Electronic supplementary information (ESI)

Development of Anti-HBV Agents Targeting HBV Capsid Proteins

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I. General information

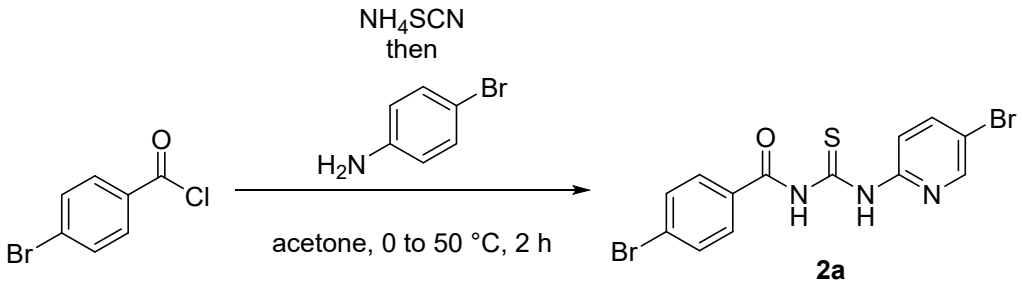
I-I. General methods

All reactions were performed using commercially supplied reagents and solvents in dried glassware under an atmosphere of nitrogen unless otherwise noted. Thin-layer chromatography (TLC) was performed on Merck $60F_{254}$ precoated silica gel plates and was visualized by fluorescence quenching under UV light and by staining with phosphomolybdic acid, *p*-anisaldehyde, or ninhydrin, respectively. Flash column chromatography was carried out with silica gel 60 N (Kanto Chemical Co., Inc.).

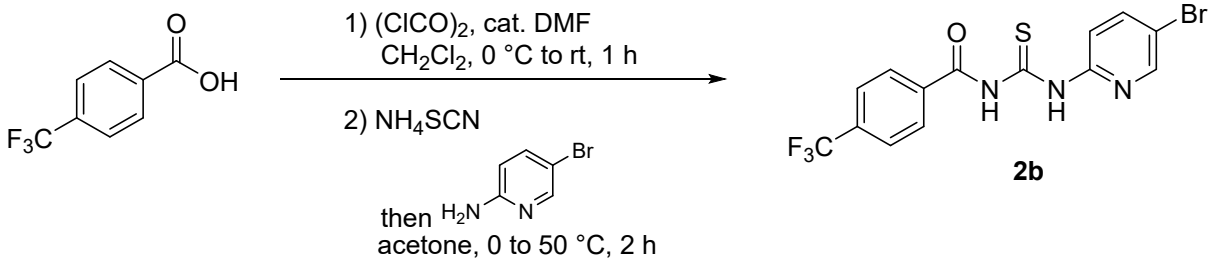
I-II. Characterization Data

^{1}H NMR (400 MHz or 500 MHz) and ^{13}C NMR (100 MHz or 125 MHz) spectra were recorded using a Bruker AVANCE III 400 spectrometer and Bruker AVANCE 500 spectrometer (Bruker, USA). Coupling constants are reported in Hertz, and peak shifts are reported in d (ppm) relative to $CDCl_3$ (^{1}H 7.26 ppm, ^{13}C 77.16 ppm) or dimethyl sulfoxide (DMSO)-d_6 (^{1}H 2.50 ppm, ^{13}C 39.52 ppm). Low- and high-resolution mass spectra were recorded on a Bruker Daltonics micrOTOF focus in the positive and negative detection mode.

II. Experimental procedures



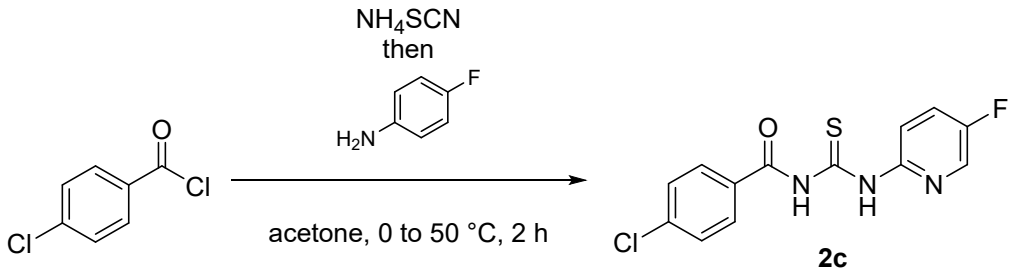
4-Bromo-*N*-((5-bromopyridin-2-yl)carbamothioyl)benzamide (**2a**): To a solution of 4-bromobenzoyl chloride (272 mg, 2.00 mmol) in acetone (3.00 mL) was added NH_4SCN (183 mg, 2.40 mmol) at 0 °C under argon. The mixture was stirred at room temperature for 30 min. 2-Amino-5-bromopyridine (346 mg, 1.00 mmol) was added to the solution, and the mixture was stirred at 50 °C for 2 h. After concentration of the mixture under reduced pressure, the residue was added MeOH to precipitate the crude compound and it was collected by filtration followed by flash column chromatography over silica gel with *n*-hexane/EtOAc (49:1 to 9:1) to obtain the title compound **2a** as a white solid (302 mg, 732 μmol, 37%): ^{1}H NMR (500 MHz, DMSO) δ 13.18 (brs, 1H), 11.96 (brs, 1H), 8.71 (s, 1H), 8.59–8.58 (m, 1H), 8.17–8.15 (m, 1H), 7.90 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 168.2, 150.6, 149.5, 141.2, 132.0 (2C), 131.9, 131.2, 127.7 (2C), 117.4, 116.2; HRMS (ESI), *m/z* calcd for $C_{13}H_8Br_2N_3OS$ $[M-H]^-$ 411.8760, found 411.8759.



***N*-((5-Bromopyridin-2-yl)carbamothioyl)-4-(trifluoromethyl)benzamide (2b)**: To a solution of 4-(trifluoromethyl)benzoic acid (190 mg, 1.00 mmol) in CH_2Cl_2 (10.0 mL) were added DMF (7.74 μL, 100 μmol) and oxalyl chloride (127 μL, 1.50 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to provide the chloride, which was used immediately in next step without purification.

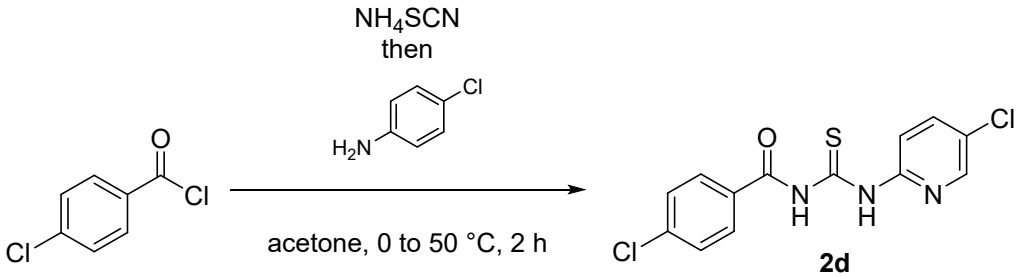
To a solution of the chloride in acetone (2.00 mL) was added NH_4SCN (91.3 mg, 1.20 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 30 min. After 2-amino-5-bromopyridine (162 mg, 1.00 mmol) was added to the solution, the mixture was stirred at 50 °C for 2 h. The reaction mixture was concentrated under reduced pressure followed by flash column chromatography over silica gel with *n*-hexane/EtOAc (99:1 to 21:4) to obtain the title compound **2b** as a white solid (323 mg, 799 μmol, 80% in 2 steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.03 (brs, 1H), 9.08 (brs, 1H), 8.80 (d, J = 9.0 Hz, 1H), 8.49 (d, J = 2.0

Hz, 1H), 8.04 (d, J = 8.0 Hz, 2H), 7.90 (dd, J = 8.5 Hz and 2.5 Hz, 1H), 7.82 (d, J = 8.5 Hz, 2H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7, 165.3, 149.7 (d, J = 33.8 Hz), 140.5, 135.5 (q, J = 32.5 Hz), 135.0, 128.4–128.1 (3C), 126.5 (q, J = 37.5 Hz, 2C), 123.4 (q, J = 271.2 Hz), 117.2, 117.1; HRMS (ESI), *m/z* calcd for $C_{14}H_{10}BrF_3N_3NaOS$ $[M+Na]^+$ 425.9494, found 425.9489.



2c

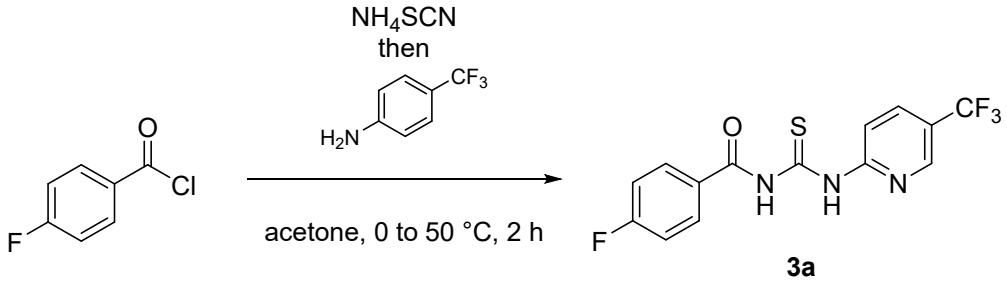
4-Chloro-*N*-((5-fluoropyridin-2-yl)carbamothioyl)benzamide (**2c**): To a solution of 4-chlorobenzoyl chloride (641 μL, 5.00 mmol) in acetone (10 mL) was added NH_4SCN (457 mg, 6.00 mmol) at 0 °C under argon. The reaction mixture was stirred at 50 °C for 30 min. After 2-amino-5-fluoropyridine (561 mg, 5.00 mmol) was added to the solution, the mixture was stirred at 50 °C for 2 h. After cooling the mixture to room temperature, the reaction was quenched by the addition of H_2O and Et_2O. The resulting precipitate was collected by filtration and washed with H_2O and Et_2O. It was then dried followed by flash column chromatography over silica gel with *n*-hexane/EtOAc (49:1 to 4:1) to obtain the title compound **2c** as a white solid (903 mg, 2.91 mmol, 58%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.05 (brs, 1H), 9.00 (brs, 1H), 8.84–8.82 (m, 1H), 8.30–8.29 (m, 1H), 7.85 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 7.54–7.49 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 165.6, 157.3 (d, J = 253.8 Hz), 147.3 (d, J = 1.3 Hz), 140.7, 136.6 (d, J = 26.2 Hz), 130.0, 129.8 (2C), 129.1 (2C), 124.6 (d, J = 31.2 Hz), 117.3 (d, J = 3.8 Hz); HRMS (ESI), *m/z* calcd for $C_{13}H_{10}ClFN_3OS$ $[M+H]^+$ 310.0212, found 310.0207.



2d

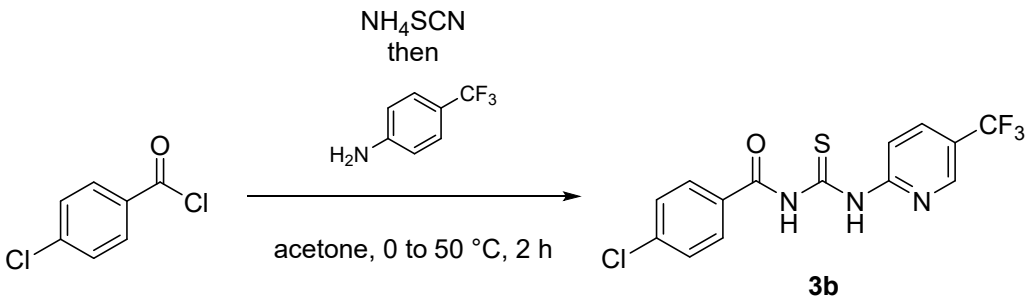
4-Chloro-*N*-((5-chloropyridin-2-yl)carbamothioyl)benzamide (**2d**): To a solution of 4-chlorobenzoyl chloride (641 μL, 5.00 mmol) in acetone (10 mL) was added NH_4SCN (457 mg, 6.00 mmol) at 0 °C under argon. The reaction mixture was stirred at 50 °C for 30 min. After 2-amino-5-chloropyridine (643 mg, 5.00 mmol) was added to the solution, the mixture was stirred at 50 °C for 2 h. After cooling the mixture to room temperature, the reaction was quenched by the addition of H_2O and Et_2O. The resulting precipitate was collected by filtration and washed with H_2O and Et_2O. It was then dried followed by flash column chromatography over

silica gel with *n*-hexane/EtOAc (49:1 to 4:1) to obtain the title compound **2d** as a white solid (1.20 g, 3.67 mmol, 73%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.09 (brs, 1H), 9.01 (brs, 1H), 8.84 (d, *J* = 9.0 Hz, 1H), 8.38 (d, *J* = 2.5 Hz, 1H), 7.86 (d, *J* = 9.0 Hz, 2H), 7.74 (dd, *J* = 9.0 Hz and 2.5 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 165.6, 149.5, 147.4, 140.7, 137.6, 130.0, 129.8 (2C), 129.1 (2C), 128.8, 116.7; HRMS (ESI), *m/z* calcd for $C_{13}H_8Cl_2N_3OS$ $[M-H]^-$ 323.9771, found 323.9770.



3a

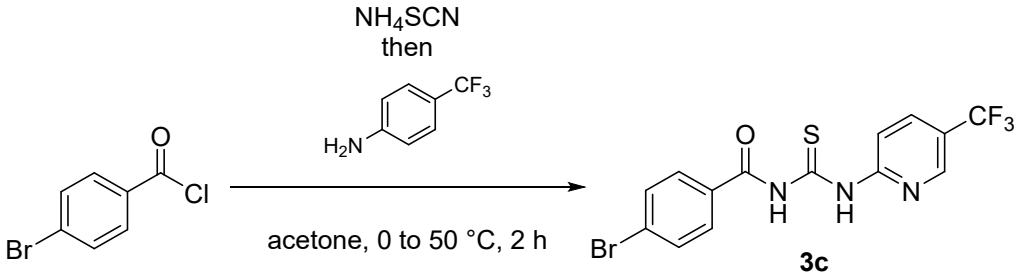
4-Fluoro-*N*-((5-(trifluoromethyl)pyridin-2-yl)carbamothioyl)benzamide (**3a**): To a solution of 4-fluorobenzoyl chloride (120 µL, 1.00 mmol) in acetone (2.00 mL) was added NH_4SCN (91.3 mg, 1.20 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 30 min. After 2-amino-5-(trifluoromethyl) pyridine (162 mg, 1.00 mmol) was added to the solution, the mixture was stirred at 50 °C for 2 h. The rection mixture was concentrated under reduced pressure. The crude compound was purified with flash column chromatography over silica gel with *n*-hexane/EtOAc (49:1 to 7:3) followed by recrystallization ($CHCl_3$/hexane) to obtain the title compound **3a** as a white solid (102 mg, 297 µmol, 30%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.31 (brs, 1H), 9.07–9.05 (m, 2H), 8.69 (d, *J* = 1.5 Hz, 1H), 8.01 (dd, *J* = 8.5 Hz and 2.0 Hz, 1H), 7.98–7.95 (m, 2H), 7.26–7.23 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5, 167.4, 165.4 (d, *J* = 30.0 Hz), 154.0, 145.9 (d, *J* = 3.8 Hz), 135.4 (d, *J* = 2.5 Hz, 2C), 130.5 (d, *J* = 10.0 Hz, 2C), 127.7 (d, *J* = 1.3 Hz), 124.0 (q, *J* = 66.3 Hz), 123.4 (q, *J* = 270.0 Hz), 116.9 (d, *J* = 22.5 Hz), 115.1; HRMS (ESI), *m/z* calcd for $C_{14}H_{10}F_4N_3OS$ $[M+H]^+$ 344.0475, found 344.0474.



3b

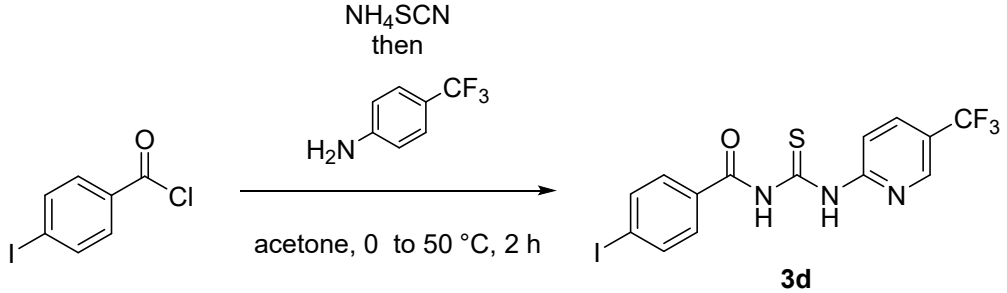
4-Chloro-*N*-((5-(trifluoromethyl)pyridin-2-yl)carbamothioyl)benzamide (**3b**, **TKB-HBV-CA-001**): To a solution of 4-chlorobenzoyl chloride (1.28 mL, 10.0 mmol) in acetone (20.0 mL) was added NH_4SCN (913 mg, 12.0 mmol) at 0 °C under argon. The reaction mixture was stirred at 50 °C for 30 min. After 2-amino-5-

(trifluoromethyl) pyridine (1.62 g, 10.0 mmol) was added to the solution, the mixture was stirred at 50 °C for 2 h. After cooling the mixture to room temperature, the reaction mixture was added H_2O and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was removed under reduced pressure followed by recrystallization (acetone/ *n*-hexane) to obtain the title compound **3b** as a white solid (422 mg, 1.18 mmol, 12%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 13.26 (brs, 1H), 9.09–9.05 (m, 2H), 8.70–8.69 (m, 1H), 8.02–7.99 (m, 1H), 7.87 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 9.0 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 177.4, 165.6, 154.0, 145.9 (d, J = 2.5 Hz), 140.8, 135.5 (d, J = 2.5 Hz), 130.1–129.2 (3C), 126.7 (2C), 124.2 (q, J = 33.8 Hz), 123.4 (q, J = 270.0 Hz), 115.1; HRMS (ESI), *m/z* calcd for $C_{14}H_{10}ClF_3N_3OS$ $[M+H]^+$ 360.0180, found 360.0178.



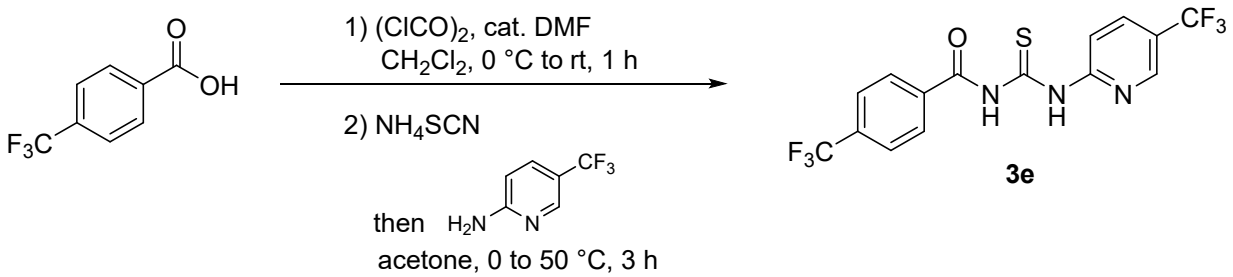
3c

4-Bromo-*N*-((5-(trifluoromethyl)pyridin-2-yl)carbamothioyl)benzamide (**3c**): To a solution of 4-bromobenzoyl chloride (681 µL, 5.00 mmol) in acetone (10.0 mL) was added NH_4SCN (457 mg, 6.00 mmol) at 0 °C under argon. The reaction mixture was stirred at 50 °C for 30 min. After 2-amino-5-(trifluoromethyl) pyridine (811 mg, 5.00 mmol) was added to the solution, the mixture was stirred at 50 °C for 2 h. After cooling the mixture to room temperature, the reaction was quenched by the addition of H_2O and Et_2O. The resulting precipitate was collected by filtration and washed with H_2O and Et_2O. It was then dried followed by flash column chromatography over silica gel with *n*-hexane/EtOAc (49:1 to 4:1) to obatin the title compound **3c** as a white solid (623 mg, 1.54 mmol, 31%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.25 (brs, 1H), 9.06–9.05 (m, 2H), 8.69 (s, 1H), 8.01–7.99 (m, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 165.7, 154.0, 146.0 (d, J = 2.5 Hz), 135.4 (d, J = 2.5 Hz), 132.8 (2C), 130.3, 129.4, 129.2 (2C), 124.3 (q, J = 33.8 Hz), 123.4 (q, J = 270.0 Hz), 115.1; HRMS (ESI), *m/z* calcd for $C_{14}H_{10}BrF_3N_3OS$ $[M+H]^+$ 403.9675, found 403.9672.



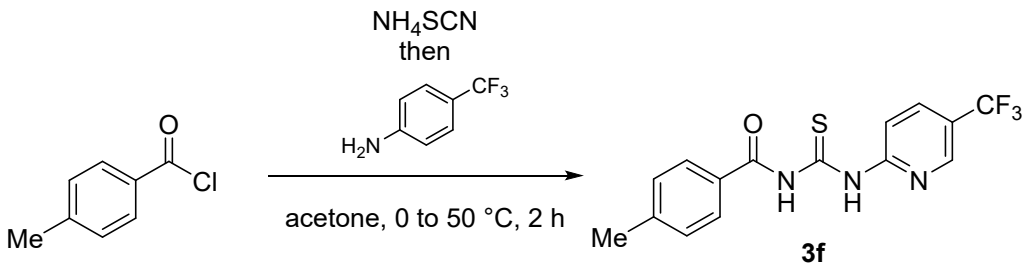
3d

4-Iodo-*N*-((5-(trifluoromethyl)pyridin-2-yl)carbamothioyl)benzamide (**3d**): To a solution of 4-iodobenzoyl chloride (266 mg, 1.00 mmol) in acetone (2.00 mL) was added NH_4SCN (91.3 mg, 1.20 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 30 min. After 2-amino-5-(trifluoromethyl) pyridine (162 mg, 1.00 mmol) was added to the solution, mixture was stirred at 50 °C for 2 h. The reaction mixture was concentrated under reduced pressure. The crude was purified by flash column chromatography over silica gel with *n*-hexane/EtOAc (49:1 to 4:1) and recrystallization ($CHCl_3$/hexane) to give the title compound **3d** as a light yellow solid (162 mg, 359 μmol, 36%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.26 (brs, 1H), 9.06–9.04 (m, 2H), 8.69–8.63 (m, 1H), 8.02–8.00 (m, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 166.0, 154.0, 145.9 (d, J = 2.5 Hz), 138.8 (2C), 135.5, 130.9, 129.0 (2C), 124.6–124.1 (m), 122.4 (q, J = 272.5 Hz), 115.1, 102.1; HRMS (ESI), *m/z* calcd for $C_{14}H_{10}F_3IN_3OS$ $[M+H]^+$ 451.9536, found 451.9535.

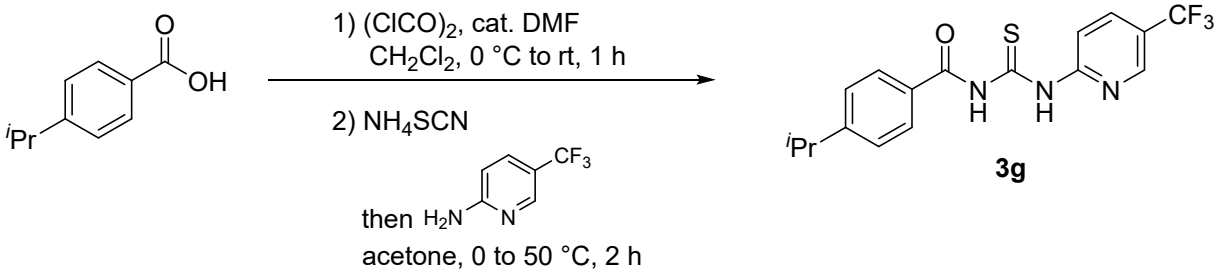


4-(Trifluoromethyl)-*N*-((5-(trifluoromethyl)pyridin-2-yl)carbamothioyl)benzamide (**3e**): To a solution of 4-(trifluoromethyl)benzoic acid (190 mg, 1.00 mmol) in CH_2Cl_2 (10.0 mL) were added DMF (7.74 μL, 100 μmol) and oxalyl chloride (127 μL, 1.50 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure to obtain the chloride, which was used immediately in next step without purification.

To a solution of the chloride in acetone (2.00 mL) was added NH_4SCN (91.3 mg, 1.20 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 30 min. After 2-amino-5-(trifluoromethyl) pyridine (162 mg, 1.00 mmol) was added to the solution, the mixture was stirred at 50 °C for 2 h. The reaction mixture was concentrated under reduced pressure followed by flash column chromatography over silica gel with *n*-hexane/EtOAc (19:1 to 4:1) to give the title compound **3e** as white solid (302 mg, 768 μmol, 77% in 2 steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.20 (brs, 1H), 9.12 (brs, 1H), 9.07–9.05 (m, 1H), 8.70 (m, 1H), 8.05 (d, J = 8.5 Hz, 2H), 8.03–8.01 (m, 1H), 7.83 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 165.4, 153.8, 146.0, 136.0–134.6 (m, 3C), 128.3 (2C), 126.5 (q, J = 3.8 Hz, 2C), 124.3 (d, J = 3.8 Hz), 123.4 (q, J = 270.0 Hz), 123.3 (d, J = 271.2 Hz), 115.1; HRMS (ESI), *m/z* calcd for $C_{15}H_{10}F_6N_3OS$ $[M+H]^+$ 394.0443, found 394.0443.



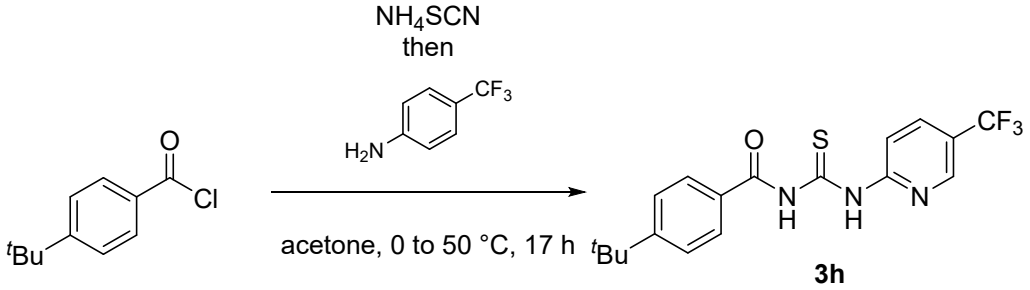
4-Methyl-*N*-((5-(trifluoromethyl)pyridin-2-yl)carbamothioyl)benzamide (**3f**): To a solution of *p*-toluoyl chloride (132 µL, 1.00 mmol) in acetone (2.00 mL) was added NH_4SCN (91.3 mg, 1.20 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 30 min. After 2-amino-5-(trifluoromethyl) pyridine (162 mg, 1.00 mmol) was added to the solution, the mixture was stirred at 50 °C for 2 h. The reaction mixture was concentrated under reduced pressure followed by flash column chromatography over silica gel with *n*-hexane/EtOAc (49:1 to 17:3) to give the title compound **3f** as a white solid (120 mg, 354 µmol, 35%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.41 (brs, 1H), 9.08–9.07 (m, 2H), 8.69–8.68 (m, 1H), 8.01–7.99 (m, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 166.6, 154.1, 145.9 (d, J = 3.8 Hz), 145.3, 135.4 (d, J = 3.8 Hz), 130.2 (2C), 128.6, 127.8 (2C), 124.1 (q, J = 32.5 Hz), 123.5 (q, J = 264.4 Hz), 115.1, 21.8; HRMS (ESI), *m/z* calcd for $C_{15}H_{13}F_3N_3OS$ $[M+H]^+$ 340.0726, found 340.0727.



4-Isopropyl-*N*-((5-(trifluoromethyl)pyridin-2-yl)carbamothioyl)benzamide (**3g**): To a solution of 4-isoprorylbenzoic acid (164 mg, 1.00 mmol) in CH_2Cl_2 (10.0 mL) were added DMF (7.74 µL, 100 µmol) and oxalyl chloride (127 µL, 1.50 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then concentrated under reduced pressure to obtain the chloride, which was used immediately in next step without purification.

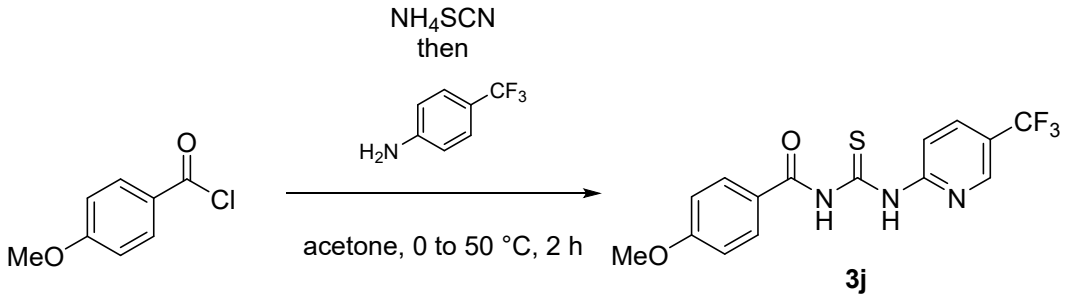
To a solution of the chloride in acetone (4.00 mL) was added NH_4SCN (91.3 mg, 1.20 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 30 min. After 2-amino-5-(trifluoromethyl) pyridine (162 mg, 1.00 mmol) was added to the solution, the mixture was stirred at 50 °C for 2 h. The reaction mixture was concentrated under reduced pressure followed by flash column chromatography over silica gel with *n*-hexane/EtOAc (49:1 to 17:3) to obtain the title compound **3g** as a white solid (145 mg, 395 µmol, 40% in 2 steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.42 (brs, 1H), 9.09-9.07 (m, 2H), 8.70-8.69 (m, 1H), 8.02-7.99 (m, 1H), 7.85 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 3.01 (sep, J = 7.0 Hz, 1H), 1.30 (d, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 166.6, 156.0, 154.1, 145.9 (d, J = 2.5 Hz) 135.4 (d, J = 3.8 Hz), 128.9, 128.0 (2C), 127.6 (2C), 123.5 (q, J = 33.8 Hz), 123.4 (q, J = 270.0 Hz), 115.1, 34.5, 23.2 (2C); HRMS (ESI), *m/z* calcd for

$C_{17}H_{17}F_3N_3OS$ $[M+H]^+$ 368.1039, found 368.1039.



3h

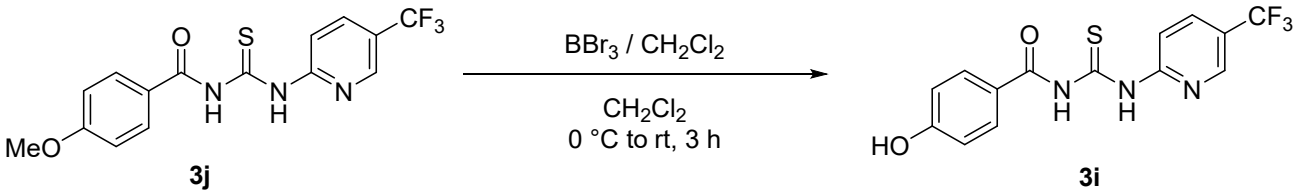
4-(*tert*-Butyl)-*N*-((5-(trifluoromethyl)pyridin-2-yl)carbamothioyl)benzamide (**3h**): To a solution of *tert*-butylbenzoyl chloride (195 µL, 1.00 mmol) in acetone (2.00 mL) was added NH_4SCN (91.3 mg, 1.20 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 30 min. After 2-amino-5-(trifluoromethyl) pyridine (162 mg, 1.00 mmol) was added to the solution, the mixture was stirred at 50 °C for 2 h. The reaction mixture was concentrated under reduced pressure followed by flash column chromatography over silica gel with *n*-hexane/EtOAc (49:1 to 17:3) to obtain the title compound **3h** as a white solid (219 mg, 574 µmol, 57%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 13.42 (brs, 1H), 9.09–9.07 (m, 2H), 8.70–8.69 (m, 1H), 8.02–7.99 (m, 1H), 7.86 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 1.36 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 177.8, 166.6, 158.3, 154.1, 145.9 (d, J = 2.5 Hz), 135.4 (d, J = 3.8 Hz), 128.5, 127.7 (2C), 127.5 (2C), 124.0 (q, J = 32.5 Hz), 123.5 (q, J = 270.0 Hz), 115.1, 35.4, 31.2 (3C); HRMS (ESI), *m/z* calcd for $C_{18}H_{19}F_3N_3OS$ $[M+H]^+$ 382.1195, found 382.1195.



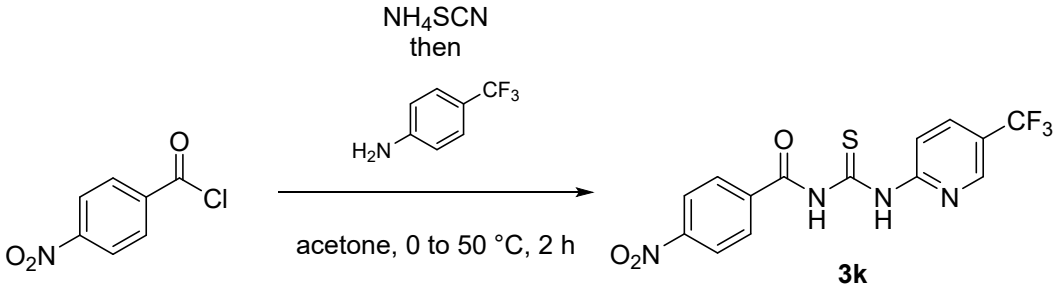
3j

4-Methoxy-*N*-((5-(trifluoromethyl)pyridin-2-yl)carbamothioyl)benzamide (**3j**): To a solution of 4-methoxybenzoyl chloride (135 µL, 1.00 mmol) in acetone (2.00 mL) was added NH_4SCN (91.3 mg, 1.20 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 30 min. After 2-amino-5-(trifluoromethyl) pyridine (162 mg, 1.00 mmol) was added to the solution, the mixture was stirred at 50 °C for 2 h. The reaction mixture was concentrated under reduced pressure followed by flash column chromatography over silica gel with *n*-hexane/EtOAc (49:1 to 17:3) to obtain the title compound **3j** as a white solid (114 mg, 321 µmol, 32%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.45 (brs, 1H), 9.08–9.05 (m, 2H), 8.69 (s, 1H), 8.01–7.99 (m, 1H), 7.89 (d, J = 9.0 Hz, 2H), 7.02 (d, J = 9.0 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9,

166.0, 164.4, 154.2, 145.9 (d, J = 3.8 Hz), 135.3 (d, J = 2.5 Hz), 130.0 (2C), 124.0 (q, J = 33.8 Hz), 123.3 (1C), 122.2 (q, J = 270.0 Hz), 115.1, 114.7 (2C), 55.8; HRMS (ESI), *m/z* calcd for $C_{15}H_{13}F_3N_3O_2S$ $[M+H]^+$ 356.0675, found 356.0677.

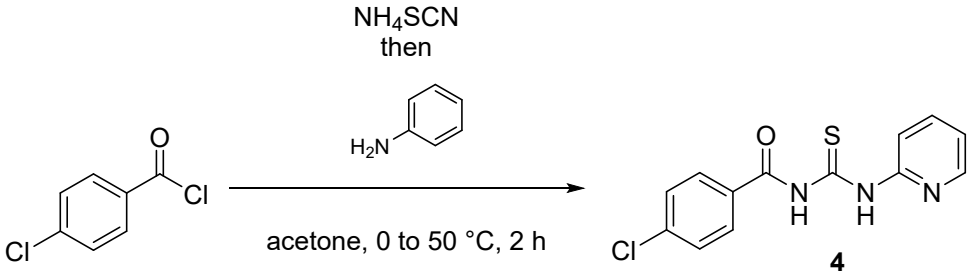


4-Hydroxy-*N*-((5-(trifluoromethyl)pyridin-2-yl)carbamothioyl)benzamide (**3i**): To a solution of **3j** (83.3 mg, 234 μmol) in CH_2Cl_2 (2.30 mL) was added BBr_3 in CH_2Cl_2 (1.40 mL, 1.40 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 3 h. After cooling the mixture to 0 °C, the reaction was quenched by the addition of H_2O. The mixture was extracted with $CHCl_3$. The organic layer was washed with brine and dried over $MgSO_4$ and concentrated under reduced pressure followed by purification with flash column chromatography over silica gel with *n*-hexane/EtOAc (23:2 to 16:9) to obtain the title compound **3i** as light yellow solid (21.9 mg, 64.1 μmol, 31% yield brsm): ^{1}H-NMR (500 MHz, MeOD) δ 9.09 (brs, 1H), 8.69 (s, 1H), 8.14–8.13 (m, 1H), 7.89 (d, J = 8.5 Hz, 2H), 6.91 (d, J = 8.5 Hz, 2H); ^{13}C-NMR (125 MHz, MeOD) δ 178.8, 167.6, 162.7, 154.6, 145.1 (d, J = 2.5 Hz), 135.1 (d, J = 2.5 Hz), 130.5 (2C), 123.6 (q, J = 270.0 Hz), 122.9 (q, J = 32.5 Hz), 122.5, 115.2–115.1 (3C); HRMS (ESI), *m/z* calcd for $C_{14}H_{10}F_3N_3NaO_2S$ $[M+Na]^+$ 364.0338, found 364.0335.



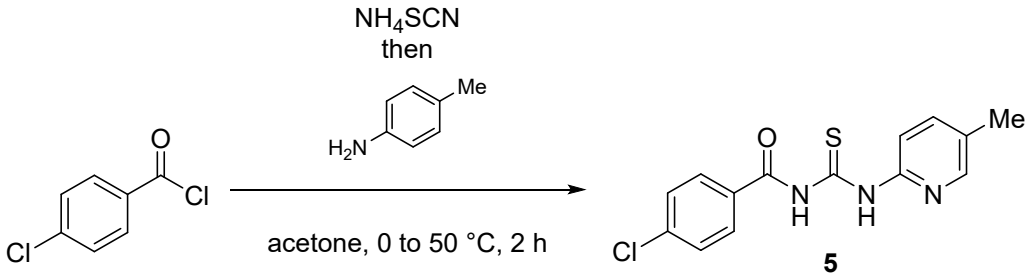
4-Nitro-*N*-((5-(trifluoromethyl)pyridin-2-yl)carbamothioyl)benzamide (**3k**): To a solution of 4-nitrobenzoyl chloride (371 mg, 2.00 mmol) in acetone (4.00 mL) was added NH_4SCN (183 mg, 2.40 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 30 min. After 2-amino-5-(trifluoromethyl) pyridine (324 mg, 2.00 mmol) was added to the solution, the mixture was stirred at 50 °C for 2 h. The reaction mixture was concentrated under reduced pressure followed by flash column chromatography over silica gel with *n*-hexane/EtOAc (49:1 to 3:1) to obtain the title compound **3k** as a white solid (212 mg, 572 μmol, 29%): ^{1}H NMR (500 MHz, DMSO) δ 13.38–12.30 (m, 2H), 8.88–8.87 (m, 1H), 8.69 (s, 1H), 8.38 (d, J

= 8.5 Hz, 2H), 8.35–8.33 (m, 1H), 8.18 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 166.5, 154.3, 149.9, 145.5, 138.2, 136.3, , 130.2 (2C), 123.6 (2C), 123.5 (q, *J* = 270.0 Hz), 121.8 (q, *J* = 30.0 Hz), 114.7; HRMS (ESI), *m/z* calcd for $C_{14}H_8F_3N_4O_3S$ $[M-H]^-$ 369.0275, found 369.0270.



4

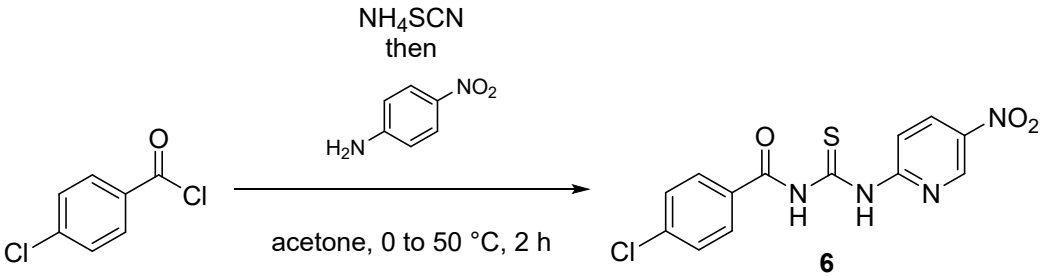
4-Chloro-*N*-(pyridin-2-ylcarbamothioyl)benzamide (**4**): To a solution of 4-chlorobenzoyl chloride (641 μL, 5.00 mmol) in acetone (10.0 mL) was added NH_4SCN (457 mg, 6.00 mmol) at 0 °C under argon. The reaction mixture was stirred at 50 °C for 30 min. After 2-aminopyridine (811 mg, 5.00 mmol) was added to the solution, the mixture was stirred at 50 °C for 2 h. The reaction mixture was added H_2O and extracted with Et_2O. The extract was washed with brine and dried by over $MgSO_4$. The organic layer was removed under reduced pressure followed by recrystallization (acetone/ *n*-hexane) to obtain the title compound **4** as a white solid (715 mg, 2.45 mmol, 49%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.04 (brs, 1H), 9.08 (brs, 1H), 8.80–8.79 (m, 1H), 8.45–8.44 (m, 1H), 7.86 (d, *J* = 8.5 Hz, 2H), 7.80–7.77 (m, 1H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.19–7.17 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 165.5, 151.2, 148.7, 140.5, 138.0, 130.1, 129.7 (2C), 129.2 (2C), 121.7, 116.2; HRMS (ESI), *m/z* calcd for $C_{13}H_{11}ClN_3OS$ $[M+H]^+$ 292.0306, found 292.0306.



5

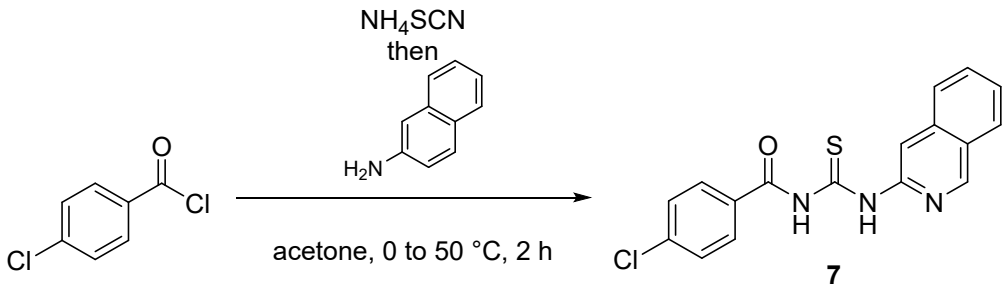
4-Chloro-*N*-((5-methylpyridin-2-yl)carbamothioyl)benzamide (**5**): To a solution of 4-chlorobenzoyl chloride (641 μL, 5.00 mmol) in acetone (10.0 mL) was added NH_4SCN (457 mg, 6.00 mmol) at 0 °C under argon, and the mixture was stirred at 50 °C for 30 min. After 2-amino-5-methylpyridine (541 mg, 5.00 mmol) was added to the solution, the mixture was stirred at 50 °C for 2 h. The reaction mixture was added H_2O and Et_2O. The resulting precipitate was collected by filtration and washed with H_2O and Et_2O. It was then dried and followed by flash column chromatography over silica gel with *n*-hexane/EtOAc (49:1 to 4:1) to obtain the title compound **5** as white solid (736 mg, 2.40 mmol, 48%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 12.97 (brs, 1H), 9.07 (brs, 1H), 8.62 (d, *J* = 8.5 Hz, 1H), 8.26 (d, *J* = 1.0 Hz, 1H), 7.86 (d, *J* = 9.0 Hz, 2H), 7.59 (dd, *J* = 8.5 Hz and 1.5 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 2H), 2.35 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 176.8, 165.5, 149.0, 148.6,

140.5, 138.4, 131.5, 130.2, 129.7 (2C), 129.1 (2C), 116.0, 18.2; HRMS (ESI), *m/z* calcd for $C_{14}H_{12}ClN_3NaOS$ $[M+Na]^+$ 328.0282, found 328.0278.



6

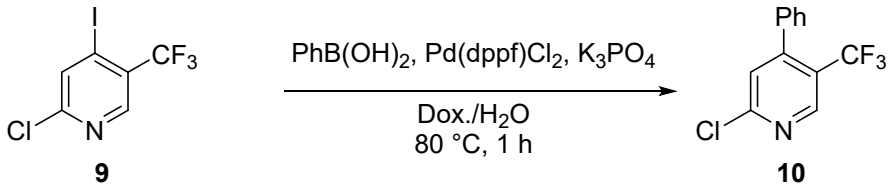
4-Chloro-*N*-((5-nitropyridin-2-yl)carbamothioyl)benzamide (**6**): To a solution of 4-chlorobenzoyl chloride (641 μL, 5.00 mmol) in acetone (10.0 mL) was added NH_4SCN (457 mg, 6.00 mmol) at 0 °C under argon. The reaction mixture was stirred at 50 °C for 30 min. After 2-amino-5-nitropyridine (696 mg, 5.00 mmol) was added to the solution, the reaction mixture was stirred at 50 °C for 2 h. The reaction was quenched by the addition of H_2O and Et_2O. The resulting precipitate was collected by filtration and washed with H_2O and Et_2O. It was then dried followed by flash column chromatography over silica gel with *n*-hexane/EtOAc (49:1 to 4:1) to obtain the title compound **6** as a light yellow solid (1.03 g, 3.06 mmol, 61%): ^{1}H-NMR (500 MHz, DMSO) δ 13.26 (brs, 1H), 12.60 (brs, 1H), 9.28–9.27 (m, 1H), 8.80–8.71 (m, 2H), 8.00 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.5 Hz, 2H); ^{13}C-NMR (125 MHz, DMSO) δ 178.3, 167.2, 155.2, 144.7, 140.8, 138.2, 134.4, 131.1, 130.7 (2C), 128.7 (2C), 114.1; HRMS (ESI), *m/z* calcd for $C_{13}H_8ClN4O3S$ $[M-H]^-$ 335.0011, found 335.0010.



7

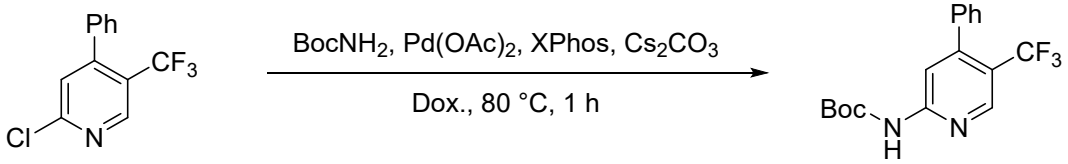
4-Chloro-*N*-(isoquinolin-3-ylcarbamothioyl)benzamide (**7**): To a solution of 4-chlorobenzoyl chloride (641 μL, 5.00 mmol) in acetone (10.0 mL) was added NH_4SCN (457 mg, 6.00 mmol) at 0 °C under argon. The reaction mixture was stirred at 50 °C for 30 min. After 3-aminoisoquinoline (721 mg, 5.00 mmol) was added to the solution, the mixture was stirred at 50 °C for 2 h. The reaction mixture was added H_2O and Et_2O. The resulting precipitate was collected by filtration and washed with H_2O and Et_2O. It was then dried in vacuo followed by flash column chromatography over silica gel with *n*-hexane/EtOAc (49:1 to 4:1) to give the title compound **7** as a light yellow solid (147 mg, 430 μmol, 9%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.27 (brs, 1H), 9.28 (s, 1H), 9.11 (s, 1H), 9.05 (brs, 1H), 7.97–7.96 (m, 1H), 7.92–7.88 (m, 1H), 7.89 (d, J = 8.5 Hz, 2H), 7.72–7.70 (m, 1H), 7.60–7.56 (m, 1H), 7.53 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 165.5, 151.6,

146.0, 140.5, 137.3, 131.2, 130.2, 129.7 (2C), 129.1 (2C), 127.7, 127.5, 127.4, 127.2, 111.0; HRMS (ESI), *m/z* calcd for $C_{17}H_{13}ClN_3OS$ $[M+H]^+$ 342.0462, found 342.0458.



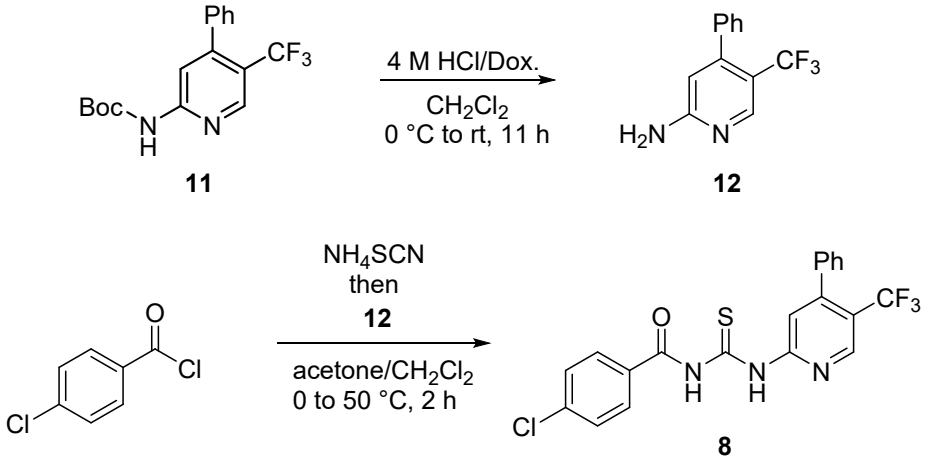
9 **10**

2-Chloro-4-phenyl-5-(trifluoromethyl)pyridine (**10**): To a solution of 2-chloro-4-iodo-5-(trifluoromethyl)pyridine (307 mg, 1.00 mmol) **9** in Dox./H_2O (4:1, 8.9 mL) was added phenylboronic acid (128 mg, 1.05 mmol), K_3PO_4 (743 mg, 3.50 mmol), and $Pd(dppf)Cl_2$ (58.5 mg, 80.0 μmol) at room temperature. The mixture was stirred at 80 °C for 1 h. The reaction mixture was added H_2O and extracted with $CHCl_3$. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was removed under reduced pressure followed by flash column chromatography over silica gel with *n*-hexane/$CHCl_3$ (5:1) to obtain the title compound **10** as a light yellow oil (202 mg, 784 μmol, 78%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.49–7.43 (m, 3H), 7.35–7.32 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 152.4, 147.7 (q, J = 6.2 Hz), 135.9, 129.4–126.7 (m, 6C), 123.8 (q, J = 5.0 Hz), 123.4 (q, J = 272.5 Hz); HRMS (ESI), *m/z* calcd for $C_{12}H_8ClF_3N$ $[M+H]^+$ 258.0292, found 258.0288.



10 **11**

***tert*-Butyl (4-phenyl-5-(trifluoromethyl)pyridin-2-yl)carbamate** (**11**): To a solution of **10** (202 mg, 784 μmol) in Dox. (7.80 mL) was added *tert*-butyl carbamate (137.8 mg, 1.18mmol), Cs_2CO_3 (510 mg, 1.57 mmol), XPhos (67.2 mg, 141 μmol), $Pd(OAc)_2$ (10.6 mg, 47.0 μmol) at room temperature under argon. The reaction mixture was stirred at 80 °C for 1 h. The mixture was added H_2O and extracted with $CHCl_3$. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was concentrated under reduced pressure followed by flash column chromatography over silica gel with *n*-hexane/$CHCl_3$ (3:1) to obtain the title compound **11** as a light yellow solid (147 mg, 447 μmol, 57%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26–9.16 (m, 1H), 8.67 (s, 1H), 8.06 (s, 1H), 7.43–7.41 (m, 3H), 7.37–7.35 (m, 2H), 1.55 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 152.3 (d, J = 22.5 Hz), 146.1 (d, J = 5.0 Hz), 137.7, 128.7–128.2 (m, 6C), 124.0 (q, J = 270.0 Hz), 119.4 (q, J = 30.0 Hz), 114.4, 82.0, 28.4 (3C); HRMS (ESI), *m/z* calcd for $C_{17}H_{18}F_3N_2O_2$ $[M+H]^+$ 339.1315 found 399.1310.



4-Chloro-*N*-((4-phenyl-5-(trifluoromethyl)pyridin-2-yl)carbamothioyl)benzamide (**8**): To the solution of compound **11** (147 mg, 447 μmol) in CH_2Cl_2 (2.20 mL) was added 4 M HCl/Dox. (3.35 mL, 13.4 mmol) at 0 °C, and the mixture was stirred at room temperature for 11 h. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was concentrated under reduced pressure to obtain crude amine **12**, which was used immediately in next step without further purification.

To a solution of 4-chlorobenzoyl chloride (59 μL, 447 μmol) in acetone (2.00 mL) was added NH_4SCN (40.8 mg, 536 μmol) at 0 °C under argon. The mixture was stirred at room temperature for 30 min, and then crude amine **12** dissolved in CH_2Cl_2 (1.10 mL) was added to the solution. The mixture was stirred at 50 °C for 2 h. The reaction mixture was added H_2O and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was concentrated under reduced pressure followed by flash column chromatography over silica gel with *n*-hexane/EtOAc (99:1 to 7:13) and recrystallization ($CHCl_3$/ *n*-hexane) to obtain the title compound **8** as a yellow solid (52.3 mg, 120 μmol, 27 %): ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.30 (brs, 1H), 9.08 (brs, 1H), 8.94 (brs, 1H), 8.76 (s, 1H), 7.88 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 7.49–7.46 (m, 3H), 7.42–7.40 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 165.6, 153.6, 151.9, 146.7 (d, J = 5.0 Hz), 140.8, 137.3, 129.8 (3C), 129.2 (2C), 129.1, 128.5 (2C), 128.4 (2C), 123.7 (q, J = 271.2 Hz), 122.2 (q, J = 31.3 Hz), 117.6; HRMS (ESI), *m/z* calcd for $C_{20}H_{14}ClF_3N_3OS$ $[M+H]^+$ 436.0493, found 436.0491.