Structure Guided Generation of Thieno[3,2-*d*]pyrimidin-4-amine *Mycobacterium tuberculosis bd* oxidase Inhibitors†

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Electronic supplementary information

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1. Experimental Section, Chemistry

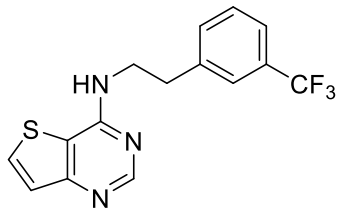
All anhydrous solvents, reagent grade solvents for chromatography and starting materials were purchased from either Aldrich Chemical Co. (Milwaulkee, WI) or Fisher Scientific (Suwanee, GA) unless otherwise noted. The reactions were monitored by TLC on precoated Merck 60 F254 silica gel plates and visualized using UV light (254 nm). All compounds were analyzed for purity by a Bruker micrOTOF with Agilent 1290 UHPLC or Agilent 6520 Q-TOF with Agilent 1100 nano-HPLC and were characterized by ^{1}H and ^{13}C NMR using a Bruker DPX Avance I NMR Spectrometer (300 MHz) and/or a Bruker Ascend Avance III HD Spectrometer (500 MHz) and/or Bruker Avance III Spectrometer (600 MHz). Chemical shifts are reported in ppm (δ) relative to the residual solvent peak in the corresponding spectra; chloroform δ 7.27 and δ 77.23, methanol δ 3.31 and δ 49.00 and coupling constants (*J*) are reported in hertz (Hz) (where, s = singlet, br s = broad singlet, d = doublet, dd = double doublet, bd = broad doublet, ddd = double doublet of doublet, t = triplet, tt–triple triplet, q = quartet, m = multiplet) and analyzed using MestreNova NMR data processing. ^{19}F NMR were run without a standard and are uncorrected. Mass spectra values are reported as m/z. Melting points were measured on a Buchi B-545 melting point instrument and are uncorrected, measured against benzoic acid 118.8-120.2°C.

General procedure A for the preparation of **7**, **10**, **11**, **13**, **17**,**19**, **22**.

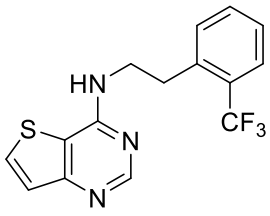
In a sealed vial, 4-chlorothieno[3,2-*d*]pyrimidine (100 mg, 0.57 mmol), desired amine (0.57 mmol) and K_2CO_3 (79 mg, 0.57 mmol) were dissolved in DMSO (4 mL). The reaction was heated to 100ºC for 12 h. The reaction mixture was concentrated to dryness and the residue was dissolved in CH_2Cl_2 and washed with 5% aqueous acetic acid solution (2x), water and brine. The organic phase was collected, dried over sodium sulfate, filtered, and concentrated in vacuo. Crude material obtained was purified by either silica gel column chromatography with a gradient of CH_2Cl_2 : ethyl acetate : solvent system (0 to 80%) or recrystallized from hot isopropanol or acetonitrile to afford the product.

General procedure B for the preparation of **12**, **14**-**16**, **18**, **20**, **21**.

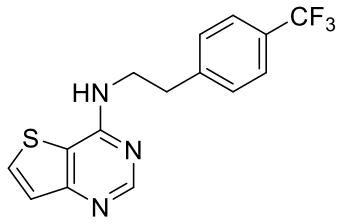
In a sealed vial, 4-chlorothieno[3,2-*d*]pyrimidine (100 mg, 0.57 mmol, 1 equiv.) and amine (1 equiv.) were dissolved in a 3:1 tetrahydrofuran: 2-propanol solution (4 mL). Next, 12 M HCl (11 μL, “drop”, ~0.4 equiv.) was added. The solution heated to 70°C for 24 h. The reaction was concentrated to dryness and the residue was dissolved in CH_2Cl_2 and washed with saturated aqueous NaHCO3 solution, water, and brine. The organic phase was collected, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Crude material obtained was purified by either silica gel column chromatography with a gradient of CH_2Cl_2 : ethyl acetate : solvent system (0-80%) or recrystallized from hot isopropanol or acetonitrile to afford the product.



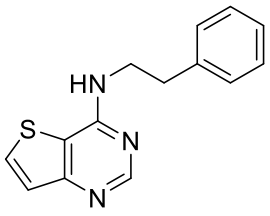
N-(3-(Trifluoromethyl)phenethyl)thieno[3,2-*d*]pyrimidin-4-amine (**7**). The reaction was carried out according to the general procedure A using 4-chlorothieno[3,2-*d*]pyrimidine (50 mg, 0.28 mmol), 2-(3-(trifluoromethyl)phenyl)ethan-1-amine (55 mg, 0.38 mmol), potassium carbonate (39 mg, 0.28 mmol) to give **7** as a yellow flaky solid (32 mg, 33% yield). m.p. 109.8-111.4°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.68 (s, 1H), 7.72 (d, *J* = 5.4 Hz, 1H), 7.55-7.51 (m, 2H), 7.47-7.43 (m, 3H), 5.06 (br s, 1H), 3.97 (q, *J* = 6.7 Hz, 2H), 3.11 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 159.8, 157.2, 155.0, 139.7, 132.3, 130.9, 129.1, 125.5, 123.5, 115.2, 42.2, 35.6. ^{19}F (282 MHz, $CDCl_3$) δ ppm -62.56 (s, 3F). HRMS (EI), M + 1 calculated for $C_{15}H_{12}F_3N_3S$, 324.0777, found 324.0890; HPLC t_R = 5.9 min, >95% pure.



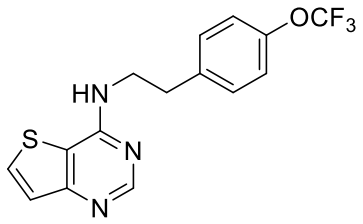
N-(2-(Trifluoromethyl)phenethyl)thieno[3,2-*d*]pyrimidin-4-amine (**10**). The reaction was carried out according to the general procedure A using 4-chlorothieno[3,2-*d*]pyrimidine (100 mg, 0.57 mmol), 2-(2-(trifluoromethyl)phenyl)ethan-1-amine (0.09 mL, 0.57 mmol), potassium carbonate (79 mg, 0.57 mol) to give **10** as white, fluffy crystals (80.8 mg, 42%). m.p. 141.5-141.8°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 8.68 (s, 1H), 7.72 (d, *J* = 5.3 Hz, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1 H), 7.46-7.42 (m, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 5.13 (s, 1H), 3.96 (q, *J* = 6.6 Hz, 2H), 3.24 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 159.8, 157.2, 155.1,137.4, 131.9, 131.7, 130.8, 126.7, 125.5, 123.5, 121.3, 115.2, 42.2, 23.5. ^{19}F (470 MHz, $CDCl_3$) δ ppm -59.2 (s, 3F). HRMS (EI), M + 1 calculated for $C_{15}H_{12}F_3N_3S$, 324.0777, found 324.0786; HPLC t_R = 6.4 min, >95% pure.



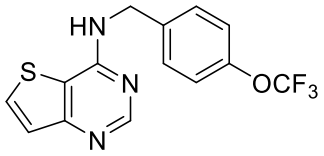
N-(4-(Trifluoromethyl)phenethyl)thieno[3,2-*d*]pyrimidin-4-amine (**11**). The reaction was carried out according to the general procedure A using 4-chlorothieno[3,2-*d*]pyrimidine (100 mg, 0.57 mmol), 2-(4-(trifluoromethyl)phenyl)ethan-1-amine (108 mg, 0.57 mmol), and potassium carbonate (79 mg, 0.57 mmol) to give **11** as yellow crystals (75.1 mg, 39%). m.p. 171.0-171.5°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.68 (s, 1H), 7.72 (d, *J* = 5.4 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 5.4 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 2H), 5.08 (s, 1H), 3.97 (q, *J* = 6.7 Hz, 2H), 3.11 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 159.89, 157.16, 155.03, 142.98, 130.89, 129.23, 125.10 (q, *J* = 15.0 Hz), 125.52, 123.13, 120.97, 115.22, 42.13, 35.60. ^{19}F (470 MHz, $CDCl_3$) δ ppm -62.43 (s, 3F). HRMS (EI), M + 1 calculated for $C_{15}H_{12}F_3N_3S$, 324.0777, found 324.0780; HPLC t_R = 6.5 min, >95% pure.



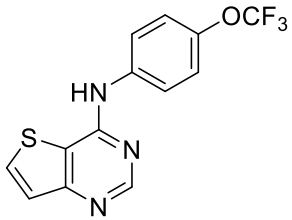
N-Phenethylthieno[3,2-*d*]pyrimidin-4-amine amine (**12**). The reaction was carried out according to the general procedure B using 4-chlorothieno[3,2-*d*]pyrimidine (100 mg, 0.57 mmol), 2-phenylethan-1-amine (0.07 mL, 0.57 mmol) and 12 N HCl (11 μL, 0.13 mmol) to give **12** as yellow, sand-like crystals (35.1 mg, 24%). m.p. 173.0-173.5°C. ^{1}H NMR (500 MHz, DMSO) δ ppm 8.46 (s, 1H), 8.08 (d, *J* = 5.4 Hz, 1H), 7.94 (t, *J* = 5.3 Hz, 1H), 7.37 (d, *J* = 5.4 Hz, 1H), 7.32-7.24 (m, 4H), 7.20 (t, *J* = 7.0 Hz, 1H), 3.72 (q, *J* = 6.9 Hz, 2H), 2.94 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, DMSO) δ ppm 159.69, 157.30, 155.04, 139.99, 133.26, 129.15, 128.81, 126.56, 124.91, 115.15, 42.29, 35.34. HRMS (EI), M + 1 calculated for $C_{14}H_{13}N_3S$, 256.0903, found 256.0911; HPLC t_R = 5.6 min, >95% pure.



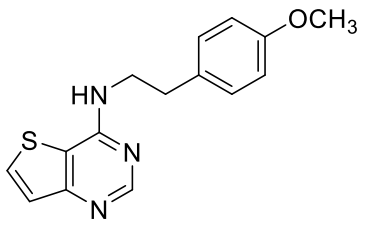
N-(4-(Trifluoromethoxy)phenethyl)thieno[3,2-*d*]pyrimidin-4-amine (**13**). The reaction was carried out according to the general procedure A using 4-chlorothieno[3,2-*d*]pyrimidine (100 mg, 0.57 mmol), 2-(4-(trifluoromethoxy)phenyl)ethan-1-amine (120 mg, 0.57 mmol), and potassium carbonate (81 mg, 0.57 mmol) to give **13** as a white solid (39.2 mg, 20%). m.p. 129.0-130.8°C. ^{1}H NMR (600 MHz, DMSO) δ ppm 8.46 (s, 1H), 8.09 (d, *J* = 5.3 Hz, 1H), 7.95 (t, *J* = 5.5 Hz, 1H, NH), 7.40-7.36 (m, 3H), 7.28 (d, *J* = 7.9 Hz, 2H), 3.73 (q, *J* = 6.7 Hz, 2H), 2.98 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR (150 MHz, DMSO) δ ppm 159.7, 157.3, 155.0, 147.3, 139.6, 133.3, 130.9, 124.9, 121.4, 119.7, 115.1, 42.0, 34.5. ^{19}F (282 MHz, DMSO) δ ppm -56.8 (s, 3F). HRMS (EI), M + 1 calculated for $C_{15}H_{12}F_3N_3OS$, 340.0726, found 340.0741; HPLC t_R = 5.5 min, >95% pure.



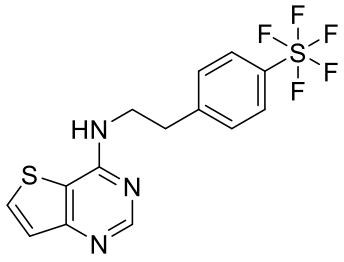
N-(4-(Trifluoromethoxy)benzyl)thieno[3,2-*d*]pyrimidin-4-amine (**14**). The reaction was carried out according to the general procedure B using 4-chlorothieno[3,2-*d*]pyrimidine (50 mg, 0.29 mmol), 4-(trifluoromethoxy)benzylamine (56 mg, 0.29 mmol), and 12 M HCl (11 μL, 0.13 mmol). Crude material was purified through column chromatography (ethyl acetate) to give **14** as an orange solid (21.2 mg, 22%). m.p. 109.5-109.9°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 8.60 (s, 1H), 7.67 (d, *J* = 5.3 Hz, 1H), 7.40 (d, *J* = 5.3 Hz, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.20-7.17 (m, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 5.30 (br.s, 1H), 4.84 (d, *J* = 5.9 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 157.1, 154.8, 149.6, 140.6, 131.3, 130.2, 126.0, 125.4, 120.3, 120.0, 115.2, 44.4. ^{19}F (282 MHz, $CDCl_3$) δ ppm -57.7 (s, 3F). HRMS (EI), M + 1 calculated for $C_{14}H_{10}F_3N_3OS$, 326.0569, found 326.0568; HPLC t_R = 6.5 min, >95% pure.



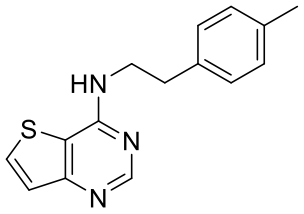
N-(4-(Trifluoromethoxy)phenyl)thieno[3,2-*d*]pyrimidin-4-amine (**15**). The reaction was carried out according to the general procedure B using 4-chlorothieno[3,2-*d*]pyrimidine (60 mg, 0.35 mmol), 4-(trifluoromethoxy)aniline (62 mg, 0.35 mmol), and 12 M HCl (11 μL, 0.13 mmol) to give **15** as a yellow solid (49.6 mg, 45%). m.p. 151.2-151.8°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 8.77 (s, 1H), 7.79 (d, *J* = 5.4 Hz, 1H), 7.70 (dt, *J* = 9.0, 3.3 Hz, 2H), 7.49 (d, *J* = 5.3 Hz, 1H), 7.31-7.26 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 161.2, 155.6, 154.6, 146.1, 136.4, 123.4, 125.4, 124.3, 121.8, 115.5. ^{19}F (282 MHz, DMSO) δ ppm -58.0 (s, 3F). HRMS (EI), M + 1 calculated for $C_{13}H_8F_3N_3OS$, 312.0413, found 312.0425; HPLC t_R = 5.8 min, >95% pure.



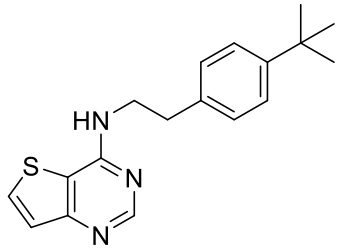
N-(4-Methoxyphenethyl)thieno[3,2-*d*]pyrimidin-4-amine (**16**). The reaction was carried out according to the general procedure B using 4-chlorothieno[3,2-*d*]pyrimidine (100 mg, 0.57 mmol), 2-(4-methoxyphenyl)ethan-1-amine (0.09 mL, 0.57 mmol), and 12 M HCl (11 μL, 0.13 mmol) to give **16** as a shiny bronze solid (75.4 mg, 46%). m.p. 151.5-151.7°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 8.67 (s, 1H), 7.71 (d, J = 5.3 Hz, 1H), 7.44 (d, J = 5.3 Hz, 1H), 7.18 (dt, J = 8.6, 3.0 Hz, 2H), 6.89 (dt, J = 8.6, 3.0 Hz, 2H), 3.92 (q, J = 6.8 Hz, 2H), 3.83 (s, 3H), 2.98 (t, J = 6.8 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 159.7, 158.4, 157.3, 155.0, 130.8, 130.6, 129.8, 12525, 115.2, 114.2, 55.3, 42.6, 34.8. HRMS (EI), M + 1 calculated for $C_{15}H_{15}N_3OS$, 286.1009, found 286.0998; HPLC t_R = 5.6 min, >95% pure.



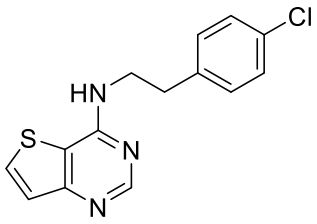
N-(4-(Pentafluoro-λ^6-sulfaneyl)phenethyl)thieno[3,2-d]pyrimidin-4-amine (**17**). The reaction was carried out according to the general procedure A using 4-chlorothieno[3,2-*d*]pyrimidine (72 mg, 0.42 mmol), 2-(4-(pentafluoro-λ^6-sulfaneyl)phenyl)ethan-1-amine (105 mg, 0.42 mmol), and potassium carbonate (59 mg, 0.42 mmol) to give **17** as a white solid (59.3 mg, 36%). m.p. 288.1-288.2°C. ^{1}H NMR (500 MHz, DMSO) δ ppm 8.46 (s, 1H), 8.09 (d, J = 5.4 Hz, 1H), 7.94 (t, J = 5.4 Hz, 1H), 7.82 (d, J = 8.6 Hz, 2H), 7.48 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 5.4 Hz, 3.76 (q, J = 6.8 Hz, 2H), 3.05 (t, J = 6.8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 159.7, 157.3, 155.0, 145.2, 133.4, 130.2, 126.2, 124.9, 115.2, 41.7, 34.7; ^{19}F NMR (282 MHz, DMSO) δ ppm 84.5 (penta, *J* = 150.0 Hz, 1F), 63.0 (d, *J* = 150.0 Hz, 4F); HRMS (EI), M + 1 calculated for $C_{14}H_{12}F_5N_3S_2$, 382.0466; found 382.0476; HPLC t_R = 6.8 min, >95% pure.



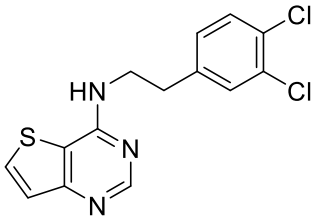
N-(4-Methylphenethyl)thieno[3,2-*d*]pyrimidin-4-amine (**18**). The reaction was carried out according to the general procedure B using 4-chlorothieno[3,2-*d*]pyrimidine (100 mg, 0.57 mmol), 2-(*p*-tolyl)ethan-1-amine (79 mg, 0.57 mmol), and 12 M HCl (11 μL, 0.13 mmol) to give **18** as pale yellow crystals (75.1 mg, 47%). m.p. 186.8-190.0°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.46 (s, 1H), 8.08 (d, *J* = 5.4 Hz, 1H), 7.91 (t, *J* = 5.4 Hz, 1H), 7.37 (d, *J* = 5.4 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 2H), 7.90 (d, *J* = 7.9 Hz, 2H), 3.69 (q, *J* = 7.1 Hz, 2H), 2.89 (t, *J* = 7.1 Hz, 2H), 2.27 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 159.7, 157.3, 155.0, 136.9, 135.5, 133.2, 129.4, 129.0, 124.9, 42.4, 34.9, 21.1. HRMS (EI), M + 1 calculated for $C_{15}H_{15}N_3S$, 270.1059, found 270.1051; HPLC t_R = 6.1 min, >95% pure.



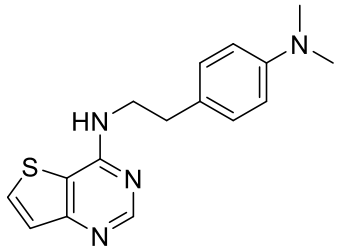
N-(4-(*tert*-Butyl)phenethyl)thieno[3,2-*d*]pyrimidin-4-amine (**19**). The reaction was carried out according to the general procedure A using 4-chlorothieno[3,2-*d*]pyrimidine (100 mg, 0.57 mmol), 2-(4-(*tert*-butyl)phenyl)ethan-1-amine (106 mg, 0.57 mmol), and potassium carbonate (79 mg, 0.57 mmol) to give **19** as a yellow solid (103 mg, 55%). m.p. 133.8-134.5°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.66 (s, 1H), 7.70 (d, *J* = 5.4 Hz, 1H), 7.44 (d, *J* = 5.4Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 5.03 (s, 1H), 3.95 (q, *J* = 6.7 Hz, 2H), 3.01 (t, *J* = 6.7 Hz, 2H), 1.35 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 159.9, 157.3, 155.1, 149.6, 135.6, 130.7, 128.5, 125.6, 125.5, 115.2, 64.41, 42.4, 35.2, 34.5, 31.4. HRMS (EI), M + 1 calculated for $C_{18}H_{21}N_3S$, 312.1534 found, 312.1520; HPLC t_R = 5.8 min, >95% pure.



N-(4-Chlorophenethyl)thieno[3,2-*d*]pyrimidin-4-amine (**20**). The reaction was carried out according to the general procedure B using 4-chlorothieno[3,2-*d*]pyrimidine (100 mg, 0.57 mmol), 2-(4-chlorophenyl)ethan-1-amine (0.08 mL, 0.57 mmol), and 12 M HCl (11 μL, 0.13 mmol) to give **20** as a pale yellow, flaky solid (34.7 mg, 20%). m.p. 174.2-175.0°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.67 (s, 1H), 7.72 (d, *J* = 5.4 Hz, 1H), 7.45 (d, *J* = 5.4 Hz, 1H), 7.31 (dt, *J* = 8.4, 2.6 Hz, 2H), 7.21-7.16 (m, 2H), 5.00 (br.s, 1H), 3.92 (q, *J* = 6.7 Hz, 2H), 3.02 (t, *J* = 6.7 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 159.7, 157.2, 154.9, 137.2, 132.5, 130.9, 130.2, 128.8, 125.5, 115.2, 42.3, 35.1. HRMS (EI), M + 1 calculated for $C_{14}H_{12}ClN_3S$, 290.0513 found, 290.0513; HPLC t_R = 6.2 min, >95% pure.

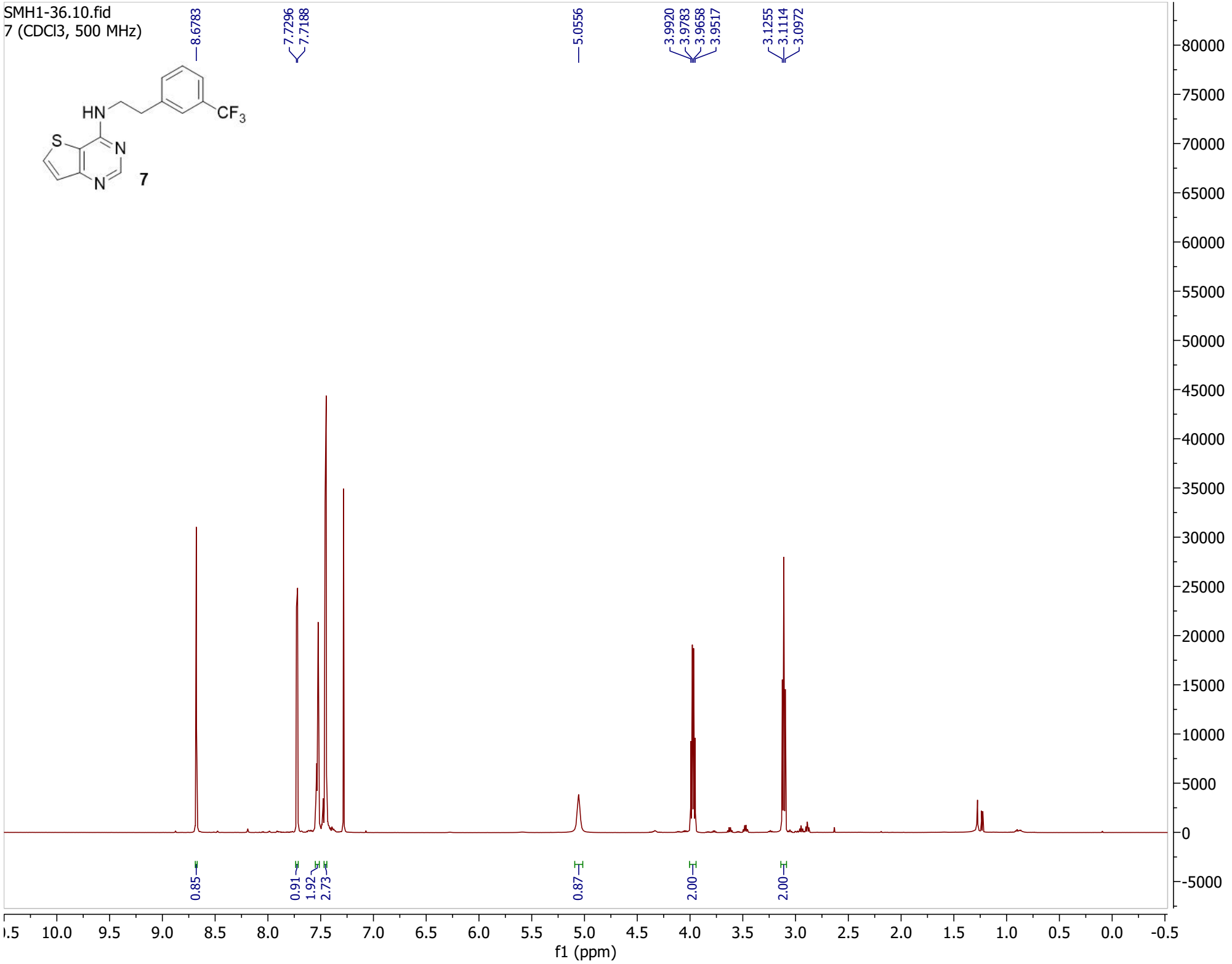


N-(3,4-Dichlorophenethyl)thieno[3,2-*d*]pyrimidin-4-amine (**21**). The reaction was carried out according to the general procedure B using 4-chlorothieno[3,2-*d*]pyrimidine (100 mg, 0.57 mmol), 2-(3,4-dichlorophenyl)ethan-1-amine (0.09 mL, 0.57 mmol), and 12 M HCl (11 μL, 0.13 mmol) to give **21** as a yellow brown pebble-like solid (35.1 mg, 18%). m.p. 186.1-187.2°C. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.45 (s, 1H), 7.97 (d, *J* = 5.4 Hz, 1H), 7.44 (d, *J* = 1.9 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.35 (d, J = 5.4 Hz, 1H), 7.18 (dd, *J* = 8.2, 1.9 Hz, 1H), 3.83 (t, *J* = 7.2 Hz, 2H), 3.00 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (125 MHz, MeOD) δ ppm 158.2, 157.4, 154.0, 140.2, 132.4, 131.7, 130.7,130.0, 129.7, 128.6, 123.4, 115.4, 41.5, 34.2. HRMS (EI), M + 1 calculated for $C_{14}H_{11}Cl_2N_3S$, 324.0124, found 324.0132; HPLC t_R = 6.7 min, >95% pure.

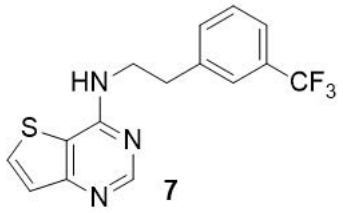


N-(4-(Dimethylamino)phenethyl)thieno[3,2-*d*]pyrimidin-4-amine (**22**). The reaction was carried out according to the general procedure A using 4-chlorothieno[3,2-*d*]pyrimidine (100 mg, 0.57 mmol), 4-(2-aminoethyl)-*N,N*-dimethylaniline (0.10 mL, 0.57 mmol), and potassium carbonate (79 mg, 0.57 mmol) to give **22** as pale yellow crystals (88.3 mg, 49%). m.p. 169.5-171.7°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 8.66 (s, 1H), 7.69 (d, *J* = 5.3 Hz, 1H), 7.43 (d, *J* = 5.3 Hz, 1H), 7.14 (d, *J* = 7.1 Hz, 1H), 6.74 (d, *J* = 7.1 Hz,), 5.02 (br.s, 1H), 3.90 (q, *J* = 6.6 Hz, 2H), 2.96 (s, 6H), 2.93 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 162.26, 159.71, 157.33, 155.06, 149.57, 130.74, 129.51, 125.44, 113.10, 42.67, 40.77, 34.65. HRMS (EI), M + 1 calculated for $C_{16}H_{18}N_4S$ 299.1325 found, 299.1320; HPLC t_R = 4.2 min, >95% pure.

2. NMR spectra


SMH1-36.10.fid
7 (CDCl3, 500 MHz)
8.6783
7.7296
7.7188
5.0556
3.9920
3.9783
3.9658
3.9517
3.1255
3.1114
3.0972
HN
CF3
S
N
N
7
0.85
0.91
1.92
2.73
0.87
2.00
2.00
f1 (ppm)

SMH1-36.12.fid
7 (CDCl3, 125 MHz)

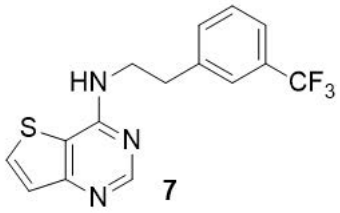


7

159.7861
157.1588
154.9610
139.7314
132.3197
130.9490
129.1285
125.4695
123.5671
115.2330
42.1813
35.6295

f1 (ppm)

SMH1-36-19F.1.fid
7 (CDCl3, 282 MHz)



7

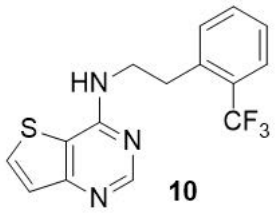
-62.5618

34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000

20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140

f1 (ppm)

SMH1-31-13307-proton.10.fid
10 (CDCl3, 600 MHz)



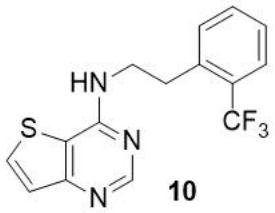
10

8.6772
7.7157
7.7069
7.6883
7.6754
7.5183
7.5058
7.4936
7.3731
7.3606
7.3486
5.1983
3.9790
3.9678
3.9566
3.9460
3.2450
3.2332
3.2220

0.95 0.89 0.95 0.98 1.92 0.98 0.95 2.00 2.00

f1 (ppm)

SMH1-31-13307-carbon 10.fid
10 (CDCl3, 150 MHz)



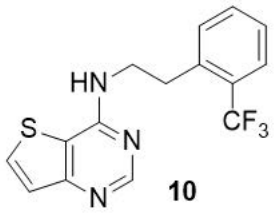
10

159.2360
157.1705
155.0834
137.3934
131.9357
131.7152
130.8159
126.7241
125.4766
123.6755
115.2490
42.1917
32.4442

20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

SMH1-31.12.fid
10 (CDCl3, 470 MHz)



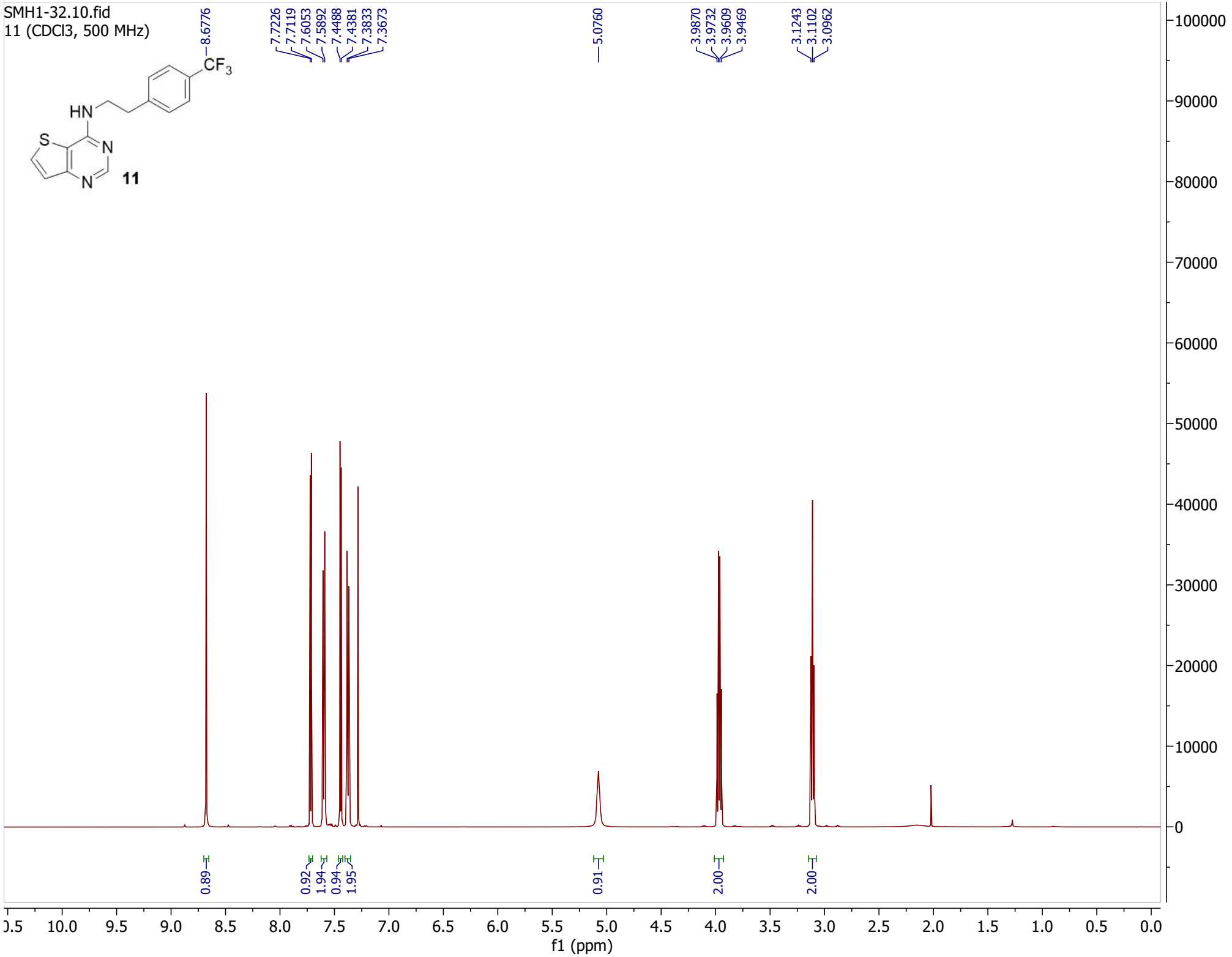
10

-59.2431

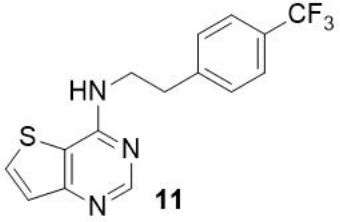
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500

5 0 -5 -10 -15 -20 -25 -30 -35 -40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120

f1 (ppm)


SMH1-32.10.fid
11 (CDCl3, 500 MHz)
8.6776
7.7226
7.7119
7.6053
7.5892
7.4488
7.4381
7.3833
7.3673
5.0760
3.9870
3.9732
3.9609
3.9469
3.1243
3.1102
3.0962
CF3
HN
S
N
N
11
0.89
0.92
1.94
0.94
1.95
0.91
2.00
2.00
f1 (ppm)

SMH1-32.12.fid
11 (CDCl3, 125 MHz)



11

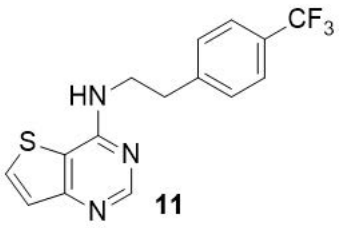
159.8936
157.1605
155.0335
142.9585
130.8921
129.2260
125.6475
125.6175
125.5875
125.5577
125.5212
123.1288
120.9670
115.2206
42.1316
35.6032

15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

SMH1-32.11.fid
11 (CDCl3, 470 MHz)



11

-62.4268

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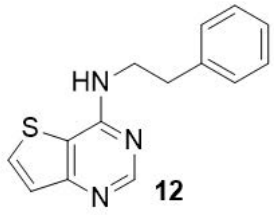
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500

5 0 -5 -10 -15 -20 -25 -30 -35 -40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120

f1 (ppm)

SMH1-6.10.fid
12 (DMSO, 500 MHz)



12

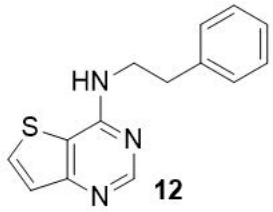
8.4616
8.0855
8.0748
7.9535
7.9429
7.9322
7.3757
7.3650
7.2147
7.2006
7.1866
3.7426
3.7294
3.7137
3.7015
2.9552
2.9399
2.9252

0.94
0.97
0.99
0.97
4.04
1.01
2.04
2.04

f1 (ppm)

SMH1-6.11.fid
12 (DMSO, 125 MHz)

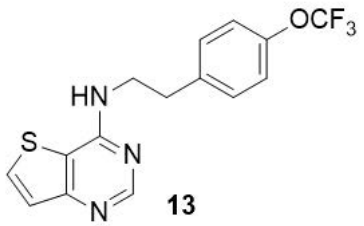
159.6909
157.3039
155.0449
139.9909
133.2574
129.1482
128.8085
126.5579
124.9054
115.1474
42.2888
35.3380



12

f1 (ppm)

GM34-60-1-11978-proton.10.fid
13 (DMSO, 600 MHz)



13

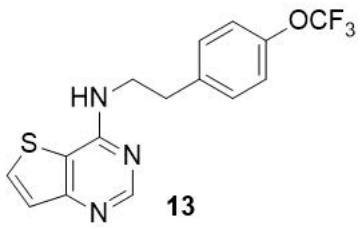
8.4557
8.0912
8.0823
7.9621
7.9530
7.9439
7.2872
7.2740
3.7492
3.7384
3.7258
3.7155
2.9906
2.9782
2.9661

0.87
0.94
0.95
2.90
2.01
1.99
2.00

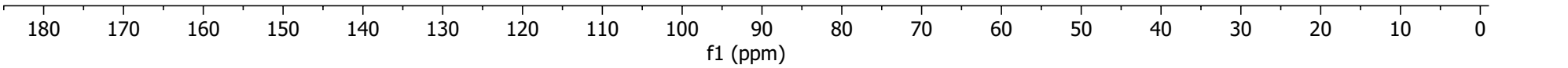
f1 (ppm)

GM34-60-1-11978-carbon.10.fid
13 (DMSO, 150 MHz)

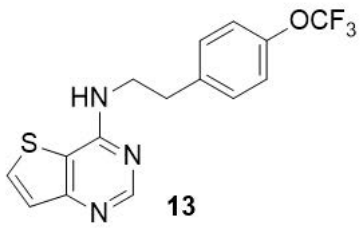
159.6900
157.2911
154.9914
147.2558
139.6023
133.3215
130.9754
124.8982
121.3810
42.0377
34.5062



13



GM34-60-1-11978-19F.1.fid
13 (DMSO, 282 MHz)



13

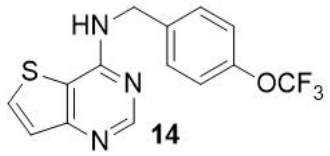
-56.8069

7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500

20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140

f1 (ppm)

GM44-41-3-13541-proton.10.fid
14 (CDCl3, 600 MHz)



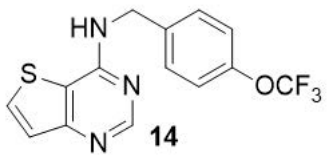
14

8.596
7.6741
7.6652
7.4015
7.3926
7.3261
7.3130
7.2999
7.2690
7.2561
7.0969
7.0834

0.88
0.89
0.90
1.03
0.96
2.37
0.97
0.80
2.00

f1 (ppm)

GM44-41-3-13541-carbon.10.fid
14 (CDCl3, 150 MHz)

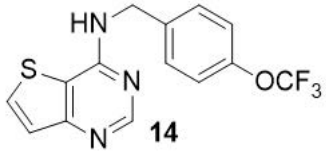


14

157.0727
154.7844
149.5770
140.6444
131.2850
130.1872
125.9952
125.3735
120.3020
120.0258
115.1628
44.4187

f1 (ppm)

GM44-41-3-13541-19F.1.fid
14 (CDCl3, 282 MHz)



14

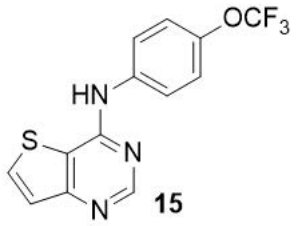
-57.6964

13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000

20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140

f1 (ppm)

GM44-36-1-13312-proton.10.fid
15 (CDCl3, 600 MHz)



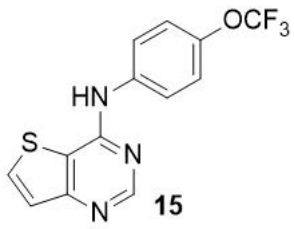
15

8.7670
7.7924
7.7836
7.7110
7.7055
7.7018
7.6942
7.6905
7.6849
7.4903
7.4814

0.90
0.98
2.09
1.00
3.27

f1 (ppm)

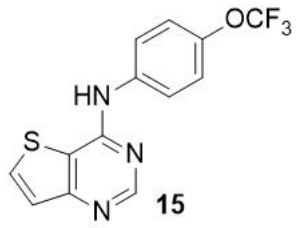
GM44-36-1-13312-carbon-10.fid
15 (CDCl3, 150 MHz)



161.1593
161.1593
155.6122
154.6262
146.1395
136.3713
132.3765
125.3524
124.2801
121.7859
119.6483
115.5010

f1 (ppm)

GM44-36-1-13312-19F.1.fid
15 (CDCl3, 282 MHz)



15

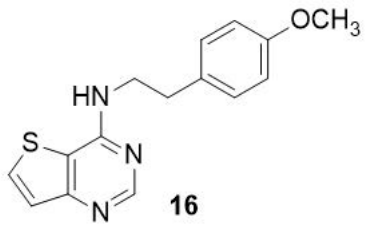
-58.0123

26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000

20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140

f1 (ppm)

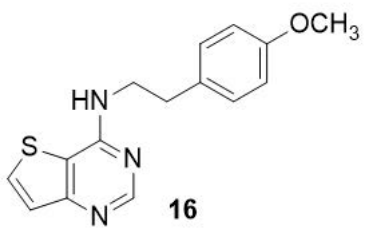
SMH1-8-13297-proton.10.fid
16 (CDCl3, 600 MHz)



16

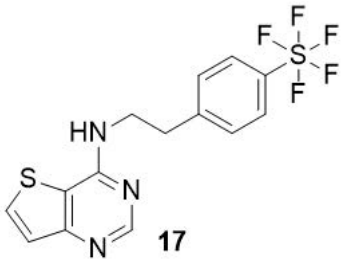
SMH1-8-13297-carbon-10.fid
16 (CDCl3, 150 MHz)

159.7441
158.4227
157.2744
155.0428
130.7856
130.6106
129.8265
125.4707
115.1807
114.1753
55.3053
42.5790
34.8049



16

GM34-86-1-12066.10.fid
17 (DMSO, 500 MHz)



17

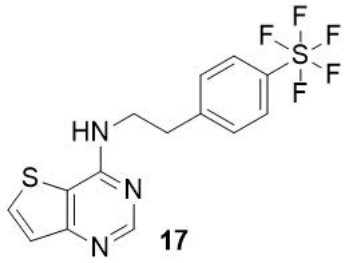
8.4647
8.0922
8.0815
7.9527
7.9419
7.9310
7.8242
7.8068
7.4918
7.4751
7.3823
7.3716
3.7824
3.7688
3.7565
3.7428
3.0595
3.0452
3.0310

1.00
1.03
1.01
2.13
2.10
1.03
2.11
2.09

f1 (ppm)

GM34-86-1-12066.11.fid
17 (DMSO, 125 MHz)

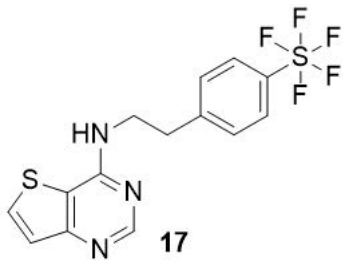
159.7498
157.2931
154.9846
145.1984
133.3506
130.1704
126.2307
124.9157
115.1855
41.7103
34.6862



17

f1 (ppm)

GM34-86-1-SF5.1.fid
17 (DMSO, 282 MHz)



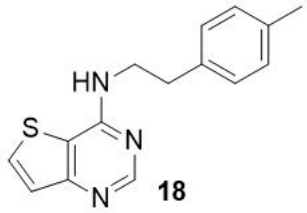
17

89.0956
88.5549
88.0212
87.4862
86.9640
64.5934
64.0611

0.99
4.00

f1 (ppm)

smh-2-13-1-13304.10.fid
18 (DMSO, 500 MHz)

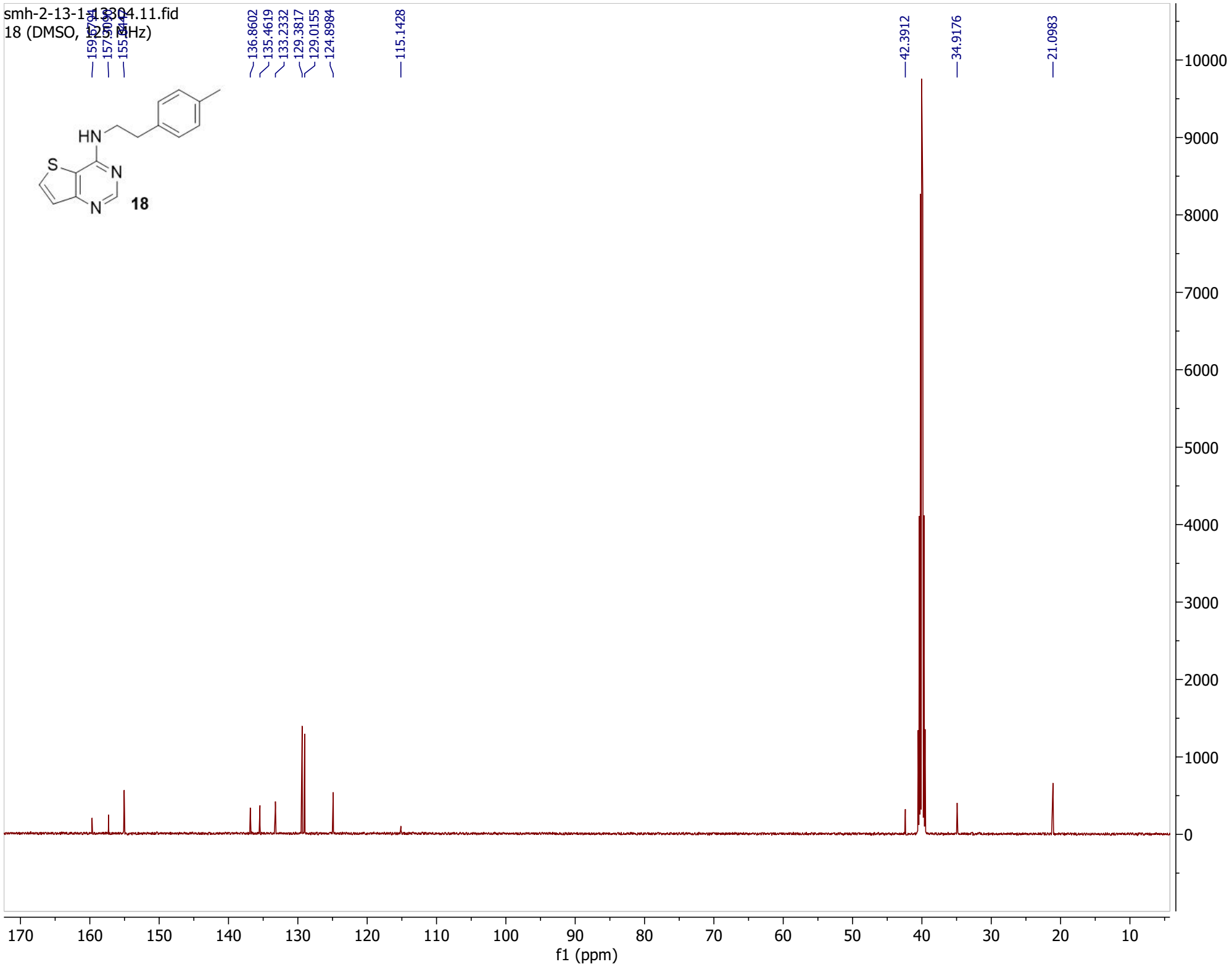


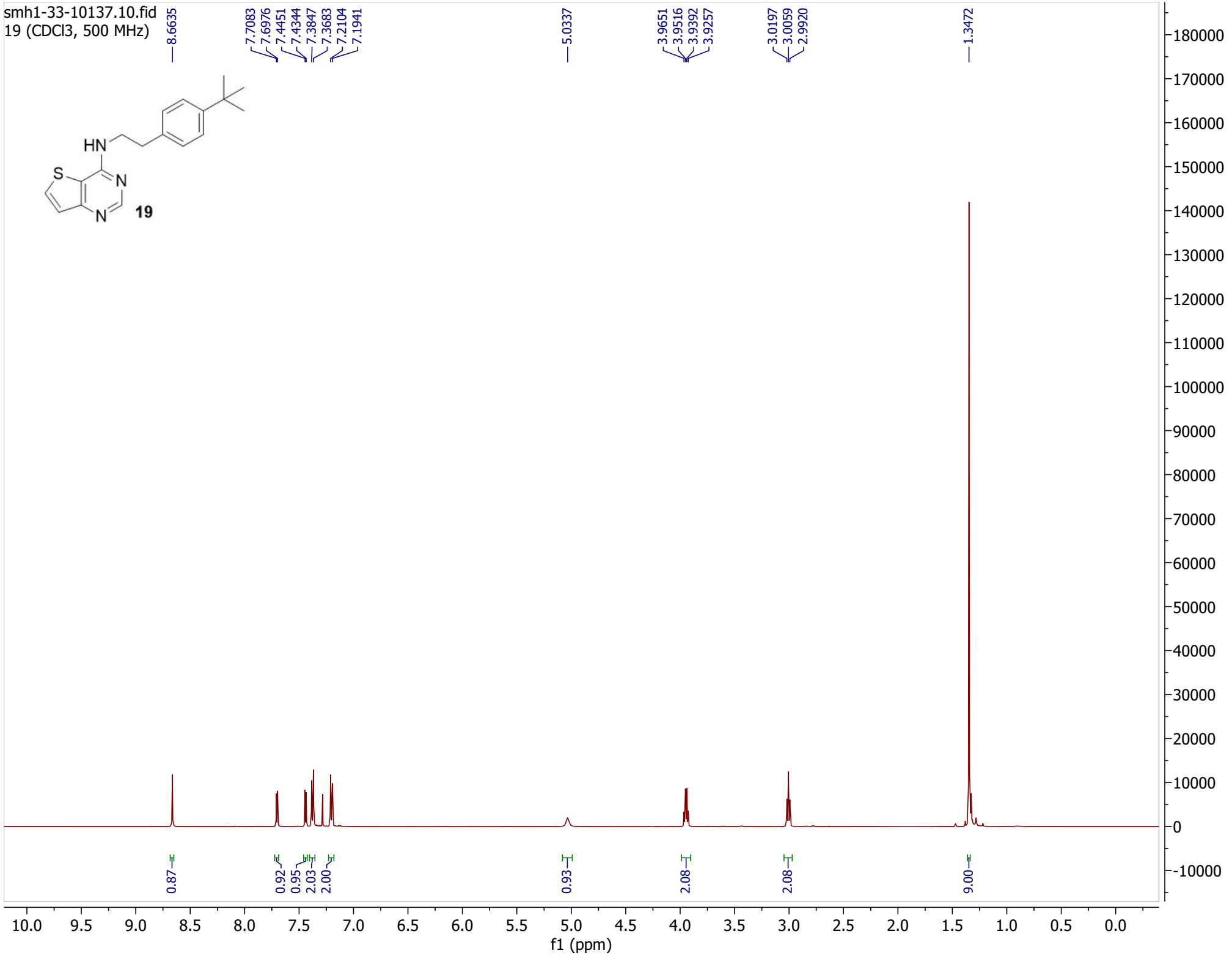
18

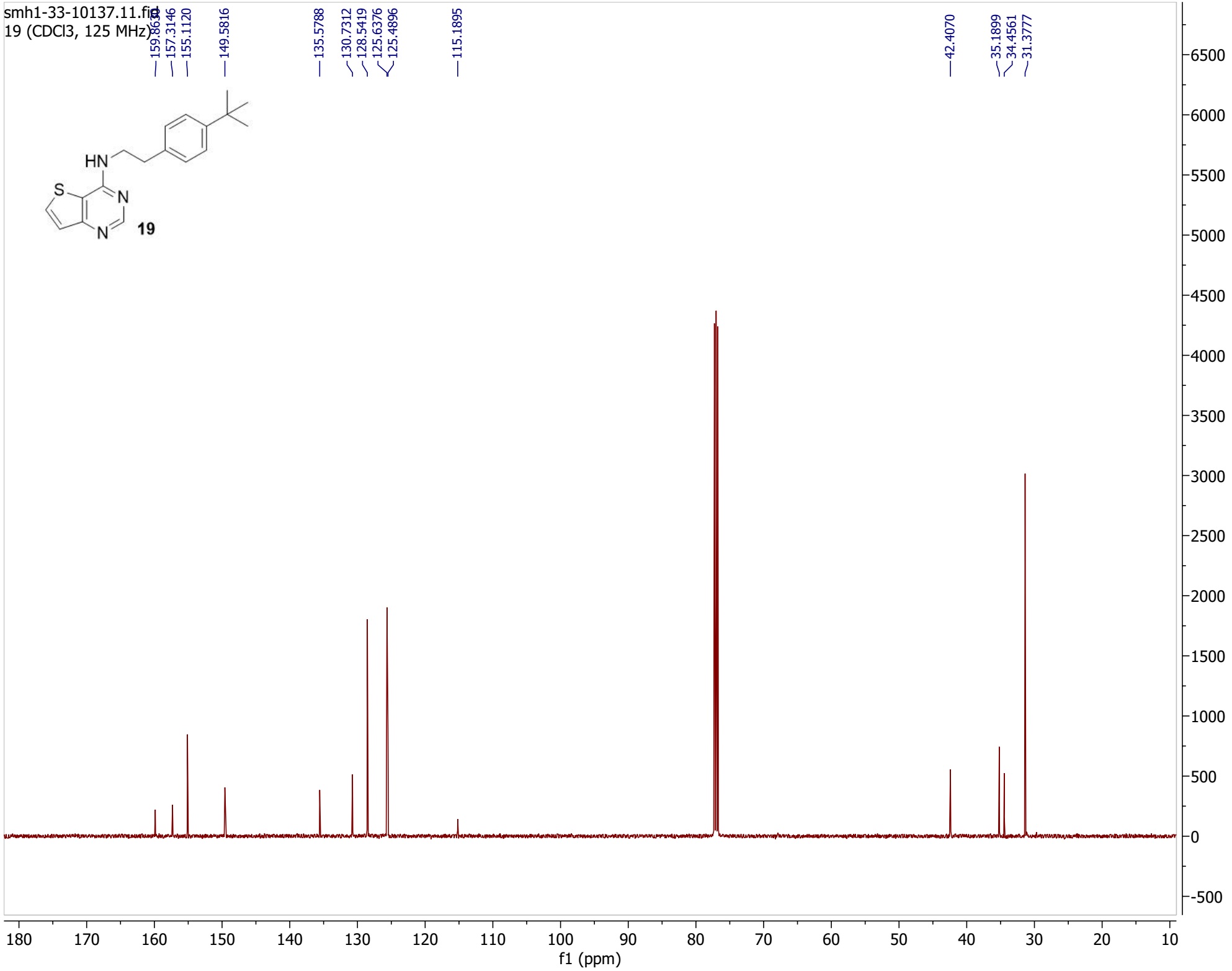
8.4609 8.0849 8.0742 7.9206 7.9099 7.8991 7.3751 7.3644 7.1530 7.1371 7.1094 7.0936 3.7143 3.7018 3.6876 3.6851 3.6731 2.9075 2.8922 2.8775 2.2657

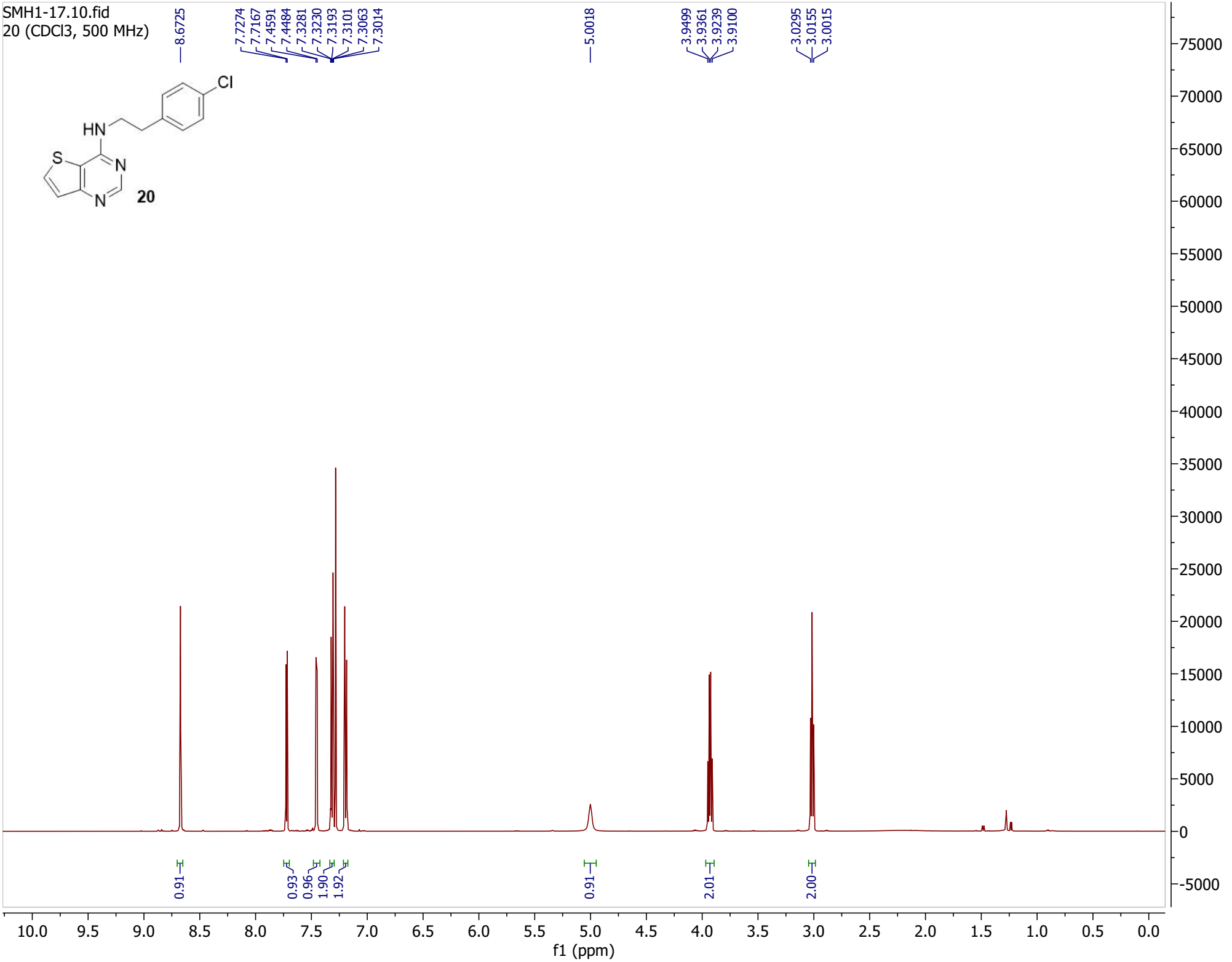
0.87 0.95 0.97 0.95 1.99 2.07 2.04 2.03 3.00

f1 (ppm)


smh-2-13-1-13304.11.fid
18 (DMSO, 125.7 MHz)
159.1779
157.2093
155.7414
136.8602
135.4619
133.2332
129.3817
129.0155
124.8984
115.1428
42.3912
34.9176
21.0983
HN
S
N
N
18
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

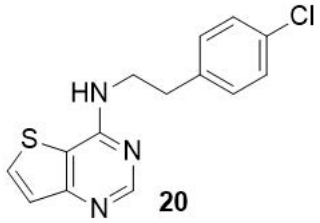

smh1-33-10137.10.fid
19 (CDCl3, 500 MHz)
8.6635
7.7083
7.6976
7.4451
7.4344
7.3847
7.3683
7.2104
7.1941
5.0337
3.9651
3.9516
3.9392
3.9257
3.0197
3.0059
2.9920
1.3472
HN
S
N
N
19
0.87
0.92
0.95
2.03
2.00
0.93
2.08
2.08
9.00
f1 (ppm)


smh1-33-10137.11.fid
19 (CDCl3, 125 MHz)
159.8630
157.3146
155.1120
149.5816
135.5788
130.7312
128.5419
125.6376
125.4896
115.1895
42.4070
35.1899
34.4561
31.3777
HN
S
N
N
19
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

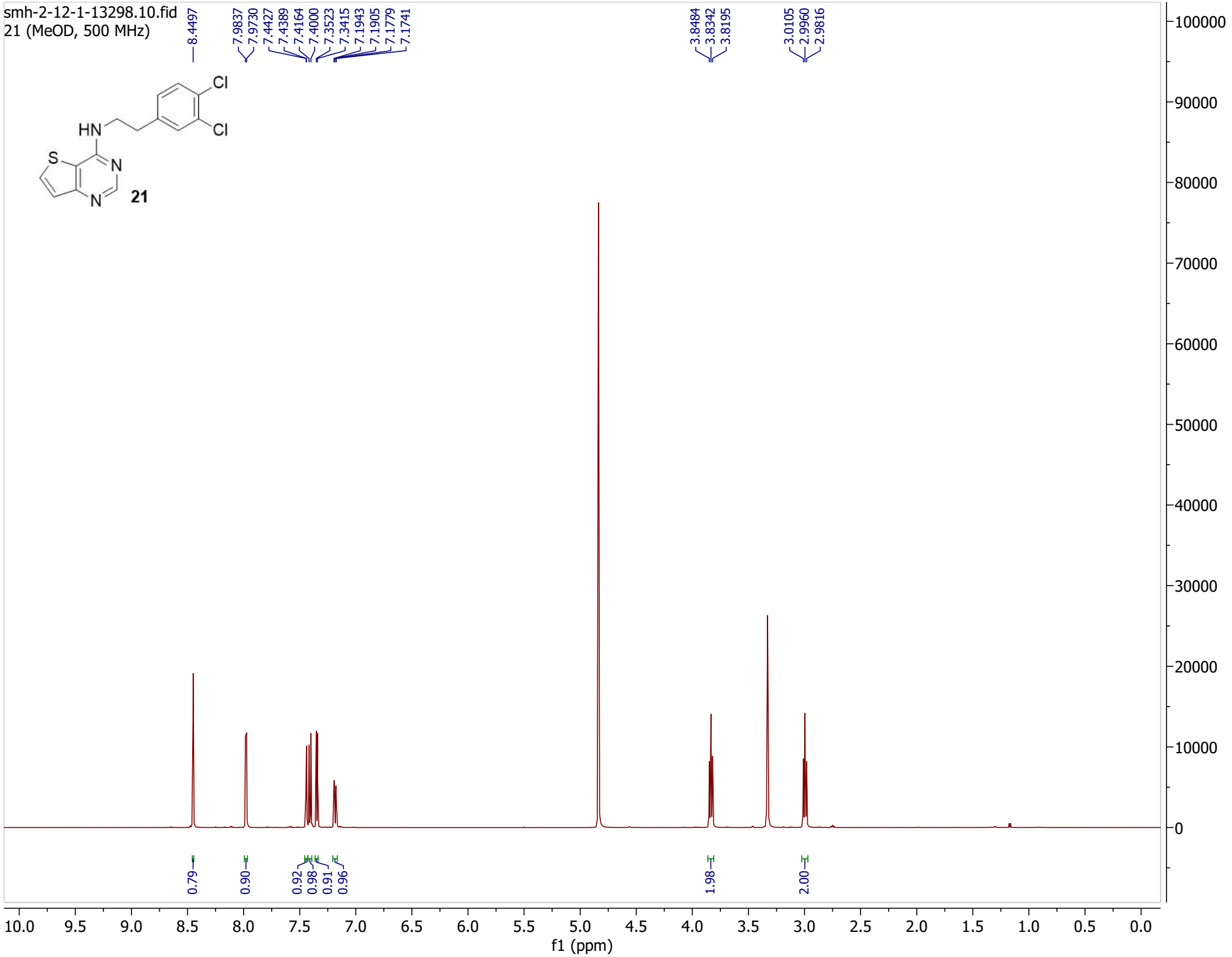

SMH1-17.10.fid
20 (CDCl3, 500 MHz)
8.6725
7.7274
7.7167
7.4591
7.4484
7.3281
7.3230
7.3193
7.3101
7.3063
7.3014
5.0018
3.9499
3.9361
3.9239
3.9100
3.0295
3.0155
3.0015
Cl
HN
S
N
N
20
0.91
0.93
0.96
1.90
1.92
0.91
2.01
2.00
f1 (ppm)

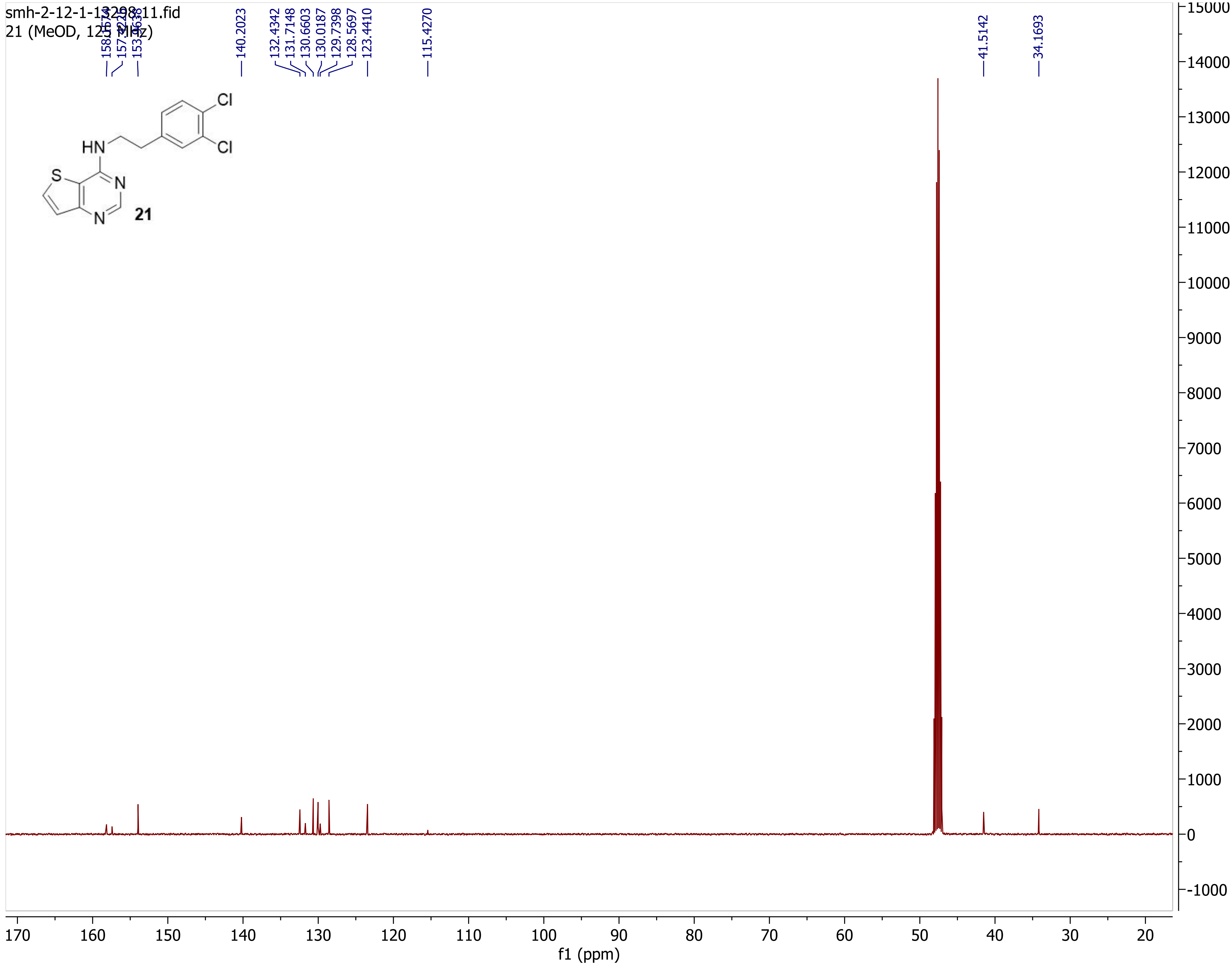
SMH1-17.12.fid
20 (CDCl3, 125 MHz)

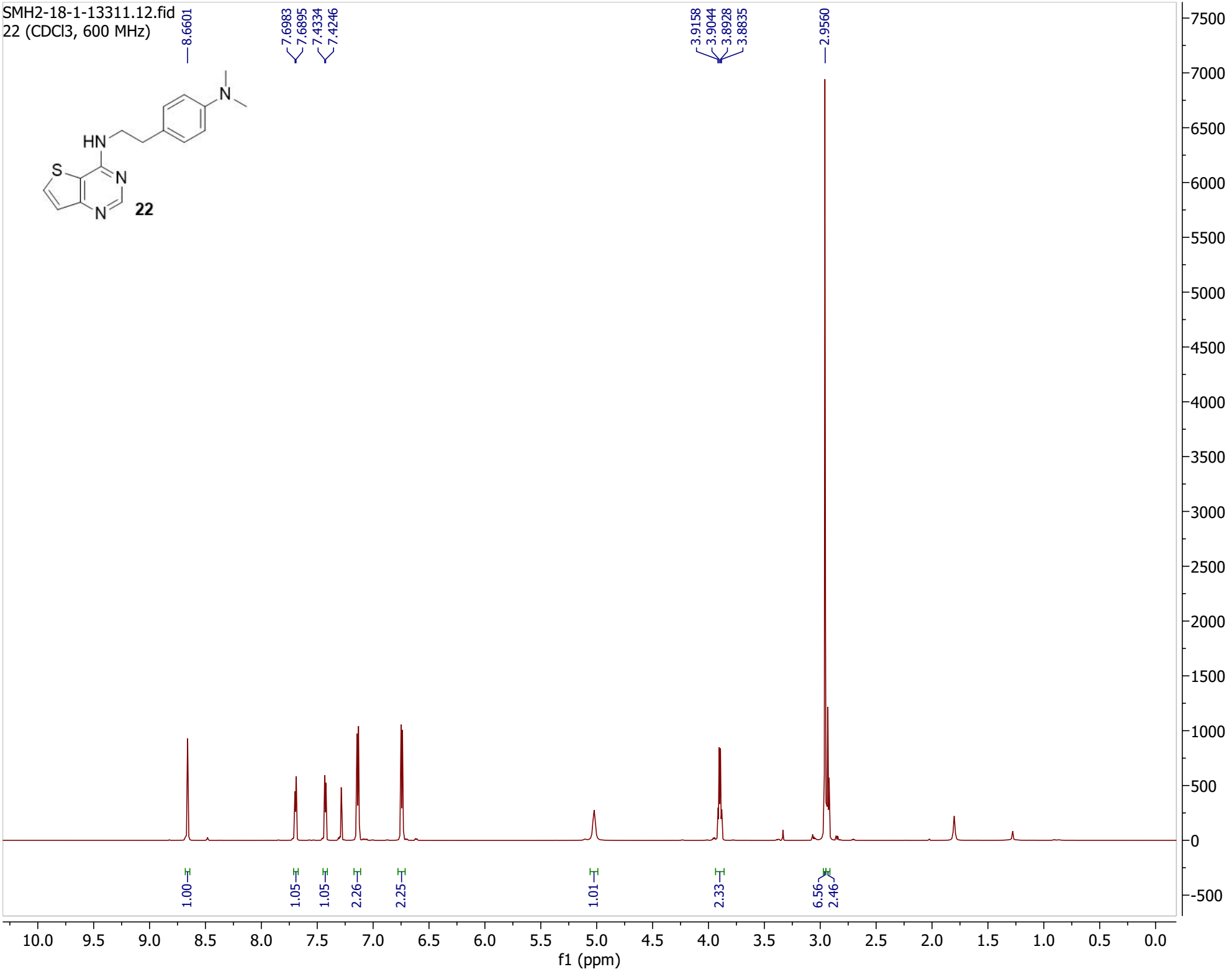
159.4560
157.3889
154.7484
137.1686
132.5243
130.9142
130.2166
128.8404
125.4694
115.1975
42.2944
35.1004

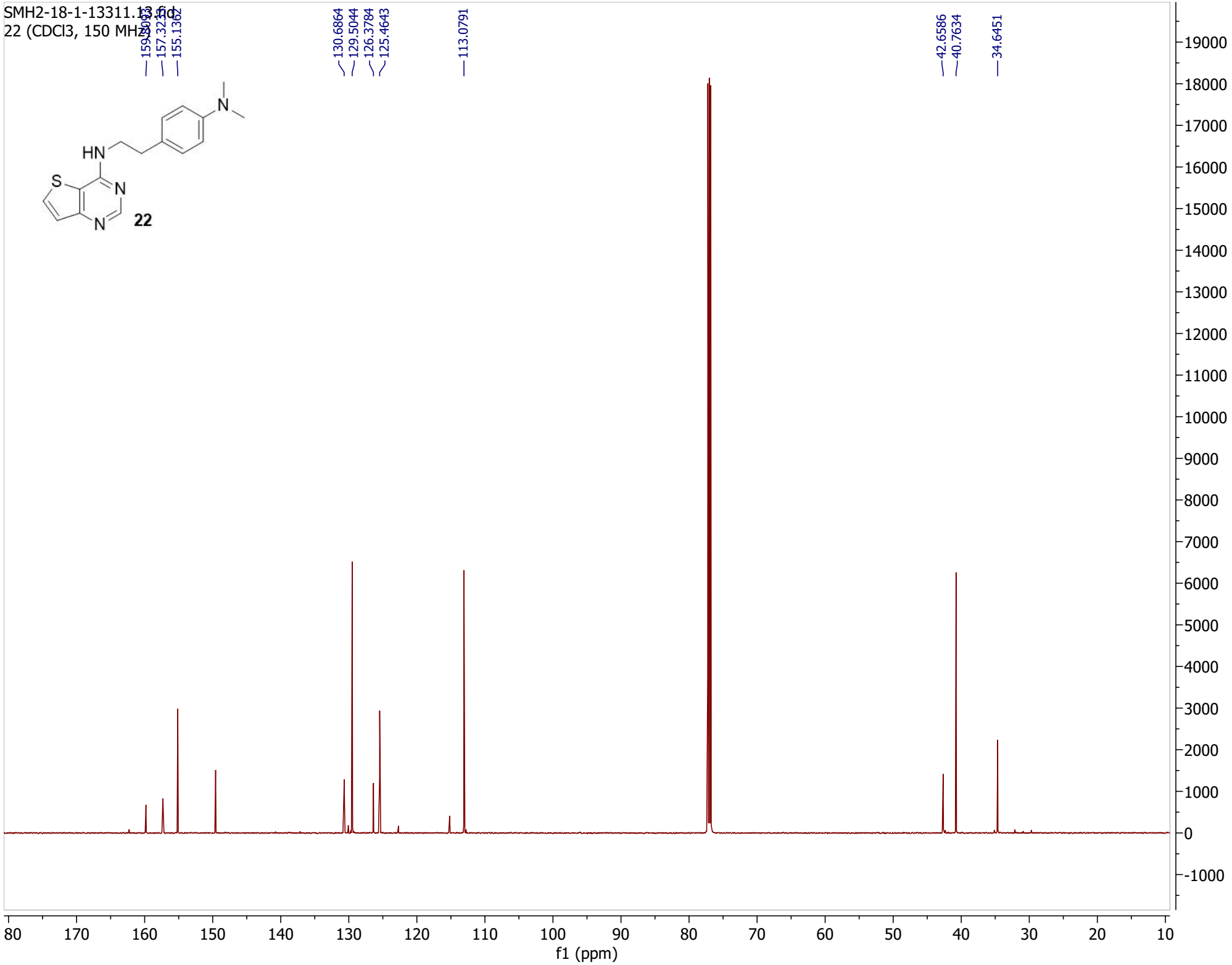


20


smh-2-12-1-13298.10.fid
21 (MeOD, 500 MHz)
8.4497
7.9837
7.9730
7.4427
7.4389
7.4164
7.4000
7.3523
7.3415
7.1943
7.1905
7.1779
7.1741
3.8484
3.8342
3.8195
3.0105
2.9960
2.9816
Cl
Cl
HN
S
N
N
21
0.79
0.90
0.92
0.98
0.91
0.96
1.98
2.00
f1 (ppm)


smh-2-12-1-13298.11.fid
21 (MeOD, 125 MHz)
158.1574
157.4225
153.9638
140.2023
132.4342
131.7148
130.6603
130.0187
129.7398
128.5697
123.4410
115.4270
41.5142
34.1693
Cl
Cl
HN
S
N
N
21
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)


SMH2-18-1-13311.12.fid
22 (CDCl3, 600 MHz)
8.6601
7.6983
7.6895
7.4334
7.4246
3.9158
3.9044
3.8928
3.8835
2.9560
HN
S
N
N
N
22
1.00
1.05
1.05
2.26
2.25
1.01
2.33
6.56
2.46
f1 (ppm)


SMH2-18-1-13311.13.fid
22 (CDCl3, 150 MHz)
159.2001
157.3225
155.1362
130.6864
129.5044
126.3784
125.4643
113.0791
42.6586
40.7634
34.6451
HN
S
N
N
N
22
f1 (ppm)

3. Experimental section, Biology

Screening assay

Mycobacterium bovis BCG and *Mycobacterium tuberculosis* strains were cultured in Middlebrook 7H9 medium (Becton Dickson and Company Limited, USA) supplemented with 0.05% tween 80, 0.5% glycerol, Bovine Serum Albumin Fraction V, D-glucose, and NaCl. *M. tuberculosis* clinical isolate N0145 was a gift from Sebastien Gagneux. Prior to use, bacteria cells were pelleted and resuspended in medium without glycerol and adjusted to an approximated cell density of 10^7 CFU/mL. 1 µL of test compounds of varying concentrations were added to each well of 96-well white plates, and 100 µL of bacterial culture was subsequently added to each well. The assay plates were incubated at 37ºC for 15 hours, after which the BacTiter-Glo™ (Promega, USA) reagent was added. Following a 12-minute delay, the luminescence of each plate was measured using a BioTek Cytation 3 Cell Imaging Multiple-mode reader.

IC_{50} values were determined using GraphPad Prism 9. The values reflected in the table represent the average and standard deviation, which were calculated from the IC_{50} values of replicates from two experimental repeats.