Synthesis of novel 3-substituted benzamides related to imatinib

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Twelve new 3-substituted benzamide derivatives structurally related to tyrosine kinase inhibitor imatinib have been synthesised by a Cu(I)-catalysed coupling of three previously synthesised (5-iodo-2-methylphenyl)-[4-(pyridin-3-yl)-6-perfluoroalkylpyrimidin-2-yl]amines with four synthesised 3-substituted 4-(4-methylpiperazin-1-ylmethyl)benzamides.

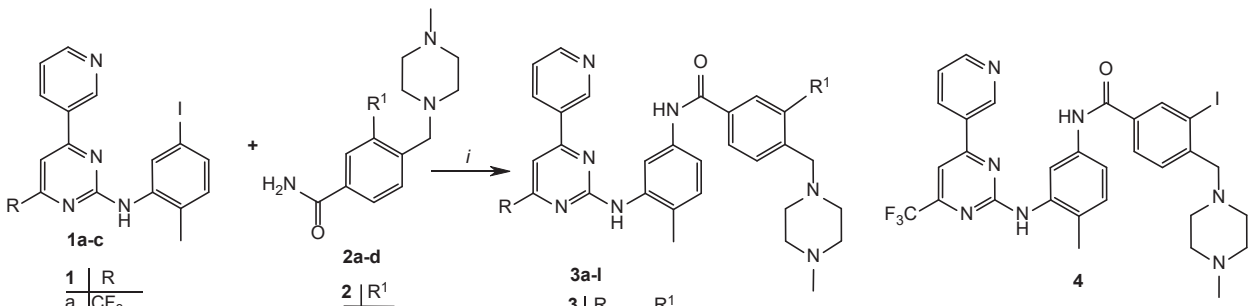
Keywords: (6-perfluoroalkylpyrimidin-2-yl)amines, 3,4-substituted benzamides, Cu(I) catalysed coupling

N-Arylamides are prevalent in numerous compounds that are of pharmaceutical interest. Imatinib – 4-(4-methylpiperazin-1-ylmethyl)-*N*-{4-methyl-3-[4-(pyridin-3-yl)pyrimidin-2-ylamino]phenyl} benzamide (**3**, R = R^1 = H) mesylate – a selective tyrosine kinase inhibitor belongs to this class of compounds. The imatinib success story has stimulated the discovery of many novel inhibitors of protein kinases and further studies of imatinib derivatives promise to enhance understanding of how changes in drug structure affect biological activity.[1,2] A series of 3-substituted benzamide derivatives structurally related to imatinib was prepared and found[3] to be much more potent than the parent compound. In continuation of our research[4,5] on the synthesis of perfluoroalkyl imatinib analogous, 12 new derivatives have been prepared for biological testing by coupling three (5-iodo-2-methylphenyl)-[4-(pyridin-3-yl)-6-perfluoroalkylpyrimidin-2-yl]amines **1a**–**c** obtained previously[5] with four 3-substituted-4-(4-methylpiperazin-1-ylmethyl)benzamides **2a**–**d.**

Results and discussion

The synthetic route designed for obtaining the target compounds **3a**–**l** is shown in Scheme 1 and employs the same Cu(I)-catalysed coupling method described by us[5] for synthesising the parent analogues **3** (R = CF_3, C_2F_5, C_3F_7, R^1 = H). The starting amides **2a**–**d** were prepared from commercially available disubstituted benzoic acids by standard methods as shown in Scheme 2. Esterification[6] of the carboxylic acids gave methyl or ethyl esters, α-bromination[7] of which with *N*-bromosuccinimide and coupling[3,8] of the products with 1-methylpiperazine afforded the corresponding 3-substituted 4-(4-methylpiperazin-1-yl)benzoates which were further converted into benzamides **2a**–**d.** These compounds were coupled with iodo compounds **1a**–**c** in the presence of Cu(I), K_3PO_4 and DMEDA in solvent *t*-BuOH under an argon atmosphere to give the 3-substituted 4-(4-methylpiperazin-1-ylmethyl)-*N*-[4-methyl-3-(4-pyridin-3-yl-6-polyfluoromethyl-pyrimidin-2-yl-amino)phenyl] benzamides **3a**–**l** as imatinib (**3**, R = R^1 = H) analogues in moderate to good yields.

In some cases (synthesis of **3a**, **3i**), the iodide was consumed completely after 18–24 h and good yields were obtained, but for others mainly starting material (revealed by LC/MS) was present even after 48 h. For example, the coupling of iodide **1c** with benzamides **2b** and **2d** gave low yields, which could not be improved even by a prolonged reaction time, and unconsumed iodide was recovered in 43% yield. Even when the amount of Cu(I) iodide was increased up to 100 mol%, the coupling reaction could not be effected efficiently. During the coupling of iodides **1** with bromo benzamide **2b**, minor amounts of iodo derivatives **4** originated from halogen exchange could be detected. This is in agreement with the disclosure[9] of a so called aromatic Finkelstein reaction, *i.e.* copper-catalysed halogen exchange in aryl halides. In the case of coupling iodide **1a** with amide **2b**, we



1	R
a	CF_3
b	C_2F_5
c	C_3F_7

2	R^1
a	Cl
b	Br
c	F
d	CF_3

3	R	R^1
a	CF_3	Cl
b	CF_3	Br
c	CF_3	F
d	CF_3	CF_3
e	C_2F_5	Cl
f	C_2F_5	Br
g	C_2F_5	F
h	C_2F_5	CF_3
i	C_3F_7	Cl
j	C_3F_7	Br
k	C_3F_7	F
l	C_3F_7	CF_3

Scheme 1 (*i*) Cu(I), DMEDA, K_3PO4, *t*-BuOH, reflux.

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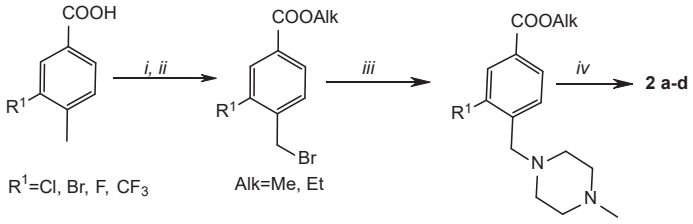

Scheme 2 (*i*) MeOH or EtOH, H_2SO_4, 60 °C, 18 h; (*ii*) NBS, $(PhCOO)_2$, benzene, 250W, reflux, 4 h; (*iii*) *N*-methylpiperazine, K_2CO_3, THF, 18 h, rt; (*iv*) NH_3, 150 °C, 50 atm, 18 h.

managed to characterise compound **4** as a reaction by-product. Minor iodo products of type **4** are easily distinguishable from major bromo derivatives by MS and NMR methods. Halogen exchange causes dramatic changes in the ^{13}C spectra and in the chemical shifts of protons (H and CH_2) next to halogen.

All the compounds were characterised by their ^1H and ^{13}C NMR spectra. 2D COSY spectroscopy was applied for correct chemical shift attributions in *N*-aryl amide and benzoic acid subunits.

Experimental

^1H, ^{19}F and ^{13}C NMR spectra were obtained on a Varian 300-MR, 400-MR or a 600-MR spectrometer in DMSO-d_6, except **2a**–**c** (in CD_3OD), **2d** (in $CDCl_3$) and **3e** (^{19}F NMR spectrum obtained in $CDCl_3$). The residual solvent protons served as internal standard in DMSO-d_6 (2.50 ppm for ^1H nuclei and 39.5 ppm for ^{13}C nuclei), in $CHCl_3$ (7.26 ppm for ^1H nuclei and 77.16 ppm for ^{13}C nuclei) and in CD_3OD (3.31 ppm for ^1H nuclei). Chemical shifts (δ) are given in ppm and coupling constants (*J*) in Hz. The assignment of resonance signals to individual protons of compounds **3** was based on COSY spectra. The COSY spectra recorded for compounds **3e**–**h** served as a basis for analysis of related compounds **3a**–**d** and **3i**–**l** spectra.

The high resolution mass spectra were done on an Agilent UPLC (Agilent 6230 TOF LC/MS) instrument. The mass spectra were obtained with an Acquity UPLC liquid chromato-mass spectrometer of the Waters-Q-TOF (Micromass) system. Elemental analyses were determined on a Carlo Erba Instrument (EA-1106). The melting points of derivatives were determined on a Boetius apparatus. Unless noted below, starting compounds were supplied by Alfa Aesar or Acros, and used without purification. The assay of the DMEDA used was 85%.

3-Fluoro-4-(4-methylpiperazin-1-ylmethyl)benzamide (**2c**). Methyl 3-fluoro-4-(4-methyl-piperazin-1-ylmethyl)benzoate[6] (2.37 g, 8.9 mmol) and ~5 mL of liquid ammonia (acetone/CO_2) in a stainless steel reactor were stirred and heated for 15 h at 150 °C and 50 bar pressure. Then the reactor was cooled to –50 °C and kept for 15 min at this temperature. After release of pressure the autoclave was opened and the remaining ammonia was volatilised warming by allowing the mass to warm slowly to room temperature. The yellowish residue was taken up in methanol (10–15 mL), with addition of 2.5 g of silica gel. The solvent was distilled off on a rotary evaporator to give the crude product absorbed on silica gel which was purified by column chromatography using EtOAc–MeOH–NH_4OH (3:1:0.1) as eluent. The crude product was crystallised from toluene and dried in a vacuum (70 °C, 1–10 mbar, 18 h) to obtain 1.73 g (77%) of amide **2c** as a white solid; m.p. 145–148 °C; ^1H NMR (400 MHz): δ 2.24 (3H, s, CH_3), 2.35–2.65 (8H, br s, CH_2 piperazine), 3.61 (1H, d, *J* = 1.2 Hz, CH_2), 4.84 (2H, s, NH_2), 7.49 (1H, t, *J* = 7.8 Hz, H-5 Ar), 7.58 (1H, dd, *J* = 10.6, 1.8 Hz, H-2 Ar), 7.66 (1H, dd, *J* = 7.8, 1.8 Hz, H-6 Ar); ^{13}C NMR (100 MHz): δ 44.9 (CH_3), 53.3 (C piperazine), 55.5 (d, *J* = 1.9 Hz, CH_2), 55.6 (C piperazine), 114.2 (d, *J* = 24.5 Hz, C-2), 122.9 (d, *J* = 3.4, C-6), 127.8 (d, *J* = 15.0, C-4), 131.7 (d, *J* = 4.4, C-5), 135.0 (d, *J* = 7.3, C-1), 161.1 (d, *J* = 246.4 Hz, C–F), 169.1 (C=O); Mass *m/z* (%): 252 $[M + 1]^+$ (100); Anal. calcd for $C_{13}H_{18}FN_3O$: C, 62.13; H, 7.22; N, 16.72; found: C, 62.12; H, 7.23; N, 16.60%.

The same synthesis protocol was used to obtain the other amides **2a**,**b**,**d**.

3-Chloro-4-(4-methylpiperazin-1-ylmethyl)benzamide (**2a**): Yield 2.07 g (87%); white solid; m.p. 88–91 °C (toluene); ^1H NMR (400 MHz): δ 2.27 (3H, s, CH_3), 2.42–2.53 (4H, br s, CH_2 piperazine), 2.52–2.63 (4H, br s, CH_2 piperazine), 3.67 (2H, s, CH_2), 4.83 (2H, s, NH_2), 7.58 (1H, d, *J* = 8.0 Hz, H-5 Ar), 7.76 (1H, dd, *J* = 8.0, 1.8 Hz, H-6 Ar), 7.89 (1H, d, *J* = 1.8 Hz, H-2 Ar); ^{13}C NMR (100 MHz): δ 46.0 (CH_3), 53.6 (C piperazine), 55.8 (C piperazine), 59.7 (CH_2), 127.0 (C-6), 129.8 (C-2), 132.1 (C-5), 135.4 and 135.6 (C-1 and C–Cl), 140.5 (C-4), 170.4 (C=O); HRMS (ESI) for $C_{13}H_{19}ClN_3O$ $[M + 1]^+$: calcd 268.1217, found: 268.1217.

3-Bromo-4-(4-methylpiperazin-1-ylmethyl)benzamide (**2b**): Yield 2.23 g (80%); white solid; m.p. 163–165 °C; ^1H NMR (400 MHz): δ 2.26 (3H, s, *N*–CH_3), 2.35–2.50 (4H, br s, CH_2 piperazine), 2.50–2.65 (4H, br s, CH_2 piperazine), 3.63 (2H, s, CH_2), 4.84 (2H, s, NH_2), 7.55 (1H, d, *J* = 7.8 Hz, H-5 Ar), 7.80 (1H, d, *J* = 7.8 Hz, H-6 Ar), 8.07 (1H, s, H-2 Ar); ^{13}C NMR (100 MHz): δ 46.0 (CH_3), 53.6 (C piperazine), 55.9 (C piperazine), 62.3 (CH_2), 125.5 (C–Br), 127.6 (C-6), 131.9 (C-5), 133.1 (C-2), 135.5 (C-1), 142.3(C-4), 170.3 (C=O). MS *m/z* (%): 312, 314 $[M + 1]^+$ (100); Anal. calcd for $C_{13}H_{18}BrN_3O$: C, 50.01; H, 5.81; N, 13.46; found: C, 49.99; H, 5.76; N, 13.40%.

4-(4-Methylpiperazin-1-ylmethyl)-3-trifluoromethylbenzamide (**2d**): Yield 2.2 g (81%), white solid; m.p. 83–86 °C; ^1H NMR (400 MHz): δ 2.29 (3H, s, *N*–CH_3), 2.48 (8H, br s, CH_2 piperazine), 3.68 (2H, s, CH_2), 5.91 (1H, br s, NH_2), 6.19 (1H, br s, NH_2), 7.90 (1H, d, *J* = 8.1 Hz, H-5 Ar), 7.93 (1H, dd, *J* = 8.1, 1.6 Hz, H-6 Ar), 8.06 (1H, br s, H-2 Ar). ^{13}C NMR (100 MHz): δ 45.9 (CH_3), 53.1 (C piperazine), 55.1 (C piperazine), 57.9 (d, *J* = 1.9 Hz, CH_2), 124.0 (q, *J* = 274.2 Hz, CF_3), 125.0 (q, *J* = 5.7 Hz, C-2), 129.0 (q, *J* = 30.9 Hz, C-3), 130.4 (q, *J* = 0.9 Hz, C-5), 130.7 (C-6); 132.0 (C-1); 142.2 (q, *J* = 1.3 Hz, C-4), 168.0 (C=O); HRMS (ESI) for $C_{14}H_{19}F_3N_3O\cdot[M + 1]^+$: calcd 302.1480, found: 302.1484.

2-Arylamino-4-(pyridin-3-yl)-6-perfluoroalkylpyrimidines (**3**)*; general procedure*

To a suspension of (5-iodo-2-methylphenyl)pyrimidin-2-ylamine **1** (0.80 mmol), the corresponding amide **2** (0.80 mmol), Cu(I) iodide (0.1 g, 0.56 mmol) and finely powdered K_3PO_4 (0.34 g, 1.60 mmol) in *t*-BuOH (10 mL), DMEDA (71 µl, 0.56 mmol, 85%) was added by syringe under an argon atmosphere. The heterogenous mixture was refluxed for 18–72 h (conversion monitoring by LC/MS), cooled and diluted with 5% aqueous solution of NH_4OH (10 mL) and dichloromethane (20 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were washed sequentially once with NH_4OH (8 mL) and water (8 mL), and dried (Na_2SO_4). The extract was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using CH_2Cl_2–MeOH as eluent (6:1 for **3a**,**c**,**d**,**g**–**l** and 10:1 for **3b**,**e**,**f**). From the first fraction unreacted (5-iodo-2-methylphenyl)pyrimidin-2-ylamine **1** could be recovered. From the second fraction 2-arylamino-4-(pyridin-3-yl)-6-perfluoroalkylpyrimidine **3** was isolated and crystallised from an appropriate solvent.

3-Chloro-4-(4-methylpiperazin-1-ylmethyl)-N-*[4-methyl-3-(4-pyridin-3-yl-6-trifluoromethyl-pyrimidin-2-ylamino)phenyl] benzamide* (**3a**): Yellow solid, 0.32 g (67%); m.p. 234–236 °C (toluene); ^1H NMR (400 MHz): δ 2.17 (3H, s, *N*–CH_3), 2.21 (3H, s, *C*–CH_3), 2.35 (4H, br s, H piperazine), 2.40–2.50 (4H, br s, H piperazine, overlap with DMSO), 3.61 (2H, s, CH_2), 7.26 (1H, d, *J* = 8.4 Hz, H-5 Ar), 7.51 (1H, dd, *J* = 8.4, 1.8 Hz, H-6 Ar), 7.54 (1H, ddd, *J* = 8.1, 4.9, 0.6 Hz, H-5 Py), 7.62 (1H, d, *J* = 8.0 Hz, H-5), 7.86 (1H, s, H Pm), 7.89 (1H, dd, *J* = 8.0, 1.9 Hz, H-6), 7.98–8.03 (2H, m, H-2 Ar and H-2), 8.54 (1H, ddd, *J* = 8.1, 1.9, 1.6 Hz, H-4 Py), 8.72 (1H, dd, *J* = 4.9, 1.6 Hz, H-6 Py), 9.33 (1H, dd, *J* = 1.9, 0.6 Hz, H-2 Py), 9.70 (1H, s, NH), 10.29 (1H, s, NH); ^{13}C NMR (100 MHz): 17.6 (*C*–$\underline{C}H_3$), 45.6 (*N*–CH_3), 52.6 (C piperazine), 54.6 (C piperazine), 58.4 (CH_2), 102.7 (C-5 Pm), 117.6, 117.7, 120.7 (q, *J* = 277 Hz, CF_3), 123.8, 126.3, 128.2, 128.7, 130.3, 130.6, 131.2, 133.2, 134.9, 135.2, 136.9, 137.0, 139.2, 148.6,

152.0, 156.3 (q, *J* = 34 Hz, C–CF_3), 161.2, 163.8, 165.1. Anal. calcd for $C_{30}H_{29}ClF_3N_7O$: C, 60.45; H, 4.90; N, 16.45; found: C, 60.11; H, 4.89; N, 16.13%.

3-Bromo-4-(4-methylpiperazin-1-ylmethyl)-N-*[4-methyl-3-(4-pyridin-3-yl-6-trifluoromethyl-pyrimidin-2-ylamino)phenyl] benzamide* (**3b**) was purified by preparative TLC (PLC plates, 20 × 20 cm, silica gel 60 F_{254}, 2 mm, Merck) using CH_2Cl_2–MeOH–NH_3 (10:20:0.1) as eluent to give a yellow solid, 0.30 g (59%); m.p. 203–205 °C (Et_2O); ^{1}H NMR (600 MHz): δ 2.12 (3H, s, *N*–CH_3), 2.17 (3H, s, *C*–CH_3), 2.35 (4H, br s, H piperazine), 2.46 (4H, br s, H piperazine), 3.55 (2H, s, CH_2), 7.21 (1H, d, *J* = 8.3 Hz, H-5 Ar), 7.48 (1H, dd, *J* = 8.3, 1.7 Hz, H-6 Ar), 7.50 (1H, dd, *J* = 8.1, 4.8 Hz, H-5 Py), 7.57 (1H, d, *J* = 8.1 Hz, H-5), 7.80 (1H, s, H Pm), 7.90 (1H, dd, *J* = 8.1, 1.7 Hz, H-6), 7.97 (1H, d, *J* = 1.7 Hz, H-2 Ar), 8.13 (1H, d, *J* = 1.7 Hz, H-2), 8.50 (1H, ddd, *J* = 8.1, 2.0, 1.7 Hz, H-4 Py), 8.68 (1H, dd, *J* = 4.8, 1.7 Hz, H-6 Py), 9.29 (1H, d, *J* = 2.0 Hz, H-2 Py), 9.68 (1H, s, NH), 10.26 (1H, s, NH); ^{13}C NMR (150 MHz): δ 18.4 (*C*–$\underline{C}H_3$), 46.2 (*N*–CH_3), 53.1 (C piperazine), 55.2 (C piperazine), 61.4 (CH_2), 103.2 (C-5 Pm), 118.1 (C-6 Ar), 118.2 (C-2 Ar), 121.2 (q, *J* = 273 Hz, CF_3), 124.1 (C–Br), 124.4 (C-5 Py), 127.4 (C-6), 129.2 (C-4 Ar), 130.8 (C-5 Ar), 131.1 (C-1), 131.7 (C-5), 131.9 (C-2), 135.5 (C-3 Py), 135.8 (C-4 Py), 137.4 (C-1 Ar), 137.5 (C-3 Ar), 141.4 (C-4), 149.1 (C-2 Py), 152.7 (C-6 Py), 156.9 (q, *J* = 34 Hz, C–CF_3), 161.6 (C-2 Pm), 164.2 (C=O), 165.6 (C-4 Pm); HRMS (ESI) for $C_{30}H_{30}BrF_3N_7O$ $[M + 1]^+$: calcd 640.1642, found: 640.1641.

3-Iodo-4-(4-methylpiperazin-1-ylmethyl)-N-*[4-methyl-3-(4-pyridin-3-yl-6-trifluoromethyl-pyrimidin-2-ylamino)phenyl] benzamide* (**4**) was detected in mixture with **3b** (ratio **3b**:**4** was 4:1). ^{1}H NMR (600 MHz): δ 2.12 (3H, s, *N*–CH_3), 2.17 (3H, s, *C*–CH_3), 2.35 (4H, br s, H piperazine), 2.46 (4H, br s, H piperazine), 3.47 (2H, s, CH_2), 7.21 (1H, d, *J* = 8.3 Hz, H-5 Ar), 7.48 (1H, dd, *J* = 8.3, 1.7 Hz, H-6 Ar), 7.50 (1H, dd, *J* = 8.1, 4.8 Hz, H-5 Py), 7.47 (1H, d, *J* = 8.1 Hz, H-5), 7.80 (1H, s, H Pm), 7.89 (1H, dd, *J* = 8.1, 1.7 Hz, H-6), 7.96 (1H, d, *J* = 1.7 Hz, H-2 Ar), 8.35 (1H, d, *J* = 1.7 Hz, H-2), 8.50 (1H, ddd, *J* = 8.1, 2.0, 1.7 Hz, H-4 Py), 8.68 (1H, dd, *J* = 4.8, 1.7 Hz, H-6 Py), 9.29 (1H, d, *J* = 2.0 Hz, H-2 Py), 9.68 (1H, s, NH), 10.26 (1H, s, NH); ^{13}C NMR (150 MHz): δ 18.4 (*C*–$\underline{C}H_3$), 46.2 (*N*–CH_3), 53.0 (C piperazine), 56.5 (C piperazine), 65.9 (CH_2), 100.9 (C–I), 103.2 (C-5 Pm), 118.1 (C-6 Ar), 118.2 (C-2 Ar), 121.2 (q, *J* = 273 Hz, CF_3), 124.4 (C-5 Py), 127.9 (C-6), 129.2 (C-4 Ar), 130.4 (C-5), 130.8 (C-5 Ar), 131.1 (C-1), 138.4 (C-2), 135.5 (C-3 Py), 135.8 (C-4 Py), 137.4 (C-1 Ar), 137.5 (C-3 Ar), 144.3 (C-4), 149.1 (C-2 Py), 152.7 (C-6 Py), 156.9 (q, *J* = 34 Hz, C–CF_3), 161.6 (C-2 Pm), 164.2 (C=O), 165.6 (C-4 Pm); HRMS (ESI) for $C_{30}H_{30}N_7OF_3I$ $[M + 1]^+$: calcd 688.1509, found: 688.1487.

3-Fluoro-4-(4-methylpiperazin-1-ylmethyl)-N-*[4-methyl-3-(4-pyridin-3-yl-6-trifluoromethyl-pyrimidin-2-ylamino)phenyl] benzamide* (**3c**): Yellow solid, 0.27 g (59%); m.p. 239–241 °C (toluene); ^{1}H NMR (300 MHz): δ 2.14 (3H, s, *N*–CH_3), 2.21 (3H, s, *C*–CH_3), 2.31 (4H, br s, H piperazine), 2.41 (4H, br s, H piperazine), 3.57 (1.7H, s, CH_2), 7.26 (1H, d, *J* = 8.0 Hz, H-5 Ar), 7.51 (1H, dd, *J* = 8.0, 2.1 Hz, H-6 Ar), 7.53 (1H, t, *J* = 7.5 Hz, H-5), 7.55 (1H, ddd, *J* = 8.0, 4.7, 0.6 Hz, H-5 Py), 7.73 (1H, dd, *J* = 11.0, 1.6 Hz, H-2), 7.77 (1H, dd, *J* = 7.5, 1.6 Hz, H-6), 7.86 (1H, s, H Pm), 8.01 (1H, d, *J* = 2.1 Hz, H-2 Ar), 8.54 (1H, ddd, *J* = 8.0, 2.2, 1.6 Hz, H-4 Py), 8.72 (1H, dd, *J* = 4.7, 1.6 Hz, H-6 Py), 9.33 (1H, dd, *J* = 2.2, 0.6 Hz, H-2 Py), 9.70 (1H, s, NH), 10.25 (1H, s, NH); ^{13}C NMR (100 MHz): δ 17.8 (*C*–$\underline{C}H_3$), 46.1 (*N*–CH_3), 52.9 (C piperazine), 55.0 (CH_2), 55.2 (C piperazine), 103.6 (C-5 Pm), 113.9, 114.6 (d, *J* = 25 Hz, C-2), 116.2, 120.6 (q, *J* = 275 Hz, CF_3), 122.3, 124.0, 125.2, 129.1 (d, *J* = 15 Hz, C-4), 131.0, 131.6 (d, *J* = 7 Hz, C-5), 131.9, 135.3, 135.9 (d, *J* = 7 Hz, C-1), 136.4, 137.2, 148.8, 152.3, 157.8 (q, *J* = 36 Hz, C–CF_3), 160.7, 161.3 (d, *J* = 249 Hz, C-3), 164.4, 165.6; Anal. calcd for $C_{30}H_{29}F_4N_7O$: C, 62.17; H, 5.04; N, 16.92; found: C, 61.97; H, 4.98; N, 16.69%.

4-(4-Methylpiperazin-1-ylmethyl)-N-*[4-methyl-3-(4-pyridin-3-yl-6-trifluoromethylpyrimidin-2-ylamino)phenyl]-3-trifluoromethylbenzamide* (**3d**): Yellow solid, 0.40 g (80%); m.p. 211–213 °C (MeOH); ^{1}H NMR (400 MHz): δ 2.18 (3H, s, *N*–CH_3), 2.21 (3H, s, *C*–CH_3), 2.37 (4H, br s, H piperazine), 2.42 (4H, br s, H piperazine), 3.68 (1H, s, CH_2), 7.27 (1H, d, *J* = 8.3 Hz, H-5 Ar), 7.51 (1H, dd, *J* = 8.3, 1.8 Hz, H-6 Ar), 7.54 (1H, dd, *J* = 8.0, 4.8 Hz, H-5 Py), 7.86 (1H, s, H Pm), 7.91 (1H, d, *J* = 8.1 Hz, H-5), 7.97 (1H, d, *J* = 1.8 Hz, H-2 Ar), 8.20 (1H, d, *J* = 8.1 Hz, H-6), 8.22 (1H, s, H-2), 8.55 (1H, ddd, *J* = 8.0, 2.3, 1.6 Hz, H-4 Py), 8.73 (1H, dd, *J* = 4.8, 1.6 Hz, H-6 Py), 9.34 (1H, d, *J* = 2.3 Hz, H-2 Py), 9.72 (1H, s, NH), 10.4 (1H, s, NH); ^{13}C NMR (100 MHz): δ 17.6 (*C*–$\underline{C}H_3$), 45.6 (*N*–CH_3), 52.7 (C piperazine), 54.6 (C piperazine), 57.5 (CH_2), 102.7 (C-5 Pm), 117.8 (2C), 120.6 (q, *J* = 275 Hz, CF_3), 121.4 (q, *J* = 275 Hz, CF_3), 123.8 (C-5 Py), 125.0, 127.2 (q, *J* = 30 Hz, C–CF_3), 128.8, 130.3, 130.7, 131.2, 131.5, 133.9, 134.9, 136.90, 136.95, 141.0, 148.6, 152.2, 156.5 (q, *J* = 34 Hz, C–CF_3), 161.2, 163.9, 165.1; HRMS (ESI) for $C_{31}H_{30}F_6N_7O$ $[M + 1]^+$: calcd 630.2411, found: 630.2387.

3-Chloro-N-*[4-methyl-3-(4-pentafluoroethyl-6-pyridin-3-ylpyrimidin-2-ylamino)phenyl]-4-(4-methylpiperazin-1-ylmethyl) benzamide* (**3e**): Yellow solid, 0.30 g (59%), m.p. 223–224 °C (MeOH); ^{1}H NMR (400 MHz): δ 2.18 (3H, s, *N*–CH_3), 2.20 (3H, s, *C*–CH_3), 2.37 (4H, br s, H piperazine), 2.46 (4H, br s, H piperazine), 3.62 (2H, s, CH_2), 7.26 (1H, d, *J* = 8.2 Hz, H-5 Ar), 7.50 (1H, dd, *J* = 8.2, 2.1 Hz, H-6 Ar), 7.54 (1H, dd, *J* = 8.0, 4.9 Hz, H-5 Py), 7.62 (1H, d, *J* = 8.0 Hz, H-5), 7.87 (1H, s, H Pm); 7.89 (1H, dd, *J* = 8.0, 1.7 Hz, H-6), 7.98 (1H, d, *J* = 2.1 Hz, H-2 Ar), 7.99 (1H, d, *J* = 1.7 Hz, H-2), 8.54 (1H, ddd, *J* = 8.0, 2.0, 1.7 Hz, H-4 Py), 8.72 (1H, dd, *J* = 4.9, 1.7 Hz, H-6 Py), 9.33 (1H, d, *J* = 2.0 Hz, H-2 Py), 9.71 (1H, s, NH), 10.28 (1H, s, NH); ^{19}F NMR (400 MHz): δ −82.0 (CF_3), −118.1 (CF_2); Anal. calcd for $C_{31}H_{29}ClF_5N_7O$: C, 57.63; H, 4.52; N, 15.18; found: C, 57.57; H, 4.46; N, 14.96%.

3-Bromo-N-*[4-methyl-3-(4-pentafluoroethyl-6-pyridin-3-ylpyrimidin-2-ylamino)phenyl]-4-(4-methylpiperazin-1-ylmethyl) benzamide* (**3f**): Yellow solid, 0.27 g (49%), m.p. 211.5–212.5 °C (toluene); ^{1}H NMR (300 MHz): δ 2.16 (3H, s, *N*–CH_3), 2.20 (3H, s, *C*–CH_3), 2.34 (4H, br s, H piperazine), 2.45–2.50 (4H, br s, H piperazine, overlap with DMSO), 3.51 (2H, s, CH_2), 7.25 (1H, d, *J* = 8.2 Hz, H-5 Ar), 7.50 (1H, dd, *J* = 8.2, 2.2 Hz, H-6 Ar), 7.55 (1H, dd, *J* = 8.0, 4.8 Hz, H-5 Py), 7.60 (1H, d, *J* = 8.0 Hz, H-5), 7.87 (1H, s, H Pm), 7.92 (1H, dd, *J* = 8.0, 1.9 Hz, H-6), 7.97 (1H, d, *J* = 2.2 Hz, H-2 Ar), 8.15 (1H, d, *J* = 1.9 Hz, H-2), 8.54 (1H, ddd, *J* = 8.0, 2.0, 1.9 Hz, H-4 Py), 8.73 (1H, dd, *J* = 4.8, 1.9 Hz, H-6 Py), 9.33 (1H, d, *J* = 2.0 Hz, H-2 Py), 9.71 (1H, s, NH), 10.28 (1H, s, NH); ^{19}F NMR (400 MHz): δ −82.0 (CF_3), −118.1 (CF_2); HRMS (ESI) for $C_{31}H_{30}BrF_5N_7O$ $[M + 1]^+$: calcd 690.1610; found: 690.1587.

3-Fluoro-N-*[4-methyl-3-(4-pentafluoroethyl-6-pyridin-3-ylpyrimidin-2-ylamino)phenyl]-4-(4-methylpiperazin-1-ylmethyl) benzamide* (**3g**): 0.36 g (71%), m.p. 230–231 °C (toluene); ^{1}H NMR (400 MHz): δ 2.15 (3H, s, *N*–CH_3), 2.20 (3H, s, *C*–CH_3), 2.33 (4H, br s, H piperazine), 2.41 (4H, br s, H piperazine), 3.57 (2H, s, CH_2), 7.25 (1H, d, *J* = 8.3 Hz, H-5 Ar), 7.50 (1H, dd, *J* = 8.3, 2.1 Hz, H-6 Ar), 7.51 (1H, ddd, *J* = 8.0, 4.8, 0.5 Hz H-5 Py), 7.54 (1H, dd, *J* = 7.9, 7.4 Hz, H-5), 7.72 (1H, dd, *J* = 10.6, 1.5 Hz, H-2), 7.77 (1H, dd, *J* = 7.9, 1.5 Hz, H-6), 7.86 (1H, s, H Pm), 7.99 (1H, d, *J* = 2.1 Hz, H-2 Ar), 8.53 (1H, ddd, *J* = 8.0, *J* = 2.0, 1.6 Hz, H-4 Py), 8.72 (1H, dd, *J* = 4.8, 1.6 Hz, H-6 Py), 9.33 (1H, dd, *J* = 2.0, 0.5, H-2 Py), 9.68 (1H, s, NH), 10.21 (1H, s, NH); ^{19}F NMR (400 MHz): δ −82.0 (CF_3), −117.6 (F Ar), −118.1 (CF_2); Anal. calcd for $C_{31}H_{29}F_6N_7O$: C, 59.14; H, 4.64; N, 15.57; found: C, 59.41; H, 4.61; N, 15.46%.

N-*[4-Methyl-3-(4-pentafluoroethyl-6-pyridin-3-yl-pyrimidin-2-ylamino)phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-3-trifluoromethylbenzamide* (**3h**): 0.39 g (71%), m.p. 162–164 °C (toluene); ^{1}H NMR (300 MHz): δ 2.16 (3H, s, *N*–CH_3), 2.21 (3H, s, *C*–CH_3), 2.36 (4H, br s, H piperazine), 2.41 (4H, br s, H piperazine), 3.67 (2H, s, CH_2), 7.26 (1H, d, *J* = 8.3 Hz, H-5 Ar), 7.51 (1H, dd, *J* = 8.3, 2.0 Hz, H-6 Ar), 7.54 (1H, dd, *J* = 8.0, 4.8 Hz, H-5 Py), 7.87 (1H, s, H Pm), 7.91 (1H, d, *J* = 8.1 Hz, H-5), 7.97 (1H, d, *J* = 2.0 Hz, H-2 Ar), 8.20 (1H, dd, *J* = 8.1, 1.6 Hz, H-6), 8.22 (1H, d, *J* = 1.6 Hz, H-2), 8.55 (1H, dt, *J* = 8.0, 1.6 Hz, H-4 Py), 8.72 (1H, dd, *J* = 4.8, 1.6 Hz, H-6 Py), 9.33 (1H, d, *J* = 1.6 Hz, H-2 Py), 9.71 (1H, s, NH), 10.40 (1H, s, NH); ^{19}F NMR (400 MHz): δ −58.2 (CF_3 Ar), −82.0 ($C\underline{F}_3CF_2$), −118.1 (CF_2); HRMS (ESI) calcd for $C_{32}H_{30}F_8N_7O$ $[M + 1]^+$ 680.2379; found: 680.2351.

3-Chloro-N-*[3-(4-heptafluoropropyl-6-pyridin-3-ylpyrimidin-2-ylamino)-4-methylphenyl]-4-(4-methylpiperazin-1-ylmethyl) benzamide* (**3i**): 0.41 g (74%), m.p. 215–216 °C (MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.16 (3H, s, *N*–CH_3), 2.20 (3H, s, *C*–CH_3), 2.34 (4H, br s, H piperazine), 2.45–2.50 (4H, br s, H piperazine, overlap with DMSO), 3.61 (2H, s, CH_2), 7.26 (1H, d, *J* = 8.3 Hz, H-5 Ar), 7.51 (1H, dd, *J* = 8.3, 1.6 Hz, H-6 Ar), 7.54 (1H, dd, *J* = 7.6, 4.6 Hz, H-5 Py), 7.62 (1H, d, *J* = 8.0 Hz, H-5), 7.86 (1H, s, H Pm), 7.88 (1H, dd, *J* = 8.0, 1.5 Hz, H-6), 7.97 (1H, d, *J* = 1.6 Hz, H-2 Ar), 7.99 (1H, d, *J* = 1.5 Hz, H-2), 8.55 (1H, ddd, *J* = 7.6, 1.8, 1.6 Hz, H-4 Py), 8.73 (1H, dd, *J* = 4.6, 1.6 Hz, H-6 Py), 9.33 (1H, d, *J* = 1.8 Hz, H-2 Py), 9.71 (1H, s, NH), 10.28 (1H, s, NH); ^{19}F NMR (400 MHz): δ –79.8 (CF_3), –115.9 ($CF_3C\underline{F}_2CF_2$), –125.8 ($CF_3CF_2C\underline{F}_2$). HRMS (ESI) for $C_{32}H_{30}ClF_7N_7O$ $[M + 1]^+$: calcd 696.2083, found: 696.2078.

3-Bromo-N-*[3-(4-heptafluoropropyl-6-pyridin-3-ylpyrimidin-2-ylamino)-4-methylphenyl]-4-(4-methylpiperazin-1-ylmethyl) benzamide* (**3j**): 0.18 g (32%), m.p. 186–188 °C (toluene); ^{1}H NMR (400 MHz): δ 2.16 (3H, s, *N*–CH_3), 2.20 (3H, s, *C*–CH_3), 2.34 (4H, br s, H piperazine), 2.45–2.50 (4H, br s, H piperazine overlap with DMSO), 3.58 (2H, s, CH_2), 7.25 (1H, d, *J* = 8.2 Hz, H-5 Ar), 7.50 (1H, dd, *J* = 8.2, 2.0 Hz, H-6 Ar), 7.54 (1H, dd, *J* = 8.0, 4.8 Hz, H-5 Py), 7.60 (1H, d, *J* = 8.0 Hz, H-5), 7.86 (1H, s, H Pm), 7.93 (1H, dd, *J* = 8.0, 1.7 Hz, H-6), 7.97 (1H, d, *J* = 2.0 Hz, H-2 Ar), 8.16 (1H, d, *J* = 1.7 Hz, H-2), 8.55 (1H, ddd, *J* = 8.0, 2.2, 1.7 Hz, H-4 Py), 8.72 (1H, dd, *J* = 4.8, 1.7 Hz, H-6 Py), 9.33 (1H, d, *J* = 2.2 Hz, H-2 Py), 9.71 (1H, s, NH), 10.28 (1H, s, NH); ^{19}F NMR (400 MHz): δ–79.8 (CF_3), –115.9 ($CF_3C\underline{F}_2CF_2$), –125.8 ($CF_3CF_2C\underline{F}_2$); HRMS (ESI) for $C_{32}H_{30}BrF_7N_7O$ $[M + 1]^+$: calcd 740.1578, found: 740.1569.

3-Fluoro-N-*[3-(4-heptafluoropropyl-6-pyridin-3-ylpyrimidin-2-ylamino)-4-methylphenyl]-4-(4-methylpiperazin-1-ylmethyl) benzamide* (**3k**): 0.29 g (53%), m.p. 226–227 °C (toluene); ^{1}H NMR (300 MHz): δ 2.14 (3H, s, *N*–CH_3), 2.20 (3H, s, *C*–CH_3), 2.32 (4H, br s, H piperazine), 2.41 (4H, br s, H piperazine), 3.57 (2H, s, CH_2), 7.25 (1H, d, *J* = 8.2 Hz, H-5 Ar), 7.48–7.58 (3H, m, H-5 Py, H-6 Ar, H-5), 7.73 (1H, dd, *J* = 10.8, 1.5 Hz, H-2), 7.77 (1H, dd, *J* = 7.8, 1.5 Hz, H-6), 7.86 (1H, s, H Pm), 7.98 (1H, d, *J* = 1.5 Hz, H-2 Ar), 8.55 (1H, ddd, *J* = 8.0, 2.2, 1.7 Hz, H-4 Py), 8.72 (1H, dd, *J* = 4.8, 1.7 Hz, H-6 Py), 9.33 (1H, d, *J* = 2.2 Hz, H-2 Py), 9.72 (1H, s, NH), 10.24 (1H, s, NH); ^{19}F NMR (400 MHz): δ –79.9 (CF_3), –115.8 ($CF_3C\underline{F}_2CF_2$), –117.6 (F Ar), –125.8 ($CF_3CF_2C\underline{F}_2$); Anal. calcd for $C_{32}H_{29}F_8N_7O$: C, 56.55; H, 4.30; N, 14.43; found: C, 56.75; H, 4.27; N, 14.16%.

N-*[3-(4-Heptafluoropropyl-6-pyridin-3-ylpyrimidin-2-ylamino)-4-methylphenyl]-4-(4-methyl-piperazin-1-ylmethyl)-3-trifluoromethylbenzamide* (**3l**): 0.19 g (32%), m.p. 183–185 °C (MeOH); ^{1}H NMR (300 MHz): δ 2.16 (3H, s, *N*–CH_3), 2.20 (3H, s, *C*–CH_3), 2.35 (4H, br s, H piperazine), 2.42 (4H, br s, H piperazine), 3.67 (2H, s, CH_2), 7.26 (1H, d, *J* = 8.3 Hz, H-5 Ar), 7.51 (1H, dd, *J* = 8.3, 1.6 Hz, H-6 Ar), 7.54 (1H, dd, *J* = 8.0, *J* = 4.8 Hz, H-5 Py), 7.86 (1H, s, H Pm), 7.91 (1H, d, *J* = 8.0 Hz, H-5), 7.97 (1H, d, *J* = 1.6 Hz, H-2 Ar), 8.19 (1H, dd, *J* = 8.0, 1.4 Hz, H-6), 8.22 (1H, br s, H-2), 8.55 (1H, ddd, *J* = 8.0, 2.1, 1.7 Hz, H-4 Py), 8.72 (1H, dd, *J* = 4.8, 1.7 Hz, H-6 Py), 9.34 (1H, d, *J* = 2.1 Hz, H-2 Py), 9.73 (1H, s, NH), 10.40 (1H, s, NH); ^{19}F NMR (400 MHz): δ –58.2 ($C\underline{F}_3$ Ar), –79.8 ($C\underline{F}_3CF_2CF_2$), –115.9 ($CF_3C\underline{F}_2CF_2$), –125.8 ($CF_3CF_2C\underline{F}_2$); HRMS (ESI) for $C_{33}H_{30}F_{10}N_7O$ $[M + 1]^+$: calcd 730.2347, found: 730.2343.

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