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Regioselective nucleophilic addition of 3-aryl-5-difluoromethyl-isoxazoles to aldehydes

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ABSTRACT

A series of 5-difluoromethyl-isoxazoles 2 were prepared, and their regioselective nucleophilic addition to aldehydes was investigated. It was found that the nucleophilic difluoromethylation of aldehydes with 5-difluoromethyl-isoxazoles could be efficiently and uniquely achieved in the presence of LDA as a base that provides a large steric hindrance. In contrast, 3,4,5-trisubstituted 5-difluoromethyl isoxazoles were alternatively afforded as the sole product in moderate yields when *n*-BuLi was used as the base.

1. Introduction

Selective introduction of fluorine atoms or fluorine-containing moieties to organic molecules has become a common and powerful strategy in different research fields, such as pharmaceuticals, biochemistry, and material science [1–4]. Among the various fluorination methods, nucleophilic fluoroalkylation of the substrate with fluorinated carbanions represents the most widely used for the synthesis of fluorinated derivatives [5–9]. Currently, (fluoroalkyl)silanes R_fSiR_3 (such as $TMSCF_3$) [10,11,8,12] and hydrofluorocarbons (such as CF_3H, $PhSO_2CF_2H$, $PhSCF_2H$, $HCF_2PO(OEt)_2$) are the most frequently used nucleophilic fluoroalkylation agents [13–19]. The advantage of using R_fH as a fluoroalkylation agent lies on the fact that functionalization of a C–H bond is the most atom-economical way in organic synthesis [20].

Recently, synthesis of fluorinated heterocyclic compounds, especially isoxazoles, is of particular interest to chemists because they exhibit various bioactivities [21]. Many examples have been reported with respect to the synthesis of trifluoromethylated isoxazoles. However, to the best of our knowledge, preparation of difluoromethyl isoxazoles in using nucleophilic addition reactions is rarely described in the literature [22,23]. The difluoromethyl isoxazoles exert two nucleophilic positions, which, under the treatment of a proper base, may generate a difluoromethyl anion or a 4-position isoxazole anion (Scheme 1). In continuation of our ongoing research on the difluoromethylation reaction [24], we report here a specific and efficient strategy toward the regioselective nucleophilic addition reaction of 5-difluoromethyl isoxazoles to aldehyde. The selection of bases as well as addition order of starting materials has proven crucial for the reactivity.

2. Results and discussion

General methods known for the preparation of fluoroalkyl isoxazoles involve the 1,3-dipolarcycloaddition and addition of hydroxylamine to conjugated ynone or β-diketone derivatives [25–29]. Using the latter reaction, we prepared the starting materials, 5-difluoromethyl-isoxazoles **2a**–**2d**, in 75–85% yields by condensation of 1-difluoromethylated with a range of 1,3-dicarbonyl derivatives in the presence of excess hydroxylamine hydrochloride at reflux in ethanol (Scheme 2).

Subsequently, we carried out a model nucleophilic addition reaction in which benzaldehyde **3a** was used as a model substrate to react with isoxazole **2a**. As shown in Table 1, no reaction took place when NaOH and DBU were applied as the base at room temperature (Table 1, entry 1–2). However, when *n*-BuLi was employed, the reaction proceeded, and a further optimization revealed that the addition order of the materials was critical for the regioselectivity. In our first procedure (A), the 5-difluoromethyl-isoxazoles **2a**,

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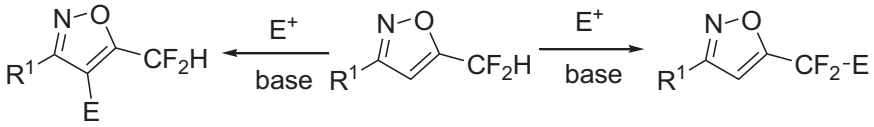
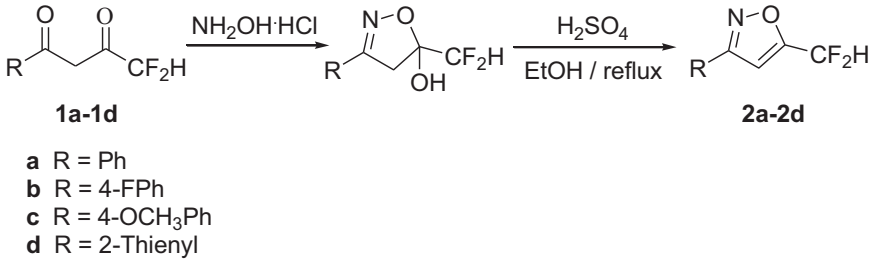


Scheme 1. Possible nucleophilic reactions of difluoromethyl isoxazoles.



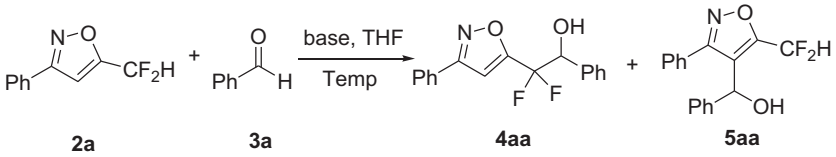
Scheme 2. Preparation of the 5-difluoromethyl-isoxazoles **2**.

benzaldehyde **3a** and *n*-BuLi were mixed at −78 °C in one-pot, and the mixture was allowed gradually to room temperature. After stirring overnight, the difluoromethylated product **4aa** as well as the 3,4,5-trisubstituted isoxazole **5aa** was obtained in low yields (Entries 3–5) with a significant amount of unreacted starting materials.

In the second procedure (B), to a solution of **2a** in THF at −78 °C, *n*-BuLi was added dropwise. After first stirring for 1 h, **3a** was added dropwise at −78 °C, and the mixture was allowed gradually to room temperature, stirring over night. To our delight, the sole nucleophilic addition product, 3,4,5-trisubstituted isoxazole **5aa**, was afforded in 56%, 69% and 75% yields in terms of the different final reaction temperatures (Entries 8–10). Notably, addition of an excess amount of *n*-BuLi only led to a slightly increased yield in procedure A (Entries 6–7), while a mixture of **4aa** and **5aa** was provided with 3 equiv. *n*-BuLi in procedure B (Entry 12). In contrast, when LDA (1.2 equiv.) with a relatively large steric hindrance was used as a base under the same condition, the difluoromethylated product **4aa** was solely afforded in both procedures. Procedure A seems to be superior in this case over B since the former gave the desired unique product in a higher yield of 75% (Entry 13) than the latter (51% Yield, entry 14). So, the optimal reaction conditions for the regioselective nucleophilic addition of 3-aryl-5-difluoromethyl-isoxazoles to aldehydes as follows: 3,4,5-trisubstituted isoxazole **5aa** was produced in 75% yield when benzaldehyde **3a** was added dropwise to a mixture of **2a** and 1.2 equiv. of *n*-BuLi at −78 °C (Entry 10) and the difluoromethylated product **4aa** was afforded in 75% yield by treatment of **2a**, **3a** and 1.2 equiv. of LDA in one-pot (Entry 13).

Having established the optimized reaction condition, a variety of aldehydes were used to probe the substrate scope of the reaction and the results are summarized in Table 2. Use of LDA (according to procedure A) and BuLi (according to procedure B) as the base led to the formation of the desired product **4** and **5** in

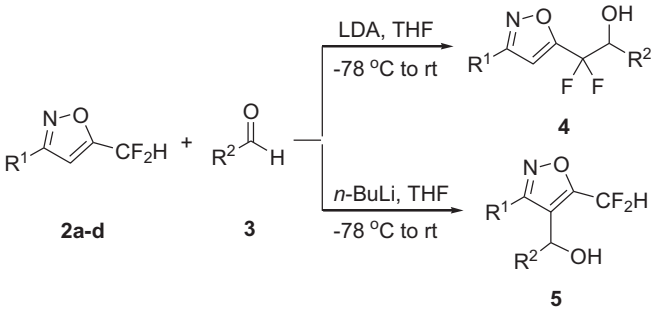
Table 1
Survey of reaction conditions.



Entry	Base	2a:3a:base	Temperature	Procedure[a,b]	Product	Yield %[c]
1	NaOH	1:1.2:2	rt			0
2	DBU	1:1.2:1.2	rt			0
3	*n*-BuLi	1:1.2:1.2	−78 °C to −30 °C	A	**4aa+5aa**	26[d]
4	*n*-BuLi	1:1.2:1.2	−78 °C to 0 °C	A	**4aa+5aa**	20[d]
5	*n*-BuLi	1:1.2:1.2	−78 °C to rt	A	**4aa+5aa**	21[d]
6	*n*-BuLi	1:1.2:1.5	−78 °C to rt	A	**4aa+5aa**	37[d]
7	*n*-BuLi	1:1.2:3	−78 °C to rt	A	**4aa**	47
8	*n*-BuLi	1:1.2:1.2	−78 °C to −30 °C	B	**5aa**	56
9	*n*-BuLi	1:1.2:1.2	−78 °C to 0 °C	B	**5aa**	69
10	**n-BuLi**	**1:1.2:1.2**	**−78 °C to rt**	**B**	**5aa**	**75**
11	*n*-BuLi	1:1.2:1.5	−78 °C to rt	B	**5aa**	69
12	*n*-BuLi	1:1.2:3	−78 °C to rt	B	**4aa+5aa**	80
13	**LDA**	**1:1.2:1.2**	**−78 °C to rt**	**A**	**4aa**	**75**
14	LDA	1:1.2:1.2	−78 °C to rt	B	**4aa**	51

[a] Procedure A: A mixture of **2a**, **3a** and base was stirred at −78 °C in one-pot.
[b] Procedure B: A mixture of **2a** and base was stirred at −78 °C for 1 h, and then **3a** was added dropwise.
[c] Isolated yield.
[d] A large amount of unreacted starting materials.

Table 2
Regioselective nucleophilic addition of different aldehydes with 5-difluoromethyl-isoxazoles **2a–d**.



Entry	R^1	R^2	Base	Product		Yield %[a]
1	Ph (**2a**)	Ph (**3a**)	LDA[b]	**4aa**		75
			BuLi[c]		**5aa**	75
2	Ph (**2a**)	2-Furyl (**3b**)	LDA[b]	**4ab**		63
			BuLi[c]		**5ab**	64
3	Ph (**2a**)	4-$MeOC_6H_4$ (**3c**)	LDA[b]	**4ac**		56
			BuLi[c]		**5ac**	55
4	Ph (**2a**)	4-$CF_3C_6H_4$ (**3d**)	LDA[b]	**4ad**		77
			BuLi[c]		**5ad**	76
5	4-FC_6H_4 (**2b**)	Ph (**3a**)	LDA[b]	**4ba**		53
			BuLi[c]		**5ba**	59
6	4-FC_6H_4 (**2b**)	2-Furyl (**3b**)	LDA[b]	**4bb**		48
			BuLi[c]		**5bb**	55
7	4-FC_6H_4 (**2b**)	4-$MeOC_6H_4$ (**3c**)	LDA[b]	**4bc**		47
			BuLi[c]		**5bc**	54
8	4-FC_6H_4 (**2b**)	4-$CF_3C_6H_4$ (**3d**)	LDA[b]	**4bd**		66
			BuLi[c]		**5bd**	68
9	4-$MeOC_6H_4$ (**2c**)	Ph (**3a**)	LDA[b]	**4ca**		62
			BuLi[c]		**5ca**	57
10	4-$MeOC_6H_4$ (**2c**)	4-$MeOC_6H_4$ (**3c**)	LDA[b]	**4cc**		58
			BuLi[c]		**5cc**	56
11	4-$MeOC_6H_4$ (**2c**)	4-$NO_2C_6H_4$ (**3e**)	BuLi[c]		**5ce**	70
12	4-$MeOC_6H_4$ (**2c**)	n-C_3H_7 (**3g**)	BuLi[c]			Complicated
13	2-Thienyl (**2d**)	Ph (**3a**)	BuLi[c]		**5da**	55
14	2-Thienyl (**2d**)	2-Furyl (**3b**)	BuLi[c]		**5db**	51
15	2-Thienyl (**2d**)	4-$MeOC_6H_4$ (**3c**)	LDA[b]	**4dc**		54
			BuLi[c]		**5dc**	44
16	2-Thienyl (**2d**)	4-$CF_3C_6H_4$ (**3d**)	LDA[b]	**4dd**		66
			BuLi[c]		**5dd**	60

[a] Isolated yield.
[b] Procedure A: A mixture of **2**, **3** and LDA was stirred at −78 °C in one-pot.
[c] Procedure B: A mixture of **2** and *n*-BuLi was stirred at −78 °C for 1 h, then **3** was added dropwise.

moderate-to-reasonable yields, respectively. For the aldehydes with electron-withdrawing substituents on the aromatic ring (such as **3d** and **3e**), the yields are generally higher than those with electron-donating substituents (such as **3c**), which can be ascribed to the intrinsic reactivity of the aldehyde derivatives.

As for the different 5-difluoromethyl-isoxazole substrates, the electronic nature of the substituents on the aromatic ring (such as **2b** vs **2c**) does not impact evidently the reactivity, giving the corresponding adducts in similarly moderate yields. Although 5-difluoromethyl-isoxazole could react with non-enolizable aldehydes [18], we note that, in the present case, **2c** did not react efficiently with an enolizable aldehyde (**3g**) (Table 2, entry 12).

3. Conclusions

In conclusion, we have developed a versatile regioselective nucleophilic reaction of aldehydes with 5-difluoromethyl isoxazoles. The reaction depended on the base employed and different procedures of adding the aldehydes to give the different products. A variety of aldehydes could be difluoromethylated with different 5-difluoromethyl-isoxazoles by treatment of LDA as a base with a large steric hindrance. In contrast, the 3,4,5-trisubstituted 5-difluoromethyl isoxazoles were alternatively produced in moderate yields using *n*-BuLi as a base. Compared to the previously developed difluoromethylation reagents, 5-difluoromethyl isoxazoles merit their relatively easy availability and superior atom-economical feature in fluoroalkylation reactions.

4. Experimental

All melting points were uncorrected. IR spectra were measured on a Nicolet Magna IR-550 spectrometer. High-resolution mass spectra were carried out on a Finnigan GC-MS-4021 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-500 spectrometer with Me_4Si as an internal standard. ^{19}F NMR spectra were obtained on a Bruker AC-500 spectrometer in $CDCl_3$ with $CFCl_3$ as an external standard, in which downfield shifts were designated as negative. All chemical shifts (δ) are expressed in parts per million and coupling constants (J) are given in Hertz.

4.1. General procedure for the preparation of 5-difluoromethyl isoxazoles **2**

A mixture of 1-difluoromethyl β-diketone 1 (5 mmol) and hydroxylamine hydrochloride (6 mmol in 20 mL ethanol) and concentrated sulfuric acid (5 mmol) was stirred for 2–10 h at

reflux. Then the reaction mixture was poured slowly to a 10 mL 10% sodium carbonate solution and extracted with ethyl acetate (3× 10 mL). After dried with sodium sulfate and removal of the solvent, the residue was purified by flash chromatography (petroleum ether/ethyl acetate = 10:1) to give **2** in 75–85% yields.

*4.1.1. 5-(Difluoromethyl)-3-phenylisoxazole (**2a**)*

White solid, m.p. 49.1–49.5 °C; IR (cm^{-1}, KBr): 3426, 3117, 1619, 1370, 1106, 1060, 770, 695. ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.84–7.80 (m, 2H), 7.52–7.48 (m, 3H), 6.89 (s, 1H), 6.80 (t, 1H, J = 53.8 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −118.6 (d, 2F, J_{F-H} = 53.8 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 164.7, 163.2, 131.3, 129.8, 128.6, 127.6, 107.9 (t, J = 239.4 Hz), 102.6. EI-MS (m/z) 195 (M^+, 87), 144 (100), 116 (19), 77 (21). HRMS (EI) calcd for $C_{10}H_7F_2NO$: 195.0496, found: 195.0497.

*4.1.2. 5-Difluoromethyl-3-(4-fluoro-phenyl)-isoxazole (**2b**)*

White solid, m.p. 68.5–69.5 °C; IR (cm^{-1}, KBr): 3379, 3223, 2720, 2471, 1685, 1597, 1254, 774. ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.8 (d, 2H, J = 8.4 Hz), 7.4 (d, 2H, J = 8.4 Hz), 6.83 (s, 1H), 6.77 (t, 1H, J = 53.8 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −109.4 (s, 1F), −117.8 (d, 2F, J_{F-H} = 53.8 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 164.2 (t, J = 30.7 Hz), 164.1 (d, J = 251.5 Hz), 161.6, 128.9, 124.1, 116.3 (d, J = 22 Hz), 107.2 (t, J = 239.4 Hz), 101.9. EI-MS (m/z) 213 (M^+, 100), 162 (78), 134 (43). HRMS (EI): $C_{10}H_6F_3NO$, calcd: 213.0401, found: 213.0402.

*4.1.3. 5-(Difluoromethyl)-3-(4-methoxyphenyl)isoxazole (**2c**)*

White solid, m.p. 71.9–72.1 °C; IR (cm^{-1}, KBr): 3433, 3118, 2940, 2842, 2041, 1614, 1437, 1256, 1067, 830. ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.76 (d, 2H, J = 8.65 Hz), 7.0 (d, 2H, J = 8.63 Hz), 6.83 (s, 1H), 6.78 (t, 1H, J = 53.8 Hz), 3.86 (s, 3H). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −118.6 (d, 2F, J_{F-H} = 53.8 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 164.8 (t, J = 30.9 Hz), 162.8, 162.2, 129.1, 121.0, 115.2, 108.0 (t, J = 239.3 Hz), 102.4, 56.1. EI-MS (m/z) 225 (M^+, 100), 174 (72), 146 (53). HRMS (EI): calcd for $C_{11}H_9F_2NO_2$: 225.0601, found: 225.0602.

*4.1.4. 5-(Difluoromethyl)-3-(thiophen-2-yl)isoxazole (**2d**)*

Yellow oil; IR (cm^{-1}, KBr): 3135, 2964, 2927, 1737, 1617, 1553, 1467, 1104, 1059. ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.50 (dd, 1H, J_1 = 3.65 Hz, J_2 = 1.16 Hz), 7.47 (dd, 1H, J_1 = 5.06 Hz, J_2 = 1.16 Hz), 7.14 (dd, 1H, J_1 = 5.06 Hz, J_2 = 3.65 Hz), 6.82 (s, 1H), 6.77 (t, 1H, J = 53.70 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −118.8 (d, 2F, J_{F-H} = 53.70 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 165.6 (t, J = 31.1 Hz), 159.4, 131.0, 130.1, 129.9, 129.5, 108.8 (t, J = 239.7 Hz), 103.7. EI-MS (m/z) 201 (M^+, 100), 150 (77), 122 (66). HRMS (EI) calcd for $C_8H_5F_2NOS$: 201.0060, found: 201.0058.

*4.2. General procedures for reaction of **2** with different aldehydes **3***

Procedure A: Under nitrogen atmosphere, to a stirred solution of isoxazole (**2a**) (0.5 mmol) and benzaldehyde (**3a**) (0.6 mmol) with 1 mL THF in a Schlenk tube, LDA (0.6 mmol) (dissolved in 1 mL THF) was added dropwise at −78 °C. The mixture was stirred at this temperature for 1 h, and then was raised to room temperature, stirring overnight. The reaction was quenched with saturated aqueous ammonium chloride or brine. The aqueous layer was extracted with ethyl acetate (3× 5 mL) and the combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated under vacuum. The resulting residue was purified by flash chromatography (petroleum ether/ethyl acetate = 10:1) to give **4aa** (113 mg, 75% yield) as a white solid.

Procedure B: Under nitrogen atmosphere, to a stirred solution of isoxazole (**2a**) (0.5 mmol) and 1 mL THF in a Schlenk tube, *n*-BuLi (0.6 mmol) (dissolved in 1 mL THF) was added dropwise at −78 °C, The mixture was stirred at this temperature for 1 h, and then benzaldehyde (**3a**) (0.6 mmol) was added dropwise at −78 °C. Then the mixture was raised to room temperature, stirring overnight. The reaction was then quenched with saturated aqueous ammonium chloride or brine. The aqueous layer was extracted with ethyl acetate (3× 5 mL) and the combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated under vacuum. The resulting residue was purified by flash chromatography (petroleum ether/ethyl acetate = 10:1) to give **5aa** (113 mg, 75% yield) as a white solid.

*4.2.1. 2,2-Difluoro-1-phenyl-2-(3-phenyl-isoxazol-5-yl)-ethanol (**4aa**)*

White solid, m.p. 105.6–106.6 °C; IR (cm^{-1}, KBr): 3359, 2937, 1612, 1443, 1404, 1280, 1184, 772, 692. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.78–7.76 (m, 2H), 7.47 (d, 2H, J = 2.4 Hz), 7.45 (d, 1H, J = 1.2 Hz), 7.41 (d, 1H, J = 4 Hz), 7.37–7.35 (m, 4H), 6.71 (s, 1H), 5.34 (s, 1H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −105.9 (dd, 1F, J_{F-F} = 268 Hz, J_{F-H} = 9 Hz), −109.9 (dd, 1F, J_{F-F} = 268 Hz, J_{F-H} = 13 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 164.1 (t, J = 33.9 Hz), 162.3, 134.6, 130.5, 129.0, 128.7, 128.6, 128.4, 127.6, 126.9, 115.8 (t, J = 247.1 Hz), 103.3, 74.8 (t, J = 28.6 Hz). EI-MS (m/z) 301 (M^+, 6), 195 (100), 145 (9), 77 (22). HRMS (EI) calcd for $C_{17}H_{13}F_2NO_2$: 301.0914, found: 301.0913.

*4.2.2. (5-Difluoromethyl-3-phenyl-isoxazol-4-yl)-phenyl-methanol (**5aa**)*

Light yellow solid, m.p. 166–167 °C; IR (cm^{-1}, KBr): 3335, 2924, 1446, 1352, 1283, 1181, 1067, 1042, 751, 693. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.43–7.40 (m, 1H), 7.36–7.35 (m, 4H), 7.32–7.30 (m, 3H), 7.22–7.20 (m, 2H), 7.04 (t, 1H, J = 53.4 Hz), 5.97 (s, 1H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −115.0 (dd, 1F, J_{F-F} = 307 Hz, J_{F-H} = 50 Hz), −118.4 (dd, 1F, J_{F-F} = 312 Hz, J_{F-H} = 51 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 162.2, 159.9 (t, J = 25.5 Hz), 140.7, 130.0, 128.9, 128.7, 128.6, 127.8, 127.0, 126.7, 121.1, 107.3 (t, J = 238.6 Hz), 68.2. EI-MS (m/z) 301 (M^+, 100), 77 (43). HRMS (EI) calcd for $C_{17}H_{13}F_2NO_2$: 301.0914, found: 301.0911.

*4.2.3. 2,2-Difluoro-1-furan-2-yl-2-(3-phenyl-isoxazol-5-yl)-ethanol (**4ab**)*

Yellow solid, m.p. 112–113 °C; IR (cm^{-1}, KBr): 3376, 2927, 1755, 1663, 1612, 1443, 1404, 1280, 1184, 769, 693. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.81–7.78 (m, 2H), 7.47 (t, 3H, J = 6.4 Hz), 7.44 (s, 1H), 6.85 (s, 1H), 6.48 (d, 1H, J = 3.6 Hz), 6.39 (dd, 1H, J = 3.2 Hz, J = 2.0 Hz), 5.35 (t, 1H, J = 10.6 Hz), 2.97 (s, 1H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −105.3 (dd, 1F, J_{F-F} = 268 Hz, J_{F-H} = 9 Hz), −110.1 (dd, 1F, J_{F-F} = 268 Hz, J_{F-H} = 11 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 163.8 (t, J = 34.6 Hz), 162.4, 147.7, 143.5, 130.6, 129.0, 127.8, 126.9, 114.9 (t, J = 247.8 Hz), 110.8, 110.2, 103.2, 69.4 (t, J = 29.2 Hz). EI-MS (m/z) 291 (M^+, 1), 195 (100), 97 (42.6), 77 (7). HRMS (EI) calcd for $C_{15}H_{11}F_2NO_3$: 291.0707, found: 291.0708.

*4.2.4. 2,2-Difluoro-1-furan-2-yl-2-(3-phenyl-isoxazol-5-yl)-ethanol (**5ab**)*

Light gray solid, m.p. 103.9–104.5 °C; IR (cm^{-1}, KBr): 3327, 2917, 1639, 1500, 1468, 1449, 1361, 1279, 1067, 946, 738, 698. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.49–7.40 (m, 6H), 7.13 (t, 1H, J = 52.4 Hz), 6.35 (dd, 1H, J = 3.4 Hz, J = 1.8 Hz), 6.20 (d, 1H, J = 3.2 Hz), 5.92 (s, 1H), 2.66 (s, 1H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −116.7 (dd, 1F, J_{F-F} = 312 Hz, J_{F-H} = 51 Hz), −118.3 (dd, 1F, J_{F-F} = 312 Hz, J_{F-H} = 51 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 161.7, 160.9 (t, J = 25.3 Hz), 152.9, 143.5, 130.2, 128.9, 128.6, 127.5, 118.7, 110.8, 108.9, 106.9 (t, J = 238.5 Hz), 61.6. EI-MS (m/z) 291 (M^+, 100), 222 (61.5), 144 (54.5), 77 (56.4). HRMS (EI) calcd for $C_{15}H_{11}F_2NO_3$: 291.0707, found: 291.0701.

*4.2.5. 2,2-Difluoro-1-(4-methoxy-phenyl)-2-(3-phenyl-isoxazol-5-yl)-ethanol (**4ac**)*

White solid, m.p. 150.2–151.2 °C; IR (cm^{-1}, KBr): 3423, 2922, 1610, 1514, 1442, 1252, 1172, 1082, 1034, 765, 689. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.79–7.75 (m, 2H), 7.48–7.44 (m, 3H), 7.32 (d, 2H, J = 8.8 Hz), 6.89–6.86 (m, 2H), 6.72 (s, 1H), 5.28 (t, 1H, J = 11.0 Hz), 3.80 (s, 3H), 2.69 (s, 1H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −106.3 (dd, 1F, J_{F-F} = 265 Hz, J_{F-H} = 8 Hz), −109.7 (dd, 1F, J_{F-F} = 268 Hz, J_{F-H} = 11 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 160.9 (t, J = 34.6 Hz), 158.9, 133.2, 129.8, 129.7, 128.5, 127.0, 116.3 (t, J = 247.3 Hz), 114.3, 103.2, 74.8 (t, J = 28.2 Hz), 56.0. EI-MS (*m/z*) 331 (M^+, 1), 195, 137 (100), 109 (9.7), 94 (4.4), 77 (6.5). HRMS (EI) calcd for $C_{18}H_{15}F_2NO_3$: 331.1020, found: 331.1017.

*4.2.6. (5-Difluoromethyl-3-phenyl-isoxazol-4-yl)-(4-methoxy-phenyl)-methanol (**5ac**)*

White solid, m.p. 132–133 °C; IR (cm^{-1}, KBr): 3380, 2922, 1610, 1512, 1465, 1359, 1258, 1174, 1042, 943, 805. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.45–7.40 (m, 1H), 7.37–7.34 (m, 4H), 7.15–7.12 (m, 2H), 7.12 (t, 1H, J = 52.8 Hz), 6.85–6.82 (m, 2H), 5.90 (s, 1H), 3.79 (s, 3H), 2.29 (s, 1H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −114.6 (dd, 1F, J_{F-F} = 310 Hz, J_{F-H} = 53 Hz), −118.9 (dd, 1F, J_{F-F} = 312 Hz, J_{F-H} = 51 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 160.9 (t, J = 34.6 Hz), 158.8, 136.5, 133.2, 129.0, 128.5, 127.0, 114.3, 106.9 (t, J = 237.8 Hz), 100.5, 65.4, 56.0. EI-MS (*m/z*) 331 (M^+, 1), 222 (71.9), 135 (75.8), 109 (51.8), 94 (9), 77 (27.4). HRMS (EI) calcd for $C_{18}H_{15}F_2NO_3$: 331.1020, found: 331.1004.

*4.2.7. 2,2-Difluoro-2-(3-phenyl-isoxazol-5-yl)-1-(4-trifluoromethyl-phenyl)-ethanol (**4ad**)*

Yellow oil; IR (cm^{-1}, KBr): 3302, 2927, 1701, 1619, 1411, 1327, 1166, 1117, 1066, 772, 692. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.79–7.75 (m, 2H), 7.63 (d, 2H, J = 8.4 Hz), 7.56 (d, 2H, J = 8.4 Hz), 7.48–7.45 (m, 3H), 6.76 (s, 1H), 5.43 (dd, 1H, J = 11.4 Hz, J = 9.6 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −62.7 (s, 3F), −105.2 (dd, 1F, J_{F-F} = 268 Hz, J_{F-H} = 9 Hz), −110.1 (dd, 1F, J_{F-F} = 268 Hz, J_{F-H} = 11 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 163.8 (t, J = 34.6 Hz), 150.0, 144.2, 136.5, 129.7, 129.0, 127.0, 125.5, 114.9 (t, J = 243.6 Hz), 106.7, 100.5, 73.6 (t, J = 29.2 Hz). EI-MS (*m/z*) 369 (M^+, 1), 190, 173 (100), 145 (54.9), 95 (5.2), 75 (4). HRMS (EI) calcd for $C_{18}H_{12}F_5NO_2$: 369.0788, found: 369.0796.

*4.2.8. (5-Difluoromethyl-3-phenyl-isoxazol-4-yl)-(4-trifluoromethyl-phenyl)-methanol (**5ad**)*

Light yellow solid, m.p. 157–158 °C; IR (cm^{-1}, KBr): 3379, 2922, 1701, 1462, 1331, 1114, 1044, 836, 771, 701. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.97 (s, 1H), 7.52 (d, 2H, J = 8.0 Hz), 7.37 (d, 4H, J = 4.0 Hz), 7.30 (d, 2H, J = 8.4 Hz), 7.06 (t, 1H, J = 52.6 Hz), 6.07 (s, 1H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −62.6 (s, 3F), −114.8 (dd, 1F, J_{F-F} = 312 Hz, J_{F-H} = 51 Hz), −118.4 (dd, 1F, J_{F-F} = 312 Hz, J_{F-H} = 51 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 160.2 (t, J = 34.6 Hz), 159.1, 148.9, 144.4, 138.1, 130.6, 130.2, 128.8, 126.8, 126.7, 125.7, 106.7 (t, J = 243.5 Hz), 100.5, 67.0. EI-MS (*m/z*) 369 (M^+, 1), 242 (4.6), 190 (64.5), 173 (100), 145 (57.7), 125 (4.5), 95 (5.9), 75 (4.6). HRMS (EI) calcd for $C_{18}H_{12}F_5NO_2$: 369.0788, found: 369.0786.

*4.2.9. 2,2-Difluoro-2-[3-(4-fluoro-phenyl)-isoxazol-5-yl]-1-phenyl-ethanol (**4ba**)*

Colorless solid, m.p. 60.9–61.9 °C; IR (cm^{-1}, KBr): 3413, 2923, 1604, 1527, 1431, 1238, 1163, 1078, 829, 731. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.78–7.74 (m, 2H), 7.42–7.40 (m, 2H), 7.38–7.35 (m, 3H), 7.15 (t, 2H, J = 8.6 Hz), 6.68 (s, 1H), 5.34 (t, 1H, J = 10.8 Hz), 2.69 (s, 1H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −105.7 (dd, 1F, J_{F-F} = 266 Hz, J_{F-H} = 8 Hz), −109.5 (s, 1F), −110.0 (dd, 1F, J_{F-F} = 266 Hz, J_{F-H} = 10 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 162.1 (d, J = 250.4 Hz), 158.9, 150.6, 140.9, 132.1, 128.7, 127.6, 116.2, 114.7 (t, J = 243.7 Hz), 104.7, 86.8. EI-MS (*m/z*) 319 (M^+, 1), 214 (7.2), 213 (100), 107 (29.2), 105 (6.6), 79 (14.4). HRMS (EI) calcd for $C_{17}H_{12}F_3NO_2$: 319.0820, found: 319.0821.

*4.2.10. [5-Difluoromethyl-3-(4-fluoro-phenyl)-isoxazol-4-yl]-phenyl-methanol (**5ba**)*

White solid, m.p. 105.5–106.5 °C; IR (cm^{-1}, KBr): 3352, 1608, 1527, 1467, 1228, 1064, 945, 829, 739, 697. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.37–7.30 (m, 5H), 7.21–7.18 (m, 2H), 7.06–7.01 (m, 2H), 6.92 (t, 1H, J = 8.4 Hz), 5.97 (s, 1H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −110.2 (s, 1F), −114.9 (dd, 1F, J_{F-F} = 312 Hz, J_{F-H} = 51 Hz), −118.4 (dd, 1F, J_{F-F} = 312 Hz, J_{F-H} = 51 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 163.7 (d, J = 250.5 Hz), 161.4 (t, J = 21.7 Hz), 140.4, 130.8, 130.7, 128.9, 128.8, 128.4, 127.6, 126.6, 123.8, 120.9, 115.8 (d, J = 21.7 Hz), 107.3 (t, J = 238.7 Hz), 68.1. EI-MS (*m/z*) 319 (M^+, 100), 240 (25.1), 213 (21.9), 162 (47.5), 105 (48.6), 95 (12.5), 77 (21.4). HRMS (EI) calcd for $C_{17}H_{12}F_3NO_2$: 319.0820, found: 319.0818.

*4.2.11. 2,2-Difluoro-2-[3-(4-fluoro-phenyl)-isoxazol-5-yl]-1-furan-2-yl-ethanol (**4bb**)*

Brown solid, m.p. 103.7–104.9 °C; IR (cm^{-1}, KBr): 3384, 2924, 1605, 1432, 1238, 1106, 823, 746. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.81–7.77 (m, 2H), 7.44 (s, 1H), 7.16 (t, 2H, J = 8.6 Hz), 6.81 (s, 1H), 6.49 (d, 1H, J = 3.2 Hz), 6.40 (dd, 1H, J = 3.2 Hz, J = 1.6 Hz), 5.34 (dd, 1H, J = 12.4 Hz, J = 8.8 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −105.1 (dd, 1F, J_{F-F} = 268 Hz, J_{F-H} = 10 Hz), −109.5 (s, 1F), −110.3 (dd, 1F, J_{F-F} = 268 Hz, J_{F-H} = 11 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 164.1 (d, J = 250.7 Hz), 161.3 (t, J = 23 Hz), 143.5, 128.9, 128.4, 116.3, 110.8, 110.2, 105.3 (t, J = 236.7 Hz), 103.2, 73.6 (t, J = 32.4 Hz). EI-MS (*m/z*) 309 (M^+, 1), 213 (100), 97 (50.9). HRMS (EI) calcd for $C_{15}H_{10}F_3NO_3$: 309.0613, found: 309.0616.

*4.2.12. [5-Difluoromethyl-3-(4-fluoro-phenyl)-isoxazol-4-yl]-furan-2-yl-methanol (**5bb**)*

White solid, m.p. 100.5–102.8 °C; IR (cm^{-1}, KBr): 3381, 1607, 1465, 1367, 1277, 1044, 930, 811, 749. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.46–7.42 (m, 3H), 7.12 (t, 1H, J = 52.4 Hz), 7.13–7.09 (m, 2H), 6.34 (dd, 1H, J = 3.2 Hz, J = 1.6 Hz), 6.19 (d, 1H, J = 3.2 Hz), 5.89 (s, 1H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −109.8 (s, 1F), −116.7 (dd, 1F, J_{F-F} = 312 Hz, J_{F-H} = 51 Hz), −118.3 (dd, 1F, J_{F-F} = 312 Hz, J_{F-H} = 51 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 163.9 (d, J = 250.8 Hz), 161.0 (t, J = 25.6 Hz), 152.7, 143.5, 130.6, 123.6, 118.6, 116.2, 115.9, 110.8, 108.8, 106.9 (t, J = 238.7 Hz), 61.5. EI-MS (*m/z*) 309 (M^+, 100), 240 (39.1), 230 (26.2), 162 (57.5), 95 (29.6). HRMS (EI) calcd for $C_{15}H_{10}F_3NO_3$: 309.0613, found: 309.0611.

*4.2.13. 2,2-Difluoro-2-[3-(4-fluoro-phenyl)-isoxazol-5-yl]-1-(4-methoxy-phenyl)-ethanol (**4bc**)*

White solid, m.p. 115.6–116.6 °C; IR (cm^{-1}, KBr): 3405, 2922, 1603, 1512, 1239, 1032, 840. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.78–7.75 (m., 2H), 7.33 (d, 2H, J = 8.8 Hz), 7.15 (t, 2H, J = 8.6 Hz), 6.88 (d, 2H, J = 8.8 Hz), 6.69 (s, 1H), 5.27 (t, 1H, J = 10.8 Hz), 3.80 (s, 3H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −105.8 (dd, 1F, J_{F-F} = 266 Hz, J_{F-H} = 8 Hz), −109.58 (s, 1F), −110.1 (dd, 1F, J_{F-F} = 266 Hz, J_{F-H} = 10 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 162.1 (d, J = 250.7 Hz), 160.9, 158.9, 150.3, 133.2, 132.1, 128.3, 116.0, 114.7 (t, J = 243.7 Hz), 100.5, 83.4, 54.7. EI-MS (*m/z*) 349 (M^+, 1), 213 (8.1), 137 (100), 109 (9.3), 94 (4.4), 77 (3.2). HRMS (EI) calcd for $C_{18}H_{14}F_3NO_3$: 349.0926, found: 349.0930.

*4.2.14. [5-Difluoromethyl-3-(4-fluoro-phenyl)-isoxazol-4-yl]-(4-methoxy-phenyl)-methanol (**5bc**)*

Light yellow solid, m.p. 116.1–117.1 °C; IR (cm^{-1}, KBr): 3401, 2919, 1609, 1513, 1259, 1174, 1069, 1037, 944, 806. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.35–7.30 (m, 2H), 7.12 (d, 2H, J = 8.8 Hz), 7.11

(t, 1H, J = 52.8 Hz), 7.07–7.01 (m, 2H), 6.86–6.82 (m, 2H), 5.88 (s, 1H), 3.79 (s, 3H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −110.3 (s, 1F), −114.42 (dd, 1F, J_{F-F} = 312 Hz, J_{F-H} = 51 Hz), −118.90 (dd, 1F, J_{F-F} = 308 Hz, J_{F-H} = 50 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 162.1 (d, J = 250.5 Hz), 159.9, 132.8, 130.8, 130.7, 128.2, 121.2, 115.9, 115.7, 106.4 (t, J = 238.5 Hz), 68.9, 55.8. EI-MS (m/z) 349 (M^+, 100), 162 (13.5), 135 (61.7), 109 (72.9), 94 (9.8), 77 (12.4). HRMS (EI) calcd for $C_{18}H_{14}F_3NO_3$: 349.0926, found: 349.0925.

4.2.15. 2,2-Difluoro-2-[3-(4-fluoro-phenyl)-isoxazol-5-yl]-1-(4-trifluoromethyl-phenyl)-ethanol (**4bd**)

Yellow solid, m.p. 92.4–93.4 °C; IR (cm^{-1}, KBr): 3447, 2923, 1609, 1465, 1431, 1327, 1167, 1129, 1068, 839. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.77 (dd, 2H, J = 8.8 Hz, J = 5.2 Hz), 7.59–7.54 (m, 4H), 7.16 (t, 2H, J = 8.6 Hz), 6.72 (s, 1H), 5.42 (dd, 1H, J = 12.0 Hz, J = 9.2 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −62.3 (s, 3F), −105.0 (dd, 1F, J_{F-F} = 266 Hz, J_{F-H} = 9 Hz), −109.58 (s, 1F), −110.11 (dd, 1F, J_{F-F} = 266 Hz, J_{F-H} = 11 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 161.2 (d, J = 250.7 Hz), 158.3, 150.7, 144.2, 132.7, 130.0, 128.3, 127.6, 119.3, 114.6 (t, J = 243.7 Hz), 100.3, 83.5. EI-MS (m/z) 387 (M^+, 1), 213 (100), 175 (31), 127 (20.5). HRMS (EI) calcd for $C_{18}H_{11}F_6NO_2$: 387.0694, found: 387.0691.

4.2.16. [5-Difluoromethyl-3-(4-fluoro-phenyl)-isoxazol-4-yl]-(4-trifluoromethyl-phenyl)-methanol (**5bd**)

White solid, m.p. 95.5–96.5 °C; IR (cm^{-1}, KBr): 3334, 2924, 1695, 1327, 1126, 1066, 860. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.22 (d, 2H, J = 8.0 Hz), 7.75 (d, 2H, J = 8.0 Hz), 7.30 (d, 2H, J = 8.0 Hz), 7.07–7.03 (m, 2H), 7.03 (t, 1H, J = 52.8 Hz), 6.10 (s, 1H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −62.5 (s, 3F), −109.8 (s, 1F), −114.5 (dd, 1F, J_{F-F} = 314 Hz, J_{F-H} = 51 Hz), −118.20 (dd, 1F, J_{F-F} = 314 Hz, J_{F-H} = 52 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 162.3 (d, J = 250.8 Hz), 158.4, 158.3, 144.2, 130.9, 130.6, 126.8, 125.6, 115.9, 107.6 (t, J = 138.7 Hz), 100.8, 64.5. EI-MS (m/z) 387 (M^+, 1), 190 (62.5), 173 (100), 145 (56.7), 127 (13.2), 107 (10.6), 95 (6), 75 (3.3). HRMS (EI) calcd for $C_{18}H_{11}F_6NO_2$: 387.0694, found: 387.0691.

4.2.17. 2,2-Difluoro-2-[3-(4-methoxy-phenyl)-isoxazol-5-yl]-1-phenyl-ethanol (**4ca**)

White solid; m.p. 99.3–100.1 °C; IR (cm^{-1}, KBr): 3426, 3136, 2937, 1612, 1462, 1430, 1255, 1101, 1078, 1036, 831, 812. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.68 (d, 2H, J = 8.8 Hz), 7.42–7.39 (m, 2H), 7.37–7.34 (m, 3H), 6.95 (d, 2H, J = 8.8 Hz), 6.66 (s, 1H), 5.32 (dd, 1H, J = 12.0 Hz, J = 9.6 Hz), 3.84 (s, 3H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −106.9 (dd, 1F, J_{F-F} = 268 Hz, J_{F-H} = 9 Hz), −110.9 (dd, 1F, J_{F-F} = 268 Hz, J_{F-H} = 12 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 167.2, 161.4, 155.8, 134.6, 130.1, 129.2, 129.0, 128.4, 128.3, 127.7, 126.7, 115.8, 114.4 (t, J = 247.8 Hz), 103.0, 74.8 (t, J = 28.2 Hz), 55.4. EI-MS (m/z) 331 (M^+, 34), 225 (100), 107 (17). HRMS (EI) calcd for $C_{18}H_{15}F_2NO_3$: 331.1020, found: 331.1021.

4.2.18. (5-(Difluoromethyl)-3-(4-methoxyphenyl)isoxazol-4-yl)(phenyl)methanol (**5ca**)

White solid, m.p. 125.6–126.6 °C; IR (cm^{-1}, KBr) 3501, 2979, 1610, 1515, 1456, 1387, 1249, 1054, 855, 702. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.59–7.55 (m, 2H), 7.33–7.30 (m, 5H), 6.90 (d, 2H, J = 12 Hz), 6.70 (t, 1H, J = 52.0 Hz), 6.15 (s, 1H), 3.81 (s, 3H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −115.0 (dd, 1F, J_{F-F} = 308 Hz, J_{F-H} = 50 Hz), −116.5 (dd, 1F, J_{F-F} = 308 Hz, J_{F-H} = 50 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 168.9, 161.5, 158.0, 141.0, 129.6, 128.6, 127.9, 127.0, 126.1, 119.2, 114.3, 109.7 (t, J = 237.9 Hz), 66.4, 55.4. EI-MS (m/z) 331 (M^+, 100), 252 (17.5), 135 (74.3), 105 (15.6), 77 (13.1). HRMS (EI) calcd for $C_{18}H_{15}F_2NO_3$: 331.1020, found: 331.1017.

4.2.19. 2,2-Difluoro-1-(4-methoxy-phenyl)-2-[3-(4-methoxy-phenyl)-isoxazol-5-yl]-ethanol (**4cc**)

White solid; m.p. 109.1–110.3 °C; IR (cm^{-1}, KBr): 3426, 3136, 2937, 1612, 1462, 1430, 1255, 1101, 1078, 1036, 831, 812. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.71 (d, 2H, J = 8.8 Hz), 7.32 (d, 2H, J = 8.8 Hz), 6.97 (d, 2H, J = 8.6 Hz), 6.87 (d, 2H, J = 8.8 Hz), 6.67 (s, 1H), 5.27 (t, 1H, J = 10.6 Hz), 3.85 (s, 3H), 3.79 (s, 3H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −106.8 (dd, 1F, J_{F-F} = 268 Hz, J_{F-H} = 9 Hz), −110.8 (dd, 1F, J_{F-F} = 268 Hz, J_{F-H} = 11 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 165.3, 161.5, 158.6, 134.6, 130.1, 129.4, 129.0, 128.4, 128.1, 127.7, 126.5, 115.8, 114.7 (t, J = 245.8 Hz), 103.0, 74.8, 60.1, 55.2. EI-MS (m/z) 361 (M^+, 37), 225 (100), 137 (67). HRMS (EI) calcd for $C_{19}H_{17}F_2NO_4$: 361.1126, found: 361.1113.

4.2.20. (5-(Difluoromethyl)-3-(4-methoxyphenyl)isoxazol-4-yl)(4-methoxyphenyl)methanol (**5cc**)

White solid, m.p. 85.3–87.1 °C; IR (cm^{-1}, KBr) 3359, 2840, 1611, 1512, 1463, 1253, 1034, 808. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.54 (d, 2H, J = 8.0 Hz), 7.25 (d, 2H, J = 8.0 Hz), 6.88 (d, 2H, J = 8.0 Hz), 6.83 (d, 2H, J = 8.0 Hz), 6.75 (t, 1H, J = 56.0 Hz), 6.08 (s, 1H), 3.80 (s, 3H), 3.76 (s, 3H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −114.8 (dd, 1F, J_{F-F} = 308 Hz, J_{F-H} = 50 Hz), −117.1 (dd, 1F, J_{F-F} = 307 Hz, J_{F-H} = 50 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 168.4, 161.4, 159.3, 133.3, 129.5, 128.1, 127.6, 119.2, 114.7, 114.3, 113.9, 109.7 (t, J = 238.4 Hz), 66.4, 60.5, 55.4. EI-MS (m/z) 361 (M^+, 85), 252 (46.3), 135 (100), 109 (40.6), 77 (10.3). HRMS (EI) calcd for $C_{19}H_{17}F_2NO_4$: 361.1126, found: 361.1118.

4.2.21. (5-(Difluoromethyl)-3-(4-methoxyphenyl)isoxazol-4-yl)(4-nitrophenyl)methanol (**5ce**)

Yellow oil; IR (cm^{-1}, KBr) 3359, 1614, 1532, 1353, 1256, 1043, 803. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.08 (d, 2H, J = 8.8 Hz), 7.49 (d, 1H, J = 7.6 Hz), 7.43 (t, 1H, J = 8.0 Hz), 7.33 (d, 2H, J = 8.8 Hz), 7.02 (t, 1H, J = 52.8 Hz), 6.86 (d, 2H, J = 8.8 Hz), 6.18 (s, 1H), 3.81 (s, 3H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −115.0 (dd, 1F, J_{F-F} = 320 Hz, J_{F-H} = 55 Hz), −117.3 (dd, 1F, J_{F-F} = 320 Hz, J_{F-H} = 55 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 162.2, 161.1, 160.3, 148.2, 142.6, 132.2, 130.2, 129.6, 123.1, 121.4, 120.0, 119.4, 114.2, 107.5 (t, J = 237.5 Hz), 66.0, 55.4. HRMS (EI) calcd for $C_{18}H_{14}F_2N_2O_5$: 376.0871, found: 376.0873.

4.2.22. (5-Difluoromethyl-3-thiophen-3-yl-isoxazol-4-yl)-phenyl-methanol (**5da**)

Light yellow solid, m.p. 66.2–67.2 °C; IR (cm^{-1}, KBr): 3410, 3107, 1558, 1463, 1353, 1280, 1177, 1116, 1041, 922, 845, 817, 763, 699. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.41 (dd, 1H, J = 5.2 Hz, J = 1.2 Hz), 7.38–7.35 (m, 3H), 7.34–7.31 (m, 2H), 7.18 (dd, 1H, J = 3.6 Hz, J = 0.8 Hz), 7.03 (t, 1H, J = 52.8 Hz), 7.02 (t, 1H, J = 4.4 Hz), 6.13 (s, 1H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −114.9 (dd, 1F, J_{F-F} = 312 Hz, J_{F-H} = 51 Hz), −118.8 (dd, 1F, J_{F-F} = 312 Hz, J_{F-H} = 51 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 160.5, 156.5, 140.2, 129.2, 129.1, 1298.96, 128.6, 128.5, 127.7, 126.9, 120.3, 110.1 (t, J = 234.1 Hz), 107.2, 68.1. EI-MS (m/z) 307 (M^+, 62), 256 (31.2), 228 (24.7), 201 (25.5), 150 (51.2), 105 (100), 84 (60.4), 77 (49). HRMS (EI) calcd for $C_{15}H_{11}F_2NO_2S$: 307.0479, found: 307.0475.

4.2.23. (5-Difluoromethyl-3-thiophen-3-yl-isoxazol-4-yl)-furan-3-yl-methanol (**5db**)

Yellow solid, m.p. 73.6–74.6 °C; IR (cm^{-1}, KBr): 3340, 1551, 1466, 1363, 1279, 1149, 1042, 921, 822, 723. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.66 (d, 1H, J = 0.8 Hz), 7.45 (d, 1H, J = 4.8 Hz), 7.39 (d, 1H, J = 4.0 Hz), 7.27 (s, 1H), 7.05 (dd, 1H, J = 5.0 Hz, J = 3.8 Hz), 6.79 (t, 1H, J = 52.6 Hz), 6.61 (dd, 1H, J = 3.8 Hz, J = 1.6 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −116.7 (dd, 1F, J_{F-F} = 312 Hz, J_{F-H} = 51 Hz), −118.3 (dd, 1F, J_{F-F} = 312 Hz, J_{F-H} = 51 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 162.5 (t, J = 27.8 Hz), 156.1, 152.1, 148.7, 129.9,

129.1, 127.9, 127.3, 121.8, 113.4, 106.4 (t, J = 241.7 Hz), 58.3. EI-MS (m/z) 297 (M^+, 1), 295 (68.4), 150 (17.2), 95 (100). HRMS (EI) calcd for $C_{13}H_9F_2NO_3S$: 297.0271, found: 297.0130.

*4.2.24. 2,2-Difluoro-1-(4-methoxy-phenyl)-2-(3-thiophen-3-yl-isoxazol-5-yl)-ethanol (**4dc**)*

Yellow solid, m.p. 96.8–97.8 °C; IR (cm^{-1}, KBr): 3435, 2925, 1609, 1512, 1464, 1249, 1174, 1030, 839, 712. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.46–7.44 (m, 2H), 7.32 (d, 2H, J = 8.4 Hz), 7.12 (dd, 1H, J = 4.8 Hz, J = 4.0 Hz), 6.90 (d, 2H, J = 6.0 Hz), 6.56 (s, 1H), 5.27 (t, 1H, J = 11.0 Hz), 3.81 (s, 3H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −106.3 (dd, 1F, $J_{F\text{-}F}$ = 266 Hz, $J_{F\text{-}H}$ = 8 Hz), −109.7 (dd, 1F, $J_{F\text{-}F}$ = 266 Hz, $J_{F\text{-}H}$ = 10 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 159.8, 159.2, 133.1, 129.1, 128.7, 128.4, 128.2, 127.8, 114.7 (t, J = 243.9 Hz), 113.8, 73.8 (t, J = 28 Hz), 55.3. EI-MS (m/z) 337 (M^+, 3.6), 201 (21.9), 137 (100), 135 (5.4), 94 (3.7). HRMS (EI) calcd for $C_{16}H_{13}F_2NO_3S$: 337.0584, found: 337.0590.

*4.2.25. (5-Difluoromethyl-3-thiophen-3-yl-isoxazol-4-yl)-(4-methoxy-phenyl)-methanol (**5dc**)*

Yellow oil; IR (cm^{-1}, KBr): 3379, 2923, 1610, 1512, 1461, 1255, 1028, 820, 719. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.40 (d, 1H, J = 4.8 Hz), 7.23 (s, 2H), 7.15 (d, 1H, J = 3.6 Hz), 7.09 (t, 1H, J = 52.8 Hz), 7.02 (t, 1H, J = 4.4 Hz), 6.89 (d, 2H, J = 8.4 Hz), 6.07 (s, 1H), 3.80 (s, 3H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −114.4 (dd, 1F, $J_{F\text{-}F}$ = 310 Hz, $J_{F\text{-}H}$ = 52 Hz), −119.4 (dd, 1F, $J_{F\text{-}F}$ = 312 Hz, $J_{F\text{-}H}$ = 51 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 160.5, 160.0, 139.2, 133.0, 129.2, 128.5, 127.7, 122.6, 114.5, 107.8 (t, J = 241.7 Hz), 68.1, 55.4. EI-MS (m/z) 337 (M^+, 68), 286 (20.5), 202 (34.9), 135 (100), 109 (32.6), 77 (15.1). HRMS (EI) calcd for $C_{16}H_{13}F_2NO_3S$: 337.0584, found: 337.0583.

*4.2.26. 2,2-Difluoro-2-(3-thiophen-3-yl-isoxazol-5-yl)-1-(4-trifluoromethyl-phenyl)-ethanol (**4dd**)*

White solid, m.p. 119–120 °C; IR (cm^{-1}, KBr): 3356, 2924, 1699, 1330, 1114, 1064, 716. ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.22 (d, 2H, J = 8.0 Hz), 7.75 (d, 2H, J = 8.0 Hz), 7.55 (d, 2H, J = 8.0 Hz), 7.13 (t, 1H, J = 4.2 Hz), 6.69 (s, 1H), 5.42 (dd, 1H, J = 11.6 Hz, J = 9.6 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −63.2 (s, 3F), −105.2 (dd, 1F, $J_{F\text{-}F}$ = 268 Hz, $J_{F\text{-}H}$ = 9 Hz), −110.2 (dd, 1F, $J_{F\text{-}F}$ = 268 Hz, $J_{F\text{-}H}$ = 11 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 162.5, 156.1, 128.9, 128.7, 128.4, 128.3, 127.8, 114.7 (t, J = 243.6 Hz), 113.9, 73.8. EI-MS (m/z) 375 (M^+, 13.8), 201 (100), 175 (26.2), 127 (23.1). HRMS (EI) calcd for $C_{16}H_{10}F_5NO_2S$: 375.0352, found: 375.0356.

*4.2.27. (5-Difluoromethyl-3-thiophen-3-yl-isoxazol-4-yl)-(4-trifluoromethyl-phenyl)-methanol (**5dd**)*

White solid, m.p. 101.9–102.9 °C; IR (cm^{-1}, KBr): 3381, 1335, 1271, 1159, 1108, 816, 719. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.61 (d, 2H, J = 8.0 Hz), 7.44 (d, 2H, J = 8.4 Hz), 7.42 (d, 1H, J = 1.2 Hz), 7.24 (dd, 1H, J = 3.6 Hz, J = 1.2 Hz), 7.04 (dd, 1H, J = 5.2 Hz, J = 3.6 Hz), 7.01 (t, 1H, J = 52.6 Hz), 6.25 (s, 1H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ: −62.69, −114.5 (dd, 1F, $J_{F\text{-}F}$ = 312 Hz, $J_{F\text{-}H}$ = 51 Hz), −118.6 (dd, 1F, $J_{F\text{-}F}$ = 312 Hz, $J_{F\text{-}H}$ = 51 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 155.2, 152.4, 143.9, 129.6, 128.8, 127.8, 127.0, 121.8, 119.6, 117.7, 116.5, 114.8 (t, J = 234.8 Hz), 107.0, 66.9. EI-MS (m/z) 375 (M^+, 84.5), 324 (29.5), 201 (45.2), 173 (57.3), 150 (100), 127 (40.4), 84 (80.4). HRMS (EI) calcd for $C_{16}H_{13}F_2NO_3S$: 375.0352, found: 375.0349.

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