Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Novel Pyrazolo[1,5-*a*]pyridines as PI3 Kinase Inhibitors: Variation of the Central Linker Group

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Contents of Supporting Information

Table S1. Isosteres generated by BROOD v1.1.1.

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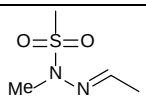
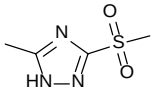
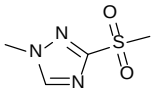
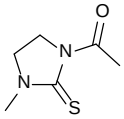
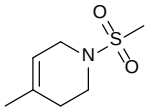
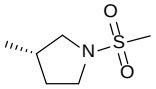
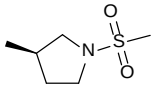
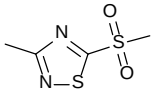
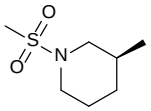
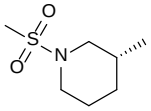
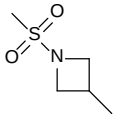
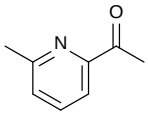
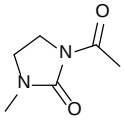
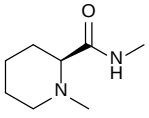
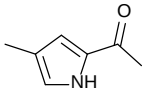
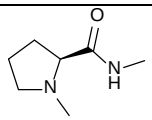
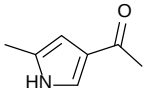
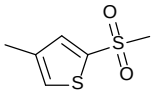
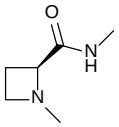
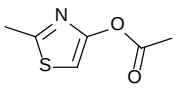
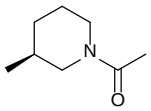
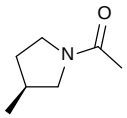
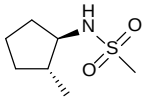
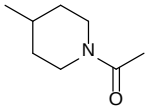
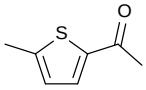
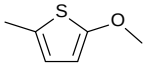
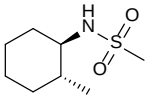
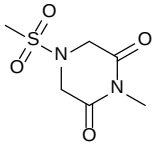
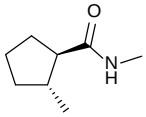
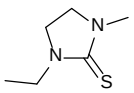
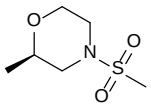
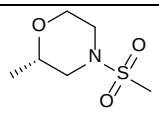
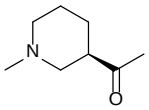
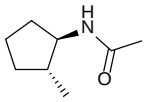
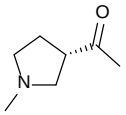
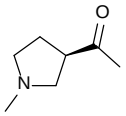
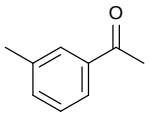
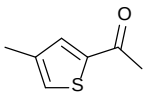
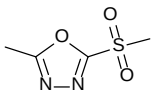
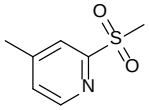
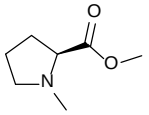
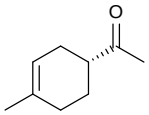
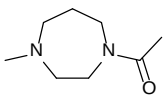
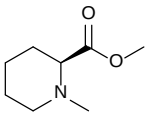
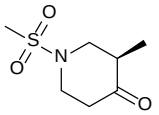
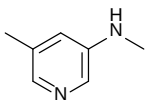
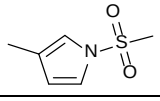
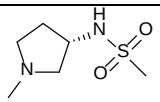
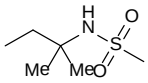
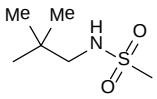
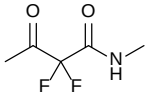
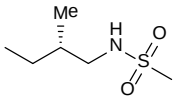
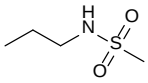
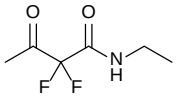
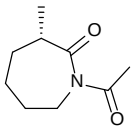
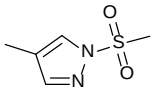
0		BROOD query				2.43
1		0.72	0.9	0.89	1.63	2.44
2		0.7	0.86	0.92	1.56	2.30
3		0.69	0.81	0.83	1.49	1.19
4		0.66	0.8	0.92	1.47	3.47
5S		0.57	0.9	0.9	1.47	3.03
5R		0.45	0.83	0.94	1.27	3.03
6		0.52	0.91	0.92	1.43	3.27
7S		0.6	0.8	0.84	1.4	3.55
7R		0.41	0.75	0.92	1.16	3.55
8		0.51	0.89	0.79	1.4	2.54
9		0.62	0.75	0.83	1.37	2.97
10		0.59	0.78	0.84	1.37	0.58
11		0.61	0.73	0.89	1.34	2.93
12		0.51	0.82	0.79	1.32	2.49

13		0.59	0.73	0.93	1.32	2.37
14		0.49	0.81	0.78	1.31	2.91
15		0.47	0.83	0.84	1.3	3.33
16		0.53	0.78	0.88	1.3	1.99
17		0.56	0.71	0.84	1.28	3.60
18		0.49	0.78	0.85	1.27	2.26
19		0.43	0.83	0.96	1.26	1.74
20		0.57	0.69	0.9	1.26	3.55
21		0.44	0.79	0.81	1.24	2.25
22		0.44	0.79	0.83	1.22	3.85
23		0.43	0.79	0.81	1.22	5.57
24		0.57	0.63	0.91	1.2	4.11
25		0.55	0.66	0.87	1.2	3.55
26		0.45	0.74	0.97	1.19	3.17
27		0.44	0.72	0.83	1.16	1.47
28R		0.36	0.79	0.85	1.16	2.76

28S		0.37	0.75	0.92	1.12	2.76
29		0.35	0.8	0.91	1.15	2.87
30		0.48	0.67	0.82	1.15	3.12
31S		0.34	0.81	0.8	1.15	2.38
31R		0.22	0.84	0.81	1.06	2.38
32		0.38	0.77	0.85	1.14	3.33
33		0.27	0.87	0.92	1.14	3.73
34		0.23	0.91	0.93	1.14	2.68
35		0.38	0.75	0.88	1.13	2.76
36		0.37	0.76	0.89	1.13	2.84
37		0.41	0.72	0.8	1.13	4.12
38		0.41	0.71	0.88	1.12	1.35
39		0.38	0.73	0.86	1.1	3.41
40		0.37	0.73	0.86	1.1	2.39
41		0.35	0.73	0.84	1.07	3.53
42		0.59	0.91	0.88	1.51	3.61

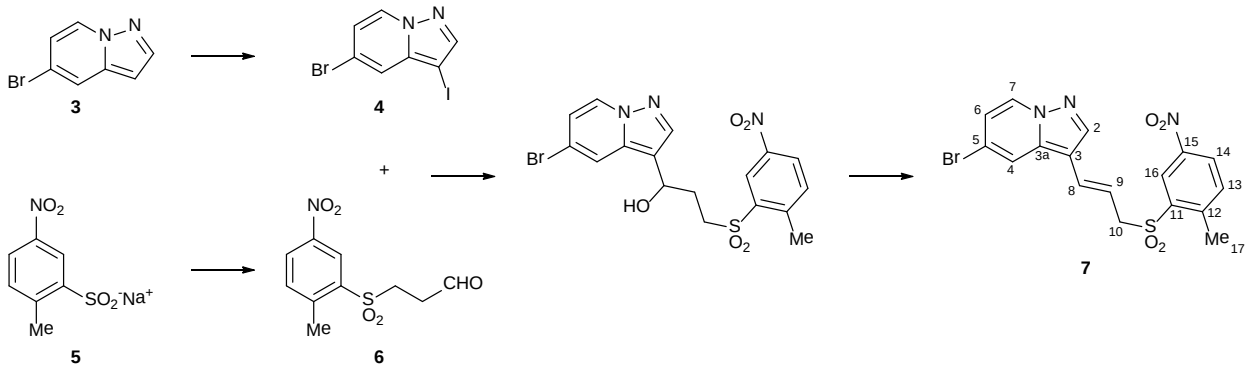
43		0.68	0.76	0.78	1.45	2.13
44		0.65	0.79	0.84	1.44	3.44
45		0.63	0.81	0.85	1.44	3.44
46		0.6	0.82	0.92	1.42	2.78
47		0.68	0.74	0.81	1.41	3.62
48		0.53	0.87	0.79	1.4	2.74
49		0.61	0.67	0.84	1.29	2.71
50		0.54	0.74	0.9	1.28	2.07
51		0.4	0.86	0.9	1.26	2.85

[a]Electrostatic Tanimoto similarity between the query and fragment hit based on a Poisson-Boltzmann calculation (external dielectric = 80); [b]Shape overlap between the query and the replacement when measuring the Electrostatic Tanimoto; [c]Shape overlap between the attachment points of the query and the replacement when measuring the Electrostatic Tanimoto; [d]Calculated using ACD/PhysChem v. 7.10 for the entire molecule analogue of **1** (i.e. BROOD query entry 0 is compound **1**).

Synthesis of Compounds 7 – 60.

NMR spectra were recorded on a Bruker Avance 400 spectrometer; chemical shifts are reported in δ using $SiMe_4$ as the internal standard when measured in $CDCl_3$, the residual DMSO as internal standard when measured in d_6-DMSO, and the residual methanol as internal standard when measured in CD_3OD. Low resolution mass spectra were recorded on a Thermo Finnigan MSQ single quadrupole mass spectrometer. High resolution mass spectra were obtained on a Bruker micrOTOF-QII mass spectrometer using either electrospray ionisation (ESI) or atmospheric pressure chemical ionisation (APCI). HPLC was carried out using an Agilent HP1100 equipped with a diode-array detector, with an Altima C18 5 μm reverse phase column, 150 × 3.2 mm (Alltech Associated, Inc., Deerfield, IL) eluting with an acetonitrile:water aqueous ammonium formate buffer gradient. Analyses were carried out in The Campbell Microanalytical Laboratory, University of Otago, Dunedin, New Zealand. Melting points were determined on an Electrothermal 2300 Melting Point Apparatus. Silica gel chromatography was performed using 200-320 mesh silica gel obtained from APS Finechem Ltd. Yields have not been optimised.

Synthesis of 5-bromo-3-(3-(2-methyl-5-nitrophenylsulfonyl)prop-1-enyl)pyrazolo[1,5-*a*]-pyridine (7).



5-Bromo-3-iodopyrazolo[1,5-*a*]pyridine (4). A solution of 5-bromopyrazolo[1,5-*a*]pyridine[1] (**3**) (282 mg, 1.43 mmol) and NIS (354 mg, 1.57 mmol) in MeCN (10 mL) was stirred at room temperature for 1 h. The reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, then brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. Chromatography (eluting with hexanes:EtOAc 98:2 to 97:3 to 19:1) gave **4** as a white solid (410 mg, 89%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.29 (dd, J = 7.3, 0.7 Hz, 1H), 7.94 (s, 1H), 7.66 (dd, J = 2.0, 0.7 Hz, 1H), 6.87 (dd, J = 7.3, 2.0 Hz, 1H). LCMS (APCI$^+$) 325 (MH^+ with ^{81}Br, 100%), 323 (MH^+ with ^{79}Br, 95%).

3-(2-Methyl-5-nitrophenylsulfonyl)propanal (6). A solution of sodium 2-methyl-5-nitrobenzenesulfinate (**5**) (334 mg, 1.50 mmol) and acrolein (0.10 mL, 1.50 mmol) in acetic acid (5 mL) was stirred at room temperature for 18 h. The solution was diluted with CH_2Cl_2, washed three times with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and the solvent removed

in vacuo to leave **6** as a white solid (344 mg, 89%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 9.75 (s, 1H), 8.84 (d, *J* = 2.4 Hz, 1H), 8.38 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 3.51 (t, *J* = 7.1 Hz, 2H), 3.07 (t, *J* = 7.1 Hz, 2H), 2.85 (s, 3H).

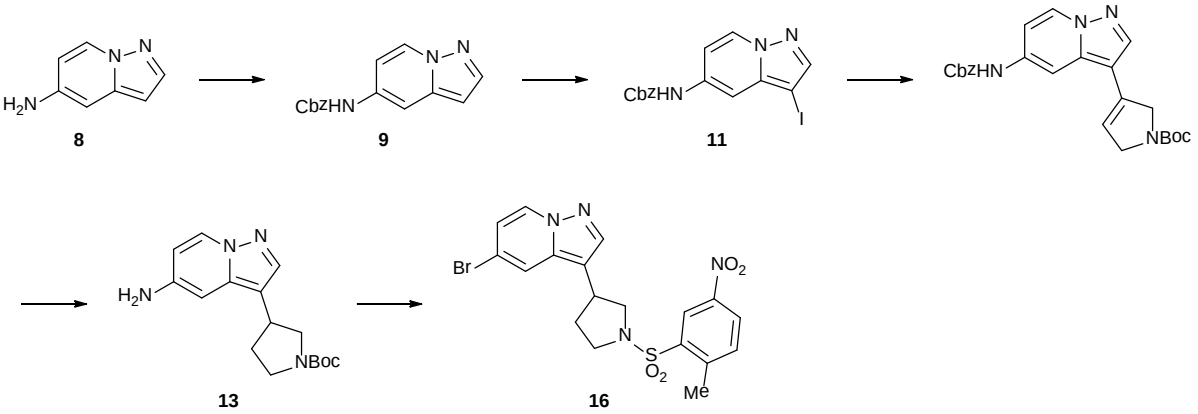
1-(5-Bromopyrazolo[1,5-*a*]pyridin-3-yl)-3-(2-methyl-5-nitrophenylsulfonyl)propan-1-ol. ^{i}PrMgCl.LiCl (0.25 mL of a 1.3M solution in THF) was added to a solution of **4** (70 mg, 0.22 mmol) in dry THF (5 mL) at -40 ºC. After 30 mins, a solution of **6** (84 mg, 0.33 mmol) in dry THF (3 mL) was added. The reaction mixture was slowly warmed to room temperature over 2 h, and then quenched by the addition of 10% aqueous NH_4Cl. This was extracted twice with CH_2Cl_2, the combined extracts were dried (Na_2SO_4) and the solvents removed *in vacuo*. Chromatography (eluting with hexanes: EtOAc 2:1 to 1:1 to 1:2) gave the title compound as a yellow solid (36 mg, 37%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.86 (d, *J* = 2.4 Hz, 1H), 8.36 (dd, *J* = 8.4, 2.4 Hz, 1H), 8.28 (dd, *J* = 7.4, 0.7 Hz, 1H), 7.85 (s, 1H), 7.76 (dd, *J* = 2.1, 0.7 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 6.86 (dd, *J* = 7.4, 2.1 Hz, 1H), 5.17 (td, *J* = 6.8, 4.0 Hz, 1H), 3.38 (m, 2H), 2.82 (m, 1H), 2.78 (s, 3H), 2.34 (m, 1H), 2.03 (d, *J* = 4.0 Hz, 1H). LCMS (APCI^{+}) 456 (MH^{+} with ^{81}Br, 100%), 454 (MH^{+} with ^{79}Br, 80%).

5-Bromo-3-(3-(2-methyl-5-nitrophenylsulfonyl)prop-1-enyl)pyrazolo[1,5-*a*]pyridine (7). DBU (47 µL, 0.31 mmol) was added to a solution of the above alcohol (36 mg, 79 µmol) and MsCl (11 mg, 96 µmol) in MeCN (2 mL), and stirred at room temperature for 30 mins. The solution was diluted with water and extracted twice with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and the solvents removed *in vacuo*. Chromatography (eluting with hexanes: EtOAc 3:1 to 2:1) gave **7** as a yellow solid (17 mg, 49%). NMR data presented in Table S2. LCMS (APCI^{+}) 438 (MH^{+} with ^{81}Br, 100%), 436 (MH^{+} with ^{79}Br, 95%). Found: C, 46.85; H, 3.4; N, 9.2. Calc. for $C_{17}H_{14}BrN_3O_4S$.0.2 EtOAc: C, 47.1; H, 3.5; N, 9.3%.

Table S2. NMR assignment for **7** (recorded in $CDCl_3$).

C/H	^{1}H (ppm)	Coupling	NOESY	HMBC	^{13}C (ppm)
2	7.95	s		C3, C3a	141.4
3					108.5
3a					137.8
4	7.65	dd (*J* 2.0, 0.7 Hz)	H8	C3a, C4/5, C6	119.1
5					119.1
6	6.87	dd (*J* 7.3, 2.0 Hz)		C4/5, C7	116.3
7	8.26	dd (*J* 7.3, 0.7 Hz)		C3a, C4/5, C6	129.7
8	6.52	d (*J* 15.9 Hz)	H4	C2, C3a, C9, C10	128.9
9	5.92	dt (*J* 15.9, 7.6 Hz)		C3, C10	111.1
10	4.07	dd (*J* 7.6, 1.0 Hz)	H17	C8, C9	60.5
11					138.7
12					145.7
13	7.54	d (*J* 8.4 Hz)		C11, C15, C17	133.9
14	8.34	dd (*J* 8.4, 2.4 Hz)		C12, C16	127.9
15					146.4
16	8.85	d (*J* 2.4 Hz)		C12, C14	126.1
17	2.85	s	H10	C11, C12, C13	20.9

Synthesis of 5-bromo-3-(1-(2-methyl-5-nitrophenylsulfonyl)pyrrolidin-3-yl)pyrazolo[1,5-*a*]pyridine (16).



Benzyl pyrazolo[1,5-*a*]pyridin-5-ylcarbamate (9). Benzyl chloroformate (0.13 mL, 0.92 mmol) was added to a solution of pyrazolo[1,5-*a*]pyridin-5-amine (**8**)[1] (98 mg, 0.74 mmol) in acetone (1 mL) and 2M aqueous Na_2CO_3 (0.75 mL) at 0 °C. After warming to room temperature, the reaction was stirred for 18 h. The reaction mixture was filtered, washed with THF, and the solvents removed from the filtrate *in vacuo*. Chromatography (eluting with hexanes: EtOAc 7:3) gave **9** as an off-white solid (100 mg, 51%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.35 (d, *J* = 7.5 Hz, 1H), 7.89 (d, *J* = 2.2 Hz, 1H), 7.72 (m, 1H), 7.44-7.33 (m, 5H), 6.74 (s, 1H), 6.67 (dd, *J* = 7.5, 2.4 Hz, 1H), 6.39 (dd, *J* = 2.2, 0.8 Hz, 1H), 5.23 (s, 2H). LCMS (APCI$^+$) 268 (MH^+, 100%).

Benzyl 3-iodopyrazolo[1,5-*a*]pyridin-5-ylcarbamate (11). NIS (101 mg, 0.45 mmol) was added to a solution of **9** (100 mg, 0.37 mmol) in acetonitrile (10 mL) and stirred for 1 h. The reaction was diluted with saturated aqueous $NaHCO_3$, and extracted with EtOAc. The organic extract was dried (Na_2SO_4) and the solvent removed *in vacuo*. Chromatography (eluting with hexanes: EtOAc 7:3) gave **11** as a white powder (122 mg, 83%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.33 (d, *J* = 7.5 Hz, 1H), 7.89 (s, 1H), 7.58 (d, *J* = 2.2 Hz, 1H), 7.44-7.35 (m, 5H), 6.90 (s, 1H), 6.81 (dd, *J* = 7.5, 2.2 Hz, 1H), 5.24 (s, 2H). LCMS (APCI$^+$) 394 (MH^+, 100%).

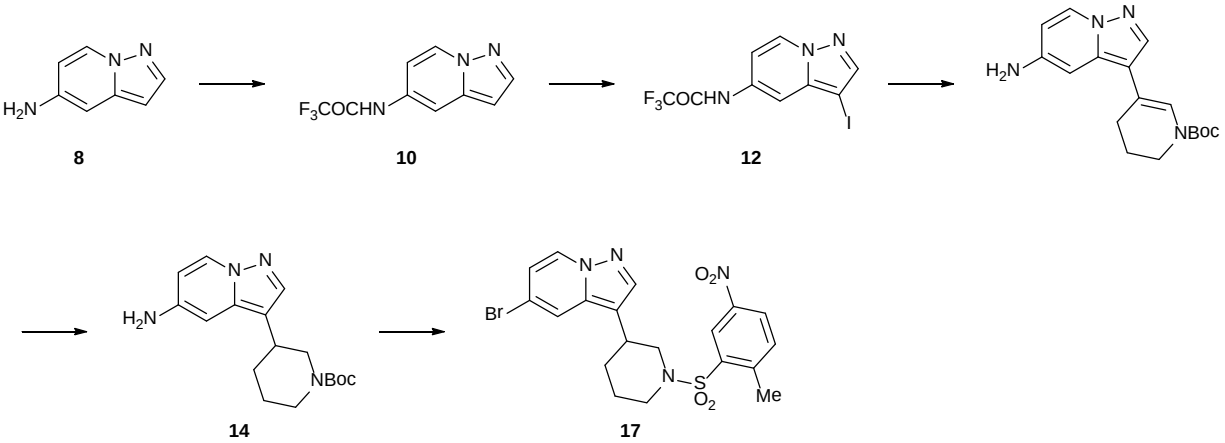
***tert*-Butyl 3-(5-(benzyloxycarbonylamino)pyrazolo[1,5-*a*]pyridin-3-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate.** A mixture of **11** (43 mg, 0.11 mmol), *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (38 mg, 0.13 mmol) and $PdCl_2$(dppf) (9 mg, 0.01 mmol) in toluene (4 mL) and EtOH (2 mL) was purged with N_2 for 10 mins. Then 2M aqueous Na_2CO_3 (0.16 mL) was added and the mixture purged with N_2 for a further 10 mins before heating to 90 °C for 18 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted four times with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. Chromatography (eluting with hexanes: EtOAc 4:1) gave the title compound as a yellow powder (19 mg, 40%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.35 (d, *J* = 7.5 Hz, 1H), 7.89

(d, *J* = 2.3 Hz, 1H), 7.72 (s, 1H), 7.44-7.32 (m, 5H), 6.73 (s, 1H), 6.68 (dd, *J* = 7.5, 2.3 Hz, 1H), 6.39 (d, *J* = 1.7 Hz, 1H), 5.23 (s, 2H), 4.53 (m, 1H), 4.31 (m, 1H), 3.85 (m, 1H), 3.07 (m, 1H), 1.56 (s, 9H).

***tert*-Butyl 3-(5-aminopyrazolo[1,5-*a*]pyridin-3-yl)pyrrolidine-1-carboxylate (13).** The above compound (252 mg, 0.58 mmol) was hydrogenated (1 atm.) in DMF (20 mL) in the presence of 10% Pd/C for 2 h. The reaction mixture was filtered through silica gel, washed with CH_2Cl_2-MeOH and the solvent removed from the filtrate *in vacuo*. Chromatography (eluting with hexanes: EtOAc 3:2 to 1:1 to 1:4) gave **13** (138 mg, 79%). ^{1}H NMR δ (400 MHz, C_6D_6) 8.11 (d, *J* = 7.4 Hz, 1H), 7.59 (s, 1H), 6.41 (s, 1H), 6.18 (d, *J* = 7.4 Hz, 1H), 3.75 (m, 1H), 3.53 (m, 1H), 3.42-3.20 (m, 3H), 2.19 (m, 1H), 1.97 (m, 1H), 1.43 (s, 9H). LCMS (APCI$^+$) 303 (MH^+, 100%).

5-Bromo-3-(1-(2-methyl-5-nitrophenylsulfonyl)pyrrolidin-3-yl)pyrazolo[1,5-*a*]pyridine (16). A solution of $NaNO_2$ (48 mg, 0.70 mmol) in water (1 mL) was added to a solution of **13** (131 mg, 0.43 mmol) in 47% HBr (1 mL) at 0 °C. After 15 mins, a solution of CuBr (31 mg, 0.22 mmol) in 47% HBr (1 mL) was added, and the stirring continued for a further 15 mins. The reaction mixture was heated to 50 °C for 15 mins, then cooled to room temperature and basified to pH 12 with 6M aqueous NaOH. The solvent was removed *in vacuo*, then the residue was triturated with EtOAc, the inorganic salts filtered off, and the solvent removed from the filtrate to give the crude product which was taken on immediately to the next step. The crude amine was taken up in CH_2Cl_2 (1 mL) and cooled to 0 °C, then NEt_3 (67 µL, 0.48 mmol) and 2-methyl-5-nitrobenzenesulfonyl chloride (100 mg, 0.42 mmol) was added. After 1 h, the solution was diluted with water and extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and the solvent removed *in vacuo*. Chromatography (eluting with hexanes: EtOAc 4:1) gave **16** as a brown solid (10 mg, 5%). HPLC purity 87%. ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.75 (d, *J* = 2.4 Hz, 1H), 8.31-8.25 (m, 2H), 7.78 (s, 1H), 7.62 (d, *J* = 2.0 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 6.83 (dd, *J* = 7.4, 2.0 Hz, 1H), 3.89 (dd, *J* = 9.5, 7.5 Hz, 1H), 3.71-3.54 (m, 3H), 3.37 (dd, *J* = 9.5, 8.6 Hz, 1H), 2.78 (s, 3H), 2.46 (m, 1H), 2.18 (m, 1H). LCMS (APCI$^+$) 465 (MH^+ with ^{79}Br, 90%), 467 (MH^+ with ^{81}Br, 100%). HRMS (FAB$^+$) Calcd for $C_{18}H_{18}{}^{79}BrN_4O_4S$: 465.02321; found ($MH^+$) 465.02240.

Synthesis of 5-bromo-3-(1-(2-methyl-5-nitrophenylsulfonyl)piperidin-3-yl)pyrazolo[1,5-*a*]pyridine (17).



2,2,2-Trifluoro-*N*-(pyrazolo[1,5-*a*]pyridin-5-yl)acetamide (10). TFAA (0.43 mL, 3.0 mmol) was added dropwise to a solution of **8** (270 mg, 2.03 mmol) and NEt_3 (0.42 mL, 3.0 mmol) in CH_2Cl_2 (20 mL) at 0 ºC over 5 mins. After 1 h, the reaction mixture was washed with water, dried (Na_2SO_4) and the solvent removed *in vacuo*. Chromatography (eluting with hexanes: EtOAc 3:1) gave **10** as a yellow solid (242 mg, 52%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.46 (d, *J* = 7.5 Hz, 1H), 8.04 (d, *J* = 2.3 Hz, 1H), 7.98 (d, *J* = 2.3 Hz, 1H), 7.87 (s, 1H), 6.78 (dd, *J* = 7.5, 2.3 Hz, 1H), 6.54 (dd, *J* = 2.3, 0.8 Hz, 1H). LCMS (APCI$^+$) 230 (MH^+, 100%).

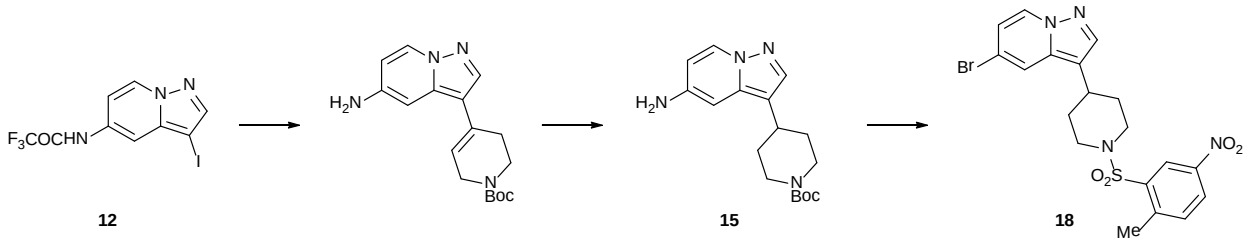
2,2,2-Trifluoro-*N*-(3-iodopyrazolo[1,5-*a*]pyridin-5-yl)acetamide (12). Reaction of **10** (97 mg, 0.42 mmol) by the same method as **11** gave **12** as a white solid (125 mg, 83%). ^{1}H NMR δ (400 MHz, d_6-DMSO) 11.59 (s, 1H), 8.75 (dd, *J* = 7.5, 0.7 Hz, 1H), 8.11 (s, 1H), 8.02 (dd, *J* = 2.3, 0.7 Hz, 1H), 7.19 (dd, *J* = 7.5, 2.3 Hz, 1H). LCMS (APCI$^+$) 356 (MH^+, 100%).

***tert*-Butyl 5-(5-aminopyrazolo[1,5-*a*]pyridin-3-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate.** Reaction of **12** (567 mg, 1.60 mmol) and *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate (597 mg, 1.93 mmol) by the above Suzuki coupling method, after chromatography (eluting with hexanes: EtOAc 7:3 to 1:1) gave the title compound as a brown oil (177 mg, 35%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.22 (d, *J* = 7.4 Hz, 1H), 7.79 (d, *J* = 2.1 Hz, 1H), 7.76 (s, 1H), 6.57 (dd, *J* = 2.4 Hz, 1H), 6.22 (dd, *J* = 7.4, 2.4 Hz, 1H), 3.63 (m, 2H), 2.45 (m, 2H), 1.97 (m, 2H), 1.53 (s, 9H). LCMS (APCI$^+$) 315 (MH^+, 100%).

***tert*-Butyl 3-(5-aminopyrazolo[1,5-*a*]pyridin-3-yl)piperidine-1-carboxylate (14).** Reaction of the above compound (177 mg, 0.56 mmol) by the same method as **13**, after chromatography (eluting with hexanes: EtOAc 2:3 to 1:4) gave **14** as a brown powder (57 mg, 32%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.17 (d, *J* = 7.4 Hz, 1H), 7.65 (s, 1H), 6.56 (s, 1H), 6.21 (dd, *J* = 7.4, 2.4 Hz, 1H), 4.10 (m, 2H), 3.87 (m, 2H), 2.79 (m, 1H), 1.80-1.55 (m, 4H), 1.48 (s, 9H). LCMS (APCI$^+$) 317 (MH^+, 100%).

5-Bromo-3-(1-(2-methyl-5-nitrophenylsulfonyl)piperidin-3-yl)pyrazolo[1,5-*a*]pyridine (17). Reaction of **14** (57 mg, 0.18 mmol) and 2-methyl-5-nitrobenzenesulfonyl chloride (36 mg, 0.15 mmol) by the same method as **16**, after chromatography (eluting with hexanes: EtOAc 7:3) gave **17** as a yellow powder (18 mg, 21%). HPLC purity 91%. ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.73 (d, *J* = 2.4 Hz, 1H), 8.28 (dd, *J* = 8.4, 2.4 Hz, 1H), 8.26 (dd, *J* = 7.4, 0.7 Hz, 1H), 7.77 (s, 1H), 7.61 (dd, *J* = 2.0, 0.7 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 6.81 (dd, *J* = 7.4, 2.0 Hz, 1H), 3.88 (m, 2H), 3.11 (tt, *J* = 11.2, 3.8 Hz, 1H), 2.91 (td, *J* = 12.0, 3.1 Hz, 1H), 2.83 (dd, *J* = 12.5, 11.2 Hz, 1H), 2.73 (s, 3H), 2.15 (m, 1H), 1.98-1.65 (m, 3H). LCMS (APCI$^+$) 479 (MH^+ with ^{79}Br, 90%), 481 (MH^+ with ^{81}Br, 100%). HRMS (ESI$^+$) Calcd for $C_{19}H_{20}{}^{79}BrN_4O_4S$: 479.0383; found ($MH^+$) 479.0408.

Synthesis of 5-bromo-3-(1-(2-methyl-5-nitrophenylsulfonyl)piperidin-4-yl)pyrazolo[1,5-*a*]pyridine (18).



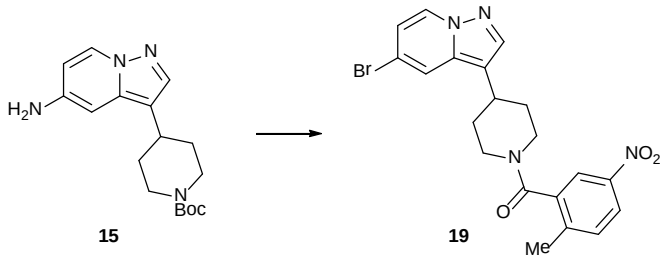
***tert*-Butyl 4-(5-aminopyrazolo[1,5-*a*]pyridin-3-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate.** Reaction of **12** (108 mg, 0.30 mmol) and (*N*-*tert*-butoxycarbonyl)-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester (131 mg, 0.43 mmol) by the above Suzuki coupling method, after chromatography (eluting with hexanes: EtOAc 7:3) gave *tert*-butyl 4-(5-aminopyrazolo[1,5-*a*]pyridin-3-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate as a white solid (110 mg, 99%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.18 (d, *J* = 7.4 Hz, 1H), 7.77 (s, 1H), 6.74 (d, *J* = 2.4 Hz, 1H), 6.23 (dd, *J* = 7.4, 2.4 Hz, 1H), 5.81 (s, 1H), 4.11-3.99 (m, 4H), 3.65 (t, *J* = 5.7 Hz, 2H), 2.53 (m, 2H), 1.50 (s, 9H). LCMS (APCI$^+$) 315 (MH^+, 100%).

***tert*-Butyl 4-(5-aminopyrazolo[1,5-*a*]pyridin-3-yl)piperidine-1-carboxylate (15).** Reaction of the above compound (137 mg, 0.44 mmol) by the same method as **13**, after chromatography (eluting with hexanes: EtOAc 3:2) gave **15** as a brown oil (60 mg, 47%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.17 (d, *J* = 7.3 Hz, 1H), 7.62 (s, 1H), 6.50 (s, 1H), 6.21 (dd, *J* = 7.3, 2.3 Hz, 1H), 4.21 (m, 2H), 3.80 (br s, 2H), 2.86-2.70 (m, 3H), 1.89 (m, 2H), 1.65 (m, 2H), 1.49 (s, 9H). LCMS (APCI$^+$) 317 (MH^+, 100%).

5-Bromo-3-(1-(2-methyl-5-nitrophenylsulfonyl)piperidin-4-yl)pyrazolo[1,5-*a*]pyridine (18). Reaction of **15** (254 mg, 0.80 mmol) and 2-methyl-5-nitrobenzenesulfonyl chloride (98 mg, 0.42 mmol) by the same method as **16**, after chromatography (eluting with hexanes: EtOAc 9:1) gave **18** as a white solid (75 mg, 19%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.77 (d, *J* = 2.4 Hz, 1H), 8.31 (dd, *J* = 8.4, 2.4 Hz, 1H), 8.27 (dd, *J* = 7.4, 0.6 Hz, 1H), 7.78 (s, 1H), 7.61 (m, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 6.80 (dd, *J* = 7.4, 2.1 Hz, 1H), 3.95 (m, 2H), 2.96-2.80

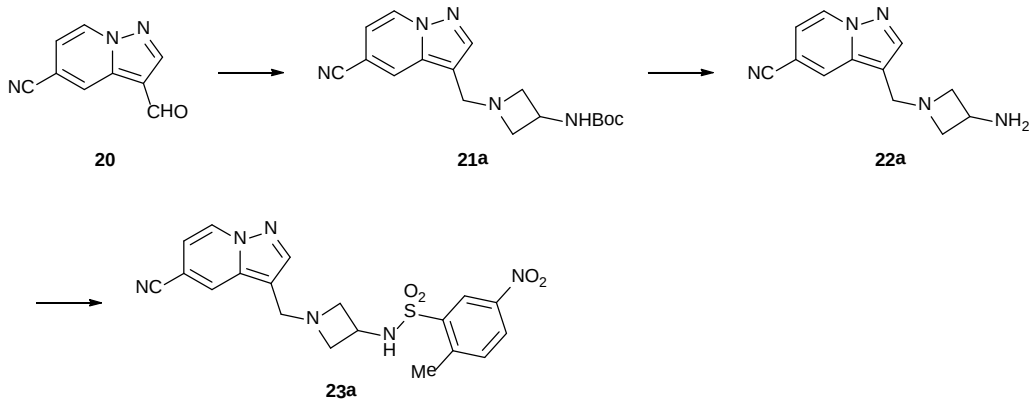
(m, 3H), 2.79 (s, 3H), 2.04 (m, 2H), 1.86 (m, 2H). LCMS (APCI$^+$) 479 (MH^+ with ^{79}Br, 95%), 481 (MH^+ with ^{81}Br, 100%). Anal. Calcd for $C_{19}H_{19}BrN_4O_4S$: C, 47.6; H, 4.0; N, 11.7. Found C, 47.9; H, 4.1; N, 11.4.

Synthesis of (4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)piperidin-1-yl)(2-methyl-5-nitrophenyl)methanone (19).



Reaction of **15** (145 mg, 0.46 mmol) and 2-methyl-5-nitrobenzoyl chloride (57 mg, 0.29 mmol) by the same method as **16**, after chromatography (eluting with hexanes: EtOAc 3:2) gave **19** as a yellow oil (81 mg, 40%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.28 (dd, J = 7.4, 0.5 Hz, 1H), 8.17-8.05 (m, 2H), 7.80 (m, 1H), 7.65 (d, J = 2.0 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 6.80 (dd, J = 7.4, 2.0 Hz, 1H), 4.94 (m, 1H), 3.55 (m, 1H), 3.30-2.93 (m, 3H), 2.48 (m, 3H), 2.20-1.53 (m, 4H). LCMS (APCI$^+$) 443 (MH^+ with ^{79}Br, 95%), 445 (MH^+ with ^{81}Br, 100%). Anal. Calcd for $C_{20}H_{19}BrN_4O_3$.0.15 hexane: C, 55.0; H, 4.7; N, 12.3. Found C, 55.0; H, 4.6; N, 12.0.

Synthesis of *N*-(1-((5-cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)azetidin-3-yl)-2-methyl-5-nitrobenzenesulfonamide (23a).



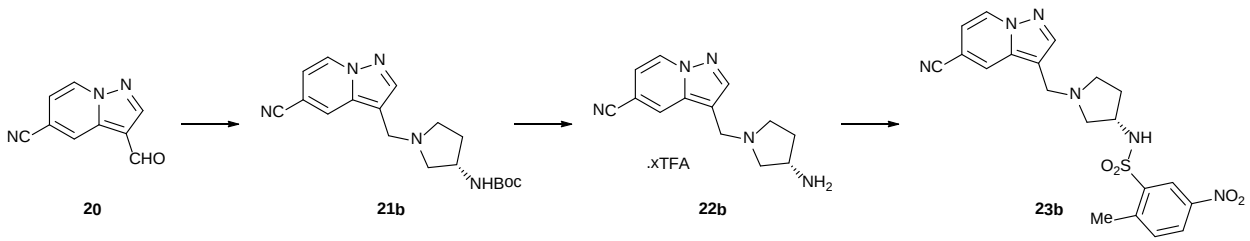
***tert*-Butyl 1-((5-cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)azetidin-3-ylcarbamate (21a).** Glacial acetic acid (3 drops) was added to a solution of 3-formylpyrazolo[1,5-*a*]pyridine-5-carbonitrile (**20**)[1] (216 mg, 1.26 mmol) and *tert*-butyl azetidin-3-ylcarbamate (260 mg, 1.51 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was refluxed for 1 h. Sodium cyanoborohydride (119 mg, 1.89 mmol) and EtOH (5 mL) were added and the mixture stirred at room temperature for 17 h. The solvents were removed *in vacuo*. Chromatography (eluting with CH_2Cl_2: MeOH 99:1 to 98:2 to 99.7) gave **21a** as a cream-coloured powder (308 mg, 75%).

^{1}H NMR δ (400 MHz, $CDCl_3$) 8.47 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.11 (dd, *J* = 1.8, 1.0 Hz, 1H), 7.98 (s, 1H), 6.86 (dd, *J* = 7.2, 1.8 Hz, 1H), 4.85 (m, 1H), 4.28 (m, 1H), 3.79 (s, 2H), 3.61 (m, 2H), 2.94 (m, 2H), 1.44 (s, 9H). LCMS (APCI$^+$) 328 (MH^+, 100%).

3-((3-Aminoazetidin-1-yl)methyl)pyrazolo[1,5-*a*]pyridine-5-carbonitrile (22a). TFA (1.5 mL) was added to a solution of **21a** (308 mg, 0.94 mmol) in CH_2Cl_2 (6 mL) and the mixture stirred at room temperature for 4 h. The solvent was removed *in vacuo* to leave the trifluoroacetate salt of the amine. This was converted to the free base by the addition of K_2CO_3 (391 mg, 2.82 mmol) to a CH_2Cl_2-MeOH solution. After 10 mins, water was added, the layers were separated and the aqueous layer extracted with CH_2Cl_2 until all amine had been extracted. The combined organic phases were dried (Na_2SO_4), and the solvent removed *in vacuo* to give crude **22a** as a pale yellow solid (544 mg). ^{1}H NMR δ (400 MHz, d_6-DMSO) 8.80 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.44 (dd, *J* = 1.8, 1.0 Hz, 1H), 8.08 (s, 1H), 7.12 (dd, *J* = 7.2, 1.8 Hz, 1H), 3.70 (s, 2H), 3.45-3.33 (m, 3H), 2.65-2.58 (m, 2H). LCMS (APCI$^+$) 228 (MH^+, 100%).

***N*-(1-((5-Cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)azetidin-3-yl)-2-methyl-5-nitrobenzenesulfonamide (23a).** A solution of **22a** (0.47 mmol), 2-methyl-5-nitrobenzenesulfonyl chloride (111 mg, 0.47 mmol) and NEt_3 (0.13 mL, 0.93 mmol) in MeCN (5 mL) was stirred at room temperature for 24 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2 until all of the product had been extracted. The combined organic phases were dried (Na_2SO_4), and the solvent removed *in vacuo*. Chromatography (eluting with CH_2Cl_2: MeOH 100:0 to 97.5:2.5) followed by recrystallisation from CH_2Cl_2-hexanes gave **23a** as a yellow powder (50 mg, 25% over 2 steps). ^{1}H NMR δ (400 MHz, d_6-DMSO) 8.80 (dd, *J* = 7.2, 0.9 Hz, 1H), 8.64 (br s, 1H), 8.50 (d, *J* = 2.5 Hz, 1H), 8.40 (dd, *J* = 1.8, 0.9 Hz, 1H), 8.34 (dd, *J* = 8.4, 2.5 Hz, 1H), 8.04 (s, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.12 (dd, *J* = 7.2, 1.8 Hz, 1H), 3.77 (m, 1H), 3.69 (s, 2H), 3.28 (m, 2H), 2.80 (m, 2H), 2.68 (s, 3H). LCMS (APCI$^+$) 427 (MH^+, 100%). Anal. Calcd for $C_{19}H_{18}N_6O_4S.0.1\ CH_2Cl_2$: C, 52.7; H, 4.2; N, 19.3. Found C, 53.0; H, 4.25; N, 19.2.

<u>Synthesis of (*S*)-*N*-(1-((5-cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)pyrrolidin-3-yl)-2-methyl-5-nitrobenzenesulfonamide (23b).</u>



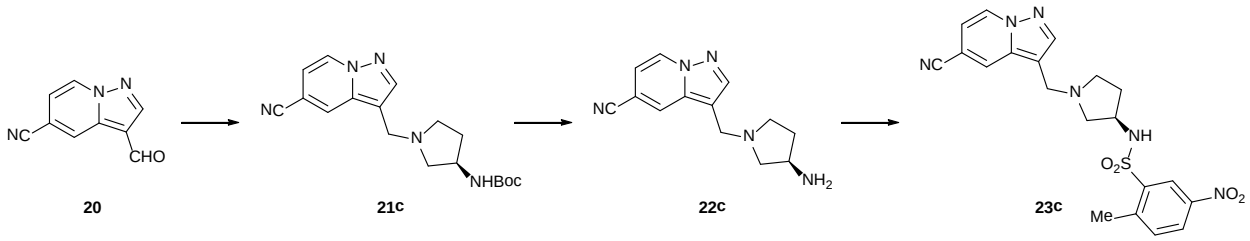
(*S*)-*tert*-Butyl 1-((5-cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)pyrrolidin-3-ylcarbamate (21b). Reaction of **20** (200 mg, 1.17 mmol) and (*S*)-*tert*-butyl pyrrolidin-3-ylcarbamate (260 mg, 1.40 mmol) by the same method as **21a**, after chromatography (eluting with CH_2Cl_2:

MeOH 100:0 to 97.5:2.5) gave **21b** as a pale yellow powder (338 mg, 85%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.49 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.09 (dd, *J* = 1.8, 1.0 Hz, 1H), 8.02 (s, 1H), 6.87 (dd, *J* = 7.2, 1.8 Hz, 1H), 4.82 (m, 1H), 4.19 (m, 1H), 3.86 (s, 2H), 2.87 (m, 1H), 2.72 (m, 1H), 2.62 (m, 1H), 2.45 (m, 1H), 2.30 (m, 1H), 1.66 (m, 1H), 1.43 (s, 9H). LCMS (APCI$^+$) 342 (MH^+, 100%).

(*S*)-3-((3-Aminopyrrolidin-1-yl)methyl)pyrazolo[1,5-*a*]pyridine-5-carbonitrile trifluoroacetate (22b). Reaction of **21b** (338 mg, 0.99 mmol) by the same method as **22a** without conversion to the free base gave crude trifluoroacetate salt **22b** as a yellow gum (675 mg). ^{1}H NMR δ (400 MHz, d_6-DMSO) 8.91 (d, *J* = 7.2 Hz, 1H), 8.65 (m, 1H), 8.28 (s, 1H), 7.25 (d, *J* = 7.2 Hz, 1H), 4.39 (m, 2H), 3.86 (m, 1H), 3.60-2.70 (m, 4H), 2.28 (m, 1H), 1.93 (m, 1H). LCMS (APCI$^+$) 242 (MH^+, 100%).

(*S*)-*N*-(1-((5-Cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)pyrrolidin-3-yl)-2-methyl-5-nitrobenzenesulfonamide (23b). Reaction of **22b** (0.25 mmol) by the same method as **23a**, after chromatography (eluting with CH_2Cl_2 to CH_2Cl_2: MeOH 97.5:2.5) gave **23b** as a yellow powder (49 mg, 45% over 2 steps). ^{1}H NMR δ (400 MHz, CD_3OD) 8.70-8.65 (m, 2H), 8.32-8.28 (m, 2H), 8.07 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.07 (dd, *J* = 7.3, 1.8 Hz, 1H), 4.50 (br s, 1H), 4.08-3.81 (m, 3H), 2.95-2.48 (m, 7H), 2.18 (m, 1H), 1.75 (m, 1H). LCMS (APCI$^+$) 441 (MH^+, 100%). Anal. Calcd for $C_{20}H_{20}N_6O_4S.0.4\ CH_2Cl_2.0.6$ MeOH: C, 51.1; H, 4.7; N, 17.0. Found C, 51.2; H, 4.6; N, 16.8.

Synthesis of (*R*)-*N*-(1-((5-cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)pyrrolidin-3-yl)-2-methyl-5-nitrobenzenesulfonamide (23c).



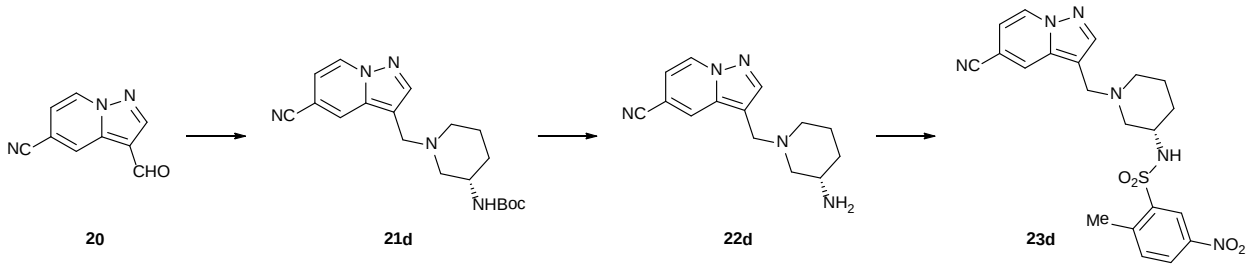
(*R*)-*tert*-Butyl 1-((5-cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)pyrrolidin-3-ylcarbamate (21c). Reaction of **20** (209 mg, 1.22 mmol) and (*R*)-*tert*-butyl pyrrolidin-3-ylcarbamate (250 mg, 1.34 mmol) by the same method as **21a**, after chromatography (eluting with CH_2Cl_2: MeOH 100:0 to 97:3) gave **21c** as a pale yellow powder (311 mg, 75%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.50 (dd, *J* = 7.2, 0.8 Hz, 1H), 8.11 (s, 1H), 8.04 (s, 1H), 6.89 (dd, *J* = 7.2, 1.7 Hz, 1H), 4.84 (m, 1H), 4.20 (m, 1H), 3.93 (s, 2H), 3.03-2.26 (m, 5H), 1.66-1.38 (m, 10H). LCMS (APCI$^+$) 342 (MH^+, 100%).

(*R*)-3-((3-Aminopyrrolidin-1-yl)methyl)pyrazolo[1,5-*a*]pyridine-5-carbonitrile (22c). Reaction of **21c** (156 mg, 0.46 mmol) by the same method as **22a**, gave crude **22c** as a pale yellow solid (399 mg). ^{1}H NMR δ (400 MHz, d_6-DMSO) 8.84 (dd, *J* = 7.2, 0.9 Hz, 1H), 8.54

(dd, *J* = 1.8, 0.9 Hz, 1H), 8.15 (s, 1H), 7.15 (dd, *J* = 7.2, 1.8 Hz, 1H), 3.87 (ABq, app. *J* = 20.5, 13.7 Hz, 2H), 3.64 (m, 1H), 2.76 (td, *J* = 8.6, 4.8 Hz, 1H), 2.62-2.53 (m, 2H), 2.36 (m, 1H), 2.13 (m, 1H), 1.65 (m, 1H). LCMS (APCI$^+$) 242 (MH$^+$, 100%).

(*R*)-*N*-(1-((5-Cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)pyrrolidin-3-yl)-2-methyl-5-nitrobenzenesulfonamide (23c). Reaction of **22c** (0.46 mmol) by the same method as **23a**, after chromatography (on alumina, eluting with CH_2Cl_2 to CH_2Cl_2: MeOH 99.75:0.25) followed by recrystallisation from CH_2Cl_2-$^i Pr_2O$ gave **23c** as yellow crystals (30 mg, 15% over 2 steps). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.79 (d, *J* = 2.4 Hz, 1H), 8.50 (dd, *J* = 7.2, 0.9 Hz, 1H), 8.27 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.98 (m, 1H), 7.95 (s, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 6.88 (dd, *J* = 7.2, 1.8 Hz, 1H), 4.93 (br d, *J* = 7.6 Hz, 1H), 3.90 (m, 1H), 3.76 (ABq, app. *J* = 25.0, 13.5 Hz, 2H), 2.82 (m, 1H), 2.70 (s, 3H), 2.55 (dd, *J* = 9.8, 3.0 Hz, 1H), 2.47 (dd, *J* = 9.8, 5.9 Hz, 1H), 2.31-2.16 (m, 2H), 1.67 (m, 1H). LCMS (APCI$^+$) 441 (MH$^+$, 100%). Anal. Calcd for $C_{20}H_{20}N_6O_4S.0.1\ CH_2Cl_2$: C, 53.8; H, 4.5; N, 18.7. Found C, 53.55; H, 4.6; N, 18.7.

Synthesis of (*S*)-*N*-(1-((5-cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)piperidin-3-yl)-2-methyl-5-nitrobenzenesulfonamide (23d).



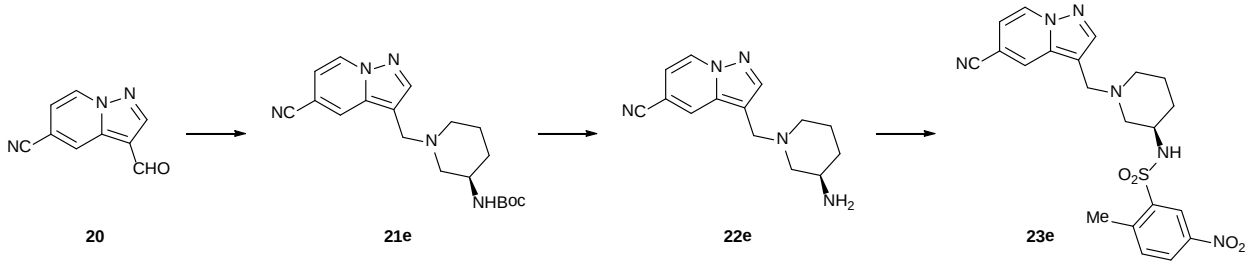
20 21d 22d 23d

(*S*)-*tert*-Butyl 1-((5-cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)piperidin-3-ylcarbamate (21d). Reaction of **20** (183 mg, 1.07 mmol) and (*S*)-*tert*-butyl piperidin-3-ylcarbamate (218 mg, 1.09 mmol) by the same method as **21a**, after chromatography (on alumina, eluting with CH_2Cl_2: MeOH 100:0 to 99.7:0.3) gave **21d** as a pale yellow foam (216 mg, 57%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.48 (dd, *J* = 7.3, 1.0 Hz, 1H), 8.06 (dd, *J* = 1.7, 1.0 Hz, 1H), 7.97 (s, 1H), 6.85 (dd, *J* = 7.3, 1.7 Hz, 1H), 4.80 (br s, 1H), 3.79-3.61 (m, 3H), 2.66-2.18 (m, 6H), 1.75-1.62 (m, 2H), 1.42 (s, 9H). LCMS (APCI$^+$) 356 (MH$^+$, 100%).

(*S*)-3-((3-Aminopiperidin-1-yl)methyl)pyrazolo[1,5-*a*]pyridine-5-carbonitrile (22d). Reaction of **21d** (209 mg, 0.59 mmol) by the same method as **22a**, after chromatography (on alumina, eluting with EtOAc: MeOH 95:5 to 9:1 to EtOAc: MeOH:c. NH_3 88:12:0.2) gave **22d** as a pale yellow solid (111 mg, 74%). ^{1}H NMR δ (400 MHz, d_6-DMSO) 8.82 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.47 (dd, *J* = 1.8, 1.0 Hz, 1H), 8.10 (s, 1H), 7.13 (dd, *J* = 7.2, 1.8 Hz, 1H), 3.70 (ABq, app. *J* = 23.1, 13.7 Hz, 2H), 2.74-2.58 (m, 3H), 1.95 (m, 1H), 1.75-1.55 (m, 3H), 1.42 (m, 1H), 0.96 (m, 1H). LCMS (APCI$^+$) 256 (MH$^+$, 100%).

(*S*)-*N*-(1-((5-Cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)piperidin-3-yl)-2-methyl-5-nitrobenzenesulfonamide (23d). Reaction of **22d** (56 mg, 0.22 mmol) by the same method as **23a**, after chromatography (eluting with CH_2Cl_2: MeOH 99:1 to 98:2 to 97:3 to 96:4 to 99.5 to 94:6) followed by recrystallisation from CH_2Cl_2-$^{i}Pr_2O$ gave **23d** as a yellow powder (40 mg, 40%). ^{1}H NMR δ (400 MHz, CD_3OD) 8.79 (d, *J* = 7.2 Hz, 1H), 8.62 (s, 1H), 8.41 (s, 1H), 8.33 (dd, *J* = 8.4, 2.4 Hz, 1H), 8.18 (br s, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.22 (dd, *J* = 7.2, 1.7 Hz, 1H), 4.57-4.39 (m, 3H), 3.48-3.36 (m, 2H), 2.86-2.65 (m, 5H), 2.04-1.39 (m, 4H). LCMS (APCI$^+$) 455 (MH^+, 100%). Anal. Calcd for $C_{21}H_{22}N_6O_4S.0.6\ CH_2Cl_2.0.4\ H_2O$: C, 50.6; H, 4.7; N, 16.4. Found C, 50.5; H, 4.9; N, 16.7.

Synthesis of (*R*)-*N*-(1-((5-cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)piperidin-3-yl)-2-methyl-5-nitrobenzenesulfonamide (23e).



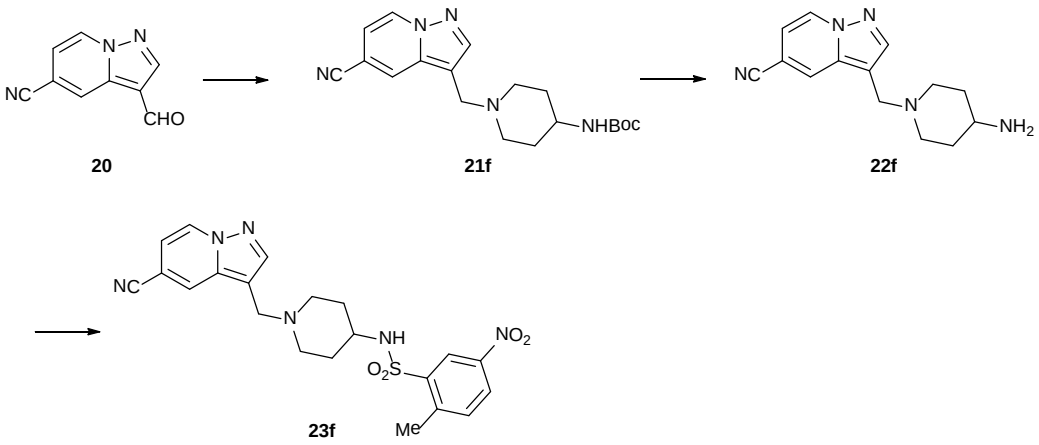
(*R*)-*tert*-Butyl 1-((5-cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)piperidin-3-ylcarbamate (21e). Reaction of **20** (200 mg, 1.17 mmol) and (*R*)-*tert*-butyl piperidin-3-ylcarbamate (280 mg, 1.40 mmol) by the same method as **21a**, after chromatography (eluting with CH_2Cl_2: MeOH 99.7:0.3 to 99.4:0.6 to 98:2) gave **21e** as a pale yellow foam (192 mg, 46%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.49 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.07 (dd, *J* = 1.7, 1.0 Hz, 1H), 7.98 (s, 1H), 6.86 (dd, *J* = 7.2, 1.7 Hz, 1H), 4.82 (br s, 1H), 3.79-3.62 (m, 3H), 2.67-2.18 (m, 6H), 1.78-1.62 (m, 2H), 1.43 (s, 9H). LCMS (APCI$^+$) 356 (MH^+, 100%).

(*R*)-3-((3-Aminopiperidin-1-yl)methyl)pyrazolo[1,5-*a*]pyridine-5-carbonitrile (22e). Reaction of **21e** (192 mg, 0.54 mmol) by the same method as **22a**, after chromatography (on alumina, eluting with EtOAc: MeOH 95:5 to 90:10 to EtOAc: MeOH: c. NH_3 88:12:0.2) gave **22e** as a pale yellow solid (91 mg, 66%). ^{1}H NMR δ (400 MHz, d_6-DMSO) 8.82 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.47 (dd, *J* = 1.8, 1.0 Hz, 1H), 8.10 (s, 1H), 7.12 (dd, *J* = 7.2, 1.8 Hz, 1H), 3.69 (ABq, app. *J* = 23.2, 13.8 Hz, 2H), 2.75-2.55 (m, 3H), 1.91 (m, 1H), 1.72-1.54 (m, 3H), 1.42 (m, 1H), 0.90 (m, 1H). LCMS (APCI$^+$) 256 (MH^+, 100%).

(*R*)-*N*-(1-((5-Cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)piperidin-3-yl)-2-methyl-5-nitrobenzenesulfonamide (23e). Reaction of **22e** (45 mg, 0.18 mmol) by the same method as **23a**, after chromatography (eluting with CH_2Cl_2: MeOH 99:1 to 98:2) followed by recrystallisation from CH_2Cl_2-$^{i}Pr_2O$ gave **23e** as a yellow powder (43 mg, 54%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.78 (d, *J* = 2.4 Hz, 1H), 8.53 (dd, *J* = 7.2, 0.9 Hz, 1H), 8.27 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.96 (dd, *J* = 1.7, 0.9 Hz, 1H), 7.95 (s, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 6.90 (dd, *J*

= 7.2, 1.7 Hz, 1H), 5.17 (br s, 1H), 3.67 (ABq, app. *J* = 24.4, 13.8 Hz, 2H), 3.55 (m, 1H), 2.68 (s, 3H), 2.58 (m, 1H), 2.41-2.34 (m, 2H), 2.26 (m, 1H), 1.79-1.56 (m, 4H). LCMS (APCI$^+$) 455 (MH$^+$, 100%). Anal. Calcd for $C_{21}H_{22}N_6O_4S.0.05\ CH_2Cl_2$: C, 55.1; H, 4.9; N, 18.3. Found C, 54.95; H, 5.1; N, 18.3.

Synthesis of *N*-1-(5-cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl-4-piperidinyl-2-methyl-5-nitrobenzenesulfonamide (23f).



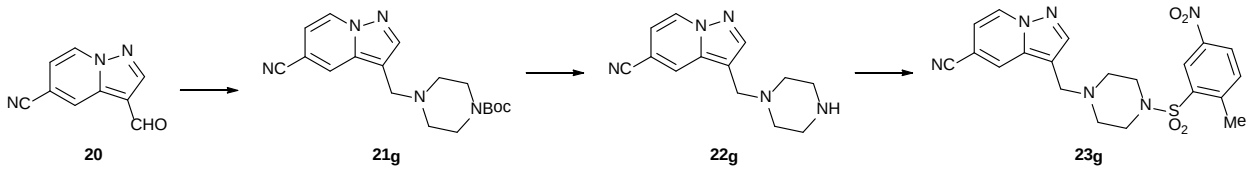
***tert*-Butyl 1-(5-cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl-4-piperidinylcarbamate (21f).** Reaction of **20** (50 mg, 0.29 mmol) and 4-(*N*-Boc-amino)piperidine (70 mg, 0.35 mmol) by the same method as **21a**, after chromatography (eluting with CH_2Cl_2: MeOH 100:0 to 96:4) gave **21f** as a pale yellow solid (73 mg, 70%). ^{1}H NMR δ (400 MHz, CD_3OD) 8.68 (dd, *J* = 7.3, 0.6 Hz, 1H), 8.35 (m, 1H), 8.14 (s, 1H), 7.08 (dd, *J* = 7.3, 1.7 Hz, 1H), 3.99 (m, 2H), 3.41 (m, 1H), 3.06 (m, 2H), 2.45 (m, 2H), 1.93 (m, 2H), 1.54 (m, 2H), 1.42 (s, 9H). LCMS (APCI$^+$) 356 (MH$^+$, 100%).

3-(4-Amino-1-piperidinyl)methylpyrazolo[1,5-*a*]pyridine-5-carbonitrile (22f). Reaction of **21f** (180 mg, 0.51 mmol) by the same method as **22a**, after chromatography (on alumina, eluting with CH_2Cl_2: MeOH 100:0 to 90:10 to EtOAc: MeOH 90:10) gave **22f** as a pale yellow solid (114 mg, 88%). ^{1}H NMR δ (400 MHz, d_6-DMSO) 8.81 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.46 (dd, *J* = 1.8, 1.0 Hz, 1H), 8.09 (s, 1H), 7.12 (dd, *J* = 7.3, 1.9 Hz, 1H), 3.68 (s, 2H), 2.74 (m, 2H), 1.95 (dt, *J* = 11.4, 2.2 Hz, 3H), 1.63-1.66 (m, 3H), 1.16-1.26 (m, 3H). LCMS (APCI$^+$) 256 (MH$^+$, 100%).

***N*-1-(5-Cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl-4-piperidinyl-2-methyl-5-nitrobenzenesulfonamide (23f).** Reaction of **22f** (57 mg, 0.22 mmol) by the same method as **23a**, after chromatography (eluting with CH_2Cl_2: MeOH 100:0 to 97:3) gave **23f** as a cream-coloured solid (67 mg, 66%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.83 (d, *J* = 2.5 Hz, 1H), 8.47 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.29 (dd, *J* = 8.3, 2.4 Hz, 1H), 8.06 (dd, *J* = 1.8, 1.0 Hz, 1H), 7.94 (s, 1H), 7.51 (d, *J* = 8.7 Hz, 1H), 6.85 (dd, *J* = 7.3, 1.8 Hz, 1H), 4.54 (d, *J* = 8.0 Hz, 1H), 3.66 (s, 2H), 3.28 (m, 1H), 2.77 (s, 3H), 2.74 (m, 2H), 2.06 (t, *J* = 10.8 Hz, 2H), 1.83 (m,

2H), 1.49 (m, 2H). LCMS (APCI$^+$) 455 (MH$^+$, 100%). Anal. Calcd for $C_{21}H_{22}N_6O_4S.0.17$ hexane: C, 56.4; H, 5.2; N, 17.9. Found C, 56.3; H, 5.3; N, 17.7.

Synthesis of 3-((4-(2-methyl-5-nitrophenylsulfonyl)piperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridine-5-carbonitrile (23g).



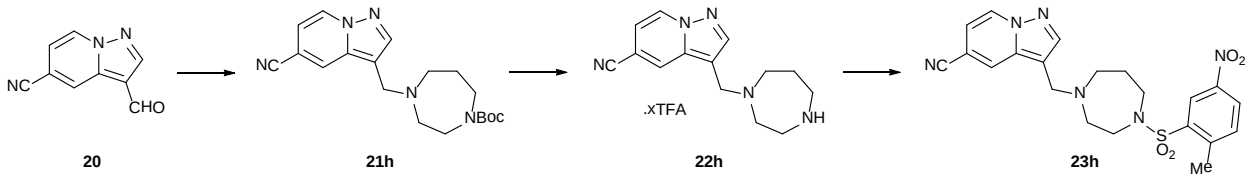
20 **21g** **22g** **23g**

***tert*-Butyl 4-((5-cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)piperazine-1-carboxylate (21g).** Reaction of **20** (30 mg, 0.18 mmol) and *tert*-butyl piperazine-1-carboxylate (53 mg, 0.28 mmol) by the same method as **21a**, after chromatography (eluting with CH_2Cl_2: MeOH 99:1 to 95:5) gave **21g** (42 mg, 70%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.48 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.12 (dd, *J* = 1.8, 1.0 Hz, 1H), 7.99 (s, 1H), 6.86 (dd, *J* = 7.2, 1.8 Hz, 1H), 3.71 (s, 2H), 3.43 (m, 4H), 2.39 (m, 4H), 1.46 (s, 9H). LCMS (APCI$^+$) 342 (MH$^+$, 100%).

3-(Piperazin-1-ylmethyl)pyrazolo[1,5-*a*]pyridine-5-carbonitrile (22g). Reaction of **21g** (174 mg, 0.51 mmol) by the same method as **22a**, gave crude **22g** as a pale yellow solid (62 mg, 50%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.48 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.13 (dd, *J* = 1.8, 1.0 Hz, 1H), 7.99 (s, 1H), 6.86 (dd, *J* = 7.2, 1.8 Hz, 1H), 3.71 (s, 2H), 2.94 (m, 4H), 2.48 (m, 4H). LCMS (APCI$^+$) 242 (MH$^+$, 100%).

3-((4-(2-Methyl-5-nitrophenylsulfonyl)piperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridine-5-carbonitrile (23g). Reaction of **22g** (20 mg, 0.083 mmol) by the same method as **23a**, after chromatography (eluting with CH_2Cl_2 to CH_2Cl_2: MeOH 99.5:0.5 to 99:1) gave **23g** as a yellow solid (22 mg, 59%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.72 (d, *J* = 2.4 Hz, 1H), 8.48 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.30 (dd, *J* = 8.3, 2.4 Hz, 1H), 8.03 (dd, *J* = 1.8, 1.0 Hz, 1H), 7.97 (s, 1H), 7.52 (d, *J* = 8.3 Hz, 1H), 6.86 (dd, *J* = 7.2, 1.8 Hz, 1H), 3.73 (s, 2H), 3.28 (m, 4H), 2.74 (s, 3H), 2.55 (m, 4H). LCMS (APCI$^+$) 156 (MH$^+$ - piperazinyl sulfonamide, 100%), 441 (MH$^+$, 60%). Anal. Calcd for $C_{20}H_{20}N_6O_4S$: C, 54.5; H, 4.6; N, 19.1. Found C, 54.6; H, 4.6; N, 19.2.

Synthesis of 3-((4-(2-methyl-5-nitrophenylsulfonyl)-1,4-diazepan-1-yl)methyl)pyrazolo[1,5-*a*]pyridine-5-carbonitrile (23h).



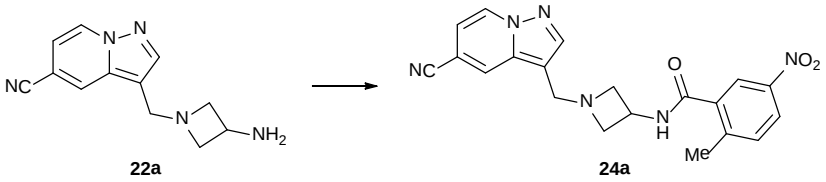
20 **21h** **22h** **23h**

***tert*-Butyl 4-((5-cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)-1,4-diazepane-1-carboxylate (21h).** Reaction of **20** (150 mg, 0.88 mmol) and 1-Boc-hexahydro-1,4-diazepine (0.20 mL, 1.05 mmol) by the same method as **21a**, after chromatography (eluting with CH_2Cl_2: MeOH 100:0 to 99:1 to 98:2) gave **21h** as a pale yellow solid (309 mg, 99%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.50 (dd, *J* = 7.2, 0.9 Hz, 1H), 8.13 (m, 1H), 8.02 (s, 1H), 6.88 (dd, *J* = 7.2, 1.7 Hz, 1H), 3.88 (s, 2H), 3.59-3.41 (m, 4H), 2.78-2.62 (m, 4H), 1.87 (m, 2H), 1.47 (s, 9H). LCMS (APCI$^+$) 356 (MH^+, 100%).

3-((1,4-Diazepan-1-yl)methyl)pyrazolo[1,5-*a*]pyridine-5-carbonitrile trifluoroacetate (22h). Reaction of **21h** (210 mg, 0.59 mmol) by the same method as **22a** without conversion to the free base, gave crude trifluoroacetate salt **22h** as a pale yellow foam (265 mg). ^{1}H NMR δ (400 MHz, CD_3OD) 8.73 (dd, *J* = 7.3, 1.0 Hz, 1H), 8.43 (dd, *J* = 1.7, 1.0 Hz, 1H), 8.24 (s, 1H), 7.14 (dd, *J* = 7.3, 1.7 Hz, 1H), 4.43 (s, 2H), 3.53-3.23 (m, 8H), 2.18 (m, 2H). LCMS (APCI$^+$) 256 (MH^+, 100%).

3-((4-(2-Methyl-5-nitrophenylsulfonyl)-1,4-diazepan-1-yl)methyl)pyrazolo[1,5-*a*]pyridine-5-carbonitrile (23h). Reaction of **22h** (133 mg) by the same method as **23a**, after chromatography (eluting with CH_2Cl_2: MeOH 100:0 to 99.5:0.5 to 99:1) followed by recrystallisation from CH_2Cl_2-^{i}Pr_2O gave **23h** as a yellow powder (52 mg, 42%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.65 (d, *J* = 2.4 Hz, 1H), 8.49 (dd, *J* = 7.3, 1.0 Hz, 1H), 8.27 (dd, *J* = 8.4, 2.4 Hz, 1H), 8.13 (dd, *J* = 1.8, 1.0 Hz, 1H), 7.99 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 6.87 (dd, *J* = 7.3, 1.8 Hz, 1H), 3.88 (s, 2H), 3.53-3.47 (m, 4H), 2.82-2.76 (m, 4H), 2.74 (s, 3H), 1.91 (m, 2H). LCMS (APCI$^+$) 455 (MH^+, 100%). Anal. Calcd for $C_{21}H_{22}N_6O_4S$: C, 55.5; H, 4.9; N, 18.5. Found C, 55.3; H, 5.1; N, 18.5.

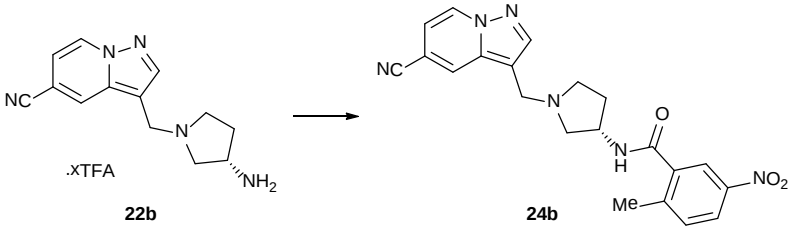
Synthesis of *N*-(1-((5-cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)azetidin-3-yl)-2-methyl-5-nitrobenzamide (24a).



A solution of **22a** (0.47 mmol), 2-methyl-5-nitrobenzoyl chloride (94 mg, 0.47 mmol) and NEt_3 (0.13 mL, 0.93 mmol) in MeCN (5 mL) was stirred at room temperature for 24 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2 until all of the product had been extracted. The combined organic phases were dried (Na_2SO_4), and the solvent removed *in vacuo*. Chromatography (eluting with CH_2Cl_2: MeOH 100:0 to 97:3) followed by recrystallisation from CH_2Cl_2-MeOH-hexanes gave **24a** as a cream-coloured powder (37 mg, 20% over 2 steps from **21a**). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.49 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.23 (d, *J* = 2.4 Hz, 1H), 8.18 (dd, *J* = 8.4, 2.4 Hz, 1H), 8.11 (dd, *J* = 1.8, 1.0 Hz, 1H), 8.00 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 6.87 (dd, *J* = 7.2, 1.8 Hz, 1H), 6.27 (br s, 1H), 4.73 (m, 1H),

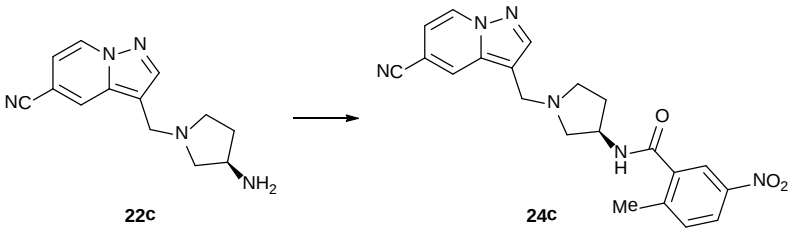
3.84 (s, 2H), 3.69 (m, 2H), 3.11 (m, 2H), 2.55 (s, 3H). LCMS (APCI$^+$) 391 (MH$^+$, 100%). Anal. Calcd for $C_{20}H_{18}N_6O_3$.0.25 H_2O: C, 60.8; H, 4.7; N, 21.2. Found C, 60.8; H, 4.6; N, 21.0.

Synthesis of (*S*)-*N*-(1-((5-cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)pyrrolidin-3-yl)-2-methyl-5-nitrobenzamide (24b).



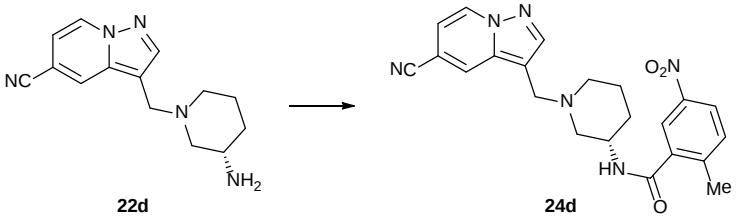
Reaction of **22b** (0.25 mmol) by the same method as **24a**, after chromatography (eluting with CH_2Cl_2: MeOH 99:1 to 97.5:2.5) gave **24b** as a white powder (32 mg, 32% over 2 steps from **21b**). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.49 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.19-8.14 (m, 2H), 8.04 (dd, *J* = 1.8, 1.0 Hz, 1H), 8.01 (s, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 6.86 (dd, *J* = 7.2, 1.8 Hz, 1H), 6.13 (br d, *J* = 7.6 Hz, 1H), 4.65 (m, 1H), 3.85 (ABq, app. *J* = 14.4, 13.8 Hz, 2H), 2.93 (td, *J* = 8.5, 3.8 Hz, 1H), 2.74-2.67 (m, 2H), 2.52 (s, 3H), 2.49-2.34 (m, 2H), 1.76 (m, 1H). LCMS (APCI$^+$) 405 (MH$^+$, 100%). Anal. Calcd for $C_{21}H_{20}N_6O_3$.0.05 CH_2Cl_2.0.05 hexanes: C, 62.1; H, 5.1; N, 20.3. Found C, 62.4; H, 5.15; N, 20.0.

Synthesis of (*R*)-*N*-(1-((5-cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)pyrrolidin-3-yl)-2-methyl-5-nitrobenzamide (24c).



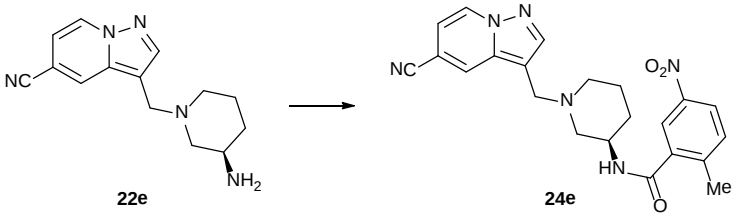
Reaction of **22c** (0.23 mmol) by the same method as **24a**, after chromatography (eluting with CH_2Cl_2: MeOH 99:1 to 98:2 to 97:3) followed by recrystallisation from CH_2Cl_2-MeOH-hexanes gave **24c** as a yellow powder (22 mg, 24% over 2 steps from **21c**). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.49 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.18-8.14 (m, 2H), 8.05 (dd, *J* = 1.8, 1.0 Hz, 1H), 8.01 (s, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 6.86 (dd, *J* = 7.2, 1.8 Hz, 1H), 6.15 (br d, *J* = 7.8 Hz, 1H), 4.66 (m, 1H), 3.85 (ABq, app. *J* = 15.0, 13.7 Hz, 2H), 2.94 (td, *J* = 8.7, 3.8 Hz, 1H), 2.75-2.67 (m, 2H), 2.52 (s, 3H), 2.50-2.35 (m, 2H), 1.76 (m, 1H). LCMS (APCI$^+$) 405 (MH$^+$, 100%). Anal. Calcd for $C_{21}H_{20}N_6O_3$: C, 62.4; H, 5.0; N, 20.8. Found C, 62.3; H, 5.3; N, 20.6.

Synthesis of (*S*)-*N*-(1-((5-cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)piperidin-3-yl)-2-methyl-5-nitrobenzamide (24d).



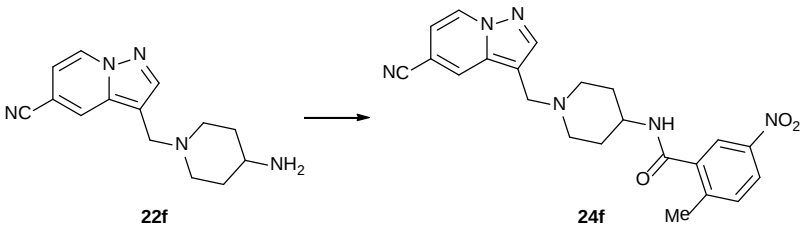
Reaction of **22d** (56 mg, 0.22 mmol) by the same method as **24a**, after chromatography (eluting with CH_2Cl_2: MeOH 99:1 to 98:2) followed by recrystallisation from CH_2Cl_2-$^{i}Pr_2O$ gave **24d** as a white powder (46 mg, 50%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.49 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.17 (dd, *J* = 8.4, 2.4 Hz, 1H), 8.13 (d, *J* = 2.4 Hz, 1H), 7.99 (s, 1H), 7.98 (dd, *J* = 1.7, 1.0 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 6.85 (dd, *J* = 7.2, 1.7 Hz, 1H), 6.25 (br s, 1H), 4.29 (m, 1H), 3.73 (ABq, app. *J* = 37.8, 13.8 Hz, 2H), 2.69-2.28 (m, 7H), 1.83-1.64 (m, 4H). LCMS (APCI$^+$) 419 (MH^+, 100%). Anal. Calcd for $C_{22}H_{22}N_6O_3$: C, 63.15; H, 5.3; N, 20.1. Found C, 63.1; H, 5.3; N, 20.15.

Synthesis of (*R*)-*N*-(1-((5-cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)piperidin-3-yl)-2-methyl-5-nitrobenzamide (24e).



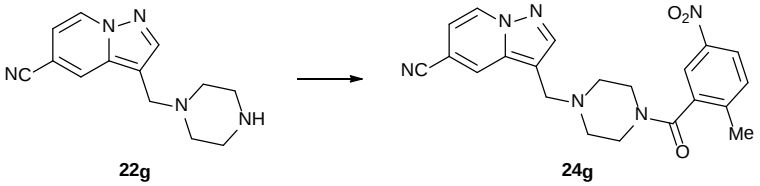
Reaction of **22e** (45 mg, 0.18 mmol) by the same method as **24a**, after chromatography (eluting with CH_2Cl_2: MeOH 99:1 to 98:2) gave **24e** as a cream-coloured powder (45 mg, 61%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.50 (dd, *J* = 7.2, 0.9 Hz, 1H), 8.17 (dd, *J* = 8.4, 2.4 Hz, 1H), 8.12 (d, *J* = 2.4 Hz, 1H), 7.99 (s, 1H), 7.98 (m, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 6.85 (dd, *J* = 7.2, 1.8 Hz, 1H), 6.28 (br s, 1H), 4.30 (m, 1H), 3.73 (ABq, app. *J* = 38.1, 13.8 Hz, 2H), 2.71-2.52 (m, 3H), 2.50 (s, 3H), 2.33 (m, 1H), 1.83-1.64 (m, 4H). LCMS (APCI$^+$) 419 (MH^+, 100%). Anal. Calcd for $C_{22}H_{22}N_6O_3$.0.05 CH_2Cl_2: C, 62.65; H, 5.3; N, 19.9. Found C, 62.5; H, 5.3; N, 19.6.

Synthesis of *N*-(1-((5-cyanopyrazolo[1,5-*a*]pyridin-3-yl)methyl)piperidin-4-yl)-2-methyl-5-nitrobenzamide (24f).



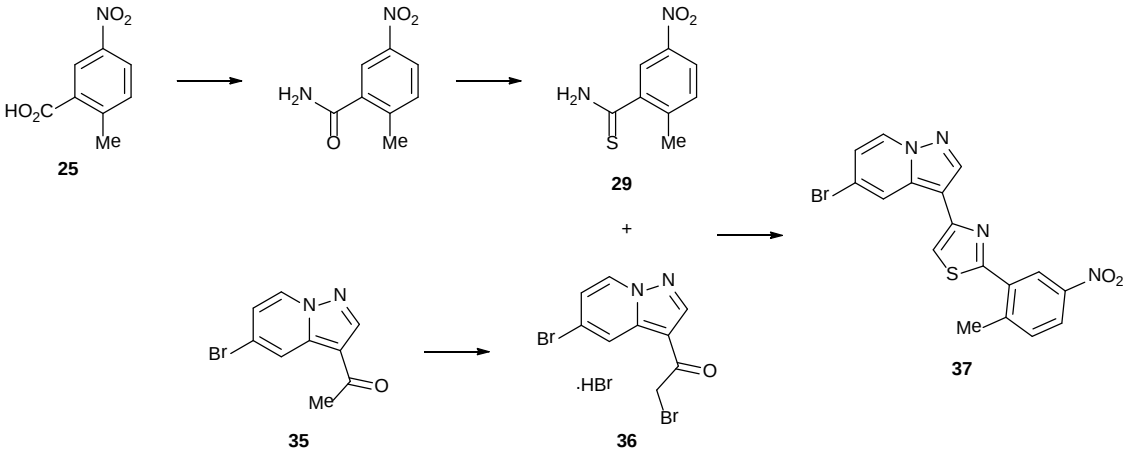
Reaction of **22f** (57 mg, 0.22 mmol) by the same method as **24a**, after chromatography (eluting with CH_2Cl_2 to CH_2Cl_2: MeOH 97:3), then recrystallisation from CH_2Cl_2-hexanes gave **24f** as a yellow solid (42 mg, 45%). ^{1}H NMR δ (400 MHz, d_6-DMSO) 8.85 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.51 (dd, *J* = 1.8, 1.0 Hz, 1H), 8.48 (d, *J* = 7.7 Hz, 1H), 8.18 (dd, *J* = 8.5, 2.5 Hz, 1H), 8.14 (s, 1H), 8.07 (d, *J* = 2.5 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.15 (dd, *J* = 7.2, 1.8 Hz, 1H), 3.68-3.75 (m, 3H), 2.84 (m, 2H), 2.42 (s, 3H), 2.06 (m, 2H), 1.82 (m, 2H), 1.50 (m, 2H). LCMS (APCI$^+$) 419 (MH^+, 100%). Anal. Calcd for $C_{22}H_{22}N_6O_3$: C, 63.15; H, 5.3; N, 20.1. Found C, 63.1; H, 5.5; N, 20.0.

Synthesis of 3-((4-(2-methyl-5-nitrobenzoyl)piperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridine-5-carbonitrile (24g).



Reaction of **22g** (40 mg, 0.17 mmol) by the same method as **24a**, after chromatography (eluting with CH_2Cl_2 to CH_2Cl_2: MeOH 99:1 to 97:3) gave **24g** as a yellow solid (43 mg, 64%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.50 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.14 (dd, *J* = 8.4, 2.4 Hz, 1H), 8.10 (dd, *J* = 1.8, 1.0 Hz, 1H), 8.05 (d, *J* = 2.4 Hz, 1H), 7.99 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 6.88 (dd, *J* = 7.2, 1.8 Hz, 1H), 4.02-3.69 (m, 4H), 3.26 (m, 2H), 2.58 (m, 2H), 2.43 (s, 3H), 2.39 (m, 2H). LCMS (APCI$^+$) 156 (MH^+ - piperazinyl amide, 100%), 405 (MH^+, 30%). Anal. Calcd for $C_{21}H_{20}N_6O_3$: C, 62.4; H, 5.0; N, 20.8. Found C, 62.3; H, 4.9; N, 20.5.

Synthesis of 4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)-2-(2-methyl-5-nitrophenyl)thiazole (37).



2-Methyl-5-nitrobenzamide. A suspension of 2-methyl-5-nitrobenzoic acid (**25**) (295 mg, 1.63 mmol) in $SOCl_2$ (5 mL) was refluxed for 15 mins. The resulting solution was concentrated *in vacuo*, the cream coloured semi-solid was taken up in CH_2Cl_2 (10 mL), cooled to 0 °C and then conc. aqueous NH_3 (4 mL) was added. The reaction was stirred for 5 mins, then the white precipitate was collected by filtration, washed with water and ice cold CH_2Cl_2, and dried to give the title compound as a white solid (293 mg, 99%). ^{1}H NMR δ (400 MHz, d_6-DMSO) 8.18 (dd, *J* = 8.1, 2.1 Hz, 1H), 8.16 (s, 1H), 7.99 (br s, 1H), 7.63 (br s, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 2.49 (s, 3H). LCMS (APCI$^+$) 181 (MH^+, 100%).

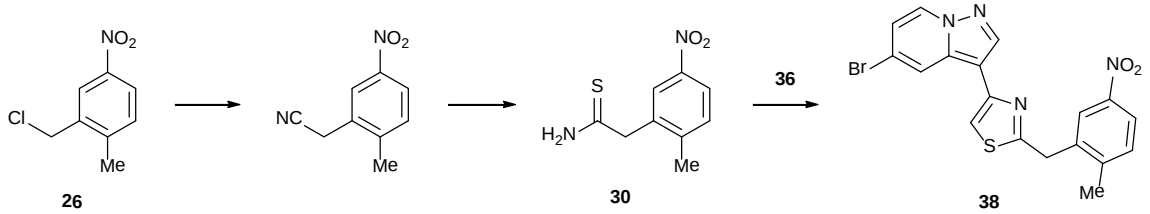
2-Methyl-5-nitrobenzothioamide (29). A solution of the above amide (150 mg, 0.83 mmol) and Lawesson's reagent (673 mg, 1.66 mmol) in MeOH (10 mL) was refluxed overnight. The solvent was removed *in vacuo*, then chromatography (eluting with EtOAc: CH_2Cl_2 15:85) gave **29** as pale green solid (69 mg, 50%). ^{1}H NMR δ (400 MHz, d_6-DMSO) 10.25 (br s, 1H), 9.72 (br s, 1H), 8.10 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.99 (d, *J* = 2.5 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 2.43 (s, 3H). LCMS (APCI$^+$) 197 (MH^+, 100%).

2-Bromo-1-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)ethanone hydrobromide (36). A solution of Br_2 (805 mg, 5.04 mmol) in AcOH (5 mL) was added to a suspension of 1-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)ethanone[1] (**35**) (1.21g, 5.04 mmol) in 30% HBr/AcOH (15 mL). The orange solution was stirred at room temperature overnight and then diluted with cold Et_2O. The resulting precipitate was filtered off, washed with ice cold EtOH then Et_2O to give **36** as a cream coloured solid (1.52 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) 8.60 (d, *J* = 2.1 Hz, 1H), 8.40 (m, 2H), 7.16 (dd, *J* = 7.2, 2.1 Hz, 1H), 4.28 (s, 2H). LCMS (APCI$^+$) 317 (MH^+ with $^{79}Br_2$, 80%), 319 (MH^+ with $^{79}Br^{81}Br$, 100%), 321 (MH^+ with $^{81}Br_2$, 60%).

4-(5-Bromopyrazolo[1,5-*a*]pyridin-3-yl)-2-(2-methyl-5-nitrophenyl)thiazole (37). A solution of **36** (60 mg, 0.15 mmol) and **29** (32 mg, 0.16 mmol) in EtOH (10 mL) was heated at 40 °C for 18 hrs. The reaction mixture was cooled to 0 °C and then the precipitate filtered off and dried to leave **37** as a white solid (25 mg, 40%). HPLC purity 99.5%. Mp 239-242 ºC (CH_2Cl_2). ^{1}H NMR δ (400 MHz, d_6-DMSO) 8.74 (dd, *J* = 7.3, 0.7 Hz, 1H), 8.67 (d, *J* = 2.5 Hz, 1H), 8.65 (s, 1H), 8.53 (dd, *J* = 2.2, 0.7 Hz, 1H), 8.26 (dd, *J* = 8.5, 2.5, 1H), 8.24 (s, 1H), 7.75 (d, *J* = 8.5 Hz,1H), 7.14 (dd, *J* = 7.3, 2.2 Hz, 1H), 2.79 (s, 3H). ^{13}C NMR δ (100

MHz, d_6-DMSO) 164.1 (C), 148.2 (C), 146.1 (C), 143.8 (C), 141.6 (CH), 136.9 (C), 133.3 (CH), 133.2 (C), 130.5 (CH), 123.8 (CH), 123.7 (CH), 120.4 (CH), 118.4 (C), 116.9 (CH), 113.9 (CH), 106.8 (C), 21.7 (CH_3). LCMS (APCI$^+$) 415 (MH^+ with ^{79}Br, 100%), 417 (MH^+ with ^{81}Br, 90%). HRMS (ESI$^+$) Calcd for $C_{17}H_{12}{}^{79}BrN_4O_2S$: 414.9859; found ($MH^+$) 414.9858.

Synthesis of 4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)-2-(2-methyl-5-nitrobenzyl)thiazole (38).



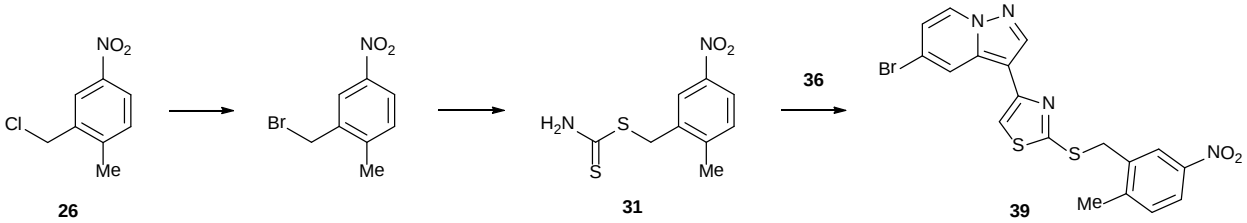
2-(2-Methyl-5-nitrophenyl)acetonitrile. KCN (136 mg, 2.09 mmol) and 2-(chloromethyl)-1-methyl-4-nitrobenzene[2] (**26**) (128 mg, 0.7 mmol) were stirred overnight in DMSO (5 mL) at room temperature. The reaction was then poured into ice-water (100 mL), the resulting precipitate collected by filtration, washed with water and dried to give the title compound as a white solid (110 mg, 89%). ^{1}H NMR δ (400 MHz, d_6-DMSO) 8.26 (d, J = 2.5 Hz, 1H), 8.13 (dd, J = 8.3, 2.5 Hz, 1H), 7.56 (d, J = 8.3, 1H), 4.19 (s, 2H), 2.44 (s, 3H). LCMS (APCI$^-$) 175 ($M\text{-}H^+$, 100%).

2-(2-Methyl-5-nitrophenyl)ethanethioamide (30). P_2S_5 (252 mg, 1.14 mmol) was stirred in EtOH (10 mL) for 1 h until it had dissolved, and then the above nitrile (77 mg, 0.437 mmol) was added and the reaction mixture refluxed for 6 h. The reaction was allowed to cool and subsequently purged with nitrogen for 15 mins and the solvent removed *in vacuo*. Chromatography (eluting with CH_2Cl_2) gave **30** as a pale tan oil (54 mg, 60%). ^{1}H NMR δ (400 MHz, d_6-DMSO) 8.14 (d, J = 2.5 Hz, 1H), 8.02 (dd, J = 8.4, 2.5 Hz, 1H), 7.45 (d, J = 8.4, 1H), 7.53 (br s, 1H), 7.00 (br s, 1H), 3.98 (s, 2H), 2.41 (s, 3H). LCMS (APCI$^-$) 209 ($M\text{-}H^+$, 100%).

4-(5-Bromopyrazolo[1,5-*a*]pyridin-3-yl)-2-(2-methyl-5-nitrobenzyl)thiazole (38). A solution of **36** (60 mg, 0.15 mmol) and **30** (31.5 mg, 0.15 mmol) in EtOH (10 mL) was heated at 40 °C for 18 hrs. The reaction mixture was poured onto ice, extracted three times with EtOAc, dried (Na_2SO_4) and the solvent removed *in vacuo*. Chromatography (eluting with CH_2Cl_2: EtOAc 85:15) followed by a second chromatography (on alumina, eluting with CH_2Cl_2: EtOAc 95:5) gave **38** as a yellow solid (10 mg, 16%). HPLC purity 92.3%. ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.33-8.28 (m, 2H), 8.23 (s, 1H), 8.22 (d, J = 2.4 Hz, 1H), 8.10 (dd, J = 8.4, 2.4 Hz, 1H), 7.40 (d, J = 8.4, 1H), 7.20 (s, 1H), 6.86 (dd, J = 7.3, 2.2 Hz, 1H), 4.48 (s, 2H), 2.51 (s, 3H). ^{13}C NMR δ (100 MHz, $CDCl_3$) 167.2 (C), 147.8 (C), 146.2 (C), 144.4 (C), 140.4 (CH), 137.3 (C), 130.9 (CH), 130.8 (C), 128.7 (CH), 124.4 (CH), 122.1 (CH), 121.1 (CH), 117.8 (C), 115.6 (CH), 110.0 (CH), 107.0 (C), 36.8 (CH_2), 19.5 (CH_3).

LCMS (APCI$^+$) 429 (MH^+ with ^{79}Br, 100%), 431 (MH^+ with ^{81}Br, 80%). HRMS (APCI$^+$) Calcd for $C_{18}H_{14}{}^{79}BrN_4O_2S$: 429.0015; found ($MH^+$) 429.0002.

Synthesis of 4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)-2-((2-methyl-5-nitrobenzyl)thio)-thiazole (39).

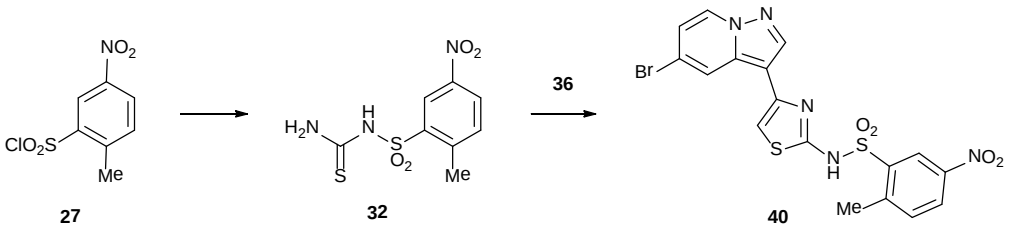


2-(Bromomethyl)-1-methyl-4-nitrobenzene. Chloride **26** (50 mg, 0.27 mmol) and LiBr (467 mg, 5.39 mmol) were refluxed in THF (75 mL) for 24 h. The solvent was removed *in vacuo*, and the residue taken up in CH_2Cl_2 (100 mL) and water (50 mL). The phases were separated and the organic layer dried (Na_2SO_4) to give the title compound as a white solid (59 mg, 95%). ^1H NMR δ (400 MHz, $CDCl_3$) 8.19 (d, *J* = 2.4, 1H), 8.07 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 4.53 (s, 2H), 2.52 (s, 3H).

2-Methyl-5-nitrobenzyl carbamodithioate (31). A solution of the above bromide (200 mg, 0.87 mmol) and ammonium dithiocarbamate (475 mg, 4.3 mmol) in EtOH (20 mL) was refluxed overnight. The reaction was cooled to room temperature then poured onto ice. The resulting solid was filtered, then purified twice by chromatography (on alumina, firstly eluting with EtOAc to EtOAc: AcOH 98:2, and secondly eluting with CH_2Cl_2: EtOH 9:1) gave **31** as yellow needles (189 mg, 90%). ^1H NMR δ (400 MHz, d_6-DMSO) 9.70 (br, 1H), 9.37 (br, 1H), 8.24 (s, 1H), 8.03 (m, 1H), 7.47 (m, 1H), 4.55 (s, 2H), 2.58 (s, 3H). LCMS (APCI$^+$) 243 (MH^+, 100%).

4-(5-Bromopyrazolo[1,5-*a*]pyridin-3-yl)-2-((2-methyl-5-nitrobenzyl)thio)thiazole (39). Reaction of **36** (60 mg, 0.15 mmol) and **31** (43 mg, 0.18 mmol) by the same method as **37**, gave **39** as a pale yellow solid (50 mg, 72%). HPLC purity 99.7%. ^1H NMR δ (400 MHz, $CDCl_3$) 8.31 (dd, *J* = 7.3, 0.7 Hz, 1H), 8.28 (dd, *J* = 2.1, 0.7 Hz, 1H), 8.27 (s, 1H), 8.25 (d, *J* = 2.4 Hz, 1H), 8.04 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.20 (s, 1H), 6.89 (dd, *J* = 7.3, 2.1 Hz, 1H), 4.59 (s, 2H), 2.57 (s, 3H). ^{13}C NMR δ (100 MHz, $CDCl_3$) 162.6 (C), 148.6 (C), 146.5 (C), 144.7 (C), 141.2 (CH), 137.7 (C), 136.2 (C), 131.4 (CH), 129.4 (CH), 124.7 (CH), 122.8 (CH), 121.3 (CH), 118.5 (C), 116.2 (CH), 111.2 (CH), 107.3 (C), 36.2 (CH_2), 19.7 (CH_3). LCMS (APCI$^+$) 461 (MH^+ with ^{79}Br, 100%), 463 (MH^+ with ^{81}Br, 80%). HRMS (APCI$^+$) Calcd for $C_{18}H_{14}{}^{79}BrN_4O_2S_2$: 460.9736; found ($MH^+$) 460.9739.

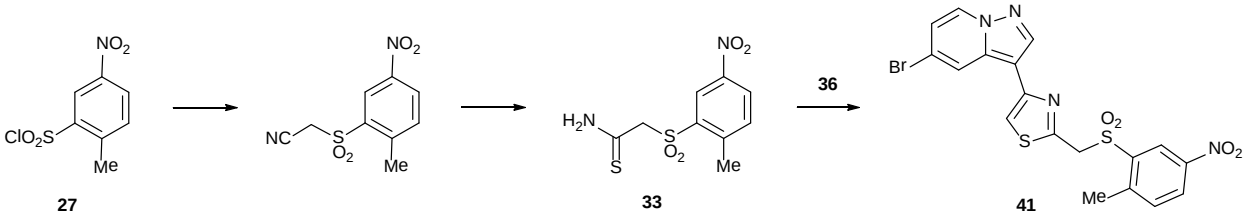
Synthesis of *N*-(4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)thiazol-2-yl)-2-methyl-5-nitro-benzenesulfonamide (40).



***N*-Carbamothioyl-2-methyl-5-nitrobenzenesulfonamide (32).** 2-Methyl-5-nitrobenzene-sulfonyl chloride (**27**) (2.35 g, 10 mmol) was added in small portions to a solution of Na_2NCN (1.01 g, 11 mmol) in water (40 mL) at 40 °C over 1 h. The reaction was stirred for an additional 1 h then cooled to room temperature. Next $Na_2S_2O_3$ (3.7 g, 15 mmol) was added in one portion, followed by the dropwise addition of 4.5 M H_2SO_4 (10 mL). The reaction mixture was stirred overnight at room temperature, then the resulting suspension was cooled to 0 °C and the precipitate collected by filtration. The solid was taken up in CH_2Cl_2-MeOH 9:1, dried (Na_2SO_4) and the solvent removed *in vacuo* to give **32** as an orange solid (700 mg, 25%). ^{1}H NMR δ (400 MHz, d_6-DMSO) 12.00 (br s, 1H) 8.98 (s, 1H), 8.72 (d, *J* = 2.5 Hz, 1H), 8.41 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.63 (s, 1H), 2.70 (s, 3H). LCMS (APCI$^+$) 276 (MH^+, 100%).

***N*-(4-(5-Bromopyrazolo[1,5-*a*]pyridin-3-yl)thiazol-2-yl)-2-methyl-5-nitrobenzene-sulfonamide (40).** Reaction of **36** (60 mg, 0.15 mmol) and **32** (49.5 mg, 0.18 mmol) by the same method as **37**, gave **40** as an orange solid (50 mg, 67%). HPLC purity 98.2%. Mp 250-254 °C. ^{1}H NMR δ (400 MHz, d_6-DMSO) 13.36 (s, 1H), 8.73 (dd, *J* = 7.3, 0.4 Hz, 1H), 8.67 (d, *J* = 2.5 Hz, 1H), 8.42 (s, 1H), 8.33 (dd, *J* = 8.4, 2.5 Hz, 1H), 8.22 (d, *J* = 2.1 Hz, 1H), 7.70 (d, *J* = 8.4, 1H), 7.18 (dd, *J* = 7.3, 2.1 Hz, 1H), 7.17 (s, 1H), 2.77 (s, 3H). ^{13}C NMR δ (100 MHz, d_6-DMSO) 168.7 (C), 145.2 (C), 144.6 (C), 144.2 (C), 144.2 (CH), 136.9 (C) 133.9 (CH), 130.6 (CH), 129.0 (C), 126.4 (CH), 122.2 (CH), 119.6 (C), 119.4 (CH), 116.8 (CH), 101.5 (CH), 101.1 (C), 20.2 (CH_3). LCMS (APCI$^+$) 494 (MH^+ with ^{79}Br, 85%), 496 (MH^+ with ^{81}Br, 100%). HRMS (ESI$^+$) Calcd for $C_{17}H_{12}{}^{79}BrN_5NaO_4S_2$: 515.9406; found ($MNa^+$) 515.9406.

<u>Synthesis of 4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)-2-(((2-methyl-5-nitrophenyl)sulfonyl)methyl)thiazole (41).</u>



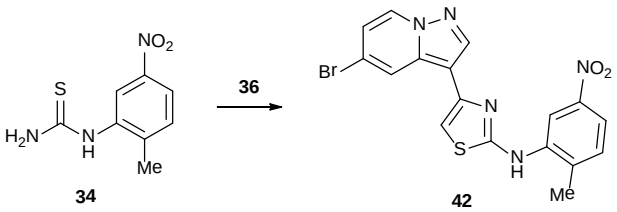
2-((2-Methyl-5-nitrophenyl)sulfonyl)acetonitrile. 27 (5.0 g, 21 mmol) was added in small portions to a stirred suspension of Na_2SO_3 (5.3 g, 21 mmol) and $NaHCO_3$ (3.57 g, 42.5 mmol) in water (40 mL) over 1 h. Stirring was continued overnight, followed by removal of

the solvent *in vacuo*. The yellow solid was triturated with MeOH (100 mL) and filtered through celite. The solvent was removed from the filtrate *in vacuo*, and then the crude sulfinate salt was reacted with bromoacetonitrile (3.36 g, 28 mmol) in DMF (50 mL) at room temperature overnight. The solvent was removed *in vacuo*. Chromatography (eluting with CH_2Cl_2) gave the title compound as white solid (1.00 g, 20%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.65 (d, *J* = 2.5 Hz, 1H), 8.55 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 5.38 (s, 2H), 2.80 (s, 3H). LCMS (APCI$^-$) 239 (M-H$^+$, 100%).

2-((2-Methyl-5-nitrophenyl)sulfonyl)ethanethioamide (33). H_2S was bubbled for 5 mins through a solution of the above nitrile (200 mg, 0.83 mmol) and NEt_3 (1 drop) in EtOH (30 mL) at 0 °C. The solution was stirred overnight at room temperature, and then purged with nitrogen for 30 min. The reaction mixture was diluted with water, extracted twice with CH_2Cl_2, and then the combined organic extracts were washed with brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. Chromatography (eluting with (CH_2Cl_2: EtOH 98:2) gave **33** as a light red oil (180 mg, 81%). ^{1}H NMR δ (400 MHz, d_6-DMSO) 9.91 (s, 1H), 9.52 (s, 1H), 8.55 (d, *J* = 2.5 Hz, 1H), 8.45 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 4.70 (s, 2H), 2.78 (s, 3H). LCMS (APCI$^-$) 273 (M-H$^+$, 100%).

4-(5-Bromopyrazolo[1,5-*a*]pyridin-3-yl)-2-(((2-methyl-5-nitrophenyl)sulfonyl)methyl)-thiazole (41). Reaction of **36** (60 mg, 0.15 mmol) and **33** (40 mg, 0.18 mmol) by the same method as **37**, gave **41** as a pale yellow solid (40 mg, 54%). HPLC purity 99.9%. ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.61 (d, *J* = 2.5 Hz, 1H), 8.27 (dd, *J* = 7.3, 0.7 Hz, 1H), 8.26 (dd, *J* = 8.4, 2.5 Hz, 1H), 8.11 (s, 1H), 7.74 (dd, *J* = 2.1, 0.7 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.34 (s, 1H), 6.87 (dd, *J* = 7.3, 2.1 Hz, 1H), 4.92 (s, 2H), 2.75 (s, 3H). ^{13}C NMR δ (100 MHz, $CDCl_3$) 154.4 (C), 148.7 (C), 145.9 (C), 145.7 (C), 140.4 (CH), 136.9 (C), 136.8 (C), 133.2 (CH), 128.8 (CH), 127.9 (CH), 125.8 (CH), 120.4 (CH), 117.9 (C), 115.7 (CH), 112.8 (CH), 106.0 (C), 58.5 (CH_2), 20.1 (CH_3). LCMS (APCI$^+$) 493 (MH$^+$ with ^{79}Br, 100%), 495 (MH$^+$ with ^{81}Br, 80%). HRMS (APCI$^+$) Calcd for $C_{18}H_{14}{}^{79}BrN_4O_4S_2$: 492.9634; found (MH$^+$) 492.9625.

<u>Synthesis of 4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)-*N*-(2-methyl-5-nitrophenyl)thiazol-2-amine hydrobromide (42).</u>

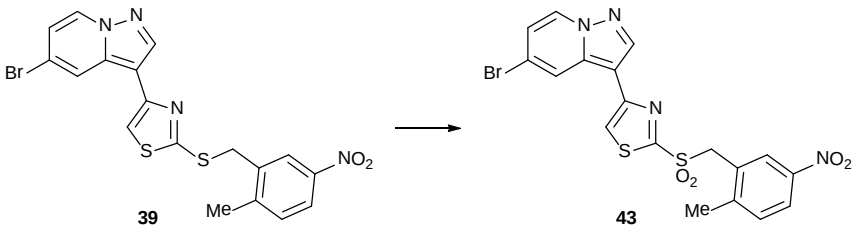


34 42

Reaction of **36** (60 mg, 0.15 mmol) and 1-(2-methyl-5-nitrophenyl)thiourea[3] (**34**) (38 mg, 0.18 mmol) by the same method as **37**, gave **42** as a white solid (40 mg, 62%). HPLC purity 99.1%. Mp 269-271 °C. ^{1}H NMR δ (400 MHz, d_6-DMSO) 9.77 (br s, 1H), 9.32 (d, *J* = 2.4 Hz, 1H), 8.66 (dd, *J* = 7.4, 0.7 Hz, 1H), 8.52 (s, 1H), 8.40 (dd, *J* = 2.2, 0.7 Hz, 1H), 7.84 (dd,

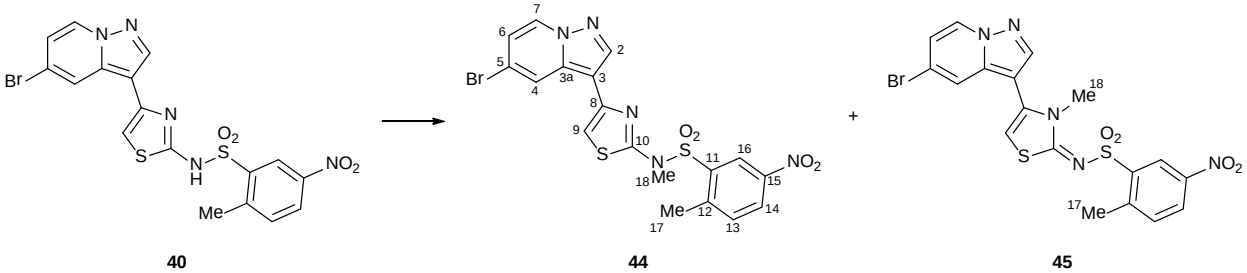
J = 8.3, 2.4 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.30 (s, 1H), 7.05 (dd, *J* = 7.4, 2.2 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR δ (100 MHz, d_6-DMSO) 163.6 (C), 146.2 (C), 142.5 (C), 141.0 (CH), 140.0 (C), 136.5 (C), 134.7 (C), 131.4 (CH), 130.3 (CH), 120.7 (CH), 117.7 (C), 116.4 (CH), 115.7 (CH), 113.0 (CH), 107.6 (C), 102.0 (CH), 18.4 (CH_3). LCMS (APCI$^+$) 430 (MH^+ with ^{79}Br, 100%), 432 (MH^+ with ^{81}Br, 70%). HRMS (ESI$^+$) Calcd for $C_{17}H_{13}{}^{79}BrN_5O_2S$: 429.9968; found ($MH^+$) 429.9965.

Synthesis of 4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)-2-((2-methyl-5-nitrobenzyl)sulfonyl)thiazole (43).



MMPP (133 mg, 0.27 mmol) was added to a suspension of **39** in CH_2Cl_2 (3 mL) and MeOH (20 mL). The reaction mixture was stirred for three days at room temperature, and then 5% aqueous Na_2SO_3 was added. The reaction mixture was diluted with CH_2Cl_2 and washed with 10% aqueous $NaHCO_3$. The aqueous layer was back extracted with CH_2Cl_2 (75 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and the solvent removed *in vacuo* to leave **43** as a yellow solid (29 mg, 76%). HPLC purity 94.4%. Mp 188-192 ºC. ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.36 (dd, *J* = 7.3, 0.7 Hz, 1H), 8.33 (s, 1H), 8.24 (dd, *J* = 2.1, 0.7 Hz, 1H), 8.10 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.97 (d, *J* = 2.4 Hz, 1H), 7.66 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 6.97 (dd, *J* = 7.3, 2.1 Hz, 1H), 4.85 (s, CH_2), 2.55 (s, CH_3). ^{13}C NMR δ (100 MHz, $CDCl_3$) 163.7 (C), 151.6 (C), 146.6 (C), 146.3 (C), 141.5 (CH), 137.9 (C), 131.9 (CH), 129.5 (CH), 127.2 (C), 126.8 (CH), 124.2 (CH), 120.9 (CH), 119.7 (C), 117.7 (CH), 116.8 (CH), 105.7 (C), 58.4 (CH_2), 20.1 (CH_3). LCMS (APCI$^+$) 493 (MH^+ with ^{79}Br, 100%), 495 (MH^+ with ^{81}Br, 80%). HRMS (APCI$^+$) Calcd for $C_{18}H_{14}{}^{79}BrN_4O_2S_2$: 492.9634; found ($MH^+$) 492.9623.

Synthesis of *N*-(4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)thiazol-2-yl)-*N*,2-dimethyl-5-nitrobenzenesulfonamide (44) and *N*-(4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)-3-methylthiazol-2(3*H*)-ylidene)-2-methyl-5-nitrobenzenesulfonamide (45).



MeI (33 µL, 5.36 mmol) was added to a suspension of **40** (53 mg, 0.107 mmol) and K_2CO_3 (40 mg, 0.27 mmol) in anhydrous DMF (10 mL) and stirred at room temperature overnight. The reaction mixture was poured onto ice and the precipitate collected by filtration. Chromatography (eluting with CH_2Cl_2 to CH_2Cl_2: EtOAc 9:1 to 85:15 to 6:4) gave firstly **44** as a red oil (20 mg, 36%). NMR data presented in Table S3. LCMS (APCI$^+$) 508 (MH^+ with ^{79}Br, 95%), 510 (MH^+ with ^{81}Br, 100%). HRMS (APCI$^+$) Calcd for $C_{18}H_{15}{}^{79}BrN_5O_4S_2$: 507.9743; found ($MH^+$) 507.9747. Followed by **45** as a red oil (20 mg, 36%). HPLC purity 81.3%. NMR data presented in Table S4. LCMS (APCI$^+$) 508 (MH^+ with ^{79}Br, 95%), 510 (MH^+ with ^{81}Br, 100%). HRMS (APCI$^+$) Calcd for $C_{18}H_{15}{}^{79}BrN_5O_4S_2$: 507.9743; found ($MH^+$) 507.9743.

Table S3. NMR assignment for **44** (recorded in $CDCl_3$).

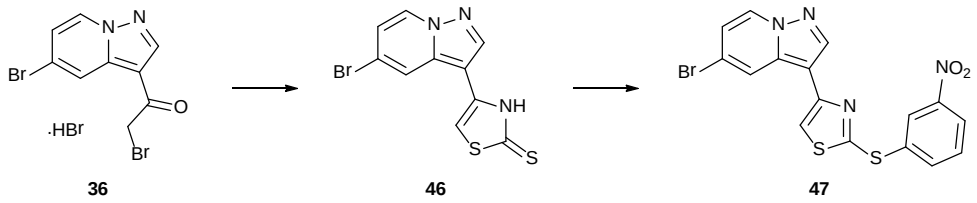
C/H	^{1}H (ppm)	Coupling	NOESY	HMBC	^{13}C (ppm)
2	8.19	s	H9	C3, C3a	141.0
3					107.2
3a					137.6
4	8.16	d (*J* 2.1 Hz)	H9	C3a, C5, C6	121.2
5					118.4
6	6.87	dd (*J* 7.3, 2.1 Hz)		C4, C5, C7	116.1
7	8.29	dd (*J* 7.3, 0.7 Hz)		C3a, C5, C6	129.3
8					144.2
9	7.00	s	H2, H4	C3, C8, C10	107.5
10					160.9
11					138.1
12					145.5
13	7.53	d (*J* 8.4 Hz)	H17	C11, C15, C17	134.2
14	8.32	dd (*J* 8.4, 2.4 Hz)		C12, C16	127.7
15					146.1
16	8.88	d (*J* 2.4 Hz)	H18	C11, C12, C14	125.4
17	2.67	s	H13, H18	C11, C12, C13	20.9
18	3.65	s	H16, H17	C10	37.4

Table S4. NMR assignment for **45** (recorded in $CDCl_3$).

C/H	^{1}H (ppm)	Coupling	NOESY	HMBC	^{13}C (ppm)
2	7.97	s	H18	C3, C3a	142.6
3					99.8
3a					139.7
4	7.65	dd (*J* 2.1, 0.7 Hz)	H9, H18	C3a, C5, C6	118.8
5					120.5
6	7.01	dd (*J* 7.3, 2.1 Hz)		C4, C5, C7	117.3
7	8.38	dd (*J* 7.3, 0.7 Hz)		C3a, C5, C6	129.8
8					130.9
9	6.49	s	H4	C3, C8, C10	105.6
10					167.3
11					141.8
12					145.1

13	7.48	d (*J* 8.4 Hz)	H17	C11, C15, C17	133.2
14	8.25	dd (*J* 8.4, 2.4 Hz)		C12, C16	126.2
15					145.8
16	8.95	d (*J* 2.4 Hz)		C12, C14	123.4
17	2.89	s	H13	C11, C12, C13	21.0
18	3.46	s	H2, H4	C8, C10	34.1

Synthesis of 4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)-2-((3-nitrophenyl)thio)thiazole (47).

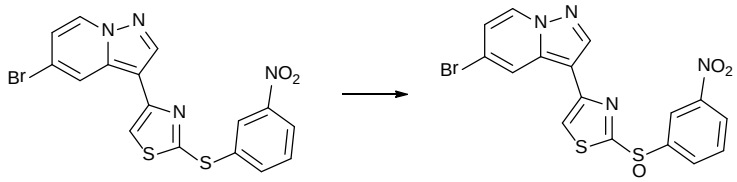


36 **46** **47**

4-(5-Bromopyrazolo[1,5-*a*]pyridin-3-yl)thiazole-2(3*H*)-thione (46). A suspension of ammonium dithiocarbamate (208 mg, 1.89 mmol) and **36** (200 mg, 0.63 mmol) in anhydrous MeOH (10 mL) was stirred for 10 mins. The precipitate was filtered off, resuspended in acetic acid (10 mL) and refluxed for 1 h. The reaction mixture was cooled to room temperature and diluted with ice cold water. The precipitate was filtered, and then redissolved in CH_2Cl_2: MeOH 95:5, dried (Na_2SO_4) and the solvent removed i*n vacuo* to leave **46** as a pale green solid (136 mg, 70%). ^{1}H NMR (400 MHz, d_6-DMSO) 13.59 (br s, 1H), 8.74 (d, *J* = 7.3 Hz, 1H), 8.51 (s, 1H), 8.22 (d, *J* = 2.1 Hz, 1H), 7.27 (s, 1H), 7.19 (dd, *J* = 7.3, 2.1 Hz, 1H). LCMS (APCI$^+$) 312 (MH^+ with ^{79}Br, 100%), 314 (MH^+ with ^{81}Br, 100%).

4-(5-Bromopyrazolo[1,5-*a*]pyridin-3-yl)-2-((3-nitrophenyl)thio)thiazole (47). A solution of **46** (50 mg, 0.15 mmol), $Cu(OAc)_2$, (29 mg, 0.15 mmol), 1,10-phenanthroline (58 mg, 0.30 mmol) and (3-nitrophenyl)boronic acid (107 mg, 0.64 mmol) were dissolved in 1,2-dichloro-ethane (10 mL) and the mixture stirred at room temperature for 30 mins. The reaction mixture was refluxed for 48 h, and then the solvent removed i*n vacuo*. Chromatography (eluting with CH_2Cl_2) gave **47** as a yellow solid (46 mg, 72%). HPLC purity 98.7%. Mp 140-142 ºC. ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.54 (dd, *J* = 2.2, 1.7 Hz, 1H), 8.29 (*J* = 7.3, 0.7 Hz, 1H), 8.28 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1H), 8.23 (s, 1H), 8.19 (dd, *J* = 2.1, 0.7 Hz, 1H), 7.98 (ddd, *J* = 7.8, 1.7, 1.0 Hz, 1H), 7.64 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.30 (s, 1H), 6.87 (dd, *J* = 7.3, 2.1 Hz, 1H). ^{13}C NMR δ (100 MHz, $CDCl_3$) 161.4 (C), 149.4 (C), 148.8 (C), 140.9 (CH), 138.5 (CH), 137.8 (C), 134.6 (C), 130.3 (CH), 129.2 (CH), 127.4 (CH), 123.9 (CH), 121.5 (CH), 118.6 (C), 116.3 (CH), 112.6 (CH), 107.0 (C). LCMS (APCI$^+$) 433 (MH^+ with ^{79}Br, 100%), 435 (MH^+ with ^{81}Br, 85%). HRMS (ESI$^+$) Calcd for $C_{16}H_9{}^{79}BrN_4NaO_2S_2$: 454.9243; found ($MNa^+$) 454.9241.

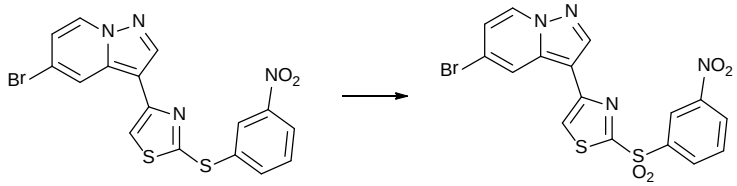
Synthesis of 4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)-2-((3-nitrophenyl)sulfinyl)thiazole (48).



47 48

Sulfide **47** (22 mg, 0.05 mmol) was added to a stirred solution of Oxone® (156 mg, 0.25 mmol) in MeOH (3 mL) and water (3 mL). The reaction was stirred at room temperature for 3 days, then the methanol was removed i*n vacuo*. The aqueous residue was diluted with water, extracted twice with CH_2Cl_2, dried (Na_2SO_4), the solvent removed i*n vacuo*. Chromatography (eluting with CH_2Cl_2 to CH_2Cl_2: EtOAc 9:1) gave **48** as a lime green solid (15 mg, 66%). HPLC purity 99.8%. Mp 206-208 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) 8.79 (dd, *J* = 2.2, 1.6 Hz, 1H), 8.39 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1H), 8.31 (dd, *J* = 7.3, 0.7 Hz, 1H), 8.25 (ddd, *J* = 7.8, 1.6, 1.0 Hz, 1H), 8.23 (s, 1H), 8.21 (dd, *J* = 2.1, 0.7 Hz, 1H), 7.80 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.55 (s, 1H), 6.93 (dd, *J* = 7.3, 2.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) 174.9 (C), 151.3 (C), 149.0 (C), 146.4 (C), 141.3 (CH), 138.0 (C), 130.9 (CH), 130.2 (CH), 129.6 (CH), 126.7 (CH), 121.3 (CH), 119.9 (CH), 119.4 (C), 116.8 (CH), 115.4 (CH), 106.5 (C). LCMS (APCI$^+$) 449 (MH^+ with ^{79}Br, 100%), 451 (MH^+ with ^{81}Br, 85%). HRMS (ESI$^+$) Calcd for $C_{16}H_9{}^{79}BrN_4NaO_3S_2$: 470.9192; found ($MNa^+$) 470.9183.

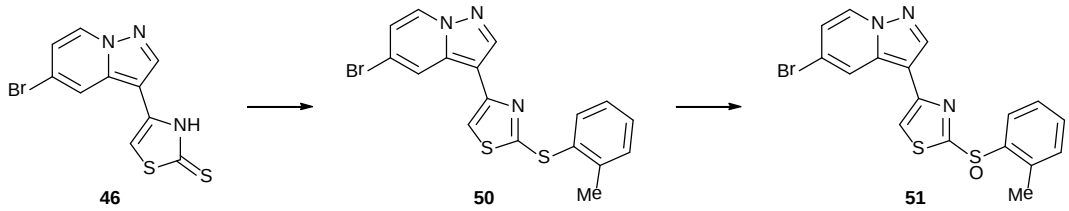
Synthesis of 4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)-2-((3-nitrophenyl)sulfonyl)thiazole (49).



47 49

A solution of MMPP (285 mg, 0.57 mmol) in EtOH (10 mL) was added dropwise to a solution of **47** (50 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) and stirred at room temperature overnight. The reaction was diluted with 5% aqueous $NaHCO_3$, extracted three times with EtOAc, dried (Na_2SO_4), the solvent removed i*n vacuo*. Chromatography (eluting with CH_2Cl_2 to CH_2Cl_2: EtOAc 7:3) gave **49** as a brown solid (7 mg, 14%). HPLC purity 99.8%. Mp 189-191 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) 9.02 (t, *J* = 1.8 Hz, 1H), 8.55 (m, 2H), 8.31 (dd, *J* = 7.3, 0.7 Hz, 1H), 8.24 (s, 1H), 8.15 (dd, *J* = 2.1, 0.7 Hz, 1H), 7.87 (t, *J* = 8.0 Hz, 1H), 7.63 (s, 1H), 6.93 (dd, *J* = 7.3, 2.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) 165.3 (C), 151.7 (C), 148.6 (C), 141.2 (CH), 141.1 (C), 138.0 (C), 134.3 (CH), 130.9 (CH), 129.4 (CH), 128.8 (CH), 124.1 (CH), 121.1 (CH), 119.6 (C), 117.1 (CH), 116.8 (CH), 105.7 (C). LCMS (APCI$^+$) 465 (MH^+ with ^{79}Br, 95%), 467 (MH^+ with ^{81}Br, 100%). HRMS (ESI$^+$) Calcd for $C_{16}H_{10}{}^{79}BrN_4O_4S_2$: 464.9321; found ($MH^+$) 464.9317.

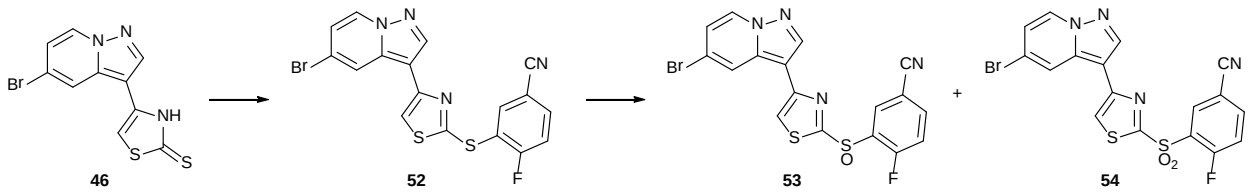
Synthesis of 4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)-2-(*o*-tolylsulfinyl)thiazole (51).



4-(5-Bromopyrazolo[1,5-*a*]pyridin-3-yl)-2-(*o*-tolylthio)thiazole (50). A solution of **46** (94 mg, 0.30 mmol), $Cu(OAc)_2$, (55 mg, 0.30 mmol), 1,10-phenanthroline (109 mg, 0.60 mmol) 2-tolylboronic acid (163 mg, 1.2 mmol) were dissolved in 1,2-dichloroethane (30 mL) and the mixture stirred at room temperature for 30 mins. The reaction mixture was refluxed for 48 h, and then diluted with CH_2Cl_2 and stirred vigorously with 0.5% aqueous $Na_4EDTA.xH_2O$ for 15 mins. The layers were separated, and then the organic layer was washed with water, dried (Na_2SO_4) and the solvent removed i*n vacuo*. Chromatography (eluting with CH_2Cl_2) gave **50** as a pale green oil (52 mg, 43%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.30-8.25 (m, 2H), 8.21 (s, 1H), 7.71 (d, *J* = 7.4 Hz, 1H), 7.45-7.38 (m, 2H), 7.29 (td, *J* = 7.4, 2.3 Hz, 1H), 7.12 (s, 1H), 6.86 (dd, *J* = 7.2, 2.2 Hz, 1H), 2.54 (s, 3H). ^{13}C NMR δ (100 MHz, $CDCl_3$) 166.9 (C), 159.3 (C), 148.7 (C), 142.5 (C), 140.9 (CH), 137.8 (C), 136.0 (CH), 131.3 (CH), 130.7 (CH), 129.1 (CH), 127.3 (CH), 121.7 (CH), 118.3 (C), 116.2 (CH), 110.6 (CH), 107.0 (C) 20.9 (CH_3).

4-(5-Bromopyrazolo[1,5-*a*]pyridin-3-yl)-2-(*o*-tolylsulfinyl)thiazole (51). MMPP (270 mg, 0.47 mmol) and water (one drop) were added to a solution **50** (37.5 mg, 0.093 mmol) in CH_2Cl_2 (8 mL). The reaction mixture was heated in a microwave (temperature profile: 0 – 1.5 mins ramp from room temperature to 60 °C; hold 1.5 mins - 2 h at 60 °C). After cooling to room temperature, the reaction was diluted with CH_2Cl_2, washed with 5% aqueous Na_2SO_3, water and brine, then dried (Na_2SO_4) and the solvent removed i*n vacuo*. Chromatography (eluting with CH_2Cl_2 to CH_2Cl_2: EtOAc 85:15) gave **51** as a pale green solid (10 mg, 25%). HPLC purity 98.6%. Mp 172-174 °C. ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.29 (dd, *J* = 7.3, 0.6 Hz, 1H), 8.25 (d, *J* = 2.1 Hz, 1H), 8.21 (s, 1H), 8.04 (m, 1H), 7.49 (s, 1H), 7.47-7.40 (m, 2H), 7.32 (m, 1H), 6.89 (dd, *J* = 7.3, 2.2 Hz, 1H), 2.71 (s, 3H). ^{13}C NMR δ (100 MHz, $CDCl_3$) 175.6 (C), 149.9 (C), 141.4 (C), 140.4 (CH), 137.6 (C), 136.0 (C), 131.3 (CH), 130.8 (CH), 128.8 (CH), 126.8 (CH), 123.2 (CH),120.9 (CH), 118.3 (C), 115.9 (CH), 114.2 (CH), 106.2 (C), 18.2 (CH_3). LCMS (APCI$^+$) 418 (MH^+ with ^{79}Br, 90%), 420 (MH^+ with ^{81}Br, 100%). HRMS (ESI$^+$) Calcd for $C_{17}H_{12}{}^{79}BrN_3NaOS_2$: 439.9497; found ($MNa^+$) 439.9496.

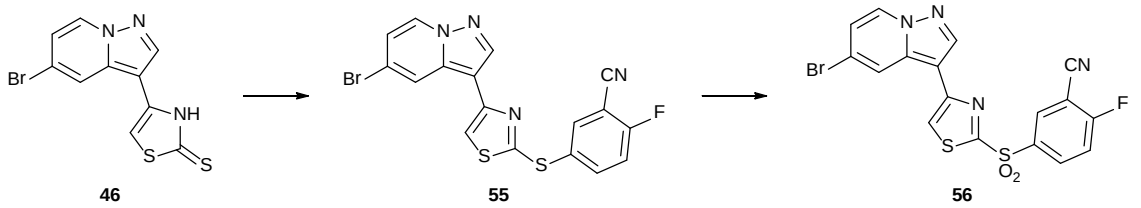
Synthesis of 3-((4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)thiazol-2-yl)sulfinyl)-4-fluoro-benzonitrile (53) and 3-((4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)thiazol-2-yl)sulfonyl)-4-fluorobenzonitrile (54).



3-((4-(5-Bromopyrazolo[1,5-*a*]pyridin-3-yl)thiazol-2-yl)thio)-4-fluorobenzonitrile (52). Reaction of **46** (50 mg, 0.15 mmol) and (5-cyano-2-fluorophenyl)boronic acid (98 mg, 0.64 mmol) by the same method as **50**, after chromatography (eluting with CH_2Cl_2) gave **52** as a yellow solid (46 mg, 72%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.29 (dd, *J* = 7.3, 0.7 Hz, 1H), 8.22 (s, 1H), 8.11 (dd, *J* = 2.1, 0.7 Hz, 1H), 7.95 (dd, *J* = 6.4, 2.1 Hz, 1H), 7.76 (ddd, *J* = 8.5, 4.6, 2.1, 1H), 7.35 (t, *J* = 8.5 Hz, 1H), 7.30 (s, 1H), 6.87 (dd, *J* = 7.3, 2.1 Hz, 1H). ^{13}C NMR δ (100 MHz, $CDCl_3$) 163.5 (C, d, *J* = 257 Hz), 159.2 (C), 148.8 (C), 140.3 (CH), 138.5 (CH, d, *J* = 2 Hz), 137.3 (C), 135.1 (CH, d, *J* = 9 Hz), 128.7 (CH), 121.5 (C, d, *J* = 20 Hz), 120.9 (CH) 118.1 (C), 117.2 (CH, d, *J* = 24 Hz), 116.6 (C), 115.8 (CH), 112.1 (CH), 109.3 (C, d, *J* = 3Hz), 106.3 (C). LCMS (APCI$^+$) 431 (MH^+ with ^{79}Br, 100%), 433 (MH^+ with ^{81}Br, 80%).

3-((4-(5-Bromopyrazolo[1,5-*a*]pyridin-3-yl)thiazol-2-yl)sulfinyl)-4-fluorobenzonitrile (53) and 3-((4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)thiazol-2-yl)sulfonyl)-4-fluorobenzonitrile (54). Reaction of **52** (100 mg, 0.23 mmol) by the same method as **49** for 3 weeks, after chromatography (eluting with CH_2Cl_2: EtOAc 4:1 then EtOAc) gave firstly **54** as a pale yellow solid (30 mg, 30%). HPLC purity 95.1%. ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.54 (dd, *J* = 6.2, 2.2 Hz, 1H), 8.32 (dd, *J* = 7.3, 0.7 Hz, 1H), 8.25 (s, 1H), 8.18 (dd, *J* = 2.1, 0.7 Hz, 1H), 7.99 (ddd, *J* = 8.6, 4.4, 2.2 Hz, 1H), 7.69 (s, 1H), 7.41 (t, *J* = 8.6 Hz, 1H), 6.94 (dd, *J* = 7.3, 2.1 Hz, 1H). ^{13}C NMR δ (100 MHz, $CDCl_3$) 164.13 (C), 161.5 (C, d, *J* = 269 Hz), 150.7 (C), 140.4 (CH), 140.0 (CH, d, *J* = 10 Hz), 138.0 (C), 137.6 (C), 135.0 (CH), 128.9 (CH), 120.7 (CH), 119.3 (C), 118.7 (CH, d, *J* = 23 Hz), 117.1 (CH), 116.4 (CH), 115.5 (C), 109.6 (C, d, *J* = 4 Hz), 105.2 (C). LCMS (APCI$^+$) 463 (MH^+ with ^{79}Br, 70%), 465 (MH^+ with ^{81}Br, 100%). HRMS (APCI$^+$) Calcd for $C_{17}H_9{}^{79}BrFN_4O_2S_2$: 462.9329; found ($MH^+$) 462.9330. Followed by **53** as a pale yellow solid (30 mg, 30%). HPLC purity 92.5%. ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.34-8.30 (m, 2H), 8.26 (dd, *J* = 2.1, 0.7 Hz, 1H), 8.23 (s, 1H), 7.88 (ddd, *J* = 8.5, 4.7, 2.1 Hz, 1H) 7.60 (s, 1H), 7.39 (t, *J* = 8.5 Hz, 1H), 6.93 (dd, *J* = 7.3, 2.1 Hz, 1H). ^{13}C NMR δ (100 MHz, $CDCl_3$) 172.7 (C), 161.1 (C, d, *J* = 261 Hz), 151.1 (C), 141.0 (CH), 138.2 (C), 138.0 (CH, d, *J* = 9 Hz), 133.8 (C, d, *J* = 19 Hz), 130.3 (CH, d, *J* = 3 Hz), 129.5 (CH), 121.6 (CH), 119.3 (C), 118.1 (CH, d, *J* = 22 Hz), 116.9 (C), 116.7 (CH), 115.6 (CH), 110.7 (C, d, *J* = 4 Hz), 106.5 (C). LCMS (APCI$^+$) 447 (MH^+ with ^{79}Br, 70%), 449 (MH^+ with ^{81}Br, 100%). HRMS (APCI$^+$) Calcd for $C_{17}H_9{}^{79}BrFN_4OS_2$: 446.9380; found ($MH^+$) 446.9373.

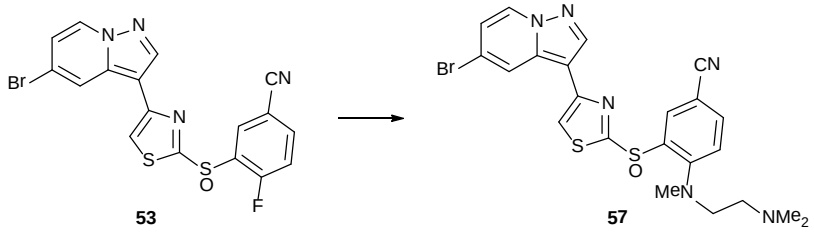
Synthesis of 5-((4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)thiazol-2-yl)sulfonyl)-2-fluoro-benzonitrile (56).



5-((4-(5-Bromopyrazolo[1,5-*a*]pyridin-3-yl)thiazol-2-yl)thio)-2-fluorobenzonitrile (55). Reaction of **46** (100 mg, 0.32 mmol) and (3-cyano-4-fluorophenyl)boronic acid (210 mg, 1.28 mmol) by the same method as **50**, after chromatography (on alumina, eluting with hexanes to hexanes: CH_2Cl_2 4:1) gave **55** as a white solid (100 mg, 78%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.29 (dd, *J* = 7.3, 0.7 Hz, 1H), 8.22 (s, 1H), 8.14 (dd, *J* = 2.1, 0.7 Hz, 1H), 7.98-7.91 (m, 2H), 7.34 (dd, *J* = 9.4, 8.4 Hz, 1H), 7.27 (s, 1H), 6.88 (dd, *J* = 7.3, 2.1 Hz, 1H). LCMS (APCI$^+$) 431 (MH^+ with ^{79}Br, 100%), 433 (MH^+ with ^{81}Br, 80%).

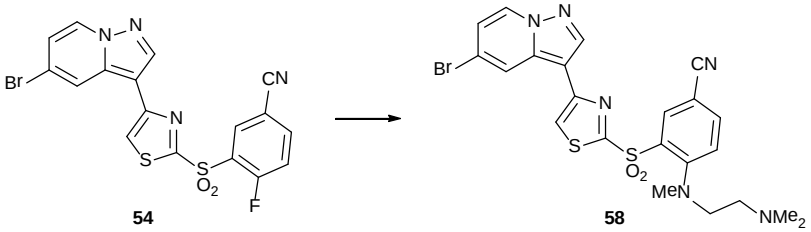
5-((4-(5-Bromopyrazolo[1,5-*a*]pyridin-3-yl)thiazol-2-yl)sulfonyl)-2-fluorobenzonitrile (56). Reaction of **55** (80 mg, 0.19 mmol) by the same method as **49**, gave **56** as a yellow solid (80 mg, 93%). HPLC purity 92.9%. Mp 199-202 °C. ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.49-8.41 (m, 2H), 8.32 (dd, *J* = 7.3, 0.7 Hz, 1H), 8.24 (s, 1H), 8.14 (dd, *J* = 2.1, 0.7 Hz, 1H), 7.63 (s, 1H), 7.51 (dd, *J* = 9.5, 8.1 Hz, 1H), 6.95 (dd, *J* = 7.3, 2.1 Hz, 1H). LCMS (APCI$^+$) 463 (MH^+ with ^{79}Br, 70%), 465 (MH^+ with ^{81}Br, 100%). HRMS (APCI$^+$) Calcd for $C_{17}H_9{}^{79}BrFN_4O_2S_2$: 462.9329; found ($MH^+$) 462.9327.

Synthesis of 3-((4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)thiazol-2-yl)sulfinyl)-4-((2-(dimethylamino)ethyl)(methyl)amino)benzonitrile (57).



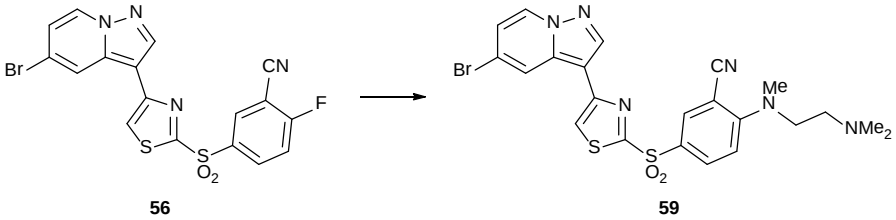
A solution of **53** (20 mg, 0.047 mmol) and *N*,*N*,*N'*-trimethylethylenediamine (28 mg, 0.28 mmol) in THF (10 mL) was stirred overnight at room temperature. The solvent was removed *in vacuo*. Chromatography (on alumina, eluting with CH_2Cl_2: EtOH 95:5) gave **57** as a pale green oil (21 mg, 86%). HPLC purity 95.5%. ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.32 (d, *J* = 2.0 Hz, 1H), 8.31 (dd, *J* = 7.3, 0.7 Hz, 1H), 8.23 (m, 2H), 7.63 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.54 (s, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 6.91 (dd, *J* = 7.3, 2.2 Hz, 1H), 3.53 (m, 2H), 3.13 (s, 3H), 2.50 (m, 2H), 2.17 (s, 6H). ^{13}C NMR δ (100 MHz, $CDCl_3$) 174.8 (C), 152.8 (C), 149.8 (C), 140.5 (CH), 137.3 (C), 135.3 (CH), 133.9 (C), 130.3 (CH), 128.9 (CH), 120.7 (CH), 118.6 (CH), 118.4 (C), 117.9 (C), 116.9 (CH), 114.7 (CH), 106.0 (C), 103.6 (C), 56.2 (CH_2), 54.2 (CH_2), 45.2 (CH_3), 41.6 (CH_3). LCMS (APCI$^+$) 529 (MH^+ with ^{79}Br, 100%), 531 (MH^+ with ^{81}Br, 90%). HRMS (ESI$^+$) Calcd for $C_{22}H_{22}{}^{79}BrN_6OS_2$: 529.0474; found ($MH^+$) 529.0478.

Synthesis of 3-((4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)thiazol-2-yl)sulfonyl)-4-((2-(dimethylamino)ethyl)(methyl)amino)benzonitrile (58).



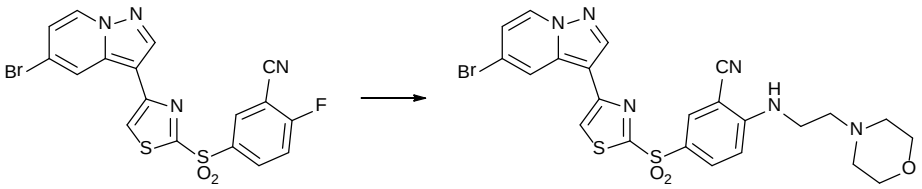
Reaction of **54** (20 mg, 0.043 mmol) and *N*,*N*,*N*'-trimethylethylenediamine (28 mg, 0.278 mmol) by the same method as **57**, after chromatography (on alumina, eluting with CH_2Cl_2: EtOH 95:5) gave **58** as a pale green solid (20 mg, 88%). HPLC purity 92.1%. ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.63 (d, *J* = 2.0 Hz, 1H), 8.28 (dd, *J* = 7.3, 0.7 Hz, 1H), 8.22 (s, 1H), 7.91 (dd, *J* = 2.1, 0.7 Hz, 1H), 7.86 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.59 (s, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 6.89 (dd, *J* = 7.3, 2.1 Hz, 1H), 3.15 (m, 2H), 2.70 (s, 3H), 2.14 (m, 2H), 2.02 (s, 6H). ^{13}C NMR δ (100 MHz, $CDCl_3$) 166.4 (C), 156.7 (C), 149.5 (C), 140.4 (CH), 137.6 (CH), 137.6 (C), 136.2 (CH), 133.8 (C), 129.8 (CH), 123.9 (CH), 120.6 (CH), 118.9 (C), 116.9 (C), 116.2 (CH), 115.5 (CH), 106.8 (C), 105.3 (C), 56.0 (CH_2), 54.6 (CH_2), 49.9 (CH_3), 42.6 (CH_3). LCMS (APCI$^+$) 545 (MH^+ with ^{79}Br, 100%), 547 (MH^+ with ^{81}Br, 90%). HRMS (ESI$^+$) Calcd for $C_{22}H_{22}{}^{79}BrN_6O_2S_2$: 545.0424; found ($MH^+$) 545.0418.

Synthesis of 5-((4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)thiazol-2-yl)sulfonyl)-2-((2-(dimethylamino)ethyl)(methyl)amino)benzonitrile (59).



Reaction of **56** (25 mg, 0.055 mmol) and *N*,*N*,*N*'-trimethylethylenediamine (28 mg, 0.278 mmol) by the same method as **57**, after chromatography (on alumina, eluting with CH_2Cl_2: EtOH 95:5) gave **59** as a pale green solid (29 mg, 98%). HPLC purity 92.9%. ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.31 (dd, *J* = 7.3, 0.7 Hz, 1H), 8.27-8.20 (m, 3H), 8.07 (dd, *J* = 9.3, 2.4 Hz, 1H), 7.55 (s, 1H), 6.98 (d, *J* = 9.3 Hz, 1H), 6.92 (dd, *J* = 7.3, 2.1 Hz, 1H), 3.71 (t, *J* = 7.0 Hz, 2H), 3.27 (s, 3H), 2.62 (t, *J* = 7.0 Hz, 2H), 2.26 (s, 6H). LCMS (APCI$^+$) 545 (MH^+ with ^{79}Br, 100%), 547 (MH^+ with ^{81}Br, 90%). HRMS (ESI$^+$) Calcd for $C_{22}H_{22}{}^{79}BrN_6O_2S_2$: 545.0424; found ($MH^+$) 545.0432.

Synthesis of 5-((4-(5-bromopyrazolo[1,5-*a*]pyridin-3-yl)thiazol-2-yl)sulfonyl)-2-((2-morpholinoethyl)amino)benzonitrile (60).



Reaction of **56** (15 mg, 0.033 mmol) and 4-(2-aminoethyl)morpholine (22 mg, 0.16 mmol) by the same method as **57**, after chromatography (on alumina, eluting with CH_2Cl_2: EtOH 98:2) gave **60** as a pale green solid (29 mg, 17%). HPLC purity 94%. ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.31 (dd, *J* = 7.3, 0.7 Hz, 1H), 8.25-8.21 (m, 2H), 8.17 (d, *J* = 2.2 Hz, 1H), 8.14 (ddd, *J* = 9.0, 2.2, 0.5 Hz, 1H), 7.54 (s, 1H), 6.92 (dd, *J* = 7.3, 2.2 Hz, 1H), 6.78 (d, *J* = 9.0 Hz, 1H), 6.27 (s, 1H), 3.74 (m, 4H), 3.31 (m, 2H), 2.71 (m, 2H), 2.50 (m, 4H). LCMS ($APCI^+$) 573 (MH^+ with ^{79}Br, 100%), 575 (MH^+ with ^{81}Br, 90%). HRMS (ESI^+) Calcd for $C_{23}H_{22}{}^{79}BrN_6O_3S_2$: 573.0373; found ($MH^+$) 573.0366.

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