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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 tranylcypromine (*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 the inhibition of MAO B. The corresponding *cis*-compounds were shown to be 10–100 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 tranylcypromines, and the geometry of the active site of the enzymes.

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 moclobemid[4] whereas MAO B is associated with neurodegenerative disorders such as Parkinson's disease[5] 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 types 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

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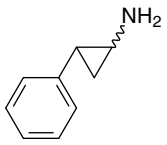
lead to damages of different tissues, capillary vessels in the eyes, kidneys, and others.

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-phenylcyclopropylamine, **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, for example, for the treatment of resistant depressions.[11]



1 (*trans*-isomer)
2 (*cis*-isomer)

The strategy of our investigations[12] has been to explore the development of highly active and selective inhibitors of MAO A and B as well as tyramine oxidase using tranylcypromine as a lead compound. A particular goal was to find more selective inhibitors that would have fewer side effects.

2. Results

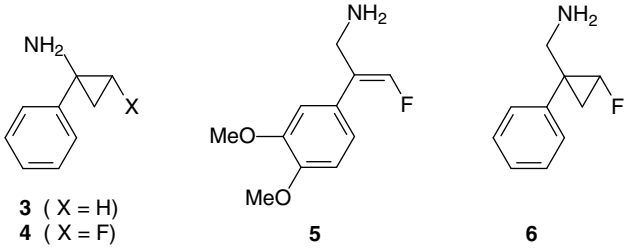
We have previously reported the syntheses of various racemic and enantiopure fluorinated tranylcypromine analogues and have described the results of their evaluation as inhibitors of the FAD-dependent amine oxidases, MAO A and B, and of tyramine oxidase, a copper-containing amine oxidase.[13–16] In the 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-cyclopropylamine (**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 (Fig. 1). For example, Palfreyman et al. found 3-fluoroallylamine **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 μM 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 μM).[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 tranylcypromine (**1**). The MAO A/B selectivity was found to be approximately 1:15 (320:24 μM), but it showed stronger inhibition of tyramine oxidase (IC_{50} = 12 μM).[12,15]

A further promising class of tranylcypromine derivatives is 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** (Fig. 2). The *cis*-isomers were also tested which 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 (–CH_3) 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 and 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-tranylcypromine derivatives.

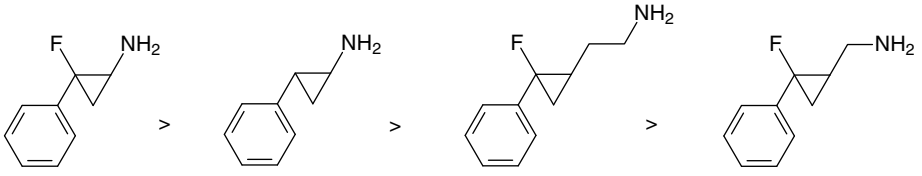


3 (X = H)
4 (X = F)
5
6

Figure 1. Monoamine oxidase inhibitors.

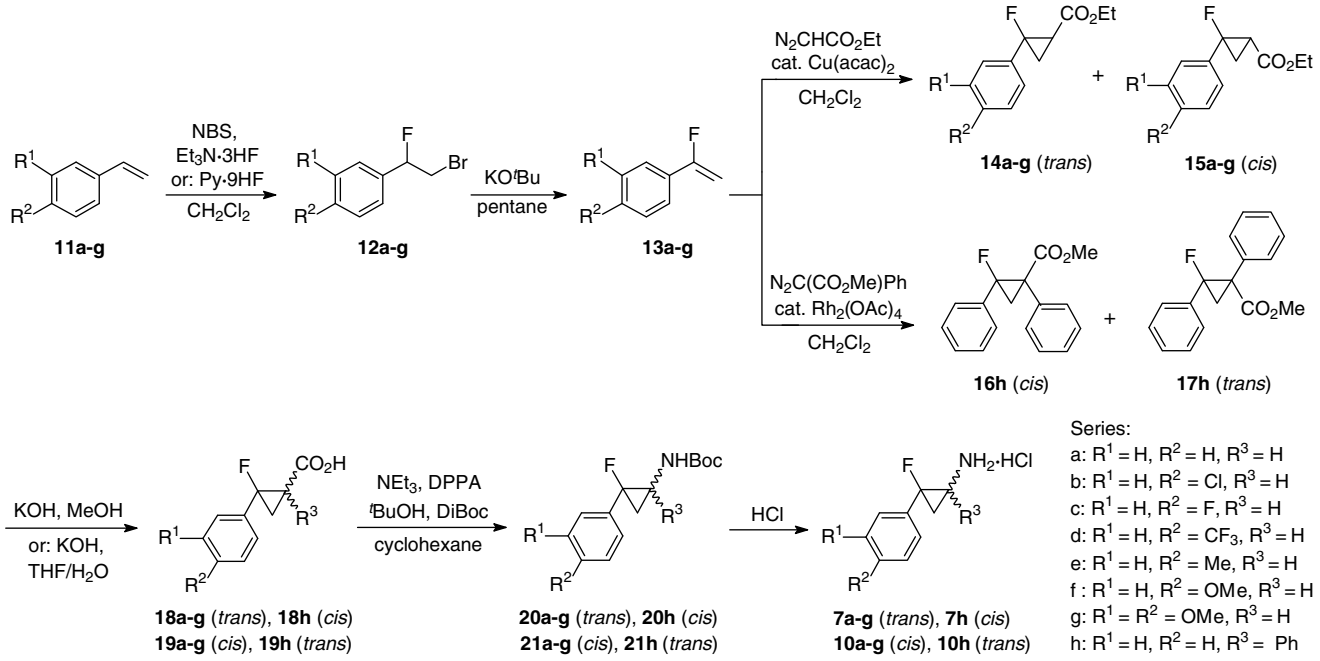
2.1. Synthesis of fluorinated arylcylopropylamines

The racemic, monofluorinated tranylcypromine derivatives were synthesized by a six step sequence from substituted styrenes **11a**–**g**. Bromofluorination with NBS and a nucleophilic fluorinating agent ($Et_3N{\cdot}3HF$ 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



7a (*trans*) **1** (*trans*) **8** (*trans*) **9** (*trans*)

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



Scheme 1. Synthesis of substituted tranylcypromine analogues.[‡]

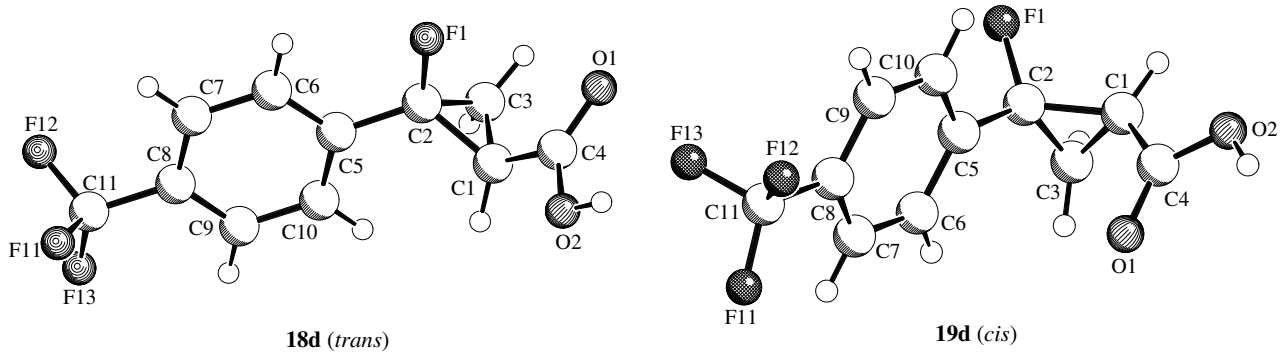


Figure 3. Crystal structures of the racemic *para*-trifluoromethylcyclopropane carboxylic acids **18d** and **19d**.

1:1.[‡] The reaction of α-fluorostyrene (**13a**) with methyl phenyl diazo acetate leads 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** which 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 tranylcypromine 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** (Fig. 3) and several more analogues (see Section 5).

2.2. Physical–chemical properties

The pharmacokinetics of biologically active compounds can be predicted by means of physical–chemical properties. These properties include the pK_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 (Fig. 4 and Table 1).

As expected, introduction of the highly electronegative fluorine atom into the 2-position of the cyclopropane ring decreases the pK_a value. Similar observations have been reported for other fluorinated amines.[23,24] For *trans*-2-fluorotranylcypromine (**7a**) the pK_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 unit difference between the corresponding *cis*-isomers **2** and **10a**. While the two isomeric non-fluorinated tranylcypromines exhibit similar acidities (ca. 8.50), the fluorinated *cis*-isomer **10a** (pK_a = 6.98) is about 0.4 units more acidic than the fluorinated *trans*-isomer **7a** (pK_a = 7.35). This difference can also be observed for the aryl-ring substituted fluoro-tranylcypromine 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 σ(C–N) and σ^*(C–F) in the fluorinated

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

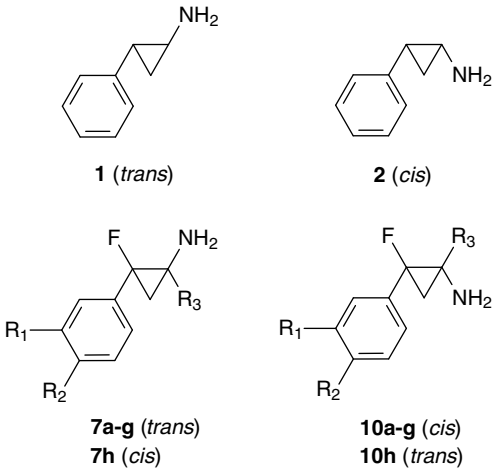


Figure 4. Compounds investigated in this study.

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** vs 2.39 for **10h**). Thus, although the pK_as 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 NH_2, 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 sp^2-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*-CF_3), **7f** and **10f** (*para*-OMe), **7g** and **10g** (*para*- and *meta*-OMe), and **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]

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]	–[d]
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 titrametrically in 0.1 M KNO_3 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] 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* refer to the arrangement of the two phenyl rings.

Among the *para*-substituted compounds, the *trans*-isomers (relationship of NH_2 to aryl) were better inhibitors for both MAO A and B than the *cis*-isomers. The *para*-CF_3 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 (Fig. 6A). Introduction of other *para*-substituents, such as Cl, F, and CF_3 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, Fig. 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

Table 2
IC_{50} 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)[a]		Selectivity
				MAO A	MAO B	MAO A:B
H	H	H	**1**[b]	20 ± 0 (irr.)	19 ± 0 (irr.)	1:1
			2[b]	11 ± 1 (irr.)	19 ± 1 (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]	470 ± 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* refer to the arrangement of the two phenyl rings.

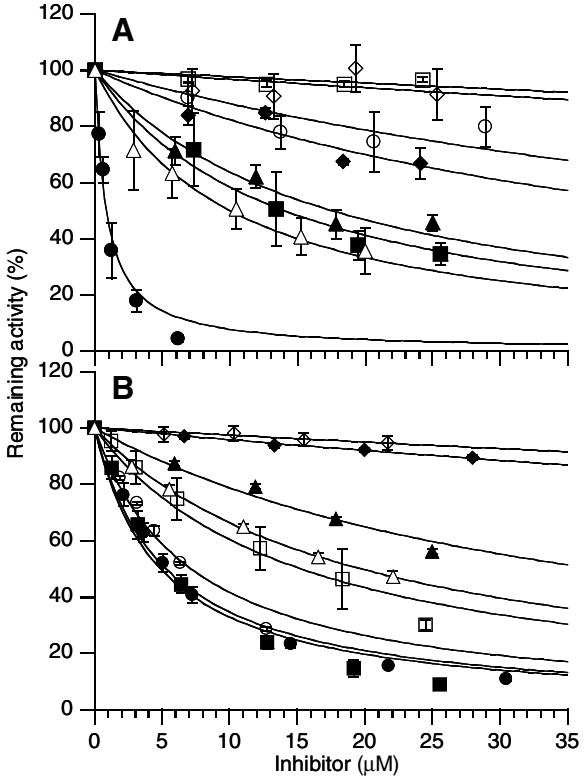


Figure 5. Effect of concentration of fluorinated phenylcyclopropylamines (closed circle, **7d**; open circle, **10d**; closed square, **7f**; open square, **10f**; closed diamond, **7g**; open diamond, **10g**; closed triangle, **7f**; open triangle, **10f**) on MAO A (**A**) and B (**B**) activity.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

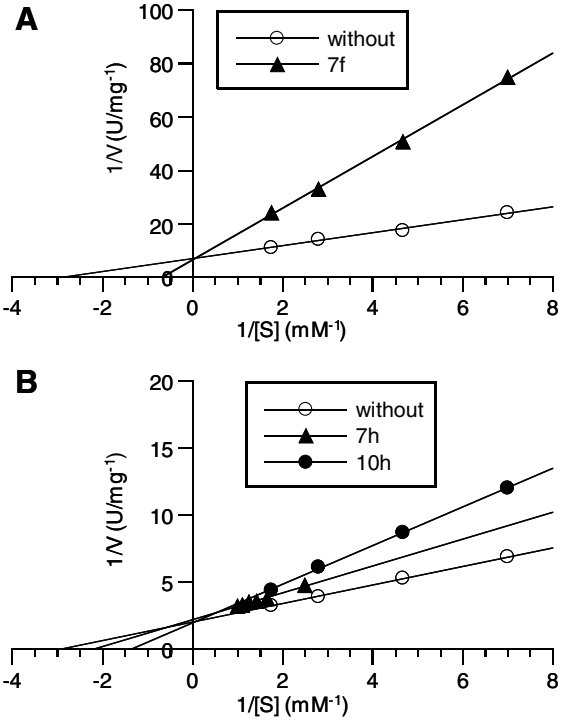


Figure 6. Lineweaver-Burk plot for inactivation of MAO A by *trans*-2-fluoro-2-(4-methoxy)phenylcyclopropylamine·HCl (**7f**, 9.7 μM) (**A**) and MAO B by *cis*-(±)-2-fluoro-1,2-diphenylcyclopropylamine·HCl (**7h**, 28.2 μM) and *trans*-2-fluoro-1,2-diphenylcyclopropylamine·HCl (**10h**, 8.4 μM) (**B**). Data were collected after the inhibition by **7f**, **7h**, and **10h** was checked to be independent of time and concentration.

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 tranylcypromine 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 (Fig. 7).[28,29]

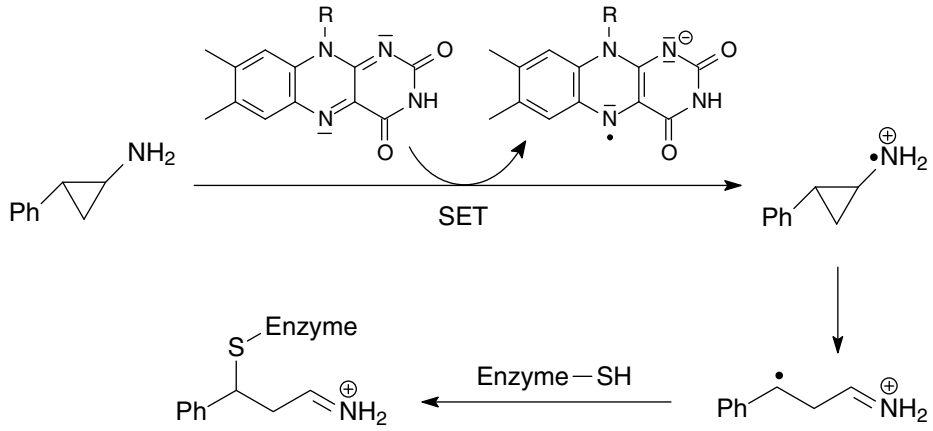


Figure 7. SET mechanism adapted from Ref. 28.

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-phenylcyclopropylamines and *N*-benzylcyclopropylamines.[30–39] Moreover, the results of biotransformation of tranylcypromine in rat liver microsomes also support such a pathway.[40] This also would be consistent with the increased activity of our fluorinated analogues of tranylcypromine since a fluorine substituent increases the strain of a cyclopropane ring.[41–44] 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 (Fig. 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_α-atom of the amine. Extrusion of the cofactor with the formation of an imine intermediate **III** and subsequent hydrolysis to benzaldehyde, ammonia and the fully reduced flavin, completes the process.

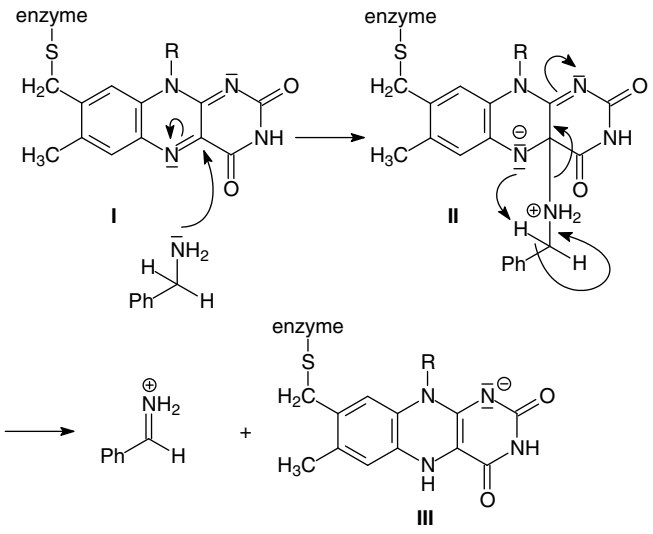


Figure 8. Polar nucleophilic mechanism.[2]

The most striking evidence against the SET mechanism is the big difference in one-electron oxidation-reduction potentials of primary or secondary amines (1.0–1.5 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 tranylcypromine 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 tranylcypromine 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** (Fig. 9), which (X = H) was found in the crystal structure of the tranylcypromine-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

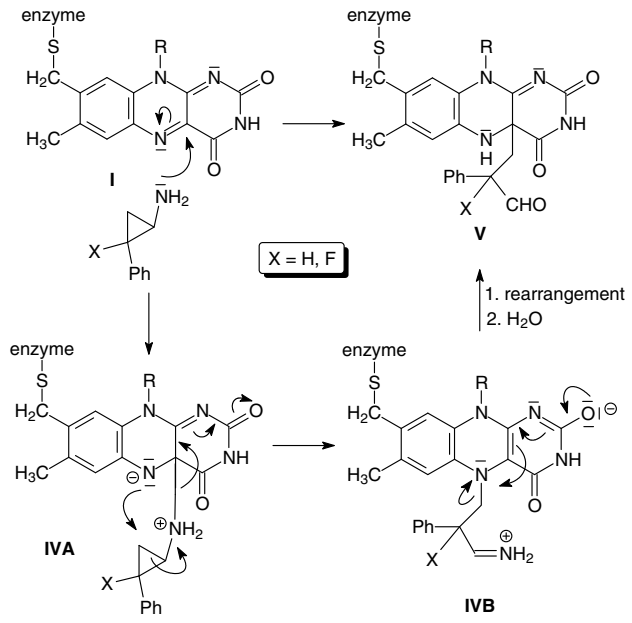


Figure 9. Suggested inhibition mechanism of tranylcypromine derivatives.

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 serves to increase the nucleophilicity of the amine (see Fig. 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 Å^3 and is overall shorter but wider than that of MAO B. The latter cavity has a volume of 700 Å^3 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 fluorotranylcypromine derivatives on MAO A and B

As described above, fluorine-containing tranylcypromines have a 1–1.5 units lower pK_a than their non-fluorinated parent compounds. Fluorine thus decreases the electron density of the neighboring NH_2-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 pK_a would lower the concentration of protonated amine. However, a lower pK_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 IC_{50} value of an inhibitor. This might explain the higher activity of fluorotranylcypromines in comparison to tranylcypromine. 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*-CF_3 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*-substitutent, 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*-substitutent. 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 that some alterations in the 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 CF_3-substituents have lower IC_{50} values compared to non-substituted 2-fluorotranylcypromine **7a** (*trans*) as inhibitors of both MAO A and B. In contrast, the IC_{50} 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: $CF_3 > Cl > F > H \sim Me$ ($IC_{50} = 0.8 > 1.6 > 3.6 > 12 \sim 13$ μM)
MAO B: $Cl > F \sim OMe \sim CF_3 > H > Me$ ($IC_{50} = 3.7 > 4.9 \sim 5.1 \sim 5.4 > 6.4 > 13$ μM)

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-fluor-

otranylcypromine **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 (Fig. 10). Furthermore, the IC_{50} values calculated for the level of deprotonated amine at pH 7.2 by Eq. 1 showed good linear correlation with hydrophobicity '$\log D$' for the inhibition of MAO A. (Table 3 and Fig. 11B). Interestingly, as shown in Figure 10, 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 effect 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.

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

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 (Figs. 10 and 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 ≈500 Å^3, which combines substrate recognition and conversion. MAO B consists of two cavities which has a total size of ≈700 Å^3 ('entrance cavity' with a volume of 290 Å^3, and a larger hydrophobic substrate cavity with a volume of about 400 Å^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

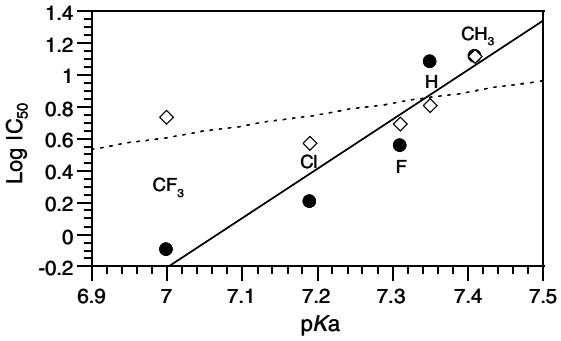


Figure 10. Correlation of MAO A and B activities with pK_a values of 2-fluoro-2-phenylcyclopropylamines. Fitting lines for MAO A and B are $\log IC_{50} = 3.09 \times pK_a - 21.87$ ($R^2 = 0.89$), and $\log IC_{50} = 0.71 \times pK_a - 4.40$ ($R^2 = 0.32$), respectively.

Table 3
IC_{50} 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}[a] (μM)	
				MAO A	MAO B	MAO A	MAO B
H	H	H	**7a**	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

[a] Corrected IC_{50} values were derived with the use of Eq. 1.

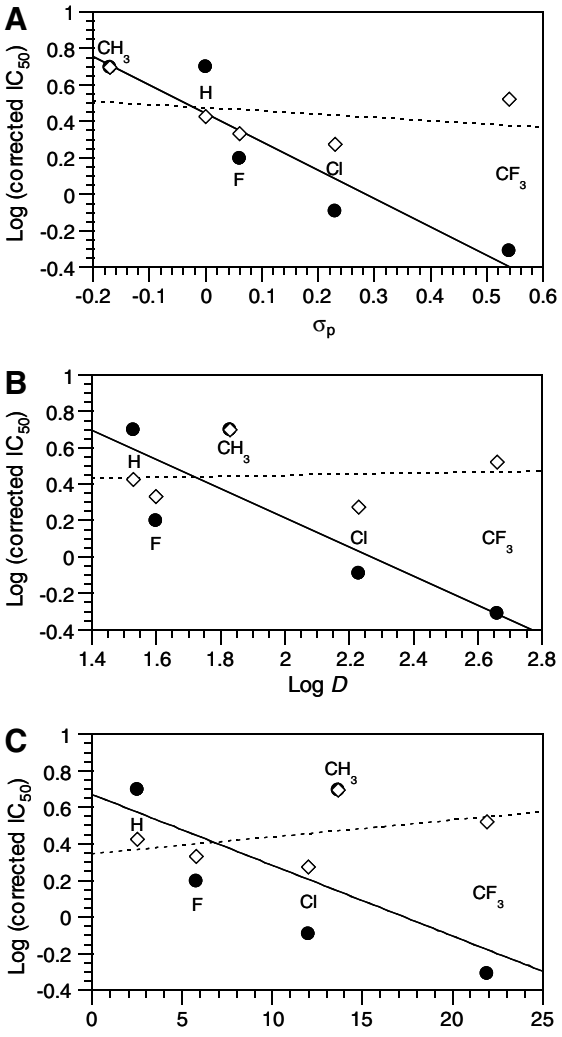


Figure 11. Correlation of corrected IC_{50} values with σ_p (A), $\log D$ (B), and van der Waals volume (C) of 2-fluoro-2-phenylcyclopropylamines for MAO A (closed circle) and B (open diamond). Equations of the fitting lines are as follows: MAO A, $\log IC_{50} = -1.56 \times \sigma_p + 0.44$ ($R^2 = 0.85$); $\log IC_{50} = -0.80 \times \log D + 1.81$ ($R^2 = 0.69$); $\log IC_{50} = -0.04 \times V_w + 0.67$ ($R^2 = 0.49$); MAO B, $\log IC_{50} = -0.18 \times \sigma_p + 0.47$ ($R^2 = 0.08$); $\log IC_{50} = 0.03 \times \log D + 0.40$ ($R^2 = 0.01$); $\log IC_{50} = 0.01 \times V_w + 0.35$ ($R^2 = 0.17$).

(Fig. 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 tranylcypromine (**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 (Fig. 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 have not found a relation between hydrophobicity and binding affinity of our inhibitors, whereas Edmondson observed such a relation for benzylamines, which are substrates. Once more does this stress 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 parameters might also reflect difference of hydrophobicity of the active site cavity of MAO A and B. Hydrophobic interaction might also be an 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 μM), comparable to the activity of tranylcypromine (**1**), is somewhat higher than that 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 tranylcypromine (**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-time 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 μM, which is two times higher than that of tranylcypromine (**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-time higher IC_{50}-value (230 μM) for **7g** than was observed for **2**. 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**

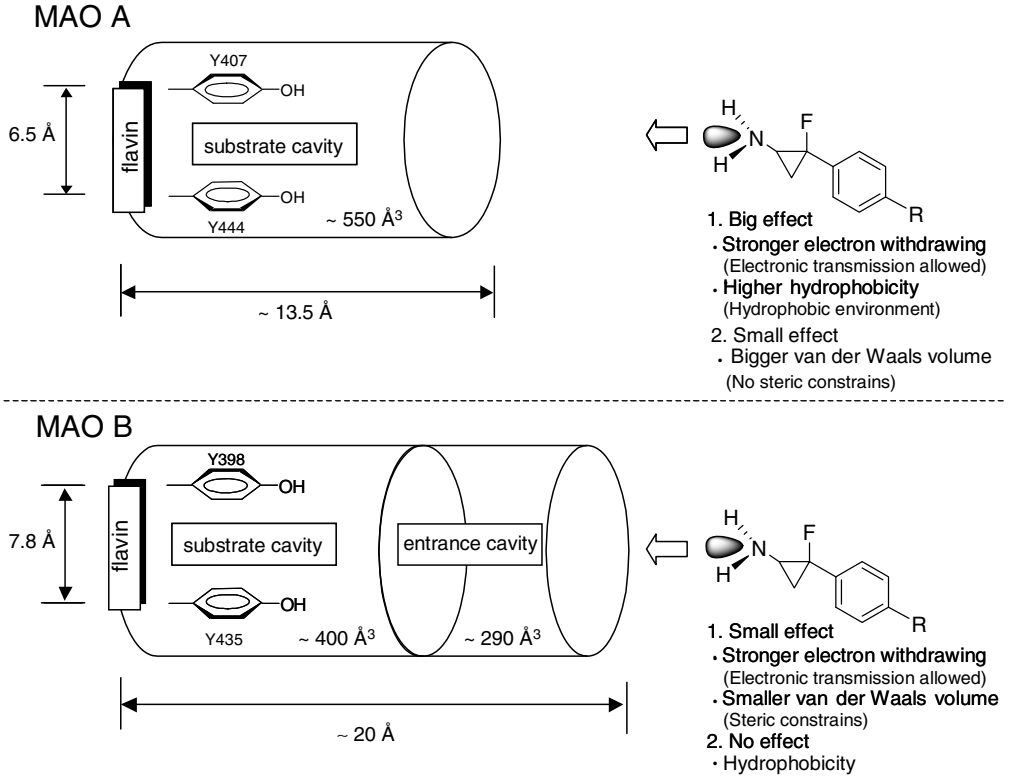


Figure 12. Differences in inhibition of MAO A and B by fluorinated phenylcyclopropylamines.[2,53]

(*cis*) are similar to those of the *para*-chloro derivative **7b** (*trans*) and therefore one could expect similar IC_{50} values, at least towards MAO A, if these parameters are the only consideration. But the IC_{50} value of **7h** (18 μM) was found to be ten times higher compared to **7b** and similar to the value of tranylcypromine (**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 IC_{50} 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 tranylcypromine (**2**) towards MAO B and *trans*-2-fluorotranylcypromine (**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 a 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 towards MAO B.[61]

4. Conclusion

A series of racemic tranylcypromine (*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 10–100 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 IC_{50} 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

5.1. General methods

NMR spectra were recorded on a Varian 600 Unity Plus (600.0 MHz for ^1H, 150.66 MHz for ^{13}C and 564.3 MHz for ^{19}F), Varian INOVA 500 (499.84 MHz for ^1H, 125.70 MHz for ^{13}C and 470.28 MHz for ^{19}F) and a Bruker ARX300 (300.13 MHz for ^1H, 75.48 MHz for ^{13}C and 282.37 MHz for ^{19}F) in $CDCl_3$ solution. Chemical shifts are reported in ppm relative to TMS or $CFCl_3$ as internal standards. The multiplicities of the ^{13}C signals, other than ^{13}C-^{19}F 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. 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. All analytical measurements were performed by the staff of Organisch-Chemisches Institut, Universität Münster. Thin layer chromatography was performed with TLC plates 60 F_{254} by Merck. Column chromatography was performed using silica gel (Merck, particle size 0.063–0.200 mm, 70–230 mesh) and preparative MPLC was carried out on silica gel (Merck, particle size 0.040–0.063 mm, 230–400 mesh). Solvents and 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, GA, USA,[62,63] were used for the inhibition experiments. The assays were carried out by the method previously reported.[12–14] 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 X-100 (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 min. The activity of MAO B was also measured spectrophotometrically at 25 °C by the modified method of Houslay and Tipton,[64] 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 min. Protein concentration was determined by the method of Bradford[65] 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 min at 10 °C. The reaction was started by the addition of substrate

stock, and the time course of the absorption increase of the reaction product was monitored as described above.

5.3. Determination of the inhibition type

The type of inhibition was determined by examining time- and concentration-dependent inactivation[66] 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, Olah's reagent, 3.2 mL, 13.8 mmol, 1.1 equiv) and subsequently *N*-bromosuccinimide (NBS, 2.46 g, 13.8 mmol, 1.1 equiv) were added in small portions. After 30 min at 0 °C the solution was allowed to warm to room temperature and stirred overnight. 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× 70 mL). The combined organic layers were washed with 6 M hydrochloric acid and 5% NaOH solution (each 1× 70 mL). The phases were dried over magnesium sulfate and the solvent was removed in vacuo. After silica gel chromatography (25× 3 cm, pentane) **12d** was obtained as a colorless liquid (yield: 2.51 g, 74%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.59–3.72 (m, 2-CH_2Br), 5.70 (dt, 1 H, $J_{H,F}$ = 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, $J_{F,H}$ = 40.2 Hz, $J_{F,H}$ = 20.1 Hz, 1-CHF). MS (GCToF, 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 procedure[20] 4-methoxystyrene (**11f**) (4.37 g, 32.6 mmol) was treated with triethylamine–trishydrofluoride (Et_3N·3HF) 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 the 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 (Et_3N·3HF) and NBS. Several side products were separated partially by silica gel chromatography (15 × 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. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.98 (dd, 1 H, 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 (GCToF, 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 procedure[21] 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 two steps). Bp 80 °C/3 mbar. The spectroscopic data agreed with published ones.[67]

5.5.3. 1-(1-Fluorovinyl)-3,4-dimethoxybenzene (13g)

According to the general procedure[21] 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. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.89 (s, 6H, 9-OCH_3 and 10-OCH_3), 4.75 (dd, 1H, J = 18.9 Hz and 3.6 Hz, H_A), 4.89 (dd, 1 H, J = 49.9 Hz and 3.5 Hz, H_B), 6.75-7.16 (m, 3H, 4-CH, 7-CH and 8-CH). ^{13}C NMR ($CDCl_3$, 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). ^{19}F NMR ($CDCl_3$, 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 equiv, 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%): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.30 (t, 3H, J = 7.1 Hz, 13-CH_3), 1.66 (ddd, 1H, J = 10.5 Hz, 9.5 Hz and 7.0 Hz, H_B), 2.23 (ddd, 1H, J = 9.3 Hz, 7.8 Hz and 3.0 Hz, H_X), 2.37 (ddd, 1H, J = 20.2 Hz, 7.8 Hz and 7.1 Hz, H_A), 4.24 (qm, 2H, J = 7.2 Hz, 12-CH_2), 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). ^{13}C NMR ($CDCl_3$,

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). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −63.34 (s, CF_3), −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^+) $C_{13}H_{12}F_4O_2$ + Na^+: calcd 299.0666, found 299.0655. $C_{13}H_{12}F_4O_2$ (276.2): calcd C 56.53% H 4.38%, found C 56.99% H 4.27%.

Data for ***15d***. Yield: 326 mg (46%): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.03 (t, 3 H, J = 7.2 Hz, 13-CH_3), 1.87 (ddd, 1H, J = 19.4 Hz, 10.5 Hz and 7.2 Hz, H_A), 2.02 (ddd, 1H, J = 15.1 Hz, 7.4 Hz and 7.4 Hz, H_B), 2.60 (ddd, 1H, J = 18.2 Hz, 10.4 Hz and 7.8 Hz, H_X), 3.94 (qm, 2H, J = 7.2 Hz, 12-CH_2), 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). ^{13}C NMR ($CDCl_3$, 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). $C_{13}H_{12}F_4O_2$ (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 equiv) in the presence of $Cu(acac)_2$ (98 mg, 0.375 mmol, 5 mol% relating to one portion of EDA). After silica gel column chromatography (20× 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***. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.27–1.33 (m, 3 H, 13-CH_3), 1.55 (ddd, J = 10.3 Hz, 9.2 Hz and 6.9 Hz, 1H, H_B), 2.12 (ddd, J = 9.2 Hz, 7.6 Hz, and 3.2 Hz, 1H, H_X), 2.23 (ddd, J = 19.5 Hz, 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 (2m, 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). $C_{13}H_{15}FO_3$ (238.25) calcd C 65.54% H 6.35%, found C 65.63% H 6.63%.

Data for ***15f***. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.03 (t, J = 7.2 Hz, 3H, 13-CH_3), 1.76 (ddd, J = 19.1 Hz, 10.2 Hz, and 6.9 Hz, 1H, H_A), 1.91 (ddd, J = 12.1 Hz, 7.5 Hz, and 6.9 Hz, 1H, H_B), 2.52 (ddd, J = 17.5 Hz, 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 (2m, 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). $C_{13}H_{15}FO_3$ (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-dimethoxy benzene (**13g**) (2.73 g, 15 mmol) was treated with (2.30 g, 2.1 mL, 22.5 mmol, 1.5 equiv) in the presence of $Cu(acac)_2$ (294 mg, 1.125 mmol, 5 mol% relating to one portion of EDA). After silica gel column chromatography (20 × 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^+): $C_{14}H_{17}FO_4$ + Na^+ calcd 291.1003, found 291.1001. $C_{14}H_{17}FO_4$ (268.3): calcd C 62.68%, H 6.39%, found C 61.96% H 6.42%. Subsequently the mixture of diasteromers was separated on a silica gel column (30 × 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): ^{1}H 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, 9.0 Hz and 6.6 Hz, H_B), 2.15 (ddd, 1H, J = 10.0 Hz, 7.7 Hz and 2.8 Hz, H_X), 2.24 (ddd, 1H, J = 19.4 Hz, 7.6 Hz and 6.6 Hz, H_A), 3.88 and 3.90 (2s, 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, 1 F, J = 19.1 Hz, 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). ^{1}H 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, 10.3 Hz, and 7.0 Hz, H_A), 1.93 (ddd, 1H, J = 14.4 Hz, 6.9 Hz, and 6.9 Hz, H_B), 2.53 (ddd, 1H, J = 17.7 Hz, 10.3 Hz, and 7.6 Hz, H_X), 3.88 and 3.89 (2s, each 3H, 11-OCH_3 and 12-OCH_3), 3.95 (q, 2 H, 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 (2q, 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. Mp 117 °C (cyclohexane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.76 (ddd, 1H, J = 7.4 Hz, 9.4 Hz and 10.9 Hz, H_B), 2.25 (ddd, 1H, J = 7.9 Hz, 9.4 Hz, and 2.9 Hz, H_X), 2.40 (ddd, 1H, J = 7.6 Hz, 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, 2 H, 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^+) $C_{11}H_8F_4O_2 + Na^+$: calcd 271.0353, found 271.0359. HRMS (ESI^-) $C_{11}H_7F_4O_2 - H^+$: 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. Mp 80 °C (cyclohexane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.92 (ddd, 1H, J = 19.1 Hz, 10.2 Hz, and 7.4 Hz, H_A), 1.99 (ddd, 1H, J = 13.3 Hz, 7.6 Hz, and 7.6 Hz, H_B), 2.55 (ddd, 1H, J = 18.0 Hz, 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-CO_2H). ^{13}C NMR ($CDCl_3$, 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). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −63.40 (s, 3F, 11-CF_3), −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^-) $C_{11}H_8F_4O_2 - H^+$: calcd 247.0377, found 247.0390. $C_{11}H_8F_4O_2$ (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 diasteromeres 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%). Mp 112 °C (cyclohexane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.65 (ddd, 1H, J = 10.5 Hz, 9.2 Hz, and 6.9 Hz, H_B), 2.14 (ddd, 1H, J = 7.6 Hz, 9.6 Hz, and 2.2 Hz, H_X), 2.26 (ddd, 1H, J = 19.5 Hz, 7.3 Hz, and 7.3 Hz, H_A), 3.80 (s, 3H, 11-OCH_3), 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-CO_2H). ^{13}C NMR ($CDCl_3$, 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). ^{19}F NMR ($CDCl_3$, 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^+) $C_{11}H_{11}FO_3 + Na^+$ calcd 233.0584, found 233.0597, $C_{11}H_{11}FO_3 - H^+$: calcd 209.0619, found 209.0630. $C_{11}H_{11}FO_3$ (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%). Mp 102 °C (cyclohexane/ethyl acetate, **19f**/**18f** = 89:11). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.80 (ddd, 1H, J = 18.2 Hz, 10.1 Hz, and 7.0 Hz, H_A), 1.86 (ddd, 1H, J = 13.7 Hz, 7.3 Hz, and 7.3 Hz, H_B), 2.47 (ddd, 1H, J = 17.4 Hz, 10.0 Hz, and 7.5 Hz, H_X), 3.80 (s, 3H, 11-OCH_3), 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-CO_2H). ^{13}C NMR ($CDCl_3$, 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). ^{19}F NMR ($CDCl_3$, 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). $C_{11}H_{11}FO_3$ (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%). $C_{12}H_{13}FO_4$ (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**.* ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.65 (dt, 1H, J = 10.0 Hz, 9.2 Hz, and 6.8 Hz, H_B), 2.12 (ddd, 1H, J = 7.7 Hz, 10.0 Hz, and 2.8 Hz, H_X), 2.22 (ddd, 1H, J = 19.8 Hz, 7.1 Hz, and 7.5 Hz, H_A), 3.90 (2s, 6H, 11-OCH_3 and 12-OCH_3), 6.83–7.06 (m, 3H, 6-CH, 9-CH and 10-CH), 8.65 (br s, 4-CO_2H). ^{13}C NMR ($CDCl_3$, 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 (2q, 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). ^{19}F NMR ($CDCl_3$, 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**.* ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.84 (ddd, 1H, J = 18.8 Hz, 10.0 Hz, and 7.2 Hz, H_A), 1.92 (ddd, 1H, J = 12.2 Hz, 7.2 Hz, and 7.2 Hz, H_B), 2.53 (ddd, 1H, J = 17.5 Hz, 10.0 Hz, and 7.5 Hz, H_X), 3.90 (2s, 6H, 11-OCH_3 and 12-OCH_3), 6.83–7.06 (m, 3H, 6-CH, 9-CH and 10-CH), 8.65 (br s, 1H, 4-CO_2H). ^{13}C NMR ($CDCl_3$, 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). ^{19}F NMR ($CDCl_3$, 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 petane diethyl ether furnished **20d** as a white solid (yield: 198 mg, 62%). Mp 164–165 °C (pentane/diethyl ether). ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ 1.40–1.67 (m, 2H, H_B and H_X), 1.46 (s, 9H, 13-CH_3–15-CH_3), 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). ^{1}H NMR (C_6D_6, 500 MHz, 298 K): δ 0.86–0.99 (br m, 2H, H_B and H_X), 1.44 (s, 9H, 13-CH_3–15-CH_3), 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). ^{1}H NMR (C_6D_6, 500 MHz, 343 K): δ 0.94–1.00 (m, 2H, H_B and H_X), 1.43 (s, 9H, 13-CH_3–15-CH_3), 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 −195.8 3 (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 −197.0 2 (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). $C_{15}H_{17}F_4NO_2$ (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%). Mp 168–170 °C (pentane/diethyl ether). ^{1}H 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, 9.6 Hz, and 21.7 Hz, H_A), 3.31 (ddd, 1H, J = 6.2 Hz, 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). ^{1}H 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, 8.6 Hz, and 21.6 Hz, H_A), 3.31 (ddd, 1H, J = 7.7 Hz, 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 −177.3 1 (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). $C_{15}H_{17}F_4NO_2$ (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%). Mp 104 °C (cyclohexane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.35 (ddd, J = 21.8 Hz, 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 −185.7 7 (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 diasteromeric mixture was separated by recrystallization from cyclohexane/ethyl acetate to give diasteromerically pure **21f** (yield: 131 mg, 31% relating to the ratio of **19f** in the diastereomeric mixture of the reactand). Mp 131 °C (cyclohexane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.29–1.42 (m, 1H, H_B), 1.35 (s, 9H, 14-CH_3−16-CH_3), 1.72 (ddd, J = 21.4 Hz, 9.5 Hz and 9.5 Hz, 1H, H_A), 3.29 (m, 1H, H_X), 3.82 (s, 3H, 11-OCH_3), 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). ^{13}C NMR ($CDCl_3$, 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). ^{19}F NMR ($CDCl_3$, 282 MHz, 298 K): δ −164.27 (br s, 0.76H, 2-CF) and −168.47 (br m, 0.24H, 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-dimethoxyphenyl)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). Mp 108 °C (cyclohexane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.36 (ddd, J = 21.8 Hz, 7.9 Hz, and 6.0 Hz, 1H, H_A), 1.48 (s, 9H, 14-CH_3−16-CH_3), 1.45–1.54 (m, 1H, H_B), 2.96 (br s, 1H, H_X), 3.87 and (2s, 3H, 11-OCH_3 and 12-OCH_3), 4.98 (br s, 1H, NH), 6.83–6.97 (m, 3H, 6-CH, 9-CH and 10-CH). ^{13}C NMR ($CDCl_3$, 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 (2q, 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). ^{19}F NMR ($CDCl_3$, 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^+-$(CH_3O)_2C_6H_3$], 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). Mp 135 °C (cyclohexane/ethyl acetate).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.29–1.42 (m, 1H, H_B), 1.36 (s, 9H, 14-CH_3−16-CH_3), 1.73 (ddd, J = 8.1 Hz, 9.2 Hz, and 21.1 Hz, 1H, H_A), 3.27–3.32 (m, 1H, H_X), 3.89 and 3.90 (2s, 3H, 11-OCH_3 and 12-OCH_3), 4.25 (br s, 1H, NH), 6.86–7.05 (m, 3H, 6-CH, 9-CH and 10-CH). ^{13}C NMR ($CDCl_3$, 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 (2q, 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). ^{19}F NMR ($CDCl_3$, 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). $C_{16}H_{22}FNO_4$ (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-diphenylcyclopropanecarboxylic 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). Mp 108 °C (pentane/diethyl ether). ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ 1.43 (s, 9H, 18-CH–20-CH_3), 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). ^{1}H NMR (C_6D_6, 600 MHz, 298 K): δ 1.39 (s, 9H, 18-CH_3–20-CH_3), 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). ^{1}H NMR (C_6D_6, 600 MHz, 348 K): δ 1.40 (s, 9H, 18-CH_3–20-CH_3), 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). ^{13}C NMR (C_6D_6, 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). ^{19}F NMR ($CDCl_3$, 282 MHz, 298 K): δ −170.90 (m, 0.71F, 2-CF) and −170.23 (br s, 0.29 F, 2-CF), signals of rotamers. ^{19}F NMR (C_6D_6, 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. ^{19}F NMR (C_6D_6, 564 MHz, 343 K): δ −170.58 (br s, 1F, 2-CF). MS (GCToF, EI, in a range from m/z 240 to 430) m/z 327 (0) [M^+], 307 (1) [M^+−HF], 295 (3), 294 (1) [M^+−CH_2F], 273 (1), 272 (18), 271 (100) [M^+−C_4H_7], 270 (15) [M^+−C_4H_8], 254 (12), 253 (41), 251 (75) [271-HF], 248 (10). MS (GCToF, EI, in a range from m/z 40 to 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^+) $C_{20}H_{22}FNO_2$ + 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). Mp 128 °C (pentane/diethyl ether). ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ 1.28 (s, 9H, 18-CH_3−20-CH_3), 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). ^{1}H NMR (C_6D_6, 600 MHz, 298 K): δ 1.91 (s, 9H, 18-CH_3−20-CH_3), 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). ^{1}H NMR (C_6D_6, 600 MHz, 348 K): δ 1.20 (s, 9H, 18-CH_3−20-CH_3), 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 (br s, 0.63F, 2-CF), signals of rotamers. MS (GCToF, 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 (GCToF, 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^+) $C_{20}H_{22}FNO_2$ + 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%). Mp 165 °C (methanol/diethyl ether, decomposition). ^{1}H 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, NH_2·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) [M-–I$^-$], 203 (89), 200 (100), 183 (6), 180 (13), 131 (7). HRMS (ESI$^+$) $C_{10}H_{10}ClF_4N$−Cl$^-$: calcd 220.0749, found 220.0742. $C_{10}H_{10}ClF_4N$ (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%). Mp 156 °C (methanol/diethyl ether, decomposition). ^{1}H 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, 10.2 Hz, and 6.3 Hz, H_X), 4.79 (s, 3H, NH_2·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$^+$): $C_{10}H_{10}ClF_4N$−Cl$^-$: calcd 220.0749, found 220.0742. $C_{10}H_{10}ClF_4N$ (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%). Mp 166 °C (methanol/diethyl ether, decomposition). ^{1}H 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-OCH_3), 4.91 (s, 3H, NH_2·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). ^{13}C NMR (methanol-d_4, 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). ^{19}F NMR (methanol-d_4, 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-CH_3], 132 (23) [162-CH_2O], 131 (28) [162-CH_3O], 130 (14) [147-NH_3], 119 (10) [147-CHO], 118 (6) [147-CH_2O]. HRMS (ESI$^+$) $C_{10}H_{13}ClFNO$−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%). Mp 156 °C (methanol/diethyl ether, decomposition). ^{1}H NMR (methanol-d_4, 300 MHz): δ 1.71 (ddd, 1 H, J = 9.4 Hz, 9.4 Hz, and 5.8 Hz, H_B), 1.88 (ddd, 1H, J = 19.2 Hz, 9.9 Hz, and 9.0 Hz, H_A), 3.36 (ddd, 1H, J = 13.7 Hz, 10.1 Hz, and 5.9 Hz, H_X), 3.84 (s, 3H, 10-OCH_3), 4.89 (s, 3H, NH_2·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). ^{13}C NMR (methanol-d_4, 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). ^{19}F NMR (methanol-d_4, 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-NH_3], 162 (29) [182-HF], 153 (71) [182-CHO], 145 (15) [162-NH_3], 139 (9), 135 (20) [165-HF], 119 (4) [139-HF], 117 (6) [145-CO], 115 (4) [145-CH_2O], 91 (7) [$C_7H_7^+$], 30 (100) [CH_2O^+]. HRMS (ESI$^+$) $C_{10}H_{13}ClFNO$−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%). Mp 155 °C (methanol/diethyl ether, decomposition). ^{1}H NMR (methanol-d_4, 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 (2s, 3H, 10-OCH_3 and 11-OCH_3), 4.77 (s, 3H, NH_2·HCl), 6.98–7.10 (m, 3H, 5-CH, 8-CH and 9-CH). ^{13}C NMR (methanol-d_4, 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 (2q, 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). ^{19}F NMR (methanol-d_4, 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$^+$) $C_{11}H_{15}ClFNO_2$−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%). Mp 156 °C (methanol/diethyl ether, decomposition). ^{1}H NMR (methanol-d_4, 300 MHz): δ 1.74 (ddd, 1H, J = 9.3 Hz, 9.3 Hz, and 5.9 Hz, H_B), 1.89 (ddd, 1H, J = 19.3 Hz, 9.9 Hz, and 9.3 Hz, H_A), 3.37 (ddd, 1H, J = 13.4 Hz, 10.0 Hz, and 5.9 Hz, H_X), 3.87 and 3.92 (2s, 3H, 10-OCH_3 or 11-OCH_3), 3.92 (s, 3H, 10- or 11-OCH_3), 4.88 (s, 3H, NH_2·HCl), 7.08 (dm, 1H, J = 8.2 Hz, 8-CH), 7.21 (dd, 1H, J = 8.2 Hz, $J_{H,F}$ = 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 (2q, 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$^+$) $C_{11}H_{15}ClFNO_2$−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%). Mp 155 °C (methanol/diethyl ether, decomposition). ^{1}H 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, NH_2·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$^+$) $C_{15}H_{15}ClFN-Cl^-$: 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%). Mp 143 °C (methanol/diethyl ether, decomposition). ^{1}H NMR (methanol-d_4, 300 MHz): δ 2.26–2.39 (m, 2H, H_A and H_B), 4.79 (br s, 3H, NH_2·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$^+$) $C_{15}H_{15}ClFN-Cl^-$: calcd 228.1183, found 228.1176.

5.10. X-ray structures

Datasets 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-SMN[70], absorption correction SORTAV[71] and Denzo[72], structure solution SHELXS-97,[73] structure refinement SHELXL-97,[74] graphics SCHAKAL.[75]

5.10.1. X-ray crystal structure analysis for 18d

Formula $C_{11}H_8F_4O_2$, M = 248.17, colorless crystal 0.40 × 0.35 × 0.15 mm, a = 23.478(1), b = 7.074(1), c = 14.505(1) Å, β = 118.19(1)°, V = 2123.3(3) Å^3, ρ_{calc} = 1.553 g cm^{-3}, μ = 1.354 mm^{-1}, empirical absorption correction (0.613 ⩽ T ⩽ 0.823), Z = 8, monoclinic, space group $C2/c$ (No. 15), λ = 1.54178 Å, T = 223 K, ω and φ scans, 6490 reflections collected (±h, ±k, ±l), [(sin θ)/λ] = 0.60 Å^{-1}, 1891 independent (R_{int} = 0.030) and 1748 observed reflections [I ⩾ 2σ(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 $C_{11}H_{11}FO_3$, M = 210.20, colorless crystal 0.30 × 0.20 × 0.10 mm, a = 5.528(1), b = 7.348(1), c = 25.592(1) Å, β = 94.91(1)°, V = 1035.7(2) Å^3, ρ_{calc} = 1.348 g cm^{-3}, μ = 0.929 mm^{-1}, empirical absorption correction (0.768 ⩽ T ⩽ 0.913), Z = 4, monoclinic, space group $P2_1/c$ (No. 14), λ = 1.54178 Å, T = 293 K, ω and φ scans, 6736 reflections collected (±h, ±k, ±l), [(sin θ)/λ] = 0.59 Å^{-1}, 1772 independent (R_{int} = 0.037) and 1611 observed reflections [I ⩾ 2σ(I)], 139 refined parameters, R = 0.043, wR^2 = 0.136, max. residual electron density 0.17 (−0.14) e Å^{-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 × 0.25 × 0.20 mm, a = 5.534(1), b = 10.323(1), c = 22.474(1) Å, α = 81,77(1), β = 89.29(1), γ = 76.55(1)°, V = 1235.5(3) Å^3, ρ_{calc} = 1.334 g cm^{-3}, μ = 1.164 mm^{-1}, empirical absorption correction (0.760 ⩽ T ⩽ 0.801), Z = 4, triclinic, space group P1bar (No. 2), λ = 1.54178 Å, T = 223 K, ω and φ scans, 11,148 reflections collected (±h, ±k, ±l), [(sin θ)/λ] = 0.59 Å^{-1}, 3934 independent (R_{int} = 0.045) and 3339 observed reflections [I ⩾ 2σ(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) e Å^{-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 × 0.30 × 0.20 mm, a = 14.976(1), b = 5.783(1), c = 12.932(1) Å, β = 112.90(1)°, V = 1031.7(2) Å^3, ρ_{calc} = 1.353 g cm^{-3}, μ = 0.933 mm^{-1}, empirical absorption correction (0.605 ⩽ T ⩽ 0.835), Z = 4, monoclinic, space group $P2_1/c$ (No. 14), λ = 1.54178 Å, T = 293 K, ω and φ scans, 12037 reflections collected (±h, ±k, ±l), [(sin θ)/λ] = 0.59 Å^{-1}, 1789 independent (R_{int} = 0.037) and 1671 observed reflections [I ⩾ 2σ(I)], 138 refined parameters, R = 0.042, wR^2 = 0.135, max. residual electron density 0.13 (−0.12) e Å^{-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 × 0.15 × 0.01 mm, a = 13.647(1), b = 11.542(1), c = 10.039(1) Å, β = 93.79(1)°, V = 1577.8(2) Å^3, ρ_{calc} = 1.344 g cm^{-3}, μ = 1.048 mm^{-1}, empirical absorption correction (0.744 ⩽ T ⩽ 0.990), Z = 4, monoclinic, space group $P2_1/c$ (No. 14), λ = 1.54178 Å, T = 223 K, ω and φ scans, 8932 reflections collected (±h, ±k, ±l), [(sin θ)/λ] = 0.59 Å^{-1}, 2465 independent (R_{int} = 0.074) and 1471 observed reflections [I ⩾ 2σ(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) e Å^{-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 × 0.15 × 0.03 mm, a = 10.934(1), b = 13.227(1), c = 10.156(1) Å, V = 1603.1(2) Å^3, ρ_{calc} = 1.290 g cm^{-3}, μ = 0.833 mm^{-1}, empirical absorption correction (0.635 ⩽ T ⩽ 0.975), Z = 4, orthorhombic, space group $Pca2_1$ (No. 29), λ = 1.54178 Å, T = 223 K, ω and φ scans, 5796 reflections collected (±h, ±k, ±l), [(sin θ)/λ] = 0.59Å^{-1}, 1873 independent (R_{int} = 0.037) and 1756 observed reflections [I ⩾ 2σ(I)], 207 refined parameters, R = 0.038, wR^2 = 0.103, Flack parameter 0.5(3), max. residual electron density 0.14 (-0.15) e Å^{-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 $C_{20}H_{22}FNO_2 \cdot C_5H_{12}$, M = 399.53, colorless crystal 0.35 × 0.35 × 0.30 mm, a = 25.168(1), c = 10.039(1) Å, V = 9834.6(8) Å^3, ρ_{calc} = 1.079 g cm^{-3}, μ = 0.577 mm^{-1}, empirical absorption correction (0.824 ⩽ T ⩽ 0.846), Z = 16, tetragonal, space group $I4_1/a$ (No. 88), λ = 1.54178 Å, T = 223 K, ω and φ scans, 44,801 reflections collected (±h, ±k, ±l), [(sin θ)/λ] = 0.59Å^{-1}, 4405 independent (R_{int} = 0.042) and 3897 observed reflections [I ⩾ 2σ(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) e Å^{-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 $C_{20}H_{22}FNO_2$, M = 327.39, colorless crystal 0.40 × 0.30 × 0.15 mm, a = 10.846(1), b = 16.590(1), c = 10.086(1) Å, β = 101.85(1)°, V = 1776.1(3) Å^3, ρ_{calc} = 1.224 g cm^{-3}, μ = 0.696 mm^{-1}, empirical absorption correction (0.768 ⩽ T ⩽ 0.903), Z = 4, monoclinic, space group $P2_1/c$ (No. 14), λ = 1.54178 Å, T = 223 K, ω and φ scans, 14,110 reflections collected (±h, ±k, ±l), [(sin θ)/λ] = 0.59 Å^{-1},

3113 independent (R_{int} = 0.033) and 2959 observed reflections [$I \geqslant 2\sigma(I)$], 224 refined parameters, R = 0.038, wR^2 = 0.105, max. residual electron density 0.18 (−0.15) e Å^{-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 $C_{15}H_{15}FN^+Cl^-$, M = 263.73, colorless crystal 0.35 × 0.30 × 0.25 mm, a = 12.233(1), b = 9.498(1), c = 11.404(1) Å, β = 95.02(1)°, V = 1319.9(2) Å^3, ρ_{calc} = 1.327 g cm^{-3}, μ = 0.282 mm^{-1}, empirical absorption correction (0.908 ⩽ T ⩽ 0.933), Z = 4, monoclinic, space group $P2_1/c$ (No. 14), λ = 0.71073 Å, T = 198 K, ω and φ scans, 6987 reflections collected (±h, ±k, ±l), [(sin θ)/λ] = 0.59 Å^{-1}, 2327 independent (R_{int} = 0.037) and 2072 observed reflections [$I \geqslant 2\sigma(I)$], 172 refined parameters, R = 0.030, wR^2 = 0.079, max. residual electron density 0.23 (−0.24) e Å^{-3}, hydrogen calculated and refined as riding atoms.

CCDC 642246–642254 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.cam.ac.uk/conts/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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