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Trisubstituted pyrimidine derivatives from tetrafluoropyrimidine

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ABSTRACT

The use of tetrafluoropyrimidine as a scaffold for the synthesis of 2,4,6-trisubstituted pyrimidine derivatives by three sequential nucleophilic aromatic substitution processes is assessed. Reactions of tetrafluoropyrimidine with various amine nucleophiles followed by a series of nitrogen and oxygen centred nucleophilic species gave a range of 4,6-disubstituted-2,5-difluoropyrimidine systems regioselectively and in good yield. Displacement of a further fluorine atom from representative difluoropyrimidine derivatives proceeded to give trisubstituted pyrimidine derivatives although mixtures of products could be obtained depending upon the substrate.

1. Introduction

Many pyrimidine derivatives bearing a wide range of functionality have found applications in a significant number of commercially important life-science products[1] and some examples, including two 5-fluoropyrimidine systems relevant to the chemistry described in this paper,[2] are shown in Figure 1.

There are a variety of well established synthetic processes that have been adopted by many organic and medicinal chemistry groups for the preparation of polyfunctional pyrimidine systems, such as cyclocondensation reactions of amidine, guanidine or thiourea derivatives with appropriate 1,3-diketone or 1,3-diester systems[3,4] and the use of polyhalogenated pyrimidine systems as versatile multi-functional scaffolds.[5] Chlorinated pyrimidine substrates can, for example, be utilised in various palladium catalysed cross-coupling reactions[6] and nucleophilic aromatic substitution

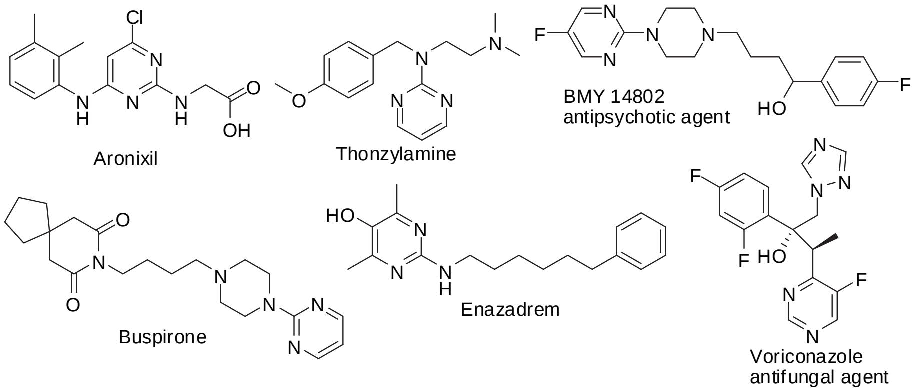

Figure 1. Pyrimidine systems with useful biological activity.

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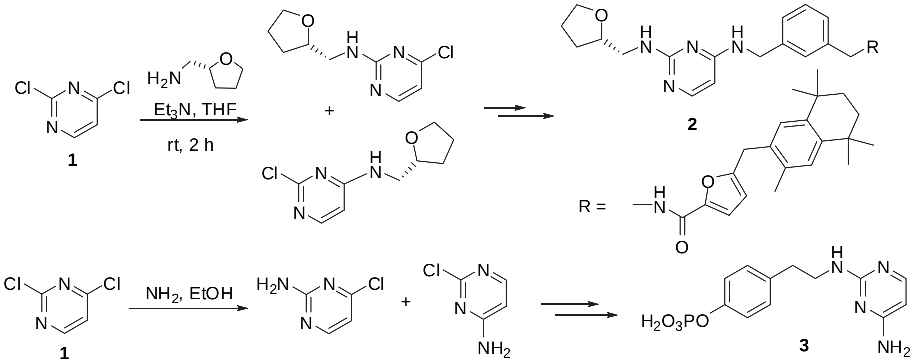
processes.[7,8] However, for many reactions involving nucleophilic aromatic substitution of chlorine from polychlorinated pyrimidine derivatives, harsh reaction conditions are frequently required. Furthermore, of particular concern, low regioselectivity is often obtained because these processes can be affected by a combination of both electronic and steric factors,[5] limiting the use of highly chlorinated scaffolds in automated parallel synthesis. For example, reaction of an amine nucleophile with 2,6-dichloropyrimidine **1** in the first step of the synthesis of the diaminated pyrimidine system **2** (Scheme 1), a potent non peptide gonadotropin releasing hormone (GnRH) receptor antagonist, leads to two products that must be separated before further processing to the desired biologically active system **2**.[9] Similarly, the synthesis of disubstituted derivative **3**, a non-peptide antagonist of the SH2 domain of GRB2, is complicated by the formation of isomeric pyrimidine systems in the first synthetic S_NAr step, leading to a low overall yield.[10]



Scheme 1. Synthesis of poly-substituted pyrimidine derivatives from polychlorinated pyrimidine scaffolds.[9,10]

In principle, highly fluorinated pyrimidine derivatives provide a range of highly effective scaffolds for sequential derivatisation by nucleophilic aromatic substitution processes because, for these systems, the regioselectivity of S_NAr processes are generally not affected by steric factors due to the relatively small size of the fluorine atom.[11] Indeed, in an ongoing research programme, we are exploiting the use of perfluorinated heteroaromatic substrates, such as pentafluoropyridine and tetrafluoropyridazine, as scaffolds for the synthesis of a wide range of poly-functional pyridine,[12] pyridazinone,[13] [5,6]- and [6,6]-ring fused bicyclic[14–16] and tricyclic[17,18] derivatives, exemplifying the use of various highly fluorinated heteroaromatic systems as useful scaffolds.

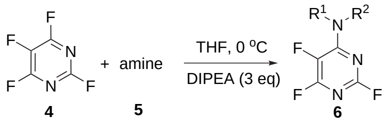
In attempts to develop a convenient scaffold for the synthesis of multi-functional pyrimidine derivatives, we assessed the use of 5-chloro-2,4,6-trifluoropyrimidine as the starting material but found that this system is not an ideal scaffold for analogue synthesis or for multiple substitution processes because of the observed low regioselectivity of reactions with nucleophiles.[19] There remains, therefore, a requirement for efficient, synthetic methodology that allows the synthesis of polysubstituted pyrimidine derivatives that undergo regioselective, sequential nucleophilic aromatic substitution, to meet the demands of rapid analogue synthesis techniques for applications in medicinal chemistry programmes.

In this paper, we report the use of tetrafluoropyrimidine **4** as a scaffold for the synthesis of a range of polysubstituted 5-fluoropyrimidine systems by sequential S_NAr processes. Whilst reactions of tetrafluoropyrimidine **4** with a variety of nucleophiles have been reported previously to give various 4-substituted systems,[20,11] the use of this polyfunctional scaffold for the synthesis of multi-substituted fluoropyrimidine systems by sequential substitution and an assessment of the regioselectivity of such processes has not been explored to any great extent.

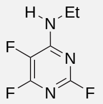
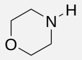
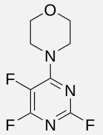
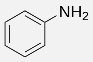
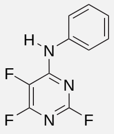
2. Results and discussion

Reactions of tetrafluoropyrimidine **4** with a representative range of nitrogen centred nucleophiles **5** in THF, with DIPEA present as an HF scavenger, proceeded very efficiently to give products **6** arising from regiospecific substitution of fluorine attached to the 4-position in high yield (Table 1), consistent with earlier observations.[20] All products were purified very readily by crystallisation of the crude product mixtures.

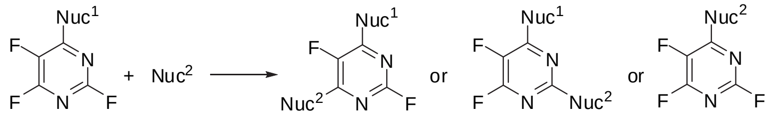
Table 1
Reactions of tetrafluoropyrimidine **4** with amines



4 **5** **6**

Amine	Product,%	
$EtNH_2$ **5a**		**6a**, 75
 **5b**		**6b**, 84
 **5c**		**6c**, 68

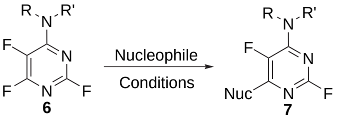
The 4-aminopyrimidine derivatives **6** are relatively electrophilic heterocyclic systems and reactions of these substrates with a nucleophilic species could, in principle, lead to three products arising from displacement of fluorine from the 2- or 6-positions or the amino substituent itself (Scheme 2).

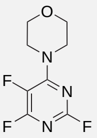
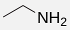
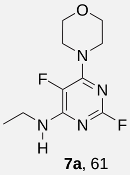
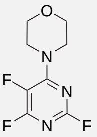
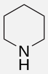
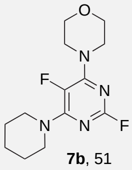
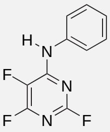
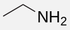
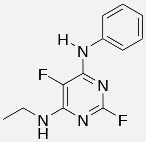
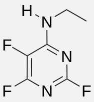
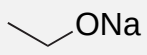
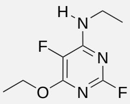
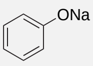
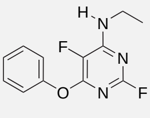
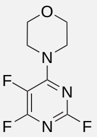
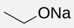
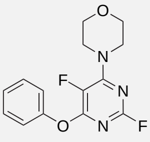
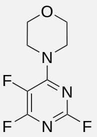
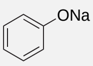
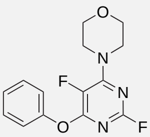
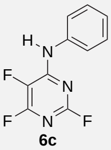
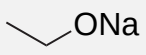
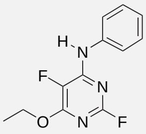
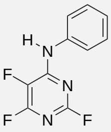
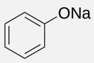
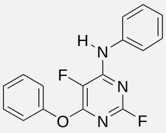


Scheme 2. Possible reactions of 4-substituted pyrimidine derivatives.

Reaction of model 4-aminopyrimidine systems **6a**–**c** with various oxygen and nitrogen centred nucleophiles was carried out and these results are collated in Table 2. In all cases, the amino derivatives **6a**–**c** gave products **7** arising from regiospecific displacement of fluorine located at the 6-position and the structures of **7c** and **7h** were confirmed by X-ray crystallography (Fig. 2).

Table 2
Reactions of 4-amino-2,5,6-trifluoropyrimidine derivatives **6a**–**c**



Substrate, **6**	Nucleophile conditions	Product **7**, %
 **6b**	 DIPEA THF, rt	 **7a**, 61
 **6b**	 DIPEA THF, rt	 **7b**, 51
 **6c**	 DIPEA THF, rt	 **7c**, 72
 **6a**	 EtOH, rt	 **7d**, 77
 **6a**	 THF, rt	 **7e**, 63
 **6b**	 EtOH, rt	 **7f**, 71
 **6b**	 THF, rt	 **7g**, 70
 **6c**	 EtOH, rt	 **7h**, 64
 **6c**	 THF, rt	 **7i**, 79

The regioselectivity of the nucleophilic substitution processes shown in Table 2 can be explained by a consideration of the activating effects of the ring substituents on each of the most reactive 2- and 6-positions of the pyrimidine ring (Fig. 3). It is well established that nitrogen *para* to the site of nucleophilic attack activates more strongly than *ortho* nitrogen by a factor of approximately 3:1 and that fluorine *para* to the site of nucleophilic attack is slightly deactivating with respect to hydrogen.[20,11] Consequently, we would expect fluorine located at the 2-position to be deactivated relative to the 6-position and nucleophilic attack to occur preferentially at the 6-position and this is indeed observed in these cases (Table 2).

Several model disubstituted difluoropyrimidine systems were then used as substrates for reactions with nucleophiles in order to assess the viability of using tetrafluoropyrimidine **4** as a scaffold for the synthesis of trisubstituted derivatives. In our initial study, **7e** was reacted with an excess of piperidine under microwave irradiation at 140 °C and gave the expected major product **8a**, confirmed by X-ray analysis (Fig. 4), arising from substitution of the fluorine atom at the 2-position and a minor product **8b**, derived from displacement of both the fluorine at the 2-position and the phenoxide group at the 6-position, in a 6:1 ratio. ^{19}F NMR and mass spectrometry analysis of the reaction mixture showed that fluorine was displaced by piperidine exclusively before substitution of the phenoxy group occurred and, consequently, when the reaction was carried out under less forcing conditions and only 2 equiv of piperidine, **8a** was the only product obtained. Similarly, reaction of **7e** with 2 equiv of ethylamine under similar conditions resulted in the formation of **8c**, which was characterised by X-ray crystallography (Fig. 4) (Scheme 3).

Furthermore, controlled reactions of the related system **7f** with butylamine and piperidine gave single products **8d** and **8e**, respectively, and their structures were also resolved by X-ray crystallography (Fig. 5) (Scheme 4).

Reaction of **7e** with a representative oxygen nucleophile, sodium ethoxide, resulted in the formation of two products **8f** and **8g** in a 1.5:1 ratio. The major product **8f** arose from displacement of both the phenoxide group and the fluorine atom located at the 2-position whilst the minor product **8g** resulted from replacement of the fluorine at the 2-position only (Scheme 5).

All attempts to reduce the formation of the bis-ethoxy product **8f** by screening multiple reaction conditions such as varying the reaction time, solvent and concentration of the reagents gave mixtures of products on all occasions. However, purification and isolation of both **8f** and **8g** was achieved by reverse phase HPLC and their structures were confirmed by X-ray crystallography (Fig. 6).

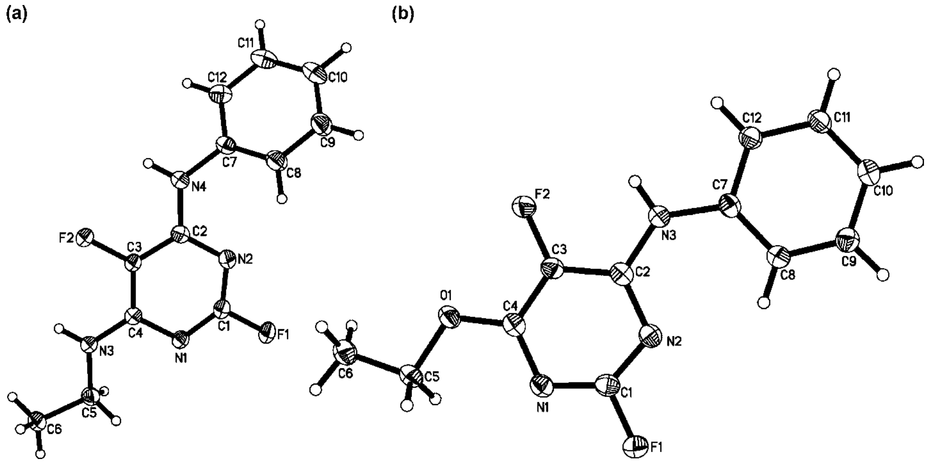


Figure 2. Molecular structures of (a) **7c** and (b) **7h**.

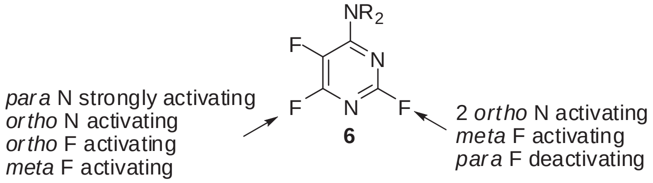


Figure 3. Activating effects for 4-amino-pyrimidine derivatives.

Similarly, reaction of **7f** with sodium ethoxide resulted in the formation of two products **8h** and **8i** in a 7:1 ratio and, again, all attempts to establish reaction conditions that gave only a single product were unsuccessful.

The results of the nucleophilic substitution reactions involving **7e** and **7f** described above reflect the fact that phenoxide is a sufficiently good leaving group that, when attached to the activated

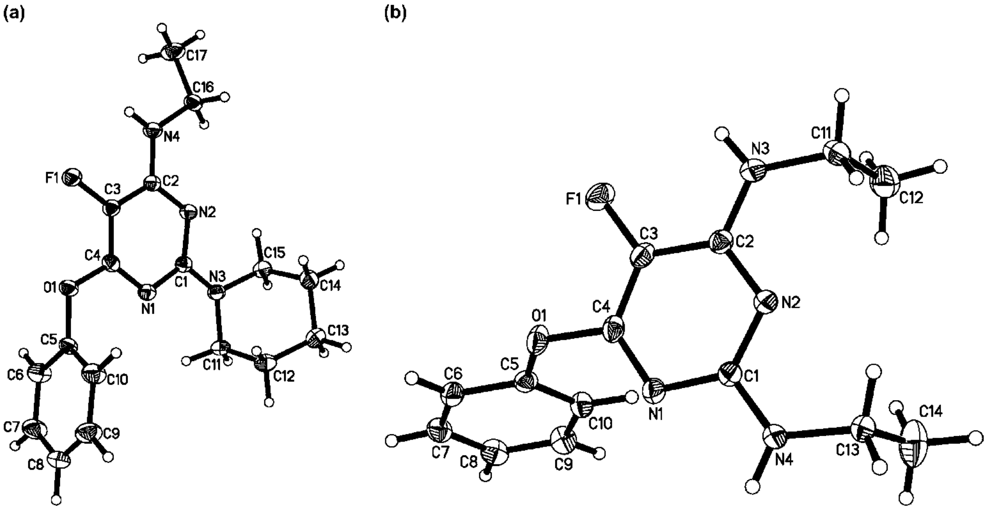
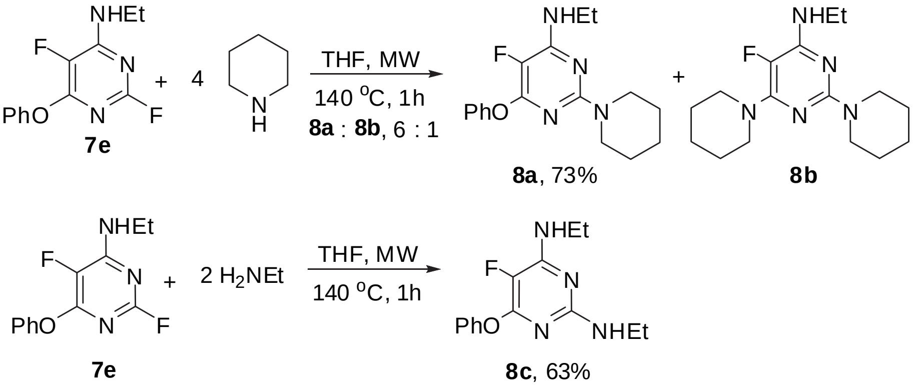


Figure 4. Molecular structures of (a) **8a** and (b) **8c**.



Scheme 3. Reactions of **7e** with nucleophiles.

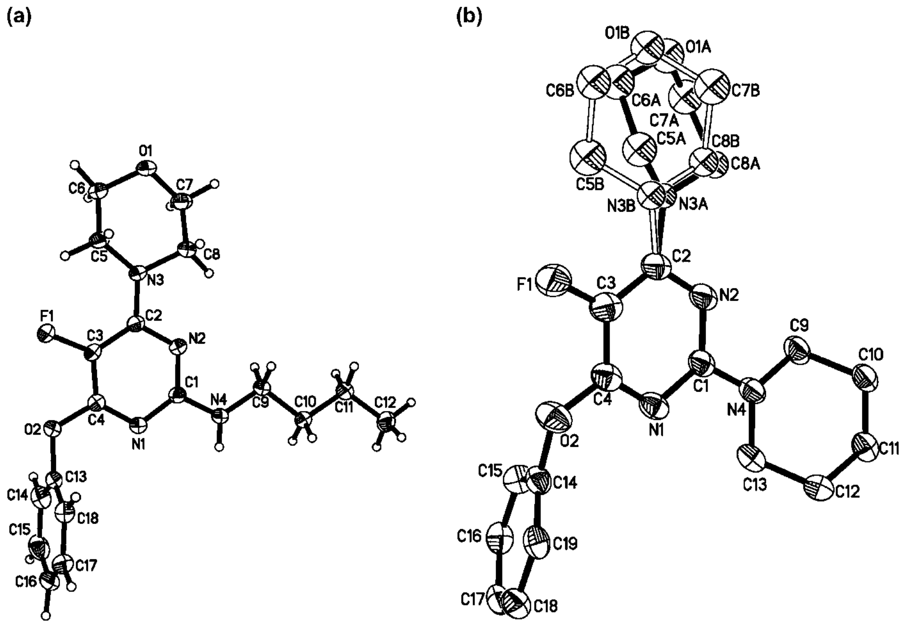
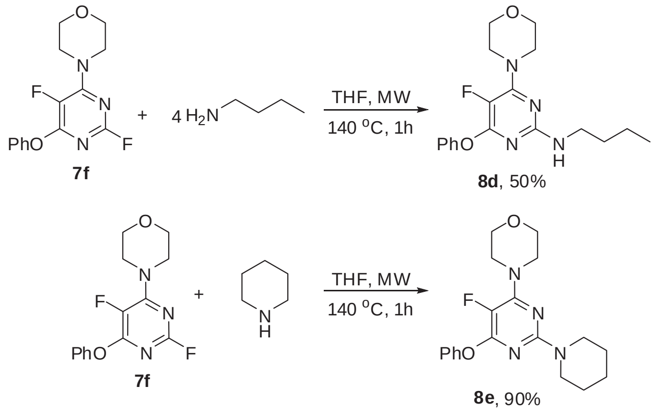


Figure 5. Molecular structures of (a) **8d** (only one of the two independent molecules is shown) and (b) **8e**.



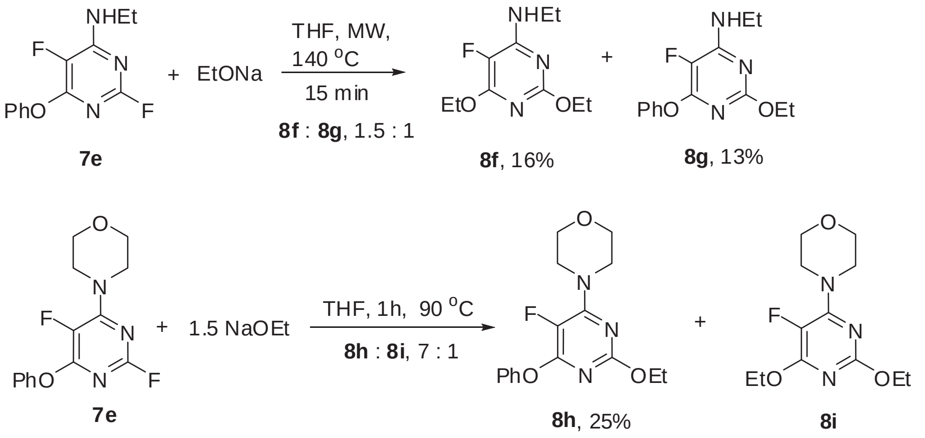
Scheme 4. Reactions of **7f** with amines.

6-position of a pyrimidine ring, it can be displaced in competing processes with the substitution of fluorine atoms located at the less activated 2-position.

Diaminated pyrimidine system **7c** was then assessed as a substrate for the synthesis of trisubstituted 5-fluoropyrimidine systems (Scheme 6) and, in this case, only single products **8j** and **8k**, the structures of which were confirmed by X-ray analysis (Fig. 6), were obtained from reactions with piperidine and sodium phenoxide, respectively. Since amino groups are much poorer leaving groups than phenoxide, competing displacement reactions are not observed in the case of this substrate.

3. Conclusions

Tetrafluoropyrimidine **4** is an effective scaffold for the synthesis of various polyfunctional pyrimidine systems by utilising sequential nucleophilic aromatic substitution processes. Reactions of tetrafluoropyrimidine **4** with nucleophiles are regioselective[20] and, in this paper, we have shown that 4-aminotrifluoropyrimidine derivatives **6** react regioselectively with various nitrogen and oxygen centred nucleophiles to give a range of disubstituted 2,5-difluorinated pyrimidine systems **7**. Reactions of model disubstituted systems **7c**,**e**,**f** allowed the synthesis, purification and isolation of a range of 2,4,6-trisubstituted pyrimidine systems but the reaction conditions required to enable the third nucleophilic substitution processes to occur can lead to the displacement of substituents already attached to activated positions of the pyrimidine ring. Consequently, the use of fluorinated pyrimidine systems for parallel



Scheme 5. Reactions of **7e** and **7f** with sodium ethoxide.

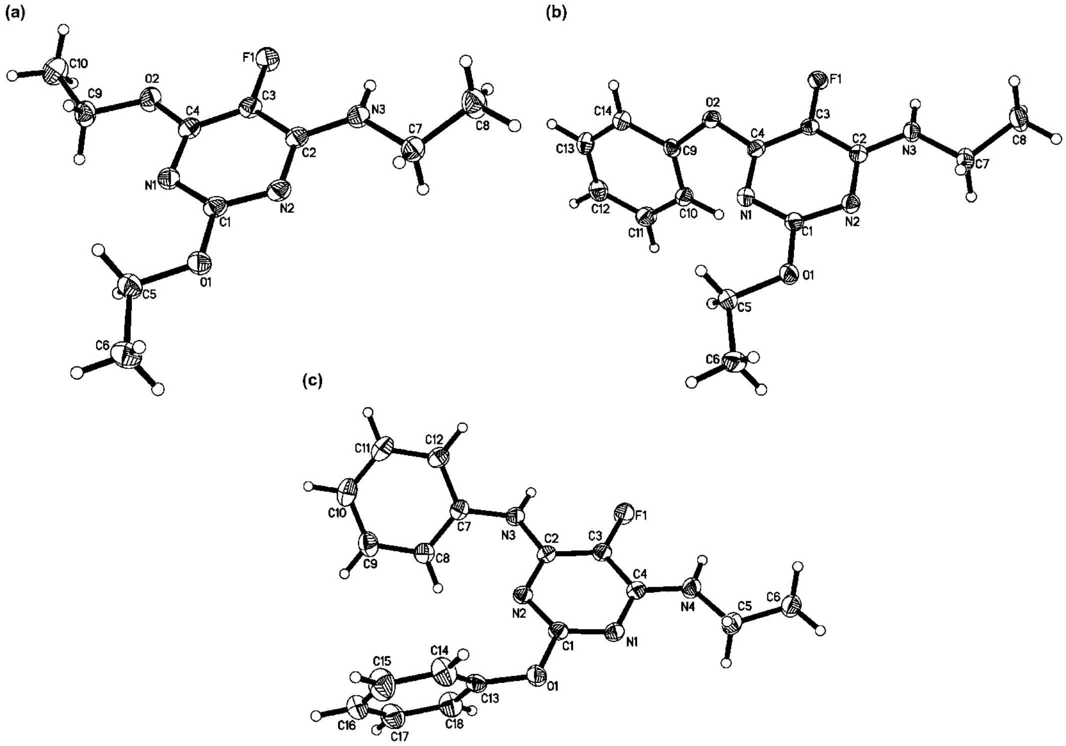
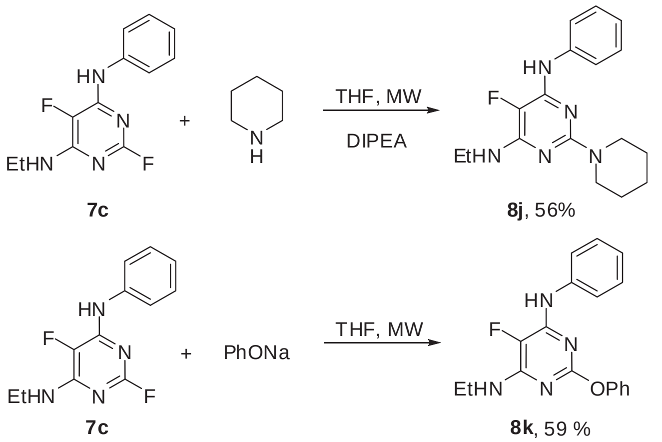


Figure 6. Molecular structures of (a) **8f**, (b) **8g** and (c) **8k** (only one independent molecule is shown).



Scheme 6. Reactions of **7c** with nucleophiles.

synthesis techniques is not general and the illustrative reactions described in this paper show that regioselective synthesis of trisubstituted derivatives may be limited to those pyrimidine systems bearing multiple substituents that are not readily displaced by nucleophiles.

4. Experimental

4.1. General

All starting materials were obtained commercially (Sigma–Aldrich) apart from tetrafluoropyrimidine, which was prepared by literature procedures.[20] and all solvents were dried using standard laboratory procedures.[21] NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a Varian VXR 400S NMR spectrometer with tetramethylsilane and trichlorofluoromethane as internal standards. Spectral assignments were made with the aid of data collected by $^{1}H-^{1}H$ COSY and $^{1}H-^{13}C$ HETCOR experiments and coupling constants are given in hertz. Mass spectra were recorded on either a VG 7070E spectrometer or a Fisons VG Trio 1000 spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph. Elemental analyses were obtained on either a Perkin–Elmer 240 or a Carlo Erba Elemental Analyser. Melting points were recorded at atmospheric pressure and are uncorrected. Column chromatography was carried out on silica gel (Merck No. 1-09385, 230–400 mesh) and TLC analysis was performed on silica gel TLC plates.

4.2. Reactions of tetrafluoropyrimidine 4

4.2.1. Reactions with amines—general procedure. A mixture of tetrafluoropyrimidine **4**, amine, DIPEA and THF was stirred at 0 °C for 2 h. The solvent was evaporated and DCM (40 mL) and brine (40 mL) were added. The mixture was stirred and passed through a hydrophobic frit and the DCM layer collected. The DCM was evaporated and column chromatography on silica gel or recrystallisation gave the product.

4.2.1.1. N-Ethyl-2,5,6-trifluoropyrimidin-4-amine ***6a***. Tetrafluoropyrimidine **4** (2.02 g, 13.3 mmol), ethylamine (6.65 mL, 13.3 mmol, 2 M in THF), DIPEA (5.16 g, 40.0 mmol) and THF (200 mL) and column chromatography using ethyl acetate–hexane (1:4) as eluent gave *N-ethyl-2,5,6-trifluoropyrimidin-4-amine* **6a** (1.76 g, 75%) as a yellow solid; mp 57–58 °C (Found: C, 40.7; H, 3.4; N, 23.7. $C_6H_6F_3N_3$ requires: C, 40.7; H, 3.4; N, 23.7%); IR (neat, ν cm^{-1}) 3313, 3001, 1644, 1596, 1448, 1389, 1276, 1136, 1039, 788, 760; δ_H 1.29 (3H, t, $^{3}J_{HH}$ 6.8, CH_3), 3.56 (2H, q, $^{3}J_{HH}$ 6.8, CH_2); δ_C 14.2 (s, CH_3), 36.2 (s, CH_2), 127.4 (ddd, $^{1}J_{CF}$ 250, $^{2}J_{CF}$ 23, $^{4}J_{CF}$ 9, C-5), 154.7 (ddd, $^{1}J_{CF}$ 217, $^{3}J_{CF}$ 21, $^{4}J_{CF}$ 3, C-2), 155.4 (ddd, $^{1}J_{CF}$ 247, $^{2}J_{CF}$ 19, $^{3}J_{CF}$ 13, C-6), 156.1 (ddd, $^{2}J_{CF}$ 18, $^{3}J_{CF}$ 11, $^{3}J_{CF}$ 6, C-4); δ_F −48.80 (1F, d, $^{4}J_{FF}$ 25, F-2), −87.72 (1F, d, $^{3}J_{FF}$ 16, F-6), −174.15 (1F, s, F-5); m/z (ES^{+}) 176 ([MH]$^{+}$, 85%).

4.2.1.2. 4-(2,5,6-Trifluoropyrimidin-4-yl)morpholine ***6b***. Tetrafluoropyrimidine **4** (1.01 g, 6.64 mmol), morpholine (0.58 g, 6.67 mmol), resin bound DIPEA (2.00 g, 8 mmol, 4 mmol/g) and THF

(150 mL) and recrystallisation from *n*-hexane gave 4-(2,5,6-*trifluoropyrimidin-4-yl)morpholine* **6b** (1.22 g, 84%) as a white solid; mp 65–66 °C (Found: C, 43.7; H, 3.7; N, 19.2. $C_8H_8F_3N_3O$ requires: C, 43.8; H, 3.7; N, 19.2%); δ_H 3.70–3.90 (8H, m, CH_2); δ_C 46.9 (s, NCH_2), 66.8 (s, OCH_2), 129.5 (ddd, $^1J_{CF}$ 251, $^2J_{CF}$ 25, $^4J_{CF}$ 9, C-5), 154.4 (ddd, $^1J_{CF}$ 217, $^3J_{CF}$ 23, $^4J_{CF}$ 4, C-2), 154.5 (ddd, $^2J_{CF}$ 16, $^3J_{CF}$ 6, $^3J_{CF}$ 6, C-4), 159.7 (ddd, $^1J_{CF}$ 281, $^2J_{CF}$ 35, $^3J_{CF}$ 16, C-6); δ_F −47.90 (1F, d, $^4J_{FF}$ 26, F-2), −84.66 (1F, d, $^3J_{FF}$ 17, F-6), −172.30 to −172.42 (1F, m, F-5); *m*/*z* (EI$^+$) 219 ([M]$^+$, 32%), 176 (60), 134 (100).

4.2.1.3. 2,5,6-Trifluoro-N-phenylpyrimidin-4-amine ***6c***. Tetrafluoropyrimidine **4** (1.01 g, 6.64 mmol), aniline (0.63 g, 6.77 mmol), resin bound DIPEA (2.02 g, 8 mmol, 4 mmol/g) and THF (150 mL) and recrystallisation from *n*-hexane gave 2,5,6-*trifluoro-N-phenylpyrimidin-4-amine* **6c** (0.64 g, 43%) as a cream solid; mp 91–93 °C (Found: C, 53.0; H, 2.7; N, 18.4. $C_{10}H_6F_3N_3$ requires: C; 53.3, H; 2.7, N; 18.7%); IR (neat, v cm^{-1}): 3413, 2364, 1628, 1583, 1536, 1478, 1446, 1390, 1290, 1228, 751; δ_H 7.20–7.65 (5H, m, Ar–H); δ_C 121.4 (s, C-2′), 125.7 (s, C-4′), 127.3 (ddd, $^1J_{CF}$ 278, $^2J_{CF}$ 32, $^4J_{CF}$ 9, C-5), 129.7 (s, C-3′), 140.9 (s, C-1′), 154.0–154.2 (m, C-4), 154.2 (ddd, $^1J_{CF}$ 218, $^3J_{CF}$ 21, $^4J_{CF}$ 3, C-2), 155.5 (ddd, $^1J_{CF}$ 283, $^2J_{CF}$ 32, $^3J_{CF}$ 9, C-6); δ_F −46.1 (1F, d, $^4J_{FF}$ 27, F-2), −84.1 (1F, d, $^3J_{FF}$ 18, F-6), −177.8 (1F, m, F-5); *m*/*z* (EI$^+$) 224 ([M]$^+$, 100%), 205 (10), 186 (6).

4.3. Disubstituted products 7—reactions of trifluoropyrimidine derivatives 6

4.3.1. Reactions of ***6*** *with amines—general procedure.* A mixture of trifluoropyrimidin-4-amine derivative **6**, amine nucleophile, DIPEA and THF was stirred at rt for 12 h. The solvent was evaporated and DCM (40 mL) and brine (40 mL) were added. The mixture was stirred and passed through a hydrophobic frit and the DCM layer collected. The DCM was evaporated and column chromatography on silica gel or recrystallisation gave the product.

4.3.1.1. N-Ethyl-2,5-difluoro-6-morpholin-4-ylpyrimidin-4-amine ***7a***. 4-(2,5,6-Trifluoropyrimidin-4-yl)morpholine **6b** (1.03 g, 4.70 mmol), ethylamine (0.27 g, 6.00 mmol), DIPEA (0.22 g, 17.1 mmol) and THF (100 mL) and recrystallisation from *n*-hexane gave 4-(2,5,6-*trifluoropyrimidin-4-yl)morpholine* **7a** (0.68 g, 61%) as a white solid; mp 61–62 °C (Found: C, 49.2; H, 5.8; N, 22.8. $C_{10}H_{14}F_2N_4O$ requires: C, 49.2; H, 5.8; N, 22.9%); δ_H 1.23 (3H, t, $^3J_{HH}$ 7.2, CH_3), 3.45–3.52 (2H, m, CH_2), 3.60–3.81 (8H, m, CH_2), 4.81 (1H, br s, NH); δ_C 15.3 (s, CH_3), 36.2 (s, CH_2CH_3), 46.7 (s, NCH_2), 67.0 (s, OCH_2), 128.0 (dd, $^1J_{CF}$ 228, $^4J_{CF}$ 7, C-5), 150.1 (dd, $^2J_{CF}$ 14, $^3J_{CF}$ 4, C-4), 154.8–154.9 (m, C-6), 157.1 (dd, $^1J_{CF}$ 206, $^4J_{CF}$ 3, C-2); δ_F −50.11 (1F, d, $^5J_{FF}$ 28, F-2), −175.77 (1F, d, $^5J_{FF}$ 28, F-5); *m*/*z* (ES$^+$) 245 ([MH]$^+$, 100%).

4.3.1.2. 4-(2,5-Difluoro-6-(piperidin-1-yl)pyrimidin-4-yl) morpholine ***7b***. 4-(2,5,6-Trifluoropyrimidin-4-yl)morpholine **6b** (1.03 g, 4.70 mmol), piperidine (0.50 g, 5.88 mmol), DIPEA (0.22 g, 17.5 mmol) and THF (100 mL) and column chromatography using ethyl acetate–hexane (1:3) as eluent gave *4-(2,5-difluoro-6-(piperidin-1-yl)pyrimidin-4-yl)morpholine* **7b** (0.68 g, 51%) as a white solid; mp 59–60 °C (Found: C, 54.7; H, 6.4; N, 19.5. $C_{13}H_{18}F_2N_4O$ requires: C, 54.9; H, 6.4; N, 19.7%); δ_H 1.50–1.75 (6H, m, CH_2), 3.21–3.85 (12H, m, CH_2); δ_C 24.9 (s, CH_2) 26.3 (s, CH_2), 47.5 (s, NCH_2), 48.3 (s, NCH_2), 67.1 (s, OCH_2), 128.0 (dd, $^1J_{CF}$ 240, $^4J_{CF}$ 8, C-5), 154.0–154.2 (m, C-4), 154.2–154.3 (m, C-6), 153.8 (dd, $^1J_{CF}$ 203, $^4J_{CF}$ 2, C-2); δ_F −50.66 (1F, d, $^5J_{FF}$ 27, F-2), −163.61 (1F, d, $^5J_{FF}$ 27, F-5); *m*/*z* (ES$^+$) 285 ([MH]$^+$, 100%).

4.3.1.3. N^4-Ethyl-2,5-difluoro-N^6-phenylpyrimidine-4,6-diamine ***7c***. 2,5,6-Trifluoro-*N*-phenylpyrimidin-4-amine **6c** (1.01 g, 4.51 mmol), ethylamine (0.26 g, 5.78 mmol), DIPEA (0.23 g, 17.5 mmol) and THF (100 mL) at 40 °C for 12 h and recrystallisation from *n*-hexane gave *N^4-ethyl-2,5-difluoro-N^6-phenylpyrimidine-4,6-diamine* **7c** (0.99 g, 88%) as an orange solid; mp 131–132 °C (Found C, 57.3; H, 4.8; N, 22.2. $C_{12}H_{12}F_2N_4$ requires C, 57.6; H, 4.8; N, 22.4%); δ_H 1.28 (3H, t, $^3J_{HH}$ 7.6, CH_3), 3.51 (2H, q, $^3J_{HH}$ 7.6, CH_2), 4.81 (1H, s, NH), 6.58 (1H, s, NH), 7.10–7.50 (5H, m, Ar–H); δ_C 15.4 (s, CH_3), 36.2 (s, CH_2), 120.5 (s, C-2′), 123.8 (s, C-4′), 128.2 (dd, $^1J_{CF}$ 234, $^4J_{CF}$ 7, C-5), 129.5 (s, C-3′), 138.4 (s, C-1′), 148.6 (dd, $^2J_{CF}$ 29, $^3J_{CF}$ 9, C-4), 152.6 (dd, $^2J_{CF}$ 31, $^3J_{CF}$ 11, C-6), 157.4 (dd, $^1J_{CF}$ 207, $^4J_{CF}$ 3, C-2); δ_F −49.1 (1F, d, $^5J_{FF}$ 27, F-2), −149.2 (1F, d, $^5J_{FF}$ 27, F-5); *m*/*z* (ES$^+$) 251 ([MH]$^+$, 100%).

4.3.2. Reactions of ***6*** *with oxygen nucleophiles—general procedure.* A mixture of 2,5,6-trifluoropyrimidin-4-amine derivative **6**, alkoxide and solvent was stirred at rt for 17 h. The solvent was evaporated and DCM (20 mL) and brine (20 mL) were added. The mixture was stirred and passed through a hydrophobic frit and the DCM layer was collected. The DCM was evaporated and recrystallisation or column chromatography on silica gel gave pure product.

4.3.2.1. 6-Ethoxy-N-ethyl-2,5-difluoropyrimidin-4-amine ***7d***. *N*-Ethyl-2,5,6-trifluoropyrimidin-4-amine **6a** (1.00 g, 5.71 mmol), sodium ethoxide (0.38 g, 5.71 mmol) and ethanol (150 mL) and recrystallisation from *n*-hexane gave *6-ethoxy-N-ethyl-2,5-difluoropyrimidin-4-amine* **7d** (0.88 g, 77%) as a white solid; mp 81–83 °C (Found: C, 47.3; H, 5.5; N, 20.7. $C_8H_{11}F_2N_3O$ requires: C, 47.3; H, 5.5; N, 20.7%); δ_H 1.24 (3H, t, $^3J_{HH}$ 7.6, CH_3), 1.41 (3H, t, $^3J_{HH}$ 7.6, CH_3), 3.49 (2H, q, $^3J_{HH}$ 7.6, NCH_2), 4.41 (2H, q, $^3J_{HH}$ 7.6, OCH_2), 4.87 (1H, s, NH); δ_C 14.8 (s, CH_3), 15.3 (s, CH_3), 36.3 (s, CH_2), 63.8 (s, CH_2), 130.5 (dd, $^1J_{CF}$ 231, $^4J_{CF}$ 9, C-5), 154.5 (dd, $^2J_{CF}$ 30, $^3J_{CF}$ 11, C-4), 154.8 (dd, $^1J_{CF}$ 214, $^4J_{CF}$ 4, C-2), 156.3 (dd, $^2J_{CF}$ 27, $^3J_{CF}$ 10, C-6); δ_F −49.33 (1F, d, $^5J_{FF}$ 27, F-2), −186.07 (1F, d, $^5J_{FF}$ 27, F-5); *m*/*z* (EI$^+$) 203 ([M]$^+$, 32%), 188(40).

4.3.2.2. N-Ethyl-2,5-difluoro-6-phenoxypyrimidin-4-amine ***7e***. *N*-Ethyl-2,5,6-trifluoropyrimidin-4-amine **6a** (1.01 g, 5.77 mmol), sodium phenoxide (0.67 g, 5.77 mmol) and THF (50 mL) after recrystallisation from *n*-hexane gave *N-ethyl-2,5-difluoro-6-phenoxypyrimidin-4-amine* **7e** (0.91 g, 63%) as a white solid; mp 97–99 °C (Found: C, 57.3; H, 4.3; N, 16.6. $C_{12}H_{11}F_2N_3O$ requires: C, 57.4; H, 4.4; N, 16.7%); δ_H 1.32 (3H, t, $^3J_{HH}$ 7.2, CH_3), 3.55–3.60 (2H, m, CH_2), 7.20–7.53 (5H, m, Ar–H); δ_F −47.8 (1F, d, $^5J_{FF}$ 25, F-2), −180.2 (1F, d, $^5J_{FF}$ 25, F-5); *m*/*z* (ES$^+$) 252 ([MH]$^+$, 100%).

4.3.2.3. 4-(6-Ethoxy-2,5-difluoropyrimidin-4-yl)morpholine ***7f***. 2,4,5-Trifluoro-6-morpholinopyrimidine **6b** (1.25 g, 5.71 mmol), sodium ethoxide (0.39 g, 5.71 mmol) and ethanol (150 mL) and recrystallisation from *n*-hexane gave 4-(6-*ethoxy-2,5-difluoropyrimidin-4-yl)morpholine* **7f** (0.99 g, 71%) as a white solid; mp 97–98 °C (Found: C, 48.8; H, 5.3; N, 17.1. $C_{10}H_{13}F_2N_3O_2$ requires: C, 49.0; H, 5.3; N, 17.1%); δ_H 1.42 (3H, t, $^3J_{HH}$ 7.2, CH_3), 3.70–3.90 (8H, m, CH_2), 4.43 (2H, q, $^3J_{HH}$ 7.2, CH_2); δ_C 14.7 (s, CH_3), 47.0 (d, $^4J_{CF}$ 7, NCH_2), 64.2 (s, OCH_2), 66.9 (s, OCH_2), 128.4 (dd, $^1J_{CF}$ 244, $^4J_{CF}$ 9, C-5), 152.6 (dd, $^2J_{CF}$ 22, $^3J_{CF}$ 4, C-4), 154.0 (dd, $^1J_{CF}$ 210, $^4J_{CF}$ 3, C-2), 160.6–160.7 (m, C-6); δ_F −49.59 (1F, d, $^5J_{FF}$ 27, F-2), −172.81 (1F, d, $^5J_{FF}$ 27, F-5); *m*/*z* (ES$^+$) 246 ([MH]$^+$, 100%).

4.3.2.4. 4-(2,5-Difluoro-6-phenoxypyrimid-4-yl)morpholine ***7g***. 2,4,5-Trifluoro-6-morpholinopyrimidine **6b** (1.07 g, 4.88 mmol), sodium phenoxide (0.56 g, 4.90 mmol) and THF (100 mL) and recrystallisation from *n*-hexane gave 4-(2,5-*difluoro*-6-*phenoxypyrimid-4-yl)morpholine* **7g** (1.12 g, 78%) as a white solid; mp 128–130 °C (Found: C, 57.3; H, 4.5; N, 14.3. $C_{14}H_{13}F_2N_3O_2$ requires: C, 57.3; H, 4.5; N, 14.3%); δ_H 3.50–3.80 (8H, m, CH_2), 7.10–7.50 (5H, m, ArH); δ_C 46.8 (s, NCH_2), 66.9 (s, OCH_2), 121.4 (s, C-2′), 126.0 (s, C-4′), 129.9 (s, C-3′), 132.0 (dd, $^1J_{CF}$ 244, $^4J_{CF}$ 9, C-5), 152.5 (s, C-1′), 153.5–153.6 (m, C-4), 154.0 (dd, $^1J_{CF}$ 213, $^4J_{CF}$ 3, C-2), 159.8–159.9 (m, C-6); δ_F −48.3 (1F, d, $^5J_{FF}$ 28, F-2), −170.7 (1F, d, $^5J_{FF}$ 28, F-5); *m*/*z* (ES$^+$) 294 ([MH]$^+$, 100%).

4.3.2.5. 6-Ethoxy-2,5-difluoro-N-phenylpyrimidin-4-amine **7h**. 2,5,6-Trifluoro-*N*-phenylpyrimidin-4-amine **6c** (1.28 g, 5.71 mmol), sodium ethoxide (0.66 g, 9.71 mmol) and ethanol (150 mL) and recrystallisation from *n*-hexane yielded *6-ethoxy-2,5-difluoro-N-phenylpyrimidin-4-amine* **7h** (0.72 g, 50%) as an off-white solid; mp 105–106 °C (Found: C, 57.2; H, 4.4; N, 16.9. $C_{12}H_{11}F_2N_3O$ requires: C, 57.4; H, 4.4; N, 16.7%); δ_H 1.47 (3H, t, $^3J_{HH}$ 7.2, CH_3), 4.49 (3H, q, $^3J_{HH}$ 7.2, CH_2), 7.10–7.65 (5H, m, Ar–H); δ_C 14.7 (s, CH_3), 64.3 (s, CH_2), 120.8 (s, C-2′), 124.5 (s, C-4′), 128.9 (dd, $^1J_{CF}$ 253, $^4J_{CF}$ 9, C-5), 129.4 (s, C-3′), 137.8 (s, C-1′), 151.5 (dd, $^2J_{CF}$ 29, $^3J_{CF}$ 9, C-6), 154.4 (dd, $^1J_{CF}$ 216, $^4J_{CF}$ 4, C-2), 158.0 (dd, $^2J_{CF}$ 27, $^3J_{CF}$ 10, C-4); δ_F −49.97 (1F, d, $^5J_{FF}$ 28, F-2), −179.31 (1F, $^5J_{FF}$ 28, F-5); *m*/*z* (ES^+) 252 ($[MH]^+$, 100%).

4.3.2.6. 2,5-Difluoro-6-phenoxy-N-phenylpyrimidin-4-amine **7i**. 2,5,6-Trifluoro-*N*-phenylpyrimidin-4-amine **6c** (1.00 g, 4.46 mmol), sodium phenoxide (0.46 g, 3.99 mmol) and THF (100 mL) and recrystallisation from *n*-hexane gave *2,5-difluoro-6-phenoxy-N-phenylpyrimidin-4-amine* **7i** (0.93 g, 70%) as a white solid; mp 128–130 °C (Found: C, 64.1; H, 3.7; N, 14.0. $C_{16}H_{11}F_2N_3O$ requires: C, 64.2; H, 3.7; N, 14.0%); δ_H 6.90 (1H, br s, NH), 7.25–7.68 (10H, m, ArH); δ_C 121.0 (s, ArH), 121.4 (s, ArH), 124.9 (s, ArH), 126.1 (s, ArH), 129.1 (dd, $^1J_{CF}$ 248, $^4J_{CF}$ 9, C-5), 129.2 (s, ArH), 129.9 (s, ArH), 137.4 (s, NH–C), 152.4 (s, C–O), 152.5 (dd, $^2J_{CF}$ 10, $^3J_{CF}$ 9, C-6), 154.3 (dd, $^1J_{CF}$ 217, $^4J_{CF}$ 4, C-2), 156.6 (dd, $^2J_{CF}$ 10, $^3J_{CF}$ 7, C-4); δ_F −46.5 (1F, br s, F-2), −176.9 (1F, br s, F-5); *m*/*z* (EI^+) 299 ($[M]^+$, 17%), 259 (5).

*4.3.3. Trisubstituted products **8**—general procedure.* A mixture of difluoropyrimidine derivative **7**, nucleophile and solvent was subjected to microwave irradiation at 140 °C for 15 min. The solvent was evaporated and DCM (40 mL) and brine (40 mL) were added. The mixture was stirred and passed through a hydrophobic frit and the DCM layer collected. The DCM layer was dried ($MgSO_4$) and evaporated to give a crude yellow solid, which was recrystallised or purified by column chromatography.

*4.3.3.1. N-Ethyl-5-fluoro-6-phenoxy-2-(piperidin-1-yl)pyrimidin-4-amine **8a**.* *N*-Ethyl-2,5-difluoro-6-(phenyloxy)-4-pyrimidinamine **7e** (1.01 g, 4.02 mmol), piperidine (0.66 g, 7.76 mmol) and THF (50 mL) and column chromatography on silica gel using ethyl acetate–hexane (1:15) as eluent gave *N-ethyl-5-fluoro-6-phenoxy-2-(piperidin-1-yl)pyrimidin-4-amine* **8a** (0.92 g, 73%) as a yellow solid; mp 78–80 °C (Found: C, 64.5; H, 6.6; N, 17.4. $C_{17}H_{21}FN_4O$ requires: C, 64.5; H, 6.7; N, 17.7%); δ_H 1.30 (3H, t, $^3J_{HH}$ 7.2, CH_3), 3.32–3.54 (4H, m, CH_2), 4.56 (1H, s, NH), 7.05–7.35 (5H, m, ArH); δ_C 15.4 (s, CH_3) 25.0 (s, CH_2), 25.8 (s, CH_2), 36.0 (s, $NHCH_2$), 45.3 (s, NCH_2), 120.9 (s, C-2′), 124.3 (s, C-4′), 125.4 (d, $^1J_{CF}$ 238, C-5), 129.2 (s, C-3′), 153.9 (s, C-1′), 153.9 (d, $^2J_{CF}$ 10, C-4), 154.1 (d, $^2J_{CF}$ 8, C-6), 156.1 (d, $^4J_{CF}$ 4, C-2); δ_F −190.7 (s); *m*/*z* (ES^+) 317 ($[MH]^+$, 100%).

*4.3.3.2. N^2,N^4-Diethyl-5-fluoro-6-phenoxypyrimidine-2,4-diamine **8c**.* *N*-Ethyl-2,5-difluoro-6-(phenyloxy)-4-pyrimidinamine **7e** (1.01 g, 5.71 mmol), ethylamine (0.66 g, 5.71 mmol) and THF (50 mL) and recrystallisation from ethyl acetate gave *N^2,N^4-diethyl-5-fluoro-6-phenoxypyrimidine-2,4-diamine* **8c** (0.69 g, 63%) as a yellow solid; mp 88–89 °C (Found: C, 60.6; H, 6.4; N, 20.4. $C_{14}H_{17}FN_4O$ requires: C, 60.9; H, 6.2; N, 20.3%); δ_H 1.30 (3H, t, $^3J_{HH}$ 7.2, CH_3), 1.40 (3H, t, $^3J_{HH}$ 7.2, CH_3), 3.35–3.50 (4H, m, CH_2), 4.56 (2H, s, NH), 7.01–7.35 (5H, m, ArH); δ_C 15.2 (s, CH_3), 15.4 (s, CH_3), 36.0 (s, CH_2), 36.8 (s, CH_2), 121.0 (s, C-2′), 124.6 (s, C-4′), 125.4 (d, $^1J_{CF}$ 237, C-5), 129.3 (s, C-3′), 153.8 (s, C-1′), 154.2 (d, $^2J_{CF}$ 10, C-4), 154.5 (d, $^2J_{CF}$ 8, C-6), 156.8 (d, $^4J_{CF}$ 6, C-2); δ_F −189.8 (s); *m*/*z* (ES^+) 277 ($[MH]^+$, 100%).

*4.3.3.3. N-Butyl-5-fluoro-4-morpholino-6-phenoxypyrimidin-2-amine **8d**.* 2,5-Difluoro-4-morpholino-6-phenoxypyrimidine **7f** (1.00 g, 4.08 mmol), butylamine (0.99 g, 13.6 mmol) and THF (15 mL) and recrystallisation from *n*-hexane gave *N-butyl-5-fluoro-4-morpholino-6-phenoxypyrimidin-2-amine* **8d** (0.71 g, 50%) as a white solid; mp 126–127 °C (Found: C, 62.4; H, 6.7; N, 16.1. $C_{18}H_{23}FN_4O_2$ requires: C, 62.4; H, 6.7; N, 16.2%); δ_H 0.89 (3H, t, $^3J_{HH}$ 7.6, CH_3), 1.25–1.50 (4H, m, CH_2), 3.10–3.20 (2H, m, CH_2), 3.65–3.85 (8H, m, CH_2), 4.76 (1H, NH), 7.10–7.40 (5H, m, ArH); δ_C 14.1 (s, CH_3), 20.3 (s, CH_2), 32.0 (s, CH_2), 41.7 (s, $NHCH_2$), 46.9 (s, NCH_2), 67.1 (s, OCH_2), 121.4 (s, C-2′), 124.8 (s, C-4′), 127.5 (d, $^1J_{CF}$ 240, C-5), 129.4 (s, C-3′), 153.1–153.2 (m, C-4), 153.6 (s, C-1′), 156.3–156.4 (m, C-2), 158.1–158.2 (m, C-6); δ_F −179.4 (s); *m*/*z* (ES^+) 347.2 ($[MH]^+$, 100%); crystals suitable for X-ray analysis were grown from MeOH.

*4.3.3.4. 4-(5-Fluoro-6-phenoxy-2-(piperidin-1-yl)pyrimidin-4-yl) morpholine **8e**.* 2,5-Difluoro-4-morpholino-6-phenoxypyrimidine **7f** (0.83 g, 3.38 mmol), piperidine (0.29 g, 3.41 mmol) and THF (15 mL) and recrystallisation from hexane gave 4-(5-*fluoro*-6-*phenoxy*-2-(*piperidin*-1-*yl*)*pyrimidin*-4-*yl*)*morpholine* **8e** (1.10 g, 90%) as a white solid; mp 128–130 °C; (Found: C, 64.0; H, 6.6; N, 15.4. $C_{19}H_{23}FN_4O_2$ requires: C, 63.7; H, 6.5; N, 15.6%); δ_H 1.40–1.63 (6H, m, CH_2), 3.42–3.84 (12H, m, CH_2), 7.10–7.35 (5H, m, ArH); δ_F −180.0 (s); *m*/*z* (ES^+) 359 ($[MH]^+$, 100%). Crystals suitable for X-ray analysis were grown from MeOH.

*4.3.3.5. 2,6-Diethoxy-N-ethyl-5-fluoropyrimidin-4-amine **8f** and 2-ethoxy-N-ethyl-5-fluoro-6-phenoxypyrimidin-4-amine **8g**.* *N*-Ethyl-2,5-difluoro-6-(phenyloxy)-4-pyrimidinamine **7e** (1.01 g, 4.02 mmol), sodium ethoxide (0.27 g, 4.02 mmol) and THF (50 mL) gave a crude yellow solid (1.56 g) containing **8f** and **8g** in a 1.5:1 ratio by ^{19}F NMR analysis. Preparative scale HPLC on a reverse phase column with a solvent gradient running from 5%:95% MeCN–H_2O (0.1% formic acid) to 85%:15% gave *2,6-diethoxy-N-ethyl-5-fluoropyrimidin-4-amine* **8f** (0.15 g, 16%) as a white solid; mp 58–60 °C (Found: C, 52.3; H, 7.0; N, 18.3. $C_{12}H_{16}FN_3O_2$ requires: C, 52.4; H, 7.0; N, 18.3%); δ_H 1.27 (3H, t, $^3J_{HH}$ 7.2, CH_3), 1.38 (6H, t, $^3J_{HH}$ 7.2, CH_3), 3.49 (2H, q, $^3J_{HH}$ 7.2, CH_2), 3.49 (4H, q, $^3J_{HH}$ 7.2, OCH_2); δ_C 14.8 (s, CH_3), 14.9 (s, CH_3), 15.5 (s, CH_3), 36.1 (s, CH_2), 62.8 (s, CH_2), 63.4 (s, CH_2), 127.3 (d, $^1J_{CF}$ 237, C-5), 153.7 (d, $^2J_{CF}$ 10, C-4), 156.2 (d, $^2J_{CF}$ 9, C-6), 158.6 (d, $^4J_{CF}$ 4, C-2); δ_F −191.2 (s); *m*/*z* (EI^+) 229 ($[M]^+$, 40%), 214 (44), 201 (42); crystals suitable for X-ray analysis were grown from MeOH; and, *2-ethoxy-N-ethyl-5-fluoro-6-phenoxypyrimidin-4-amine* **8g** (0.14 g, 13%) as a white solid; mp 109–110 °C (Found: C, 60.4; H, 5.8; N, 15.1. $C_{14}H_{16}FN_3O_2$ requires: C, 60.6; H, 5.8; N, 15.2%); δ_H 1.22–1.27 (3H, m, CH_3), 1.28–1.32 (3H, m, CH_3), 3.55 (2H, q, $^3J_{HH}$ 7.6, CH_2), 4.10–4.25 (2H, m, CH_2), 7.10–7.60 (5H, m, ArH); δ_C 14.6 (s, CH_3), 15.3 (s, CH_3), 36.2 (s, CH_2), 63.6 (s, CH_2), 121.2 (s, C-2′), 125.0 (s, C-4′), 127.7 (d, $^1J_{CF}$ 241, C-5), 129.5 (s, C-3′), 153.20 (s, C-1′), 154.7 (d, $^2J_{CF}$ 9, C-4), 154.8 (d, $^2J_{CF}$ 10, C-6), 158.7 (d, $^4J_{CF}$ 4, C-2); δ_F −185.2 (s); *m*/*z* (EI^+) 277 ($[M]^+$, 20%), 262 (8), 234 (10); crystals suitable for X-ray analysis were grown from MeOH.

*4.3.3.6. 4-(2-Ethoxy-5-fluoro-6-phenoxypyrimidin-4-yl)morpholine **8h**.* 2,5-Difluoro-4-morpholino-6-phenoxypyrimidine **7f** (0.50 g, 2.04 mmol), sodium ethoxide (0.17 g, 2.55 mmol) and THF (50 mL) and column chromatography using hexane–ethyl acetate (12:1) as eluent gave 4-(2-*ethoxy*-5-*fluoro*-6-*phenoxypyrimidin*-4-*yl*)*morpholine* **8h** (0.14 g, 26%) as a white solid; mp 87–88 °C (Found: C, 60.0; H, 5.7; N, 13.4. $C_{16}H_{18}FN_3O_3$ requires: C, 60.2; H, 5.7; N, 13.2%); δ_H 1.23 (3H, t, $^3J_{HH}$ 7.2, CH_3), 3.70–3.95 (8H, m, CH_2), 4.15 (2H, q, $^3J_{HH}$ 7.2, CH_2), 7.10–7.45 (5H, m, Ar–H); δ_F −175.0 (s); *m*/*z* (EI^+) 319 ($[M]^+$, 90%), 234 (100).

*4.3.3.7. N^4-Ethyl-5-fluoro-N^6-phenyl-2-piperidin-1-ylpyrimidine-4,6-diamine **8j**.* *N^4-Ethyl-2,5-difluoro-N^6-phenylpyrimidine-4,6-diamine* **7c** (1.03 g, 4.12 mmol), piperidine (0.49 g, 5.82 mmol) and THF (15 mL) and recrystallisation from *n*-hexane–DCM gave *N^4-ethyl-5-fluoro-N^6-phenyl-2-piperidin-1-ylpyrimidine-4,6-diamine* **8j** (0.70 g, 56%) as a pale orange solid; mp 131–132 °C (Found: C, 64.6;

H, 7.0; N, 22.1. $C_{17}H_{22}FN_5$ requires: C, 64.7; H, 7.0; N, 22.2%); δ_H 1.25 (3H, t, $^3J_{HH}$ 7.6, CH_3), 1.50–1.65 (6H, m, CH_2), 3.40–3.80 (6H, m, CH_2), 4.23 (1H, s, NH), 6.16 (1H, s, NH), 7.25–7.45 (5H, m, ArH); δ_C 15.7 (s, CH_3), 25.2 (s, CH_2), 26.0 (s, CH_2), 35.8 (s, $NHCH_2$), 45.7 (s, NCH_2), 119.4 (s, C-2′), 122.0 (s, C-4′), 127.5 (d, $^1J_{CF}$ 223, C-5), 129.0 (s, C-3′), 140.2 (s, C-1′), 147.0 (d, $^2J_{CF}$ 7, C-4), 151.1 (d, $^2J_{CF}$ 8, C-6), 156.8 (d, $^4J_{CF}$ 4, C-2); δ_F −191.96 (s); *m*/*z* (ES^+) 316 ($[MH]^+$, 100%).

4.3.3.8. N^4-Ethyl-5-fluoro-2-phenoxy-N^6-phenylpyrimidine-4,6-diamine **8k**. N^4-Ethyl-2,5-difluoro-N^6-phenylpyrimidine-4,6-diamine **7c** (1.03 g, 4.12 mmol), sodium phenoxide (0.82 g, 7.07 mmol) and THF (15 mL) and recrystallisation from *n*-hexane–DCM gave *N^4-ethyl-5-fluoro-2-phenoxy-N^6-phenylpyrimidine-4,6-diamine* **8k** (1.02 g, 79%) as a white solid; mp 124–112 °C (Found: C, 64.5; H, 6.6; N, 17.4. $C_{18}H_{17}FN_4O$ requires: C, 66.7; H, 5.3; N, 17.3%); δ_H 1.22 (3H, t, $^3J_{HH}$ 7.2, CH_3), 3.58 (2H, q, $^3J_{HH}$ 7.2, CH_2), 4.76 (1H, br s, NH), 6.42 (1H, br s, NH), 6.95–7.45 (10H, m, ArH); δ_C 15.5 (s, CH_3) 36.1 (s, CH_2), 119.2 (s, Ar), 122.6 (s, Ar), 122.7 (s, Ar), 125.0 (s, Ar), 127.4 (d, $^1J_{CF}$ 235, C-5), 129.4 (s, Ar), 129.5 (s, Ar), 139.2 (s, C–N), 147.3 (d, $^2J_{CF}$ 8, C-4), 152.3 (d, $^2J_{CF}$ 10, C-6), 153.9 (s, C–O), 156.8 (d, $^4J_{CF}$ 4, C-2); δ_F −186.3 (s); *m*/*z* (ES^+) 325 ($[MH]^+$, 100%).

4.4. X-ray crystallography

Single crystal X-ray data were collected on SMART 6000 (**7c**, **7h**, **8c**, **8e**, **8k**) and Rigaku R-AXIS Spider IP (**8a**, **8d**, **8f**, **8g**) diffractometers equipped with Cryostream (Oxford Cryosystems) nitrogen coolers 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 SHELXTL software. All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms were located on the difference map and refined isotropically in all structures except **8e** (disordered morpholine moiety) and **8k**, where they were placed in the calculated positions and refined in riding mode. Crystallographic data for the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 768245–768253.

Crystal data for **7c**: $C_{12}H_{12}F_2N_4$, *M*=250.26, orthorhombic, space group *P* bca, *a*=11.2752(4), *b*=8.5143(3), *c*=24.4971(10) Å, *U*=2351.7 (2) Å^3, *F*(000)=1040, *Z*=8, D_c=1.414 mg m^{-3}, μ=0.111 mm^{-1}. 28,797 reflections yielded 3274 unique data (R_{merg}=0.0314). Final w$R_2(F^2)$= 0.1266 for all data (211 refined parameters), conventional $R_1(F)$= 0.0428 for 2676 reflections with $I \geq 2\sigma$, GOF=1.030.

Crystal data for **7h**: $C_{12}H_{11}F_2N_3O$, *M*=251.24, monoclinic, space group *P* $2_1/n$, *a*=7.8769(3), *b*=5.4557(2), *c*=25.5645(10) Å, β=90.90 (1)°, *U*=1098.47(7) Å^3, *F*(000)=520, *Z*=4, D_c=1.519 mg m^{-3}, μ=0.124 mm^{-1}. 12,034 reflections yielded 3064 unique data (R_{merg}=0.0305). Final w$R_2(F^2)$=0.1310 for all data (207 refined parameters), conventional $R_1(F)$=0.0455 for 2452 reflections with $I \geq 2\sigma$, GOF=1.074.

Crystal data for **8a**: $C_{17}H_{21}FN_4O$, *M*=316.38, monoclinic, space group *P* $2_1/n$, *a*=15.164(3), *b*=6.5763(13), *c*=16.377(3) Å, β=93.29 (3)°, *U*=1630.5(6) Å^3, *F*(000)=672, *Z*=4, D_c=1.289 mg m^{-3}, μ=0.091 mm^{-1}. 31,813 reflections yielded 4308 unique data (R_{merg}=0.0398). Final w$R_2(F^2)$=0.1144 for all data (292 refined parameters), conventional $R_1(F)$=0.0443 for 4205 reflections with $I \geq 2\sigma$, GOF=1.117.

Crystal data for **8c**: $C_{14}H_{17}FN_4O$, *M*=276.32, monoclinic, space group *P* $2_1/c$, *a*=8.8074(2), *b*=8.1779(2), *c*=19.7704(4) Å, β=101.40 (1)°, *U*=1395.89(5) Å^3, *F*(000)=584, *Z*=4, D_c=1.315 mg m^{-3}, μ=0.096 mm^{-1}. 19,449 reflections yielded 4447 unique data (R_{merg}=0.0246). Final w$R_2(F^2)$=0.1434 for all data (249 refined parameters), conventional $R_1(F)$=0.0465 for 3606 reflections with $I \geq 2\sigma$, GOF=1.037.

Crystal data for **8d**: $C_{18}H_{23}FN_4O_2$, *M*=346.40, triclinic, space group *P* −1, *a*=9.549(2), *b*=9.985(2), *c*=20.876(2) Å, α=92.04(3), β=95.04(3), γ=118.18(3)°, *U*=1741.0(6) Å^3, *F*(000)=736, *Z*=4, D_c=1.322 mg m^{-3}, μ=0.096 mm^{-1}. 24,835 reflections yielded 8376 unique data (R_{merg}=0.0515). Final w$R_2(F^2)$=0.1750 for all data (636 refined parameters), conventional $R_1(F)$=0.0615 for 7481 reflections with $I \geq 2\sigma$, GOF=1.066.

Crystal data for **8e**: $C_{19}H_{23}FN_4O_2$, *M*=358.41, monoclinic, space group *P* $2_1/c$, *a*=17.4666(6), *b*=5.4244(2), *c*=19.3478(6) Å, β=109.29 (1)°, *U*=1730.2(1) Å^3, *F*(000)=760, *Z*=4, D_c=1.376 mg m^{-3}, μ=0.099 mm^{-1}. 16,777 reflections yielded 3411 unique data (R_{merg}=0.0247). Final w$R_2(F^2)$=0.2304 for all data (229 refined parameters), conventional $R_1(F)$=0.0839 for 2772 reflections with $I \geq 2\sigma$, GOF=1.085.

Crystal data for **8f**: $C_{10}H_{16}FN_3O_2$, *M*=229.26, monoclinic, space group *P* $2_1/c$, *a*=11.3774(6), *b*=12.0944(9), *c*=8.5144(6) Å, β=97.39 (3)°, *U*=1161.9(4) Å^3, *F*(000)=488, *Z*=4, D_c=1.311 mg m^{-3}, μ=0.103 mm^{-1}. 7167 reflections yielded 2388 unique data (R_{merg}=0.0539). Final w$R_2(F^2)$=0.1457 for all data (209 refined parameters), conventional $R_1(F)$=0.0549 for 2074 reflections with $I \geq 2\sigma$, GOF=1.090.

Crystal data for **8g**: $C_{14}H_{16}FN_3O_2$, *M*=277.30, orthorhombic, space group *P bca*, *a*=10.7762(2), *b*=8.9759(2), *c*=28.1543(6) Å, *U*=2723.3 (9) Å^3, *F*(000)=1168, *Z*=8, D_c=1.353 mg m^{-3}, μ=0.102 mm^{-1}. 24,438 reflections yielded 3610 unique data (R_{merg}=0.0465). Final w$R_2(F^2)$= 0.1022 for all data (245 refined parameters), conventional $R_1(F)$= 0.0427 for 3362 reflections with $I \geq 2\sigma$, GOF=1.138.

Crystal data for **8k**: $C_{18}H_{17}FN_4O$, *M*=324.36, monoclinic, space group *P c*, *a*=12.6975(3), *b*=12.8198(3), *c*=20.7884(5) Å, β=106.44 (1)°, *U*=3245.6(1) Å^3, *F*(000)=1360, *Z*=8, D_c=1.328 mg m^{-3}, μ=0.094 mm^{-1}. 43,044 reflections yielded 9470 unique data (R_{merg}=0.0372). Final w$R_2(F^2)$=0.0968 for all data (897 refined parameters), conventional $R_1(F)$=0.0368 for 8372 reflections with $I \geq 2\sigma$, GOF=1.026.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.05.094.

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