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Development of Cyanopyrazoles as Building-Blocks to Fungicide Fluxapyroxad and Analogues

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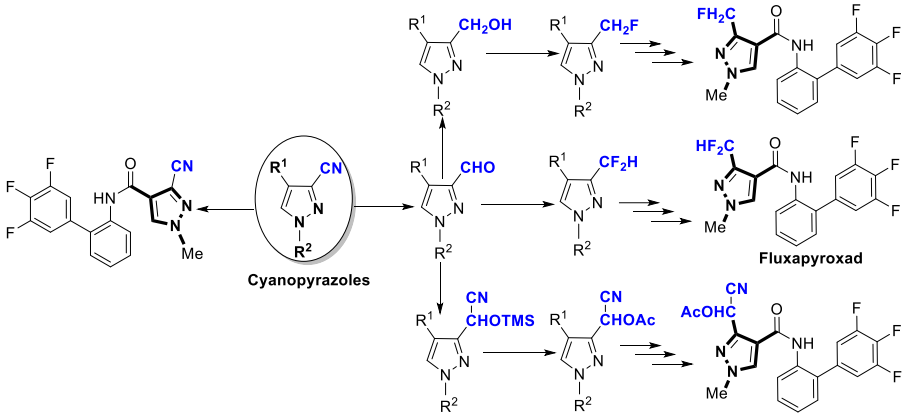
Supporting Information



ABSTRACT: Herein we present a facile approach to a diverse collection of 1,4-disubstituted-3-di- or mono-fluoromethylpyrazoles utilizing our previously developed cyanopyrazoles as key building blocks. This method features several merits, such as easily accessible starting materials, broad substrate scope, mild reaction conditions, and simple operation. This protocol further deserves to be highlighted by the successful translation into the synthesis of commercialized fungicide Fluxapyroxad and its analogues.

KEYWORDS: *cyanopyrazoles, fluoroalkyl pyrazoles, SDHI fungicide, Fluxapyroxad*

1. INTRODUCTION

3-Fluoroalkylpyrazoles belong to a family of heterocycles with a significant application in the realm of organic chemistry, pharmaceuticals, agrochemicals, and material science.[1] Among the numerous related derivatives, 1,4-disubstituted-3-difluoromethylpyrazoles particularly deserve to be highlighted as prevalent structural motifs with a significant value in various bioactive molecules.[2] These motifs can be found in a number of succinate dehydrogenase inhibitors (SDHIs) with a broad-spectrum of fungicidal activity, which represent the fastest growing mode-of-action (MoA) to protect crops against phytopathogens on the fungicide market.[3] Among them are Fluxapyroxad,[4] Bixafen,[5] Sedaxana,[6] Isopyrazam,[7] Benzovondiflupyr,[8] and Pydiflumetofen[9] (Figure 1). As a consequence, the efficient synthesis of these motifs is highly desired in the organic and medicinal community.[10] The most typical approach to 1,4-disubstituted-3-difluoromethylpyrazoles resides in the cyclocondensations of 1,1-difluoro-4-dialkoxyl- or di(alkyl)amino-3-en-2-ones with a substituted hydrazine, which features moderate to high regioselectivity (Scheme 1A).[11] To obtain a better control on the regiochemistry of these reactions, a number of recent studies have led to the discovery of protected hydrazines,

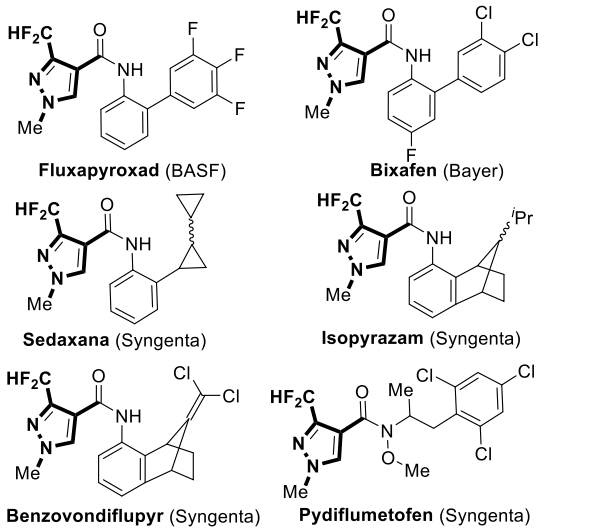
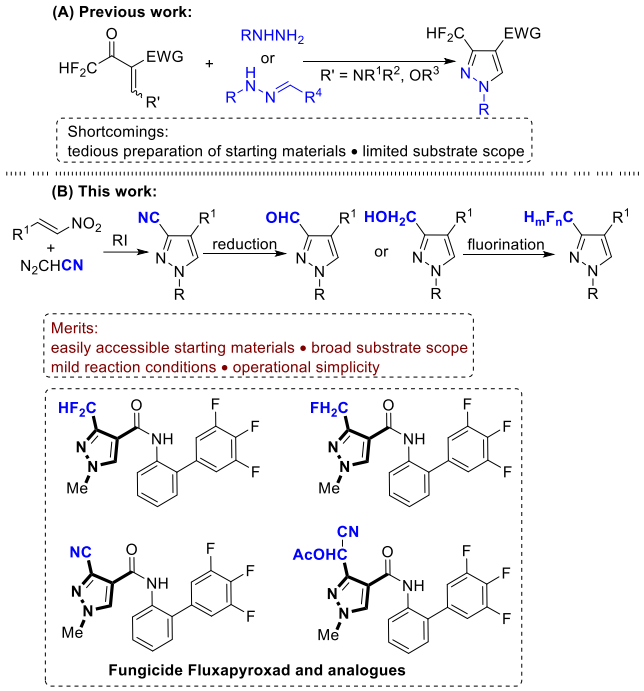


Figure 1. Commercialized SDHIs Containing 1,4-Disubstituted 3-difluoromethylpyrazole Motifs

namely hydrazones, as cyclization partners to yield the desired product as a single isomer.[12] Other approaches to the 1,4-disubstituted-3-difluoromethylpyrazoles include the cyclization reaction of difluoroacetic hydrazide with ethyl propargylate,[13] late elaboration on a pyrazole scaffold[14] as well as the successive transformation of 1,1,2,2-tetrafluoroehtyl-*N*,*N*-dimethylamine (TFEDMA).[15] However, the tedious procedure for the preparation of the required starting materials severely limited the substrate scope of these approaches, wherein only electron-withdrawing groups can be incorporated into the C4-position of the pyrazole motifs. Therefore, it is still of great importance to develop novel methods for the access to more abundant 1,4-disubstituted-3-difluoromethylpyrazoles.

Scheme 1. Synthesis of 1,4-Disubstituted-3-difluoromethyl-pyrazoles.



As part of our continuing interest in the construction of pyrazole derivatives,[16] we recently developed a multi-component reaction of nitroolefins with diazoacetonitrile and alkyl halides, thus providing a direct approach to a variety of 1,4-disubstituted-3-cyanopyrazoles in one step.[17] To pursue the further application of these cyanopyrazoles, herein we present their facile transformation to a diverse collection of 1,4-disubstituted-3-di- or mono-fluoromethylpyrazoles via a successive reduction and fluorination sequence (Scheme 1B). This transformation exhibits several features, such as easily accessible starting materials, broad substrate scope, mild reaction conditions and simple operation. Furthermore, this approach can be successfully translated into the total synthesis of the commercialized SDHI fungicide Fluxapyroxad and its several analogues.

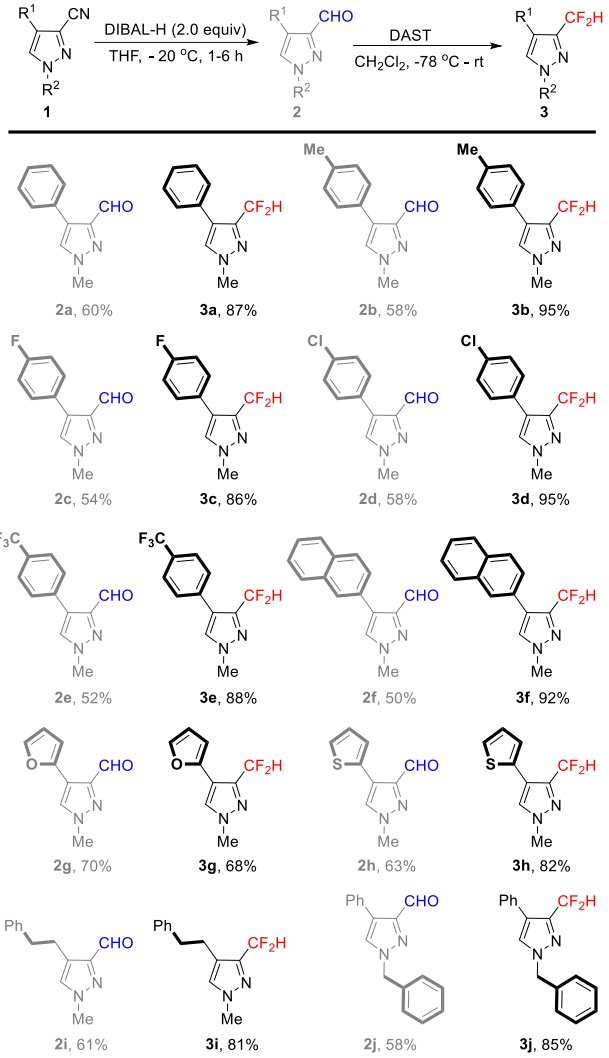
2. RESULTS AND DISCUSSION

According to our previous study,[17] we commenced this work with investigating the substrate scope of the reduction reaction of 1,4-disubstituted-3-cyanopyrazoles **1** and the follow-up difluorination reaction. As shown in Scheme 2, in the presence of diisobutylaluminum hydride (DIBAL-H), a variety of 1,4-disubstituted-3-cyanopyrazoles can be successfully transformed into the corresponding pyraozle-3-carbaldehydes **2a-j** in moderate yields (49-65%). The subsequent fluorination was readily achieved by utilizing diethylaminosulfur trifluoride (DAST) as the fluorination reagent. In the case of 1-methyl-4-phenyl-1*H*-pyrazole-3-carbonitriles **1a-e**, this synthetic approach tolerated a range of substitution patterns on the phenyl ring, including methyl, fluoro, chloro, and trifluoromethyl groups to give the corresponding products **3a-e**. 2-Naphthyl-substituted cyanopyrazole was found to be a competent substrate, thus affording the desired product **3f** in practical overall yield. Heteroaryl, such as 2-thiophenyl- and 3-pyridyl-substituted cyanopyrazoles, also underwent the desired transformations uneventfully to deliver the corresponding 1,4-disubstituted-3-difluoromethylpyrazoles **3g** and **3h** in good yields over two steps. 4-Alkyl-substituted-3-cyanopyrazole also performed well under the same reaction conditions (**3i**). Besides methyl group, other alkyl-substituent such as benzyl was also compatible at the N1 position of the pyrazole core (**3j**), which further highlights the mild reaction conditions and broad substrate scope for this method.

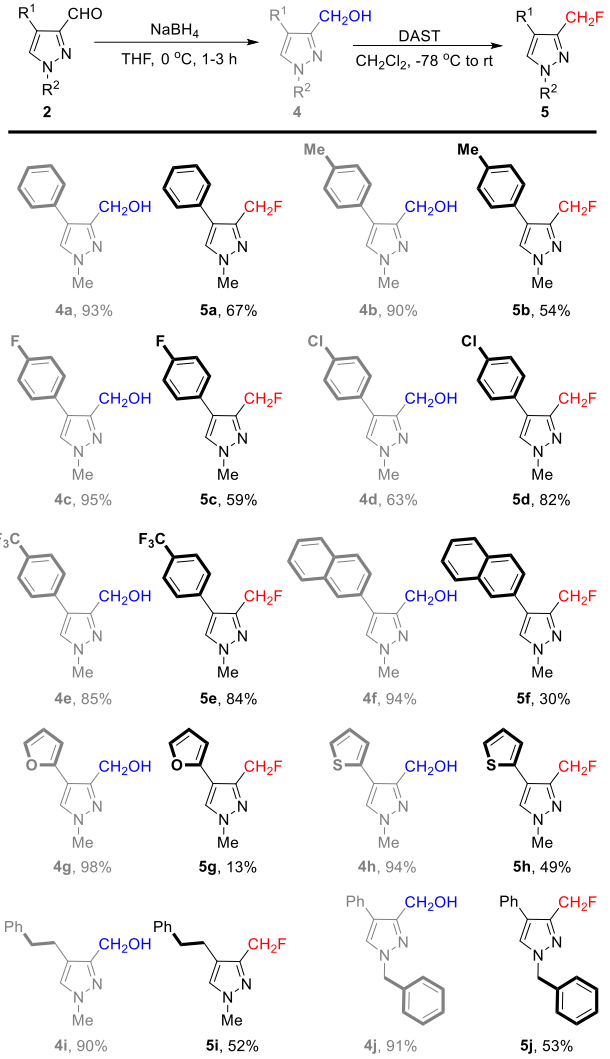
While 1,4-disubstituted-3-tri- or di-fluoromethylpyrazoles have gained much attention over the past few decades, the corresponding monofluoromethylpyrazole analogues have been largely ignored.[18] Therefore, we continued this work with evaluating the feasibility of converting the cyanopyrazoles **1** to 1,4-disubstituted-3-monofluoromethylpyrazoles. As depicted in Scheme 3, in the presence of sodium borohydride ($NaBH_4$), the previously obtained pyrazole-3-carbaldehydes **2** could be reduced to the corresponding alcohols **4** in excellent efficiencies regardless of the substituent patterns at the C4 or N1 position on the pyrazole ring. Phenyl, substituted phenyl, polycyclic aryl, heteroaryl, and alkyl groups were all compatible with this transformation, thereby providing the products **4a-j** in 83-98% yields. Subsequently, the fluorination reactions of alcohols **4** were evaluated with DAST as fluorination reagent. In the case of 4-phenyl-substituted substrates **4a-e**, the fluorination reactions proceeded smoothly to deliver the desired 1,4-disubstituted-3-monofluoromethylpyrazoles **5a-e** in good to high yields (54-90%). 4-Polycyclic aryl- and heteroaryl-substituted alcohols also underwent this reactions despite in much lower yields (**5f-h**). Lastly, 1-methyl-4-phenylethyl- and 1-benzyl-4-phenyl-substituted-3-monofluoromethylpyrazoles **5i** and **5j** were also readily isolated in 52% and 53% yields, respectively.

Having determined the broad substrate scope of the current protocol, we then turned our attention to its implementation in the synthesis of the commercialized SDHI fungicide Fluxapyroxad and its analogues. As shown in Scheme 4a, starting from compound **3g**, it was smoothly oxidized in the presence of $NaIO_4$ and catalytic amount of $RuCl_3$, thus delivering the corresponding carboxylic acid **7** in decent yield. The acid **7** was then treated with phosphorus pentachloride (PCl_5) and 3',4',5'-trifluoro-[1,1'-biphenyl]-2-amine in a one-pot manner, and the desired SDHI fungicide Fluxapyroxad (**11**) was isolated in 83% yield.[19] Utilizing a similar process, the monofluoromethyl-analogue **12**, cyano-analogue **13** and α-acetoxy-cyanoethyl-analogue **14** were readily obtained in 36-56% total yields over three steps, wherein the starting

Scheme 2. The Scope of (1H-pyrazol-3-yl)-carbaldehydes 2 and 3-Difluoromethylpyrazoles 3.



Scheme 3. The Scope of (1H-pyrazol-3-yl)-methanols 4 and 3-Fluoromethylpyrazoles 5.



Scheme 4. Synthesis of the Corresponding Intermediates and SDHI Fungicide Fluxapyroxad and Its Analogues.

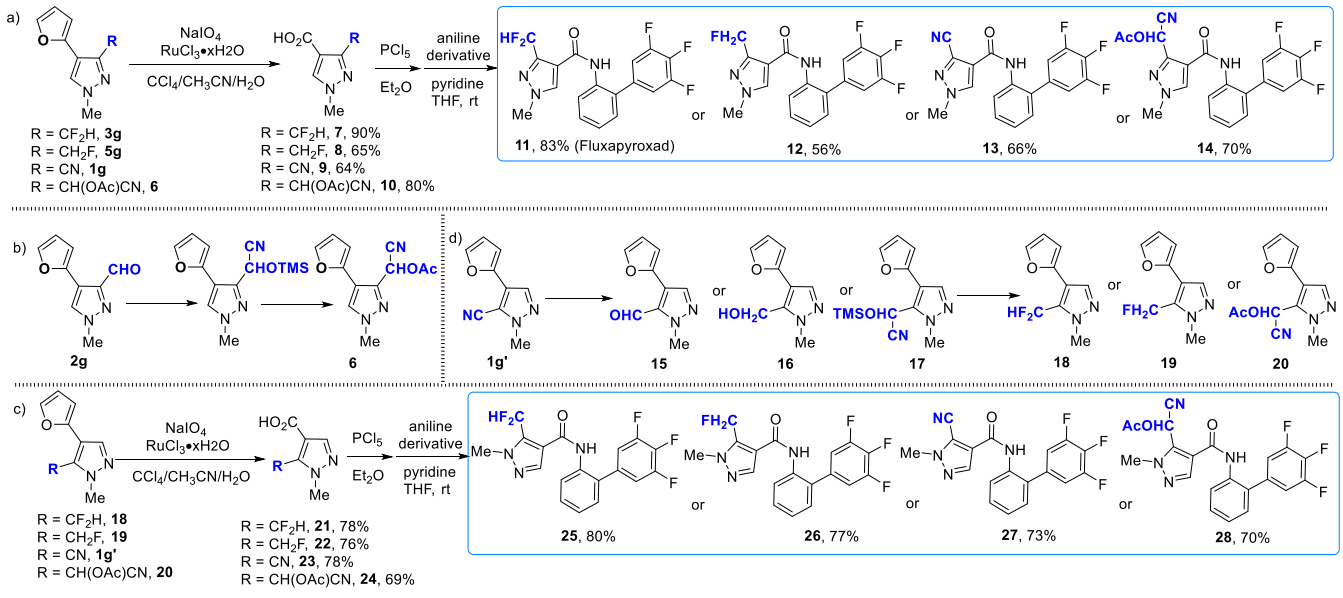


Table 1. Fungicidal Activity of Compounds 11-14 & 25-28 against 14 Kinds of Phytopathogens[a]

Compd.	Fungicidal activity (%) / 50 μm/mL													
	FC	CH	PP	RC	BM	CO	FM	AS	FG	PI	PC	SS	BC	RS
11	37.1	94.7	33.3	37.3	25.0	23.3	31.6	91.7	11.8	12.5	33.3	100	66.7	94.4
12	25.7	89.5	12.2	33.3	22.2	16.7	21.1	91.7	5.9	25.0	36.7	95.7	50.0	91.7
13	51.9	58.8	9.8	54.5	26.1	21.2	12.3	18.8	8.6	16.1	44.8	25.6	46.4	21.3
14	0	23.5	33.3	22.7	8.7	18.2	15.8	21.9	11.4	6.5	20.7	34.9	42.9	21.3
25	25.7	21.1	29.2	33.3	19.4	10.0	47.4	25.0	11.8	18.8	33.3	26.1	58.3	61.1
26	22.9	15.8	12.5	39.2	25.0	26.7	36.8	16.7	29.4	25.0	33.3	50.0	33.3	55.6
27	5.6	26.5	5.9	18.2	26.1	27.3	15.8	18.8	14.3	25.8	20.7	39.5	25.0	32.0
28	11.1	26.5	66.7	13.6	21.7	6.1	24.6	21.9	17.1	19.4	20.7	30.2	21.4	21.3

[a]FC = Fusarium oxysporum sp cucumeris, CH = Cercospora ara-chidicola Hori, PP = Physalospora piricola, RC = Rhizoctonia cerealis, BM = Bipolaris maydis, CO = Colletotrichum orbicu-lare, FM = Fusarium moniliforme, AS = Alternaria solani, FG = Fusarium graminearum, PI = Phytophthora infestans, PC = Phytophthora capsica, SS = Sclerotinia sclerotiorum, BC = Botrytis cinereal, RS = Rhizoctonia solani.

material **6** was accessed through nucleophilic cyanation of the aldehyde **2g** followed by acetylation of the resulting *O*-trimethysilyl cyanohydrin intermediate (Scheme 4b). For comparison, we also synthesized the corresponding 5-substituted analogues **25-28** via the oxidation/amidation sequence from 5-substituted-1-methyl-4-(2-furyl)-1*H*-pyrazoles **1g'** & **15-20** in practical total yields (48-62%, Scheme 4c and 4d).

With Fluxapyroxad and its analogues in hand, we next assessed the *in vitro* fungicidal activity against 14 kinds of phytopathogens,[20] including Fusarium oxysporum sp cucumeris (FC), Cercospora arachidicola Hori (CH), Physalospora piricola (PP), Rhizoctonia cerealis (RC), Bipolaris maydis (BM), Colletotrichum orbiculare (CO), Fusarium moniliforme (FM), Alternaria solani (AS), Fusarium graminearum (FG), Phytophthora infestans (PI), Phytophthora capsica (PC), Sclerotinia sclerotiorum (SS), Botrytis cinereal (BC), and Rhizoctonia solani (RS). As shown in Table 1, while no significant inhibitory activity (<70%) was observed for analogues **13**, **14** & **25-28**, the 3-monofluoromethyl-analogue **12** demonstrated excellent fungicidal activity towards several plant pathogens, including cercospora arachidicola hori (89.5%), alternaria solani (91.7%), sclerotinia sclerotiorum (95.7%) and rhizoctonia solani (91.7%) at 50 μg/mL, which is comparable to that of Fluxapyroxad (94.7%, 91.7%, 100.0% and 94.4%, respectively). These results indicated that 3-fluoroalkyl group is of great importance for the achievement of effective fungicidal activity. Moreover, 3-cyanopyrazole **13** exhibited better activity against a few kinds of fungi than **11** and **12**, such as fusarium oxysporum sp cucumeris, rhizoctonia cerealis, bipolaris maydis, and phytophthora capsica. On the contrary, the target compound **14** possessing an extended cyano group displayed very weak fungicidal activities against the fungi tested. In addition, the 5-substituted analogues **25-28** displayed seriously decreased fungicidal activities, indicating a crucial role of the 3-fluoroalkyl pyrazolic core in such succinate dehydrogenase inhibitors.

3. CONCLUSIONS

In conclusion, we have successfully developed an efficient approach to a diverse collection of 1,4-disubstituted-3-di- or mono-fluoromethylpyrzoles via elaborations on cyanopyrazoles, which were synthesized previously by our group through a multi-component reaction of nitroolefins with diazoacetonitrile and alkyl halides. This approach features several merits, such as easily accessible starting materials, broad substrate scope, mild reaction conditions, and simple operation. Furthermore, this protocol further deserves to be highlighted by the successful translation into the synthesis of commercialized SDHI fungicide Fluxapyroxad and its several analogues. Notably, the monofluoromethylated analogue **12** exhibited remarkable *in vitro* fungicidal activity towards several phytopathogens, including cercospora arachidicola hori, alternaria solani, sclerotinia sclerotiorum, and rhizoctonia solani at 50 μg/mL, which is comparable with the Fluxapyroxad. Future investigations including substrate scope expansion, and *in vivo* applications of compound **12** are still ongoing in our laboratories, and these results will be reported in due course.

■ EXPERIMENTAL SECTION

General information: ^{1}H, ^{19}F and ^{13}C NMR were recorded at 400 MHz (^{1}H NMR), 376 MHz (^{19}F NMR) and 100 MHz (^{13}C NMR) or 600 MHz (^{1}H NMR), 565 MHz (^{19}F NMR) and 150 MHz (^{13}C NMR), respectively. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.20 ppm; DMSO-d_6: δ_H = 2.50 ppm, δ_C = 39.52 ppm; CD_3OD: δ_H = 3.31 ppm, δ_C = 49.00 ppm). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet of doublets). Coupling constants were reported in Hertz (Hz). High resolution mass spectrometry (HRMS) spectra were obtained on a microTOF-QII or Waters Micromass GCT Premier Instrument. Melting points were measured on a WRS-1A digital melting point apparatus and are uncorrected.

General procedure for the synthesis of pyraozle-3-carbaldehydes 2a-j: At –20 °C, to a well-stirred solution of 3-cycnopyrazoles **1** (1 mmol) in THF (10 mL) under an argon atmosphere was added DIBAL-H (1.0 M in hexane, 2 mL, 2 equiv) dropwise, and the resulting mixture was stirred at the same temperature for 1 – 6 h. After completion of the reaction, it was quenched with 2 M HCl (5 mL), and extracted with ethyl acetate (3 ×15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel [petroleum ether (PE)/ethyl acetate (EA) = 8/1 to 6/1 as the eluent] to give the desired products **2a-j**.

*1-Methyl-4-phenyl-1H-pyrazole-3-carbaldehyde (**2a**).* White solid; mp 83 – 84 ℃; 111.7 mg, 60% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.54 – 7.48 (m, 2H), 7.44 (s, 1H), 7.36 – 7.29 (m, 2H), 7.28 – 7.22 (m, 1H), 3.85 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 186.0, 146.0, 130.9, 130.4, 128.4, 128.1, 127.3,

125.4, 39.4; HRMS (ESI) *m/z* calculated for $C_{11}H_{11}N_2O^+$ $[M + H]^+$: 187.0866, found: 187.0869.

*1-Methyl-4-(p-tolyl)-1H-pyrazole-3-carbaldehyde (**2b**).* Colorless oil; 116.1 mg, 58% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 7.50 (s, 1H), 7.47 – 7.43 (m, 2H), 7.22 – 7.18 (m, 2H), 4.01 (s, 3H), 2.37 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.3, 146.7, 137.7, 130.9, 129.3, 128.8, 127.8, 126.2, 39.9, 21.3; HRMS (ESI): *m/z* calculated for $C_{12}H_{13}N_2O^+$ $[M + H]^+$: 201.1022, found: 201.1030.

*4-(4-Fluorophenyl)-1-methyl-1H-pyrazole-3-carbaldehyde (**2c**).* White solid; mp 122 – 123 ℃; 110.3 mg, 54% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.57 – 7.51 (m, 2H), 7.50 (s, 1H), 7.10 – 7.00 (m, 2H), 4.00 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.28 – -114.36 (m). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.4, 162.5 (d, *J* = 245.5 Hz), 146.5, 131.0, 130.5 (d, *J* = 8.0 Hz), 126.8 (d, *J* = 3.3 Hz), 124.7, 115.3 (d, *J* = 21.4 Hz), 39.9; HRMS (ESI): *m/z* calculated for $C_{11}H_{10}FN_2O^+$ $[M + H]^+$: 205.0772, found: 205.0775.

*4-(4-Chlorophenyl)-1-methyl-1H-pyrazole-3-carbaldehyde (**2d**).* Colorless oil; 127.6 mg, 58% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.53 – 7.46 (m, 3H), 7.35 – 7.29 (m, 2H), 4.00 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.5, 146.6, 133.7, 131.1, 130.1, 129.3, 128.6, 124.5, 39.9; HRMS (ESI): *m/z* calculated for $C_{11}H_{10}ClN_2O^+$ $[M + H]^+$: 221.0476, found: 221.0481.

*1-Methyl-4-(4-(trifluoromethyl)phenyl)-1H-pyrazole-3-carbaldehyde (**2e**).* White solid; mp 91 – 92 ℃; 132.2 mg, 52% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.72 – 7.66 (m, 2H), 7.62 – 7.56 (m, 3H), 3.99 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.53 (s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.4, 146.5, 134.5, 131.6, 129.3 (q, *J* = 32.2 Hz), 128.8, 125.2 (q, *J* = 3.7 Hz), 124.2 (q, *J* = 270.3 Hz), 123.8, 39.7; HRMS (ESI): *m/z* calculated for $C_{12}H_{10}F_3N_2O^+$ $[M + H]^+$: 255.0740, found: 255.0745.

*1-Methyl-4-(naphthalen-2-yl)-1H-pyrazole-3-carbaldehyde (**2f**).* White solid; mp 82 – 83 ℃; 118.1 mg, 50% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.07 (s, 1H), 7.88 – 7.80 (m, 3H), 7.65 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.62 (s, 1H), 7.52 – 7.45 (m, 2H), 4.04 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.4, 147.0, 133.5, 132.9, 131.3, 128.3, 128.2, 128.2, 127.8, 127.7, 127.0, 126.5, 126.3, 126.2, 40.0; HRMS (ESI): *m/z* calculated for $C_{15}H_{13}N_2O^+$ $[M + H]^+$: 237.1022, found: 237.1027.

*4-(Furan-2-yl)-1-methyl-1H-pyrazole-3-carbaldehyde (**2g**).* Yellow solid; mp 55 – 56 ℃; 123.3 mg, 70% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.73 (s, 1H), 7.38 – 7.35 (m, 1H), 7.30 – 7.29 (m, 1H), 6.46 – 6.44 (m, 1H), 4.00 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.1, 146.2, 145.5, 141.7, 129.4, 115.9, 111.7, 109.9, 39.9; HRMS (ESI): *m/z* calculated for $C_9H_9N_2O_2^+$ $[M + H]^+$: 177.0659, found: 177.0653.

*1-Methyl-4-(thiophen-2-yl)-1H-pyrazole-3-carbaldehyde (**2h**).* Colorless oil; 121.1 mg, 63% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.61 (dd, *J* = 3.6, 1.0 Hz, 1H), 7.55 (s, 1H), 7.21 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.01 (dd, *J* = 5.1, 3.6 Hz, 1H), 3.88 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.8, 145.7, 131.9, 130.4, 127.5, 127.1, 124.7, 118.4, 39.5; HRMS (ESI): *m/z* calculated for $C_9H_9N_2OS^+$ $[M + H]^+$: 193.0430, found: 193.0431.

*1-Methyl-4-phenethyl-1H-pyrazole-3-carbaldehyde (**2i**).* White solid; mp 54.5 – 55.5 ℃; 130.7 mg, 61% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.18 – 7.14 (m, 2H), 7.09 – 7.06 (m, 3H), 6.97 (s, 1H), 3.78 (s, 3H), 2.96 – 2.92 (m, 2H), 2.79 – 2.75 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 187.3, 148.1, 141.5, 130.9, 128.5, 128.3, 126.0, 124.3, 39.6, 36.3, 25.7; HRMS (ESI): *m/z* calculated for $C_{13}H_{15}N_2O^+$ $[M + H]^+$: 215.1179, found: 215.1180.

*1-Benzyl-4-phenyl-1H-pyrazole-3-carbaldehyde (**2j**).* White solid; mp 97 – 98 ℃; 152.1 mg, 58% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.47 (s, 1H), 7.32 – 7.20 (m, 8H), 5.29 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.3, 146.4, 134.9, 130.6, 130.1, 128.9, 128.6, 128.5, 128.3, 127.9, 127.6, 125.9, 56.9. HRMS (ESI): *m/z* calculated for $C_{17}H_{15}N_2O^+$ $[M + H]^+$: 263.1179, found: 263.1181.

General procedure for the synthesis of 1,4-disubstituted-3-difluoromethylpyraozles 3a-j: To a pre-cooled (–78 °C) solution of **2** (0.5 mmol) in CH_2Cl_2 (5 mL) was added DAST (166 μL, 1.25 mmol, 2.5 equiv) dropwise. The resulting mixture was then allowed to warm to room temperature and stirred at the same temperature overnight before quenching with cooled water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 ×20 mL), and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (PE/EA = 8/1 to 4/1 as the eluent) to afford the desired products **3a-j**.

*3-(Difluoromethyl)-1-methyl-4-phenyl-1H-pyrazole (**3a**).* Colorless oil; 90.6 mg, 87% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.46 (m, 3H), 7.41 –7.37 (m, 2H), 7.33 – 7.29 (m, 1H), 6.77 (t, *J* = 54.1 Hz, 1H), 3.90 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.78 (d, *J* = 54.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 142.2 (t, *J* = 26.9 Hz), 131.2, 130.2, 128.7, 128.3 (t, *J* = 1.3 Hz), 127.3, 122.4, 111.7 (t, *J* = 233.9 Hz), 39.2; HRMS (ESI): *m/z* calculated for $C_{11}H_{11}F_2N_2^+$ $[M + H]^+$: 209.0885, found: 209.0883.

*3-(Difluoromethyl)-1-methyl-4-(p-tolyl)-1H-pyrazole (**3b**).* White solid; mp 52.5 – 53.5 ℃; 105.6 mg, 95% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 6.74 (t, *J* = 54.2 Hz, 1H), 3.94 (s, 3H), 2.38 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.93 (d, *J* = 54.2 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 142.4 (t, *J* = 26.8 Hz), 137.2, 130.1, 129.5, 128.3, 122.5, 111.7 (t, *J* = 234.0 Hz), 39.4, 21.3; HRMS (ESI): *m/z* calculated for $C_{12}H_{13}F_2N_2^+$ $[M + H]^+$: 223.1041, found: 223.1044.

*3-(Difluoromethyl)-4-(4-fluorophenyl)-1-methyl-1H-pyrazole (**3c**).* White solid; mp 53 – 54 ℃; 97.3 mg, 86% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.44 – 7.40 (m, 2H), 7.08 – 7.04 (m, 2H), 6.72 (t, *J* = 54.1 Hz, 1H), 3.93 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.66 (d, *J* = 54.1 Hz), -115.07 – -115.19 (m). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.3 (d, *J* = 246.5 Hz), 142.4 (t, *J* = 27.5 Hz), 130.3, 130.1 (dt, *J* = 8.0, 1.7 Hz), 127.4 (d, *J* = 3.3 Hz), 121.4, 115.7 (d, *J* = 21.5 Hz), 111.9 (t, *J* = 233.8 Hz), 39.4; HRMS (ESI): *m/z* calculated for $C_{11}H_{10}F_3N_2^+$ $[M + H]^+$: 227.0791, found: 227.0792.

*4-(4-Chlorophenyl)-3-(difluoromethyl)-1-methyl-1H-pyrazole (**3d**).* White solid; mp 67 – 68 ℃; 115.3 mg, 95% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.37 (dd, *J* = 21.0, 8.6 Hz, 4H), 6.72 (t, *J* = 54.1 Hz, 1H), 3.94 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.65 (d, *J* = 54.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 142.5 (t, *J* = 27.7 Hz), 133.4, 130.4, 129.8, 129.7 (t, *J* = 1.7 Hz), 129.0, 121.2, 111.9 (t, *J* = 233.9 Hz), 39.5; HRMS (ESI): *m/z* calculated for $C_{11}H_{10}ClF_2N_2^+$ $[M + H]^+$: 243.0495, found: 243.0494.

*3-(Difluoromethyl)-1-methyl-4-(4-(trifluoromethyl)phenyl)-1H-pyrazole (**3e**).* Colorless oil; 121.5 mg, 88% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (q, *J* = 8.3 Hz, 4H), 7.52 (s, 1H), 6.75 (t, *J* = 54.1 Hz, 1H), 3.91 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.55 (s, 3F), -109.57 (d, *J* = 54.1 Hz, 2F). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 142.6 (t, *J* = 28.1 Hz), 135.0, 130.8, 129.2 (q, *J* = 32.5 Hz), 128.5 (t, *J* = 1.7 Hz), 125.6 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 270.3 Hz), 120.8, 112.0 (t, *J* = 233.8 Hz), 39.3; HRMS (ESI): *m/z* calculated for $C_{12}H_{10}F_5N_2^+$ $[M + H]^+$: 277.0759, found: 277.0758.

*3-(Difluoromethyl)-1-methyl-4-(naphthalen-2-yl)-1H-pyrazole (**3f**).* White solid; mp 64 – 65 ℃; 118.8 mg, 92% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.90 – 7.80 (m, 3H), 7.59 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.54 – 7.45 (m, 3H), 6.84 (t, *J* = 54.1 Hz, 1H), 3.92 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.69 (d, *J* = 54.1 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 142.5 (t, *J* = 27.1 Hz), 133.6, 132.6, 130.5, 128.7, 128.4, 128.1, 127.8, 127.0 (t, *J* = 1.6 Hz), 126.7, 126.5, 126.1, 122.4, 111.9 (t, *J* = 234.0 Hz), 39.4.

HRMS (ESI): *m/z* calculated for $C_{15}H_{13}F_2N_2^+$ [M + H]$^+$: 259.1041, found: 259.1042.

3-(Difluoromethyl)-4-(furan-2-yl)-1-methyl-1H-pyrazole ***(3g)***. Colorless oil; 67.4 mg, 68% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.37 (d, *J* = 1.2 Hz, 1H), 6.82 (t, *J* = 54.1 Hz, 1H), 6.53 (d, *J* = 3.2 Hz, 1H), 6.41 (dd, *J* = 3.2, 1.8 Hz, 1H), 3.85 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.98 (d, *J* = 54.1 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.8, 141.4, 141.0 (t, *J* = 27.7 Hz), 129.1, 112.7, 111.6 (t, *J* = 232.3 Hz), 111.5, 106.8 (t, *J* = 3.1 Hz), 39.3; HRMS (ESI): *m/z* calculated for $C_9H_9F_2N_2O^+$ [M + H]$^+$: 199.0677, found: 199.0678.

3-(Difluoromethyl)-1-methyl-4-(thiophen-2-yl)-1H-pyrazole ***(3h)***. Colorless oil; 87.8 mg, 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.23 (dd, *J* = 5.1, 0.9 Hz, 1H), 7.19 (d, *J* = 3.3 Hz, 1H), 7.04 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.77 (t, *J* = 54.0 Hz, 1H), 3.88 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.22 (d, *J* = 54.0 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.0 (t, *J* = 27.3 Hz), 132.1, 130.3, 127.9, 126.0 (t, *J* = 2.4 Hz), 124.7, 115.3, 111.5 (t, *J* = 234.0 Hz), 39.3; HRMS (ESI): *m/z* calculated for $C_9H_9F_2N_2S^+$ [M + H]$^+$: 215.0449, found: 215.0447.

3-(Difluoromethyl)-1-methyl-4-phenethyl-1H-pyrazole ***(3i)***. Colorless oil; 95.7 mg, 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.29 (m, 2H), 7.24 – 7.20 (m, 3H), 7.04 (s, 1H), 6.67 (t, *J* = 54.5 Hz, 1H), 3.82 (s, 3H), 2.95 – 2.87 (m, 4H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.95 (d, *J* = 54.5 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.7 (t, *J* = 28.3 Hz), 141.6, 130.5, 128.6, 128.5, 126.1, 119.8, 112.6 (t, *J* = 232.5 Hz), 39.0, 37.1, 25.2; HRMS (ESI): *m/z* calculated for $C_{13}H_{15}F_2N_2^+$ [M + H]$^+$: 237.1198, found: 237.1198.

1-Benzyl-3-(difluoromethyl)-4-phenyl-1H-pyrazole ***(3j)***. White solid; mp 110 – 111 ℃; 120.8 mg, 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.50 (m, 3H), 7.43 – 7.31 (m, 8H), 6.83 (t, *J* = 54.1 Hz, 1H), 5.35 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.71 (d, *J* = 54.2 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ142.5 (t, *J* = 27.3 Hz), 135.6, 131.2, 129.4, 129.1, 128.7, 128.6, 128.4 (t, *J* = 1.5 Hz), 128.1, 127.4, 122.7, 111.9 (t, *J* = 234.1 Hz), 56.6; HRMS (ESI): *m/z* calculated for $C_{17}H_{15}F_2N_2^+$ [M + H]$^+$: 285.1198, found: 285.1197.

General procedure for the synthesis of 1,4-disubstituted-3-hydroxylmethylpyraozles 4a-j: A solution of **2** (0.5 mmol) in MeOH (5 mL) was cooled to 0 ºC, and $NaBH_4$ (37.8 mg, 1.0 mmol, 2 equiv) was added portion-wise over 10 min. The resulting suspension was stirred at the same temperature for 1 – 3 h until the disappearance of the starting material as monitored by thin layer chromatography (TLC). The reaction was then quenched with saturated aqueous solution of NH_4Cl (10 mL). The aqueous phase was extracted with ethyl acetate (3 ×20 mL), and the organic layers were dried over $NaSO_4$ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EA as the eluent) to give the desired products **4a-j**

(1-Methyl-4-phenyl-1H-pyrazol-3-yl)methanol ***(4a)***. White solid; mp 101 – 102 ℃; 87.5 mg, 93% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.46 (m, 3H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.29 – 7.26 (m, 1H), 4.76 (s, 2H), 3.89 (s, 3H), 3.07 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.9, 132.8, 129.3, 128.9, 127.8, 126.7, 121.7, 57.5, 39.0; HRMS (ESI): *m/z* calculated for $C_{11}H_{13}N_2O^+$ [M + H]$^+$: 189.1022, found: 189.1019.

(1-Methyl-4-(p-tolyl)-1H-pyrazol-3-yl)methanol ***(4b)***. White solid; mp 126 – 127 ℃; 91.0 mg, 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.41 (m, 3H), 7.21 – 7.19 (m, 2H), 4.74 (s, 2H), 4.30 (s, 1H), 3.82 (s, 3H), 2.37 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.9, 136.2, 129.7, 129.5, 129.0, 127.6, 121.6, 56.9, 38.7, 21.2; HRMS (ESI): *m/z* calculated for $C_{12}H_{15}N_2O^+$ [M + H]$^+$: 203.1179, found: 203.1187.

(4-(4-Fluorophenyl)-1-methyl-1H-pyrazol-3-yl)methanol ***(4c)***. White solid; mp 112 – 113 ℃; 97.9 mg, 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.45 (m, 2H), 7.38 (s, 1H), 7.06 – 7.01 (m, 2H), 4.67 (s, 2H), 4.47 (s, 1H), 3.81 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.01 – -116.20 (m). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.8 (d, *J* = 245.5 Hz), 148.9, 129.4 (d, *J* = 7.9 Hz), 129.1, 128.7 (d, *J* = 3.2 Hz), 120.9, 115.6 (d, *J* = 21.3 Hz), 56.6, 38.7; HRMS (ESI): *m/z* calculated for $C_{11}H_{12}FN_2O^+$ [M + H]$^+$: 207.0928, found: 207.0935.

(4-(4-Chlorophenyl)-1-methyl-1H-pyrazol-3-yl)methanol ***(4d)***. White solid; mp 140 – 141 ℃; 70.1 mg, 63% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.43 (m, 3H), 7.35 – 7.33 (m, 2H), 4.70 (s, 2H), 3.86 (s, 3H), 3.70 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 149.0, 132.5, 131.2, 129.3, 129.0, 120.8, 57.1, 39.0; HRMS (ESI): *m/z* calculated for $C_{11}H_{12}ClN_2O^+$ [M + H]$^+$: 223.0633, found: 223.0639.

(1-Methyl-4-(4-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)methanol ***(4e)***. White solid; mp 118 – 119 ℃; 108.9 mg, 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7. 65 – 7.59 (m, 4H), 7.50 (s, 1H), 4.71 (s, 2H), 4.38 (s, 1H), 3.84 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.36 (s). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 149.3, 136.4, 129.7, 128.5 (q, *J* = 32.4 Hz), 127.8, 125.8 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 271.8 Hz), 120.6, 56.8, 38.8; HRMS (ESI): *m/z* calculated for $C_{12}H_{12}F_3N_2O^+$ [M + H]$^+$: 257.0896, found: 257.0905.

(1-Methyl-4-(naphthalen-2-yl)-1H-pyrazol-3-yl)methanol ***(4f)***. White solid; mp 127 – 128 ℃; 111.9 mg, 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.82 – 7.87 (m, 3H), 7.64 – 7.62 (m, 1H), 7.54 (s, 1H), 7.49 – 7.45 (m, 2H), 4.85 (s, 2H), 3.89 (s, 3H), 3.55 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 149.2, 133.9, 132.3, 130.2, 129.6, 128.5, 128.1, 127.8, 126.5, 126.4, 126.0, 125.8, 121.7, 57.5, 39.0; HRMS (ESI): *m/z* calculated for $C_{15}H_{15}N_2O^+$ [M + H]$^+$: 239.1179, found: 239.1188.

(4-(Furan-2-yl)-1-methyl-1H-pyrazol-3-yl)methanol ***(4g)***. White solid; mp 105.6 – 106.6 ℃; 87.3 mg, 98% yield; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.60 (d, *J* = 1.1 Hz, 1H), 6.54 (d, *J* = 3.2 Hz, 1H), 6.51 – 6.50 (m, 1H), 5.04 (t, *J* = 4.7 Hz, 1H), 4.51 (d, *J* = 4.5 Hz, 2H), 3.81 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6) δ 147.8, 147.7, 141.1, 128.6, 111.7, 111.5, 105.0, 56.2, 38.5; HRMS (ESI): *m/z* calculated for $C_9H_{11}N_2O_2^+$ [M + H]$^+$: 179.0815, found: 179.0812.

(1-Methyl-4-(thiophen-2-yl)-1H-pyrazol-3-yl)methanol ***(4h)***. White solid; mp 114 – 115 ℃; 91.3 mg, 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.19 – 7.16 (m, 2H), 7.02 (dd, *J* = 5.1, 3.6 Hz, 1H), 4.75 (s, 2H), 3.80 (s, 4H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.7, 134.1, 129.2, 127.8, 124.5, 123.8, 114.9, 57.1, 38.8. HRMS (ESI): *m/z* calculated for $C_9H_{11}N_2OS^+$ [M + H]$^+$: 195.0587, found: 195.0594.

(1-Methyl-4-phenethyl-1H-pyrazol-3-yl)methanol ***(4i)***. White solid; mp 101 – 102 ℃; 97.3 mg, 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.28 (m, 2H), 7.23 – 7.18 (m, 3H), 7.01 (s, 1H), 4.55 (s, 2H), 3.77 (s, 3H), 2.87 – 2.81 (m, 4H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.1, 141.7, 129.5, 128.5, 128.3, 126.0, 119.0, 56.5, 38.5, 37.2, 25.3; HRMS (ESI): *m/z* calculated for $C_{13}H_{17}N_2O^+$ [M + H]$^+$: 217.1335, found: 217.1343.

(1-Benzyl-4-phenyl-1H-pyrazol-3-yl)methanol ***(4j)***. White solid; mp 104 – 105 ℃; 120.3 mg, 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.57 (d, *J* = 7.4 Hz, 2H), 7.50 (s, 1H), 7.45 – 7.41 (t, *J* = 7.6 Hz, 2H), 7.33 – 7.25 (m, 6H), 5.27 (s, 2H), 4.83 (s, 2H), 4.46 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 149.1, 136.1, 132.6, 128.8, 128.8, 128.3, 128.2, 127.9, 127.7, 126.6, 122.0, 57.0, 55.9; HRMS (ESI): *m/z* calculated for $C_{17}H_{17}N_2O^+$ [M + H]$^+$: 265.1335, found: 265.1345.

General procedure for the synthesis of 1,4-disubstituted-3-monofluoromethylpyraozles 5a-j: To a pre-cooled (– 78 ºC) solution of **4** (0.5 mmol) in CH_2Cl_2 (5 mL) was added DAST (133 μL, 1.0 mmol, 2.0 equiv) dropwise. The resulting mixture was then allowed to warm to room temperature and stirred at the same temperature overnight before quenching with cooled water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 ×20 mL), and the combined organic layers were washed with brine (30 mL), dried

over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (PE/EA = 4/1 to 2/1 as the eluent) to afford the desired products **5a-j**.

*3-(Fluoromethyl)-1-methyl-4-phenyl-1H-pyrazole (**5a**).* Colorless oil; 64.0 mg, 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 7.9, 6.6 Hz, 3H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 5.41 (d, *J* = 49.2 Hz, 2H), 3.93 (d, *J* = 2.0 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -199.09 (t, *J* = 49.2 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 144.2 (d, *J* = 19.7 Hz), 132.2 (d, *J* = 1.0 Hz), 129.4 (d, *J* = 2.2 Hz), 129.0, 127.9 (d, *J* = 2.3 Hz), 127.0, 123.9 (d, *J* = 2.2 Hz), 76.9 (d, *J* = 161.9 Hz), 39.2; HRMS (ESI): *m/z* calculated for $C_{11}H_{12}FN_2^+$ [M + H]$^+$: 191.0979, found: 191.0981.

*3-(Fluoromethyl)-1-methyl-4-(p-tolyl)-1H-pyrazole (**5b**).* White solid; mp 67 – 68 ℃; 55.1 mg, 54% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 5.41 (d, *J* = 49.2 Hz, 2H), 3.94 (d, *J* = 1.9 Hz, 3H), 2.39 (s, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -198.93 (td, *J* = 49.2, 1.4 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 144.1 (d, *J* = 19.7 Hz), 136.8, 129.7, 129.3, 129.2 (d, *J* = 2.2 Hz), 127.9 (d, *J* = 2.2 Hz), 123.9 (d, *J* = 2.1 Hz), 76.9 (d, *J* = 161.8 Hz), 39.2, 21.3; HRMS (ESI): *m/z* calculated for $C_{12}H_{14}FN_2^+$ [M + H]$^+$: 205.1136, found: 205.1143.

*3-(Fluoromethyl)-4-(4-fluorophenyl)-1-methyl-1H-pyrazole (**5c**).* White solid; mp 86 – 87 ℃; 61.4 mg, 59% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.45 – 7.36 (m, 2H), 7.08 (t, *J* = 8.7 Hz, 2H), 5.37 (d, *J* = 49.2 Hz, 2H), 3.93 (d, *J* = 1.8 Hz, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -115.59 (m), -198.86 (td, *J* = 49.5, 1.7 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.2 (d, *J* = 246.1 Hz), 144.1 (d, *J* = 19.9 Hz), 129.6 (dd, *J* = 7.9, 2.5 Hz), 129.3 (d, *J* = 1.9 Hz), 128.3 (d, *J* = 2.3 Hz), 123.0 (d, *J* = 2.0 Hz), 115.8 (d, *J* = 21.4 Hz), 77.4 (d, *J* = 161.8 Hz), 39.3; HRMS (ESI): *m/z* calculated for $C_{11}H_{11}F_2N_2^+$ [M + H]$^+$: 209.0885, found: 209.0889.

*4-(4-Chlorophenyl)-3-(fluoromethyl)-1-methyl-1H-pyrazole (**5d**).* White solid; mp 85 – 86 ℃; 92.1 mg, 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.39 – 7.34 (m, 4H), 5.37 (d, *J* = 49.1 Hz, 2H), 3.93 (d, *J* = 1.8 Hz, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -199.10 (td, *J* = 49.2, 1.4 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 144.1 (d, *J* = 20.0 Hz), 133.0, 130.7, 129.5 (d, *J* = 2.1 Hz), 129.2 (d, *J* = 2.6 Hz), 129.1, 122.8 (d, *J* = 2.0 Hz),77.3 (d, *J* = 162.0 Hz), 39.3; HRMS (ESI): *m/z* calculated for $C_{11}H_{11}ClFN_2^+$ [M + H]$^+$: 225.0589, found: 225.0600.

*3-(Fluoromethyl)-1-methyl-4-(4-(trifluoromethyl)phenyl)-1H-pyrazole (**5e**).* White solid; mp 65 – 66 ℃; 108.5 mg, 84% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.63 (m, 2H), 7.58 – 7.56 (m, 3H), 5.40 (d, *J* = 49.1 Hz, 2H), 3.95 (d, *J* = 1.7 Hz, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.46 (s, 3F), -199.10 (td, *J* = 49.2, 1.4 Hz, 1F). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 144.4 (d, *J* = 20.1 Hz), 136.0, 129.9 (d, *J* = 1.9 Hz), 129.0 (q, *J* = 32.4 Hz), 128.0 (d, *J* = 2.7 Hz), 125.9 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 271.8 Hz), 122.6 (d, *J* = 1.6 Hz), 76.9 (d, *J* = 162.2 Hz), 39.3; HRMS (ESI): *m/z* calculated for $C_{12}H_{11}F_4N_2^+$ [M + H]$^+$: 259.0853, found: 259.0866.

*3-(Fluoromethyl)-1-methyl-4-(naphthalen-2-yl)-1H-pyrazole (**5f**).* White solid; mp 75 – 76 ℃; 36.0 mg, 30% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.87 (t, *J* = 8.3 Hz, 3H), 7.60 – 7.58 (m, 2H), 7.53 – 7.46 (m, 2H), 5.49 (d, *J* = 49.2 Hz, 2H), 3.95 (d, *J* = 1.8 Hz, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -198.89 (td, *J* = 49.2, 1.3 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 144.4 (d, *J* = 19.8 Hz), 133.8, 132.4, 129.7 (d, *J* = 2.2 Hz), 129.7, 128.6, 128.2, 127.8, 126.5, 126.4 (d, *J* = 2.1 Hz), 126.3 (d, *J* = 2.7 Hz), 126.0, 123.9 (d, *J* = 2.1 Hz), 77.1 (d, *J* = 161.9 Hz), 39.3; HRMS (ESI): *m/z* calculated for $C_{15}H_{14}FN_2^+$ [M + H]$^+$: 241.1136, found: 241.1144.

*3-(Fluoromethyl)-4-(furan-2-yl)-1-methyl-1H-pyrazole (**5g**).* Yellow oil; 11.7 mg, 13% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.41 (t, *J* = 1.3 Hz, 1H), 6.44 (d, *J* = 1.2 Hz, 2H), 5.49 (d, *J* = 48.8 Hz, 2H), 3.91 (d, *J* = 1.9 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -206.07 (t, *J* = 49.0 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 147.1 (d, *J* = 1.6 Hz), 143.4 (d, *J* = 20.2 Hz), 141.5, 128.5 (d, *J* = 2.1 Hz), 114.4 (d, *J* = 1.6 Hz), 111.5, 105.8 (d, *J* = 3.1 Hz), 77.3 (d, *J* = 162.6 Hz), 39.3; HRMS (ESI): *m/z* calculated for $C_9H_{10}FN_2O^+$ [M + H]$^+$: 181.0772, found: 181.0773.

*3-(Fluoromethyl)-1-methyl-4-(thiophen-2-yl)-1H-pyrazole (**5h**).* White solid; mp 32 – 33 ℃; 48.0 mg, 49% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.24 (dd, *J* = 5.1, 0.9 Hz, 1H), 7.14 (dd, *J* = 3.5, 1.0 Hz, 1H), 7.06 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.44 (d, *J* = 49.0 Hz, 2H), 3.92 (d, *J* = 1.9 Hz, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -202.02 (td, *J* = 49.0, 1.6 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 144.1 (d, *J* = 19.9 Hz), 133.5 (d, *J* = 1.4 Hz), 129.5 (d, *J* = 2.2 Hz), 128.0, 125.1 (d, *J* = 2.9 Hz), 124.4, 117.1 (d, *J* = 1.8 Hz), 76.8 (d, *J* = 162.4 Hz), 39.3; HRMS (ESI): *m/z* calculated for $C_9H_{10}FN_2S^+$ [M + H]$^+$: 197.0543, found: 197.0546.

*3-(Fluoromethyl)-1-methyl-4-phenethyl-1H-pyrazole (**5i**).* Colorless oil; 56.8 mg, 52% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.28 (m, 2H), 7.23 – 7.17 (m, 3H), 7.05 (s, 1H), 5.28 (d, *J* = 49.2 Hz, 2H), 3.82 (d, *J* = 1.9 Hz, 3H), 2.90 – 2.81 (m, 4H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -204.45 (t, *J* = 49.2 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.5 (d, *J* = 20.2 Hz), 141.6, 129.8 (d, *J* = 2.2 Hz), 128.6, 128.4, 126.1, 121.0 (d, *J* = 1.7 Hz), 76.8 (d, *J* = 161.3 Hz), 38.9, 37.3, 25.4; HRMS (ESI): *m/z* calculated for $C_{13}H_{16}FN_2^+$ [M + H]$^+$: 219.1292, found: 219.1299.

*1-Benzyl-3-(fluoromethyl)-4-phenyl-1H-pyrazole (**5j**).* Colorless oil; 70.6 mg, 53% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.50 – 7.48 (m, 2H), 7.43 – 7.35 (m, 5H), 7.33 – 7.29 (m, 3H), 5.47 (d, *J* = 49.1 Hz, 2H), 5.35 (s, 2H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -199.35 (t, *J* = 49.1 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 144.3 (d, *J* = 19.8 Hz), 136.0, 132.2, 129.1, 128.9, 128.6 (d, *J* = 2.1 Hz), 128.5, 128.0, 128.0 (d, *J* = 2.4 Hz), 127.1, 124.2 (d, *J* = 2.0 Hz), 77.0 (d, *J* =162.2 Hz), 56.5; HRMS (ESI): *m/z* calculated for $C_{17}H_{16}FN_2^+$ [M + H]$^+$: 267.1292, found: 267.1306.

Syntheses of cyano(4-(furan-2-yl)-1-methyl-1-*H*-pyrazol-3-yl)methyl acetate (6): A mixture of **2g** (88.1 mg, 0.5 mmol), $LiClO_4$ (53.2 mg, 0.5 mmol) and TMSCN (130 μL, 1.0 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 12 h until disappearance of the starting material as monitored by TLC. Then water (10 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to give the crude *O*-trimethysilyl cyanohydrin intermediate, which was directly dissolved in THF (3 mL) and treated with 2 M HCl (2 mL) at room temperature for 2 h. The organic layer was successively separated, dried over Na_2SO_4, filtered, and treated with acetic anhydride (140 μL) and pyridine (100 μL) at room temperature for 5 h. The reaction mixture was then concentrated under reduced pressure and the residue was purified by flash column chromatography on the silica gel to afford the desired product **6**. White solid; mp 121 – 122 ℃; 58.3 mg, 80% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.38 (s, 1H), 6.75 (s, 1H), 6.42 (s, 1H), 6.36 (d, *J* = 2.6 Hz, 1H), 3.93 (s, 3H), 2.13 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.1, 145.8, 141.9, 138.7, 129.2, 115.2, 113.4, 111.5, 106.2, 57.0, 39.7, 20.5. HRMS (ESI): m/z calculated for $C_{12}H_{11}N_3NaO_3^+$ [M + Na]$^+$: 268.0693, found: 268.0698.

Procedure for the synthesis of SDHI fungicide fluxapyroxad 11 and its analogues: To a solution of sodium periodate (1.85 g, 8.0 mmol) in a co-solvent of $CCl_4/CH_3CN/H_2O$ (3/3/2, 6 mL) was added $RuCl_3$•xH_2O (20.7 mg, 0.1 mmol), and the resulting mixture was stirred at room temperature for 15 min before addition of the solution of **3g**, or **5g**, or **1g**, or **6** (1.0 mmol) in CCl_4 (1 mL) in one portion. After stirred for a further 30 min, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered through Celite and evaporated in vacuum. The residue was purified by flash column chromatography on silica gel to afford the corresponding carboxylic acids **7**-**10**.

A suspension of carboxylic acids **7-10** (0.55 mmol) and PCl_5 (125.0 mg, 0.6 mmol) in anhydrous Et_2O (2 mL) was stirred at room temperature for 2 h under an argon atmosphere until a transparent solution was formed (monitored by TLC, PE/EA=7/3). At that point, the solvent was evaporated under vacuum, and the residue containing the intermediate acylchloride was then dissolved in anhydrous THF (1mL), and treated with anhydrous pyridine (88 μL, 1.1 mmol) and 3',4',5'-trifluoro-[1,1'-biphenyl]-2-amine (123.1 mg, 0.55 mmol). The resulting mixture was stirred at room temperature for 2.5 h (monitored by TLC) before dilution with ethyl acetate (5 mL). The organic layer was sequentially washed with aqueous solution of 4 % HCl (10 mL), 5% $NaHCO_3$ (10 mL) and saturated brine. The organic layer was then dried over $NaSO_4$, filtered and concentrated under vacuum. The residue was purified by flash column chromatography (PE/EA=4/1 as the eluent) to give the SDHI Fungicide Fluxapyroxad **11** or its anagues **12-14**, **25-28** as a white solid.

3-(Difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic acid (7). White solid; mp 203 – 204 ℃; 158.5 mg, 90% yield; ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (s, 1H), 7.15 (t, *J* = 54.0 Hz, 1H), 3.96 (s, 3H). ^{19}F NMR (376 MHz, CD_3OD) δ -117.43 (d, *J* = 54.0 Hz). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 163.5, 146.2 (t, *J* = 24.0 Hz), 135.8, 113.1 (t, *J* = 3.5 Hz), 109.3 (t, *J* = 235.3 Hz), 38.3; HRMS (ESI): *m/z* calculated for $C_6H_7F_2N_2O_2^+$ [M + H]$^+$: 177.0470, found: 177.0471.

3-(Fluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic acid (8). Reaction performed on a 1.0 mmol scale utilizing the starting material **5g**, **8** was isolated as a white solid: 102.8 mg, 65% yield; mp 185 – 186 ℃; ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 12.54 (s, 1H), 8.25 (s, 1H), 5.48 (d, *J* = 48.0 Hz, 2H), 3.87 (s, 3H). ^{19}F NMR (565 MHz, DMSO-*d*$_6$) δ -206.59 (t, *J* = 49.1 Hz). ^{13}C{^{1}H} NMR (150 MHz, DMSO-*d*$_6$) δ 163.6, 147.4 (d, *J* = 18.3 Hz), 135.9, 112.8, 76.0 (d, *J* = 161.2 Hz), 38.8; HRMS (ESI): *m/z* calculated for $C_6H_8FN_2O_2^+$ [M + H]$^+$: 159.0564, found: 159.0563.

3-Cyano-1-methyl-1H-pyrazole-4-carboxylic acid (9). Reaction performed on a 3.0 mmol scale utilizing the starting material **1g**, **9** was isolated as a white solid: 289.0 mg, 64% yield; mp 193 – 194 ℃; ^{1}H NMR (400 MHz, CD_3OD) δ 8.26 (s, 1H), 4.02 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 162.0, 135.4, 125.1, 118.8, 112.2, 39.1; HRMS (ESI): *m/z* calculated for $C_6H_6N_3O_2^+$ [M + H]$^+$: 152.0455, found: 152.0452.

3-(Acetoxy(cyano)methyl)-1-methyl-1H-pyrazole-4-carboxylic acid (10). Reaction performed on a 1.0 mmol scale utilizing starting material **6**, **10** was isolated as a white solid: 178.2 mg, 80% yield; mp 163 – 164 ℃; ^{1}H NMR (400 MHz, CD_3OD) δ 8.18 (s, 1H), 6.96 (s, 1H), 3.98 (s, 3H), 2.15 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 169.1, 163.5, 144.2, 136.1, 114.8, 112.5, 56.3, 38.4, 18.7; HRMS (ESI): *m/z* calculated for $C_9H_9N_3NaO_4^+$ [M + Na]$^+$: 246.0485, found: 246.0485.

*3-(Difluoromethyl)-1-methyl-N-(3',4',5'-trifluoro-[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide (**11, Fluxapyroxad**).* White solid; mp 140 – 141 ℃; 174.1 mg, 83% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.2 Hz, 1H), 7.92 (s, 1H), 7.86 (s, 1H), 7.42 – 7.39 (m, 1H), 7.24 – 7.20 (m, 2H), 6.99 – 6.97 (m, 2H), 6.68 (t, *J* = 54.2 Hz, 1H), 3.89 (s, 3H). ^{19}F NMR (565 MHz, $CDCl_3$) δ -109.06 (d, *J* = 56.4 Hz), -133.74 (dd, *J* = 21.2, 8.3 Hz), -158.26 – -165.86 (m). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 159.6, 151.4 (ddd, *J* = 251.2, 9.9, 4.1 Hz), 142.5 (t, *J* = 29.0 Hz), 139.6 (dt, *J* = 252.7, 15.3 Hz), 136.2, 134.6, 134.3 (td, *J* = 7.7, 5.6 Hz), 131.5, 130.2, 129.3, 125.4, 123.7, 116.7, 113.9 (dd, *J* = 16.6, 4.6 Hz), 111.7 (t, *J* = 233.0 Hz), 39.6; HRMS (ESI): *m/z* calculated for $C_{18}H_{14}F_4N_3O^+$ [M + H]$^+$: 364.1068, found: 364.1062.

*3-(Fluoromethyl)-1-methyl-N-(3',4',5'-trifluoro-[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide (**12**).* Reaction performed on a 0.8 mmol scale utilizing the starting material **8**, **12** was isolated as a white solid: 162.8 mg, 56% yield; mp 156 – 157 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.2 Hz, 1H), 7.86 (s, 2H), 7.45 – 7.36 (m, 1H), 7.45 – 7.36 (m, 2H), 6.99 (t, *J* = 7.0 Hz, 2H), 5.35 (d, *J* = 48.4 Hz, 2H), 3.89 (s, 3H). ^{19}F NMR (565 MHz, $CDCl_3$) δ -133.46 (dd, *J* = 21.3, 8.3 Hz), -159.31 – -168.09 (m), -204.17 (dd, *J* = 60.4, 50.0 Hz). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 160.8, 151.4 (ddd, *J* = 251.4 Hz, 10.2 Hz, 4.3 Hz), 144.6 (d, *J* = 21.4 Hz), 139.6 (dt, *J* = 252.7 Hz, 15.0 Hz), 135.1, 134.8, 134.5 (dd, *J* = 7.3, 4.5 Hz), 131.3, 130.2, 129.4, 125.3, 123.7, 118.4, 113.8 (dd, *J* = 16.6, 4.6 Hz), 78.1 (d, *J* = 158.5 Hz), 39.5; HRMS (ESI): *m/z* calculated for $C_{18}H_{14}F_4N_3O^+$ [M + H]$^+$: 364.1068, found: 364.1062.

*3-Cyano-1-methyl-N-(3',4',5'-trifluoro-[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide (**13**).* Reaction performed on a 1.0 mmol scale utilizing the starting material **9**, **13** was isolated as a white solid: 235.2 mg, 66% yield; mp 203 – 204 ℃; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.96 (s, 1H), 8.41 (s, 1H), 7.48 (d, *J* = 3.3 Hz, 2H), 7.45 – 7.40 (m, 2H), 7.34 (dd, *J* = 8.6, 7.1 Hz, 2H), 3.99 (s, 3H). ^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -135.64 (dd, *J* = 22.4, 9.4 Hz), -161.53 – -166.42 (m). ^{13}C{^{1}H} NMR (100 MHz, DMSO-*d*$_6$) δ 159.2, 150.5 (ddd, *J* = 246.6, 9.6, 4.0 Hz), 138.5 (dt, *J* = 31.4, 15.4 Hz), 136.40 (td, *J* = 8.3, 4.8 Hz), 134.9 (d, *J* = 103.2 Hz), 134.4, 133.3, 130.8, 129.5, 128.4, 127.5, 124.3, 122.0, 113.7 (dd, *J* = 16.2, 5.3 Hz), 113.6, 40.6; HRMS (ESI): *m/z* calculated for $C_{18}H_{12}F_3N_4O^+$ [M + H]$^+$: 357.0958, found: 357.0960.

*Cyano(1-methyl-4-((3',4',5'-trifluoro-[1,1'-biphenyl]-2-yl)carbamoyl)-1H-pyrazol-3-yl)methyl acetate (**14**).* Reaction performed on a 0.5 mmol scale utilizing the starting material **10**, **14** was isolated as a white solid: 186.0 mg, 70% yield; mp 185 – 186 ℃; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.82 (s, 1H), 8.32 (s, 1H), 7.49 – 7.37 (m, 4H), 7.33 (dd, *J* = 9.0, 6.9 Hz, 2H), 6.90 (s, 1H), 3.95 (s, 3H), 2.07 (s, 3H). ^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -135.77 (dd, *J* = 22.4, 9.5 Hz), -158.88 – -170.32 (m). ^{13}C{^{1}H} NMR (100 MHz, DMSO-*d*$_6$) δ 169.3, 161.0, 150.5 (ddd, *J* = 246.6, 9.6, 4.1 Hz), 143.7, 138.4 (dt, *J* = 248.9, 15.5 Hz), 136.6 (td, *J* = 8.4, 4.7 Hz), 135.5, 134.6, 133.6, 130.7, 129.4, 128.6, 127.4, 116.2, 114.9, 113.7 (dd, *J* = 16.0, 5.2 Hz), 56.7, 39.9, 20.3; HRMS (ESI): *m/z* calculated for $C_{21}H_{16}F_3N_4O_3^+$ [M + H]$^+$: 429.1169, found: 429.1169.

Syntheses of 15-20: 1g' was obtained according to the procedure of literature 17 and could successfully be transformed to 1,4,5-trisubstituted pyrazoles **15-20**.

*4-(Furan-2-yl)-1-methyl-1H-pyrazole-5-carbaldehyde (**15**).* Reaction performed on a 1.0 mmol scale utilizing the same procedure for the preparation of **2g** from the starting material **1g'**, **15** was isolated as a yellow solid: 52.9 mg, 30% yield; mp 55 – 56 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.22 (s, 1H), 7.61 (s, 1H), 7.42 (d, *J* = 1.3 Hz, 1H), 6.54 (d, *J* = 3.3 Hz, 1H), 6.42 (dd, *J* = 3.3, 1.8 Hz, 1H), 4.11 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 181.4, 146.4, 143.1, 135.9, 134.0, 120.6, 111.8, 108.4, 40.3. HRMS (ESI): m/z calculated for $C_9H_9N_2O_2^+$ [M + H]$^+$: 177.0659, found: 177.0654.

*(4-(Furan-2-yl)-1-methyl-1H-pyrazol-5-yl)methanol (**16**).* Reaction performed on a 2.8 mmol scale utilizing the same procedure for the preparation of **4g** from the starting material **15**, **16** was isolated as a light yellow solid: 358.2 mg, 72% yield; mp 84 – 85 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.37 (dd, *J* = 1.8, 0.6 Hz, 1H), 6.41 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.33 (dd, *J* = 3.3, 0.5 Hz, 1H), 4.81 (s, 2H), 3.86 (s, 3H), 2.98 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.1, 141.3, 137.5, 136.0, 112.9, 111.4, 105.0, 54.0, 36.8. HRMS (ESI): m/z calculated for $C_9H_{11}N_2O_2^+$ [M + H]$^+$: 179.0815, found: 179.0815.

*2-(4-(Furan-2-yl)-1-methyl-1H-pyrazol-5-yl)-2-((trimethylsilyl)oxy)acetonitrile (**17**).* Reaction performed on a 1.0 mmol scale utilizing the same procedure for the preparation of **6** from the starting material **1g'**, **17** was isolated as a yellow solid: 261.6 mg, 95% yield; mp 122 – 123 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.41 (s, 1H), 6.43 (s, 1H), 6.38 (d, J = 3.2 Hz, 1H), 6.27 (s, 1H), 4.08 (s, 3H), 0.11 (s, 9H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 146.7, 141.7, 135.9, 131.7, 117.0, 112.9, 111.5, 106.2, 54.5, 38.3, -0.6. HRMS (ESI): m/z calculated for $C_{13}H_{18}N_3O_2Si^+$ [M + H]$^+$: 276.1163, found: 276.1161.

*5-(Difluoromethyl)-4-(furan-2-yl)-1-methyl-1H-pyrazole **(18)**.* Reaction performed on a 2.4 mmol scale utilizing the same procedure for the preparation of **3g** from the starting material **15**, **18** was isolated as a light yellow solid: 200.0 mg; 42% yield; mp 39 – 40 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.42 (d, J = 1.0 Hz, 1H), 7.19 (t, *J* = 52.8 Hz, 1H), 6.44 – 6.41 (m, 2H), 4.05 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.98 (d, *J* = 52.7 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 146.3, 142.1, 135.9, 130.1 (t, *J* = 23.5 Hz), 115.4 (t, *J* = 5.9 Hz), 111.5, 108.7 (t, *J* = 234.0 Hz), 106.6, 38.9. HRMS (ESI): m/z calculated for $C_9H_9F_2N_2O^+$ [M + H]$^+$: 199.0677, found: 199.0676.

*5-(Fluoromethyl)-4-(furan-2-yl)-1-methyl-1H-pyrazole **(19)**.* Reaction performed on a 2.0 mmol scale utilizing the same procedure for the preparation of **5g** from the starting material **16**, **19** was isolated as yellow oil: 51.4 mg, 11% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.43 (d, *J* = 1.5 Hz, 1H), 6.44 (dd, J = 3.3, 1.8 Hz, 1H), 6.39 (d, J = 3.3 Hz, 1H), 5.60 (d, *J* = 49.0 Hz, 2H), 3.95 (s, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -207.84 (t, *J* = 49.3 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 147.4 (d, *J* = 2.6 Hz), 141.8, 136.3 (d, *J* = 2.7 Hz), 132.9 (d, *J* = 19.1 Hz), 115.1 (d, *J* = 4.2 Hz), 111.4, 105.8 (d, *J* = 1.6 Hz), 72.9 (d, *J* = 164.9 Hz), 37.1. HRMS (ESI): m/z calculated for $C_9H_{10}FN_2O^+$ [M + H]$^+$: 181.0772, found: 181.0771.

*Cyano(4-(furan-2-yl)-1-methyl-1H-pyrazol-5-yl)methyl acetate **(20)**.* Reaction performed on a 1.5 mmol scale utilizing the same procedure for the preparation of **6** from the starting material **1g'**, **20** was isolated as a yellow solid: 330.0 mg, 90% yield; mp 89 – 90 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.49 – 7.42 (m, 1H), 7.15 (s, 1H), 6.47 (dd, *J* = 3.4, 0.6 Hz, 1H), 6.45 (dd, *J* = 3.3, 1.8 Hz, 1H), 4.11 (s, 3H), 2.18 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 168.3, 146.0, 142.4, 136.4, 127.6, 115.1, 114.2, 111.5, 106.9, 53.2, 38.4, 20.4. HRMS (ESI): m/z calculated for $C_{12}H_{12}N_3O_3^+$ [M + H]$^+$: 246.0873, found: 246.0870.

*5-(Difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic acid **(21)**.* Reaction performed on a 0.63 mmol scale utilizing the same procedure for the preparation of **7** from the starting material **18**, **21** was isolated as a yellow solid: 86.9 mg, 78% yield; mp 148 – 149 ℃; ^{1}H NMR (400 MHz, CD_3OD) δ 7.87 (s, 1H), 7.55 (t, *J* = 52.8 Hz, 1H), 4.07 (s, 3H). ^{19}F NMR (376 MHz, CD_3OD) δ -117.71 (d, *J* = 52.8 Hz). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 163.5, 140.2, 136.5 (t, *J* = 23.7 Hz),115.3 (t, *J* = 5.2 Hz), 107.8 (t, *J* = 234.2 Hz), 38.0; HRMS (ESI): *m/z* calculated for $C_6H_7F_2N_2O_2^+$ [M + H]$^+$: 177.0470, found: 177.0469.

*5-(Fluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic acid **(22)**.* Reaction performed on a 1.1 mmol scale utilizing the same procedure for the preparation of **8** from the starting material **19**, **22** was isolated as a white solid: 132.2 mg, 76% yield; mp 123 – 124 ℃; ^{1}H NMR (400 MHz, CD_3OD) δ 7.87 (s, 1H), 5.81 (d, *J* = 47.9 Hz, 2H), 3.97 (s, 3H). ^{19}F NMR (377 MHz, CD_3OD) δ -216.31 (t, *J* = 48.2 Hz). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 164.4, 140.4 (d, *J* = 1.9 Hz), 140.0 (d, *J* = 17.5 Hz), 113.7, 71.7 (d, *J* = 162.6 Hz), 36.0; HRMS (ESI): *m/z* calculated for $C_6H_8FN_2O_2^+$ [M + H]$^+$: 159.0564, found: 159.0561.

*5-Cyano-1-methyl-1H-pyrazole-4-carboxylic acid **(23)**.* Reaction performed on a 3 mmol scale utilizing the same procedure for the preparation of **9** from the starting material **1g'**, **23** was isolated as a white solid: 356.4 mg, 78% yield; mp 192 – 193 ℃; ^{1}H NMR (400 MHz, CD_3OD) δ 7.95 (s, 1H), 4.08 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 162.0, 140.5, 120.7, 117.5, 108.9, 37.9; HRMS (ESI): *m/z* calculated for $C_6H_6N_3O_2^+$ [M + H]$^+$: 152.0455, found: 152.0454.

*5-(Acetoxy(cyano)methyl)-1-methyl-1H-pyrazole-4-carboxylic acid **(24)**.* Reaction performed on a 1 mmol scale utilizing the same procedure for the preparation of **10** from the starting material **20**, **24** was isolated as a white solid: 200.0 mg, 86% yield; mp 199 – 200 ℃; ^{1}H NMR (400 MHz, CD_3OD) δ 7.91 (s, 1H), 7.55 (s, 1H), 4.13 (s, 3H), 2.21 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 168.4, 163.7, 140.4, 134.9, 114.1, 113.6, 52.3, 37.6, 18.5. HRMS (ESI): *m/z* calculated for $C_9H_{10}N_3O_4^+$ [M + H]$^+$: 224.0666, found: 224.0662.

*5-(Difluoromethyl)-1-methyl-N-(3',4',5'-trifluoro-[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide **(25)**.* Reaction performed on a 0.38 mmol scale utilizing the starting material **21**, **25** was isolated as a white solid: 116.5 mg, 80% yield; mp 120 – 121 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.1 Hz, 1H), 7.61 (t, *J* = 48.3 Hz, 1H), 7.46 (d, *J* = 2.9 Hz, 2H), 7.36 (s, 1H), 7.29 (s, 1H), 7.28 (s, 1H), 7.08 (t, *J* = 6.9 Hz, 2H), 4.10 (s, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -116.00 (d, *J* = 53.1 Hz), -132.22 (dd, *J* = 21.7, 8.2 Hz), -157.00 – -162.58 (m). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.2, 151.6 (ddd, *J* = 252.5, 9.9, 4.3 Hz), 139.7 (dt, *J* = 30.2, 14.9 Hz), 136.9 (t, *J* = 24.1 Hz), 135.8, 134.2 (dd, *J* = 7.8, 5.1 Hz), 133.9, 130.8, 130.2, 129.7, 125.8, 123.3, 118.0 (t, *J* = 4.9 Hz), 113.7 (dd, *J* = 15.4, 6.0 Hz), 107.7 (t, *J* = 235.6 Hz), 39.4; HRMS (ESI): *m/z* calculated for $C_{18}H_{13}F_5N_3O^+$ [M + H]$^+$: 382.0973, found: 382.0974.

*5-(Fluoromethyl)-1-methyl-N-(3',4',5'-trifluoro-[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide **(26)**.* Reaction performed on a 0.27 mmol scale utilizing the starting material **22**, **26** was isolated as a white solid: 75.4 mg, 77% yield; mp 141 – 142 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.2 Hz, 1H), 7.51 (s, 1H), 7.41 – 7.39 (m, 2H), 7.23 – 7.21 (m, 2H), 7.01 – 7.03 (m, 2H), 5.74 (d, *J* = 48.1 Hz, 2H), 3.94 (s, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -132.47 (dd, *J* = 21.3, 8.2 Hz), -156.44 – -166.83 (m), -213.58 (t, *J* = 48.4 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.9, 151.6 (ddd, *J* = 252.2, 9.9, 4.2 Hz), 139.7 (dt, *J* = 238.8,14.6 Hz), 139.2 (d, *J* = 17.7 Hz), 136.5 (d, *J* = 1.8 Hz), 134.4 (dd, *J* = 5.1, 2.7 Hz), 134.3, 130.6, 130.1, 129.7, 125.4, 123.2, 117.2 (d, *J* = 2.9 Hz), 113.7 (dd, *J* = 15.4, 6.1 Hz), 72.6 (d, *J* = 165.0 Hz), 37.7; HRMS (ESI): *m/z* calculated for $C_{18}H_{14}F_4N_3O^+$ [M + H]$^+$: 364.1068, found: 364.1072.

*5-Cyano-1-methyl-N-(3',4',5'-trifluoro-[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide **(27)**.* Reaction performed on a 1.3 mmol scale utilizing the starting material **23**, **27** was isolated as a white solid: 337.0 mg, 73% yield; mp 199 – 200 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 8.15 (s, 1H), 7.48 (dd, *J* = 12.5, 6.1 Hz, 3H), 7.43 (d, *J* = 7.1 Hz, 1H), 7.40 – 7.33 (m, 2H), 4.03 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -135.74 (dd, *J* = 22.7, 9.7 Hz), -159.30 – -167.04 (m). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 159.0, 150.5 (ddd, *J* = 246.8, 9.6, 3.8 Hz), 138.5 (dt, *J* = 249.0, 15.0 Hz), 138.2, 136.3 (td, *J* = 8.2, 4.8 Hz), 135.5, 134.3, 130.8, 129.5, 128.5, 127.7, 124.4, 117.0, 113.8 (dd, *J* = 16.0, 5.2 Hz), 110.3, 39.2; HRMS (ESI): *m/z* calculated for $C_{18}H_{12}F_3N_4O^+$ [M + H]$^+$: 357.0958, found: 357.0959.

*Cyano(1-methyl-4-((3',4',5'-trifluoro-[1,1'-biphenyl]-2-yl)carbamoyl)-1H-pyrazol-5-yl)methyl acetate **(28)**.* Reaction performed on a 0.54 mmol scale utilizing the starting material **24**, **28** was isolated as a white solid: 188.0 mg, 70% yield; mp 163 – 164 ℃; ^{1}H NMR (400 MHz, CD_3OD) δ 7.83 (s, 1H), 7.43 – 7.35 (m, 3H), 7.35 – 7.31 (m, 2H), 7.07 (dd, *J* = 8.8, 6.8 Hz, 2H), 4.02 (s, 3H), 2.09 (s, 3H). ^{19}F NMR (376 MHz, CD_3OD) δ -137.52 (dd, *J* = 20.7, 9.2 Hz), -157.84 – -171.78 (m). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 168.2, 161.9, 150.8 (ddd, *J* = 248.1, 9.9, 4.1 Hz), 138.8 (dt, *J* = 31.2, 15.4 Hz), 137.3, 136.0, 136.0 – 135.8 (m), 134.5, 133.5, 130.0, 128.9, 127.8, 127.3, 116.3, 113.7, 112.9 (dd, *J* = 16.1, 5.8 Hz), 52.3, 37.5, 18.5; HRMS (ESI): *m/z* calculated for $C_{21}H_{16}F_3N_4O_3^+$ [M + H]$^+$: 429.1169, found: 429.1169.

■ ASSOCIATED CONTENT

● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.xxxx.

Scheme S1, ^{1}H, ^{19}F and ^{13}C NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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