Supporting Information

One-Pot Synthesis of 5-Hydroxy-4*H*-1,3-thiazin-4-ones: Structure Revision, Synthesis and NMR Shift Dependence of Thiasporine A

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List of Supporting Information

General Information

^{1}H and ^{13}C NMR spectral data were recorded at 600/700 MHz (^{1}H) & 100/176 MHz (^{13}C) on a Varian System or on a Bruker Avance III 700 spectrometer. The chemical shifts were referenced to the corresponding residual solvent signal ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm; CD_3OD: δ_H = 3.31 ppm, δ_C = 49.00 ppm; DMSO-d_6: δ_H = 2.50 ppm, δ_C = 39.52 ppm). IR spectra were measured on a Jasco FT/IR-4100 equipped with an ATR unit. All IR spectra were measured with neat substances. High resolution ESI-TOF mass spectra were provided by The Scripps Research Institute, La Jolla, CA and on a ESI-MSD TOF Agilent 6210-System by Freie Universität Berlin, Germany. High resolution EI spectra were provided on a Waters Autospec Premier by Freie Universität Berlin. Melting points were determined by digital melting point apparatus (Stuart SMP30). Products were purified by flash chromatography on silica gel 300-400 mesh (Macherey & Nagel). Additives (formic acid) for eluents are given in vol%. TLC was performed on ALUGRAM® Xtra SIL G/UV_{254} form Macherey & Nagel. Unless otherwise indicated, all reagents were purchased from commercial distributors and used without further purification. Dichloromethane was used dry after purification by MBraun SPS-800. Dry *N*,*N*-Dimethylformamide was purchased from Acros Chemicals. 2-Aminobenzonitrile was obtained from Fluka Chemika. 3-Bromopyruvic acid was purchased from Sigma Aldrich. *tert*-Butyl (2-cyanophenyl)carbamate was obtained from Sigma Aldrich or was prepared by a known method.[1]

Figure S1. Comparison of the ^{1}H and ^{13}C NMR of synthetic **1a** with isolated thiasporine A in DMSO-d_6.

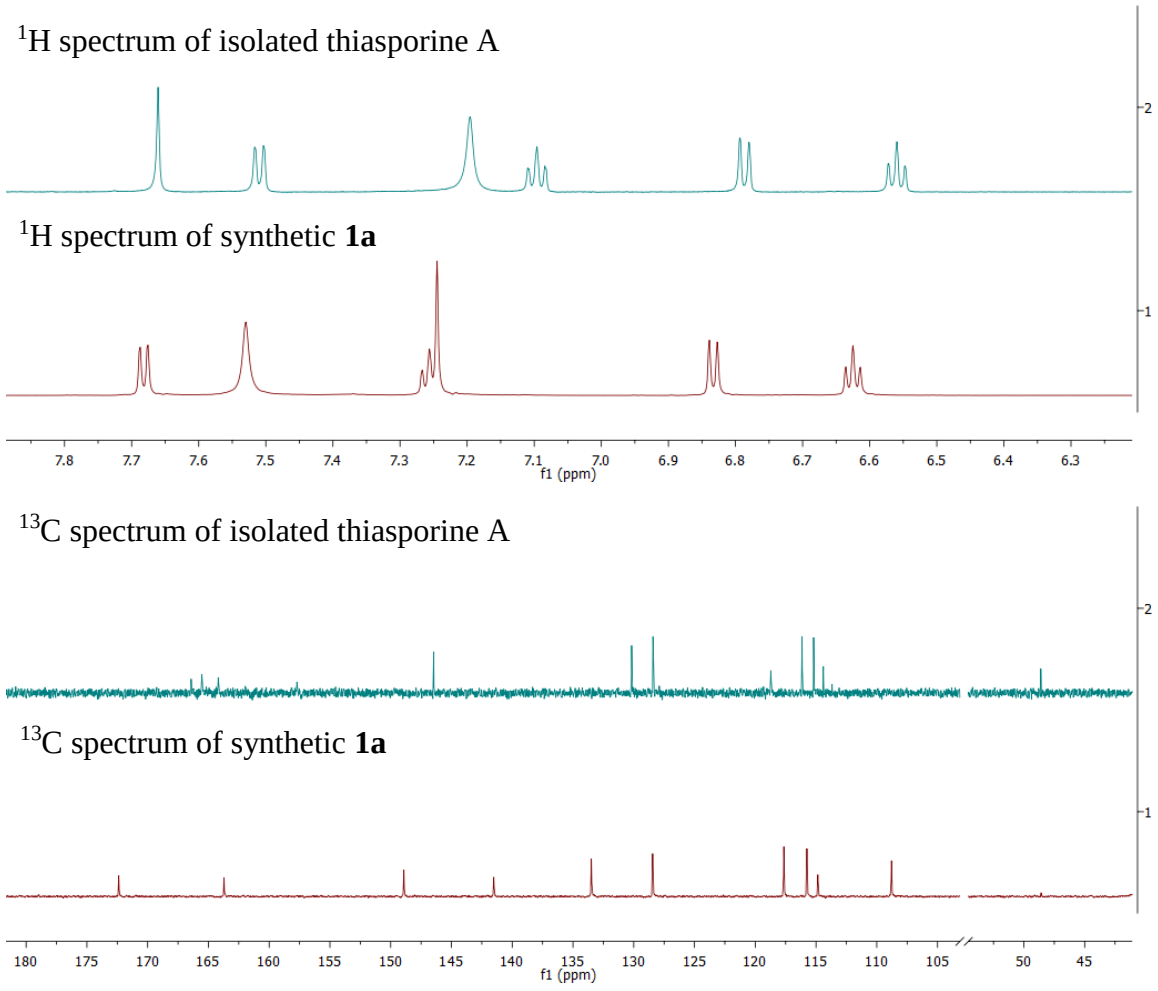


Figure S2. Comparison of the ^{1}H NMR of synthetic **12** with the methyl ester of isolated thiasporine A in CD_3OD.

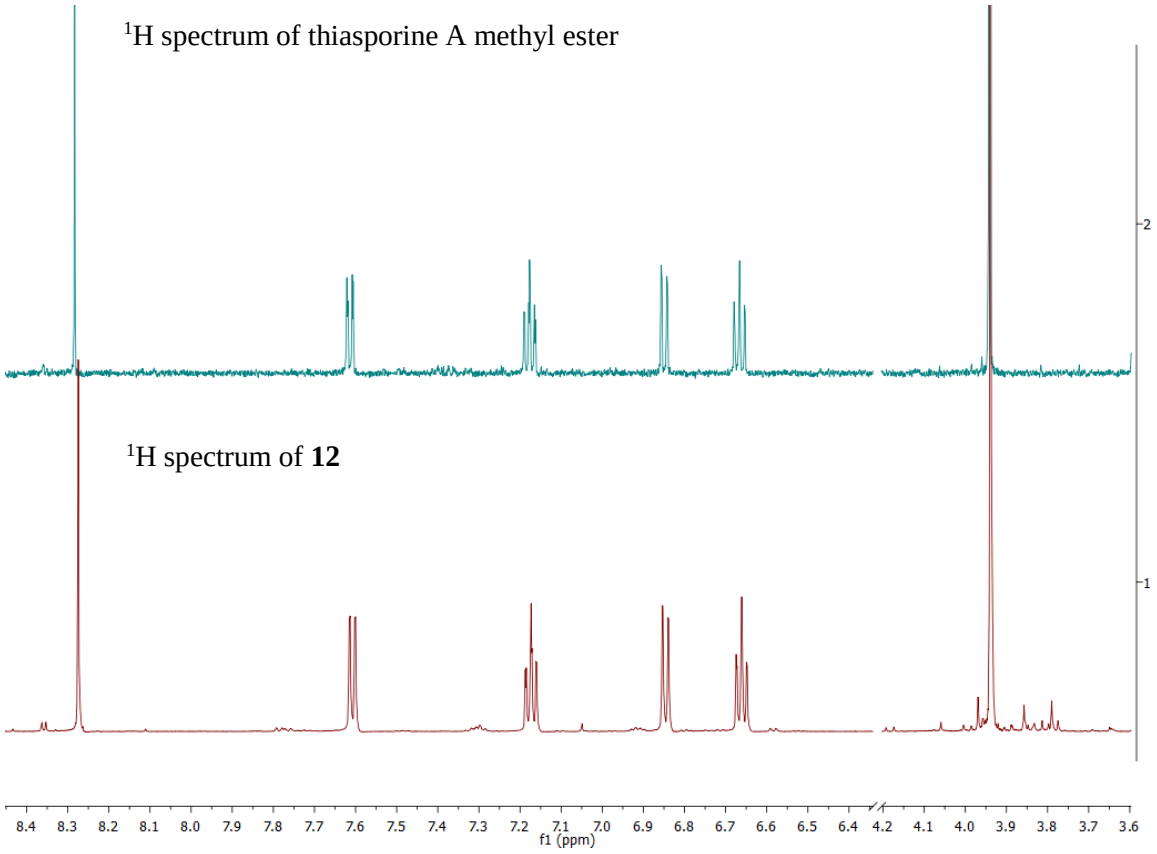


Figure S3. Histograms comparing carbon and proton chemical shifts of synthetic **1b** as different salt forms in DMSO-d_6.

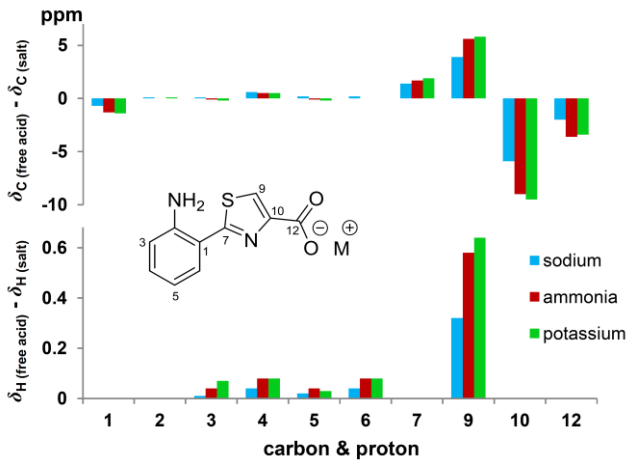


Figure S4. Variation of ^{1}H NMR resonances with added NaOH (6 *M* in H_2O) for synthetic **1b** in DMSO-d_6.

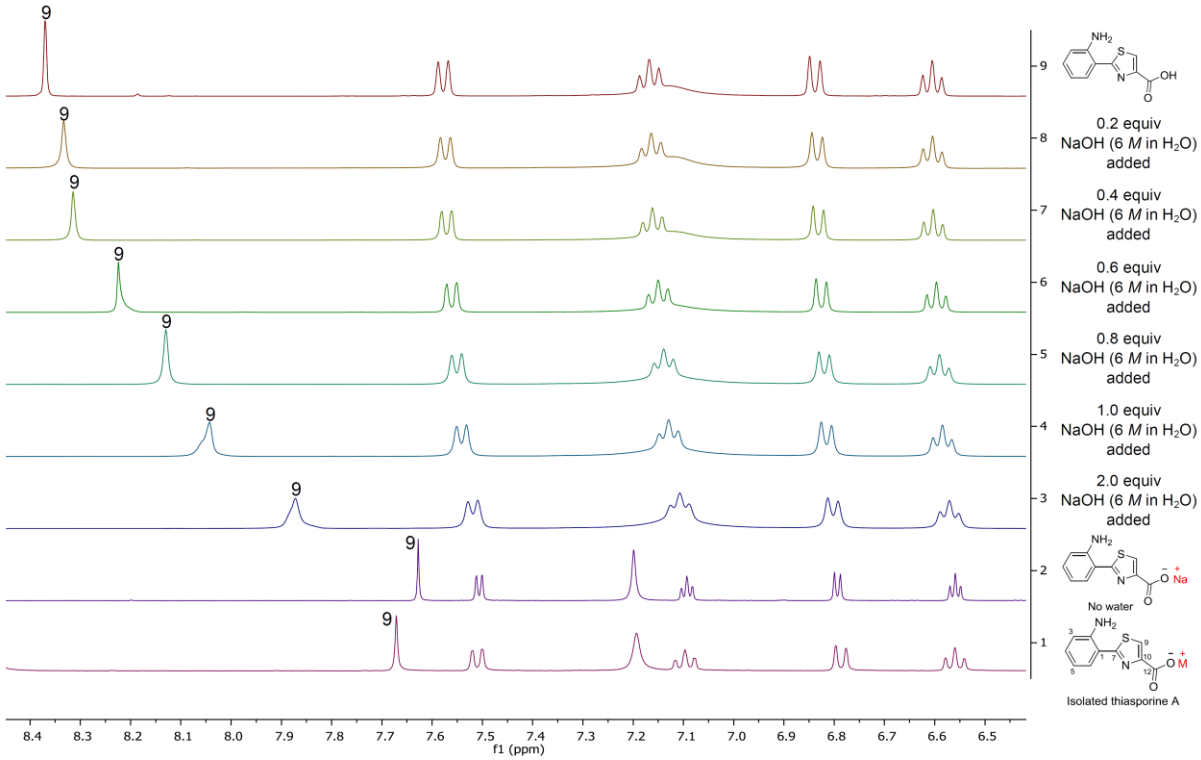
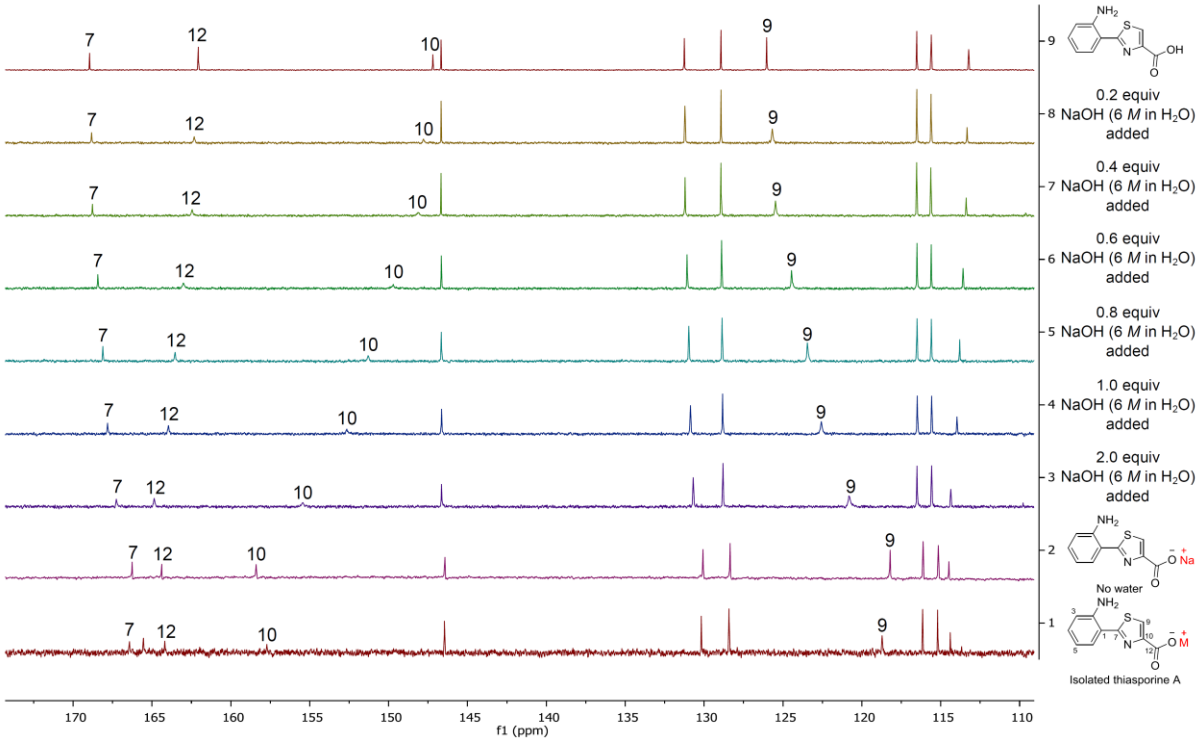
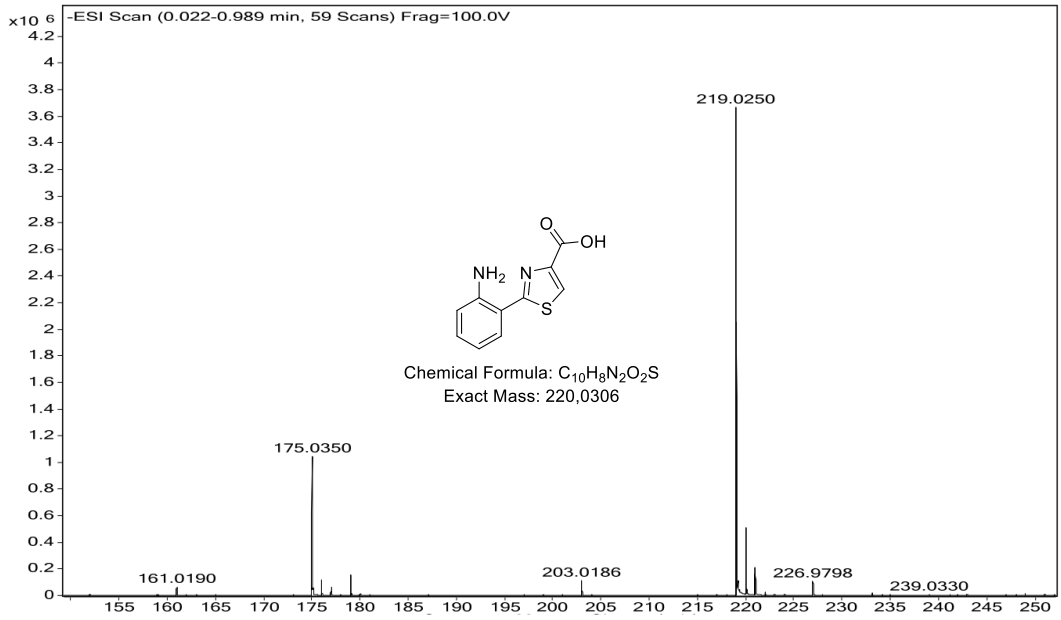


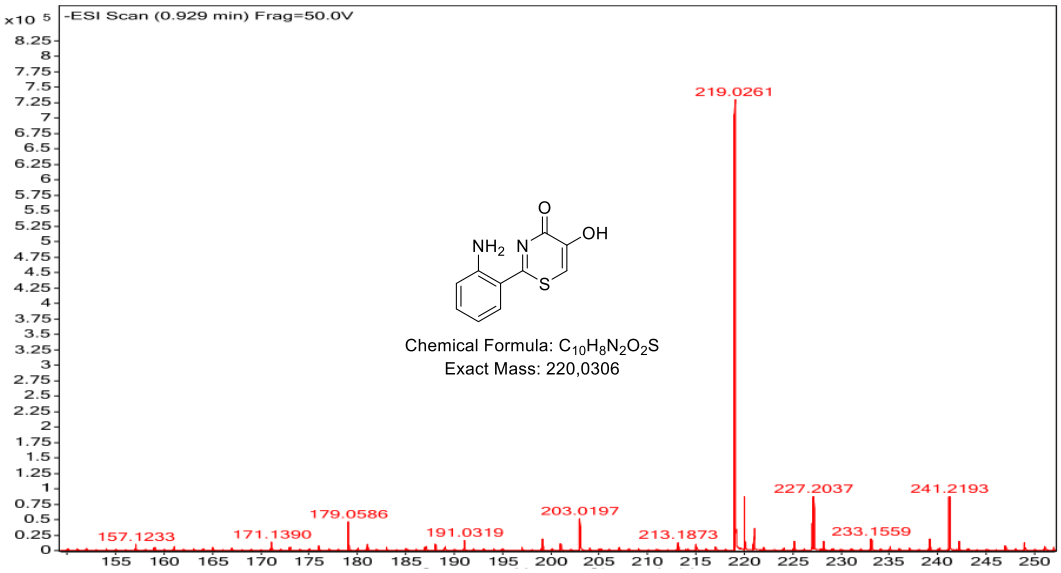
Figure S5. Variation of ^{13}C NMR resonances with added NaOH (6 *M* in H_2O) for synthetic **1b** in DMSO-d_6.



Mass spectrometric analysis of 1a and 1b

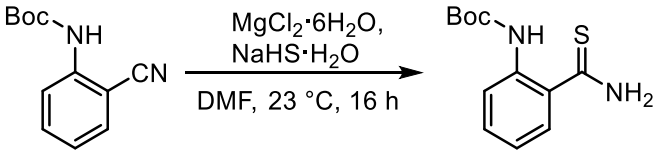
The two structures, **1a** and **1b** can be distinguished using electrospray ionization mass spectrometry in negative ion mode (–)ESI-MS, yielding $[M-H]^-$ at *m/z* 219 with a major fragment at *m/z* 175 $[M–COOH]^-$ for **1b**.





Experimental Procedure

tert-Butyl (2-carbamothioylphenyl)carbamate (5)[2]



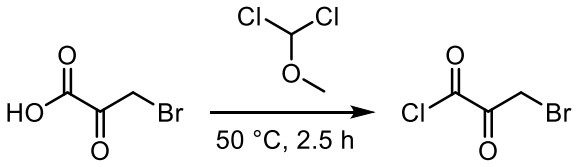
4 $C_{12}H_{14}N_2O_2$ (218.26)

5 $C_{12}H_{16}N_2O_2S$ (252.33)

An oven-dried 250 mL round-bottom-flask equipped with a Teflon-coated magnetic stirrer bar was charged with *tert*-butyl (2-cyanophenyl)carbamate **4** (4.00 g, 18.3 mmol, 1.0 equiv) and *N*,*N*-dimethylformamide (49.0 mL). This mixture was stirred at 23 °C and magnesium chloride hexahydrate (3.73 g, 18.3 mmol, 1.0 equiv) was added in portions until it was dissolved completely (~15 min). Sodium hydrosulfide monohydrate (2.72 g, 36.7 mmol, 2.0 equiv) was added and the reaction mixture was stirred for 16 h at 23 °C until TLC showed complete consumption of the starting material. The reaction was diluted with water (150 mL) and brine (20 mL) and extracted with ethyl acetate (4 × 100 mL). The combined organic phases were washed with brine (3 × 100 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (dry load, pentane–ethyl acetate, 3:1 to 2:1) to give the product **5** (3.97 g, 15.7 mmol, 86%) as a yellow solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.10 (d, *J* = 8.3 Hz, 1H), 7.64 (s, 1H), 7.41–7.37 (m, 1H), 7.33 (s, 1H), 7.31 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 1.51 (s, 9H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 202.1, 153.3, 136.8, 131.7, 129.7, 125.8, 122.7, 121.8, 80.9, 28.5 (3C) ppm; IR (neat): 3281, 3149, 3005, 2978, 2927, 2360, 1693, 1656, 1603, 1579, 1522, 1475, 1447, 1393, 1366, 1322, 1291, 1249, 1233, 1154, 1110, 1050, 1025, 909, 870, 832, 757, 734, 718, 708, 682, 669, 660, 653 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{12}H_{16}N_2O_2SNa$ $[M + Na]^+$: 275.0830; found: 275.0819; m.p. 171 °C.

3-Bromo-2-oxopropanoyl chloride (3)



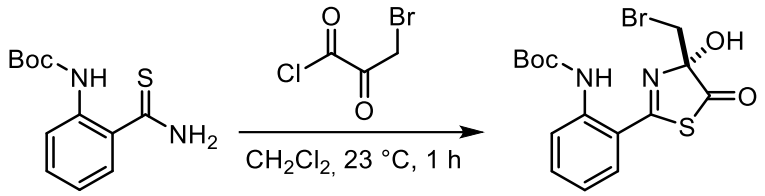
2a $C_3H_3BrO_3$ (166.96)

3 $C_3H_2BrClO_2$ (185.40)

An oven-dried 10 mL round-bottom-flask equipped with a Teflon-coated magnetic stirrer bar was charged with 3-bromopyruvic acid **2a** (1.50 g, 8.98 mmol, 1 equiv), sealed with a rubber septum and connected to a Schlenk line through a needle. Under a stream of argon, dichloro(methoxy)methane (0.85 mL, 9.43 mmol, 1.05 equiv) was added and the mixture was stirred at 50 °C for 2.5 h. The reaction mixture was concentrated on a rotary evaporator (40 °C, 20 mbar, 5 min) and purified via bulb-to-bulb distillation (50–60 °C, 8.8×10^{-2} mbar) to give **3** (834 mg, 4.50 mmol, 50%) as a yellow oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 4.32 (s, 2H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 179.8, 165.9, 28.2 ppm; IR (neat): 1762, 1738, 1415, 1387, 1274, 1226, 1195, 1158, 1108, 1091, 1022, 956, 909, 873, 756, 733, 692, 657 cm^{-1}, HRMS (EI): *m/z* calcd for $C_3H_2BrClO_2$ $[M]^+$: 183.8921; found: 183.8925.

***tert*-Butyl (2-(4-(bromomethyl)-4-hydroxy-5-oxo-4,5-dihydrothiazol-2-yl)phenyl)carbamate (6)**



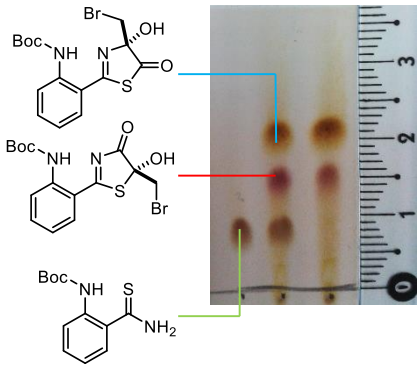
5
$C_{12}H_{16}N_2O_2S$ (252.33)

6
$C_{15}H_{17}BrN_2O_4S$ (401.28)

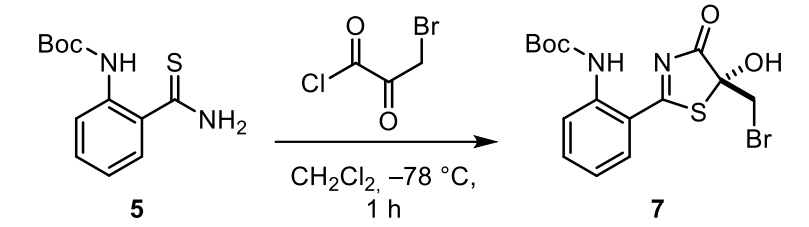
An oven-dried 25 mL round-bottom-flask equipped with a Teflon-coated magnetic stirrer bar was charged with thioamide **5** (100 mg, 396 µmol, 1.0 equiv) and dry CH_2Cl_2 (7.2 mL). 3-Bromo-2-oxopropanoyl chloride (**3**) (49.4 µL, 495 µmol, 1.25 equiv) was added slowly at 23 °C to the solution. The reaction mixture was stirred at this temperature for 1 h. The reaction was quenched with water (50 mL) and brine (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried over sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (dry load, pentane–Et_2O, 4:1 to pentane–Et_2O, 3:1) to give **6** (105 mg, 263 µmol, 66%) as orange solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 10.93 (s, 1H), 8.49 (d, *J* = 8.5 Hz, 1H), 7.50–7.49 (m, 1H), 7.46 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.10–7.07 (m, 1H), 3.83 (s, 1H), 3.82 (d, *J* = 10.6 Hz, 1H), 3.70 (d, *J* = 10.6 Hz, 1H), 1.53 (s, 9H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 201.2, 169.2, 153.2, 140.83, 134.2, 132.7, 121.9, 119.5, 117.1, 103.0, 81.1, 35.1, 28.5 (3C) ppm; IR (neat): 3357, 3228, 2978, 2929, 1731, 1699, 1607, 1592, 1577, 1530, 1474, 1448, 1415, 1392, 1368, 1307, 1240, 1154, 1075, 1048, 954, 889, 865, 826, 755, 714, 695, 665 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{17}BrN_2O_4SK$ $[M + K]^+$: 438.9729; found: 438.9746; m.p. 124 °C (decomposition).

TLC: pentane−Et_2O 1:1, stain solution: vanillin (1 g) in methanol (170 mL) + conc. acetic acid (20 mL) + conc. sulfuric acid (10 mL)



***tert*-Butyl (2-(5-(bromomethyl)-5-hydroxy-4-oxo-4,5-dihydrothiazol-2-yl)phenyl)carbamate (7)**



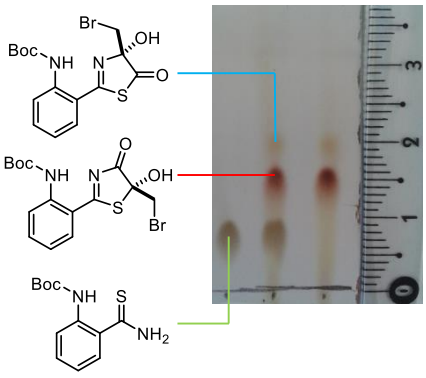
5 $C_{12}H_{16}N_2O_2S$ (252.33)

7 $C_{15}H_{17}BrN_2O_4S$ (401.28)

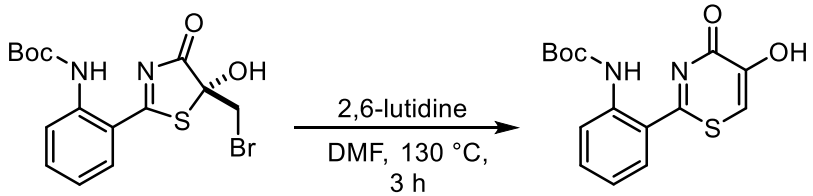
An oven-dried 25 mL round-bottom-flask equipped with a Teflon-coated magnetic stirrer bar was charged with thioamide **5** (100 mg, 396 µmol, 1.0 equiv) and dry CH_2Cl_2 (7.2 mL). The solution was cooled to –78 °C and 3-bromo-2-oxopropanoyl chloride (**3**) (49.4 µL, 495 µmol, 1.25 equiv) was added slowly at –78 °C to the suspension. The reaction mixture was stirred for 1 h at –78 °C. After complete consumption of the starting material (TLC) the cooling bath was removed, the reaction mixture was allowed to warm to 23 °C. The reaction was quenched with water (50 mL) and brine (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried over sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (dry load, pentane–Et_2O, 4:1 to pentane–Et_2O, 3:1) to give **7** (93.4 mg, 233 µmol, 59%) as yellow solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 11.19 (s, 1H), 8.55–8.53 (m, 1H), 7.76 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.63–7.59 (m, 1H), 7.07–7.04 (m, 1H), 4.06 (s, 1H), 3.98 (d, *J* = 10.9 Hz, 1H), 3.82 (d, *J* = 10.9 Hz, 1H), 1.55 (s, 9H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 193.5, 186.8, 152.8, 142.3, 137.5, 130.7, 121.7, 119.5, 116.5, 92.0, 81.5, 37.5, 28.3 (3C) ppm; IR (neat): 3341, 2956, 2920, 2851, 2361, 2341, 1733, 1608, 1582, 1524, 1494, 1438, 1393, 1368, 1320, 1305, 1229, 1146, 1051, 1022, 773, 751 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{17}BrN_2O_4SK$ [M + K]$^+$: 438.9729; found: 438.9728; m.p. 130–131 °C (decomposition).

TLC: pentane−Et_2O 1:1, stain solution: vanillin (1 g) in methanol (170 mL) + conc. acetic acid (20 mL) + conc. sulfuric acid (10 mL)



***tert*-Butyl (2-(5-hydroxy-4-oxo-4H-1,3-thiazin-2-yl)phenyl)carbamate (8)**



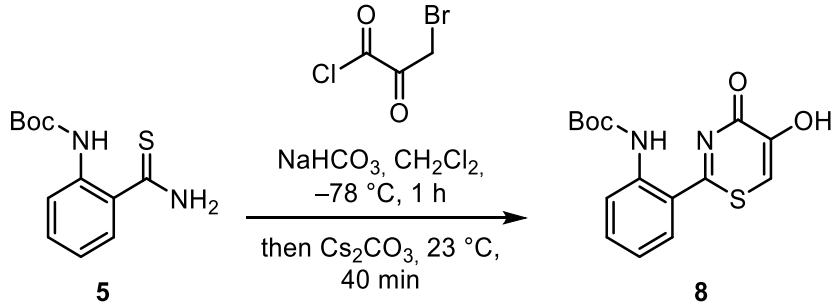
7 $C_{15}H_{17}BrN_2O_4S$ (401.28)

8 $C_{15}H_{16}N_2O_4S$ (320.36)

An oven-dried 5 mL round-bottom-flask equipped with a Teflon-coated magnetic stirrer bar was charged with thiazolinone **7** (25.0 mg, 62.3 µmol, 1.0 equiv) and dry *N*,*N*-dimethylformamide (0.61 mL). 2,6-Lutidine (14.5 µL, 125 µmol, 2.0 equiv) was added at 23 °C and the reaction mixture was stirred at 130 °C for 1 h. The reaction was quenched with hydrochloric acid (1 M, 10 mL) and the aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic phases were washed with brine (1 × 20 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (dry load, pentane–Et_2O, 1:1 + 1% formic acid to pentane–ethyl acetate, 1:1 + 1% formic acid) to give **8** (16.3 mg, 50.9 µmol, 82%) as yellow solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.4 Hz, 1H), 7.79 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.54–7.51 (m, 1H), 7.38 (s, 1H), 7.10–7.07 (m, 1H), 7.02 (s, 1H), 1.53 (s, 9H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 175.2, 164.3, 153.1, 141.6, 139.2, 134.2, 128.9, 122.4, 121.9, 121.1, 108.2, 81.0, 28.4 (3C) ppm; IR (neat): 3453, 2932, 2872, 1715, 1596, 1458, 1434, 1414, 1382, 1323, 1311, 1298, 1248, 1214, 1169, 1139, 1110, 1074, 1044, 1022, 969, 927, 892, 849, 821, 784, 766, 712, 693, 666 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{16}N_2O_4SNa$ [M + Na]$^+$: 343.0728; found: 343.0727; m.p. 177 °C (decomposition).

***tert*-Butyl (2-(5-hydroxy-4-oxo-4H-1,3-thiazin-2-yl)phenyl)carbamate (8)**



5 $C_{12}H_{16}N_2O_2S$ (252.33)

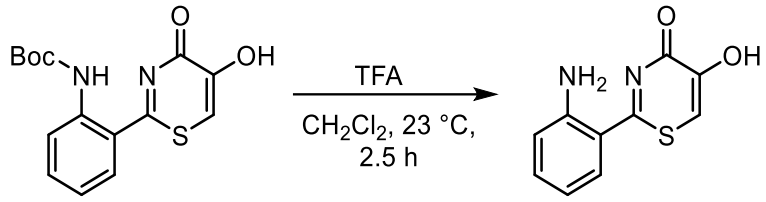
8 $C_{15}H_{16}N_2O_4S$ (320.36)

An oven-dried 25 mL round-bottom-flask equipped with a Teflon-coated magnetic stirrer bar was charged with thioamide **5** (91.3 mg, 362 µmol, 1.0 equiv) and dry CH_2Cl_2 (8.0 mL). Upon addition of sodium bicarbonate (76.0 mg, 905 µmol, 2.5 equiv), the suspension was cooled to –78 °C and 3-bromo-2-oxopropanoyl chloride (**3**) (44.7 µL, 441 µmol, 1.2 equiv) was added slowly. The reaction mixture was stirred for 1 h at –78 °C. Caesium carbonate (141.5 mg, 434 µmol, 1.2 equiv) was added and the cooling bath was removed, the reaction mixture was allowed to warm to 23 °C and stirred for 40 min at this temperature. The reaction was quenched with hydrochloric acid (1 M, 10 mL) and the aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phases were washed with hydrochloric acid (1 M, 10 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (dry load,

pentane-Et_2O, 1:1 to pentane–ethyl acetate, 2:1 + 1% formic acid) to give **8** (92.8 mg, 290 µmol, 80%) as yellow solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.4 Hz, 1H), 7.79 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.54–7.51 (m, 1H), 7.38 (s, 1H), 7.10–7.07 (m, 1H), 7.02 (s, 1H), 1.53 (s, 9H) ppm; ^{1}H NMR (700 MHz, DMSO-d6) δ 10.45 (s, 1H), 10.22 (s, 1H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.78 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.56 (td, *J* = 8.6, 8.0, 1.5 Hz, 1H), 7.35 (s, 1H), 7.22 (td, *J* = 7.9, 1.2 Hz, 1H), 1.42 (s, 5H) ppm. ^{13}C NMR (176 MHz, $CDCl_3$) δ 175.2, 164.3, 153.1, 141.6, 139.2, 134.2, 128.9, 122.4, 121.9, 121.1, 108.2, 81.0, 28.4 (3C) ppm; ^{13}C NMR (176 MHz, DMSO) δ 172.9, 163.6, 152.5, 142.5, 137.1, 132.7, 129.3, 124.8, 123.4, 121.7, 109.9, 79.8, 27.9 (3C) ppm; IR (neat): 3453, 2932, 2872, 1715, 1596, 1458, 1434, 1414, 1382, 1323, 1311, 1298, 1248, 1214, 1169, 1139, 1110, 1074, 1044, 1022, 969, 927, 892, 849, 821, 784, 766, 712, 693, 666 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{16}N_2O_4SNa$ [M + Na]$^+$: 343.0728; found: 343.0727; m.p. 177 °C (decomposition).

2-(2-Aminophenyl)-5-hydroxy-4H-1,3-thiazin-4-one (1a)



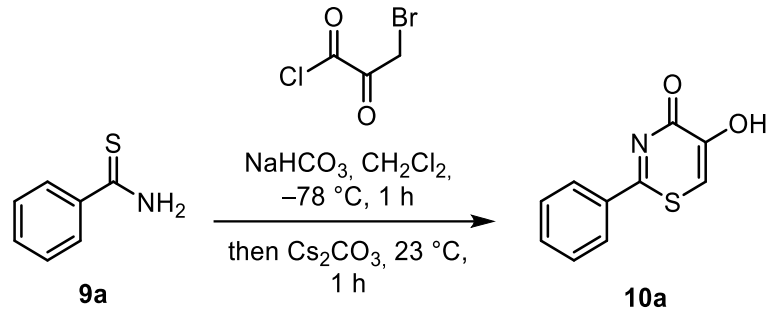
8 $C_{15}H_{16}N_2O_4S$ (320.36)

1a $C_{10}H_8N_2O_2S$ (220.25)

An oven-dried 5 mL round-bottom-flask equipped with a Teflon-coated magnetic stirrer bar was charged with 1,3-thiazin-4-one **8** (19.0 mg, 59.0 µmol, 1.0 equiv) and dry CH_2Cl_2 (0.55 mL). The solution was cooled to 0 °C and trifluoroacetic acid (54.8 µL, 712 µmol, 12.0 equiv) was added and the reaction was kept at this temperature for 30 min. Upon warming to 23 °C, the reaction was stirred for another 2 h. A pH-7 buffer solution (NaH_2PO_4 0.1 M/NaOH 0.1 M (1.72:1), 5 mL) was added to the reaction mixture and the aqueous layer was extracted with ethyl acetate (4 × 20 mL). The combined organic phases were washed with brine (20 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (dry load, pentane–Et_2O, 1:1 + 1% formic acid to pentane–ethyl acetate, 1:1 + 1% formic acid) to give **1a** (12.2 mg, 55.6 µmol, 94%) as red-brown solid.

^{1}H NMR (700 MHz, DMSO-d_6) δ 10.01 (s, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.53 (s, 2H), 7.28–7.23 (m, 1H), 7.24 (s, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.62 (t, *J* = 7.5 Hz, 1H) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 172.4, 163.7, 148.9, 141.5, 133.5, 128.5, 117.7, 115.8, 114.9, 108.8 ppm; IR (neat): 3372, 3266, 3055, 2923, 2853, 1734, 1713, 1613, 1556, 1501, 1467, 1445, 1407, 1378, 1300, 1273, 1248, 1227, 1194, 1155, 1119, 1062, 942, 915, 851, 834, 805, 785, 762, 751, 733, 709, 696, 682, 672, 661 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{10}H_8N_2O_4SNa$ [M + Na]$^+$: 243.0204; found: 243.0228; m.p. 199 °C (decomposition).

5-Hydroxy-2-phenyl-4*H*-1,3-thiazin-4-one (10a)



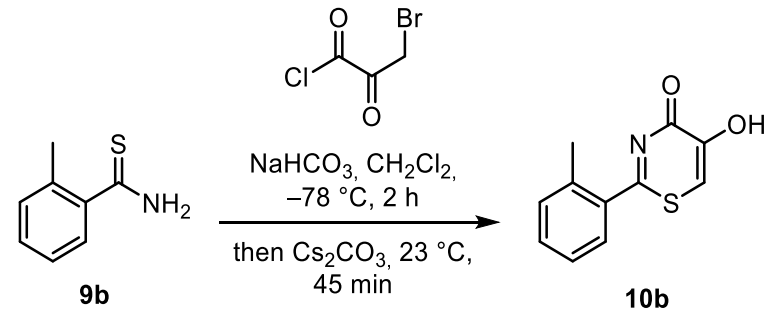
9a
C_7H_7NS (137.20)

10a
$C_{10}H_7NO_2S$ (205.23)

An oven-dried 25 mL round-bottom-flask equipped with a Teflon-coated magnetic stirrer bar was charged with thioamide **9a**[3] (100 mg, 729 µmol, 1.0 equiv) and dry CH_2Cl_2 (12 mL). Upon addition of sodium bicarbonate (153 mg, 1.82 mmol, 2.5 equiv), the suspension was cooled to –78 °C and 3-bromo-2-oxopropanoyl chloride (**3**) (74.2 µL, 729 µmol, 1.0 equiv) was added slowly. Because TLC-control showed incomplete conversion after 40 min at –78 °C, 3-bromo-2-oxopropanoyl chloride (**3**) (7.40 µL, 72.9 µmol, 0.10 equiv) was added and the reaction stirred for additional 20 min at –78 °C. Caesium carbonate (261 mg, 802 µmol, 1.1 equiv) was added and the cooling bath was removed, the reaction mixture was allowed to warm to 23 °C and stirred for 1 h at this temperature. The reaction was quenched with hydrochloric acid (1 M, 10 mL) and the aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phases were dried over sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (dry load, pentane–Et_2O, 1:1 to Et_2O + 1% formic acid) to give **10a** (114 mg, 553 µmol, 76%) as brown solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.5 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 2H), 7.45 (s, 1H), 7.01 (s, 1H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 174.5, 166.0, 142.3, 136.3, 133.5, 129.3, 127.4, 107.2 ppm; IR (neat): 3296, 3027, 2918, 2849, 1614, 1597, 1578, 1500, 1490, 1446, 1394, 1314, 1265, 1248, 1203, 1182, 1175, 1098, 1074, 1001, 951, 909, 860, 790, 766, 700, 683, 658 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{10}H_7NO_2SNa$ $[M + Na]^+$: 228.0089; found: 228.0096; m.p. 201 °C (decomposition).

5-Hydroxy-2-(o-tolyl)-4*H*-1,3-thiazin-4-one (10b)



9b
C_8H_9NS (151.23)

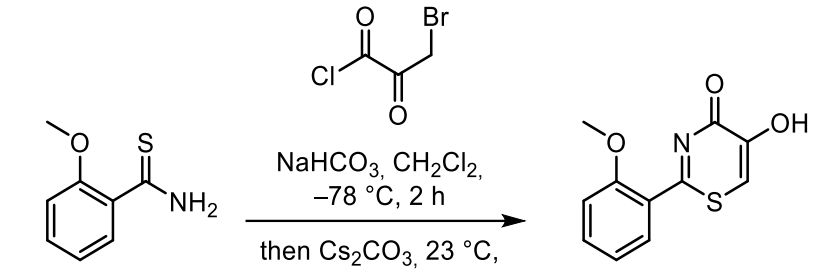
10b
$C_{11}H_9NO_2S$(219.26)

An oven-dried 25 mL round-bottom-flask equipped with a Teflon-coated magnetic stirrer bar was charged with thioamide **9b**[4] (100 mg, 661 µmol, 1.0 equiv) and dry CH_2Cl_2 (12 mL). Upon addition of sodium bicarbonate (139 mg, 1.65 mmol, 2.5 equiv), the suspension was cooled to –78 °C and 3-bromo-2-oxopropanoyl chloride (**3**) (67.4 µL, 661 µmol, 1.0 equiv) was added slowly. Because TLC-control showed incomplete conversion after 1.5 h at –78 °C, 3-bromo-2-oxopropanoyl chloride (**3**) (4.72 µL, 46.3 µmol, 0.07 equiv) was added and the reaction stirred for additional 30 min at –78 °C. Caesium carbonate (237 mg, 727 µmol, 1.2 equiv) was added and the cooling bath was removed, the reaction

mixture was allowed to warm to 23 °C and stirred for 45 min at this temperature. The reaction was quenched with hydrochloric acid (1 M, 10 mL) and the aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phases were dried over sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (dry load, pentane–Et_2O, 1:1 to Et_2O + 1% formic acid) to give **10b** (122 mg, 556 µmol, 85%) as beige solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.49–7.46 (m, 1H), 7.42 (td, *J* = 7.6, 1.3 Hz, 1H), 7.33–7.28 (m, 2H), 7.06 (s, 1H), 2.51 (s, 3H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 176.9, 165.4, 142.0, 136.8, 136.4, 131.8, 131.5, 129.1, 126.3, 108.9, 20.4 ppm; IR (neat): 3316, 3055, 2980, 2960, 2925, 2854, 1616, 1599, 1509, 1487, 1455, 1395, 1291, 1265, 1232, 1188, 1173, 1120, 938, 900, 829, 792, 759, 719, 681, 668 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{11}H_9NO_2SNa$ [M + Na]$^+$: 242.0246; found: 242.0248; m.p. 137–140 °C.

5-Hydroxy-2-(2-methoxyphenyl)-4*H*-1,3-thiazin-4-one (10c)



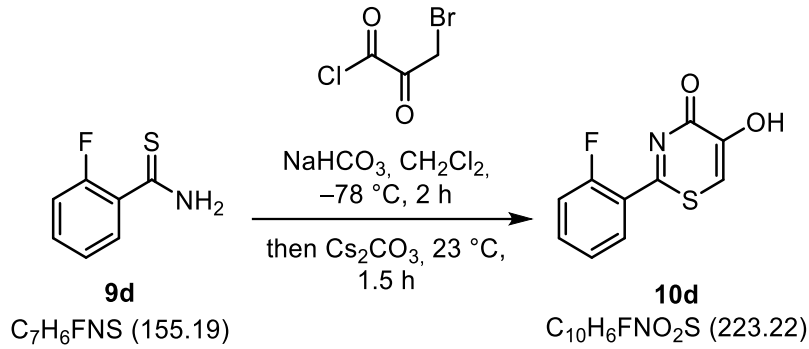
9c
C_8H_9NOS (167.23)

10c
$C_{11}H_9NO_3S$ (235.26)

An oven-dried 25 mL round-bottom-flask equipped with a Teflon-coated magnetic stirrer bar was charged with thioamide **9c**[5] (100 mg, 598 µmol, 1.0 equiv) and dry CH_2Cl_2 (10.8 mL). Upon addition of sodium bicarbonate (125.6 mg, 1.49 mmol, 2.5 equiv), the suspension was cooled to –78 °C and 3-bromo-2-oxopropanoyl chloride (**3**) (60.9 µL, 598 µmol, 1.0 equiv) was added slowly. Because TLC-control showed incomplete conversion after 1.5 h at –78 °C, 3-bromo-2-oxopropanoyl chloride (**3**) (6.09 µL, 59.8 µmol, 0.10 equiv) was added and the reaction stirred for additional 30 min at –78 °C. Caesium carbonate (312 mg, 957 µmol, 1.6 equiv) was added and the cooling bath was removed, the reaction mixture was allowed to warm to 23 °C and stirred for 15 h at this temperature. The reaction was quenched with hydrochloric acid (1 M, 10 mL) and the aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phases were dried over sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (dry load, pentane–ethyl acetate, 2:1 + 1% formic acid to pentane–ethyl acetate, 1:1 + 1% formic acid to pentane-ethyl acetate, 1:2 + 1% formic acid) to give **10c** (82.4 mg, 350 µmol, 59%) as dirty yellow solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.52 (ddd, *J* = 8.5, 7.4, 1.8 Hz, 1H), 7.10–7.07 (m, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 7.01 (s, 1H), 3.98 (s, 3H) ppm.; ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.9, 165.9, 158.5, 142.1, 134.2, 130.8, 124.9, 121.3, 111.9, 109.4, 55.9 ppm; IR (neat): 3247, 3087, 3052, 2957, 2920, 2851, 1611, 1595, 1485, 1478, 1438, 1396, 1317, 1285, 1249, 1218, 1197, 1161, 1119, 1013, 947, 910, 817, 788, 764 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{11}H_9NO_3SNa$ [M + Na]$^+$: 258.0201; found: 258.0243; m.p. 159 °C (decomposition).

2-(2-Fluorophenyl)-5-hydroxy-4*H*-1,3-thiazin-4-one (10d)



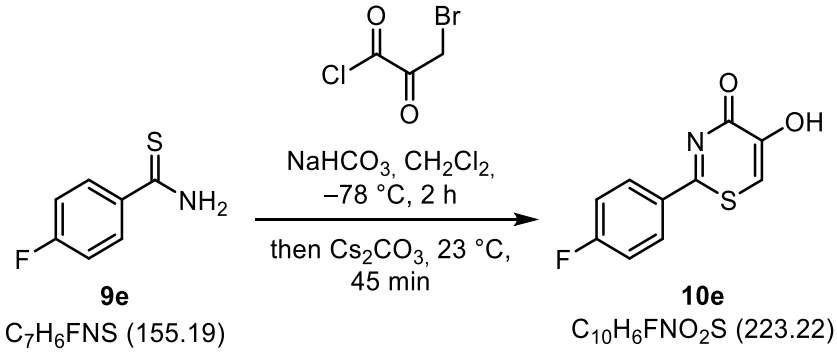
9d
C_7H_6FNS (155.19)

10d
$C_{10}H_6FNO_2S$ (223.22)

An oven-dried 25 mL round-bottom-flask equipped with a Teflon-coated magnetic stirrer bar was charged with thioamide **9d**[3] (100 mg, 644 µmol, 1.0 equiv) and dry CH_2Cl_2 (11.5 mL). Upon addition of sodium bicarbonate (135 mg, 1.61 mmol, 2.5 equiv), the suspension was cooled to –78 °C and 3-bromo-2-oxopropanoyl chloride (**3**) (65.6 µL, 644 µmol, 1.0 equiv) was added slowly. Because TLC-control showed incomplete conversion after 1.5 h at –78 °C, 3-bromo-2-oxopropanoyl chloride (**3**) (3.28 µL, 32.2 µmol, 0.05 equiv) was added and the reaction stirred for additional 30 min at –78 °C. Caesium carbonate (231 mg, 709 µmol, 1.1 equiv) was added and the cooling bath was removed, the reaction mixture was allowed to warm to 23 °C and stirred for 1.5 h at this temperature. The reaction was quenched with hydrochloric acid (1 M, 10 mL) and the aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phases were dried over sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (dry load, pentane–Et_2O, 1:1 + 1% formic acid to Et_2O + 1% formic acid) to give **10d** (104 mg, 467 µmol, 72%) as light brown solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.19 (t, *J* = 7.7 Hz, 1H), 7.59–7.54 (m, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.24–7.19 (m, 1H), 7.05 (s, 1H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.8 (d, *J* = 5.2 Hz), 165.7, 161.0 (d, *J* = 255.5 Hz), 142.4 (d, *J* = 1.3 Hz), 134.6 (d, *J* = 9.0 Hz), 130.6, 125.1 (d, *J* = 3.3 Hz), 124.1 (d, *J* = 10.4 Hz), 116.9 (d, *J* = 22.5 Hz), 108.3 (d, *J* = 7.6 Hz) ppm; IR (neat): 3284, 3033, 2980, 2921, 2851, 1592, 1575, 1484, 1450, 1392, 1306, 1270, 1226, 1200, 1176, 1105, 1031, 957, 914, 869, 854, 801, 790, 768, 723, 679, 665, 656 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{10}H_6FNO_2SNa$ $[M + Na]^+$: 246.0001; found: 246.0009; m.p. 166 °C (decomposition).

2-(4-Fluorophenyl)-5-hydroxy-4*H*-1,3-thiazin-4-one (10e)



9e
C_7H_6FNS (155.19)

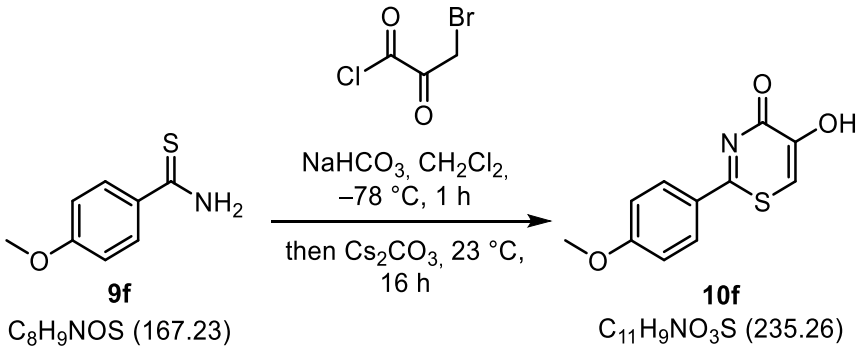
10e
$C_{10}H_6FNO_2S$ (223.22)

An oven-dried 25 mL round-bottom-flask equipped with a Teflon-coated magnetic stirrer bar was charged with thioamide **9e**[6] (100 mg, 644 µmol, 1.0 equiv) and dry CH_2Cl_2 (11.6 mL). Upon addition of sodium bicarbonate (135 mg, 1.61 mmol, 2.5 equiv), the suspension was cooled to –78 °C and 3-bromo-2-oxopropanoyl chloride (**3**) (65.6 µL, 644 µmol, 1.0 equiv) was added slowly. Because

TLC-control showed incomplete conversion after 1.5 h at –78 °C, 3-bromo-2-oxopropanoyl chloride (**3**) (6.56 µL, 64.4 µmol, 0.10 equiv) was added and the reaction stirred for additional 30 min at –78 °C. Caesium carbonate (231 mg, 709 µmol, 1.1 equiv) was added and the cooling bath was removed, the reaction mixture was allowed to warm to 23 °C and stirred for 45 min at this temperature. The reaction was quenched with hydrochloric acid (1 M, 10 mL) and the aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phases were dried over sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (dry load, pentane–Et_2O, 1:1 to pentane–Et_2O, 1:1 + 1% formic acid to Et_2O + 1% formic acid) to give **10e** (113 mg, 504 µmol, 78%) as beige solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.14–8.10 (m, 2H), 7.45 (s, 1H), 7.21–7.17 (m, 2H), 6.99 (s, 1H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 172.90, 166.07 (d, *J* = 255.9 Hz), 165.76, 142.18, 132.36 (d, *J* = 3.2 Hz), 129.65 (d, *J* = 9.4 Hz, 2C), 116.48 (d, *J* = 22.1 Hz, 2C), 106.67 ppm; IR (neat): 3289, 3058, 3030, 2924, 2852, 1741, 1683, 1615, 1600, 1513, 1493, 1412, 1392, 1300, 1234, 1202, 1179, 1159, 1123, 1102, 1012, 9523, 910, 839, 820, 808, 791, 760, 718, 685, 659 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{10}H_6FNO_2SNa$ [M + Na]$^+$: 246.0001; found: 246.0004; m.p. 216 °C (decomposition).

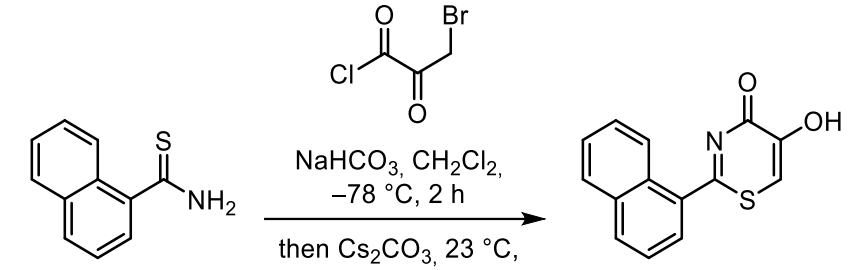
5-Hydroxy-2-(4-methoxyphenyl)-4*H*-1,3-thiazin-4-one (10f)



An oven-dried 25 mL round-bottom-flask equipped with a Teflon-coated magnetic stirrer bar was charged with thioamide **9f**[7] (100 mg, 598 µmol, 1.0 equiv) and dry CH_2Cl_2 (11 mL). Upon addition of sodium bicarbonate (126 mg, 1.50 mmol, 2.5 equiv), the suspension was cooled to –78 °C and 3-bromo-2-oxopropanoyl chloride (**3**) (60.9 µL, 598 µmol, 1.0 equiv) was added slowly. Because TLC-control showed incomplete conversion after 40 min at –78 °C, 3-bromo-2-oxopropanoyl chloride (**3**) (3.05 µL, 29.9 µmol, 0.05 equiv) was added and the reaction stirred for additional 20 min at –78 °C. Caesium carbonate (195 mg, 598 µmol, 1 equiv) was added and the cooling bath was removed, the reaction mixture was allowed to warm to 23 °C and stirred for 16 h at this temperature. The reaction was quenched with hydrochloric acid (1 M, 10 mL) and the aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phases were dried over sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (dry load, pentane–ethyl acetate, 1:2 to pentane–ethyl acetate, 1:2 + 1% formic acid) to give **10f** (99.3 mg, 422 µmol, 71%) as brown solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.7 Hz, 2H), 7.43 (s, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.93 (s, 1H), 3.89 (s, 3H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.7, 166.1, 164.2, 142.0, 129.4, 128.8, 114.7, 106.6, 55.8 ppm; IR (neat): 3297, 3026, 2921, 2850, 1602, 1574, 1508, 1485, 1418, 1394, 1322, 1308, 1258, 1196, 1175, 1114, 1035, 953, 910, 829, 793, 725, 696, 660 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{11}H_9NO_3SNa$ [M + Na]$^+$: 258.0201; found: 258.0216; m.p. 209 °C (decomposition).

5-Hydroxy-2-(naphthalen-1-yl)-4*H*-1,3-thiazin-4-one (10g)



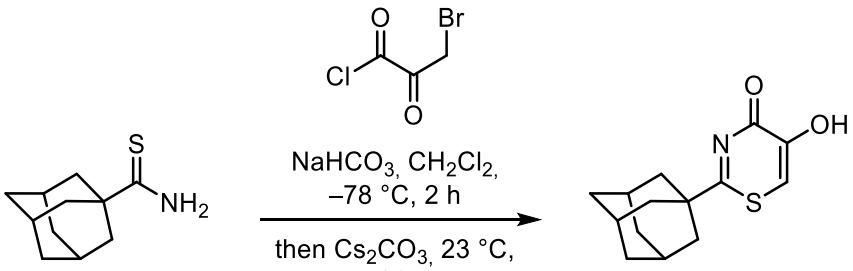
9g
$C_{11}H_9NS$ (187.26)

10g
$C_{14}H_9NO_2S$ (255.29)

An oven-dried 25 mL round-bottom-flask equipped with a Teflon-coated magnetic stirrer bar was charged with thioamide **9g**[8] (100 mg, 534 µmol, 1.0 equiv) and dry CH_2Cl_2 (9.5 mL). Upon addition of sodium bicarbonate (112 mg, 1.33 mmol, 2.5 equiv), the suspension was cooled to –78 °C and 3-bromo-2-oxopropanoyl chloride (**3**) (54.4 µL, 534 µmol, 1.0 equiv) was added slowly. The reaction mixture was stirred for 2 h at –78 °C. Caesium carbonate (191 mg, 587 µmol, 1.1 equiv) was added and the cooling bath was removed, the reaction mixture was allowed to warm to 23 °C and stirred for 1 h at this temperature. The reaction was quenched with hydrochloric acid (1 M, 10 mL) and the aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phases were dried over sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (dry load, pentane–Et_2O, 3:2 + 1% formic acid to Et_2O + 1% formic acid to ethyl acetate + 1% formic acid) to give **10g** (104 mg, 405 µmol, 76%) as brown solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.3 Hz, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.74 (d, *J* = 7.1 Hz, 1H), 7.61 – 7.55 (m, 3H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.12 (s, 1H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 176.2, 165.4, 142.2, 134.1, 134.0, 132.8, 129.8, 128.6, 128.2, 128.2, 127.1, 125.1, 124.8, 109.4 ppm; IR (neat): 3293, 3056, 3011, 1610, 1506, 1395, 1269, 1238, 1191, 1095, 929, 903, 801, 773, 754 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_9NO_2SNa$ [M + Na]$^+$: 278.0252; found: 278.0265; m.p. 165 °C (decomposition).

2-((3r,5r,7r)-adamantan-1-yl)-5-hydroxy-4*H*-1,3-thiazin-4-one (10h)



9h
$C_{11}H_{17}NS$ (195.32)

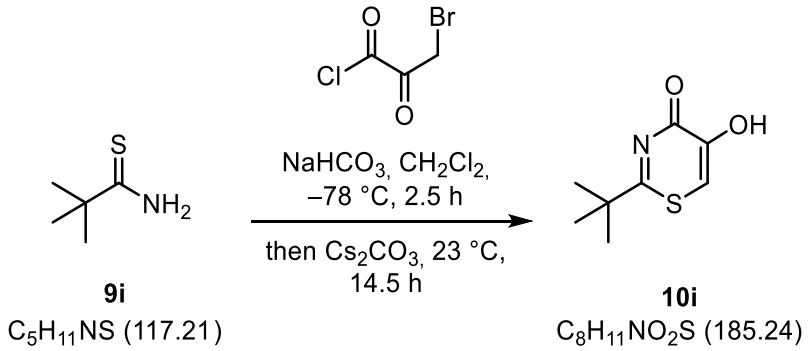
10h
$C_{14}H_{17}NO_2S$ (263.36)

An oven-dried 25 mL round-bottom-flask equipped with a Teflon-coated magnetic stirrer bar was charged with thioamide **9h**[9] (25.0 mg, 128 µmol, 1.0 equiv) and dry CH_2Cl_2 (2.3 mL). Upon addition of sodium bicarbonate (26.9 mg, 320 µmol, 2.5 equiv), the suspension was cooled to –78 °C and 3-bromo-2-oxopropanoyl chloride (**3**) (13.0 µL, 128 µmol, 1.0 equiv) was added slowly. Because TLC-control showed incomplete conversion after 1.5 h at –78 °C, 3-bromo-2-oxopropanoyl chloride (**3**) (1.30 µL, 12.8 µmol, 0.10 equiv) was added and the reaction stirred for additional 30 min at –78 °C. Caesium carbonate (45.9 mg, 141 µmol, 1.1 equiv) was added and the cooling bath was removed, the reaction

mixture was allowed to warm to 23 °C and stirred for 1 h at this temperature. The reaction was quenched with hydrochloric acid (1 M, 10 mL) and the aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phases were dried over sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (dry load, pentane–Et_2O, 2:1 + 1% formic acid to Et_2O + 1% formic acid) to give **10h** (24.0 mg, 91.1 µmol, 71%) as yellow solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.37 (s, 1H), 6.96 (s, 1H), 2.13 (s, 3H), 2.06 (s, 6H), 1.81–1.71 (m, 6H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 190.1, 165.8, 142.1, 107.8, 45.8, 41.2 (3C), 36.4 (3C), 28.5 (3C) ppm; IR (neat): 3312, 3059, 2906, 2849, 1611, 1594, 1583, 1498, 1471, 1451, 1412, 1397, 1367, 1342, 1268, 1242, 1216, 1200, 1159, 1102, 995, 909, 832, 794, 684 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{17}NO_2SNa$ [M + Na]$^+$: 286.0878; found: 286.0880; m.p. 203 °C (decomposition).

2-(tert-butyl)-5-hydroxy-4*H*-1,3-thiazin-4-one (10i)



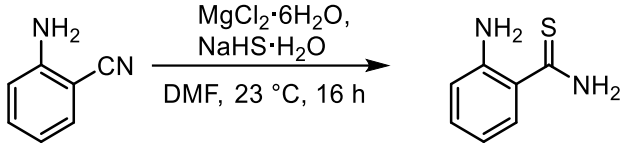
9i
$C_5H_{11}NS$ (117.21)

10i
$C_8H_{11}NO_2S$ (185.24)

An oven-dried 25 mL round-bottom-flask equipped with a Teflon-coated magnetic stirrer bar was charged with thioamide **9i**[10] (100 mg, 853 µmol, 1.0 equiv) and dry CH_2Cl_2 (15.5 mL). Upon addition of sodium bicarbonate (179 mg, 2.13 mmol, 2.5 equiv), the suspension was cooled to –78 °C and 3-bromo-2-oxopropanoyl chloride (**3**) (95.6 µL, 938 µmol, 1.1 equiv) was added slowly. Because TLC-control showed incomplete conversion after 2 h at –78 °C, 3-bromo-2-oxopropanoyl chloride (4.35 µL, 42.7 µmol, 0.05 equiv) was added and the reaction stirred for additional 30 min at –78 °C. Caesium carbonate (306 mg, 938 µmol, 1.1 equiv) was added and the cooling bath was removed, the reaction mixture was allowed to warm to 23 °C and stirred for 14.5 h at this temperature. The reaction was quenched with hydrochloric acid (1 M, 10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried over sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (dry load, pentane-ethyl acetate, 2:1 + 1% formic acid) to give **10i** (99.5 mg, 537 µmol, 63%) as beige solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.36 (s, 1H), 6.94 (s, 1H), 1.42 (s, 9H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 189.8, 165.7, 141.9, 107.6, 44.0, 29.4 (3C) ppm; IR (neat): 3310, 3044, 2962, 2930, 2867, 1616, 1599, 1584, 1502, 1477, 1455, 1405, 1365, 1274, 1246, 1201, 1178, 1040, 1011, 937, 912, 861, 834, 795, 670, 661 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_8H_{11}NO_2SNa$ [M + Na]$^+$: 208.0402; found: 208.0408; m.p. 137.0–139 °C.

2-Aminobenzothioamide (11)[2]



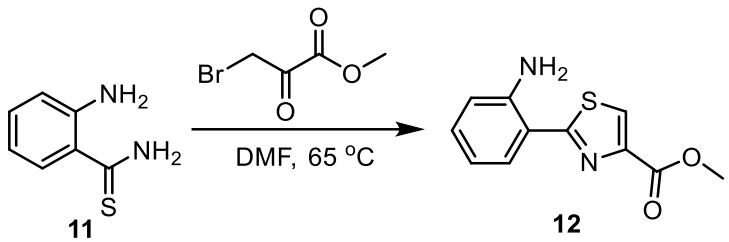
2-aminobenzonitrile
$C_7H_6N_2$ (118.14)

11
$C_7H_8N_2S$ (152.22)

An oven-dried 50 mL round-bottom-flask equipped with a Teflon-coated magnetic stirrer bar was charged with 2-aminobenzonitrile (1.00 g, 8.47 mmol, 1.0 equiv) and *N*,*N*-dimethylformamide (22.0 mL). This mixture was stirred at 23 °C and magnesium chloride hexahydrate (1.72 g, 8.47 mmol, 1.0 equiv) was added in portions until it was dissolved completely (~15 min). Sodium hydrosulfide monohydrate (1.25 g, 16.9 mmol, 2.0 equiv) was added and the reaction mixture was stirred for 16 h at 23 °C until TLC showed complete consumption of the starting material. The reaction was diluted with water (70 mL) and brine (10 mL) and extracted with ethyl acetate (4 × 50 mL). The combined organic phases were washed with brine (3 × 50 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (dry load, pentane–ethyl acetate, 3:1 to 2:1) to give the product **11** (1.25 g, 8.24 mmol, 97%) as a yellow solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.25 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.14 (td, *J* = 7.8, 1.5 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 6.65 (t, *J* = 8.1 Hz, 1H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 203.4, 147.7, 132.2, 127.9, 126.3, 118.4, 117.9 ppm. The spectra correlate with the literature data.[11]

Methyl 2-(2-aminophenyl)thiazole-4-carboxylate (12)



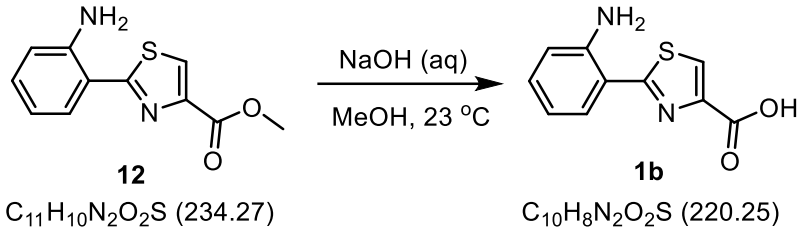
11
$C_7H_8N_2S$ (152.22)

12
$C_{11}H_{10}N_2O_2S$ (234.27)

To a solution of **11** (70.0 mg, 460 µmol, 1.0 equiv) in DMF (7 mL) was added methyl bromopyruvate (49.0 µL, 460 µmol, 1.0 equiv). The mixture was stirred under argon at 65 °C for 2.5 h. The reaction was diluted with water (20 mL) and extracted with ethyl acetate (4 × 15 mL). The combined organic phases were washed with brine (2 × 20 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (pentane–ethyl acetate, 4:1) to give the product **12** (55.9 mg, 239 µmol, 52%) as a yellow solid.

^{1}H NMR (600 MHz, CD_3OD) δ 8.27 (s, 1H), 7.61 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.17 (ddd, *J* = 8.3, 7.1, 1.5 Hz, 1H), 7.10 (s, 2H), 6.85 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.66 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 3.94 (s, 3H) ppm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 7.10 (s, 2H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.62 (t, *J* = 7.5 Hz, 1H), 3.87 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.3, 161.0, 146.7, 145.4, 131.4, 129.0, 126.9, 116.5, 115.7, 113.0, 52.2 ppm; HRMS (ESI): *m/z* calcd for $C_{11}H_{11}N_2O_2S$ $[M + H]^+$: 235.0536; found: 235.0538.

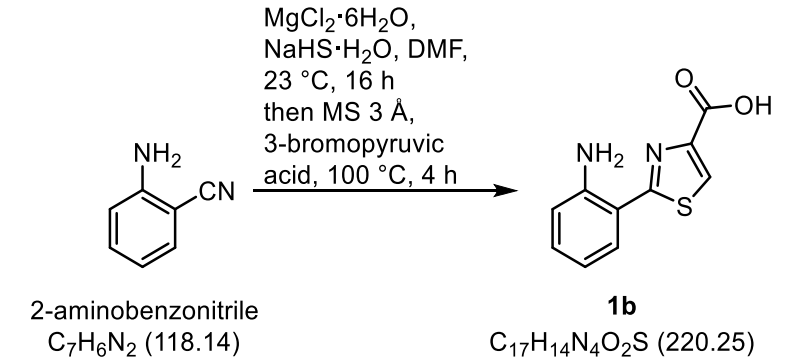
2-(2-Aminophenyl)thiazole-4-carboxylic acid (1b)



A solution of **12** (50 mg, 202 µmol, 1.0 equiv) in methanol (2 mL) was treated with a solution of NaOH (100 mg) in water (1 mL) added dropwise over 1 min and the resulting solution was stirred at 23 °C for 1 h. The pH was adjusted to ~6 by concentrated hydrochloric acid. Then, the methanol was removed under reduced pressure and 10 mL of water was added. It was extracted by ethyl acetate (2 × 30 mL). The organic layer was concentrated. The residue was purified by silica gel column chromatography (hexanes–ethyl acetate, 2:1) to yield **1b** (39 mg, 177 µmol, 88%).

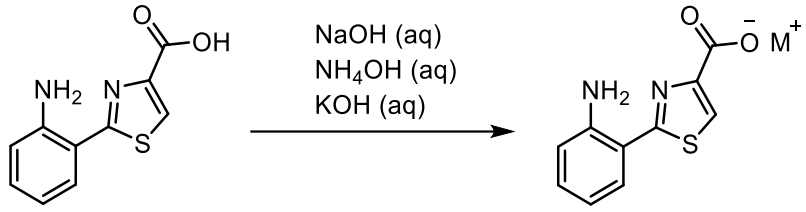
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 7.13 (s, 2H), 6.84 (d, J = 8.2 Hz, 1H), 6.61 (t, J = 7.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.0, 162.1, 147.2, 146.7, 131.3, 128.9, 126.0, 116.5, 115.6, 113.2 ppm; HRMS (ESI): *m/z* calcd for $C_{10}H_9N_2O_2S$ $[M + H]^+$: 221.0379; found: 221.0382.

2-(2-Aminophenyl)thiazole-4-carboxylic acid (1b)



An oven-dried 10 mL round-bottom-flask equipped with a Teflon-coated magnetic stirrer bar was charged with 2-aminobenzonitrile (25.0 mg, 212 µmol, 1.0 equiv) and *N*,*N*-dimethylformamide (0.55 mL). This mixture was stirred at 23 °C and magnesium chloride hexahydrate (43.0 g, 212 µmol, 1.0 equiv) was added in portions until it was dissolved completely (~15 min). Sodium hydrosulfide monohydrate (31.4 mg, 423 µmol, 2.0 equiv) was added and the reaction mixture was stirred for 20 h at 23 °C until TLC showed complete consumption of the starting material. The reaction mixture was diluted with *N*,*N*-dimethylformamide (4.5 mL) and molecular sieve (3 Å, 305 mg) was added. After stirring for 30 min at 23 °C 3-bromopyruvic acid (72.8 mg, 423 µmol, 2.0 equiv) was added and the reaction was stirred for 4 h at 100 °C. The reaction was quenched with sat. ammonium chloride solution (40 mL) and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic phases were washed with brine (2 × 50 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (pentane–Et_2O, 1:1 + 0.5% formic acid to pentane–Et_2O, 1:1 + 0.5% formic acid). To avoid side products toluene (50 mL) was added to the column fractions before removal of the solvent under reduced pressure to give the product **3** (17.3 mg, 78.5 µmol, 37%) as a yellow solid. The analytical data correlate with the saponification product **1b** form the stepwise protocol.

Preparation of different salts (1b-Na, 1b-cNH$_4$, 1b-K)

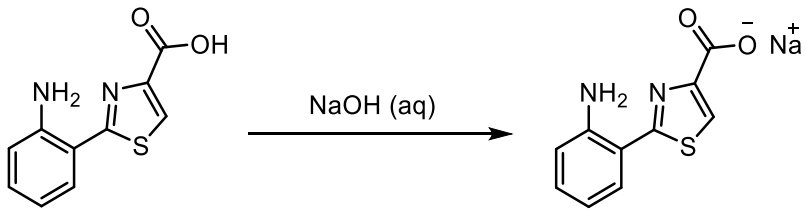


1b
$C_{17}H_{14}N_4O_2S$ (220.25)

1b-Na, 1b-NH$_4$, 1b-K

A solution of **1b** (10 mg for each salt) in DMSO-d_6 (0.5 mL) was treated with 50 µL of 2 M NaOH, 28%-30% ammonium hydroxide or 2 M KOH and the resulting solutions were used for the NMR experiments.

Preparation of the sodium salt (1b-Na, water was removed)

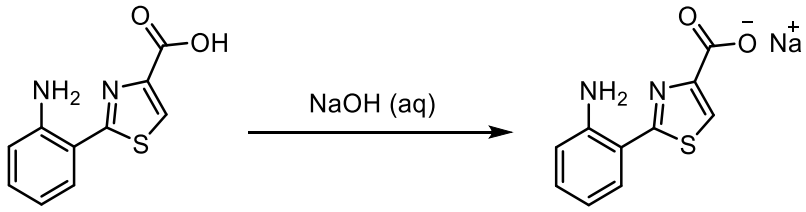


1b
$C_{17}H_{14}N_4O_2S$ (220.25)

1b-Na

To a suspension of **1b** (3.05 mg, 13.8 µmol, 1 equiv) in water (0.1 mL) was added 2 M NaOH (6.93 µL, 13.8 µmol, 1 equiv). The solvent was removed under reduced pressure with a rotary evaporator and the residue was then dried in high vacuum at 45 °C for 15 h. The NMR sample was prepared by dissolving **1b-Na** in dry DMSO-d_6.

Preparation of the sodium salt (1b-Na) with different equivalents of NaOH (aqueous, 6 M)

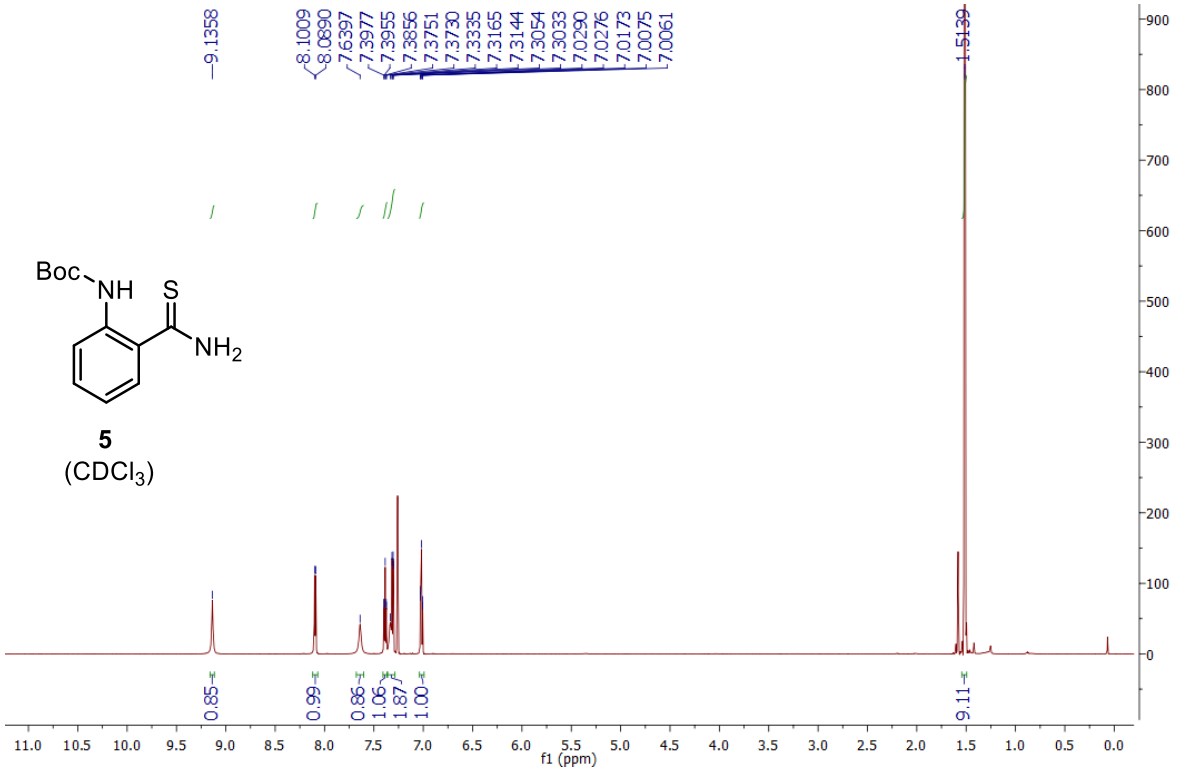


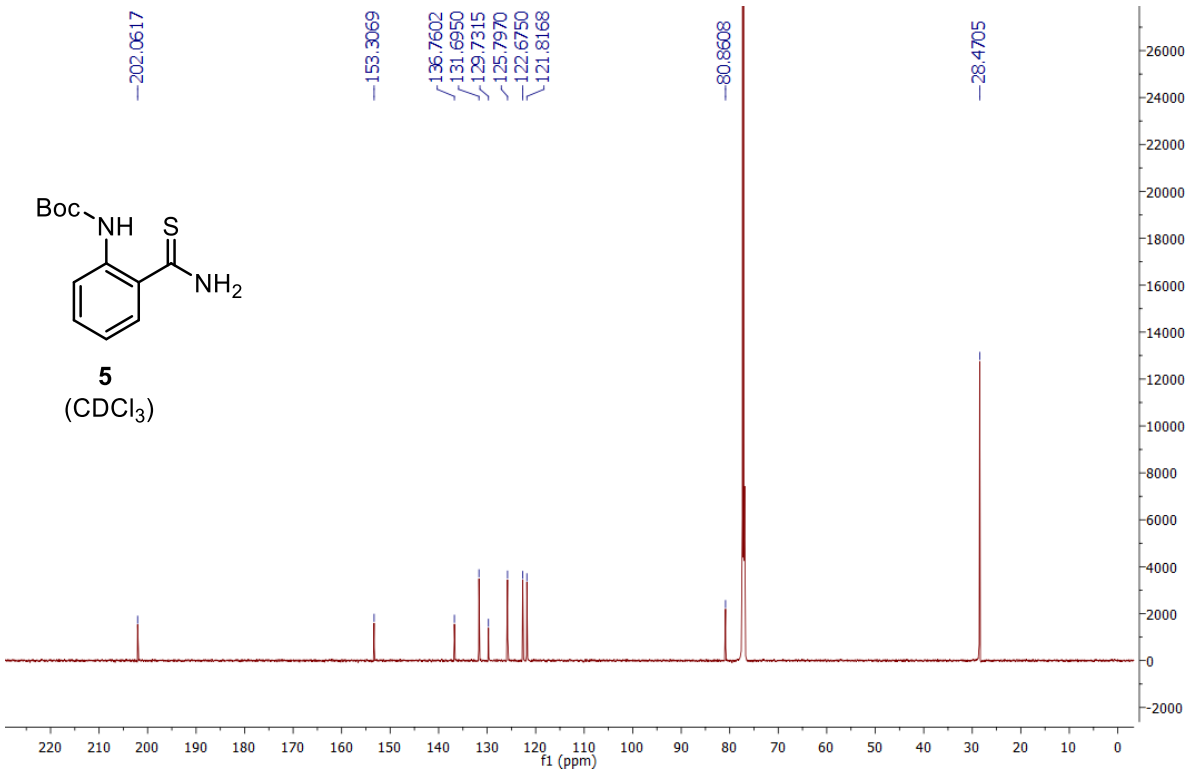
1b
$C_{17}H_{14}N_4O_2S$ (220.25)

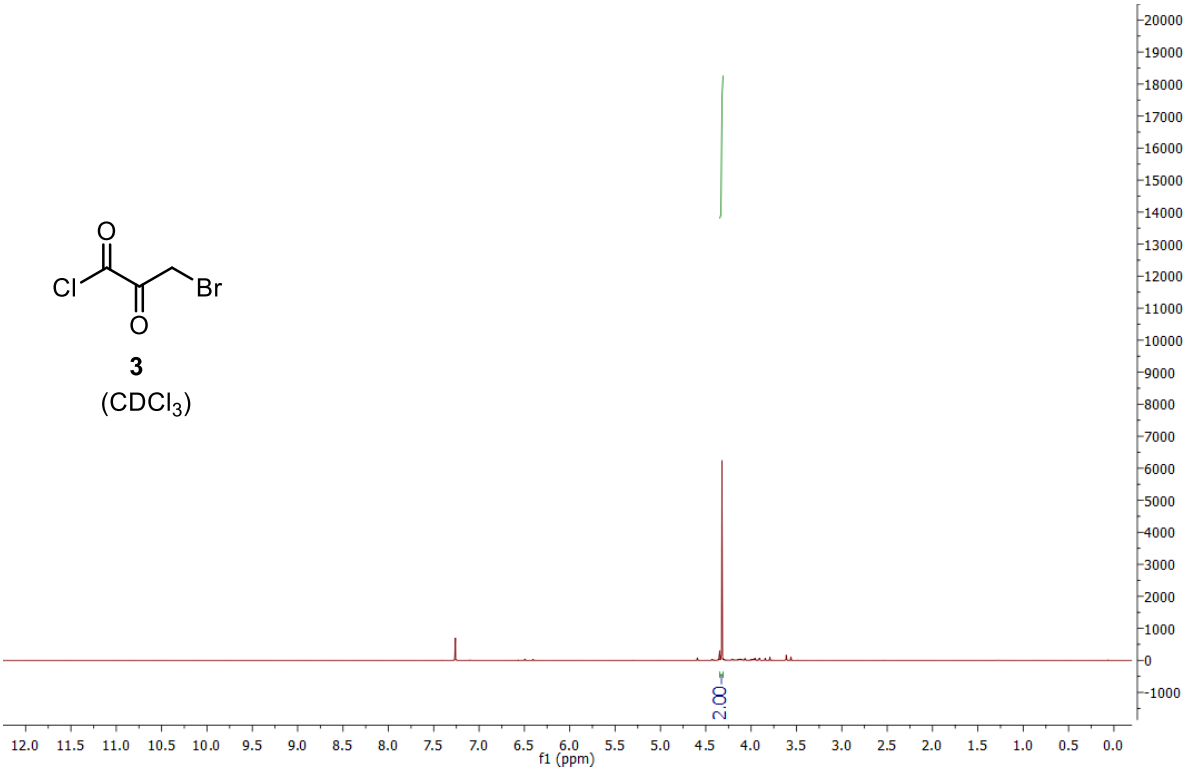
1b-Na

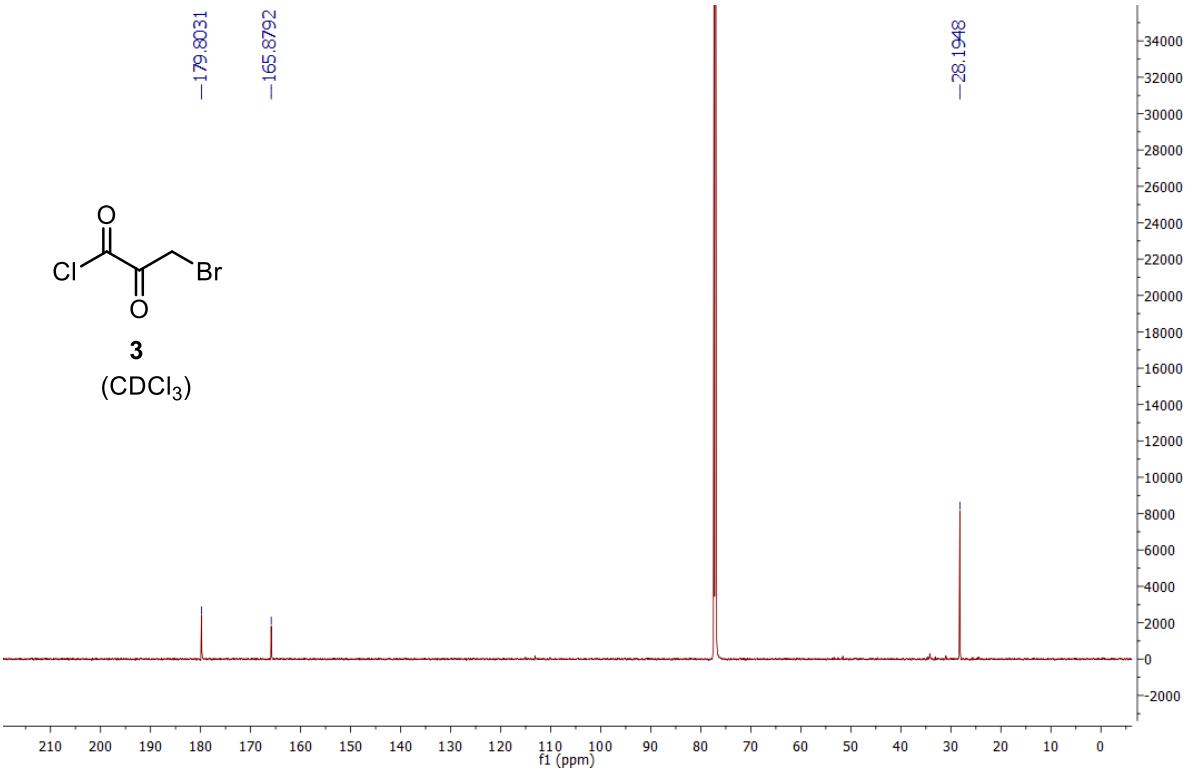
A solution of **1b** (15 mg) in DMSO-d_6 (530 µL) was treated with 0.2, 0.4, 0.6, 0.8, 1.0, and 2.0 equivalents of NaOH (aqueous, 6 M), respectively, and the resulting solutions were used for the NMR experiments.

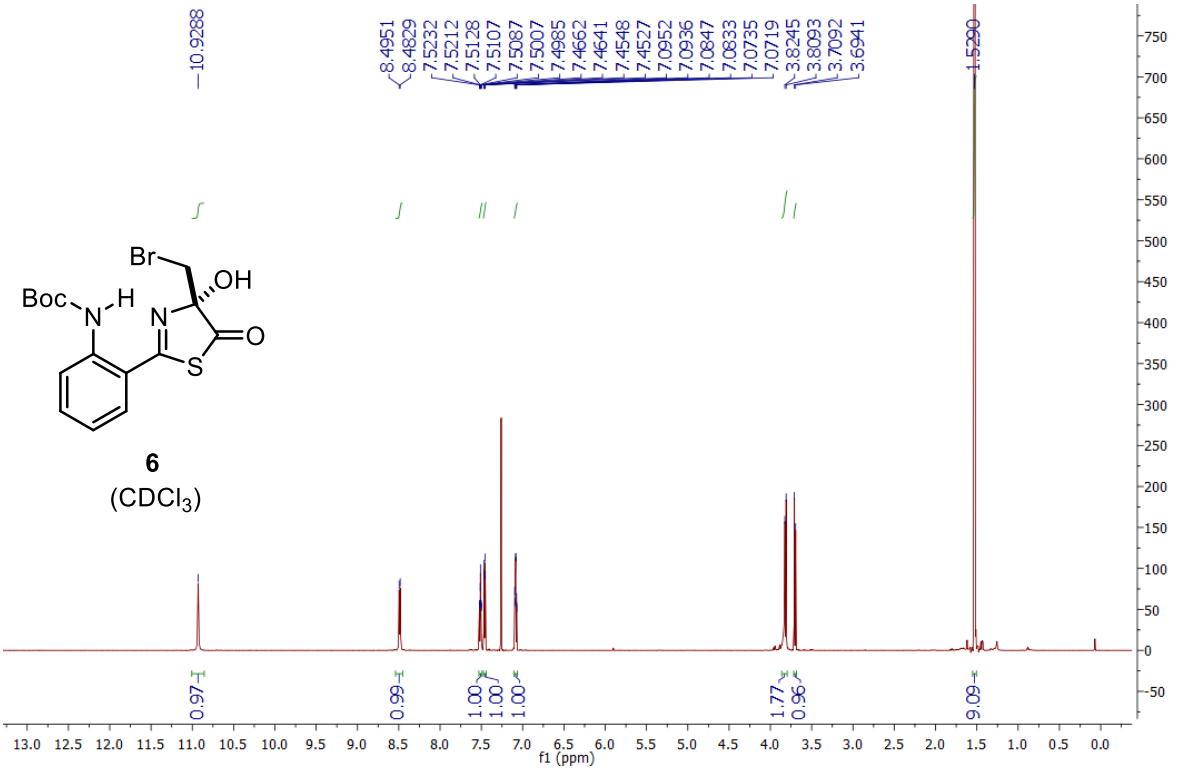
NMR Spectra


9.1358
8.1009
8.0890
7.6397
7.3977
7.3955
7.3856
7.3751
7.3730
7.3335
7.3165
7.3144
7.3054
7.3033
7.0290
7.0276
7.0173
7.0075
7.0061
1.5139
Boc
NH
S
NH2
5
(CDCl3)
0.85
0.99
0.86
1.06
1.87
1.00
9.11
f1 (ppm)


202.0617
153.3069
136.7602
131.6950
129.7315
125.7970
122.6750
121.8168
80.8608
28.4705
Boc
NH
S
NH2
5
(CDCl3)
f1 (ppm)

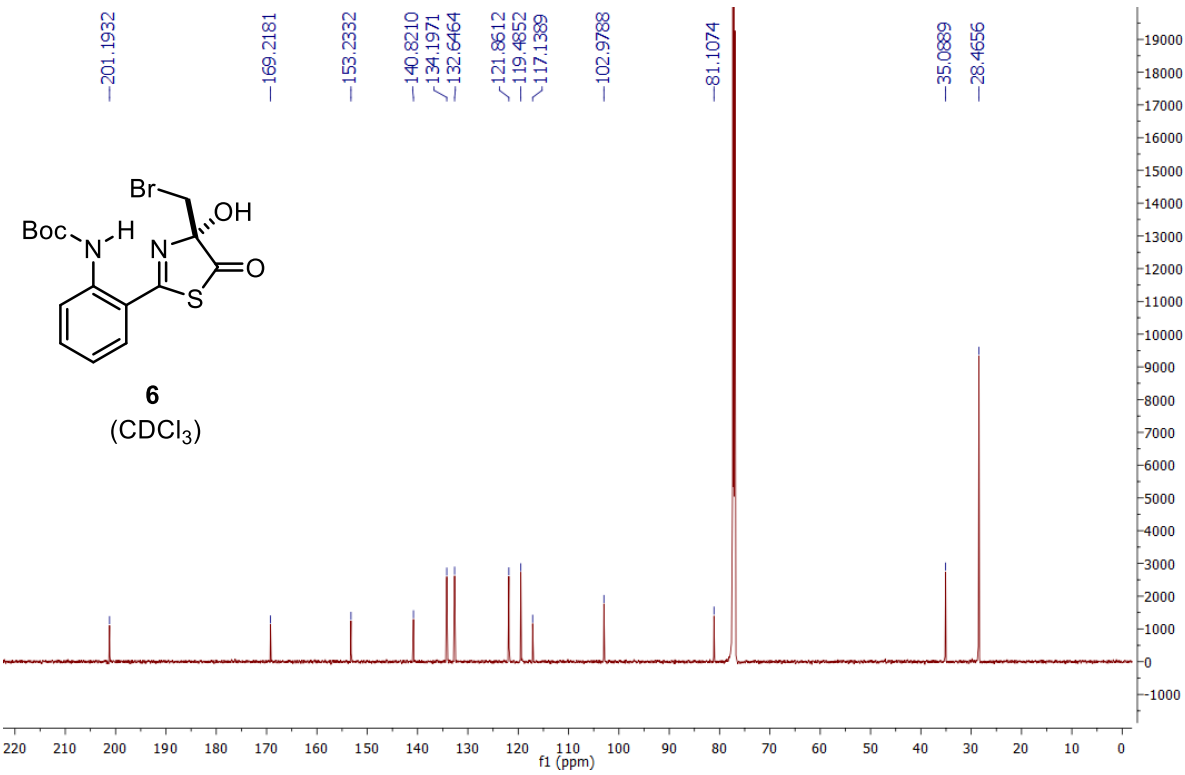

Cl
Br
O
O
3
(CDCl3)
2.00
f1 (ppm)


179.8031
165.8792
28.1948
Cl
Br
O
O
3
(CDCl3)
f1 (ppm)



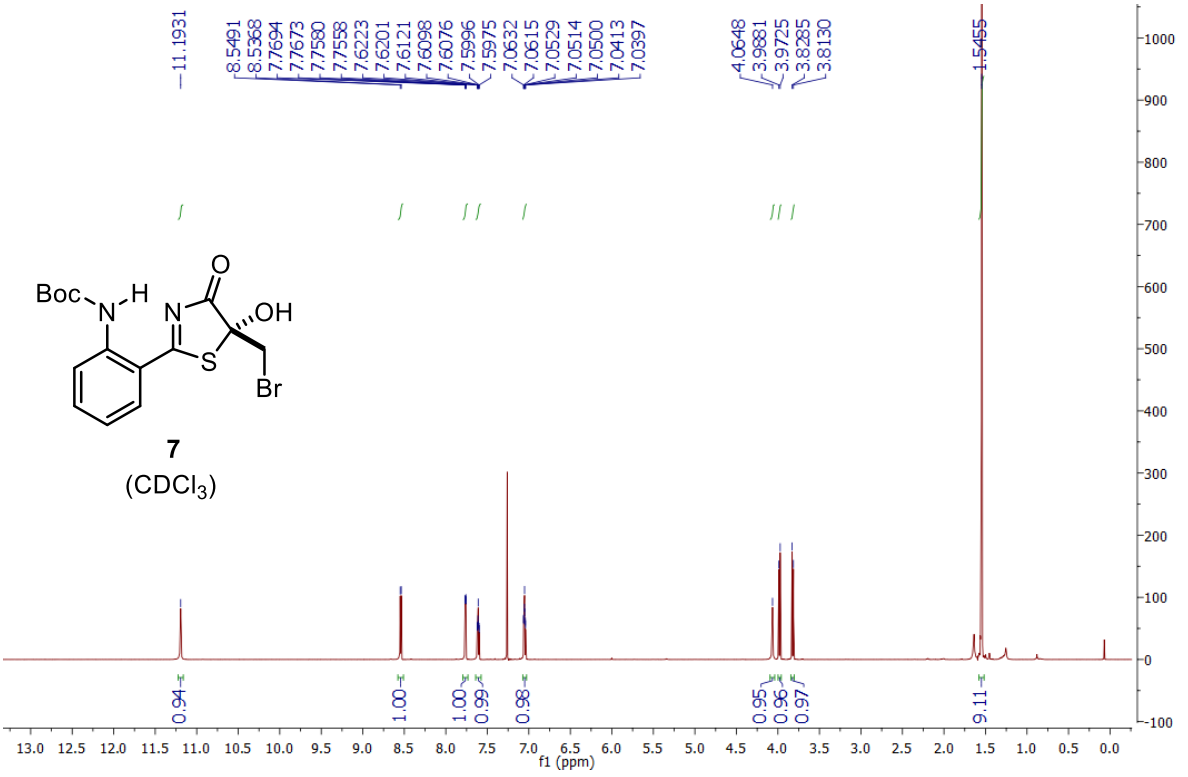
6

($CDCl_3$)



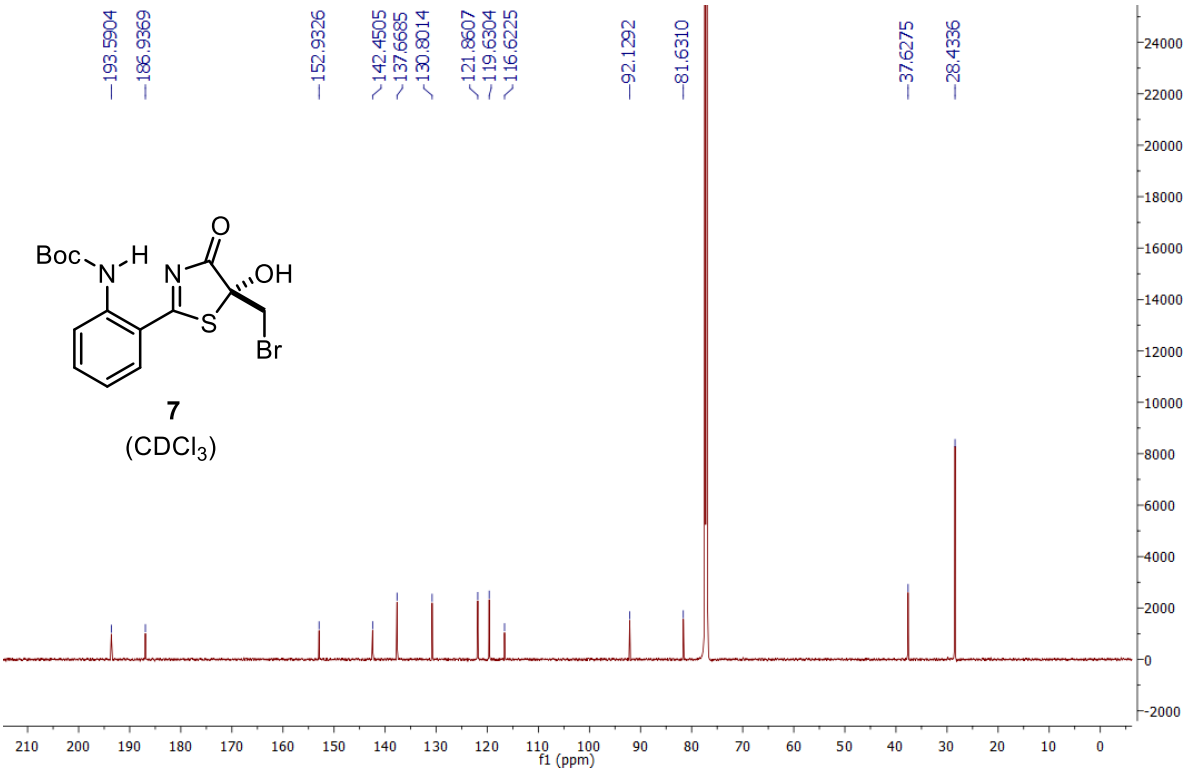
6

($CDCl_3$)



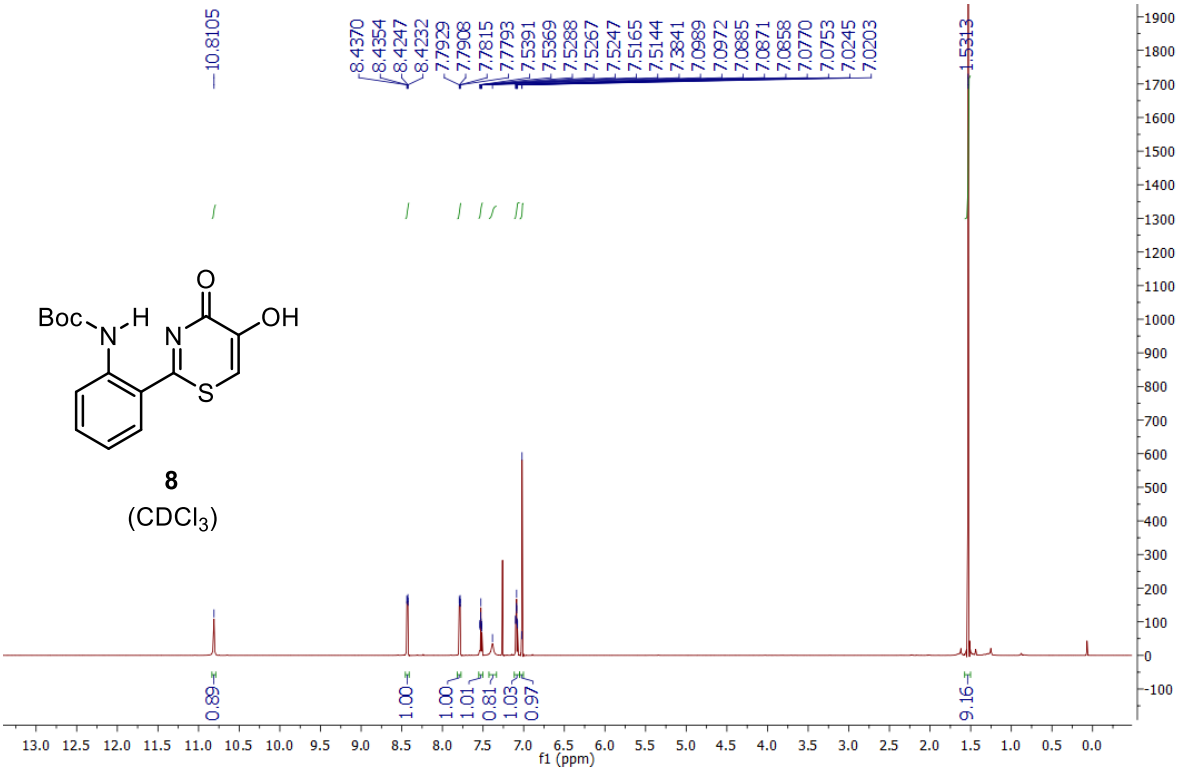
7

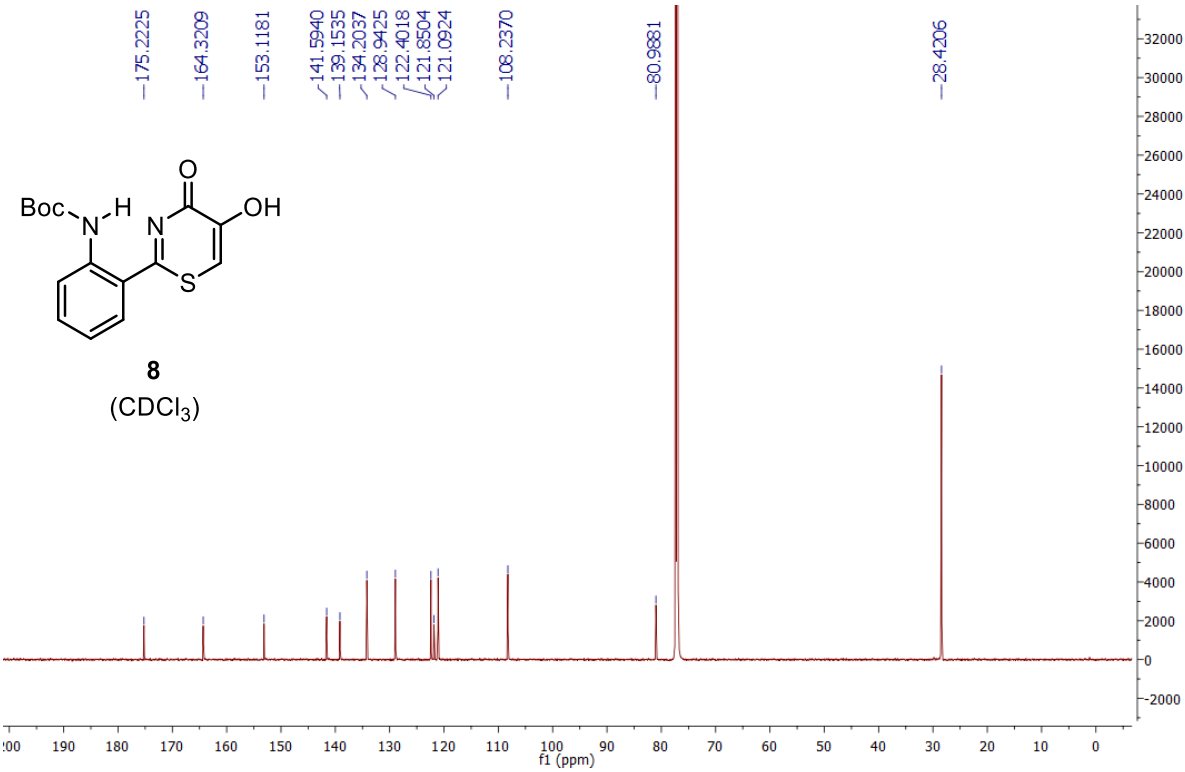
$(CDCl_3)$

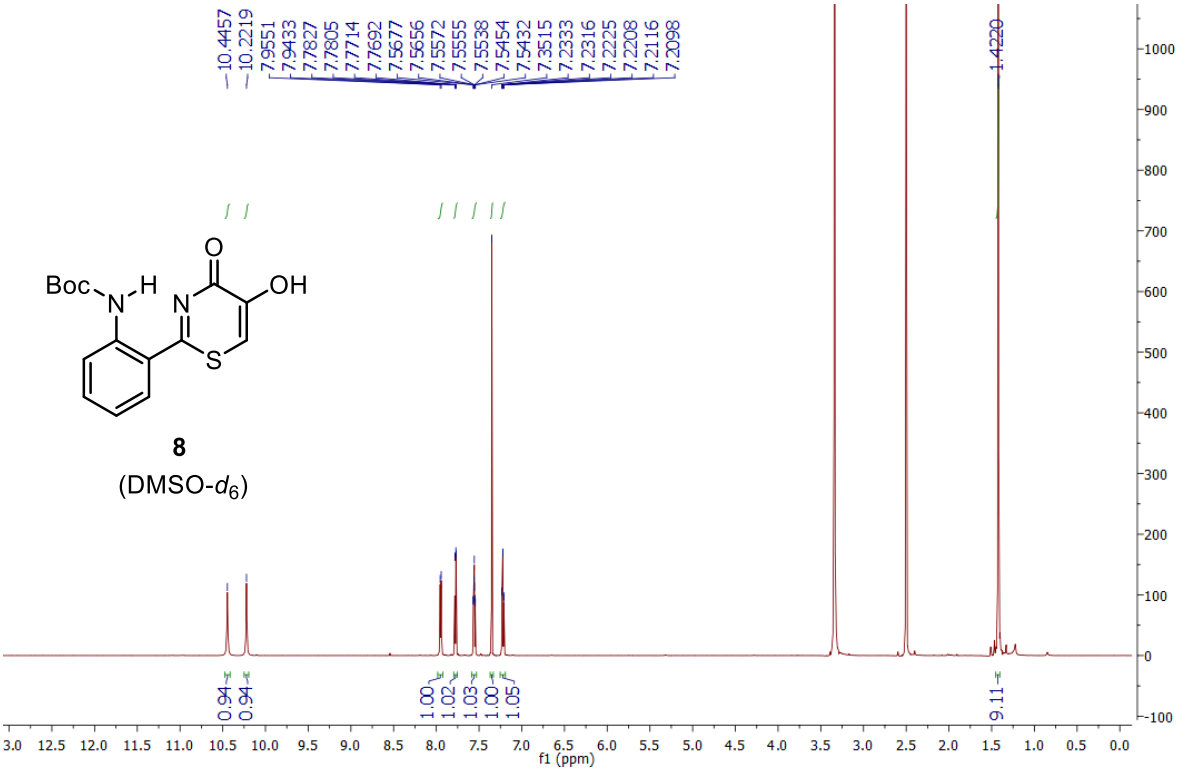


7

$(CDCl_3)$

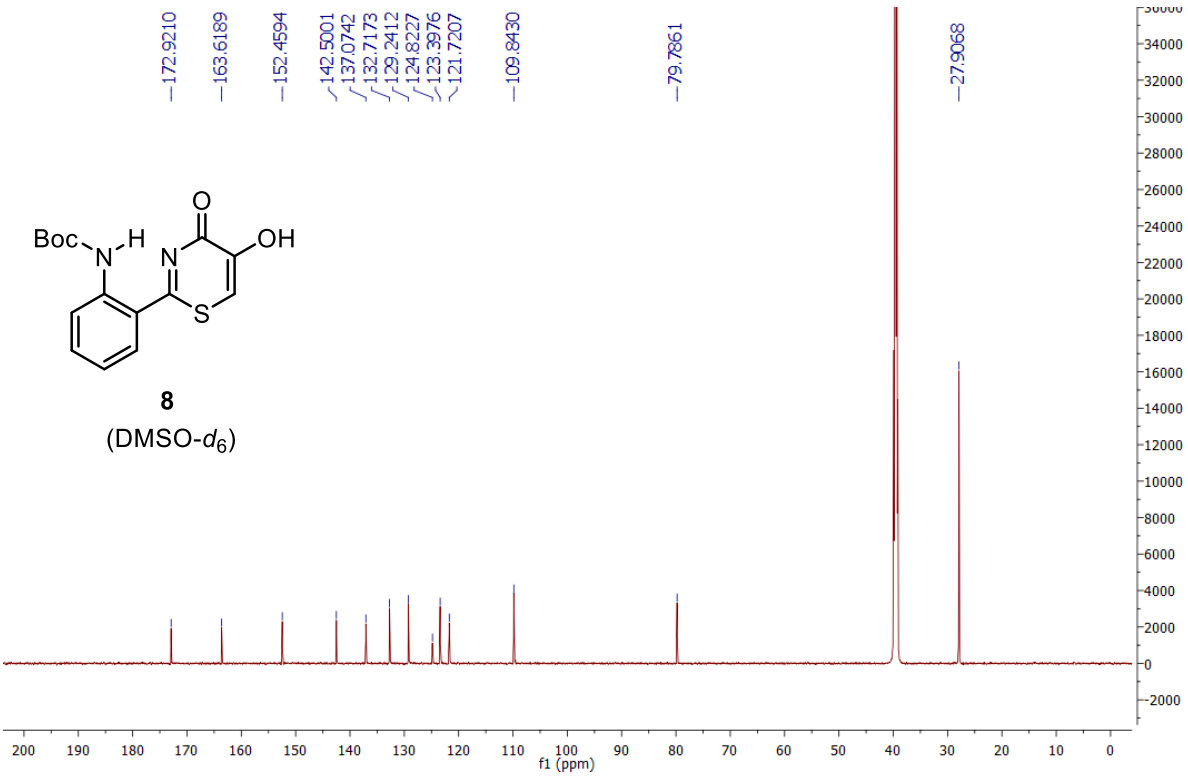

10.8105
8.4370
8.4354
8.4247
8.4232
7.7929
7.7908
7.7815
7.7793
7.5391
7.5369
7.5288
7.5267
7.5247
7.5165
7.5144
7.3841
7.0989
7.0972
7.0885
7.0871
7.0858
7.0770
7.0753
7.0245
7.0203
1.5313
Boc
N
H
N
O
OH
S
8
(CDCl3)
0.89
1.00
1.00
1.01
0.81
1.03
0.97
9.16
f1 (ppm)


175.2225
164.3209
153.1181
141.5940
139.1535
134.2037
128.9425
122.4018
121.8504
121.0924
108.2370
80.9881
28.4206
Boc
N
H
N
O
OH
S
8
(CDCl3)
f1 (ppm)



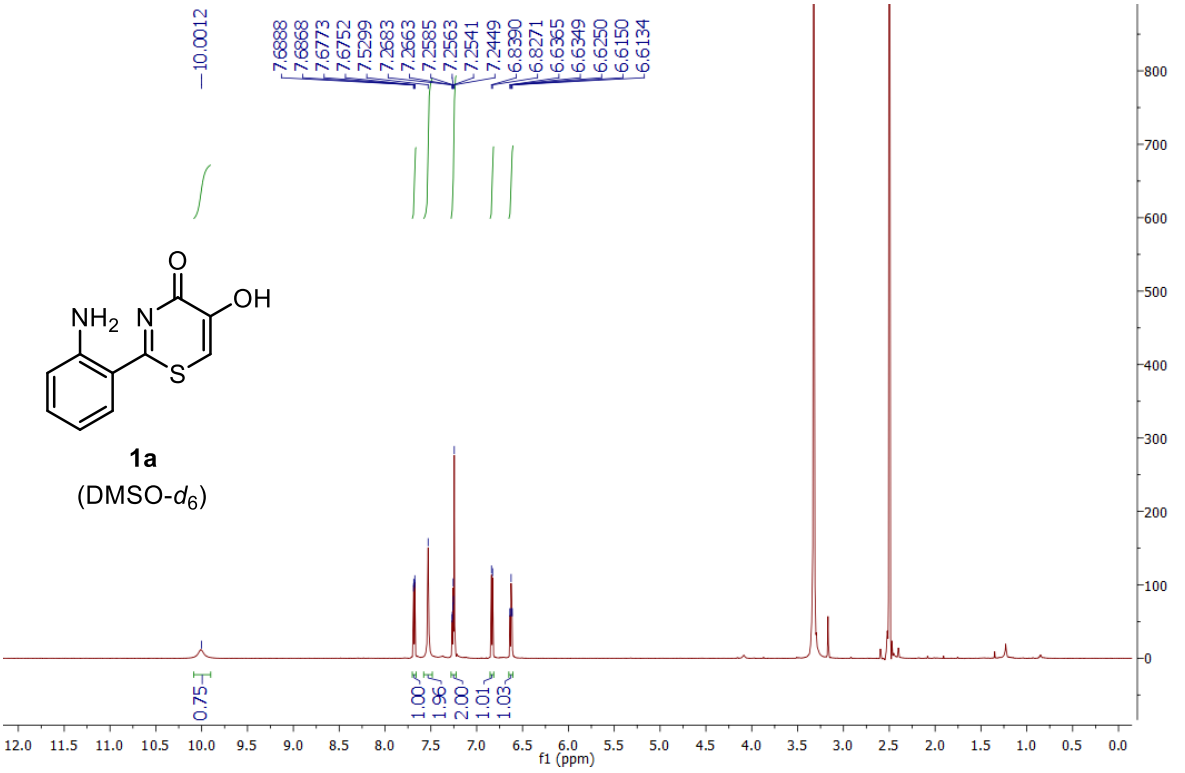
8

(DMSO-d_6)



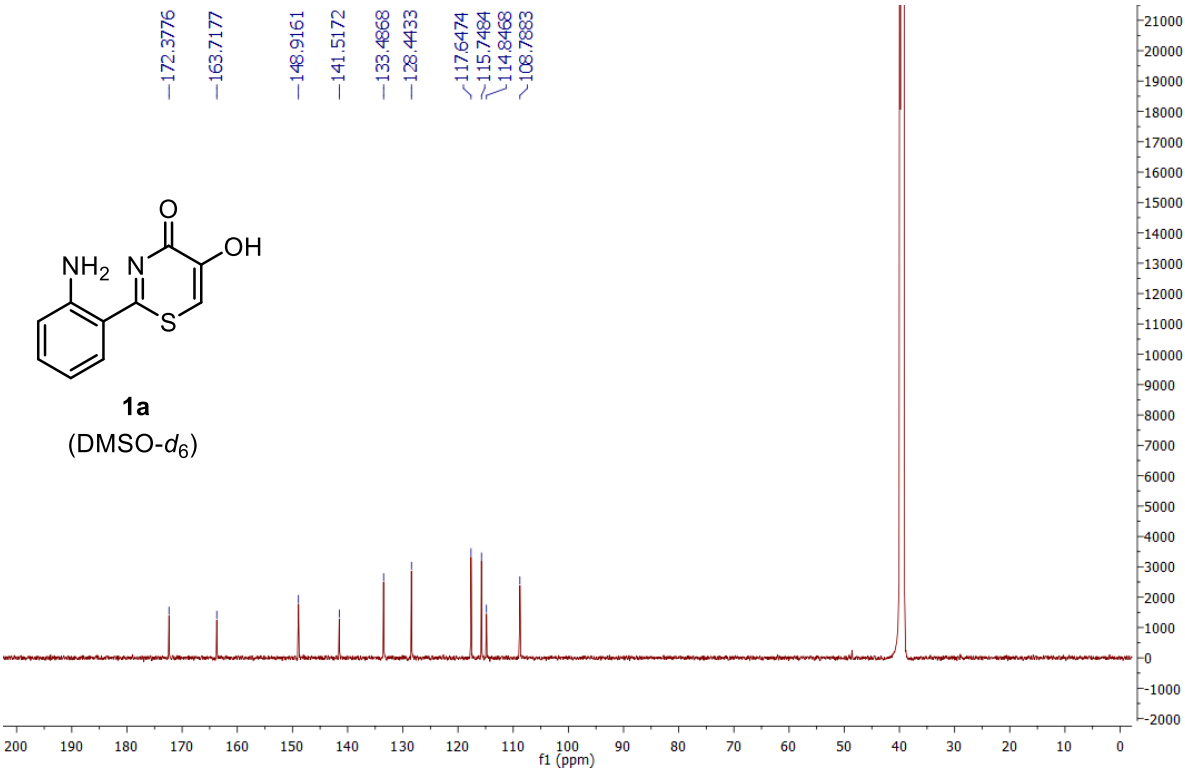
8

(DMSO-d_6)



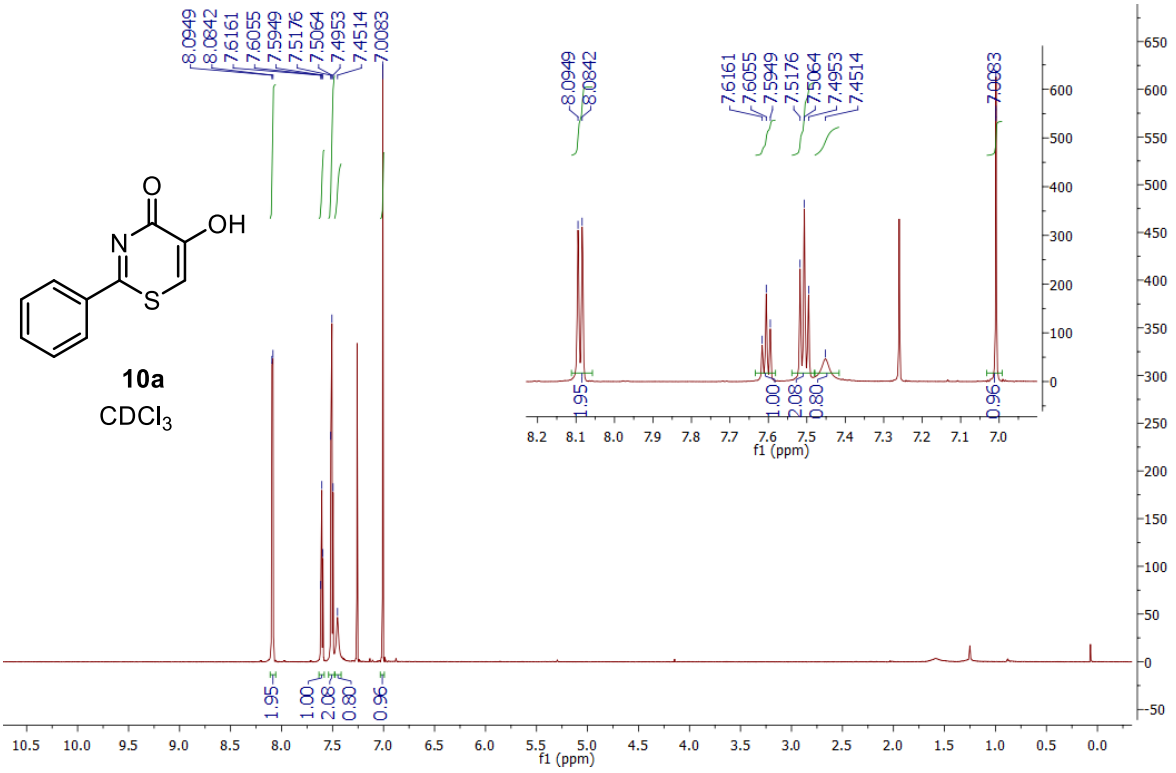
1a

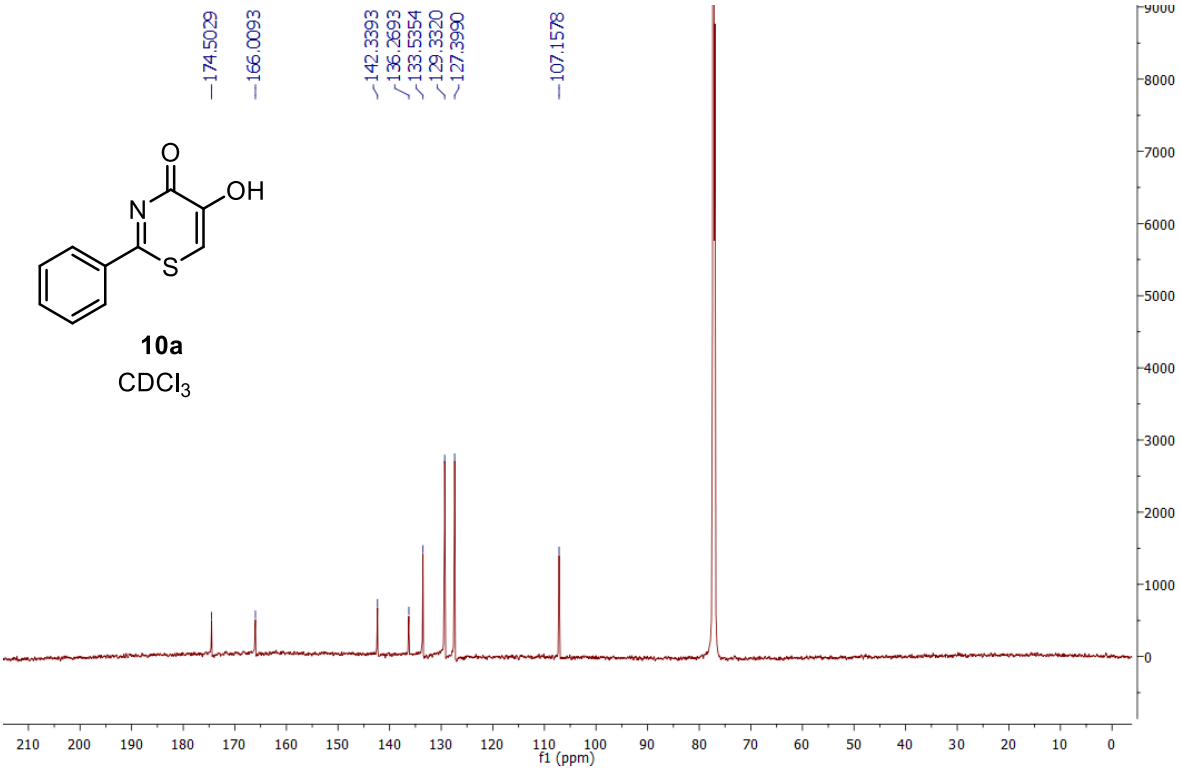
(DMSO-d_6)

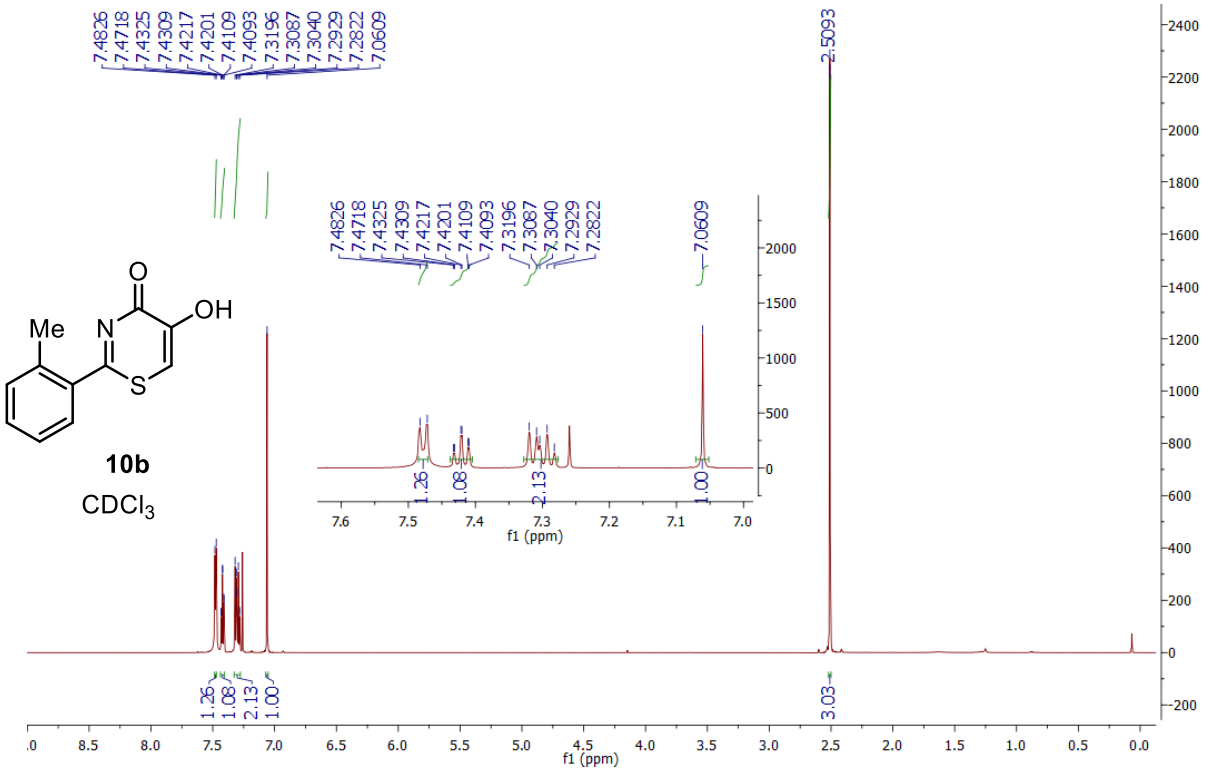


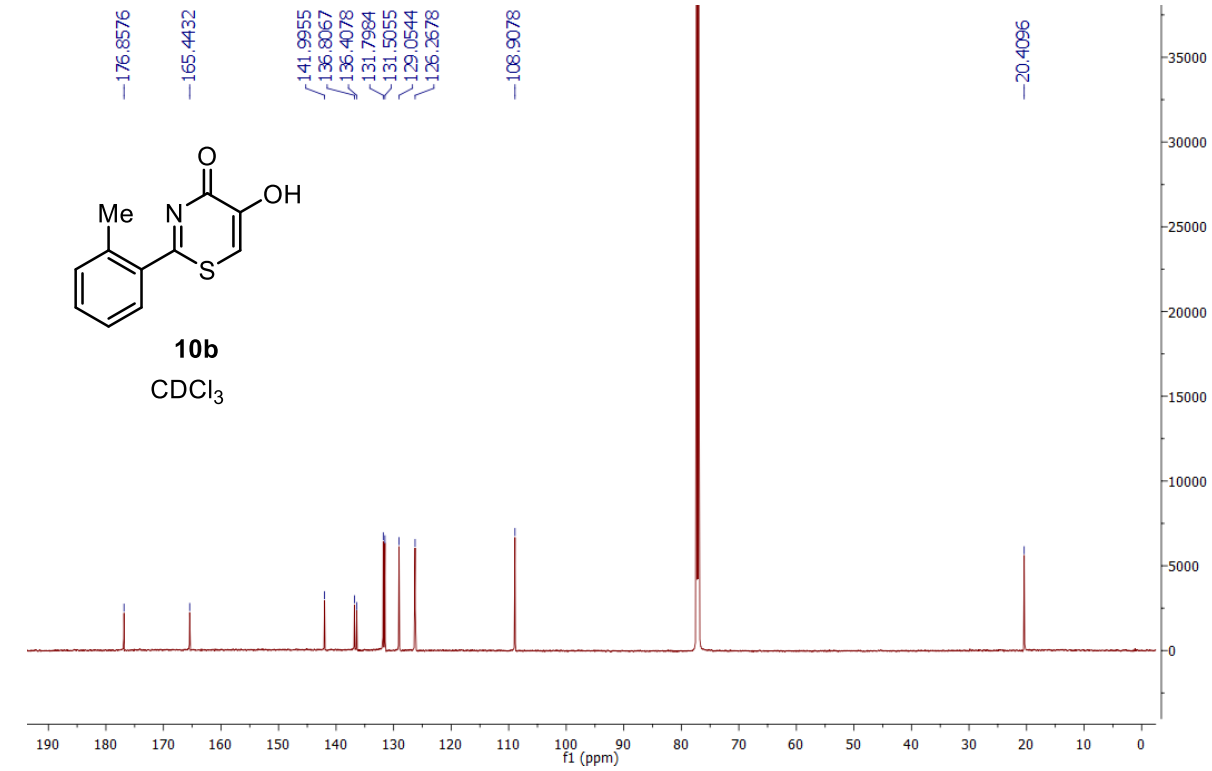
1a

(DMSO-d_6)


8.0949
8.0842
7.6161
7.6055
7.5949
7.5176
7.5064
7.4953
7.4514
7.0083
O
N
OH
S
10a
CDCl3
1.95
1.00
2.08
0.80
0.96
f1 (ppm)


174.5029
166.0093
142.3393
136.2693
133.5354
129.3320
127.3990
107.1578
O
N
OH
S
10a
CDCl3
f1 (ppm)


7.4826
7.4718
7.4325
7.4309
7.4217
7.4201
7.4109
7.4093
7.3196
7.3087
7.3040
7.2929
7.2822
7.0609
2.5093
Me
N
O
OH
S
10b
CDCl3
1.25
1.08
2.13
1.00
3.03
f1 (ppm)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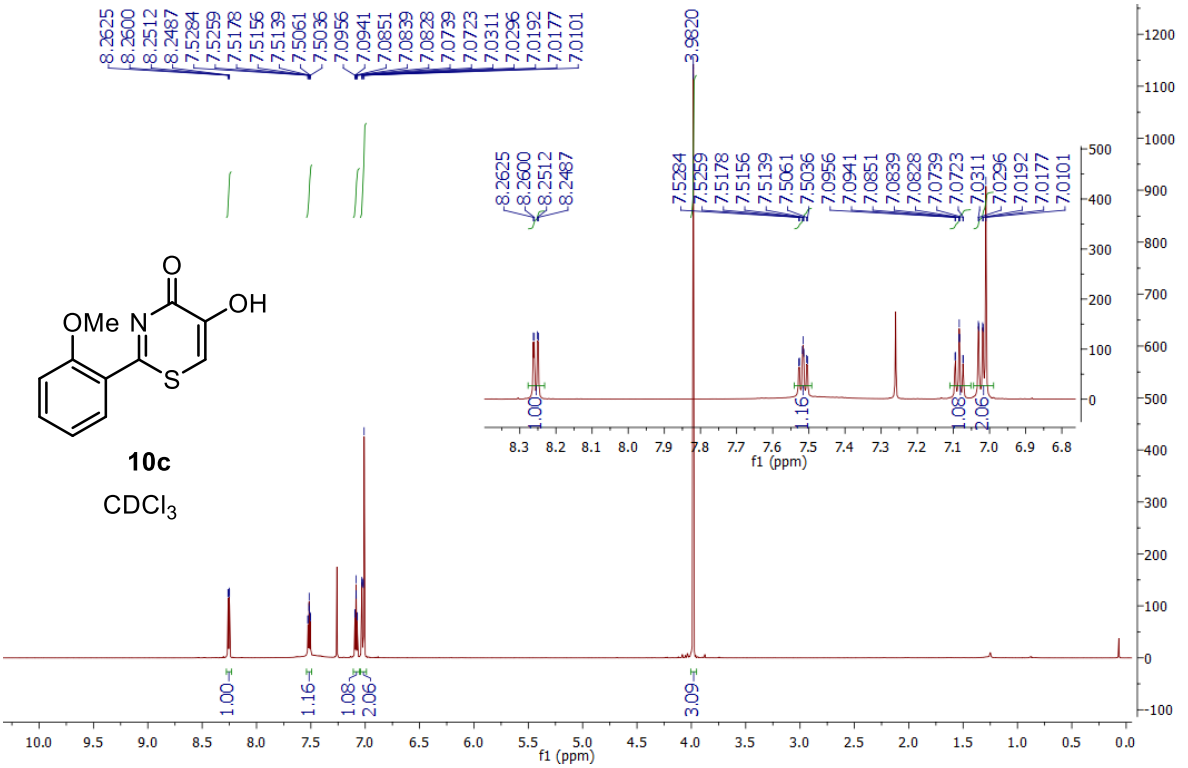
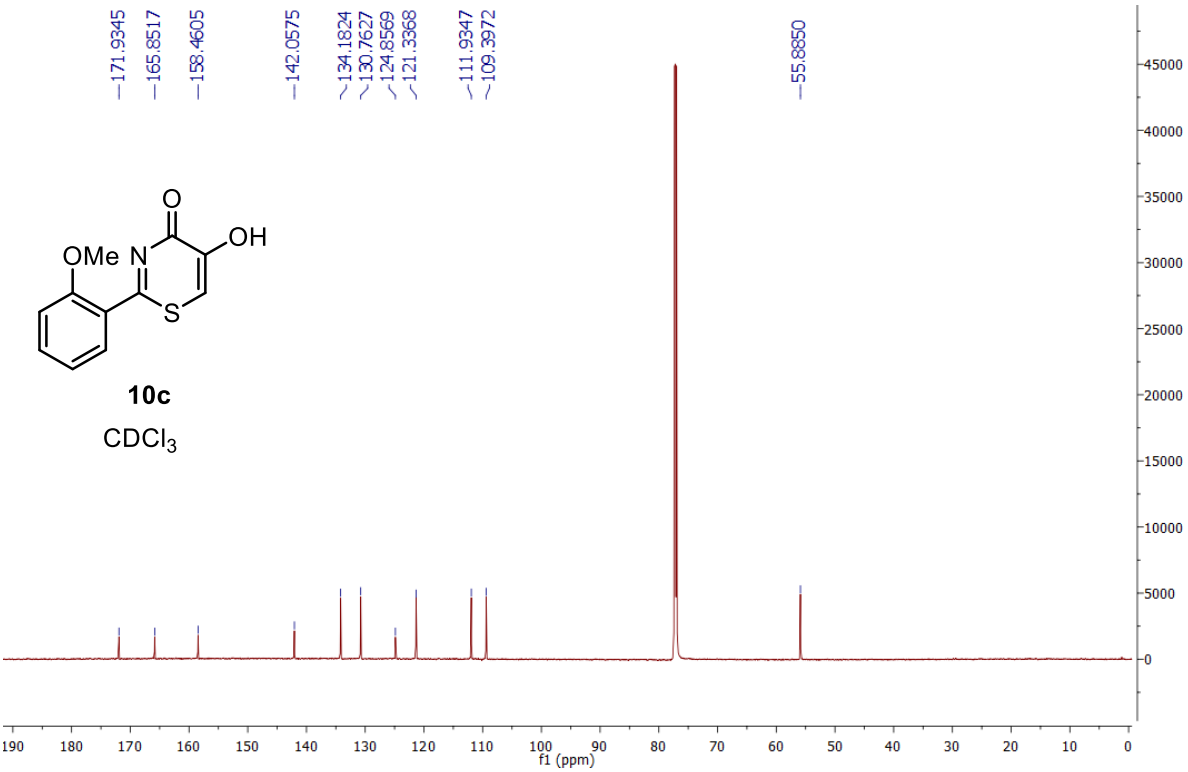
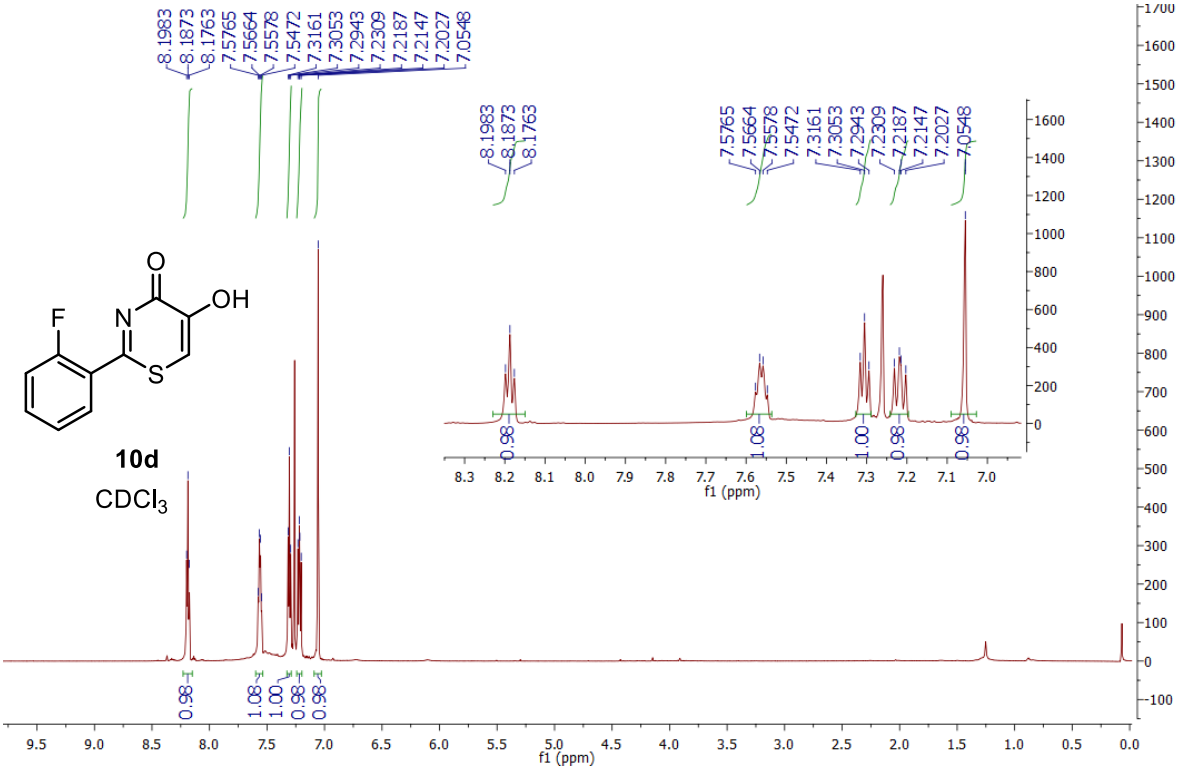
165.4432
141.9955
136.8067
136.4078
131.7984
131.5055
129.0544
126.2678
108.9078
20.4096
Me
N
O
OH
S
10b
CDCl3
f1 (ppm)


OMe
N
O
OH
S
10c
CDCl3
f1 (ppm)


OMe
N
O
OH
S
10c
CDCl3
f1 (ppm)


8.1983
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8.1763
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7.5664
7.5578
7.5472
7.3161
7.3053
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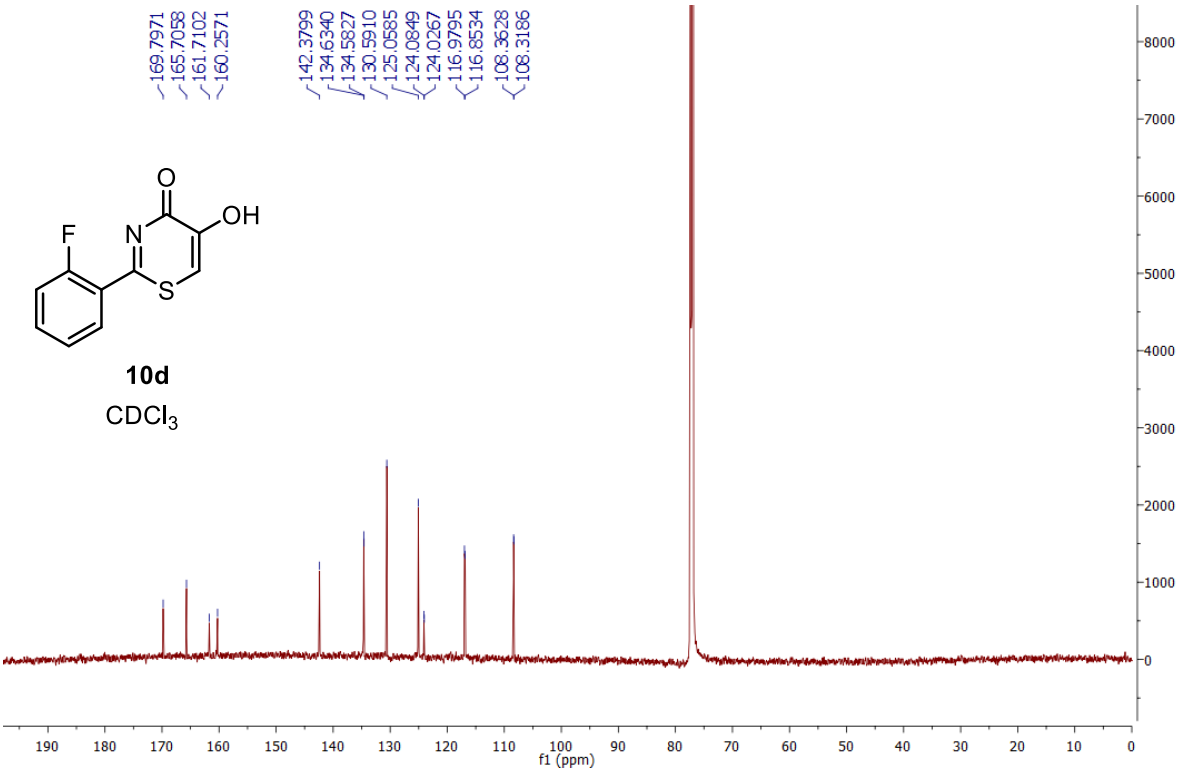
7.2309
7.2187
7.2147
7.2027
7.0548
O
OH
F
N
S
10d
CDCl3
0.98
1.08
1.00
0.98
0.98
f1 (ppm)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161.7102
160.2571
142.3799
134.6340
134.5827
130.5910
125.0585
124.0849
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116.8534
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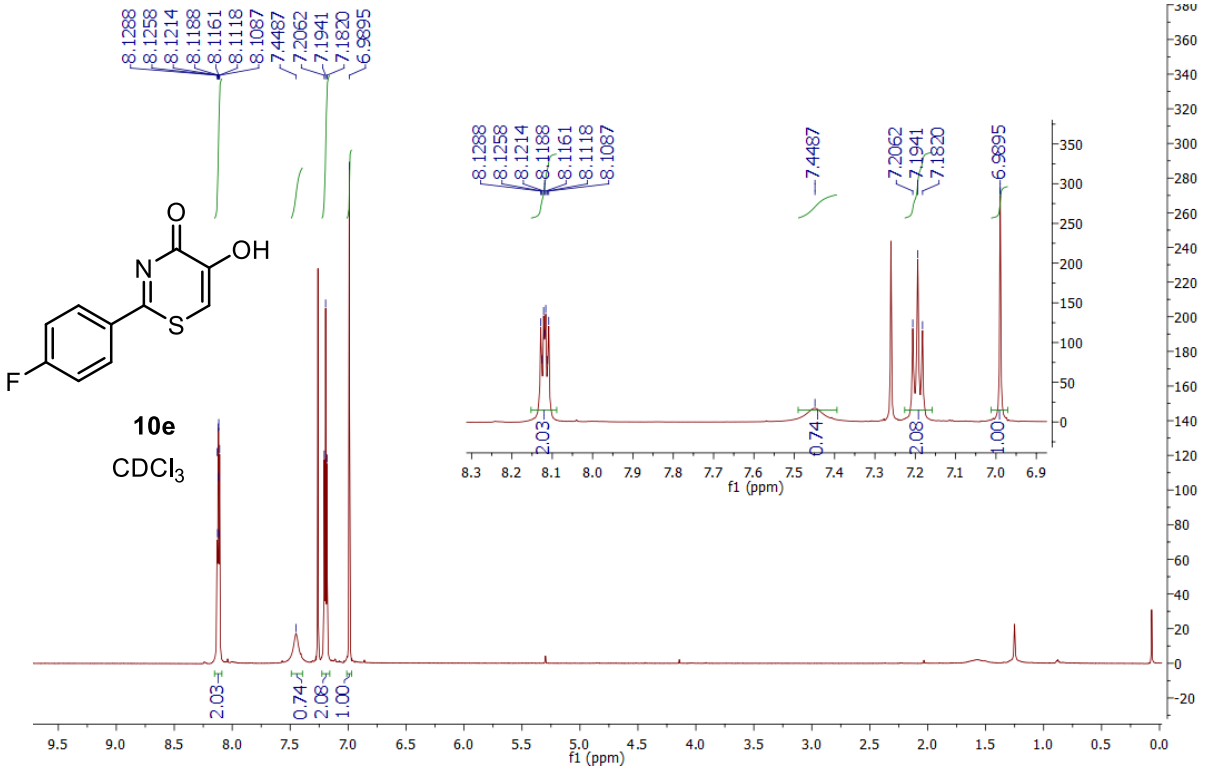
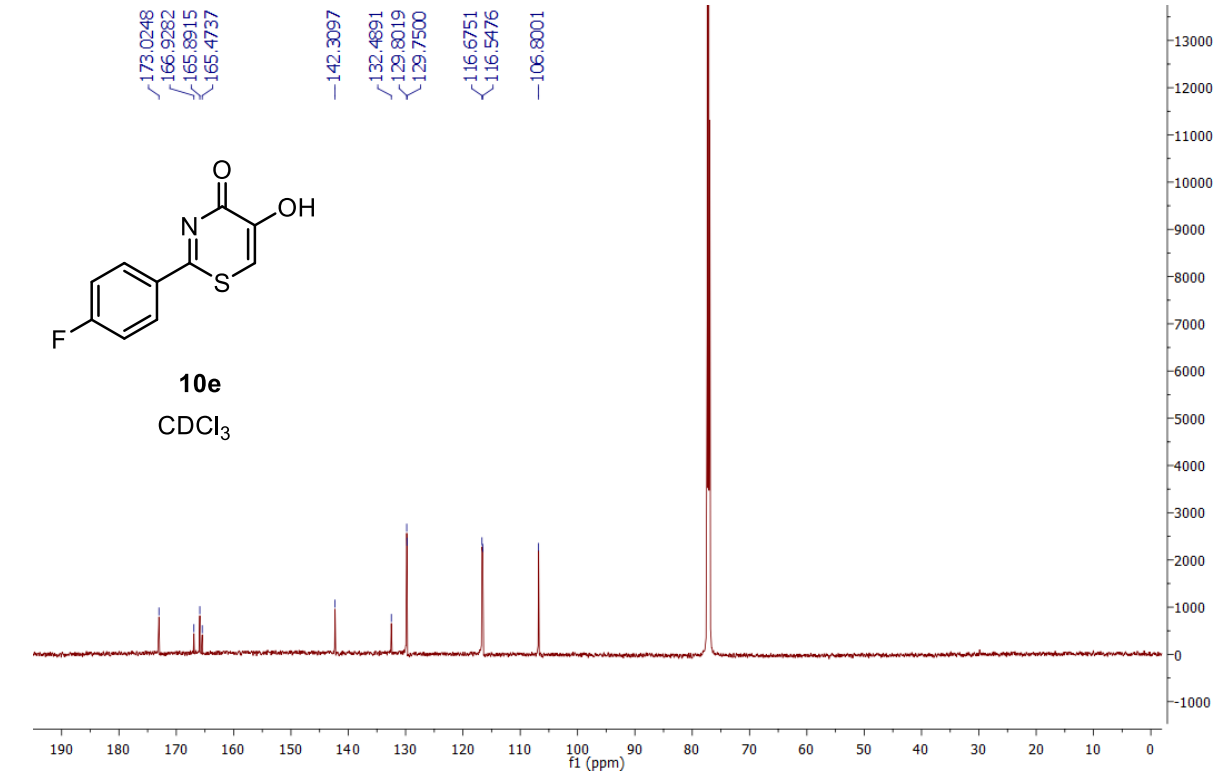
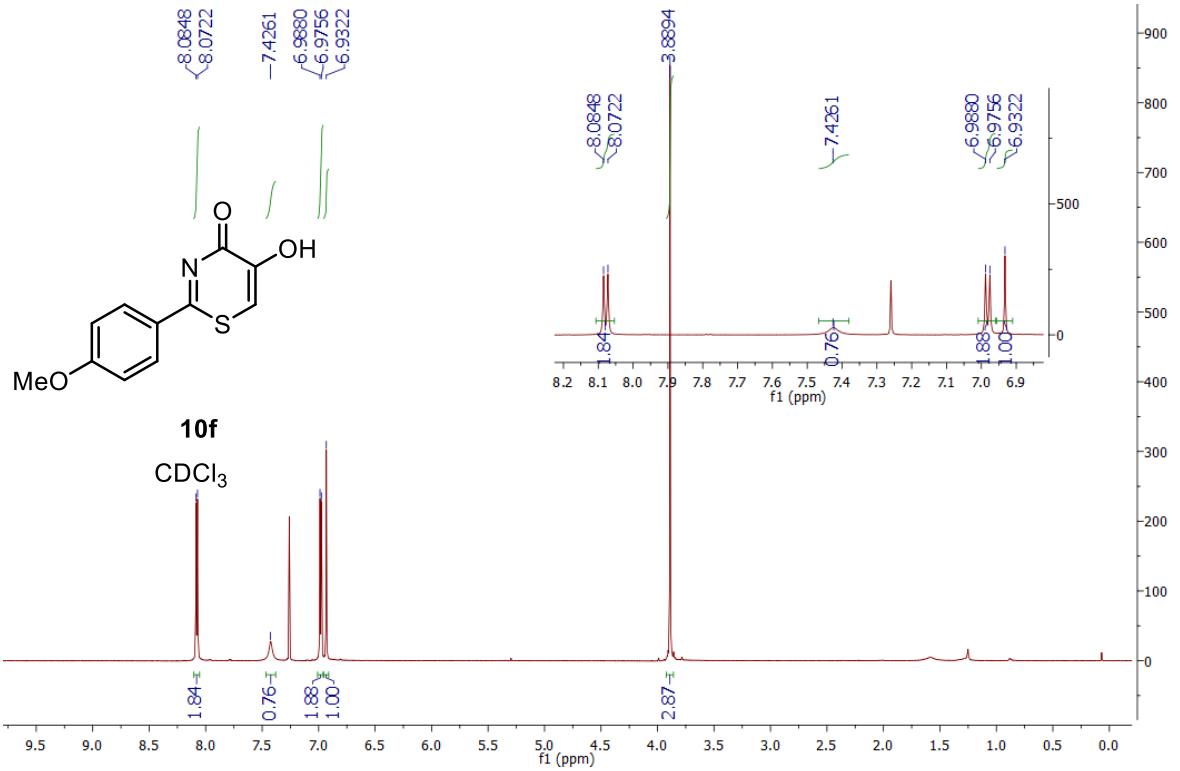
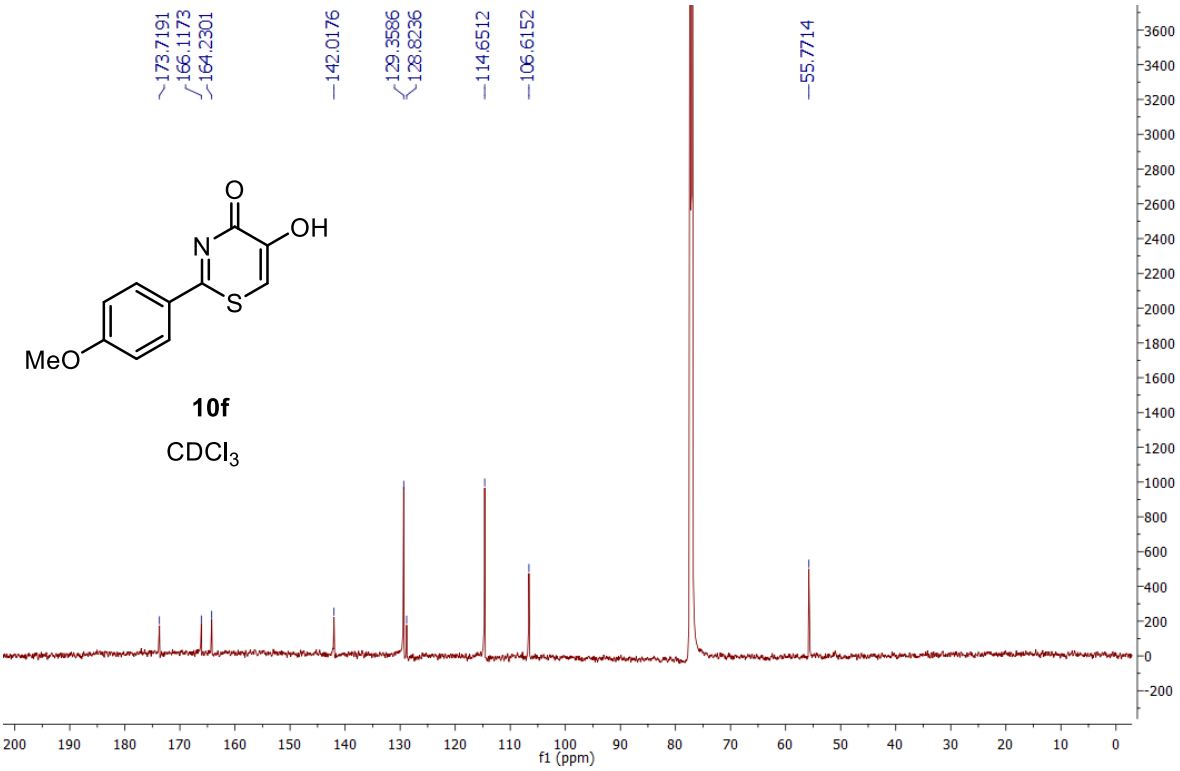
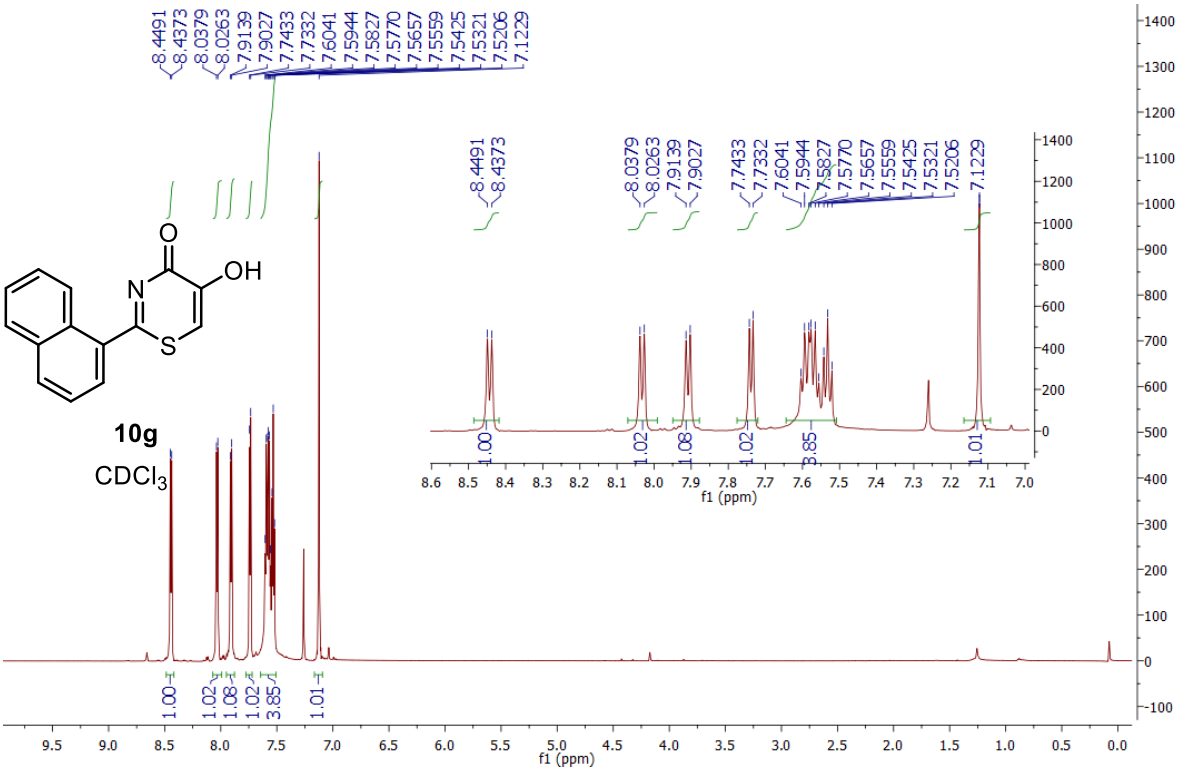
O
OH
F
N
S
10d
CDCl3
f1 (ppm)

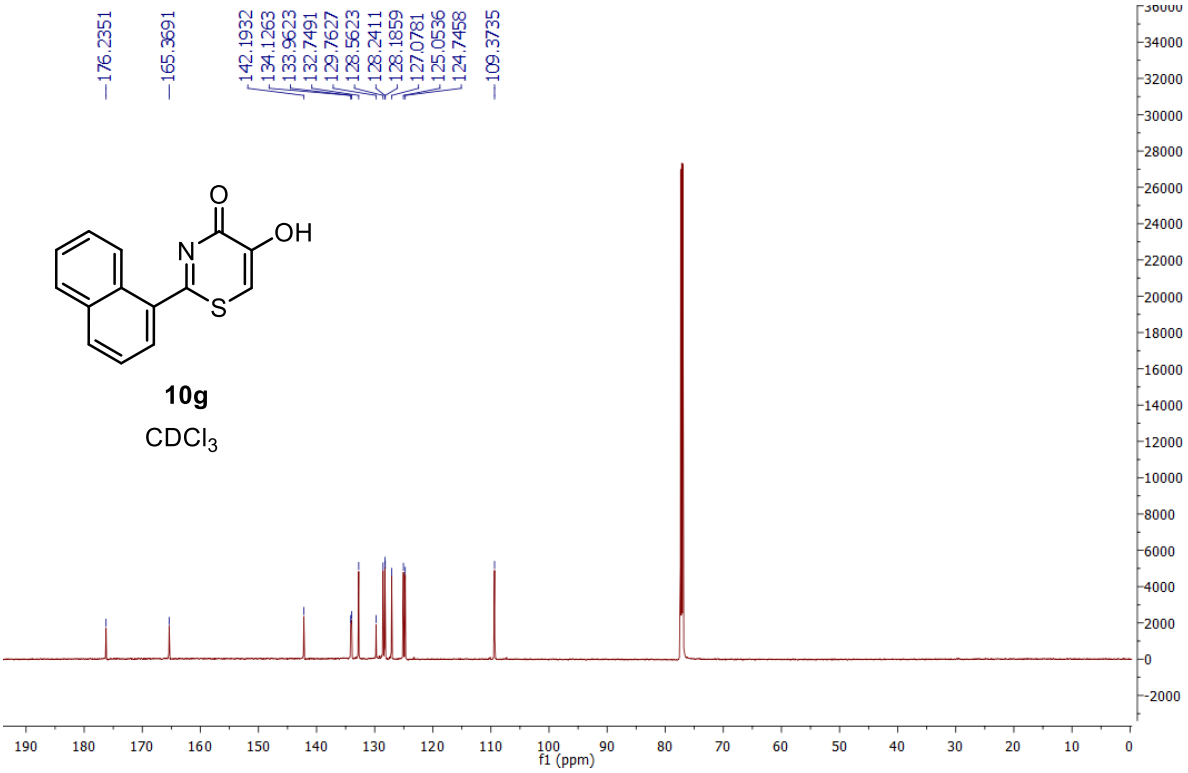

8.1288
8.1258
8.1214
8.1188
8.1161
8.1118
8.1087
7.4487
7.2062
7.1941
7.1820
6.9895
O
N
OH
S
F
10e
CDCl3
2.03
0.74
2.08
1.00
f1 (ppm)

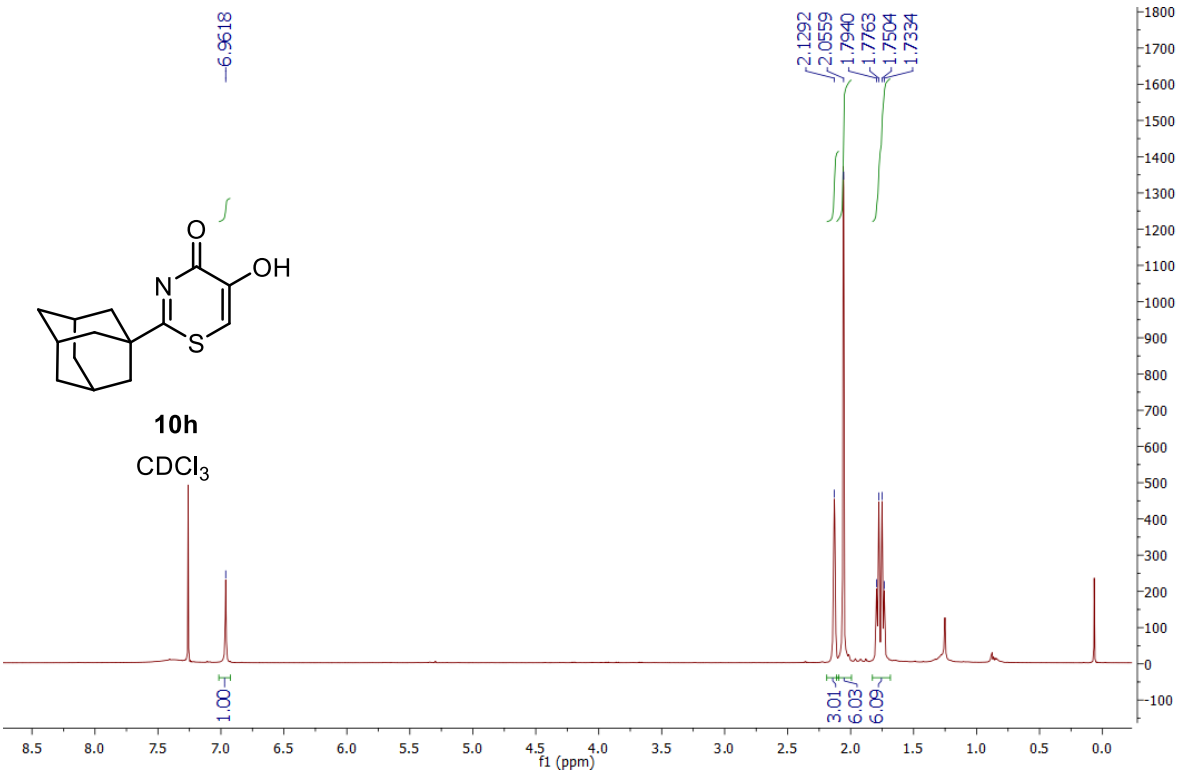

173.0248
166.9282
165.8915
165.4737
142.3097
132.4891
129.8019
129.7500
116.6751
116.5476
106.8001
O
N
OH
S
F
10e
CDCl3
f1 (ppm)

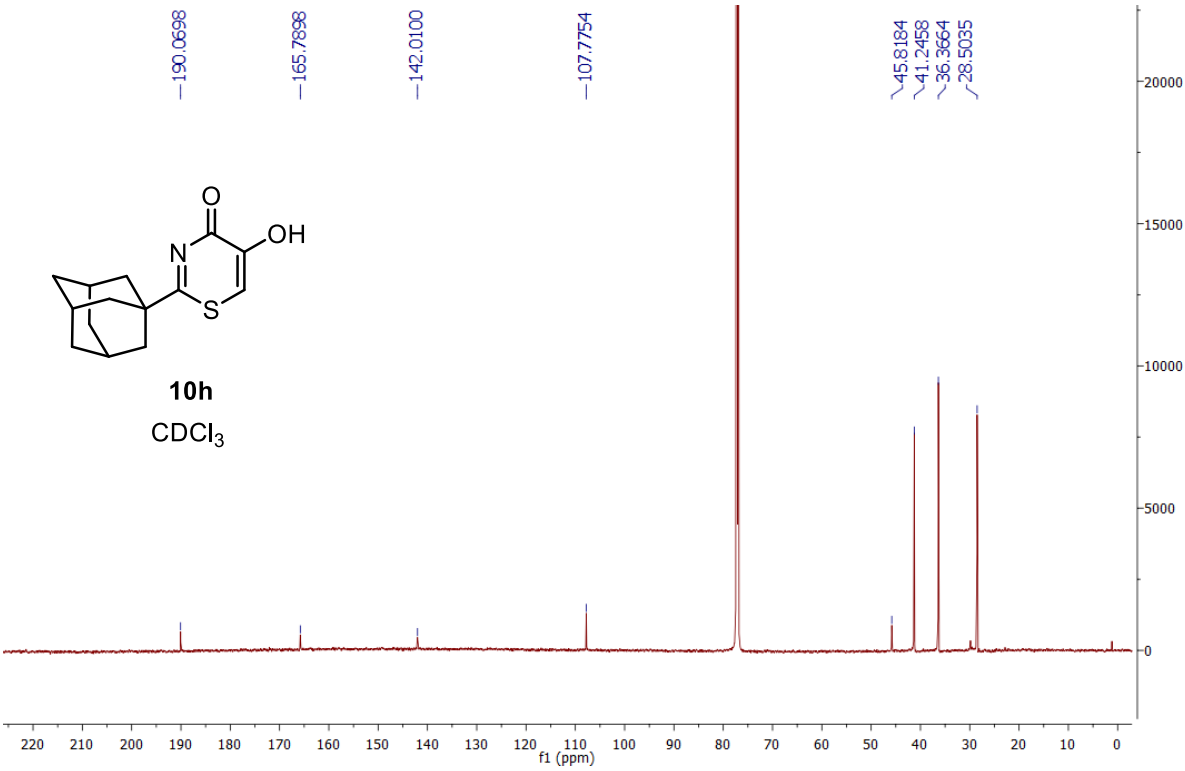

8.0848
8.0722
7.4261
6.9880
6.9756
6.9322
3.8894
O
N
S
OH
MeO
10f
CDCl3
1.84
0.76
1.88
1.00
2.87
f1 (ppm)

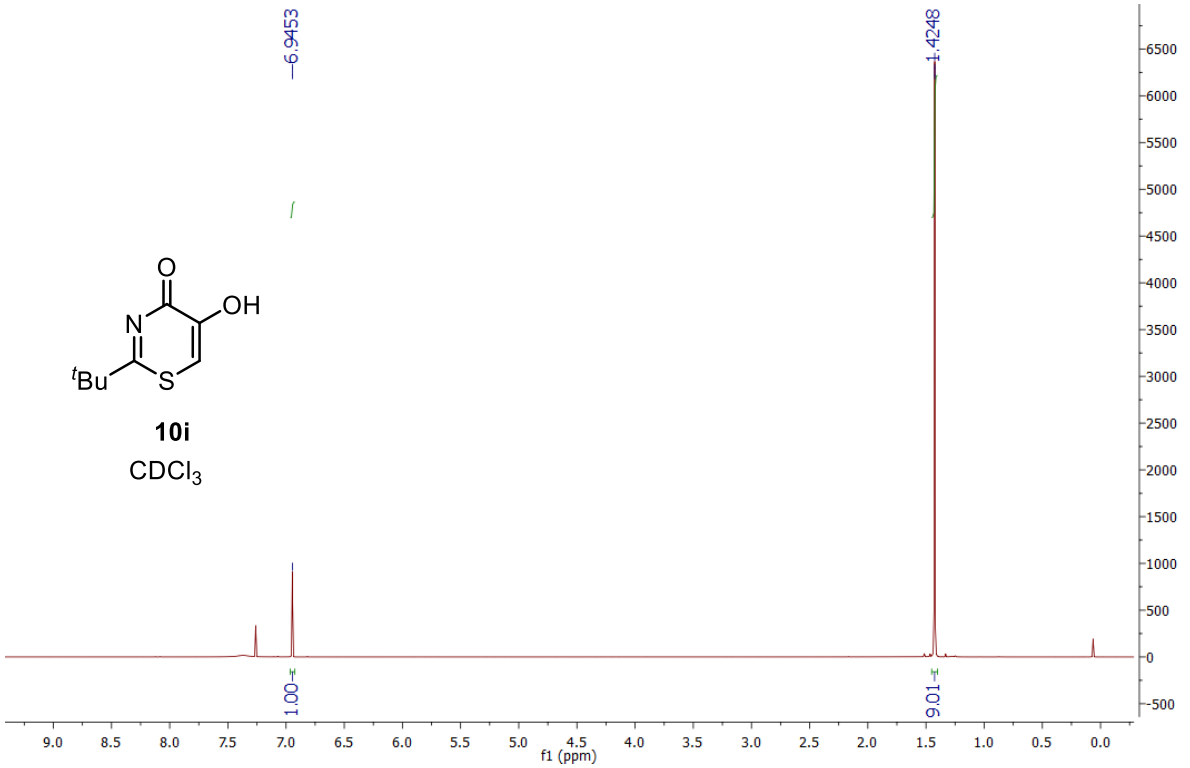

173.7191
166.1173
164.2301
142.0176
129.3586
128.8236
114.6512
106.6152
55.7714
O
N
S
OH
MeO
10f
CDCl3
f1 (ppm)

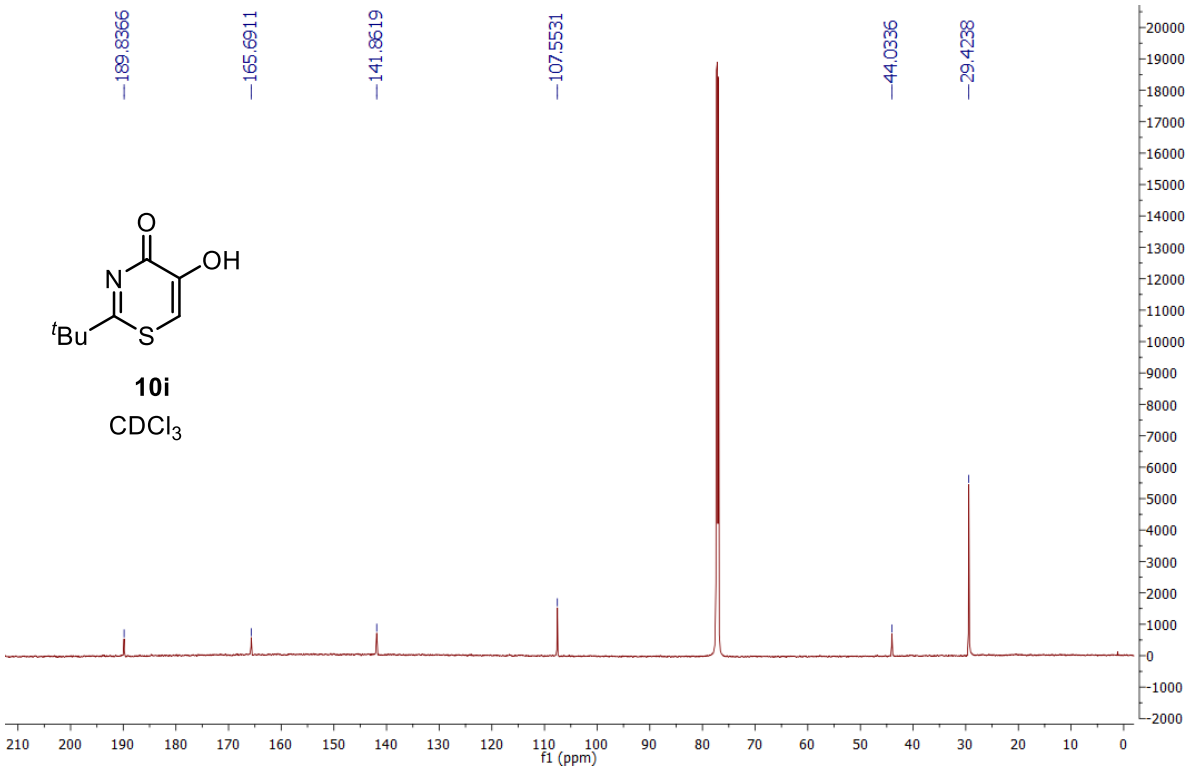

8.4491
8.4373
8.0379
8.0263
7.9139
7.9027
7.7433
7.7332
7.6041
7.5944
7.5827
7.5770
7.5657
7.5559
7.5425
7.5321
7.5206
7.1229
O
N
OH
S
10g
CDCl3
1.00
1.02
1.08
1.02
3.85
1.01
f1 (ppm)

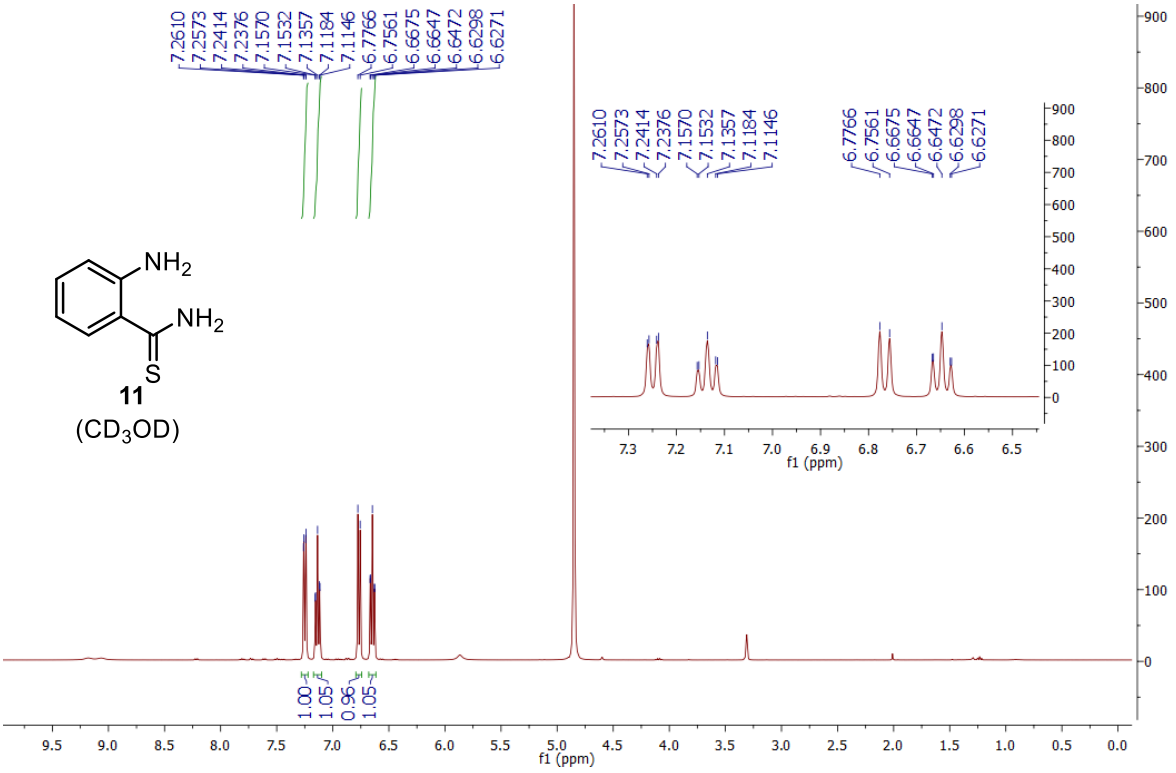

176.2351
165.3691
142.1932
134.1263
133.9623
132.7491
129.7627
128.5623
128.2411
128.1859
127.0781
125.0536
124.7458
109.3735
O
N
OH
S
10g
CDCl3
f1 (ppm)

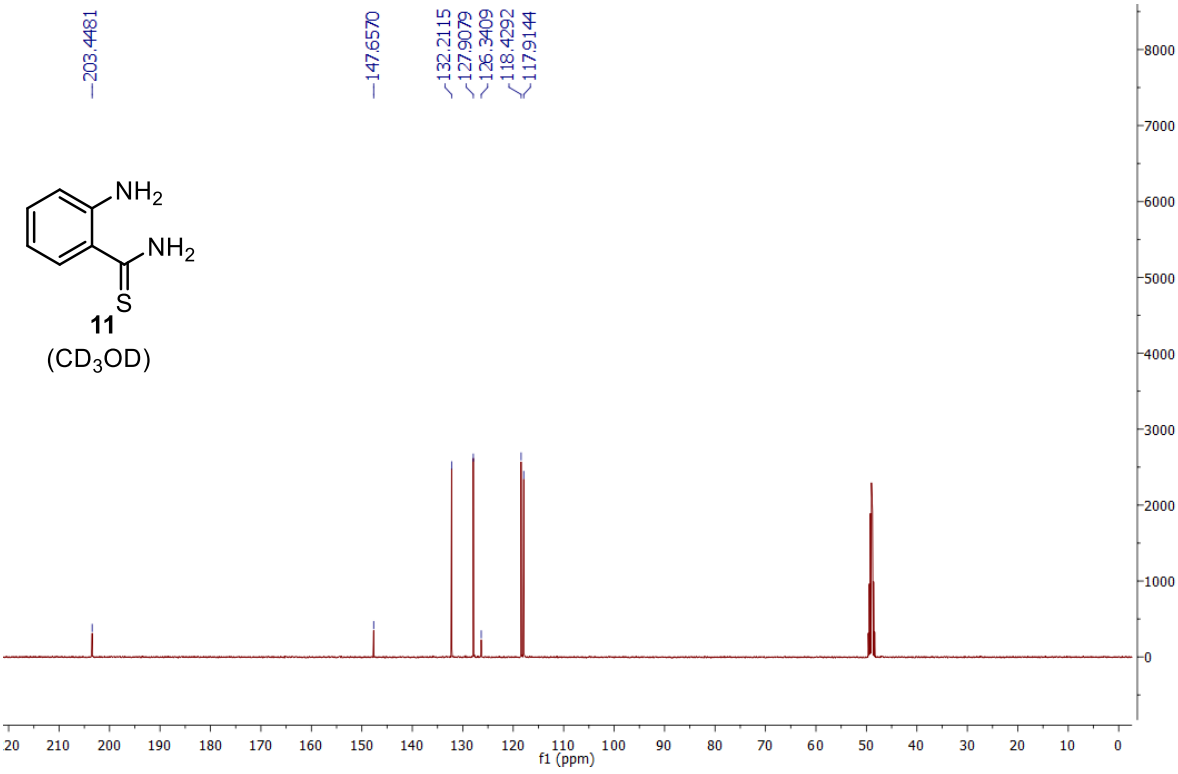

6.9618
2.1292
2.0559
1.7940
1.7763
1.7504
1.7334
O
N
S
OH
10h
CDCl3
1.00
3.01
6.03
6.09
f1 (ppm)

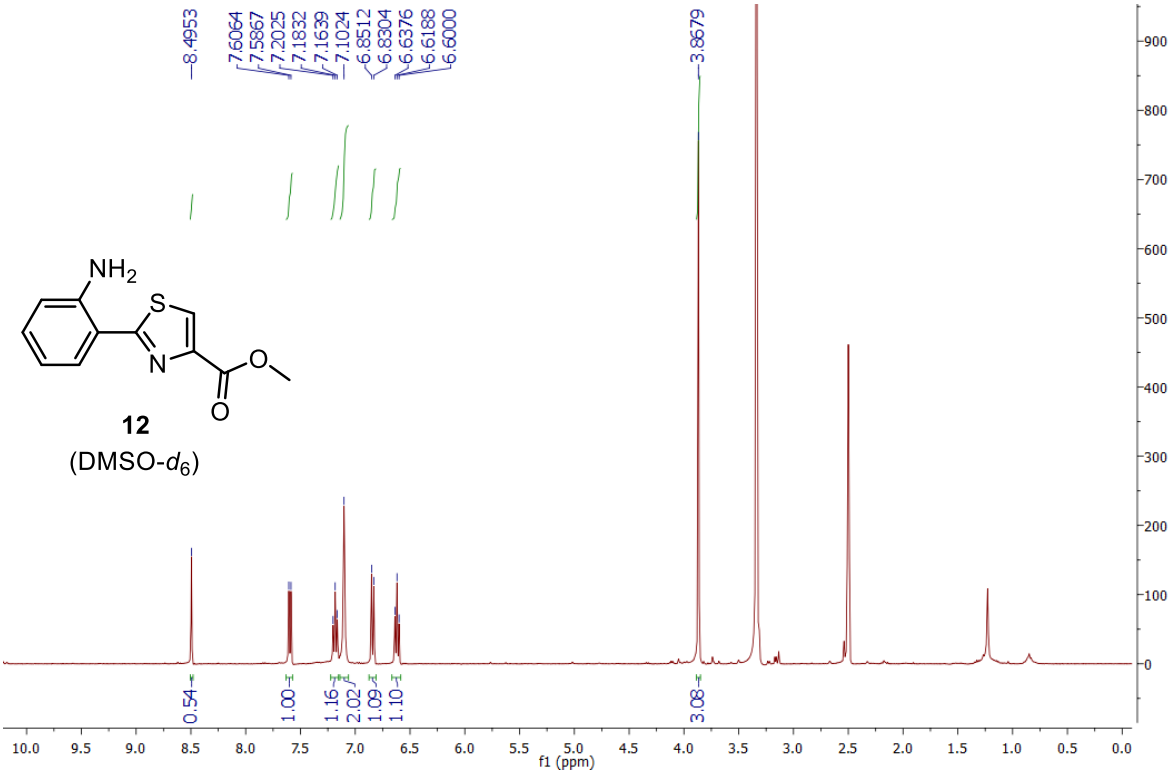

190.0698
165.7898
142.0100
107.7754
45.8184
41.2458
36.3664
28.5035
O
N
S
OH
10h
CDCl3
f1 (ppm)

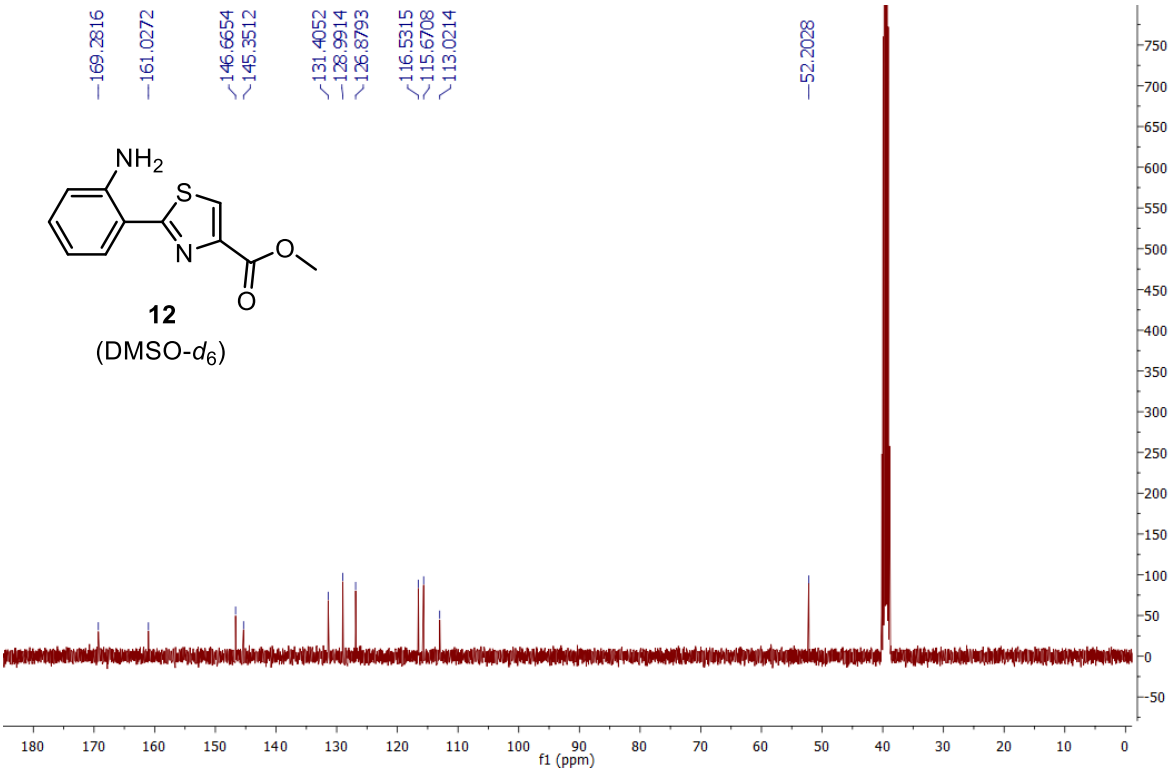

6.9453
1.4248
1.00
9.01
f1 (ppm)
10i
CDCl3

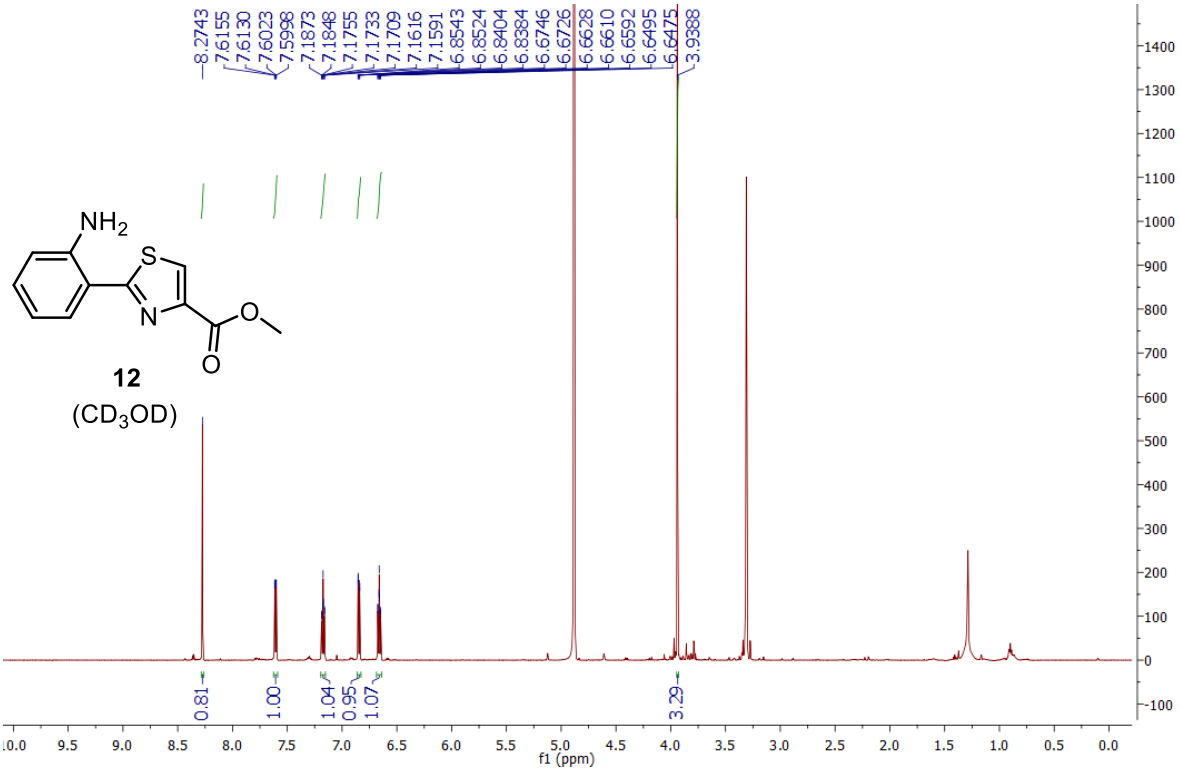

189.8366
165.6911
141.8619
107.5531
44.0336
29.4238
f1 (ppm)
10i
CDCl3

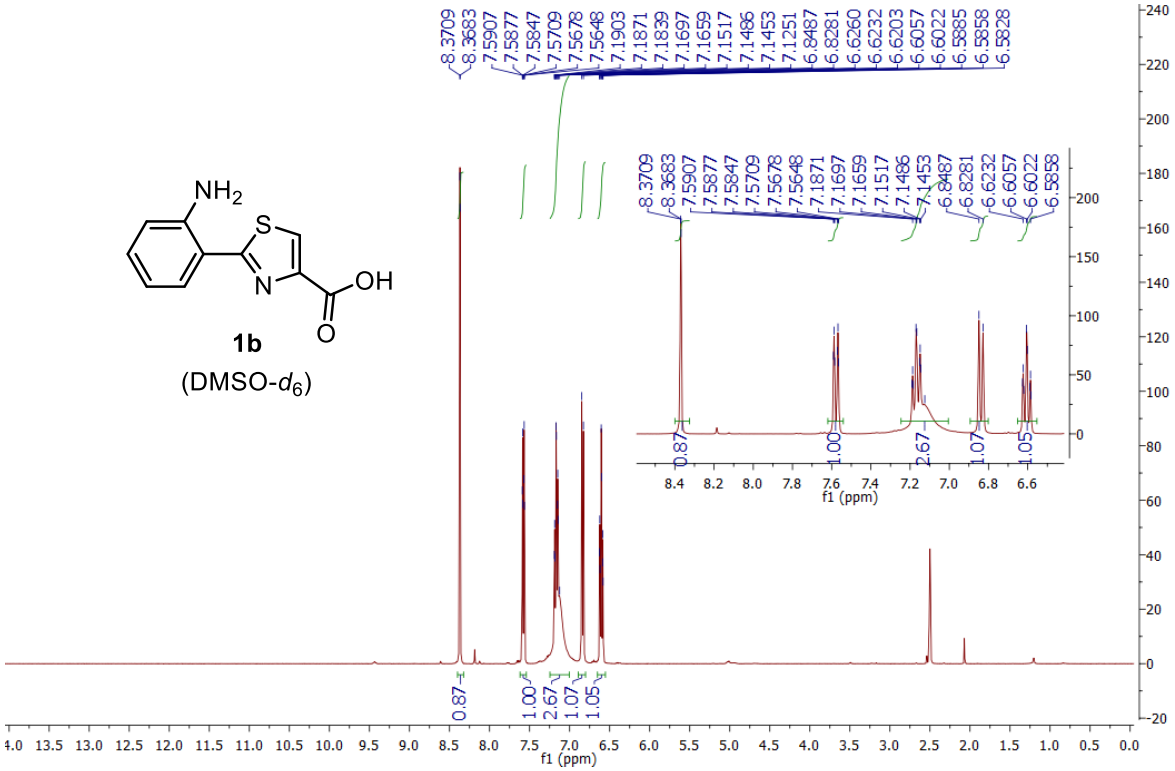

7.2610
7.2573
7.2414
7.2376
7.1570
7.1532
7.1357
7.1184
7.1146
6.7766
6.7561
6.6675
6.6647
6.6472
6.6298
6.6271
NH2
NH2
S
11
(CD3OD)
1.00
1.05
0.96
1.05
f1 (ppm)

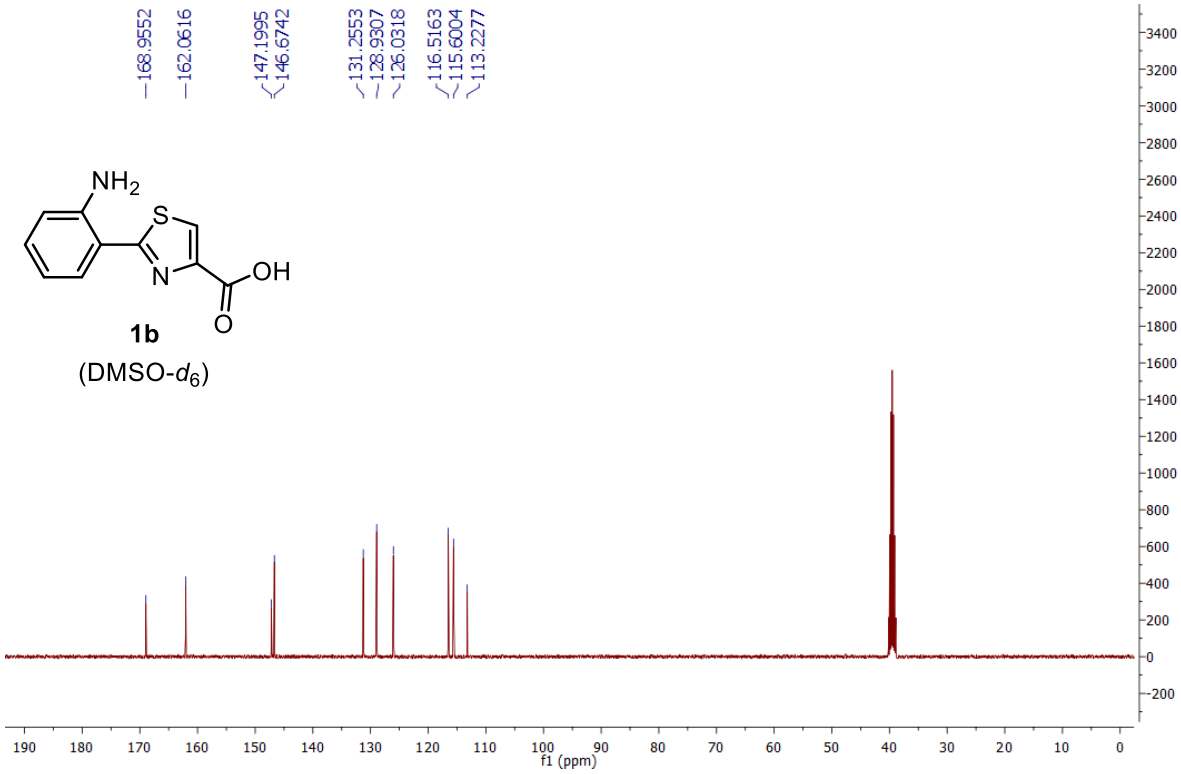

203.4481
147.6570
132.2115
127.9079
126.3409
118.4292
117.9144
NH2
NH2
S
11
(CD3OD)
f1 (ppm)

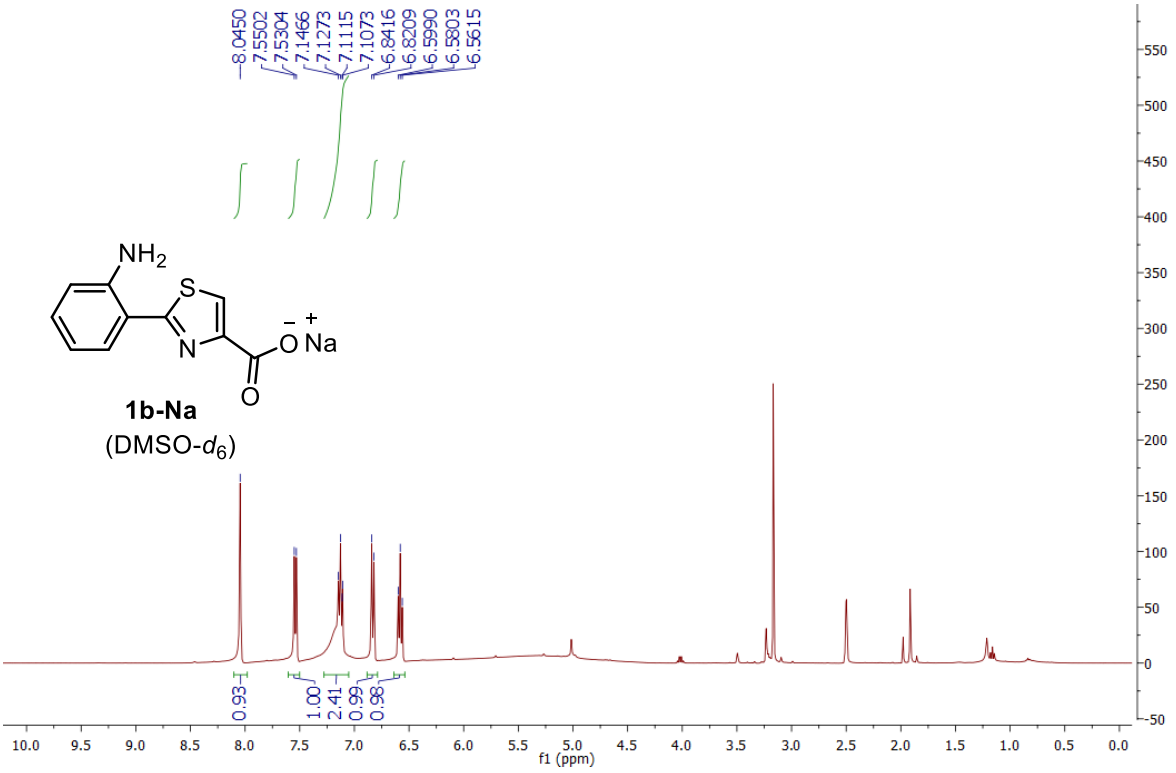

8.4953
7.6064
7.5867
7.2025
7.1832
7.1639
7.1024
6.8512
6.8304
6.6376
6.6188
6.6000
3.8679
NH2
S
N
O
O
12
(DMSO-d6)
0.54
1.00
1.16
2.02
1.09
1.10
3.08
f1 (ppm)

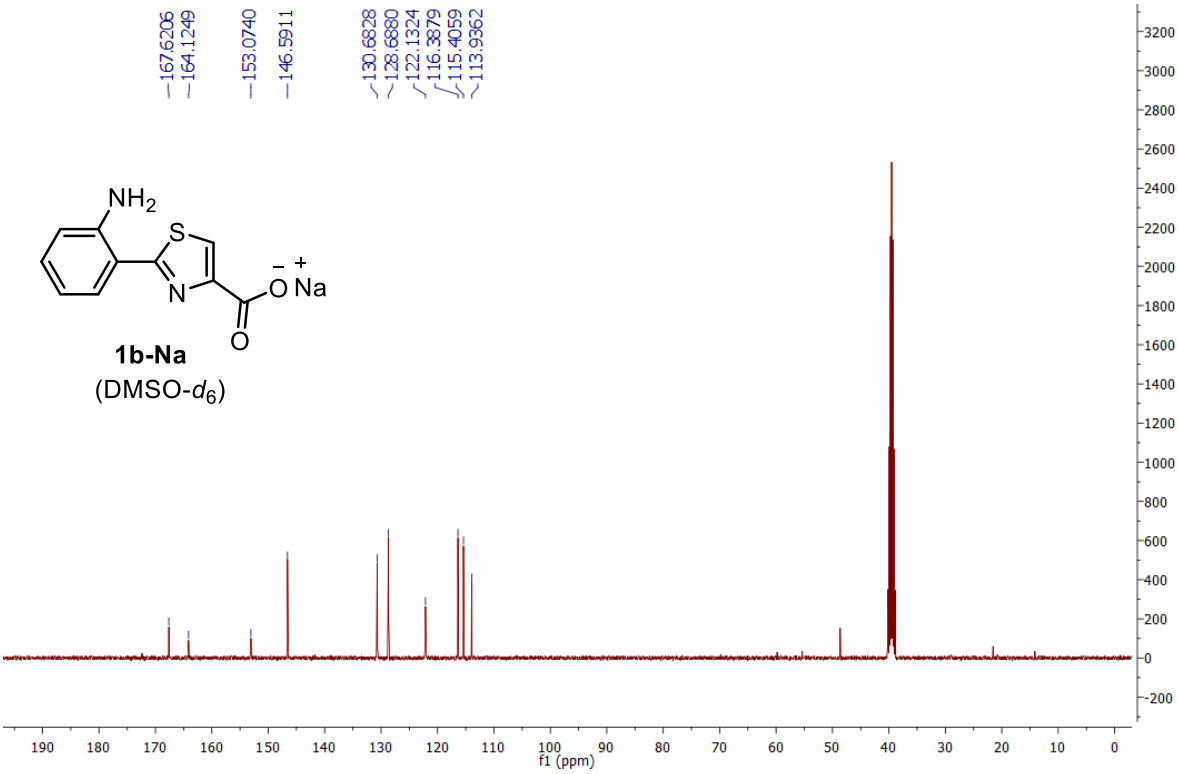

169.2816
161.0272
146.6654
145.3512
131.4052
128.9914
126.8793
116.5315
115.6708
113.0214
52.2028
NH2
S
N
O
O
12
(DMSO-d6)
f1 (ppm)

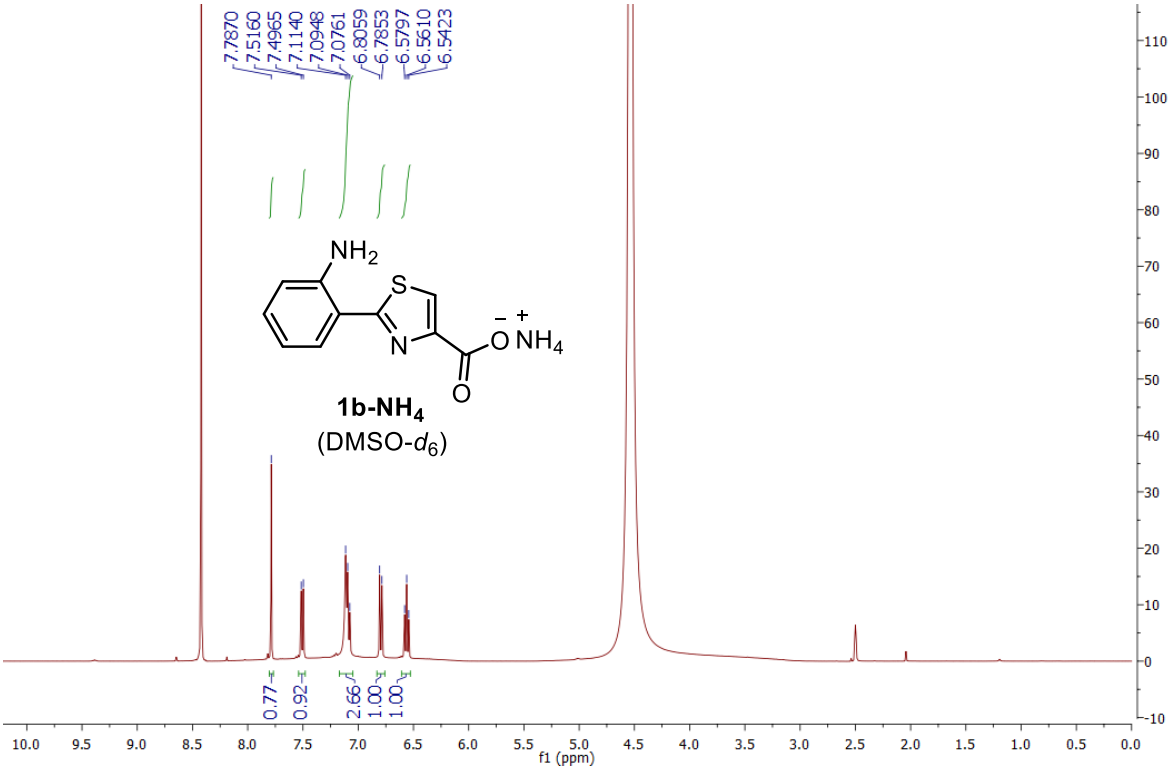

8.2743
7.6155
7.6130
7.6023
7.5998
7.1873
7.1848
7.1755
7.1733
7.1709
7.1616
7.1591
6.8543
6.8524
6.8404
6.8384
6.6746
6.6726
6.6628
6.6610
6.6592
6.6495
6.6475
3.9388
NH2
S
N
O
O
12
(CD3OD)
0.81
1.00
1.04
0.95
1.07
3.29
f1 (ppm)

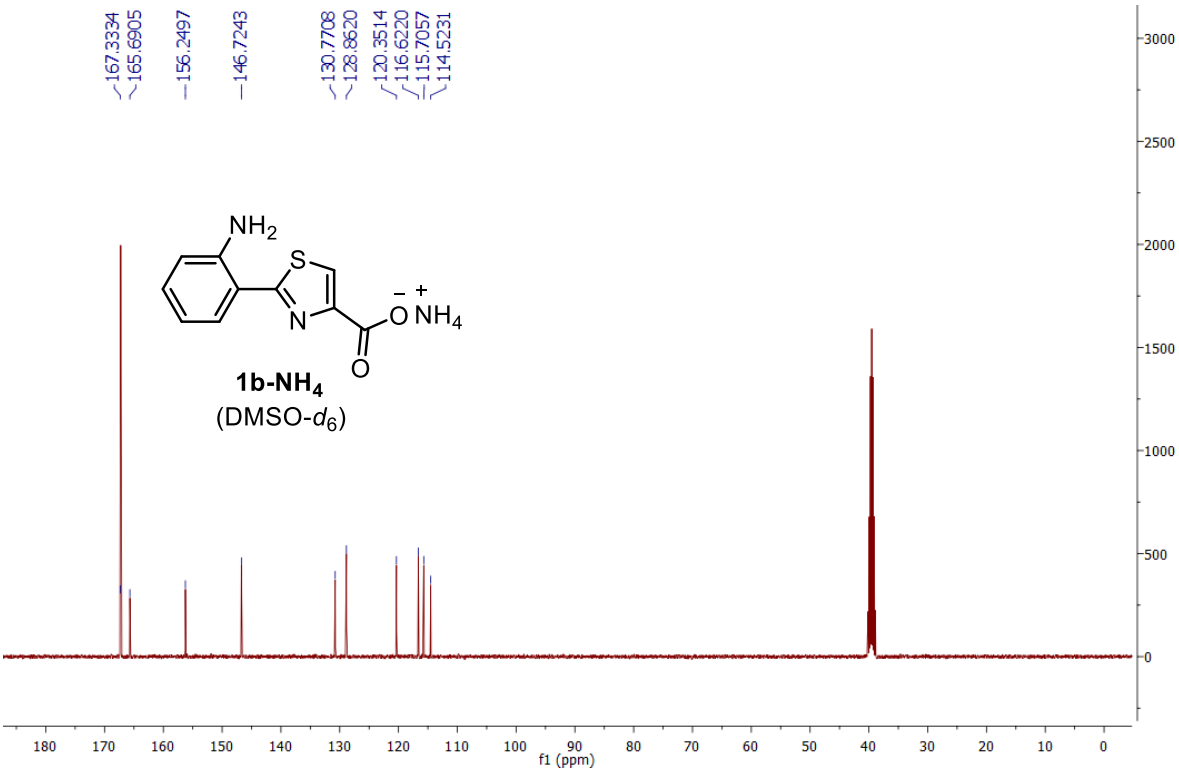

NH2
S
N
OH
O
1b
(DMSO-d6)
f1 (ppm)

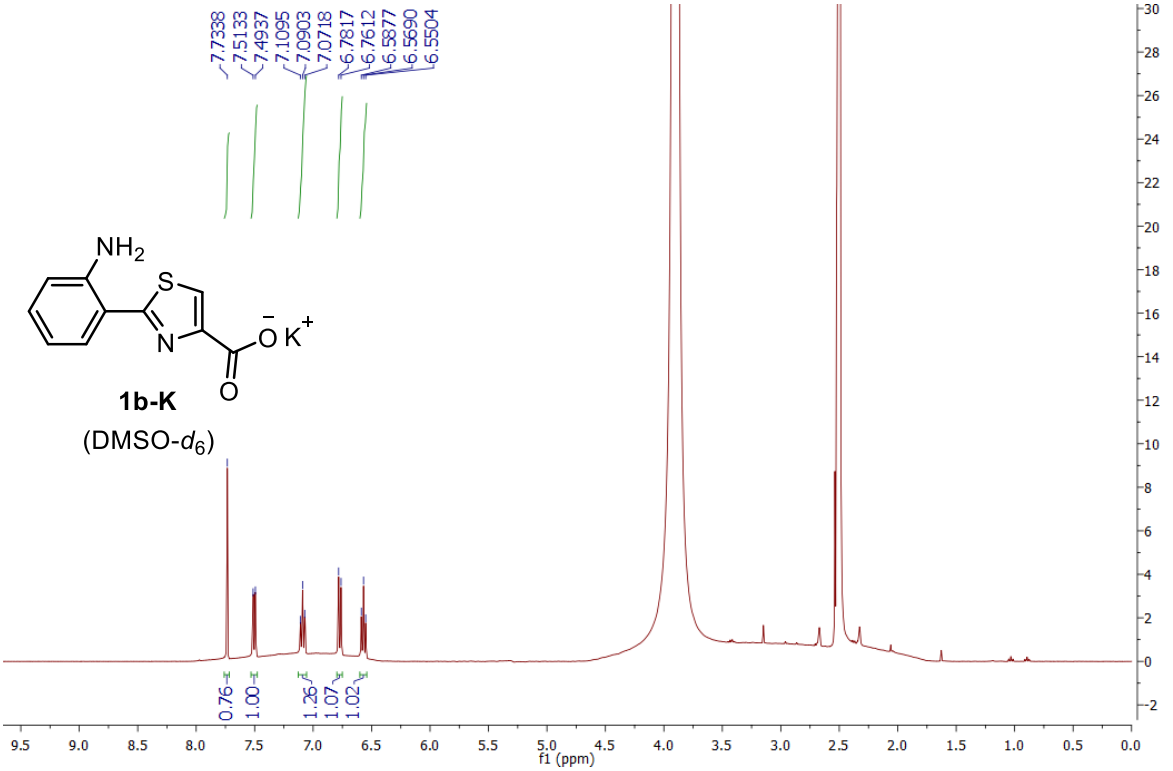

NH2
S
N
OH
O
1b
(DMSO-d6)
f1 (ppm)

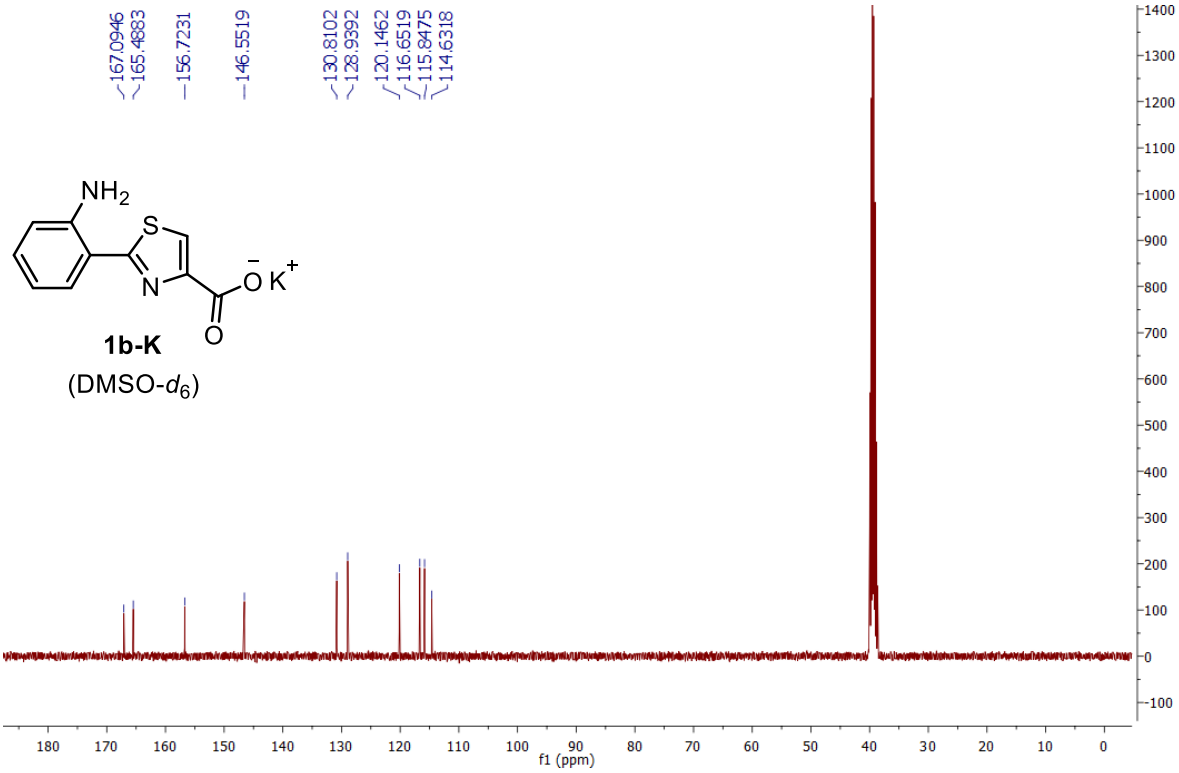

8.0450
7.5502
7.5304
7.1466
7.1273
7.1115
7.1073
6.8416
6.8209
6.5990
6.5803
6.5615
NH2
S
N
O
O Na
1b-Na
(DMSO-d6)
0.93
1.00
2.41
0.99
0.98
f1 (ppm)

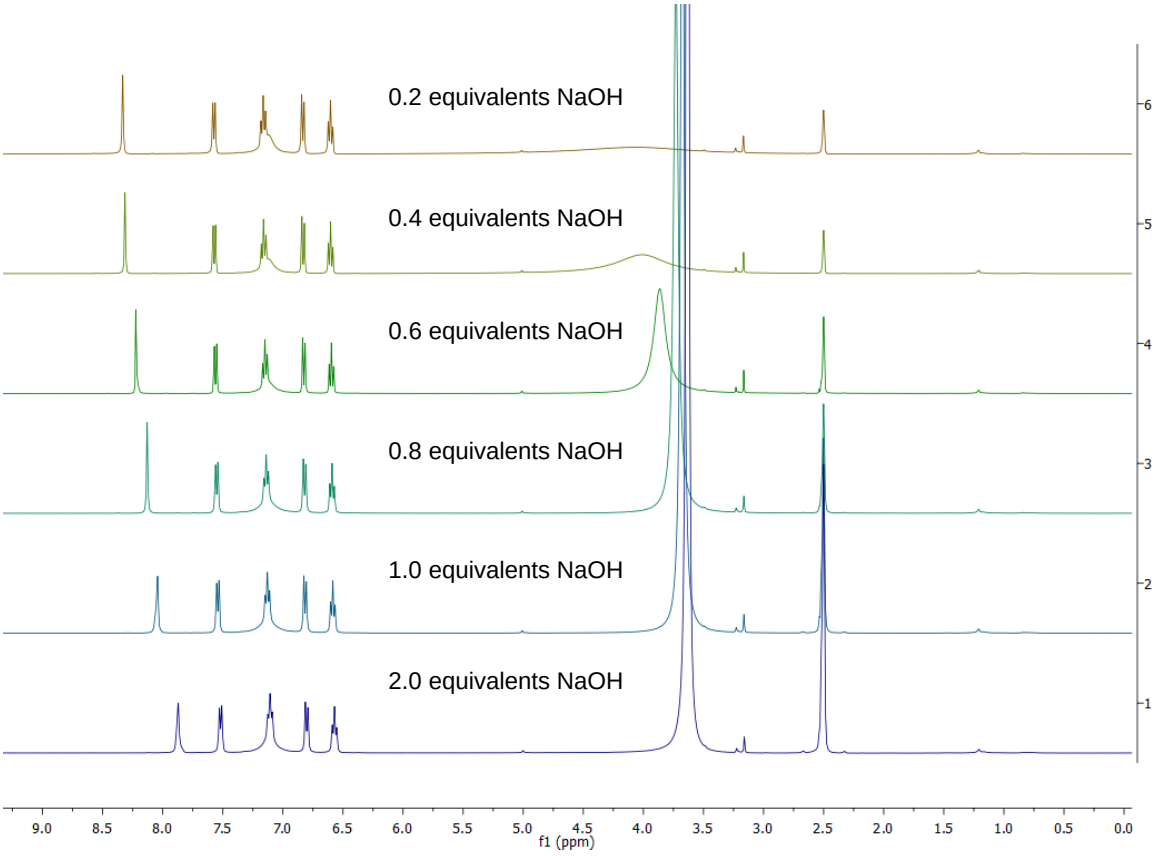

167.6206
164.1249
153.0740
146.5911
130.6828
128.6880
122.1324
116.3879
115.4059
113.9362
NH2
S
N
O
O Na
1b-Na
(DMSO-d6)
f1 (ppm)

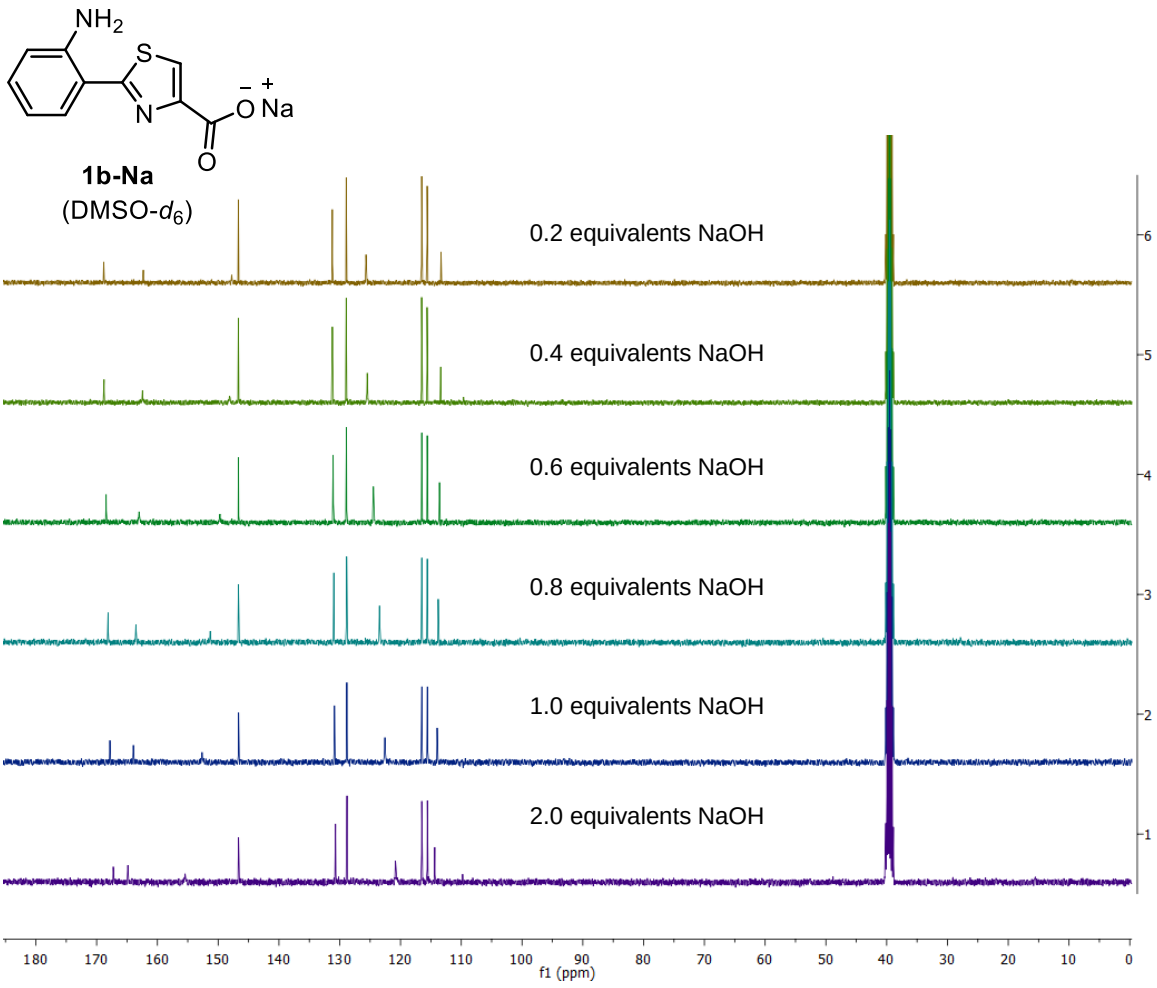

7.7870
7.5160
7.4965
7.1140
7.0948
7.0761
6.8059
6.7853
6.5797
6.5610
6.5423
NH2
S
N
O
O NH4
1b-NH4
(DMSO-d6)
0.77
0.92
2.66
1.00
1.00
f1 (ppm)

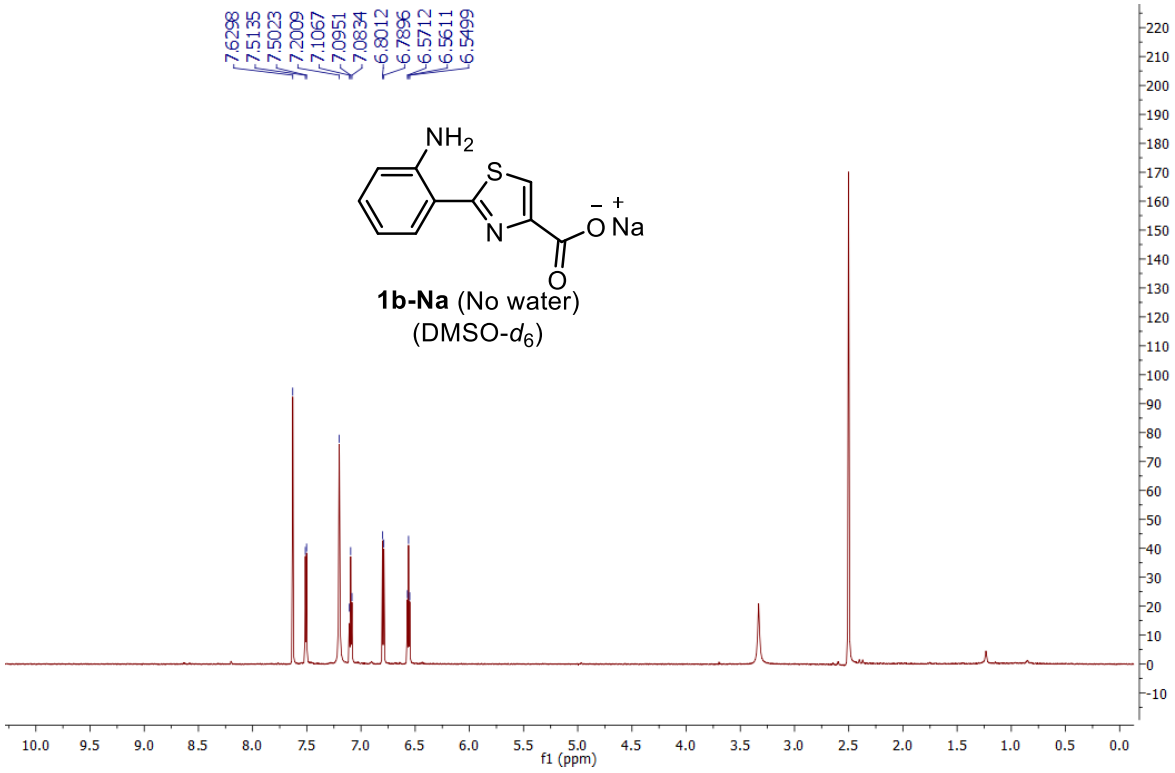

167.3334
165.6905
156.2497
146.7243
130.7708
128.8620
120.3514
116.6220
115.7057
114.5231
NH2
S
N
O
O NH4
1b-NH4
(DMSO-d6)
f1 (ppm)

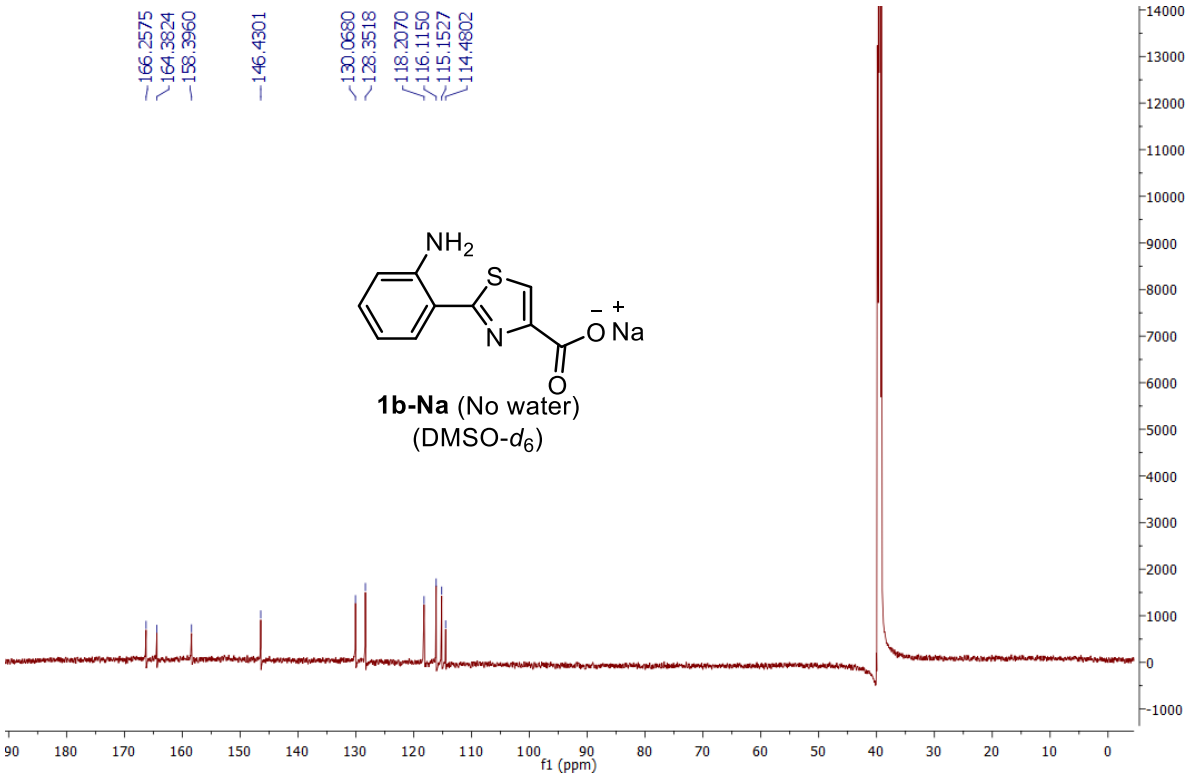

7.7338
7.5133
7.4937
7.1095
7.0903
7.0718
6.7817
6.7612
6.5877
6.5690
6.5504
NH2
S
N
O
O K+
1b-K
(DMSO-d6)
0.76
1.00
1.26
1.07
1.02
f1 (ppm)


167.0946
165.4883
156.7231
146.5519
130.8102
128.9392
120.1462
116.6519
115.8475
114.6318
NH2
S
N
O
O K+
1b-K
(DMSO-d6)
f1 (ppm)


0.2 equivalents NaOH
0.4 equivalents NaOH
0.6 equivalents NaOH
0.8 equivalents NaOH
1.0 equivalents NaOH
2.0 equivalents NaOH
f1 (ppm)


NH2
S
N
O
Na
1b-Na
(DMSO-d6)
0.2 equivalents NaOH
0.4 equivalents NaOH
0.6 equivalents NaOH
0.8 equivalents NaOH
1.0 equivalents NaOH
2.0 equivalents NaOH
f1 (ppm)


7.6298
7.5135
7.5023
7.2009
7.1067
7.0951
7.0834
6.8012
6.7896
6.5712
6.5611
6.5499
NH2
S
N
O Na
O
1b-Na (No water)
(DMSO-d6)
f1 (ppm)


166.2575
164.3824
158.3960
146.4301
130.0680
128.3518
118.2070
116.1150
115.1527
114.4802
NH2
S
N
O Na
O
1b-Na (No water)
(DMSO-d6)
f1 (ppm)

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