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Cinchona alkaloid induced chiral discrimination for the determination of the enantiomeric composition of α-trifluoromethylated-hydroxyl compounds by ^{19}F NMR spectroscopy

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Abstract—The determination of the enantiomeric composition of α-trifluoromethylated-hydroxyl compounds using cinchona alkaloids as chiral selectors is described. The interaction between the alkaloid and trifluoromethylated-hydroxyl compounds converted the enantiotopic nuclei to diastereotopic nuclei observed by ^{19}F NMR spectroscopy. A wide variety of target molecules have been studied to highlight the broad applicability of the method.

1. Introduction

The importance and contribution of fluorinated compounds in many aspects of life are enormous. Organofluorine compounds are especially important in the pharmaceutical industry, due to their unique properties.[1,2] The synthesis and application of chiral organofluorine compounds for therapeutic purposes have attracted significant attention.[1c] Obviously, the separation and enantiomeric excess purity determination are necessary elements of the use of such compounds.[2] Several techniques, such as gas and liquid chromatography or NMR spectroscopy can be applied for analytical separations and enantiomeric excess (ee) determination.[3–5]

In NMR spectroscopy several chiral reagents have been developed.[5] These include the Mosher's chloride[6] [α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride] which forms covalent diastereomeric derivatives. Another example, Pirkle's reagent [2,2,2-trifluoro-1-(9-anthracenyl)-ethanol] acts as a chiral solvating agent.[7] Chiral lanthanide complexes also provide an effective alternative for ee determination in many applications especially in ^{1}H and ^{13}C NMR spectroscopy.[8] However, based on the exceptional demand for effective chiral analytical methods, the development of new chiral selection processes for NMR spectroscopy is highly desirable. Cinchona alkaloids (Chart 1), are known to catalyze a wide range of reactions from base catalysis to hydrogenations.[9] Their application, although sporadic, has been extended to chiral discrimination in ^{1}H and ^{31}P NMR spectroscopy.[10]

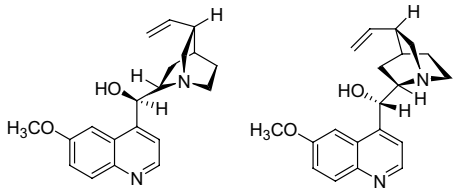

Chart 1. Chiral discriminating agents used in this study.

Herein, we report an effective and economic method[11] for the determination of the enantiomeric composition of α-trifluoromethylated-hydroxyl compounds. The enantioselection is induced by cinchona alkaloids and studied by ^{19}F NMR spectroscopy.

2. Results and discussion

The substrates investigated herein were trifluoromethylated-hydroxyl compounds, such as 2-aryl-2-hydroxyl-3,3,3-trifluoromethyl-propionic acid esters, 3-aryl-3-hydroxyl-4,4,4-trifluoromethyl-butanoic acid ethyl esters,

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and α-aryl-α-trifluoromethyl-carbinols. Although, many of these compounds have just been recently synthesized, they have already shown promising biological effects,[12] while others are important chiral building blocks.[13–16] Their structures are summarized in Chart 2.

The complex chemical structure of cinchona alkaloids makes these molecules capable of interacting with various functional groups.[9,10] Through these interactions, the alkaloid provides a sufficient chiral environment for enantioselection. It is also known that α-trifluoromethylated alcohols are fairly strong acids.[1e] Our idea originated from two basic facts: (i) solvation interactions occur when cinchona alkaloids are mixed with chiral CF_3 alcohols; (ii) such interactions can be used for enantiodifferentiation and enantiomeric excess determination. ^{19}F NMR chemical shift of trifluoromethyl group is extremely sensitive for its chemical environment, and the CF_3 group is directly attached to the stereogenic center (Chart 2). As such, ^{19}F NMR is an ideal method to detect chiral resolution.[6,7,17] The single peak in the ^{19}F NMR provides a simple and convenient way of observing resolution. Even reaction mixtures with solvents can be used directly. In addition, we can avoid the most common disadvantage; namely the complex spectrum of cinchona alkaloids that might result in overlapping peaks in ^{1}H or ^{13}C NMR investigations. The basic idea was tested in the case of compound **1c**. It was observed that each cinchona alkaloid (Chart 1) induced enantiodifferentiation to a different extent (Fig. 1).

Figure 1 shows that the most effective enantiodifferentiation took place in the presence of quinine (QN) and quinidine (QD). Thus, these pseudoenantiomers were

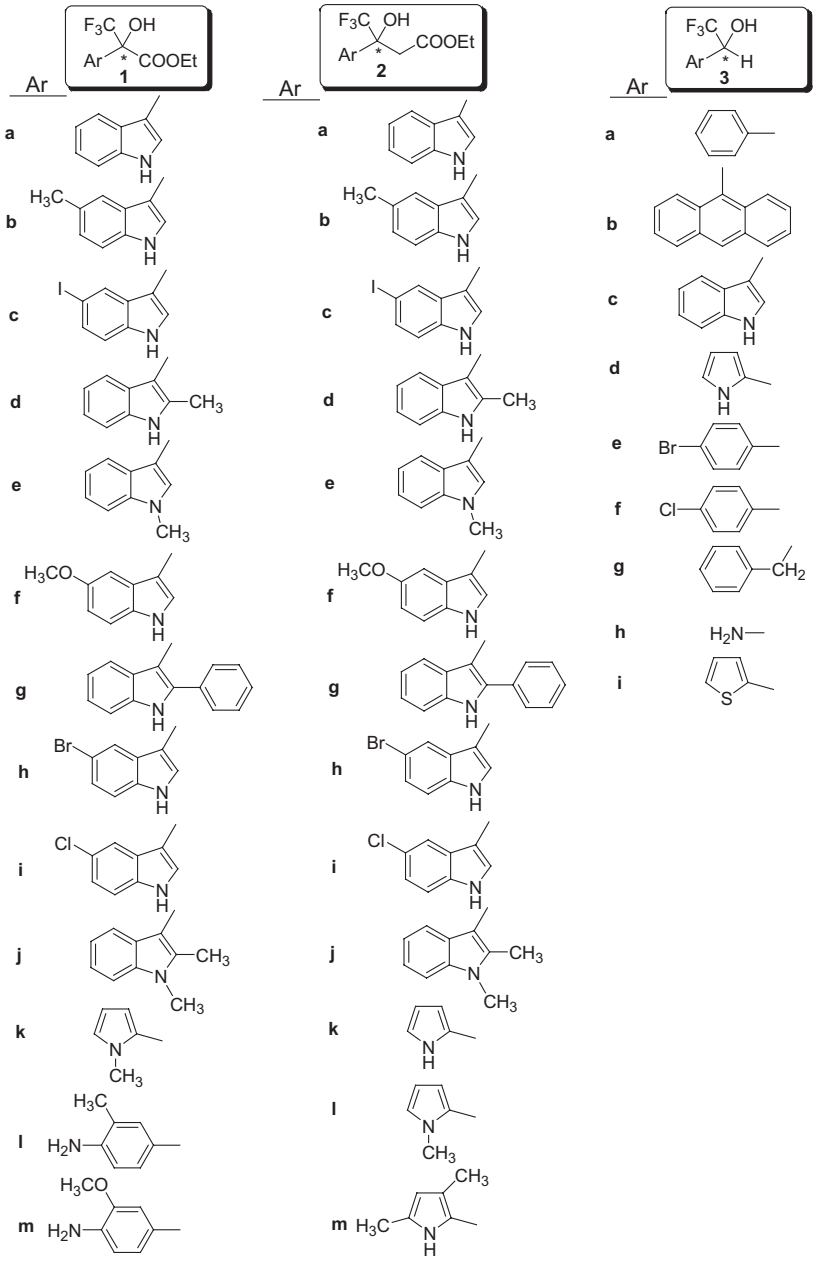

Chart 2. Chiral trifluoromethylated-hydroxyl compounds.

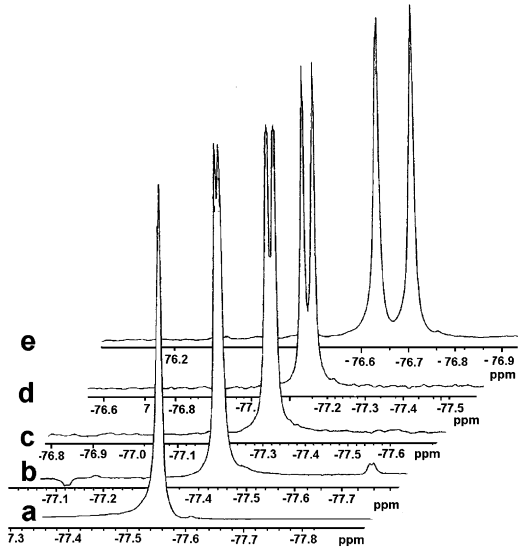

Figure 1. ^{19}F NMR resonances of CF_3 fluorines in **1c** in the presence of cinchona alkaloids: (a) no alkaloid, (b) cinchonine, (c) cinchonidine, (d) quinine, (e) quinidine (376 MHz, $CDCl_3$, 25 °C).

applied to detailed investigations. Figure 2 illustrates the application of quinidine in the signal assignment and ee determination of the enantiomers of **1c**.

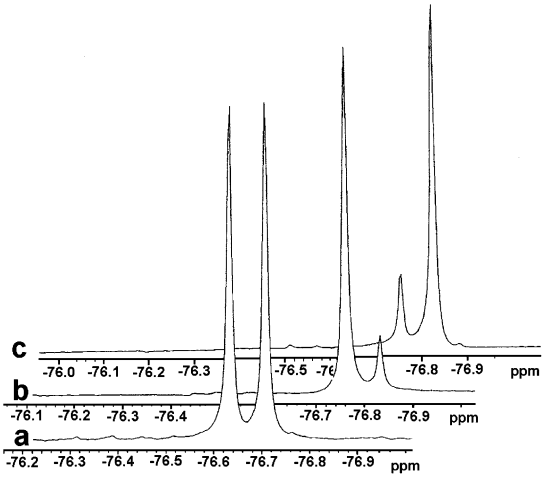

Figure 2. ^{19}F NMR resonances of CF_3 fluorines in **1c** in the presence of quinidine (QD): (a) racemic sample, (b) (*S*)-isomer in excess, (c) (*R*)-isomer in excess (376 MHz, $CDCl_3$, 25 °C).

The assignment of the individual enantiomers is based on the separate synthesis of the (*S*)-enantiomer of **1c** using a literature method.[14] This authentic sample has been used for signal assignment. Figure 2 shows the ^{19}F NMR resonances of the trifluoromethyl group in racemic and chiral samples of **1c** in the presence of quinidine. The racemic sample shows excellent resolution providing a perfect baseline separation of the CF_3 signals. The expected 1:1 ratio was obtained for the two enantiomers. When the chiral products were studied, the separation of the signals of the enantiotopic groups also proved satisfactory. This indicates that the method is sufficient for enantiomeric excess determination even for highly enantiopure samples. It was also observed that the molar ratio of the alkaloid and sample was an important factor in enantioselection. The signal separation was not satisfactory when the trifluoromethylated compound was in excess. Efforts to determine a minimum alkaloid versus target compound ratio revealed that at least a 3-fold molar excess of the alkaloid was necessary. Increasing the amount of cinchona further did not show any significant effects on the separation of the CF_3 signals. As such, a 3-fold molar excess of cinchona was always used in the investigations.

As Figure 2 shows excellent separation, a series of similar compounds (Chart 2) was subjected to solvation interaction with both QN and QD. Our investigations demonstrated that a change in substituents (usually the aryl group) did not result in deterioration during enantiodifferentiation. All three different groups of compounds showed excellent chiral resolution independent of their structure. The chemical shifts of the individual enantiomers (or diastereomeric solvates) of the target compounds including the chemical shift differences between the signals of individual enantiomers are summarized in Tables 1–3.

Table 1. ^{19}F NMR chemical shifts of the CF_3-group (A and B) in the diastereomeric solvates of 2-aryl-2-hydroxyl-3,3,3-trifluoropropionic acid esters **1a**–**m** with cinchona alkaloids and the chemical shift differences between the signals of individual enantiomers ($\Delta\delta$)[a]

Compound	Resolving agent	A (ppm)	B (ppm)	$\Delta\delta$ (ppm)
1a	QD	−76.388	−76.444	0.056
1b	QN	−76.700	−76.801	0.101
1c	QD	−76.680	−76.753	0.073
1d	QN	−76.696	−76.737	0.041
1e	QD	−76.262	−76.323	0.061
1f	QD	−76.128	−76.201	0.073
1g	QN	−75.293	−75.398	0.105
1h	QD	−76.412	−76.513	0.101
1i	QD	−76.359	−76.469	0.110
1j	QD	−76.939	−76.984	0.045
1k	QN	−75.524	−75.629	0.105
1l	QN	−76.777	−76.801	0.024
1m	QD	−76.416	−76.444	0.028

[a] ^{19}F NMR chemical shifts are referenced to $CFCl_3$ as internal standard. Experiments have been carried out in $CDCl_3$ at 376 MHz at room temperature (25 °C). The molar ratio of the cinchona and the target compounds was set at 3:1.

It was found that the alternate use of the two pseudo-enantiomeric cinchona alkaloids (QN and QD) was necessary to achieve the most effective signal separation. In some cases (e.g., **3a**–**d**) QN and QD provided the same $\Delta\delta$ values. As Table 1, shows quinine and quinidine were found to be approximately equally applicable chiral resolution agents for substituted propionic acid esters **1a**–**m**. However, substituted butanoic acid esters **2a**–**m** and aryl ethanols **3a**–**i** clearly preferred QD as the solvating agent (Tables 2 and 3).

As expected, the original CF_3 signal in α-aryl-α-trifluoromethyl carbinols **3a**–**i** were split into a doublet due

Table 2. ^{19}F NMR chemical shifts of the CF_3-group (A and B) in the diastereomeric solvates of 3-aryl-3-hydroxy-4,4,4-trifluorobutanoic acid esters **2a**–**m** with quinidine and the chemical shift differences between the signals of individual enantiomers ($\Delta\delta$)[a]

Compound	A (ppm)	B (ppm)	$\Delta\delta$ (ppm)
2a	−80.837	−80.914	0.077
2b	−80.878	−80.943	0.065
2c	−80.918	−81.008	0.090
2d	−81.442	−81.454	0.012
2e	−81.028	−81.101	0.073
2f	−80.913	−80.979	0.048
2g	−80.282	−80.302	0.020
2h	−80.943	−81.024	0.081
2i	−80.995	−81.064	0.069
2j	−81.429	−81.446	0.017
2k	−81.661	−81.786	0.125
2l	−80.350	−80.399	0.049
2m	−81.620	−81.652	0.032

[a] ^{19}F NMR chemical shifts are referenced to $CFCl_3$ as internal standard. Experiments have been carried out in $CDCl_3$ at 376 MHz at room temperature (25 °C). The molar ratio of quinidine and the target compounds was set at 3:1.

Table 3. ^{19}F NMR chemical shifts of the CF_3-group (A and B) in the diastereomeric solvates of α,α,α-trifluoromethyl-arylethanols **3a**–**i** with quinidine and the chemical shift differences between the signals of individual enantiomers ($\Delta\delta$)[a]

Compound	A (ppm)	B (ppm)	$\Delta\delta$ (ppm)
3a	−78.363	−78.383	0.020
3b	−74.055	−74.080	0.025
3c	−78.116	−78.136	0.020
3d	−78.521	−78.541	0.020
3e	−78.489	−78.509	0.020
3f	−78.521	−78.537	0.016
3g	−77.166	−77.191	0.025
3h	−80.054	−80.075	0.021
3i	−78.947	−78.963	0.016

[a] ^{19}F NMR chemical shifts are referenced to $CFCl_3$ as internal standard. Experiments have been carried out in $CDCl_3$ at 376 MHz at room temperature (25 °C). The molar ratio of quinidine and the target compounds was set at 3:1.

to the presence of an α-hydrogen. The addition of the alkaloid to these samples resulted in further splitting with double doublets being obtained. The separation of these doublets showed satisfactory enantioselection.

Chromatographic investigations of mixtures used in NMR experiments showed that the alkaloid and the target compounds could easily be separated after determination of enantiomeric excess. Thus, the studied compounds could be regenerated and isolated from the mixture. This is a significant advantage when the product molecule is synthesized by a multi-step method or obtained in very low quantities.

As expected, the relatively strong acidity of the hydroxyl group in the target compounds initiates a solvation interaction with the basic nitrogen of the cinchona alkaloids. Therefore, we suggest that the enantiodifferentiation is based on the formation of an acid–base complex between the alkaloid and the target molecules. As this complex formation is a reversible, equilibrium type process, excess cinchona (3:1 molar ratio) is necessary for the complete solvation of the target molecules. Although, the tertiary quinuclidine *N* is preferred for complex formation we observed that the other less basic quinoline *N* is also able to initiate this process.

3. Conclusion

In conclusion, our data unambiguously indicate that cinchona alkaloids are effective chiral resolution agents for a wide variety of substituted trifluoromethylated-hydroxyl compounds using the CF_3 moiety as a reporting group. Our method represents an effective, convenient, and economic way for the enantiomeric excess determination of the above mentioned compounds and possibly for an even wider range of products. The major advantages of this method are: (i) the use of the inexpensive, readily available cinchona alkaloids; (ii) the ^{19}F NMR spectrum is simple and the signal assignment is clear, even the immediate testing of reaction mixtures is possible; (iii) as they do not have fluorine in their structure, the complex spectra of cinchona alkaloids do not disturb the ee determination, and (iv) after ee determination, the products can be regenerated from the mixture.

4. Experimental

4.1. Materials

The cinchona alkaloids [cinchonidine (denoted as CD), cinchonine (denoted as CN), quinine (denoted as QN), and quinidine (denoted as QD)] used were purchased from Fluka and used without further purification. Trifluoromethyl alkyl ketones, indole derivatives, other aromatics, ethyl 3,3,3-trifluoropyruvate, and ethyl 4,4,4-trifluoroacetoacetate were Aldrich products. $CDCl_3$ used as a solvent (99.8%) for the NMR studies was a Cambridge Isotope Lab. product. ^{19}F NMR reference compound $CFCl_3$ was purchased from Aldrich. Other solvents with minimum purity of 99.5% were Fisher products. $NaBH_4$ was purchased from Fisher. An Engelhard 5% Pt/Al_2O_3 catalyst (code 4759) was used for catalytic hydrogenations, using hydrogen gas of 99.8% purity (PRAXAIR).

4.2. Preparation of substrates

The racemic samples of ethyl 3,3,3-trifluoro-2-hydroxy-2-aryl-propionates **1a**–**m** were prepared by a literature method,[13] while the (*S*)-enantiomers for the assignments were synthesized by Zhuang et al.[14] Ethyl 3,3,3-trifluoro-2-hydroxy-2-aryl-butanoates **2a**–**m** were prepared by a literature method.[18] The chiral trifluoromethyl-carbinols **3a**–**i** were prepared by either a conventional $NaBH_4$ reduction[19] or catalytic hydrogenation[15] of the corresponding ketones as described earlier. All products showed MS and NMR spectra, which were consistent with the expected structures and literature data.

4.3. NMR analysis

The ^{19}F NMR spectra were obtained on a 400 MHz superconducting Varian Inova 400 NMR spectrometer operating at 376 MHz, in $CDCl_3$ solvent with CCl_3F as an internal standard. The temperature was maintained at 25 °C (accuracy ±1 °C). In the case of nonracemic samples, the ee values determined were reproducible within 0.5%. The concentration of the CF_3 compounds was usually 8 mg/mL, while the alkaloid was added in 3-fold molar excess.

4.4. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(indol-3-yl)-propionate 1a

Colorless crystals (mp 70.5–71.8 °C); ^1H NMR (399.81 MHz, $CDCl_3$): δ (ppm) 8.25 (br s, 1H, NH), 7.89 (d, J = 8.3 Hz, 1H, Ar), 7.45 (d, J = 2.3 Hz, 1H, Ar), 7.35 (dd, J = 7.99, 1.19 Hz, 1H, Ar), 7.21 (dd, J = 7.19, 1.19 Hz, 1H, Ar), 7.14 (ddd, J = 7.19, 1.19 Hz, 1H, Ar), 4.44 (dq, J = 7.2, 3.6 Hz, 1H, CH_2), 4.39 (s, 1H, OH), 4.34 (dq, J = 7.2, 3.6 Hz, 1H, CH_2), 1.35 (td, J = 7.19 Hz, 3H, CH_3); ^{13}C NMR (100.53 MHz, $CDCl_3$): δ (ppm) 169.6, 136.5, 125.3, 125.1, 124.5, 122.9, 122.3, 121.4, 120.7, 111.5, 108.9, 64.4, 14.1; ^{19}F NMR (376.19 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −77.15 (s, 3F); MS $C_{13}H_{12}F_3NO_3$ (287), m/z (%): 287 (M^+, 33), 214 (100), 144 (65), 117 (70), 89 (30).

4.5. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(5-methyl-indol-3-yl)-propionate 1b

Light brown crystals (mp 75.2–76.5 °C); ^1H NMR (399.81 MHz, $CDCl_3$): δ (ppm) 8.16 (br s, 1H, NH), 7.66 (s, 1H, Ar), 7.40 (d, J = 2.3 Hz, 1H, Ar), 7.24 (d, J = 8.3 Hz, 1H, Ar), 7.03 (dd, J = 8.3, 1.5 Hz, 1H, Ar), 4.43 (dq, J = 7.19, 3.6 Hz, 1H, CH_2), 4.39 (s, 1H, OH), 4.34 (dq, J = 7.19, 3.5 Hz, 1H, CH_2), 2.43 (s, 3H, CH_3), 1.35 (td, J = 7.19 Hz, 3H, CH_3); ^{13}C NMR (100.53 MHz, $CDCl_3$): δ (ppm) 169.6, 151.7, 134.8, 130.0, 125.6, 124.5, 123.4, 122.3, 120.9, 111.1, 108.4, 64.3, 21.8, 14.0; ^{19}F NMR (376.19 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −77.12 (s, 3F); MS $C_{14}H_{14}F_3NO_3$ (301), m/z (%): 301 (M^+, 11), 130 (100).

4.6. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(5-iodo-indol-3-yl)-propionate 1c

Dark brown crystals (mp 74.3–76 °C); ^1H NMR (399.81 MHz, $CDCl_3$): δ (ppm) 8.35 (br s, 1H, NH), 8.27 (s, 1H, Ar), 7.45 (dd, J = 8.8, 2.0 Hz, 1H, Ar), 7.40 (d, J = 2.4 Hz, 1H, Ar), 7.11 (dd, J = 8.8, 0.4 Hz, 1H, Ar), 4.44 (dq, J = 7.2, 3.6 Hz, 1H, CH_2), 4.38 (s, 1H, OH), 4.35 (dq, J = 7.2, 3.6 Hz, 1H, CH_2), 1.36 (td, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100.54 MHz, $CDCl_3$): δ (ppm) 169.3, 135.6, 131.3, 130.4, 127.4, 125.5, 124.9, 122.1, 113.4, 108.3, 84.5, 64.7, 14.1; ^{19}F NMR (376.15 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −77.46 (s, 3F); MS $C_{13}H_{11}F_3INO_3$ (413), m/z (%): 413 (M^+, 33), 340 (60), 270 (20), 144 (100).

4.7. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(2-methyl-indol-3-yl)-propionate 1d

Red crystals (mp 67–68.5 °C); ^1H NMR (399.81 MHz, $CDCl_3$): δ (ppm) 7.99 (br s, 1H, NH), 7.79 (d, J = 7.9 Hz, 1H, Ar), 7.24 (dq, J = 6.7, 0.7 Hz, 1H, Ar), 7.12 (ddd, J = 7.1, 1.1, Hz, 1H, Ar), 7.08 (ddd, J = 6.7, 1.1 Hz, 1H, Ar), 4.43 (dq, J = 7.2, 3.6 Hz, 1H, CH_2), 4.34 (dq, J = 7.2, 3.6 Hz, 1H, CH_2), 3.95 (s, 1H, OH), 2.51 (s, 3H, CH_3), 1.33 (t, J = 7.19, 3H, CH_3); ^{13}C NMR (100.54 MHz, $CDCl_3$): δ (ppm) 169.5, 135.4, 134.8, 127, 125.5, 122.7, 121.8, 120.7, 120.4, 110.4, 104.1, 63.77, 14.4, 14.0; ^{19}F NMR (376.15 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −77.91 (s, 3F); MS $C_{14}H_{14}F_3NO_3$ (301), m/z (%): 301 (M^+, 30), 228 (100), 158 (66), 131 (90).

4.8. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(1-methyl-indol-3-yl)-propionate 1e

Dark red crystals (mp 61–62.2 °C); ^1H NMR (399.81 MHz, $CDCl_3$): δ (ppm) 7.87 (d, J = 8.3 Hz, 1H, Ar), 7.31 (d, J = 2.7 Hz, 1H, Ar), 7.29 (dd, J = 1.5 Hz, 1H, Ar), 7.24 (ddd, J = 6.7, 0.7 Hz, 1H, Ar), 7.14 (ddd, J = 6.7, 1.1 Hz, 1H, Ar), 4.45 (dq, J = 7.19, 3.5 Hz, 1H, CH_2), 4.39 (s, 1H, OH), 4.32 (dq, J = 6.7, 3.5 Hz, 1H, CH_2), 3.77 (s, 3H, CH_3), 1.35 (td, J = 7.19 Hz, 3H, CH_3); ^{13}C NMR (100.54 MHz, $CDCl_3$): δ (ppm) 169.6, 137.4, 129, 125.9, 125.1, 122.4, 121.4, 120.3, 109.7, 107.0, 64.3, 33.2, 14.1; ^{19}F NMR (376.15 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −77.17 (s, 3F); MS $C_{14}H_{14}F_3NO_3$ (301), m/z (%): 301 (M^+, 25), 228 (100), 158 (60), 131 (80).

4.9. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(5-methoxy-indol-3-yl)-propionate 1f

Colorless crystals (mp 74.5–75.8 °C); ^1H NMR (399.81 MHz, $CDCl_3$): δ (ppm) 8.25 (br s, 1H, NH), 7.40 (d, J = 2.8 Hz, 1H, Ar), 7.35 (d, J = 2.4 Hz, 1H, Ar), 7.22 (d, J = 8.8 Hz, 1H, Ar), 6.87 (dd, J = 8.8, 2.4 Hz, 1H, Ar), 4.45 (dq, J = 7.2, 3.6 Hz, 1H, CH_2), 4.40 (s, 1H, OH), 4.34 (dq, J = 7.2, 3.6 Hz, 1H, CH_2), 3.83 (s, 3H, CH_3), 1.34 (td, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100.53 MHz, $CDCl_3$): δ (ppm) 169.6, 154.7, 131.6, 125.9, 125.2, 125, 122.3, 113.4, 112.2, 108.5, 103, 64.4, 56.0, 14.2; ^{19}F NMR (376.15 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −77.15 (s, 3F); MS $C_{14}H_{14}F_3NO_4$ (317), m/z (%): 317 (M^+, 25), 244 (95), 270 (65), 147 (100).

4.10. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(2-phenyl-indol-3-yl)-propionate 1g

Light green crystals (mp 145.0–147.0 °C); ^1H NMR (399.81 MHz, $CDCl_3$): δ (ppm) 8.14 (br s, 1H, NH), 8.04 (d, J = 8.0 Hz, 1H, Ar), 7.43 (m, 5H, Ar), 7.32 (td, J = 8.0, 1.2 Hz, 1H, Ar), 7.23 (ddd, J = 5.6, 1.2 Hz, 1H, Ar), 7.18 (ddd, J = 7.2, 1.5, 1H, Ar), 3.88 (dq, J = 10.4, 7.2 Hz, 1H, CH_2), 3.72 (s, 1H, OH), 3.50 (dq, J = 14.4, 7.2 Hz, 1H, CH_2), 1.08 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100.54 MHz, $CDCl_3$): δ (ppm) 168.7, 138.0, 135.3, 132.7, 130.5, 129.2, 128.1, 126.7, 125.4, 123.0,

122.6, 122.5, 122.9, 110.8, 106.2, 63.1, 13.7; ^{19}F NMR (376.19 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −75.63 (s, 3F); MS $C_{19}H_{16}F_3NO_3$ (363), *m/z* (%): 363 (M^+, 15), 290 (66), 220 (50), 193 (100).

4.11. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(5-bromo-indol-3-yl)-propionate 1h

Reddish-brown crystals (mp 51–52.5 °C); ^{1}H NMR (399.81 MHz, $CDCl_3$): δ (ppm) 8.32 (br s, 1H, NH), 8.07 (t, J = 0.7 Hz, 1H, Ar), 7.47 (d, J = 2.7 Hz, 1H, Ar), 7.29 (dd, J = 8.8, 2.0 Hz, 1H, Ar), 7.22 (dd, J = 8.8, 0.3 Hz, 1H, Ar), 4.45 (dq, J = 7.2, 3.6 Hz, 1H, CH_2), 4.39 (s, 1H, OH), 4.36 (dq, J = 7.2, 3.9 Hz, 1H, CH_2), 1.36 (td, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100.54 MHz, $CDCl_3$): δ (ppm) 169.3, 135.2, 127.0, 125.9, 125.8, 125, 124.26, 122.1, 114.2, 112.9, 108.7, 64.7, 14.1; ^{19}F NMR (376.15 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −77.5 (s, 3F); MS $C_{13}H_{11}F_3BrNO_3$ (367), *m/z* (%): 367 (M^+, 10), 295 (45), 225 (20), 144 (100).

4.12. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(5-chloro-indol-3-yl)-propionate 1i

Red crystals (mp 51–52.3 °C); ^{1}H NMR (399.81 MHz, $CDCl_3$): δ (ppm) 8.30 (br s, 1H, NH), 7.91 (t, J = 0.8 Hz, 1H, Ar), 7.50 (d, J = 2.8 Hz, 1H, Ar), 7.28 (dd, J = 8.8, 0.8 Hz, 1H, Ar), 7.17 (dd, J = 6.8, 2.0 Hz, 1H, Ar), 4.45 (dq, J = 7.2, 3.6 Hz, 1H, CH_2), 4.41 (s, 1H, OH), 4.36 (dq, J = 7.2, 3.6 Hz, 1H, CH_2), 1.36 (td, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100.54 MHz, $CDCl_3$): δ (ppm) 169.3, 134.9, 126.5, 126.3, 125.9, 125, 123.2, 122.1, 121.1, 112.5, 108.3, 64.6, 14.0; ^{19}F NMR (376.15 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −77.53 (s, 3F); MS $C_{13}H_{11}F_3ClNO_3$ (321), *m/z* (%): 321 (M^+, 20), 248 (100), 178 (60), 151 (85).

4.13. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(1,2-dimethyl-indol-3-yl)-propionate 1j

Dark brown crystals (mp 83–84.5 °C); ^{1}H NMR (399.81 MHz, $CDCl_3$): δ (ppm) 7.77 (d, J = 7.99 Hz, 1H, Ar), 7.26 (d, J = 8.3 Hz, 1H, Ar), 7.17 (ddd, J = 6.7, 1.1 Hz, 1H, Ar), 7.08 (ddd, J = 6.7, 1.1 Hz, 1H, Ar), 4.41 (dq, J = 7.1, 3.1 Hz, 1H, CH_2), 4.39 (s, 1H, OH), 4.36 (dq, J = 7.1, 3.1 Hz, 1H, CH_2), 3.65 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 1.35 (td, J = 15.5, 3H, CH_3); ^{13}C NMR (100.54 MHz, $CDCl_3$): δ (ppm) 169.5, 137.1, 136.6, 129.2, 125.9, 124.8, 122.7, 121.4, 120.2, 109.1, 103.7, 63.5, 29.6, 14.1, 11.8; ^{19}F NMR (376.15 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −77.01 (s, 3F); MS $C_{15}H_{16}F_3NO_3$ (315), *m/z* (%): 315 (M^+, 33), 242 (100), 172 (66), 145 (85).

4.14. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(1-methyl-pyrrol-2-yl)-propionate 1k

Light yellow oil; ^{1}H NMR (399.81 MHz, $CDCl_3$): δ (ppm) 6.61 (q, J = 2.8, 2.0 Hz, 1H, Ar), 6.38 (td, J = 3.4, 1.6 Hz, 1H, Ar), 6.06 (dd, J = 3.6, 2.4 Hz, 1H, Ar), 4.46 (dq, J = 6.8, 3.2 Hz, 1H, CH_2), 4.36 (dq, J = 6.8, 3.2 Hz, 1H, CH_2), 4.29 (s, 1H, OH), 3.59 (s, 3H, CH_3), 1.35 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100.53 MHz, $CDCl_3$): δ (ppm) 169.0, 126.2, 124.5, 122.4, 121.7, 111.5, 107.1, 64.7, 36.0, 14.0; ^{19}F NMR (376.15 MHz, $CFCl_3$-Ref): δ (ppm) −75.95 (s, 3F); MS $C_{10}H_{12}F_3NO_3$ (251), *m/z* (%): 251 (M^+, 15), 178 (80), 108 (100).

4.15. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(2-methyl-4-amino-phenyl)-propionate 1l

Light brown crystals (mp 98.1–99.8 °C); ^{1}H NMR (399.81 MHz, $CDCl_3$): δ (ppm) 7.39 (m, 2H, Ar), 6.64 (d, J = 8.4 Hz, 1H, Ar), 4.45 (dq, J = 7.2, 3.6 Hz, 1H, CH_2), 4.38 (dq, J = 7.2, 3.6 Hz, 1H, CH_2), 4.21 (br s, 1H, OH), 3.71 (br s, 2H, NH_2), 2.18 (s, 3H, CH_3), 1.38 (t, J = 7.19 Hz, 3H, CH_3); ^{13}C NMR (100.53 MHz, $CDCl_3$): δ (ppm) 169.6, 145.9, 128.9, 125.7, 122.5, 122.0, 121.1, 120.7, 114.6, 64.2, 17.7, 14.1; ^{19}F NMR (376.19 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −77.03 (s, 3F); MS $C_{12}H_{14}F_3NO_3$ (277), *m/z* (%): 277 (M^+, 33), 204 (100), 134 (90), 107 (45).

4.16. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(3-methoxy-4-amino-phenyl)-propionate 1m

Brown crystals (mp 80.4–82.0 °C); ^{1}H NMR (399.81 MHz, $CDCl_3$): δ (ppm) 7.18 (m, 2H, Ar), 6.71 (d, J = 8.4 Hz, 1H, Ar), 4.42 (q, J = 7.2, 3.6 Hz, 1H, CH_2), 4.93 (s, 1H, OH), 4.35 (q, J = 7.2, 3.6 Hz, 1H, CH_2), 3.82 (s, 3H, CH_3), 1.38 (t, J = 7.19 Hz, 3H, CH_3); ^{13}C NMR (100.53 MHz, $CDCl_3$): δ (ppm) 169.6, 145.9, 128.9, 125.7, 122.5, 122.0, 121.1, 120.7, 114.6, 64.2, 17.7, 14.1; ^{19}F NMR (376.19 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −77.06 (s, 3F); MS $C_{12}H_{14}F_3NO_4$ (293), *m/z* (%): 293 (M^+, 30), 220 (100), 150 (80), 123 (90).

4.17. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(indol-3-yl)-butanoate 2a

Green oil; ^{1}H NMR (399.81 MHz, $CDCl_3$): δ 8.21 (br s, 1H, NH), 7.88 (d, J = 8 Hz, 1H, Ar), 7.35 (d, J = 8.4 Hz, 1H, Ar), 7.28 (d, J = 2.8 Hz, 1H, Ar), 7.20 (ddd, J = 8.0, 1.2 Hz, 1H, Ar), 7.14 (ddd, J = 7.2, 1.2 Hz, 1H, Ar), 5.36 (s, 1H, OH), 4.09 (m, 2H, CH_2), 3.28 (d, J = 16.4 Hz, 1H, CH_2), 3.17 (d, J = 16 Hz, 1H, CH_2), 1.13 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 171.8, 136.7, 126.7, 125.4, 123.8, 123.7, 122.7, 121.4, 120.5, 113.5, 111.5, 61.7, 38.5, 14.0; ^{19}F NMR (376.15 MHz, $CDCl_3$, $CFCl_3$-Ref): δ −81.15 (s, 3F); MS $C_{14}H_{14}F_3NO_4$ (301), *m/z* (%): 301 (M^+, 25), 232 (30), 214 (25), 144 (100), 117 (10).

4.18. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(5-methyl-indol-3-yl)-butanoate 2b

Colorless oil; ^{1}H NMR (399.81 MHz, $CDCl_3$): δ 8.10 (br s, 1H, NH), 7.66 (s, 1H, Ar), 7.23 (m, 2H, Ar), 7.03 (d, J = 6.8 Hz, 1H, Ar), 5.34 (s, 1H, OH), 4.10 (m, 2H, CH_2), 3.25 (d, J = 15.6 Hz, 1H, CH_2), 3.16 (d, J = 15.6 Hz, 1H, CH_2), 2.44 (s, 3H, CH_3), 1.15 (t, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 171.8, 135.1, 129.8, 125.9, 125.7, 124.3, 123.7, 121.0,

113.5, 111.1, 106.5, 61.7, 38.6, 21.8, 14.0; ^{19}F NMR (376.15 MHz, $CDCl_3$, $CFCl_3$-Ref): δ −81.10 (s, 3F); MS $C_{15}H_{16}F_3NO_3$ (315), *m/z* (%): 315 (M^+, 25), 246 (40), 228 (25), 158 (100), 131 (20).

4.19. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(5-iodo-indol-3-yl)-butanoate 2c

Dark green oil; ^{1}H NMR (399.81 MHz, $CDCl_3$): δ 8.32 (br s, 1H, NH), 7.45 (dd, J = 8.4, 1.6 Hz, 1H, Ar), 7.32 (d, J = 8.4 Hz, 1H, Ar), 7.21 (d, J = 2.8 Hz, 1H, Ar), 7.10 (s, 1H, Ar), 5.39 (s, 1H, OH), 4.11 (m, 2H, CH_2), 3.20 (d, J = 16.4 Hz, 1H, CH_2), 3.14 (d, J = 16 Hz, 1H, CH_2), 1.16 (t, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 169.3, 135.6, 131.2, 130.7, 129.8, 128.8, 125.3, 124.3, 113.4, 111.8, 112.5, 60.9, 40.1, 13.7; ^{19}F NMR (376.15 MHz, $CDCl_3$, $CFCl_3$-Ref): δ −81.20 (s, 3F); MS $C_{14}H_{13}F_3INO_3$ (427), *m/z* (%): 427 (M^+, 25), 358 (55), 340 (10), 270 (100).

4.20. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(2-methyl-indol-3-yl)-butanoate 2d

Light yellow oil; ^{1}H NMR (399.81 MHz, $CDCl_3$): δ 7.92 (br s, 1H, NH), 7.70 (d, J = 8 Hz, 1H, Ar), 7.23 (dt, J = 8.4, 0.8 Hz, 1H, Ar), 7.08 (m, 2H, Ar), 5.37 (s, 1H, OH), 4.062 (m, 2H, CH_2), 3.51 (d, J = 16 Hz, 1H, CH_2), 3.23 (d, J = 16 Hz, 1H, CH_2), 2.58 (s, 3H, CH_3), 1.08 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 172.1, 135.2, 135.0, 127.2, 127.0, 124.4, 121.4, 120.6, 120.2, 110.5, 107.4, 61.6, 38.8, 14.8, 13.0; ^{19}F NMR (376.15 MHz, $CDCl_3$, $CFCl_3$-Ref): δ −81.49 (s, 3F); MS $C_{15}H_{16}F_3NO_3$ (315), *m/z* (%): 315 (M^+, 25), 246 (40), 228 (25), 158 (100), 131 (20).

4.21. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(1-methyl-indol-3-yl)-butanoate 2e

Brown oil; ^{1}H NMR (399.81 MHz, $CDCl_3$): δ 7.85 (d, J = 8 Hz, 1H, Ar), 7.29 (d, J = 8 Hz, 1H, Ar), 7.23 (t, J = 7.6 Hz, 1H, Ar), 7.15 (d, J = 6.4 Hz, 1H, Ar), 7.12 (d, J = 0.8 Hz, 1H, Ar), 5.33 (s, 1H, OH), 4.10 (m, 2H, CH_2), 3.76 (s, 3H, CH_3), 3.27 (d, J = 16.0 Hz, 1H, CH_2), 3.17 (d, J = 16.0 Hz, 1H, CH_2), 1.14 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 171.8, 137.6, 128.4, 125.9, 122.1, 121.6, 121,5, 120.1, 111.5, 109.7, 101.0, 61.6, 38.6, 33.1, 14.0; ^{19}F NMR (376.15 MHz, $CDCl_3$, $CFCl_3$-Ref): δ −81.21 (s, 3F); MS $C_{15}H_{16}F_3NO_3$ (315), *m/z* (%): 315 (M^+, 15), 246 (15), 228 (25), 158 (100), 131 (15).

4.22. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(5-methoxy-indol-3-yl)-butanoate 2f

Red crystals (mp 112–113.8 °C); ^{1}H NMR (399.81 MHz, $CDCl_3$): δ 8.11 (br s, 1H, NH), 7.37 (s, 1H, Ar), 7.23 (m, 2H, Ar), 6.87 (dd, J = 8.4, 2.0 Hz, 1H, Ar), 5.33 (s, 1H, OH), 4.11 (m, 2H, CH_2), 3.85 (s, 3H, CH_3), 3.24 (d, J = 16 Hz, 1H, CH_2), 3.14 (d, J = 16 Hz, 1H, CH_2), 1.16 (t, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 171.8, 154.5, 131.8, 126.1, 124.03, 113.1, 113.0, 112.5, 112.1, 111.8, 103.4, 61.7, 56.1, 38.5, 14.1; ^{19}F NMR (376.15 MHz, $CDCl_3$, $CFCl_3$-Ref): δ −81.14 (s, 3F); MS $C_{15}H_{16}F_3NO_4$ (331), *m/z* (%): 331 (M^+, 15), 262 (25), 244 (25), 174 (100), 147 (20).

4.23. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(2-phenyl-indol-3-yl)-butanoate 2g

Colorless solid (mp 206.7–208.1 °C); ^{1}H NMR (399.81 MHz, $CDCl_3$): δ 8.04 (br s, 1H, NH), 7.44 (m, 5H, Ar), 7.31 (s, 1H, Ar), 7.30 (d, J = 1.2 Hz, 1H, Ar), 7.21 (ddd, J = 6.4, 1.2 Hz, 1H, Ar), 7.16 (ddd, J = 8.4, 1.2 Hz, 1H, Ar), 5.28 (s, 1H, OH), 3.90 (m, 2H, CH_2), 3.12 (d, J = 16.8 Hz, 1H, CH_2), 2.90 (d, J = 16.8 Hz, 1H, CH_2), 1.04 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 171.6, 136.9, 135.5, 133.8, 130.3, 129.2, 128.3, 127.4, 126.1, 123.7, 122.9, 122.7, 120.6, 115.3, 113.1, 110.7, 109.3, 61.2, 38.5, 13.9; ^{19}F NMR (376.15 MHz, $CDCl_3$, $CFCl_3$-Ref): δ −80.32 (s, 3F); MS $C_{20}H_{18}F_3NO_3$ (377), *m/z* (%): 377 (M^+, 25), 308 (30), 290 (10), 220 (100), 193 (25).

4.24. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(5-bromo-indol-3-yl)-butanoate 2h

Orange crystals (mp 89–90.1 °C); ^{1}H NMR (399.81 MHz, $CDCl_3$): δ 8.24 (br s, 1H, NH), 8.05 (s, 1H, Ar), 7.29 (d, J = 1.2 Hz, 1H, Ar), 7.27 (d, J = 3.6 Hz, 1H, Ar), 7.22 (d, J = 8.8 Hz, 1H, Ar), 5.38 (s, 1H, OH), 4.11 (m, 2H, CH_2), 3.20 (d, J = 16 Hz, 1H, CH_2), 3.14 (d, J = 16 Hz, 1H, CH_2), 1.16 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 171.6, 161.0, 135.3, 127.1, 125.8, 124.6, 124.1, 118.7, 114.0, 113.3, 112.8, 61.8, 38.5, 14.0; ^{19}F NMR (376.15 MHz, $CDCl_3$, $CFCl_3$-Ref): δ −81.24 (s, 3F); MS $C_{14}H_{13}F_3BrNO_3$ (380), *m/z* (%): 380 (M^+, 15), 310 (40), 292 (10), 224 (100).

4.25. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(5-chloro-indol-3-yl)-butanoate 2i

Red oil; ^{1}H NMR (399.81 MHz, $CDCl_3$): δ 8.30 (br s, 1H, NH), 7.88 (s, 1H, Ar), 7.16 (d, J = 6.8 Hz, 1H, Ar), 7.01 (d, J = 7.6 Hz, 1H, Ar), 6.89 (s, 1H, Ar), 5.38 (s, 1H, OH), 4.11 (m, 2H, CH_2), 3.20 (d, J = 16 Hz, 1H, CH_2), 3.14 (d, J = 16 Hz, 1H, CH_2), 1.16 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 171.6, 134.9, 127.5, 126.4, 125.7, 124.9, 123.2, 122.7, 121.0, 120.4, 112.5, 61.8, 38.5, 14.0; ^{19}F NMR (376.15 MHz, $CDCl_3$, $CFCl_3$-Ref): δ −81.23 (s, 3F); MS $C_{14}H_{13}F_3ClNO_3$ (335), *m/z* (%): 335 (M^+, 15), 266 (20), 248 (10), 178 (100), 151 (20).

4.26. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(1,2-dimethyl-indol-3-yl)-butanoate 2j

Yellow crystals (mp 102.4–103.9 °C); ^{1}H NMR (399.81 MHz, $CDCl_3$): δ 7.68 (d, J = 8 Hz, 1H, Ar), 7.23 (d, J = 8 Hz, 1H, Ar), 7.23 (ddd, J = 7.2, 1.2 Hz, 1H, Ar), 7.05 (ddd, J = 7.2, 1.2 Hz, 1H, Ar), 5.37 (s, 1H, OH), 4.04 (m, 2H, CH_2), 3.64 (s, 3H, CH_3), 3.59 (d, J = 16.4 Hz, 1H, CH_2), 3.24 (d, J = 16 Hz, 1H, CH_2), 2.62 (s, 3H, CH_3), 1.07 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 172.2, 157.3, 137.0,

135.1, 125.9, 123.9, 122.9, 120.9, 120.3, 119.8, 109.1, 106.7, 61.5, 39.1, 29.6, 13.9; ^{19}F NMR (376.15 MHz, $CDCl_3$, $CFCl_3$-Ref): δ −81.49 (s, 3F); MS $C_{16}H_{18}F_3NO_3$ (329), *m/z* (%): 329 (M^+, 20), 260 (25), 242 (10), 172 (100), 145 (15).

4.27. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(pyrrol-2-yl)-butanoate 2k

Green oil; ^{1}H NMR (399.81 MHz, $CDCl_3$): δ (ppm) 8.75 (br s, 1H, NH), 6.79 (q, J = 4.0, 2.4, Hz, 1H, Ar), 6.16 (dd, J = 6.0, 2.8 Hz, 1H, Ar), 6.12 (t, J = 3.6, 1H, Ar), 5.58 (s, 1H, OH), 4.16 (m, 2H, CH_2), 3.07 (d, J = 16.0 Hz, 1H, CH_2), 3.01 (d, J = 16.0 Hz, 1H, CH_2), 1.23 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100.53 MHz, $CDCl_3$): δ (ppm) 172.0, 126.8, 124.8, 122.8, 118.8, 109.1, 107.0, 62.0, 37.5, 14.1; ^{19}F NMR (376.15 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −81.97 (s, 3F); MS $C_{10}H_{13}F_3NO_3$ (251), *m/z* (%): 251 (M^+, 40), 182 (70), 164 (80), 94 (100).

4.28. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(1-methyl-pyrrol-2-yl)-butanoate 2l

Gray oil; ^{1}H NMR (399.81 MHz, $CDCl_3$): δ (ppm) 6.59 (t, J = 7.2 Hz, 1H, Ar), 6.08 (t, J = 3.4 Hz, 1H, Ar), 6.01 (dd, J = 3.6, 2.4 Hz, 1H, Ar), 5.52 (s, 1H, OH), 4.17 (m, 2H, CH_2), 3.82 (s, 3H, CH_3), 3.18 (d, J = 16.0 Hz, 1H, CH_2), 2.96 (d, J = 16.0 Hz, 1H, CH_2), 1.25 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100.53 MHz, $CDCl_3$): δ (ppm) 172.3, 126.6, 126.1, 123.2, 114.1, 110.2, 106.9, 61.9, 38.2, 37.0, 14.1; ^{19}F NMR (376.15 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −80.44 (s, 3F); MS $C_{11}H_{14}F_3NO_3$ (265), *m/z* (%): 265 (M^+, 30), 196 (60), 178 (80), 108 (100), 81 (10).

4.29. Ethyl 4,4,4-trifluoro-3-hydroxy-3-(3,5-dimethyl-pyrrol-2-yl)-butanoate 2m

Dark brown oil; ^{1}H NMR (399.81 MHz, $CDCl_3$): δ (ppm) 8.27 (br s, 1H, NH), 6.71 (d, J = 3.2 Hz, 1H, Ar), 5.64 (s, 1H, OH), 4.16 (q, J = 14.0, 6.8 Hz, 1H, Ar), 3.21 (d, J = 16.0 Hz, 1H, CH_2), 3.03 (d, J = 16.4 Hz, 1H, CH_2), 2.17 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 1.21 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100.53 MHz, $CDCl_3$): δ (ppm) 172.0, 126.8, 123.4, 119.8, 118.1, 116.5, 110.7, 73.4, 61.9, 36.8, 36.5, 14.0; ^{19}F NMR (376.15 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −81.73 (s, 3F); MS $C_{12}H_{16}F_3NO_3$ (279), *m/z* (%): 279 (M^+, 25), 210 (30), 192 (60), 122 (100).

4.30. 2,2,2-Trifluoro-1-phenyl ethanol 3a

^{19}F NMR (376.19 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −78.82 (d, 3F); MS $C_6H_5F_3SO$ (176), *m/z* (%): 176 (M^+, 35), 107 (100), 79 (90), 77 (60).

4.31. 2,2,2-Trifluoro-1-(anthracen-9-yl)-ethanol 3b

^{19}F NMR (376.19 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −74.44 (d, 3F); MS $C_{16}H_{11}F_3O$ (276), *m/z* (%): 276 (M^+, 55), 207 (80), 178 (100).

4.32. 2,2,2-Trifluoro-1-(indole-3-yl)-ethanol 3c

^{19}F NMR (376.19 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −78.30 (d, 3F); MS $C_{10}H_8F_3NO$ (215), *m/z* (%): 215 (M^+, 70), 146 (90), 118 (100).

4.33. 2,2,2-Trifluoro-1-(pyrrol-2-yl)-ethanol 3d

^{19}F NMR (376.19 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −78.86 (d, 3F); MS $C_6H_6F_3NO$ (165), *m/z* (%): 165 (M^+, 60), 148 (10), 96 (100), 68 (90).

4.34. 2,2,2-Trifluoro-1-(4-bromo-phenyl)-ethanol 3e

^{19}F NMR (376.19 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −79.11 (d, 3F); MS $C_8H_6BrF_3O$ (256), *m/z* (%): 256 (M^+, 30), 187 (100), 157 (25), 77 (100).

4.35. 2,2,2-Trifluoro-1-(4-chloro-phenyl)-ethanol 3f

^{19}F NMR (376.19 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −78.95 (d, 3F); MS $C_8H_6ClF_3O$ (210), *m/z* (%): 210 (M^+, 35), 141 (95), 77 (100).

4.36. 1,1,1-Trifluoro-2-hydroxy-3-phenyl-propane 3g

^{19}F NMR (376.19 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −80.03 (d, 3F); MS $C_9H_9F_3O$ (190), *m/z* (%): 190 (M^+, 20), 91 (100), 77 (5).

4.37. 2,2,2-Trifluoro-1-amino ethanol 3h

^{19}F NMR (376.19 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −77.57 (t, 3F).

4.38. 2,2,2-Trifluoro-1-(thiophen-2-yl)-ethanol 3i

^{19}F NMR (376.19 MHz, $CDCl_3$, $CFCl_3$-Ref): δ (ppm) −79.21 (d, 3F); MS $C_6H_5F_3SO$ (182), *m/z* (%): 182 (M^+, 50), 113 (100), 85 (80).

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