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# Annelation reactions of pentafluorobenzonitrile

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ABSTRACT

Annelation reactions between pentafluorobenzonitrile and *N,N*-dimethylethylene diamine and 3-methyl picoline gave [6,6]-bicyclic and [6,5,6]-tricyclic ring-fused systems, respectively. Reaction of 4-morpholino tetrafluorobenzonitrile with hydrazine and phenyl hydrazine gave [5,6] ring-fused systems arising from a tandem $S_NAr$ and cyclisation process involving annelation onto the pendant cyano group providing an indication of the synthetic possibilities for heterocycle formation using the pentafluorobenzonitrile scaffold.



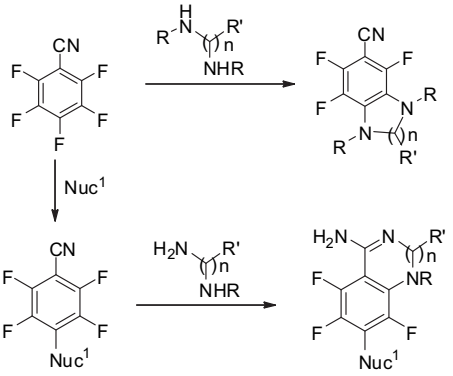
## 1. Introduction

The chemistry of perfluorinated aromatic systems has been a developing field since synthetic routes that provided ready access to hexafluorobenzene and related highly fluorinated aromatic systems were reported.[1,2] It was realised very rapidly that reactions of highly fluorinated aromatic systems occur readily with nucleophilic species, rather than electrophiles, and consequently, all of the problems of regioselectivity of nucleophilic aromatic substitution reactions, rates of reaction, control and functionalisation processes began to be addressed. Of course, the literature contains a great deal of information describing familiar electrophilic substitution reactions of hydrocarbon aromatic and heteroaromatic derivatives but research into the chemistry of corresponding perfluorinated aromatic systems has been effectively summarised in a single review article,[1] providing an indication of the vast chemistry of these systems that remains to be explored.

In a developing research programme, we have been utilising simple highly fluorinated aromatic and heteroaromatic 'building blocks' as starting materials for the construction of a variety of macrocycles,[3] glycosyl donors,[4] polyfunctional[5] and ring-fused systems[6–8] and have discussed the application of perfluoroheteroaromatic scaffolds in the drug discovery arena.[5]

In this paper, we present methodology for the synthesis of various ring-fused systems from pentafluorobenzonitrile **1**, a potentially very useful and reactive scaffold that bears multiple, complementary functionality but whose chemistry is relatively unexplored. Only a limited number of reactions involving pentafluorobenzonitrile and several nitrogen[9–11] and oxygen[9] centred nucleophiles have been reported in the literature[1] and, in general, nucleophilic substitution of fluorine located *para* to the cyano group provides access to various 4-substituted tetrafluorobenzonitrile systems.

Potentially, nucleophilic displacement of fluorine atoms and reactions involving the transformation of the cyano group may allow the synthesis of a diverse range of polyfunctional ring-fused heterocycles upon reaction with appropriate difunctional nucleophiles utilising the general strategy outlined in Scheme 1, given that reaction of the first nucleophile may be expected to occur at the site *para* to the cyano group, consistent with earlier findings.




**Scheme 1.** General synthetic strategy for annelation reactions.

## 2. Results and discussion

Reaction of pentafluorobenzonitrile **1** with a range of representative mono- and di-functional nitrogen centred nucleophiles are shown in Scheme 2.

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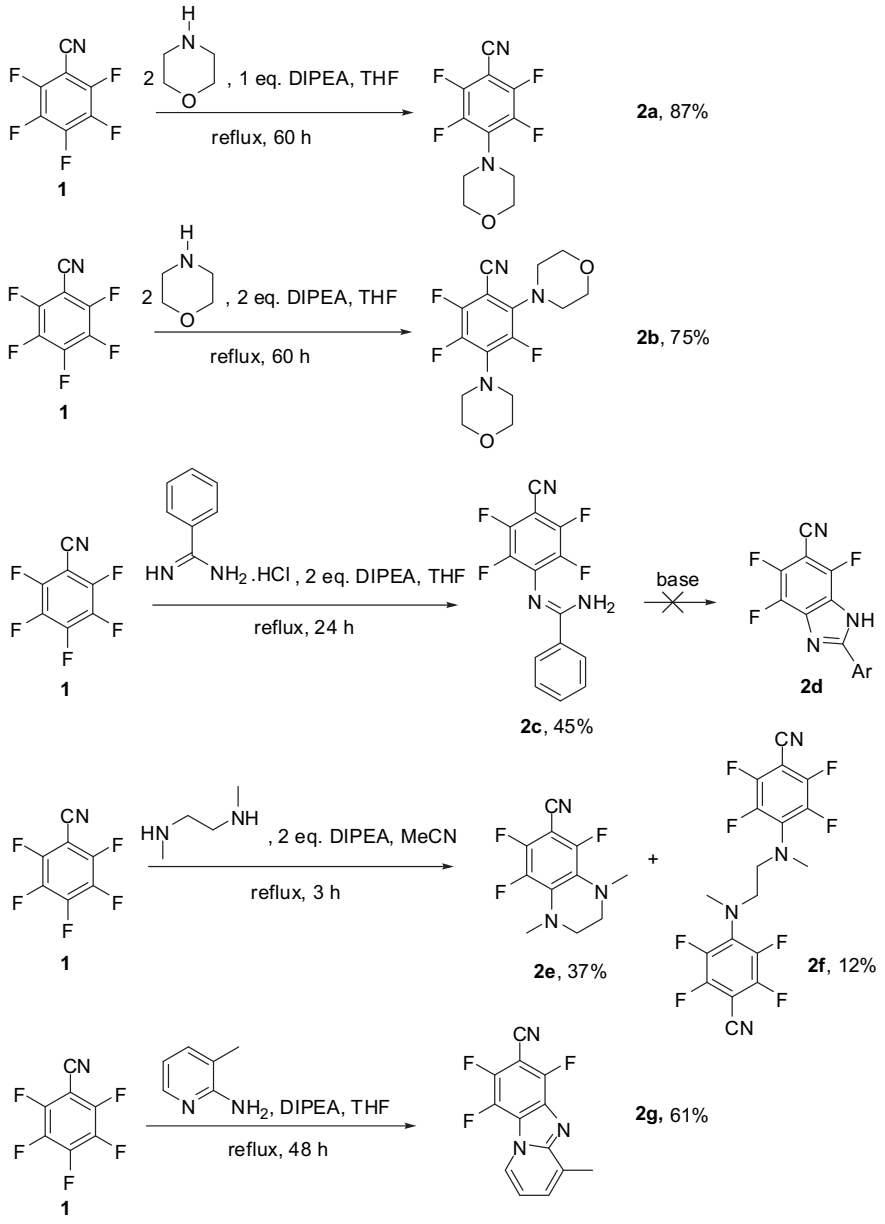



**Scheme 2.** Reactions of pentafluorobenzonitrile **1** with nitrogen centred nucleophiles.

Morpholine and **1** gave product **2a** arising from displacement of fluorine at the site *para* to the cyano group and its structure was confirmed by X-ray crystallography (Fig. 1).

Reaction of **1** with 2 equiv of morpholine gave **2b** where the second substitution was found to be regioselective and occurs at the site *ortho* to the electron withdrawing and, therefore, highly activating, cyano group. The structure of **2b** could be determined by $^{19}$F NMR spectroscopy, which showed three resonances at −134.4, −135.7 and −151.0 ppm in a 1:1:1 ratio. A consideration of the $^{19}$F NMR substituent chemical shifts from literature data[12] and this work, confirmed the structure of **2b**.

After the model reactions described above confirmed that nucleophilic substitution of nitrogen centred nucleophiles occurred at the 4- then 2-positions regioselectively, reactions of **1** with nitrogen centred difunctional nucleophiles were studied. Benzamidine gave **2c**, as confirmed by X-ray crystallography (Fig. 1), but no cyclised product **2d** could be obtained upon reaction of **2c** with various strong bases. In contrast, stronger nucleophiles, *N*,*N*′-dimethylethylene diamine and 2-amino-3-picoline gave ring-fused products **2e** and **2g**, respectively, in good yield. The structures of **2e** and **2g** follow from $^{19}$F NMR studies, in which three resonances are observed as expected, and other spectroscopic techniques are consistent with the structures proposed.

Reaction of the 4-morpholino derivative **2a** with benzamide gave the [6,6]-ring-fused system **3a** (Scheme 3) by reaction of the nitrogen centred nucleophile firstly at the site *ortho* to the ring cyano group, consistent with the regioselectivity of these processes as discussed above, and subsequent reaction with the carbon atom of the cyano group, reminiscent of reactions that we reported earlier involving tetrafluoro-4-cyanopyridine (Scheme 4).[13]

By a similar process, reaction of phenyl hydrazine with **2a** gave [5,6]-fused system **3b** while reaction of **2a** with hydrazine allowed the synthesis of the ring-fused system **3c** whose structure was confirmed by X-ray crystallography (Fig. 2).

Reaction of **2a** with *N*,*N*′-dimethylethylene diamine gave the [6,6]-ring-fused system **3d** arising from annelation of the benzene ring only, reflecting the ease of formation of a six-membered ring in the annelation step rather than a seven-membered ring, which

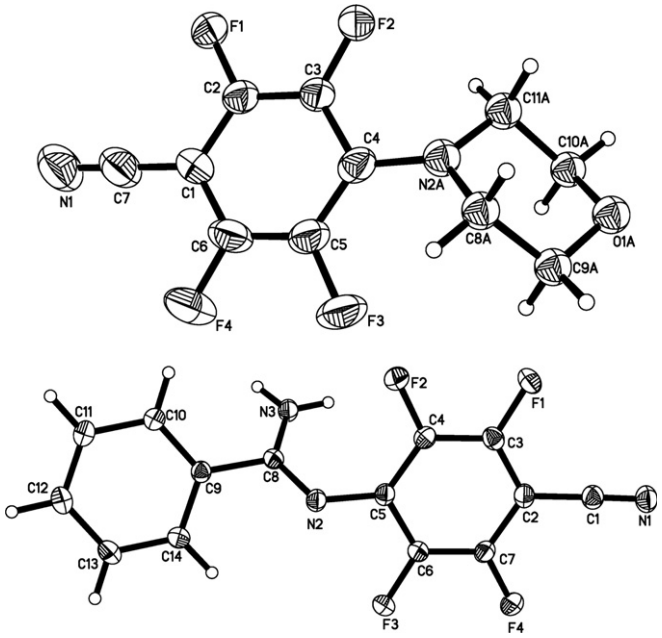
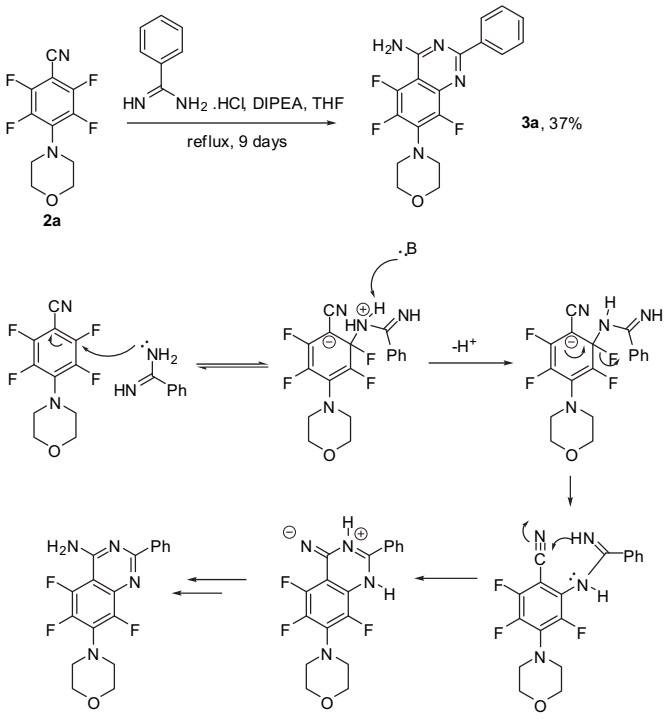



**Figure 1.** Molecular structures of 2,3,5,6-tetrafluoro-4-morpholinobenzonitrile **2a** (above, only one position of the disordered morpholine ring is shown) and (*Z*)-*N*′-(4-cyano-2,3,5,6-tetrafluorophenyl)benzimidamide **2c** (below).




**Scheme 3.** Formation of **3a**.

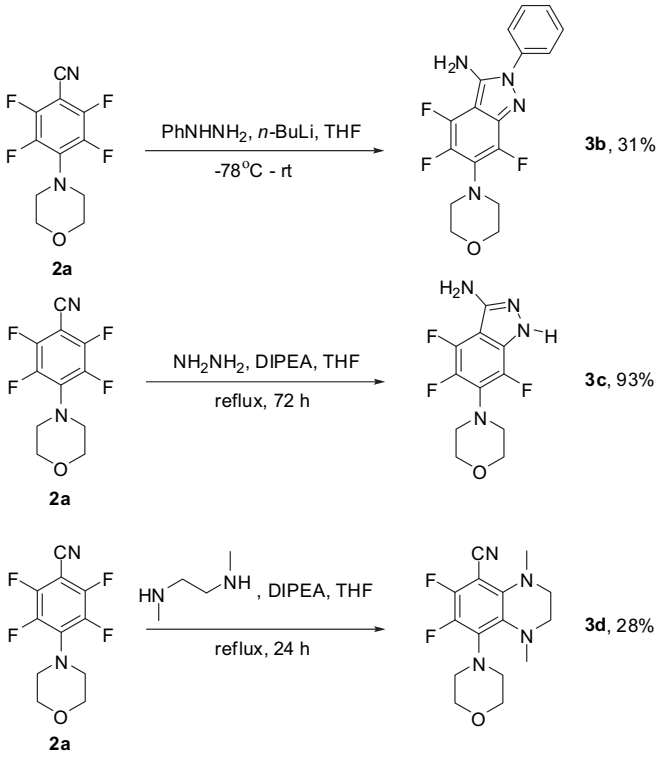
would be formed upon corresponding cyclisation involving the cyano substituent.

In summary, we have demonstrated that pentafluorobenzonitrile **1** may be used very effectively for the synthesis of various [5,6]- and [6,6]-ring-fused systems upon efficient reaction with appropriate difunctional nucleophiles, further illustrating the synthetic possibilities afforded by highly fluorinated heteroaromatic scaffolds for heterocyclic synthesis.

## 3. Experimental

### 3.1. General

All starting materials were obtained commercially (Sigma–Aldrich) and all solvents were dried using standard laboratory procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on Varian VXR NMR spectrometers with




**Scheme 4.** Reactions of 4-morpholino derivative **2a** with difunctional nucleophiles.

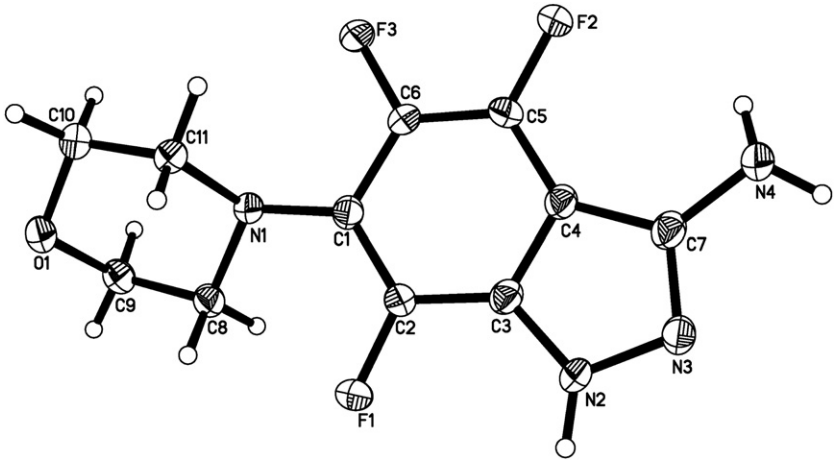



**Figure 2.** Molecular structure of 4,5,7-trifluoro-6-morpholino-1*H*-indazole-3-amine **3c**.

tetramethylsilane and trichlorofluoromethane as internal standards. Assignments were made with the aid of data collected by $^{1}H$–$^{1}H$ COSY and $^{1}H$–$^{13}C$ HETCOR experiments and coupling constants are given in hertz. Mass spectra were recorded on either a VG 7070E spectrometer or a Fisons VG Trio 1000 spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph. Elemental analyses were obtained on either a Perkin–Elmer 240 or a Carlo Erba Elemental Analyser. Melting points were recorded at atmospheric pressure and are uncorrected. Column chromatography was carried out on silica gel (Merck No. 1-09385, 230–400 mesh) and TLC analysis was performed on silica gel TLC plates.

### 3.2. Reactions of pentafluorobenzonitrile 1

*3.2.1. 2,3,5,6-Tetrafluoro-4-morpholinobenzonitrile* ***2a***. Morpholine (0.56 g, 6.4 mmol) was added to a solution of pentafluorobenzonitrile **1** (1.19 g, 6.1 mmol) and DIPEA (0.78 g, 6.0 mmol) in anhydrous acetonitrile (30 mL) under an atmosphere of dry argon and the mixture was heated and stirred under reflux for 12 h. The mixture was allowed to cool to room temperature, poured into water (100 mL) and extracted with DCM (3×40 mL). The combined organic extracts were washed with water and dried ($MgSO_4$). The mixture was filtered, volatiles removed in vacuo and the residue was purified by column chromatography on silica gel using DCM as the eluent to afford *2,3,5,6-tetrafluoro-4-morpholinobenzonitrile* **2a** (1.40 g, 87%) as a white solid, mp 78–79 °C; $R_f$ (DCM) 0.3; IR 2968, 2861, 2236, 1648, 1524 $cm^{-1}$; $^{1}H$ NMR (500 MHz, $CDCl_3$) $\delta$ 3.40–3.44 (4H, m, $NCH_2CH_2O$), 3.80–3.85 (4H, m, $NCH_2CH_2O$); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$ 51.1 (t, $^{4}J_{CF}$=4.4 Hz, $NCH_2CH_2O$), 67.2 (s, $NCH_2CH_2O$), 84.5 (tt, $^{2}J_{CF}$=8.8 Hz, $^{3}J_{CF}$=1.7 Hz, 1-*C*), 108.5 (t, $^{3}J_{CF}$=3.4 Hz, *C*N), 135.6 (tt, $^{2}J_{CF}$=9.4 Hz, $^{3}J_{CF}$=2.9 Hz, 4-*C*), 140.7 (dddd, $^{1}J_{CF}$=245 Hz, $^{2}J_{CF}$=13.8 Hz, $^{3}J_{CF}$=6.3 Hz, $^{4}J_{CF}$=4.1 Hz, 3-*C*), 148.4

(dddd, $^1J_{CF}$=245 Hz, $^2J_{CF}$=14.5 Hz, $^3J_{CF}$=6.3 Hz, $^4J_{CF}$=3.8 Hz, 2-*C*); $^{19}$F NMR (658 MHz, $CFCl_3$) $\delta$ −134.4 (2F, m, 2-*F*), −149.8 (2F, m, 3-*F*); GC–MS (probe) 70 eV *m*/*z* (rel int.): 260 $[M]^+$ (38), 202 (100), 201 (80), 174 (18), 124 (22). Anal. Calcd for $C_{11}H_8N_2OF_4$: C, 50.78; H, 3.10; N, 10.77. Found C, 50.72; H, 3.14; N, 10.90%.

*3.2.2. 2,3,5-Trifluoro-4,6-dimorpholinobenzonitrile* ***2b***. Morpholine (0.65 g, 7.4 mmol) was added to a solution of pentafluorocyanobenzene (0.57 g, 2.95 mmol) and DIPEA (0.92 g, 7.2 mmol) in anhydrous acetonitrile (30 mL) under an atmosphere of dry argon. The mixture was heated and stirred under reflux for 60 h. The mixture was allowed to cool to room temperature, poured into water (100 mL) and extracted with DCM (3×40 mL). The combined organic extracts were washed with water and dried ($MgSO_4$). The mixture was filtered, volatiles evaporated and the residue purified by column chromatography on silica gel using hexane and ethyl acetate (7:3) as the eluent to afford *2,3,5-trifluoro-4,6-dimorpholinobenzonitrile* **2b** (0.72 g, 75%) as a white solid, mp 125–126 °C; $R_f$ (hexane/ethyl acetate, 7:3) 0.4; IR 2363, 1650, 1494 $cm^{-1}$; $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 3.20–3.28 (4H, m, $CH_2$), 3.28–3.36 (4H, m, $CH_2$), 3.70–3.82 (8H, m, $CH_2$); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 51.3 (t, $^4J_{CF}$=3.6 Hz, $NCH_2CH_2O$), 52.1 (d, $^4J_{CF}$=4.4 Hz, $NCH_2CH_2O$), 67.5 (s, $NCH_2CH_2O$), 67.7 (s, $NCH_2CH_2O$), 91.9 (m, 1-*C*), 112.4 (m, *C*N), 134.9 (t, $^2J_{CF}$=11.0 Hz, 4-*C*), 138.7 (d, $^2J_{CF}$=14.3 Hz, 6-*C*), 141.0 (ddd, $^1J_{CF}$=247 Hz, $^2J_{CF}$=13.3 Hz, $^3J_{CF}$=6.7 Hz, 3-*C*), 148.4 (dm, $^1J_{CF}$=246 Hz, 5-*C*), 149.7 (dm, $^1J_{CF}$=247 Hz, 2-*C*); $^{19}$F NMR (658 MHz, $CFCl_3$) $\delta$ −134.4 (1F, dd, $^3J_{FF}$=20.7 Hz, $^5J_{FF}$=9.8 Hz, 2-*F*), −135.7 (1F, br s, 5-*F*), −151.0 (1F, d, $^3J_{FF}$=20.7, 3-*F*); GC–MS (probe) 70 eV *m*/*z* (rel int.): 327 $[M]^+$ (86), 269 (52), 211 (100), 184 (59), 157 (18). Anal. Calcd for $C_{15}H_{16}N_3O_2F_3$: C, 55.04; H, 4.93; N, 12.84. Found C, 55.10; H, 4.98; N, 12.77%.

*3.2.3. (Z)-N′-(4-Cyano-2,3,5,6-tetrafluorophenyl)benzimidamide* ***2c***. Benzamidine hydrochloride (0.95 g, 6.1 mmol) was added to a solution of pentafluorocyanobenzene (1.08 g, 5.6 mmol) and DIPEA (1.49 g, 11.5 mmol) in anhydrous acetonitrile (30 mL) under an atmosphere of dry argon. The mixture was heated and stirred under reflux for 24 h. The mixture was allowed to cool to room temperature, poured into water (100 mL) and extracted with DCM (3×40 mL). The combined organic extracts were washed with water and dried ($MgSO_4$). The mixture was filtered, volatiles evaporated and the residue purified by column chromatography on silica gel using hexane and THF (7:3) as the eluent to afford *(Z)-N′-(4-cyano-2,3,5,6-tetrafluorophenyl)benzimidamide* **2c** (0.73 g, 45%) as a white solid, mp 164–165 °C; $R_f$ 0.3 (hexane/THF, 7:3); IR 3432, 2238, 1640, 1591, 1568 $cm^{-1}$; $^1$H NMR (700 MHz, $d_6$-DMSO) $\delta$ 7.15 (1H, br s, N*H*), 7.47 (2H, dd, $^3J_{HH}$=7.7, 7.7 Hz, 3′-*H*), 7.54 (1H, t, $^3J_{HH}$=7.7 Hz, 4′-*H*), 7.89, (1H, br s, N*H*), 7.92 (2H, d, $^3J_{HH}$=7.7 Hz, 2′-*H*); $^{13}$C NMR (176 MHz, DMSO-$d_6$) $\delta$ 84.0 (t, $^2J_{CF}$=17.8 Hz, 4-*C*), 109.5 (s, *C*N), 128.0 (s, 2′-*C*), 128.8 (s, 3′-*C*), 131.8 (s, 4′-*C*), 134.1 (s, 1′-*C*), 138.1 (t, $^2J_{CF}$=14.4 Hz, 1-*C*), 140.2 (dm, $^1J_{CF}$=243 Hz, 3-*C*), 147.8 (dm, $^1J_{CF}$=255 Hz, 2-*C*), 159.1 (s, NH*C*NH); $^{19}$F NMR (658 MHz, $CFCl_3$) $\delta$ −137.4 (m, Ar–*F*), −149.7 (m, Ar–*F*); GC–MS (probe) 70 eV *m*/*z* (rel int.): 293 $[M]^+$ (58), 274 (59), 216 (15), 124 (20), 104 (36), 77 (100), 51 (34). Anal. Calcd for $C_{14}H_7N_3F_4$: C, 57.35; H, 2.41; N, 14.33. Found C, 57.20; H, 2.42; N, 14.09%.

*3.2.4. 5,7,8-Trifluoro-1,4-dimethyl-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile* ***2e*** *and 4,4′-(ethane-1,2-diylbis(methylazanediyl))bis(2,3,5,6-tetrafluorobenzonitrile)* ***2f***. *N,N′*-Dimethylethylene diamine (0.60 g, 6.8 mmol) was added to a solution of pentafluorocyanobenzene (1.19 g, 6.2 mmol) and DIPEA (2.02 g, 15.6 mmol) in anhydrous acetonitrile (30 mL) under an atmosphere of dry argon. The mixture was heated and stirred under reflux for 3 h. The mixture was allowed to cool to room temperature, poured into water (100 mL) and extracted with DCM (3×40 mL). The combined organic extracts were washed with water and dried ($MgSO_4$). The mixture was filtered, volatiles evaporated and the residue purified by column chromatography on silica gel using DCM and hexane (9:1) as the eluent to afford *5,7,8-trifluoro-1,4-dimethyl-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile* **2e** (0.55 g, 37%) as an off-white solid, mp 112–113 °C; $R_f$ 0.6 (DCM/hexane, 9:1); IR $\nu$ 2221, 1640, 1529, 1494 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 2.75 (3H, br s, $CH_3$), 3.00 (2H, t, $^3J_{HH}$=4.8 Hz, $CH_2$), 3.22 (3H, d, $^5J_{HF}$=4.9 Hz, $CH_3$), 3.26 (2H, t, $^3J_{HH}$=4.8 Hz, $CH_2$); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 42.2 (d, $^4J_{CF}$=13.4 Hz, $CH_3$), 43.5 (d, $^4J_{CF}$=5.6 Hz, $CH_3$), 46.4 (s, $CH_2$), 47.9 (s, $CH_2$), 79.6 (ddd, $^2J_{CF}$=18.7, 17.1 Hz, $^3J_{CF}$=2.1 Hz, 6-*C*), 110.6 (d, $^3J_{CF}$=3.4 Hz, *C*N), 122.3 (ddd, $^2J_{CF}$=12.4 Hz, $^3J_{CF}$=3.5 Hz, $^4J_{CF}$=2.6 Hz, 4b-*C*), 135.9 (ddd, $^2J_{CF}$=7.2 Hz, $^3J_{CF}$=5.8 Hz, $^4J_{CF}$=3.8 Hz, 4a-*C*), 136.9 (ddd, $^1J_{CF}$=243 Hz, $^2J_{CF}$=14.3 Hz, $^4J_{CF}$=2.9 Hz, 8-*C*), 147.1 (ddd, $^1J_{CF}$=252 Hz, $^2J_{CF}$=15.0 Hz, $^3J_{CF}$=8.4 Hz, 7-*C*), 151.4 (ddd, $^1J_{CF}$=252 Hz, $^3J_{CF}$=6.2 Hz, $^4J_{CF}$=1.1 Hz, 5-*C*); $^{19}$F NMR (658 MHz, $CFCl_3$) $\delta$ −123.5 (1F, dd, $^4J_{FF}$=4.6 Hz, $^5J_{FF}$=8.2 Hz, 5-*F*), −139.8 (1F, dd, $^3J_{FF}$=20.2 Hz, $^4J_{FF}$=4.6 Hz, 7-*F*), −155.9 (1F, ddq, $^3J_{FF}$=20.2 Hz, $^5J_{HF}$=4.9, 8.2 Hz, 8-*F*); GC–MS (probe) 70 eV *m*/*z* (rel int.): 241 $[M]^+$ (100), 226 (70), 211 (25), 170 (57), 42 (20). Anal. Calcd for $C_{11}H_{10}N_3F_3$: C, 54.77; H, 4.18; N, 17.42. Found: C, 54.59; H, 4.02; N, 17.47%; and *4,4′-(ethane-1,2-diylbis(methylazanediyl))bis(2,3,5,6-tetrafluorobenzonitrile)* **2f** (0.33 g, 12%) as a white solid; mp 155–156 °C; $R_f$ 0.25 (DCM/hexane, 9:1); IR $\nu$ 2236, 1640, 1520, 1494 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 3.07 (6H, t, $^5J_{HF}$=2.9 Hz, $CH_3$), 3.58 (4H, s, $CH_2$); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 40.9 (t, $^4J_{CF}$=5.2 Hz, $CH_3$), 52.8 (s, $CH_2$), 84.0 (tt, $^2J_{CF}$=17.5 Hz, $^3J_{CF}$=1.3 Hz, 4-*C*), 108.1 (t, $^3J_{CF}$=3.5 Hz, *C*N), 135.5 (tt, $^2J_{CF}$=9.7 Hz, $^3J_{CF}$=2.8 Hz, 1-*C*), 140.3 (dddd, $^1J_{CF}$=245 Hz, $^2J_{CF}$=10.2 Hz, $^3J_{CF}$=5.7 Hz, $^4J_{CF}$=3.7 Hz, 3-*C*), 148.2 (dddd, $^1J_{CF}$=259 Hz, $^2J_{CF}$=15.1 Hz, $^3J_{CF}$=7.0 Hz, $^4J_{CF}$=4.1 Hz, 2-*C*); $^{19}$F NMR (658 MHz, $CFCl_3$) $\delta$ −134.0–134.2 (4F, m, Ar–*F*), −149.8–150.1 (4F, m, Ar–*F*); GC–MS (probe) 70 eV *m*/*z* (rel int.): 434 $[M]^+$ (1), 231 (15), 217 (100), 201 (20), 188 (10). Anal. Calcd for $C_{18}H_{10}N_4F_8$: C, 49.78; H, 2.32; N, 12.90. Found: C, 49.66; H, 2.30; N, 12.96%.

*3.2.5. 6,8,9-Trifluoro-4-methyl-benzo[4,5]imidazo[1,2-α]pyridine-7-carbonitrile* ***2g***. 2-Amino-3-picoline (0.45 g, 4.2 mmol) was added to a solution of pentafluorocyanobenzene (0.85 g, 4.4 mmol) and DIPEA (0.55 g, 4.26 mmol) in anhydrous acetonitrile (30 mL) under an atmosphere of dry argon. The mixture was heated and stirred under reflux for 48 h. The mixture was allowed to cool to room temperature, poured into water (100 ml) and extracted with DCM (3×40 mL). The combined organic extracts were washed with water and dried ($MgSO_4$). The mixture was filtered, volatiles evaporated and the residue purified by column chromatography on silica gel using hexane and ethyl acetate (1:1) as the eluent to afford *6,8,9-trifluoro-4-methyl-benzo[4,5]imidazo[1,2-α]pyridine-7-carbonitrile* **2g** (0.66 g, 61%) as a yellow solid, mp 211–212 °C; $R_f$ 0.4 (hexane/ethyl acetate, 1:1); IR $\nu$ 2235, 1650, 1550 $cm^{-1}$; $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 2.70 (3H, s, $CH_3$), 6.95 (1H, t, $^3J_{HH}$=6.9 Hz, 2-*H*), 7.36–7.40 (1H, m, 3-*H*), 8.54 (1H, d, $^3J_{HH}$=6.9 Hz, 1-*H*); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 17.7 (s, $CH_3$), 89.2 (t, $^2J_{CF}$=18.1 Hz, 7-*C*), 109.5 (d, $^3J_{CF}$=3.0 Hz, *C*N), 113.6 (s, 2-*C*), 123.0 (m, Ar–*C*), 125.2 (d, $^4J_{CF}$=6.7 Hz, 1-*C*), 129.3 (s, 4-*C*), 130.2 (s, 3-*C*), 130.7 (d, $^2J_{CF}$=17.7 Hz, Ar–*C*), 135.9 (ddd, $^1J_{CF}$=252 Hz, $^2J_{CF}$=16.8 Hz, $^4J_{CF}$=5.5 Hz, 9-*C*), 143.3 (ddd, $^1J_{CF}$=253 Hz, $^2J_{CF}$=14.0 Hz, $^3J_{CF}$=3.6 Hz, 8-*C*), 151 (ddd, $^1J_{CF}$=269 Hz, $^3J_{CF}$=3.4 Hz, $^4J_{CF}$=3.4 Hz, 6-*C*), 151.4 (s, 4a-*C*); $^{19}$F NMR (658 MHz, $CFCl_3$) $\delta$ −119.9 (1F, dd, $^3J_{FF}$=19.5 Hz, $^4J_{FF}$=6.2 Hz, Ar–*F*), −141.2 (1F, dd, $^3J_{FF}$=19.5 Hz, $^4J_{FF}$=6.2 Hz, Ar–*F*), −141.2 (1F, dd, $^3J_{FF}$=19.5 Hz, $^5J_{FF}$=19.5, 9-*F*); GC–MS (probe) 70 eV *m*/*z* (rel int.): 261 $[M]^+$ (100), 208 (9), 155 (11), 105 (12), 51 (42). Anal. Calcd for $C_{13}H_6N_3F_3$: C, 59.78; H, 2.32; N, 16.09. Found: C, 59.58; H, 2.36; N, 15.95%.

### 3.3. Reactions of 2,3,5,6-tetrafluoro-4-morpholinobenzonitrile 2a

*3.3.1. 5,6,8-Trifluoro-7-morpholino-2-phenylquinazolin-4(3H)-imine* ***3a***. Benzamidine hydrochloride (0.47 g, 3.0 mmol) was added to

a solution of 2,3,5,6-tetrafluoro-4-morpholinobenzonitrile **2a** (0.72 g, 2.8 mmol) and DIPEA (0.41 g, 3.2 mmol) in anhydrous acetonitrile (30 mL) under an atmosphere of dry argon. The mixture was heated and stirred under reflux for nine days. The mixture was allowed to cool to room temperature, poured into water (100 mL) and extracted with DCM (3×40 mL). The combined organic extracts were washed with water and dried ($MgSO_4$). The mixture was filtered, volatiles evaporated and the residue purified by column chromatography on silica gel using hexane and ethyl acetate (7:3) as the eluent to afford *5,6,8-trifluoro-7-morpholino-2-phenylquinazolin-4(3H)-imine* **3a** (0.370 g, 37%) as a white solid, mp 227–228 °C; $R_f$ 0.4 (hexane/ethyl acetate, 7:3); IR $\nu$ 3515, 3311, 3213, 2863, 1631, 1569 $cm^{-1}$; $^1H$ NMR (700 MHz, DMSO-$d_6$) $\delta$ 3.31 (4H, t, $^3J_{HH}$=4.2 Hz, NC$H_2$CH$_2$O), 3.70 (4H, t, $^3J_{HH}$=4.2 Hz, NCH$_2$C$H_2$O), 7.30 (1H, br s, N*H*), 7.42–7.50 (3H, m, Ar–*H*), 8.07 (1H, br s, N*H*), 8.38–8.42 (2H, m, Ar–*H*); $^{13}C$ NMR (176 MHz, DMSO-$d_6$) $\delta$ 51.1 (s, NCH$_2$CH$_2$O), 67.1 (s, NCH$_2$CH$_2$O), 98.6 (d, $^2J_{CF}$=10.0 Hz, 4a-*C*), 128.2 (s, Ar–*C*), 128.7 (s, Ar–*C*), 130.8 (s, Ar–*C*), 132.2 (t, $^2J_{CF}$=11.3 Hz, 7-*C*), 138.1 (s, Ar–*C*), 138.6 (d, $^2J_{CF}$=12.0 Hz, 8a-*C*), 141.9 (ddd,$^1J_{CF}$=246 Hz, $^2J_{CF}$=14.5 Hz, $^3J_{CF}$=6.9 Hz, F–*C*), 143.1 (ddd, $^1J_{CF}$=252 Hz, $^2J_{CF}$=14.1 Hz, $^3J_{CF}$=2.7 Hz, F–*C*), 146.2 (d, $^1J_{CF}$=248 Hz, 8-*C*), 159.2 (s, Ar–*C*), 160.7 (s, Ar–*C*); $^{19}F$ NMR (658 MHz, $CFCl_3$) $\delta$ −140.4 (1F, d, $^5J_{FF}$=15.0 Hz, 8-*F*), −142.2 (1F, dd, $^3J_{FF}$=20.8 Hz, $^5J_{FF}$=15.0 Hz, 5-*F*), −149.3 (1F, d, $^3J_{FF}$=20.8 Hz, 6-*F*); GC–MS (probe) 70 eV *m*/*z* (rel int.): 360 $[M]^+$ (85), 302 (100), 199 (18), 151 (30), 77 (24). Anal. Calcd for $C_{18}H_{15}N_4F_3O$: C, 60.00; H, 4.20; N, 15.55. Found: C, 59.70; H, 4.23; N, 15.48%.

*3.3.2. 4,5,7-Trifluoro-6-morpholino-2-phenyl-2H-indazol-3-amine* ***3b***. Phenylhydrazine (0.30 g, 2.8 mmol) in anhydrous THF (10 mL) was cooled to −78 °C under an atmosphere of dry argon, which was maintained throughout the experiment. To the cooled solution *n*-BuLi (0.15 g, 2.3 mmol, 1.6 M in hexanes) was added in a dropwise manner with stirring, followed by the addition of a solution of 2,3,5,6-tetrafluoro-4-morpholinobenzonitrile (0.50 g, 1.9 mmol) in anhydrous THF (20 mL). The reaction mixture was allowed to warm to room temperature with stirring, poured into water (100 mL) and extracted with DCM (3×40 mL). The combined organic extracts were washed with water and dried ($MgSO_4$). The mixture was filtered, volatiles evaporated and the residue purified by column chromatography on silica gel using hexane and ethyl acetate (7:3) as the eluent to afford *4,5,7-trifluoro-6-morpholino-2-phenyl-2H-indazol-3-amine* **3b** (0.21 g, 31%) as an off-white solid, mp 178–179 °C; $R_f$ 0.3 (hexane/ethyl acetate, 7:3); IR $\nu$ 3330, 3226, 2362, 1646 $cm^{-1}$; $^1H$ NMR (700 MHz, $CDCl_3$) $\delta$ 3.25 (4H, t, $^3J_{HH}$=4.6 Hz, NC$H_2$CH$_2$O), 3.80 (4H, t, $^3J_{HH}$=4.6 Hz, NCH$_2$C$H_2$O), 4.32 (2H, s, N$H_2$), 7.31 (1H, tt, $^3J_{HH}$=7.2 Hz, $^4J_{HH}$=1.3 Hz, NCCHCHC*H*), 7.41–7.48 (4H, m, Ar–*H*); $^{13}C$ NMR (176 MHz, $CDCl_3$) $\delta$ 51.6 (t, $^4J_{CF}$=3.3 Hz, NCH$_2$CH$_2$O), 67.5 (s, NCH$_2$CH$_2$O), 103.2 (ddd, $^2J_{CF}$=21.0 Hz, $^3J_{CF}$=6.1 Hz, $^4J_{CF}$=2.6 Hz, 3a-*C*), 124.3 (s, Ar–*C*), 126.8 (s, Ar–*C*), 127.2 (m, Ar–*C*), 128.7 (s, Ar–*C*), 129.0 (t, $^2J_{CF}$=12.9 Hz, 6-*C*), 138.6 (dm, $^1J_{CF}$=241 Hz, F–*C*), 139.6 (dm, $^1J_{CF}$=252 Hz, F–*C*), 139.9 (dm, $^1J_{CF}$=250 Hz, F–*C*), 140.0 (s, Ar–*C*), 147.9 (s, 3-*C*); $^{19}F$ NMR (658 MHz, $CFCl_3$) $\delta$ −139.1 (1F, d, $^5J_{FF}$=18.4 Hz, 7-*F*), −152.6 (1F, dd, $^3J_{FF}$=20.6 Hz, $^5J_{FF}$=18.4 Hz, 4-*F*), −156.0 (1F, d, $^3J_{FF}$=20.4, 5-*F*); GC–MS (probe) 70 eV *m*/*z* (rel int.): 348 $[M]^+$ (88), 290 (91), 213 (13), 185 (19), 77 (100). Anal. Calcd for $C_{17}H_{15}N_4F_3O$: C, 58.62; H, 4.34; N, 16.08. Found: C, 58.35; H, 4.44; N, 16.15%.

*3.3.3. 4,5,7-Trifluoro-6-morpholino-1H-indazol-3-amine* ***3c***. Hydrazine monohydrate (0.340 g, 6.79 mmol) was added to a solution of 2,3,5,6-tetrafluoro-4-morpholinobenzonitrile (0.950 g, 3.65 mmol) and DIPEA (0.64 g, 4.95 mmol) in anhydrous acetonitrile (30 mL) under an atmosphere of dry argon, which was maintained throughout the experiment. The reaction mixture heated, with stirring, to reflux for a period of 72 h, after which time complete conversion of starting materials was observed by $^{19}F$ NMR spectroscopy. The reaction mixture was allowed to cool to room temperature, poured into water (100 ml) and extracted with DCM (3×40 mL). The combined organic extracts were washed with water and dried ($MgSO_4$). The mixture was filtered, volatiles removed in vacuo and purified by column chromatography on silica gel using hexane and ethyl acetate (2:1) as the eluent to afford pure *4,5,7-trifluoro-6-morpholino-1H-indazol-3-amine* **3c** (0.92 g, 93%) as a white solid, mp 188–189 °C; $R_f$ 0.35 (hexane/ethyl acetate, 2:1); IR $\nu$ 3434, 3260, 3201, 2920, 2362 $cm^{-1}$; $^1H$ NMR (700 MHz, DMSO-$d_6$) $\delta$ 3.20–3.38 (4H, m, NC$H_2$CH$_2$O), 3.75 (4H, t, $^3J_{HH}$=4.6 Hz, NCH$_2$C$H_2$O), 5.35 (2H, br s, N$H_2$), 12.2 (1H, br s, N*H*); $^{13}C$ NMR (176 MHz, DMSO-$d_6$) $\delta$ 51.3 (s, NC$H_2$CH$_2$O), 66.7 (s, NCH$_2$C$H_2$O), 100.5 (m, 3a-*C*), 126.4 (t, $^2J_{CF}$=11.4 Hz, 6-*C*), 129.4–129.6 (m, 7a-*C*), 138.2 (dm, $^1J_{CF}$=246 Hz, F–*C*), 138.5 (dm, $^1J_{CF}$=235 Hz, F–*C*), 139.6 (dm, $^1J_{CF}$=241 Hz, F–*C*), 148.1–148.3 (m, 3–*C*); $^{19}F$ NMR (658 MHz, $CFCl_3$) $\delta$ −147.9 (1F, d, $^5J_{FF}$=18.8 Hz, 7-*F*), −153.0 (1F, dd, $^3J_{FF}$=19.8 Hz, $^5J_{FF}$=18.8 Hz, 4-*F*), −160.3 (1F, d, $^3J_{FF}$=19.8 Hz, 5-*F*); GC–MS (probe) 70 eV *m*/*z* (rel int.): 272 $[M]^+$ (33), 214 (100), 185 (23), 28 (72). Anal. Calcd for $C_{11}H_{11}N_4F_3O$: C, 48.53; H, 4.07; N, 20.58. Found: C, 48.23; H, 4.07; N, 20.24%.

*3.3.4. 6,7-Difluoro-1,4-dimethyl-8-morpholino-1,2,3,4-tetrahydroquinoxaline-5-carbonitrile* ***3d***. *N,N′*-Dimethylethylene diamine (0.210 g, 2.38 mmol) was added to a solution of 2,3,5,6-tetrafluoro-4-morpholinobenzonitrile (0.640 g, 2.46 mmol) and DIPEA (0.63 g, 4.90 mmol) in anhydrous THF (30 mL) under an atmosphere of dry argon. The mixture was heated and stirred under reflux for 24 h, after which time complete consumption of pentafluorocyanobenzene was observed by $^{19}F$ NMR spectroscopy. The mixture was allowed to cool to room temperature, poured into water (100 mL) and extracted with DCM (3×40 mL). The combined organic extracts were washed with water and dried ($MgSO_4$). The mixture was filtered, volatiles removed in vacuo and purified by column chromatography on silica gel using hexane and ethyl acetate (1:1) as the eluent to afford *6,7-difluoro-1,4-dimethyl-8-morpholino-1,2,3,4-tetrahydroquinoxaline-5-carbonitrile* (0.210 g, 28%) as a white solid, mp 132–133 °C; $R_f$ 0.5 (hexane/ethyl acetate, 9:1); IR $\nu$ 2851, 2961, 2219, 1600, 1450, 1109 $cm^{-1}$; $^1H$ NMR (700 MHz, $CDCl_3$) $\delta$ 2.72 (3H, s, C$H_3$), 2.92 (2H, t, $^3J_{HH}$=4.8 Hz, NC$H_2$CH$_2$N), 3.16 (2H, t, $^3J_{HH}$=4.8 Hz, NCH$_2$C$H_2$N), 3.19 (3H, s, C$H_3$), 3.31 (4H, br s, NC$H_2$CH$_2$O), 3.78 (4H, t, $^3J_{HH}$=4.5 Hz, NCH$_2$C$H_2$O); $^{13}C$ NMR (176 MHz, $CDCl_3$) $\delta$ 41.7 (s, C$H_3$), 44.0 (s, C$H_3$), 45.4 (s, NC$H_2$CH$_2$N), 46.7 (s, NC$H_2$CH$_2$N), 50.1 (d, $^4J_{CF}$=5.1 Hz, NCH$_2$CH$_2$O), 67.6 (s, NCH$_2$C$H_2$O), 84.0 (d, $^2J_{CF}$=15.8 Hz, 5-*C*), 114.5 (d, $^3J_{CF}$=2.7 Hz, *C*N), 128.8 (s, 4a-*C*), 138.14 (dd, $^2J_{CF}$=7.5 Hz, $^3J_{CF}$=2.4 Hz, 8-*C*), 139.6 (dd, $^1J_{CF}$=250 Hz, $^2J_{CF}$=14.0 Hz, 7-*C*), 141.5 (d, $^3J_{CF}$=3.7 Hz, 4b-C), 149.3 (dd, $^1J_{CF}$=250 Hz, $^2J_{CF}$=15.8 Hz, 6-*C*); $^{19}F$ NMR (658 MHz, $CFCl_3$) $\delta$ −137.3 (1F, br s, Ar–*F*), −158.1 (1F, m, Ar–*F*); GC–MS (probe) 70 eV *m*/*z* (rel int.): 308 $[M]^+$ (100), 234 (65), 220 (38), 208 (41). Anal. Calcd for $C_{15}H_{18}N_4F_2O$: C, 58.43; H, 5.88; N, 18.17. Found: C, 58.23; H, 5.89; N, 18.15%.

### 3.4. X-ray structures

Single crystal X-ray data were collected on Bruker SMART 6000 (**2a** and **3d**) and Rigaku Spider IP (**2c**) diffractometers equipped with Cryostream (Oxford Cryosystems) nitrogen coolers at 120 K using graphite monochromated MoK$\alpha$ radiation ($\lambda$=0.71073 Å, $\omega$-scan). All structures were solved by direct methods and refined by full-matrix least squares on $F^2$ for all data using Olex2 software. All non-disordered non-hydrogen atoms were refined with anisotropic displacement parameters, non-disordered H-atoms were located on the difference map and refined isotropically.

Crystallographic data for structures **2a**, **2c** and **3c** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 751884–751886.

*3.4.1. Crystal data for* ***2a****.* $C_{11}H_8F_4N_2O$, $M$=260.19, orthorhombic, space group $Pna2_1$, $a$=16.0178(4), $b$=7.5162(2), $c$=9.0124(2) Å, $U$=1085.03(5) Å$^3$, $F$(000)=528, $Z$=4, $D_c$=1.593 mg m$^{-3}$, $\mu$=0.151 mm$^{-1}$. 11,904 reflections yielded 1322 unique data ($R_{merg}$=0.0624). Final $wR_2(F^2)$=0.1629 for all data (157 refined parameters), conventional $R_1(F)$=0.0525 for 950 reflections with $I>2\sigma$, GOF=1.039.

*3.4.2. Crystal data for* ***2c****.* $C_{11}H_8F_4N_2O$, $M$=293.23, monoclinic, space group $P2_1/c$, $a$=12.8354(4), $b$=8.9702(3), $c$=10.6272(4) Å, $\beta$=91.05(1)°, $U$=1223.37(7) Å$^3$, $F$(000)=592, $Z$=4, $D_c$=1.592 mg m$^{-3}$, $\mu$=0.141 mm$^{-1}$. 22,102 reflections yielded 3572 unique data ($R_{merg}$=0.0521). Final $wR_2(F^2)$=0.1215 for all data (218 refined parameters), conventional $R_1(F)$=0.0423 for 3261 reflections with $I>2\sigma$, GOF=1.095.

*3.4.3. Crystal data for* ***3c****.* $C_{11}H_{11}F_3N_4O$, $M$=272.24, monoclinic, space group $P2_1/n$, $a$=4.2181(2), $b$=16.4277(7), $c$=15.3824(7) Å, $\beta$=90.78(2)°, $U$=1135.09(9) Å$^3$, $F$(000)=560, $Z$=4, $D_c$=1.593 mg m$^{-3}$, $\mu$=0.141 mm$^{-1}$. 1178 reflections yielded 2756 unique data ($R_{merg}$=0.0710). Final $wR_2(F^2)$=0.1315 for all data (216 refined parameters), conventional $R_1(F)$=0.0507 for 1748 reflections with $I>2\sigma$, GOF=1.059.

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