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Fluorinated phenylcyclopropylamines. Part 5: Effects of electron withdrawing or donating aryl substituents on the inhibition of monoamine oxidases A and B by 2-aryl-2-fluoro-cyclopropylamines

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Abstract

A series of racemic, diastereoisomeric aryl cyclopropylamines substituted with fluorine in the 2-position and electron donating and electron withdrawing groups on the aromatic ring have been prepared. These represent analogues of the classic MAO inhibitor tranlycypromine (*trans*-2-phenylcyclopropylamine, **1**). Their activities as inhibitors of recombinant human liver monoamine oxidases A (MAO A) and B (MAO B) were determined. The *trans*-compounds were low micromolar inhibitors of both MAO A and MAO B with moderate MAO A selectivity while the less active *cis*-analogues were MAO B selective. In the *trans*-series, electron withdrawing *para*-substituents increased the potency of MAO A inhibition while electron donating groups such as methyl or methoxy had no influence on this activity. In contrast, aromatic ring substitution in the *trans*-series had essentially no effect on inhibition of MAO B. The corresponding *cis*-compounds were shown to be 10 to 100 times less active against MAO A, while *trans*- and *cis*-compounds were quite similar in terms of inhibition of MAO B. The best MAO A/MAO B selectivity (7:1) in the *trans*-series was found for *trans*-2-fluoro-2-(*para*-trifluoromethylphenyl)cyclopropylamine (**7d**), while a 1:27 selectivity was found for *cis*-2-fluoro-2-(*para*-fluorophenyl)cyclopropylamine (**10c**). These results are discussed in connection with the pK_a and $\log D$ values, the mechanism of action of tranlycypromines and the geometry of the active site of the enzymes.

Keywords

Monoamine oxidase; Tranlycypromine; Fluorinated phenylcyclopropylamine; Irreversible inhibition; Stereochemistry

[#]X-ray structure analysis.

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1. Introduction

Monoamine oxidases are present in mammals, plants and both eukaryotic and prokaryotic microorganisms. They metabolize amines of dietary origin as well as endogenous amines, including amine neurotransmitters, to form the corresponding aldehyde, hydrogen peroxide and ammonia. Monoamine oxidases are highly diverse and include the important copper-(EC 1.4.3.6) [CAO or SSAO (semicarbazide sensitive amine oxidases)] and flavin-dependent (MAO A and MAO B) (EC 1.4.3.4) enzymes.¹ Monoamine oxidase B (MAO B) shares 70% of the amino acid sequence with MAO A and, in particular, the active centers of both enzymes are very similar.²

Although different types of monoamine oxidase catalyze the same oxidative deamination process they serve different functions in the body.³ Therefore an abnormal activity of any particular enzyme can translate uniquely to a specific pathological condition. For example, depression is associated with an abnormally low level of amine neurotransmitters that can be alleviated by intervention with inhibitors of MAO A such as clorgyline and moclobemid⁴ whereas MAO B is associated with neurodegenerative disorders such as Parkinson's disease⁵ and Alzheimer's disease.⁶ Inhibitors of MAO B (e.g. L-deprenyl) show no antidepressant effect.

In general, increased MAO activity can lead to excessive formation of the toxic metabolites hydrogen peroxide and ammonia which in turn may contribute to tissue damage and neurodegeneration associated with oxidative stress. Adipocytes of diabetes patients have been shown to contain an increased level of copper containing amine oxidases (CAOs).⁷ The toxic metabolites formed may also be involved in typical damages that accompany diabetes mellitus type I and II.⁸ Hydrogen peroxide, in fact, can act as a mimic of insulin and activate the transport of glucose into adipocytes. In addition, oxidative stress induced by hydrogen peroxide may lead to damages of different tissues, capillary vessels in the eyes, kidneys, and others.

Recognition that monoamine oxidases represent promising targets for intervention in many amine oxidase-related disorders has led to enormous efforts to produce potent and selective inhibitors of these enzymes. Recently the therapeutic potential of monoamine oxidase inhibitors has been reviewed.^{9, 10} One such inhibitor, tranylcypromine (*trans*-2-phenylcyclopropyl amine, **1**) is a very potent antidepressant that has been in clinical use since the 1960s. However, side effects associated with this compound preclude its use as a first-line drug and it is prescribed in cases where other therapies do not work, e.g. for treatment of resistant depressions.¹¹

1 (*trans*-isomer)

2 (*cis*-isomer)

The strategy of our investigations¹² has been to explore development of highly active and selective inhibitors of MAO A and B as well as tyramine oxidase using tranlycypromine as a lead compound. A particular goal was to find more selective inhibitors that would have fewer side effects.

2. Results

We have previously reported the syntheses of various racemic, and enantiopure fluorinated tranlycypromine analogues and have described the results of their evaluation as inhibitors of the FAD-dependent amine oxidases, MAO A and B, and of tyramine oxidase, a copper-containing amine oxidase.^{13,14,15,16} In this previous work we discovered striking effects resulting from fluorine substitution. For example, in our assays 1-phenylcyclopropylamine (**3**) was found to be a modest inhibitor of MAO B, with no activity apparent for MAO A in the micromolar range. In contrast, *trans*-2-fluoro-1-phenyl-cyclopropyl amine (**4**) was a potent and selective inhibitor of MAO A (selectivity index [IC_{50} (MAO B)/ IC_{50} (MAO A)] of 100). Neither **3** nor **4** was an inhibitor of tyramine oxidase.^{12,13}

There have been previous investigations on the effects of monofluorination on other inhibitors of amine oxidases (Figure 1). For example, Palfreyman et al. found 3-fluoroallyl amine **5** to be a moderate, but very selective inhibitor of MAO A giving a ratio of [K_i (MAO B)/ K_i (MAO A)] = 100.¹⁷ At 20 °C **5** has a K_i = 231 μ M for MAO A, whereas the inhibition of MAO B was too low to be detected.¹⁸ On the other hand, this compound is highly active towards a CAO (IC_{50} = 0.006 μ M).¹⁹

Since the three-membered ring can be seen as a mimic of a double bond the observations reported by Palfreyman prompted us to synthesize and to test first the phenyl substituted cyclopropane analogue **6**. This compound turned out to be a weaker inhibitor than tranlycypromine (**1**). The MAO A/B selectivity was found to be approximately 1:15 (320 μ M : 24 μ M), but it showed stronger inhibition of tyramine oxidase (IC_{50} = 12 μ M).^{12,15}

A further promising class of tranlylcypromine derivatives are analogues with a fluorine substituent in the 2-position. Comparison of *trans*-2-fluoro-2-phenylcyclopropylamine (**7a**) with compounds **8** and **9** bearing a spacer between the amino group and the cyclopropane ring showed **7a** to be the best inhibitor of all three enzymes, and was more potent than **1** (Figure 2). The *cis*-isomers were also tested but showed much lower inhibition than the *trans*-compounds.^{12,13,15} We also demonstrated that only the (1*S*,2*S*)-2-fluoro-2-phenylcyclopropylamine [(1*S*,2*S*)-**7a**] enantiomer possessed inhibitory activity.¹³

In our previous work, we found that inhibitor activity and selectivity could be varied by substitution of the phenyl ring of *cis*- and *trans*-2-fluoro-2-phenylcyclopropylamines (**10** (*cis*) and **7** (*trans*), compare Scheme 1). Opposite trends were found for MAO and CAO. Thus, electron withdrawing groups such as –Cl and –F improved the efficiency of inhibition of MAO, whereas electron donating groups (–CH₃) enhanced the inhibition of tyramine oxidase.¹² Based on these results, we have explored these substituent effects more thoroughly with the goal both to find more potent inhibitors as well as to learn more about the interactions of these compounds with the various enzyme active sites. In this paper these earlier results will be brought into context with our new results on other substituted fluoro-tranlylcypromine derivatives.

2.1. Synthesis of fluorinated arylcyclopropylamines

The racemic, monofluorinated tranlylcypromine derivatives were synthesized by a six step sequence from substituted styrenes **11a–g**. Bromofluorination with NBS and a nucleophilic fluorinating agent (Et₃N·3HF or Py·9HF)²⁰ and subsequent HBr elimination from the bromofluoride **12a–g** produced α -fluorostyrene derivatives **13a–g**.²¹ Cyclopropanation of **13a–g** with ethyl diazoacetate (EDA) furnished the diastereomeric monofluorinated cyclopropanecarboxylic ethyl esters **14a–g** (*trans*) and **15a–g** (*cis*) in a ratio of 1:1.* The reaction of α -fluorostyrene (**13a**) with methyl phenyl diazo acetate lead to the formation of the methyl esters **16h** (*cis*) and **17h** (*trans*).^{*} The diastereomeric ratio in this case was *cis:trans* = 64:36.²² Saponification of the esters gave the corresponding acids **18a–h** and **19a–h** that were converted into the Boc-protected amines **20a–h** and **21a–h** by Curtius rearrangement with DPPA, *tert*-butanol and DiBoc. The last step in the sequence was deprotection with HCl to obtain the desired monofluorinated tranlylcypromine analogues as their hydrochlorides **7a–h** and **10a–h**. The relative stereochemistry within the series of compounds was proved by single crystal X-ray analysis of **18d** and **19d** (Figure 3) and several more analogs (see experimental part).

2.2. Physical-chemical properties

The pharmacokinetics of biologically active compounds can be predicted by means of physical-chemical properties. These properties include the p*K*_a value, which influences the solubility, adsorption and reactivity of a given molecule at physiological pH. Lipophilicity is also of high importance since it defines the permeability through membranes.

As expected, introduction of the highly electronegative fluorine atom into the 2-position of the cyclopropane ring decreases the p*K*_a value. Similar observations have been reported for other fluorinated amines.^{23,24} For *trans*-2-fluorotranlylcypromine (**7a**) the p*K*_a value of 7.35 is more than one pH unit lower than for its non-fluorinated parent compound **1** (*trans*). There is an even greater 1.5 pH units difference between the corresponding *cis*-isomers **2** and **10a**. While the two isomeric non-fluorinated tranlylcypromines exhibit similar acidities (ca 8.50), the fluorinated *cis*-isomer **10a** (p*K*_a = 6.98) is about 0.4 units more acidic than the fluorinated

*In compounds **14a–g** and **15a–g** (and resulting derivatives) *cis* and *trans* refers to the arrangement of the aryl ring towards the vicinal substituent, while in compounds **16h** and **17h** (and resulting derivatives) *cis* and *trans* refers to the arrangement of the phenyl groups.

trans-isomer **7a** ($pK_a = 7.35$). This difference can also be observed for the aryl-ring substituted fluorotranlycypromine analogues. The different relative arrangement of fluorine and the amino group and hence, different orbital interactions seem to be responsible for these differences. From quantum chemical calculations of the model compounds, cyclopropylamine and *cis*- and *trans*-2-fluorocyclopropylamine, it becomes obvious that there are hyperconjugative interactions between $\sigma(C-N)$ and $\sigma^*(C-F)$ in the fluorinated *trans*-isomer, which do not exist in the *cis*-isomer of these model compounds. Moreover, the gas phase proton affinity calculated for *cis*-2-fluorocyclopropylamine is about 6 kcal mol⁻¹ larger than that of the *trans*-compound and finally the p-character of the nitrogen lone-pair, which is a measure for the basicity, is larger for the *cis*-(sp^{4.34}) as compared to the *trans*-isomer (sp^{4.07}).²⁵

As anticipated, **7b–d** (*trans*) and **10b–d** (*cis*) have lower pK_a values due to their –I-effect substituents whereas +I and +M substituted **7e,f** and **7g** as well as **10e** and **10g** have a higher pK_a compared to **7a** or **10a**, respectively. A second phenyl group at the cyclopropane ring decreases the pK_a to give a value for **10h** ($pK_a = 7.20$) comparable to *para*-chloro **7b** ($pK_a = 7.19$). The latter compound has a lower lipophilicity (2.23 for **7b** versus 2.39 for **10h**). Thus, although the pK_a s are similar the lipophilicities are different and this could contribute to the different biological activities observed (see Table 3).

The lipophilicity is influenced by the pK_a since, at a given pH value, a greater portion of the more basic amine will be protonated. Moreover, the *trans*-isomers having both electronegative substituents, F and NH₂, in *cis*-orientation are expected to have a larger dipole moment. Both effects might contribute to the fact that all fluorinated *cis*-isomers have a higher log *D* than the *trans*-isomers at pH = 7.4. The log *D* values of the aryl ring-substituted analogues reflect the expected effects of the influence of the various substituents. Thus, as already known, non-polar groups improve the lipophilicity, while relatively polar groups decrease it. Fluorine is known to increase the lipophilicity of a given molecule if it is bonded to an sp²-center.^{26,27}

Table 1 shows that this is also true for the *pseudo*- π system of the cyclopropane ring. In addition, a trifluoromethyl group always increases the lipophilicity when introduced into an aromatic ring (compare both isomers **7d** and **10d**). A methyl group (+I) and two methoxy groups in *para* (–I/+M) and in *meta*-positions (–I) lead to similar pK_a values [compare **7e** (*trans*) and **7g** (*trans*)]. Since the methyl group is much less polar than the methoxy groups, **7e** exhibits a medium lipophilicity and **7g** has a low log *D* of 0.58.

2.3. Inhibition of flavin-dependent amine oxidases MAO A and B by fluorinated arylcyclopropylamines

Our new analogues in the series of 2-fluoro-2-phenylcyclopropylamines **7d** and **10d** (*para*-CF₃), **7f** and **10f** (*para*-OMe), **7g** and **10g** (*para*- and *meta*-OMe), **7h** and **10h** (1,2-diphenyl) were studied as inhibitors of MAO A and B. Table 2 and Figure 5 provide a summary of our results as well as the data obtained from the analogues we reported previously.^{12,13}

Among the *para*-substituted compounds, the *trans*-isomers (relationship of NH₂ to aryl) were better inhibitors for both MAO A and B than the *cis*-isomers. The *para*-CF₃ compound **7d** (*trans*) showed the best inhibition for MAO A, being 15 times more potent than the non-substituted **7a**. In contrast, as an inhibitor for MAO B, **7d** was essentially equipotent to **7a**. The *para*-OMe compound **7f** was a good inhibitor for both isozymes but did not exhibit the MAO A selectivity seen with the other *trans*-isomers. In that regard it may be significant that the inhibition type of **7f** for MAO A was different from that for MAO B. Whereas **7f** showed irreversible inhibition of MAO B similar to the related analogues, it was not a time- and concentration-dependent inhibitor for MAO A, but instead showed simple competitive inhibition (Figure 6A). Introduction of other *para*-substituents, such as Cl, F and CF₃ into the *trans* isomer resulted in MAO A selectivity. All *cis*-configured, 2-fluorinated analogues

showed MAO B selectivity. The precise K_i and k_{inact} values could not be obtained from the results of time- and concentration-dependent inactivation experiments. When the inhibitors were added to the reaction mixture containing MAO, time- and concentration-dependent inactivation was observed. However, the decrease of the relative activity at each concentration of inhibitor deviated somewhat from the exponential curves as observed and described in our previous report.¹³ One reason for this might be instability of these inhibitors under assay conditions.

Dimethoxy analogues (**7g** and **10g**) were weak inhibitors of both isozymes, although **7g** showed modest inhibition of MAO A. Diphenyl analogues (**7h**, **10h**) were modest inhibitors for both isozymes, but showed different kinetic behavior with the two enzymes, being competitive inhibitors of MAO B and irreversible inhibitors of MAO A (Table 2, Figure 6B). These analogues showed modest MAO A selectivity.

3. Discussion

3.1. Inhibition mechanism of MAO A and B

A brief review of current knowledge of the details of the mechanism of MAO A and MAO B will be useful in subsequent discussions of our inhibition studies. In particular, differences in the structure-activity relationships of the two isozymes will be important in the interpretation of our results.

Silverman based his explanation of the inhibition of MAO A and B by tranlylcypromine and other cyclopropylamines on a single electron transfer (SET) from the inhibitor to the active site oxidized flavin. This leads to an amine radical cation, which is followed by cyclopropyl ring opening and subsequent radical coupling of the inhibitor to the enzyme (Figure 7).^{28,29}

According to this formulation, the opening of the ring would be an important step in the actual mechanism of inhibition, which was further confirmed for several 1-henylcyclopropyl amines and *N*-benzylcyclopropylamines.^{30, 31, 32, 33, 34, 35, 36, 37, 38, 39} Moreover, the results of biotransformation of tranlylcypromine in rat liver microsomes also support such a pathway.⁴⁰ This also would be consistent with the increased activity of our fluorinated analogues of tranlylcypromine since a fluorine substituent increases the strain of a cyclopropane ring.^{41, 42,43,44} According to such a mechanism, from our inhibitors α -fluorobenzyl radicals would be formed, which in turn could recombine with the flavin radical to give covalent adducts. Fragmentation of these adducts would give back the oxidized flavin and α -fluorocinnamic aldehydes after hydrolysis.

The relative merits of the original SET mechanism and an alternative polar nucleophilic mechanism were discussed recently by Edmondson et al.² These authors favored the latter, the steps of which are shown as they illustrated using benzyl amine as the substrate (Figure 8). Nucleophilic attack of the substrate amino group at the C(4a) position of flavin **I** leads to formation of adduct **II**. This intermediate has an increased basicity of the N(5) nitrogen which then abstracts the *pro*-R proton at the C $_{\alpha}$ -atom of the amine. Extrusion of the cofactor with formation of an imine intermediate **III** and subsequent hydrolysis to benzaldehyde, ammonia and the fully reduced flavin, completes the process.

The most striking evidence against the SET mechanism is the big difference in one-electron oxidation-reduction potentials of primary or secondary amines (1.0 to 1.5 V)⁴⁵ and the covalent MAO B flavin potential of approximately 0.04 V.⁴⁶ Also theoretical calculations do support the polar nucleophilic mechanism.⁴⁷ However, there are also recent results supporting the SET mechanism.⁴⁰

Since tranlylcypromine forms a ring-opened adduct **V** with MAO B, ring opening presumably occurs after nucleophilic attack.^{2,48,49} However, it is not obvious at which step the ring opens, or to what degree increased strain would affect this process. One can imagine that nucleophilic attack of the amino group at C(4a) of flavin **I** gives an intermediate zwitter ion **IVA** having an increased electron density at nitrogen N(5). Succeeding nucleophilic attack at C(3) of the tranlylcypromine derivative and ring opening leads to the zwitterionic *N*-alkylated intermediate **IVB** which undergoes thermal carbon shift from N(5) to C(4a), analogous to the findings of Hemmerich et al. in a similar chemical transformation.⁵⁰ Final hydrolysis will give the σ -C-C-bonded product **V** (Figure 9), which (X = H) was found in the crystal structure of the tranlylcypromine-MAO B adduct.⁴⁸

Crystal structures of recombinant human liver MAO A and B obtained in the years 2002–2005 have revealed structural details of the active site that support the polar nucleophilic mechanism rather than the original SET mechanism.^{2,51, 52} For example, this mechanism is consistent with the presence of an “aromatic cage” located around the flavin cofactor in the active site of both enzymes that is formed by two tyrosine rings that are almost perpendicular to each other and to the flavin.⁵³ Polarization of the approaching amine by dipole-dipole interactions with these tyrosine residues serve to increase the nucleophilicity of the amine (see Figure 12). Moreover, the aromatic cage appears to provide a path to bring the substrate into the right position for reaction with the flavin.⁵⁴

As noted above, MAO A and B have 70 % homology in their amino acid sequences and their binding cavities are very similar.² There are, however, major differences in the structures of their entrance cavities. For MAO A this cavity has a volume of 500 Å³ and is overall shorter but wider than that of MAO B. The latter cavity has a volume of 700 Å³ and is divided into two parts. How those differences contribute to the substrate and inhibitor selectivities of each enzyme is yet to be clearly delineated. In addition to the differences in the sizes of the cavities, Ile-335 in MAO A and Tyr-326 in MAO B are suggested to play important roles in determining substrate and inhibitor specificities in human MAO A and B.⁵⁵

3.2. Biological testing of fluorotranlylcypromine derivatives on MAO A and B

As described above, fluorine-containing tranlylcypromines have a 1 to 1.5 units lower p*K*_a than their non-fluorinated parent compounds. Fluorine thus decreases the electron density of the neighboring NH₂-group and thereby lowers the nucleophilicity, a factor that would contribute to a lower rate of conversion involving a nucleophilic mechanism. In addition, the proposal has been made that the negative charge associated with the outer mitochondrial membrane facilitates the attraction of the protonated amine substrate to MAO B, and a lower p*K*_a would lower the concentration of protonated amine. However, a lower p*K*_a also leads to a higher concentration of free amine at physiological pH and this should provide a higher level of substrate available for inclusion in the aromatic cage of the active site. This would result in an accelerated conversion of a substrate and to a lower IC₅₀ value of an inhibitor. This might explain the higher activity of fluorotranlylcypromines in comparison to tranlylcypromine. The differences between the more active *trans*-compounds to the less active *cis*-isomers may be due to different interactions with the aromatic cage, possibly reflecting the lower degree of protonation of the *trans*-isomers. This might also hold for the more basic (+I substituted) amines, which though more nucleophilic, are present in lower concentration of non-protonated form.

Edmondson et al. examined a series of *para*-substituted benzylamines as substrates for human recombinant liver MAO A and B, as well as for bovine liver mitochondrial MAO B.^{53,56, 57} They showed that electron withdrawing substituents accelerate the MAO A-catalyzed oxidation with the *para*-CF₃ analogue being the best substrate.^{53,56} The MAO A binding data correlated with the van der Waals volume (*V*_w) of the substituents but not with electronic

properties (σ). In contrast, the turnover was strongly dependent on σ . In addition, the binding correlation with V_w could be improved by correction for the dissociation constants. This led to the conclusion that the deprotonated amine is the species that binds to the active site.

In contrast to the MAO A data, MAO B had a negative correlation with (V_w) of substituents and showed no dependence on σ .⁵⁷ The principal determinant of binding in this case was found to be the hydrophobicity (π) and the Taft steric constants (E_s). This difference in substrate specificities of the two isozymes was ascribed to the different shapes of the enzyme binding pockets. The broad cavity of MAO A allows the substrate to take an orientation in which the bond orbitals of the *para*-substituent, the aromatic ring and the α -carbon are coplanar.⁵⁶ Therefore an electron-withdrawing substituent can decrease the basicity of the amino group. A large substituent does not inhibit binding since the cavity is very broad and wide. In the flat geometry of the MAO B cavity the substrate's orbitals are not coplanar and this blocks electron transmission between the substituent and the amino group. Here the limiting factors are the hydrophobicity and the van der Waals volume since the substrate comes very close to the non-polar walls of the pocket. Substrates with a dipole into the same direction as the tyrosine rings lead to a decrease in conversion.

In the case of phenethylamine analogues, which have alkyl side chain and are more similar to native substrates than benzylamine, Edmondson and co-workers reported several interesting observations.⁵⁸ The binding affinity of the deprotonated amine to MAO A increases with increasing van der Waals volume of the *para*-substituent. The limiting of rate of enzyme reduction decreases with increasing van der Waals volume of the substituent in a linear manner with no observable electronic contribution, in contrast to the electronic effects observed with benzylamine reduction of MAO A. In addition, the alkyl side chain of arylalkylamine shows a strong interaction with the enzyme, and this interaction is linearly correlated with the Taft steric factor (E_s) of the side chain. These data suggested that the binding site for the aryl ring is identical for phenethylamine and benzylamine analogues and that steric interactions of the alkyl side chain with the enzyme strongly influence the binding affinities with MAO A. They also reported that the binding affinity of arylalkylamines to MAO B is less sensitive to the E_s values of the side chain, although they have not completed their analysis. The rate MAO B reduction by phenethylamine is considerably lower than that of benzylamine, which suggests some alterations in transition-state structure may occur simply by increasing the side chain by one methylene group.⁵⁹

These observations are in accordance with the results we obtained with our series of inhibitors, which showed that **7b**, **7c** and **7d** (*trans*) with Cl-, F-, and CF₃-substituents have lower IC₅₀ values compared to non-substituted 2-fluorotranlycpromine **7a** (*trans*) as inhibitors of both MAO A and B. In contrast, the IC₅₀ value for MAO A inhibition by the *trans*-configured *para*-methyl derivative (**7e**) was not different from that of **7a**. As described above, the corresponding *cis*-compounds were significantly less effective as inhibitors of MAO B, this difference in activity being even greater for MAO A (up to 100 times less active).

The following order of activity was observed for the *trans*-compounds:

MAO A: CF₃ > Cl > F > H ~ Me (IC₅₀ = 0.8 > 1.6 > 3.6 > 12 ~ 13 μ M)

MAO B: Cl > F ~ OMe ~ CF₃ > H > Me (IC₅₀ = 3.7 > 4.9 ~ 5.1 ~ 5.4 > 6.4 > 13 μ M)

This order matches the one postulated by Böhm et al. (Cl > F > H) for a non-specific increase of binding affinity in protein-ligand interactions due to higher lipophilicity of fluorinated compounds compared to the non-fluorinated parent compounds.⁶⁰

The *para*-trifluoromethyl substituted **7d** (*trans*) is the best inhibitor of MAO A found so far in this series. It is highly lipophilic (log D = 2.66) and therefore fits very well into the hydrophobic

center of the enzyme. Its low pK_a -value of 7.0 provides a high concentration of non-protonated amine at physiological pH. In spite of a similar $\log D$ -value, the inhibition by *para*-chloro **7b** is only half as strong. An explanation for that might be the slightly increased pK_a -value of 7.19, which leads to a lower concentration of free amine and thus a weaker inhibition. A fluorine substituent in the *para*-position results in pK_a and $\log D$ -values of **7c** (*trans*) which are of similar magnitude to the ones of non-substituted 2-fluorotranlylcypromine **7a** (*trans*). Although the IC_{50} -value of **7c** is twice as high as that of the *para*-chloro-substituted **7b** (*trans*) it is still three times lower than that of **7a** (*trans*), possibly due to attractive interactions of fluorine with the aromatic cage.

The above discussion is supported by structure-activity relation (SAR) analysis. The pK_a values of these compounds correlate with IC_{50} values with both MAO A and B, suggesting that basicity of the inhibitors is important for the inhibition activity against both isozymes (Figure 10). Furthermore, the IC_{50} values calculated for the level of deprotonated amine at pH 7.2 by Equation 1 showed good linear correlation with hydrophobicity “ $\log D$ ” for the inhibition of MAO A. (Table 3 and Figure 11B). Interestingly, as shown in Figure 10A, the corrected IC_{50} values still show good correlation with the electronic factor for *para*-substituents (σ_p), suggesting that electron withdrawing or donating properties are having some additional affect and are not related to the pK_a value of the amino group. Further work would be needed to explain this effect. However, one possibility might be an influence on the rate of opening of the cyclopropane ring of fluorinated phenylcyclopropylamines. Electron withdrawing groups, such as CF_3 , Cl, and F would be expected to accelerate the rate of ring opening, whereas electron donating group would decrease the rate of this reaction in the active site.

$$\text{corrected } IC_{50} = \frac{\text{observed } IC_{50}}{1 + 10^{(pK_a - pH)}} \quad \text{Equation 1}$$

Such a clear and demonstrative trend of the substituent effects could not be observed for the inhibition of MAO B. All activities were found to be in a very narrow range with IC_{50} values between 3.7 and 5.4 μM , marginally better than the IC_{50} of *trans*-**7a** (6.4 μM). Weak correlation was observed by SAR analysis in the case of MAO B (Figure 10 and Figure 11).

In contrast to MAO A, the active center of MAO B consists of two parts. From the crystallographic studies, MAO A was shown to have a single substrate cavity of $\approx 500 \text{ \AA}^3$, which combines substrate recognition and conversion. MAO B consists of two cavities which has a total size of $\approx 700 \text{ \AA}^3$ (“entrance cavity” with a volume of $290 \text{ \AA}^3$, and a larger hydrophobic substrate cavity with a volume of about $400 \text{ \AA}^3$).^{52,54} The cavity of MAO A is shorter in length and wider than the longer and narrower cavity in MAO B. An approaching substrate must pass the entrance cavity to reach the substrate binding region where it is metabolized. Presumably the transition from one cavity into another may be rate limiting rather than the attack on the flavin itself. A consequence of this may be that all molecules which enter the substrate binding cavity will react with the enzyme following the same mechanism as proposed for MAO A and that isozyme selectivity is determined by entrance cavity selectivity in MAO B. Thus the difference in shape between MAO A and B seems to be one of the reasons for substrate and inhibitor selectivity of both enzymes. Since the actual active site is the same for both enzymes all molecules that pass this “gate” between recognition and binding site in MAO B are expected to be converted by the enzyme.

The analogues having smaller substituents showed slightly higher inhibition activity for MAO B, while strong inhibition of MAO A was observed by the analogues having larger substituents (Figure 11C). The difference in cavity shape and size might explain our observations. Any effects of the cyclopropyl side chain of the fluorinated phenylcyclopropylamine analogues on binding affinity might need to be taken into account to discuss the inhibition mechanism, because binding affinity of tranlylcypromine (**1**) is reported to be better than that of benzylamine

and phenethylamine from the analysis of the steric effect of alkyl side chain of arylalkylamines on the binding affinity of MAO.⁵⁸ In addition to this steric effect, hydrophobicity is shown not to be an important factor for the inhibition of MAO B by fluorinated phenylcyclopropylamine in contrast to MAO A (Figure 11B). This is not consistent with the previous results that hydrophobicity of the benzylamine is the major factor influencing the binding affinity for MAO B.² It appears that other properties of phenylcyclopropylamines have major importance. So far QSAR only deals with the interactions of the enzymes and the specific compounds used for these studies. For compounds with different electronic structures/electron densities hydrophobicity may have an influence or not, depending on the nature of the compound. So it is quite probable that we haven't found a relation between hydrophobicity and binding affinity of our inhibitors, whereas Edmondson observed such a relation for benzylamines, which are substrates. Once more this stresses the difference between substrates and inhibitors and fits to the general idea of this paper.

The cavities in both isozymes are reported to be quite hydrophobic,⁵² and this difference in MAO A and B against hydrophobic parameter might also reflect difference of hydrophobicity of the active site cavity of MAO A and B. Hydrophobic interaction might be also important factor in addition to the basicity of fluorinated phenylcyclopropylamine.

The +I-effect of a methyl group in *para*-position on the inhibition can be discussed in a manner similar to the rationalization of the increased activities due to the presence of electron withdrawing groups. Thus, both pK_a and $\log D$ value of **7e** (*trans*) are slightly higher compared to the values of **7a** (*trans*). Because of this one would expect a lower inhibitory activity. This is observed with MAO A. However, the IC_{50} for MAO B (13 μ M), comparable to the activity of tranlycypromine (**1**), is somewhat higher than predicted by this analysis.

To study further the effects of electron donating substituents on inhibitory activity, the *para*-methoxy analogues **7f** (*trans*) and **10f** (*cis*) were synthesized and examined as inhibitors of MAO. In contrast to all other inhibitors in this series which showed irreversible behavior, **7f** (*trans*) proved to be a competitive inhibitor of MAO A, although it is an irreversible inhibitor of MAO B. Furthermore, **10f** (*cis*) does not inhibit MAO A at micromolar concentrations and is only a weak irreversible inhibitor of MAO B, comparable to tranlycypromine (**1**) itself. The IC_{50} values of **7f** (*trans*) and the *para*-methyl analogue **7e** (*trans*) do not significantly differ from each other, whereas the *para*-methoxy compound is a three times better inhibitor of MAO B than the *para*-methyl derivative. The stronger electron-donating effect of methoxy group that should lead to greater nucleophilicity and contribute to enhanced inhibitory activity apparently is counterbalanced by the higher polarity of this analogue.

A second methoxy group in the *meta*-position of the phenyl ring dramatically decreases the activity of **7g** (*trans*) and **10g** (*cis*) towards both MAO A and MAO B compared to the isomeric *para*-methoxy compounds **7f** and **10f**. The best inhibitory activity was observed for **7g** on MAO A with an IC_{50} -value of 47 μ M, which is two times higher than that of tranlycypromine (**1**). Although the pK_a value (7.40) of the dimethoxy compound **7g** is comparable to the other compounds **7** discussed above, its significantly lower lipophilicity ($\log D = 0.58$) might explain its lower activity. The introduction of two methoxy groups has a particularly detrimental influence on the inhibition of MAO B, leading to a ten times higher IC_{50} -value (230 μ M) for **7g** than was observed. A reason for that might be the dipole moment of the compound. Thus, both isomers of **7g** and **10g** are weak inhibitors, although they represent close structural analogies to the 3-fluoro-allylamine **5**.

An increased steric demand is to be expected for diphenylcyclopropylamines **7h** (*cis*) and **10h** (*trans*) (for the assignment of *cis* and *trans* see remarks at Scheme 1). The physicochemical data of **7h** (*cis*) are similar to those of the *para*-chloro derivative **7b** (*trans*) and therefore one

could expect similar IC₅₀ values, at least towards MAO A, if these parameters are the only consideration. But the IC₅₀ value of **7h** (18 μM) was found to be ten times higher compared to **7b** and similar to the value of tranlycypromine (**1**). Towards MAO B compound *trans*-**7h** (37 μM), the only competitive inhibitor, of this enzyme was comparable to **1** (19 μM) and as well as to the *para*-methoxy compound **7f** (*trans*) (5 μM). The IC₅₀ values of **10h** (*trans*) are 10 μM (MAO A) and 20 μM (MAO B) and only half as high as that of the corresponding *cis*-isomer, similar to the value of tranlycypromine (**2**) towards MAO B and *trans*-2-fluorotranlycypromine (**7a**) towards MAO A. Compounds **7h** and **10h** can also be viewed as analogues of 2-fluoro-1-phenylcyclopropylamine (**4**). However, a combination of structural features of both leads, **4** and **7a**, did not result in a better inhibition.

The relationship between structural parameters and efficiency of inhibition of MAO A and B by 1-fluoro-1-phenylcyclopropylamine analogues postulated from the present study are summarized in Figure 12. Electron-withdrawing groups on the *para*-position increase the ratio of the deprotonated form of the analogues, an effect that should facilitate entry into the “aromatic cage” of the active site. Since the active sites of both isomers are quite hydrophobic, hydrophobicity of the analogues might further promote the interaction with enzyme cavities. Cyclopropane ring opening is thought to be significant step in the inhibition by phenylcyclopropylamine analogues. The rate of ring opening might be increased by electron withdrawing groups, also increasing inhibitory activity. The correlation with van der Waals volume of the substituents is consistent with the larger binding pocket of MAO A, while steric constraint of the larger substituents adversely affects the inhibitory activity of the analogues toward MAO B.⁶¹

4. Conclusion

A series of racemic tranlycypromine (*trans*-2-phenylcyclopropylamine) analogues bearing a fluorine substituent at the cyclopropane ring and electron withdrawing or donating substituents in the *para*-position of the phenyl ring were synthesized and their activities as inhibitors of recombinant human liver MAO A and MAO B were examined. Electron withdrawing substituents such as chlorine, fluorine and the trifluoromethyl group in the *para*-position increased the potency of inhibition of MAO A up to a factor of 15 compared to the lead *trans*-2-fluoro-2-phenylcyclopropylamine (**7a**), while electron donating groups such as methyl or methoxy had no influence on this activity. In contrast, there is almost no difference in the action as inhibitors of MAO B of all substituted *trans*-compounds. The corresponding *cis*-compounds were shown to be 10 to 100 times less active as inhibitors of MAO A compared to the *trans*-isomers, while *trans*- and *cis*-compounds were quite similar in their inhibition of MAO B. The *trans*-compounds are moderate inhibitors of both MAO A and MAO B exhibiting IC₅₀ values in the low micromolar range. All *para*-substituted *trans*-compounds **7** (except the *para*-methoxy compound **7f**) are MAO A selective, while all *cis*-compounds **10** (except **10h**), though much less active, are MAO B selective. The best MAO A/MAO B selectivity (7:1) in the *trans*-series was found for *trans*-2-(*para*-trifluoromethylphenyl)cyclopropylamine (**7d**), while a 1:27 selectivity was found for *cis*-2-(*para*-fluorophenyl)cyclopropylamine (**10c**).

5. Experimental section

5.1. General Methods

NMR spectra were recorded on a Varian 600 Unity Plus (600.0 MHz for ¹H, 150.66 MHz for ¹³C and 564.3 MHz for ¹⁹F), Varian INOVA 500 (499.84 MHz for ¹H, 125.70 MHz for ¹³C and 470.28 MHz for ¹⁹F) and a Bruker ARX300 (300.13 MHz for ¹H, 75.48 MHz for ¹³C and 282.37 MHz for ¹⁹F) in CDCl₃ solution. Chemical shifts are reported in ppm relative to TMS or CFCl₃ as internal standards. The multiplicities of the ¹³C signals, other than ¹³C-¹⁹F couplings, were assigned using the DEPT procedure and are designated s (singlet),

d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of a doublet), dt (doublet of a triplet), mt (multiplett of a triplet) etc. Mass spectra (GC/MS, EI and GCToF, EI) were measured on a Waters-Micromass „GCT” instrument or „Quattro Micro GC” instrument or on a Thermo-Finnigan-MAT “MAT 8200” instrument, all operating at 70 eV by the staff of Organisch-Chemisches Institut, Universität Münster. Mass spectra and high resolution mass spectra (ESI⁺, ESI⁻ and HRMS ESI⁺, HRMS ESI⁻) were measured on a Waters-Micromass „Quattro LC-Z” instrument or a Bruker Daltonics „MicroTOF” instrument. Thin layer chromatography was performed with TLC plates 60 F₂₅₄ by Merck. Column chromatography was performed using silica gel (Merck, particle size 0.063–0.200 mm, 70–230 mesh), preparative MPLC was carried out on silica gel (Merck, particle size 0.040–0.063 mm, 230–400 mesh). Solvents and other reagents were purchased from Acros, Fluka or Sigma-Aldrich. Compounds **7a–c** and **10a–c** as well as **18–19h** were prepared as previously described^{15,16} and illustrated in Scheme 1. Compounds **7f–h** and **10f–h** were synthesized analogously.

5.2. Enzyme assay

Recombinant human mitochondrial MAO A and B, kindly provided by Professor D. E. Edmondson, Emory University, Atlanta, Georgia, USA,^{62, 63} were used for the inhibition experiments. The assays were carried out by the method previously reported.^{12,13,14} Prior to use, the enzyme stock solution was passed through a gel-filtration column (PD 10 desalting column, Amersham Biosciences) pre-equilibrated with 50 mM K phosphate (pH 7.2) containing 0.8% octyl-glucoside. The activity of MAO A was measured spectrophotometrically at 25°C by the modified method of Li et al.⁶³ using 0.7 mL of standard reaction mixture containing 1 mM kynuramine hydrobromide, 50 mM potassium phosphate buffer (pH 7.2), 0.5% Triton X100 (reduced), 6% dimethylsulfoxide 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 minute. The activity of MAO B was also measured spectrophotometrically at 25°C by the modified method of Houslay and Tipton⁶⁴ using 0.7 mL of standard reaction mixture containing 1 mM benzylamine, 0.1 M potassium phosphate buffer (pH 7.2), 6% dimethylsulfoxide 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 the extinction coefficient of benzaldehyde at 250 nm. One unit of the enzyme oxidizes 1 μmol of benzylamine to benzaldehyde per 1 minute. Protein concentration was determined by the method of Bradford⁶⁵ using bovine serum albumin as a standard. 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 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; MAO A, 4.4 μg; MAO B, 7.0 μg), and allowed to stand for 10 minutes 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.

5.3. Determination of the inhibition type

The type of inhibition was determined by examining time-and concentration-dependent inactivation⁶⁶ of MAO A and B in the presence of the inhibitor. The incubation of MAO B with an inhibitor was carried out at 4°C in the 0.1 mL of 0.1 M potassium phosphate (pH 7.2) containing 11.2 μg of enzyme, 6% of dimethylsulfoxide and different concentration of an inhibitor. Aliquots (20 μL) were taken out periodically from the mixture, and diluted with 0.68 mL of assay solution. The increase of absorbance at 250 nm was monitored as described above. Incubation of MAO A 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), 19.1 μg of enzyme, 6% of dimethylsulfoxide and different concentration of inhibitor. Aliquots (20 μL) were taken out periodically from the mixture and diluted with 0.68 mL of assay solution. The increase of absorbance at 316 nm was monitored as described above.

5.4. Bromofluorinations of substituted styrenes

5.4.1. 2-Bromo-1-fluoro-1-(4-trifluoromethylphenyl)ethane (**12d**)—4-

Trifluoromethylstyrene (**11d**) (2.16 g, 12.5 mmol) was dissolved in dry dichloromethane (30 mL) in a teflon flask under ice cooling. Pyridiniumhydrogenfluoride (Py 9HF, O_{LAH} 's reagent, 3.2 mL, 13.8 mmol, 1.1 equivalents) and subsequently *N*-bromosuccinimide (NBS, 2.46 g, 13.8 mmol, 1.1 equivalents) were added in small portions. After 30 min at 0°C the solution was allowed to warm to room temperature and stirred over night. The reaction mixture was poured into ice-water (100 mL) and neutralized with concentrated ammonia. After separation of the phases the aqueous layer was extracted with dichloromethane (3 $\times$ 70 mL). The combined organic layers were washed with 6 M hydrochloric acid and 5 % NaOH solution (each 1 $\times$ 70 mL). The phases were dried over magnesium sulfate and the solvent was removed in vacuo. After silica gel chromatography (25 $\times$ 3 cm, pentane) **12d** was obtained as a colorless liquid (Yield: 2.51 g, 74 %). ^1H NMR (CDCl_3 , 300 MHz): δ 3.59-3.72 (m, 2- CH_2Br), 5.70 (dt, 1H, $J_{\text{H,F}}$ = 46.5 Hz and 4.6 Hz, 1-CHF), 7.49 (dm, 2H, J = 7.9 Hz, 4-CH and 8-CH), 7.69 (dm, 2H, J = 7.9 Hz, 5-CH and 7-CH). ^{13}C NMR (CDCl_3 , 75 MHz): δ 33.6 (dt, J = 27.7 Hz, C-2), 91.7 (ds, J = 180.0 Hz, C-1), 123.8 (qs, J = 272.1 Hz, C-9), 125.7 (qd, J = 4.6 Hz, C-5 and C-7), 126.1 (dd, J = 7.3 Hz, C-4 and C-8), 131.4 (qs, J = 33.4 Hz, C-6), 141.0 (ds, J = 20.8 Hz, C-3). ^{19}F NMR (CDCl_3 , 282 MHz): δ -63.37 (s, 3F, 9- CF_3), -176.52 (dt, 1F, $J_{\text{F,H}}$ = 40.2 Hz, $J_{\text{F,H}}$ = 20.1 Hz, 1-CHF). MS (GC/ToF, EI) m/z 272/270 (13/15) [M^+], 250/252 (6/6), 251/253 (6/6), 191 (2), 190 (6), 178.0 (6), 177 (100), 172.0 (72), 171 (24), 153 (6), 151 (42), 145 (12), 127 (35), 122 (6), 103 (32), 102 (5), 77 (10), 75 (14), 69 (6), 63 (5), 50 (10).

5.4.2. 2-Bromo-1-fluoro-1-(4-methoxyphenyl)ethane (12f**)**—According to the general procedure²⁰ 4-methoxystyrene (**11f**) (4.37 g, 32.6 mmol) was treated with triethylamine-trishydrofluoride ($\text{Et}_3\text{N}\cdot 3\text{HF}$) and NBS to give **12f** (Yield: 6.12 g crude product). Due to its instability on silica gel **12f** was used in the next step without any purification. Crude product spectra agreed with published ones.⁶⁷

5.4.3. 2-Bromo-1-fluoro-1-(3,4-dimethoxyphenyl)ethane (12g**)**—According to the general procedure^{15,21} 3,4-dimethoxystyrene (**11g**) (3.28 g, 20 mmol) was treated with triethylamine-trishydrofluoride ($\text{Et}_3\text{N}\cdot 3\text{HF}$) and NBS. Several side products were separated partially by silica gel chromatography (15 $\times$ 3 cm, cyclohexane/ethyl acetate, 1:1) **12g** was obtained as a colorless liquid (Yield: 3.01 g, 75 % pure (GC), 43 %).

5.5. Synthesis of α -fluorostyrenes

5.5.1. 1-(1-Fluorovinyl)-4-trifluoromethylbenzene (13d**)**—According to the general procedure^{15,21} 2-bromo-1-fluoro-1-(4-trifluoromethylphenyl)ethane (**12d**) (3.42 g, 12.6 mmol) was treated with potassium *tert*-butoxide. After distillation **13d** was isolated as a colorless liquid (Yield: 1.41, 59 %). Bp. 49 °C / 9 mbar. ^1H NMR (CDCl_3 , 300 MHz): δ 4.98 (dd, 1H, J = 17.5 Hz and 3.7 Hz, H_A), 5.14 (dd, 1H, J = 48.9 Hz and 3.7 Hz, H_B), 7.58-7.70 (m, 4H, 4-CH, 5-CH, 7-CH and 8-CH). ^{13}C NMR (CDCl_3 , 75 MHz): δ 91.8 (dt, J = 22.5 Hz, C-2), 123.9 (qs, J = 272.2 Hz, C-9), 124.9 (dd, J = 6.8 Hz, C-4 and C-8), 125.5 (qd, J = 3.5 Hz, C-5 and C-7), 131.3 (qs, J = 33.0 Hz, C-6), 135.4 (ds, J = 29.2 Hz, C-3), 161.7 (ds, J = 250.3 Hz, C-1). ^{19}F NMR (CDCl_3 , 282 MHz): δ -63.42 (s, 3F, CF_3), -108.72 (dd, 1F, J = 50.8 Hz and 17.7 Hz, 1-CF). MS (GC/ToF, EI): m/z 190 (100) [M^+], 189 (3), 171 (15), 169 (15), 151 (5), 140 (15), 121 (35), 120 (4), 101 (16), 75 (4).

5.5.2. 1-(1-Fluorovinyl)-4-methoxybenzene (13f)—According to the general procedure²¹ 2-bromo-1-fluoro-1-(4-methoxyphenyl)ethane (**12f**) (crude product) was treated with potassium *tert*-butoxide (8.55 g). After distillation **13f** was isolated as a colorless liquid (yield: 1.85 g, 37% over 2 steps). Bp. 80 °C / 3mbar. The spectroscopic data agreed with published ones.⁶⁷

5.5.3. 1-(1-Fluorovinyl)-3,4-dimethoxybenzene (13g)—According to the general procedure²¹ 2-bromo-1-fluoro-1-(3,4-dimethoxyphenyl)-ethane (**12g**) (8.18 g, 75 % purity (GC), ca. 23 mmol) was treated with potassium *tert*-butoxide to give **13g** (yield: 5.29 g, 77 % purity (GC), 96 %). Due to polymerization **13g** was used in the next reaction without any purification. The spectroscopic data were taken from the crude product. ¹H NMR (CDCl₃, 300 MHz): δ 3.89 (s, 6H, 9-OCH₃ and 10-OCH₃), 4.75 (dd, 1H, *J* = 18.9 Hz and 3.6 Hz, H_A), 4.89 (dd, 1H, *J* = 49.9 Hz and 3.5 Hz, H_B), 6.75-7.16 (m, 3H, 4-CH, 7-CH and 8-CH). ¹³C NMR (CDCl₃, 75 MHz): δ 55.9 (q, C-9 and C-10), 87.8 (dd, *J* = 24.5 Hz, C-2), 107.8 (dd, *J* = 7.2 Hz, C-4), 110.9 (d, C-7), 117.7 (dd, *J* = 7.6 Hz, C-8), 124.9 (ds, *J* = 29.9 Hz, C-3), 148.8 (s, C-6), 150.1 (s, C-5), 162.8 (ds, *J* = 247.8 Hz, C-1). ¹⁹F NMR (CDCl₃, 282 MHz): δ -107.10 (dd, 1F, *J* = 50.1 Hz and 18.7 Hz, 1-CF). MS (GCToF, EI) *m/z* 183 (3), 182 (56) [M⁺], 180 (2), 168 (1), 167 (13), 162 (100), 148 (2), 147 (29), 146 (2), 139 (15), 137 (2), 121 (3), 119 (19), 109 (11), 104 (3), 101 (11), 96 (12), 91 (29), 89 (9), 88 (3), 83 (3), 77 (10), 76 (12), 75 (10), 74 (5), 65 (11), 62 (9), 51 (8), 50 (9).

5.6. Cyclopropanations

5.6.1. *cis*- and *trans*-2-Fluoro-2-(4-trifluoromethylphenyl)

cyclopropanecarboxylic acid ethylesters (14d and 15d)—According to the general procedure^{15, 68} (1-fluorovinyl)-4-trifluoromethyl benzene (**13d**) (0.5 g, 2.6 mmol) was treated with ethyl diazoacetate (1.19 mg, 1.12 mL, 11.7 mmol, 4.5 equivalents, EDA) in the presence of Cu(acac)₂ (153 mg, 0.59 mmol, 5 mol% relating to EDA), whereas EDA was added within 12 h. After silica gel column chromatography (25 × 3 cm, pentane/diethyl ether, 80:1) the isomers were separated and each isolated as a colorless oil.

Data for 14d: Yield: 296 mg (42 %): ¹H NMR (CDCl₃, 300 MHz): δ 1.30 (t, 3H, *J* = 7.1 Hz, 13-CH₃), 1.66 (ddd, 1H, *J* = 10.5 Hz and 9.5 Hz and 7.0 Hz, H_B), 2.23 (ddd, 1H, *J* = 9.3 Hz and 7.8 Hz and 3.0 Hz, H_X), 2.37 (ddd, 1H, *J* = 20.2 Hz and 7.8 Hz and 7.1 Hz, H_A), 4.24 (qm, 2H, *J* = 7.2 Hz, 12-CH₂), 7.39 (dm, 2H, *J* = 8.2 Hz, 6-CH and 10-CH), 7.64 (dm, 2H, *J* = 8.6 Hz, 7-CH and 9-CH). ¹³C NMR (CDCl₃, 75 MHz): δ 14.1 (q, C-13), 19.4 (dt, *J* = 11.7 Hz, C-3), 29.7 (dd, *J* = 11.6 Hz, C-1), 61.3 (t, C-12), 80.0 (ds, *J* = 228.9 Hz, C-2), 123.9 (qs, *J* = 273.1 Hz, C-11), 124.9 (dd, *J* = 8.5 Hz, C-6 and C-10), 125.6 (qd, *J* = 3.7 Hz, C-7 and C-9), 130.4 (qs, *J* = 32.5 Hz, C-8), 141.7 (ds, *J* = 21.8 Hz, C-5), 167.1 (ds, *J* = 2.8 Hz, C-4). ¹⁹F NMR (CDCl₃, 282 MHz): δ -63.34 (s, CF₃), -190.02 (not completely resolved ddd, *J* = 18.4 Hz and 8.9 Hz, aliphatic F). MS (GCToF, EI) *m/z* 276 (10 [M⁺], 257 (10), 248 (38), 232 (1), 228 (27), 221 (12), 212 (10), 203 (91), 193 (100), 184 (12), 183 (89), 171 (13), 173 (33), 151 (17), 135 (3), 134 (21), 133 (85), 131 (10), 115 (36), 107 (7), 101 (5), 81 (4), 75 (8), 69 (4), 57 (5), 55 (11), 44 (10). HRMS (ESI⁺) C₁₃H₁₂F₄O₂ + Na⁺: calcd. 299.0666, found 299.0655. C₁₃H₁₂F₄O₂ (276.2): calcd. C 56.53 % H 4.38 %, found C 56.99 % H 4.27 %.

Data for 15d: Yield: 326 mg (46 %): ¹H NMR (CDCl₃, 300 MHz): δ 1.03 (t, 3H, *J* = 7.2 Hz, 13-CH₃), 1.87 (ddd, 1H, *J* = 19.4 Hz and 10.5 Hz and 7.2 Hz, H_A), 2.02 (ddd, 1H, *J* = 15.1 Hz and 7.4 Hz and 7.4 Hz, H_B), 2.60 (ddd, 1H, *J* = 18.2 Hz and 10.4 Hz and 7.8 Hz, H_X), 3.94 (qm, 2H, *J* = 7.2 Hz, 12-CH₂), 7.63 (dm, 2H, *J* = 8.6 Hz, 6-CH and 10-CH), 7.58 (dm, 2H, *J* = 8.7 Hz, 7-CH and 9-CH). ¹³C NMR (CDCl₃, 75 MHz): δ 13.9 (q, C-13), 16.8 (dt, *J* = 10.2 Hz, C-3), 28.4 (dd, *J* = 18.3 Hz, C-1), 61.0 (t, C-12), 82.2 (ds, *J* = 221.6 Hz, C-2), 125.2 (qd, *J* = 3.6 Hz, C-7 and C-9), 125.9 (m, C-11), 128.4 (dd, *J* = 4.5 Hz, C-6 and C-10), 130.8 (qs,

$J = 32.6$ Hz, C-8), 137.2 (ds, $J = 19.3$ Hz, C-5), 168.4 (s, C-4). ^{19}F NMR (CDCl_3 , 282 MHz): δ -63.34 (s, 3F, CF_3), -158.32 (not completely resolved ddd, 1F, $J = 18.2$ Hz and 13.0 Hz, 2-CF). MS (GCToF, EI): m/z 276 (10 [M^+], 257 (10), 248 (38), 232 (1), 228 (27), 221 (12), 212 (10), 203 (82), 193 (100), 184 (12), 183 (89), 171 (13), 173 (33), 151 (17), 135 (3), 134 (21), 133 (85), 131 (10), 115 (36), 107 (7), 101 (5), 81 (4), 75 (8), 69 (4), 57 (5), 55 (11), 44 (10). $\text{C}_{13}\text{H}_{12}\text{F}_4\text{O}_2$ (276.2) calcd. C 56.53 % H 4.38 %, found C 56.60 % H 4.46 %.

5.6.2. *cis*- and *trans*-2-Fluoro-2-(4-methoxyphenyl)cyclopropanecarboxylic acid ethylesters (14f** and **15f**)**—According to the general procedure^{15,68} (1-fluorovinyl)-4-methoxybenzene (**13f**) (0.76 g, 5 mmol) was treated with two portions of ethyldiazoacetate (each 0.86 g, 1.12 mL, 7.5 mmol, 1.5 equivalents) in the presence of $\text{Cu}(\text{acac})_2$ (98 mg, 0.375 mmol, 5 mol% relating to one portion of EDA). After silica gel column chromatography (20 $\times$ 3 cm, pentane/diethyl ether, 10:1) a 1:1-mixture of both isomers of **14f** and **15f** was isolated as a colorless oil. Spectrometric data were taken from this mixture (yield: 1.06 g, 89 %, **14f** : **15f** = 1:1).

Data for **14f:** ^1H NMR (CDCl_3 , 300 MHz): δ 1.27-1.33 (m, 3H, 13- CH_3), 1.55 (ddd, $J = 10.3$ Hz and 9.2 Hz and 6.9 Hz, 1H, H_B), 2.12 (ddd, $J = 9.2$ Hz and 7.6 Hz and 3.2 Hz, 1H, H_X), 2.23 (ddd, $J = 19.5$ Hz and 7.6 Hz and 6.9 Hz, 1H, H_A), 3.80 (s, 3H, 11- OCH_3), 4.19-4.28 (m, 2H, 12- CH_2), 6.88-6.92 and 7.27-7.31 (two m, each 2H, 6-CH, 7-CH, 9-CH and 10-CH). ^{13}C NMR (CDCl_3 , 75 MHz): δ 14.2 (q, C-13), 18.3 (dt, $J = 12.6$ Hz, C-3), 28.3 (dd, $J = 12.2$ Hz, C-1), 55.3 (q, C-11), 61.1 (t, C-12), 81.0 (ds, $J = 229.7$ Hz, C-2), 114.0 (d, C-7 and C-9), 127.1 (dd, $J = 5.1$ Hz, C-6 and C-10), 129.4 (ds, $J = 22.9$ Hz, C-5), 159.9 (s, C-8), 168.0 (s, C-4). ^{19}F NMR (CDCl_3 , 282 MHz): δ -182.36 (m, 1F, 2-CF). MS (GCToF, EI): m/z 238 (27 [M^+], 220 (4), 218 (7), 209 (45), 193 (17), 189 (35), 183 (21), 174 (21), 165 (100), 161 (40), 155 (39), 149 (19), 145 (50), 135 (34), 133 (32), 121 (18), 115 (33), 109 (12), 103 (18), 101 (15), 96 (14), 91 (7), 83 (5), 77 (12), 63 (5), 57 (4), 51 (3). $\text{C}_{13}\text{H}_{15}\text{FO}_3$ (238.25) calcd. C 65.54 % H 6.35 %, found C 65.63 % H 6.63 %.

Data for **15f:** ^1H NMR (CDCl_3 , 300 MHz): δ 1.03 (t, $J = 7.2$ Hz, 3H, 13- CH_3), 1.76 (ddd, $J = 19.1$ Hz and 10.2 Hz and 6.9 Hz, 1H, H_A), 1.91 (ddd, $J = 12.1$ Hz and 7.5 Hz and 6.9 Hz, 1H, H_B), 2.52 (ddd, $J = 17.5$ Hz and 10.2 Hz and 7.5 Hz, 1H, H_X), 3.79 (s, 3H, 11- OCH_3), 3.93 (q, $J = 7.2$ Hz, 2H, 12- CH_2), 6.84-6.90 and 7.37-7.41 (two m, each 2H, 6-CH, 7-CH, 9-CH and 10-CH). ^{13}C NMR (CDCl_3 , 75 MHz): δ 14.0 (q, C-13), 16.6 (dt, $J = 13.1$ Hz, C-3), 27.6 (dd, $J = 16.6$ Hz, C-1), 55.2 (q, C-11), 60.6 (t, C-12), 82.8 (ds, $J = 220.8$ Hz, C-2), 113.7 (d, C-7 and C-9), 125.4 (ds, $J = 22.3$ Hz, C-5), 130.1 (d, C-6 and C-10), 160.3 (s, C-8), 169.0 (s, C-4). ^{19}F NMR (CDCl_3 , 282 MHz): δ -150.32 (m, 1F, 2-CF). MS (GCToF, EI): m/z 238 (62 [M^+], 220 (8), 218 (12), 209 (74), 193 (23), 189 (69), 183 (31), 174 (36), 165 (100), 163 (60), 155 (61), 149 (30), 145 (81), 135 (62), 133 (60), 121 (35), 115 (60), 109 (27), 103 (38), 101 (26), 96 (22), 91 (19), 89 (10), 77 (27), 63 (12), 55 (5), 51 (7). $\text{C}_{13}\text{H}_{15}\text{FO}_3$ (238.25) calcd. C 65.54 % H 6.35 %, found C 65.70 % H 6.65 %.

5.6.3. *cis*- and *trans*-2-Fluoro-2-(3,4-dimethoxyphenyl)cyclopropanecarboxylic acid ethylesters (14g** and **15g**)**—According to the general procedure^{15,68} (1-fluorovinyl)-3,4-dimethoxybenzene (**13g**) (2.73 g, 15 mmol) was treated with (2.30 g, 2.1 mL, 22.5 mmol, 1.5 equivalents) in the presence of $\text{Cu}(\text{acac})_2$ (294 mg, 1.125 mmol, 5 mol% relating to one portion of EDA). After silica gel column chromatography (20 $\times$ 3 cm, pentane/diethyl ether, 10:1) a 1:1 mixture of both isomers was isolated as a pale yellow oil (yield: 1.33 g, 33 %, **14g** : **15g** = 1:1). HRMS (ESI^+): $\text{C}_{14}\text{H}_{17}\text{FO}_4 + \text{Na}^+$ calcd. 291.1003, found 291.1001. $\text{C}_{14}\text{H}_{17}\text{FO}_4$ (268.3): calcd. C 62.68 %, H 6.39 %, found C 61.96 % H 6.42 %. Subsequently the mixture of diastereomers was separated on a silica gel column (30 $\times$ 3 cm, cyclohexane/

ethyl acetate, 15:1) giving a mixed fraction (1.17 g, 29 %, **14g** : **15g** = 1:1) and two diastereomeric enriched fractions of each isomer that were taken for spectroscopic analyses.

Data for 14g: Yield: 42 mg (1 %, **14g** : **15g** *cis:trans* = 93:7): ^1H NMR (CDCl_3 , 300 MHz): δ 1.31 (t, 3H, J = 7.1 Hz, 14- CH_3), 1.58 (ddd, 1H, J = 10.3 Hz and 9.0 Hz and 6.6 Hz, H_B), 2.15 (ddd, 1H, J = 10.0 Hz and 7.7 Hz and 2.8 Hz, H_X), 2.24 (ddd, 1H, J = 19.4 Hz and 7.6 Hz and 6.6 Hz, H_A), 3.88 and 3.90 (two s, each 3H, 11- OCH_3 and 12- OCH_3), 4.19 (qm, 2H, J = 7.1 Hz, 13- CH_2), 6.86-7.02 (m, 3H, 6-CH, 9-CH and 10-CH). ^{13}C NMR (CDCl_3 , 75 MHz): δ 14.1 (q, C-14), 18.4 (dt, J = 12.4 Hz, C-3), 28.4 (dd, J = 13.4 Hz, C-1), 56.0 (q, C-11 and C-12), 61.1 (t, C-13), 81.1 (ds, J = 227.8 Hz, C-2), 109.4 (dd, J = 4.9 Hz, C-6), 111.1 (d, C-9), 117.8 (dd, J = 4.6 Hz, C-10), 129.8 (ds, J = 21.5 Hz, C-5), 149.1 (s, C-8), 149.4 (dd, J = 2.6 Hz, C-7), 167.9 (ds, J = 2.4 Hz, C-4). ^{19}F NMR (CDCl_3 , 282 MHz): δ -182.53 (ddd, 1F, J = 19.1 Hz and 10.9 Hz and 4.4 Hz, 2-CF). MS (GC/MS, EI): m/z 269 (12), 268 (69) [M^+], 250 (2), 249 (1), 240 (4), 239 (26), 237 (6), 224 (2), 223 (22), 219 (12), 213 (18), 197 (3), 196 (14), 195 (100), 185 (21), 175 (9), 166 (2), 165 (17), 164 (30), 163 (14), 151 (5), 149 (16), 145 (4), 137 (6), 133 (12), 131 (4), 121 (10), 115 (5), 109 (10), 107 (5), 96 (3), 83 (6), 77 (2), 70 (1), 63 (2), 55 (2), 51 (2).

Data for 15g: Yield: 111 mg (3 %, **15g** : **14g** = 89:11). ^1H NMR (CDCl_3 , 300 MHz): δ 1.06 (t, 3H, J = 8.3 Hz, 14- CH_3), 1.78 (ddd, 1H, J = 18.9 Hz and 10.3 Hz and 7.0 Hz, H_A), 1.93 (ddd, 1H, J = 14.4 Hz and 6.9 Hz and 6.9 Hz, H_B), 2.53 (ddd, 1H, J = 17.7 Hz and 10.3 Hz and 7.6 Hz, H_X), 3.88 and 3.89 (two s, each 3H, 11- OCH_3 and 12- OCH_3), 3.95 (q, 2H, J = 7.1 Hz, 5- CH_2), 6.83-7.05 (m, 3H, 6-CH, 9-CH and 10-CH). ^{13}C NMR (CDCl_3 , 75 MHz): δ 14.1 (q, C-14), 16.7 (dt, J = 10.7 Hz, C-3), 27.8 (dd, J = 16.1 Hz, C-1), 55.9 (two q, C-11 and C-12), 60.7 (t, C-13), 83.1 (ds, J = 219.9 Hz, C-2), 110.6 (d, C-9), 111.8 (dd, J = 2.0 Hz, C-6), 121.4 (dd, J = 5.2 Hz, C-10), 130.0 (ds, J = 19.5 Hz, C-5), 148.8 (s, C-8), 149.9 (s, C-7), 169.0 (s, C-4). ^{19}F NMR (CDCl_3 , 282 MHz): δ -150.42 (not completely resolved ddd, 1F, J = 16.7 Hz and 11.7 Hz, 2-CF). MS (GC/MS, EI): m/z 269 (6), 268 (41) [M^+], 248 (1), 240 (3), 239 (19), 237 (7), 224 (2), 223 (13), 219 (10), 213 (16), 197 (2), 196 (13), 195 (100), 193 (19), 185 (24), 175 (10), 169 (2), 165 (23), 164 (40), 163 (19), 160 (4), 151 (9), 149 (25), 145 (6), 137 (10), 133 (18), 131 (6), 121 (15), 115 (8), 109 (17), 96 (6), 91 (8), 83 (17), 77 (6), 70 (2), 63 (6), 55 (9), 51 (6), 43 (2).

5.7. Synthesis of cyclopropanecarboxylic acids

5.7.1. *trans*-2-Fluoro-2-(4-trifluoromethyl phenyl)cyclopropane carboxylic acid (18d**)**—According to the general procedure^{15,68} *trans*-2-fluoro-2-(4-trifluoromethylphenyl)cyclopropane carboxylic acid ethylester (**14d**) (0.94 g, 3.39 mmol) was transferred into the corresponding carboxylic acid. Recrystallization from cyclohexane/ethyl acetate gave **18d** (Yield: 0.79 g, 92 %) as colorless needles. m.p. 117 °C (cyclohexane/ethyl acetate). ^1H NMR (CDCl_3 , 300 MHz): δ 1.76 (ddd, 1H, J = 7.4 Hz and 9.4 Hz and 10.9 Hz, H_B), 2.25 (ddd, 1H, J = 7.9 Hz and 9.4 Hz and 2.9 Hz, H_X), 2.40 (ddd, 1H, J = 7.6 Hz and 7.6 Hz and 20.3 Hz, H_A), 7.41 (dm, 2H, J = 8.2 Hz, C-6 and C-10), 7.66 (dm, 2H, J = 8.2 Hz, C-7 and C-9), 10.33 (br s, 1H, 4- CO_2H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 19.8 (dt, J = 10.9 Hz, C-3), 29.2 (dd, J = 11.6 Hz, C-1), 80.7 (ds, J = 232.2 Hz, C-2), 123.3 (qs, J = 271.8 Hz, C-11), 124.7 (dd, J = 5.8 Hz, C-6 and C-10), 125.7 (qd, J = 4.0 Hz, C-7 and C-9), 130.7 (qs, J = 31.2 Hz, C-8), 141.1 (ds, J = 21.7 Hz, C-5), 173.5 (s, C-4). ^{19}F NMR (CDCl_3 , 282 MHz): δ -63.40 (s, 3F, 11- CF_3), -190.02 (not completely resolved ddd, J = 18.4 Hz and 8.9 Hz, 2-CF). GC (GC/MS, EI, as trimethylsilyl ester): m/z 320 (9) [M^+], 305 (51), 265 (33), 230 (53), 211 (13), 202 (9), 183 (57), 173 (89), 145 (7), 133 (37), 115 (11), 73 (100), 55 (5), 45 (20). HRMS (ESI^+) $\text{C}_{11}\text{H}_8\text{F}_4\text{O}_2 + \text{Na}^+$: calcd. 271.0353, found 271.0359. HRMS (ESI^-) $\text{C}_{11}\text{H}_7\text{F}_4\text{O}_2 - \text{H}^+$: calcd. 247.0377, found 247.0386.

5.7.2. *cis*-2-Fluoro-2-(4-trifluoromethylphenyl)cyclopropane carboxylic acid

(19d)—According to the general procedure^{15,68} *cis*-2-fluoro-2-(4-trifluoromethylphenyl)-cyclopropane carboxylic acid ethylester (**15d**) (0.75 g, 2.72 mmol) was transferred into the corresponding carboxylic acid. Recrystallization from cyclohexane/ethyl acetate gave **19d** (yield: 0.61 g, 90 %) as colorless needles. m.p. 80 °C (cyclohexane/ethyl acetate). ¹H NMR (CDCl₃, 300 MHz): δ 1.92 (ddd, 1H, *J* = 19.1 Hz and 10.2 Hz and 7.4 Hz, H_A), 1.99 (ddd, 1H, *J* = 13.3 Hz and 7.6 Hz and 7.6 Hz, H_B), 2.55 (ddd, 1H, *J* = 18.0 Hz and 10.2 Hz and 7.7 Hz, H_X), 7.52 (dm, 2H, *J* = 8.4 Hz, 6-CH and 10-CH), 7.62 (dm, 2H, *J* = 8.8 Hz, 7-CH and 9-CH), 9.26 (br s, 1H, 4-CO₂H). ¹³C NMR (CDCl₃, 75 MHz): δ 17.4 (dt, *J* = 9.1 Hz, C-3), 28.0 (dd, *J* = 17.3 Hz, C-1), 82.7 (ds, *J* = 222.7 Hz, C-2), 123.8 (q, *J* = 272.5 Hz, C-11), 125.2 (qd, *J* = 4.0 Hz, C-7 and C-9), 126.9 (dd, *J* = 5.7 Hz, C-6 and C-10), 131.4 (qs, *J* = 33.3 Hz, C-8), 136.4 (ds, *J* = 20.8 Hz, C-5), 174.3 (s, C-4). ¹⁹F NMR (CDCl₃, 282 MHz): δ -63.40 (s, 3F, 11-CF₃), -156.57 (not completely resolved ddd, 1F, *J* = 19.8 Hz, 2-CF). GC (GC/MS, EI, as trimethyl silyl ester): m/z 320 (4) [M⁺], 305 (12), 265 (9), 230 (19), 183 (18), 173 (41), 145 (7), 133 (16), 115 (6), 73 (100), 45 (13). HRMS (ESI⁻) C₁₁H₈F₄O₂ – H⁺: calcd. 247.0377, found 247.0390. C₁₁H₈F₄O₂ (248.18): calcd. C 53.24 % H 3.25 %, found C 50.49 % H 3.11 %.

5.7.3. *cis*- and *trans*-2-Fluoro-2-(4-methoxyphenyl)cyclopropanecarboxylic acids (18f and 19f)

—According to the general procedure^{15,68} a mixture of *cis* and *trans*-2-fluoro-2-(4-methoxyphenyl)cyclopropanecarboxylic acid ethylester (**14f** and **15f**) (1.06 g, 4.44 mmol, **14f** : **15f** = 1:1) was transferred into the corresponding mixture of carboxylic acids **16f** and **17f** (yield: 0.77 g, **18f** : **19f** = 1:1, 83 %). Subsequently, the mixture of diastereomers was separated by recrystallization from cyclohexane/ethyl acetate giving diastereomerically pure **18f**, a mixed fraction (440 mg, **19f** : **18f** = 70:30, 47 %) and diastereomerically enriched **19f**.

Data for 18f: Yield: 225 mg (24 %). M.p. 112 °C (cyclohexane/ethyl acetate). ¹H NMR (CDCl₃, 300 MHz): δ 1.65 (ddd, 1H, *J* = 10.5 Hz and 9.2 Hz and 6.9 Hz, H_B), 2.14 (ddd, 1H, *J* = 7.6 Hz and 9.6 Hz and 2.2 Hz, H_X), 2.26 (ddd, 1H, *J* = 19.5 Hz and 7.3 Hz and 7.3 Hz, H_A), 3.80 (s, 3H, 11-OCH₃), 6.91 (dm, 2H, *J* = 8.4 Hz, 6-CH and 10-CH), 7.30 (dm, 2H, *J* = 8.1 Hz, 7-CH and 9-CH), 11.67 (br s, 1H, 4-CO₂H). ¹³C NMR (CDCl₃, 75 MHz): δ 18.9 (dt, *J* = 13.1 Hz, C-3), 28.0 (dd, *J* = 11.9 Hz, C-1), 55.3 (q, C-11), 81.7 (ds, *J* = 229.2 Hz, C-2), 114.1 (d, C-7 and C-9), 127.3 (dd, *J* = 6.3 Hz, C-6 and C-10), 128.8 (ds, *J* = 21.2 Hz, C-5), 160.0 (s, C-8), 174.5 (s, C-4). ¹⁹F NMR (CDCl₃, 282 MHz): δ -180.65 (not completely resolved ddd, 1F, *J* = 20.2 Hz and 11.3 Hz, 2-CF). MS ESI⁻ (daughter ion experiment): m/z 210 (40) [M⁺], 190 (30), 146 (7), 132 (100), 63 (30). HRMS (ESI⁺) C₁₁H₁₁FO₃ + Na⁺ calcd. 233.0584, found 233.0597, C₁₁H₁₁FO₃ – H⁺: calcd. 209.0619, found 209.0630. C₁₁H₁₁FO₃ (210.20): calcd. C 62.85 %, H 5.27 %, found C 62.84 % H 5.15 %.

Data for 19f: Yield: 97 mg (**19f** : **18f** = 89:11, 10 %). M.p. 102 °C (cyclohexane/ethyl acetate, **19f** : **18f** = 89:11). ¹H NMR (CDCl₃, 300 MHz): δ 1.80 (ddd, 1H, *J* = 18.2 Hz and 10.1 Hz and 7.0 Hz, H_A), 1.86 (ddd, 1H, *J* = 13.7 Hz and 7.3 Hz and 7.3 Hz, H_B), 2.47 (ddd, 1H, *J* = 17.4 Hz and 10.0 Hz and 7.5 Hz, H_X), 3.80 (s, 3H, 11-OCH₃), 6.86 (d, 2H, *J* = 8.5 Hz, 6-CH and 10-CH), 7.36 (dd, 2H, *J* = 8.6 Hz, *J*_{H,F} = 1.7 Hz, 7-CH and 9-CH), 9.65 (br s, 1H, 4-CO₂H). ¹³C NMR (CDCl₃, 75 MHz): δ 17.4 (dt, *J* = 11.6 Hz, C-3), 27.2 (dd, *J* = 19.4 Hz, C-1), 55.2 (q, C-11), 83.3 (ds, *J* = 221.0 Hz, C-2), 113.8 (d, C-7 and C-9), 124.8 (ds, *J* = 20.2 Hz, C-5), 130.1 (dd, *J* = 3.3 Hz, C-6 and C-10), 160.3 (ds, *J* = 2.7 Hz, C-8), 175.0 (s, C-4). ¹⁹F NMR (CDCl₃, 282 MHz): δ -148.24 (m, 1F, 2-CF). MS (GCToF, EI, as trimethylsilyl ester): m/z 282 (26) [M⁺], 267 (14), 262 (27), 247 (4), 239 (4), 227 (12), 223 (16), 209 (1), 208 (4), 207 (9), 195 (1), 193 (5), 192 (46), 190 (16), 189 (2), 177 (6), 174 (27), 173 (1), 165 (16), 161 (6), 159 (4), 149 (19), 146 (29), 145 (34), 136 (2), 135 (26), 131 (32), 130 (9), 121 (16), 115

(12), 109 (9), 103 (26), 102 (16), 96 (6), 89 (6), 78 (4), 77 (36), 76 (35), 73 (100), 64 (5), 63 (9), 55 (5), 51 (5), 47 (8), 45 (12). C₁₁H₁₁FO₃ (210.20): calcd. C 62.85 % H 5.27 %, found C 62.59 % H 5.46 %.

5.7.4. *cis*- and *trans*-2-Fluoro-2-(3,4-dimethoxyphenyl)cyclopropanecarboxylic acids (18g and 19g)—According to the general procedure^{15,68} a mixture of *cis* and *trans*-2-fluoro-2-(3,4-dimethoxyphenyl)cyclopropanecarboxylic acid ethylester (**14g** and **15g**) (0.81 g, 3 mmol, **14g** : **15g** = 1:1) was transferred into the corresponding mixture of carboxylic acids **18g** and **19g** (yield: 0.72 g, **18g** : **19g** = 1:1, 99 %). C₁₂H₁₃FO₄ (240.23): calcd. C 60.00 % H 5.45 %, found C 59.79 % H 5.45 %. All spectroscopic data were taken from a 1:1 mixture of **18g** and **19g**.

Data for 18g: ¹H NMR (CDCl₃, 300 MHz): δ 1.65 (dt, 1H, *J* = 10.0 Hz and 9.2 Hz and 6.8 Hz, H_B), 2.12 (ddd, 1H, *J* = 7.7 Hz and 10.0 Hz and 2.8 Hz, H_X), 2.22 (ddd, 1H, *J* = 19.8 Hz and 7.1 Hz and 7.5 Hz, H_A), 3.90 (two s, 6H, 11-OCH₃ and 12-OCH₃), 6.83-7.06 (m, 3H, 6-CH, 9-CH and 10-CH), 8.65 (br s, 4-CO₂H). ¹³C NMR (CDCl₃, 75 MHz): δ 18.8 (dt, *J* = 14.0 Hz, C-3), 28.0 (dd, *J* = 13.4 Hz, C-1), 55.8 and 55.9 (two q, C-11 and C-12), 81.7 (ds, *J* = 228.3 Hz, C-2), 109.6 (dd, *J* = 6.4 Hz, C-6), 111.1 (d, C-9), 118.0 (dd, *J* = 5.3 Hz, C-10), 129.3 (d, *J* = 21.6 Hz, C-5), 149.2 (s, C-7), 149.6 (s, C-8), 174.5 (s, C-4). ¹⁹F NMR (CDCl₃, 282 MHz): δ -180.67 (not completely resolved ddd, 1F, *J* = 18.7 Hz and 8.5 Hz, 2-CF). MS (GCToF, EI, as trimethyl silyl ester): *m/z* 313 (2), 312 (16) [M⁺], 297 (11), 292 (10), 277 (2), 257 (2), 253 (14), 238 (1), 223 (5), 220 (58), 204 (72), 195 (18), 189 (10), 176 (20), 165 (74), 161 (48), 149 (16), 145 (6), 133 (22), 131 (12), 115 (16), 103 (16), 92 (4), 89 (16), 77 (70), 73 (100), 63 (12), 51 (8), 47 (16).

Data for 19g: ¹H NMR (CDCl₃, 300 MHz): δ 1.84 (ddd, 1H, *J* = 18.8 Hz and 10.0 Hz and 7.2 Hz, H_A), 1.92 (ddd, 1H, *J* = 12.2 Hz and 7.2 Hz and 7.2 Hz, H_B), 2.53 (ddd, 1H, *J* = 17.5 Hz and 10.0 Hz and 7.5 Hz, H_X), 3.90 (two s, 6H, 11-OCH₃ and 12-OCH₃), 6.83-7.06 (m, 3H, 6-CH, 9-CH and 10-CH), 8.65 (br s, 1H, 4-CO₂H). ¹³C NMR (CDCl₃, 75 MHz): δ 17.4 (dd, *J* = 10.9 Hz, C-3), 27.4 (dd, *J* = 17.6 Hz, C-1), 56.0 (q, C-11 and C-12), 83.5 (ds, *J* = 223.4 Hz, C-2), 110.7 (d, C-9), 111.8 (dd, *J* = 3.3 Hz, C-6), 121.5 (dd, *J* = 4.9 Hz, C-10), 125.2 (ds, *J* = 20.1 Hz, C-5), 148 (s, C-8), 150.0 (s, C-7), 173.7 (s, C-4). ¹⁹F NMR (CDCl₃, 282 MHz): δ -148.72 (not completely resolved ddd, 1F, *J* = 18.3 Hz and 13.1 Hz, 2-CF). MS (GCToF, EI, as trimethylsilyl ester): *m/z* 313 (2), 312 (17) [M⁺], 298 (2), 297 (11), 292 (10), 277 (2), 257 (6), 253 (18), 238 (1), 223 (4), 222 (28), 220 (96), 219 (2), 205 (22), 204 (70), 195 (21), 191 (22), 176 (26), 175 (25), 165 (96), 161 (74), 149 (16), 145 (6), 133 (22), 131 (12), 115 (15), 103 (15), 92 (4), 89 (13), 77 (93), 73 (100), 63 (12), 51 (9), 47 (16).

5.8. Curtius rearrangements

5.8.1. *tert*-Butyl *trans*-[2-fluoro-2-(4-trifluoromethylphenyl)cyclopropyl] carbamate (20d)—According to the general procedure^{15,68} *trans*-2-fluoro-2-(4-trifluoromethylphenyl)cyclopropane carboxylic acid (**18d**) (248 mg, 1 mmol) was transferred into the corresponding Boc-protected amine Silica gel column chromatography (10 × 3 cm, pentane/diethyl ether, 10:1) and subsequent recrystallization from pentane diethyl ether furnished **20d** as a white solid (yield: 198 mg, 62 %). m.p. 164–165 °C (pentane/diethyl ether). ¹H NMR (CDCl₃, 300 MHz, 298 K): δ 1.40-1.67 (m, 2H, H_B and H_X), 1.46 (s, 9H, 13-CH₃ – 15-CH₃), 3.02 (br s, 1H, H_A), 4.97 (br s, 1H, NH), 7.38 (d, 2H, *J* = 8.1, Hz 6-CH and 10-CH), 7.62 (d, 2H, *J* = 8.2 Hz, 7-CH and 9-CH). ¹H NMR (C₆D₆, 500 MHz, 298 K): δ 0.86-0.99 (br m, 2H, H_B and H_X), 1.44 (s, 9H, 13-CH₃ – 15-CH₃), 2.68 (br s, 1H, H_A), 4.42 (br s, 1H, NH), 6.87 (d, 2H, *J* = 7.1, Hz 6-CH and 10-CH), 7.23 (d, 2H, *J* = 7.8 Hz, 7-CH and 9-CH). ¹H NMR (C₆D₆, 500 MHz, 343 K): δ 0.94-1.00 (m, 2H, H_B and H_X), 1.43 (s, 9H, 13-CH₃ – 15-CH₃), 2.69 (br s, 1H, H_A), 4.41 (br s, 1H, NH), 6.96 (d, 2H, *J* = 8.2, Hz 6-CH and

10-CH), 7.29 (d, 2H, $J = 8.1$ Hz, 7-CH and 9-CH). ^{13}C NMR (CDCl_3 , 75 MHz, 298 K): δ 20.7 (m, C-3), 28.3 (q, C-13 – C-15), 34.9 (m, C-1), 76.9 (m, C-12), 80.0 (m, C-2), 124.0 (q, $J = 271.4$ Hz, C-11), 124.5 (m, C-6 and C-10), 125.5 (qd, $J = 3.6$ Hz, C-7 and C-9), 130.1 (m, C-8), 141.9 (m, C-5), 156.1 (s, C-4). ^{19}F NMR (CDCl_3 , 282 MHz, 298 K): δ [ppm]: –62.92 (s, 3F, CF_3); –194.69 (br m, 0.83F, 2-CF) and –195.83 (br m, 0.17 F, 2-CF), signals of rotamers. ^{19}F NMR (C_6D_6 , 470 MHz, 298 K): δ –62.40 (s, 3F, 11- CF_3); –194.93 (not completely resolved ddd, 0.81F, 2-CF) and –197.02 (br s, 0.19 F, 2-CF), signals of rotamers. ^{19}F NMR (C_6D_6 , 470 MHz, 343 K): δ –62.82 (s, 3F, 11- CF_3), –194.12 (br s, 1F, 2-CF). MS (GCToF, EI): m/z 319 (0) [M^+], 245 (1), 226 (1), 219 (5), 218 (5), 216 (4), 199 (4), 198 (59), 190 (8), 176 (11), 171 (11), 169 (5), 151 (18), 133 (8), 130 (17), 121 (8), 103 (6), 101 (5), 99 (4), 75 (4), 74 (3), 59 (7), 57 (55), 56 (60), 55 (24), 53 (8), 44 (100). $\text{C}_{15}\text{H}_{17}\text{F}_4\text{NO}_2$ (319.30): calcd. C 56.43 % H 5.37 % N 4.39 %, found C 56.16 % H 5.34 % N 4.25 %.

5.8.2. *tert*-Butyl *cis*-[2-fluoro-2-(4-trifluoromethylphenyl)cyclopropyl]carbamate (21d)

—According to the general procedure^{15,68} *cis*-2-fluoro-2-(4-trifluoromethylphenyl)-cyclopropane carboxylic acid (**19d**) (310 mg, 1.25 mmol) was transferred into the corresponding Boc-protected amine. Silica gel column chromatography (13 × 3 cm, cyclohexane/ethyl acetate, 20:1) and subsequent recrystallization from pentane diethyl ether furnished **21d** as a white solid (yield: 383 mg, 95 %). m.p. 168–170 °C (pentane/diethyl ether). ^1H NMR (CDCl_3 , 300 MHz, 298 K): δ 1.27 (s, 9H, 13- CH_3 – 15- CH_3), 1.44–1.56 (m, 1H, H_B), 1.86 (ddd, 1H, $J = 8.4$ Hz and 9.6 Hz and 21.7 Hz, H_A), 3.31 (ddd, 1H, $J = 6.2$ Hz and 9.9 Hz and 15.3 Hz, H_X), 4.42 (br s, 1H, NH), 7.49 (dm, 2H, $J = 8.5$ Hz, C-6 and 10-CH), 7.64 (dm, 2H, $J = 8.2$ Hz, 7-CH and 9-CH). ^1H NMR (CDCl_3 , 500 MHz, 328 K): δ 1.28 (s, 9H, 13- CH_3 – 15- CH_3), 1.43–1.51 (m, 1H, H_B), 1.85 (ddd, 1H, $J = 8.6$ Hz and 8.6 Hz and 21.6 Hz, H_A), 3.31 (ddd, 1H, $J = 7.7$ Hz and 7.7 Hz and 15.4 Hz, H_X), 4.34 (br s, 1H, NH), 7.49 (dm, 2H, $J = 7.9$ Hz, C-6 and 10-CH), 7.63 (dm, 2H, $J = 8.2$ Hz, 7-CH and 9-CH). ^{13}C NMR (CDCl_3 , 125 MHz, 328 K): δ 19.1 (m, C-3), 28.0 (q, C-13 – C-15), 35.2 (m, C-1), 80.3 (m, C-12), 80.6 (ds, $J = 218.1$ Hz, C-2), 124.1 (q, $J = 272.6$ Hz, C-11), 125.1 (qd, $J = 3.1$ Hz, C-7 and C-9), 126.5 (m, C-6 and C-10), 130.4 (qs, $J = 33.3$ Hz, C-8), 138.5 (m, C-5), 155.5 (s, C-4). ^{19}F NMR (CDCl_3 , 282 MHz, 298 K): δ –63.25 (s, 1F, CF_3); –174.31 (br m, 0.67 F, 2-CF) and –177.31 (br m, 0.33F, 2-CF), signals of rotamers. ^{19}F NMR (CDCl_3 , 470 MHz, 328 K): δ –63.39 (s, 3F, 11- CF_3), –173.91 (br m, 1F, 2-CF). MS (GCToF, EI): m/z 319 (0) [M^+], 245 (2), 220 (3), 218 (11), 216 (11), 207 (2), 202 (4), 199 (44), 198 (94), 190 (16), 178 (9), 176 (20), 171 (16), 169 (5), 156 (1), 152 (4), 151 (18), 145 (8), 134 (3), 133 (12), 130 (30), 121 (10), 120 (4), 107 (1), 103 (7), 101 (7), 95 (2), 81 (1), 77 (3), 75 (7), 74 (12), 69 (1), 63 (1), 59 (14), 57 (100), 56 (36), 55 (14), 50 (8), 44 (63), 41 (76). $\text{C}_{15}\text{H}_{17}\text{F}_4\text{NO}_2$ (319.30): calcd. C 56.43 % H 5.37 % N 4.39 %, found C 56.11 % H 5.10 % N 4.29 %.

5.8.3. *tert*-Butyl *trans*-[2-fluoro-2-(4-methoxyphenyl)cyclopropyl]carbamate (20f)

—According to the general procedure^{15,68} *trans*-2-fluoro-2-(4-methoxyphenyl)-cyclopropane carboxylic acid (**18f**) (0.190 g, 0.80 mmol) was transferred into the corresponding Boc-protected amine Silica gel column chromatography (20 × 3 cm, cyclohexane/ethyl acetate, 10:1) and subsequent recrystallization from cyclohexane/ethyl acetate furnished **20f** as a white solid (yield: 161 mg, 71 %). m.p. 104 °C (cyclohexane/ethyl acetate). ^1H NMR (CDCl_3 , 300 MHz): δ 1.35 (ddd, $J = 21.8$ Hz and 7.8 Hz and 5.9 Hz, 1H, H_A), 1.48 (s, 9H, 14- CH_3 – 16- CH_3), 1.44–1.54 (m, 1H, H_B), 2.93 (br s, 1H, H_X), 3.81 (s, 3H, 11- OCH_3), 4.99 (br s, 1H, NH), 6.90 (d, 2H, $J = 8.2$ Hz, 7-CH and 9-CH), 7.35 (dd, 2H, $J = 7.8$ Hz, 6-CH and 10-CH). ^{13}C NMR (CDCl_3 , 75 MHz): δ 19.2 (dt, $J = 11.0$ Hz, C-3), 28.3 (q, C-13 – C-15), 33.0 (dd, $J = 10.3$ Hz, C-1), 55.3 (q, C-11), 80.2 (ms, C-2), 113.9 (d, C-7 and C-9), 128.0 (md, C-6 and C-10), 128.9–129.8 (ms, C-5), 156.4 (s, C-4) 159.7 (s, C-8). ^{19}F NMR (CDCl_3 , 282 MHz, 298 K): δ –183.85 (not completely resolved ddd, 0.83F, 2-CF) and –185.77

(br m, 0.17 F, 2-CF), signals of rotamers. MS (GCToF, EI): m/z 281 (<0.1) [M^+], 225 (2), 205 (2), 188 (2), 180 (3), 164 (3), 161 (19), 160 (100), 159 (9), 146 (20), 145 (14), 144 (4), 133 (15), 130 (43), 119 (5), 118 (20), 117 (16), 116 (15), 103 (9), 92 (3), 91 (12), 90 (13), 89 (20), 79 (3), 77 (12), 65 (6), 63 (12), 57 (16), 56 (27), 55 (12), 51 (8), 44 (27), 41 (45). $C_{15}H_{20}FNO_3$ (281.33): calcd. C 64.04 % H 7.17 % N 4.98 %, found C 63.80 % H 7.05 % N 4.95 %.

5.8.4. *tert*-Butyl *cis*-[2-fluoro-2-(4-methoxyphenyl)cyclopropyl]carbamate (**21f**)

—According to the general procedure^{15,68} a mixture of *cis*- and *trans*-2-fluoro-2-(4-methoxyphenyl) cyclopropanecarboxylic acid (0.440 g, 2.1 mmol, **19f** : **18f** = 70:30) was transferred into the corresponding Boc-protected amines. After silica gel column chromatography (20 × 3 cm, cyclohexane/ethyl acetate, 10:1) a mixture of both isomers was isolated as a white solid (yield: 404 mg, **21f** : **20f** = 70:30, 69 %). Subsequently the diastereomeric mixture was separated by recrystallization from cyclohexane/ethyl acetate to give diastereomerically pure **21f** (yield: 131 mg, 31 % relating to the ratio of **19f** in the diastereomeric mixture of the reactand). m.p. 131 °C (cyclohexane/ethyl acetate). ¹H NMR (CDCl₃, 300 MHz): δ 1.29-1.42 (m, 1H, H_B), 1.35 (s, 9H, 14-CH₃ – 16-CH₃), 1.72 (ddd, J = 21.4 Hz and 9.5 Hz and 9.5 Hz, 1H, H_A), 3.29 (m, 1H, H_X), 3.82 (s, 3H, 11-OCH₃), 4.26 (br s, 1H, NH), 6.92 (d, 2H, J = 8.3 Hz, 7-CH and 9-CH), 7.37-7.46 (m, 2H, 6-CH and 10-CH). ¹³C NMR (CDCl₃, 75 MHz): δ 17.9-18.1 (mt, C-3), 28.2 (q, C-13 – C-15), 33.3-33.6 (md, C-1), 55.3 (q, C-11), 79.8 (s, C-12), 81.0 (ds, J = 218.2 Hz, C-2), 113.8 (d, C-7 and C-9), 125.5 (ms, C-5), 129.5 (md, C-6 and C-10), 155.8 (s, C-4), 160.0 (ms, C-8). ¹⁹F NMR (CDCl₃, 282 MHz, 298 K): δ -164.27 (br s, 0.76H, 2-CF) and -168.47 (br m, 0.24 H, 2-CF), signals of rotamers. MS (GCToF, EI): m/z 281 (0) [M^+], 226 (1), 225 (3), 205 (4), 188 (2), 180 (4), 164 (4), 161 (21), 160 (100), 159 (11), 152 (8), 146 (21), 145 (15), 144 (4), 133 (19), 130 (45), 119 (6), 118 (21), 117 (18), 116 (6), 103 (10), 102 (6), 92 (4), 91 (13), 90 (14), 89 (23), 74 (4), 77 (13), 65 (6), 63 (13), 57 (18), 56 (31), 55 (14), 51 (10), 44 (37), 41 (56). $C_{15}H_{20}FNO_3$ (281.33): calcd. C 64.04 % H 7.17 % N 4.98 %, found C 63.69 % H 7.12 % N 4.93 %.

5.8.5. *tert*-Butyl *cis*- and *trans*-[2-fluoro-2-(3,4-dimethoxyphenyl)cyclopropyl] carbamate (**20g** and **21g**)

—According to the general procedure^{15,68} a mixture of *cis*- and *trans*-2-fluoro-2-(3,4-dimethoxy phenyl)cyclopropanecarboxylic acid (0.77 g, 2.81 mmol, **19g** : **18g** = 1:1) was transferred into the corresponding Boc-protected amines. Silica gel column chromatography (45 × 3 cm, pentane/diethyl ether, 4:1, then 3:1) furnished diastereomerically pure products as white solids.

Data for 20g: Yield: 241 mg (55 % relating to the ratio of **18g** in the diastereomeric mixture of the reactand). M.p. 108 °C (cyclohexane/ethyl acetate). ¹H NMR (CDCl₃, 300 MHz): δ 1.36 (ddd, J = 21.8 Hz and 7.9 Hz and 6.0 Hz, 1H, H_A), 1.48 (s, 9H, 14-CH₃ – 16-CH₃), 1.45-1.54 (m, 1H, H_B), 2.96 (br s, 1H, H_X), 3.87 and (two s, 3H, 11-OCH₃ and 12-OCH₃), 4.98 (br s, 1H, NH), 6.83-6.97 (m, 3H, 6-CH, 9-CH and 10-CH). ¹³C NMR (CDCl₃, 75 MHz): δ 19.6 (dt, J = 10.5 Hz, C-3), 28.3 (q, C-14 – C-16), 33.3 (md, C-1), 55.9 (2 q, C-11 and C-12), 79.3 (ds, J = 220.6 Hz, C-2), 79.9 (s, C-13), 109.9 (dd, J = 5.9 Hz, C-6), 111.1 (d, C-9), 118.6 (md, C-10), 129.7 (ds, J = 21.2 Hz, C-5), 149.1 (s, C-8), 149.3 (ds, J = 2.4 Hz, C-7), 156.3 (s, C-4). ¹⁹F NMR (CDCl₃, 282 MHz): δ -184.64 (br s, 0.82 F, 2-CF) and -186.24 (br s, 0.18 F, 2-CF), signals of rotamers. MS (GCToF, EI): m/z 311 (0) [M^+], 235 (1), 210 (1), 190 (17), 174 (12) [M^+ -(CH₃O)₂C₆H₃], 160 (45), 117 (6), 116 (2), 77 (4), 57 (25), 56 (52), 44 (100). $C_{16}H_{22}FNO_4$ (311.35): calcd. C 61.72 % H 7.12 % N 4.50 %, found C 61.61 % H 7.14 % N 4.41 %.

Data for 21g: Yield: 240 mg (55 % relating to the ratio of **19g** in the diastereomeric mixture of the reactand). M.p. 135 °C (cyclohexane/ethyl acetate). ¹H NMR (CDCl₃, 300 MHz): δ 1.29-1.42 (m, 1H, H_B), 1.36 (s, 9H, 14-CH₃ – 16-CH₃), 1.73 (ddd, *J* = 8.1 Hz and 9.2 Hz and 21.1 Hz, 1H, H_A), 3.27-3.32 (m, 1H, H_X), 3.89 and 3.90 (two s, 3H, 11-OCH₃ and 12-OCH₃), 4.25 (br s, 1H, NH), 6.86-7.05 (m, 3H, 6-CH, 9-CH and 10-CH). ¹³C NMR (CDCl₃, 75 MHz): δ 17.8-18.2 (mt, C-3), 28.2 (q, C-14 – C-16), 33.5-33.7 (md, C-1), 55.9 (two q, C-11 and C-12), 79.8 (s, C-13), 81.3 (ds, *J* = 218.0 Hz, C-2), 110.9 (d, C-9), 111.3-111.6 (md, C-6), 120.4 (md, C-10), 125.8 (ds, *J* = 18.9 Hz, C-5), 149.0 (s, C-8), 149.6 (ms, C-7), 155.8 (s, C-4). ¹⁹F NMR (CDCl₃, 282 MHz): δ –163.93 (br s, 0.78 F, 2-CF) and –168.50 (br s, 0.22 F, 2-CF), signals of rotamers. MS (GCToF, EI): *m/z* 311 (0) [M⁺], 235 (3), 210 (3), 190 (17), 174 (18), 160 (71), 117 (8), 116 (5), 77 (8), 57 (28), 56 (68), 44 (100). C₁₆H₂₂FNO₄ (311.35): calcd. C 61.72 % H 7.12 % N 4.50 %, found C 61.39 % H 7.13 % N 4.39 %.

5.8.6. *tert*-Butyl *cis*-(±)- and *trans*-(±)-(2-fluoro-1,2-diphenylcyclopropyl) carbamates (20h and 21h)—According to the general procedure^{15,68} a mixture of *cis*- and *trans*-2-fluoro-1,2-diphenyl cyclopropanecarboxylic acid (0.83 g, 3.25 mmol, **18h** : **19h** = 60:40) was transferred into the corresponding Boc-protected amines. Silica gel column chromatography (30 × 3 cm, pentane/diethyl ether, 20:1) furnished diastereomerically pure products as white solids and a mixed fraction (Yield: 159 mg, **20h** : **21h** = 33:67, 15 %).

Data for 20h: Yield: 442 mg (69 % relating to the ratio of **18h** in the diastereomeric mixture of the reactand). M.p. 108 °C (pentane/diethyl ether). ¹H NMR (CDCl₃, 300 MHz, 298 K): δ 1.43 (s, 9H, 18-CH – 20-CH₃), 1.94 (dd, 1H, *J* = 21.0 Hz and 9.0 Hz, H_A), 2.30 (dd, 1H, *J* = 11.8 Hz and 8.4 Hz, H_B), 5.66 (br s, 1H, NH), 7.10-7.17 (m, 10H, 6-CH – 10-CH and 12-CH – 16-CH). ¹H NMR (C₆D₆, 600 MHz, 298 K): δ 1.39 (s, 9H, 18-CH₃ – 20-CH₃), 1.76-1.81 (m, 1H, H_A), 1.96-1.99 (m, 1H, H_B), 5.39 (br s, 1H, NH), 6.80-7.12 (m, 6-CH – 10-CH and 12-CH – 16-CH). ¹H NMR (C₆D₆, 600 MHz, 348 K): δ 1.40 (s, 9H, 18-CH₃ – 20-CH₃), 1.76 (dd, 1H, *J* = 22.5 Hz and 7.7 Hz, H_A), 1.99 (dd, 1H, *J* = 12.3 Hz and 8.4 Hz, H_B), 5.36 (br s, 1H, NH), 6.82-7.16 (m, 6-CH – 10-CH and 12-CH – 16-CH). ¹³C NMR (C₆D₆, 600 MHz, 343 K): δ 23.9 (dt, *J* = 9.5 Hz, C-3), 28.5 (q, C-18 – C-20), 44.9 (ms, C-1), 79.4 (s, C-17), 84.5 (ds, *J* = 227.6 Hz, C-2), 127.1, 127.8, 127.9, 128.0, 128.3, 128.9 (d, C-6 – C-10 and C-12 – C-16), 135.1 (ds, *J* = 21.8 Hz, C-5), 138.8 (br s, C-11), 155.5 (br s, C-4). ¹⁹F NMR (CDCl₃, 282 MHz, 298 K): δ –170.90 (m, 0.71F, 2-CF) and –170.23 (brs, 0.29 F, 2-CF), signals of rotamers. ¹⁹F NMR (C₆D₆, 470 MHz, 298 K): δ –170.32 (m, 0.93F, 2-CF) and –170.23 (br s, 0.7 F, 2-CF), signals of rotamers. ¹⁹F NMR (C₆D₆, 564 MHz, 343 K): δ –170.58 (br s, 1F, 2-CF). MS (GCToF, EI, in a range from *m/z* = 240–430) *m/z* 327 (0) [M⁺], 307 (1) [M⁺-HF], 295 (3), 294 (1) [M⁺-CH₂F], 273 (1), 272 (18), 271 (100) [M⁺-C₄H₇], 270 (15) [M⁺-C₄H₈], 254 (12), 253 (41), 251 (75) [271-HF], 248 (10). MS (GCToF, EI, in a range from *m/z* = 40–430): *m/z* 327 (0) [M⁺], 272 (1), 271 (4), 270 (1), 251 (4), 228 (1), 227 (4), 226 (11), 224 (5), 208 (3), 207 (21), 206 (100), 204 (9), 191 (3), 180 (3), 179 (14), 178 (11), 176 (2), 150 (2), 133 (3), 130 (25), 122 (8), 105 (3), 104 (40), 103 (18), 102 (10), 101 (3), 89 (2), 78 (5), 77 (40), 76 (8), 75 (4), 73 (1), 56 (9), 51 (13), 41 (18). HRMS (ESI⁺) C₂₀H₂₂FNO₂ + Na⁺: calcd. 350.1527, found 350.1515.

Data for 21h: Yield: 210 mg (49 % relating to the ratio of **19h** in the diastereomeric mixture of the reactand). M.p. 128 °C (pentane/diethyl ether). ¹H NMR (CDCl₃, 300 MHz, 298 K): δ 1.28 (s, 9H, 18-CH₃ – 20-CH₃), 2.13 (br s, 1H, H_B), 2.27 (dd, 1H, *J* = 21.5 Hz and 7.8 Hz, H_A), 4.71 (br s, 1H, NH), 7.24-7.50 (m, 6-CH – 10-CH and 12-CH – 16-CH). ¹H NMR (C₆D₆, 600 MHz, 298 K): δ 1.91 (s, 9H, 18-CH₃ – 20-CH₃), 2.00 (br s, 1H, H_B), 2.08-2.10 (m, 1H, H_A), 4.56 (br s, 1H, NH), 7.05-7.53 (m, 6-CH – 10-CH and 12-CH – 16-CH). ¹H NMR (C₆D₆, 600 MHz, 348 K): δ 1.20 (s, 9H, 18-CH₃ – 20-CH₃), 1.93 (br s, 1H, H_B), 2.06 (dd, 1H, *J* = 21.8 Hz and 8.2 Hz, H_A), 4.53 (br s, 1H, NH), 7.07-7.22 (m, C-7 – C-9 and C-13 – C-15),

7.35 (d, 2H, $J = 7.5$ Hz, 6-CH and 10-CH), 7.51 (d, 2H, $J = 7.5$ Hz, 12-CH and 16-CH). ^{13}C NMR (C_6D_6 , 600 MHz, 298 K): δ 22.3 (mt, C-3), 27.2 (q, C-18 – C-20), 43.8 (ms, C-1), 78.9 (s, C-17), 82.7 (ds, $J = 220.0$ Hz, C-2), 125.6, 125.7, 126.4, 127.2, 127.4, 127.5, 127.6 (d, C-6 – C-10 and C-12 – C-16), 132.9 (ms, C-5), 136.6 (br s, C-11), 153.5 (br s, C-4). ^{19}F NMR (CDCl_3 , 282 MHz, 298 K): δ -172.52 (m, 0.37 F, 2-CF) and -173.28 (brs, 0.63 F, 2-CF), signals of rotamers. MS (GC/ToF, EI, in the of $m/z = 240$ –390) m/z 327 (0) [M^+], 320 (1), 307 (2), 306 (2), 295 (3), 294 (2), 273 (1), 272 (16), 271 (100), 270 (15), 254 (14), 253 (73), 252 (48), 251 (79), 248 (7). MS (GC/ToF, EI, in the range of $m/z = 0$ –390): m/z 327 (0), 272 (1), 271 (3), 270 (1), 251 (2), 232 (1), 227 (4), 226 (8), 224 (5), 208 (4), 207 (20), 206 (100), 204 (10), 191 (4), 179 (12), 176 (2), 165 (3), 156 (3), 133 (3), 130 (20), 122 (8), 120 (1), 105 (4), 104 (37), 103 (19), 102 (8), 101 (4), 89 (3), 78 (5), 77 (32), 76 (8), 75 (4), 63 (4), 56 (10), 51 (11), 41 (18). HRMS (ESI^+) $\text{C}_{20}\text{H}_{22}\text{FNO}_2 + \text{Na}^+$: calcd. 350.1527, found 350.1522.

5.9. Synthesis of cyclopropylamine hydrochlorides

5.9.1. *trans*-2-Fluoro-2-(4-trifluoromethylphenyl)cyclopropylamine

hydrochloride (7d)—According to the general procedure^{15,68} *tert*-butyl *trans*-[2-fluoro-2-(4-trifluoromethylphenyl) cyclopropyl]carbamate (**20d**) (132 mg, 0.41 mmol) was transferred into the corresponding free amine. Recrystallization from methanol/diethyl ether furnished **7d** as a white solid (yield: 66 mg, 63 %). m.p. 165 °C (methanol/diethyl ether, decomposition). ^1H NMR (methanol- d_4 , 300 MHz): δ 1.90–2.00 (m, 2H, H_A and H_B), 3.17–3.22 (m, 1H, H_X), 4.80 (br s, 3H, $\text{NH}_2\cdot\text{HCl}$), 7.60 (dm, 2H, $J = 8.0$ Hz, 5-CH and 9-CH), 7.75 (dm, 2H, $J = 7.9$ Hz, 6-CH and 8-CH). ^{13}C NMR (methanol- d_4 , 75 MHz): δ 18.9 (dt, $J = 10.3$ Hz, C-3), 33.4 (dd, $J = 13.1$ Hz, C-1), 78.9 (ds, $J = 220.3$ Hz, C-2), 123.9 (ms, C-10), 126.9 (dd, $J = 6.9$ Hz, C-5 and C-9), 127.1 (qd, $J = 3.9$ Hz, C-6 and C-8), 132.2 (qs, $J = 32.9$ Hz, C-7), 141.5 (ds, $J = 20.7$ Hz, C-4). ^{19}F NMR (methanol- d_4 , 282 MHz): δ -62.65 (s, 3F, 10- CF_3), -192.59 (m, 1F, 2-CF). MS ESI^- (daughter ion experiment): m/z 220 (51) [$\text{M}-\text{Cl}^-$], 203 (89), 200 (100), 183 (6), 180 (13), 131 (7). HRMS (ESI^+) $\text{C}_{10}\text{H}_{10}\text{ClF}_4\text{N} - \text{Cl}^-$: calcd. 220.0749, found 220.0742. $\text{C}_{10}\text{H}_{10}\text{ClF}_4\text{N}$ (255.64): calcd. C 46.98 % H 3.94 % N 5.48 %, found C 46.25 % H 3.78 % N 5.46 %.

5.9.2. *cis*-2-Fluoro-2-(4-trifluoromethylphenyl)cyclopropylamine hydrochloride

(10d)—According to the general procedure^{15,68} *tert*-butyl *cis*-[2-fluoro-2-(4-trifluoromethylphenyl) cyclopropyl]carbamate (**21d**) (155 mg, 0.48 mmol) was transferred into the corresponding free amine. Recrystallization from methanol/diethyl ether furnished **10d** as a white solid (yield: 100 mg, 81 %). m.p. 156 °C (methanol/diethyl ether, decomposition). ^1H NMR (methanol- d_4 , 300 MHz): δ 1.90–2.11 (m, 2H, H_B and H_A), 3.46 (ddd, 1H, $J = 14.4$ Hz and 10.2 Hz and 6.3 Hz, H_X), 4.79 (s, 3H, $\text{NH}_2\cdot\text{HCl}$), 7.80–7.87 (m, 4H, 5-CH – 9-CH). ^{13}C NMR (methanol- d_4 , 75 MHz): δ 16.5 (dt, $J = 12.4$ Hz, C-3), 33.3 (dd, $J = 20.5$ Hz, C-1), 79.9 (ds, $J = 220.7$ Hz, C-2), 123.8 (q, $J = 272.5$ Hz, C-10), 127.5 (qd, $J = 4.2$ Hz, C-8 and C-6), 131.2 (dd, $J = 4.0$ Hz, C-5 and C-9), 133.6 (qs, $J = 33.1$ Hz, C-7), 136.5 (ds, $J = 21.5$ Hz, C-4). ^{19}F NMR (methanol- d_4 , 282 MHz): δ -62.82 (s, 3F, 10- CF_3), -163.41 (not completely resolved ddd, 1F, $J = 21.1$ Hz and 12.7 Hz, 2-CF). MS (direct injection, EI): m/z 257/255 (0/0) [M^+], 219 (21), 218 (27), 198 (100), 183 (5), 171 (16), 151 (23), 130 (34), 121 (5), 103 (6), 74 (31), 73 (5), 54 (3). HRMS (ESI^+): $\text{C}_{10}\text{H}_{10}\text{ClF}_4\text{N} - \text{Cl}^-$: calcd. 220.0749, found 220.0742. $\text{C}_{10}\text{H}_{10}\text{ClF}_4\text{N}$ (255.64): calcd. C 46.98 % H 3.94 % N 5.48 %, found C 46.62 % H 3.95 % N 5.43 %.

5.9.3. *trans*-2-Fluoro-2-(4-methoxyphenyl)cyclopropylamine hydrochloride (7f)

—According to the general procedure^{15,68} *tert*-butyl *trans*-[2-fluoro-2-(4-methoxyphenyl) cyclopropyl] carbamate (**20f**) (132 mg, 0.41 mmol) was transferred into the corresponding free amine. Recrystallization from methanol/diethyl ether furnished **7f** as a white solid (yield: 84 mg, 94 %). m.p. 166 °C (methanol/diethyl ether, decomposition). ^1H NMR (methanol- d_4 , 300

MHz): δ 1.69–1.82 (m, 2H, H_A and H_B), 2.97–3.02 (m, 1H, H_X), 3.81 (s, 3H, 10-OCH₃), 4.91 (s, 3H, NH₂-HCl), 6.98 (d, 1H, J = 8.1 Hz, 6-CH and 8-CH), 7.43 (dd, 1H, J = 8.7 Hz, $J_{H,F}$ = 1.3 Hz, 5-CH and 9-CH). ¹³C NMR (methanol-d₄, 75 MHz): δ 17.4 (dt, J = 15.1 Hz, C-3), 32.1 (dd, J = 10.5 Hz, C-1), 56.2 (q, C-10), 79.4 (ds, J = 218.9 Hz, C-2), 115.5 (d, C-6 and C-8), 128.3 (ds, J = 19.8 Hz, C-4), 129.8 (ds, J = 4.4 Hz, C-5 and C-9), 162.3 (ds, J = 2.5 Hz, C-7). ¹⁹F NMR (methanol-d₄, 282 MHz): δ –181.05 (not completely resolved ddd, 1F, J = 19.4 Hz and 15.4 Hz, 2-CF). MS ESI⁺ (daughter ion experiment): m/z 182 (5) [M-Cl⁻], 162 (100) [182-HF], 147 (53) [162-CH₃], 132 (23) [162-CH₂O], 131 (28) [162-CH₃O], 130 (14) [147-NH₃], 119 (10) [147-CHO], 118 (6) [147-CH₂O]. HRMS (ESI⁺) C₁₀H₁₃ClFNO – Cl⁻: calcd. 182.0976, found 182.0913.

5.9.4. *cis*-2-Fluoro-2-(4-methoxyphenyl)cyclopropylamine hydrochloride (**10f**)—

According to the general procedure^{15,68} *tert*-butyl *cis*-[2-fluoro-2-(4-methoxyphenyl)cyclopropyl] carbamate (**21f**) (74 mg, 0.26 mmol) was transferred into the corresponding free amine. Recrystallization from methanol/diethyl ether furnished **10f** as a white solid (yield: 55 mg, 96 %). m.p. 156 °C (methanol/diethyl ether, decomposition). ¹H NMR (methanol-d₄, 300 MHz): δ 1.71 (ddd, 1 H, J = 9.4 Hz and 9.4 Hz and 5.8 Hz, H_B), 1.88 (ddd, 1H, J = 19.2 Hz and 9.9 Hz and 9.0 Hz, H_A), 3.36 (ddd, 1H, J = 13.7 Hz and 10.1 Hz and 5.9 Hz, H_X), 3.84 (s, 3H, 10-OCH₃), 4.89 (s, 3H, NH₂-HCl), 7.06 (d, 1H, J = 8.6 Hz, 6-CH and 8-CH), 7.59 (dd, 1H, J = 8.7 Hz, $J_{H,F}$ = 1.8 Hz, 5-CH and 9-CH). ¹³C NMR (methanol-d₄, 75 MHz): δ 16.3 (dt, J = 14.4 Hz, C-3), 32.6 (dd, J = 22.9 Hz, C-1), 56.2 (q, C-10), 80.1 (ds, J = 220.0 Hz, C-2), 115.9 (d, C-6 and C-8), 123.9 (ds, J = 20.6 Hz, C-4), 132.9 (dd, J = 2.2 Hz, C-5 and C-9), 163.1 (ds, J = 2.3 Hz, C-7). ¹⁹F NMR (methanol-d₄, 282 MHz): δ –155.36 (not completely resolved ddd, 1F, J = 21.1 Hz and 11.1 Hz, 2-CF). MS ESI⁺ (daughter ion experiment): m/z 182 (35) [M-Cl⁻], 165 (83) [182-NH₃], 162 (29) [182-HF], 153 (71) [182-CHO], 145 (15) [162-NH₃], 139 (9), 135 (20) [165-HF], 119 (4) [139-HF], 117 (6) [145-CO], 115 (4) [145-CH₂O], 91 (7) [C₇H₇⁺], 30 (100) [CH₂O⁺]. HRMS (ESI⁺) C₁₀H₁₃ClFNO – Cl⁻: calcd. 182.0976, found 182.0978.

5.9.5. *trans*-2-Fluoro-2-(3,4-dimethoxyphenyl)cyclopropylamine hydrochloride (**7g**)—

According to the general procedure^{15,68} *tert*-butyl *trans*-[2-fluoro-2-(3,4-dimethoxyphenyl)cyclopropyl]carbamate (**20g**) (156 mg, 0.5 mmol) was transferred into the corresponding free amine. Recrystallization from methanol/diethyl ether furnished **7g** as a white solid (yield: 90 mg, 77 %). m.p. 155 °C (methanol/diethyl ether, decomposition). ¹H NMR (methanol-d₄, 300 MHz): δ 1.73–1.81 (m, 2H, H_A and H_B), 3.00–3.05 (m, 1H, H_X), 3.84 and 3.86 (two s, 3H, 10-OCH₃ and 11-OCH₃), 4.77 (s, 3H, NH₂-HCl), 6.98–7.10 (m, 3H, 5-CH, 8-CH and 9-CH). ¹³C NMR (methanol-d₄, 75 MHz): δ 17.5 (dt, J = 17.5 Hz, C-3), 32.3 (dd, J = 10.7 Hz, C-1), 56.8 and 57.0 (two q, C-10 and C-11), 79.6 (ds, J = 218.4 Hz, C-2), 112.3 (dd, J = 3.3 Hz, C-5), 113.2 (d, C-8), 121.1 (dd, J = 5.2 Hz, C-9), 128.9 (ds, J = 19.7 Hz, C-4), 151.0 (s, C-7), 151.9 (ds, J = 3.2 Hz, C-6). ¹⁹F NMR (methanol-d₄, 282 MHz): δ –181.26 (m, 1F, 2-CF). MS ESI⁺ (daughter ion experiment): m/z 212 (21) [M⁺-HCl], 192 (100), 161 (6). HRMS (ESI⁺) C₁₁H₁₅ClFNO₂ – Cl⁻: calcd. 212.1081, found 212.1080.

5.9.6. *cis*-2-Fluoro-2-(3,4-dimethoxyphenyl)cyclopropylamine hydrochloride (**10g**)—

According to the general procedure^{15,68} *tert*-butyl *cis*-[2-fluoro-2-(3,4-methoxyphenyl)cyclopropyl]carbamate (**21g**) (35 mg, 0.11 mmol) was transferred into the corresponding free amine. Recrystallization from methanol/diethyl ether furnished **10g** as a white solid (yield: 26 mg, 84 %). m.p. 156 °C (methanol/diethyl ether, decomposition). ¹H NMR (methanol-d₄, 300 MHz): δ 1.74 (ddd, 1H, J = 9.3 Hz and 9.3 Hz and 5.9 Hz, H_B), 1.89 (ddd, 1H, J = 19.3 Hz and 9.9 Hz and 9.3 Hz, H_A), 3.37 (ddd, 1H, J = 13.4 Hz and 10.0 Hz and 5.9 Hz, H_X), 3.87 and 3.92 (two s, 3H, 10-OCH₃ or 11-OCH₃), 3.92 (s, 3H, 10-or 11-OCH₃), 4.88 (s, 3H, NH₂-HCl), 7.08 (dm, 1H, J = 8.2 Hz, 8-CH), 7.21 (dd, 1H, J = 8.2 Hz,

$J_{\text{H,F}} = 2.2$ Hz, 9-CH), 7.25 (m, 1H, 5-CH). ^{13}C NMR (methanol- d_4 , 75 MHz): δ 16.3 (dt, $J = 12.8$ Hz, C-3), 32.7 (dd, $J = 22.7$ Hz, C-1), 56.8 and 57.0 (two q, C-10 and C-11), 57.0 (q, C-10 or C-11), 80.4 (ds, $J = 221.3$ Hz, C-2), 113.2 (d, C-8), 114.6 (d, C-5), 124.4 (d, C-9), 124.3 (ds, $J = 17.7$ Hz, C-4), 151.1 (s, C-7), 152.6 (ms, C-6). ^{19}F NMR (methanol- d_4 , 282 MHz): δ -155.88 (m, 1F, 2-CF). MS ESI⁺ (daughter ion experiment): m/z 212 (2) [M-Cl⁻], 192 (100), 165 (8). HRMS (ESI⁺) $\text{C}_{11}\text{H}_{15}\text{ClFNO}_2 - \text{Cl}^-$: calcd. 212.1081, found 212.1081.

5.9.7. *cis*-(±)-2-Fluoro-1,2-diphenylcyclopropylamine hydrochloride (7h)—

According to the general procedure^{15,68} *tert*-butyl *cis*-[2-fluoro-1,2-diphenylcyclopropyl] carbamate (**20h**) (164 mg, 0.5 mmol) was transferred into the corresponding free amine. Recrystallization from methanol/diethyl ether furnished **7h** as a white solid (yield: 132 mg, 99 %). m.p. 155 °C (methanol/diethyl ether, decomposition). ^1H NMR (methanol- d_4 , 300 MHz): δ 2.21 (dd, 1H, $J = 23.6$ Hz and 9.8 Hz, H_A), 2.64 (dd, 1H, $J = 13.3$ Hz and 9.8 Hz, H_B), 4.77 (br s, 3H, $\text{NH}_2\cdot\text{HCl}$), 7.23-7.30 (m, 10H, 4-CH – 9-CH and 11-CH -15-CH). ^{13}C NMR (methanol- d_4 , 75 MHz): δ 20.4 (dt, $J = 11.0$ Hz, C-3), 45.5 (ds, $J = 11.4$ Hz, C-1), 83.7 (ds, $J = 225.6$ Hz, C-2), 128.2, 129.6, 130.3, 130.4, 130.8 (d, C-5 – C-9, C-11 – C-15), 133.3 (s, C-10), 133.9 (ds, $J = 22.4$ Hz, C-4). ^{19}F NMR (methanol- d_4 , 282 MHz): δ -175.28 (dd, 1F, $J = 22.0$ Hz and 13.3 Hz, 2-CF). MS ESI⁺ (daughter ion experiment): m/z 228 (20) [M-Cl⁻], 211 (23), 208 (100), 191 (12), 133 (5). HRMS (ESI⁺) $\text{C}_{15}\text{H}_{15}\text{ClFN} - \text{Cl}^-$: calcd. 228.1183, found 228.1186.

5.9.8. *trans*-(±)-2-Fluoro-1,2-diphenylcyclopropylamine hydrochloride (10h)—

According to the general procedure^{15,68} *tert*-butyl *trans*-(2-fluoro-1,2-diphenylcyclopropyl) carbamate (**21h**) (80 mg, 0.24 mmol) was transferred into the corresponding free amine. Recrystallization from methanol/diethyl ether furnished **10h** as a white solid (yield: 62 mg, 96 %). m.p. 143 °C (methanol/diethyl ether, decomposition). ^1H NMR (methanol- d_4 , 300 MHz): δ 2.26-2.39 (m, 2H, H_A and H_B), 4.79 (br s, 3H, $\text{NH}_2\cdot\text{HCl}$), 7.47-7.79 (m, 10H, 5-CH – 9-CH and 11-CH -15-CH). ^{13}C NMR (methanol- d_4 , 75 MHz): δ 20.6 (dt, $J = 11.5$ Hz, C-3), 45.4 (ds, $J = 17.3$ Hz, C-1), 82.7 (ds, $J = 224.2$ Hz, C-2), 130.6, 130.8, 130.9, 131.2, 131.4, 132.4 (d, C-5 – C-9, C-11 – C-15), 133.3 (ms, C-10), 133.9 (ds, $J = 1.9$ Hz, C-4). ^{19}F NMR (methanol- d_4 , 282 MHz): δ -158.43 (dd, 1F, $J = 18.2$ Hz and 12.6 Hz, 2-CF). MS ESI⁺ (daughter ion experiment): m/z 228 (39) [M-Cl⁻], 211 (19), 208 (100), 191 (8), 133 (5), 106 (8), 105 (33), 104 (90). HRMS (ESI⁺) $\text{C}_{15}\text{H}_{15}\text{ClFN} - \text{Cl}^-$: calcd. 228.1183, found 228.1176.

5.10. X-Ray structures

Data sets were collected with Nonius KappaCCD diffractometers, in the case of Mo-radiation equipped with a rotating anode generator. Programs used: data collection COLLECT,⁶⁹ data reduction Denzo-SMN⁷⁰, absorption correction SORTAV⁷¹ and Denzo⁷², structure solution SHELXS-97,⁷³ structure refinement SHELXL-97,⁷⁴ graphics SCHAKAL.⁷⁵

5.10.1. X-ray crystal structure analysis for 18d—formula $\text{C}_{11}\text{H}_8\text{F}_4\text{O}_2$, $M = 248.17$, colorless crystal $0.40 \times 0.35 \times 0.15$ mm, $a = 23.478(1)$, $b = 7.074(1)$, $c = 14.505(1)$ Å, $\beta = 118.19(1)^\circ$, $V = 2123.3(3)$ Å³, $\rho_{\text{calc}} = 1.553$ g cm⁻³, 1.354 mm⁻¹, empirical absorption correction ($0.613 \leq T \leq 0.823$), $Z = 8$, monoclinic, space group $C2/c$ (No. 15), $\lambda = 1.54178$ Å, $T = 223$ K, ω and ϕ scans, 6490 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.60\text{Å}^{-1}$, 1891 independent ($R_{\text{int}} = 0.030$) and 1748 observed reflections [$I \geq 2\sigma(I)$], 155 refined parameters, $R = 0.057$, $wR^2 = 0.153$, max. residual electron density 0.54 (−0.39) e Å⁻³, hydrogens calculated and refined as riding atoms.

5.10.2. X-ray crystal structure analysis for 18f—formula $\text{C}_{11}\text{H}_{11}\text{FO}_3$, $M = 210.20$, colorless crystal $0.30 \times 0.20 \times 0.10$ mm, $a = 5.528(1)$, $b = 7.348(1)$, $c = 25.592(1)$ Å, $\beta = 94.91(1)^\circ$, $V = 1035.7(2)$ Å³, $\rho_{\text{calc}} = 1.348$ g cm⁻³, 0.929 mm⁻¹, empirical absorption correction

($0.768 \leq T \leq 0.913$), $Z = 4$, monoclinic, space group $P2_1/c$ (No. 14), $\lambda = 1.54178 \text{ \AA}$, $T = 293 \text{ K}$, ω and ϕ scans, 6736 reflections collected ($\pm h, \pm k, \pm l$), $[(\sin\theta)/\lambda] = 0.59 \text{ \AA}^{-1}$, 1772 independent ($R_{int} = 0.037$) and 1611 observed reflections [$I \geq 2 \sigma(I)$], 139 refined parameters, $R = 0.043$, $wR^2 = 0.136$, max. residual electron density $0.17 (-0.14) \text{ e \AA}^{-3}$, hydrogen calculated and refined as riding atoms.

5.10.3. X-ray crystal structure analysis for 19d—Formula $C_{11}H_8F_4O_2$, $M = 248.17$, colorless crystal $0.25 \times 0.25 \times 0.20 \text{ mm}$, $a = 5.534(1)$, $b = 10.323(1)$, $c = 22.474(1) \text{ \AA}$, $\alpha = 81.77(1)^\circ$, $\beta = 89.29(1)^\circ$, $\gamma = 76.55(1)^\circ$, $V = 1235.5(3) \text{ \AA}^3$, $\rho_{calc} = 1.334 \text{ g cm}^{-3}$, 1.164 mm^{-1} , empirical absorption correction ($0.760 \leq T \leq 0.801$), $Z = 4$, triclinic, space group $P1bar$ (No. 2), $\lambda = 1.54178 \text{ \AA}$, $T = 223 \text{ K}$, ω and ϕ scans, 11148 reflections collected ($\pm h, \pm k, \pm l$), $[(\sin\theta)/\lambda] = 0.59 \text{ \AA}^{-1}$, 3934 independent ($R_{int} = 0.045$) and 3339 observed reflections [$I \geq 2 \sigma(I)$], 365 refined parameters, $R = 0.089$, $wR^2 = 0.283$, two almost identical molecules in the asymmetric unit, CF_3 -groups heavily disordered, refined with split positions, max. residual electron density $0.47 (-0.28) \text{ e \AA}^{-3}$, hydrogens calculated and refined as riding atoms.

5.10.4. X-ray crystal structure analysis for 19f—Formula $C_{11}H_{11}FO_3$, $M = 210.20$, colorless crystal $0.60 \times 0.30 \times 0.20 \text{ mm}$, $a = 14.976(1)$, $b = 5.783(1)$, $c = 12.932(1) \text{ \AA}$, $\beta = 112.90(1)^\circ$, $V = 1031.7(2) \text{ \AA}^3$, $\rho_{calc} = 1.353 \text{ g cm}^{-3}$, 0.933 mm^{-1} , empirical absorption correction ($0.605 \leq T \leq 0.835$), $Z = 4$, monoclinic, space group $P2_1/c$ (No. 14), $\lambda = 1.54178 \text{ \AA}$, $T = 293 \text{ K}$, ω and ϕ scans, 12037 reflections collected ($\pm h, \pm k, \pm l$), $[(\sin\theta)/\lambda] = 0.59 \text{ \AA}^{-1}$, 1789 independent ($R_{int} = 0.037$) and 1671 observed reflections [$I \geq 2 \sigma(I)$], 138 refined parameters, $R = 0.042$, $wR^2 = 0.135$, max. residual electron density $0.13 (-0.12) \text{ e \AA}^{-3}$, hydrogen calculated and refined as riding atoms.

5.10.5. X-ray crystal structure analysis for 20d—Formula $C_{15}H_{17}F_4NO_2$, $M = 319.30$, colorless crystal $0.30 \times 0.15 \times 0.01 \text{ mm}$, $a = 13.647(1)$, $b = 11.542(1)$, $c = 10.039(1) \text{ \AA}$, $\beta = 93.79(1)^\circ$, $V = 1577.8(2) \text{ \AA}^3$, $\rho_{calc} = 1.344 \text{ g cm}^{-3}$, 1.048 mm^{-1} , empirical absorption correction ($0.744 \leq T \leq 0.990$), $Z = 4$, monoclinic, space group $P2_1/c$ (No. 14), $\lambda = 1.54178 \text{ \AA}$, $T = 223 \text{ K}$, ω and ϕ scans, 8932 reflections collected ($\pm h, \pm k, \pm l$), $[(\sin\theta)/\lambda] = 0.59 \text{ \AA}^{-1}$, 2465 independent ($R_{int} = 0.074$) and 1471 observed reflections [$I \geq 2 \sigma(I)$], 216 refined parameters, $R = 0.063$, $wR^2 = 0.152$, CF_3 -groups disordered, refined with split positions, max. residual electron density $0.19 (-0.15) \text{ e \AA}^{-3}$, hydrogen at N1 from difference fourier map, other calculated and refined as riding atoms.

5.10.6. X-ray crystal structure analysis for 20g—Formula $C_{16}H_{22}FNO_4$, $M = 311.35$, colorless crystal $0.60 \times 0.15 \times 0.03 \text{ mm}$, $a = 10.934(1)$, $b = 13.227(1)$, $c = 10.156(1) \text{ \AA}$, $V = 1603.1(2) \text{ \AA}^3$, $\rho_{calc} = 1.290 \text{ g cm}^{-3}$, 0.833 mm^{-1} , empirical absorption correction ($0.635 \leq T \leq 0.975$), $Z = 4$, orthorhombic, space group $Pca2_1$ (No. 29), $\lambda = 1.54178 \text{ \AA}$, $T = 223 \text{ K}$, ω and ϕ scans, 5796 reflections collected ($\pm h, \pm k, \pm l$), $[(\sin\theta)/\lambda] = 0.59 \text{ \AA}^{-1}$, 1873 independent ($R_{int} = 0.037$) and 1756 observed reflections [$I \geq 2 \sigma(I)$], 207 refined parameters, $R = 0.038$, $wR^2 = 0.103$, Flack parameter $0.5(3)$, max. residual electron density $0.14 (-0.15) \text{ e \AA}^{-3}$, hydrogen at N1 from difference fourier map, other calculated and refined as riding atoms.

5.10.7. X-ray crystal structure analysis for 20h—Formula $C_{20}H_{22}FNO_2^* C_5H_{12}$, $M = 399.53$, colorless crystal $0.35 \times 0.35 \times 0.30 \text{ mm}$, $a = 25.168(1)$, $c = 10.039(1) \text{ \AA}$, $V = 9834.6(8) \text{ \AA}^3$, $\rho_{calc} = 1.079 \text{ g cm}^{-3}$, 0.577 mm^{-1} , empirical absorption correction ($0.824 \leq T \leq 0.846$), $Z = 16$, tetragonal, space group $I4_1/a$ (No. 88), $\lambda = 1.54178 \text{ \AA}$, $T = 223 \text{ K}$, ω and ϕ scans, 44801 reflections collected ($\pm h, \pm k, \pm l$), $[(\sin\theta)/\lambda] = 0.59 \text{ \AA}^{-1}$, 4405 independent ($R_{int} = 0.042$) and 3897 observed reflections [$I \geq 2 \sigma(I)$], 240 refined parameters, $R = 0.063$, $wR^2 = 0.208$, disordered solvent molecule refined with geometrical constraints, max. residual electron

density $0.37 (-0.26) \text{ e } \text{\AA}^{-3}$, hydrogen at N1 from difference fourier map, other calculated and refined as riding atoms.

5.10.8. X-ray crystal structure analysis for 21h—Formula $\text{C}_{20}\text{H}_{22}\text{FNO}_2$, $M = 327.39$, colorless crystal $0.40 \times 0.30 \times 0.15 \text{ mm}$, $a = 10.846(1)$, $b = 16.590(1)$, $c = 10.086(1) \text{ \AA}$, $\beta = 101.85(1)^\circ$, $V = 1776.1(3) \text{ \AA}^3$, $\rho_{\text{calc}} = 1.224 \text{ g cm}^{-3}$, 0.696 mm^{-1} , empirical absorption correction ($0.768 \leq T \leq 0.903$), $Z = 4$, monoclinic, space group $P2_1/c$ (No. 14), $\lambda = 1.54178 \text{ \AA}$, $T = 223 \text{ K}$, ω and ϕ scans, 14110 reflections collected ($\pm h, \pm k, \pm l$), $[(\sin\theta)/\lambda] = 0.59 \text{ \AA}^{-1}$, 3113 independent ($R_{\text{int}} = 0.033$) and 2959 observed reflections [$I \geq 2 \sigma(I)$], 224 refined parameters, $R = 0.038$, $wR^2 = 0.105$, max. residual electron density $0.18 (-0.15) \text{ e } \text{\AA}^{-3}$, hydrogen at N1 from difference fourier map, other calculated and refined as riding atoms.

5.10.9. X-ray crystal structure analysis for 7h—Formula $\text{C}_{15}\text{H}_{15}\text{FN}^+\text{Cl}^-$, $M = 263.73$, colorless crystal $0.35 \times 0.30 \times 0.25 \text{ mm}$, $a = 12.233(1)$, $b = 9.498(1)$, $c = 11.404(1) \text{ \AA}$, $\beta = 95.02(1)^\circ$, $V = 1319.9(2) \text{ \AA}^3$, $\rho_{\text{calc}} = 1.327 \text{ g cm}^{-3}$, 0.282 mm^{-1} , empirical absorption correction ($0.908 \leq T \leq 0.933$), $Z = 4$, monoclinic, space group $P2_1/c$ (No. 14), $\lambda = 0.71073 \text{ \AA}$, $T = 198 \text{ K}$, ω and ϕ scans, 6987 reflections collected ($\pm h, \pm k, \pm l$), $[(\sin\theta)/\lambda] = 0.59 \text{ \AA}^{-1}$, 2327 independent ($R_{\text{int}} = 0.037$) and 2072 observed reflections [$I \geq 2 \sigma(I)$], 172 refined parameters, $R = 0.030$, $wR^2 = 0.079$, max. residual electron density $0.23 (-0.24) \text{ e } \text{\AA}^{-3}$, hydrogen calculated and refined as riding atoms.

CCDC 642246 – 642254 contain the supplementary crystallographic data for this paper. This data can be obtained free of charge at www.cam.ac.uk/contents/retrieving.html [or from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44(1223)336-033, E-mail: deposit@ccdc.cam.ac.uk].

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Figure 1.
Monoamine oxidase inhibitors.

Figure 2.
Rank order of activity as inhibitors of MAO A and B and tyramine oxidase.

Figure 3. Crystal structures of the racemic *para*-trifluoromethylcyclopropane carboxylic acids **18d** and **19d**.

1 (*trans*) **2** (*cis*) **7a-g** (*trans*)**7h** (*cis*) **10a-g** (*cis*)**10h** (*trans*)

Figure 4.
Compounds investigated in this study.

Figure 5. Effect of concentration of fluorinated phenylcyclopropylamines (closed circle, **7d**; open circle, **10d**; closed square, **7f**; open square, **10f**; closed diamond, **7g**; open diamond, **10g**; closed triangle, **7f**; open triangle, **10f**) on MAO A (A) and B (B) activity. The procedure is described in section 5.2.

Figure 6.

Lineweaver-Burk plot for inactivation of MAO A by *trans*-2-fluoro-2-(4-methoxy) phenylcyclopropylamine·HCl (**7f**, 9.7 μ M) (A) and MAO B by *cis*-($\pm$)-2-fluoro-1,2-diphenylcyclopropylamine·HCl (**7h**, 28.2 μ M) and *trans*-2-fluoro-1,2-diphenylcyclopropylamine·HCl (**10h**, 8.4 μ M) (B). Data were collected after the inhibition by **7f**, **7h** and **10h** was checked to be independent from time and concentration.

Figure 7.
SET mechanism adapted from ref. [28].

Figure 8.
Polar nucleophilic mechanism.²

Figure 9.

Suggested inhibition mechanism of tranylcypromine derivatives (GH: I changed the drawing according to reviewer 2)

Figure 10.

Correlation of MAO A and B activities with pK_a values of 2-fluoro-2-phenylcyclopropylamines. Fitting lines for MAO A and B are $\log IC_{50} = 3.09 \times pK_a - 21.87$ ($R^2 = 0.89$), and $\log IC_{50} = 0.71 \times pK_a - 4.40$ ($R^2 = 0.32$), respectively.

Figure 11.

Correlation of corrected IC₅₀ values with σ_p (A), log D (B) and van der Waals volume (C) of 2-fluoro-2-phenylcyclopropylamines for MAO A (closed circle) and B (open diamond).

Equations of the fitting lines are as follows: MAO A, $\log IC_{50} = -1.56 \times \sigma_p + 0.44$ ($R^2 = 0.85$); $\log IC_{50} = -0.80 \times \log D + 1.81$ ($R^2 = 0.69$); $\log IC_{50} = -0.04 \times V_w + 0.67$ ($R^2 = 0.49$); MAO B, $\log IC_{50} = -0.18 \times \sigma_p + 0.47$ ($R^2 = 0.08$); $\log IC_{50} = 0.03 \times \log D + 0.40$ ($R^2 = 0.01$); $\log IC_{50} = 0.01 \times V_w + 0.35$ ($R^2 = 0.17$).

Figure 12.
Differences in inhibition of MAO A and B by fluorinated phenylcyclopropyl amines.^{2,51}

Scheme 1.
 Synthesis of substituted transylcypromine analogues.*

Table 1
Physical-chemical properties of known and new inhibitors of MAO A and MAO B.

R ¹	R ²	R ³	Compound	pK _a ^a	log D (lipo class) ^b
H	H	H	1^c	8.50	^d
			2^c	8.47	1.41 (medium)
H	H	H	7a^c	7.35	1.53 (medium)
			10a^c	6.98	1.78 (medium)
H	Cl	H	7b^c	7.19	2.23 (medium)
			10b^c	6.81	2.66 (high)
H	F	H	7c^c	7.31	1.60 (medium)
			10c^c	6.88	2.14 (medium)
H	CF ₃	H	7d	7.00	2.66 (high)
			10d	6.60	3.13 (high)
H	Me	H	7e^c	7.41	1.83 (medium)
			10e^c	7.04	^e
H	OMe	H	7f	7.50	^d
			10f	^e	
OMe	OMe	H	7g	7.40	0.58 (low)
			10g	^e	^d
H	H	Ph	7h^f	7.20	2.39 (medium)
			10h^f	5.80	^d

^a pK_a values were determined titrimetrically in 0.1 M KNO₃ at 21 °C.

^b log D values were determined from the partition coefficient for 1-octanol/0.05 N NaOH + 5 Vol% DMSO at pH = 7.4.

^c The corresponding data were taken from the literature. ¹²

^d was not determined.

^e could not be determined.

^f **7h** (*cis*) and **10h** (*trans*): in contrast to the other compounds **7** and **10** here *cis* and *trans* refers to the arrangement of the two phenyl rings.

Table 2
IC₅₀ values and types of inhibition of known and new inhibitors of MAO A and MAO B.

R ¹	R ²	R ³	Compound	IC ₅₀ [μM] (type of inhibition) ^d		Selectivity MAO A : B
				MAO A	MAO B	
H	H	H	1^b	20 ± 0 (irr.)	19 ± 1 (irr.)	1 : 1
			2^b	11 ± 1 (irr.)	19 ± 0 (irr.)	1.7 : 1
H	H	H	7a^b	12 ± 1 (irr.)	6.4 ± 0.1 (irr.)	1 : 2
			10a^b	65 ± 42 (irr.)	19 ± 1 (irr.)	1 : 3.4
H	Cl	H	7b^b	1.6 ± 0 (irr.)	3.7 ± 0.1 (irr.)	2.3 : 1
			10b^b	89 ± 9 (irr.)	4.8 ± 0.1 (irr.)	1 : 18.5
H	F	H	7c^b	3.6 ± 0.2 (irr.)	4.9 ± 0.1 (irr.)	1.4 : 1
			10c^b	270 ± 70 (irr.)	10 ± 0 (irr.)	1 : 27
H	CF ₃	H	7d	0.8 ± 0.1 (irr.)	5.4 ± 0.5 (irr.)	6.8 : 1
			10d	76 ± 17 (irr.)	7.1 ± 0.2 (irr.)	1 : 10.7
H	Me	H	7e^b	13 ± 0 (irr.)	13 ± 0 (irr.)	1 : 1
			10e^b	230 ± 120 (irr.)	30 ± 1 (irr.)	1 : 7.7
H	OMe	H	7f	14 ± 5 (comp.)	5.1 ± 0.8 (irr.)	1 : 2.8
			10f	^c (-) ^d	18 ± 6 (irr.)	-
OMe	OMe	H	7g	47 ± 5 (irr.)	230 ± 26 (irr.)	4.9 : 1
			10g	^c (-) ^d	± 310 (-) ^d	-
H	H	Ph	7h^e	18 ± 3 (irr.)	37 ± 2 (comp.)	2 : 1
			10h^e	10 ± 3 (irr.)	20 ± 1 (comp.)	2 : 1

^a irr. = irreversible, comp. = competitive. For the determination of the inhibition type see section 5.3.

^b The corresponding data were taken from the literature.¹²

^c No inhibition was observed in micromolar range.

^d could not be determined.

^e **7h** (*cis*) and **10h** (*trans*): in contrast to the other compounds **7** and **10** here *cis* and *trans* refers to the arrangement of the two phenyl rings.

Table 3

IC₅₀ values corrected by pK_a of inhibitors and pH of the assay solution (*trans*-2-aryl-2-fluorocyclopropylamines).

R ¹	R ²	R ³	Compound	Observed IC ₅₀ [μM]		Corrected IC ₅₀ [μM] ^I	
				MAO A	MAO B	MAO A	MAO B
H	H	H	7a^b	12	6.4	5.0	2.7
H	Cl	H	7b	1.6	3.7	0.8	1.9
H	F	H	7c	3.6	4.9	1.6	2.1
H	CF ₃	H	7d	0.8	5.4	0.5	3.3
H	Me	H	7e	13	13	5.0	5.0
H	OMe	H	7f	14	5.1	4.7	1.7
OMe	OMe	H	7g	47	230	18	89
H	H	Ph	7h	18	37	9.0	19

^I Corrected IC₅₀ values were derived with the use of Equation 1.