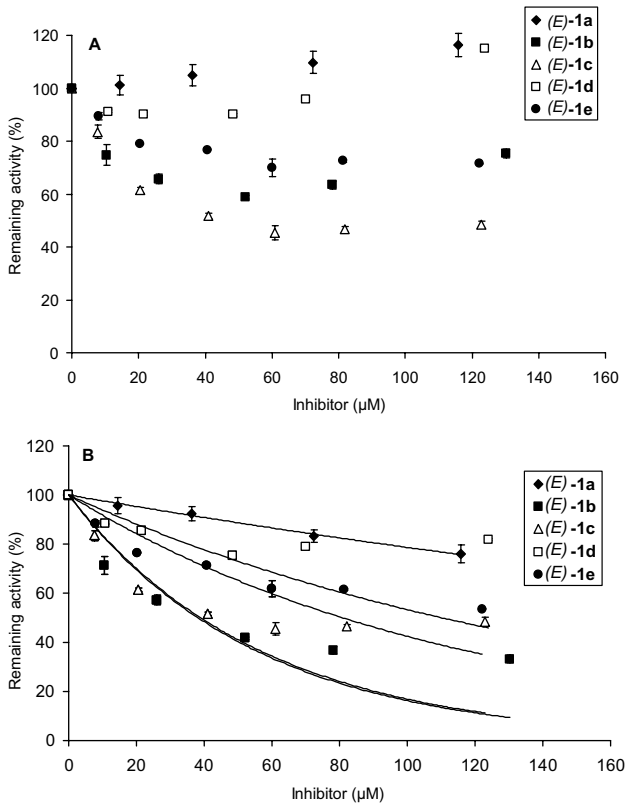


Figure 3. Inhibition curves of MAO B by *p*-aromatic substituted (*E*)-2-fluoro-1-phenylcyclopropylamines. (A) Without correction by the control data. (B) Subtracted control data from complete experiments data. Exponential fitting curves for (*E*)-**1b**,**d**,**e** were made by using the relative activity values at inhibitor concentrations below 60 μM, because good correlations were not obtained if data at higher concentrations were used. For **1c** data at inhibitor concentration below 50 μM were used, and for **1a** data obtained at all inhibitor concentrations were used for fitting. IC_{50} values were calculated by using these fitting curves (see Table 1).

((*Z*)-**1c** vs (*E*)-**1c**) to 4-fold ((*Z*)-**1a** vs (*E*)-**1a**) more potent inhibitors of MAO B than were the (*E*)-isomers. For both (*E*)- and (*Z*)-isomers, *para*-aromatic substitution increased the potency of inhibition of MAO B, and the most effective inhibitor, (*Z*)-**1b** (*para*-fluorine) had an IC_{50} of 13 μM. The difluoro analogue **4** showed no inhibition of MAO B. Under our conditions, 1-phenylcyclopropylamine **3** had an IC_{50} of 190 μM for inhibition of MAO B.[8]

2.2.2. Inhibition of MAO A. Figure 5 shows the inhibition curve of (*E*)- and (*Z*)-**1a**–**e** and **4** for MAO A. In preliminary control experiments for all compounds examined, no increase of absorbance at 316 nm in the reaction system without enzyme and substrate was observed. Therefore, the data obtained were not corrected.

All compounds were more potent inhibitors of MAO A than of MAO B. There was very little effect of relative configuration of the fluorine. The (*Z*)-diastereomers were equal or only slightly more potent than the (*E*)-diastereomers (Table 1). The *para*-methyl derivatives, (*E*)- and (*Z*)-**1d**, were the most potent inhibitors (IC_{50} = 0.2 μM). In contrast, the nonfluorinated parent 1-phenylcyclopropylamine **3** had an IC_{50} of 730 μM.[8] The difluoro analogue **4** was a much weaker inhibitor (IC_{50} = 110 μM) than the mono-fluoro compounds (Fig. 5).

2.2.3. Enantioselectivity in the inhibition of MAO A and B. To investigate the effect of absolute stereochemistry in the inhibition of MAO A and B, the two enantiomers of 2-fluoro-1-phenylcyclopropylamine ((1*R*,2*S*)-**1a** and (1*S*,2*R*)-**1a**) were examined as inhibitors. No significant enantioselectivity was observed for both isoforms of MAO (Fig. 6).

2.2.4. Inhibition of tyramine oxidase. Commercially available tyramine oxidase was used as a model for copper-containing amine oxidase in this study.[6] None of the compounds in this series was a potent inhibitor of tyramine oxidase (Fig. 7, Table 2). The (*Z*-isomers of *para*-fluoro- and *para*-methyl-substituted compounds ((*Z*)-**1b** and (*Z*)-**1d**) showed weak irreversible inhibition (IC_{50} = 110 and 220 μM, respectively). The low or absent inhibition by 1-aryl-2-fluorocyclopropylamines stands in contrast to our results with the isomeric 2-aryl-2-fluorocyclopropylamines.[6,7]

3. Discussion

Substitution of fluorine on the cyclopropyl ring of MAO B-selective 1-phenylcyclopropylamine (**3**) (IC_{50} = 190 μM) produced a potent and selective inhibitor of MAO A. Both (*E*)- and (*Z*)-**1a** were comparably potent and selective inhibitors of MAO A (IC_{50} = 1.1 and 0.9 μM, respectively) and both showed only weak inhibition of MAO B (IC_{50} = 290 and 72 μM, respectively).

1-Phenylcyclopropylamine (**3**) had an IC_{50} of 730 μM for MAO A. The presence of electron donating (Me, OMe) or electron withdrawing (Cl, F) groups substituted on the *para*-position caused a modest increase on the inhibition of MAO A. The most potent compounds, (*E*)- and (*Z*)-**1d** (*p*-Me), had IC_{50} values of 0.2 μM, about 3600 times lower than the parent 1-phenylcyclopropylamine (**3**).

The most striking feature of these results is the dramatic increase in inhibitory activity for MAO A that is caused by substitution of fluorine on the cyclopropane of 1-arylcyclopropylamines. Together with the accompanying decrease in potency as an MAO B inhibitor, this represents a very substantial reversal of MAO A versus MAO B selectivity (about 1000-fold). That this effect is independent of relative or absolute stereochemistry is noteworthy. Assuming the aryl ring and amino substituent occupy the same position when interacting with the enzyme, this suggests that the fluorine substituent is accommodated with equal facility when in either of four positions (Fig. 8). The lowered activity of the difluoro analogue **4** is difficult to reconcile with this, although p*K*a considerations may be appropriate. In this regard, there is ample evidence that the unprotonated amine is the active species, and this should favor binding of **4** at physiological pH.[3]

Table 1. IC_{50} values and inhibition type for *p*-aromatic substituted 2-fluoro-1-phenylcyclopropylamines (MAO A and B)

Compound	R[a]	Isomer type[b]	MAO A		MAO B	
			IC_{50} (μM)[e]	Inhibition type[h]	IC_{50} (μM)[e]	Inhibition type[h]
(*E*)-**1a**	H	*trans*	1.1 ± 0.1	Irreversible	290 ± 50	Irreversible
(*Z*)-**1a**	H	*cis*	0.9 ± 0.1	Irreversible	72 ± 1	Irreversible
(*E*)-**1b**	F	*trans*	1.2 ± 0.0	Irreversible	38 ± 0	Irreversible
(*Z*)-**1b**	F	*cis*	0.6 ± 0.0	Irreversible	13 ± 1	Irreversible
(*E*)-**1c**	Cl	*trans*	0.7 ± 0.1	Irreversible	39 ± 1	Irreversible
(*Z*)-**1c**	Cl	*cis*	0.5 ± 0.0	Irreversible	24 ± 1	Irreversible
(*E*)-**1d**	CH_3	*trans*	0.2 ± 0.0	Irreversible	110 ± 0[f]	Irreversible
(*Z*)-**1d**	CH_3	*cis*	0.2 ± 0.0	Irreversible	40 ± 2	Irreversible
(*E*)-**1e**	OMe	*trans*	0.7 ± 0.0	Irreversible	81 ± 5	Irreversible
(*Z*)-**1e**	OMe	*cis*	0.6 ± 0.1	Irreversible	23 ± 0	Irreversible
3[g]	—	—	730 ± 150	ND[d]	190 ± 20	Irreversible
4	—	—	110 ± 10	Irreversible	NI[c]	ND[d]

[a] *p*-Aromatic substituent.
[b] Relative configuration of fluorine and amine-containing side chain.
[c] No inhibition was observed.
[d] Could not be determined.
[e] Refer to the legend of Figures 3–5.
[f] In Figure 3B, IC_{50} values for **1d** could not be correctly estimated, because the relative activity values at high inhibitor concentrations is still high even after the data were corrected by subtraction of the control data. Therefore, the IC_{50} value for this compound was mathematically predicted from the inhibition curve fitted by the data at below 60 μM inhibitor concentrations (Fig. 3B).
[g] From Ref. 8.
[h] The term 'irreversible' was used when both time- and concentration-dependent inhibitions were observed under conditions described in Experimental.

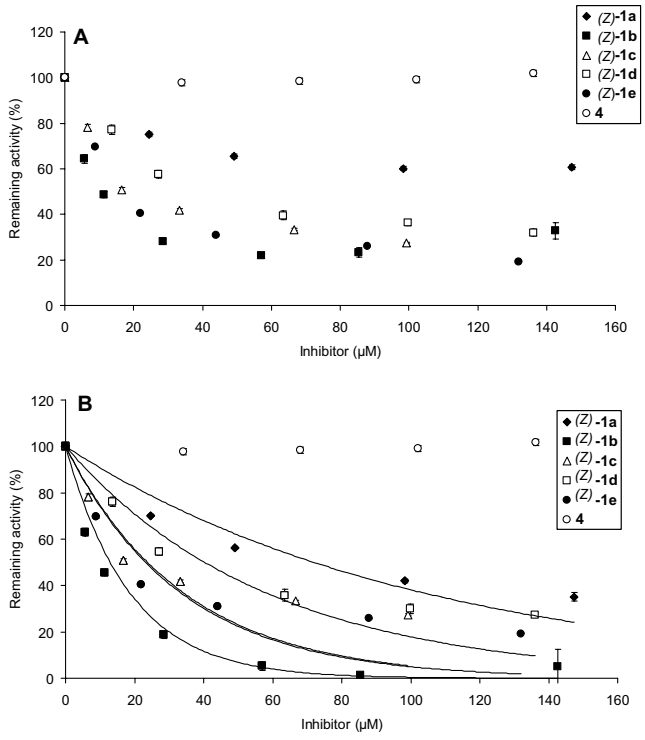


Figure 4. Inhibition curves of MAO B by *p*-aromatic substituted (*Z*)-2-fluoro-1-phenylcyclopropylamines and 2,2-difluoro-1-phenylcyclopropylamine. (A) Without correction by the control data. (B) Subtracted control data from complete experiments data. For (*Z*)-**1b**,**c**,**e** the relative activity values at inhibitor concentrations below 60 μM were used. For (*Z*)-**1a**, data at inhibitor concentrations below 100 μM and for (*Z*)-**1d**, data at concentration below 70 μM were used to obtain exponential fitting curves, because good correlations were not obtained including the data at higher concentrations. For **4**, values at all inhibitor concentrations were used for fitting. IC_{50} values were calculated by using these fitting curves (see Table 1).

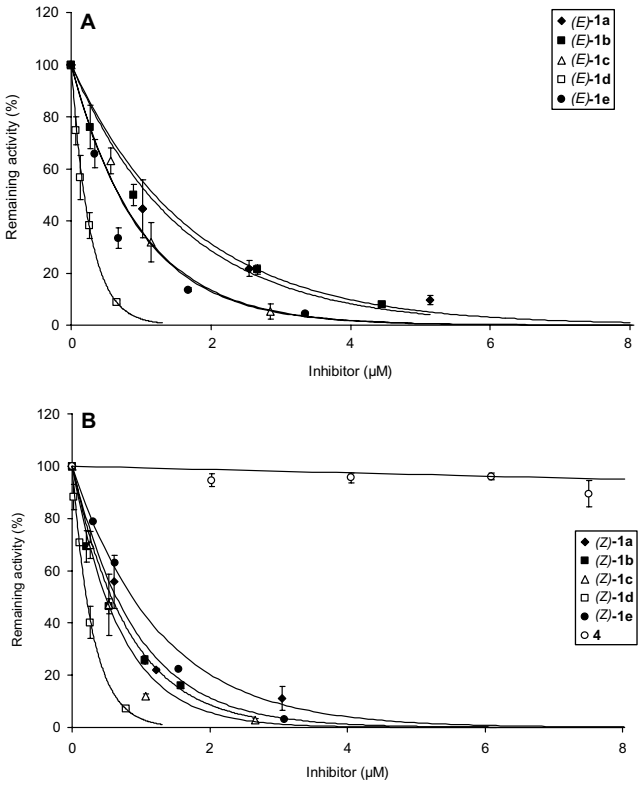


Figure 5. Inhibition curves of MAO A by *p*-aromatic substituted (*E*)- and (*Z*)-2-fluoro-1-phenylcyclopropylamines, and 2,2-difluoro-1-phenylcyclopropylamine. (A) (*E*)-**1a**–**e**. (B) (*Z*)-**1a**–**e** and difluoroanalogue **4**. For all compounds, except for (*E*)-**1a**, the relative activity values at all inhibitor concentrations were used to obtain exponential fitting curves. For (*E*)-**1a**, the values at inhibitor concentrations below 4 μM of were used for fitting, because good correlations were not obtained including the data above this concentration. IC_{50} values were calculated by using these fitting curves (see Table 1).

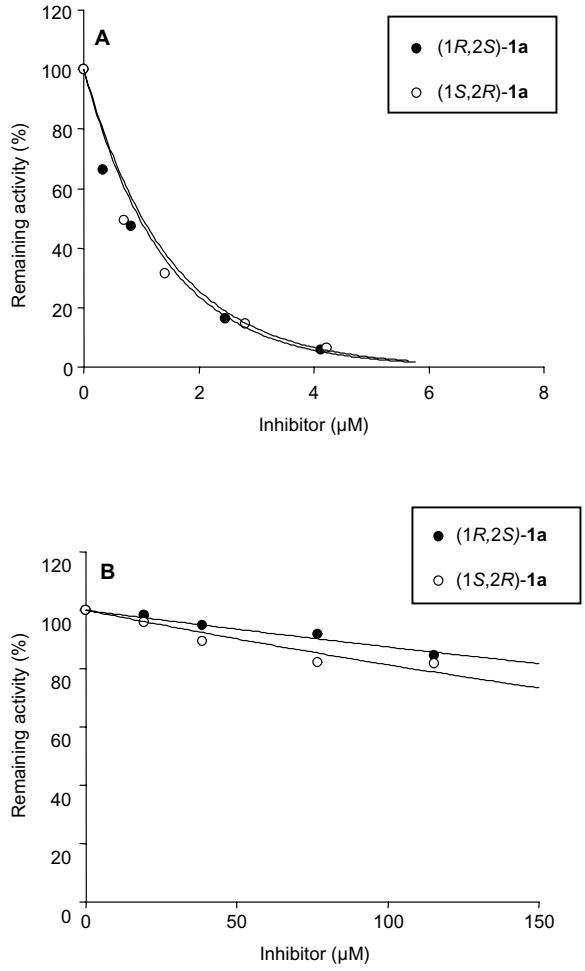


Figure 6. Effect of enantiomers of 2-fluoro-1-phenylcyclopropylamine ((1*S*,2*R*)-**1a**, (1*R*,2*S*)-**1a**) on monoamine oxidase activity (A: for MAO A; B: for MAO B).

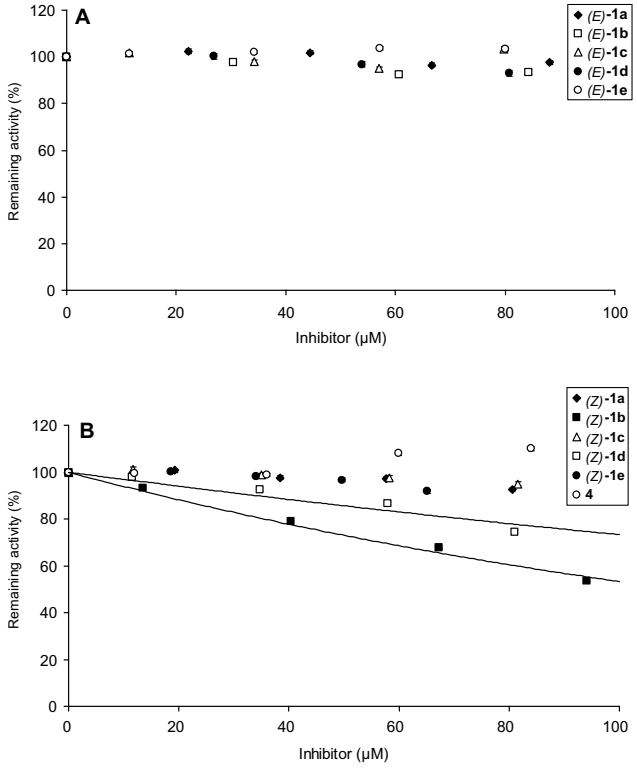


Figure 7. Effect of concentration of 2-fluoro-1-phenylcyclopropylamines on inhibition of tyramine oxidase (A: (*E*)-isomers; B: (*Z*)-isomers).

The significant loss of potency of inhibition of MAO B that results from fluorine substitution is also noteworthy. This result makes more striking the effect of fluorine substitution on MAO A versus MAO B selectivity. Because of the greater activity as an inhibitor of MAO B shown by the (*Z*)-diastereomers, this effect on selectivity is more pronounced with the (*E*)-diastereomers. There was no obvious correlation with electronic effects on the effect of *para*-substituents on activity with either enzyme. Both electron donating (Me, OMe) and electron withdrawing (Cl, F) substituents increased activity, particularly toward MAO B.

Enzyme-mediated opening of the cyclopropane ring has been implicated in the inhibition mechanism of 1- and 2-phenylcyclopropylamines. This is supported by the iso-

Table 2. IC_{50} values and inhibition type for *p*-aromatic substituted 2-fluoro-1-phenylcyclopropylamines (tyramine oxidase)

Compound	R[a]	Isomer type[b]	IC_{50} (μM)	Inhibition type[e]
(*E*)-**1a**	H	*trans*	NI[c]	ND[d]
(*Z*)-**1a**	H	*cis*	NI[c]	ND[d]
(*E*)-**1b**	F	*trans*	NI[c]	ND[d]
(*Z*)-**1b**	F	*cis*	110 ± 0	Irreversible
(*E*)-**1c**	Cl	*trans*	NI[c]	ND[d]
(*Z*)-**1c**	Cl	*cis*	NI[c]	ND[d]
(*E*)-**1d**	CH_3	*trans*	NI[c]	ND[d]
(*Z*)-**1d**	CH_3	*cis*	220 ± 10	Irreversible
(*E*)-**1e**	OMe	*trans*	NI[c]	ND[d]
(*Z*)-**1e**	OMe	*cis*	NI[c]	ND[d]
4	—	—	ND[d]	ND[d]

[a] *p*-Aromatic substituent.
[b] Relative configuration of fluorine and amine-containing side chain.
[c] No inhibition was observed.
[d] Could not be determined.
[e] The term 'irreversible' was used when both time- and concentration-dependent inhibitions were observed under conditions described in Experimental.

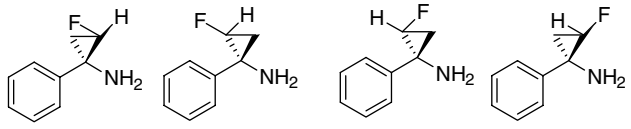


Figure 8. Position of the fluorine substituent in the four isomers of 2-fluoro-1-phenylcyclopropylamine.

lation of ring-opened products covalently attached to the enzyme.[3,4,9] A fluorine substituent should facilitate this ring opening due to the increased ring strain.[10] However, this does not explain the unusual MAO A selectivity exhibited by these compounds. In addition, the expectation that the presence of two fluorine substituents would increase activity was not realized. It is apparent that more detailed examination of the behavior of these compounds will be required to determine the mechanism of increased MAO A inhibition, and such experiments will be pursued.

4. Experimental

4.1. General

All reactions were performed under an atmosphere of N_2 in oven (90 °C) dried glassware unless otherwise stated. Anhydrous solvents were purchased from Aldrich and used as received. Chromatography was performed on ICN SiliTech 60 Å silica gel purchased from Bodman. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Varian Gemini-300 FT spectrometer. ^{19}F chemical shifts are expressed in δ ppm upfield (minus sign) from CCl_3F. Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Optical rotations were determined on a Perkin–Elmer Polarimeter 241. Chiral HPLC was performed on an HPLC system from GBC using an analytical CHIRACEL OD column.

The X-ray data set was collected with an Enraf-Nonius CAD4 diffractometer. Programs used: data collection EXPRESS (Nonius, B. V., 1994), data reduction MOLEN (Fair, K.; Enraf-Nonius B.V., 1990), structure solution SHELXS-97 (Ref. 15), structure refinement SHELXL-97 (Sheldrick, G. M. Universität Göttingen, 1997), graphics SCHAKAL (Keller, E. Universität Freiburg, 1997).

4.2. 1-Aryl-2-fluoro-1-ethoxycarbonylcyclopropane (5). Typical procedure

Our published procedure[6] with modifications was used. An ethereal solution of diazomethane, prepared in situ from diazald (17.1 g, 79.6 mmol), was added dropwise to a solution of ethyl 2-phenyl-3-fluoroacrylate (15 g, 70.4 mmol), prepared according to the literature procedure,[5] in anhydrous ether while stirring at 0 °C. After addition, the reaction mixture was allowed to warm to room temperature and was stirred overnight. The excess diazomethane was removed by treatment with $MgSO_4$. The clear solution was filtered and the solvent was removed at reduced pressure to give an oil. The oil was dissolved in acetone (150 mL) and irradiated (Rayonette apparatus) at 3500 Å for 4 days. The solvent was removed at reduced pressure and the residue was purified by chromatography on silica gel (*n*-hexane/ethyl acetate, 20:1) to give cyclopropane **5a** as a mixture of (*E*)- and (*Z*)-isomers (13.1 g, 86%, *E*:*Z* = 4:1).

4.2.1. Compound 5a (Ar = Ph) mixture of (*E*)- and (*Z*)-isomers. ^1H NMR ($CDCl_3$/TMS): 7.4–7.2 (m, 5H), 5.08 (ddd, J = 65.4, 6.3, 3.6 Hz, 0.8H), 4.86 (ddd, J = 64.2, 6.0, 3.9 Hz, 0.2H), 4.2–4.0 (m, 2H), 2.37 (ddd, J = 22.5, 6.9, 3.6 Hz, 0.2H), 1.89 (dt, J = 13.2, 6.6 Hz, 0.8H), 1.72 (ddd, J = 21.9, 6.6, 3.6 Hz, 0.8H), 1.46 (dt, J = 13.5, 6.6 Hz, 0.2H), 1.4–1.1 (m, 3H).

4.2.2. Compound 5b (Ar = *p*-FC_6H_4) mixture of (*E*)- and (*Z*)-isomers. ^1H NMR ($CDCl_3$/TMS): 7.4–7.0 (m, 4H), 5.07 (ddd, J = 65.1, 6.0, 3.3 Hz, 0.8H), 4.82 (ddd, J = 64.8, 6.3, 3.6 Hz, 0.2H), 4.4–4.0 (m, 2H), 2.37 (ddd, J = 22.5, 7.2, 3.9 Hz, 0.2H), 1.88 (dt, J = 13.5, 6.6 Hz, 0.8H), 1.68 (ddd, J = 21.9, 6.9, 3.6 Hz, 0.8H), 1.5–1.4 (m, 0.2H), 1.3–1.1 (m, 3H).

4.2.3. Compound 5c (Ar = *p*-ClC_6H_4) mixture of (*E*)- and (*Z*)-isomers. ^1H NMR ($CDCl_3$/TMS): 7.4–7.2 (m, 4H), 5.07 (ddd, J = 65.1, 6.3, 3.6 Hz, 0.8H), 4.81 (ddd, J = 64.5, 6.0, 3.6 Hz, 0.2H), 4.3–4.0 (m, 2H), 2.38 (ddd, J = 22.5, 7.2, 3.9 Hz, 0.2H), 1.89 (dt, J = 13.2, 6.3 Hz, 0.8H), 1.68 (ddd, J = 21.9, 6.9, 3.6 Hz, 0.8H), 1.5–1.4 (m, 0.2H), 1.3–1.1 (m, 3H).

4.2.4. Compound 5d (Ar = *p*-$CH_3C_6H_4$) mixture of (*E*)- and (*Z*)-isomers. ^1H NMR ($CDCl_3$/TMS): 7.3–7.0 (m, 4H), 5.06 (ddd, J = 65.4, 6.3, 3.6 Hz, 0.8H), 4.83 (ddd, J = 64.8, 6.6, 3.9 Hz, 0.2H), 4.3–4.0 (m, 2H), 2.35 (s, 0.8 × 3H), 2.33 (s, 0.2 × 3H), 2.34 (ddd, J = 22.5, 7.2, 3.6 Hz, 0.2H), 1.85 (dt, J = 13.2, 6.6 Hz, 0.8H), 1.70 (ddd, J = 21.6, 6.6, 3.3 Hz, 0.8H), 1.48–1.38 (m, 0.2H), 1.3–1.1 (m, 3H).

4.2.5. Compound 5e (Ar = *p*-$CH_3OC_6H_4$) mixture of (*E*)- and (*Z*)-isomers. ^1H NMR ($CDCl_3$/TMS): 7.27 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.06 (ddd, J = 65.4, 6.3, 3.3 Hz, 0.8H), 4.82 (ddd, J = 66.0, 6.6, 3.9 Hz, 0.2H), 4.4–4.0 (m, 2H), 3.81 (s, 0.8 × 3H), 3.80 (s, 0.2 × 3H), 2.33 (ddd, J = 23.1, 7.2, 3.9 Hz, 0.2H), 1.85 (dt, J = 13.2, 6.3 Hz, 0.8H), 1.68 (ddd, J = 21.6, 6.6, 3.6 Hz, 0.8H), 1.5–1.3 (m, 0.2H), 1.3–1.1 (m, 3H).

4.2.6. Compound 5f (R_1 = R_2 = F, R_3 = H). ^1H NMR ($CDCl_3$/TMS): 7.4–7.2 (m, 5H), 4.17 (q, J = 7.22 Hz, 2H), 2.62 (ddd, J = 12.6, 8.1, 6.0 Hz, 1H), 1.92 (ddd, J = 12.9, 7.8, 4.2 Hz, 1H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz): 167.05, 130.46, 130.43, 128.49, 128.42, 111.23 (t, $^1J_{CF}$ = 289.1 Hz), 62.27, 39.72 (t, $^2J_{CF}$ = 10.9 Hz), 21.93 (t, $^1J_{CF}$ = 10.0 Hz), 14.01.

4.3. 2-Fluoro-1-phenylcyclopropane carboxyhydrazide (6a). Typical procedure

Hydrazine monohydrate (30 equiv, 54 mL) was added to a solution of an (*E*/*Z*)-mixture of ethyl 2-fluoro-1-phenylcyclopropanecarboxylate (**5a**) (7.7 g, 37 mmol) in EtOH (50 mL). After the reaction mixture was stirred overnight, the solvent was removed at reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH, 20:1) to give 6.9 g (96%, (*E*/*Z*) = 4:1) of carboxyhydrazide **6a** as a colorless oil. Small amount of pure (*E*)- and (*Z*)-isomers were obtained by careful chromatography for characterization.

4.3.1. Compound 6a (Ar = C_6H_5) mixture of (*E*)- and (*Z*)-isomers. ^{1}H NMR ($CDCl_3$/TMS): 7.5–7.3 (m, 5H), 6.68 (br, 0.2H), 6.54 (br, 0.8H), 5.13 (ddd, *J* = 65.4, 6.3, 3.6 Hz, 0.8H), 4.91 (ddd, *J* = 63.6, 6.3, 3.9 Hz, 0.2H), 3.75 (br, 2H), 2.49 (ddd, *J* = 22.8, 6.9, 3.9 Hz, 0.2H), 1.92 (dt, *J* = 13.8, 6.6 Hz, 0.8H), 1.60 (ddd, *J* = 22.2, 6.3, 3.3 Hz, 0.8H), 1.39 (dt, *J* = 13.2, 6.3 Hz, 0.2H).

4.3.2. Compound 6b (Ar = *p*-FC_6H_4) mixture of (*E*)- and (*Z*)-isomers (*E*/*Z* = 4:1). ^{1}H NMR ($CDCl_3$/TMS), 7.4–7.3 (m, 2H), 7.2–7.0 (m, 2H), 6.6 (br, 0.2H), 6.5 (br, 0.8H), 5.11 (ddd, *J* = 65.1, 6.3, 3.6 Hz, 0.8H), 4.88 (ddd, *J* = 64.8, 6.6, 3.9 Hz, 0.2H), 3.78 (br, 2H), 2.45 (ddd, *J* = 22.8, 7.2, 4.2 Hz, 0.2H), 1.93 (dt, *J* = 13.8, 6.3 Hz, 0.8H), 1.56 (ddd, *J* = 22.5, 6.3, 3.3 Hz, 0.8H), 1.37 (dt, *J* = 13.2, 6.6 Hz, 0.2H).

4.3.3. Compound 6c (Ar = *p*-ClC_6H_4) (*E*)-isomer. ^{1}H NMR ($CDCl_3$/TMS): 7.41 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.51 (br, 1H), 5.12 (ddd, *J* = 65.1, 6.3, 3.3 Hz, 1H), 3.78 (br, 2H), 1.93 (dt, *J* = 13.5, 6.3 Hz, 1H), 1.57 (ddd, *J* = 22.5, 6.6, 3.6 Hz, 1H). (*Z*)-Isomer: ^{1}H NMR ($CDCl_3$/TMS): 7.4–7.2 (m, 4H), 5.23 (br, 1H), 4.88 (ddd, *J* = 64.8, 6.6, 3.9 Hz, 1H), 3. 31 (br, 2H), 2.41 (ddd, *J* = 22.8, 7.2, 3.9 Hz, 1H), 1.4–1.2 (m, 1H).

4.3.4. Compound 6d (Ar = *p*-$CH_3C_6H_4$) mixture of (*E*)- and (*Z*)- isomers (*E*/*Z* = 4:1). ^{1}H NMR ($CDCl_3$/TMS): 8.05 (br, 0.2H), 7.95 (br, 0.8H), 7.4–7.2 (m, 4H), 5.19 (ddd, *J* = 65.4, 6.0, 3.6 Hz, 0.8H), 4.92 (ddd, *J* = 64.8, 6.3, 3.9 Hz, 0.2H), 2.57 (ddd, *J* = 22.8, 6.9, 3.9 Hz, 0.2H), 2.39 (s, 0.8 × 3H), 2.36 (s, 0.2 × 3H), 2.1–1.9 (m, 0.8H), 1.60 (ddd, *J* = 22.5, 6.6, 3.6 Hz, 0.8H), 1.5–1.3 (m, 0.2H).

4.3.5. Compound 6e (Ar = *p*-$CH_3OC_6H_4$) (*E*)-isomer. ^{1}H NMR ($CDCl_3$/TMS): 7.31 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.56 (br, 1H), 5.10 (ddd, *J* = 65.4, 6.3, 3.6 Hz, 1H), 3.83 (s, 3H), 1.88 (dt, *J* = 13.5, 6.3 Hz, 1H), 1.56 (ddd, *J* = 22.2, 6.3, 3.6 Hz, 1H). (*Z*)-Isomer: ^{1}H NMR ($CDCl_3$/TMS): 7.3–7.2 (m, 2H), 7.0–6.9 (m, 2H), 6.78 (br, 1H), 4.87 (ddd, *J* = 65.1, 6.3, 3.9 Hz, 1H), 3.83 (s, 3H), 2.44 (ddd, *J* = 22.8, 6.9, 3.6 Hz, 1H), 1.35 (dt, *J* = 13.2, 6.6 Hz, 1H).

4.3.6. Compound 6f (R_1 = R_2 = F, R_3 = H). ^{1}H NMR ($CDCl_3$/TMS): 7.5–7.3 (m, 5H), 6.71 (br, 1H), 4.82 (br, 2H), 2.80 (dt, *J* = 14.4, 7.2 Hz, 1H), 1.84 (ddd, *J* = 12.6, 7.8, 4.8 Hz, 1H).

4.4. *t*-Butyl (*E*)- and (*Z*)-2-fluoro-1-arylcyclopropane carbamate (8a). Typical procedure

A suspension of carboxyhydrazide **6a** (1.53 g, 7.88 mmol) in water (30 mL) was topped with 30 mL of ether. Then 6 N HCl (19.5 mL) was added dropwise at 0 °C. After several minutes, an aqueous solution of sodium nitrite (1.0 M, 12 mL) was added dropwise. The reaction mixture was stirred for additional 40 min at 0 °C. The mixture was extracted with ether, washed with brine, dried over $MgSO_4$, and evaporated at reduced pressure. The residue was dissolved in anhydrous *tert*-butanol, and the solution was refluxed overnight. The solvent was evaporated, and the residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 9:1) to give (*Z*)-**8a** (173 mg, 9%, white solid) and (*E*)-**8a** (360 mg, 18%, white solid).

4.4.1. Compound (*E*)-8a (Ar = Ph). ^{1}H NMR ($CDCl_3$/TMS): 7.5–7.2 (m, 5H), 5.1 (br, 1H), 4.87 (br d, *J* = 66.0 Hz, 1H), 1.7–1.2 (m, 2H), 1.43 (s, 9H).

4.4.2. Compound (*Z*)-8a. ^{1}H NMR ($CDCl_3$/TMS): 7.4–7.2 (m, 5H), 5.37 (br, 1H), 4.67 (br d, *J* = 62.4 Hz, 1H), 1.8–1.2 (m, 2H), 1.45 (s, 9H).

4.4.3. Compound (*E*)-8b (Ar = *p*-FC_6H_4). ^{1}H NMR ($CDCl_3$/TMS): 7.6–7.4 (m, 2H), 7.1–6.9 (m, 2H), 5.03 (br, 1H), 4.85 (br d, *J* = 64.5 Hz, 1H), 1.64 (ddd, *J* = 22.5, 8.1, 3.6 Hz, 2H), 1.6–1.4 (m, 1H), 1.41 (s, 9H).

4.4.4. Compound (*Z*)-8b. ^{1}H NMR ($CDCl_3$/TMS): 7.3–7.1 (m, 2H), 7.1–6.9 (m, 2H), 5.36 (br, 1H), 4.64 (br d, *J* = 63.9 Hz, 1H), 1.8–1.2 (m, 2H).

4.4.5. Compound (*E*)-8c (Ar = *p*-ClC_6H_4). ^{1}H NMR ($CDCl_3$/TMS): 7.4–7.2 (m, 4H), 5.1 (br, 1H), 4.86 (br, d, *J* = 65.1 Hz, 1H), 1.7–1.2 (m, 2H), 1.41 (s, 9H). MS-FAB 286.2 (MH^+).

4.4.6. Compound (*Z*)-8c. ^{1}H NMR ($CDCl_3$/TMS): 7.28 (d, *J* = 7.3 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 5.38 (br, 1H), 4.63 (br d, *J* = 63.6 Hz, 1H), 1.8–1.2 (m, 2H).

4.4.7. Compound (*E*)-8d (Ar = *p*-$CH_3C_6H_4$). ^{1}H NMR ($CDCl_3$/TMS): 7.5–7.2 (m, 4H), 5.0 (br, 1H), 4.86 (br d, *J* = 65.1 Hz, 1H), 2.34 (s, 3H), 1.7–1.2 (m, 2H), 1.41 (s, 9H).

4.4.8. Compound (*Z*)-8d. ^{1}H NMR ($CDCl_3$/TMS): 7.2–7.0 (m, 4H), 5.35 (br, 1H), 4.63 (br d, *J* = 62.1 Hz, 1H), 2.31 (s, 3H), 1.8–1.2 (m, 2H), 1.44 (s, 9H).

4.4.9. Compound (*E*)-8e (Ar = *p*-$CH_3OC_6H_4$). ^{1}H NMR ($CDCl_3$/TMS): 7.40 (d, *J* = 8.1 Hz 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.0 (br, 1H), 4.82 (br d, *J* = 66 Hz, 1H), 3.80 (s, 3H), 1.7–1.2 (m, 2H), 1.41 (s, 9H).

4.4.10. Compound (*Z*)-8e. ^{1}H NMR ($CDCl_3$/TMS): 7.17 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 9.6 Hz, 2H), 5.35 (br,

1H), 4.63 (br d, J = 64.2 Hz, 1H), 3.79 (s, 3H), 1.7–1.2 (m, 2H), 1.43 (s, 9H).

4.4.11. Compound 8f ($R_1 = R_2 = F$, $R_3 = H$). ^{1}H NMR ($CDCl_3$/TMS): 7.5–7.2 (m, 5H), 5.46 (br, 1H), 2.17 (br, 1H), 1.94 (br, 1H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz): 154.81, 135.17, 128.61, 128.19, 128.14, 112.42 (t, $^1J_{CF}$ = 289.2 Hz), 80.70, 42.48, 28.41, 24.36; ^{19}F NMR ($CDCl_3$/TMS, 282 MHz): −137.7 (d, J = 152.4 Hz), −140.1 (d, J = 155.8 Hz).

4.5. (*E*)-2-Fluoro-1-phenylcyclopropylamine hydrochloride (1a). Typical procedure

Using a procedure modified from our previous report,[6] the carbamate (*E*)-**8a** (1.43 mmol, 360 mg) was dissolved in 7.2 mL of 2 N HCl in ether. The reaction mixture was stirred overnight at room temperature. The mixture was centrifuged and the precipitate was collected and washed with ether to give a white solid (178 mg, 66%).

4.5.1. Compound (*E*)-1a (Ar = Ph). Mp 159 °C (decomp.). ^{1}H NMR (D_2O): 7.5–7.2 (m, 5H), 5.26 (ddd, J = 62.1, 7.5, 3.6 Hz, 1H), 1.97 (ddd, J = 23.4, 9.6, 3.6 Hz, 1H), 1.83–1.75 (m, 1H). ^{19}F NMR (D_2O, 282 MHz): −214.6 (ddd, J = 62.6, 24.7, 13.7 Hz).

4.5.2. Compound (*Z*)-1a. Mp 154 °C (decomp.). ^{1}H NMR (D_2O): 7.51 (br, 4H), 5.12 (ddd, J = 63.0, 6.6, 3.6 Hz, 1H), 2.0–1.7 (m, 2H).

4.5.3. Compound (*E*)-1b (Ar = *p*-FC_6H_4). ^{1}H NMR (D_2O): 7.7–7.5 (m, 2H), 7.4–7.2 (m, 2H), 5.26 (ddd, J = 62.7, 7.5, 3.9 Hz, 1H), 1.94 (ddd, J = 21.9, 9.3, 2.4 Hz, 1H), 1.86–1.76 (m, 1H).

4.5.4. Compound (*Z*)-1b. ^{1}H NMR (D_2O): 7.6–7.5 (m, 2H), 7.3–7.1 (m, 2H), 5.13 (ddd, J = 63.0, 6.6, 3.3 Hz, 1H), 2.0–1.6 (m, 2H).

4.5.5. Compound (*E*)-1c (Ar = *p*-ClC_6H_4). Mp 164 °C (decomp.). ^{1}H NMR (D_2O): 7.62 (d, J = 8.7 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 5.33 (ddd, J = 61.8, 7.5, 3.9 Hz, 1H), 1.7–1.2 (m, 2H). FAB-MS 186.0 (M^+). HRMS (FAB): calcd for (M^+, $C_9H_{10}ClFN$) 186.0486. Found: 186.0484.

4.5.6. Compound (*Z*)-1c. Mp 146 °C (decomp.). ^{1}H NMR (D_2O): 7.6–7.4 (m, 4H), 5.11 (ddd, J = 63.0, 6.6, 3.6 Hz, 1H), 2.0–1.7 (m, 2H). HRMS (FAB): calcd for (M^+, $C_9H_{10}ClFN$) 186.0486. Found: 186.0486.

4.5.7. Compound (*E*)-1d (Ar = *p*-$CH_3C_6H_4$). ^{1}H NMR (D_2O): 7.56 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 5.26 (ddd, J = 62.1, 7.2, 3.6 Hz, 1H), 2.41 (s, 3H), 1.95 (ddd, J = 23.1, 9.6, 3.3 Hz, 1H), 1.86–1.75 (m, 1H).

4.5.8. Compound (*Z*)-1d. ^{1}H NMR (D_2O): 7.43 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 7.8 Hz, 2H), 5.1 (br d, J = 63 Hz, 1H), 2.38 (s, 3H), 2.0–1.7 (m, 2H).

4.5.9. Compound (*E*)-1e (Ar = *p*-$CH_3OC_6H_4$). ^{1}H NMR (D_2O): 7.59 (d, J = 9.0 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 5.21 (ddd, J = 61.8, 7.2, 3.6 Hz, 1H), 3.87 (s, 3H), 2.0–1.7 (m, 2H).

4.5.10. Compound (*Z*)-1e. ^{1}H NMR (D_2O): 7.49 (d, J = 15.3 Hz, 2H), 7.07 (d, J = 15.3 Hz, 2H), 5.08 (ddd, J = 63.0, 6.6, 3.3 Hz, 1H), 3.86 (s, 3H), 1.9–1.7 (m, 2H).

4.5.11. Compound 4 ($R_1 = R_2 = F$, $R_3 = H$). ^{1}H NMR (D_2O): 7.4–7.2 (m, 5H), 5.42 (br), 2.17 (br, 1H), 1.93 (br, 1H).

4.6. The resolution of (*E*)-2-fluoro-1-phenylcyclopropylamine ((*E*)-1a)

(*E*)-2-Fluoro-1-phenylcyclopropylamine hydrochloride ((*E*)-**1a**) (439 mg, 2.34 mmol), (*R*)-*O*-acetylmandelic acid (908 mg, 4.68 mmol) and DMAP (144 mg, 0.94 mmol) were dissolved in anhydrous dichloromethane (40 mL) and cooled to 0 °C in an ice bath. A solution of dicyclohexylcarbodiimide (1.93 g, 9.36 mmol) in dichloromethane (15 mL) was added dropwise. The reaction mixture was gradually warmed to rt and stirred for 24 h. The white precipitate that formed was removed by filtration and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 4:1) to give 568 mg (74%, dr = 1:1, determined by ^{1}H NMR) of (*R*)-*O*-acetylmandelic cyclopropylamides (**9a**,**b**) as a white solid.

To a solution of *O*-acetylmandelic amides **9a**,**b** (470 mg, 1.44 mmol) in methanol (22 mL) was added triethylamine (220 μL, 1.58 mmol). The resulting mixture was stirred at rt for 3 d. The solvent was removed under reduced pressure and the residue was carefully purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 4:1 then 7:3) to give 155 mg (38%) mandelic amide **10a** (R_f = 5.0 (*n*-hexane/ethyl acetate, 1:1), dr (**10a**/**10b**) = 94:6 (HPLC: Chiralcel OD, *n*-hexane/2-propanol = 80/20, 0.6 mL/min; t_R = 16.56 min (minor), 26.12 min (major)) followed by 231 mg mandelic amide **10b**, dr (**10b**/**10a**) = 5:1 (^{1}H NMR)), which was further recrystallized to give amide **10b** (148 mg, 36%, dr (**10b**/**10a**) = 93:7 (HPLC: Chiralcel OD, *n*-hexane/2-propanol = 80/20, 0.6 mL/min; t_R = 16.76 min (major), 27.02 min (minor)) as colorless crystals.

4.6.1. Amide 10a. White solid, mp 121–123 °C, $[\alpha]_D^{20}$ −57.6 (*c* 0.217, CH_2Cl_2). ^{1}H NMR ($CDCl_3$/TMS): 7.4–7.2 (m, 9H), 6.59 (s, 1H), 4.97 (d, J = 3.3 Hz, 1H), 4.86 (dd, J = 63.3, 6.9, 3.3 Hz, 1H), 3.36 (d, J = 3.6 Hz, 1H), 1.80 (ddd, J = 22.8, 8.4, 3.6 Hz, 1H), 1.41 (ddd, J = 13.2, 8.4, 6.9 Hz, 1H). ^{13}C NMR (CD_3OD): 175.79, 141.57, 138.08, 129.52, 129.25, 129.12, 128.35, 127.96, 77.43 (d, J = 226.5 Hz), 75.66, 39.25 (d, J = 12.5 Hz), 21.13 (d, J = 10.3 Hz).

4.6.2. Amide 10b. Colorless crystals, mp 121–123 °C, $[\alpha]_D^{20}$ −35.7 (*c* 0.213, CH_2Cl_2). ^{1}H NMR ($CDCl_3$/TMS): 7.4–7.2 (m, 9H), 6.67 (s, 1H), 4.94 (d, J = 3.6 Hz, 1H), 4.94 (dd, J = 63.0, 6.6, 3.3 Hz, 1H), 3.40 (d, J = 3.3 Hz, 1H), 1.74 (ddd, J = 22.5, 8.4, 3.6 Hz, 1H), 1.44 (ddd, J = 12.9, 8.1, 6.6 Hz, 1H). ^{13}C NMR

(CD_3OD): 175.76, 141.55, 138.10, 129.57, 129.50, 129.23, 129.12, 128.35, 127.93, 77.50 (d, J = 227.0 Hz), 75.68, 39.22 (d, J = 12.5 Hz), 21.22 (d, J = 10.2 Hz).

4.6.3. (+)-(1*S*,2*R*)-2-Fluoro-1-phenylcyclopropylamine hydrochloride ((+)-(1*S*,2*R*)-1a). A suspension of amide **10a** (66 mg, 0.23 mmol) in 2.3 mL 2 N HCl (aq) was heated to reflux until it becomes a clear solution (about 1 day). The solvent was removed under reduced pressure and the residue was washed with ether and collected by centrifugation to give a white solid (34.7 mg, 80.4%). The ^{1}H NMR spectrum is identical to racemic (*E*)-**1a**. Mp 169 °C (decomp.), $[\alpha]_D^{20}$ +28.3 (*c* 0.13, H_2O).

4.6.4. (−)-(1*R*,2*S*)-2-Fluoro-1-phenylcyclopropylamine hydrochloride ((−)-(1*R*,2*S*)-1a). This enantiomer was prepared from amide **10b** by the same procedure as above. The ^{1}H NMR spectrum is identical to racemic **1a**. Mp 169 °C (decomp.), $[\alpha]_D^{20}$ −35.7 (*c* 0.20, H_2O).

4.7. X-ray crystallographic study

4.7.1. *N*-[(1*R*,2*S*)-2-Fluoro-1-phenylcyclopropyl]-(2*R*)-2-hydroxy-2-phenyl-acetamide (10b). Formula $C_{17}H_{16}FNO_2$, M = 285.31, colorless crystal 0.25 × 0.20 × 0.15 mm, a = 8.965(1), b = 9.835(1), c = 15.674(1) Å, V = 1382.0(2) Å^3, ρ_{calcd} = 1.371 g cm^{-3}, μ = 8.16 cm^{-1}, empirical absorption correction via ψ scan data ($0.822 \leqslant T \leqslant 0.887$), Z = 4, orthorhombic, space group $P2_12_12_1$ (No. 19), λ = 1.54178 Å, T = 223 K, $\omega/2\theta$ scans, 1630 reflections collected ($-h$, $-k$, $-l$), [$(\sin\theta)/\lambda$]=0.62 Å^{-1}, 1630 independent and 1446 observed reflections [$I \geqslant 2\sigma(I)$], 196 refined parameters, R = 0.037, wR^2 = 0.113, Flack parameter 0.2(3), max. residual electron density 0.18 (−0.19) e Å^{-3}, hydrogens calculated and refined as riding atoms.

Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-254590. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44 (1223) 336 033, e-mail: deposit@ccdc.cam.ac.uk].

4.8. Enzyme assay

4.8.1. MAO A and MAO B. Stock solutions of human liver mitochondrial outer membrane MAO A and MAO B, expressed in the methylotrophic yeast, *Pichia pastoris*, were kindly provided by Professor Dale E. Edmondson, Departments of Biochemistry and Chemistry, Emory University, Atlanta, GA, USA. Enzyme assays for MAO A and MAO B were performed by modified procedures of Li et al.[11] and Houslay and Tipton,[12] respectively, as described in our previous publication.[8] Protein concentration was determined by the method of Bradford.[13]

Prior to use, the stock solution of MAO A was passed through a gel-filtration column (PD 10 desalting column, Amersham Biosciences) pre-equilibrated with 50 mM potassium phosphate (pH 7.2) containing 0.8% octyl-glucoside. The activity of MAO A was measured spectrometrically at 25 °C by the modified method of Li et al.[11] using 0.7 mL of standard reaction mixture containing 1 mM kynuramine hydrobromide, 50 mM potassium phosphate buffer (pH 7.2), 0.5% Triton × 100 (reduced), 6% DMSO and MAO A. The reaction was monitored at 316 nm, which is the maximum absorption wavelength of 4-hydroxyquinoline. The enzyme activity was calculated by using 12,300 M^{-1} cm^{-1} as the extinction coefficient of 4-hydroxyquinoline at 316 nm. One unit of the enzyme oxidizes 1 μmol of kynuramine to 4-hydroxyquinoline per 1 min.

The activity of MAO B was measured spectrophotometrically at 25 °C by using 0.7 mL of standard reaction mixture containing 1 mM benzylamine, 0.1 M potassium phosphate buffer (pH 7.2), 6% DMSO, and MAO B. The reaction was monitored at 250 nm, which is the maximum absorption wavelength of benzaldehyde. The enzyme activity was calculated by using 13,800 M^{-1} cm^{-1} as extinction coefficient of benzaldehyde at 250 nm. One unit of the enzyme oxidizes 1 μmol of benzylamine to benzaldehyde per 1 min.

Each inhibitor was dissolved in DMSO and diluted with the same solvent to give the appropriate concentration. The solution was immediately divided into several vials and wrapped with aluminum foil. These vials were stocked in an ice bath until used for inhibition experiments. Inhibition experiments were carried out as follows: varying concentrations of inhibitor were added to the reaction mixture described above (without substrate), and allowed to stand for 10 min at 10 °C. The reaction was started by the addition of substrate stock, and the time course of the absorption increase of the reaction product was monitored as described above. Control experiments were carried out by using the reaction mixture omitting both benzylamine and MAO B from the standard assay solution.

4.8.2. Tyramine oxidase. Tyramine oxidase was purchased from Sigma and dissolved in 25 mM potassium phosphate buffer (pH 7.2). The enzyme activity was measured spectrophotometrically at 30 °C as described in the MAO B assay method, using 0.7 mL of standard reaction mixture containing 0.6 mM benzylamine, 0.1 M potassium phosphate buffer (pH 7.2), 6% DMSO, and tyramine oxidase. Inhibition experiments were carried out using the same method as for MAO B after letting the mixture stand for 10 min at 25 °C without substrate. Control experiments were also carried out by using the reaction mixture omitting both benzylamine and tyramine oxidase from the standard assay solution. One unit of the enzyme oxidizes 1 μmol of benzylamine to benzaldehyde per 1 min.

4.8.3. Time- and concentration-dependent inhibition experiments. Time- and concentration-dependent inhibition experiments were carried out by the previously described method of Kitz and Wilson.[14] The incubation of MAO A with inhibitor was carried out at 4 °C in

0.1 mL of 50 mM potassium phosphate (pH 7.2) containing 0.5% of Triton X-100 (reduced), 15 μg of enzyme, 6% of DMSO and different concentration of inhibitor. The incubation of MAO B with inhibitor was carried out at 4 °C in 0.1 mL of 100 mM potassium phosphate (pH 7.2), 10 μg of enzyme, 6% of DMSO and different concentrations of inhibitor. A lower incubation temperature (4 °C) was used in this study for two reasons. First, this reduced spontaneous inactivation of the MAO during the incubation. In addition, for some compounds it was necessary to work at a lower temperature in order to reduce the rate of inactivation to a readily measurable rate. Aliquots (20 μL) were taken out periodically from the mixture, and diluted with 0.68 mL of each enzyme assay solution. The incubation of tyramine oxidase with inhibitor was carried out at 25 °C in the 0.05 mL of 100 mM potassium phosphate (pH 7.2), 12 μg of enzyme, 6% of dimethylsulfoxide and different concentrations of inhibitor. Aliquots (10 μL) were taken out periodically from the mixture, and diluted with 0.24 mL of each enzyme assay solution. The increase of absorbance at 316 nm for MAO A, and at 250 nm for MAO B and tyramine oxidase was monitored as described above.

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