Supporting Information

6-Nitro-2,3-dihydroimidazo[2,1-*b*][1,3]thiazoles: facile synthesis and comparative appraisal against tuberculosis and neglected tropical diseases

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Table S1. Complete *in vitro* antitubercular and antiparasitic data for nitroimidazothiazoles, selected nitroimidazooxazoles, and nitrotriazole-related analogues

	MIC[a,b] (μM)		IC_{50}[c,b] (μM)			
compd	MABA	LORA	*L. inf*	*T. cruzi*	*T. bruc*	MRC-5
8	4.4 ± 2.5	15 ± 1	64 ± 0	0.87 ± 0.20	>64	>64
9	4.4 ± 2.0	3.4 ± 0.3	48 ± 16	0.62 ± 0.12	6.2 ± 2.5	>64
10	14 ± 8	43 ± 4	0.11 ± 0.03	0.60 ± 0.23	>64	>64
11	11 ± 4	63 ± 8	1.5 ± 0	6.9 ± 1.2	61 ± 3	>64
12	0.24 ± 0.03	7.9 ± 4.5	57 ± 8	0.67 ± 0.12	56 ± 9	>64
13	0.20 ± 0.05	5.8 ± 1.3	>64	0.57 ± 0.05	>64	43 ± 21
14	6.1 ± 1.6	51 ± 1	>64	1.6 ± 0.5	>64	>64
15	3.2 ± 0.1	12 ± 0	56 ± 14	0.28 ± 0.14	31 ± 20	64 ± 1
16	0.24 ± 0.15	34 ± 6	0.28 ± 0.14	0.42 ± 0.06	60 ± 2	60 ± 4
17	0.30 ± 0.10	50 ± 13	7.3 ± 0.7	3.2 ± 1.6	60 ± 4	>64
18	>128	>128	>64	1.6 ± 1.0	>64	>64
19	>128	>128	>64	3.0 ± 0.2	>64	>64
20	>128	>128	56 ± 14	0.08 ± 0.03	0.33 ± 0.19	>64
21	>128	>128	>64	0.49 ± 0.07	2.3 ± 0.1	>64
22	>128	21 ± 9	>64	0.97 ± 0.41	>64	>64
23	>128	>128	56 ± 14	0.09 ± 0.01	0.98 ± 0.53	62 ± 3
24	55 ± 5	59 ± 6	>64	7.3 ± 0.2	22 ± 1	47 ± 17
25	>128	>128	55 ± 9	19 ± 6	53 ± 11	>64
26	1.5 ± 0.4	>64	>64	0.15 ± 0.01	>64	>64
27	1.1 ± 0.6	>64	56 ± 14	0.04 ± 0	1.1 ± 0.5	>64
28	1.4 ± 0.4	>64	56 ± 14	0.14 ± 0.05	2.8 ± 0.4	>64
29	4.5 ± 2.6	8.2 ± 3.9	>64	0.85 ± 0.41	>64	>64
30	>128	29 ± 4	56 ± 14	1.6 ± 0.6	11 ± 5	56 ± 8
31	2.0 ± 0.9	73 ± 46	0.15 ± 0.03	1.5 ± 0.8	>64	>64
32	0.96 ± 0.45	>128	3.4 ± 0.6	3.1 ± 1.4	>64	19 ± 11
33	0.49 ± 0.20	10 ± 5	>64	0.38 ± 0.19	>64	>64
34	0.76 ± 0.23	5.3 ± 2.3	>64	0.14 ± 0.02	>64	>64
35	0.077 ± 0.026	55 ± 2	0.33 ± 0.03	1.8 ± 1.1	>64	>64
36	0.79 ± 0.40	24 ± 10	1.3 ± 0.3	1.9 ± 0.1	28 ± 8	>64
37	>128	>128	>64	2.3 ± 1.3	>64	>64
38	26 ± 2	58 ± 4	>64	1.7 ± 0.3	41 ± 5	>64
39	>128	>128	55 ± 9	0.19 ± 0.05	0.36 ± 0.12	53 ± 12
40	>128	25 ± 1	42 ± 22	0.75 ± 0.29	0.98 ± 0.43	51 ± 13
41	14 ± 2	15 ± 1	>64	1.8 ± 1.1	>64	>64
42	>128	>128	55 ± 9	0.46 ± 0.13	3.8 ± 1.8	45 ± 19
43	0.21 ± 0.11	>64	>64	0.21 ± 0.02	>64	>64
44	0.12 ± 0.07	46 ± 12	>64	0.035 ± 0.005	52 ± 21	>64
45	0.063 ± 0.019	>128	45 ± 19	0.085 ± 0.005	>64	>64
46	0.043 ± 0.005	11 ± 3	3.3 ± 0.1	0.52 ± 0.15	9.2 ± 1.2	>64
47	0.081 ± 0.040	>128	11 ± 0	1.5 ± 0.6	1.0 ± 0.3	>64
48	0.088 ± 0.035	64 ± 31	5.3 ± 1.8	0.89 ± 0.46	0.85 ± 0.15	>64
49	0.073 ± 0.010	71 ± 39	53 ± 19	0.055 ± 0.005	59 ± 9	>64

50	0.051 ± 0.031	26 ± 1	13 ± 2	0.40 ± 0.08	3.4 ± 0.8	>64
51	10 ± 1	>128				
52	16 ± 7	116 ± 10	18 ± 0	52 ± 12	>64	>64
53	21 ± 8	>128	53 ± 15	0.49 ± 0.05	10 ± 4	>64
54	>128	>128	>64	0.59 ± 0.11	20 ± 10	>64
55	6.4 ± 1.2	61 ± 3	16 ± 5	0.60 ± 0.10	7.1 ± 1.7	1.2 ± 0.7
56	9.3 ± 1.9	90 ± 26	0.90 ± 0.53	1.2 ± 0.6	3.0 ± 1.4	0.74 ± 0.34
57	2.2 ± 1.0	27 ± 1	1.3 ± 0.6	1.3 ± 0.7	2.1 ± 0.7	0.42 ± 0.23
58	24 ± 5	>128	>64	6.2 ± 0.1	34 ± 9	42 ± 10
59	46 ± 7	>128	>64	13 ± 1	60 ± 6	43 ± 3

[a]Minimum inhibitory concentration against *M. tb*, determined under aerobic (MABA) or hypoxic (LORA) conditions. [b]Each value is the mean of at least two independent determinations. [c]IC_{50} values for inhibition of growth of the parasites *Leishmania infantum*, *Trypanosoma cruzi*, and *Trypanosoma brucei*, or for cytotoxicity toward human lung fibroblasts (MRC-5 cells).

Representative experimental for the compounds of Tables 1 and 2

Combustion analyses were performed by the Campbell Microanalytical Laboratory, University of Otago, Dunedin, New Zealand. Melting points were determined using an Electrothermal IA9100 melting point apparatus, and are as read. NMR spectra were measured on a Bruker Avance 400 spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C and are referenced to Me_4Si or solvent resonances. Chemical shifts and coupling constants are recorded in units of ppm and hertz, respectively. High-resolution electron impact (HREIMS), chemical ionisation (HRCIMS), and fast atom bombardment (HRFABMS) mass spectra were determined on a VG-70SE mass spectrometer at nominal 5000 resolution. Low-resolution atmospheric pressure chemical ionisation (APCI) mass spectra were obtained for organic solutions using a ThermoFinnigan Surveyor MSQ mass spectrometer, connected to a Gilson autosampler. Optical rotations were measured on a Schmidt + Haensch Polartronic NH8 polarimeter. Column chromatography was performed on silica gel (Merck 230-400 mesh). Thin-layer chromatography was carried out on aluminium-backed silica gel plates (Merck 60 F_{254}), with visualization of components by UV light (254 nm), I_2, or $KMnO_4$ staining. Tested compounds (including batches screened *in vivo*) were ≥ 95% pure, as determined by combustion analysis (results within 0.4% of theoretical values) and/or by HPLC conducted on an Agilent 1100 system, using a 150 mm x 3.2 mm Altima 5 µm reversed phase C18 column with diode array detection. Preparative chiral HPLC was carried out on a Gilson Unipoint system (322-H pump, 156 UV/vis detector) by employing a 250 mm x 20 mm CHIRALCEL OD 10 µm semipreparative column, while chiral purity was assessed using a 250 mm x 4.6 mm CHIRALCEL OD 10 µm analytical column.

Synthesis of 8 (Scheme 1A):

Procedure A: *tert*-Butyldimethyl(thiiran-2-ylmethoxy)silane (61). A solution of *tert*-butyldimethyl(oxiran-2-ylmethoxy)silane (**60**) (1.00 g, 5.31 mmol) in CH_2Cl_2 (75 mL) was treated with thiourea on silica gel[1] (15.0 g, containing 10.0 mmol of thiourea). The mixture was stirred at 20 °C for 3 h and then filtered, washing with CH_2Cl_2, and the filtrate was concentrated under reduced pressure (at 20 °C). The resulting oil was chromatographed on silica gel, eluting with pentane, to give **61** (406 mg, 37%) as a volatile colourless oil; ^{1}H NMR ($CDCl_3$) δ 3.88 (ddd, *J* = 11.1, 5.2, 0.7 Hz, 1 H), 3.55 (dd, *J* = 11.1, 6.7 Hz, 1 H), 3.05 (tt, *J* = 6.4, 5.4 Hz, 1 H), 2.49 (dt, *J* = 6.2, 0.9 Hz, 1 H), 2.21 (dd, *J* = 5.4, 1.1 Hz, 1 H), 0.91 (s, 9 H), 0.08 (2 s, 2 x 3 H); HREIMS calcd for $C_9H_{20}OSSi$ *m*/*z* (M^+) 204.1004, found 204.1014.

Procedure B: 2-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]thiazole (62). A mixture of thiirane **61** (393 mg, 1.92 mmol), 2-bromo-4-nitro-1*H*-imidazole (408 mg, 2.13 mmol), and DIPEA (1.70 mL, 9.76 mmol) in a sealed vial was stirred at 109 °C for 21 h. The resulting cooled mixture was dissolved in CH_2Cl_2 and added to ice/aqueous $NaHCO_3$ (50 mL), then extracted with CH_2Cl_2 (5 x 50 mL). The extracts were evaporated to dryness under reduced pressure and the residue was chromatographed on silica gel. Elution with 0-20% EtOAc/petroleum ether first gave foreruns, and then further elution with 20% EtOAc/petroleum ether and CH_2Cl_2 gave **62** (448 mg, 74%) as a pale yellow solid: mp (CH_2Cl_2/hexane) 116-118 °C; ^{1}H NMR ($CDCl_3$) δ 7.78 (s, 1 H), 4.37-4.23 (m, 3 H), 3.88 (dd, *J* = 10.7, 5.1 Hz, 1 H), 3.74 (dd, *J* = 10.6, 7.6 Hz, 1 H), 0.87 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H). Anal. ($C_{12}H_{21}N_3O_3SSi$) C, H, N.

(6-Nitro-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-2-yl)methanol (63). Silyl ether **62** (425 mg, 1.35 mmol) was treated with a solution of 1% HCl in 95% EtOH[2] (21.5 mL, 5.16 mmol). The mixture was stirred at 20 °C for 7 h and then neutralised with a solution of NH_3 in MeOH (1.7 mL of 7 M). The resulting mixture was evaporated to dryness under reduced pressure (at 30 °C) and the residue was chromatographed on silica gel. Elution with 0-10% EtOAc/CH_2Cl_2 first gave foreruns and then further elution with 10-25% EtOAc/CH_2Cl_2 gave **63** (271 mg, 100%) as a bright yellow solid: mp (MeOH/CH_2Cl_2/hexane) 149-151 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.42 (s, 1 H), 5.40 (br s, 1 H), 4.58-4.48 (m, 1 H), 4.37 (dd, *J* = 12.0, 7.6 Hz, 1 H), 4.22 (dd, *J* = 12.0, 4.8 Hz, 1 H), 3.72-3.58 (m, 2 H). Anal. ($C_6H_7N_3O_3S$) C, H, N.

Procedure C: 6-Nitro-2-({[4-(trifluoromethoxy)benzyl]oxy}methyl)-2,3-dihydroimidazo[2,1-*b*][1,3]thiazole (8). A solution of alcohol **63** (41.5 mg, 0.206 mmol) in anhydrous DMF (3 mL) under N_2 at 0 °C was treated with 60% NaH (29 mg, 0.725 mmol), then quickly degassed, and resealed under N_2. 4-(Trifluoromethoxy)benzyl bromide (66 µL, 0.413 mmol) was added, and the mixture was stirred at 20 °C for 1 h. The resulting mixture was cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (50 mL), and extracted with EtOAc (7 x 50 mL). The extracts were washed with brine (50 mL) and then evaporated to dryness under reduced pressure (at 30 °C), and the residue was chromatographed on silica gel. Elution with 3:1 CH_2Cl_2/petroleum ether first gave foreruns, and then further elution with CH_2Cl_2 gave **8** (54 mg, 70%) as a light yellow solid: mp (CH_2Cl_2/hexane) 90-91 °C; ^{1}H NMR ($CDCl_3$) δ 7.77 (s, 1 H), 7.32 (br d, *J* = 8.6 Hz, 2 H), 7.21 (br d, *J* = 8.0 Hz, 2 H), 4.56 (s, 2 H), 4.52-4.43 (m, 1 H), 4.31 (dd, *J* = 11.5, 6.5 Hz, 1 H), 4.27 (dd, *J* = 11.5, 5.0 Hz, 1 H), 3.75 (dd, *J* = 9.8, 5.7 Hz, 1 H), 3.67 (dd, *J* = 9.8, 8.1 Hz, 1 H). Anal. ($C_{14}H_{12}F_3N_3O_4S$) C, H, N.

Syntheses of 12 and 51 (Scheme 1A):

***tert*-Butyldimethyl[(2-methylthiiran-2-yl)methoxy]silane (65).** Reaction of *tert*-butyldimethyl[(2-methyloxiran-2-yl)methoxy]silane[3] (**64**) with thiourea on silica gel in CH_2Cl_2, using procedure A for 2.5 h, followed by chromatography of the product on silica gel, eluting with petroleum ether, gave **65** (77%) as a slightly volatile colourless oil; ^{1}H NMR ($CDCl_3$) δ 3.80 (dd, *J* = 10.5, 1.2 Hz, 1 H), 3.53 (d, *J* = 10.5 Hz, 1 H), 2.40 (d, *J* = 0.6 Hz, 1 H), 2.34 (t, *J* = 1.1 Hz, 1 H), 1.62 (s, 3 H), 0.90 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H); HRFABMS calcd for $C_{10}H_{23}OSSi$ *m*/*z* $[M + H]^+$ 219.1239, found 219.1245.

2-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]thiazole (66). Reaction of thiirane **65** with 2-bromo-4-nitro-1*H*-imidazole and DIPEA, using procedure B for 15 h, followed by chromatography of the product on silica gel, eluting with 0-15% EtOAc/petroleum ether (foreruns) and then with 5:1 CH_2Cl_2/petroleum ether, gave **66** (83%) as a cream solid: mp (CH_2Cl_2/pentane) 141-143 °C; ^{1}H NMR ($CDCl_3$) δ 7.76 (s, 1 H), 4.33 (d, *J* = 11.4 Hz, 1 H), 3.87 (d, *J* = 11.4 Hz, 1 H), 3.71 (s, 2 H), 1.68 (s, 3 H), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H). Anal. ($C_{13}H_{23}N_3O_3SSi$) C, H, N.

(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-2-yl)methanol (51). A solution of silyl ether **66** (459 mg, 1.39 mmol) in anhydrous THF (15 mL) was treated with TBAF (1.55 mL of a 1 M solution in THF, 1.55 mmol). The mixture was stirred at 20 °C for 4 h and then concentrated under reduced pressure, treated with ice/aqueous $NaHCO_3$ (50 mL), and extracted with EtOAc (6 x 50 mL). The extracts were washed with brine (50 mL) and then evaporated to dryness under reduced pressure (at 30 °C), and then the residue was chromatographed on silica gel. Elution with 0-3% EtOAc/CH_2Cl_2 first gave foreruns and then

further elution with 10% EtOAc/CH_2Cl_2 gave **51** (289 mg, 96%) as a pale yellow solid: mp (THF/CH_2Cl_2/hexane) 161-163 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.42 (s, 1 H), 5.57 (t, *J* = 5.5 Hz, 1 H), 4.30 (d, *J* = 12.0 Hz, 1 H), 4.07 (d, *J* = 12.0 Hz, 1 H), 3.61 (dd, *J* = 11.4, 5.6 Hz, 1 H), 3.57 (dd, *J* = 11.4, 5.5 Hz, 1 H), 1.60 (s, 3 H). Anal. ($C_7H_9N_3O_3S$) C, H, N.

2-Methyl-6-nitro-2-({[4-(trifluoromethoxy)benzyl]oxy}methyl)-2,3-dihydroimidazo[2,1-*b*][1,3]thiazole (12). Reaction of alcohol **51** with 4-(trifluoromethoxy)benzyl bromide (1.4 equiv) and NaH (1.5 equiv), using procedure C for 6 h, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2, gave **12** (81%) as a cream solid: mp (CH_2Cl_2/hexane) 98-100 °C; ^{1}H NMR ($CDCl_3$) δ 7.76 (s, 1 H), 7.31 (br d, *J* = 8.8 Hz, 2 H), 7.20 (br d, *J* = 8.6 Hz, 2 H), 4.58 (d, *J* = 12.5 Hz, 1 H), 4.55 (d, *J* = 12.5 Hz, 1 H), 4.36 (d, *J* = 11.5 Hz, 1 H), 3.93 (d, *J* = 11.5 Hz, 1 H), 3.64 (d, *J* = 9.6 Hz, 1 H), 3.62 (d, *J* = 9.7 Hz, 1 H), 1.74 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 150.6, 149.7, 149.2, 136.0, 129.2 (2 C), 121.3 (2 C), 120.6 (q, J_{C-F} = 257.3 Hz), 117.7, 75.5, 72.9, 62.7, 55.1, 23.9. Anal. ($C_{15}H_{14}F_3N_3O_4S$) C, H, N.

Synthesis of 13 (Scheme 1A):

(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-2-yl)methyl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (67). (2*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyl chloride (0.230 mL, 1.23 mmol) was added to a solution of alcohol **51** (216 mg, 1.00 mmol) and DMAP (12.9 mg, 0.106 mmol) in anhydrous pyridine (3 mL) under N_2. The mixture was stirred at 20 °C for 6 h and then concentrated under a stream of N_2. The resulting oil was diluted with ice-water (50 mL) and then extracted with CH_2Cl_2 (4 x 50 mL). The extracts were evaporated to dryness under reduced pressure (at 30 °C) and then the residue was chromatographed on silica gel. Elution with 1:1 and 3:1 CH_2Cl_2/petroleum ether first gave foreruns, and then further elution with 3:1 CH_2Cl_2/petroleum ether and CH_2Cl_2 gave **67** (427 mg, 99%) as a cream solid (a 1:1 mixture of diastereomers): mp (CH_2Cl_2/pentane) 112-114 °C; ^{1}H NMR ($CDCl_3$) δ 7.71, 7.53 (2 s, 2 x 0.5 H), 7.50-7.38 (m, 5 H), 4.52 (d, *J* = 11.6 Hz, 0.5 H), 4.51 (d, *J* = 11.5 Hz, 0.5 H), 4.41 (d, *J* = 11.5 Hz, 0.5 H), 4.39 (d, *J* = 11.6 Hz, 0.5 H), 4.10 (d, *J* = 11.9 Hz, 0.5 H), 4.05 (d, *J* = 11.7 Hz, 0.5 H), 3.93 (d, *J* = 11.8 Hz, 0.5 H), 3.93 (d, *J* = 11.7 Hz, 0.5 H), 3.49 (br s, 3 H), 1.71, 1.70 (2 s, 2 x 1.5 H); HRFABMS calcd for $C_{17}H_{17}F_3N_3O_5S$ *m/z* $[M + H]^+$ 432.0841, found 432.0843.

[(2*R*)-2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-2-yl]methyl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (68) and [(2*S*)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-2-yl]methyl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (69). Mosher's ester **67** (552 mg) was separated into pure diastereomers by preparative chiral HPLC (using a CHIRALCEL OD column and an isocratic solvent system of 40% *i*PrOH in hexane, at a flow rate of 10 mL/min) to first give **68** (231 mg, 42%) as a cream solid: mp (CH_2Cl_2/pentane) 108-110 °C; ^{1}H NMR ($CDCl_3$) δ 7.53 (s, 1 H), 7.48-7.38 (m, 5 H), 4.52 (d, *J* = 11.6 Hz, 1 H), 4.39 (d, *J* = 11.6 Hz, 1 H), 4.05 (d, *J* = 11.7 Hz, 1 H), 3.93 (d, *J* = 11.7 Hz, 1 H), 3.48 (q, J_{H-F} = 1.0 Hz, 3 H), 1.70 (s, 3 H); $[\alpha]^{22}_D$ -79 (*c* 1.00, $CHCl_3$); HRFABMS calcd for $C_{17}H_{17}F_3N_3O_5S$ *m/z* $[M + H]^+$ 432.0841, found 432.0833; HPLC purity: 100%.

Second eluted was **69** (222 mg, 40%) as a cream solid: mp (CH_2Cl_2/hexane) 141-143 °C; ^{1}H NMR ($CDCl_3$) δ 7.71 (s, 1 H), 7.50-7.39 (m, 5 H), 4.51 (d, *J* = 11.5 Hz, 1 H), 4.41 (d, *J* = 11.5 Hz, 1 H), 4.10 (d, *J* = 11.8 Hz, 1 H), 3.93 (d, *J* = 11.8 Hz, 1 H), 3.49 (br s, 3 H), 1.71 (s, 3 H); $[\alpha]^{22}_D$ 28 (*c* 1.00, $CHCl_3$); HRFABMS calcd for $C_{17}H_{17}F_3N_3O_5S$ *m/z* $[M + H]^+$ 432.0841, found 432.0837; HPLC purity: 100%.

[(2*R*)-2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-2-yl]methanol (70). A stirred solution of ester **68** (226 mg, 0.524 mmol) in MeOH (20.7 mL) was treated with K_2CO_3 (81 mg, 0.586 mmol) and then water (2.3 mL) was added dropwise. The mixture was stirred at 20 °C for 3.5 h and then cooled (CO_2/acetone) and neutralised with 0.1 M HCl (12 mL) and 7 M NH_3 in MeOH (0.4 mL). The resulting mixture was evaporated to dryness under reduced pressure (at 20 °C) and then the residue was chromatographed on silica gel. Elution with 0-5% EtOAc/CH_2Cl_2 first gave foreruns and then further elution with 10-15% EtOAc/CH_2Cl_2 gave **70** (113 mg, 100%) as a light yellow solid: mp (MeOH/CH_2Cl_2/hexane) 161-163 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.42 (s, 1 H), 5.57 (t, *J* = 5.0 Hz, 1 H), 4.30 (d, *J* = 12.0 Hz, 1 H), 4.07 (d, *J* = 12.0 Hz, 1 H), 3.61 (dd, *J* = 11.5, 5.1 Hz, 1 H), 3.57 (dd, *J* = 11.2, 4.8 Hz, 1 H), 1.60 (s, 3 H); $[\alpha]^{24}_D$ -36 (*c* 1.00, MeOH). Anal. ($C_7H_9N_3O_3S$) C, H, N.

(2*R*)-2-Methyl-6-nitro-2-({[4-(trifluoromethoxy)benzyl]oxy}methyl)-2,3-dihydroimidazo[2,1-*b*][1,3]thiazole (13). Reaction of alcohol **70** with 4-(trifluoromethoxy)-benzyl bromide (2.5 equiv) and NaH (2.9 equiv), using procedure C for 1.5 h, followed by chromatography of the product on silica gel, eluting with 2:1 CH_2Cl_2/petroleum ether (foreruns) and then with 3:1 CH_2Cl_2/petroleum ether and CH_2Cl_2, gave **13** (59%) as a cream solid: mp (CH_2Cl_2/pentane) 73-75 °C; ^{1}H NMR ($CDCl_3$) δ 7.74 (s, 1 H), 7.30 (br d, *J* = 8.6 Hz, 2 H), 7.20 (br d, *J* = 8.1 Hz, 2 H), 4.56 (s, 2 H), 4.34 (d, *J* = 11.4 Hz, 1 H), 3.92 (d, *J* = 11.5 Hz, 1 H), 3.64 (d, *J* = 9.7 Hz, 1 H), 3.61 (d, *J* = 9.6 Hz, 1 H), 1.74 (s, 3 H); $[\alpha]^{24}_D$ -39 (*c* 1.00, $CHCl_3$). Anal. ($C_{15}H_{14}F_3N_3O_4S$) C, H, N.

Synthesis of 18, 19 and 22 (Scheme 1B):

Procedure D: 2-Methyl-6-nitro-2-({[4-(trifluoromethoxy)benzyl]oxy}methyl)-2,3-dihydroimidazo[2,1-*b*][1,3]thiazole 1-oxide (18 and 19) and 2-methyl-6-nitro-2-({[4-(trifluoromethoxy)benzyl]oxy}methyl)-2,3-dihydroimidazo[2,1-*b*][1,3]thiazole 1,1-dioxide (22). 3-Chloroperoxybenzoic acid (403 mg of 50%, 1.17 mmol) was added to a mixture of thiazole **12** (150 mg, 0.385 mmol) and disodium hydrogen phosphate (248 mg, 1.75 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at 20 °C for 22 h and then added to an ice-cold aqueous solution of sodium sulphite (50 mL of 10%) and extracted with CH_2Cl_2 (50 mL) and EtOAc (3 x 50 mL). The extracts were sequentially washed with ice-cold aqueous sodium sulphite solution (50 mL of 10%), aqueous $NaHCO_3$ (50 mL), and brine (50 mL), and then the combined extracts were concentrated under reduced pressure (at 30 °C) and the remaining oil was chromatographed on silica gel. Elution with 1:1 and 3:1 CH_2Cl_2/petroleum ether first gave foreruns and then further elution with CH_2Cl_2 gave **22** (67 mg, 41%) as a white solid: mp (CH_2Cl_2/pentane) 150-151 °C; ^{1}H NMR ($CDCl_3$) δ 7.78 (s, 1 H), 7.19 (br d, *J* = 8.9 Hz, 2 H), 7.16 (br d, *J* = 8.9 Hz, 2 H), 4.60 (d, *J* = 12.1 Hz, 1 H), 4.51 (d, *J* = 11.6 Hz, 1 H), 4.47 (d, *J* = 11.6 Hz, 1 H), 4.26 (d, *J* = 12.1 Hz, 1 H), 3.91 (d, *J* = 10.2 Hz, 1 H), 3.79 (d, *J* = 10.2 Hz, 1 H), 1.63 (s, 3 H). Anal. ($C_{15}H_{14}F_3N_3O_6S$) C, H, N.

Further elution of the above column with 1% EtOAc/CH_2Cl_2 gave **18** (26 mg, 17%) as a white solid: mp (CH_2Cl_2/hexane) 159-160 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1 H), 7.38 (br d, *J* = 8.7 Hz, 2 H), 7.23 (br d, *J* = 7.9 Hz, 2 H), 4.71 (d, *J* = 12.0 Hz, 1 H), 4.60 (d, *J* = 12.0 Hz, 1 H), 4.50 (d, *J* = 12.2 Hz, 1 H), 4.09 (d, *J* = 12.2 Hz, 1 H), 4.05 (d, *J* = 9.9 Hz, 1 H), 3.78 (d, *J* = 9.9 Hz, 1 H), 1.45 (s, 3 H). Anal. ($C_{15}H_{14}F_3N_3O_5S$) C, H, N.

Further elution of the above column with 1-2% EtOAc/CH_2Cl_2 gave a mixture of **18** and **19** (47 mg, 30%) and then continued elution with 2-5% EtOAc/CH_2Cl_2 gave **19** (16 mg, 10%) as a white solid: mp (CH_2Cl_2/pentane) 138-141 °C; ^{1}H NMR ($CDCl_3$) δ 7.87 (s, 1 H), 7.16 (br d,

J = 8.2 Hz, 2 H), 7.11 (br d, *J* = 8.7 Hz, 2 H), 4.43 (br s, 2 H), 4.40 (s, 2 H), 3.75 (d, *J* = 10.0 Hz, 1 H), 3.70 (d, *J* = 10.0 Hz, 1 H), 1.61 (s, 3 H). Anal. ($C_{15}H_{14}F_3N_3O_5S$) C, H, N.

Synthesis of 24 (Scheme 1B):

2-Methyl-2-({[4-(trifluoromethoxy)benzyl]oxy}methyl)thiirane (80). Reaction of 2-methyl-2-({[4-(trifluoromethoxy)benzyl]oxy}methyl)oxirane[4] (**79**) with thiourea on silica gel in CH_2Cl_2, using procedure A for 4 h, followed by chromatography of the product on silica gel, eluting with pentane (foreruns) and then with 25% CH_2Cl_2/pentane, gave **80** (94%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 7.37 (br d, *J* = 8.7 Hz, 2 H), 7.20 (br d, *J* = 8.6 Hz, 2 H), 4.57 (s, 2 H), 3.65 (dd, *J* = 10.2, 1.1 Hz, 1 H), 3.51 (d, *J* = 10.2 Hz, 1 H), 2.41 (d, *J* = 0.9 Hz, 1 H), 2.39 (t, *J* = 1.1 Hz, 1 H), 1.67 (s, 3 H); HRFABMS calcd for $C_{12}H_{14}F_3O_2S$ *m/z* $[M + H]^+$ 279.0667, found 279.0662.

2-Methyl-5-nitro-2-({[4-(trifluoromethoxy)benzyl]oxy}methyl)-2,3-dihydroimidazo[2,1-*b*][1,3]thiazole (24). Reaction of thiirane **80** with 2-bromo-4-nitro-1*H*-imidazole and DIPEA, using procedure B for 16 h, followed by chromatography of the product on silica gel, eluting with 0-15% EtOAc/petroleum ether (foreruns) and then with more 15% EtOAc/petroleum ether, first gave **24** (2%) as a yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.88 (s, 1 H), 7.31 (br d, *J* = 8.7 Hz, 2 H), 7.20 (br d, *J* = 8.0 Hz, 2 H), 4.71 (d, *J* = 12.2 Hz, 1 H), 4.59 (s, 2 H), 4.22 (d, *J* = 12.3 Hz, 1 H), 3.67 (d, *J* = 9.5 Hz, 1 H), 3.64 (d, *J* = 9.5 Hz, 1 H), 1.76 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.4, 149.1 (q, J_{C-F} = 1.6 Hz), 138.6, 136.5, 136.0, 129.2 (2 C), 121.3 (2 C), 120.6 (q, J_{C-F} = 257.2 Hz), 75.7, 72.9, 64.1, 56.4, 24.5; HRFABMS calcd for $C_{15}H_{15}F_3N_3O_4S$ *m/z* $[M + H]^+$ 390.0735, found 390.0737; HPLC purity: 97.6%.

Further elution of the above column with 30% EtOAc/petroleum ether and CH_2Cl_2 gave **12** (89%); see data above.

Synthesis of 26 (Scheme 1B):

2-{[(4-Iodobenzyl)oxy]methyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]thiazole (82). A solution of alcohol **51** (186 mg, 0.864 mmol) and 4-iodobenzyl bromide (348 mg, 1.17 mmol) in anhydrous DMF (6 mL) under N_2 at 0 °C was treated with 60% NaH (53 mg, 1.33 mmol), then quickly degassed and resealed under N_2. The resulting mixture was stirred at 20 °C for 2.5 h and then cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (50 mL), and extracted with EtOAc (4 x 50 mL). The extracts were washed with brine (50 mL) and then evaporated to dryness under reduced pressure (at 30 °C), and the residue was chromatographed on silica gel. Elution with 1:1 CH_2Cl_2/petroleum ether first gave foreruns, and then further elution with 3:2 CH_2Cl_2/petroleum ether and CH_2Cl_2 gave **82** (293 mg, 79%) as a light yellow solid: mp (CH_2Cl_2/hexane) 168-170 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 (s, 1 H), 7.69 (br d, *J* = 8.3 Hz, 2 H), 7.02 (br d, *J* = 8.3 Hz, 2 H), 4.50 (s, 2 H), 4.32 (d, *J* = 11.5 Hz, 1 H), 3.90 (d, *J* = 11.5 Hz, 1 H), 3.61 (d, *J* = 9.6 Hz, 1 H), 3.58 (d, *J* = 9.7 Hz, 1 H), 1.72 (s, 3 H). Anal. ($C_{14}H_{14}IN_3O_3S$) C, H, N.

Procedure E: 2-{[(4'-Fluoro[1,1'-biphenyl]-4-yl)methoxy]methyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]thiazole (26). A stirred mixture of iodide **82** (40.1 mg, 93.0 μmol), 4-fluorophenylboronic acid (19.9 mg, 142 μmol), and Pd(dppf)Cl_2 (14.0 mg, 19.1 μmol) in toluene (2.0 mL) and EtOH (0.8 mL) was degassed for 5 min (vacuum pump) and then N_2 was added. An aqueous solution of Na_2CO_3 (0.40 mL of 2 M, 0.80 mmol) was added by syringe and the stirred mixture was again degassed for 5 min, and then N_2 was added. The

resulting mixture was stirred at 90 °C for 60 min, and then cooled, diluted with aqueous $NaHCO_3$ (50 mL), and extracted with CH_2Cl_2 (4 x 50 mL). The extracts were evaporated to dryness under reduced pressure (at 30 °C) and the residue was chromatographed on silica gel. Elution with 3:1 CH_2Cl_2/petroleum ether first gave foreruns, and then further elution with 3:1 CH_2Cl_2/petroleum ether and CH_2Cl_2 gave **26** (25 mg, 67%) as a pale yellow solid: mp (CH_2Cl_2/pentane) 151-153 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.44 (s, 1 H), 7.69 (br dd, *J* = 8.9, 5.4 Hz, 2 H), 7.61 (br d, *J* = 8.3 Hz, 2 H), 7.37 (br d, *J* = 8.2 Hz, 2 H), 7.29 (br t, *J* = 8.9 Hz, 2 H), 4.61 (s, 2 H), 4.35 (d, *J* = 12.1 Hz, 1 H), 4.16 (d, *J* = 12.1 Hz, 1 H), 3.74 (d, *J* = 9.7 Hz, 1 H), 3.71 (d, *J* = 9.7 Hz, 1 H), 1.67 (s, 3 H); ^{13}C NMR [$(CD_3)_2SO$] δ 161.9 (d, J_{C-F} = 244.1 Hz), 149.0, 148.7, 138.4, 137.0, 136.3 (d, J_{C-F} = 2.8 Hz), 128.6 (d, J_{C-F} = 8.2 Hz, 2 C), 128.0 (2 C), 126.5 (2 C), 120.8, 115.7 (d, J_{C-F} = 21.1 Hz, 2 C), 75.3, 72.2, 64.3, 54.6, 23.8. Anal. ($C_{20}H_{18}FN_3O_3S$) C, H, N.

Synthesis of 29 (Scheme 2A):

2-{[4-(Trifluoromethoxy)phenoxy]methyl}thiirane (85). Reaction of 2-{[4-(trifluoromethoxy)phenoxy]methyl}oxirane[4,5] (**84**) with thiourea on silica gel in CH_2Cl_2, using procedure A for 4 h, followed by chromatography of the product on silica gel, eluting with pentane (foreruns) and then with 25% CH_2Cl_2/pentane, gave **85** (83%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 7.14 (br d, *J* = 9.0 Hz, 2 H), 6.89 (br d, *J* = 9.1 Hz, 2 H), 4.18 (dd, *J* = 10.1, 5.6 Hz, 1 H), 3.92 (dd, *J* = 10.1, 6.9 Hz, 1 H), 3.30-3.21 (m, 1 H), 2.61 (br d, *J* = 6.2 Hz, 1 H), 2.32 (dd, *J* = 5.2, 1.4 Hz, 1 H); HRFABMS calcd for $C_{10}H_9F_3O_2S$ *m*/*z* (M^+) 250.0275, found 250.0276.

6-Nitro-2-{[4-(trifluoromethoxy)phenoxy]methyl}-2,3-dihydroimidazo[2,1-*b*][1,3]thiazole (29). Reaction of thiirane **85** with 2-bromo-4-nitro-1*H*-imidazole and DIPEA, using procedure B at 107 °C for 13 h, followed by chromatography of the product on silica gel, eluting with 3:1 CH_2Cl_2/petroleum ether (foreruns) and then with additional 3:1 CH_2Cl_2/petroleum ether and CH_2Cl_2, gave **29** (65%) as a cream solid: mp (CH_2Cl_2/hexane) 131-133 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.46 (s, 1 H), 7.30 (br d, *J* = 9.1 Hz, 2 H), 7.04 (br d, *J* = 9.2 Hz, 2 H), 4.93-4.84 (m, 1 H), 4.50 (dd, *J* = 12.2, 7.6 Hz, 1 H), 4.36 (dd, *J* = 12.2, 4.1 Hz, 1 H), 4.32 (d, *J* = 6.4 Hz, 2 H); ^{13}C NMR [$(CD_3)_2SO$] δ 156.7, 149.4, 148.7, 142.2 (q, J_{C-F} = 1.6 Hz), 122.6 (2 C), 120.8, 120.1 (q, J_{C-F} = 255.3 Hz), 115.9 (2 C), 69.5, 50.5, 48.5. Anal. ($C_{13}H_{10}F_3N_3O_4S$) C, H, N.

Synthesis of 33 (Scheme 2A):

2-Methyl-2-{[4-(trifluoromethoxy)phenoxy]methyl}thiirane (92). Reaction of 2-methyl-2-{[4-(trifluoromethoxy)phenoxy]methyl}oxirane[4] (**91**) with thiourea on silica gel in CH_2Cl_2, using procedure A, followed by chromatography of the product on silica gel, eluting with pentane (foreruns) and then with 25% CH_2Cl_2/pentane, gave **92** (82%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 7.14 (br d, *J* = 9.1 Hz, 2 H), 6.88 (br d, *J* = 9.1 Hz, 2 H), 4.13 (dd, *J* = 9.5, 1.2 Hz, 1 H), 3.89 (d, *J* = 9.5 Hz, 1 H), 2.51 (d, *J* = 1.2 Hz, 1 H), 2.47 (t, *J* = 1.2 Hz, 1 H), 1.74 (s, 3 H); HRFABMS calcd for $C_{11}H_{11}F_3O_2S$ *m*/*z* (M^+) 264.0432, found 264.0428.

2-Methyl-6-nitro-2-{[4-(trifluoromethoxy)phenoxy]methyl}-2,3-dihydroimidazo[2,1-*b*][1,3]thiazole (33). Reaction of thiirane **92** with 2-bromo-4-nitro-1*H*-imidazole and DIPEA, using procedure B at 107 °C for 14 h, followed by chromatography of the product on silica gel, eluting with 1:1 and 3:1 CH_2Cl_2/petroleum ether (foreruns) and then with additional 3:1 CH_2Cl_2/petroleum ether and CH_2Cl_2, gave **33** (88%) as a cream solid: mp (CH_2Cl_2/hexane)

144-146 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.47 (s, 1 H), 7.30 (br d, *J* = 9.0 Hz, 2 H), 7.01 (br d, *J* = 9.2 Hz, 2 H), 4.46 (d, *J* = 12.2 Hz, 1 H), 4.31 (d, *J* = 10.4 Hz, 1 H), 4.28 (d, *J* = 10.4 Hz, 1 H), 4.26 (d, *J* = 12.2 Hz, 1 H), 1.76 (s, 3 H); ^{13}C NMR [$(CD_3)_2SO$] δ 156.8, 149.1, 148.4, 142.2 (q, J_{C-F} = 1.6 Hz), 122.6 (2 C), 120.9, 120.1 (q, J_{C-F} = 255.1 Hz), 116.0 (2 C), 73.5, 63.4, 54.5, 23.3. Anal. ($C_{14}H_{12}F_3N_3O_4S$) C, H, N.

Synthesis of 37, 38 and 41 (Scheme 2A):

2-Methyl-6-nitro-2-{[4-(trifluoromethoxy)phenoxy]methyl}-2,3-dihydroimidazo[2,1-*b*][1,3]thiazole 1-oxide (37 and 38) and 2-methyl-6-nitro-2-{[4-(trifluoromethoxy)-phenoxy]methyl}-2,3-dihydroimidazo[2,1-*b*][1,3]thiazole 1,1-dioxide (41). Oxidation of thiazole **33** with 70% *m*-CPBA (1.7 equiv for 24 h and then an additional 1.0 equiv for 40 h) and disodium hydrogen phosphate (2.2 equiv), using procedure D, followed by chromatography of the product on silica gel, eluting with 4:1 CH_2Cl_2/petroleum ether (foreruns) and then with CH_2Cl_2, first gave **41** (45%) as a white solid: mp (CH_2Cl_2/pentane) 158-158.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.91 (s, 1 H), 7.16 (br d, *J* = 9.1 Hz, 2 H), 6.80 (br d, *J* = 9.2 Hz, 2 H), 4.79 (d, *J* = 12.3 Hz, 1 H), 4.40 (d, *J* = 12.3 Hz, 1 H), 4.33 (d, *J* = 9.9 Hz, 1 H), 4.27 (d, *J* = 9.9 Hz, 1 H), 1.79 (s, 3 H). Anal. ($C_{14}H_{12}F_3N_3O_6S$) C, H, N.

Further elution of the above column with 0.25% MeOH/CH_2Cl_2 gave **37** (25%) as a white solid: mp (CH_2Cl_2/pentane) 161-163 °C; ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1 H), 7.20 (br d, *J* = 8.5 Hz, 2 H), 6.99 (br d, *J* = 9.2 Hz, 2 H), 4.66 (d, *J* = 12.3 Hz, 1 H), 4.57 (d, *J* = 9.7 Hz, 1 H), 4.28 (d, *J* = 9.7 Hz, 1 H), 4.27 (d, *J* = 12.3 Hz, 1 H), 1.58 (s, 3 H). Anal. ($C_{14}H_{12}F_3N_3O_5S$) C, H, N.

Further elution of the above column with additional 0.25% MeOH/CH_2Cl_2 gave **38** (25%) as a white solid: mp (CH_2Cl_2/pentane) 119-121 °C; ^{1}H NMR ($CDCl_3$) δ 7.97 (s, 1 H), 7.12 (br d, *J* = 9.1 Hz, 2 H), 6.67 (br d, *J* = 9.2 Hz, 2 H), 4.59 (d, *J* = 12.4 Hz, 1 H), 4.56 (d, *J* = 12.4 Hz, 1 H), 4.23 (s, 2 H), 1.76 (s, 3 H). Anal. ($C_{14}H_{12}F_3N_3O_5S$) C, H, N.

Synthesis of 45 (Scheme 2B):

2-[(4-Iodophenoxy)methyl]-2-methylthiirane (99). Reaction of 2-[(4-iodophenoxy)-methyl]-2-methyloxirane[4] (**98**) with thiourea on silica gel in CH_2Cl_2, using procedure A for 4 h, followed by chromatography of the product on silica gel, eluting with pentane (foreruns) and then with 25% CH_2Cl_2/pentane, gave **99** (78%) as a white solid (on freezing): mp (pentane) 41-43 °C; ^{1}H NMR ($CDCl_3$) δ 7.55 (br d, *J* = 9.0 Hz, 2 H), 6.67 (br d, *J* = 9.0 Hz, 2 H), 4.11 (dd, *J* = 9.6, 1.2 Hz, 1 H), 3.86 (d, *J* = 9.6 Hz, 1 H), 2.50 (d, *J* = 1.3 Hz, 1 H), 2.46 (t, *J* = 1.3 Hz, 1 H), 1.73 (s, 3 H). Anal. ($C_{10}H_{11}IOS$) C, H.

2-[(4-Iodophenoxy)methyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]thiazole (100). Reaction of thiirane **99** with 2-bromo-4-nitro-1*H*-imidazole and DIPEA, using procedure B at 108 °C for 15 h, followed by chromatography of the product on silica gel, eluting with 3:1 CH_2Cl_2/petroleum ether (foreruns) and then with CH_2Cl_2, gave **100** (91%) as a pale yellow solid: mp (MeOH/CH_2Cl_2/hexane) 196-198 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.48 (s, 1 H), 7.60 (br d, *J* = 9.0 Hz, 2 H), 6.77 (br d, *J* = 9.0 Hz, 2 H), 4.44 (d, *J* = 12.2 Hz, 1 H), 4.27 (d, *J* = 10.2 Hz, 1 H), 4.25 (d, *J* = 12.2 Hz, 1 H), 4.24 (d, *J* = 10.2 Hz, 1 H), 1.74 (s, 3 H). Anal. ($C_{13}H_{12}IN_3O_3S$) C, H, N.

2-Methyl-6-nitro-2-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy}methyl)-2,3-dihydroimidazo[2,1-*b*][1,3]thiazole (45). Reaction of iodide **100** with 4-(trifluoromethoxy)-

phenylboronic acid (2.0 equiv) and Pd(dppf)Cl_2 (0.40 equiv), using procedure E for 3 h (but with only 6 equiv of Na_2CO_3), followed by chromatography of the product on silica gel, eluting with CH_2Cl_2, gave **45** (58%) as a cream solid: mp (CH_2Cl_2/pentane) 171-172 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.49 (s, 1 H), 7.73 (br d, *J* = 8.9 Hz, 2 H), 7.63 (br d, *J* = 8.8 Hz, 2 H), 7.41 (br d, *J* = 8.7 Hz, 2 H), 7.02 (br d, *J* = 8.8 Hz, 2 H), 4.48 (d, *J* = 12.2 Hz, 1 H), 4.35 (d, *J* = 10.1 Hz, 1 H), 4.32 (d, *J* = 10.0 Hz, 1 H), 4.28 (d, *J* = 12.2 Hz, 1 H), 1.78 (s, 3 H); ^{13}C NMR [$(CD_3)_2SO$] δ 158.0, 149.1, 148.5, 147.4 (q, J_{C-F} = 1.5 Hz), 139.0, 131.8, 128.0 (4 C), 121.4 (2 C), 120.9, 120.1 (q, J_{C-F} = 256.7 Hz), 115.2 (2 C), 73.2, 63.5, 54.6 23.5. Anal. ($C_{20}H_{16}F_3N_3O_4S$) C, H, N.

Synthesis of 49 (Scheme 2B):

1-{4-[(2-Methyloxiran-2-yl)methoxy]phenyl}-4-[4-(trifluoromethoxy)phenoxy]-piperidine (101). 2-(Chloromethyl)-2-methyloxirane (**97**) (0.068 mL, 0.703 mmol) was added to a mixture of 4-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}phenol[6] (200 mg, 0.566 mmol), powdered K_2CO_3 (198 mg, 1.43 mmol), and sodium iodide (27.7 mg, 0.185 mmol) in anhydrous DMF (0.6 mL) and the reaction vial was sealed. The mixture was stirred at 82 °C for 24 h and then additional K_2CO_3 (102 mg, 0.738 mmol) and **97** (0.034 mL, 0.352 mmol) were added. The mixture was stirred at 82 °C for a further 36 h, and then cooled, added to aqueous $NaHCO_3$ (15 mL), and extracted with EtOAc (4 x 15 mL). The extracts were washed with water (30 mL) and concentrated under reduced pressure (at 25 °C), and the remaining oil was chromatographed on silica gel. Elution with 0-10% EtOAc/petroleum ether first gave foreruns, and then further elution with 10% EtOAc/petroleum ether gave **101** (118 mg, 49%) as a white solid: mp (CH_2Cl_2/pentane) 70-71 °C; ^{1}H NMR ($CDCl_3$) δ 7.13 (br d, *J* = 8.6 Hz, 2 H), 6.95-6.88 (m, 4 H), 6.85 (br d, *J* = 9.1 Hz, 2 H), 4.44-4.36 (m, 1 H), 3.97 (d, *J* = 10.5 Hz, 1 H), 3.91 (d, *J* = 10.5 Hz, 1 H), 3.42-3.32 (m, 2 H), 3.04-2.94 (m, 2 H), 2.85 (d, *J* = 4.8 Hz, 1 H), 2.71 (d, *J* = 4.8 Hz, 1 H), 2.15-2.06 (m, 2 H), 2.00-1.89 (m, 2 H), 1.47 (s, 3 H); HRFABMS calcd for $C_{22}H_{24}F_3NO_4$ *m/z* (M^+) 423.1657, found 423.1661.

1-{4-[(2-Methylthiiran-2-yl)methoxy]phenyl}-4-[4-(trifluoromethoxy)phenoxy]-piperidine (102). Reaction of epoxide **101** with thiourea on silica gel in CH_2Cl_2, using procedure A for 4 h, followed by chromatography of the product on silica gel, eluting with 0-10% EtOAc/petroleum ether (foreruns) and then with additional 10% EtOAc/petroleum ether, gave **102** (64%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 7.13 (br d, *J* = 9.1 Hz, 2 H), 6.95-6.88 (m, 4 H), 6.84 (br d, *J* = 9.1 Hz, 2 H), 4.45-4.36 (m, 1 H), 4.13 (dd, *J* = 9.7, 1.3 Hz, 1 H), 3.84 (d, *J* = 9.7 Hz, 1 H), 3.42-3.32 (m, 2 H), 3.04-2.94 (m, 2 H), 2.50 (d, *J* = 1.1 Hz, 1 H), 2.45 (t, *J* = 1.3 Hz, 1 H), 2.16-2.05 (m, 2 H), 2.01-1.89 (m, 2 H), 1.74 (s, 3 H); HRFABMS calcd for $C_{22}H_{24}F_3NO_3S$ *m/z* (M^+) 439.1429, found 439.1431.

2-Methyl-6-nitro-2-[(4-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}phenoxy)-methyl]-2,3-dihydroimidazo[2,1-*b*][1,3]thiazole (49). Reaction of thiirane **102** with 2-bromo-4-nitro-1*H*-imidazole and DIPEA (10 equiv), using procedure B at 108 °C for 15 h, followed by chromatography of the product on silica gel, eluting with 0-40% EtOAc/petroleum ether (foreruns) and then with additional 40% EtOAc/petroleum ether and EtOAc, gave **49** (86%) as a pale yellow-brown solid: mp (CH_2Cl_2/pentane) 150-151 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.47 (s, 1 H), 7.27 (br d, *J* = 8.4 Hz, 2 H), 7.07 (br d, *J* = 9.2 Hz, 2 H), 6.91 (br d, *J* = 9.2 Hz, 2 H), 6.81 (br d, *J* = 9.2 Hz, 2 H), 4.58-4.50 (m, 1 H), 4.43 (d, *J* = 12.2 Hz, 1 H), 4.24 (d, *J* = 12.2 Hz, 1 H), 4.20 (d, *J* = 10.0 Hz, 1 H), 4.17 (d, *J* = 9.9 Hz, 1 H), 3.42-3.30 (m, 2 H), 2.98-2.87 (m, 2 H), 2.09-1.97 (m, 2 H), 1.80-1.66 (m, 5 H); ^{13}C NMR [$(CD_3)_2SO$] δ 155.9, 151.5, 149.1, 148.6, 145.9, 141.7 (q, J_{C-F} = 2.0 Hz), 122.5 (2 C), 120.8,

120.2 (q, $J_{C\text{-}F}$ = 255.2 Hz), 117.7 (2 C), 117.0 (2 C), 115.4 (2 C), 73.7, 72.5, 63.7, 54.6, 47.1 (2 C), 30.1 (2 C), 23.6. Anal. ($C_{25}H_{25}F_3N_4O_5S$) C, H, N.

Synthesis of 53 and 58 (Scheme 2C):

5-Methyl-2-nitro-5-{[4-(trifluoromethoxy)phenoxy]methyl}-5,6-dihydro[1,3]thiazolo-[3,2-*b*][1,2,4]triazole (53) and 2-bromo-5-methyl-5-{[4-(trifluoromethoxy)phenoxy]-methyl}-5,6-dihydro[1,3]thiazolo[3,2-*b*][1,2,4]triazole (58). Reaction of thiirane **92** with 5-bromo-3-nitro-1*H*-1,2,4-triazole (**103**) and DIPEA (10 equiv), using procedure B at 105 °C for 14 h, followed by chromatography of the product on silica gel, eluting with 0-20% Et_2O/petroleum ether (foreruns) and then with 33% Et_2O/petroleum ether, first gave **58** (17%) as a cream solid (on freezing and trituration in pentane): mp 72-74 °C; ^{1}H NMR ($CDCl_3$) δ 7.17 (br d, *J* = 9.1 Hz, 2 H), 6.88 (br d, *J* = 9.2 Hz, 2 H), 4.55 (d, *J* = 11.4 Hz, 1 H), 4.14 (d, *J* = 9.4 Hz, 1 H), 4.11 (d, *J* = 11.3 Hz, 1 H), 4.09 (d, *J* = 9.2 Hz, 1 H), 1.87 (s, 3 H). Anal. ($C_{13}H_{11}BrF_3N_3O_2S$) C, H, N.

Further elution of the above column with 50% Et_2O/petroleum ether gave **53** (50%) as a cream solid: mp (CH_2Cl_2/pentane) 110-112 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.30 (br d, *J* = 9.1 Hz, 2 H), 7.02 (br d, *J* = 9.2 Hz, 2 H), 4.69 (d, *J* = 12.1 Hz, 1 H), 4.53 (d, *J* = 12.1 Hz, 1 H), 4.39 (d, *J* = 10.4 Hz, 1 H), 4.36 (d, *J* = 10.3 Hz, 1 H), 1.83 (s, 3 H); ^{13}C NMR [$(CD_3)_2SO$] δ 164.2, 159.0, 156.7, 142.3 (q, $J_{C\text{-}F}$ = 2.0 Hz), 122.6 (2 C), 120.1 (q, $J_{C\text{-}F}$ = 255.4 Hz), 116.0 (2 C), 73.7, 63.9, 55.4, 23.8. Anal. ($C_{13}H_{11}F_3N_4O_4S$) C, H, N.

Synthesis of 55-57 (Scheme 2C):

5-Methyl-2-nitro-5-{[4-(trifluoromethoxy)phenoxy]methyl}-5,6-dihydro[1,3]thiazolo-[3,2-*b*][1,2,4]triazole 4-oxide (55 and 56) and 5-methyl-2-nitro-5-{[4-(trifluoromethoxy)-phenoxy]methyl}-5,6-dihydro[1,3]thiazolo[3,2-*b*][1,2,4]triazole 4,4-dioxide (57). Oxidation of thiazole **53** with *m*-CPBA (1.8 equiv) and disodium hydrogen phosphate (2.4 equiv), using procedure D for 70 h, followed by chromatography of the product on silica gel, eluting with 1:1 CH_2Cl_2/petroleum ether (foreruns) and then with 3:2 CH_2Cl_2/petroleum ether, first gave **57** (19%) as a white solid: mp (CH_2Cl_2/pentane) 150-151 °C; ^{1}H NMR ($CDCl_3$) δ 7.16 (br d, *J* = 9.0 Hz, 2 H), 6.78 (br d, *J* = 9.1 Hz, 2 H), 5.01 (d, *J* = 12.8 Hz, 1 H), 4.61 (d, *J* = 12.8 Hz, 1 H), 4.46 (d, *J* = 10.0 Hz, 1 H), 4.31 (d, *J* = 10.0 Hz, 1 H), 1.85 (s, 3 H). Anal. ($C_{13}H_{11}F_3N_4O_6S$) C, H, N.

Further elution of the above column with 3:1 and 4:1 CH_2Cl_2/petroleum ether gave **55** (32%) as a white solid: mp (CH_2Cl_2/pentane) 149-150 °C; ^{1}H NMR ($CDCl_3$) δ 7.20 (br d, *J* = 9.1 Hz, 2 H), 6.99 (br d, *J* = 9.2 Hz, 2 H), 4.80 (d, *J* = 12.8 Hz, 1 H), 4.58 (d, *J* = 9.9 Hz, 1 H), 4.49 (d, *J* = 12.8 Hz, 1 H), 4.34 (d, *J* = 9.9 Hz, 1 H), 1.68 (s, 3 H). Anal. ($C_{13}H_{11}F_3N_4O_5S$) C, H, N.

Further elution of the above column with CH_2Cl_2 gave **56** (32%) as a white solid: mp (CH_2Cl_2/pentane) 121-123 °C; ^{1}H NMR ($CDCl_3$) δ 7.13 (br d, *J* = 9.1 Hz, 2 H), 6.67 (br d, *J* = 9.2 Hz, 2 H), 4.81 (d, *J* = 12.9 Hz, 1 H), 4.72 (d, *J* = 12.9 Hz, 1 H), 4.41 (d, *J* = 10.1 Hz, 1 H), 4.33 (d, *J* = 10.1 Hz, 1 H), 1.79 (s, 3 H). Anal. ($C_{13}H_{11}F_3N_4O_5S$) C, H, N.

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