Supporting Information for:

Creating an antibacterial with *in vivo* efficacy: synthesis and characterisation of potent inhibitors of the bacterial cell-division protein FtsZ with improved pharmaceutical properties

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Contents:

Experimental and spectroscopic details of compounds not disclosed in the main article

2,6-Difluoro-3-(hexyloxy)benzamide (6a). Compound **6a** was prepared from **4** (140 mg, 0.8 mmol) and n-hexyl bromide (**5a**) (150 mg, 0.9 mmol, 1.1 equiv) using 1.5 equiv K_2CO_3, according to the general procedure (60 ºC, overnight, aqueous work-up). The crude product was triturated with n-pentane (20 mL), filtered and dried *in vacuo* to give **6a** as a white solid (79 mg, 38%); mp 93-95 °C. ^{1}H-NMR ($CDCl_3$): δ 0.89 (t, J = 6.3 Hz, 3H), 1.32 (m, 4H), 1.44 (m, 2H), 1.78 (m, 2H), 3.99 (t, J = 6.5 Hz, 2H), 6.00 (br s, 1H), 6.13 (br s, 1H), 6.85 (m, 1H), 6.97 (m, 1H). HPLC-MS (APCI) *m/z* 258 $[M+H]^+$, (method 5) Rt = 4.38 min.

2,6-Difluoro-3-[(4-methyl-1,3-thiazol-2-yl)methoxy]benzamide (6b). Compound **6b** was prepared from **4** (260 mg, 1.5 mmol) and 2-(chloromethyl)-4-methyl-1,3-thiazole hydrochloride (**5b**) (304 mg, 1.65 mmol,

1.1 equiv) using 2 equiv of K_2CO_3, according to the general procedure (60 ºC, overnight, EtOAc/H_2O work-up). The crude product was recrystallised from CH_3CN to give **6b** as an off-white solid (210 mg, 49%); mp 172-173 °C. ^{1}H-NMR (DMSO-d_6): δ 2.38 (s, 3H), 5.45 (s, 2H), 7.09 (app dt, J = 9.0, 1.8 Hz, 1H), 7.32-7.38 (m, 2H), 7.81 (br s, 1H), 8.10 (br s, 1H). HPLC-MS (APCI) *m/z* 285 $[M+H]^+$, (method 5) Rt = 2.80 min.

2,6-Difluoro-3-[(5-methyl-1,3-thiazol-2-yl)methoxy]benzamide (6c). Compound **6c** was prepared from **4** (260 mg, 1.5 mmol) and 2-(chloromethyl)-5-methyl-1,3-thiazole hydrochloride (**5c**) (304 mg, 1.65 mmol, 1.1 equiv) using 2 equiv of K_2CO_3, according to the general procedure (60 ºC, overnight, aqueous work-up). The crude product was recrystallised from CH_3CN to give **6c** as an off-white solid (195 mg, 46%); mp 172-174 °C. ^{1}H-NMR (DMSO-d_6): δ 2.45 (s, 3H), 5.42 (s, 2H), 7.08 (app dt, J = 9.0, 1.8 Hz, 1H), 7.35 (m, 1H), 7.51 (s, 1H), 7.81 (br s, 1H), 8.10 (br s, 1H). HPLC-MS (APCI) *m/z* 285 $[M+H]^+$, (method 5) Rt = 2.85 min.

2,6-Difluoro-3-[(2-phenyl-1,3-thiazol-4-yl)methoxy]benzamide (6d). Compound **6d** was prepared from **4** (346 mg, 2 mmol) and 4-(chloromethyl)-2-phenyl-1,3-thiazole (**5d**) (460 mg, 2.2 mmol, 1.1 equiv) using 1.5 equiv K_2CO_3, according to the general procedure (60 ºC, overnight, aqueous work-up). The crude product was recrystallised from CH_3CN to give **6d** as an off-white solid (400 mg, 58%); mp 207-209 °C. ^{1}H-NMR (DMSO-d_6): δ 5.31 (s, 2H), 7.09 (app dt, J = 9.0, 1.8 Hz, 1H), 7.41 (m, 1H), 7.50-7.55 (m, 3H), 7.79-7.82 (m, 2H), 7.94-7.97 (m, 2H), 8.09 (br s, 1H). HPLC-MS (APCI) *m/z* 347 $[M+H]^+$, (method 5) Rt = 3.96 min.

3-[2-(1H-Pyrazol-1-yl)ethoxy]-2,6-difluorobenzamide (6e). Compound **6e** was prepared from **4** (150 mg, 0.86 mmol) and 1-(2-bromoethyl)-1H-pyrazole (**5e**) (150 mg, 0.86 mmol, 1 equiv) using 3 equiv K_2CO_3 according to the general procedure (room temperature, 3 h, EtOAc/H_2O work-up, with additional 1N NaOH wash). The residue was triturated with diethyl ether to obtain the title compound **6e** (60 mg, 26%). ^{1}H-NMR (DMSO-d_6): δ 4.40 (t, J = 4.8 Hz, 2H), 4.50 (t, J = 4.8 Hz, 2H), 6.25 (t, J = 1.6 Hz, 1H), 7.05 (m, 1H), 7.15 (m, 1H), 7.46 (d, J = 1.6 Hz, 1H), 7.76 (d, J = 1.6 Hz, 1H), 7.83 (br s, 1H), 8.10 (br s, 1H). MS (ESI) *m/z* 268.13 $[M+H]^+$. HPLC purity (method 1) 93.29% Rt = 13.38 min.

3-(1,3-Benzothiazol-2-yloxy)-2,6-difluorobenzamide (6f). Compound **6f** was prepared from **4** (346 mg, 2 mmol) and 2-chloro-1,3-benzothiazole (**5f**) (373 mg, 2.2 mmol, 1.1 equiv) using 1.5 equiv K_2CO_3,

according to the general procedure (60 ºC, overnight, EtOAc/H_2O work-up). The crude product was purified by flash column chromatography on silica, eluting with EtOAc:Hexane (1:1), to give **6f** as a white solid (132 mg, 22%); mp 163-164 °C. ^{1}H-NMR (DMSO-d_6): δ 7.28-7.39 (m, 2H), 7.45 (m, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.77 (app dt, J = 9.0, 5.4 Hz, 1H), 7.95 (br s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 8.27 (br s, 1H). HPLC-MS (APCI) m/z 307 $[M+H]^+$, (method 5) Rt = 3.66 min.

3-(1,3-Benzothiazol-2-ylmethoxy)-2,6-difluorobenzamide (6g). Compound **6g** was prepared from **4** (346 mg, 2 mmol) and 2-(chloromethyl)-1,3-benzothiazole (**5g**) (404 mg, 2.2 mmol, 1.1 equiv) using 1.5 equiv K_2CO_3, according to the general procedure (60 ºC, overnight, aqueous work-up). The crude product was recrystallised from EtOAc to give **6g** as a pale yellow solid (96 mg, 15%); mp 185-186 °C. ^{1}H-NMR (DMSO-d_6): δ 5.69 (s, 2H), 7.10 (app dt, J = 9.0, 1.8 Hz, 1H), 7.39 (m, 1H), 7.48 (m, 1H), 7.55 (m, 1H), 7.83 (br s, 1H), 8.03 (d, J = 7.9 Hz, 1H), 8.13-8.16 (m, 2H). HPLC-MS (APCI) m/z 321 $[M+H]^+$, (method 5) Rt = 3.46 min.

2,6-Difluoro-3-(quinolin-2-ylmethoxy)benzamide (6h). Compound **6h** was prepared from **4** (346 mg, 2 mmol) and 2-(chloromethyl)quinoline hydrochloride (**5h**) (470 mg, 2.2 mmol, 1.1 equiv) using 3 equiv of K_2CO_3, according to the general procedure (60 ºC, overnight, aqueous work-up). The crude product was recrystallised from CH_3CN to give **6h** as a white solid (300 mg, 48%); mp 216-218 °C. ^{1}H-NMR (DMSO-d_6): δ 5.46 (s, 2H), 7.07 (app dt, J = 9.0, 1.8 Hz, 1H), 7.32 (m, 1H), 7.64 (m, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.80 (m, 1H), 7.89 (br s, 1H), 8.02 (m, 2H), 8.17 (br s, 1H), 8.45 (d, J = 8.5 Hz, 1H). HPLC-MS (APCI) m/z 315 $[M+H]^+$, (method 5) Rt = 3.43 min.

3-(1,3-Benzoxazol-2-ylmethoxy)-2,6-difluorobenzamide (6i). Compound **6i** was prepared from **4** (346 mg, 2 mmol) and 2-(chloromethyl)-1,3-benzoxazole (**5i**) (369 mg, 2.2 mmol, 1.1 equiv) using 1.5 equiv K_2CO_3, according to the general procedure (60 ºC, overnight, EtOAc/H_2O work-up). The crude product was triturated with diethyl ether (20 mL), filtered and dried *in vacuo* at 40 °C to give **6i** as a white solid (224 mg, 37%); mp 138-139 °C. ^{1}H-NMR (DMSO-d_6): δ 5.56 (s, 2H), 7.10 (app dt, J = 9.0, 1.8 Hz, 1H), 7.39-7.46 (m, 3H), 7.76-7.81 (m, 3H), 8.11 (br s, 1H). HPLC-MS (APCI) m/z 305 $[M+H]^+$, (method 5) Rt = 3.28 min.

2,6-Difluoro-3-[(4-methyl-2-thienyl)methoxy]benzamide (6j). To a solution of triphenyl phosphine (787 mg, 3 mmol, 1.5 equiv) in THF (20 mL) at room temperature under N_2 atmosphere, was added **4** (346 mg,

2 mmol), (4-methyl-thiophene-2-yl)-methanol (**5j**) (256 mg, 2 mmol, 1 equiv) and triethylamine (0.28 mL, 2 mmol, 1 equiv). After stirring at room temperature for 10 min, the reaction mixture was cooled at 0 °C and diisopropyl azadicarboxylate (DIAD, 0.47 mL, 2.4 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred at room temperature under N_2 atmosphere for 4 days. The mixture was evaporated to dryness under reduced pressure and the residue was purified by flash column chromatography on silica eluting with EtOAc:Hexane (1:1), to give **6j** as a white solid (52 mg, 9%); mp 111-112 °C. ^{1}H-NMR (DMSO-d_6): δ 2.19 (s, 3H), 5.30 (s, 2H), 7.02 (s, 1H), 7.06 (m, 1H), 7.13 (s, 1H), 7.32 (m, 1H), 7.79 (br s, 1H), 8.08 (br s, 1H). HPLC-MS (APCI) *m/z* 284 $[M+H]^+$, (method 5) Rt = 3.73 min.

2,6-Difluoro-3-[(6-methylpyridin-2-yl)methoxy]benzamide (6k). Compound **6k** was prepared from **4** (346 mg, 2 mmol) and (6-methylpyridin-2-yl)methanol (**5k**) (246 mg, 2 mmol, 1 equiv) following the procedure described for compound **6j**. The crude product was triturated with diethyl ether (20 mL), filtered and dried *in vacuo* at 40 °C to give **6k** as an off-white solid (316 mg, 57%); mp 201-202 °C. ^{1}H-NMR (DMSO-d_6): δ 2.49 (s, 3H), 5.20 (s, 2H), 7.05 (app dt, J = 9.0, 1.8 Hz, 1H), 7.21-7.32 (m, 3H), 7.74 (app t, J = 7.7 Hz, 1H), 7.80 (br s, 1H), 8.10 (br s, 1H). HPLC-MS (APCI) *m/z* 279 $[M+H]^+$, (method 5) Rt = 2.89 min.

2,6-Difluoro-3-[(5-phenyl-1,3-benzothiazol-2-yl)methoxy]benzamide (8a). Compound **8a** was prepared from **4** (130 mg, 0.75 mmol) and 2-bromomethyl-5-phenyl-benzothiazole (**7a**) (230 mg, 0.75 mmol, 1.07 equiv) using 3 equiv of K_2CO_3, according to the general procedure (25 ºC, overnight). The reaction mixture was evaporated to dryness under reduced pressure and the residue was purified by chromatography on silica eluting with 30% EtOAc-Hexane to provide the title compound **8a** as a light yellow solid (12 mg, 4%). ^{1}H-NMR (DMSO-d_6): δ 5.73 (s, 2H), 7.11 (app t, J = 9.2 Hz, 1H), 7.36-7.43 (m, 2H), 7.51 (app t, J = 7.6 Hz, 2H), 7.78-7.81 (m, 3H), 7.90 (br s, 1H), 8.16 (br s, 1H), 8.28 (d, J = 1.6 Hz, 1H), 8.29 (d, J = 8.4 Hz, 1H). MS (ESI) *m/z* 397.11 $[M+H]^+$. HPLC purity (method 1) 94.12% Rt = 10.28 min.

3-[(5-Ethoxy-1,3-benzothiazol-2-yl)methoxy]-2,6-difluorobenzamide (8b). Compound **8b** was prepared from **4** (34 mg, 0.20 mmol) and 2-(bromomethyl)-5-ethoxybenzothiazole (**7b**) (60 mg, 0.22 mmol, 1.1 equiv) using 3 equiv of K_2CO_3, according to the general procedure (25 ºC, 3 h, EtOAc/H_2O work-up, with additional 1N NaOH wash). The residue was chromatographed on silica eluting with 40% EtOAc-Hexane to obtain the title compound **8b** (12 mg, 15%), mp 231 ºC. ^{1}H-NMR (DMSO-d_6): δ 1.36 (t, J = 7.2 Hz, 3H),

4.10 (q, *J* = 7.2 Hz, 2H), 5.66 (s, 2H), 7.10 (m, 2H), 7.37 (m, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.89 (br s, 1H), 7.99 (d, *J* = 8.8 Hz, 1H), 8.17 (br s, 1H). MS (ESI) *m/z* 365.05 $[M+H]^+$. HPLC purity (method 3) 93.80% Rt = 15.86 min.

2,6-Difluoro-3-[(5-nitro-1,3-benzothiazol-2-yl)methoxy]benzamide (8c). Compound **8c** was prepared from **4** (180 mg, 1.02 mmol) and 2-(bromomethyl)-5-nitrobenzothiazole (**7c**) (310 mg, 1.13 mmol, 1.1 equiv) using 3 equiv of K_2CO_3, according to the general procedure (25 ºC, 16 h, EtOAc/H_2O work-up). The residue was chromatographed on silica eluting with 30% EtOAc-Hexane to obtain the title compound **8c** (130 mg, 31%). ^{1}H-NMR (DMSO-d_6): δ 5.77 (s, 2H), 7.12 (m, 1H), 7.43 (m, 1H), 7.90 (br s, 1H), 8.18 (br s, 1H), 8.33 (dd, *J*= 8.8, 2.0 Hz, 1H), 8.47 (d, *J*= 9.2 Hz, 1H), 8.83 (s, 1H). MS (ESI) *m/z* 366.06 $[M+H]^+$. HPLC (method 1) Rt = 15.63 min.

3-[(5-Bromo-1,3-benzothiazol-2-yl)methoxy]-2,6-difluorobenzamide (8d). Compound **8d** was prepared from **4** (620 mg, 3.58 mmol) and 5-bromo-2-(bromomethyl)benzothiazole (**7d**) (1.10 g, 3.58 mmol, 1 equiv) using 3 equiv of K_2CO_3, according to the general procedure (25 ºC, 16 h, aqueous work-up). Filtration and washing with diethyl ether gave the title compound **8d** as yellow solid (1.10 g, 77%). ^{1}H-NMR (DMSO-d_6): δ 5.71 (s, 2H), 7.11 (app dt, *J* = 8.8, 2.0 Hz, 1H), 7.38 (m, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.90 (br s, 1H), 8.14 (d, *J* = 8.8 Hz, 1H), 8.18 (s, 1H), 8.26 (br s, 1H). MS (ESI) *m/z* 400.90 $[M+H]^+$. HPLC (method 1) 97.74% Rt = 16.57 min.

2,6-Difluoro-3-{[5-(trifluoromethyl)-1,3-benzothiazol-2-yl]methoxy}benzamide (8e). Compound **8e** was prepared from **4** (400 mg, 2.31 mmol) and 2-(bromomethyl)-5-(trifluoromethyl)-1,3-benzothiazole (**7e**) (684 mg, 2.31 mmol, 1 equiv) using 3 equiv of K_2CO_3 according to the general procedure (60 ºC, 3.5 h, aqueous work-up). The crude product was triturated with CH_2Cl_2 (30 mL), by stirring overnight, filtered and dried *in vacuo* to give **8e** as an off-white solid (541 mg, 60%); mp 223-224 °C. ^{1}H-NMR (DMSO-d_6): δ 5.75 (s, 2H), 7.11 (app dt, *J* = 9.0, 1.8 Hz, 1H), 7.41 (m, 1H), 7.79-7.85 (m, 2H), 8.13 (br s, 1H), 8.39-8.43 (m, 2H). HPLC-MS (APCI) *m/z* 389 $[M+H]^+$, (method 5) Rt = 4.15 min.

2,6-Difluoro-3-[(5-methyl-1,3-benzothiazol-2-yl)methoxy]benzamide (8f). Compound **8f** was prepared from **4** (43 mg, 0.25 mmol) and 2-bromomethyl-5-methyl-benzothiazole (**7f**) (60 mg, 0.25 mmol, 1 equiv) using 3 equiv of K_2CO_3, according to the general procedure (25 ºC, overnight) followed by evaporation to dryness. The residue was purified by column chromatography on silica eluting with 35% EtOAc-Hexane to

provide the title compound **8f** as yellow solid (23 mg, 27%). ^{1}H-NMR (DMSO-d_6): δ 2.46 (s, 3H), 5.67 (s, 2H), 7.10 (m, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.37 (m, 1H), 7.83 (s, 1H), 7.88 (br s, 1H), 8.00 (d, J = 8.4 Hz, 1H), 8.17 (br s, 1H). MS (ESI) m/z 335.09 $[M+H]^+$. HPLC (method 2) Rt = 15.29 min.

3-{[5-(Dimethylamino)-1,3-benzothiazol-2-yl]methoxy}-2,6-difluorobenzamide (8g). Compound **8g** was prepared from **4** (35 mg, 0.20 mmol) and 2-(bromomethyl)-N,N-dimethylbenzothiazol-5-amine (**7g**) (62 mg, 0.23 mmol, 1.15 equiv) using 3 equiv of K_2CO_3, according to the general procedure (25 ºC, 16 h, EtOAc/H_2O work-up). The residue was triturated with diethyl ether to obtain the title compound **8g** (44 mg, 53%), mp 265 ºC (d). ^{1}H-NMR (DMSO-d_6): δ 2.96 (s, 6H), 5.61 (s, 2H), 7.01 (dd, J= 9.2, 2.8 Hz, 1H), 7.08 (m, 1H), 7.23 (d, J= 2.4 Hz, 1H), 7.35 (m, 1H), 7.86 (d, J= 8.8 Hz, 1H), 7.87 (br s, 1H), 8.17 (br s, 1H). MS (ESI) m/z 364.16 $[M+H]^+$. HPLC purity (method 3) 94.70% Rt = 14.96 min.

2,6-Difluoro-3-[(5-methoxy-1,3-benzothiazol-2-yl)methoxy]benzamide (8h). Compound **8h** was prepared from **4** (90 mg, 0.53 mmol) and 2-(2-bromomethyl-5-methoxybenzothiazole (**7h**) (150 mg, 0.58 mmol, 1.1 equiv) using 3 equiv of K_2CO_3, according to the general procedure (25 ºC, 3 h, EtOAc/H_2O work-up). The residue was triturated with diethyl ether to obtain the title compound **8h** (180 mg, 88%). ^{1}H-NMR (DMSO-d_6): δ 3.84 (s, 3H), 5.66 (s, 2H), 7.10 (m, 2H), 7.38 (m, 1H), 7.55 (d, J= 2.8 Hz, 1H), 7.88 (br s, 1H), 8.0 (d, J= 9.2 Hz, 1H), 8.17 (br s, 1H). MS (ESI) m/z 351.10 $[M+H]^+$. HPLC purity (method 2) 84.54% Rt 15.69 min.

Methyl 2-[(3-carbamoyl-2,4-difluorophenoxy)methyl]-1,3-benzothiazole-5-carboxylate (8i). Compound **8i** was prepared from **4** (770 mg, 4.40 mmol) and methyl 2-(bromomethyl)benzothiazole-5-carboxylate (**7i**) (1.40 g, 4.90 mmol, 1.1 equiv) using 3 equiv of K_2CO_3, according to the general procedure (25 ºC, 16 h, EtOAc/H_2O work-up). The residue thus obtained was triturated with diethyl ether to obtain the title compound **8i** (1.20 g, 65%). ^{1}H-NMR (DMSO-d_6): δ 3.91 (s, 3H), 5.35 (s, 2H), 7.12 (m, 1H), 7.40 (m, 1H), 7.90 (br s, 1H), 8.04 (d, J = 8.4 Hz, 1H), 8.18 (br s, 1H), 8.32 (d, J = 8.4 Hz, 1H), 8.52 (s, 1H). MS (ESI) m/z 379.11 $[M+H]^+$. HPLC (method 2) Rt = 15.22 min.

3-[(5-Chloro-1,3-benzothiazol-2-yl)methoxy]-2,6-difluorobenzamide (8j). Compound **8j** was prepared from **4** (3.12 g, 18 mmol) and 5-chloro-2-(chloromethyl)-1,3-benzothiazole (**7j**) (4.12 g, 18.9 mmol, 1.05 equiv) using 1.5 equiv K_2CO_3, according to the general procedure (60 ºC, overnight, aqueous work-up). The crude product was recrystallised from CH_3CN to give **8j** as an off-white solid (5.18 g, 81%); mp 235-

236 °C. ^{1}H-NMR (DMSO-d_6): δ 5.70 (s, 2H), 7.10 (app dt, J = 9.0, 1.8 Hz, 1H), 7.39 (m, 1H), 7.53 (dd, J = 8.6, 2.0 Hz, 1H), 7.84 (br s, 1H), 8.11-8.13 (m, 2H), 8.19 (d, J = 8.6 Hz, 1H). HPLC-MS (APCI) *m/z* 355 $[M+H]^+$, (method 5) Rt = 3.89 min.

3-[(5-Amino-1,3-benzothiazol-2-yl)methoxy]-2,6-difluorobenzamide (9). To a solution of **8c** (130 mg, 0.36 mmol) in EtOH (5 mL) was added $SnCl_2.2H_2O$ (240 mg, 1.06 mmol, 3 equiv) and the resulting reaction mixture was refluxed for 3 h. The reaction mixture was basified (pH 8) by a saturated solution of $NaHCO_3$, filtered and the filtrate was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified over silica eluting with 80% EtOAc-Hexane to obtain the title compound **9** (12 mg, 17%). ^{1}H-NMR (DMSO-d_6): δ 5.31 (br s, 2H), 5.58 (s, 2H), 6.76 (m, 1H), 7.09 (m, 1H), 7.35 (m, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.87 (br s, 1H), 8.16 (br s, 1H), 8.50 (s, 1H). MS (ESI) *m/z* 336.02 $[M+H]^+$. HPLC purity (method 3) 91.70% Rt = 12.63 min.

3-[(5-Allyl-1,3-benzothiazol-2-yl)methoxy]-2,6-difluorobenzamide (10). To a solution of **8d** (100 mg, 0.25 mmol) in DMF (5 mL) was added allyl tributyltin (83 mg, 0.25 mmol, 1 equiv) and the reaction mixture was degassed for 10 min. Tetrakis (triphenylphosphine)palladium(0) (29 mg, 0.025 mmol, 0.1 equiv) was added and the reaction mixture was again degassed for 10 min. The reaction mixture was heated at 120 °C for 1 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature, water was added and the mixture extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, and evaporated to dryness under reduced pressure. The compound was crystallized from EtOAc-Hexane to give the title compound **10** as brown solid (50 mg, 55%). MS (ESI) *m/z* 361.05 $([M+H]^+$.

2,6-Difluoro-3-[(5-propyl-1,3-benzothiazol-2-yl)methoxy]benzamide (11). To a solution of **10** (100 mg, 0.27 mmol) in methanol (5 mL) was added 10% palladium on charcoal (20 mg). The reaction mixture was stirred at room temperature for 16 h under a hydrogen atmosphere then filtered over a celite bed and the filtrate evaporated to dryness. The residue was crystallized with EtOAc-Hexane to give the title compound **11** as light yellow solid (14 mg, 14%). ^{1}H-NMR (DMSO-d_6): δ 0.92 (t, J = 7.2 Hz, 3H), 1.64 (m, 2H), 2.71 (t, J = 7.2 Hz, 2H), 5.67 (s, 2H), 7.12 (dt, J = 8.8 Hz, 1H), 7.32 (d, J = 8.4, 1H), 7.38 (m, 1H), 7.83 (s, 1H),

7.89 (br s, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 8.17 (br s, 1H). MS (ESI) *m/z* 363.08 $[M+H]^+$. HPLC (method 2) 90.69% Rt =17.64 min.

2,6-Difluoro-3-{[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-benzothiazol-2-yl]methoxy}benzamide (12). A solution of **8d** (150 mg, 0.38 mmol), bispinacolatodiboron (105 mg, 0.41 mmol, 1.08 equiv) and KOAc (56 mg, 0.57 mmol, 1.5 equiv) in 1,4-dioxane (5 mL) was degassed by flushing with nitrogen for 15 min. Tricyclohexylphosphine (11 mg, 0.04 mmol) and tris(dibenzyledineacetone)dipalladium(0) (20 mg, 0.02 mmol) was then added to the reaction mixture, which was again degassed by nitrogen for 15 min. The resulting reaction mixture was heated to 80 - 85 ºC for 2 h. The reaction mixture was filtered through a celite bed and the filtrate was concentrated to obtain crude **12** (100 mg) that was carried forward to the next step without further purification. MS (ESI) *m/z* 447.13 $[M+H]^+$.

3-{[5-(1H-Imidazol-2-yl)-1,3-benzothiazol-2-yl]methoxy}-2,6-difluorobenzamide (13). To a solution of **12** (100 mg, 0.22 mmol) in DMF-H_2O (6 mL, 2:1) was added 2-iodoimidazole (85 mg, 0.44 mmol, 2 equiv) and potassium phosphate (57 mg, 0.26 mmol, 1.18 equiv). The reaction mixture was degassed for 10 min followed by addition of dichlorobis(triphenylphosphine)palladium(II) (70 mg, 0.10 mmol). The reaction mixture was again degassed for 10 min and then heated at 120 °C for 3 h under nitrogen atmosphere. Water (25 mL) was added and the mixture extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with water, brine, dried (Na_2SO_4), filtered and concentrated. The crude residue was purified over silica eluting with 60% EtOAc-Hexane to obtain the title compound **13** (2 mg, 2.5%). ^{1}H-NMR (DMSO-d_6): δ 5.71 (s, 2H), 7.11 (m, 2H), 7.40 (m, 2H), 7.88 (br s, 1H), 8.08 (d, *J* = 9.6 Hz, 1H), 8.19 (m, 2H), 8.36 (br s, 1H), 8.53 (br s, 1H). MS (ESI) *m/z* 386.97 $[M+H]^+$. HPLC purity (method 2) 94.48% Rt = 12.42 min.

2-[(3-Carbamoyl-2,4-difluorophenoxy)methyl]benzothiazole-5-carboxylic acid (14). To a solution of **8i** (1 g, 2.60 mmol) in THF (30 mL) was added a solution of LiOH (330 mg, 7.90 mmol) in H_2O (5 mL) and the resulting reaction mixture was refluxed for 5 h. The solvent was evaporated, water was added and the mixture extracted with EtOAc (2 × 50 mL). The organic layer was discarded and the aqueous layer was acidified with 2N HCl to pH 4-5 followed by extraction with EtOAc (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to obtain the title compound **14** (550

mg, 57%). ^{1}H-NMR (DMSO-d_6): δ 5.73 (s, 2H), 7.12 (m, 1H), 7.40 (m, 1H), 7.90 (br s, 1H), 8.0 (d, *J*= 8.4 Hz, 1H), 8.18 (br s, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 8.50 (s, 1H), 13.22 (br s, 1H). MS (ESI) *m/z* 364.93 $[M+H]^+$. HPLC (method 3) Rt = 13.88 min.

2-[(3-Carbamoyl-2,4-difluorophenoxy)methyl]benzothiazole-5-carbonyl chloride (15). To a solution of **14** (100 mg, 0.27 mmol) in toluene (3 mL) was added $SOCl_2$ (0.1 mL, 1.35 mmol) and the resulting mixture was refluxed for 4 h. The solvent was evaporated under reduced pressure and the residue, compound **15**, thus obtained was further carried forward as such for the next step.

2-((3-Carbamoyl-2,4-difluorophenoxy)methyl)benzothiazole-5-carboxamide (16). The above obtained carbonyl chloride derivative **15** was dissolved in THF (10 mL), cooled to 0 ºC and treated with gaseous NH_3 for 10 min. The reaction mixture was left to stir at room temperature for 16 h. The solvent was evaporated, water was added and the mixture extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried (anhydrous Na_2SO_4), filtered and concentrated. The residue was purified over silica eluting with 5% MeOH-CH_2Cl_2 to obtain the title compound **16** (20 mg, 20%). ^{1}H-NMR (DMSO-d_6): δ 5.73 (s, 2H), 7.11 (m, 1H), 7.39 (m, 1H), 7.48 (br s, 1H), 7.90 (br s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 8.15 (br s, 1H), 8.20 (m, 2H), 8.53 (br s, 1H). LCMS (ESI) *m/z* 364.32 $[M+H]^+$. HPLC (method 4, with a flow rate of 0.30 mL/min) Rt = 2.46 min.

2,6-Difluoro-3-{[5-(3-methyl-1,2,4-oxadiazol-5-yl)-1,3-benzothiazol-2-yl]methoxy}benzamide (17). A solution of **15** (40 mg, 0.10 mmol), acetamide oxime (30 mg, 0.26 mmol, 2.6 equiv) and K_2CO_3 (50 mg, 0.36 mmol, 3.6 equiv) in toluene was refluxed for 16 h. The solvent was evaporated, water was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure. The residue was chromatographed on silica eluting with 60% EtOAc-Hexane to obtain the title compound **17** (2.5 mg, 6%). ^{1}H-NMR (DMSO-d_6): δ 2.45 (s, 3H), 5.76 (s, 2H), 7.12 (m, 1H), 7.42 (m, 1H), 7.90 (br s, 1H), 8.14 (s, 1H), 8.18 (d, *J*= 8.4 Hz, 1H), 8.43 (d, *J*= 8.4 Hz, 1H), 8.66 (s, 1H). MS (ESI) *m/z* 403.06 $[M+H]^+$. HPLC purity (method 3) 91.49% Rt = 15.34 min.

2,6-Difluoro-3-[(5-hydroxy-1,3-benzothiazol-2-yl)methoxy]benzamide (18). A solution of **8h** (100 mg, 0.29 mmol) in CH_2Cl_2 (10 mL) was cooled to –78 ºC followed by dropwise addition of BBr_3 (55 µL, 0.58 mmol, 2 equiv). The resulting reaction mixture was allowed to reach room temperature over 30 min. The

reaction mixture was cooled again to –78 ºC followed by quenching with dropwise addition of a saturated solution of $NaHCO_3$. The reaction mixture was then extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified over silica eluting with 60% EtOAc-Hexane to obtain the title compound **18** (22 mg, 23%), mp 221 ºC. ^{1}H-NMR (DMSO-d_6): δ 5.63 (s, 2H), 6.95 (m, 1H), 7.10 (m, 1H), 7.32 (d, *J*= 2.4 Hz, 1H), 7.36 (m, 1H), 7.89 (d, *J*= 8.8 Hz, 2H), 8.17 (br s, 1H), 9.76 (br s, 1H). MS (ESI) *m/z* 337.13 $[M+H]^+$. HPLC (method 3) Rt = 13.98 min.

3-[(4-Chloro-1,3-benzothiazol-2-yl)methoxy]-2,6-difluorobenzamide (22a). A solution of KOH (15.15 g, 270 mmol, 20 equiv) in water (25 mL) was added to a solution of 4-chloro-1,3-benzothiazol-2-amine (**20a**) (2.5 g, 13.5 mmol) in 2-methoxy-ethanol (25 mL) and the reaction mixture was heated to reflux overnight. After cooling at room temperature, the mixture was diluted with water (200 mL), acidified with 5N HCl solution to pH 4 and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure to dryness, to give crude 2-amino-3-chlorobenzenethiol (**21a**) (1.5 g, 70%). A portion of this material (167 mg, 1.05 mmol, 1.5 equiv) were mixed with **19** (150 mg, 0.7 mmol) and the mixture was stirred at 120 °C, in a pre-heated oil bath, under N_2, for 2 h. EtOH (2 mL) was added and the reaction mixture was heated at 120 °C for a further 2 h. After cooling at room temperature, the precipitant solid was filtered, washed with EtOH and recrystallised from EtOAc/pentane, to give **22a** as a pale yellow solid (62 mg, 25%; overall yield: 18%). ^{1}H-NMR (DMSO-d_6): δ 5.74 (s, 2H), 7.12 (app dt, *J* = 9.0, 1.8 Hz, 1H), 7.41 (m, 1H), 7.48 (app t, *J* = 7.9 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.84 (br s, 1H), 8.12-8.16 (m, 2H). HPLC-MS (APCI) *m/z* 355 $[M+H]^+$, (method 5) Rt = 3.75 min.

3-[(6-Chloro-1,3-benzothiazol-2-yl)methoxy]-2,6-difluorobenzamide (22b). Compound **22b** was prepared from **19** (150 mg, 0.7 mmol) and 6-chloro-1,3-benzothiazol-2-amine (**20b**) following the same procedure as **22a**. After the end of the reaction, the solvent was removed by evaporation under reduced pressure and the residue was triturated with CH_3OH:CH_2Cl_2 (1:1, 4 mL). The solid was filtered, washed with CH_2Cl_2 (2 × 2 mL) and hexane (2 × 5 mL) and dried *in vacuo* at 40 °C to give **22b** as an off-white solid (95 mg, 38%); mp 190-191 °C. ^{1}H-NMR (DMSO-d_6): δ 5.69 (s, 2H), 7.10 (app dt, *J* = 9.0, 1.8 Hz,

1H), 7.39 (m, 1H), 7.58 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.84 (br s, 1H), 8.03 (d, *J* = 8.7 Hz, 1H), 8.13 (br s, 1H), 8.31 (d, *J* = 2.0 Hz, 1H). HPLC-MS (APCI) *m/z* 355 $[M+H]^+$, (method 5) Rt = 3.85 min.

2,6-Difluoro-3-[(4-methyl-1,3-benzothiazol-2-yl)methoxy]benzamide (22c). Compound **22c** was prepared from **19** (150 mg, 0.7 mmol) and 4-methyl-1,3-benzothiazol-2-amine (**20c**) following the same procedure as **22a**. After the end of the reaction, CH_2Cl_2 (4 mL) was added and the precipitant solid was filtered, washed with CH_2Cl_2 (2 × 5 mL) and hexane (5 mL) and dried *in vacuo* at 40 °C to give **22** as an off-white solid (87 mg, 36%); mp 201-202 °C. ^{1}H-NMR (DMSO-d_6): δ 2.68 (s, 3H), 5.69 (s, 2H), 7.10 (app dt, *J* = 9.0, 1.8 Hz, 1H), 7.35-7.43 (m, 3H), 7.83 (br s, 1H), 7.94 (m, 1H), 8.12 (br s, 1H). HPLC-MS (APCI) *m/z* 335 $[M+H]^+$, (method 5) Rt = 3.79 min.

2,6-Difluoro-3-[(6-methyl-1,3-benzothiazol-2-yl)methoxy]benzamide (22d). Compound **22d** was prepared from **19** (150 mg, 0.7 mmol) and 6-methyl-1,3-benzothiazol-2-amine (**20d**) following the same procedure as **22a**. After the end of the reaction, EtOAc (4 mL) was added and the precipitant solid was filtered hot. This crude product was triturated with hot CH_3CN, under reflux, undissolved solids were filtered off and the filtrate was concentrated to dryness under reduced pressure to give brown solid (40 mg, 17%). ^{1}H-NMR (DMSO-d_6): δ 2.46 (s, 3H), 5.65 (s, 2H), 7.09 (app dt, *J* = 9.0, 1.8 Hz, 1H), 7.35-7.41 (m, 2H), 7.83 (br s, 1H), 7.89-7.93 (m, 2H), 8.12 (br s, 1H). HPLC-MS (APCI) *m/z* 335 $[M+H]^+$, purity (method 5) 94% Rt = 3.70 min.

2-Aminobiphenyl-3-thiol (21e). A solution of 4-phenylbenzothiazol-2-amine (**20e**) (1 g, 4.42 mmol) and 10 N NaOH (25 mL) was refluxed for 16 h. A thick precipitate was observed that was dissolved in acetic acid and EtOAc. The solvent was removed, water was added (500 mL) and extracted with EtOAc (3 × 500 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to obtain the title compound **21e** (1 g crude yield) as oil that was carried forward to the next step without further purification. MS (ESI) *m/z* 202.10 $[M+H]^+$.

2,6-Difluoro-3-[(4-phenyl-1,3-benzothiazol-2-yl)methoxy]benzamide (22e). A mixture of **21e** (1 g, 4.97 mmol) and **19** (1.05 g, 4.97 mmol, 1 equiv) in EtOH was heated to 150 ºC in an autoclave for 16 h. The reaction mixture was diluted with MeOH and evaporated under reduced pressure. The residue was directly loaded onto a silica column and eluted with 35-50% EtOAc-Hexane to obtain the title compound **22e** (103 mg, 5%). ^{1}H-NMR (DMSO-d_6): δ 5.70 (s, 2H), 7.10 (app t, *J* = 8.4 Hz, 1H), 7.42 (m, 2H), 7.50 (m, 3H),

7.62 (m, 1H), 7.81 (d, J = 6.8 Hz, 2H), 7.89 (br s, 1H), 8.14 (br s, 1H), 8.17 (m, 1H). MS (ESI) *m/z* 397.09 $[M+H]^+$. HPLC purity (method 1) 89.87% Rt = 10.47 min.

2,6-Difluoro-3-[(6-phenyl-1,3-benzothiazol-2-yl)methoxy]benzamide (24a). Compound **24a** was prepared from **4** (17 mg, 0.10 mmol) and 2-(bromomethyl)-6-phenylbenzothiazole (**23a**) (30 mg, 0.10 mmol, 1 equiv) using 3.5 equiv K_2CO_3 according to the general procedure (25 ºC, 16 h, EtOAc/H_2O work-up, with additional 1N NaOH wash). The residue was triturated with diethyl ether to obtain the title compound **24a** (10 mg, 25%). ^{1}H-NMR (DMSO-d_6): δ 5.72 (s, 2H), 7.11 (app t, J = 8.8 Hz, 1H), 7.40 (m, 2H), 7.50 (m, 2H), 7.76 (d, J = 7.6 Hz, 2H), 7.85 (d, J = 8.4 Hz, 1H), 7.89 (br s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 8.18 (br s, 1H), 8.46 (s, 1H). MS (ESI) *m/z* 397.13 $[M+H]^+$. HPLC (method 1) Rt = 10.29 min.

2,6-Difluoro-3-[(6-methoxy-1,3-benzothiazol-2-yl)methoxy]benzamide (24b). Compound **24b** was prepared from **4** (405 mg, 2.3 mmol) and 2-(chloromethyl)-6-methoxy-1,3-benzothiazole (**23b**) (500 mg, 2.3 mmol, 1 equiv) using 1.5 equiv K_2CO_3, according to the general procedure (60 ºC, overnight, EtOAc/H_2O work-up). The crude product was triturated with CH_2Cl_2 (10 mL), filtered and dried *in vacuo* at 40 °C to give **24b** as a white solid (150 mg, 19%); mp 190-192 °C. ^{1}H-NMR (DMSO-d_6): δ 3.84 (s, 3H), 5.62 (s, 2H), 7.06-7.15 (m, 2H), 7.38 (m, 1H), 7.70 (d, J = 2.5 Hz, 1H), 7.83 (br s, 1H), 7.90 (d, J = 9.0 Hz, 1H), 8.12 (br s, 1H). HPLC-MS (APCI) *m/z* 351 $[M+H]^+$, purity (method 5) 92% Rt = 3.50 min.

3-[(5/7-Bromo-4-methoxy-1,3-benzothiazol-2-yl)methoxy]-2,6-difluorobenzamide (24c). Compound **24c** was prepared from **4** (180 mg, 1.05 mmol) and 5/7-bromo-2-(bromomethyl)-4-methoxybenzothiazole (**23c**) (0.35 g, 1.05 mmol, 1 equiv) using 3.5 equiv K_2CO_3, according to the general procedure (25 ºC, 2 h, EtOAc/H_2O work-up). The residue was chromatographed on silica eluting with 5% EtOAc-Hexane to obtain the title compound **24c** (60 mg, 14%), mp 236 ºC. ^{1}H-NMR (DMSO-d_6): δ 3.96 (s, 3H), 5.68 (s, 2H), 7.10 (d, J = 8.8 Hz, 1H), 7.14 (m, 1H), 7.40 (m, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.90 (br s, 1H), 8.18 (br s, 1H). MS (ESI) *m/z* 429.11 $[M+H]^+$. HPLC (method 3) Rt = 15.97 min.

2,6-Difluoro-3-[(7-phenyl-1,3-benzothiazol-2-yl)methoxy]benzamide (24d). Compound **24d** was prepared from **4** (37 mg, 0.21 mmol) and 2-(bromomethyl)-7-phenylbenzothiazole (**23d**) (66 mg, 0.21 mmol, 1 equiv) using 3.5 equiv K_2CO_3, according to the general procedure (25 ºC, 16 h, EtOAc/H_2O work-up, with additional 1N NaOH wash). The residue was triturated with diethyl ether to obtain the title compound **24d** (23 mg, 27%). ^{1}H-NMR (DMSO-d_6): δ 5.70 (s, 2H), 7.12 (m, 1H), 7.38 (m, 1H), 7.50 (m,

1H), 7.55 (m, 3H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.88 (br s, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 8.16 (br s, 1H). MS (ESI) *m/z* 397.15 $[M+H]^+$. HPLC (method 1) Rt = 10.51 min.

3-[(7-Chloro-1,3-benzothiazol-2-yl)methoxy]-2,6-difluorobenzamide (24e). Compound **24e** was prepared from **4** (198 mg, 1.14 mmol) and 2-bromomethyl-7-chloro-benzothiazole (**23e**) (300 mg, 1.14 mmol, 1 equiv) according to the general procedure (25 ºC, 24 h). The reaction mixture was evaporated to dryness under reduced pressure and the residue was purified by chromatography on silica eluting with 30% EtOAc-Hexane to provide the title compound **24e** as a light yellow solid (20 mg, 5%). ^{1}H-NMR (DMSO-d_6): δ 5.73 (s, 2H), 7.12 (app dt, *J* = 9.2, 1.6 Hz, 1H), 7.41 (m, 1H), 7.61 (m, 2H), 7.91 (br s, 1H), 8.04 (dd, *J* = 7.2, 1.6 Hz, 1H), 8.19 (br s, 1H). MS (ESI) *m/z* 355.04 $[M+H]^+$. HPLC (method 1) Rt = 9.85 min.

2,6-Difluoro-3-[(4-methoxy-1,3-benzothiazol-2-yl)methoxy]benzamide (25). To a solution of **24c** (250 mg, 0.58 mmol) in MeOH (10 mL) and aqueous NH_3 (25% solution, 5 mL) was added Pd-C (50 mg) and the resulting reaction mixture was stirred at room temperature under a hydrogen atmosphere for 2 h. The reaction mixture was then filtered through a celite bed and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica eluting with 50% EtOAc-Hexane to obtain the title compound **25** (27 mg, 14%). ^{1}H-NMR (DMSO-d_6): δ 3.96 (s, 3H), 5.68 (s, 2H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.30-7.45 (m, 3H), 7.65 (dd, *J* = 8.0, 3.6 Hz, 1H), 7.89 (br s, 1H), 8.17 (br s, 1H). MS (ESI) *m/z* 351.02 $[M+H]^+$. HPLC purity (method 3) 80.41% Rt = 14.95 min.

3-({6-bromopyrido[3,2-d][1,3]thiazol-2-yl}methoxy)-2,6-difluorobenzamide (28a). Compound **28a** was prepared from **4** (1.01 g, 5.84 mmol) and 6-bromo-2-(bromomethyl)pyrido[3,2-d][1,3]thiazole (**27a**) (2 g, 6.50 mmol, 1.1 equiv) using 3.5 equiv K_2CO_3, according to the general procedure (25 ºC, 16 h). The reaction mixture was evaporated to dryness under reduced pressure and the residue was purified by chromatography on silica eluting with 50% EtOAc-Hexane to provide the title compound **28a** (1.80 g, 69%). ^{1}H NMR (DMSO-d_6): δ 5.72 (s, 2H), 7.12 (app t, *J* = 7.6 Hz, 1H), 7.39 (m, 1H), 7.90 (br s, 1H), 8.18 (br s, 1H), 8.80 (m, 2H). MS (ESI) *m/z* 402.08 $[M+H]^+$. HPLC (method 3) Rt = 15.50 min.

3-({5-bromo-6-ethoxypyrido[3,2-d][1,3]thiazol-2-yl}methoxy)-2,6-difluorobenzamide (28b). Compound **24d** was prepared from **4** (110 mg, 0.64 mmol, 1.5 equiv) and 5-bromo-2-(bromomethyl)-6-ethoxypyrido[3,2-d][1,3]thiazole (**27b**) (150 mg, 0.43 mmol) using 3.5 equiv K_2CO_3, according to the general procedure (25 ºC, 2 h, EtOAc/H_2O work-up, with additional 1N NaOH wash). The residue thus

obtained was triturated with diethyl ether to obtain the title compound **28b** (150 mg, 79%). ^{1}H-NMR (DMSO-d_6): δ 1.43 (t, J = 7.2 Hz, 3H), 4.27 (q, J = 7.2 Hz, 2H), 5.68 (s, 2H), 7.11 (m, 1H), 7.39 (m, 1H), 7.90 (br s, 1H), 8.16 (s, 1H), 8.17 (br s, 1H). MS (ESI) *m/z* 443.90 $[M+H]^+$.

3-({6-chloropyrido[4,3-d][1,3]thiazol-2-yl}methoxy)-2,6-difluorobenzamide (28c). Compound **28c** was prepared from **4** (33 mg, 0.19 mmol) and 2-(bromomethyl)-6-chloropyrido[4,3-d][1,3]thiazole (**27c**) (50 mg, 0.19 mmol, 1 equiv) using 3.5 equiv K_2CO_3, according to the general procedure (25 ºC, 16 h). The reaction mixture was evaporated to dryness under reduced pressure and the residue was purified by chromatography on silica eluting with 50% EtOAc-Hexane to provide the title compound **28c** (12 mg, 18%). ^{1}H NMR (DMSO-d_6): δ 5.78 (s, 2H), 7.12 (m, 1H), 7.40 (m, 1H), 7.91 (br s, 1H), 8.19 (br s, 1H), 8.20 (s, 1H), 9.25 (s, 1H). MS (ESI) *m/z* 355.94 $[M+H]^+$. HPLC purity (method 2) 92.16% Rt = 15.25min.

3-({5-chloro-6-methoxypyrido[3,2-d][1,3]thiazol-2-yl}methoxy)-2,6-difluorobenzamide (28d). Compound **28d** was prepared from **4** (50 mg, 0.29 mmol) and 2-(bromomethyl)-5-chloro-6-methoxypyrido[3,2-d][1,3]thiazole (**27d**) (86 mg, 0.29 mmol, 1 equiv) using 3.5 equiv K_2CO_3, according to the general procedure (25 ºC, 3 h, EtOAc/H_2O work-up with additional 1N NaOH wash). The residue thus obtained was triturated with diethyl ether to obtain the title compound **28d** (30 mg, 27%), mp 256 ºC. ^{1}H-NMR (DMSO-d_6): δ 4.0 (s, 3H), 5.69 (s, 2H), 7.09 (m, 1H), 7.39 (m, 1H), 7.89 (br s, 1H), 8.17 (br s, 1H), 8.24 (s, 1H). MS (ESI) *m/z* 386.16 $[M+H]^+$. HPLC purity (method 4) 94.79% Rt = 5.34 min.

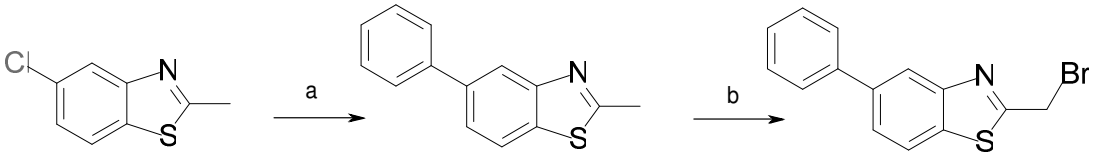
3-({6-ethoxypyrido[3,2-d][1,3]thiazol-2-yl}methoxy)-2,6-difluorobenzamide (29). To a solution of **28b** (150 mg, 0.33 mmol) in DMF-H_2O (6 mL, 5:1) was added 2,4,6-trifluoro-3-methoxyphenylboronic acid (83 mg, 0.40 mmol, 1.2 equiv) and potassium phosphate (210 mg, 1 mmol, 3 equiv). The reaction mixture was degassed for 10 min followed by addition of dichlorobis(triphenylphosphine)palladium(II) (23 mg, 0.03 mmol, 0.1 equiv). The reaction mixture was again degassed for 10 min and then heated at 90 °C for 16 h under a nitrogen atmosphere. Water (25 mL) was added and the mixture was extracted with EtOAc (4 × 25 mL). The combined organic extracts were washed with water, brine, dried (Na_2SO_4), filtered and concentrated. The crude residue was chromatographed on silica eluting with 1% MeOH- CH_2Cl_2 to obtain the title compound **29** (15 mg, 12%), mp 206 ºC. (The desired Suzuki product was not formed). ^{1}H-NMR (DMSO-d_6): δ 1.38 (t, J = 7.2 Hz, 3H), 4.20 (q, J = 7.2 Hz, 2H), 5.67 (s, 2H), 7.11 (m, 1H), 7.40 (m, 1H),

7.88 (br s, 1H), 8.02 (d, J = 2.4 Hz, 1H), 8.16 (br s, 1H), 8.40 (d, J = 2.4 Hz, 1H). MS (ESI) *m/z* 366.04 $[M+H]^+$. HPLC (method 4) Rt = 5.23 min.

2,6-difluoro-3-({6-phenylpyrido[3,2-d][1,3]thiazol-2-yl}methoxy)benzamide (30). To a solution of **28a** (200 mg, 0.50 mmol) in DMF-H_2O (6 mL, 2:1) was added phenyl boronic acid (120 mg, 1 mmol, 2 equiv) and potassium phosphate (120 mg, 0.60 mmol, 1.2 equiv). The reaction mixture was degassed for 10 min followed by addition of dichlorobis(triphenylphosphine)palladium(II) (70 mg, 0.10 mmol, 0.2 equiv). The reaction mixture was again degassed for 10 min and then heated at 110 °C for 4 h under nitrogen atmosphere. Water (25 mL) was added and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water, brine, dried (Na_2SO_4), filtered and concentrated. The crude residue was chromatographed on silica eluting with 60% EtOAc-Hexane to obtain the title compound **30** (80 mg, 40%), mp 195 ºC. ^{1}H NMR (DMSO-d_6): δ 5.74 (s, 2H), 7.10 (m, 1H), 7.40-7.48 (m, 2H), 7.52-7.59 (m, 2H), 7.85 (d, J = 7.2 Hz, 2H), 7.91 (br s, 1H), 8.19 (br s, 1H), 8.70 (d, J = 2.4 Hz, 1H), 8.98 (d, J = 2.0 Hz, 1H). MS (ESI) *m/z* 398.09 $[M+H]^+$. HPLC (method 3) Rt = 16.15 min.

Synthesis of intermediates

Supplementary Scheme 1. Reagents and conditions: (a) Phenylboronic acid, K_3PO_4, $Pd(dppf)_2Cl_2$, DMF-H_2O, 110 ºC; (b) NBS, AIBN, CCl_4.



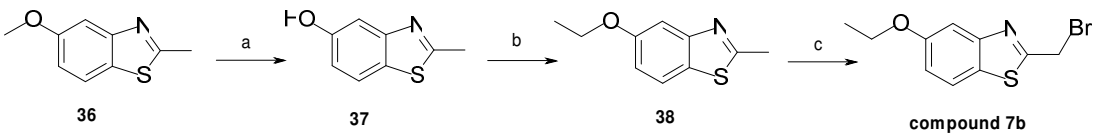
34 **35** **compound 7a**

2-Methyl-5-phenylbenzothiazole (35). To a solution of 5-chloro-2-methylbenzothiazole (**34**) (200 mg, 1.08 mmol) in DMF-H_2O (9 mL, 2:1) was added phenyl boronic acid (160 mg, 1.31 mmol) and potassium phosphate (280 mg, 1.30 mmol). The reaction mixture was degassed for 20 min followed by addition of [1,1'-Bis(diphenylphosphino)-ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (130 mg, 0.16 mmol). The reaction mixture was again degassed for 20 min and then heated at 110 °C for 2 h under N_2 atmosphere. Water (25 mL) was added and extracted with EtOAc (3 × 50 mL). The combined organic

extracts were washed with water, brine, dried (Na_2SO_4), filtered and concentrated. The crude residue was purified over silica eluting with 5% EtOAc-Hexane to obtain the title compound **35** (50 mg, 21%). MS *m/z* 226.06 $[M+H]^+$.

2-(Bromomethyl)-5-phenylbenzothiazole (7a). To a solution of **35** (330 mg, 1.46 mmol) in CCl_4 (20 mL) was added NBS (520 mg, 2.93 mmol) and AIBN (65 mg, catalytic). The resulting reaction mixture was refluxed for 7-8 h. The solvent was evaporated and the residue was purified over silica eluting with 5% EtOAc-Hexane to obtain the title compound **7a** (240 mg, 54%). MS *m/z* 303.98 $[M+H]^+$.

Supplementary Scheme 2. Reagents and conditions: (a) BBr_3, CH_2Cl_2; (b) NaH, EtI; (c) NBS, AIBN, CCl_4.



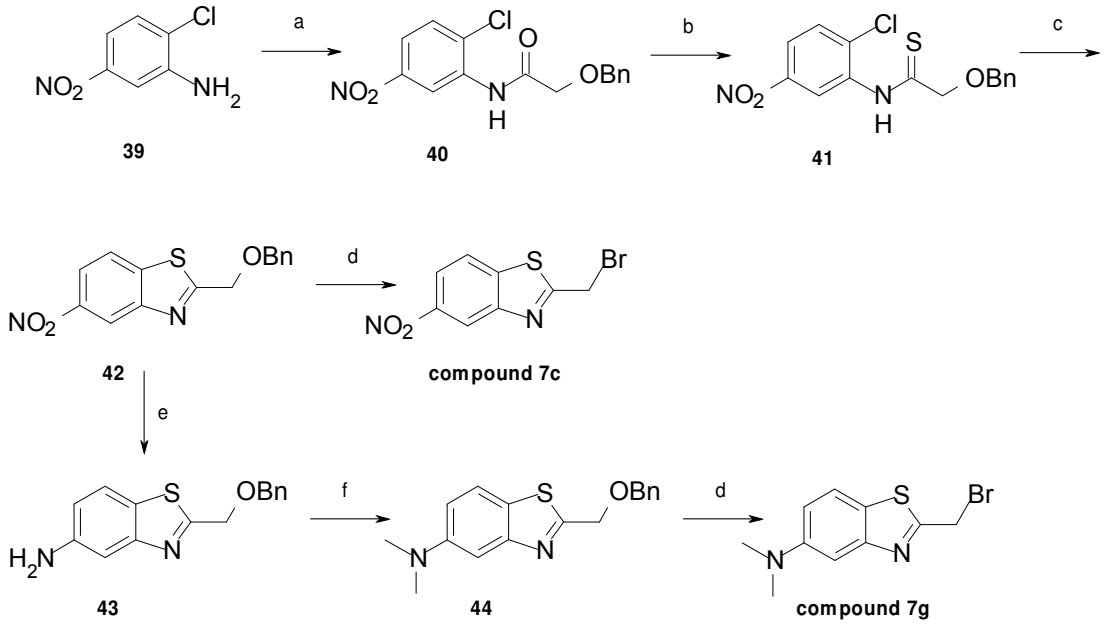
2-Methylbenzothiazol-5-ol (37). A solution of 5-methoxy-2-methylbenzothiazole (**36**) (500 mg, 2.70 mmol) in CH_2Cl_2 (7 mL) was cooled to –78 ºC followed by addition of BBr_3 (1.30 mL, 13.90 mmol). The resulting reaction mixture was allowed to come to room temperature and then stirred for 30 min. The reaction mixture was cooled to –78 ºC followed by quenching with dropwise addition of H_2O. The reaction mixture was then extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was triturated with diethyl ether to obtain the title compound **37** (400 mg, 89%). ^{1}H-NMR (DMSO-d_6): δ 2.77 (s, 3H), 6.88 (dd, *J*= 2.4, 8.8 Hz, 1H), 7.23 (d, *J* = 2.4 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 9.62 (br s, 1H).

5-Ethoxy-2-methylbenzothiazole (38). To an ice-cold suspension of NaH (60% dispersion in mineral oil, 30 mg, 0.73 mmol) in THF (5 mL) was added a solution of **37** (100 mg, 0.61 mmol) in THF (2 mL) dropwise. The resulting reaction mixture was stirred at room temperature for 30 min. The reaction mixture was again cooled to 0 ºC followed by addition of ethyl iodide (73 μL, 0.92 mmol) and continued to stir at 40 ºC for 16 h. The reaction mixture was cooled to 0 ºC followed by quenching with H_2O and extraction with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified over silica eluting with 40% EtOAc-

Hexane to obtain the title compound **38** (65 mg, 55%). ^{1}H-NMR ($CDCl_3$): δ 1.45 (t, J = 6.8 Hz, 3H), 2.81 (s, 3H), 4.10 (q, J = 6.8 Hz, 2H), 6.99 (dd, J = 2.4, 8.8 Hz, 1H), 7.43 (d, J = 2.8 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H).

2-(Bromomethyl)-5-ethoxybenzothiazole (7b). To a solution of **38** (250 mg, 0.92 mmol) in CCl_4 (5 mL) was added NBS (190 mg, 1.10 mmol) and AIBN (20 mg, 0.12 mmol). The resulting reaction mixture was refluxed for 3 h. The solvent was evaporated and the residue was directly loaded onto a silica column and eluted with 2% EtOAc-Hexane to obtain the title compound **7b** (60 mg, 24%). ^{1}H-NMR ($CDCl_3$): δ 1.46 (t, J = 7.2 Hz, 3H), 4.10 (q, J = 6.8 Hz, 2H), 4.79 (s, 2H), 7.07 (d, J = 2.4, 8.80 Hz, 1H), 7.48 (d, J = 2.4 Hz, 1H), 7.72 (d, J = 9.2 Hz, 1H).

Supplementary Scheme 3. Reagents and conditions: (a) 2-(benzyloxy)acetyl chloride, triethyl amine, CH_2Cl_2; (b) Lawesson's Reagent, toluene, reflux; (c) NaH, NMP, 140 ºC; (d) BBr_3, CH_2Cl_2; (e) Fe-AcOH, 100 ºC; (f) NaH, MeI, THF.



2-(Benzyloxy)-N-(2-chloro-5-nitrophenyl)acetamide (40). To an ice cold solution of 2-chloro-5-nitroaniline (**39**) (5 g, 28.97 mmol) in CH_2Cl_2 (50 mL) was added triethyl amine (6.04 mL, 43.46 mmol) followed by the addition of a solution of 2-(benzyloxy)acetyl chloride (6.32 g, 34.76 mmol) in CH_2Cl_2 (50 mL). The resulting reaction mixture was stirred at room temperature for 3 - 4 h. Water was added and the

organic layer was extracted. The aqueous fraction was re-extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified over silica eluting with 5% EtOAc-Hexane to obtain the title compound **40** (8 g, 86%). MS *m/z* 321.10 $[M+H]^+$.

2-(Benzyloxy)-N-(2-chloro-5-nitrophenyl)ethanethioamide (41). To a solution of **40** (2 g, 6 mmol) in toluene (50 mL) was added Lawesson's reagent (1.70 g, 4.20 mmol) and the reaction mixture was refluxed for 8 - 10 h. The solvent was evaporated and the residue was diluted with water and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified over silica eluting with 5% EtOAc-Hexane to obtain the title compound **41** (2 g, 99%). ^{1}H-NMR ($CDCl_3$): δ 4.52 (s, 2H), 4.73 (s, 2H), 7.34-7.40 (m, 5H), 7.62 (d, *J* = 8.8 Hz, 1H), 8.08 (dd, *J* = 2.4, 8.4 Hz, 1H), 10.06 (d, *J* = 2.8 Hz, 1H), 10.55 (br s, 1H).

2-(Benzyloxymethyl)-5-nitrobenzothiazole (42). To a solution **41** (1 g, 2.96 mmol) in NMP (4 mL) was added NaH (60% dispersion in mineral oil, 120 mg, 2.96 mmol) portion wise. The reaction mixture was then heated to 140 ºC for 30 min. The reaction mixture was cooled to room temperature and poured onto crushed ice followed by extraction with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to obtain the title compound **42** (850 mg, quantitative yield). ^{1}H-NMR ($CDCl_3$): δ 4.73 (s, 2H), 4.97 (s, 2H), 7.32-7.42 (m, 5H), 8.02 (d, *J* = 8.8 Hz, 1H), 8.28 (dd, *J* = 2.4, 8.8 Hz, 1H), 8.43 (d, *J* = 2.0 Hz, 1H).

2-(Bromomethyl)-5-nitrobenzothiazole (7c). A solution of **42** (400 mg, 1.33 mmol) in CH_2Cl_2 (10 mL) was cooled to –78 ºC followed by dropwise addition of BBr_3 (0.63 mL, 6.66 mmol). The resulting reaction mixture was stirred at room temperature for 4 h. The reaction mixture was cooled again to –78 ºC followed by quenching with MeOH and water. The reaction mixture was then extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified over silica eluting with 2% EtOAc-Hexane to obtain the title compound **7c** (310 mg, 86%). ^{1}H-NMR ($CDCl_3$): δ 5.02 (s, 2H), 8.04 (d, *J* = 8.8 Hz, 1H), 8.30 (dd, *J* = 2.4, 8.8 Hz, 1H), (d, *J* = 2.0 Hz, 1H).

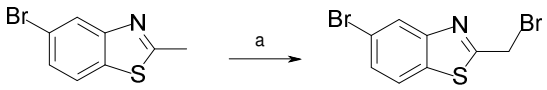
2-(Benzyloxymethyl)benzothiazol-5-amine (43). To a solution of **42** (1 g, 3.33 mmol) in AcOH (15 mL) was added Fe powder (930 mg, 16.65 mmol) and the resulting reaction mixture was refluxed for 15 min.

The reaction mixture was filtered through celite bed, the filtrate was diluted with water, basified with 10% NaOH solution and extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified over silica eluting with 25% EtOAc-Hexane to obtain the title compound **43** (600 mg, 67%). MS *m/z* 271.10 $[M+H]^+$.

2-(Benzyloxymethyl)-N,N-dimethylbenzothiazol-5-amine (44). To an ice cold solution of **43** (400 mg, 1.48 mmol) in THF (25 mL) was added NaH (60% dispersion in mineral oil, 150 mg, 3.70 mmol) portion wise and the resulting reaction mixture was stirred at room temperature for 15 min. The reaction mixture was again cooled to 0 ºC followed by addition of methyl iodide (0.23 mL, 3.70 mmol) and left to stir at room temperature for 16 h and under reflux for 2 h. The reaction mixture was cooled to 0 ºC and quenched by dropwise addition of water followed by extraction with EtOAc (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified over silica eluting with 6% EtOAc-Hexane to obtain the title compound **44** (110 mg, 25%). MS *m/z* 299.17 $[M+H]^+$.

2-(Bromomethyl)-N,N-dimethylbenzothiazol-5-amine (7g). A solution of **44** (110 mg, 0.37 mmol) in CH_2Cl_2 (10 mL) was cooled to –70 ºC followed by addition of BBr_3 (0.11 mL, 1.10 mmol) and the resulting reaction mixture was stirred at room temperature for 1 h. The reaction mixture was cooled to –30 ºC, quenched by dropwise addition of H_2O followed by extraction with EtOAc (3 × 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified over silica eluting with 2% EtOAc-Hexane to obtain the title compound **7g** (62 mg, 62%). MS *m/z* 271.04 $[M+H]^+$.

Supplementary Scheme 4. Reagents and conditions: (a) NBS, AIBN, CCl_4.

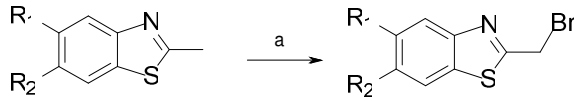


45 compound 7d

5-Bromo-2-(bromomethyl)benzothiazole (7d). To a solution of 2-methyl-5-bromobenzothiazole (**45**) (5 g, 22.04 mmol) in CCl_4 (90 mL) was added NBS (8 g, 44.94 mmol) and AIBN (750 mg). The resulting reaction mixture was heated to 90 ºC for 3 - 4 h. The solvent was evaporated and the residue was purified

over silica eluting with 5% EtOAc-Hexane to obtain the title compound **7d** (1.10 g, 16%). MS *m/z* 305.90 $[M+H]^+$.

Supplementary Scheme 5. Reagents and conditions: (a) NBS, AIBN, CCl_4.



R1=H;R2=Ph **46**
R1=Me; R2=H **47**
R1=OMe; R2=H **48**

R1=H;R2=Ph **compound 23a**
R1=Me; R2=H **compound 7f**
R1=OMe; R2=H **compound 7h**

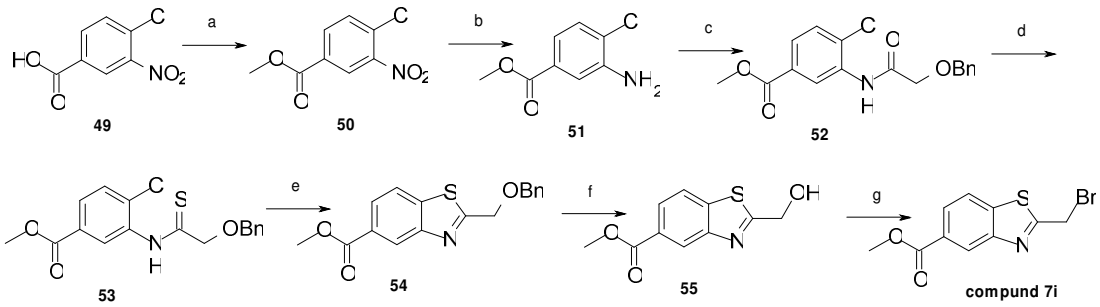
2-(Bromomethyl)-6-phenylbenzothiazole (23a). To a solution of 2-methyl-6-phenylbenzothiazole (**46**) (80 mg, 0.35 mmol) in CCl_4 (5 mL) was added NBS (95 mg, 0.53 mmol) and AIBN (10 mg, catalytic). The resulting reaction mixture was refluxed for 7 - 8 h. The solvent was evaporated and the residue was purified over silica eluting with 2% EtOAc-Hexane to obtain the title compound **23a** (32 mg, 30%). MS *m/z* 303.97 $[M+H]^+$.

2-(Bromomethyl)-5-methylbenzothiazole (7f). To a solution of 2,5-dimethylbenzothiazole (**47**) (600 mg, 3.67 mmol) in CCl_4 (15 mL) was added NBS (650 mg, 3.67 mmol) and AIBN (50 mg, catalytic) and the resulting reaction mixture was refluxed for 3 h. The solvent was evaporated and the residue was purified over silica eluting with 10% EtOAc-Hexane to obtain the title compound **7f** (60 mg, 7%). MS *m/z* 241.98 $[M+H]^+$.

2-(Bromomethyl)-5-methoxybenzothiazole (7h). To a solution of 5-methoxy-2-methylbenzothiazole (**48**) (200 mg, 1.11 mmol) in CCl_4 (25 mL) was added NBS (200 mg, 1.11 mmol) and AIBN (18 mg, 0.11 mmol). The resulting reaction mixture was refluxed for 3 h. The reaction mixture was filtered through a celite bed and the filtrate was evaporated under reduced pressure. The residue was purified over silica eluting with 1.50% EtOAc-Hexane to obtain the title compound **7h** (50 mg, 17%). ^{1}H-NMR (DMSO-d_6): δ 3.88 (s, 3H), 4.79 (s, 2H), 7.08 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.50 (d, *J* = 2.8 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 1H). MS *m/z* 257.95 $[M+H]^+$.

Supplementary Scheme 6. Reagents and conditions: (a) MeOH, H_2SO_4, reflux; (b) $SnCl_2$, MeOH, reflux; (c) 2-(benzyloxy)acetyl chloride, triethylamine, CH_2Cl_2; (d) Lawesson's Reagent, toluene, reflux; (e) NaH,

NMP, reflux; (f) Methanesulfonic acid, CH_2Cl_2; (g) PBr_3, toluene, reflux.



Methyl 4-chloro-3-nitrobenzoate (50). To a solution of 4-chloro-3-nitrobenzoic acid (**49**) (20 g, 99.23 mmol) in MeOH (150 mL) was added concentrated H_2SO_4 (4 mL) and the reaction mixture was refluxed for 16 h. The solvent was evaporated, water was added and the mixture extracted with EtOAc (3 × 250 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to obtain the title compound **50** (21.50 g, 98%). ^{1}H-NMR ($CDCl_3$): δ 3.97 (s, 3H), 7.66 (d, J = 8.4 Hz, 1H), 8.15 (dd, J = 2.0, 8.4 Hz, 1H), 8.51 (d, J = 2.0 Hz, 1H).

Methyl 3-amino-4-chlorobenzoate (51). To a solution of **50** (2.50 g, 11.59 mmol) in MeOH (100 mL) was added anhydrous $SnCl_2$ (21.90 g, 115.90 mmol). The resulting reaction mixture was refluxed for 1 h. The reaction mixture was cooled to 0 ºC followed by dropwise addition of a saturated solution of $NaHCO_3$ to pH 8. The reaction mixture was then filtered and the filtrate was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain the title compound **51** (2 g, 92%). ^{1}H-NMR (DMSO-d_6): δ 3.80 (s, 3H), 5.67 (br s, 2H), 7.08 (dd, J = 2.0, 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 2.0 Hz, 1H). MS m/z 186.17 $[M+H]^+$.

Methyl 3-(2-(benzyloxy)acetamido)-4-chlorobenzoate (52). A solution of **51** (10.50 g, 56.70 mmol) in CH_2Cl_2 (150 mL) was cooled to –78 ºC followed by sequential addition of triethyl amine (12 mL, 62.40 mmol) and a solution of 2-(benzyloxy)acetyl chloride (10.50 g, 62.40 mmol) in CH_2Cl_2 (100 mL). The resulting reaction mixture was stirred at room temperature for 2 h. Water was added and the organic layer was extracted. The aqueous fraction was re-extracted with CH_2Cl_2 (2 × 250 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4 followed by the removal of solvent under reduced pressure. The residue was then purified over silica eluting with 10% EtOAc-Hexane to obtain the title compound **52** (8.10 g, 43%). MS m/z 334.01 $[M+H]^+$.

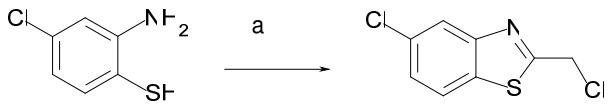
Methyl 3-(2-(benzyloxy)ethanethioamido)-4-chlorobenzoate (53). To a solution of **52** (8.10 g, 24.30 mmol) in toluene (80 mL) was added Lawesson's reagent (4.90 g, 12.10 mmol) and the reaction mixture was refluxed for 3 h. The solvent was evaporated and the residue was purified over silica eluting with 5% EtOAc-Hexane to obtain the title compound **53** (6 g, 71%). ^{1}H-NMR (DMSO-d_6): δ 3.87 (s, 3H), 4.50 (s, 2H), 4.71 (s, 2H), 7.31-7.47 (m, 5H), 7.76 (d, J = 8.4 Hz, 1H), 7.93 (dd, J = 1.2, 8.4 Hz, 1H), 8.08 (s, 1H), 11.38 (br s 1H). MS *m/z* 350.10 $[M+H]^+$.

Methyl 2-(benzyloxymethyl)benzothiazole-5-carboxylate (54). To a solution of **53** (6 g, 17.20 mmol) in NMP (50 mL) was added NaH (60% dispersion in mineral oil, 620 mg, 15.50 mmol) portion wise over a period of 15 - 20 min. The resulting reaction mixture was refluxed at 160 ºC for 1 h. The reaction mixture was poured onto crushed ice and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine, dried (anhydrous Na_2SO_4), filtered and concentrated to obtain the title compound **54** (4.10 g, 76%). ^{1}H-NMR (DMSO-d_6): δ 3.90 (s, 3H), 4.72 (s, 2H), 5.01 (s, 2H), 7.31-7.43 (m, 5H), 8.01 (d, J = 8.4 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 8.48 (br s, 1H). MS *m/z* 314.06 $[M+H]^+$.

Methyl 2-(hydroxymethyl)benzothiazole-5-carboxylate (55). To a solution of **54** (1.20 g, 3.82 mmol) in CH_2Cl_2 (25 mL) was added methanesulfonic acid (5.20 mL, 76.40 mmol) and the resulting reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water followed by extraction with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with saturated solution of $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain the title compound **55** (690 mg, 81%). ^{1}H-NMR (DMSO-d_6): δ 3.90 (s, 3H), 4.90 (s, 2H), 6.38 (t, J = 6.0 Hz, 1H), 7.98 (dd, J = 1.6, 8.4 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 8.48 (s, 1H). MS *m/z* 224.07 $[M+H]^+$.

Methyl 2-(bromomethyl)benzothiazole-5-carboxylate (7i). To a solution of **55** (200 mg, 0.89 mmol) in toluene (10 mL) was added PBr_3 (130 µL, 1.34 mmol) and the resulting reaction mixture was refluxed for 15 min. After cooling to room temperature, water was added followed by extraction with EtOAc (3 × 50 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution, brine, dried (anhydrous Na_2SO_4), filtered and concentrated to obtain the title compound **7i** (200 mg, 78%) that was carried forward without further purification. MS *m/z* 285.95 $[M+H]^+$.

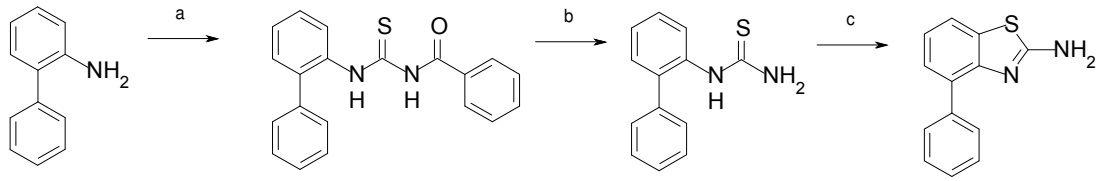
Supplementary Scheme 7. Reagents and conditions: (a) 2-chloro-1,1,1-trimethoxy ethane, 60 °C.



56 **compound 7j**

5-Chloro-2-(chloromethyl)-1,3-benzothiazole (7j). 2-Amino-4-chlorobenzenethiol (**56**) (4.05 g, 25.4 mmol) and 2-chloro-1,1,1-trimethoxy ethane (5 mL, 37 mmol, 1.45 equiv) were heated with stirring at 60 °C for 2 h. The reaction mixture was cooled at room temperature and triturated with diethyl ether (10 mL). The un-dissolved solid was filtered and rinsed with diethyl ether and pentane, to give 1.54 g (28% yield) of **7j**. The mother liquors were evaporated to dryness, the orange solid residue was dissolved in diethyl ether (50 mL) and washed consecutively with 1N HCl (25 mL), water (25 mL), 5% $NaHCO_3$ solution (25 mL) and brine (25 mL). The organic layer was dried (MgSO4) and evaporated to smaller volume, under reduced pressure. The precipitant solid was filtered and washed with diethyl ether and pentane, to give a second crop of **7j**, 1.88 g (34% yield). Total yield 62%; mp 102-104 °C. ^{1}H-NMR (DMSO-d_6): δ 5.24 (s, 2H), 7.55 (dd, J = 8.4, 2.0 Hz, 1H), 8.12 (d, J = 2.0 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H).

Supplementary Scheme 8. Reagents and conditions: (a) Benzoylisothiocyanate, acetone; (b) NaOH, THF-H_2O, reflux; (c) Br_2, CH_2Cl_2, 40 ºC, 2 h.



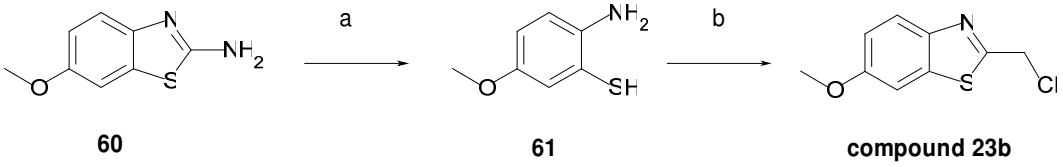
57 **58** **59** **compound 20e**

N-(Biphenyl-2-ylcarbamothioyl)benzamide (58). To a solution of 2-aminobiphenyl (**57**) (5 g, 29.55 mmol) in acetone (100 mL) was added benzoylisothiocyanate (5.30 g, 32.50 mmol) and the resulting reaction mixture was stirred at room temperature for 30 min. The solvent was evaporated and the residue was repeatedly washed with hexane to obtain the title compound **58** (9.67 g, 98%). ^{1}H-NMR ($CDCl_3$): δ 7.33-7.44 (m, 8H), 7.48 (m, 2H), 7.61 (t, J = 7.2 Hz, 1H), 7.80 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 7.6 Hz, 1H), 9.02 (br s, 1H), 12.10 (br s, 1H). MS m/z 333.05 $[M+H]^+$.

1-(Biphenyl-2-yl)thiourea (59). To a solution of **58** (9.60 g, 28.91 mmol) in THF (125 mL) was added a solution of NaOH (5.80 g, 145 mmol) in H_2O (50 mL). The resulting reaction mixture was heated to 85 ºC for 16 h. THF was evaporated, water was added and the mixture extracted with EtOAc (3 × 250 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain the title compound **59** (5.30 g, 80%). MS *m/z* 229.12 $[M+H]^+$.

4-Phenylbenzothiazol-2-amine (20e). To a solution of **59** (5.30 g, 23.25 mmol) in CH_2Cl_2 (70 mL) was added dropwise a solution of bromine (2.30 mL, 46.47 mmol) in CH_2Cl_2 (10 mL). The resulting reaction mixture was heated to 40 ºC for 2 h. The solvent was evaporated and the residue was basified by NH_4OH solution followed by extraction with EtOAc (3 × 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified over silica eluting with 50% EtOAc-Hexane to obtain the title compound **20e** (4.50 g, 86%). ^{1}H-NMR (DMSO-d_6): δ 7.09 (t, J = 4.6 Hz, 1H), 7.30 (m, 2H), 7.41 (t, J = 8.0 Hz, 2H), 7.55 (br s, 2H), 7.66 (d, J = 7.6 Hz, 1H), 7.75 (d, J,= 7.2 Hz, 2H). MS *m/z* 227.13 $[M+H]^+$.

Supplementary Scheme 9. Reagents and conditions: (a) NaOH, H_2O, reflux; (b) 2-chloro-1,1,1-trimethoxy ethane, 60 °C.

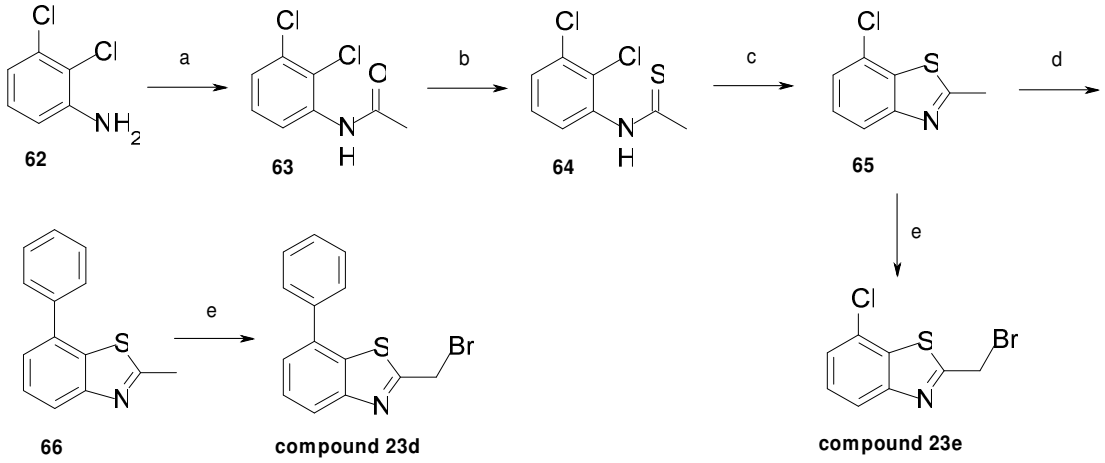


60 **61** **compound 23b**

2-(Chloromethyl)-6-methoxy-1,3-benzothiazole (23b). A mixture of 6-methoxy-1,3-benzothiazol-2-amine (**60)** (1.6 g, 9 mmol) and NaOH (8 g, 200 mmol, 22.2 equiv) in water (20 mL) was stirred under N_2 and under reflux, for 20 h. After cooling at 10 °C, the mixture was poured into water (30 mL) and acidified to pH 4 with conc. HCl. The suspension was extracted with CH_2Cl_2 (2 × 80 mL) and the combined extracts were washed with brine (80 mL) and dried ($MgSO_4$). The solvent was evaporated to dryness under reduced pressure, to give 2-amino-5-methoxybenzenethiol (**61)** as a viscous orange oil which solidified on standing (1 g, 72%, 6.4 mmol). This was mixed with 2-chloro-1,1,1-trimethoxy ethane (1.3 mL, 9.7 mmol, 1.5 equiv) and the mixture was stirred, under N_2, at 60 °C, for 2 h. Volatiles were removed by evaporation

under reduced pressure and the residue was purified by column chromatography on silica, eluted with EtOAc/hexane (10-50 %), to give **23b** as an orange oil which partially solidified on standing (940 mg, 49 % yield over two steps). ^{1}H-NMR (DMSO-d_6): δ 3.85 (s, 3H), 5.17 (s, 2H), 7.14 (dd, J = 9.0, 2.6 Hz, 1H), 7.70 (d, J = 2.6 Hz, 1H), 7.90 (d, J = 9.0 Hz, 1H).

Supplementary Scheme 10. Reagents and conditions: (a) acetyl chloride, triethyl amine, CH_2Cl_2; (b) Lawesson's reagent, toluene, reflux; (c) 1,1,3,3-tetramethyl guanidine, NMP, 130 ºC, 30 min; (d) phenylboronic acid, K_3PO_4, $Pd(dppf)_2Cl_2$, DMF-H_2O, 110 ºC; (e) NBS, AIBN, CCl_4, reflux.



N-(2,3-Dichlorophenyl)acetamide (63). To an ice-cold solution of 2,3-dichloroaniline (**62**) (7.50 g, 46.30 mmol) in CH_2Cl_2 (150 mL) was added triethylamine (9.66 mL, 69.40 mmol) followed by the addition of acetyl chloride (4 mL, 55.50 mmol) and the resulting reaction mixture was stirred at room temperature for 3 - 4 h. Water was added to the reaction mixture and the organic layer was separated. The aqueous layer was re-extracted with CH_2Cl_2 (2 × 150 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified over silica eluting with 5% EtOAc-Hexane to obtain the title compound **63** (8 g, 85%). MS *m/z* 204.0 $[M+H]^+$.

N-(2,3-Dichlorophenyl)ethanethioamide (64). To a solution of **63** (7.50 g, 36.75 mmol) in toluene (200 mL) was added Lawesson's reagent (14.90 g, 36.75 mmol) and the resulting reaction mixture was refluxed for 3 h. The solvent was evaporated and the residue was directly purified over silica eluting with 5% EtOAc-Hexane to obtain the title compound **64** (5.25 g, 65%). MS *m/z* 220.0 $[M+H]^+$.

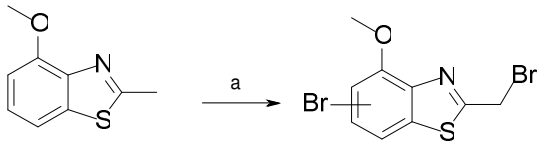
7-Chloro-2-methylbenzothiazole (65). To a solution of **64** (5 g, 22.72 mmol) in NMP (20 mL) was added 1,1,3,3-tetramethyl guanidine (8.70 mL, 69.45 mmol) and the resulting reaction mixture was heated to 150 ºC for 30 min. After cooling to room temperature, it was poured onto crushed ice (200 g) and extracted with EtOAc (3 × 250 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was again washed with water and filtered to obtain the title compound **65** (3.70 g, 89%). MS *m/z* 184.0 $[M+H]^+$.

2-Methyl-7-phenylbenzothiazole (66). To a solution of **65** (770 mg, 4.19 mmol) in DMF-H_2O (12 mL, 2:1) was added phenyl boronic acid (2.55 g, 20.95 mmol) and potassium phosphate (1 g, 4.72 mmol). The reaction mixture was degassed for 20 min followed by addition of [1,1'-Bis(diphenylphosphino)-ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (510 mg, 0.63 mmol). The reaction mixture was again degassed for 20 min and then heated at 110 °C for 16 h under N_2 atmosphere. Water (25 mL) was added and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water, brine, dried (Na_2SO_4), filtered and concentrated. The crude residue was purified over silica eluting with 5% EtOAc-Hexane to obtain the title compound **66** (340 mg, 36%). MS *m/z* 226.06 $[M+H]^+$.

2-(Bromomethyl)-7-phenylbenzothiazole (23d). To a solution of **66** (100 mg, 0.44 mmol) in CCl_4 (10 mL) was added NBS (160 mg, 0.88 mmol) and AIBN (20 mg, catalytic). The resulting reaction mixture was refluxed for 16 h. The solvent was evaporated, water was added and the mixture was extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to obtain the title compound **23d** (66 mg, 49%) that was carried forward to the next step without further purification. MS: 304.10 $[M+H]^+$.

2-Bromomethyl-7-chlorobenzothiazole (23e). To a solution of **65** (500 mg, 2.72 mmol) in CCl_4 (50 mL) was added NBS (970 mg, 5.45 mmol) and AIBN (50 mg, catalytic). The resulting reaction mixture was refluxed for 4-5 h. The solvent was evaporated, water was added and the mixture was extracted with EtOAc (3× 100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified over silica eluting with 5% EtOAc-Hexane to give the desired compound **23e** (310 mg, 43%). MS *m/z* 261.92 $[M+H]^+$.

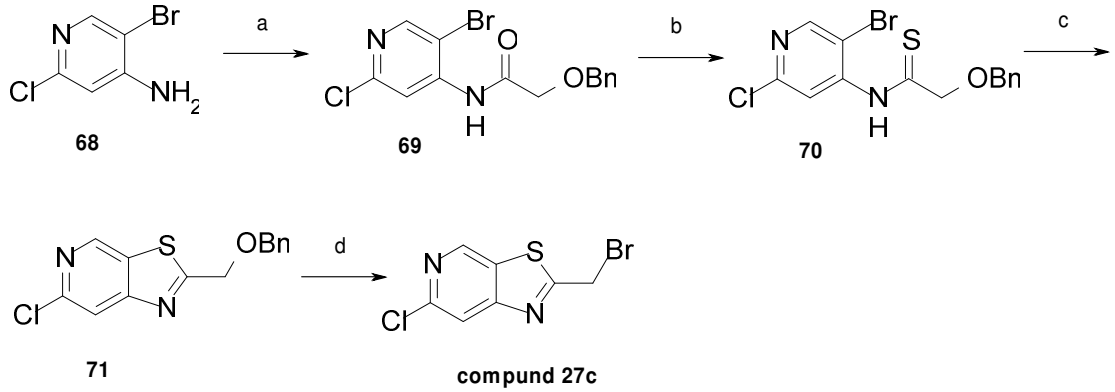
Supplementary Scheme 11. Reagents and conditions: (a) NBS, AIBN, CCl_4, reflux.



67 compound 23c

5/7-Bromo-2-(bromomethyl)-4-methoxybenzothiazole (23c). To a solution of 4-methoxy-2-methylbenzothiazole (**67**) (500 mg, 2.79 mmol) in CCl_4 (50 mL) was added NBS (1 g, 5.58 mmol) and AIBN (50 mg, catalytic). The resulting reaction mixture was refluxed for 16 h. The solvent was evaporated and the residue was purified over silica eluting with 5% EtOAc-Hexane to give the title compound **23c** (420 mg, 45%). MS *m/z* 338.10 $[M+H]^+$.

Supplementary Scheme 12. Reagents and conditions: (a) 2-(Benzyloxy)acetyl chloride, triethyl amine, CH_2Cl_2; (b) Lawesson's Reagent, toluene, reflux; (c) NaH, NMP, 160 ºC; (d) BBr_3, CH_2Cl_2.



68 69 70 71 compund 27c

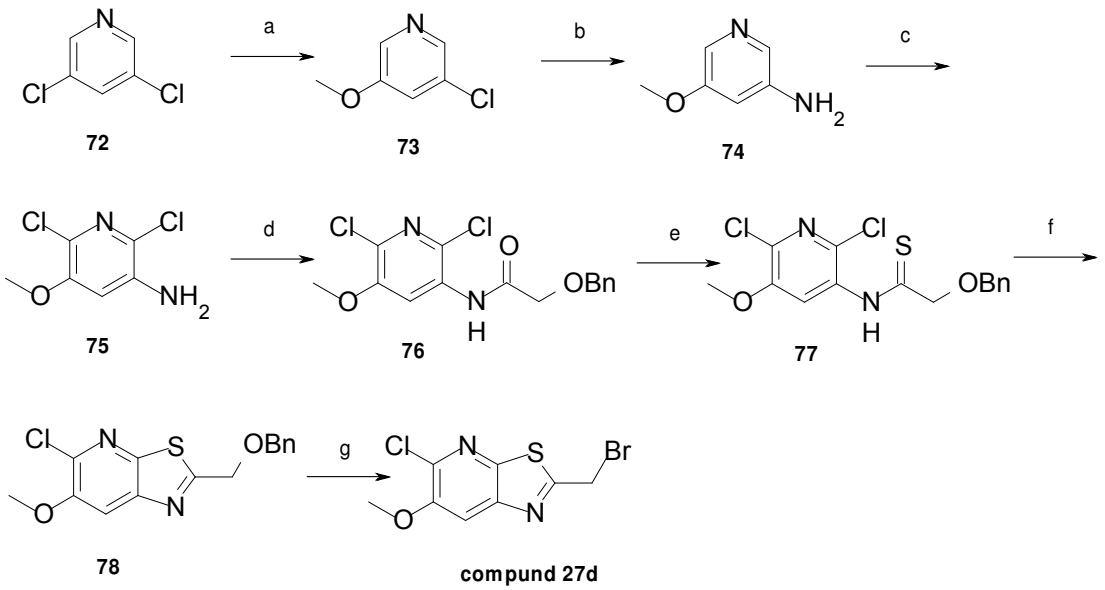
2-(Benzyloxy)-N-(5-bromo-2-chloropyridin-4-yl)acetamide (69). To an ice-cold solution of 5-bromo-2-chloropyridin-4-amine (**68**) (5.80 g, 28.16 mmol) in CH_2Cl_2 (150 mL) was added triethylamine (5.80 mL, 42.25 mmol) followed by the addition of 2-(benzyloxy)acetyl chloride (5.20 g, 28.16 mmol). The resulting reaction mixture was stirred at room temperature for 16 h. Water was added and the organic layer was separated. The aqueous fraction was re-extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified over silica eluting with 10% EtOAc-Hexane to obtain the title compound **69** (2.90 g, 29%). MS *m/z* 355.0 $[M+H]^+$.

2-(Benzyloxy)-N-(5-bromo-2-chloropyridin-4-yl)ethanethioamide (70). To a solution of **69** (2.90 g, 8.20 mmol) in toluene (50 mL) was added Lawesson's reagent (2.47 g, 6.10 mmol) and the resulting reaction mixture was refluxed for 3 h. The solvent was evaporated and the residue was purified over silica eluting with 4% EtOAc-Hexane to obtain the title compound **70** (2.30 g, 76%). MS *m/z* 370.0 $[M+H]^+$.

2-[(Benzyloxy)methyl]-6-chloropyrido[4,3-d][1,3]thiazole (71). To a solution of **70** (2.30 g, 6.18 mmol) in NMP (30 mL) was added NaH (60% dispersion in mineral oil, 220 mg, 5.56 mmol) portion wise and the resulting reaction mixture was heated to 160 ºC for 1 h. The reaction mixture was allowed to reach room temperature and poured onto ice cold water followed by extraction with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude residue **71** was carried forward to the next step without further purification. MS *m/z* 291.10 $[M+H]^+$.

2-(Bromomethyl)-6-chloropyrido[4,3-d][1,3]thiazole (27c). A solution of **71** (350 mg, 1.20 mmol) in CH_2Cl_2 (10 mL) was cooled to –78 ºC followed by dropwise addition of BBr_3 (570 μL, 5.98 mmol).The resulting reaction mixture was allowed to reach room temperature and then left to stir for 16 h. The reaction mixture was again cooled to –78 ºC and quenched by dropwise addition of water. The organic layer was separated and the aqueous layer was re-extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified over silica eluting with 4% EtOAc-Hexane to obtain the title compound **27c** (110 mg, 35%). MS *m/z* 262.91 $[M+H]^+$.

Supplementary Scheme 13. Reagents and conditions: (a) NaOMe, DMSO; (b) NH_3 (aq), $CuSO_4.5H_2O$, 160 ºC, autoclave; (c) H_2O_2, 12 N HCl; (d) 2-(benzoyloxy)acetyl chloride, triethylamine, CH_2Cl_2; (e) P_2S_5, THF, 55 ºC, 16 h; (f) NaH, NMP; (g) BBr_3, CH_2Cl_2.



3-Chloro-5-methoxypyridine (73). To a stirred solution of 3,5-dichloropyridine (**72**) (10 g, 67.56 mmol) in DMSO (100 mL) was added NaOMe (9.10 g, 168.90 mmol) portion wise and the resulting reaction mixture was heated to 80 ºC for 1 h. Water was added to the mixture and extracted with EtOAc (3 × 250 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude residue was purified over silica eluting with 15% EtOAc-Hexane to obtain the title compound **73** (6 g, 62%). ^{1}H-NMR (DMSO-d_6): δ 3.84 (s, 3H), 7.58 (br s, 1H), 8.19 (br s, 1H), 8.25 (d, J = 2.0 Hz, 1H). MS m/z 144.11 $[M+H]^+$.

5-Methoxypyridin-3-amine (74). A mixture of **73** (2.50 g, 17.40 mmol), $CuSO_4.5H_2O$ (21 g, 87 mmol) and 25% aqueous ammonia (250 mL) was heated at 160 ºC in a pressure vessel for 16 h. The reaction mixture was poured onto the ice-cold water and extracted with EtOAc (5 × 250 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified over silica eluting with 100% EtOAc to obtain the title compound **74** (600 mg, 28%). ^{1}H-NMR (DMSO-d_6): δ 3.70 (s, 3H), 5.31 (br s, 2H), 6.48 (br s, 1H), 7.45 (br s, 1H), 7.53 (br s, 1H).

2,6-Dichloro-5-methoxypyridin-3-amine (75). To an ice-cold solution of **74** (430 mg, 3.11 mmol) in 12 N HCl (5 mL) was added H_2O_2 (30% solution, 1.76 mL, 15.56 mmol) dropwise and the resulting reaction mixture was heated to 70 ºC for 1 h. The reaction mixture was then cooled to room temperature, water was added and basified with 1N NaOH solution followed by extraction with EtOAc (3× 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure

to obtain the title compound **75** (120 mg, 19%) that was carried forward to the next step without further purification. ^{1}H-NMR ($CDCl_3$): δ 3.86 (s, 3H), 4.10 (br s, 2H), 6.64 (s, 1H).

2-(Benzyloxy)-N-(2,6-dichloro-5-methoxypyridin-3-yl)acetamide (76). A solution of **75** (120 mg, 0.58 mmol) in CH_2Cl_2 (10 mL) was cooled to –10 ºC followed by addition of triethyl amine (90 µL, 0.64 mmol) and then 2-(benzoyloxy)acetyl chloride (130 mg, 0.70 mmol). The resulting reaction mixture was stirred at room temperature for 2 h. Water was added and the mixture was basified with 1N NaOH solution followed by extraction with EtOAc (3× 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified over silica eluting with 5% EtOAc-Hexane to obtain the title compound **76** (90 mg, 43%). ^{1}H-NMR (DMSO-d_6): δ 3.89 (s, 3H), 4.21 (s, 2H), 4.67 (s, 2H), 7.31-7.43 (m, 5H), 8.22 (s, 1H), 9.48 (br s, 1H).

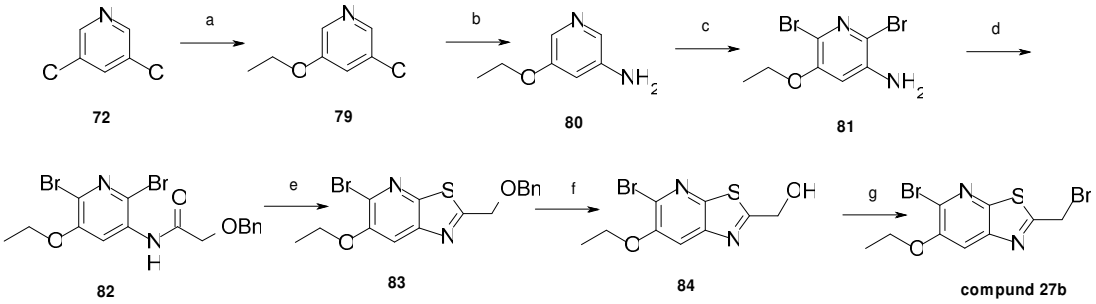
2-(Benzyloxy)-N-(2,6-dichloro-5-methoxypyridin-3-yl)ethanethioamide (77). To a solution **76** (90 mg, 0.25 mmol) in THF (10 mL) was added P_2S_5 (85 mg, 0.38 mmol) and the resulting reaction mixture was heated to 55 ºC for 16 h. The solvent was evaporated and the residue was directly loaded onto a silica column and eluted with 2% EtOAc-Hexane to obtain the title compound **77** (80 mg, 83%). ^{1}H-NMR (DMSO-d_6): δ 3.87 (s, 3H), 4.45 (s, 2H), 4.53 (s, 2H), 7.30-7.45 (m, 5H), 7.94 (s, 1H), 11.42 (br s, 1H).

2-[(Benzyloxy)methyl]-5-chloro-6-methoxypyrido[3,2-d][1,3]thiazole (78). To a solution of **77** (140 mg, 0.39 mmol) in NMP (1 mL) was added NaH (60% dispersion in mineral oil, 15 mg, 0.39 mmol) and the resulting solution was heated to 130 ºC for 30 min. Ice-cold water was added to the reaction mixture and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to obtain the title compound **78** (100 mg, 79%) that was carried forward without further purification. MS *m/z* 321.20 $[M+H]^+$.

2-(Bromomethyl)-5-chloro-6-methoxypyrido[3,2-d][1,3]thiazole (27d). A solution of **78** (100 mg, 0.31 mmol) in CH_2Cl_2 (5 mL) was cooled to –78 ºC followed by addition of BBr_3 (170 µL, 1.55 mmol). The resulting reaction mixture was stirred at room temperature for 30 min. The reaction mixture was cooled to 0 ºC and quenched by ice-cold $NaHCO_3$ solution followed by extraction with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified over silica eluting with 5% EtOAc-Hexane to obtain the title

compound **27d** (90 mg, quantitative yield). ^{1}H-NMR (DMSO-d_6): δ 3.60 (s, 3H), 5.01 (s, 2H), 8.22 (s, 1H). MS *m/z* 293.04 $[M+H]^+$.

Supplementary Scheme 14. Reagents and conditions: (a) NaOEt, DMSO; (b) NH_3 (aq), $CuSO_4.5H_2O$, 160 ºC, autoclave; (c) NBS, AcOH; (d) 2-(benzoyloxy)acetyl chloride, triethylamine, CH_2Cl_2; (e) P_2S_5, THF, 55 ºC, 16 h; (f) Methanesulfonic acid, CH_2Cl_2; (g) PBr_3, toluene, reflux.



3-Chloro-5-ethoxypyridine (79). To a stirred solution of 3,5-dichloropyridine (**72**) (25 g, 169 mmol) in DMSO (250 mL) was added NaOEt (34 g, 500 mmol) portion wise and the resulting reaction mixture was heated to 80 ºC for 1 h. Water was added to the mixture and extracted with EtOAc (3 × 500 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude residue **79** (16 g, 64% crude yield) thus obtained was carried forward to the next step without further purification. ^{1}H-NMR (DMSO-d_6): δ 1.28 (t, J = 7.20 Hz, 3H), 4.12 (q, J = 7.2 Hz, 2H), 7.57 (t, J = 2.0 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 8.25 (d, J = 2.4 Hz, 1H). MS *m/z* 158.11 $[M+H]^+$.

5-Ethoxypyridin-3-amine (80). A mixture of **79** (4 g, 25.50 mmol), $CuSO_4 \cdot 5H_2O$ (30 g, 102 mmol) and 25% aqueous ammonia (300 mL) was heated at 160 ºC in a pressure vessel for 16 h. The reaction mixture was poured onto ice-cold water and extracted with EtOAc (5 × 100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified over silica eluting with 2% MeOH- CH_2Cl_2 to obtain the title compound **80** (1.30 g, 37%). ^{1}H-NMR (DMSO-d_6): δ 1.29 (t, J = 6.8 Hz, 3H), 3.97 (q, J = 6.8 Hz, 2H), 5.29 (br s, 2H), 6.47 (t, J = 2.0 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H),7.52 (d, J = 2.4 Hz, 1H).

2,6-Dibromo-5-ethoxypyridin-3-amine (81). To a stirred solution of **80** (100 mg, 0.72 mmol) in acetic acid (5 mL) was added NBS (260 mg, 1.46 mmol) and the resulting mixture was stirred at room temperature for 30 min. Water was added and the pH of the reaction mixture was adjusted to 8-9 by addition of 10% aqueous NaOH solution followed by extraction with EtOAc (3 × 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified over silica eluting with CH_2Cl_2 100% to obtain the title compound **81** (150 mg, 70%). ^{1}H-NMR (DMSO-d_6): δ 1.34 (t, J = 7.2 Hz, 3H), 4.03 (q, J = 7.2 Hz, 2H), 5.68 (br s, 2H), 6.83 (s, 1H). MS m/z 294.95 $[M+H]^+$.

2-(Benzyloxy)-N-(2,6-dibromo-5-ethoxypyridin-3-yl)acetamide (82). To a solution of **81** (200 mg, 0.97 mmol) in CH_2Cl_2 (10 mL) was added triethyl amine (150 μL, 1.06 mmol) and the resulting solution was cooled to –10 ºC followed by addition of 2-(benzyloxy)acetyl chloride (230 mg, 1.15 mmol). The resulting reaction mixture was then stirred at room temperature for 2 h. Water was added and the pH of the solution adjusted to 7 by the addition of a saturated $NaHCO_3$ solution followed by extraction with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified over silica eluting with CH_2Cl_2 100% to obtain the title compound **82** (160 mg, 37%). MS m/z 442.98 $[M+H]^+$.

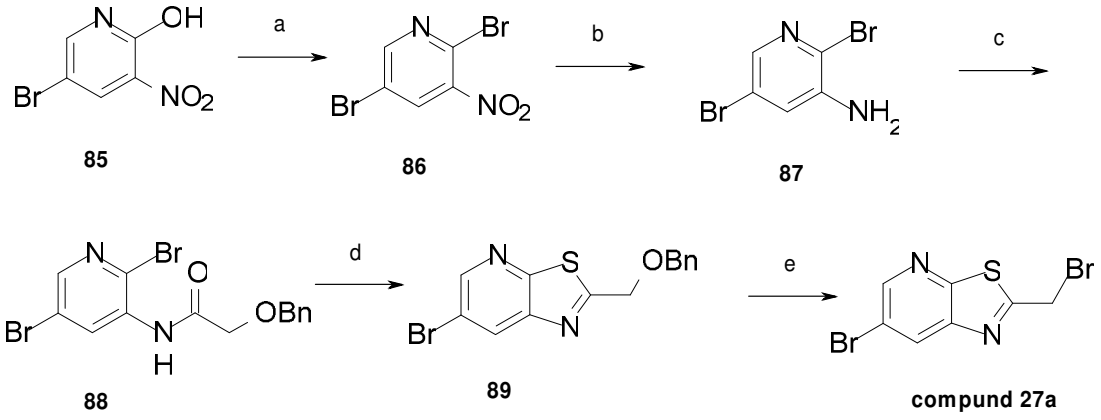
2-(Benzyloxymethyl)-5-bromo-6-ethoxythiazolo[5,4-b]pyridine (83). To a solution of **82** (230 mg, 0.51 mmol) in THF (20 mL) was added P_2S_5 (170 mg, 0.76 mmol) and the resulting solution was heated to 55 ºC for 16 h. The solvent was evaporated and the residue was directly loaded onto a silica column and eluted with CH_2Cl_2 100% to obtain the title compound **83** (180 mg, 77%). ^{1}H-NMR (DMSO-d_6): δ 1.35 (t, J = 7.2 Hz, 3H), 4.15 (q, J = 7.2 Hz, 2H), 4.42 (s, 2H), 4.72 (s, 2H), 7.33 (m, 2H), 7.39 (m, 2H), 7.47 (m, 1H), 7.83 (s, 1H).

2-[(Benzyloxy)methyl]-5-bromo-6-ethoxypyrido[3,2-d][1,3]thiazole (84). To a solution of **83** (1.50 g, 3.90 mmol) in CH_2Cl_2 (25 mL) was added methanesulfonic acid (2 mL, 20 mmol) and the resulting reaction mixture was stirred at room temperature for 16 h. The reaction mixture was then poured onto ice-cold water, the pH of the reaction adjusted to neutral by addition of saturated $NaHCO_3$ solution and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified over silica eluting

with 40% EtOAc-Hexane to obtain the title compound **84** (1 g, 88%). ^{1}H-NMR (DMSO-d_6): δ 1.37 (t, J = 7.2 Hz, 3H), 4.10 (q, J = 7.2 Hz, 2H), 4.68 (d, J = 6.0 Hz, 2H), 6.41 (t, J = 6.0 Hz, 1H), 8.04 (s, 1H). MS m/z 289.04 $[M+H]^+$.

5-Bromo-2-(bromomethyl)-6-ethoxypyrido[3,2-d][1,3]thiazole (27b). To a solution of **84** (1 g, 3.46 mmol) in toluene (25 mL) was added PBr_3 (490 μL, 5.20 mmol) and the resulting reaction mixture was refluxed for 2 h. The reaction mixture was cooled to room temperature, saturated $NaHCO_3$ solution was added and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified over silica eluting with 10% EtOAc-Hexane to obtain the title compound **27b** (400 mg, 33%). ^{1}H-NMR (DMSO-d_6): δ 1.41 (t, J = 7.2 Hz, 3H), 4.27 (q, J = 7.2 Hz, 2H), 5.12 (s, 2H), 8.14 (s, 1H).

Supplementary Scheme 15. Reagents and conditions: (a) PBr_3, toluene, reflux; (b) $SnCl_2.2H_2O$, EtOH, reflux; (c) 2-(benzoyloxy)acetyl chloride, triethylamine, CH_2Cl_2; (d) Lawesson's reagent, toluene, reflux; (e) BBr_3, CH_2Cl_2.



2,5-Dibromo-3-nitro-pyridine (86). To a solution of 5-bromo-3-nitro-pyridin-2-ol (**85**) (10 g, 45.66 mmol) in toluene (70 mL) and DMF (7 mL) was added PBr_3 (6.60 mL, 68.49 mmol) and the reaction mixture was heated at 120 ºC for 20 min under N_2 atmosphere. Water (100 mL) was added and the mixture was extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with water, brine, dried (Na_2SO_4), filtered and concentrated to obtain the title compound **86** (10.30 g, 80.0%). ^{1}H-NMR (DMSO-d_6): δ 8.85 (d, J = 2.0 Hz, 1H), 8.88 (d, J = 2.4 Hz, 1H).

2,5-Dibromo-pyridin-3-ylamine (87). To a solution of **86** (10.30 g, 35.47 mmol) in EtOH (100 mL) was added $SnCl_2.2H_2O$ (24 g, 106.42 mmol) portion wise. The reaction mixture was heated at 80 ºC for 2 h. The reaction mixture was evaporated to dryness under reduced pressure. Water (250 mL) was added, white solid separated out, then the reaction mixture was basified with 10% NaOH solution followed by extraction with hot EtOAc (3 × 250 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the desired product **87** (6.20 g, 69%). MS *m/z* 250.78 $[M+H]^+$.

2-Benzyloxy-N-(2,5-dibromo-pyridin-3-yl)-acetamide (88). To an ice cold solution of **87** (4.60 g, 18.26 mmol) in CH_2Cl_2 (50 mL) was added triethylamine (2.79 mL, 20.09 mmol) followed by addition of a solution of 2-(benzyloxy)acetyl chloride (4.05 g, 21.91 mmol) in 20 mL of CH_2Cl_2. The reaction mixture was stirred at 25 ºC for 16 h. The reaction mixture was evaporated, water was added and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica eluting with 2.5% EtOAc-Hexane, to provide the title compound **88** (3.20 g, 44%). MS *m/z* 398.71 $[M+H]^+$.

2-[(Benzyloxy)methyl]-6-bromopyrido[3,2-d][1,3]thiazole (89). To a solution of **88** (3.20 g, 7.97 mmol) in toluene (60 mL) was added Lawesson's reagent (1.94 g, 4.78 mmol) and the reaction mixture was heated at 120 ºC for 1-2 h. The solvent was evaporated off under reduced pressure, water was added and the mixture was extracted with EtOAc (3× 100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica eluting with 2% EtOAc-Hexane, to provide the title compound **89** (2.60 g, 97%). ^{1}H-NMR (DMSO-d_6): δ 4.72 (s, 2H), 4.99 (s, 2H), 7.40 (m, 5H), 8.71 (d, J = 2.4 Hz, 1H), 8.74 (d, J = 2.0 Hz, 1H). MS *m/z* 334.77 $[M+H]^+$.

6-Bromo-2-(bromomethyl)pyrido[3,2-d][1,3]thiazole (27a). A solution of **89** (1.60 g, 4.77 mmol) CH_2Cl_2 (15 mL) was cooled to –78° C followed by addition of BBr_3 (2.27 mL, 23.86 mmol). The reaction mixture was stirred at 25 ºC for 2 h. The reaction mixture was cooled to 0 ºC and quenched by dropwise addition of a saturated solution of $NaHCO_3$ (20 mL) followed by extraction with EtOAc (3 × 50 mL). The combined organic extracts were washed with water, brine, dried (Na_2SO_4), filtered and concentrated to obtain the title compound **27a** (2 g, crude yield) that was carried forward to the next step without further purification. MS *m/z* 306.90 $[M+H]^+$.