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A general strategy for the synthesis of difluoromethyl-containing pyrazoles, pyridines and pyrimidines

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ABSTRACT

Difluoromethyl-containing heteroannulated pyridines, pyrimidines and pyrazoles are prepared by a two step method. The regioselective cyclizations of electron-excessive aminoheterocycles, hydrazines and amidines with CF_2Cl-substituted 1,3-dicarbonyl compounds provide the corresponding CF_2Cl-substituted heterocycles. Subsequent radical reactions with trimethylstannane or allyltrimethylstannane gave difluoromethyl-containing heteroannulated pyridines, pyrimidines and pyrazoles, respectively.

1. Introduction

The introduction of fluorine-containing functional groups to biomolecules often results in an improvement of the biological activity.[1] It has been demonstrated that CF_2H-containing molecules possess strong anti-cancer activity. In general, compounds containing CF_2-groups have been reported to exhibit herbicidal,[2] potential antitumour[3] and antileishmanial activity.[4] Although difluoromethylated compounds have significant applications in drug and pesticide discovery, only a limited number of them are synthetically available as compared to their CF_3 analogues.

On the other side, there are a number of drugs on the market, which contain a CF_2-group (Fig. 1).[5–9] Pantoprazole (**I**) developed by Altana Pharma (presently Nicomed) is a proton pump inhibitor used for short-term treatment of erosion and ulceration of the oesophagus caused by gastroesophageal reflux disease.[5] Eflornithine (α-difluoromethylornithine or DFMO) **IV**, a rationally designed ornithine decarboxylase inhibitor, is active against infections with *Trypanosoma gambiense*. Eflornithine is a drug used for the treatment of facial hirsutism (excessive hair)[6] as well as in African *trypanosomiasis* (sleeping sickness).[7]

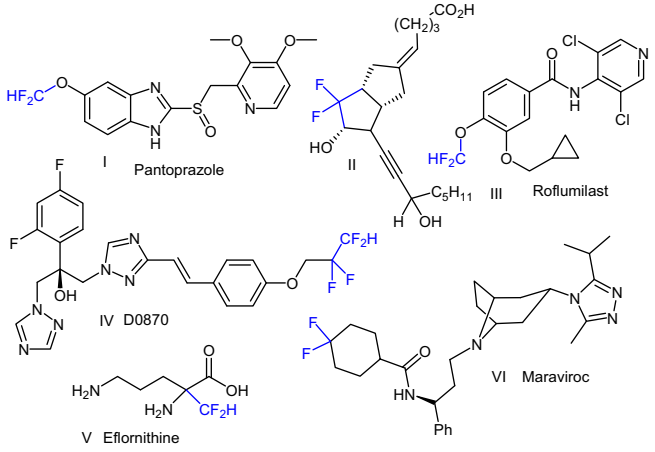

Fig. 1. Drugs containing a CF_2-group.

In general, molecules containing a CF_2-function are relatively rare in the literature, due to the lack of synthetic methods available for their introduction. A number of methods for the preparation of CF_2-containing compounds have been developed in recent years.[10] The commercial availability of several fluorinating agents, such as DAST, SF_4,[11] SeF_4,[12] TBAF[13] and BrF_3,[14] has paved the way for the

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synthesis of various difluorinated compounds. However, most of these methods rely on harsh reaction conditions and aggressive medias. Thus, the development of alternative synthetic approaches to CF_2-containing molecules represents an important area of current research.

2. Results and discussion

Continuing our research program[15] dedicated to the design and synthesis of fluorinated drug-like scaffolds and their functionalization, we started the project reported herein. Our initial purpose was to develop a facile and straightforward synthetic pathway towards small heterocycles bearing CF_2H and CF_2R substituents in the heteroaromatic ring. Based on the retrosynthetic analysis and our previous experience in the synthesis of fluorinated heterocycles, based on cyclocondensation of electron-rich systems with fluorinated 1,3-CCC- and 1,3-CNC-dielectrophiles, we envisaged the two-step strategy depicted in Fig. 2. The first step is built upon the initial assembly of the heterocyclic scaffold by formal [2+3] or [3+3]-cycloaddition reactions. As a second step, the exchange of the Cl-atom by free radical conditions, using AIBN, Bu_3SnH or Bu_3Sn–allyl, was carried out.

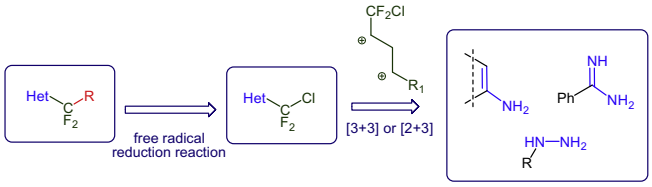


Fig. 2. Retrosynthetic analysis.

Hereby, we report a general method for the synthesis of 4-CF_2R-substituted heteroannulated pyridines as well as CF_2R-substituted pyrimidines and pyrazoles. The syntheses follow a two step procedure, which consists of the formal [3+3]- and [2+3]-cyclization of CF_2Cl-containing 1,3-CCC-dielectrophiles with electron-excessive heteroaromatic systems, hydrazines and amidines. Subsequently, radical-induced substitutions of the chlorine atom of the CF_2Cl moiety using Bu_3SnH or Bu_3Sn–allyl and AIBN are carried out.[16] Previously, this method was used for the synthesis of complex organic molecules,[16] but the scope and limitations have not yet been studied.

Starting with electron-excessive aminoheterocycles available in our laboratories (Fig. 3) and CF_2Cl-substituted 1,3-diketones, we have elaborated a facile synthesis of γ-CF_2Cl-substituted pyridines **7** (Scheme 1). The reaction proceeds in acetic acid under reflux delivering the correspondent annulated pyridines in good to

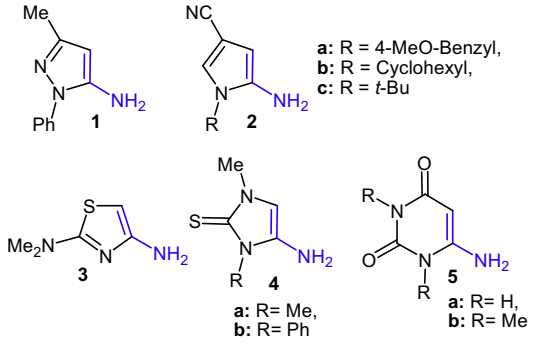
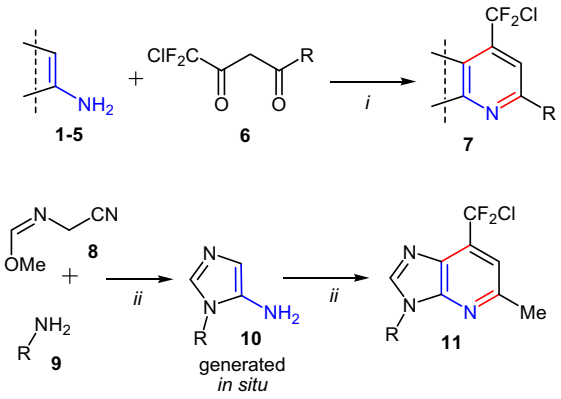


Fig. 3. Amines used for the synthesis of heteroanulated pyridines.



Scheme 1. Synthesis of heteroannulated pyridines **7**. Reagents and conditions: (i): AcOH, reflux. (ii) CH_2Cl_2, argon, reflux, 2 h.

excellent yields (Table 1). At the same time, 5-aminoimidazoles **10**, in situ generated by our recently reported method,[17] reacted with **6** to give the 7-(chlorodifluoromethyl)-imidazo[4,5-*b*]pyridines **11**.

After construction of the condensed pyridine scaffolds, we have concentrated our efforts on the functionalization of the CF_2–Cl bond by free radical reactions initiated by AIBN with Bu_3SnH or Bu_3Sn–allyl. This reaction takes place smoothly in dry benzene at 80 °C and usually was finished within 18 h. All pyridines tested here have shown high reactivity and gave the correspondent CF_2-substituted pyridines **12**, **13** in good to excellent yields (Scheme 2, Table 2).

The bicyclic structures of scaffolds **12** and **13** were in accordance with the NMR spectroscopic data. The assignments of scaffolds **12**

Table 1
Yields of compounds **7**, **11**

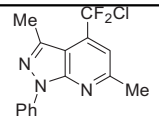
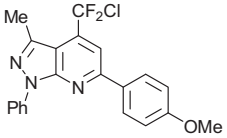
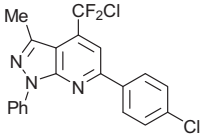
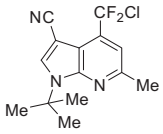
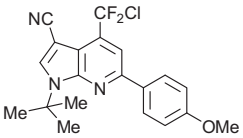
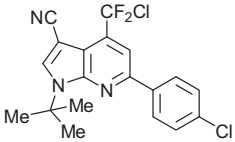
N	Structure	%[a]
7a		84
7b		60
7c		65
7d		67
7e		82
7f		72

Table 1 (*continued*)

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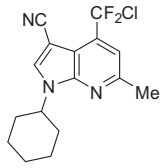
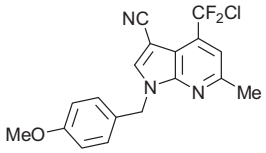
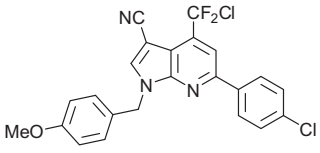
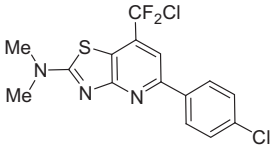
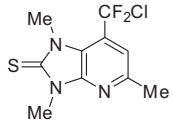
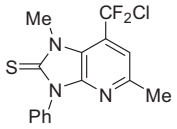
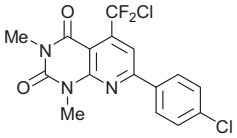
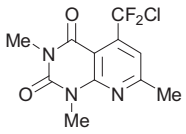
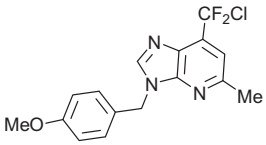
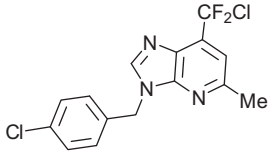
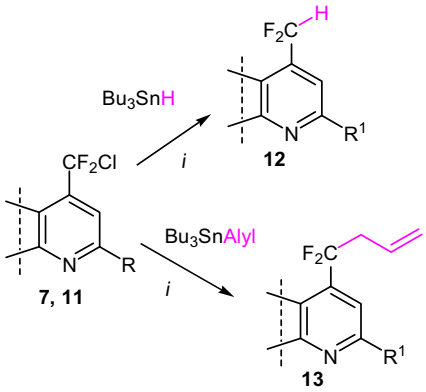
7g		87
7h		85
7i		70
7j		55
7k		59
7l		75
7m		75
7n		73
11a		89
11b		85

[a] Yields of isolated products.



Scheme 2. Synthesis of pyridines **12** and **13**. Reagents and conditions: (i): AIBN, C_6H_6, 18 h, 80 °C.

and **13** were additionally confirmed by X-ray crystal structure analysis of compounds **12f** and **13d** (Figs. 4 and 5).[18] The 1-*tert*-butyl-4-(1,1-difluorobut-3-enyl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile **13d** is, as expected, a plane molecule. In the crystal, the angle F(1)C(13)F(2) is 105.0° and the angle C(5)C(13)C(14) is 105.8°, which are typical for CF_2–alkyl substituents. The torsion angle C(2)C(5)–C(13)C(14) is 71.4° (Fig. 5).

Table 2
Yields of compounds **12**, **13**

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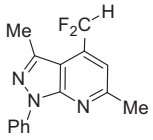
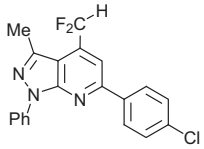
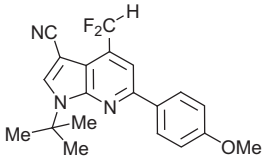
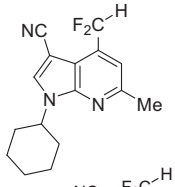
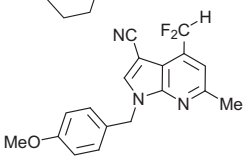
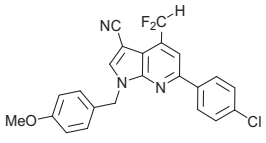
12a		68
12b		87
12c		84
12d		73
12e		78
12f		58

(*continued on next page*)

Table 2 (*continued*)

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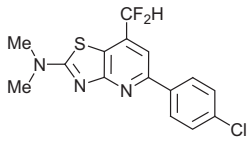
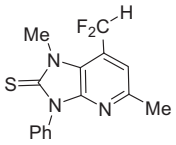
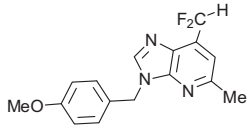
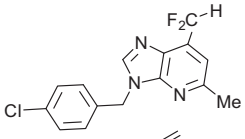
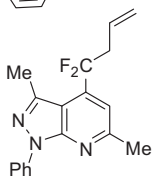
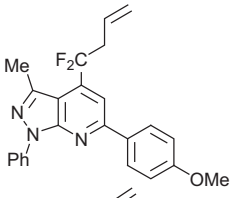
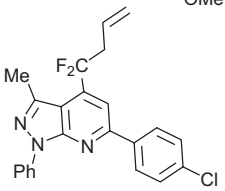
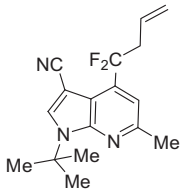
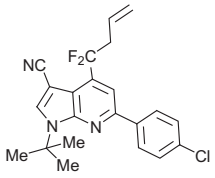
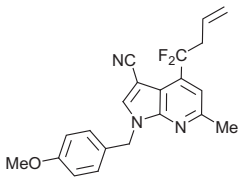
12g		56
12h		60
12i		74
12j		90
13a		95
13b		65
13c		72
13d		68
13e		68
13f		61

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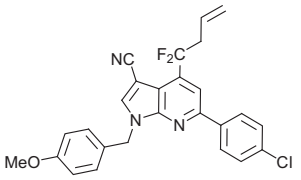
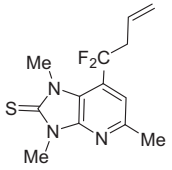
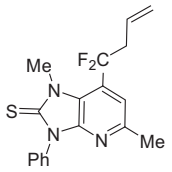
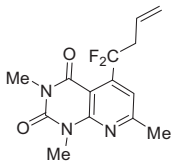
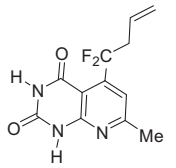
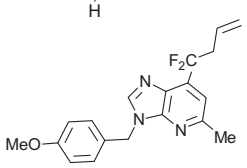
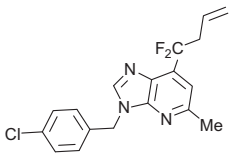
13g		68
13h		69
13i		55
13j		43
13k		29
13l		98
13m		59

[a] Yields of isolated products.

For the synthesis of 4-(difluoromethyl)pyrimidines we have applied the same synthetic pathway as described above for the synthesis of heteroannulated pyridines. As a model compound, phenylamidine **14** was chosen. For the synthesis of the cyclic CF_2Cl-precursors **16a**,**b** we have used two different building blocks, namely, CF_2Cl-substituted 1,3-diketones **6** and (*E*)-1-chloro-4-ethoxy-1,1-difluorobut-3-en-2-one **15** (Scheme 3). The reaction of phenylamidine with CF_2Cl-substituted 1,3-dielectrophiles **6** and **15** afforded the 4-(chlorodifluoromethyl)-2-phenylpyrimidines **16a**,**b** in good yields. The reaction with Bu_3SnH and Bu_3Sn–allyl resulted in the formation of the correspondent CF_2H- and CF_2Allyl-substituted derivatives **17**, **18** (Scheme 4).

The structure of pyrimidine **16b** was unambiguously proved by X-ray crystal structure analysis (Fig. 6).[18] The molecule has a plane structure, the corresponding torsion angle N(1)C(1)–C(5)C(10) is close to 0°.

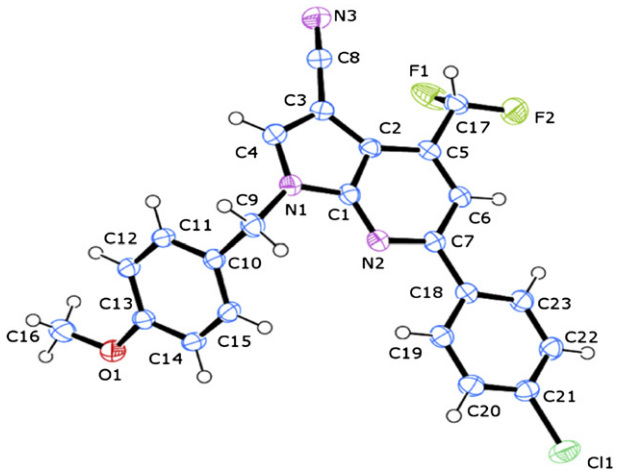


Fig. 4. Molecular structure of compound **12f**.

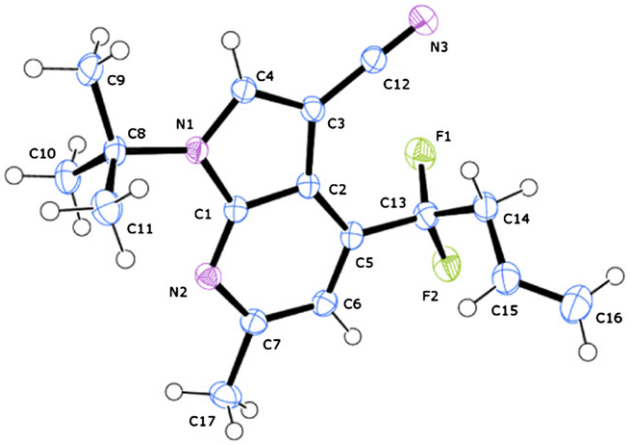
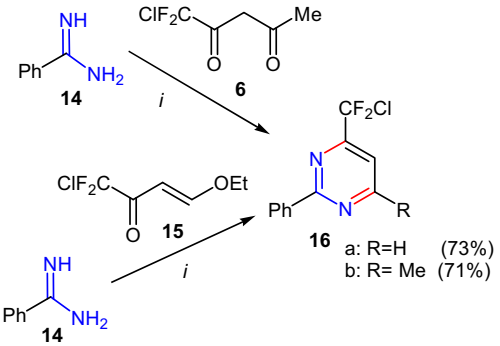
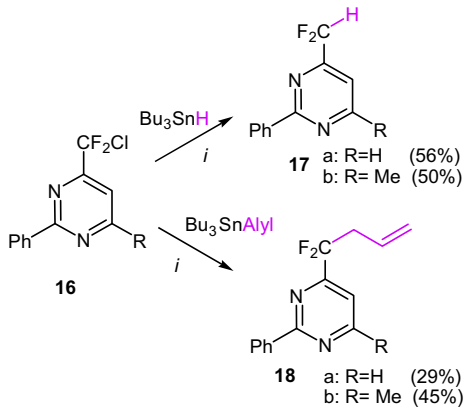


Fig. 5. Molecular structure of compound **13d**.

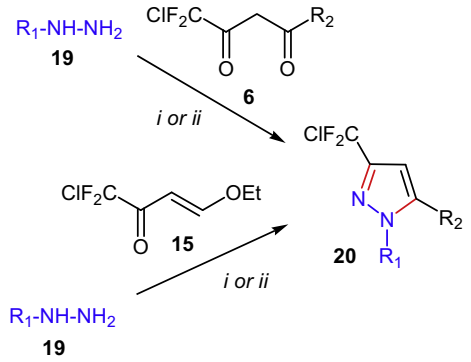


Scheme 3. Synthesis of pyrimidines **16**. Reagents and conditions: (i): 1.1 equiv NaOAc, xylol, 7.5 h, reflux.

Pyrazoles have a wide range of biological activities and occur in numerous drugs. Pyrazoles are present in B-Raf inhibitors,[19] CARM1 inhibitors,[20] CB1 receptor antagonists,[21] and EP1 receptor antagonists.[22] Fluorinated pyrazoles are relatively rare. In spite of extensive studies related to the biological activities of pyrazole derivatives, syntheses of pyrazoles suffer from their poor regioselectivity, especially in the case of the condensation reaction of 1,3-diketones with unsymmetrical hydrazines. Therefore, we were strongly encouraged to pursue the synthesis of a focused library of CF_2-substituted pyrazoles, which is based on formal [3+2]-cyclizations of hydrazines with CF_2Cl-substituted 1,3-CCC-dielectrophiles followed by functionalization of the CF_2Cl-group (Scheme 5).



Scheme 4. Synthesis of pyrimidines **17**, **18**. Reagents and conditions: (i): AIBN, C_6H_6, 18 h, 80 °C.



Scheme 5. Synthesis of 3-chlorodifluoromethyl-1*H*-pyrazoles **20**. Reagents and conditions: (i): EtOH, reflux, 5 h (ii): AcOH, 20 °C.

As the starting point, we have chosen two previously described methods for the synthesis of pyrazole using diketones **6** and (*E*)-1-chloro-4-ethoxy-1,1-difluorobut-3-en-2-one **15**. We have identified two reported reaction conditions for the synthesis of pyrazoles, namely, acetic acid at 20 °C,[23] and ethanol under reflux.

The reaction of hydrazines with **6** and **15** regioselectively afforded the 3-(chlorodifluoromethyl)-1*H*-pyrazoles **20** in 10–94% yields (Table 3, Scheme 5). The yields are dependent on the choice of the reaction medium. The modification of the CF_2Cl-group, again conducted using Bu_3SnH or Bu_3Sn–allyl in the presence of AIBN, led to the formation of the CF_2-substituted pyrazoles **21** and **22** in fair yields (Scheme 6).

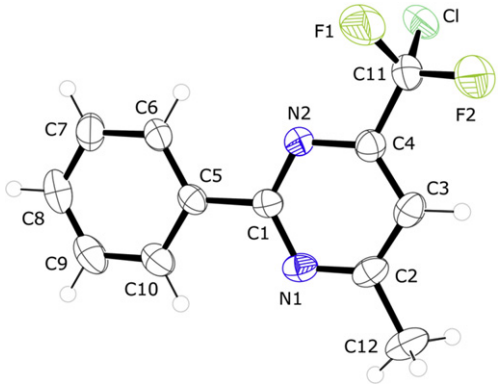
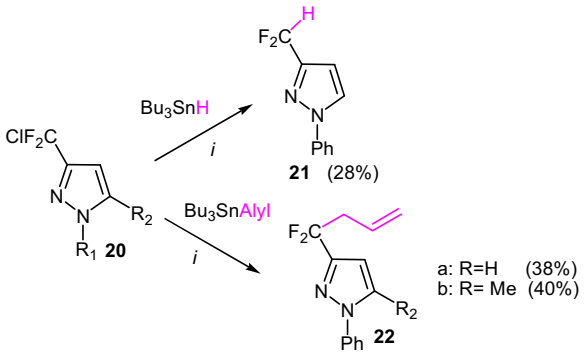


Fig. 6. Molecular structure of compound **16b**.

Table 3
Yields of compounds **20**

20	R_1	R_2	% (**20**)[a]
a	H	H	79 (ii)
b	Ph	H	94 (i)
c	4–$(NO_2)C_6H_4$	H	0 (i,ii)
d	H	Me	73 (ii)
e	Me	Me	47 (ii)
f	Ph	Me	88 (ii)
g	4–$(NO_2)C_6H_4$	Me	73 (i)

[a] Yields of isolated products; in brackets: reactions conditions applied.



Scheme 6. Synthesis of pyrazoles **21**, **22**. Reagents and conditions: (i): AIBN, C_6H_6, 18 h, 80 °C.

In conclusion, we have elaborated a practical and short synthetic route to CF_2-containing drug-like heteroannulated pyridines, pyrimidines and pyrazoles using a new two step sequence. This protocol relies on the assembly of the CF_2Cl-containing heterocyclic moiety by [3+2]- and [3+3]-cyclizations and subsequent substitution reactions by free radical conditions.

3. Experimental section

3.1. General comments

Chemical yields refer to pure isolated substances. ^1H and ^{13}C NMR spectra were obtained using a Bruker DPX-300 spectrometer. Chemical shifts of the ^1H and ^{13}C NMR are reported in parts per million using the solvent internal standard ($CDCl_3$ 7.26 ppm and 77.0 ppm, DMSO-d_6 2.49 ppm and 39.7 ppm). IR spectra were recorded on a Perkin–Elmer FTIR 1600 spectrometer for samples in KBr discs. Mass spectra were obtained on a Hewlett–Packard HP GC/MS 5890/5972 instrument (EI, 70 eV) by GC inlet or on an MX-1321 instrument (EI, 70 eV) by direct inlet. Elemental analyses were carried out at the Microanalytical laboratory of the University of Rostock Germany. Melting points are uncorrected. The solvents were purchased directly from ACROS and used without further purification. Analytical thin layer chromatography was performed on 0.20 mm 60 A silica gel plates. Column chromatography was performed using 60 A silica gel (60–200 mesh).

3.2. General procedure for the synthesis of compounds 6

To a solution of NaH (1.1 equiv) in ether (2.0 mL/mmol SM) was added acetophenone (1.0 equiv) at 0 °C. The solution was stirred at 0 °C for 10 min before methyl 2-chloro-2,2-difluoroacetate (1.0 equiv) was added. The temperature was allowed to rise to 20 °C over 14 h. To the solution was added HCl (10%) and the mixture was extracted with Et_2O. The organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (heptane/EtOAc) to give the chlorodifluoroketones.

3.3. General procedure for the synthesis of compounds 7a–n

A solution of chlorodifluorodiketone (1.0 equiv) and amine (1.0 equiv) in acetic acid (10 mL per 1 mmol of starting material) was heated for 3–6 h under reflux. The solvent was evaporated, and the obtained crude product was purified by column chromatography to give the pure product.

3.4. General procedure for the synthesis of compounds 12a–j, 13a–m, 17a,b, 18a,b, 21, 22a,b

To a solution of chlorodifluorinated heterocycle (0.5 equiv) and of the stannane (1.25 equiv) in benzene (10 mL per 1 mmol of starting material) was added AiBN (0.06 equiv). The mixture was heated for 16 h under reflux (TLC control). The solvent was evaporated and the crude product was purified by column chromatography (silica gel, heptanes/EtOAc, 100:1) to give the crude product. The residue was purified by preparative chromatography (silica gel, heptane).

3.5. General procedure for the synthesis of compound 7j

A solution of 1.0 equiv of the chlorodifluorodiketone and of 1.0 equiv of the amine in acetic acid (3 mL per 1 mmol of the starting material) was added NaOAc (4 equiv). The mixture was heated for 6 h under reflux. The solvent was evaporated, and the obtained crude product was purified by column chromatography to give the pure product.

3.6. General procedure for the synthesis of compounds 16a,b

A solution of 1.0 equiv of the chlorodifluorodiketone, 1.0 equiv of benzamidine and 1.1 equiv of sodium acetate in xylol (1 mL per 1 mmol of starting material) was heated at 139 °C. The crude product was poured into ice water. After standing for 12 h at room temperature, the precipitate formed was filtered, washed with water and dried.

3.7. General procedure for the synthesis of compounds 20a, 20c, 20e–f

A solution of 1.0 equiv of the chlorodifluorodiketone or of (*Z*)-1-chloro-4-ethoxy-1,1-difluorbut-3-en-2-one and of 1.0 equiv of the hydrazine in acetic acid (8 mL per 1 mmol of starting material) was stirred for 2 h at room temperature. The solvent was evaporated, and the crude product was purified by column chromatography to give the pure product.

3.8. General procedure for the synthesis of compounds 20b, 20g

A solution of 1.0 equiv of the chlorodifluorodiketone or of (*Z*)-1-chloro-4-ethoxy-1,1-difluorbut-3-en-2-one and of 1.0 equiv of the hydrazine in ethanol (8 mL per 1 mmol of starting material) was heated for 5 h under reflux and stirred for 12 h at room temperature. The solvent was evaporated, and the obtained crude product was purified by column chromatography to give the pure product.

*3.8.1. 4-(Chlorodifluoromethyl)-3,6-dimethyl-1-phenyl-1H-pyrazolo [3,4-b]pyridine (**7a**).* Brown solid isolated by recrystallization from acetic acid, mp 67–69 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ=2.74–2.75 (m, 6H, CH_3), 7.27–7.33 (m, 1H, CH), 7.44–7.53 (m, 3H, $C_{Ar}H$), 8.19–8.22 (m, 2H, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=15.5 (t, $J_{C,F}$=4.5 Hz, CH_3), 25.1 (CH_3), 108.3 (t, $J_{C,F}$=2.2 Hz, C), 112.4 (t, $J_{C,F}$=6.6 Hz, CH), 121.6 (CH), 124.3 (t, $J_{C,F}$=35.0 Hz, C), 126.1, 129.0 (CH), 137.4 (t, $J_{C,F}$=28.6 Hz, *C*–CF_2Cl), 139.0, 140.9, 152.0 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−49.54 (CF_2Cl). IR (ATR, cm^{-1}): ν=3082 (w), 2922 (w), 2851 (w), 1681 (w), 1595 (m), 1573 (w), 1502 (s), 1438 (m),

1412 (s), 1391 (w), 1378 (w), 1343 (s), 1305 (w), 1295 (w), 1271 (w), 1219 (s), 1162 (s), 1122 (s), 1071 (m), 1034 (m), 1009 (m). MS (EI, 70 eV): *m*/*z* (%)=309 ([M$^+$] [^{37}Cl], 51), 308 (34), 307 ([M$^+$] [^{35}Cl], 100), 292 (16), 272 (52), 266 (22), 257 (11), 77 (16). HRMS (EI, 70 eV): calcd for $C_{15}H_{12}N_3ClF_2$ ([M$^+$], [^{35}Cl]) 307.06823, found 307.067620. Anal. Calcd for $C_{15}H_{12}ClF_2N_3$ (307.73): C, 58.55, H, 3.93, N, 13.66. Found: C, 58.290, H, 3.960, N, 12.910.

*3.8.2. 4-(Chlorodifluoromethyl)-6-(4-methoxyphenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine (**7b**).* White solid isolated by recrystallization from acetic acid; mp 158–159 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.77 (t, ^3J=1.9 Hz, 3H, CH_3), 3.89 (s, 3H, OCH_3), 7.01–7.04 (m, ^3J=8.9 Hz, 2H, $C_{Ar}H$), 7.32 (t, ^3J=7.4 Hz, 1H, $C_{Ar}H$), 7.51–7.57 (m, 2H, $C_{Ar}H$), 7.79 (s, 1H, CH), 8.10–8.13 (m, 2H, $C_{Ar}H$), 8.30–8.32 (m, 2H, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=15.5 (t, $J_{C,F}$=4.4 Hz, CH_3), 55.4 (OCH_3), 108.6 (t, $J_{C,F}$=2.2 Hz, C), 108.8 (t, $J_{C,F}$=6.6 Hz, CH), 114.3 (CH), 121.4 (CH), 124.4 (t, $J_{C,F}$=290.5 Hz, CF_2Cl), 125.9 (CH), 128.9 (CH), 129.0 (CH), 130.5 (C), 137.9 (t, $J_{C,F}$=29.2 Hz, *C*–CF_2Cl), 139.2 (C), 141.1 (C), 152.2 (C), 156.5 (C), 161.4 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=–49.55 (CF_2Cl). IR (ATR, cm^{-1}): ν=3107 (w), 3076 (w), 3040 (w), 3007 (w), 2938 (w), 2842 (w), 1593 (w), 1582 (w), 1568 (w), 1504 (w), 1493 (w), 1478 (w), 1458 (m), 1435 (w), 1417 (s), 1386 (w), 1347 (s), 1311 (w), 1297 (w), 1255 (w), 1236 (s), 1167 (w), 1157 (w), 1118 (m), 1084 (m), 1050 (w), 1042 (w), 1028 (m), 1002 (w). MS (EI, 70 eV): *m*/*z* (%)=401 ([M$^+$], [^{37}Cl], 35), 400 (25), 399 ([M$^+$], [^{35}Cl], 100), 364 (14). HRMS (EI, 70 eV): calcd for $C_{21}H_{16}N_3ClF_2O$ ([M$^+$], [^{35}Cl]) 399.09445, found 399.094692. Anal. Calcd for $C_{21}H_{16}ClF_2N_3O$ (399.82): C, 63.08, H, 4.03, N, 10.51. Found: C, 62.600, H, 3.620, N, 9.920.

*3.8.3. 4-(Chlorodifluoromethyl)-6-(4-chlorophenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine (**7c**).* White solid isolated by recrystallization from acetic acid; mp 157–158 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.79 (s, 3H, CH_3), 7.34 (t, ^3J=7.4 Hz, 1H, $C_{Ar}H$), 7.47–7.57 (m, 4H, $C_{Ar}H$), 7.80 (s, 1H, CH), 8.08 (d, ^3J=8.5 Hz, 2H, $C_{Ar}H$), 8.27 (d, ^3J=7.7 Hz, 2H, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=15.5 (t, $J_{C,F}$=4.4 Hz, CH_3), 109.0 (t, $J_{C,F}$=6.6 Hz, CH), 109.3 (t, $J_{C,F}$=2.2 Hz, C), 121.5 (CH), 124.1 (t, $J_{C,F}$=290.5 Hz, CF_2Cl), 126.2 (CH), 127.5 (C), 128.7, 129.0, 129.2 (CH), 136.4 (d, $J_{C,F}$=4.4 Hz, C), 138.3 (t, $J_{C,F}$=29.2 Hz, *C*–CF_2Cl), 139.0, 141.2, 152.1, 155.5 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=–49.62. IR (ATR, cm^{-1}): ν=3061 (w), 2979 (w), 2937 (w), 2861 (w), 2355 (w), 2138 (w), 1592 (w), 1581 (w), 1562 (w), 1503 (s), 1489 (w), 1476 (w), 1456 (w), 1438 (w), 1418 (m), 1403 (m), 1388 (w), 1345 (s), 1312 (w), 1298 (w), 1268 (w), 1242 (s), 1176 (m), 1152 (m), 1026 (m), 1094 (w), 1084 (w), 1051 (m), 1031 (w), 1013 (w), 1002 (w). MS (EI, 70 eV): *m*/*z* (%)=407 ([M$^+$], [^{37}Cl] [^{37}Cl], 12), 405 ([M$^+$], [^{35}Cl] [^{37}Cl], 67), 404 (28), 403 ([M$^+$], [^{35}Cl] [^{35}Cl], 100), 402 (9), 368 (23). HRMS (EI, 70 eV): calcd for $C_{20}H_{13}N_3Cl_2F_2$ ([M$^+$], [^{35}Cl]) 403.04491, found 403.043839. Anal. Calcd for $C_{20}H_{13}Cl_2F_2N_3$ (404.24): C, 59.42, H, 3.24, N, 10.39. Found: C, 58.996, H, 3.187, N, 10.144.

*3.8.4. 1-tert-Butyl-4-(chlorodifluoromethyl)-6-methyl-1H-pyrrolo [2,3-b]pyridine-3-carbonitrile (**7d**).* White solid isolated recrystallization from acetic acid; mp 161–162 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.82 (s, 9H, C(CH_3)$_3$), 2.69 (s, 3H, CH_3), 7.29 (s, 1H, CH), 7.95 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=24.7 (CH_3), 29.1 (C(CH_3)$_3$), 59.1 (*C*(CH_3)$_3$), 82.8 (C), 112.4 (t, $J_{C,F}$=6.1 Hz, CH), 115.4 (C≡N), 121.6 (C), 124.3 (t, $J_{C,F}$=290.5 Hz, CF_2Cl), 135.7 (t, $J_{C,F}$=29.2 Hz, *C*–CF_2Cl), 135.4 (CH), 148.0, 153.4 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=–49.76. IR (ATR, cm^{-1}): ν=3141 (w), 2988 (w), 2975 (w), 2929 (w), 2225 (m), 1597 (w), 1579 (w), 1515 (m), 1483 (w), 1444 (w), 1395 (w), 1367 (w), 1356 (w), 1367 (w), 1314 (m), 1303 (w), 1217 (w), 1199 (w), 1055 (m), 1026 (s), 1036 (m), 1022 (m). MS (EI, 70 eV): *m*/*z* (%)=299 ([M$^+$], [^{37}Cl], 12), 297 ([M$^+$], [^{35}Cl], 37), 262 (10), 243 (49), 242 (22). 241 (100), 207 (21), 206 (100). HRMS (ESI-TOF/MS): calcd for $C_{14}H_{14}ClF_2N_3$ ([M+H]$^+$, [^{35}Cl]) 298.0918, found 298.0917. Anal. Calcd for $C_{14}H_{14}ClF_2N_3$ (297.73): C, 56.48, H, 4.74, N, 14.11. Found: C, 55.350, H, 4.380, N, 13.810.

*3.8.5. 1-tert-Butyl-4-(chlorodifluoromethyl)-6-(4-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**7e**).* White solid isolated recrystallization from acetic acid; mp 178–179 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.90 (s, 9H, C(CH_3)$_3$), 3.89 (s, 3H, OCH_3), 7.01–7.06 (m, 2H, $C_{Ar}H$), 7.85 (s, 1H, CH), 8.00 (s, 1H, CH), 8.03–8.08 (m, 2H, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=29.3 (C(CH_3)$_3$), 55.4 (OCH_3), 59.2 (*C*(CH_3)$_3$), 83.2 (C), 109.0 (t, $J_{C,F}$=6.1 Hz, CH), 112.8 (t, $J_{C,F}$=2.2 Hz, C), 114.4 (C), 115.6 (C≡N), 124.4 (t, $J_{C,F}$=290.5 Hz, CF_2Cl), 128.3 (CH), 130.9 (C), 136.0 (CH), 136.4 (t, $J_{C,F}$=29.0 Hz, *C*–CF_2Cl), 143.3 (C), 151.9 (C), 160.9 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=–49.83 (CF_2Cl). IR (ATR, cm^{-1}): ν=3140 (w), 3089 (w), 2986 (w), 2931 (w), 2836 (w), 2632 (w), 2271 (w), 2225 (s), 1750 (w), 1643 (w), 1606 (w), 1592 (m), 1575 (w), 1515 (s), 1465 (w), 1450 (w), 1440 (w), 1396 (s), 1365 (s), 1320 (s), 1297 (s), 1240 (w), 1204 (m), 1172 (m), 1061 (w), 1134 (s), 1117 (w), 1068 (w), 1033 (s), 1015 (w), 1007 (w). MS (EI, 70 eV): *m*/*z* (%)=391 ([M$^+$], [^{37}Cl], 11), 390 (8), 389 ([M$^+$], [^{35}Cl], 32), 335 (35), 334 (19), 333 (100). 298 (29). HRMS (EI, 70 eV): calcd for $C_{20}H_{18}N_3ClF_2O$ ([M$^+$], [^{35}Cl]) 389.11010, found 389.110212.

*3.8.6. 1-tert-Butyl-4-(chlorodifluoromethyl)-6-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**7f**).* White solid isolated recrystallization from acetic acid; mp 244–245 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.90 (s, 9H, C(CH_3)$_3$), 7.46–7.51 (m, 2H, $C_{Ar}H$), 7.88 (s, 1H, CH), 8.01–8.06 (m, 3H, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=29.3 (C(CH_3)$_3$), 59.4 (*C*(CH_3)$_3$), 83.4 (C), 109.4 (t, $J_{C,F}$=6.6 Hz, CH), 113.6 (t, $J_{C,F}$=2.2 Hz, C), 115.0 (C≡N), 124.2 (t, $J_{C,F}$=291 Hz, CF_2Cl), 128.2 (CH), 129.2 (CH), 135.7 (C), 136.6 (t, $J_{C,F}$=29.2 Hz, *C*–CF_2Cl), 136.7 (C), 136.8 (CH), 148.2, 150.9 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=–49.90. IR (ATR, cm^{-1}): ν=3136 (w), 3094 (w), 2993 (w), 2945 (w), 2224 (s), 1756 (w), 1591 (w), 1514 (m), 1494 (m), 1471 (m), 1398 (s), 1370 (w), 1359 (w), 1320 (s), 1294 (w), 1275 (w), 1239 (m), 1203 (s), 1177 (w), 1163 (m), 1136 (s), 1116 (w), 1103 (w), 1090 (s), 1064 (m), 1038 (w), 1010 (s). MS (EI, 70 eV): *m*/*z* (%)=397 ([M$^+$], [^{37}Cl] [^{37}Cl], 16), 395 ([M$^+$], [^{37}Cl] [^{35}Cl], 16), 393 ([M$^+$], [^{35}Cl] [^{35}Cl], 25), 339 (66), 337 (100), 303 (13), 302 (56). HRMS (ESI-TOF/MS): calcd for $C_{19}H_{15}Cl_2F_2N_3$ ([M+H]$^+$, [^{35}Cl] [^{35}Cl]) 394.0684, found 394.0689. Anal. Calcd for $C_{19}H_{15}Cl_2F_2N_3$ (394.25): C, 57.88, H, 3.83, N, 10.66. Found: C, 57.900, H, 3.420, N, 9.980.

*3.8.7. 4-(Chlorodifluoromethyl)-1-cyclohexyl-6-methylds1H-pyrrolo [2,3-b]pyridine-3-carbonitrile (**7g**).* Brown solid isolated recrystallization from acetic acid; mp 173–174 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.24–2.15 (m, 10H, CH_2), 2.70 (s, 3H, CH_3), 4.81–4.90 (m, 1H, CH), 7.31 (s, 1H, $C_{Ar}H$), 7.90 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=24.5 (CH_3), 25.3, 25.5, 33.4 (CH_2), 54.2 (CH), 83.9 (C), 111.0 (C), 113.2 (t, $J_{C,F}$=6.0 Hz, CH), 115.2 (C≡N), 124.3 (t, $J_{C,F}$=290.7 Hz, CF_2Cl), 134.6 (CH), 135.9 (t, $J_{C,F}$=29.3 Hz, *C*–CF_2Cl), 147.3 (C), 154.5 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=–49.78 (CF_2Cl). IR (ATR, cm^{-1}): ν=3126 (w), 2934 (m), 2857 (w), 2225 (s), 1693 (w), 1598 (w), 1581 (w), 1581 (w), 1537 (w), 1520 (s), 1494 (w), 1464 (w), 1451 (w), 1416 (w), 1394 (w), 1361 (w), 1348 (w), 1332 (m), 1306 (w), 1291 (m), 1272 (w), 1250 (w), 1223 (m), 1210 (w), 1191 (w), 1172 (w), 1146 (w), 1123 (s), 1028 (s). MS (EI, 70 eV): *m*/*z* (%)=325 ([M$^+$], [^{37}Cl], 9), 323 ([M$^+$], [^{35}Cl], 28), 288 (17), 243 (35), 242 (19), 241 (100), 206 (57). HRMS (ESI-TOF/MS): calcd for $C_{16}H_{16}ClF_2N_3Na$ ([M+Na]$^+$, [^{35}Cl]) 346.0893, found 346.089.

*3.8.8. 1-(4-Methoxybenzyl)-4-(chlorodifluoromethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile(**7h**).* Brown solid isolated recrystallization from acetic acid; mp 104–106 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.73 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 5.44 (s, 2H, CH_2), 6.87–6.90 (m, 2H, ^3J=8.7 Hz, $C_{Ar}H$), 7.23–7.26 (m, 2H, ^3J=8.7 Hz, $C_{Ar}H$), 7.34 (s, 1H, CH), 7.73 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=24.5 (CH_3), 48.4 (CH_2), 55.3 (OCH_3), 84.4 (C), 110.9 (t, $J_{C,F}$=2.2 Hz,

C), 113.3 (t, $J_{C,F}$=5.5 Hz, CH), 114.5 (CH), 114.9 (C≡N), 124.2 (t, $J_{C,F}$=290.5 Hz, CF_2Cl), 127.2 (C), 128.1 (C), 129.7 (CH), 136.1 (t, $J_{C,F}$=29.2 Hz, *C*–CF_2Cl), 136.7 (CH), 147.7 (C), 155.0 (C), 159.8 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−49.76 (CF_2Cl). IR (ATR, cm^{-1}): ν=3099 (w), 3034 (w), 3001 (w), 2935 (w), 2838 (w), 2226 (s), 1753 (w), 1710 (m), 1612 (w), 1601 (w), 1578 (w), 1524 (w), 1513 (s), 1463 (w), 1441 (w), 1415 (m), 1385 (m), 1350 (m), 1328 (w), 1298 (m), 1245 (s), 1217 (m), 1175 (m), 1122 (br m), 1031 (s). MS (EI, 70 eV): *m*/*z* (%)=363 ([M^+], [^{37}Cl], 6), 361 ([M^+], [^{35}Cl], 17), 121 (100). HRMS (ESI-TOF/MS): calcd for $C_{18}H_{14}ClF_2N_3NaO$ ([M+Na]$^+$, [^{35}Cl]) 384.0686, found 384.0680.

*3.8.9. 1-(4-Methoxybenzyl)-4-(chlorodifluoromethyl)-6-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**7i**).* Yellow solid isolated recrystallization from acetic acid; mp 218–219 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ=3.80 (s, 3H, OCH_3), 5.53 (s, 2H, CH_2), 6.88–6.93 (m, 2H, ^3J=8.7 Hz, $C_{Ar}H$), 7.28–7.31 (m, 2H, ^3J=8.9 Hz, $C_{Ar}H$), 7.47–7.52 (m, 2H, ^3J=8.9 Hz, $C_{Ar}H$), 7.85 (s, 1H, CH), 7.90 (s, 1H, CH), 8.06–8.10 (m, 2H, ^3J=8.7 Hz, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=48.8 (CH_2), 55.3 (CH_3), 84.9 (C), 111.2 (t, $J_{C,F}$=6.1 Hz, CH), 112.3 (t, $J_{C,F}$=2.2 Hz, C), 114.5 (C≡N), 114.6 (CH), 124.1 (t, $J_{C,F}$=291.0 Hz, CF_2Cl), 127.0 (C), 128.3, 129.2, 129.8 ($C_{Ar}H$), 136.0 (C), 136.4 (C), 137.0 (t, $J_{C,F}$=29.2 Hz, *C*–CF_2Cl), 138.0 (CH), 147.9 (C), 152.2 (C), 159.9 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−49.93 (CF_2Cl). IR (ATR, cm^{-1}): ν=3091 (w), 3047 (w), 3004 (w), 2961 (w), 2936 (w), 2906 (w), 2837 (w), 2226 (s), 1682 (w), 1612 (w), 1588 (w), 1516 (m), 1496 (w), 1477 (w), 1467 (w), 1456 (w), 1440 (w), 1425 (w), 1413 (w), 1406 (w), 1382 (m), 1347 (w), 1336 (w), 1317 (w), 1306 (w), 1295 (w), 1280 (w), 1234 (m), 1208 (w), 1177 (m), 1159 (m), 1142 (m), 1129 (w), 1118 (w), 1105 (w), 1095 (m), 1072 (w), 1025 (s), 1010 (s). MS (EI, 70 eV): *m*/*z* (%)=461 ([M^+], [^{37}Cl] [^{37}Cl], 1), 459 ([M^+], [^{37}Cl] [^{35}Cl], 6), 457 ([M^+], [^{35}Cl] [^{35}Cl], 9), 122 (10), 121 (100). HRMS (ESI-TOF/MS): calcd for $C_{23}H_{15}Cl_2F_2N_3NaO$ ([M+Na]$^+$, [^{35}Cl] [^{35}Cl]) 480.0452, found 480.0451. Anal. Calcd for $C_{23}H_{15}Cl_2F_2N_3O$ (458.29): C, 60.28, H, 3.30, N, 9.17. Found: C, 58.896, H, 3.254, N, 8.860.

*3.8.10. 7-(Chlorodifluoromethyl)-5-(4-chlorophenyl)-N,N-dimethylthiazolo[4,5-b]pyridin-2-amine (**7j**).* Brown solid isolated by column chromatography (heptane/EtOAc, 20:1); mp 194–196 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ=3.31 (s, 6H, CH_3), 7.14 (d, 2H, ^3J=8.5 Hz, $C_{Ar}H$), 7.55 (s, 1H, CH), 8.06 (d, 2H, ^3J=8.5 Hz, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=40.3 (CH_3), 107.5 (t, $J_{C,F}$=5.0 Hz, CH), 118.8 (C), 124.7 (t, $J_{C,F}$=290.5 Hz, CF_2Cl), 128.4, 128.8 ($C_{Ar}H$), 131.5 (C), 136.7 (C), 137.7 (t, $J_{C,F}$=29.2 Hz, *C*–CF_2Cl), 154.4 (C), 166.6 (C), 171.1 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−52.58. IR (ATR, cm^{-1}): ν=2928 (w), 1681 (m), 1600 (s), 1539 (s), 1492 (s), 1414 (w), 1394 (w), 1365 (w), 1349 (w), 1272 (w), 1248 (w), 1229 (m), 1167 (w), 1130 (m), 1105 (w), 1088 (s), 1043 (w), 1012 (w). MS (EI, 70 eV): *m*/*z* (%)=377 ([M^+], [^{37}Cl] [^{37}Cl], 14), 375 ([M^+], [^{37}Cl] [^{35}Cl], 72), 373 ([M^+], [^{35}Cl] [^{35}Cl], 97), 360 (31), 358 (44), 348 (14). 346 (72), 344 (100), 323 (15). HRMS (ESI-TOF/MS): calcd for $C_{15}H_{11}Cl_2F_2N_3NaS$ ([M+Na]$^+$, [^{35}Cl] [^{35}Cl]) 395.9911, found 395.9911. Anal. Calcd for $C_{15}H_{11}Cl_2F_2N_3S$ (374.24): C, 48.14, H, 2.96, N, 11.23. Found: C, 48.283, H, 2.951.

*3.8.11. 7-(Chlorodifluoromethyl)-1,3,5-trimethyl-1H-imidazo[4,5-b]pyridine-2(3H)-thione (**7k**).* Yellow solid isolated by column chromatography (heptane/EtOAc, 10:1); mp 90–92; ^1H NMR ($CDCl_3$, 300 MHz): δ=2.62 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 4.05 (t, $^3J_{H,F}$=2.4 Hz, 3H, CH_3), 7.17 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=23.9 (CH_3), 30.8 (CH_3), 34.6 (t, $J_{C,F}$=6.1 Hz, CH_3), 112.4 (t, $J_{C,F}$=6.6 Hz, CH), 118.9 (t, $J_{C,F}$=2.2 Hz, C), 123.5 (t, $J_{C,F}$=289.4 Hz, CF_2Cl), 124.9 (t, $J_{C,F}$=29.0 Hz, *C*–CF_2Cl), 146.7 (C), 152.3 (C), 172.9 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−49.71 (CF_2Cl). IR (ATR, cm^{-1}): ν=3043 (w), 3010 (w), 2958 (w), 2922 (w), 2853 (w), 1825 (w), 1718 (w), 1610 (s), 1588 (w), 1472 (s), 1435 (s), 1409 (s), 1389 (s), 1359 (s), 1325 (w), 1312 (w), 1283 (w), 1225 (s), 1211 (w), 1172 (m), 1117 (s), 1082 (s), 1027 (s). MS (EI, 70 eV): *m*/*z* (%)=279 ([M^+], [^{37}Cl], 37), 278 (18), 277 ([M^+], [^{35}Cl], 100), 244 (23), 242 (34). HRMS (ESI-TOF/MS): calcd for $C_{10}H_{11}ClF_2N_3S$ ([M+H]$^+$, [^{35}Cl]) 278.0325, found 278.0325.

*3.8.12. 7-(Chlorodifluoromethyl)-1,5-dimethyl-3-phenyl-1H-imidazo[4,5-b]pyridine-2(3H)-thione (**7l**).* Yellow solid isolated by column chromatography (heptane/EtOAc, 10:1); mp 173–174 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ=2.53 (s, 3H, CH_3), 4.14 (t, $^3J_{H,F}$=2.3 Hz, 3H, CH_3), 7.22 (s, 1H, CH), 7.48–7.61 (m, 5H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=23.9 (CH_3), 34.9 (t, $^3J_{C,F}$=6.0 Hz, 3H, CH_3), 113.1 (t, $J_{C,F}$=6.6 Hz, CH), 119.0 (t, $^3J_{C,F}$=2.2 Hz, C), 124.5 (t, $J_{C,F}$=290.0 Hz, CF_2Cl), 125.1 (t, $J_{C,F}$=29.2 Hz, *C*–CF_2Cl), 128.4, 129.2 (CH), 134.7 (C), 147.2 (C), 152.9 (C), 173.4 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−49.50 (CF_2Cl). IR (ATR, cm^{-1}): ν=3047 (w), 2962 (w), 1811 (w), 1722 (w), 1607 (w), 1504 (s), 1442 (m), 1425 (m), 1387 (s), 1377 (w), 1355 (m), 1325 (s), 1294 (w), 1283 (w), 1219 (s), 1167 (w), 1147 (w), 1103 (m), 1073 (m), 1042 (s). MS (EI, 70 eV): *m*/*z* (%)=341 ([M^+], [^{37}Cl], 31), 340 (83), 339 ([M^+], [^{35}Cl], 83), 338 (100), 304 (18), 302 (11). HRMS (EI, 70 eV): calcd for $C_{15}H_{12}N_3ClF_2S$ ([M^+], [^{35}Cl]) 339.04030, found 339.039725. Anal. Calcd for $C_{15}H_{12}ClF_2N_3S$ (339.79): C, 53.02, H, 3.56, N, 12.37. Found: C, 53.277, H, 3.693, N, 12.150.

*3.8.13. 5-(Chlorodifluoromethyl)-7-(4-chlorophenyl)-1,3-dimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (**7m**).* White solid isolated recrystallization from acetic acid; mp 293 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ=3.51 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 7.49–7.54 (m, ^3J=8.9 Hz, 2H, $C_{Ar}H$), 7.86 (s, 1H, $C_{Ar}H$), 8.06–8.11 (m, ^3J=8.9 Hz, 2H, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=28.9 (CH_3), 30.7 (CH_3), 104.5 (C), 111.3 (t, $J_{C,F}$=9.4 Hz, CH), 123.3 (t, $J_{C,F}$=290.5 Hz, CF_2Cl), 128.9 ($C_{Ar}H$), 129.5 ($C_{Ar}H$), 134.9 (C), 138.1 (C), 146.2 (t, $J_{C,F}$=28.6 Hz, *C*–CF_2Cl), 150.9 (C), 152.7 (C), 158.0 (C), 160.1 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−50.19 (CF_2Cl). IR (ATR, cm^{-1}): ν=3092 (w), 3065 (w), 3042 (w), 2953 (w), 1716 (m), 1663 (br s), 1579 (m), 1556 (m), 1516 (w), 1503 (w), 1384 (w), 1452 (w), 1417 (w), 1404 (w), 1387 (w), 1367 (w), 1349 (w), 1306 (w), 1289 (w), 1282 (w), 1254 (w), 1199 (m), 1119 (s), 1085 (w), 1072 (w), 1009 (s). MS (EI, 70 eV): *m*/*z* (%)=389 ([M^+], [^{37}Cl] [^{37}Cl], 13), 387 ([M^+], [^{37}Cl] [^{35}Cl], 67), 385 ([M^+], [^{35}Cl] [^{35}Cl], 100), 365 (15), 350 (50), 300 (24), 275 (39), 273 (60). HRMS (EI, 70 eV): calcd for $C_{16}H_{11}N_3Cl_2F_2O_2$ ([M^+], [^{35}Cl] [^{35}Cl]) 385.01909, found 385.019348.

*3.8.14. 5-(Chlorodifluoromethyl)-1,3,7-trimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (**7n**).* Yellow solid isolated recrystallization from acetic acid; mp 273 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ=2.67 (s, 3H, CH_3), 3.46 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 7.30 (s, 1H, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=25.4 (CH_3), 28.7 (CH_3), 30.5 (CH_3), 103.5 (t, $^3J_{C,F}$=1.7 Hz, C), 114.9 (t, $J_{C,F}$=9.0 Hz, CH), 123.3 (t, $J_{C,F}$=290.5 Hz, CF_2Cl), 116.9 ($C_{Ar}H$), 145.0 (t, $J_{C,F}$=28.6 Hz, *C*–CF_2Cl), 150.9 (C), 152.4 (C), 158.3 (C), 161.2 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−50.19 (CF_2Cl). IR (ATR, cm^{-1}): ν=3393 (w), 3360 (w), 3230 (w), 3084 (w), 2997 (w), 2954 (w), 2917 (w), 2851 (w), 1711 (s), 1661 (br s), 1592 (w), 1567 (m), 1503 (w), 1454 (w), 1417 (m), 1381 (w), 1368 (w), 1343 (m), 1286 (m), 1263 (m), 1235 (w), 1213 (m), 1179 (m), 1118 (s), 1093 (w), 1065 (w), 1031 (w), 1001 (w). MS (EI, 70 eV): *m*/*z* (%)=291 ([M^+], [^{37}Cl], 28), 289 ([M^+], [^{35}Cl], 86), 269 (18), 254 (45), 204 (25), 179 (33), 177 (100), 169 (13), 142 (12). HRMS (ESI-TOF/MS): calcd for $C_{11}H_{11}N_3ClF_2O_2$ ([M+H]$^+$, [^{35}Cl]) 292.0476, found 292.0476.

*3.8.15. 3-(4-Methoxybenzyl)-7-(chlorodifluoromethyl)-5-methyl-3H-imidazo[4,5-b]pyridine (**11a**).* Yellow solid isolated by column chromatography (heptane/EtOAc, 20:1); mp 59–60 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ=2.72 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 5.39 (s, 2H, CH_2), 6.85–6.87 (m, ^3J=8.9 Hz, 2H, $C_{Ar}H$), 7.26–7.29 (m, ^3J=8.9 Hz, 3H, $C_{Ar}H$), 8.03 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=24.6 (CH_3), 46.8 (CH_2), 55.3 (OCH_3), 113.0 (t, $J_{C,F}$=5.5 Hz, CH),

114.3 (CH), 126.6 (t, $J_{C,F}$=291.1 Hz, CF_2Cl), 128.2 (t, $^3J_{C,F}$=2.2 Hz, C), 129.5 (CH), 133.9 (t, $J_{C,F}$=28.1 Hz, *C*–CF_2Cl), 144.3 (CH), 148.1 (C), 154.2 (C), 159.7 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−50.57 (CF_2Cl). IR (ATR, cm^{-1}): ν=3070 (w), 3030 (w), 2955 (w), 2937 (w), 2916 (w), 2839 (w), 1613 (m), 1588 (m), 1510 (s), 1482 (m), 1463 (w), 1441 (w), 1434 (w), 1420 (w), 1397 (m), 1382 (m), 1364 (w), 1355 (w), 1287 (s), 1240 (s), 1217 (w), 1204 (m), 1179 (m), 1162 (w), 1133 (s), 1114 (w), 1096 (s), 1027 (m). MS (EI, 70 eV): *m*/*z* (%)=339 ([M^+], [^{37}Cl], 13), 339 ([M^+], [^{35}Cl], 37), 122 (12), 121 (100). HRMS (EI, 70 eV): calcd for $C_{16}H_{14}N_3ClF_2O$ ([M^+], [^{35}Cl]) 337.07880, found 337.078831.

*3.8.16. 3-(4-Chlorobenzyl)-7-(chlorodifluoromethyl)-5-methyl-3H-imidazo[4,5-b]pyridine (**11b**).* Yellow oil isolated by preparative chromatography (heptane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.73 (s, 3H, CH_3), 5.46 (s, 2H, CH_2), 7.26–7.28 (m, ^3J=8.7 Hz, 2H, $C_{Ar}H$), 7.32–7.35 (m, ^3J=8.7 Hz, 3H, $C_{Ar}H$), 8.09 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=24.6 (CH_3), 46.5 (CH_2), 113.2 (t, $J_{C,F}$=5.5 Hz, CH), 124.2 (t, $J_{C,F}$=290.6 Hz, CF_2Cl), 128.2 (t, $^3J_{C,F}$=2.7 Hz, C), 129.2 (CH), 129.3 (CH), 129.5 (C), 133.9 (C), 134.1 (t, $J_{C,F}$=28.2 Hz, *C*–CF_2Cl), 144.2 (CH), 148.0 (C), 154.3 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−50.62 (CF_2Cl). IR (ATR, cm^{-1}): ν=3115 (w), 3068 (w), 3034 (w), 2923 (w), 2852 (w), 1736 (w), 1593 (s), 1507 (w), 1489 (s), 1431 (m), 1397 (m), 1382 (w), 1372 (w), 1353 (s), 1296 (w), 1285 (s), 1254 (w), 1213 (w), 1205 (w), 1189 (w), 1170 (w), 1129 (s), 1095 (m), 1011 (m). MS (EI, 70 eV): *m*/*z* (%)=345 ([M^+], [^{37}Cl] [^{37}Cl], 8), 343 ([M^+], [^{37}Cl] [^{35}Cl], 49), 341 ([M^+], [^{35}Cl] [^{35}Cl], 77), 307 (14), 306 (39), 127 (36), 125 (100), 89 (22). HRMS (ESI-TOF/MS): calcd for $C_{15}H_{12}N_3Cl_2F_2$ ([M^+], [^{35}Cl]) 342.0371, found 342.0373.

*3.8.17. 4-(Difluoromethyl)-3,6-dimethyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine (**12a**).* White solid isolated by preparative chromatography (heptane); mp 75–76 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.63 (t, ^3J=1.1 Hz, 3H, CH_3), 2.66 (s, 3H, CH_3), 6.89 (t, ^3J=55.0 Hz, 1H, CF_2H), 7.09 (s, 1H, $C_{Ar}H$), 7.19–7.24 (m, 1H, $C_{Ar}H$), 7.40–7.45 (m, 2H, $C_{Ar}H$), 8.15–8.18 (m, ^3J=7.4 Hz, 2H, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=14.9 (t, $J_{C,F}$=3.3 Hz, CH_3), 25.1 (CH_3), 110.4 (t, $J_{C,F}$=3.3 Hz, C), 112.9 (t, $J_{C,F}$=240.0 Hz, CF_2H), 114.2 (t, $J_{C,F}$=7.7 Hz, CH), 121.3 ($C_{Ar}H$), 125.8 ($C_{Ar}H$), 129.0 ($C_{Ar}H$), 135.8 (t, $J_{C,F}$=23.7 Hz, *C*–CF_2H), 139.2 (C), 141.1 (C), 151.7 (C), 159.2 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−111.78 (CF_2H). IR (ATR, cm^{-1}): ν=3088 (w), 3065 (w), 2959 (w), 2920 (w), 2857 (w), 1589 (w), 1504 (s), 1482 (w), 1458 (w), 1444 (w), 1415 (m), 1398 (w), 1375 (w), 1347 (w), 1331 (w), 1302 (w), 1271 (w), 1199 (w), 1141 (w), 1127 (w), 1080 (s), 1043 (w), 1028 (w), 1009 (w). MS (EI, 70 eV): *m*/*z* (%)=273 ([M^+], 100), 272 (29), 258 (23), 232 (15), 77 (15). HRMS (ESI-TOF/MS): calcd for $C_{15}H_{14}F_2N_3$ [$(M+H)^+$] 274.115, found 274.1153. Anal. Calcd for $C_{15}H_{13}F_2N_3$ (273.28): C, 65.93, H, 4.79, N, 15.38. Found: C, 66.066, H, 4.832, N, 14.783.

*3.8.18. 6-(4-Chlorophenyl)-4-(difluoromethyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine (**12b**).* White solid isolated by preparative chromatography (heptane); mp 152–154 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.73 (s, 3H, CH_3), 7.04 (t, $^3J_{H,F}$=55.0 Hz, 1H, CF_2H), 7.32 (t, ^3J=7.4 Hz, 1H, CH), 7.45–7.56 (m, 4H, $C_{Ar}H$), 7.71 (s, 1H, $C_{Ar}H$), 8.04–8.08 (m, 2H, $C_{Ar}H$), 8.28–8.31 (m, 2H, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=14.9 (t, $J_{C,F}$=3.0 Hz, CH_3), 110.7 (t, $J_{C,F}$=8.0 Hz, CH), 111.5 (t, $J_{C,F}$=3.3 Hz, C), 112.8 (t, $J_{C,F}$=240.0 Hz, CF_2), 121.1 ($C_{Ar}H$), 125.9 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 129.0 ($C_{Ar}H$), 129.1 ($C_{Ar}H$), 136.2 (C), 136.7 (C), 137.7 (t, $J_{C,F}$=24.0 Hz, *C*–CF_2), 139.2 (C), 141.3 (C), 151.7 (C), 155.6 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−112.03 (CF_2H). IR (ATR, cm^{-1}): ν=3107 (w), 3084 (w), 3063 (w), 2960 (w), 2921 (w), 2856 (w), 1593 (w), 1584 (w), 1569 (w), 1505 (s), 1490 (w), 1477 (m), 1459 (w), 1438 (w), 1417 (m), 1404 (w), 1393 (w), 1369 (w), 1359 (w), 1346 (m), 1331 (w), 1311 (w), 1295 (w), 1269 (m), 1223 (s), 1184 (w), 1174 (w), 1150 (s), 1129 (s), 1110 (w), 1093 (s), 1043 (w), 1032 (w), 1007 (s). MS (EI, 70 eV): *m*/*z* (%)=371 ([M^+], [^{37}Cl], 34), 370 (28), 369 ([M^+], [^{35}Cl], 100), 368 (18), 354 (15), 328 (10). HRMS (ESI-TOF/MS): calcd for $C_{20}H_{15}N_3ClF_2$ ([$M+H]^+$, [^{35}Cl]) 370.0917, found 370.0924. Anal. Calcd for $C_{20}H_{14}ClF_2N_3$ (369.80): C, 64.96, H, 3.82, N, 11.36. Found: C, 64.825, H, 3.939, N, 11.033.

*3.8.19. 1-tert-Butyl-4-(difluoromethyl)-6-(4-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**12c**).* Yellow solid isolated by preparative chromatography (heptane); mp 180–182 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.88 (s, 9H, $C(CH_3)_3$), 3.88 (s, 3H, OCH_3), 7.00–7.05 (m, ^3J=8.9 Hz, 2H, $C_{Ar}H$), 7.26 (t, $^3J_{H,F}$=55.0 Hz, 1H, CF_2H), 7.84 (s, 1H, CH), 7.93 (s, 1H, CH), 8.04–8.08 (m, ^3J=8.9 Hz, 2H, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=29.2 ($C(CH_3)_3$), 55.4 (OCH_3), 59.0 ($C(CH_3)_3$), 81.9 (*C*–C≡N), 110.2 (t, $J_{C,F}$=6.6 Hz, CH), 111.8 (t, $J_{C,F}$=240.4 Hz, CF_2), 114.3 ($C_{Ar}H$), 115.2 (t, $J_{C,F}$=4.4 Hz, C), 115.7 (C≡N), 128.2 ($C_{Ar}H$), 131.2 (C), 134.8 (t, $J_{C,F}$=24.2 Hz, *C*–CF_2), 134.8 ($C_{Ar}H$), 147.7 (C), 152.2 (C), 160.8 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−113.81 (CF_2H). IR (ATR, cm^{-1}): ν=3137 (w), 2978 (w), 2961 (w), 2934 (w), 2840 (w), 2220 (s), 1595 (m), 1579 (w), 1515 (s), 1472 (m), 1456 (w), 1417 (w), 1392 (w), 1367 (m), 1320 (s), 1305 (w), 1297 (m), 1246 (s), 1210 (w), 1198 (w), 1176 (s), 1135 (w), 1121 (w), 1110 (w), 1066 (w), 1024 (s). MS (EI, 70 eV): *m*/*z* (%)=355 ([M^+], 31), 300 (18), 299 (100), 284 (10), 256 (12). HRMS (ESI/TOF, MS): calcd for $C_{20}H_{19}F_2N_3NaO$ ([$M+Na]^+$) 378.1388, found 378.1389.

*3.8.20. 1-Cyclohexyl-4-(difluoromethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**12d**).* White solid isolated by preparative chromatography (heptane); mp 157–158 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.23–2.14 (m, 10H, CH_2), 2.68 (s, 3H, CH_3), 4.79–4.90 (m, 1H, CH), 7.18 (t, $^3J_{H,F}$=54.8 Hz, 1H, CF_2H), 7.29 (s, 1H, CH), 7.84 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=24.6 (CH_3), 25.3, 25.5, 33.5 (CH_2), 54.1 (CH), 82.7 (*C*–C≡N), 111.8 (t, $J_{C,F}$=240.0 Hz, CF_2H), 113.5 (t, $J_{C,F}$=4.4 Hz, C), 114.5 (t, $J_{C,F}$=6.6 Hz, CH), 115.7 (C≡N), 133.3 (CH), 134.5 (t, $J_{C,F}$=23.7 Hz, *C*–CF_2), 146.7 (C), 154.8 (C). 150.6 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−113.70 (CF_2H). IR (ATR, cm^{-1}): ν=3123 (w), 3106 (w), 2941 (m), 2859 (w), 2217 (s), 1714 (w), 1596 (w), 1588 (w), 1523 (s), 1485 (w), 1468 (w), 1448 (w), 1416 (w), 1399 (w), 1386 (w), 1356 (m), 1324 (s), 1288 (s), 1272 (w), 1250 (w), 1197 (s), 1135 (s), 1111 (s), 1036 (s). MS (EI, 70 eV): *m*/*z* (%)=289 (M^+, 21), 208 (17), 207 (100). HRMS (ESI/TOF, MS): calcd for $C_{16}H_{18}N_3F_2$ ([$M+H]^+$) 290.1463, found 290.1464.

*3.8.21. 1-(4-Methoxybenzyl)-4-(difluoromethyl)-6-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**12e**).* White solid isolated by preparative chromatography (heptane); mp 116–118 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.72 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 5.43 (s, 2H, CH_2), 6.85–6.90 (m, ^3J=8.7 Hz, 2H, $C_{Ar}H$), 7.18 (t, $^3J_{H,F}$=54.8 Hz, 1H, CF_2H), 7.21–7.24 (m, ^3J=8.7 Hz, 2H, $C_{Ar}H$), 7.32 (s, 1H, CH), 7.65 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=24.6 (CH_3), 48.2 (CH_2), 55.3 (OCH_3), 83.3 (*C*–C≡N), 111.7 (t, $J_{C,F}$=240.0 Hz, CF_2H), 113.4 (t, $J_{C,F}$=4.4 Hz, C), 114.4 ($C_{Ar}H$), 114.6 (t, $J_{C,F}$=6.6 Hz, CH), 115.4 (C≡N), 127.4 (C), 129.7 ($C_{Ar}H$), 134.7 (t, $J_{C,F}$=24.0 Hz, *C*–CF_2), 135.6 (CH), 147.1 (C), 155.3 (C), 159.7 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−113.66 (CF_2H). IR (ATR, cm^{-1}): ν=3131 (w), 3115 (w), 3067 (w), 3031 (w), 3006 (w), 2967 (w), 2929 (w), 2835 (w), 2229 (s), 1711 (w), 1610 (w), 1584 (w), 1528 (m), 1509 (s), 1454 (w), 1439 (s), 1415 (s), 1381 (s), 1358 (w), 1324 (s), 1304 (w), 1291 (s), 1242 (s), 1196 (w), 1171 (w), 1161 (w), 1118 (w), 1107 (w), 1032 (s), 1005 (w). MS (EI, 70 eV): *m*/*z* (%)=327 ([M^+], 27), 122 (9), 123 (100). HRMS (ESI/TOF, MS): calcd for $C_{18}H_{16}N_3F_2O$ ([$M+H]^+$) 328.1256, found 328.1255. Anal. Calcd for $C_{18}H_{15}F_2N_3O$ (327.33): C, 66.05, H, 4.62, N, 12.84. Found: C, 65.731, H, 4.638, N, 12.426.

*3.8.22. 1-(4-Methoxybenzyl)-6-(4-chlorophenyl)-4-(difluoromethyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**12f**).* Yellow solid isolated by preparative chromatography (heptane); mp 184–185 °C; ^{1}H

NMR ($CDCl_3$, 300 MHz): δ=3.79 (s, 3H, OCH_3), 5.51 (s, 2H, CH_2), 6.87–6.90 (m, ^3J=8.7 Hz, 2H, $C_{Ar}H$), 7.26 (t, $^3J_{H,F}$=54.7 Hz, 1H, CF_2H), 7.26–7.29 (m, ^3J=8.7 Hz, 2H, $C_{Ar}H$), 7.46–7.49 (m, ^3J=8.7 Hz, 2H, $C_{Ar}H$), 7.77 (s, 1H, CH), 7.89 (s, 1H, CH), 8.06–8.09 (m, ^3J=8.7 Hz, 2H, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 126 MHz): δ=48.6 (CH_2), 55.3 (OCH_3), 83.8 (*C*–C≡N), 111.4 (t, $J_{C,F}$=7.2 Hz, CH), 111.6 (t, $J_{C,F}$=240.6 Hz, CF_2H), 114.5 ($C_{Ar}H$), 114.8 (t, $J_{C,F}$=4.3 Hz, C), 115.0 (C≡N), 127.2 (C), 128.3 (CH), 129.1 (CH), 129.7 (CH), 135.5 (t, $J_{C,F}$=23.6 Hz, *C*–CF_2), 135.7 (C), 136.8 (C), 136.9 (CH), 147.4 (C), 152.5 (C), 159.9 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−113.77 (CF_2H). IR (ATR, cm^{-1}): ν=3105 (w), 2955 (w), 2919 (w), 2848 (w), 2221 (s), 1611 (m), 1585 (w), 1574 (w), 1556 (w), 1520 (w), 1512 (s), 1477 (w), 1455 (w), 1445 (w), 1417 (w), 1406 (w), 1384 (m), 1354 (w), 1328 (w), 1315 (w), 1302 (w), 1292 (w), 1246 (s), 1217 (m), 1175 (s), 1150 (m), 1116 (w), 1104 (w), 1093 (s), 1078 (w), 1046 (m), 1026 (m), 1009 (m). MS (EI, 70 eV): *m*/*z* (%)=425 ([M^+], [^{37}Cl], 6), 423 ([M^+], [^{35}Cl], 17), 121 (100). HRMS (ESI/TOF, MS): calcd for $C_{23}H_{16}ClF_2N_3O$ ([M+Na]$^+$, ^{35}Cl]) 446.0842, found 446.0842.

*3.8.23. 5-(4-Chlorophenyl)-7-(difluoromethyl)-N,N-dimethylthiazolo [4,5-b]pyridin-2-amine (**12g**).* Yellow solid isolated by preparative chromatography (heptane); mp 186–188 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ=3.30 (s, 6H, CH_3), 6.78 (t, $J_{H,F}$=55.5 Hz, CF_2H), 7.40–7.43 (m, *J*=8.9 Hz, 2H, $C_{Ar}H$), 7.44 (s, 1H, CH), 8.04–8.08 (m, *J*=8.9 Hz, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=40.1 (CH_3), 109.3 (t, $J_{C,F}$=6.6 Hz, CH), 113.1 (t, $J_{C,F}$=242.0 Hz, CF_2), 119.9 (t, $J_{C,F}$=2.2 Hz, C), 128.3 ($C_{Ar}H$), 128.8 ($C_{Ar}H$), 135.2 (C), 135.7 (t, $J_{C,F}$=24.2 Hz, *C*–CF_2), 137.0 (C), 154.2 (C), 166.3 (C), 171.2 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−116.17 (CF_2H). IR (ATR, cm^{-1}): ν=2927 (w), 2859 (w), 2792 (w), 1600 (s), 1538 (s), 1492 (m), 1415 (w), 1403 (w), 1392 (w), 1369 (w), 1348 (w), 1322 (w), 1302 (w), 1270 (w), 1246 (w), 1215 (w), 1182 (w), 1133 (w), 1110 (w), 1091 (w), 1066 (w), 1034 (w), 1011 (m). MS (EI, 70 eV): *m*/*z* (%)=341 ([M^+], [^{37}Cl], 38), 339 ([M^+], [^{35}Cl], 97), 326 (20), 324 (53), 312 (39), 310 (100). HRMS (ESI/TOF, MS): calcd for $C_{15}H_{13}F_2ClN_3O_2$ ([M+H]$^+$, [^{35}Cl]) 340.0481, found 340.0485.

*3.8.24. 7-(Difluoromethyl)-1,5-dimethyl-3-phenyl-1H-imidazo[4,5-b]pyridine-2(3H)-thione (**12h**).* White solid isolated by preparative chromatography (heptane); mp 199–200 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ=2.52 (s, 3H, CH_3), 4.06 (t, ^3J=1.7 Hz, 3H, CH_3), 6.93 (t, ^3J=54.4 Hz, 1H, CF_2H), 7.11 (s, 1H, CH), 7.48–7.61 (m, 5H, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=23.9 (CH_3), 34.0 (t, $^3J_{C,F}$=4.4 Hz, CH_3), 112.9 (t, $J_{C,F}$=240.0 Hz, CF_2H), 115.7 (t, $J_{C,F}$=7.7 Hz, CH), 120.7 (t, $J_{C,F}$=2.8 Hz, C), 122.8 (t, $J_{C,F}$=24.0 Hz, *C*–CF_2), 128.4, 129.2, 129.2 ($C_{Ar}H$), 134.8 (C), 146.6 (C), 153.0 (C), 172.8 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−106.07 (CF_2H). IR (ATR, cm^{-1}): ν=3109 (w), 3053 (w), 3015 (w), 2953 (w), 2918 (w), 1621 (w), 1589 (w), 1504 (s), 1470 (w), 1438 (w), 1425 (m), 1405 (m), 1385 (m), 1357 (s), 1325 (s), 1295 (m), 1277 (w), 1230 (s), 1197 (s), 1158 (w), 1134 (s), 1004 (w), 1082 (s), 1038 (s). MS (EI, 70 eV): *m*/*z* (%)=305 ([M^+], 80), 304 (100), 290 (7), 289 (10), 77 (4). HRMS (ESI/TOF, MS): calcd for $C_{15}H_{14}N_3F_2S$ ([M+H]$^+$) 306.0871, found 306.0871. Anal. Calcd for $C_{15}H_{13}F_2N_3S$ (305.35): C, 59.00, H, 4.29, N, 13.76. Found: C, 58.914, H, 4.351, N, 13.313.

*3.8.25. 3-(4-Methoxybenzyl)-7-(difluoromethyl)-5-methyl-3H-imidazo[4,5-b]pyridine (**12i**).* White solid isolated by preparative chromatography (heptane); mp 102–103 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ=2.71 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 5.38 (s, 2H, CH_2), 6.83–6.88 (m, ^3J=8.7 Hz, 2H, $C_{Ar}H$), 7.24 (t, ^3J=55.0 Hz, 1H, CF_2H), 7.23–7.30 (m, 3H, $C_{Ar}H$), 7.96 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=24.6 (CH_3), 46.6 (CH_2), 55.3 (OCH_3), 111.4 (t, $J_{C,F}$=239.0 Hz, CF_2), 113.9 (t, $J_{C,F}$=5.0 Hz, CH), 114.3 (CH), 127.6 (C), 129.4 (CH), 130.2 (t, $J_{C,F}$=5.0 Hz, C), 132.5 (t, $J_{C,F}$=24.0 Hz, *C*–CF_2), 143.9 (CH), 147.4 (C), 154.4 (C), 159.6 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−116.01 (CF_2H). IR (ATR, cm^{-1}): ν=3070 (w), 3029 (w), 2967 (w), 2939 (w), 2841 (w), 1611 (w), 1596 (w), 1584 (w), 1510 (s), 1465 (w), 1442 (w), 1432 (w), 1418 (w), 1399 (w), 1385 (w), 1366 (w), 1355 (w), 1285 (s), 1241 (s), 1213 (m), 1183 (w), 1173 (w), 1161 (w), 1096 (m), 1028 (s). MS (EI, 70 eV): *m*/*z* (%)=303 ([M^+], 50), 302 (11), 121 (100). HRMS (ESI/TOF, MS): calcd for $C_{16}H_{16}F_2N_3O$ ([M+H]$^+$) 304.1251, found 304.1256. Anal. Calcd for $C_{16}H_{15}F_2N_3O$ (303.31): C, 63.36, H, 4.98, N, 13.85. Found: C, 63.439, H, 5.212, N, 13.501.

*3.8.26. 3-(4-Chlorobenzyl)-7-(difluoromethyl)-5-methyl-3H-imidazo [4,5-b]pyridine (**12j**).* White solid isolated by preparative chromatography (heptane); mp 92–93 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ=2.70 (s, 3H, CH_3), 5.43 (s, 2H, CH_2), 7.21–7.32 (m, 5H, CH), 7.24 (t, ^3J=55.0 Hz, 1H, CF_2H), 7.99 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=24.6 (CH_3), 46.4 (CH_2), 111.4 (t, $J_{C,F}$=239.0 Hz, CF_2H), 114.1 (t, $J_{C,F}$=5.5 Hz, CH), 129.2 ($C_{Ar}H$), 130.1 (t, $J_{C,F}$=5.0 Hz, C), 132.7 (t, $J_{C,F}$=23.7 Hz, *C*–CF_2), 134.2 (C), 134.3 (C), 143.8 (CH), 147.3 (C), 154.7 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−116.05 (CF_2H). IR (ATR, cm^{-1}): ν=3063 (w), 2972 (w), 2926 (w), 2857 (w), 1805 (w), 1756 (w), 1593 (m), 1494 (s), 1444 (w), 1426 (w), 1413 (w), 1394 (w), 1384 (w), 1375 (w), 1367 (w), 1344 (w), 1332 (w), 1306 (w), 1286 (m), 1277 (w), 1234 (w), 1214 (s), 1197 (w), 1178 (s), 1153 (m), 1109 (w), 1089 (s), 1051 (s), 1017 (m). MS (EI, 70 eV): *m*/*z* (%)=309 ([M^+], [^{37}Cl], 35), 308 (50), 307 ([M^+], [^{35}Cl], 94), 306 (100), 287 (13), 256 (15), 196 (23), 127 (32), 125 (96), 89 (22). HRMS (ESI/TOF, MS): calcd for $C_{15}H_{12}ClF_2N_3Na$ ([M+Na]$^+$, [^{35}Cl]) 330.058, found 330.0581. Anal. Calcd for $C_{15}H_{12}ClF_2N_3$ (307.73): C, 58.55, H, 3.93, N, 13.66. Found: C, 58.667, H, 3.983, N, 13.398.

*3.8.27. 4-(1,1-Difluorobut-3-enyl)-3,6-dimethyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine (**13a**).* Yellow solid isolated by preparative chromatography (heptane); mp 51–52 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ=2.70 (t, $J_{H,F}$=2.5 Hz, 3H, CH_3), 2.72 (s, 3H, CH_3), 2.96–3.10 (m, 2H, CH_2), 5.18–5.26 (m, 2H, CH_2), 5.74–5.88 (m, 1H, CH), 7.11 (s, 1H, $C_{Ar}H$), 7.26–7.31 (m, 1H, $C_{Ar}H$), 7.47–7.53 (m, 2H, $C_{Ar}H$), 8.22–8.25 (m, 2H, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=15.8 (t, $J_{C,F}$=6.0 Hz, CH_3), 25.1 (CH_3), 43.6 (t, $J_{C,F}$=27.0 Hz, CH_2), 109.9 (t, $J_{C,F}$=2.8 Hz, C), 114.1 (t, $J_{C,F}$=7.7 Hz, CH), 120.6 (t, $J_{C,F}$=243.7 Hz, CF_2), 121.3 (CH_2), 121.5 ($C_{Ar}H$), 125.8 ($C_{Ar}H$), 128.0 (t, $J_{C,F}$=5.0 Hz, CH), 128.9 ($C_{Ar}H$), 139.0 (t, $J_{C,F}$=28.5 Hz, *C*–CF_2), 139.2, 141.1, 151.9, 158.6 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−93.05 (CF_2). IR (ATR, cm^{-1}): ν=3081 (w), 3065 (w), 3014 (w), 2985 (w), 2940 (w), 2921 (w), 2853 (w), 1643 (w), 1596 (s), 1584 (w), 1572 (w), 1504 (s), 1486 (w), 1456 (w), 1439 (w), 1429 (w), 1418 (m), 1383 (w), 1373 (w), 1343 (m), 1320 (w), 1306 (w), 1295 (w), 1284 (w), 1258 (s), 1201 (m), 1168 (w), 1152 (s), 1094 (s), 1068 (m), 1028 (m). MS (EI, 70 eV): *m*/*z* (%)=314 (21), 313 ([M^+], 100), 273 (10), 272 (57). HRMS (EI, 70 eV): calcd for $C_{18}H_{17}N_3F_2$ ([M^+]) 313.13851, found 313.138641. Anal. Calcd for $C_{18}H_{17}F_2N_3$ (313.14): C, 69.00, H, 5.47, N, 13.41. Found: C, 68.880, H, 5.470.

*3.8.28. 4-(1,1-Difluorobut-3-enyl)-6-(4-methoxyphenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine (**13b**).* White solid isolated by preparative chromatography (heptane); mp 94–96 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ=2.73 (t, ^3J=2.3 Hz, 3H, CH_3), 3.02–3.15 (m, 2H, CH_2), 3.88 (s, 3H, CH_3), 5.21–5.28 (m, 2H, CH_2), 5.76–5.91 (m, 1H, CH), 7.02–7.05 (m, ^3J=9.1 Hz, 2H, $C_{Ar}H$), 7.31 (t, ^3J=7.4 Hz, 1H, $C_{Ar}H$), 7.54 (t, ^3J=7.4 Hz, 2H, $C_{Ar}H$), 7.67 (s, 1H, $C_{Ar}H$), 8.11–8.14 (m, ^3J=9.1 Hz, 2H, $C_{Ar}H$), 8.32–8.36 (m, ^3J=8.7 Hz, 2H, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=15.9 (t, $J_{C,F}$=6.1 Hz, CH_3), 43.6 (t, $J_{C,F}$=27.0 Hz, CH_2), 55.4 (OCH_3), 110.2 (t, $J_{C,F}$=2.8 Hz, C), 110.5 (t, $J_{C,F}$=8.3 Hz, CH), 114.3 (CH), 120.7 (t, $J_{C,F}$=243.7 Hz, CF_2), 121.3 (CH), 121.4 (CH_2), 125.7 ($C_{Ar}H$), 128.0 (t, $J_{C,F}$=5.0 Hz, CH), 128.9 ($C_{Ar}H$), 128.9 ($C_{Ar}H$), 131.0 (C), 139.4 (C), 139.9 (t, $J_{C,F}$=28.6 Hz, *C*–CF_2), 141.2 (C), 152.1 (C), 156.1 (C), 161.2 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−93.05 (CF_2). IR (ATR, cm^{-1}): ν=3116 (w), 3081 (w), 3011 (w), 2957 (w), 2929 (w), 2840 (w), 1645 (w), 1610 (w), 1593 (w), 1584 (w), 1566 (s), 1504 (s), 1481 (m), 1456 (w), 1441 (w), 1412 (s), 1388 (m), 1348 (m), 1325 (w), 1311 (w), 1295 (w), 1247 (w), 1230 (w), 1175 (w), 1167 (w), 1142 (w),

1130 (w), 1110 (w), 1088 (w), 1053 (m), 1027 (s). MS (EI, 70 eV): *m/z* (%)=406 ([M$^+$], 27), 405 (100), 364 (27), 321 (7). HRMS (ESI-TOF/MS): calcd for $C_{24}H_{22}F_2N_3O$ [(M+H)$^+$] 406.1725, found 406.1732.

*3.8.29. 6-(4-Chlorophenyl)-4-(1,1-difluorobut-3-enyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine (**13c**).* White solid isolated by preparative chromatography (heptane); mp 124–126 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.74 (t, ^3J=2.3 Hz, 3H, CH_3), 3.02–3.15 (m, 2H, CH_2), 5.21–5.28 (m, 2H, CH_2), 5.77–5.91 (m, 1H, CH), 7.32 (t, ^3J=7.4 Hz, 1H, CH), 7.46–7.57 (m, 4H, $C_{Ar}H$), 7.68 (s, 1H, $C_{Ar}H$), 8.07–8.11 (m, ^3J=8.7 Hz, 2H, $C_{Ar}H$), 8.29–8.32 (m, ^3J=8.7 Hz, 2H, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=15.9 (t, $J_{C,F}$=6.0 Hz, CH_3), 43.3 (t, $J_{C,F}$=27.0 Hz, CH_2), 110.8 (t, $J_{C,F}$=8.3 Hz, CH), 110.8 (t, $J_{C,F}$=2.3 Hz, C), 120.7 (t, $J_{C,F}$=243.7 Hz, CF_2), 121.4 (CH), 121.6 (CH_2), 126.0 ($C_{Ar}H$), 128.2 (t, $J_{C,F}$=5.0 Hz, CH), 128.8 ($C_{Ar}H$), 129.0 ($C_{Ar}H$), 129.1 ($C_{Ar}H$), 136.1 (C), 136.9 (C), 139.2 (C), 140.3 (t, $J_{C,F}$=28.1 Hz, *C*–CF_2), 141.3 (C), 151.9 (C), 155.2 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−93.64 (CF_2). IR (ATR, cm^{-1}): ν=3115 (w), 3083 (w), 3020 (w), 2969 (w), 2929 (w), 2859 (w), 1644 (w), 1592 (m), 1578 (m), 1564 (w), 1503 (s), 1489 (w), 1477 (w), 1456 (w), 1437 (w), 1412 (m), 1400 (m), 1387 (m), 1348 (m), 1324 (w), 1309 (w), 1294 (w), 1267 (w), 1249 (w), 1231 (w), 1166 (s), 1141 (w), 1129 (m), 1107 (w), 1095 (m), 1052 (s), 1021 (w), 1011 (w). MS (EI, 70 eV): *m/z* (%)=411 ([M$^+$], [^{37}Cl], 36), 410 (29), 409 ([M$^+$], [^{35}Cl], 100), 370 (12), 368 (35). HRMS (ESI-TOF/MS): calcd for $C_{23}H_{19}ClF_2N_3$ ([M+H]$^+$, [^{35}Cl]) 410.123, found 410.1234. Anal. Calcd for $C_{23}H_{18}ClF_2N_3$ (409.86): C, 67.40, H, 4.43, N, 10.25. Found: C, 67.463, H, 4.616, N, 9.744.

*3.8.30. 1-tert-Butyl-4-(1,1-difluorobut-3-enyl)-6-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**13d**).* Yellow solid isolated by preparative chromatography (heptane); mp 80–81 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.81 (s, 9H, $C(CH_3)_3$), 2.66 (s, 3H, CH_3), 3.03–3.17 (m, 2H, CH_2), 5.18–5.24 (m, 2H, CH_2), 5.72–5.86 (m, 1H, CH), 7.16 (s, 1H, $C_{Ar}H$), 7.89 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=24.7 (CH_3), 29.0 (CH_3), 43.2 (t, $J_{C,F}$=27.0 Hz, CH_2), 58.8 ($C(CH_3)_3$), 82.4 (*C*–C≡N), 113.3 (t, $J_{C,F}$=3.3 Hz, C), 114.1 (t, $J_{C,F}$=7.3 Hz, CH), 116.2 (C≡N), 120.7 (CH_2), 120.7 (t, $J_{C,F}$=244.3 Hz, CF_2), 128.1 (t, $J_{C,F}$=5.0 Hz, CH), 134.7 (CH), 137.5 (t, $J_{C,F}$=28.6 Hz, *C*–CF_2), 147.8 (C), 153.2 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−93.84 (CF_2). IR (ATR, cm^{-1}): ν=3156(w), 2980 (w), 2924 (w), 2220 (s), 1859 (w), 1784 (w), 1679 (w), 1649 (s), 1593 (w), 1580 (w), 1522 (s), 1473 (w), 1435 (w), 1425 (m), 1399 (w), 1290 (m), 1368 (s), 1356 (w), 1350 (w), 1320 (s), 1300 (w), 1266 (s), 1245 (m), 1232 (w), 1199 (s), 1164 (w), 1150 (s), 1111 (m), 1061 (s), 1034 (m), 1014 (m). MS (EI, 70 eV): *m/z* (%)=303 ([M$^+$], 32), 247 (58), 246 (30), 207 (19), 206 (100), 194 (23). HRMS (ESI/TOF, MS): calcd for $C_{17}H_{19}N_3F_3$ ([M+H]$^+$) 304.162, found 304.1617. Anal. Calcd for $C_{17}H_{19}F_2N_3$ (303.35): C, 67.31, H, 6.31, N, 13.85. Found: C, 67.309, H, 6.396, N, 13.500.

*3.8.31. 1-tert-Butyl-6-(4-chlorophenyl)-4-(1,1-difluorobut-3-enyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**13e**).* White solid isolated by preparative chromatography (heptane); mp 190–191 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.89 (s, 9H, $C(CH_3)_3$), 3.10–3.23 (m, 2H, CH_2), 5.21–5.27 (m, 2H, CH_2), 5.76–5.90 (m, 1H, CH), 7.45–7.48 (m, ^3J=8.7 Hz, 2H, $C_{Ar}H$), 7.76 (s, 1H, CH), 8.01 (s, 1H, $C_{Ar}H$), 8.03–8.05 (m, ^3J=8.7 Hz, 2H, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=29.3 ($C(CH_3)_3$), 43.3 (t, J=27.0 Hz, CH_2), 59.1 ($C(CH_3)_3$), 83.1 (*C*–C≡N), 111.0 (t, $J_{C,F}$=7.7 Hz, CH), 114.9 (t, $J_{C,F}$=3.3 Hz, C), 115.9 (C≡N), 120.8 (t, $J_{C,F}$=244.8 Hz, CF_2), 121.5 (CH), 128.0 (t, $J_{C,F}$=5.0 Hz, CH), 128.2, 129.1 (CH), 135.4 (C), 136.2 (CH), 137.2 (C), 138.5 (t, $J_{C,F}$=28.6 Hz, *C*–CF_2), 149.0 (C), 150.6 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−93.80 (CF_2). IR (ATR, cm^{-1}): ν=3137 (w), 3086 (w), 2987 (w), 2921 (w), 2223 (s), 1747 (w), 1645 (w), 1583 (w), 1568 (w), 1518 (s), 1495 (w), 1470 (w), 1396 (s), 1366 (s), 1316 (s), 1293 (w), 1279 (w), 1268 (w), 1235 (w), 1207 (s), 1152 (w), 1124 (w), 1103 (w), 1089 (m), 1054 (w), 1040 (w), 1012 (w). MS (EI, 70 eV): *m/z* (%)=401 ([M$^+$], [^{37}Cl], 14), 399 ([M$^+$], [^{35}Cl], (42), 345 (34), 344 (28), 343 (100), 342 (21), 304 (32), 302 (87), 290 (16). HRMS (ESI/TOF, MS): calcd for $C_{22}H_{20}ClF_2N_3Na$ [(M+Na)$^+$, [^{35}Cl]) 422.1206, found 422.1202. Anal. Calcd for $C_{22}H_{20}ClF_2N_3$ (399.86): C, 66.08, H, 5.04, N, 10.51. Found: C, 65.825, H, 5.206, N, 10.321.

*3.8.32. 1-(4-Methoxybenzyl)-4-(1,1-difluorobut-3-enyl)-6-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**13f**).* Yellow solid isolated by preparative chromatography (heptane); mp 86–87 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.74 (s, 3H, CH_3) 3.07–3.21 (m, 2H, CH_2), 3.84 (s, 3H, OCH_3), 5.21–5.26 (m, 2H, CH_2), 5.47 (s, 2H, CH_2), 5.76–5.89 (m, 1H, CH), 6.90–6.95 (m, ^3J=8.7 Hz, 2H, $C_{Ar}H$), 7.27–7.30 (m, ^3J=8.7 Hz, 3H, $C_{Ar}H$), 7.71 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=24.5 (CH_3), 43.2 (t, $^3J_{C,F}$=27.0 Hz, CH_2), 48.2 (CH_2), 55.3 (OCH_3), 84.2 (*C*–C≡N), 112.1 (t, $J_{C,F}$=3.3 Hz, C), 114.4 (CH), 114.9 (t, $J_{C,F}$=7.2 Hz, CH), 115.7 (C≡N), 120.7 (t, $J_{C,F}$=244.3 Hz, CF_2), 121.3 (CH_2), 127.4 (C), 128.0 (t, $J_{C,F}$=4.8 Hz, CH), 129.7 (CH), 136.1 (CH), 138.0 (t, $J_{C,F}$=28.6 Hz, *C*–CF_2), 147.4 (C), 154.8 (C), 159.7 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−93.80 (CF_2). IR (ATR, cm^{-1}): ν=3097 (w), 3076 (w), 3029 (w), 2937 (w), 2844 (w), 2222 (s), 1722 (w), 1644 (w), 1614 (w), 1595 (w), 1575 (m), 1530 (m), 1511 (s), 1493 (w), 1455 (w), 1442 (m), 1416 (s), 1388 (s), 1356 (m), 1326 (m), 1295 (s), 1246 (s), 1211 (w), 1198 (w), 1182 (w), 1173 (s), 1154 (m), 1007 (s), 1025 (s), 1011 (w). MS (EI, 70 eV): *m/z* (%)=367 ([M$^+$], 28), 121 (100). HRMS (ESI/TOF, MS): calcd for $C_{21}H_{20}N_3F_2O$ ([M+H]$^+$) 368.1569, found 368.1563.

*3.8.33. 1-(4-Methoxybenzyl)-6-(4-chlorophenyl)-4-(1,1-difluorobut-3-enyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**13g**).* White solid isolated by preparative chromatography (heptane); mp 158–159 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.08–3.22 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 5.19–5.24 (m, 2H, CH_2), 5.52 (s, 2H, CH_2), 5.74–5.88 (m, 1H, CH), 6.88–6.91 (m, ^3J=8.7 Hz, 2H, $C_{Ar}H$), 7.28–7.31 (m, ^3J=8.7 Hz, 2H, $C_{Ar}H$), 7.46–7.49 (m, ^3J=8.7 Hz, 2H, $C_{Ar}H$), 7.78 (s, 1H, CH), 7.79 (s, 1H, CH), 8.07–8.09 (m, ^3J=8.7 Hz, 2H, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 126 MHz): δ=43.3 (t, $^3J_{C,F}$=27.0 Hz, CH_2), 48.6 (CH_2), 55.3 (OCH_3), 84.6 (*C*–C≡N), 111.8 (t, $J_{C,F}$=7.1 Hz, CH), 113.6 (t, $J_{C,F}$=2.4 Hz, C), 114.5 (CH), 115.4 (C≡N), 120.8 (t, $J_{C,F}$=244.6 Hz, CF_2), 121.6 (CH_2), 127.3 (C), 127.9 (t, $J_{C,F}$=4.8 Hz, CH), 128.4, 129.1, 129.8 (CH), 135.6, 136.9 (C), 137.4 (CH), 138.9 (t, $J_{C,F}$=28.6 Hz, *C*–CF_2), 147.7 (C), 152.0 (C), 159.9 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−113.76 (CF_2). IR (ATR, cm^{-1}): ν=3098 (w), 3076 (w), 2952 (w), 2920 (w), 2837 (w), 2217 (s), 1739 (w), 1722 (w), 1704 (w), 1642 (w), 1611 (w), 1594 (w), 1584 (m), 1513 (s), 1478 (w), 1464 (w), 1455 (w), 1442 (w), 1415 (s), 1405 (w), 1387 (m), 1365 (w), 1347 (w), 1332 (w), 1305 (w), 1294 (w), 1275 (w), 1247 (s), 1227 (m), 1212 (w), 1172 (s), 1147 (w), 1137 (w), 1122 (w), 1112 (w), 1092 (s), 1033 (s), 1012 (w). MS (EI, 70 eV): *m/z* (%)=465 ([M$^+$], [^{37}Cl], 6), 463 ([M$^+$], [^{35}Cl], 17), 121 (100). HRMS (ESI/TOF, MS): calcd for $C_{26}H_{21}N_3ClF_2O$ ([M+H]$^+$, [^{35}Cl]) 464.1336, found 464.1335. Anal. Calcd for $C_{26}H_{20}ClF_2N_3O$ (463.91): C, 67.31, H, 4.35, N, 9.06. Found: C, 67.389, H, 4.452, N, 8.517.

*3.8.34. 7-(1,1-Difluorobut-3-enyl)-1,3,5-trimethyl-1H-imidazo[4,5-b]pyridine-2(3H)-thione (**13h**).* White solid isolated by preparative chromatography (heptane); mp 100–101 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.59 (s, 3H, CH_3), 2.98–3.12 (m, 2H, CH_2), 3.83 (s, 3H, CH_3), 3.98 (t, ^3J=2.6 Hz, 3H, CH_3), 5.22–5.29 (m, 2H, CH_2), 5.73–5.87 (m, 1H, CH), 7.03 (s, 1H, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=23.9 (CH_3), 30.7 (CH_3), 34.8 (t, $^3J_{C,F}$=8.3 Hz, CH_3), 43.2 (t, $^3J_{C,F}$=27.0 Hz, CH_2), 114.6 (t, $J_{C,F}$=7.7 Hz, CH),120.0 (t, $J_{C,F}$=243.0 Hz, CF_2), 120.3 (t, $J_{C,F}$=2.2 Hz, C), 121.7 (CH), 126.7 (t, $J_{C,F}$=29.0 Hz, *C*–CF_2), 127.6 (t, $J_{C,F}$=5.0 Hz, CH), 146.4 (C), 152.0 (C), 172.5 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−86.55 (CF_2). IR (ATR, cm^{-1}): ν=3093 (w), 3051 (w), 2941 (w), 2916 (w), 1643 (m), 1615 (m), 1469 (s), 1435 (w), 1408 (br m), 1390 (w), 1361 (s), 1322 (s), 1309 (w), 1282 (m), 1260 (w), 1223 (w), 1215 (w), 1174 (w), 1157 (m), 1108 (m), 1077 (m),

1022 (w), 1003 (s). MS (EI, 70 eV): *m*/*z* (%)=283 ([M^+], 100), 282 (16), 268 (22), 232 (11), 220 (11), 219 (44), 218 (63). HRMS (ESI/TOF, MS): calcd for $C_{13}H_{15}N_3F_2NaS$ ([M+Na]$^+$) 306.0847, found 306.0849. Anal. Calcd for $C_{13}H_{15}F_2N_3S$ (283.34): C, 55.11, H, 5.34, N, 14.83. Found: C, 55.268, H, 5.522, N, 14.619.

*3.8.35. 7-(1,1-Difluorobut-3-enyl)-1,5-dimethyl-3-phenyl-1H-imidazo[4,5-b]pyridine-2(3H)-thione (**13i**).* White solid isolated by preparative chromatography (heptane); mp 184–185 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.50 (s, 3H, CH_3), 3.05–3.18 (m, 2H, CH_2), 4.07 (t, ^3J=2.6 Hz, 3H, CH_3), 5.27–5.35 (m, 2H, CH_2), 5.79–5.92 (m, 1H, CH), 7.08 (s, 1H, $C_{Ar}H$), 7.49–7.68 (m, 5H, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=23.9 (CH_3), 30.7 (CH_3), 34.8 (t, $^3J_{C,F}$=8.3 Hz, CH_3), 43.2 (t, $^3J_{C,F}$=27.0 Hz, CH_2), 114.6 (t, $J_{C,F}$=7.7 Hz, CH),120.0 (t, $J_{C,F}$=243.0 Hz, CF_2), 120.3 (t, $J_{C,F}$=2.2 Hz, C), 121.7 (CH), 126.7 (t, $J_{C,F}$=29.0 Hz, *C*–CF_2), 127.6 (t, $J_{C,F}$=5.0 Hz, CH), 146.4 (C), 152.0 (C), 172.5 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=–86.18 (CF_2). IR (ATR, cm^{-1}): ν=3049 (w), 2956 (w), 2923 (w), 2853 (w), 1713 (w), 1614 (m), 1503 (s), 1483 (w), 1470 (w), 1442 (w), 1425 (s), 1394 (s), 1381 (w), 1358 (m), 1320 (w), 1294 (w), 1286 (w), 1255 (w), 1229 (w), 1219 (w), 1171 (w), 1143 (w), 1128 (w), 1108 (w), 1075 (s), 1028 (s), 1007 (m). MS (EI, 70 eV): *m*/*z* (%)=345 ([M^+], 100), 344 (47), 330 (18), 281 (50), 280 (67), 254 (12). HRMS (EI, 70 eV): calcd for $C_{18}H_{17}N_3F_2S$ ([M^+]) 345.11058, found 345.110147.

*3.8.36. 5-(1,1-Difluorobut-3-enyl)-1,3,7-trimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (**13j**).* White solid isolated by preparative chromatography (heptane); mp 88–90 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.63 (s, 3H, CH_3), 3.30–3.43 (m, 2H, CH_2), 3.45 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 5.13–5.19 (m, 2H, CH_2), 5.69–5.83 (m, 1H, CH), 7.23 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=25.2 (CH_3), 28.7 (CH_3), 30.4 (CH_3), 41.3 (t, J=24.8 Hz, CH_2), 104.7 (t, $J_{C,F}$=2.2 Hz, C), 117.1 (t, $J_{C,F}$=11.0 Hz, CH), 120.7 (CH_2), 121.2 (t, $J_{C,F}$=245.4 Hz, CF_2), 129.0 (t, $J_{C,F}$=5.0 Hz, CH), 147.4 (t, $J_{C,F}$=27.5 Hz, *C*–CF_2), 151.0 (C), 152.1 (C), 159.5 (C), 164.3 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=–91.50 (CF_2). IR (ATR, cm^{-1}): ν=3366 (w), 3120 (w), 3080 (w), 2957 (w), 1713 (s), 1666 (m), 1641 (w), 1614 (w), 1593 (s), 1565 (s), 1500 (m), 1451 (w), 1416 (s), 1382 (w), 1355 (s), 1329 (w), 1284 (w), 1263 (w), 1254 (w), 1234 (w), 1196 (w), 1171 (w), 1154 (w), 1140 (w), 1078 (s), 1025 (w), 1009 (w). MS (EI, 70 eV): *m*/*z* (%)=295 ([M^+], 24), 275 (35), 274 (32), 254 (34), 231 (21), 230 (100), 190 (26), 189 (38), 162 (49), 161 (31). HRMS (ESI/TOF, MS): calcd for $C_{14}H_{16}F_2N_3O_2$ [(M+H)$^+$] 296.1205, found 296.1206. Anal. Calcd for $C_{14}H_{15}F_2N_3O_2$ (295.28): C, 56.94, H, 5.12, N, 14.23. Found: C, 57.082, H, 5.411, N, 13.797.

*3.8.37. 5-(1,1-Difluorobut-3-enyl)-7-methylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (**13k**).* White solid isolated by preparative chromatography (heptane); mp 208–209 °C; ^{1}H NMR ($(CD_3)_2CO$, 300 MHz): δ=2.59 (s, 3H, CH_3), 3.30–3.44 (m, 2H, CH_2), 5.12–5.21 (m, 2H, CH_2), 5.71–5.85 (m, 1H, CH), 7.27 (s, 1H, CH), 10.29 (s, 1H, NH), 10.51 (s, 1H, NH). ^{13}C NMR ($(CD_3)_2CO$, 75 MHz): δ=24.4 (CH_3), 41.2 (t, J=24.8 Hz, CH_2), 104.4 (t, $J_{C,F}$=2.8 Hz, C), 117.1 (t, $J_{C,F}$=11.0 Hz, CH), 121.5 (t, $J_{C,F}$=244.3 Hz, CF_2), 120.3 (CH_2), 129.7 (t, $J_{C,F}$=5.0 Hz, CH), 147.2 (t, $J_{C,F}$=27.5 Hz, *C*–CF_2), 149.7 (C), 154.5 (C), 160.8 (C), 165.7 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=–92.38 (CF_2). IR (ATR, cm^{-1}): ν=3207 (w), 3078 (w), 3023 (w), 2873 (w), 1693 (br s), 1601 (m), 1566 (s), 1467 (w), 1440 (w), 1394 (s), 1372 (w), 1352 (m), 1316 (w), 1263 (s), 1211 (w), 1182 (w), 1157 (w), 1131 (w), 1114 (w), 1101 (w), 1084 (w), 1062 (w), 1033 (w). MS (EI, 70 eV): *m*/*z* (%)=267 ([M^+], 26), 247 (45), 246 (64), 232 (27), 227 (26), 226 (66), 203 (70), 202 (100), 176 (70). HRMS (ESI/TOF, MS): calcd for $C_{12}H_{10}F_2N_3O_2$ [(M–H)$^-$] 266.0747, found 266.0753.

*3.8.38. 3-(4-Methoxybenzyl)-7-(1,1-difluorobut-3-enyl)-5-methyl-3H-imidazo[4,5-b]pyridine (**13l**).* Yellow oil isolated by preparative chromatography (heptane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.71 (s, 3H, CH_3), 3.27–3.41 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 5.11–5.19 (m, 2H, CH_2), 5.40 (s, 2H, CH_2), 5.68–5.82 (m, 1H, CH), 6.68–6.91 (m, ^3J=8.9 Hz, 2H, $C_{Ar}H$), 7.27–7.31 (m, ^3J=8.9 Hz, 2H, $C_{Ar}H$), 7.97 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=24.6 (CH_3), 42.3 (t, J=26.0 Hz, CH_2), 46.6 (CH_2), 55.3 (OCH_3), 114.3 (t, $J_{C,F}$=6.1 Hz, CH), 120.5 (t, $J_{C,F}$=243.7 Hz, CF_2), 120.6 (CH_2), 127.7 (C), 128.7 (t, $J_{C,F}$=5.0 Hz, CH), 129.3 (t, $J_{C,F}$=4.4 Hz, C), 129.5 (CH), 135.4 (t, $J_{C,F}$=27.5 Hz, *C*–CF_2), 143.3 (CH), 147.5 (C), 154.1 (C), 159.6 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=–95.75 (CF_2). IR (ATR, cm^{-1}): ν=3078 (w), 2954 (w), 2930 (w), 2837 (w), 1717 (w), 1675 (w), 1644 (w), 1612 (w), 1588 (m), 1513 (s), 1492 (w), 1463 (w), 1435 (w), 1396 (w), 1381 (m), 1357 (m), 1300 (w), 1284 (m), 1246 (s), 1194 (w), 1176 (w), 1156 (w), 1109 (w), 1071 (m), 1029 (s). MS (EI, 70 eV): *m*/*z* (%)=343 ([M^+], 21), 122 (10), 121 (100). HRMS (ESI/TOF, MS): calcd for $C_{19}H_{19}F_2N_3NaO$ [(M+Na)$^+$] 366.1388, found 366.1393.

*3.8.39. 3-(4-Chlorobenzyl)-7-(1,1-difluorobut-3-enyl)-5-methyl-3H-imidazo[4,5-b]pyridine (**13m**).* Yellow oil isolated by preparative chromatography (heptane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.67 (s, 3H, CH_3), 3.27–3.40 (m, 2H, CH_2), 5.10–5.18 (m, 2H, CH_2), 5.42 (s, 2H, CH_2), 5.67–5.81 (m, 1H, CH), 7.22–7.31 (m, 5H, $C_{Ar}H$), 7.99 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 126 MHz): δ=24.5 (CH_3), 42.2 (t, J=27.9 Hz, CH_2), 46.3 (CH_2), 114.4 (t, $J_{C,F}$=6.7 Hz, CH), 120.4 (t, $J_{C,F}$=244.3 Hz, CF_2), 120.5 (CH_2), 128.6 (t, $J_{C,F}$=5.3 Hz, CH), 129.0 ($C_{Ar}H$), 129.1 ($C_{Ar}H$), 129.3 (t, $J_{C,F}$=3.6 Hz, C), 134.2 (C), 134.3 (C), 135.5 (t, $J_{C,F}$=28.6 Hz, *C*–CF_2), 143.1 (CH), 147.4 (C), 154.3 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=–95.68 (CF_2). IR (ATR, cm^{-1}): ν=3080 (w), 3019 (w), 2954 (w), 2923 (w), 2854 (w), 1730 (w), 1714 (w), 1697 (w), 1681 (w), 1644 (w), 1591 (s), 1539 (w), 1491 (s), 1463 (w), 1431 (w), 1410 (w), 1396 (w), 1381 (m), 1358 (m), 1288 (s), 1233 (w), 1194 (s), 1155 (s), 1072 (w), 1029 (w), 1015 (m). MS (EI, 70 eV): *m*/*z* (%)=349 ([M^+], [^{37}Cl], 8), 347 ([M^+], [^{35}Cl], (32), 222 (60), 127 (31), 125 (100), 89 (18). HRMS (ESI/TOF, MS): calcd for $C_{18}H_{16}ClF_2N_3Na$ ([M+Na)$^+$, [^{35}Cl]) 370.0893, found 370.089.

*3.8.40. 4-(Chlorodifluoromethyl)-2-phenylpyrimidine (**16a**).* Orange-yellow solid isolated recrystallization from water; mp 139 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.46 (d, $^3J_{H,H}$=5.1 Hz, 1H, CH), 7.51–7.53 (m, 3H, Ar), 8.50–8.53 (m, 2H, Ar), 9.00 (d, $^3J_{H,H}$=5.1 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=113.0 (t, $^3J_{C,F}$=3.3 Hz, CH) 123.6 (t, $^1J_{C,F}$=291.1 Hz, CF_2Cl), 128.6, 128.7, 131.6 ($C_{Ar}H$), 136.2 (C_{Ar}), 159.6 (CH), 160.2 (t, $^2J_{C,F}$=30.8 Hz, *C*–CF_2Cl), 165.4 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=–58.28 (CF_2Cl). IR (ATR, cm^{-1}): ν=3201 (w), 3134 (w), 3066 (w), 3045 (w), 2962 (w), 2922 (w), 2851 (w), 1965 (w), 1909 (w), 1621 (w), 1601 (w), 1588 (w), 1559 (m), 1520 (m), 1458 (w), 1430 (m), 1390 (s), 1368 (m), 1322 (m), 1308 (m), 1298 (m), 1276 (m), 1185 (w), 1172 (w), 1144 (s), 1093 (s), 1067 (s), 1025 (m), 1002 (m). MS (EI, 70 eV): *m*/*z* (%)=242 ([M]$^+$, [^{37}Cl], 32), 240 ([M]$^+$, [^{35}Cl], 100), 241 (12), 205 (15), 155 (91), 104 (12), 103 (22), 77 (13).HRMS (EI, 70 eV): calcd for $C_{11}H_7ClF_2N_2$ ([M]$^+$, [^{35}Cl]) 240.02603, found 240.025859.

*3.8.41. 4-(Chlorodifluoromethyl)-6-methyl-2-phenylpyrimidine (**16b**).* Orange-brown solid isolated recrystallization from water; mp 58–59 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.69 (s, 3H, CH_3), 7.32 (s, 1H, CH), 7.49–7.51 (m, 3H, Ar), 8.50–8.53 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=24.8 (CH_3), 112.5 (t, $^3J_{C,F}$=3.3 Hz, CH), 123.9 (t, $^1J_{C,F}$=291.1 Hz, CF_2Cl), 127.3, 128.6, 131.3 ($C_{Ar}H$), 136.5 (C_{Ar}), 160.0 (t, $^2J_{C,F}$=30.0 Hz, *C*–CF_2Cl), 165.0, 170.1 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=–58.17 (CF_2Cl). IR (ATR, cm^{-1}): ν=3365 (w), 3168 (w), 3067 (w), 2964 (w), 1660 (w), 1623 (w), 1590 (w), 1576 (m), 1546 (m), 1460 (w), 1448 (w), 1405 (w), 1370 (s), 1289 (w), 1260 (w), 1213 (m), 1202 (m), 1175 (w), 1148 (m), 1120 (s), 1091 (s), 1071 (m), 1027 (m). MS (EI, 70 eV): *m*/*z* (%)=256 ([M]$^+$, [^{37}Cl], 34), 254 ([M]$^+$, [^{35}Cl], 100), 255 (15), 219 (17), 169 (62), 104 (28), 103 (22). HRMS (EI, 70 eV): calcd for $C_{12}H_9ClF_2N_2$ ([M]$^+$, [^{35}Cl]) 254.04168, found 254.041507.

Anal. Calcd for $C_{12}H_9ClF_2N_2$ (254.66): C, 56.60, H, 3.56, N, 11.00. Found: C, 56.610, H, 3.143, N, 10.834.

*3.8.42. 4-(Difluoromethyl)-2-phenylpyrimidine (**17a**).* White-yellow solid isolated by preparative chromatography (heptane); mp 55–57 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=6.61 (t, $^2J_{H,F}$=54.9 Hz, 1H, CF_2H), 7.46–7.48 (m, 1H, CH), 7.49–7.51 (m, 3H, Ar), 8.46–8.49 (m, 2H, Ar), 8.97 (d, $^3J_{H,H}$=4.9 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=112.9 (t, $^1J_{C,F}$=242.1 Hz, CF_2H), 114.3 (t, $^3J_{C,F}$=3.0 Hz, CH), 128.4, 128.7, 131.3 ($C_{Ar}H$), 136.6 (C_{Ar}), 159.0 (CH), 160.5 (t, $^2J_{C,F}$=26.7 Hz, *C*–CF_2H), 164.9 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−119.11 (CF_2). IR (ATR, cm^{-1}): ν=3139 (w), 3092 (w), 3070 (w), 3046 (w), 2956 (w), 2922 (w), 2871 (w), 2853 (w), 1587 (w), 1566 (s), 1531 (w), 1520 (w), 1462 (w), 1435 (w), 1396 (s), 1353 (m), 1335 (m), 1307 (w), 1294 (w), 1252 (w), 1178 (w), 1155 (w), 1120 (m), 1090 (m), 1045 (s), 1025 (s), 1002 (m). MS (EI, 70 eV): *m*/*z* (%)=206 ([M]$^+$, 100), 207 (13), 155 (77), 104 (12), 103 (22), 77 (13). HRMS (EI, 70 eV): calcd for $C_{11}H_8F_2N_2$ ([M]$^+$) 206.06501, found 206.064908.

*3.8.43. 4-(Difluoromethyl)-6-methyl-2-phenylpyrimidine (**17b**).* Colourless oil isolated by preparative chromatography (heptane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.66 (s, 3H, CH_3), 6.58 (t, $^2J_{H,F}$=55.0 Hz, 1H, CF_2H), 7.33 (s, 1H, CH), 7.47–7.51 (m, 3H, Ar), 8.46–8.49 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=24.7 (CH_3), 113.1 (t, $^1J_{C,F}$=241.8 Hz, CF_2H), 113.8 (t, $^3J_{C,F}$=3.3 Hz, CH), 128.4, 128.6, 131.1 ($C_{Ar}H$), 136.9 (C_{Ar}), 160.2 (t, $^2J_{C,F}$=26.4 Hz, *C*–CF_2H), 164.5 (C), 169.4 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−119.20. IR (ATR, cm^{-1}): ν=3068 (w), 3043 (w), 2959 (w), 2925 (w), 2872 (w), 2855 (w), 1593 (m), 1578 (m), 1556 (m), 1497 (w), 1459 (w), 1445 (w), 1409 (s), 1395 (s), 1373 (s), 1331 (m), 1287 (w), 1201 (w), 1174 (m), 1157 (w), 1137 (m), 1092 (s), 1049 (s), 1028 (s), 1002 (m). MS (EI, 70 eV): *m*/*z* (%)=220 ([M]$^+$, 100), 221 (14), 169 (44), 104 (21), 103 (16). HRMS (EI, 70 eV): calcd for $C_{12}H_{10}F_2N_2$ ([M]$^+$) 220.08066, found 220.080431.

*3.8.44. 4-(1,1-Difluorobut-3-enyl)-2-phenylpyrimidine (**18a**).* Yellow oil isolated by preparative chromatography (heptane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.12–3.26 (m, $^3J_{H,F}$=7.2 Hz, 2H, CH_2), 5.18–5.26 (m, 2H, CH_2), 5.73–5.87 (m, $^4J_{H,F}$=7.0 Hz, 1H, CH), 7.46 (d, $^3J_{H,H}$=5.1 Hz, 1H, CH), 7.50–7.52 (m, 3H, Ar), 8.48–8.51 (m, 2H, Ar), 8.93 (d, $^3J_{H,H}$=5.1 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): 40.1 (t, $^2J_{C,F}$=25.3 Hz, CH_2), 114.5 (t, $^3J_{C,F}$=4.1 Hz, CH), 119.7 (t, $^1J_{C,F}$=243.2 Hz, CF_2), 121.2 (CH_2), 128.2 (t, $^3J_{C,F}$=5.5 Hz, CH), 128.4, 128.6, 131.2 ($C_{Ar}H$), 136.8 (C_{Ar}), 158.8 (CH), 162.3 (t, $^2J_{C,F}$=30.5 Hz, *C*–CF_2), 164.7 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−100.37 (CF_2Cl). IR (ATR, cm^{-1}): ν=3070 (w), 3045 (w), 2984 (w), 2925 (w), 1645 (w), 1588 (w), 1563 (s), 1460 (w), 1428 (m), 1386 (s), 1347 (m), 1333 (m), 1314 (m), 1286 (w), 1260 (w), 1243 (w), 1172 (m), 1143 (m), 1108 (w), 1090 (m), 1064 (m), 1044 (m), 1029 (m). MS (EI, 70 eV): *m*/*z* (%)=246 ([M]$^+$, 18), 245 (100), 225 (17), 104 (18), 103 (11), 77 (12). HRMS (ESI-TOF/MS): calcd for $C_{14}H_{12}F_2N_2$ ([M+H]$^+$) 247.1041, found 247.1042. Anal. Calcd for $C_{14}H_{12}F_2N_2$ (246.26): C, 68.28, H, 4.91, N, 11.38. Found: C, 68.417, H, 4.952, N, 11.122.

*3.8.45. 4-(1,1-Difluorobut-3-enyl)-6-methyl-2-phenylpyrimidine (**18b**).* Colourless oil isolated by preparative chromatography (heptane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.65 (s, 3H, CH_3), 3.10–3.24 (m, 2H, CH_2), 5.17–5.26 (m, 2H, CH_2), 5.72–5.86 (m, 1H, CH), 7.33 (s, 1H, CH), 7.45–7.50 (m, 3H, Ar), 8.47–8.51 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=24.7 (CH_3), 40.2 (t, $^2J_{C,F}$=24.8 Hz, CH_2), 114.0 (t, $^3J_{C,F}$=4.4 Hz, CH), 119.9 (t, $^1J_{C,F}$=243.2 Hz, CF_2), 121.1 (CH_2), 128.4 ($C_{Ar}H$), 128.5 (t, $^3J_{C,F}$=5.5 Hz, CH), 128.5, 131.0 ($C_{Ar}H$), 137.1 (C_{Ar}), 161.0 (t, $^2J_{C,F}$=30.3 Hz, *C*–CF_2), 164.4, 169.2 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−100.5 (CF_2). IR (ATR, cm^{-1}): ν=3081 (w), 3069 (w), 2985 (w), 2959 (w), 2925 (w), 2855 (w), 1645 (w), 1592 (m), 1577 (m), 1548 (m), 1558 (w), 1429 (w), 1372 (s), 1318 (w), 1268 (s), 1197 (w), 1175 (w), 1140 (w), 1071 (w), 1060 (w), 1028 (m). MS (EI, 70 eV): *m*/*z* (%)=260 ([M]$^+$, 68), 259 (100), 239 (36), 104 (31), 103 (14), 77 (12). HRMS (EI, 70 eV): calcd for $C_{15}H_{14}F_2N_2$ ([M]$^+$) 259.10413, found 259.104744. Anal. Calcd for $C_{15}H_{14}F_2N_2$ (260.28): C, 69.22, H, 5.42. Found: C, 68.870, H, 5.440.

*3.8.46. 3-(Chlorodifluoromethyl)-1H-pyrazole (**20a**).* Colourless oil isolated by column chromatography (heptane/EtOAc, 5:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=6.63 (d, $^4J_{H,F}$=2.5 Hz, 1H, CH), 7.69–7.70 (m, 1H, CH), 11.99 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=103.5 (CH), 123.1 (t, $^1J_{C,F}$=284.7 Hz, CF_2Cl), 130.3 (CH), 147.6 (t, $^2J_{C,F}$=31.6 Hz, *C*–CF_2Cl). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−47.1 (CF_2Cl). IR (ATR, cm^{-1}): ν=3167 (m), 3065 (w), 2979 (m), 2933 (m), 2848 (w), 2774 (w), 2703 (w), 2533 (w), 2342 (w), 2141 (w), 1635 (w), 1553 (w), 1481 (w), 1372 (m), 1304 (s), 1242 (w), 1226 (m), 1117 (s), 1079 (s), 1053 (s). MS (EI, 70 eV): *m*/*z* (%)=154 ([M]$^+$, [^{37}Cl], 5), 152 ([M]$^+$, [^{35}Cl], 15), 117 (100), 39 (13). HRMS (ESI-TOF/MS): calcd for $C_4H_3ClF_2N_2$ ([M+H]$^+$, [^{35}Cl]) 153.0026, found 153.0025. Anal. Calcd for $C_4H_3ClF_2N_2$ (152.53): C, 31.50, H, 1.98, N, 18.37. Found: C, 31.556, H, 1.934, N, 17.438.

*3.8.47. 3-(Chlorodifluoromethyl)-1-phenyl-1H-pyrazole (**20b**).* Yellow oil isolated by column chromatography (heptane/EtOAc, 100:1→10:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=6.77 (d, $^4J_{H,F}$=2.1 Hz, 1H, CH), 7.48 (s, 5H, Ar), 7.66 (d, $^5J_{H,F}$=1.9 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=108.3 (t, $^3J_{C,F}$=2.7 Hz, CH), 119.9 (CH), 120.8 (t, $^1J_{C,F}$=286.0 Hz, CF_2Cl), 126.5, 128.9, 129.4 ($C_{Ar}H$), 137.5 (t, $^2J_{C,F}$=33.4 Hz, *C*–CF_2Cl), 139.2 (C_{Ar}). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−43.2 (CF_2Cl). IR (ATR, cm^{-1}): ν=3144 (w), 3112 (w), 3066 (w), 1598 (m), 1533 (m), 1502 (s), 1459 (m), 1397 (s), 1331 (s), 1272 (m), 1228 (s), 1147 (w), 1133 (w), 1097 (w), 1083 (w), 1072 (w), 1027 (m). MS (EI, 70 eV): *m*/*z* (%)=230 ([M]$^+$, [^{37}Cl], 20), 228 ([M]$^+$, [^{35}Cl], 57), 194 (12), 193 (100), 173 (43), 77 (18), 51 (12). HRMS (EI, 70 eV): calcd for $C_{10}H_7ClF_2N_2$ ([M]$^+$, [^{35}Cl]) 228.02603, found 248.025981. Anal. Calcd for $C_{12}H_9ClF_2N_2$ (228.63): C, 52.53, H, 3.09, N, 12.25. Found: C, 52.790, H, 2.890, N, 12.210.

*3.8.48. 3-(Chlorodifluoromethyl)-5-methyl-1H-pyrazole (**20d**).* White-yellow solid isolated by column chromatography (heptane/EtOAc, 10:1→5:1); mp 83–84 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.32 (d, $^6J_{H,F}$=0.6 Hz, 3H, CH_3), 6.28 (s, 1H, CH), 12.41 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=10.6 (CH_3), 102.5 (t, $^3J_{C,F}$=2.1 Hz, CH), 123.1 (t, $^1J_{C,F}$=284.7 Hz, CF_2Cl), 142.2 (C), 147.8 (t, ^2J=31.4 Hz, *C*–CF_2Cl). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−46.91 (CF_2Cl). IR (ATR, cm^{-1}): ν=3182 (w), 3140 (w), 3098 (w), 3030 (w), 2980 (w), 2937 (w), 2876 (w), 2781 (w), 1582 (w), 1477 (w), 1423 (m), 1382 (w), 1306 (w), 1221 (s), 1162 (m), 1112 (m), 1072 (s), 1031 (m). MS (EI, 70 eV): *m*/*z* (%)=168 ([M]$^+$, [^{37}Cl], 6), 166 ([M]$^+$, [^{35}Cl], 19), 131 (100). HRMS (ESI-TOF/MS): calcd for $C_5H_5ClF_2N_2$ ([M+H]$^+$, [^{35}Cl]) 166.0182, found 166.0183. Anal. Calcd for $C_5H_5ClF_2N_2$ (166.56): C, 36.06, H, 3.03, N, 16.82. Found: C, 36.354, H, 2.992, N, 15.639.

*3.8.49. 3-(Chlorodifluoromethyl)-1,5-dimethyl-1H-pyrazole (**20e**).* Yellow oil isolated by column chromatography (heptane/EtOAc, 10:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.28, 3.80 (s, 3H, CH_3), 6.25 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=11.1, 36.6 (CH_3), 103.2 (CH), 123.1 (t, $^1J_{C,F}$=284.5 Hz, CF_2Cl), 140.1 (C), 145.9 (t, $^2J_{C,F}$=31.6 Hz, *C*–CF_2Cl). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−46.82 (CF_2Cl). IR (ATR, cm^{-1}): ν=3138 (w), 2952 (w), 1553 (w), 1463 (w), 1433 (w), 1426 (w), 1407 (w), 1381 (w), 1298 (w), 1201 (s), 1173 (m), 1116 (m), 1090 (m), 1036 (m), 1000 (s). MS (EI, 70 eV): *m*/*z* (%)=182 ([M]$^+$, [^{37}Cl], 14), 180 ([M]$^+$, [^{35}Cl], 42), 146 (19), 145 (100). HRMS (EI, 70 eV): calcd for $C_6H_7ClF_2N_2$ ([M]$^+$, [^{35}Cl]) 180.02603, found 180.026362.

*3.8.50. 3-(Chlorodifluoromethyl)-5-methyl-1-phenyl-1H-pyrazole (**20f**).* Yellow oil isolated by column chromatography (heptane/EtOAc, 10:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.33 (d, $^6J_{H,F}$=0.6 Hz, 3H, CH_3), 6.44 (s, 1H, CH), 7.42–7.49 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$,

75 MHz): δ=12.3 (CH_3), 104.4 (t, $^3J_{C,F}$=1.9 Hz, CH), 123.1 (t, $^1J_{C,F}$=285.0 Hz, CF_2Cl), 125.3, 128.6, 129.2 ($C_{Ar}H$), 138.9 (C_{Ar}), 140.7 (C), 147.5 (t, $^2J_{C,F}$=31.6 Hz, *C*–CF_2Cl). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−47.23 (CF_2Cl). IR (ATR, cm^{-1}): ν=3136 (w), 3066 (w), 2966 (w), 2928 (w), 1598(w), 1549 (w), 1503 (m), 1449 (m), 1317 (w), 1295 (w), 1277 (w), 1210 (s), 1149 (m), 1087 (s), 1073 (s), 1041 (w), 1017 (m), 1001 (s). MS (EI, 70 eV): *m*/*z* (%)=244 ($[M]^+$, $[^{37}Cl]$, 8), 242 ($[M]^+$, $[^{35}Cl]$, 26), 208 (12), 207 (100), 77 (27), 51 (16). HRMS (ESI-TOF/MS): calcd for $C_{11}H_9ClF_2N_2$ ($[M+H]^+$, $[^{35}Cl]$) 243.0495, found 243.0495. Anal. Calcd for $C_{11}H_9ClF_2N_2$ (242.65): C, 54.45, H, 3.74, N, 11.54. Found: C, 54.846, H, 3.759, N, 11.332.

*3.8.51. 5-(Chlorodifluoromethyl)-3-methyl-1-(4-nitrophenyl)-1H-pyrazole (**20g**).* Orange-brown solid isolated by column chromatography (heptane/EtOAc, 10:1); mp 52–53 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ=2.36 (s, 3H, CH_3), 6.65 (s, 1H, CH), 7.68–7.73 (m, 2H, Ar), 8.31–8.36 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=13.3 (CH_3), 109.9 (t, $^3J_{C,F}$=2.7 Hz, CH), 120.5 (t, $^1J_{C,F}$=285.6 Hz, CF_2Cl), 124.4 ($C_{Ar}H$), 126.5 (t, $^5J_{C,F}$=1.8 Hz, $C_{Ar}H$), 138.0 (t, $^2J_{C,F}$=33.4 Hz, *C*–CF_2Cl), 144.2, 147.4, 150.1 (C). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−42.93 (CF_2Cl). IR (ATR, cm^{-1}): ν=3122(w), 3091 (w), 2932 (w), 2863 (w), 1612 (w), 1597 (m), 1555 (w), 1523 (s), 1503 (s), 1454 (m), 1438 (m), 1382 (w), 1343 (s), 1314 (m), 1275 (m), 1193 (m), 1154 (m), 1099 (m), 1075 (s), 1017 (s), 1002 (s). MS (EI, 70 eV): *m*/*z* (%)=289 ($[M]^+$, $[^{37}Cl]$, 33), 287 ($[M]^+$, $[^{35}Cl]$, 90), 252 (63), 206 (100), 205 (25), 165 (17), 75 (16). HRMS (EI, 70 eV): calcd for $C_{11}H_8ClF_2N_3O_2$ ($[M]^+$, $[^{35}Cl]$) 287.02676, found 287.025954. Anal. Calcd for $C_{11}C_8ClF_2N_3O_2$ (287.65): C, 45.93, H, 2.80. Found: C, 45.528, H, 2.509.

*3.8.52. 3-(Difluoromethyl)-1-phenyl-1H-pyrazole (**21**).* Colourless oil isolated by preparative chromatography (heptane); ^1H NMR ($CDCl_3$, 300 MHz): δ=6.63 (t, $^2J_{H,F}$=53.6 Hz, 1H, CF_2H), 6.74–6.75 (m, 1H, CH), 7.44–7.51 (m, 5H, Ar), 7.71 (m, 1H, CH). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=107.3 (t, $^3J_{C,F}$=2.3 Hz, CH), 108.5 (t, $^1J_{C,F}$=235.5 Hz, CF_2H), 124.9, 128.8, 129.4 ($C_{Ar}H$), 136,2 (t, $^2J_{C,F}$=30.0 Hz, *C*–CF_2H), 138.9 (C_{Ar}), 140.1 (t, $^4J_{C,F}$=1.6 Hz, CH). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−109.77 (CF_2). IR (ATR, cm^{-1}): ν=3142 (w), 3111 (w), 3066 (w), 2957 (w), 2925 (w), 2854 (w), 1620 (w), 1597 (w), 1545 (w), 1503 (s), 1465 (w), 1458 (w), 1401 (m), 1370 (m), 1344 (w), 1329 (m), 1296 (w), 1275 (w), 1208 (m), 1177 (w), 1159 (w), 1132 (m), 1081 (s), 1072 (s), 1035 (s), 1025 (s), 1006 (s). MS (EI, 70 eV): *m*/*z* (%)=194 ($[M]^+$, 100), 193 (34), 173 (12), 116 (12), 77 (23), 51 (16). HRMS (ESI-TOF/MS): calcd for $C_{10}H_8F_2N_2$ ($[M]^+$) 195.0728, found 195.0728.

*3.8.53. 3-(1,1-Difluorobut-3-enyl)-1-phenyl-1H-pyrazole (**22a**).* Colourless oil isolated by preparative chromatography (heptane); ^1H NMR ($CDCl_3$, 300 MHz): δ=3.07–3.21 (m, $^3J_{H,F}$=7.0 Hz, 2H, CH_2), 5.20–5.29 (m, 2H, CH_2), 5.83–5.97 (m, $^4J_{H,F}$=7.0 Hz, 1H, CH), 6.63 (d, $^4J_{H,F}$=2.5 Hz, 1H, CH), 7.29–7.49 (m, 3H, Ar), 7.66–7.71 (m, 2H, Ar), 7.89 (d, $^5J_{H,F}$=2.5 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=41.5 (t, $^2J_{C,F}$=26.4 Hz, CH_2), 105.5 (t, $^3J_{C,F}$=2.2 Hz, CH), 118.9 (t, $^1J_{C,F}$=237.1 Hz, CF_2), 119.5 (CH), 120.4 (CH_2), 127.1, 127.8 ($C_{Ar}H$), 129.2 (t, $^3J_{C,F}$=5.0 Hz, CH), 129.5 ($C_{Ar}H$), 139.8 (C_{Ar}), 150.0 (t, $^2J_{C,F}$=33.6 Hz, *C*–CF_2). ^{19}F NMR($CDCl_3$, 282 MHz): δ=−92.05 (CF_2). IR (ATR, cm^{-1}): ν=3150 (w), 3081 (w), 3050 (w), 3022 (w), 2957 (w), 2923 (w), 2872 (w), 2854 (w), 1645 (w), 1601 (m), 1529 (w), 1497 (s), 1473 (w), 1463 (w), 1429 (w), 1416 (w), 1382 (m), 1327 (w), 1281 (s), 1244 (m), 1171 (m), 1153 (m), 1086 (m), 1072 (m), 1045 (s). MS (EI, 70 eV): *m*/*z* (%)=234 ($[M]^+$, 38), 233 (34), 213 (18), 194 (13), 193 (100), 77 (19). HRMS (EI, 70 eV): calcd for $C_{13}H_{12}F_2N_2$ ($[M]^+$) 234.09631, found 234.096137.

*3.8.54. 3-(1,1-Difluorobut-3-enyl)-5-methyl-1-phenyl-1H-pyrazole (**22b**).* Colourless oil isolated by preparative chromatography (heptane); ^1H NMR ($CDCl_3$, 300 MHz): δ=2.33 (d, $^6J_{H,F}$=0.6 Hz, 3H, CH_3), 3.03–3.17 (m, $^3J_{H,F}$=7.2 Hz, 2H, CH_2), 5.22–5.28 (m, 2H, CH_2), 5.83–5.96 (m, $^4J_{H,F}$=7.0 Hz, 1H, CH), 6.37 (s, 1H, CH), 7.40–7.50 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=12.4 (CH_3), 41.4 (t, $^2J_{C,F}$=26.3 Hz, CH_2), 104.5 (t, $^3J_{C,F}$=2.3 Hz, CH), 119.0 (t, $^1J_{C,F}$=236.9 Hz, CF_2), 120.2 (CH_2), 125.1, 128.2, 129.1 ($C_{Ar}H$), 129.3 (t, $^3J_{C,F}$=5.0 Hz, CH), 139.3 (C_{Ar}), 140.0 (C), 148.7 (t, $^3J_{C,F}$=33.6 Hz, *C*–CF_2). ^{19}F NMR ($CDCl_3$, 282 MHz): δ=−92.05 (CF_2Cl). IR (ATR, cm^{-1}): ν=3137 (w), 3079 (w), 3021 (w), 2985 (w), 2958 (w), 2925 (w), 2872 (w), 2856 (w), 1645 (w), 1598 (w), 1552 (w), 1503 (s), 1481 (w), 1465 (w), 1450 (m), 1429 (w), 1378 (m), 1327 (w), 1318 (w), 1295 (w), 1270 (m), 1247 (w), 1198 (m), 1171 (m), 1138 (m), 1114 (w), 1063 (m), 1016 (s). MS (EI, 70 eV): *m*/*z* (%)=248 ($[M]^+$, 51), 247 (57), 228 (18), 227 (42), 207 (100), 157 (30). HRMS (ESI-TOF/MS): calcd for $C_{14}H_{14}F_2N_2$ ($[M+Na]^+$) 271.1017, found 271.1020.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.05.085.

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18. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-821637 (**7b**), CCDC-821639 (**12f**), CCDC-821638 (**13d**) and CCDC-821636 (**16b**) and can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk, or via www.ccdc.cam.ac.uk/data_request/cif
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