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Imidazopyridine and pyrimidinopyridine systems from perfluorinated pyridine derivatives

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Abstract—Annelation of pentafluoropyridine via an intramolecular nucleophilic aromatic substitution process with benzamidine gave an imidazopyridine system in high yield in a two step process whilst alkyl amidines gave 4-aminotetrafluoropyridine by a competing elimination reaction. 4-Phenylsulfonyl tetrafluoropyridine reacts with amidines to give the corresponding imidazo[4,5-*b*]pyridine systems. In contrast, 4-cyanotetrafluoropyridine gave a [6,6]-fused pyrimidinopyridine system arising from initial nucleophilic substitution at the C-3 position of the pyridine ring followed by intramolecular cyclization onto the pendant cyano group. The systems prepared by this annelation methodology further demonstrate the utility of perfluorinated heterocyclic substrates for the synthesis of heterocyclic scaffolds that possess multiple functionality and have potential applications in the drug discovery arena.

1. Introduction

An essential part of a drug discovery programme is the identification and ready synthesis of new chemical entities that may provide leads to novel classes of valuable, pharmacologically important systems.[1] Consequently, for an increased chance of discovering lead compounds, libraries of molecules that maximise structural diversity are keenly sought. In particular, syntheses of molecules possessing multiple functionality and skeletal diversity, which can act as scaffolds for subsequent analogue synthesis, are an essential component of library design and construction. For example, the concept of privileged structures,[2] in which common structural sub-units of naturally occurring biologically active systems are identified, has led to the synthesis of libraries based upon an increasing variety of such core scaffolds. By differing strategies, Diversity Orientated Synthesis[3–5] (DOS) aims to develop wide ranging structural diversity from simple polyfunctional starting materials while Rapid Analogue Synthesis[6,7] (RAS) is a complementary approach that seeks to synthesise many analogues of structurally related derivatives of a biologically active system. Although these strategies are different in many respects, each relies upon the ready availability of low molecular weight, core scaffold molecules that bear multiple functionality and can be efficiently processed into more sophisticated molecular systems by a series of regio- and stereo-selective reactions.

A wide variety of low molecular weight heterocyclic systems have found application in the life science industries,[8,9] in part, due to the favourable combination of pharmacological properties possessed by these systems, according to the well-known Lipinski parameters.[10] Consequently, the synthesis of polyfunctional heterocyclic core scaffolds, such as benzopyrans, pyranocoumarins, benzimidazoles and benzofuran systems,[2] that may be used as privileged structures in parallel synthesis are increasingly valuable.[2] However, although, for example, polyfunctional pyridine systems and related bicyclic ring fused derivatives possessing a pyridine substructure have wide ranging bioactivity, it is surprising that even some of the most structurally simple nitrogenated bicyclic heterocycles are very difficult to access. Consequently, there exists a demand for the development of effective methodology for the synthesis of new nitrogen containing polyfunctional bicyclic scaffolds for library synthesis and subsequent biological screening programmes. Of course, many synthetic approaches to the synthesis of bicyclic systems have been developed to meet the demands of academia and industry with varying degrees of success.[8]

Recently, we described a general approach towards the synthesis of highly substituted [6,6]-ring fused nitrogen bicyclic heterocyclic systems from highly fluorinated heterocyclic

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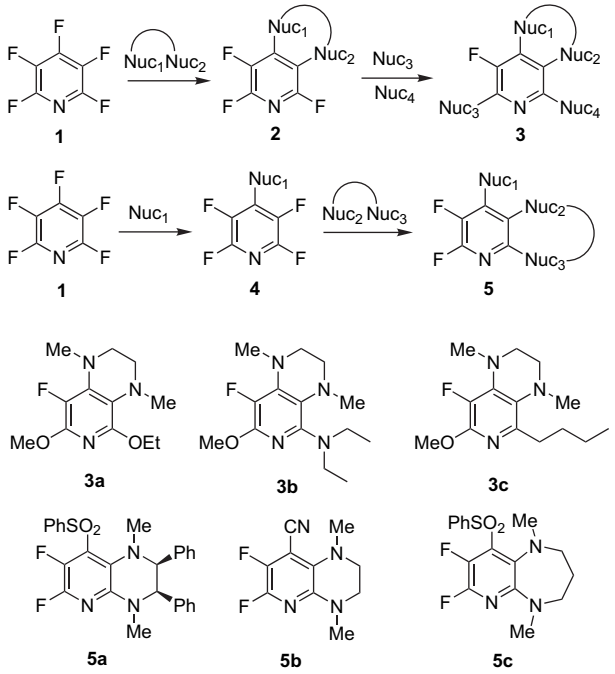
derivatives.[11–13] Reaction of pentafluoropyridine **1** with various 1,2-diamine nucleophiles gave tetrahydropyrido[3,4-*b*]pyridine systems **2**, which could be used as core scaffolds for the synthesis of substituted analogues **3** upon sequential reaction with successive nucleophiles. By an adaptation of this strategy, related tetrahydropyrido[2,3-*b*]pyridine systems **5**, for example, could also be accessed by reaction of **1** with a nucleophile to give **4** followed by subsequent annelation (Scheme 1).

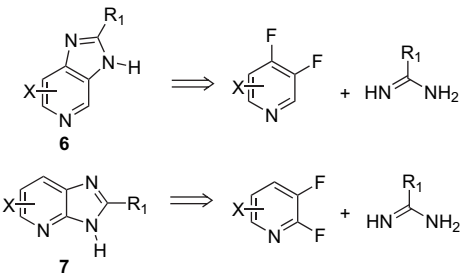


Scheme 1. Strategy for fused ring synthesis from perfluorinated pyridine derivatives.

This strategy relies upon the fact that highly fluorinated pyridine systems are very susceptible towards nucleophilic attack due to the presence of highly electronegative fluorine atoms attached to the heterocyclic ring[14,15] and the high regioselectivity of subsequent nucleophilic aromatic substitution processes on the 'core scaffolds'. In particular, we found that pentafluoropyridine, 4-phenylsulfonyl and 4-cyanotetrafluoropyridine derivatives were excellent starting materials for the synthesis of core tetrahydropyridopyrazine scaffolds that bear multiple functionality.

In this paper, we further develop our general annelation strategy to the synthesis of [5,6]-ring fused bicyclic systems by carrying out reactions of highly fluorinated pyridines and appropriate difunctional nitrogen nucleophiles. We targeted the synthesis of core scaffolds based upon the imidazopyridine structural units **6** and **7** (Scheme 2), in part, because molecules containing this heterocyclic skeleton possess a range of bioactivities.[16–20] Retrosynthetic analysis of imidazopyridine systems **6** and **7** shows that ring fused scaffolds should be accessible by reaction of a polyfluorinated pyridine system and an appropriate amidine.

Reported syntheses of imidazopyridines of type **6** and **7** almost always involve reaction of aldehyde or acid derivatives with 3,4- and 2,3-diaminopyridine systems, respectively.[21–26] However, multi-step syntheses of the



Scheme 2. Strategy for the synthesis of imidazopyridine systems.

diaminopyridine precursors and related analogues are not trivial and subsequent derivatisation to give a range of systems can be very difficult.

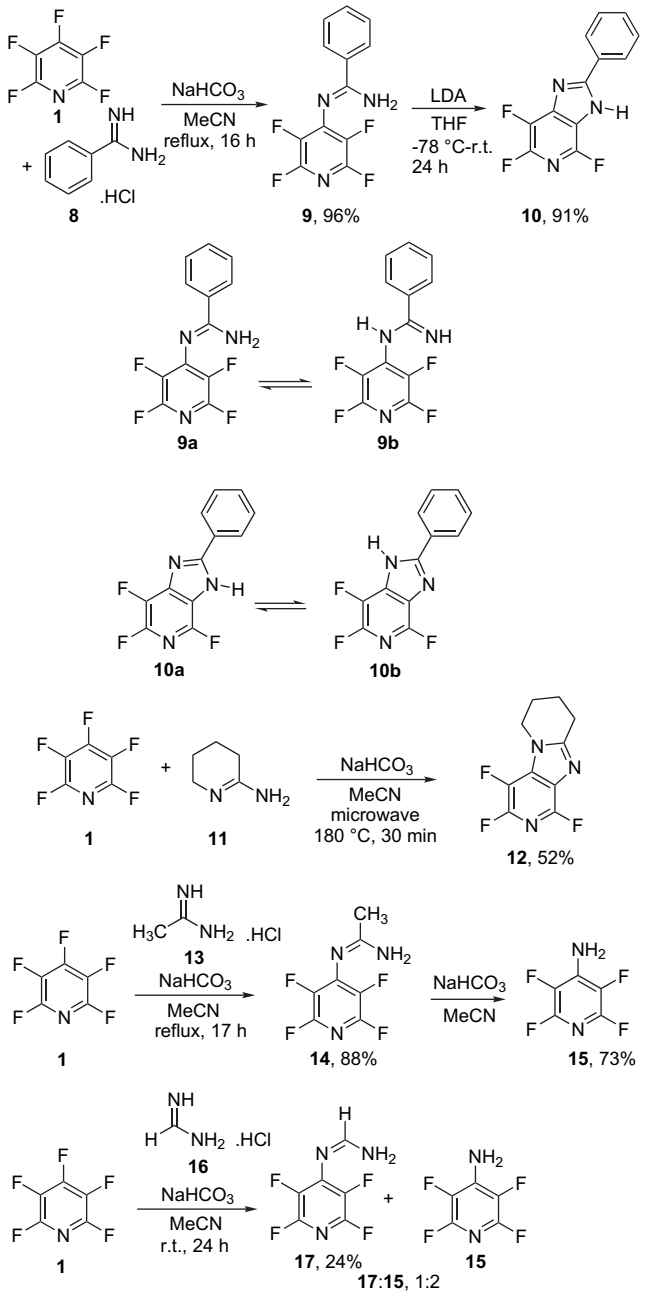
Here we report syntheses of imidazopyridine scaffolds **6** and **7** by reaction of perfluorinated pyridine substrates and various amidines, following the retrosynthetic strategy shown in Scheme 2. No reports of reactions between highly fluorinated pyridines and amidines have been described previously although related reactions involving urea and guanidine, which did not give bicyclic products, have been described by Coe.[27] Various imidazopyridine systems have been synthesised from highly fluorinated pyridine precursors, using complex multi-step strategies, and have been processed to deazaadenosine derivatives that possess useful biological activity.[28,29]

2. Results and discussion

Reaction of pentafluoropyridine **1** with benzamidine hydrochloride **8**, in the presence of sodium bicarbonate, led to the amidine **9**, arising from substitution of the most activated fluorine atom at the 4-position of the pyridine ring (Scheme 3). Subsequent addition of LDA to a solution of **9** in THF gave rise to the desired annelation product **10**, which could be readily purified by recrystallisation.

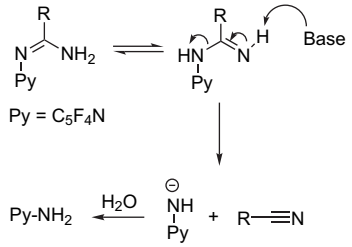
Both **9** and **10** exist as pairs of tautomers **9a/9b** and **10a/10b**, respectively, but, for simplicity, **9a** and **10a** are used to denote these scaffolds throughout this paper. The structure of **10** followed from NMR data and, in particular, the ^{19}F NMR spectrum showed three resonances at −82, −102 and −162 ppm in a 1:1:1 ratio. In attempts to synthesise **10** in a one-pot procedure from **1** using LDA in THF, we found that **10** was, indeed, formed but isolation from tarry material made purification tedious. Since microwave heating did not yield any cyclised product **10** by a one-step process either, we prefer to synthesise **10** by the two stage process described above.

2-Iminopiperidine **11** gave the tricyclic system **12** upon heating with **1** under microwave irradiation. (Scheme 3) Acetamidine **13** and **1** gave the analogous amidine **14** but all attempts to promote cyclisation to the desired imidazopyridine, using a variety of organic bases, gave 4-aminotetrafluoropyridine **15** as the only product in this particular case. Formamidine **16** and **1** gave a mixture of 4-amidine derivatives **17** and **15** in a 1:2 ratio upon reflux in acetonitrile. Attempted cyclization also led to conversion of **17** to 4-aminotetrafluoropyridine.



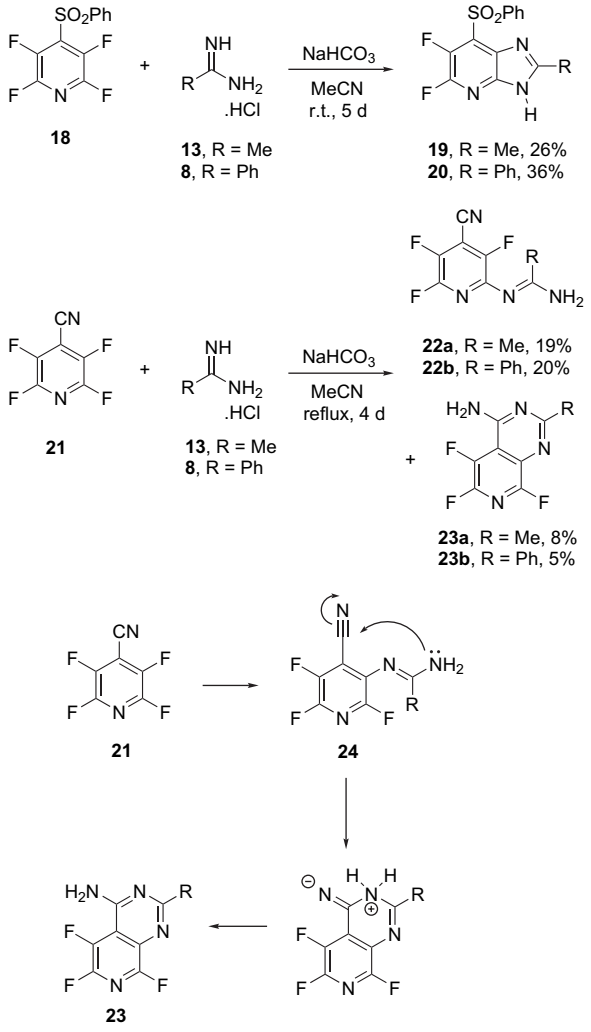
Scheme 3. Reactions of pentafluoropyridine with amidines.

A postulated mechanism for the elimination process that leads to **15** is shown in Scheme 4 and involves elimination of acetonitrile from the amidine substituent, adapting a mechanism postulated by Coe[27] concerning reactions between pentafluoropyridine and urea.



Scheme 4. Elimination reaction mechanism.

Given the successful synthesis of imidazopyridines **10** and **12**, we studied analogous reactions involving 4-phenylsulfonyl tetrafluoropyridine **18**. Both **13** and **8** gave annelated products **19** and **20** in one-pot processes in good yield, albeit after prolonged heating, following recrystallisation of the crude products (Scheme 5).



Scheme 5. Annelation reactions of **18** and **21**.

The reactions were monitored by ^{19}F NMR and we observed that initial nucleophilic attack of the amidine system on **18** occurs at both the 2 and the 3 positions of the pyridine ring in approximately 2:1 ratio, consistent with our earlier findings involving other nitrogen nucleophiles. Heating the reaction permitted cyclisation to occur, which for this system, of course, gives the ring fused product regardless of the site of initial attack.

The identity of **19** was confirmed by an X-ray crystallographic study of its methanol hemi-solvate. The molecular geometry of **19** does not show any unexpected features (Fig. 1a), and the molecules in the crystal are linked together in infinite chains along the *c*-axis by N–H···N and N–H···O (methanol) hydrogen bonds. The heterocyclic systems of adjacent molecules from the different chains are in an anti-parallel arrangement with the shortest interatomic distance equal to 3.185 Å (C1···C1).

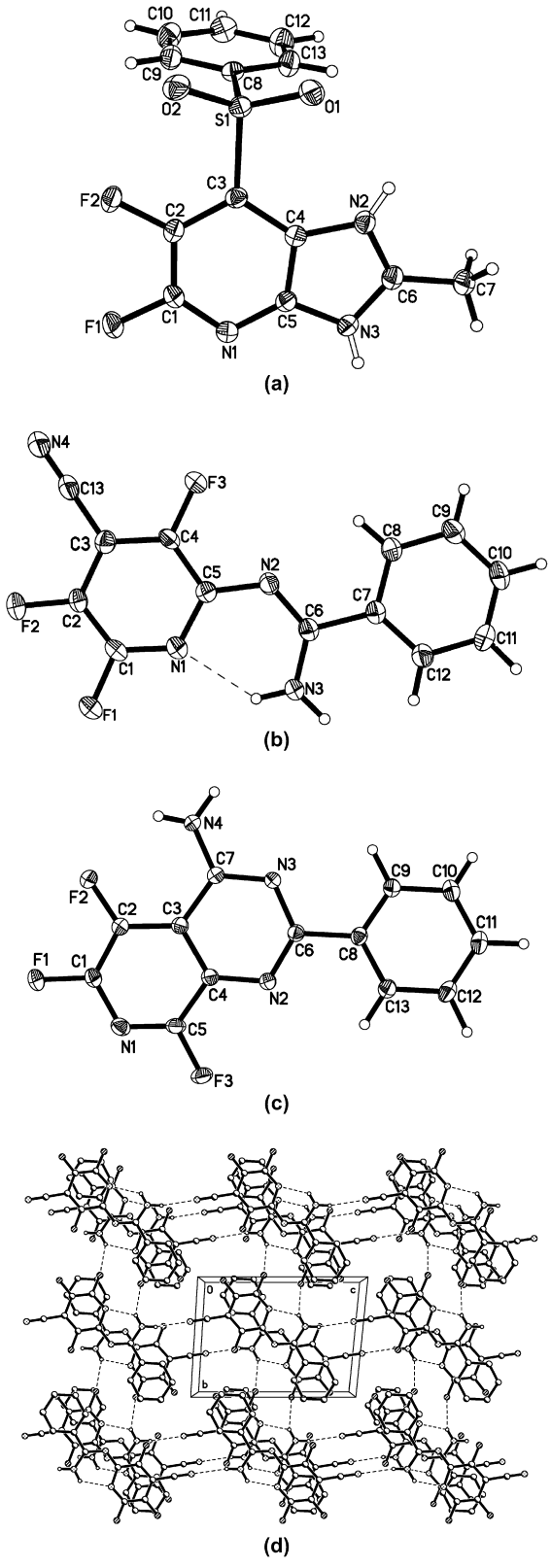
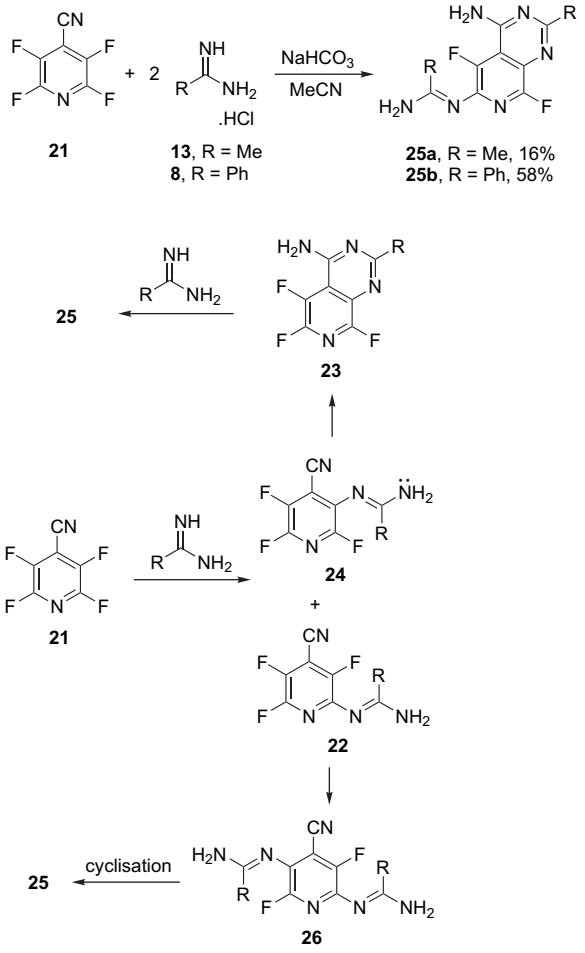


Figure 1. (a) Molecular structure of **19**. The hydrogen atom of the imidazole ring is disordered over two positions; (b) molecular structure of **22b**; (c) molecular structure of **23b**; (d) H-bonded stacks of the molecules in **22b**.

In contrast, reaction of 4-cyanopyridine **21** with 1 equiv of either **13** or **8** gave a mixture of two products **22** and **23** in a 1:1 ratio (Scheme 5), whose structures were confirmed by X-ray crystallography. Both molecules are planar (Fig. 1b–d) and the anti-parallel stacking in the crystals are typical for bicyclic fluoropyridine derivatives.[11–13] Molecule **22b** form the stacks along the *a*-axis while the molecule **23b** form layers, where each molecule is sandwiched between four adjacent molecules. Both stacks in the structure of **22b** and layers in the structure of **23b** are linked together by networks of N–H···N hydrogen bonds.

In both reactions, **22** is formed by nucleophilic substitution of the 2-fluorine whereas **23** arises from competing substitution of the 3-fluorine to give **24**, which is activated towards nucleophilic attack by the adjacent cyano group, as discussed in our previous paper,[13] followed by intramolecular cyclization onto the cyano group as outlined in the mechanism in Scheme 5.

Reaction of **21** with 2 equiv of either **13** or **8** gave only **25**, which could be formed by either of two possible pathways (Scheme 6).



Scheme 6. Formation of **25**.

Initially, **21** reacts with the amidine derivatives **13** and **8** to give **22** and **24**, in a 1:1 ratio. Then **22** reacts with a further equivalent of **8** to give **26**, arising from selective displacement of fluorine located at the 5-position. The 5-site is activated towards nucleophilic attack by the presence of *ortho*

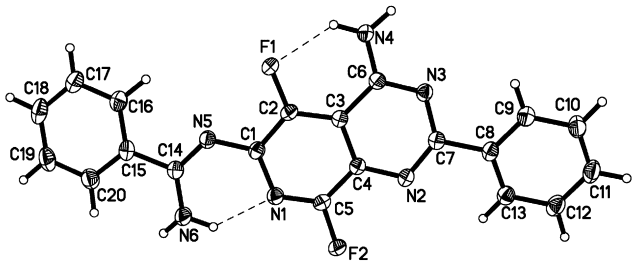
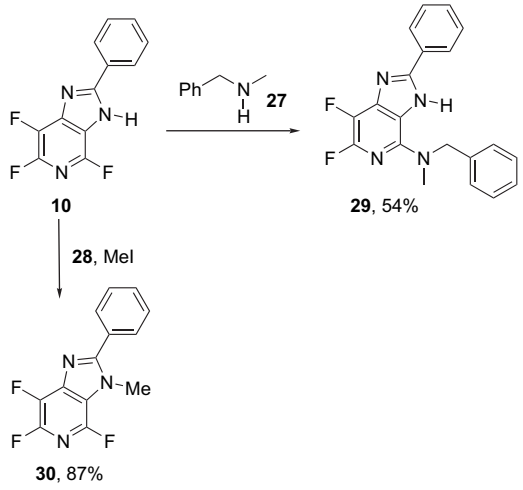


Figure 2. Molecular structure of **25b**.

cyano and fluorine substituents, *meta* fluorine and the absence of deactivating *para* fluorine atoms. Of course, the other sites on the pyridine ring in **26** are slightly deactivated by *para* fluorine atoms. Intramolecular cyclization of **26** gives **25** by the process indicated in Scheme 5. Cyclization of **24** gives **23**, which undergoes further regioselective nucleophilic substitution at the 6-position to give **25**. In **23**, the 6-position is activated by the *ortho* fluorine and ring nitrogen atoms and bears similarities to the regioselectivity of nucleophilic substitution processes of perfluoroisoquinoline.[14,15] Similar to molecules **22b** and **23b**, the molecule **25b** is planar (Fig. 2) and in the crystal lattice the molecules are arranged in anti-parallel dimers, linked in layers by N–H···N hydrogen bonds.

Reactions of scaffold **10** with *N*-methylbenzylamine **27** and methyl iodide **28** gave **29** and **30** (as a mixture of isomers), respectively, providing an indication of the types of molecules that could be readily accessed from this system (Scheme 7). Nucleophilic substitution occurs at the 2-position, in agreement with earlier work.[28]



Scheme 7. Reactions of scaffold **10**.

The structure of **29** has been determined by X-ray crystallographic study of its methanol solvate (1:2). The most noteworthy feature of the crystal packing of molecule **29** is the pattern of hydrogen bonds, which link molecules into chains along the *b*-axis and the molecules are connected by double methanol bridges (Fig. 3). The usual anti-parallel stacking arrangement exists between the molecules of adjacent chains.

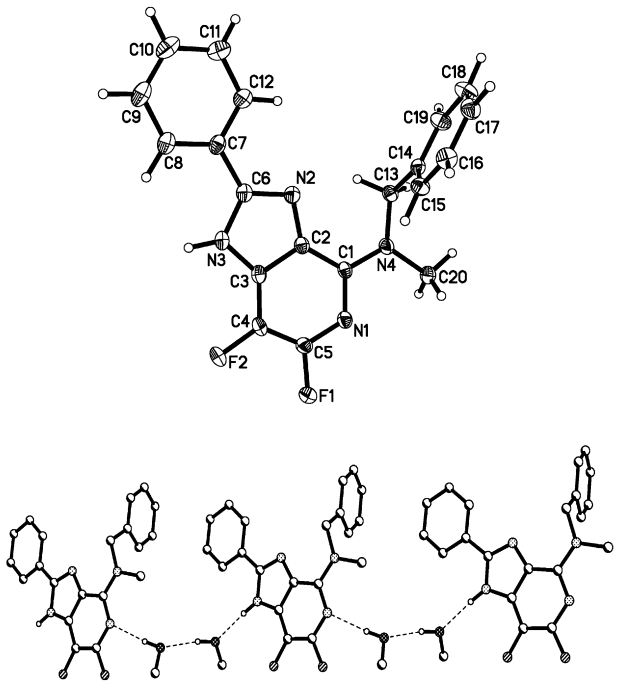


Figure 3. (a) Molecular structure of **29**; (b) H-bonded chains in the structure of **29**.

3. Conclusion

The strategy outlined in Schemes 1 and 2 has allowed short and efficient syntheses of target [5,6]-ring fused systems of types **6** and **7** by reaction of pentafluoropyridine and 4-phenylsulfonyl-tetrafluoropyridine, respectively, with appropriate difunctional amidine nucleophiles. In contrast, 4-cyanopyridine gave [6,6]-ring fused pyrimidino–pyridine system by intramolecular cyclization involving the cyano group. These initial studies and our earlier work[11,12] provide an indication of the large number of new fused [5,6] and [6,6]-bicyclic polyfunctional heterocyclic scaffolds that can, potentially, be accessed using our general annelation strategy involving reactions between highly fluorinated heterocycles and appropriate difunctional nucleophiles.

4. Experimental

4.1. General

All starting materials were obtained commercially. All solvents were dried using literature procedures. NMR spectra were recorded in deuterochloroform, unless otherwise stated, on a Varian VXR 400S NMR spectrometer operating at 500 MHz (^{1}H NMR), 376 MHz (^{19}F NMR) and 100 MHz (^{13}C NMR) with tetramethylsilane and trichlorofluoromethane as internal standards. 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. Accurate mass measurements were performed by the EPSRC National Mass Spectrometry service, Swansea, UK. Elemental analyses were obtained on an Exeter Analytical CE-440 elemental analyser. Melting

points and boiling points were recorded at atmospheric pressure unless otherwise stated and are uncorrected. The progress of reactions were monitored by ^{19}F NMR. Column chromatography was carried out on silica gel.

4.2. Formation of tetrafluoro-pyridin-4-yl amidine derivatives

4.2.1. *N*-(2,3,5,6-Tetrafluoro-pyridin-4-yl)benzamidine 9. Pentafluoropyridine **1** (6.76 g, 40 mmol), benzamidine hydrochloride **8** (13.78 g, 88 mmol) and sodium hydrogen carbonate (6.72 g, 80 mmol) were stirred under an atmosphere of argon in acetonitrile (400 ml) for 16 h at reflux temperature. The reaction mixture was poured into water (50 ml) and extracted with dichloromethane (3×40 ml). Drying ($MgSO_4$) and evaporation of the solvent gave *N*-(2,3,5,6-tetrafluoro-pyridin-4-yl)benzamidine **9** (10.35 g, 96%) as a white solid. Mp 157–159 °C (Found: C, 53.4; H, 2.6; N, 15.7. $C_{12}H_7F_4N_3$ requires: C, 53.54; H, 2.6; N, 15.6%); δ_H (Acetone-d_6) 8.01 (2H, m, H-2′), 7.56 (1H, m, H-4′), 7.49 (2H, m, H-3′), 7.02 (2H, s, NH_2); δ_F −94.90 (2F, m, F-2), −153.88 (2F, m, F-3); δ_C 159.44 (s, C=N), 144.73 (dm, $^1J_{CF}$ 236.6, C-2), 143.72 (m, C-4), 136.53 (dm, $^1J_{CF}$ 236.8, C-3), 134.94 (s, C-1′), 132.31 (s, C-4′), 129.32 (s, C-3′), 128.37 (s, C-2′); *m*/*z* (EI^+) 269 (100%, $[M]^+$), 253 (72), 249 (90), 77 (94).

4.2.2. *N*-(2,3,5,6-Tetrafluoro-pyridin-4-yl)acetamidine 14. Pentafluoropyridine **1** (3.38 g, 20.0 mmol), acetamidine hydrochloride **13** (4.16 g, 44.0 mmol) and sodium hydrogen carbonate (3.36 g, 40.0 mmol) were stirred under argon in dry acetonitrile for 17 h at reflux temperature. The reaction solvent was evaporated and the remaining residue treated with water (50 ml). Extraction by dichloromethane (3×40 ml), drying ($MgSO_4$) and evaporation of the solvent gave *N*-(2,3,5,6-tetrafluoro-pyridin-4-yl)acetamidine **14** (3.64 g, 88%) as an off-white solid. Mp 142–145 °C (Found: C, 40.6; H, 2.4; N, 20.2. $C_7H_5F_4N_3$ requires: C, 40.6; H, 2.4; N, 20.3%); δ_H (DMSO-d_6) 7.42 and 6.94 (2H, br s, NH_2), 1.97 (3H, s, CH_3); δ_F −94.96 (m, F-2), −154.09 (m, F-3); δ_C 161.15 (s, C-7), 143.34 (dm, $^1J_{CF}$ 237.3, C-2), 142.96 (m, C-4), 135.49 (dm, $^1J_{CF}$ 249.5, C-3), 20.65 (s, CH_3); *m*/*z* (EI^+) 207 (100%, $[M]^+$), 192 (82).

4.2.3. *N*-(2,3,5,6-Tetrafluoro-pyridin-4-yl)formamidine 17. Pentafluoropyridine **1** (1.69 g, 10 mmol), formamidine hydrochloride **16** (1.61 g, 20 mmol) and sodium hydrogen carbonate (3.36 g, 40 mmol) were stirred under argon in acetonitrile for 23 h at room temperature. The reaction mixture was treated with water (50 ml) and the organic products extracted into dichloromethane (3×40 ml). The organic phase was dried ($MgSO_4$) and evaporated to leave a brown waxy solid that consisted of **17** and 2,3,5,6-tetrafluoro-pyridin-4-ylamine **15** in a 1:2 ratio by ^{19}F NMR analysis.[30] Recrystallisation of this residue from acetonitrile gave *N*-(2,3,5,6-tetrafluoro-pyridin-4-yl)formamidine **17** (0.47 g, 24%) as a white crystalline solid. Mp 168–170 °C (Found: C, 37.2; H, 1.5; N, 21.8. $C_6H_3N_3F_4$ requires: C, 37.3; H, 1.6; N, 21.8%); δ_H (DMSO-d_6) 7.95 (3H, br m, NH_2, $NCHNH_2$); δ_F −95.17 (2F, m, F-2), −156.89 (2F, br m, F-3); δ_C 157.66 (s, $NCHNH_2$), 143.73 (m, C-4), 143.38 (dm, $^1J_{CF}$ 236.5, C-2), 135.97 (dm, $^1J_{CF}$ 248.9, C-3); *m*/*z* (EI^+) 193 (95%, $[M]^+$).

4.3. Attempted cyclisation of *N*-(2,3,5,6-tetrafluoro-pyridin-4-yl)acetamidine 14

LDA (1.11 ml, 1.8 M solution in heptane/THF/ethylbenzene, 2.0 mmol) was added to a stirred solution of *N*-(2,3,5,6-tetrafluoro-pyridin-4-yl)acetamidine **14** (0.21 g, 1.0 mmol) in dry THF (25 ml) at −78 °C, under an atmosphere of dry argon. After warming to room temperature, the solution was stirred for 65 h. After the addition of water (50 ml), the aqueous phase was extracted into DCM (3×40 ml). The organic phase was dried ($MgSO_4$) and evaporated to leave a brown oil, which was identified as 2,3,5,6-tetrafluoro-pyridin-4-ylamine **15** (0.12 g, 73%), which was not purified further. δ_F −96.2 (2F, m, F-2), −165.6 (2F, br m, F-3); *m*/*z* (EI^+) 166 ($[M]^+$, 100%); as compared to the literature data.[30]

4.4. Formation of imidazopyridine systems

4.4.1. 4,6,7-Trifluoro-2-phenyl-3*H*-imidazo[4,5-*c*]pyridine 10. LDA (17.19 ml, 1.8 M solution in heptane/THF/ethylbenzene, 30.9 mmol) was added to a stirred solution of *N*-(2,3,5,6-tetrafluoro-pyridin-4-yl)benzamidine **9** (3.79 g, 14.1 mmol) in dry THF (250 ml) at −78 °C, under an atmosphere of dry argon. After warming to room temperature, the solution was stirred for 24 h. The reaction mixture was evaporated and 0.5 M HCl solution (50 ml) added. Extraction of the aqueous layer by dichloromethane (3×40 ml) and drying ($MgSO_4$) followed by evaporation gave a brown crude solid. Recrystallisation from acetonitrile gave 4,6,7-trifluoro-2-phenyl-3*H*-imidazo[4,5-*c*]pyridine **10** (3.20 g, 91%) as an off-white solid. Mp 208–209 °C (Found: C, 57.8; H, 2.4; N, 17.0. $C_{12}H_6F_3N_3$ requires: C, 57.8; H, 2.4; N, 16.9%); δ_H (DMSO-d_6) 8.18 (2H, br m, H-2′), 7.56–7.52 (3H, br m, H-3′,4′); δ_F major tautomer (67% by ^{19}F NMR) −83.08 (1F, br s, F-6), −102.02 (1F, br s, F-4), −161.60 (1F, br s, F-7); minor tautomer (33%) −82.60 (1F, br s, F-6), −104.33 (1F, br s, F-4), −163.00 (1F, br s, F-7); δ_C 155.42 (br m, C-2), 143.80 (m, C-4), 142.50 (dm, $^1J_{CF}$ 228.5, C-6), 135.20 (br m, C-5c), 131.25 (s, C-4′), 129.53 (m, C-7), 128.95 (s, C-3′), 128.07 (s, C-1′), 127.26 (s, C-2′); *m*/*z* (EI^+) 249 ($[M]^+$, 100).

4.4.2. 1,3,4-Trifluoro-6,7,8,9-tetrahydro-dipyrido[1,2-*a*; 3′,4′-*d*]imidazole 12. Pentafluoropyridine **1** (0.30 g, 1.77 mmol), 2-iminopiperidine hydrochloride **11** (0.36 g, 2.67 mmol) and triethylamine (0.54 g, 5.34 mmol) were stirred together in a mixture of THF (11.25 ml) and DMSO (4.50 ml), in a sealed 20 ml vial, under microwave heating, for 30 min at 180 °C. The reaction mixture was evaporated to dryness, heated in THF (50 ml) and filtered to remove excess starting material. The product mixture was absorbed onto silica gel and purified by column chromatography (120 g silica column, 40–80% ethyl acetate in hexane) to give 1,3,4-trifluoro-6,7,8,9-tetrahydro-dipyrido[1,2-*a*; 3′,4′-*d*]imidazole **12** (0.21 g, 52%) as a white solid. Mp 175–178 °C (Found: C, 52.8; H, 3.4; N, 18.1. $C_{10}H_8F_3N_3$ requires: C, 52.9; H, 3.6; N, 18.5%); δ_H (DMSO-d_6) 4.36 (2H, t, $^3J_{HH}$ 6.0, H-6), 3.01 (2H, t, $^3J_{HH}$ 6.0, H-9), 2.05 (2H, m, H-7), 1.93 (2H, m, H-8); δ_C 156.11 (q, $^4J_{CF}$ 1.3, C-2a), 143.06 (dd, $^1J_{CF}$ 244.5, $^3J_{CF}$ 14.2, C-1), 141.02 (ddd, $^1J_{CF}$ 227.7, $^2J_{CF}$ 15.2, $^3J_{CF}$ 15.0, C-3), 134.44 (ddd, $^2J_{CF}$ 11.7, $^3J_{CF}$ 7.7, $^3J_{CF}$ 5.8, C-4′d), 129.57

(ddd, $^{1}J_{CF}$ 253.71, $^{2}J_{CF}$ 32.0, $^{4}J_{CF}$ 7.8, C-4), 125.57 (dd, $^{2}J_{CF}$ 34.8, $^{3}J_{CF}$ 3.2, C-3′d), 44.91 (d, $^{4}J_{CF}$ 2.8, C-6), 24.97 (s, C-9), 21.65 (s, C-7), 19.17 (s, C-8); δ_F −85.36 (dd, $^{3}J_{FF}$ 31.8, $^{4}J_{FF}$ 13.3, F-3), −104.36 (dd, $^{5}J_{FF}$ 22.0, $^{4}J_{FF}$ 13.4, F-1), −167.93 (m, F-4); *m*/*z* (ES$^+$) 228 (100%, [MH]$^+$).

4.4.3. 7-Benzenesulfonyl-5,6-difluoro-2-methyl-1*H*-imidazo[4,5-*b*]pyridine 19. 4-Benzenesulfonyl-2,3,5,6-tetrafluoropyridine **18** (1.46 g, 5 mmol), acetamidine **13** (0.95 g, 10 mmol) and sodium hydrogen carbonate (1.68 g, 20 mmol) were stirred together at room temperature under argon in acetonitrile (200 ml) for 120 h. The reaction mixture was poured into water (50 ml) and extracted into dichloromethane (4×30 ml). Drying ($MgSO_4$) and evaporation of the solvent gave a yellow solid. Recrystallisation from acetonitrile gave 7-benzenesulfonyl-5,6-difluoro-2-methyl-1*H*-imidazo[4,5-*b*]pyridine **19** (0.40 g, 26%) as yellow crystals. Mp 225–227 °C (Found: C, 50.5; H, 3.0; N, 13.8. $C_{13}H_9F_2N_3O_2S$ requires: C, 50.5; H, 2.9; N, 13.6%); δ_H (DMSO-d_6) 13.14 (1H, br s, NH), 8.11 (2H, m, H-2′), 7.77 (1H, m, H-4′), 7.68 (2H, m, H-3′), 2.42 (3H, s, CH_3); δ_F −93.18 (1F, d, $^{3}J_{FF}$ 28.2, C-5), −148.80 (1F, d, $^{3}J_{FF}$ 27.5, C-6); δ_C 159.44 (s, C-2), 147.80 (br m, C-4b), 147.05 (dd, $^{1}J_{CF}$ 232.0, $^{2}J_{CF}$ 17.3, C-5), 139.53 (s, C-1′), 136.94 (dd, $^{1}J_{CF}$ 257.7, $^{2}J_{CF}$ 32.5, C-6), 135.34 (s, C-4′), 130.05 (s, C-3′), 127.71 (s, C-2′), 122.91 (m, C-7), 121.55 (br m, C-5b), 15.31 (s, CH_3); *m*/*z* (EI$^+$) 309 (80%, [M]$^+$), 77 (100). Crystals suitable for X-ray crystallography were grown from MeOH.

4.4.4. 7-Benzenesulfonyl-5,6-difluoro-2-phenyl-1*H*-imidazo[4,5-*b*]pyridine 20. 4-Benzenesulfonyl-2,3,5,6-tetrafluoropyridine **18** (2.33 g, 8 mmol), benzamidine hydrochloride **8** (2.51 g, 16 mmol) and sodium hydrogen carbonate (2.69 g, 32 mmol) were stirred together at room temperature under argon in acetonitrile (300 ml) for 120 h. The reaction mixture was poured into water (50 ml) and extracted into dichloromethane (4×30 ml). Drying ($MgSO_4$) and evaporation of the solvent gave a yellow solid. Recrystallisation from acetonitrile gave 7-benzenesulfonyl-5,6-difluoro-2-phenyl-1*H*-imidazo[4,5-b]pyridine **20** (1.1 g, 36%) as a yellow powder. Mp 241–245 °C (Found: C, 58.3; H, 3.0; N, 11.6. $C_{18}H_{11}F_2N_3O_2S$ requires: C, 58.2; H, 3.0; N, 11.3%); δ_H (DMSO-d_6) 8.25 (2H, m, C-2′), 8.22 (2H, m, C-2″), 7.80 (1H, m, C-4′), 7.70 (2H, m, C-3′), 7.61–7.58 (3H, m, C-3″,4″); δ_F −91.33 (1F, d, $^{3}J_{FF}$ 27.9, F-5), −147.73 (1F, m, F-6); δ_C 156.42 (br m, C-2, C-4b), 147.92 (dd, $^{1}J_{CF}$ 236.1, $^{2}J_{CF}$ 18.0, C-5), 139.99 (s, C-1′), 138.06 (dd, $^{1}J_{CF}$ 259.6, $^{2}J_{CF}$ 31.1, C-6), 135.13 (s, C-4′), 131.43 (s, C-4″), 129.70 (s, C-3′), 129.08 (s, C-3″), 128.63 (s, C-2′), 128.34 (s, C-2″), 127.52 (br s, C-1″, C-7), 125.99 (br m, C-5b); *m*/*z* (EI$^+$) 371 ([M]$^+$, 100%).

4.4.5. *N*-(4-Cyano-3,5,6-trifluoro-pyridin-2-yl)acetamidine 22a and 5,6,8-trifluoro-2-methyl-pyrido[3,4-*d*]pyrimidin-4-ylamine 23a. 2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile **21** (0.44 g, 2.5 mmol), acetamidine **13** (0.24 g, 2.5 mmol) and sodium hydrogen carbonate (0.42 g, 5.0 mmol) were stirred together under argon in acetonitrile (100 ml) for 7 d. Evaporation under reduced pressure was followed by treatment with water (50 ml). Extraction of the organic products by dichloromethane (3×40 ml), drying ($MgSO_4$), filtering and evaporation gave a brown/black solid. Filtration of the crude material through alumina (dichloromethane as eluent) gave *N*-(4-cyano-3,5,6-trifluoro-pyridin-2-yl)acetamidine **22a** (0.09 g, 17%) as a yellow solid. ([MH]$^+$ 215.0540. $C_8H_6F_3N_4$ requires [MH]$^+$ 215.0539); δ_H (DMSO-d_6) 8.02–7.76 (2H, br m, NH_2), 2.04 (3H, s, CH_3); δ_F −88.94 (dd, $^{3}J_{FF}$ 29.5, $^{5}J_{FF}$ 26.2, F-6), −124.26 (m, F-5), −145.02 (dd, $^{5}J_{FF}$ 23.2, $^{4}J_{FF}$ 6.9, F-3); δ_C 163.35 (s, C-7), 147.91 (ddd, $^{1}J_{CF}$ 266.6, $^{2}J_{CF}$ 6.2, $^{4}J_{CF}$ 3.1, C-6), 144.61 (m, C-2), 143.38 (ddd, $^{1}J_{CF}$ 232.1, $^{2}J_{CF}$ 13.1, $^{3}J_{CF}$ 3.3, C-5), 136.55 (dd, $^{1}J_{CF}$ 263.2, $^{3}J_{CF}$ 34.6, C-3), 108.43 (m, C-8), 102.19 (m, C-4), 21.26 (s, CH_3); *m*/*z* (EI) 214 (90%, [M]$^+$), 197 (100). Washing the alumina with methanol followed by recrystallisation of the residue from acetonitrile gave 5,6,8-trifluoro-2-methyl-pyrido[3,4-*d*]pyrimidin-4-ylamine **23a** (0.04 g, 8%) as an orange solid. ([MH]$^+$ 215.0541. $C_8H_6N_4F_3$ requires [MH]$^+$ 215.0545); δ_H (DMSO-d_6) 8.56 (2H, br s, NH_2), 2.46 (3H, s, CH_3); δ_F −77.42 (dd, $^{3}J_{FF}$ 35.1, $^{4}J_{FF}$ 14.0, F-6), −100.78 (dd, $^{5}J_{FF}$ 22.1, $^{4}J_{FF}$ 14.0, F-8), −145.35 (dd, $^{3}J_{FF}$ 35.0, $^{5}J_{FF}$ 22.2, F-5); δ_C 166.42 (s, C-2), 158.18 (d, $^{3}J_{CF}$ 3.4, C-4), 149.36 (ddd, $^{1}J_{CF}$ 252.4, $^{2}J_{CF}$ 11.0, $^{3}J_{CF}$ 2.2, C-6), 140.99 (ddd, $^{1}J_{CF}$ 234.4, $^{3}J_{CF}$ 18.3, $^{4}J_{CF}$ 13.3, C-8), 136.74 (ddd, $^{1}J_{CF}$ 258.6, $^{2}J_{CF}$ 27.0, $^{4}J_{CF}$ 7.1, C-5), 134.30 (dm, $^{2}J_{CF}$ 28.3, C-3d), 112.78 (m, C-4d), 25.80 (s, CH_3).

4.4.6. *N*-(4-Cyano-3,5,6-trifluoro-pyridin-2-yl)benzamidine 22b and 5,6,8-trifluoro-2-phenyl-pyrido[3,4-*d*]-pyrimidin-4-ylamine 23b. 2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile **21** (0.44 g, 2.5 mmol), benzamidine hydrochloride **8** (0.39 g, 2.5 mmol) and sodium hydrogen carbonate (0.42 g, 5.0 mmol) were stirred together under argon in acetonitrile (100 ml) for 7 d at 80 °C. The reaction mixture was treated with water (50 ml) and extracted into dichloromethane (3×40 ml). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure to give an orange/red crude solid. Column chromatography on alumina (dichloromethane/hexane 3:2) gave *N*-(4-cyano-3,5,6-trifluoro-pyridin-2-yl)benzamidine **22b** (0.14 g, 20%) as a pale yellow solid. Mp 123–124 °C (Found; C 56.2; H, 2.6; N, 20.2. $C_{13}H_7F_3N_4$ requires; C, 56.5; H, 2.6; N, 20.3%); δ_H (DMSO-d_6) 8.37 (2H, br s, NH_2), 8.02 (2H, m, H-2′), 7.58 (1H, m, H-4′), 7.51 (2H, m, H-3′); δ_F −88.90 (dd, $^{3}J_{FF}$ 30.0, $^{5}J_{FF}$ 25.2, F-6), −123.03 (dd, $^{3}J_{FF}$ 29.4, $^{4}J_{FF}$ 7.0, F-5), −144.10 (dd, $^{5}J_{FF}$ 25.0, $^{4}J_{FF}$ 6.5, F-3); δ_C 159.44 (s, C-7), 148.53 (ddd, $^{1}J_{CF}$ 268.0, $^{2}J_{CF}$ 7.5, $^{4}J_{CF}$ 3.2, C-6), 145.01 (m, C-2), 143.39 (ddd, $^{1}J_{CF}$ 234.2, $^{2}J_{CF}$ 13.7, $^{3}J_{CF}$ 3.9, C-5), 136.88 (dd, $^{1}J_{CF}$ 264.6, $^{3}J_{CF}$ 34.1, C-3), 134.60 (s, C-1′), 131.51 (s, C-4′), 128.40 (s, C-3′), 127.75 (s, C-2′), 108.39 (m, C-8), 102.50 (m, C-4); *m*/*z* (EI$^+$) 276 (78%, [M]$^+$), 257.0 (100). Crystals suitable for X-ray crystallography were grown from acetonitrile. Recrystallisation of the remaining crude material recovered from the silica column from acetonitrile gave 5,6,8-trifluoro-2-phenyl-pyrido[3,4-*d*]pyrimidin-4-ylamine **23b** (0.036 g, 5%) as a yellow solid. Mp 220–223 °C (Found; C 56.1; H, 2.5; N, 20.4. $C_{13}H_7F_3N_4$ requires; C, 56.5; H, 2.6; N, 20.3%); δ_H (DMSO-d_6) 8.67 and 7.9 (2H, br s, NH_2), 8.40 (2H, m, H-2′), 7.54–7.48 (3H, m, H-3′,4′); δ_F −76.92 (dd, $^{3}J_{FF}$ 34.9, $^{4}J_{FF}$ 14.0, F-6), −100.11 (dd, $^{5}J_{FF}$ 21.7, $^{4}J_{FF}$ 13.8, F-8), −145.26 (dd, $^{3}J_{FF}$ 35.3, $^{5}J_{FF}$ 22.0, F-5); δ_C 161.84 (s, C-2), 158.65 (d, $^{3}J_{CF}$ 3.4, C-4), 149.93 (ddd, $^{1}J_{CF}$ 253.8, $^{3}J_{CF}$ 10.7, $^{4}J_{CF}$ 2.0, C-8), 141.40 (ddd, $^{1}J_{CF}$ 236.5, $^{3}J_{CF}$ 18.6, $^{3}J_{CF}$ 13.5, C-6), 136.87 (ddd,

$^{1}J_{CF}$ 259.6, $^{2}J_{CF}$ 27.5, $^{4}J_{CF}$ 7.1, C-5), 136.81 (s, C-1′), 134.76 (dm, $^{2}J_{CF}$ 31.4, C-3d), 131.19 (s, C-4′), 128.52 (s, C-3′), 128.10 (s, C-2′), 113.41 (m, C-4d); *m/z* (EI^{+}) 276 (100%, [M]$^{+}$), 260 (49). Crystals suitable for X-ray crystallography were grown from acetonitrile.

4.4.7. *N*-(4-Amino-5,8-difluoro-2-methyl-pyrido[3,4-*d*]pyrimidin-6-yl)acetamidine 25a. 2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile **21** (0.44 g, 2.5 mmol), acetamidine **13** (0.47 g, 5.0 mmol) and sodium hydrogen carbonate (0.84 g, 10.0 mmol) were stirred together under argon in acetonitrile (100 ml) for 72 h at 80 °C. The reaction mixture was treated with water (100 ml) and the organic products were extracted into DCM (3×100 ml). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting crude was recrystallised from acetonitrile to give *N*-(4-amino-5,8-difluoro-2-methyl-pyrido[3,4-*d*]pyrimidin-6-yl)acetamidine **25a** (0.10 g, 16%) as a yellow solid. Mp 224–228 °C; ([MH]$^{+}$ 253.1009. $C_{10}H_{11}F_2N_6$ requires [MH]$^{+}$ 253.1013); δ_H (DMSO-d_6) 8.02 and 7.17 (4H, br s, NH_2), 2.41 (3H, s, C-10), 1.92 (3H, s, C-11); δ_F −98.58 (d, $^{5}J_{FF}$ 28.12, C-8), −155.18 (d, $^{5}J_{FF}$ 27.88, C-5); δ_C 163.69 (s, C-2), 160.61 (s, C-9), 158.92 (m, C-4), 154.29 (dd, $^{2}J_{CF}$ 12.9, $^{3}J_{CF}$ 3.0, C-6), 143.52 (dd, $^{1}J_{CF}$ 226.2, $^{4}J_{CF}$ 15.6, C-8), 140.05 (m, C-3d), 132.30 (dd, $^{1}J_{CF}$ 254.9, $^{4}J_{CF}$ 30.7, C-5), 110.06 (dd, $^{2}J_{CF}$ 8.2, $^{3}J_{CF}$ 3.2, C-4d), 25.80 (s, C-11), 20.78 (s, C-10).

4.4.8. *N*-(4-Amino-5,8-difluoro-2-phenyl-pyrido[3,4-*d*]pyrimidin-6-yl)benzamidine 25b. 2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile **21** (0.44 g, 2.5 mmol), benzamidine hydrochloride **8** (0.78 g, 5.0 mmol) and sodium hydrogen carbonate (0.84 g, 10.0 mmol) were stirred together under argon in acetonitrile (100 ml) for 170 h at 80 °C. The reaction mixture was treated with water (50 ml) and the organic products extracted into dichloromethane (3×40 ml). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. Recrystallisation from acetonitrile gave *N*-(4-amino-5,8-difluoro-2-phenyl-pyrido[3,4-*d*]pyrimidin-6-yl)benzamidine **25b** (1.09 g, 58%) as a yellow solid. Mp 215–216 °C; ([MH]$^{+}$ 377.1320. $C_{20}H_{15}F_2N_6$ requires [MH]$^{+}$ 377.1321); δ_H (DMSO-d_6) 8.41 (2H, m, H-2′), 8.21, 7.76 and 7.38 (4H, br s, NH_2), 8.11 (2H, m, H-2″), 7.55–7.47 (6H, m, H-3′,3″,4′,4″); δ_F −97.79 (d, $^{5}J_{FF}$ 28.0, F-8), −153.97 (d, $^{5}J_{FF}$ 29.3, F-5); δ_C 159.59 (s, C-2), 159.35 (m, C-4), 157.80 (s, C-9), 154.90 (dd, $^{2}J_{CF}$ 12.8, $^{3}J_{CF}$ 3.7, C-6), 144.19 (dd, $^{1}J_{CF}$ 227.9, $^{4}J_{CF}$ 16.9, C-8), 140.25 (m, C-3d), 137.82 (s, C-1′), 135.64 (s, C-1″), 132.99 (dd, $^{1}J_{CF}$ 254.8, $^{4}J_{CF}$ 30.8, C-5), 130.87 (s, C-4″), 130.42 (s, C-4′), 128.35 (s, C-3′), 128.31 (s, C-3″), 127.80 (s, C-2′), 127.65 (s, C-2″), 110.99 (dd, $^{2}J_{CF}$ 8.3, $^{3}J_{CF}$ 3.6, C-4d); *m/z* (ES^{+}) 377 (100%, [MH]$^{+}$). Crystals suitable for X-ray crystallography were grown from acetonitrile.

4.4.9. Benzyl(6,7-difluoro-2-phenyl-3*H*-imidazo[4,5-*c*]pyridine-4-yl)methyl-amine 29. 4,6,7-Trifluoro-2-phenyl-3*H*-imidazo[4,5-*c*]pyridine **10** (0.0555 g, 0.2227 mmol) and *N*-benzylmethylamine **27** (0.1349 g, 1.1136 mmol) were stirred together in THF (2.25 ml) and DMSO (0.90 ml) at 180 °C (microwave) for 30 min. The reaction solvents were evaporated and the crude material dissolved in methanol/DMSO (1:1 mixture, 2 ml). Mass directed auto purification gave benzyl-(6,7-difluoro-2-phenyl-3*H*-imidazo[4,5-*c*]pyridine-4-yl)methyl-amine **29** (0.0424 g, 54%) as a white solid. Mp 79–83 °C; ([MH]$^{+}$ 351.1416. $C_{20}H_{16}F_2N_4$ requires [MH]$^{+}$ 351.1416); δ_H (DMSO-d_6) 10.05 (1H, br s, NH), 7.99–7.89 (2H, m, H-2′), 7.50–7.43 (3H, m, H-3′,4′), 7.37 (2H, d, $^{3}J_{HH}$ 7.6, H-2″), 7.33 (2H, t, $^{3}J_{HH}$ 7.6, H-3″), 7.27 (1H, t, $^{3}J_{HH}$ 7.6, H-4″), 5.34 (2H, s, CH_2), 3.35 (3H, s, CH_3); δ_F (DMSO-d_6) −100.09 (1F, d, $^{3}J_{FF}$ 27.1, F-6), −174.97 (1F, d, $^{3}J_{FF}$ 26.9, F-7); *m/z* (ES^{+}) 351 (100%, [MH]$^{+}$).

4.4.10. 4,6,7-Trifluoro-*N*-methyl-2-phenyl-3*H*-imidazo[4,5-*c*]pyridine 30. Butyllithium (1.4 ml, 1.6 M solution in hexanes) was added to a stirring solution of 4,6,7-trifluoro-2-phenyl-3*H*-imidazo[4,5-*c*]pyridine **10** (0.49 g, 2.0 mmol) in THF (40 ml), at −78 °C. After 1 h, methyl iodide **28** (0.37 ml, 6.0 mmol) was added to the reaction mixture and the vessel allowed to warm to room temperature. After 18 h, the resulting mixture was poured into water (50 ml) and extracted into dichloromethane (3×40 ml). Drying ($MgSO_4$) and evaporation gave a pale yellow solid. Column chromatography on silica gel (ethyl acetate/hexane, 1:1) gave 4,6,7-trifluoro-*N*-methyl-2-phenyl-3*H*-imidazo[4,5-*c*]pyridine **30** (0.46 g, 87%) as a mixture of isomers. Mp 103–106 °C (Found: C, 59.3; H, 3.0; N, 16.0. $C_{13}H_8F_3N_3$ requires: C, 59.3; H, 3.1; N, 16.0%); δ_H 7.77–7.52 (5H, m, Ar-H), 4.05 (3H, m, CH_3); δ_F major isomer (52% by ^{19}F NMR) −81.59 (dd, $^{3}J_{FF}$ 32.3, $^{4}J_{FF}$ 12.9, F-6), −100.51 (dd, $^{5}J_{FF}$ 20.6, $^{4}J_{FF}$ 13.1, F-4), −169.39 (dd, $^{3}J_{FF}$ 32.6, $^{5}J_{FF}$ 20.8, F-7); minor isomer (48%) −86.67 (dd, $^{3}J_{FF}$ 32.8, $^{4}J_{FF}$ 13.9, F-6), −102.59 (dd, $^{5}J_{FF}$ 18.8, $^{4}J_{FF}$ 14.2, F-4), −162.18 (dd, $^{3}J_{FF}$ 33.0, $^{5}J_{FF}$ 19.1, F-7); δ_C 159.79–119.61, 34.09 (m, CH_3); *m/z* (EI^{+}) 263 (60%, [M]$^{+}$), 262 (100).

4.5. X-ray crystallography

The data were collected on a Bruker SMART CCD 6K (**19**, **22b**, **23b** and **25b**) and Bruker APEX Proteum-M CCD (**29**) at 120 K using graphite monochromated Mo Kα radiation (λ=0.71073 Å). All structures were solved by direct method and refined by full-matrix least squares on F^2 for all data using SHELXL software. All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms were found in the difference Fourier maps and refined isotropically except those of the disordered solvent methanol molecules in the structure of **19**, which were placed in calculated positions and refined using 'riding model'. Crystallographic data for the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 636999–637003.

4.5.1. Crystal data for 19. $C_{13}H_9F_2N_3O_2S\cdot 0.5CH_3OH$, M=325.31, monoclinic, space group $C2/c$, a=16.2592(3), b=10.1481(2), c=17.6509(3) Å, β=112.20(1)°, U=2696.48(9) Å^3, $F(000)$=1336, Z=8, D_c=1.603 mg m^{-3}, μ=0.278 mm^{-1}, 12,057 reflections ($2.42\leq\theta\leq29.00°$), 3579 unique data (R_{merg}=0.0449). Final $wR_2(F^2)$=0.0972 for all data (244 refined parameters), conventional $R_1(F)$=0.0349 for 3107 reflections with $I\geq2\sigma$, GOF=1.021.

4.5.2. Crystal data for 22b. $C_{13}H_7F_3N_4$, M=276.23, triclinic, space group P-1, a=6.7260(8), b=8.175(1), c=10.908(1) Å, α=94.36(1), β=90.07(1), γ=104.96(1)°,

U=577.7(1) Å^3, F(000)=280, Z=2, D_c=1.588 mg m^{-3}, μ=0.134 mm^{-1}; 4956 reflections (1.87≤θ≤28.00°), 2757 unique data (R_{merg}=0.079). Final $wR_2(F^2)$=0.0946 for all data (209 refined parameters), conventional $R_1(F)$=0.0508 for 1380 reflections with $I\geq 2\sigma$, GOF=0.941.

4.5.3. Crystal data for 23b. $C_{13}H_7F_3N_4$, M=276.23, orthorhombic, space group *Fdd*2, a=25.0648(3), b=25.7841(3), c=6.9063(1) Å, U=4463.4(1) Å^3, F(000)=2240, Z=16, D_c=1.644 mg m^{-3}, μ=0.139 mm^{-1}, 13,639 reflections (2.27≤θ≤29.00°), 1602 unique data (R_{merg}=0.0584). Final $wR_2(F^2)$=0.0918 for all data (209 refined parameters), conventional $R_1(F)$=0.0321 for 1543 reflections with $I\geq 2\sigma$, GOF=1.108.

4.5.4. Crystal data for 25b. $C_{20}H_{14}F_2N_6$, M=376.37, orthorhombic, space group *Pbca*, a=11.3937(2), b=8.9080(2), c=33.5493(7) Å, U=3405.1(1) Å^3, F(000)=1552, Z=8, D_c=1.468 mg m^{-3}, μ=0.108 mm^{-1}, 23,179 reflections (2.16≤θ≤28.00°), 4108 unique data (R_{merg}=0.0538). Final $wR_2(F^2)$=0.1106 for all data (309 refined parameters), conventional $R_1(F)$=0.0388 for 2817 reflections with $I\geq 2\sigma$, GOF=1.030.

4.5.5. Crystal data for 29. $C_{20}H_{16}F_2N_4\cdot 2CH_3OH$, M=414.45, triclinic, space group *P*1, a=10.0524(9), b=11.0747(9), c=11.3796(10) Å, α=111.62(3), β=94.38(3), γ=116.04(3)°, U=1014.3(2) Å^3, F(000)=436, Z=2, D_c=1.357 mg m^{-3}, μ=0.101 mm^{-1}, 10,683 reflections (2.62≤θ≤29.00°), 5260 unique data (R_{merg}=0.0337). Final $wR_2(F^2)$=0.1119 for all data (367 refined parameters), conventional $R_1(F)$=0.0389 for 4070 reflections with $I\geq 2\sigma$, GOF=1.010.

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References and notes

1. Gordon, E. M.; Kerwin, J. F. *Combinatorial Chemistry and Molecular Diversity in Drug Discovery*; John Wiley and Sons: New York, NY, 1998.
2. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.
3. Schrieber, S. L. *Science* **2000**, *287*, 1964.
4. Schrieber, S. L. *Chem. Eng. News* **2003**, *March 3*, 51.
5. Spring, D. R. *Org. Biomol. Chem.* **2003**, *1*, 3867.
6. Collins, I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2845.
7. Collins, I. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1921.
8. Katritzky, A. R.; Rees, C. W. *Comprehensive Heterocyclic Chemistry*; Pergamon: Oxford, 1984; Vols. 1–8.
9. Pozharskii, A. F.; Soldantenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society*; John Wiley and Sons: New York, NY, 1997.
10. Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Delivery Rev.* **1997**, *23*, 3.
11. Sandford, G.; Slater, R.; Yufit, D. S.; Howard, J. A. K.; Vong, A. *J. Org. Chem.* **2005**, *70*, 7208.
12. Baron, A.; Sandford, G.; Slater, R.; Yufit, D. S.; Howard, J. A. K.; Vong, A. *J. Org. Chem.* **2005**, *70*, 9377.
13. Hargreaves, C. A.; Sandford, G.; Slater, R.; Yufit, D.; Howard, J. A. K.; Vong, A. *Tetrahedron* **2007**, *63*, 5204.
14. Chambers, R. D.; Sargent, C. R. *Adv. Heterocycl. Chem.* **1981**, *28*, 1.
15. Brooke, G. M. *J. Fluorine Chem.* **1997**, *86*, 1.
16. Montgomery, J. A.; Hewson, K. *J. Med. Chem.* **1966**, *9*, 105.
17. Montgomery, J. A.; Salemink, C. A. *J. Med. Chem.* **1966**, *9*, 354.
18. De Roos, K. B.; Salemink, C. A. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 1166.
19. Benedict, W. F.; Baker, M. S.; Haroun, L.; Choi, E.; Ames, B. N. *Cancer Res.* **1977**, *37*, 2209.
20. Barraclough, P.; Gillam, J.; King, W. R.; Nobbs, M. S.; Vine, S. J. *J. Chem. Res., Synop.* **1997**, 196.
21. Middleton, R. W.; Wibberley, D. G. *J. Heterocycl. Chem.* **1980**, *17*, 1757.
22. Temple, C.; Rose, J. D.; Comber, R. N.; Rener, G. A. *J. Med. Chem.* **1987**, *30*, 1746.
23. Viscardi, G.; Savarino, P.; Barni, E.; Carigano, R. *J. Heterocycl. Chem.* **1990**, *27*, 1825.
24. Katner, A. S.; Brown, R. F. *J. Heterocycl. Chem.* **1990**, *27*, 563.
25. Bakke, J. M.; Riha, J. *J. Heterocycl. Chem.* **1999**, *36*, 1143.
26. Yang, D.; Fokas, D.; Li, J.; Yu, L.; Baldino, C. M. *Synthesis* **2005**, 47.
27. Coe, P. L.; Rees, A. J.; Whittaker, J. *J. Fluorine Chem.* **2001**, *107*, 13.
28. Liu, M. C.; Luo, M. Z.; Mozdziesz, D. E.; Lin, T. S.; Dutschmann, G. E.; Gullen, E. A.; Cheng, Y. C.; Sartorelli, A. C. *Nucleosides, Nucleotides, Nucleic Acids* **2001**, *20*, 1975.
29. Sakthivel, K.; Cook, P. D. *Tetrahedron Lett.* **2005**, *46*, 3883.
30. Banks, R. E.; Burgess, J. E.; Haszeldine, R. N. *J. Chem. Soc.* **1965**, 575.