Supporting Information for

Photooxygenation of an Amino-Thienopyridone Yields a More Potent PTP4A3 Inhibitor

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General. All air-sensitive reactions were performed under an N_2 or Ar atmosphere in flame-dried or oven-dried glassware. Reactions carried out at temperatures above room temperature (rt) employed an oil bath, Lab Armor Beads™ (SKU # 42370), or a Biotage Initiator 2.0 microwave, where indicated. EtOH was stored over 4 Å molecular sieves. Pyridine, CH_2Cl_2, and $CHCl_3$ were distilled from CaH_2. Et_3N was stored over KOH. 1,4-Dioxane and H_2O were deoxygenated by sparging with Ar for 20 min immediately before use, where indicated. All commercial reagents were used as received. Concentrating under reduced pressure refers to removing solvents by the use of a rotary evaporator connected to a PIAB Lab Vac H40.

Reactions were monitored by thin layer chromatography analysis (EMD, pre-coated silica gel 60 F_{254} plates, 250 μm layer thickness) and visualization was accomplished with a 254 or 365 nm UV light and by staining with a phosphomolybdic acid solution (5.00 g of phosphomolybdic acid in 100 mL of 95% EtOH), *p*-anisaldehyde solution (2.50 mL of *p*-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH), $KMnO_4$ solution (1.50 g of $KMnO_4$, 10 g of K_2CO_3, and 1.25 mL of 10% NaOH in 200 mL of H_2O), or Vaughn's reagent (4.80 g of $(NH_4)_6Mo_7O_{24}$•4 H_2O and 0.20 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 M H_2SO_4) when needed. Column chromatography on SiO_2 (Silicycle, Silia-P Flash, or SiliaFlash® P60; 40-63 μm) was used to purify the crude reaction mixtures where indicated. All products were placed under high vacuum (0.5-4 mmHg) to remove trace solvents. Purities of products for bio-analysis were determined using an Agilent Technologies 385-ELSD. ELSD conditions: evaporator and nebulizer set at 45 °C; gas flow set at 1.80 standard liter / min; X Bridge BEH C18 2.5 μM; 2.1 x 50 mm column XP.

Melting points were determined using a Laboratory Devices Mel-Temp II in open capillary tubes and are uncorrected. Infrared spectra were obtained from neat solids or oils on a Smiths Detection IdentifyIR FT-IR or PerkinElmer® Spectrum 100 FT-IR spectrometers. High-resolution mass spectra were obtained on a Micromass UK Limited, Q-TOF Ultima API or a Thermo Scientific Exactive Orbitrap LC-MS. ^{1}H NMR spectra were obtained on a Bruker Avance at 300 MHz, 400 MHz, or 500 MHz in $CDCl_3$, $(CD_3)_2SO$, and THF-*d*8. Chemical shifts (δ) were reported in parts per million with the residual solvent peak used as an internal standard δ ^{1}H / ^{13}C (solvent): 7.26 / 77.16 ($CDCl_3$); 2.50 / 39.52 ($(CD_3)_2SO$); 1.72 and 3.58 / 67.21 and 25.31 (THF-d_8). ^{1}H NMR spectra were obtained and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m =

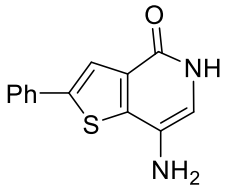
multiplet, bs = broad singlet), number of protons, and coupling constant(s). ^{13}C NMR spectra were recorded using a proton-decoupled pulse sequence run at 75 MHz, 100 MHz, or 125 MHz and are tabulated by chemical shifts.

Supercritical fluid chromatography (SFC) semi-prep purification used a Mettler Toledo AG - Berger SFC™ MiniGram instrument. Sample preparation involved dissolving the analyte (10 mg/mL) in HPLC-grade MeOH and filtering with a 13 mm Millex® Syringe Filter (0.45 μm pore size). Separation was accomplished with a SiO_2 column (250 x 10 mm) at 100 bar pressure with a detection wavelength of 220 nm, an oven temp. of 35 °C, an evaporator temp. of 27 °C, a trimmer temp. of 27 °C and using MeOH as a modifier under isocratic conditions.

The cDNA for the full length *Ptp4a3* was obtained from OriGene (SC308739). The cDNA was amplified and cloned into a pET-15b vector to attach the N-terminal His-tag required for purification. The pET-15b construct containing *Ptp4a3* sequence was confirmed by sequencing and transformed into *E. coli* BL21 (DE3).

Experimental Procedures:

Compound Index:



1

7-Amino-2-phenylthieno[3,2-*c*]pyridin-4(5*H*)-one (1).

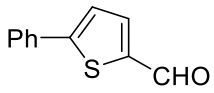
Route 1:

A solution of **8** (0.280 g, 0.915 mmol) and conc. H_2SO_4 (7 mL) was heated to 80 °C, treated with conc. HNO_3 (0.5 mL), and heated at 80 °C for 1 h. The reaction mixture was allowed to cool to rt, stirred for 5 h, neutralized with 5 N NaOH, washed with water, and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a yellow solid that was purified by chromatography on SiO_2 (0-100% EtOAc/hexanes) to obtain crude 7-nitro-2-phenylthieno[3,2-*c*]pyridin-4(5*H*)-one (0.142 g, ca. 44%) as a yellow solid. The crude solid (0.0272 g) was dissolved in EtOH (50 mL) and was reduced and debrominated using a 10% Pd/C cartridge in an H-cube instrument (pressure: 1 atm, temp. 50 °C, flow rate 1 mL/min) for 1 h. The reaction mixture was evaporated under reduced pressure to obtain the crude product as a white powder which turned red upon standing at room temperature. The crude product was purified by SFC (MeOH, isocratic at 35% and 10 mL/min; retention time: 4.66 min) to obtain **1** (0.00370 g, 0.0153 mmol, 9% over 2 steps) as a pink solid.

Route 2:

A solution of HNO_3 (0.100 g, 1.10 mmol, 69% grade) in glacial AcOH (1 mL) was added to a solution of **12** (0.075 g, 0.33 mmol) in AcOH (2 mL). The yellow reaction mixture was stirred at rt for 15.5 h and turned dark orange. It was diluted with water (15 mL) and the yellow precipitate was filtered and washed with water (3 x 5 mL) to yield a yellow solid. A solution of the solid in

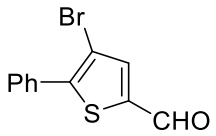
EtOAc was washed with water (15 mL), sat. aq. $NaHCO_3$ (2 x 15 mL), and brine (15 mL), dried (Na_2SO_4), and concentrated to yield a yellow residue (ca. 0.070 g) that was treated with 10% Pd/C (0.047 g, 0.044 mmol, 17 mol%) in EtOH (10 mL). The reaction flask was flushed with N_2 (3x) and then H_2 was bubbled through the solution. The reaction mixture was stirred at rt under H_2 (1 atm, balloon) for 5 h, filtered through basic Celite (EtOH), and concentrated to a dark residue that was purified by semi-prep SFC (MeOH, isocratic at 27% and 7.5 mL/min; collection/retention time: 7.25-10.25 min) to yield **1** (15.3 mg, 19% over 2 steps) as a yellow-brown solid: ^{1}H NMR ($(CD_3)_2SO$, 300 MHz) δ 10.85 (bs, 1 H), 7.83 (s, 1 H), 7.75 (d, 2 H, J = 7.2 Hz), 7.46 (t, 2 H, J = 7.2 Hz), 7.38-7.33 (m, 1 H), 6.66 (s, 1 H), 4.46 (s, 2 H); ^{13}C NMR ($(CD_3)_2SO$, 100 MHz) δ 156.5, 142.9, 141.0, 133.2, 131.1, 129.3, 128.2, 125.6, 124.3, 120.7, 112.21; HRMS (ESI^+) *m/z* calcd for $C_{13}H_{11}ON_2S$ (M+H) 243.0587, found 243.0586.



4

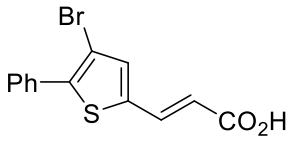
5-Phenylthiophene-2-carbaldehyde (4).[1] A mixture of phenyl boronic acid (0.770 g, 6.32 mmol), Na_2CO_3 (1.21 g, 11.4 mmol), and $Pd(PPh_3)_4$ (0.300 g, 0.286 mmol) in a microwave vial was evacuated and refilled with Ar (3x), dissolved in deoxygenated 1,4-dioxane/H_2O (2:1, 17 mL), and treated with 5-bromothiophene-2-carboxaldehyde (**3**) (1.12 g, 5.69 mmol). The vial was sealed and heated in a microwave reactor at 90 °C for 2 h. The biphasic mixture was diluted with water (15 mL), and the precipitate was filtered and washed with water (100 mL). The residue was purified by chromatography on SiO_2 (0-25% EtOAc/hexanes) to yield **4** (1.01 g, 95%) as a light pink solid: Mp 94.6-95.1 °C (CH_2Cl_2; lit. 92-94 °C); IR (ATR) 3092, 1637, 1439, 1228, 1062 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.89 (s, 1 H), 7.74 (d, 1 H, J = 3.6 Hz), 7.68-

7.65 (m, 2 H), 7.45-7.37 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.9, 154.4, 142.6, 137.5, 133.2, 129.6, 129.3, 126.5, 124.2; HRMS (ESI^+) *m/z* calcd for $C_{11}H_9OS$ (M+H) 189.0369, found 189.0368.



5

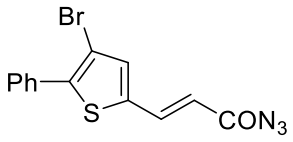
4-Bromo-5-phenylthiophene-2-carbaldehyde (5).[2] Bromine (0.09 mL, 2 mmol) was added to a solution of **4** (0.300 g, 1.59 mmol) in $CHCl_3$/AcOH (1:1, 4 mL). The reaction mixture was shielded from light, stirred for 20 h, and diluted with EtOAc (15 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 x 15 mL), aq. $Na_2S_2O_3$ (2 x 15 mL), and brine (15 mL), dried (Na_2SO_4), and concentrated to yield **5** (0.418 g, 98%) as yellow oil, which solidified upon standing to a light pink solid: Mp 81.7-82.5 °C (CH_2Cl_2) (lit. 83 °C); IR (ATR) 3051, 1677, 1663, 1430, 1217, 1124 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.85 (s, 1 H), 7.72 (s, 1 H), 7.70-7.67 (m, 2 H), 7.49-7.45 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.9, 148.2, 141.5, 140.0, 131.9, 129.8, 129.1, 128.9, 108.9; HRMS (ESI^+) *m/z* calcd for $C_{11}H_8BrOS$ (M+H) 266.9474, found 266.9473.



6

(*E*)-3-(4-Bromo-5-phenylthiophen-2-yl)acrylic acid (6). Malonic acid (0.094 g, 0.90 mmol) was added to a solution of **5** (0.200 g, 0.749 mmol) in pyridine (5 mL) and piperidine (0.25 mL).

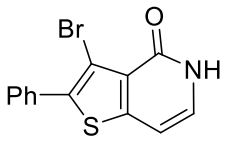
The reaction mixture was stirred at reflux for 5.5 h, allowed to cool to rt, poured over ice and dropwise treated with 12 N HCl (15 mL). The aqueous layer was extracted with EtOAc (100 mL) and the combined organic layers were washed with 1 N HCl (100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated to give **6** (0.203 g, 88%) as a yellow solid: Mp 169.1-171.9 °C (EtOAc); IR (ATR) 3300-2200 (br), 1676, 1614, 1413, 1273, 1195 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 400 MHz) δ 12.6 (bs, 1 H), 7.70 (d, 1 H, J = 16.0 Hz), 7.66-7.64 (m, 3 H), 7.55-7.45 (m, 3 H), 6.28 (d, 1 H, J = 16.0 Hz); ^{13}C NMR ($(CD_3)_2SO$, 100 MHz) δ 166.8, 139.6, 138.2, 135.1, 134.7, 131.6, 129.0, 128.9, 128.5, 119.1, 107.9; HRMS (ESI^+) *m/z* calcd for $C_{13}H_{10}BrO_2S$ (M+H) 308.9579, found 308.9578.



7

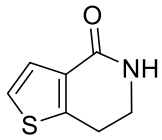
(*E*)-3-(4-Bromo-5-phenylthiophen-2-yl)acryloyl azide (7). A stirred suspension of **6** (0.650 g, 2.10 mmol) and DMF (0.1 mL) in toluene (10 mL) was treated dropwise with thionyl chloride (0.183 mL, 2.52 mmol) at room temperature, heated to reflux for 2.5 h, cooled to room temperature, and concentrated under reduced pressure to obtain crude acid chloride (0.660 g) as a brown oil that was used without further purification. A stirred suspension of NaN_3 (0.261 g, 4.03 mmol) in a mixture of toluene (2.5 mL) and water (2.5 mL) was treated dropwise with a solution of the crude oil (0.660 g) in toluene (2.5 mL) at 0 °C. The suspension was stirred for 1.5 h at room temperature. The toluene layer was then isolated and concentrated in vacuo, dissolved in EtOAc (5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (0-10% EtOAc/hexanes) to give **7** (0.310 g, 44% over 2

steps) as a yellow solid: IR (ATR) 2135, 1677, 1610, 1431, 1129 cm^{-1}; ^1H NMR (THF-*d*8, 500 MHz) δ 7.81 (d, 1 H, *J* = 15.5 Hz), 7.70-7.67 (m, 2 H), 7.54 (s, 1 H), 7.47-7.40 (m, 3 H), 6.34 (d, 1 H, *J* = 15.5 Hz); ^{13}C NMR (THF-*d*8, 75 MHz) δ 171.3, 142.7, 138.7, 137.9, 136.9, 132.9, 129.8, 129.4 (2 C), 119.3, 109.2; EIMS *m/z* 335 (50), 333 (35), 307 (95), 293 (55), 198 (95), 171 (100); HRMS (EI) *m/z* calcd for $C_{13}H_8BrN_3OS$ 332.9571, found 332.9571.



8

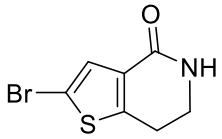
3-Bromo-2-phenylthieno[3,2-*c*]pyridin-4(5*H*)-one (8). A solution of azide **7** (0.101 g, 0.302 mmol) in diphenyl ether (2.5 mL) was heated in a microwave vial to 250 °C for 30 min. The dark brown reaction mixture was purified by chromatography on SiO_2 (20-70% EtOAc/hexanes) to give **8** (0.0481 g, 0.157 mmol, 52%) as a buff colored solid: Mp 239-240 °C; IR (ATR) 3313, 1684, 1638, 1602, 1591, 1494, 1440, 1192 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 11.96 (bs, 1 H), 7.68-7.66 (m, 2 H), 7.50-7.46 (m, 3 H), 7.33 (d, 1 H, *J* = 6.6 Hz), 6.74 (d, 1 H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.5, 148.9, 137.0, 132.5, 130.0, 129.6, 129.1, 128.8, 127.1, 105.7, 102.2; HRMS (TOF MS ES+) *m/z* calcd for $C_{13}H_9BrNOS$ (M+H) 305.9588, found 305.9583.



10

6,7-Dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (10).[3] Thiophene-2-ethylamine (**9**) (1.0 mL, 8.4 mmol) was added dropwise to a three neck flask (one gas inlet, two rubber septa) containing a

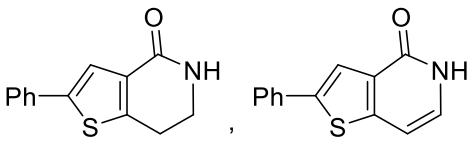
solution of triphosgene (1.25 g, 4.21 mmol) in anhydrous CH_2Cl_2 (12 mL) at 0 °C under Ar, followed by addition of sat. aq. $NaHCO_3$ (12 mL) over 5 min. The resulting biphasic mixture was stirred at 0 °C under Ar for 5 h. The organic layer was dried (Na_2SO_4), passed through a short SiO_2 column (CH_2Cl_2), and concentrated to yield crude 2-(2-isocyanatoethyl)thiophene as an oil: IR (ATR) 2263 (NCO) cm^{-1}. A solution of this oil in anhydrous CH_2Cl_2 (25 mL) was added to a mixture of anhydrous $FeCl_3$ (1.36 g, 8.37 mmol) in anhydrous CH_2Cl_2 (100 mL) under N_2. The flask was equipped with a condenser and the reaction mixture was stirred at 50 °C for 40 min, poured into sat. aq. NH_4Cl (25 mL), extracted with CH_2Cl_2 (2 x 25 mL), and dried (Na_2SO_4). The solution was passed through a short basic Al_2O_3 column (10% MeOH/CH_2Cl_2) and concentrated to yield **10** (0.976 g, >90% pure based on NMR analysis, 71% over two steps) as a viscous dark oil with minor solvent impurities: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, 1 H, *J* = 5.2 Hz), 7.10 (d, 1 H, *J* = 5.2 Hz), 6.46 (bs, 1 H), 3.64 (dt, 2 H, *J* = 6.8, 2.8 Hz), 3.05 (t, 2 H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.2, 146.3, 132.2, 126.0, 123.2, 41.3, 24.5.



11

2-Bromo-6,7-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (11).[4] After addition of Br_2 (0.11 mL, 2.1 mmol) to a solution of **10** (0.300 g, 1.96 mmol) in AcOH (6 mL), the red reaction mixture was shielded from light and stirred at rt for 12 h, neutralized (Na_2CO_3) and diluted with EtOAc (30 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (30 mL), aq. $Na_2S_2O_3$ (30 mL), and brine (30 mL), dried (Na_2SO_4), and concentrated to yield **11** (0.340 g, 75%) as a brown solid: Mp >100 °C (dec., CH_2Cl_2); IR (ATR) 3195, 3059, 2930, 1664, 1478, 1430, 1286 cm^{-1}; ^{1}H NMR

($CDCl_3$, 400 MHz) δ 7.36 (s, 1 H), 6.24 (bs, 1 H), 3.63 (dt, 2 H, *J* = 6.8, 2.8 Hz), 2.97 (t, 2 H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.6, 147.4, 132.9, 128.5, 110.4, 41.2, 24.5; HRMS (ESI^+) *m/z* calcd for C_7H_7BrNOS (M+H) 231.9426, found 231.9425.

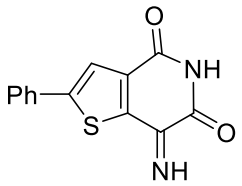


12-a, **12**

2-Phenylthieno[3,2-*c*]pyridin-4(5*H*)-one (**12**).[5] A mixture of bromide **11** (0.200 g, 0.862 mmol), phenyl boronic acid (0.127 g, 1.04 mmol), $Pd(PPh_3)_4$ (0.045 g, 0.043 mmol), and Na_2CO_3 (0.211 g, 2.00 mmol) in a microwave vial was flushed with Ar (3x), diluted with deoxygenated 1,4-dioxane/H_2O (2:1, 10 mL) and sealed. The reaction mixture was heated in an oil bath to 90 °C for 24 h, concentrated, and purified by chromatography on SiO_2 (50-100% EtOAc/hexanes) to yield 2-phenyl-6,7-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (**12-a**) as a crude solid (0.178 g) with minor aromatic impurities. The solid was typically used in the next step without further purification. Analytically pure compound was acquired by washing with ether in a sonication bath: Mp 173.3-175.1 °C (CH_2Cl_2); IR (ATR) 3211 (br.), 3062, 2947, 2901, 1657, 1483, 1430, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.63 (s, 1 H), 7.59-7.56 (m, 2H), 7.39-7.36 (m, 2 H), 7.31-7.27 (m, 1 H), 6.75 (bs, 1 H), 3.67 (dt, 2 H, *J* = 6.8, 2.8 Hz), 3.06 (t, 2 H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.1, 145.6, 142.3, 133.7, 133.1, 129.1, 128.0, 125.8, 121.3, 41.2, 24.5; HRMS (ESI^+) *m/z* calcd for $C_{13}H_{12}NOS$ (M+H) 230.0634, found 230.0632.

After addition of DDQ (0.218 g, 0.932 mmol) under an atmosphere of Ar to a solution of crude **12-a** (0.178 g) in 1,4-dioxane (15 mL), the dark reaction mixture was stirred at 101 °C in a sealed vial under an Ar atmosphere for 1.5 d. Additional DDQ (0.218 g, 0.932 mmol) was added

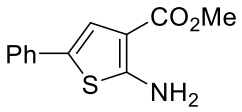
and heating was continued for another 24 h. The dark solution was concentrated to a crude brown solid that was purified by chromatography on SiO_2 (0-100% EtOAc/hexanes) to yield a crude light yellow solid with red and orange impurities. The crude solid was suspended in a small amount of EtOAc (<5 mL), filtered, and dried under vacuum to yield **12** (0.094 g, 48% over 2 steps) as light yellow solid: Mp >245 °C (dec., EtOAc); IR (ATR) 2828 (br), 1638, 1597, 1500, 1215, 749, 686 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 400 MHz) δ 11.47 (bs, 1 H), 7.86 (s, 1 H), 7.75 (d, 2 H, *J* = 7.2 Hz), 7.45 (t, 2 H, *J* = 7.2 Hz), 7.38-7.34 (m, 1 H), 7.27 (d, 1 H, *J* = 7.2 Hz), 6.85 (d, 1 H, *J* = 7.2 Hz); ^{13}C NMR ($(CD_3)_2SO$, 100 MHz) δ 158.6, 147.6, 141.2, 133.0, 131.6, 130.0, 129.3, 128.3, 125.7, 119.9, 100.9; HRMS (ESI^+) *m/z* calcd for $C_{13}H_{10}NOS$ (M+H) 228.0478, found 228.0474.



13

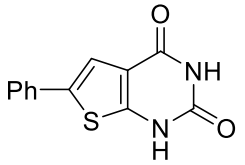
7-Imino-2-phenylthieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (13). A solution of **1** (32.51 mg, 0.1342 mmol) in MeOH (30 mL) in a 50 mL Pyrex® round bottom flask was placed 15 cm away from a 23 W compact fluorescent lamp and stirred at 23-24 °C until the starting material was consumed (2.5 days), as determined by high resolution LC-MS. Brown product **13** started to precipitate after 1 day. The mixture was concentrated under reduced pressure to remove about half of the solvent and the brown precipitate was filtered, washed with MeOH (5 mL) and dried under vacuum to yield a brown solid (14.86 mg). The filtrate was concentrated under reduced pressure to remove all of the solvent. The brown residue was washed with MeOH (5 mL) and dried under vacuum to yield a brown solid (11.72 mg). The solids were combined to yield **13**

(26.58 mg, 77%) as an amorphous brown solid. Both precipitates had the same purity based on ^{1}H NMR analysis. Yellow-green crystals were obtained from the slow evaporation of a solution of **13** in MeCN: Mp >260 °C (dec., MeOH); IR (ATR) 3239, 3095, 2823, 1695, 1598, 1453 cm^{-1}; ^{1}H NMR ($(CD_3)_2SO$, 400 MHz) δ 11.87 (bs, 1H), 11.59 (s, 1 H), 7.98 (s, 1 H), 7.87 (d, 2 H, J = 6.8 Hz), 7.52-7.43 (m, 3 H); ^{13}C NMR ($(CD_3)_2SO$, 100 MHz) δ 160.1, 157.9, 153.4, 149.3, 141.9, 136.8 132.0, 129.6, 129.5, 126.2, 122.1; HRMS (ESI$^+$) *m/z* calcd for $C_{13}H_9O_2N_2S$ (M+H) 257.0379, found 257.0378. The X-ray structure of **13** was deposited with the Cambridge Crystallographic Data Centre (CCDC 1476250).



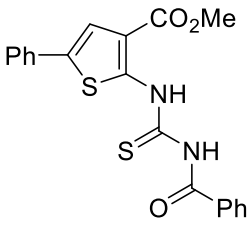
20

Methyl 2-amino-5-phenylthiophene-3-carboxylate (20).[6] After addition of Et_3N (1.2 mL, 8.5 mmol) to a stirred mixture of phenylacetaldehyde (**18**) (1.0 mL, 8.4 mmol), methyl cyanoacetate (**19**) (0.80 mL, 8.8 mmol) and elemental sulfur (0.269 g, 8.40 mmol) in DMF (8.4 mL, 1 M), the reaction mixture was stirred at rt for 21 h and then diluted with water (10 mL). The yellow precipitate was filtered, washed with water (40 mL) and then hexanes (50 mL), and dried under vacuum to yield **20** (1.77 g, 90%) as a light yellow solid: Mp 183.8-185.1 °C (lit. 194.5 °C); IR (ATR) 3459, 3348, 2943, 1664, 1569, 1543, 1484, 1230 cm^{-1}; ^{1}H NMR ($(CD_3)_2SO$, 400 MHz) δ 7.50 (bs, 2 H), 7.46-7.43 (m, 2 H), 7.35-7.31 (m, 2 H), 7.24 (s, 1 H), 7.20-7.16 (m, 1 H), 3.73 (s, 3 H); ^{13}C NMR ($(CD_3)_2SO$, 100 MHz) δ 164.6, 163.5, 133.7, 128.9, 126.2, 124.0, 122.3, 121.0, 104.7, 50.7; HRMS (ESI$^+$) *m/z* calcd for $C_{12}H_{12}NO_2S$ (M+H) 234.0583, found 234.0576.



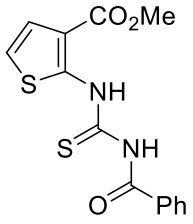
21

6-Phenylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (21).[7] Chlorosulfonyl isocyanate (0.15 mL, 1.7 mmol) was added slowly at -78 °C to a solution of **20** (0.200 g, 0.857 mmol) in CH_2Cl_2 (1.5 mL). The reaction mixture was allowed to warm to rt and stirred for 40 min. The slurry was concentrated and then diluted with wet 1,4-dioxane (4 mL), stirred at rt for 15 min and then at 85 °C for 30 min and treated with conc. NaOH (1 mL) so that the final concentration of the base was 1 M. Heating at 85 °C was continued for 30 min and then the reaction mixture was allowed to cool to rt, diluted with water (5 mL), and acidified with conc. HCl with stirring until precipitation stopped. The precipitate was filtered, washed with water (20 mL), and dried under vacuum to yield **21** (0.120 g, 57%) as a colorless solid: Mp >300 °C (dec.); IR (ATR) 3159, 3044, 2806, 1707, 1653, 1555, 1256 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 400 MHz) δ 12.03 (s, 1 H), 11.21 (s, 1 H), 7.65-7.63 (m, 2 H), 7.55 (s, 1 H), 7.42-7.38 (m, 2 H), 7.32-7.29 (m, 1 H); ^{13}C NMR ($(CD_3)_2SO$, 100 MHz) δ 159.1, 151.4, 150.5, 133.3, 132.6, 129.2, 127.8, 125.1, 117.6, 116.2; HRMS (ESI^+) *m/z* calcd for $C_{12}H_9N_2O_2S$ (M+H) 245.0379, found 245.0378.



23-a (tentative structural assignment)

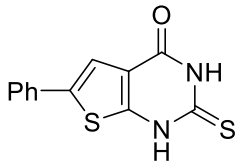
Methyl 2-(3-benzoylthioureido)-5-phenylthiophene-3-carboxylate (23-a). A solution of benzoyl chloride (0.50 mL, 4.3 mmol) and anhydrous ammonium thiocyanate (0.489 g, 6.43 mmol) in anhydrous CH_3CN (10 mL) was stirred at reflux for 30 min under N_2 and then treated with a suspension of **20** (0.500 g, 2.14 mmol) in anhydrous CH_3CN (5 mL). The reaction mixture was stirred for 6 h at reflux, cooled, and the precipitate was filtered, washed with water (75 mL), and dried under vacuum to yield **23-a** (0.583 g, 69%) as a fine bright yellow powder: Mp 229.6-231.2 °C (CH_3CN); IR (ATR) 3275, 2943, 1694, 1670, 1508, 1221 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 14.78 (bs, 1 H), 9.17 (bs, 1 H), 7.98-7.96 (m, 2 H), 7.67-7.61 (m, 3 H), 7.57-7.52 (m, 3 H), 7.41-7.37 (m, 2 H), 7.32-7.27 (m, 1 H), 4.02 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.0, 165.5, 164.9, 147.7, 134.8, 133.9, 133.7, 131.5, 129.3, 129.1, 127.9 (2 C), 125.9, 120.4, 118.3, 52.4; HRMS (ESI^+) *m/z* calcd for $C_{20}H_{17}N_2O_3S_2$ (M+H) 397.0675, found 397.0673.



24-a (tentative structural assignment)

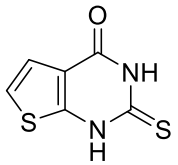
Methyl 2-(3-benzoylthioureido)thiophene-3-carboxylate (24-a). A mixture of benzoyl chloride (0.59 mL, 5.1 mmol) and anhydrous ammonium thiocyanate (0.581 g, 7.63 mmol) in anhydrous CH_3CN (10 mL) was stirred at reflux for 30 min under N_2, treated with a suspension of **22** (0.400 g, 2.54 mmol) in anhydrous CH_3CN (5 mL), and stirred for 6 h at reflux and then cooled to 0 °C. The precipitate was filtered, washed with cold CH_3CN (50 mL) and then water (75 mL), and dried under vacuum to yield **24-a** (0.543 g, 67%) as a yellow solid: Mp 179.7-181.6 °C (EtOH); IR (ATR) 3422, 2934, 1683, 1543, 1148 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ

14.77 (bs, 1 H), 9.16 (bs, 1 H), 7.97-7.95 (m, 2 H), 7.66-7.62 (m, 1 H), 7.55-7.51 (m, 2 H), 7.37 (d, 1 H, J = 6.0 Hz), 6.85 (dd, 1 H, J = 5.6, 0.4 Hz), 3.99 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.4, 165.5, 165.0, 148.7, 133.9, 131.6, 129.3, 127.9, 125.1, 117.5, 117.4, 52.3; HRMS (ESI^+) *m/z* calcd for $C_{14}H_{13}N_2O_3S_2$ (M+H) 321.0362, found 321.0360.



23

6-Phenyl-2-thioxo-2,3-dihydrothieno[2,3-*d*]pyrimidin-4(1*H*)-one (23).[8] A suspension of **23-a** (0.100 g, 0.252 mmol) and KOH (0.100 g, 1.78 mmol) in EtOH (5 mL) was stirred at reflux for 14 h, cooled to rt, and acidified with aq. HCl. The colorless precipitate was filtered and washed with water (20 mL). The solid was then precipitated from EtOH, filtered and dried under vacuum to yield **23** (0.032 g, 49%) as an off-white solid: Mp >230 °C (dec., EtOH) (lit. >305 °C, dec.); IR (ATR) 3059, 2932, 1653, 1543, 1199, 1126, 744 cm^{-1}; ^{1}H NMR ($(CD_3)_2SO$, 400 MHz) δ 13.54 (bs, 1 H), 12.51 (bs, 1 H), 7.69 (d, 2 H, J = 7.6 Hz), 7.65 (s, 1 H), 7.43 (t, 2 H, J = 7.6 Hz), 7.36-7.33 (m, 1 H); ^{13}C NMR ($(CD_3)_2SO$, 100 MHz) δ 173.4, 156.5, 150.8, 135.9, 132.3, 129.3, 128.3, 125.4, 119.8, 117.5; HRMS (ESI^+) *m/z* calcd for $C_{12}H_9N_2OS_2$ (M+H) 261.0151, found 261.0148.



24

2-Thioxo-2,3-dihydrothieno[2,3-*d*]pyrimidin-4(1*H*)-one (24).[9] A suspension of **24-a** (0.350 g, 1.09 mmol) and KOH (0.350 g, 6.24 mmol) in EtOH (15 mL) was stirred at reflux for 19 h, cooled to rt and concentrated under reduced pressure. The residue was diluted with 1 N HCl (25 mL). The precipitate was filtered and washed with water (50 mL) to yield a brown solid. The solid was stirred in hot EtOH, cooled, filtered and dried under vacuum to yield **24** (0.115 g, 57%) as a fine yellow powder: Mp >280 °C (dec., EtOH) (lit. 305-307 °C, EtOH); IR (ATR) 3059, 2898, 1629, 1553, 1523, 1450, 1187, 1128, 701 cm^{-1}; ^{1}H NMR ($(CD_3)_2SO$, 400 MHz) δ 13.44 (bs, 1 H), 12.44 (bs, 1 H), 7.27 (d, 1 H, J = 5.6 Hz), 7.20 (d, 1 H, J = 5.6 Hz); ^{13}C NMR ($(CD_3)_2SO$, 100 MHz) δ 173.5, 156.7, 151.7, 121.8, 119.8, 118.7; HRMS (ESI^+) *m/z* calcd for $C_6H_5N_2OS_2$ (M+H) 184.9838, found 184.9838.

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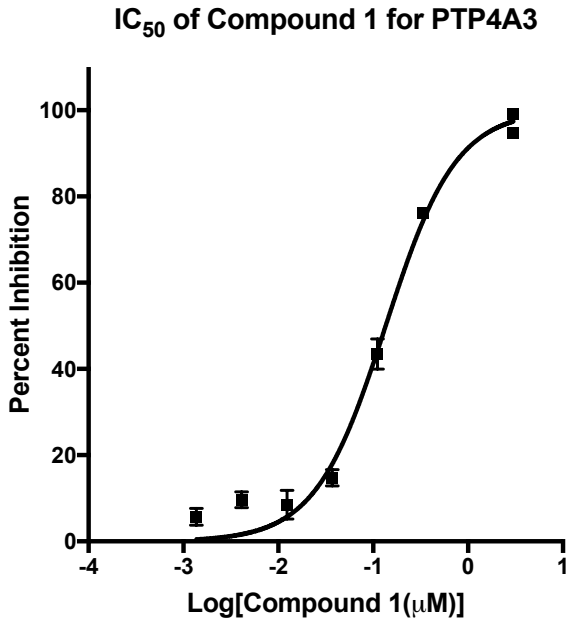
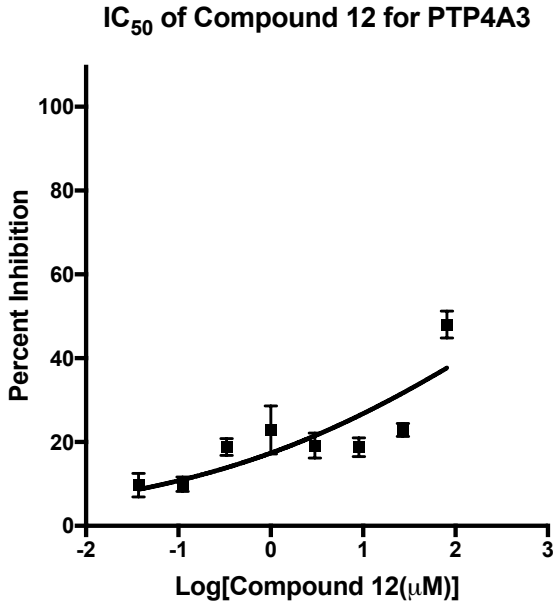
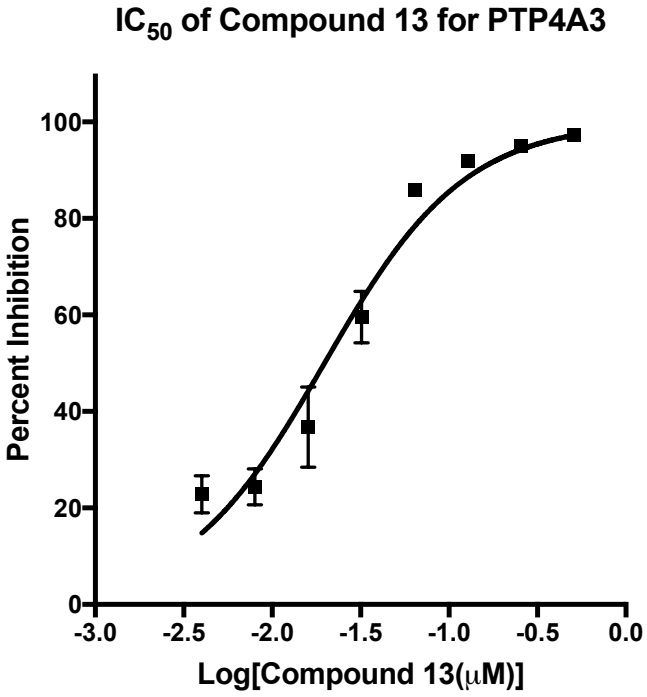
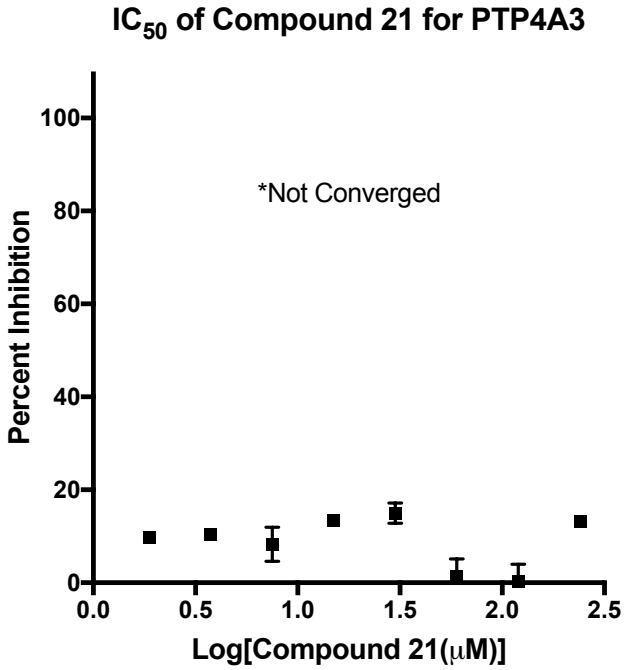
Biological Data






IC50 of Compound 13 for PTP4A3
Percent Inhibition
100
80
60
40
20
0
-3.0
-2.5
-2.0
-1.5
-1.0
-0.5
0.0
Log[Compound 13(μM)]


IC50 of Compound 21 for PTP4A3
*Not Converged
Percent Inhibition
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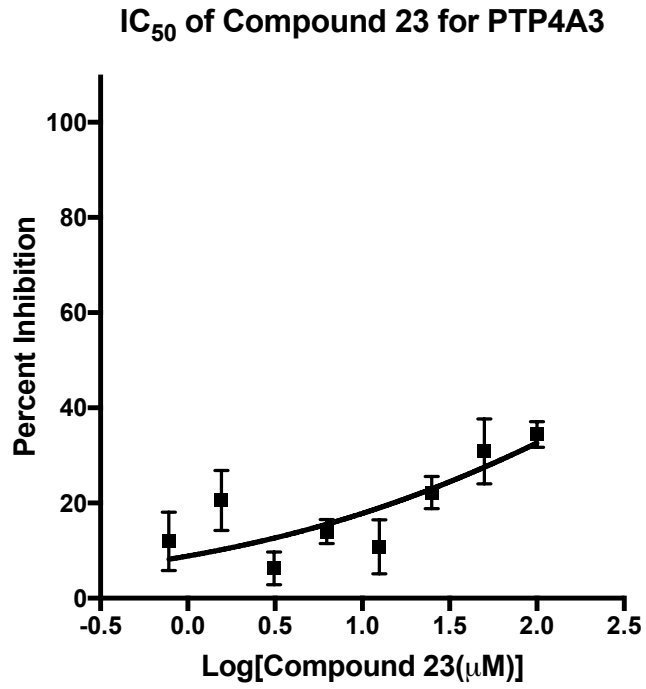
60
40
20
0
0.0
0.5
1.0
1.5
2.0
2.5
Log[Compound 21(μM)]


IC50 of Compound 23 for PTP4A3
Percent Inhibition
100
80
60
40
20
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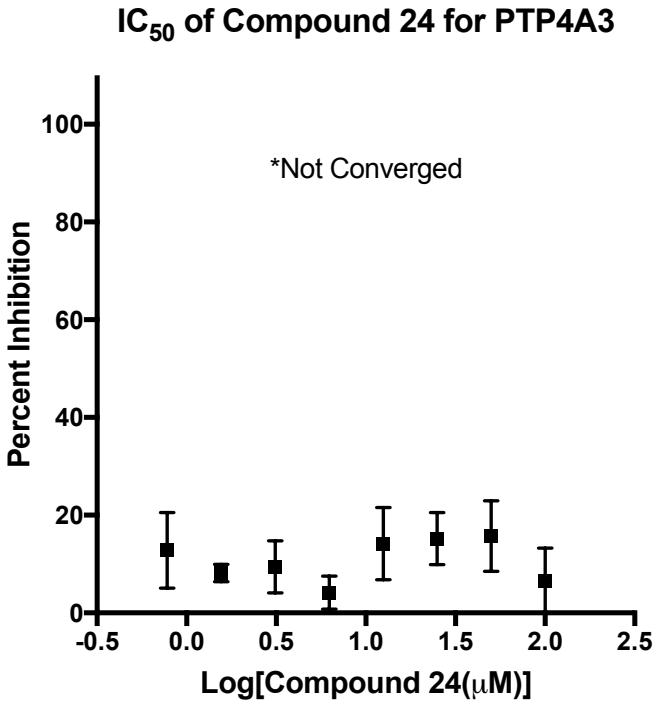
0.5
1.0
1.5
2.0
2.5
Log[Compound 23(μM)]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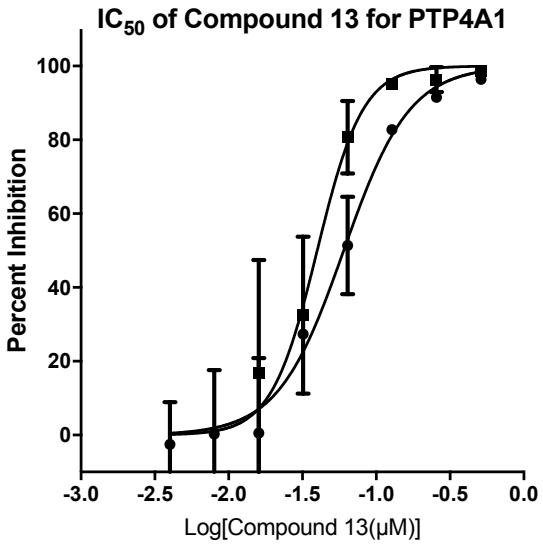
1.5
2.0
2.5
Log[Compound 24(μM)]



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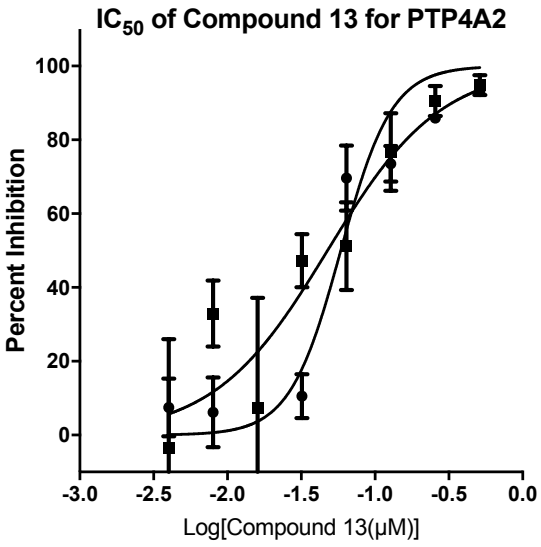

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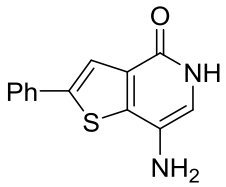

1

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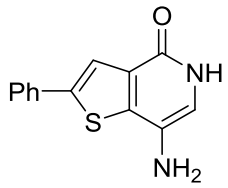

1

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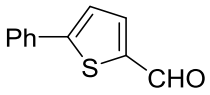

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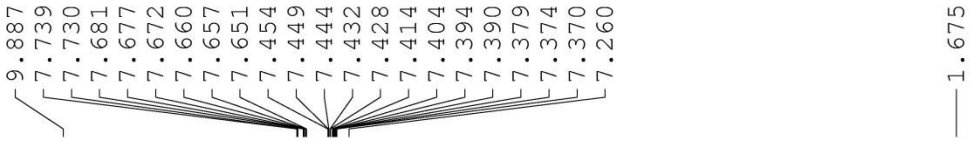

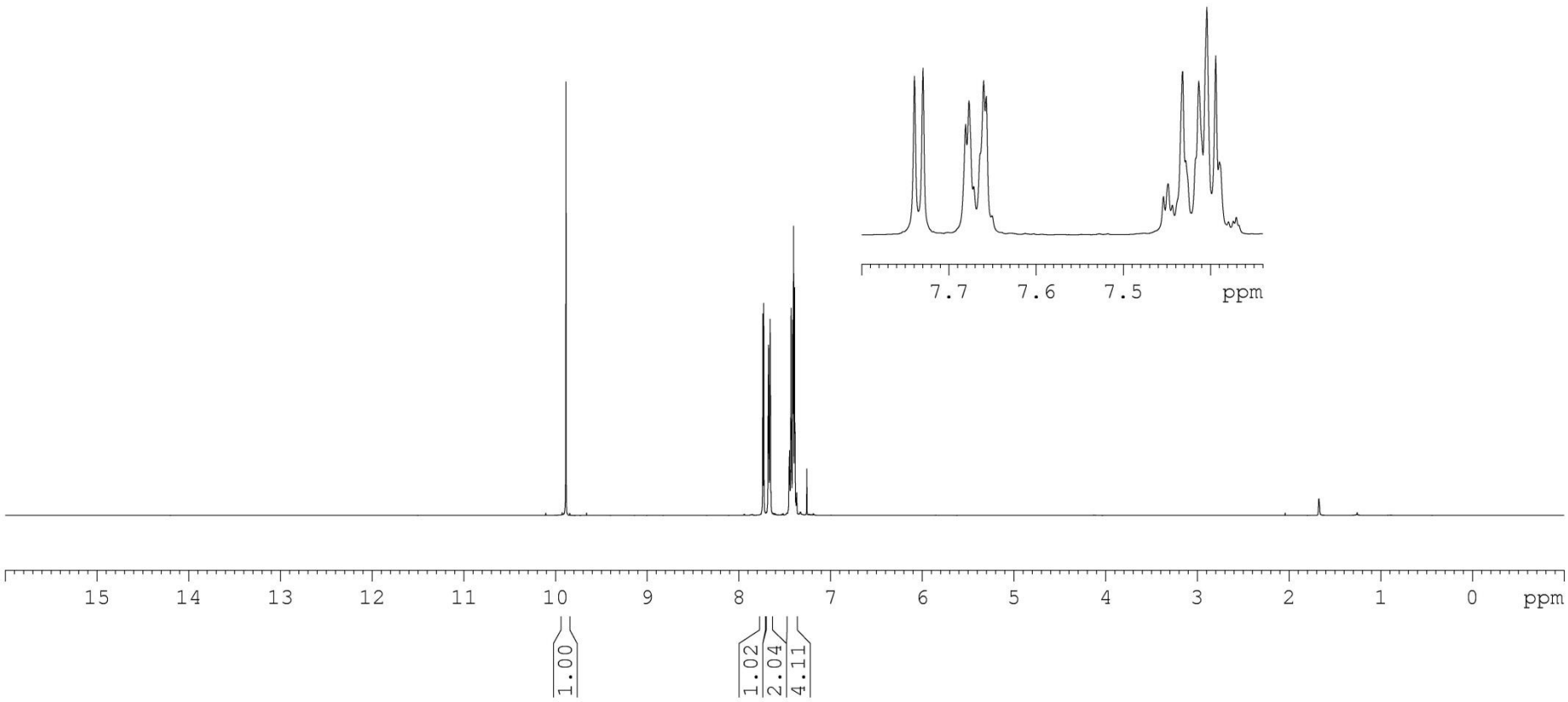

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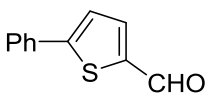

4

182.92
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137.53
133.15
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124.21
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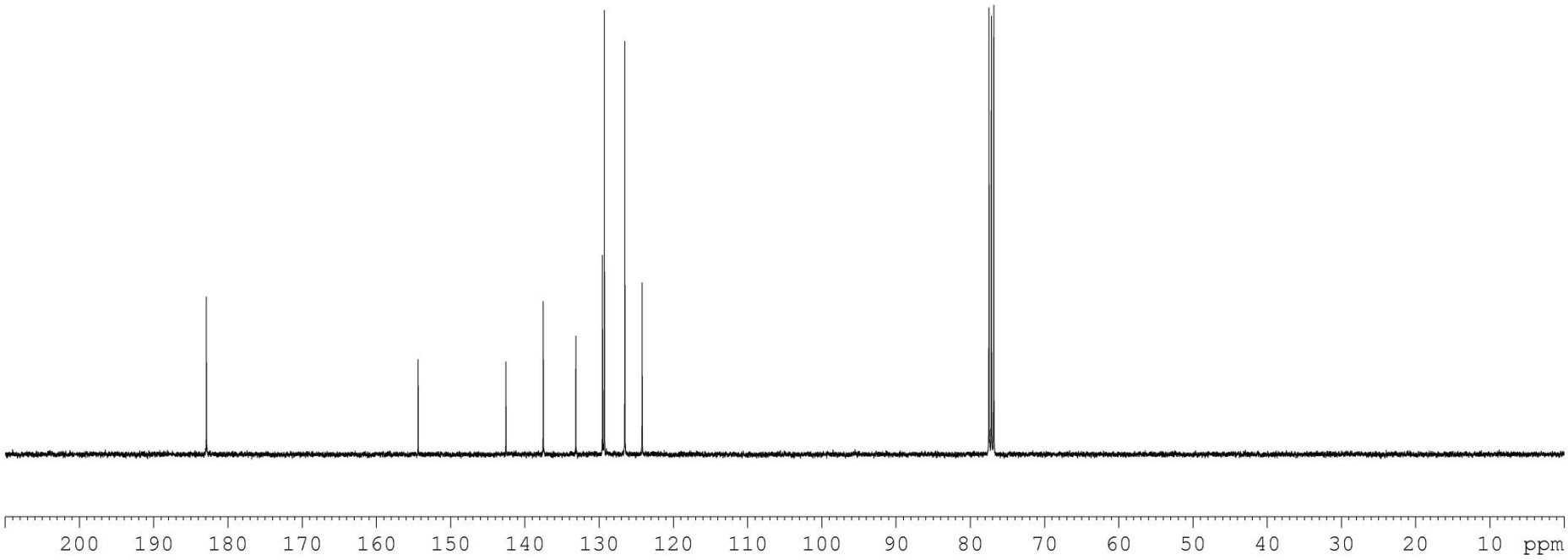
77.16
76.84



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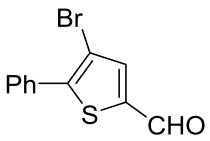

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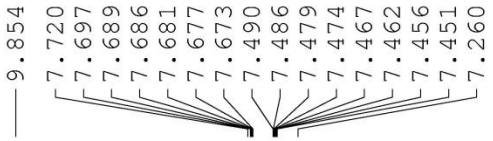

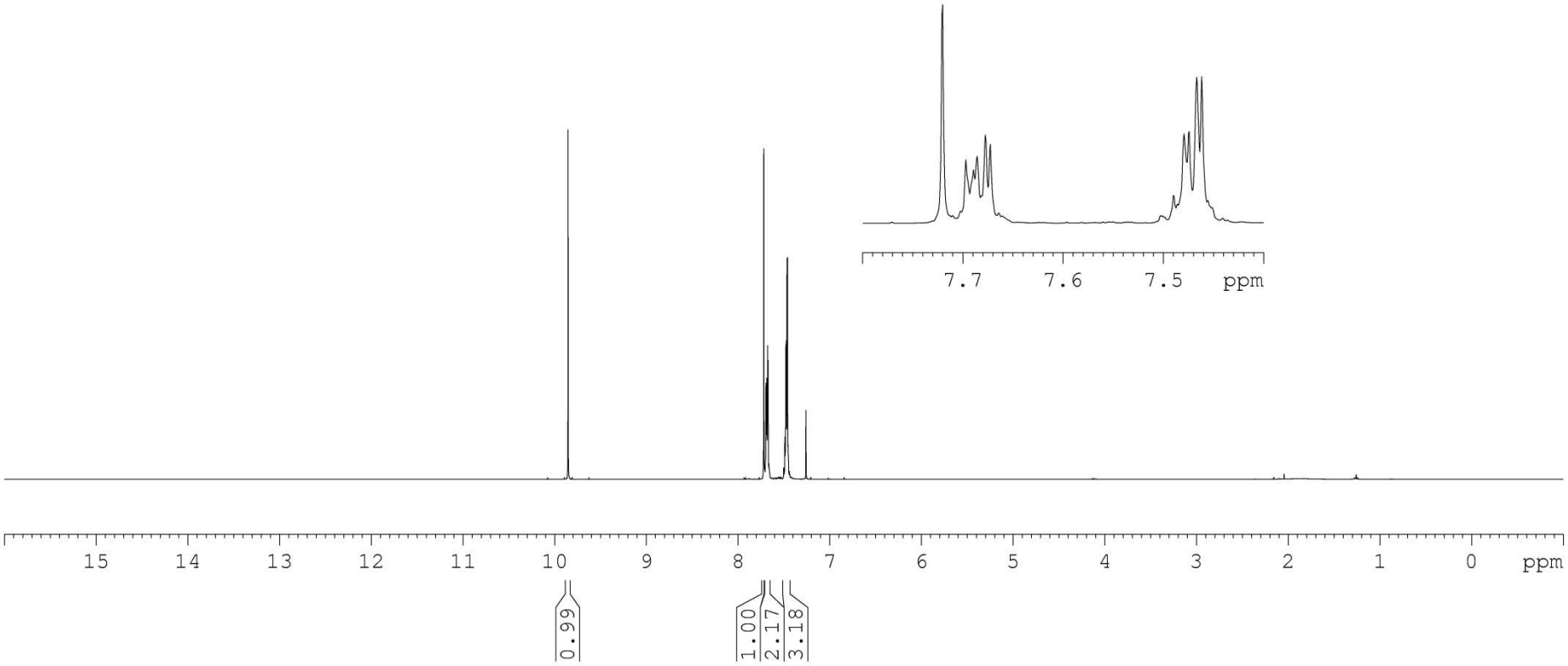

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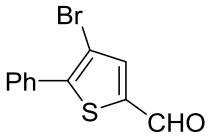

5

181.94
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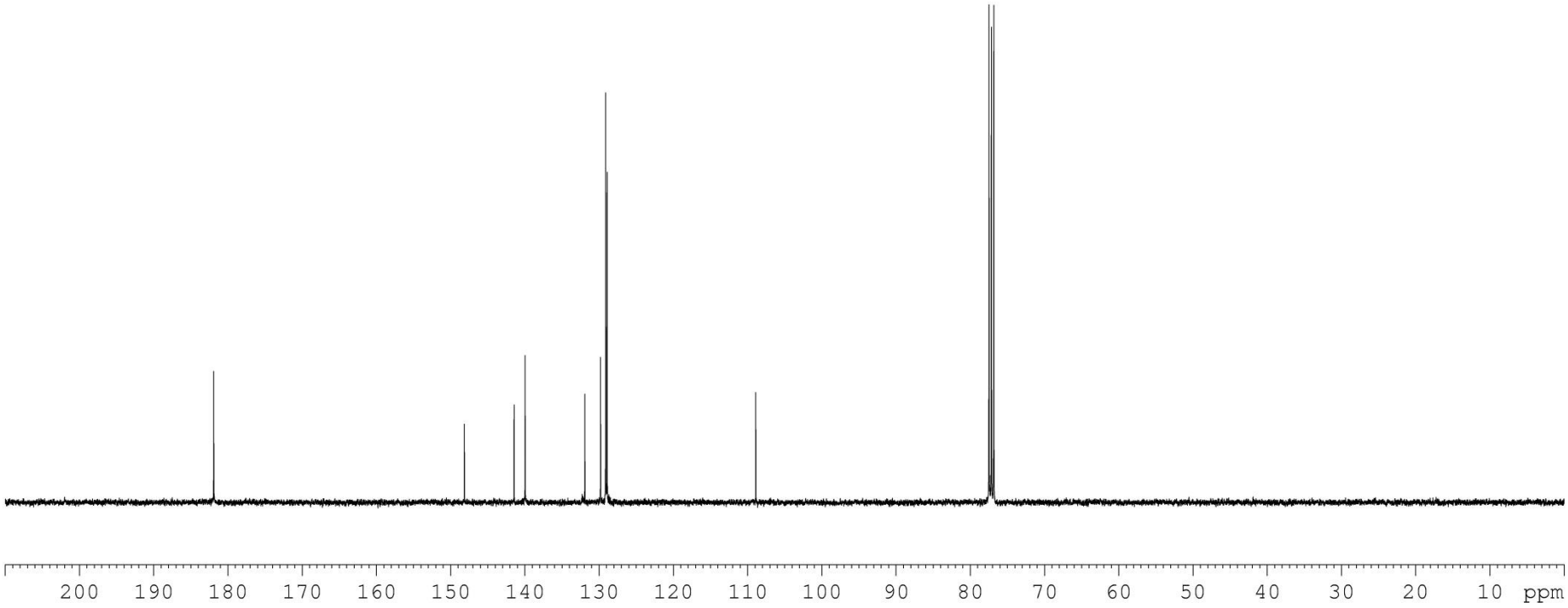
129.12
128.93
108.90
77.48
77.16
76.84



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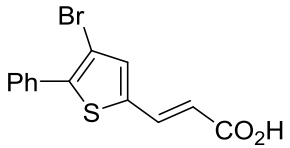

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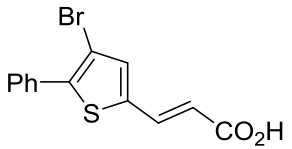

6

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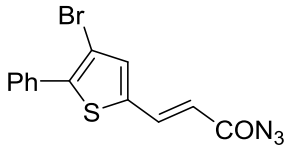

7

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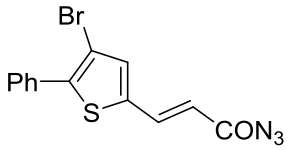
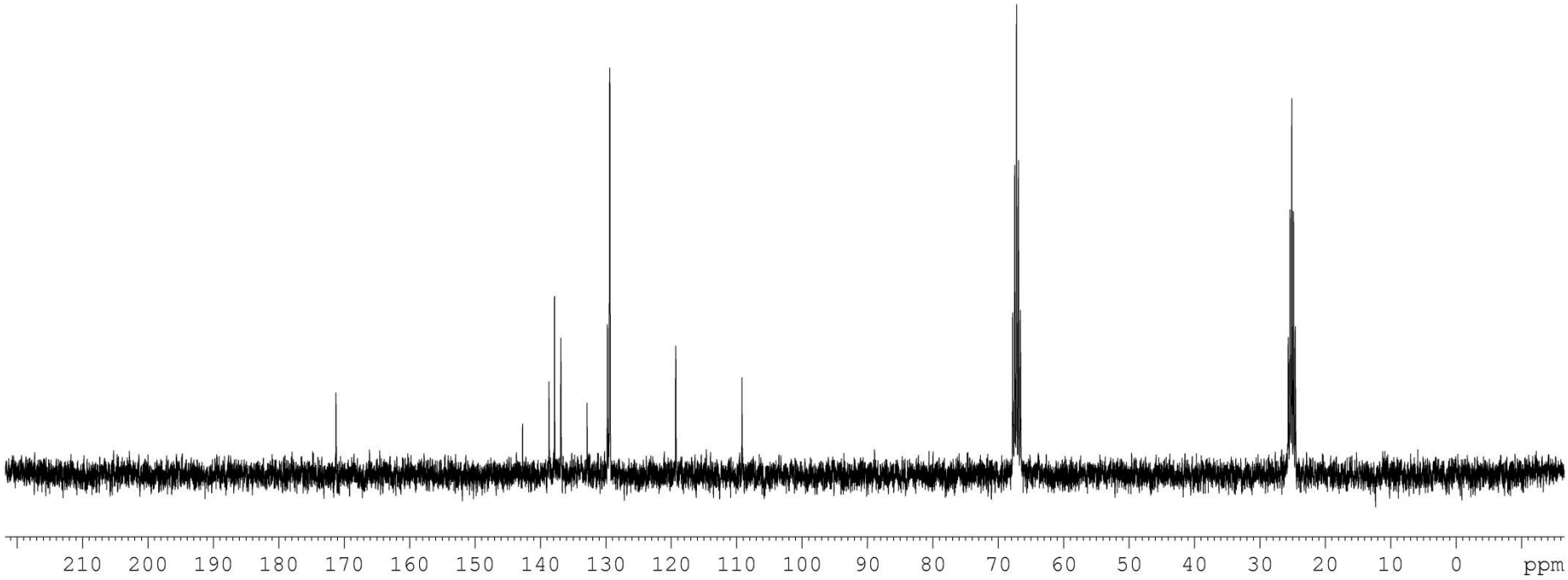
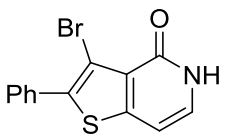


7

171.27
142.73
138.70
137.86
136.88
132.88
129.76
129.44
129.39
119.32
109.19
67.80
67.50
67.21
66.92
66.63
25.67
25.40
25.14
24.87
24.60

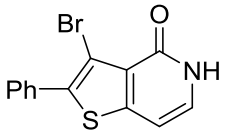


^{1}H NMR ($CDCl_3$, 300 MHz)



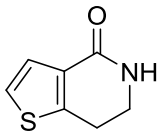
8

^{13}C NMR ($CDCl_3$, 125 MHz)



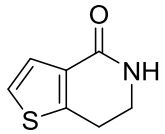
8

^{1}H NMR ($CDCl_3$, 400 MHz)



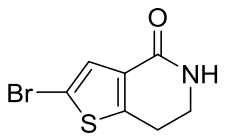
Crude **10** with MeOH Impurity

^{13}C NMR ($CDCl_3$, 100 MHz)



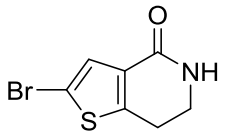
Crude **10** with MeOH Impurity

^{1}H NMR ($CDCl_3$, 400 MHz)



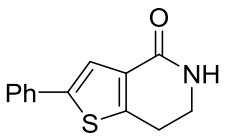
11

^{13}C NMR ($CDCl_3$, 100 MHz)



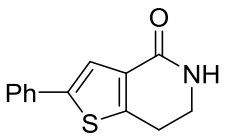
11

^{1}H NMR ($CDCl_3$, 400 MHz)



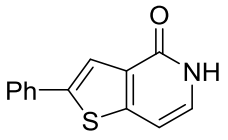
12-a

^{13}C NMR ($CDCl_3$, 100 MHz)



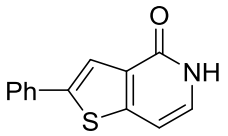
12-a

^{1}H NMR ((CD$_3$)$_2$SO, 400 MHz)



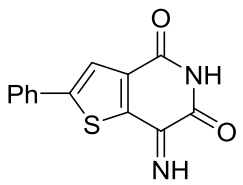
12

^{13}C NMR ((CD$_3$)$_2$SO, 100 MHz)



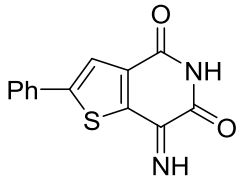
12

^{1}H NMR ((CD$_3$)$_2$SO, 400 MHz)



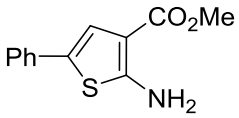
13

^{13}C NMR ((CD$_3$)$_2$SO, 100 MHz)



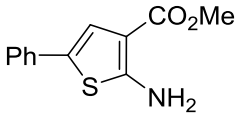
13

^{1}H NMR ($(CD_3)_2SO$, 400 MHz)



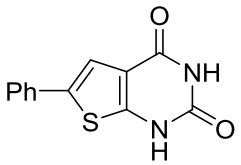
20

^{13}C NMR ((CD$_3$)$_2$SO, 100 MHz)



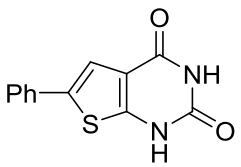
20

^{1}H NMR ((CD$_3$)$_2$SO, 400 MHz)

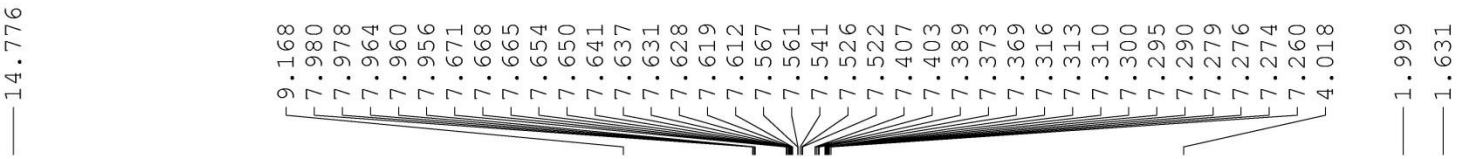


21

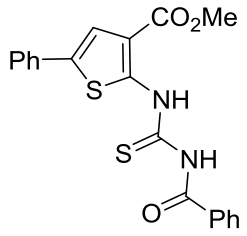
^{13}C NMR ((CD$_3$)$_2$SO, 100 MHz)



21

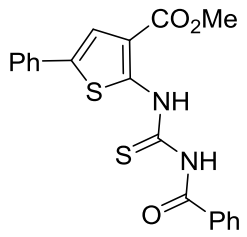


^{1}H NMR ($CDCl_3$, 400 MHz)



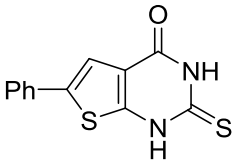
23-a

^{13}C NMR ($CDCl_3$, 100 MHz)



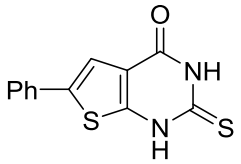
23-a

^{1}H NMR ((CD$_3$)$_2$SO, 400 MHz)



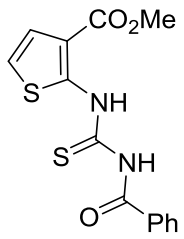
23

^{13}C NMR ((CD$_3$)$_2$SO, 100 MHz)



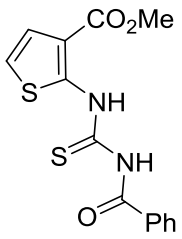
23

^{1}H NMR ($CDCl_3$, 400 MHz)



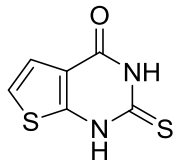
24-a

^{13}C NMR ($CDCl_3$, 100 MHz)



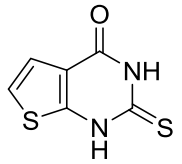
24-a

^{1}H NMR ((CD$_3$)$_2$SO, 400 MHz)



24

^{13}C NMR ((CD$_3$)$_2$SO, 100 MHz)



24