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Synthesis of fluorinated 3-aminobenzofurans *via* a tandem S_NAr-cyclocondensation strategy†

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A small library of twenty-seven novel 3-amino-2,6-disubstituted-4,5,7-trifluorobenzofurans was successfully synthesized with the compounds formed in low to good yield using a tandem S_NAr-cyclocondensation reaction of 4-substituted perfluorobenzonitriles with α-hydroxycarbonyl compounds employing DBU as base. The compounds were prepared as part of a medicinal chemistry project to develop novel fluorinated heterocyclic leads and were characterised by ^1H and ^{19}F NMR spectroscopy, IR spectroscopy, high resolution mass spectrometry and elemental analysis. The X-ray crystal structure of the 2-(4-methoxybenzoyl)-6-morpholino derivative was determined, which showed the benzoyl substituent to be coplanar with the benzofuran ring, and to form a hydrogen bond to the 3-amino group. Attempts to synthesise the corresponding 3-unsubstituted or 3-methyl analogues using 4-substituted perfluoro-benzaldehydes or acetophenones were unsuccessful, with cleavage of the carbonyl group occurring. A mechanistic study indicated that alkoxide ions attacked the carbonyl group, rather than effecting S_NAr reaction at C-2, leading to loss of a perfluoroaryl anion which was trapped with D_2O.

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Introduction

Benzofurans are an important class of heterocyclic compound and have found diverse application in medicinal chemistry as antibacterial, antimicrobial, anti-ulcer and antimalarial agents,[1] and as ischemic cell death inhibitors.[2] Methods to prepare both synthetic[3,4] and naturally occurring[5] benzofurans have been reviewed recently. As part of a programme to develop new leads based on polyfluorinated scaffolds, we have applied our general approach to the rapid construction of fluorinated heterocycles through the use of reliable S_NAr reactions of perfluorinated arene building blocks to effect easy annelation of a new heteroatom ring. Having demonstrated this strategy in the synthesis of benzothiophene[6] derivatives, in this paper we report the preparation of polyfluorinated benzofuran derivatives. The presence of fluorine imparts desirable properties for drug development, and also allows additional functionalisation through further S_NAr reaction.

Results and discussion

The synthesis of the benzofuran targets first required the preparation of 4-substituted tetrafluorobenzonitrile derivatives **2** (Scheme 1). Sandford and co-workers have shown[7] that nucleophilic substitution in pentafluorobenzonitrile **1** occurred regioselectively, at first the 4-, and then the 2-position, and reported the synthesis of the 4-morpholino derivative **2e** by heating **1** with morpholine in THF or MeCN in the presence of diisopropylethylamine. We found substitution of the 4-fluorine atom by amines, imidazoles and phenols occurred more rapidly in DMF as solvent, and the benzonitriles **2a–h** were formed in good yield (typically >80%) after 15 h at room temperature.

After successfully obtaining the benzonitrile precursors **2**, conversion to substituted fluorinated benzofurans was explored. Reaction with α-hydroxy carbonyl compounds **3** (Scheme 1) as bis-nucleophilic reagents was investigated. Suh and co-workers have synthesised non-fluorinated benzofurans, active as ischemic cell death inhibitors, utilising a related strategy.[2] Methyl glycolate, hydroxyacetone and two hydroxyacetophenones were employed as nucleophiles to react with benzonitriles **2**. The latter were prepared by reaction of the corresponding bromoacetophenones with sodium formate in ethanol (Scheme 2). The intermediate formate esters were not observed, presumably undergoing transesterification *in situ*. The use of DBU as base was then found to be effective in promoting attack of the alcohol at the 2-position of the tetrafluorobenzontriles **2**, and subsequent enolisation and cyclo-

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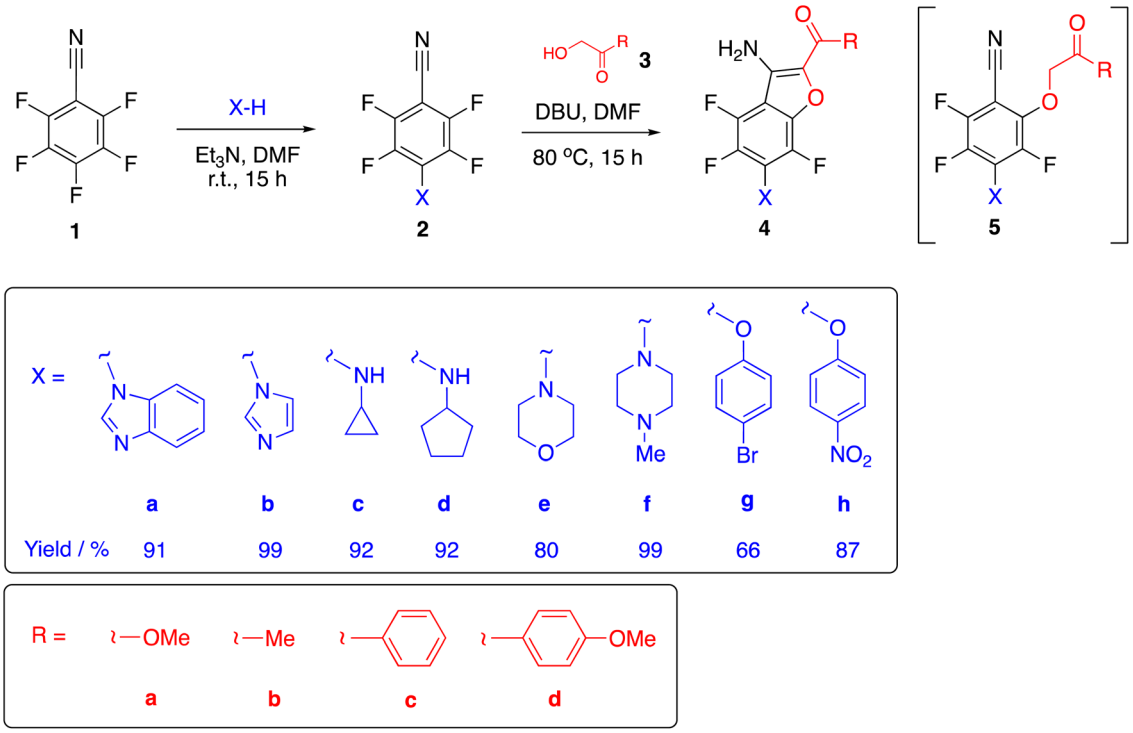
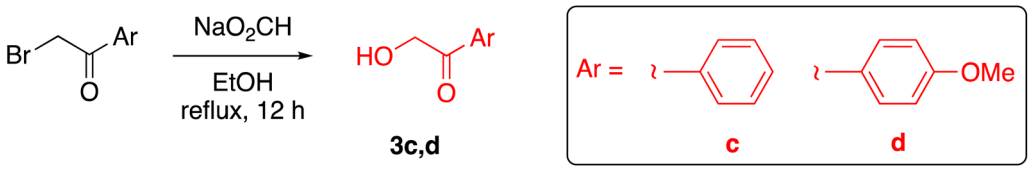


Scheme 1 Synthesis of 4-substituted tetrafluorobenzonitriles and their conversion to 3-amino-2,6-disubstituted-4,5,7-trifluorobenzofurans.



Scheme 2 Preparation of α-hydroxyacetophenone bis-nucleophiles.

condensation with the nitrile group to close the five-membered furan ring forming compounds **4** in low to high yield (Fig. 1).

Reaction was found to proceed well in DMF at 80 °C in 2–3 h although boiling THF was also suitable as a solvent. None of the intermediate **5** was observed indicating the enolisation and cyclisation was rapid in either solvent. On completion of the reaction, the crude products, in most cases, precipitated as solids on dilution of the reaction mixture with water. Products were chromatographed to analytical purity or recrystallized from ethanol as they were to be screened for biological activity. The structures of compounds isolated were confirmed by ^{1}H, ^{19}F and ^{13}C NMR and IR spectroscopy. Composition and purity were confirmed by HRMS and combustion analysis. The ^{19}F NMR spectra in most cases showed three distinct signals in the range 5–20 ppm (relative to C_6F_6) for the trifluorinated products. For example the 2-acetyl-6-morpholino compound **4eb** showed doublet signals at 11.5 (J 17 Hz) and 9.3 (J 20 Hz) and a matching double doublet at 10.3 for the F-5 atom. The amino group protons of **4eb** exhibited a singlet peak at 5.88 in the ^{1}H NMR spectrum with the other derivatives having signals in the range 5.6–6.2 ppm. The structure of the 2-(4-methoxybenzoyl)-6-morpholino substituted benzofuran **4ed** was confirmed by single crystal X-ray diffraction analysis (Fig. 2). This showed the 4-methoxybenzoyl group to be coplanar with the benzofuran ring (plane twist angle = 1.21(3)°, plane fold angle = 7.43(3)°) and to form an intramolecular hydrogen bond to the neighbouring 3-amino substituent (N1···O1 = 2.7709(11) Å).

The synthesized compounds are currently undergoing evaluation as cytotoxic agents against a range of pathogens.

We then investigated the possibility of synthesising the analogous 3-unsubstituted, or 3-methyl benzofurans using 4-substituted tetrafluorobenzaldehydes **6a** or acetophenones **6b** (Scheme 3) as substrates. However, despite precedent from our earlier work using methyl thioglycolate which afforded benzothiophenes,[6] attempted reactions with methyl glycolate in the presence of base (DBU or NaH) failed to give the desired benzofurans **7**, and deacylation of the substrates **6** was observed. The tetrafluorobenzene derivatives **8** were identified by the characteristic triplet of triplets signal around 6.9 ppm (tt, J = 9, 7 Hz) in the ^{1}H NMR spectra of the products. It appears that the alkoxide ion generated (Scheme 4) attacks the carbonyl group forming a hemi-acetal anion **9a** which then collapses expelling

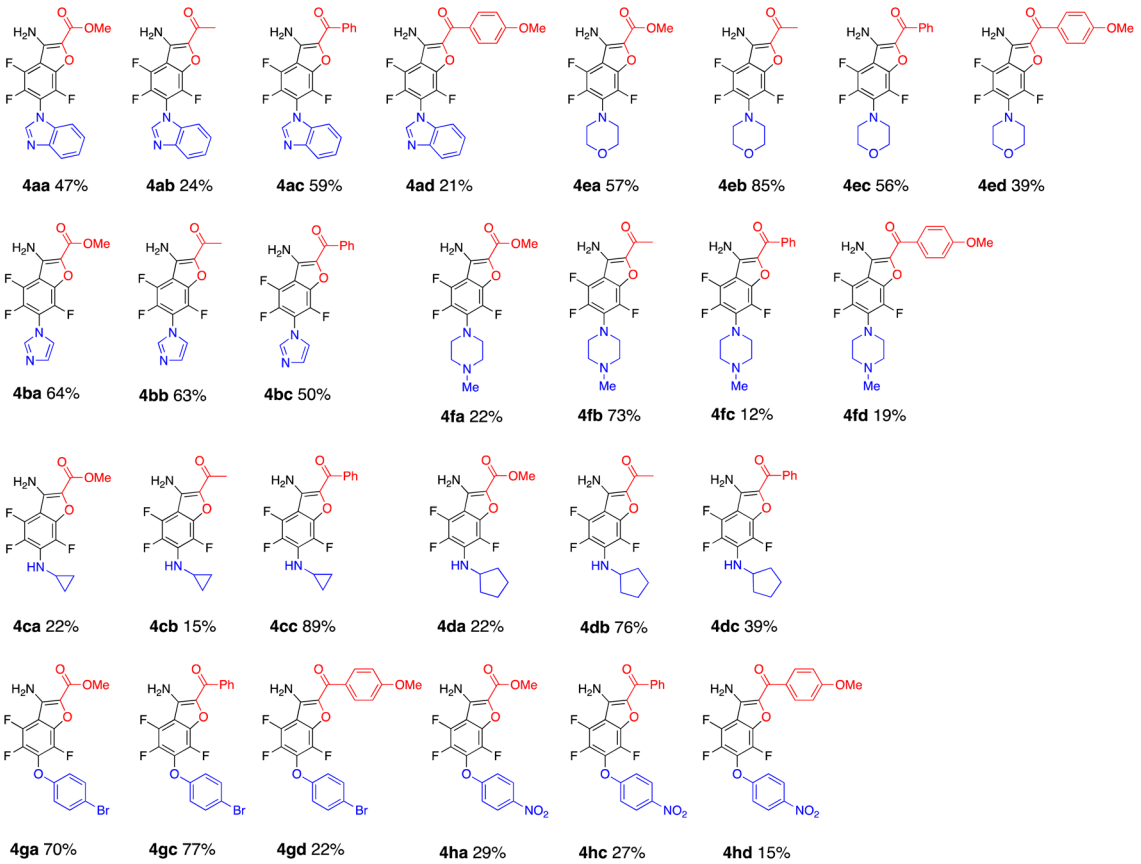


Fig. 1 Structures and isolated yields of the novel fluorinated benzofurans synthesised.

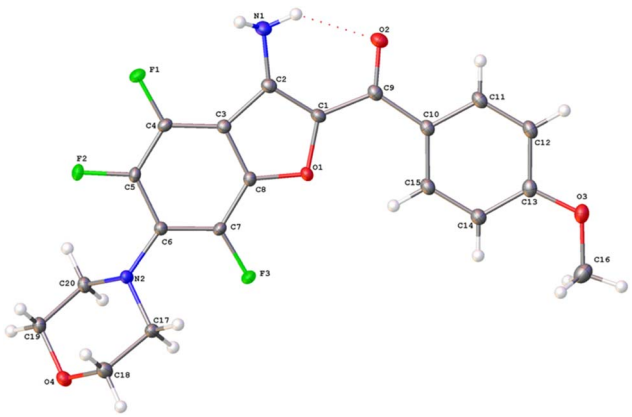
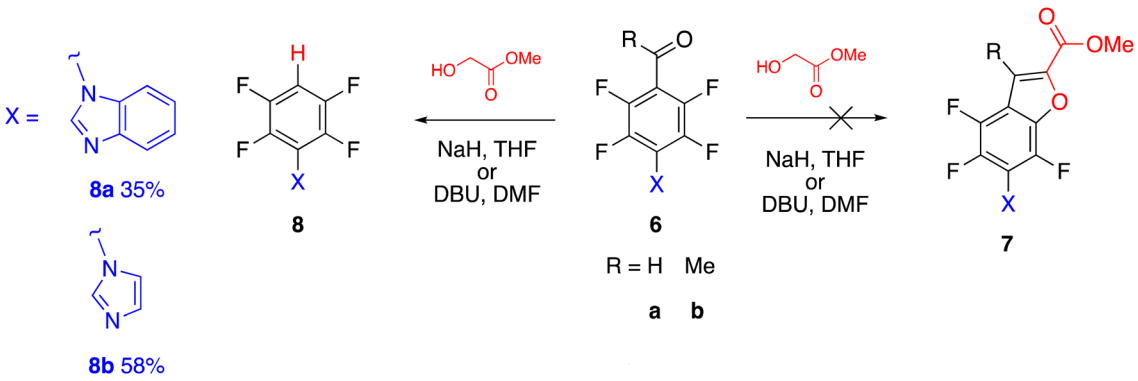


Fig. 2 Molecular structure of benzofuran **4ed** determined by single crystal X-ray diffraction. ADP ellipsoids shown at 50% probability.

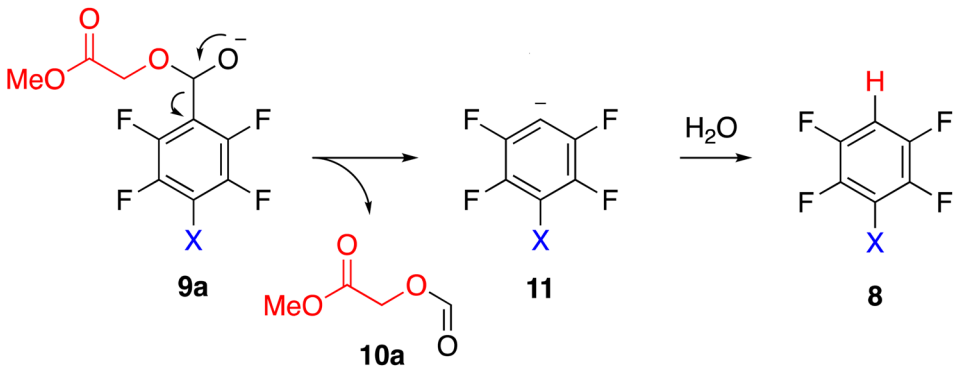
the fluoroaryl anion **11**. This was confirmed by conducting a reaction of the 4-morpholinotetrafluorobenzaldehyde **6ea** in deuterated methanol which led to the benzene derivative **8e** with up to 95% deuterium incorporation (Scheme 5). This finding is in line with early reports that pentafluorobenzaldehyde fails to undergo the Cannizzaro reaction. Isolation of *S*-benzylthiouronium formate indicated the aldehyde group was lost as formate.[8] The reaction appears to be a particularly facile version of the Haller–Bauer reaction.[9] Base catalysed ring opening of cyclic perfluorobenzocycloalkenones has recently been reported, which also involves cleavage of the aryl carbonyl bond, generating tetrafluoroarylperfluoroalkanoic acids.[10] A related study on the rate of protodeboronation of arylboronic acids, also invoking an aryl anion intermediate, showed the perfluoroaryl derivative had a half-life of only 2.6 ms in aqueous dioxane at pH 13.[11]

When either pentafluorobenzaldehyde **12a** or pentafluoroacetophenone **12b** was treated with methoxide (Scheme 6) and the reaction followed by NMR spectroscopy we were able to identify the mono- and di-substitution products, **13** and **14**, and the deacylated 1,3-dimethoxybenzene **15** which indicated that substitution occurs before deacylation. In the reaction with methyl glycolate it is thought that the more bulky nucleophile will attack the carbonyl group preferentially rather than adding to the more hindered 2-position of the benzene ring.

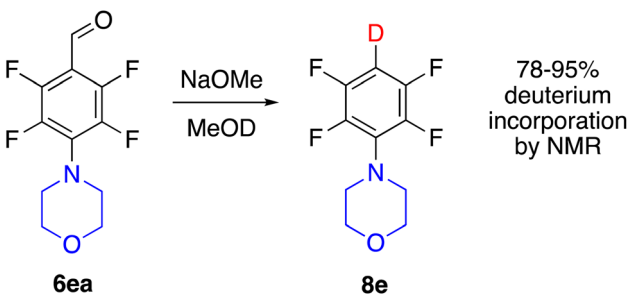
In conclusion twenty-seven fluorinated 3-aminobenzofurans have been accessed *via* a tandem S_NAr cyclo-condensation reaction of perfluorobenzonitriles with α-hydroxycarbonyl compounds, and were characterized by IR spectroscopy, NMR spectroscopy, HRMS, and elemental analysis. Single crystal X-ray diffraction analysis of the 2-methoxybenzoyl-6-morpholino-derivative confirmed the formation of the core 3-aminobenzofuran ring. The compounds are undergoing screening for biological activity against a number of pathogens and the biological results will be reported in due course.



Scheme 3 Attempted synthesis of 4,5,7-trifluorobenzofurans from perfluorobenzaldehydes or perfluoroacetophenones.



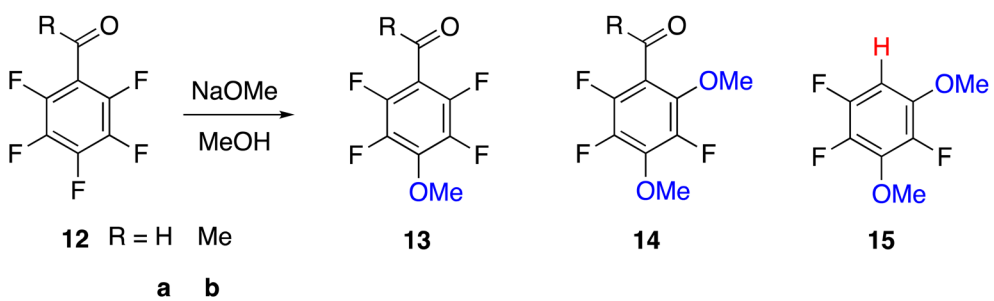
Scheme 4 Alkoxide induced cleavage mechanism leading to protio-deacylation.



Scheme 5 Deuterium incorporation confirmed tetrafluoroaryl anion formation.

Experimental

Starting materials for the synthesis of new compounds were obtained from Sigma Aldrich, Alfa Aesar or Fluorochem and used as received. 40–60 Micron silica was used for column chromatography and thin layer chromatography (TLC) was performed using Supleco pre-cut aluminium backed silica gel plates. Compounds on TLC plates were visualised under UV radiation at 254 nm wavelength. Melting points were carried out on a Stuart SMP10 melting point apparatus. IR spectroscopy was carried out on a PerkinElmer Spectrum 65 FT-IR, and NMR spectra were recorded on JEOL ECS400 or JEOL ESZ500 spectrometers with ^{1}H spectra recorded at 400 or 500 MHz, ^{13}C



Scheme 6 Methoxide induced substitution and deacylation in pentafluorobenzaldehyde and pentafluoroacetophenone.

spectra at 100 or 125 MHz and ^{19}F spectra at 376 or 470 MHz respectively. High resolution mass spectrometry (HRMS) was carried out on a ThermoFisher Exactive (Orbitrap) instrument with an ESI probe and a max ion source. X-ray crystallography was carried out at the UK National Crystallography Service, Southampton.

General procedure for the synthesis of 4-substituted perfluorobenzonitriles

Nucleophile R-H (15 mmol, 1 eq.) was dissolved in DMF (5 mL) and triethylamine (3.04 g, 30 mmol, 2 eq.) was added. Pentafluorobenzonitrile (2.90 g, 15 mmol, 1 eq.) was added and the reaction mixture was stirred at room temperature for 15 h. Water (10 mL) was added to the reaction mixture which was filtered under suction if a solid precipitated, and the solid product dried under vacuum, or, if no solid formed on addition of water, the mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine (3 × 10 mL), dried over $MgSO_4$, filtered and evaporated to dryness on a rotary evaporator to give the following compounds.

4-(1*H*-Benzo[*d*]imidazol-1-yl)-2,3,5,6-tetrafluorobenzonitrile (2a). Yellow solid (3.97 g, 91%), mp 160–167 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 8.01 (t, J = 1.5 Hz, 1H), 7.88 (m, 1H), 7.41 (m, 2H), 7.25 (m, 1H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 32.3 (m, 2F), 20.2 (m, 2F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C {^{1}H, ^{19}F} 148.0, 143.2, 142.1, 141.7, 132.7, 125.2, 124.3, 121.5, 121.2, 110.6, 106.7, 94.3. IR, ν_{max}/cm^{-1} 3022, 2244, 1726, 1652, 1609, 1496, 1476, 1455, 1385, 1345, 1304, 1265, 1208, 1128, 1114, 1013, 990, 887 and 867. HRMS expected for $C_{14}H_6F_4N_3$ 292.0492 observed m/z 292.0492 [M + H$^+$].[12]

2,3,5,6-Tetrafluoro-4-(1*H*-imidazol-1-yl)benzonitrile (2b). Colourless solid (3.56 g, 99%), mp 52–56 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.78 (d, J = 0.8 Hz, 1H), 7.22 (d, J = 18.0, 1.6 Hz, 2H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ_F 31.7 (m, 2F), 16.9 (m, 2F). IR, ν_{max}/cm^{-1} 3584, 3344, 3137, 2919, 2233, 1696, 1667, 1655, 1520, 1504, 1437, 1362, 1314, 1287, 1226, 1169, 1107, 1085, 1040, 993, 809 and 738. HRMS expected for $C_{10}H_4F_4N_3$ 274.0962 observed m/z 274.0961 [M + H$^+$].[13]

4-(Cyclopropylamino)-2,3,5,6-tetrafluorobenzonitrile (2c). White solid (3.16 g, 92%), mp 115–122 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 4.82 (s, 1H), 2.96 (m, 1H), 0.86 (m, 2H), 0.66 (m, 2H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 26.2 (m, 2F), 2.9 (d, J = 14.1 Hz, 2F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C {^{1}H, ^{19}F} 148.0, 135.8, 134.0, 109.1, 79.3, 27.2, 8.8. IR, ν_{max}/cm^{-1} 3420, 3336, 3095, 3019, 2989, 2919, 2849, 2236, 1657, 1537, 1513, 1458, 1361, 1266, 1019, 836 and 737. HRMS expected for $C_{10}H_7F_4N_2$ 231.0540 observed m/z 231.0547 [M + H$^+$].

4-(Cyclopentylamino)-2,3,5,6-tetrafluorobenzonitrile (2d). White solid (3.55 g, 92%), mp 99–107 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 4.40 (s, 2H), 4.25 (m, 1H), 2.03 (m, 2H), 1.70 (m, 4H), 1.52 (m, 2H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 26.4 (m, 2F), 1.9 (d, J = 14.3 Hz, 2F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C {^{1}H, ^{19}F} 148.1, 135.7, 133.1, 109.2, 78.5, 56.6, 34.7, 23.7. IR, ν_{max}/cm^{-1} 3467, 3336, 2959, 2924, 2854, 2239, 1655, 1535, 1513, 1480, 1438, 1365, 1314, 1288, 1189, 1126, 1072, 988, 960 and 721. HRMS expected for $C_{12}H_{10}F_4N_2Na$ 281.0672 observed m/z 281.0673 [M + Na$^+$].

2,3,5,6-Tetrafluoro-4-morpholinobenzonitrile (2e).[7] White solid (3.11 g, 80%), mp 76–82 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 3.82 (t, J = 4.5 Hz, 4H), 3.42 (m, 4H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 27.8 (m, 2F), 12.2 (m, 2F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C {^{1}H, ^{19}F} 148.2, 140.6, 135.4, 108.4, 84.5, 67.1, 51.0. IR, ν_{max}/cm^{-1} 2968, 2920, 2860, 2235, 1647, 1491, 1444, 1372, 1339, 1263, 1172, 1110, 1067, 1031, 981, 963, 916,858 and 725. HRMS expected for $C_{11}H_8F_4N_2ONa$ 283.0465 observed m/z 283.0465 [M + Na$^+$]. In agreement with literature values.[7]

2,3,5,6-Tetrafluoro-4-(4-methylpiperazin-1-yl)benzonitrile (2f). White solid (4.04 g, 99%), mp 72–80 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 3.40 (t, J = 4.5 Hz, 4H), 2.49 (t, J = 4.5 Hz, 4H), 2.31 (s, 3H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 27.2 (m, 2F), 12.1 (m, 2F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C {^{1}H, ^{19}F} 148.2, 140.5, 135.8, 108.5, 83.6, 55.2, 50.6, 46.2. IR, ν_{max}/cm^{-1} 3436, 3031, 2984, 2947, 2922, 2849, 2804, 2777, 2755, 2709, 2589, 2236, 1860, 1790, 1723, 1647, 1498, 1455, 1390, 1377, 1336, 1292, 1233, 1184, 1153, 1137, 1076, 988, 935, 816 and 782. HRMS expected for $C_{12}H_{12}F_4N_3$ 274.0962 observed m/z 274.0961 [M + H$^+$].

4-(4-Bromophenoxy)-2,3,5,6-tetrafluorobenzonitrile (2g). White solid (3.41 g, 66%), mp 58–65 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.44 (dt, J = 9.0, 3.5 Hz, 2H), 6.89 (dt, J = 9.5, 3.0 Hz, 2H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 29.9 (m, 2F), 11.4 (m, 2F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C {^{1}H, ^{19}F} 155.5, 148.1, 141.4, 139.1, 133.1, 118.0, 117.6, 107.1, 90.3. IR, ν_{max}/cm^{-1} 3681, 3448, 3095, 3063, 2936, 2856, 2774, 2648, 2559, 2436, 2323, 2274, 2243, 2042, 1889, 1869, 1787, 1651, 1581, 1497, 1482, 1437, 1404, 1317, 1297, 1277, 1209, 1168, 1102, 1010, 996, 936, 812, 699 and 581. HRMS expected for $C_{13}H_4{}^{79}BrF_4NO{\cdot}Na$ 367.9305 observed m/z 367.9306 [M + Na$^+$].

2,3,5,6-Tetrafluoro-4-(4-nitrophenoxy)benzonitrile (2h). White solid (4.10 g, 87%), mp 124–131 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 8.27 (dt, J = 9.6, 3.2 Hz, 2H), 7.12 (dt, J = 9.5, 2.4 Hz, 2H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 31.3 (m, 2F), 12.4 (m, 2F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C {^{1}H, ^{19}F} 160.3, 148.2, 144.6, 141.4, 137.7, 126.4, 116.4, 106.9, 91.6. IR, ν_{max}/cm^{-1} 3114, 3082, 2249, 1706, 1646, 1615, 1589, 1487, 1438, 1340, 1331, 1317, 1298, 1217, 1166, 1117, 994, 958, 855, 751 and 686.

2-Hydroxy-1-(4-methoxyphenyl)ethanone (3d). 2-Bromo-4-methoxyacetophenone (5.66 g, 24.7 mmol) was dissolved in ethanol (90 mL) and sodium formate (10.8 g, 159 mmol) was added and the mixture was refluxed for 12 h. The reaction was cooled to room temperature and concentrated under vacuum. Water (10 mL) was then added to the residue and the mixture extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried with $MgSO_4$, filtered and evaporated to dryness to give an orange solid (3.41 g, 83%), mp 105–111 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.88 (dt, J = 9.0, 2.0 Hz, 2H), 6.95 (dt, J = 9.0, 2.0 Hz, 2H), 4.81 (s, 2H), 3.87 (s, 3H), 3.58 (s, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C 196.8, 164.5, 130.1, 126.4, 114.3, 65.0, 55.4. IR, ν_{max}/cm^{-1} 3388, 3080, 3058, 3018, 2975, 2927, 2844, 2054, 1914, 1733, 1681, 1674, 1603, 1577, 1512, 1474, 1464, 1444, 1425, 1406, 1315, 1250, 1185, 1108, 1030, 1008, 992, 979, 836, 822, 635, 609, 569, 497 and 473. GC-MS 166.10.

General procedure for the synthesis of 2,6-disubstututed 3-amino-4,5,7-trifluoro-1-benzofurans 4

The appropriate benzonitrile derivative **2a–h** (2 mmol) and hydroxy carbonyl compound **3a–d** (2 mmol) were dissolved in the minimum convenient volume of either anhydrous THF (3 mL) or DMF (4 mL) and DBU (0.75 mL, 5 mmol) added. The resulting solution was heated under reflux if THF was employed, or at 80 °C for reactions in DMF, for 1–3 h until consumption of starting material was complete by TLC analysis. The cooled mixture was diluted with water (20 mL) and product collected by suction filtration if solid precipitated, or by extraction with ethyl acetate (3 × 50 mL) if no solid formed. The product was then purified by column chromatography over silica, using gradient elution with dichloromethane : methanol (99 : 1 to 95 : 5), or by recrystallisation from ethanol.

Methyl 3-amino-6-(1*H*-1,3-benzodiazol-1-yl)-4,5,7-trifluoro-1-benzofuran-2-carboxylate 4aa. Methyl glycolate (0.16 mL, 2.0 mmol) and 4-benzimidazol-1-yltetrafluorobenzonitrile (0.603 g, 2.07 mmol) in DMF afforded **4aa** as an off-white solid (0.337 g; 47%), after recrystallization from ethanol, mp 195–206 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 8.05 (s, 1H), 7.90 (td, J = 10.0, 4.0 Hz, 1H), 7.37 (m, 2H), 7.24 (m, 1H), 5.25 (s, 2H), 3.97 (s, 3H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ_F 19.0 (d, J = 16.9 Hz, 1F), 12.4 (d, J = 20.7 Hz, 1F), 12.2 (dt, J = 21.1, 1.9 Hz, 1F). ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C 160.9, 143.3, 142.7, 141.0 (d, J 248 Hz), 140.7 (dd, J 251, 16 Hz), 139.8 (d, J 257 Hz), 137.5–137.3 (m), 137.0, 133.8, 127.7, 124.5, 123.5, 120.9, 114.7–114.6 (m), 113.5–113.4 (m), 110.3, 51.9. IR, ν_{max}/cm^{-1} 3400, 1632, 1582, 1531, 1501, 1467, 1427, 1398, 1343, 1300, 1283, 1257, 1212, 1133, 1048, 1000, 960, 892, 873, 847, 762, 743 and 457. HRMS expected for $C_{17}H_{11}F_3N_3O_3$ 362.0747 observed m/z 362.0746 [M + H$^+$]. Elemental Analysis $C_{17}H_{10}F_3N_3O_3.0.5H_2O$ requires C 55.15%, H 2.99% and N 11.35%. Found C 55.26%, H 2.81% and N 11.16%.

1-[3-Amino-6-(1H-1,3-benzodiazol-1-yl)-4,5,7-trifluoro-1-benzofuran-2-yl]ethan-1-one 4ab. Hydroxyacetone (0.14 mL, 2.0 mmol) and 4-benzimidazol-1-yltetrafluorobenzonitrile (0.554 g, 1.87 mmol) in DMF gave **4ab** as a yellow solid (0.169 g; 24%), purified by column chromatography, mp 138–144 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 8.03 (s, 1H), 7.87 (m, 1H), 7.33 (m, 2H), 7.23 (m, 1H), 5.88 (s, 2H), 2.48 (s, 3H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 18.3 (dd, J = 18.4, 4.5 Hz, 1F), 13.3 (dd, J = 21.1, 18.8 Hz, 1F), 11.9 (dd, J = 21.1, 4.5 Hz, 1F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C {^{1}H, ^{19}F} 189.7, 143.2, 142.8, 141.3, 140.4, 139.7, 137.1, 137.1, 136.6, 133.7, 124.5, 123.5, 120.8, 113.3, 110.4, 110.4, 26.2 and (101 MHz, $CDCl_3$) δ_C 189.7, 143.2, 142.8, 141.3 (ddd, J 250, 14, 4 Hz), 140.5 (dd, J 249, 13 Hz), 139.7 (d, J 256 Hz), 137.2 (dd, J 11, 8 Hz), 136.64, 136.58, 133.7, 124.5, 123.5, 120.8, 114.8 (t, J 11 Hz), 113.3 (d, J 16 Hz), 110.4, 26.2. IR, ν_{max}/cm^{-1} 3584, 3424, 3312, 3203, 3105, 2918, 2849, 1647, 1614, 1554, 1518, 1501, 1464, 1422, 1390, 1361, 1339, 1297, 1279, 1256, 1210, 1175, 1154, 1124, 1096, 1004, 953, 890, 832, 814, 779, 764, 743, 700, 666 and 470. HRMS expected for $C_{17}H_{11}F_3N_3O_3$ 346.0798 observed m/z 346.0797 [M + H$^+$]. Elemental analysis requires $C_{17}H_{10}F_3N_3O_2$ C 59.14%, H 2.92% and N 12.17%. Found C 59.12%, H 3.07% and N 11.83%.

2-Benzoyl-6-(1H-1,3-benzodiazol-1-yl)-4,5,7-trifluoro-1-benzofuran-3-amine 4ac. Hydroxyacetophenone (0.282 g, 2.07 mmol) and 4-benzimidazol-1-yltetrafluorobenzonitrile (0.524 g, 2.01 mmol) in THF gave **4ac** as a red brown solid (0.310 g; 59%) purified by chromatography, mp 165–171 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 8.22 (dt, J = 7.0, 1.5 Hz, 2H), 8.11 (m, 1H), 7.92 (m, 1H), 7.60 (tt, J = 7.0, 1.5 Hz, 1H), 7.53 (tt, J = 7.0, 1.5 Hz, 2H), 7.40 (m, 2H), 7.28 (d, J = 6.5 Hz, 1H), 6.28 (s, 2H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 18.8 (dd, J = 18.4, 3.3 Hz, 1F), 13.5 (dd, J = 21.2, 18.8 Hz, 1F), 12.3 (dd, J = 20.7, 3.8 Hz, 1F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C {^{1}H, ^{19}F} 183.3, 143.2, 141.3, 140.5 139.7, 137.4, 132.9, 129.3, 128.7, 123.7, 120.9, 115.3, 113.0, 110.5. IR, ν_{max}/cm^{-1} 3584, 3350, 3306, 3091, 3059, 2919, 2850, 2218, 1630, 1615, 1600, 1578, 1544, 1501, 1460, 1343, 1322, 1301, 1281, 1259, 1211, 1183, 1154, 1126, 1101, 1042, 1006, 932, 889, 846, 824, 813, 793, 779, 763, 742, 718, 695, 678 and 462. HRMS expected for $C_{22}H_{13}N_3O_2F_3$ 408.0954 observed m/z 408.0947 [M + H$^+$].

(3-Amino-6-(1*H*-benzo[*d*]imidazole-1-yl)-4,5,7-trifluorobenzofuran-2-yl)(4-methoxyphenyl)methanone 4ad. Hydroxyketone **3d** (0.345 g, 2.08 mmol) and 4-benzimidazolyltetrafluorobenzonitrile **2a** (0.382 g, 1.31 mmol) in DMF gave **4ad** as a yellow solid (0.118 g, 21%) purified *via* column chromatography, ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 8.28 (dt, J = 9.0, 2.5 Hz, 2H), 8.06 (m, 1H), 7.91 (m, 1H), 7.39 (m, 2H), 7.28 (m, 1H), 7.03 (dt, J = 9.0, 2.0 Hz, 2H), 6.15 (s, 2H), 3.89 (s, 3H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 18.5 (dd, J = 18.4, 3.8 Hz, 1F), 13.1 (dd, J = 20.7, 18.4 Hz, 1F), 12.1 (dd, 21.2, 4.2 Hz, 1F). ^{13}C-NMR (126 MHz, $CDCl_6$) δ_C {^{1}H, ^{19}F} 181.9, 163.5, 143.2, 142.8, 141.3, 140.6, 139.8, 139.3, 137.2, 136.7, 133.8, 131.7, 129.4, 124.6, 123.6, 120.9, 114.9, 114.0, 113.1, 110.5 55.6. IR ν_{max}/cm^{-1} 3584, 3339, 2921, 2853, 1629, 1600, 1543, 1504, 1457, 1342, 1304, 1255, 1211, 1171, 1105, 1027, 1005, 963, 933, 843, 763 and 745. HRMS expected for $C_{23}H_{15}F_3N_3O_3$ 438.1060 observed m/z 438.1060 [M + H$^+$].

Methyl 3-amino-4,5,7-trifluoro-6-(1*H*-imidazol-1-yl)-1-benzofuran-2-carboxylate 4ba. Methyl glycolate (0.21 mL, 2.8 mmol) and 4-imidazol-1-yltetrafluorobenzonitrile **2b** (0.664 g, 2.8 mmol) in THF (3 mL) gave **4ba** as a red brown solid (0.547 g; 64%), mp 175–181 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.79 (s, 1H), 7.28 (t, J = 1.5 Hz, 1H), 7.22 (t, J = 1.5 Hz, 1H), 5.22 (s, 2H), 3.97 (m, 3H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 15.8 (d, J = 17.9 Hz, 1F), 12.1 (t, J = 19.8 Hz, 1F), 9.9 (dt, J = 21.2, 2.4 Hz, 1F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C {^{1}H, ^{19}F} 160.9, 140.9, 139.8, 138.6, 138.0, 137.3, 137.0, 130.1, 127.6, 120.5, 116.2, 112.6, 52.0. IR, ν_{max}/cm^{-1} 3584, 3437, 3359, 2956, 2862, 2218, 1690, 1633, 1581, 1535, 1519, 1502, 1459, 1426, 1395, 1346, 1316, 1285, 1258, 1207, 1135, 1083, 1040, 1006, 996, 958, 908, 846, 813, 794, 761, 736 and 655. HRMS expected for $C_{13}H_9F_3N_3O_3$ 312.0591 observed m/z 312.0590 [M + H$^+$].

1-[3-Amino-4,5,7-trifluoro-6-(1*H*-imidazol-1-yl)-1-benzofuran-2-yl]ethan-1-one 4bb. Hydroxyacetone (0.18 mL, 2.6 mmol) and 4-imidazol-1-yltetrafluorobenzonitrile **2b** (0.634 g, 2.6 mmol) in THF gave **4bb** as a red solid (0.491 g; 63%), mp 108–112 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.77 (m, 1H), 7.28 (t, J = 1.0 Hz, 2H), 7.22 (t, J = 1.5 Hz, 1H) 5.74 (s, 2H), 2.51 (s, 3H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 15.3 (dt, J = 18.4, 2.83 Hz, 1F),

12.9 (dd, J = 21.2, 18.4 Hz, 1F), 10.0–9.9 (m, 1F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C 189.8, 141.3 (ddd, J 250, 14, 4), 139.6 (dd, J 247, 14), 138.7 (dd, J 253, 3), 138.0, 137.1 (dd, J 13, 8), 136.7, 136.4 (d, J 3), 130.2, 120.4, 116.6 (t, J 14), 112.5 (dd, J 17, 2), 26.2. IR, ν_{max}/cm^{-1} 3584, 3401, 3306, 3207, 3120, 2918, 2850, 2218, 1647, 1621, 1555, 1519, 1501, 1465, 1361, 1343, 1314, 1271, 1205, 1136, 1108, 1083, 1040, 1005, 952, 906, 876, 829, 812, 734 and 653. HRMS expected for $C_{13}H_9F_3N_3O_2$ 296.0641 observed m/z 296.0641 [M + H^+].

2-Benzoyl-4,5,7-trifluoro-6-(1*H*-imidazol-1-yl)-1-benzofuran-3-amine 4bc. 2-Hydroxyacetophenone (0.076 g, 0.56 mmol) and 4-imidazol-1-yltetrafluorobenzonitrile **2b** (0.134 g, 0.56 mmol) in THF gave **4bc** as an orange solid (0.091 g; 50%), purified by column chromatography, mp 196–204 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 8.21 (dt, J = 7.0, 1.5 Hz, 2H), 7.86 (s, 1H), 7.60 (tt, J = 7.0, 1.5 Hz, 1H), 7.53 (m, 2H) 7.34 (s, 1H), 7.26 (s, 1H), 6.18 (s, 2H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 15.7 (dd, J = 18.4, 3.8 Hz, 1F), 13.3 (dd, J = 20.7, 18.4 Hz, 1F), 10.1 (dt, J = 21.2, 2.4 Hz, 1F). IR, ν_{max}/cm^{-1} 3584, 3369, 2917, 2849, 1630, 1599, 1577, 1547, 1507, 1462, 1441, 1346, 1317, 1284, 1208, 1183, 1153, 1104, 1079, 1040, 1008, 928, 909, 822, 812 and 714. HRMS expected for $C_{18}H_{11}F_3N_3O_2$ 358.0798 observed m/z 358.0792 [M + H^+].

Methyl 3-amino-6-(cyclopropylamino)-4,5,7-trifluoro-1-benzofuran-2-carboxylate 4ca. Methyl glycolate (0.16 mL, 2.0 mmol) and 4-cyclopropylaminotetrafluorobenzonitrile **2c** (0.345 g, 1.5 mmol) in DMF gave **4ca** as a light brown solid (0.103 g; 22%) purified by column chromatography, ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 5.10 (s, 2H), 4.20 (s, 1H), 3.90 (s, 3H), 2.89 (m, 1H), 0.76 (m, 2H), 0.60 (m, 2H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 8.5 (m, 1F), 2.6 (m, 1F), 1.0 (dd, J = 20.3, 3.3 Hz, 1F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C {^{19}F} 161.3, 140.7, 138.9, 138.5, 137.1, 133.5, 128.6, 125.2, 125.0, 102.1, 51.5 (q, $^1J_{CH}$ 183 Hz), 27.8 (d, $^1J_{CH}$ 226 Hz), 8.74 (t, $^1J_{CH}$ 202 Hz). IR, ν_{max}/cm^{-1} 3585, 3494–3372, 3091, 3010, 2956, 2919, 2851, 1675, 1624, 1575, 1534, 1509, 1453, 1423, 1384, 1363, 1348, 1300, 1269, 1229, 1183, 1128, 1022, 1049, 965, 953, 927, 847, 832, 819, 797, 759, 734 and 457. HRMS expected for $C_{13}H_{12}F_3N_2O_3$ 301.0795 observed m/z 301.0794 [M + H^+]. Elemental analysis expected for $C_{19}H_{18}F_3N_5$ C 50.49% H 3.88% N 9.05%, found C 50.79% H 3.51% N 9.01%.

1-[3-Amino-6-(cyclopropylamino)-4,5,7-trifluoro-1-benzofuran-2-yl]ethan-1-one 4cb. Hydroxyacetone (0.14 mL, 2.00 mmol) and 4-cyclopropylaminotetrafluorobenzonitrile **2c** (0.516 g, 2.24 mmol) in DMF gave **4cb** as an off-white solid (0.086 g; 15%) purified by chromatography, mp 123–129 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 5.71 (s, 2H), 4.34 (s, 1H), 2.93 (m, 1H), 2.44 (s, 3H), 0.80 (m, 2H), 0.62 (m, 2H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 9.3 (dd, J = 20.3, 16.0 Hz, 1F), 2.0 (dt, J = 16.0, 3.3 Hz, 1F), 0.9 (dd, J = 20.3, 3.3 Hz, 1F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C {^{19}F} 188.3, 141.1, 139.0, 138.4, 136.8, 135.4133.4, 129.1, 101.8, 27.8 (d, $^1J_{CH}$ 180 Hz), 25.7 (q, $^1J_{CH}$ 127 Hz), 8.79 (t, $^1J_{CH}$ 164 Hz). IR, ν_{max}/cm^{-1} 3584, 3497, 3313, 3016, 1775, 1732, 1661, 1640, 1596, 1555, 1503, 1452, 1392, 1361, 1300, 1269, 1232, 1172, 1130, 1105, 1046, 1017, 946, 931, 848, 833, 799, 765, 739, 693, 675, 656 and 459. HRMS expected for $C_{13}H_{12}F_3N_2O_2$ 285.0845 observed m/z 285.0845 [M + H^+]. Elemental analysis expected for $C_{13}H_{11}F_3N_2O_2$ C 53.61% H 4.12% N 9.62%, found C 53.19% H 3.74% N 9.57%.

2-Benzoyl-*N*^{6}-cyclopropyl-4,5,7-trifluoro-1-benzofuran-3,6-diamine 4cc. 2-Hydroxyacetophenone (0.273 g, 2.01 mmol) and 4-cyclopropylaminotetrafluorobenzonitrile **2c** (0.516 g, 2.24 mmol) in DMF gave **4cc** as a brown solid (0.617 g; 89%) purified by chromatography, ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 8.18 (m, 2H), 7.52 (m, 3H), 6.15 (m, 2H), 4.38 (m, 1H), 2.94 (m, 1H), 0.84 (m, 2H), 0.65 (m, 2H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ_F 9.6 (dd, J = 20.3, 16.0 Hz, 1F), 2.2 (d, J = 16.0 Hz, 1F), 0.9 (dd, J = 20.3, 4.2 Hz, 1F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C 181.7, 142.1, 141.1, 137.4, 137.1, 135.2, 133.4, 132.0, 132.0, 129.2, 128.4, 124.7, 101.4, 27.8 (d, $^1J_{CH}$ 181 Hz), 8.84 (t, $^1J_{CH}$ 164 Hz). IR, ν_{max}/cm^{-1} 3584, 3492, 3346, 3060, 2957, 2850, 2230, 1665, 1618, 1600, 1576, 1554, 1494, 1453, 1438, 1382, 1361, 1350, 1306, 1272, 1230, 1182, 1123, 1074, 1048, 1022, 961, 947, 912, 847, 743, 712, 694, 677 and 458. HRMS expected for $C_{18}H_{14}F_3N_2O_2$ 347.1002 observed m/z 347.1001 [M + H^+].

Methyl 3-amino-6-(cyclopentylamino)-4,5,7-trifluoro-1-benzofuran-2-carboxylate 4da. Methyl glycolate (0.16 mL, 2.0 mmol) and 4-cyclopentylaminotetrafluorobenzonitile **2d** (0.516 g, 2.0 mmol) in DMF gave **4da** as an orange solid (0.145 g, 22%) purified by chromatography, ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 5.07 (s, 2H), 4.18 (m, 1H), 3.89 (s, 3H), 3.66 (s, 1H), 1.96 (m, 2H), 1.66 (m, 4H), 1.46 (m, 2H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 8.7 (m, 1F), 2.3 (m, 1F), 0.8 (dq, J = 20.3, 2.4 Hz, 1F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C 161.3, 140.8, 138.9, 137.4, 134.8, 133.6, 132.5, 124.9, 101.9 57.0, 51.5, 34.4, 23.7. IR, ν_{max}/cm^{-1} 3584, 3379, 2956, 2871, 2225, 1826, 1678, 1624, 1575, 1532, 1454, 1422, 1384, 1344, 1314, 1294, 1263, 1191, 1149, 1130, 995, 974, 950, 896, 878, 819, 760, 733 and 455. HRMS expected for $C_{15}H_{16}F_3N_2O_3$ 329.1108 observed m/z 329.1107 [M + H^+].

1-[3-Amino-6-(cyclopentylamino)-4,5,7-trifluoro-1-benzofuran-2-yl]ethan-1-one 4db. Hydroxyacetone (0.14 mL, 2.00 mmol) and 4-cyclopentylaminotetrafluorobenzonitrile **2d** (0.501 g, 1.94 mmol) in DMF gave **4db** as a brown solid (0.464 g; 76%) purified by chromatography, mp 98–105 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 5.74 (s, 2H), 4.23 (s, 1H, NH), 3.89 (s, 1H), 2.44 (s, 3H), 2.01 (m, 2H), 1.64 (m, 4H), 1.53 (m, 2H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 9.4 (dd, J = 20.7, 16.0 Hz, 1F), 1.6 (d, J = 16.0 Hz, 1F), 0.8 (d, J = 20.3 Hz, 1F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C 188.3, 145.0, 140.4, 140.3, 138.4, 136.2, 135.4, 128.6, 101.8, 57.0, 34.5, 25.9, 23.7. IR, ν_{max}/cm^{-1} 3584, 3498, 3429, 3338, 3205, 2959, 2872, 1664, 1638, 1604, 1558, 1510, 1455, 1392, 1380, 1361, 1342, 1311, 1294, 1265, 1173, 1095, 1002, 975, 944, 741 and 460. HRMS expected for $C_{15}H_{16}F_3N_2O_2$ 313.1158 observed m/z 313.1158 [M + H^+].

2-Benzoyl-*N*^{6}-cyclopentyl-4,5,7-trifluoro-1-benzofuran-3,6-diamine 4dc. 2-Hydroxyacetophenone (0.272 g, 2.00 mmol) and 4-cyclopentylaminotetrafluorobenzonitrile **2d** (0.202 g, 0.78 mmol) in DMF gave **4dc** as a brown solid (0.293 g; 39%) purified by chromatography, mp 105–111 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 8.20 (m, 2H), 7.45 (m, 3H), 6.20 (s, 2H), 4.29 (s, 1H), 3.77 (m, 1H, NH), 2.00 (m, 2H), 1.69 (m, 4H), 1.51 (m, 2H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 9.8 (dd, J = 20.7, 16.5 Hz, 1F), 1.7 (d, J = 16.0 Hz, 1F), 0.7 (dd, J = 20.3, 1.9 Hz, 1F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C 181.6, 142.1, 141.2, 139.5, 137.5, 137.3, 135.2, 134.4, 133.4,

131.9, 129.2, 128.4, 107.2, 57.0, 34.5, 29.8, 23.7. IR, ν_{max}/cm^{-1} 3584, 3427, 3340, 3061, 3026, 2960, 2872, 2247, 2223, 1818, 1664, 1620, 1575, 1554, 1494, 1455, 1438, 1380, 1346, 1323, 1313, 1295, 1266, 1183, 1157, 1101, 1073, 1003, 970, 931, 914, 847, 793, 733, 710, 695, 678, 632 and 647. HRMS expected for $C_{20}H_{18}F_3N_2O_2$ 375.1315 observed *m*/*z* 375.1314 [M + H$^+$].

Methyl-3-amino-4,5,7-trifluoro-6-(morpholin-4-yl)-1-benzofuran-2-carboxylate 4ea. Methyl glycolate (0.16 mL, 2.0 mmol) and 4-morpholinotetrafluorobenzonitrile **2e** (0.522 g, 2.0 mmol) in DMF gave **4ea** as an off-white solid (0.375 g; 57%) purified by chromatography, mp 138–143 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 5.12 (s, 2H), 3.95 (m, 3H), 3.81 (m, J = 4.4 Hz, 4H), 3.28 (t, J = 4.0 Hz, 4H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ_F 12.2 (m, 1F), 9.4 (m, 2F). ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C 161.2, 141.8, 140.9, 139.5, 138.3, 137.8, 130.0, 125.9, 107.3, 67.5, 51.7, 51.5. IR, ν_{max}/cm^{-1} 3583, 3449, 3380, 2958, 2850, 1682, 1658, 1627, 1573, 1520, 1449, 1424, 1388, 1375, 1340, 1305, 1290, 1264, 1194, 1153, 1115, 1069, 1033, 1000, 990, 958, 923, 864, 833, 808, 797, 760 and 733. HRMS expected for $C_{14}H_{14}F_3N_2O_4$ 331.0900 observed *m*/*z* 331.0899 [M + H$^+$]. Elemental analysis $C_{14}H_{13}F_3N_3O_4$ requires C 50.92%, H 3.97% and N 8.48%, found C 50.84%, H 3.99% and N 8.67%.

1-[3-Amino-4,5,7-trifluoro-6-(morpholin-4-yl)-1-benzofuran-2-yl]ethan-1-one 4eb. Hydroxyacetone (0.14 mL, 2.0 mmol) and 4-morpholinotetrafluorobenzonitrile **2e** (0.535 g, 2.00 mmol) in DMF (3 mL) gave **4eb** as a brown oil (0.537 g; 85%) purified by chromatography which then solidified, mp 198–204 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 5.69 (s, 2H), 3.83 (m, J = 5.0 Hz, 4H), 3.31 (m, 4H), 2.46 (s, 3H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 11.5 (d, J = 17.0 Hz, 1F), 10.3 (dd, J = 20.3, 16.5 Hz, 1F), 9.3 (d, J = 20.3 Hz, 1F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C 189.2, 141.6, 141.4, 139.5, 138.3, 137.4, 135.9, 130.5 107.0, 67.5, 51.6, 26.0. IR, ν_{max}/cm^{-1} 3585, 3429, 3318, 3209, 2965, 2853, 1815, 1731, 1647, 1614, 1545, 1508, 1446, 1385, 1359, 1334, 1304, 1287, 1264, 1215, 1174, 1153, 1116, 1068, 998, 947, 923, 864, 818, 807, 734 and 712. HRMS expected for $C_{14}H_{14}F_3N_2O_3$ 315.0951 observed *m*/*z* 315.0951 [M + H$^+$].

2-Benzoyl-4,5,7-trifluoro-6-(morpholin-4-yl)-1-benzofuran-3-amine 4ec. 2-Hydroxyacetophenone (0.273 g, 2.0 mmol) and 4-morpholinetetrafluorobenzonitrile **2e** (0.355 g, 1.4 mmol) in DMF gave as a yellow solid **4ec** (0.421 g, 56%) purified by chromatography, mp 109–113 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 8.21 (m, 2H), 7.54 (m, 3H), 6.14 (s, 2H), 3.82 (t, J = 4.8 Hz, 4H), 3.29 (m, 4H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ_F 11.8 (d, J = 16.5 Hz, 1F), 10.6 (dd, J = 20.3, 16.9 Hz, 1F), 9.4 (d, J = 20.3 Hz, 1F). ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C 182.5, 141.5, 141.4, 139.4, 138.7, 137.2, 135.2, 132.3, 132.3, 130.8, 129.2, 128.5, 106.6, 67.5, 51.6. IR, ν_{max}/cm^{-1} 3434, 3325, 2960–2853, 2758, 2692, 2230, 1823, 1721, 1657, 1626, 1600, 1536, 1493, 1450, 1440, 1386, 1374, 1341, 1307, 1290, 1264, 1181, 1153, 1115, 1069, 1029, 1000, 926, 861, 747, 694, 678 and 463. HRMS expected for $C_{19}H_{16}F_3N_2O_3$ 377.1108 observed *m*/*z* 377.1106 [M + H$^+$].

(3-Amino-4,5,7-trifluoro-6-morpholinobenzofuran-2-yl)(4-methoxyphenyl)methanone 4ed. 2-Hydroxy-1-(4-methoxyphenyl) ethan-1-one (0.326 g, 1.96 mmol) and 4-morpholinotetrafluorobenzonitrile **2e** (0.570 g, 2.19 mmol) in DMF gave **4ed** as a yellow solid (0.316 g, 39%) purified by chromatography eluting with ethyl acetate, mp 159–164 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 8.24 (dt, J = 9.0, 3.0 Hz, 2H), 6.99 (dt, J = 9.0, 2.5 Hz, 2H), 6.07 (s, 2H), 3.88 (s, 3H), 3.36 (t, J = 3.5 Hz, 4H), 3.32 (t, J = 3.5 Hz, 4H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 11.8 (d, J = 16.5 Hz, 1F), 10.1 (dd, J = 20.7, 17.0 Hz, 1F), 9.4 (d, J = 20.3 Hz, 1F). ^{13}C-NMR (126 MHz, $CDCl_6$) δ_C {^{1}H, ^{19}F} 181.2, 163.0, 141.6, 141.3, 140.4, 139.4, 138.4, 135.7, 131.5, 130.5, 129.9, 113.8, 106.8, 55.5, 51.6, 46.3. IR, ν_{max}/cm^{-1} 3401, 2929, 2799, 1661, 1623, 1602, 1569, 1540, 1512, 1488, 1456, 1417, 1391, 1372, 1301, 1286, 1255, 1175, 1139, 112, 1029, 1002, 925, 908, 843, 762, 732, 560, 507 and 471. GC-MS for $C_{20}H_{18}F_3N_2O_4$ found *m*/*z* 406.20 (M$^+$).

Methyl 3-amino-4,5,7-trifluoro-6-(4-methylpiperazin-1-yl)-1-benzofuran-2-carboxylate 4fa. Methyl glycolate (0.15 mL, 2.0 mmol) and 4-(4-methylpiperazin-1-yl)tetrafluorobenzonitrile **2f** (0.545 g, 1.99 mmol) in DMF gave **4fa** as a brown solid (0.153 g; 22%) crystallised from ethanol, mp 138–145 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 5.11 (s, 2H), 3.92 (m, 3H), 3.32 (t, J = 4.5 Hz, 4H), 2.55 (m, 4H), 2.30 (m, 3H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 12.5 (d, J = 12.7 Hz, 1F), 9.5 (d, J = 20.3 Hz, 1F), 9.2 (m, 1F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C 161.3, 141.8, 140.9, 139.5, 138.4, 137.9, 125.9, 130.4, 107.0, 51.7, 51.0, 46.3, 46.3. IR, ν_{max}/cm^{-1} 3584, 3468, 3368, 3189, 2943, 2888, 2849, 2801, 2748, 1682, 1626, 1572, 1520, 1452, 1425, 1391, 1373, 1341, 1301, 1285, 1258, 1230, 1194, 1171, 1132, 1076, 1051, 1035, 1004, 991, 957, 936, 802, 779, 760, 735, 699, 638 and 455. HRMS expected for $C_{15}H_{17}F_3N_3O_3$ 344.1217 observed *m*/*z* 344.1209 [M + H$^+$]. Elemental analysis expected for $C_{15}H_{16}F_3N_3O_3.0.5H_2O$ C 51.40% H 4.79% N 11.99%, found C 51.84% H 4.69% N 11.94%.

1-[3-Amino-4,5,7-trifluoro-6-(4-methylpierazin-1-yl)-1-benzofuran-2-yl]ethan-1-one 4fb. Methyl glycolate (0.15 mL, 2.0 mmol) and 4-(4-methylpiperazin-1-yl)tetrafluorobenzonitrile **2f** (0.543 g, 1.99 mmol) in DMF gave **4fb** as a brown solid (0.477 g; 73%) crystallised from ethanol, mp 128–135 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 5.69 (s, 2H, NH_2), 3.33 (t, J = 4.5 Hz, 4H), 2.55 (t, J = 4.0 Hz, 4H), 2.43 (m, 3H), 2.34 (s, 3H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 11.6 (d, J = 16.5 Hz, 1F), 10.0 (dd, J = 20.7, 17.0 Hz, 1F), 9.4 (d, J = 20.3 Hz, 1F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C {^{1}H, ^{19}F} 189.1, 141.5, 141.4, 139.5, 138.4, 137.5, 135.8, 130.8, 106.6, 55.5, 51.0, 46.3, 26.0. IR, ν_{max}/cm^{-1} 3583, 3414, 2938, 2888, 2850, 2803, 2747, 2694, 2219, 1863, 1841, 1787, 1643, 1545, 1507, 1450, 1391, 1372, 1361, 1333, 1300, 1284, 1259, 1230, 1171, 1154, 1139, 1076, 1052, 999, 950, 833, 810, 781, 732 and 466. HRMS expected for $C_{15}H_{17}F_3N_3O_2$ 328.1267 observed *m*/*z* 328.1258 [M + H$^+$]. Elemental analysis $C_{15}H_{16}F_3N_3O_2$ requires C 55.05%, H 4.93% N 12.84, found C 55.24%, H 5.14% N 12.66%.

2-Benzoyl-4,5,7-trifluoro-6-(4-methylpiperazin-1-yl)-1-benzofuran-3-amine 4fc. 2-Hyroxyacetophenone (0.293 g, 2.15 mmol) and 4-(4-methylpiperazin-1-yl)tetrafluorobenzonitrile **2f** (0.566 g, 2.07 mmol) in THF gave **4fc** as a yellow-orange solid (0.065 g; 12%) purified by chromatography, mp 138–144 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 8.20 (dd, J = 8.5, 1.0 Hz, 2H), 7.55 (tt, J = 7.0, 1.5 Hz, 1H), 7.50 (tt, J = 7.5, 1.5 Hz, 2H), 6.13 (s, 2H), 3.43 (m, 4H), 2.70 (m, 4H), 2.44 (m, 3H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 12.1 (d, J = 16.0 Hz, 1F), 10.6 (t, J = 19.3 Hz, 1F), 9.5 (d, J = 20.7 Hz, 1F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C 182.5, 141.5, 141.4, 140.9, 139.3, 138.7, 137.2, 135.7, 132.3, 130.8, 129.2, 128.5, 106.4, 55.3, 50.6, 45.9. IR, ν_{max}/cm^{-1} 3488, 3323, 3193, 3059,

2936, 2888, 2849, 2799, 1658, 1625, 1601, 1577, 1536, 1494, 1452, 1440, 1391, 1373, 1341, 1285, 1261, 1231, 1182, 1168, 1155, 1139, 1075, 1029, 1002, 934, 926, 736, 717, 696, 678, 631, 616, 564 and 458. HRMS expected for $C_{20}H_{19}F_3N_3O_2$ 390.1424 observed *m/z* 390.1416 [M + H$^+$]. Elemental analysis $C_{20}H_{18}F_3N_3O_2.H_2O$ requires C 58.97%, H 4.91% N 10.32%, found C 58.56%, H 4.43% N 10.17%.

(3-Amino-4,5,7-trifluoro-6-(4-methylpiperazin-1-yl) benzofuran-2-yl)(4-methoxyphenyl)methanone 4fd. 2-Hydroxy-1-(4-methoxyphenyl)ethan-1-one **3d** (0.347 g, 2.09 mmol) and 4-(4-methylpiperazin-1-yl)tetrafluorobenzonitrile **2f** (0.580 g, 2.12 mmol) in DMF gave **4fd** as a yellow solid (0.157 g, 19%) purified by chromatography eluting with ethyl acetate, mp 162–168 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 8.22 (d, J = 9.0 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H), 6.07 (s, 2H), 3.88 (s, 3H), 3.35 (m, 4H), 2.56 (m, 4H), 2.36 (s, 3H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 11.8 (d, J = 16.5 Hz, 1F), 10.1 (t, J = 19.8 Hz, 1F), 9.3 (d, J = 20.3 Hz, 1F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C {^{19}F, ^{1}H} 181.0, 162.8, 141.5, 141.3, 140.5, 139.4, 138.5, 135.7, 131.5, 130.9, 130.0, 113.8, 106.4, 55.5 (2xC, O$\underline{C}$H$_3$ and MeN$\underline{C}$H$_2$), 51.1, 46.3. IR, ν_{max}/cm^{-1} 3386, 3288, 2979, 2840, 1659, 1600, 1573, 1536, 1509, 1492, 1447, 1439, 1418, 1385, 1366, 1347, 1302, 1290, 1263, 1250, 1176, 1166, 1033, 1001, 927, 853, 762, 684, 619, 523 and 469. HRMS expected for $C_{21}H_{21}F_3N_3O_3$ 420.1530 observed *m/z* 420.1528 [M + H$^+$].

Methyl 3-amino-6-(4-bromophenoxy)-4,5,7-trifluoro-1-benzofuran-2-carboxylate 4ga. Methyl glycolate (0.15 mL, 2.00 mmol) and 4-(4-bromophenoxy)tetrafluorobenzonitrile **2g** (0.704 g, 2.03 mmol) in THF gave **4ga** as a red brown solid (0.580 g; 70%) crystallised from ethanol, mp 74–79 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.41 (dt, J = 9.0, 3.5 Hz, 2H), 6.85 (dt, J = 9.5, 3.5 Hz, 2H), 5.19 (s, 2H), 3.96 (s, 3H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 11.1 (t, J = 18.8 Hz, 1F), 9.0 (d, J = 17.0 Hz, 1F), 5.2 (dd, J = 20.7, 1.9 Hz, 1F). ^{13}C-NMR (126 MHz, $CDCl_6$) δ_C {^{1}H, ^{19}F} 161.1, 156.6, 140.9, 140.1, 138.6, 137.5, 136.7, 133.0, 132.8, 117.2, 116.2, 109.9, 107.6, 51.9. IR, ν_{max}/cm^{-1} 3490, 3370, 2954, 1690, 1627, 1579, 1524, 1483, 1456, 1343, 1309, 1269, 1208, 1168, 1130, 1069, 1008, 950, 825, 761 and 737. HRMS expected for $C_{16}H_{10}BrF_3NO_4$ 415.9740 observed *m/z* 415.9740 [M + H$^+$].

2-Benzoyl-6-(4-bromophenoxy)-4,5,7-trifluoro-1-benzofuran-3-amine 4gc. 2-Hydroxyacetophenone (0.272 g, 2.00 mmol) and 4-(4-bromophenoxy)tetrafluorobenzonitrile (0.792 g, 2.29 mmol) in DMF gave **4gc** as a bright yellow solid (0.705 g; 77%) purified by chromatography and preparative TLC (eluting with light petroleum-ethyl acetate), mp 135–142 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 8.20 (tt, J = 8.4, 2.0 Hz, 2H), 7.58 (tt, J = 7.2, 1.8 Hz, 1H), 7.51 (tt, J = 6.8, 1.6 Hz, 2H), 7.43 (dt, J = 9.2, 3.2 Hz, 2H), 6.88 (dt, J = 9.2, 3.2 Hz, 2H), 6.17 (s, 2H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ_F 12.3 (dd, J = 20.7, 17.3 Hz, 1F), 9.8 (dd, J = 17.3, 1.5 Hz, 1F), 5.3 (m, J = 20.7, 1.5 Hz, 1F). ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C 183.0, 156.6, 141.3, 140.2, 140.0, 138.8, 137.7, 136.8, 136.2, 133.8, 132.8, 132.6, 129.2, 128.6, 117.5, 116.4, 109.3. IR, ν_{max}/cm^{-1} 3416, 3308, 2924, 1625, 1574, 1540, 1482, 1461, 1437, 1385, 1345, 1313, 1267, 1211, 1186, 1168, 1153, 1099, 1071, 1008, 916, 824, 735, 704, 683, 608, 549 and 493. HRMS expected for $C_{21}H_{12}BrF_3NO_3$ 461.9947 observed *m/z* 461.9942 [M + H$^+$].

(3-Amino-6-(4-bromophenoxy)-4,5,7-trifluorobenzofuran-2-yl)(4-methoxyphenyl)methanone 4gd. 2-Hydroxy-1-(4-methoxyphenyl)ethan-1-one **3d** (0.377 g, 2.27 mmol) and 4-(4-bromophenoxy)tetrafluorobenzonitrile (0.690 g, 1.99 mmol) in DMF gave **4gd** as a yellow solid (0.219 g, 22%) purified by chromatography eluting with light petroleum-ethyl acetate, mp 192–198 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 8.25 (dt, J = 10.0, 3.0 Hz, 2H), 7.43 (dt, J = 9.0, 2.0 Hz, 2H), 7.00 (dt, J = 9.0, 2.0 Hz, 2H), 6.89 (dt, J = 9.0, 2.0 Hz, 2H), 6.10 (s, 2H), 3.89 (s, 3H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 12.0 (dd, J = 20.7, 17.4 Hz, 1F), 9.5 (dd, J = 17.4, 1.4 Hz, 1F), 5.0 (dd, J = 20.7, 1.4 Hz, 1F). ^{13}C-NMR (126 MHz, $CDCl_6$) δ_C {^{1}H, ^{19}F} 181.6, 163.2, 156.7, 141.3, 140.0, 139.7, 138.7, 137.5, 136.3, 133.5, 132.8, 131.6, 129.6, 117.4, 116.3, 113.9, 109.4, 55.5. IR ν_{max}/cm^{-1} 3494, 3338, 2931, 2840, 1632, 1603, 1541, 1512, 1483, 1449, 1384, 1348, 1309, 1260, 1216, 1169, 1098, 1072, 1026, 1008, 920, 882, 846, 821, 760, 697, 631, 604, 582, 565 and 551.

Methyl 3-amino-4,5,7-trifluoro-6-(4-nitrophenoxy)-1-benzofuran-2-carboxylate 4ha. Methyl glycolate (0.15 mL, 2.00 mmol) and 4-(4-nitrophenoxy)tetrafluorobenzonitrile (0.656 g, 2.10 mmol) in DMF gave **4ha** as a light brown solid (0.222 g; 29%) purified by trituration with ether, mp 91–96 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 8.24 (dt, J = 9.5, 3.0 Hz, 2H), 7.06 (dt, J = 9.5, 3.0 Hz, 2H), 5.21 (s, 2H), 3.96 (m, 3H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 11.8 (t, J = 20.3 Hz, 1F), 10.5 (d, J = 17.0 Hz, 1F), 5.3 (dd, J = 20.7, 2.8 Hz, 1F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C 161.7, 161.1, 143.8, 141.0, 139.7, 138.5, 137.5, 137.2, 131.8, 127.2, 126.2, 115.7, 110.6, 52.0. IR, ν_{max}/cm^{-1} 3490, 3377, 2929, 2854, 1691, 1615, 1590, 1521, 1490, 1457, 1345, 1308, 1222, 1168, 1113, 1010, 949, 863 and 749. HRMS expected for $C_{16}H_{10}F_3N_2O_6$ 383.0485 observed *m/z* 383.0477 [M + H$^+$].

2-Benzoyl-4,5,7-trifluoro-6-(4-nitrophenoxy)-1-benzofuran-3-one 4hc. 2-Hydroxyacetophenone (0.269 g, 1.97 mmol) and 4-(4-nitrophenoxy)tetrafluorobenzonitrile (0.666 g, 2.13 mmol) in DMF gave **4hc** as a light brown solid (0.235 g; 27%) purified by trituration with ether, mp 121–127 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 8.25 (tt, J = 9.5, 3.5 Hz, 2H), 8.18 (m, 2H), 7.58 (tt, J = 7.0, 1.5 Hz, 1H), 7.52 (tt, J = 7.5, 1.5 Hz, 2H), 7.09 (tt, J = 9.0, 3.5 Hz, 2H), 6.18 (s, 2H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 12.9 (dd, J = 20.7, 17.4 Hz, 1F), 10.3 (dd, J = 17.4, 2.8 Hz, 1F), 5.4 (dd, J = 20.7, 2.8 Hz, 1F). ^{13}C-NMR (126 MHz, $CDCl_3$) δ_C 183.1, 161.7, 143.9, 141.4, 139.7, 138.6, 137.6, 136.7, 136.4, 132.7, 132.6, 129.2, 128.6, 126.2, 126.1, 115.8, 110.1. IR, ν_{max}/cm^{-1} 3056, 2934, 2853, 1617, 1592, 1523, 1490, 1456, 1346, 1265, 1222, 1167, 1113, 1011, 862, 738, 704 and 464. HRMS expected for $C_{21}H_{12}F_3N_2O_5$ 429.0693 observed *m/z* 429.0694 [M + H$^+$]. Elemental analysis requires $C_{21}H_{11}F_3N_2O_5$ C 58.89%, H 2.59% and N 6.54%, found C 58.54%, H 2.84% and N 6.42%.

(3-Amino-4,5,7-trifluoro-6-(4-nitrophenoxy)benzofuran-2-yl)(4-methoxyphenyl)methanone 4hd. 2-Hydroxy-1-(4-methoxyphenyl)ethan-1-one **3d** (0.335 g, 2.02 mmol) and 4-(4-nitrophenoxy)tetrafluorobenzonitrile (0.683 g, 2.19 mmol) in DMF gave an off-white solid **4hd** (0.138 g, 15%) purified by chromatography eluting with light petroleum-ethyl acetate, mp 172–180 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 8.28–8.23 (m, 4H), 7.12–7.08 (m, 2H), 7.03–7.00 (m, 2H), 6.12 (bs, 2H), 3.89 (s, 3H). ^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 12.7 (dd, J = 20.7, 17.4 Hz, 1F),

10.1 (dd, $J = 17.0$, 2.4 Hz, 1F), 5.2 (dd, $J = 20.7$, 2.8 Hz, 1F). ^{13}C-NMR (126 MHz, $CDCl_6$) δ_C {^{1}H, ^{19}F} 181.7, 163.4, 161.7, 143.9, 141.4, 139.6, 139.5, 138.5, 137.4, 136.5, 132.3, 131.5, 129.5, 126.2, 115.8, 113.9, 110.3, 55.6. IR, ν_{max}/cm^{-1} 3485, 3361, 2930, 2850, 1633, 1601, 1574, 1543, 1513, 1489, 1452, 1418, 1346, 1308, 1257, 1217, 1176, 1160, 1112, 1007, 918, 864, 851, 761, 695, 679, 645, 632, 570, 544 and 471. HRMS expected for $C_{22}H_{14}F_3N_2O_6$ 459.0798 observed m/z 459.0800 [M + H$^+$].

Investigations of carbonyl group cleavage

4-Benzimidazol-1-yltetrafluorobenzene **8a** was identified from cleavage of 4-benzimidazol-1-yltetrafluorobenzaldehyde in the presence of sodium methoxide.

4-Benzimidazol-1-yltetrafluorobenzene 8a. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 8.05 (s, 1H), 7.91–7.87 (m, 1H), 7.41–7.37 (m, 2H), 7.29–7.25 (m, 1H), 6.97 (m, 1H).

^{19}F-NMR (376 MHz, CDCl3) δ_F 25.8–25.6 (m, 2F), 16.5–16.3 (m, 2F).

IR, ν_{max}/cm^{-1} 3429, 2926, 2854, 2119, 1646, 1614, 1517, 1452, 1411, 1305, 1289, 1266, 1253, 1207, 1180, 1152, 1136, 1086, 1008, 991, 946, 889, 839, 782, 764, 742, 714 and 702.

LC-MS m/z 266.80.

HRMS calculated for $C_{13}H_7F_4N_2$ 267.0540, observed m/z 267.0540 [M + H]$^+$.

4-(2,3,5,6-Tetrafluorophenyl)morpholine 8e. Attempted reaction of 4-morpholinotetrafluorobenzaldehyde with methyl glycolate and DBU led to formation of an off-white solid **8e** in low yield.

^{1}H-NMR δ_H (400 MHz, $CDCl_3$) δ_H 6.69 (tt, $J = 9.9$, 7.1 Hz, 1H, H-1), 3.84–3.75 (m, 4H, H-2′/H-6′), 3.28–3.22 (m, 4H, H-3′/H-5′).

^{19}F-NMR δ_F (376 MHz, $CDCl_3$) δ_F 29.0–28.8 (2F, m), 18.2–18.0 (2F, m).

^{13}C-NMR δ_C (101 MHz, $CDCl_3$), 147.6 (dtd, $J = 245$, 12.5, 3.75 Hz), 145.6 (dtd, $J = 245$, 12.5, 3.75 Hz), 143.3 (ddt, $J = 244$, 14, 4 Hz) 141.4 (ddt, $J = 244$, 14, 4 Hz) 130.6 (t, $J = 11$ Hz), 99.7–98.6 (m), 67.4 (s, CH_2, C-3'/C-5′), 51.2 (s, CH_2, C-2′/C-6′).

IR, ν_{max}/cm^{-1} 3048 (C–H, aromatic), 2966–2863 (C–H, saturated), 1641–1450 (C=C, aromatic), 1378 (C–F), 1184 (C–N), 1137 (C–O).

LC-MS 236.15 [M + H]$^+$.

HRMS expected for $C_{10}H_{10}F_4NO$ 236.0676, observed m/z 236.0676 [M + H]$^+$.

Reaction of 4-morpholinotetrafluorobenzaldehyde 6ea with sodium methoxide in deuterated methanol – *D*-8e

Sodium (0.004 g, 0.2 mmol, 1.1 eq.) was dissolved in CD_3OD (1 mL). Then 4-morpholinotetrafluorobenzaldehyde **6ea** (0.050 g, 0.18 mmol, 1 eq.) was added and dissolved. The solution was heated under reflux for 2 h. Water (15 mL) was poured into the reaction mixture which was then extracted with ethyl acetate (3 × 15 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The residue (0.026 g) was taken up in CD_3OCD_3 and shown by NMR to be a mixture containing:

***D*-8e.** NMR δ_H (400 MHz, CD_3OCD_3) 6.69 (tt, $J = 9.9$, 7.1 Hz, integrates at <0.05 H, 95% deuterium incorporation).

IR ν_{max}/cm^{-1} 3584, 2960, 2893, 2855, 2225, 2132, 2073, 1693, 1629, 1472, 1389, 1375, 1342, 1298, 1264, 1148, 1113, 1069, 1047, 1034, 1047, 1008, 927, 895, 859 and 843.

HRMS expected for $C_{10}H_9DF_4NO$ 237.0756, observed m/z 237.0750 [M + H]$^+$. Deuterated product ***D*-8e**.

HRMS expected for $C_{10}H_{10}F_4NO$ 236.0693, observed m/z 236.0716 [M + H]$^+$. Non-deuterated product **8e**.

Reaction of pentafluorobenzaldehyde or pentafluoroacetophenone with sodium methoxide

Pentafluorobenzaldehyde or pentafluoroacetophenone (2 mmol) was dissolved in MeOH (3 mL) and NaOMe (10 mmol) was added at −10 °C and the solution was stirred and then heated under reflux for 15 h, during the course of the reaction the solution turned yellow. Water (10 mL) was then poured into the reaction mixture and extracted with $CDCl_3$ (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and filtered and submitted for NMR spectroscopy which showed mixtures from which the following were identified.

From pentafluorobenzaldehyde:

1,2,4,5-Tetrafluoro-3-methoxybenzene (minor). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.57–7.53 (m, 1H, CH), 4.01 (t, $J = 1.6$ Hz, 3H, OMe).

^{19}F-NMR (376 MHz, $CDCl_3$) δF 21.6–21.4 (m, 1F), 4.2–4.0 (m, 1F).

IR, ν_{max}/cm^{-1} 3467, 1623, 1509, 1469, 1378, 1285, 1196, 1125, 990, 896, 823, 759 and 562.

2,3,5-Trifluoro-4,6-dimethoxybenzaldehyde 14a. IR, ν_{max}/cm^{-1} 3584, 3391, 2951, 2852, 1696, 1649, 1611, 1493, 1479, 1430, 1400, 1361, 1292, 1268, 1203, 1141, 1039, 1003, 903, 811, 739, 703 and 622.

HRMS calculated for $C_9H_8F_3O_3$ 221.0420, observed m/z 221.0422 [M + H]$^+$.

From reaction with pentafluoroacetophenone:

2,3,5-Trifluoro-4,6-dimethoxyacetophenone 14b. HRMS calculated for $C_{10}H_{10}F_3O_3$ 235.0577, observed m/z 235.0576 [M + H]$^+$.

From both reactions:

1,2,4-Trifluoro-3,5-dimethoxybenzene 15. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 6.74–6.63 (m, 1H), 3.98 (t, $J = 2.0$ Hz, 3H), 3.93 (t, $J = 1.0$ Hz, 3H).

^{19}F-NMR (471 MHz, $CDCl_3$) δ_F 21.6–21.4 (m, 1F), 10.9 (s, 1F), 3.8–3.6 (m, 1F).

IR, ν_{max}/cm^{-1} 3584, 3400, 3003, 2950, 2844, 2586, 2420, 2345, 2308, 2043, 1986, 1943, 1893, 1711, 1616, 1515, 1476, 1424, 1380, 1352, 1295, 1263, 1206, 1179, 1130, 1099, 1045, 1003, 942, 896, 853, 774, 743, 700 and 600.

Conclusions

Twenty-seven aminobenzofurans, as potential drug leads were accessed *via* tandem S_NAr-cyclocondensation reaction of substituted perfluorobenzonitriles and α-hydroxycarbonyl compounds using DBU as base. The new compounds were characterized by IR spectroscopy, NMR spectroscopy, HRMS, and elemental analysis. The structure of (3-amino-4,5,7-trifluoro-6-morpholinobenzofuran-2-yl)(4-methoxyphenyl) methanone was determined by single crystal X-ray diffraction analysis.

Data availability

The data supporting this article have been included as part of the ESI.† Crystallographic data for compound **4ed** has been deposited at the CCDC under 231984 at **https://www.ccdc.cam.ac.uk/**.

Conflicts of interest

The authors declare no conflicts of interest.

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