Supporting Information

Investigation of Thiazolyl-Benzothiophenamides as Potential Agents for African Sleeping Sickness

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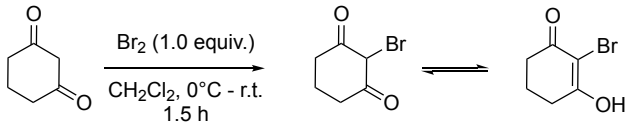
1. General Experimental

All commercial reagents were used as received, unless otherwise noted. Anhydrous solvents were either purchased from commercial suppliers or passed over activated alumina, before being dried over pre-activated 3, 4 or 5 Å molecular sieves and stored under nitrogen gas. Reaction vessels were oven-dried (120 °C) overnight before use and all reactions were carried out under a nitrogen atmosphere, unless otherwise noted. Reactions were monitored via thin-layer chromatography (TLC) analysis using aluminium-backed silica gel sheets coated with fluorescent indicator F254 and visualized under UV light (254 nm) and either potassium permanganate stain (1.5 g $KMnO_4$, 10 g K_2CO_3, 1.25 mL aqueous NaOH (10% v/v) in 200 mL water) or anisaldehyde stain (4 mL anisaldehyde, 5 mL concentrated H_2SO_4, 2 mL glacial AcOH in 150 mL EtOH). Column chromatography was performed under compressed air using flash grade silica gel (40–60 nm). NMR spectroscopy was conducted using a Bruker 500 (500 MHz, ^{1}H, 125 MHz, ^{13}C), Bruker 400 (400 MHz, ^{1}H, 100 MHz, ^{13}C), Varian 500 (500 MHz, ^{1}H, 125 MHz, ^{13}C) or Varian 300 (300 MHz, ^{1}H, 75 MHz, ^{13}C) spectrometer. For samples dissolved in $CDCl_3$ (0.1% v/v TMS), chemical shifts (δ) have been reported in parts per million (ppm) and referenced to the $CDCl_3$ signal (7.26 ppm, ^{1}H, 77.0 ppm, ^{13}C) or TMS signal (0.00 ppm, ^{1}H and ^{13}C). Those dissolved in DMSO-d_6 have been referenced to the $(CD_3)_2SO$ signal (2.50 ppm, ^{1}H, 39.5 ppm, ^{13}C) and those dissolved in acetone-d_6 have been referenced to the $(CD_3)_2CO$ signal (2.05 ppm, ^{1}H, 29.9, ^{13}C). Coupling constants (*J*) are reported in hertz (Hz). Multiplicities of NMR signals have been abbreviated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), dq (doublet of quartets) or m (multiplet) and some denoted as app (apparent) or br. (broad). High resolution mass spectrometry (HRMS) was carried out using a Waters Xevo G1 QTof mass spectrometer. Infrared data was collected on either a Shimadzu IRAffinity-1 Miracle 10 Fourier transform infrared (FTIR) or Bruker Vertex 70 FTIR instrument. High-performance liquid chromatography (HPLC) was conducted using a Shimadzu Prominence-i LC-2030C HPLC system equipped with a PDA detector, under reversed-phase conditions. Purity analysis was conducted using a Waters SunFire C18 column at 1.0 mL/min and 25 °C, with detection at 254 nm or 280 nm. Unless otherwise noted, analytes were eluted using a concentration gradient of 50 – 100% solvent B in A over 10 minutes, followed by 100% B for a further 10 minutes, where A = water/TFA (99.9:0.1) and B = MeCN. The precatalysts $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$[1a] and $Ni(dppe)Cl_2$[1b] were prepared as per the literature. Biological assays against *T. brucei*/HEK293 cells were performed within the group of Prof Vicky Avery (Discovery Biology, Griffith Institute for Drug Discovery, Griffith University) using a modified version of their previously reported method.[2] The *T. b. rhodesiense*/L6 assay was performed by Dr Marcel Kaiser (Swiss Tropical and Public Health Institute/University of Basel) using his previously reported method.[3]

*2. Synthesis of Building Blocks for Derivatives of WEHI-0086109 (**1**)*

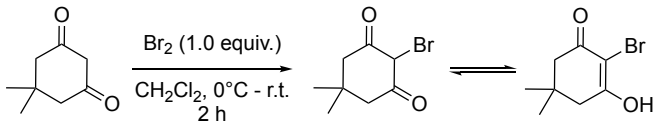
Synthesis of 2-bromocyclohexane-1,3-dione:



A suspension of 1,3-cyclohexanedione (2.99 g, 26.67 mmol, 1.0 equiv.) in CH_2Cl_2 (12 mL) was stirred at 0 °C and Br_2 (1.4 mL, 27.18 mmol, 1.0 equiv.) added dropwise over 15 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 1.5 hours before the precipitate was filtered and washed with a solution of toluene/CH_2Cl_2 (50:50). The crude product was recrystallised in water and EtOH to give the pure product as off-white crystals (4.21 g, 22.04 mmol, 83%).

MS(ESI) *m/z*: 191, $[M+H]^+$; 193, $[M+2+H]^+$. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.58 (t, *J* = 6.4 Hz, 4H, *C*H_2-CO), 1.99 (quint, *J* = 6.4 Hz, 2H, CH_2) ppm. The signal arising from the CH(Br) proton was not detected, presumably due to rapid keto-enol tautomerisation. **^{13}C NMR** (125 MHz, $CDCl_3$/DMSO-d_6, 95:5): δ 99.8 (CH_2, 2×*C*H_2-CO), 33.6 (br., CH, CH(Br)), 20.4 (CH_2, CH_2) ppm. The signal arising from the CO carbons could be detected at approximately 191.1 ppm, and a second signal at 175.0 ppm (presumably arising from the CO or =C-OH carbon of the enol tautomer), but these were too broadened to report. Apart from the aforementioned discrepancies, the NMR data match that previously reported.[4a]

Synthesis of 2-bromo-5,5-dimethylcyclohexane-1,3-dione:

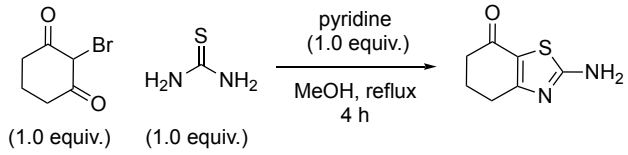


A suspension of dimedone (3.00 g, 21.40 mmol, 1.0 equiv.) in CH_2Cl_2 (40 mL) was stirred at 0 °C and Br_2 (1.1 mL, 21.34 mmol, 1.0 equiv.) added dropwise over 15 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours before the precipitate was filtered and washed with cold Et_2O to leave the pure product as an off-white powder (4.70 g, 21.40 mmol, > 99%).

MS(ESI) *m/z*: 219, $[M+H]^+$; 221, $[M+2+H]^+$.**^{1}H NMR** (500 MHz, $CDCl_3$/DMSO-d_6, 95:5): δ 6.52 (br. s, 1H, CH(Br)), 2.46 (s, 4H, *C*H_2-CO), 1.10 (s, 6H, CH_3) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$/DMSO-d_6, 95:5): δ 181.3 (br., CO or =C-OH), 98.6 (CH, CH(Br) or =C-Br), 47.1 (CH_2, 2×*C*H_2-CO), 31.8 (QC, *C*$(CH_2)_2$, 27.8 (CH_3, 2×CH_3) ppm. The signal at 98.6 ppm was significantly downfield from that observed in the literature (66.6 ppm) and may have arisen from the =C-Br carbon of the enol tautomer. Similarly, the signal at 181.3 ppm was comparatively upfield (lit. 193.0 ppm) and may therefore have

arisen from the CO or =C-OH carbon of the enol tautomer. Apart from these discrepancies, the NMR data match that previously reported.[4b]

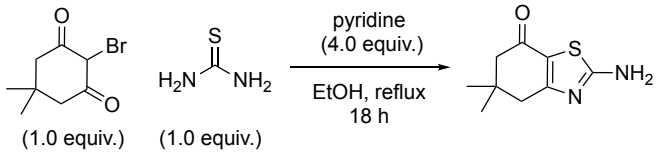
*Synthesis of 2-amino-5,6-dihydrobenzo[d]thiazol-7(4H)-one (**2a**):*



A solution of 2-bromocyclohexane-1,3-dione (4.00 g, 20.94 mmol, 1.0 equiv.), thiourea (1.63 g, 21.41 mmol, 1.0 equiv.) and pyridine (1.8 mL, 22.30 mmol, 1.0 equiv.) in MeOH (20 mL) was heated at reflux for 4 hours. The precipitate was filtered and washed with cold MeOH to leave the pure product as yellow crystals (2.46 g, 14.62 mmol, 70%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.09 (s, 2H, NH_2), 2.67 (t, J = 6.2 Hz, 2H, CH_2-C-N), 2.36 (t, J = 6.0 Hz, 2H, CH_2-CO), 1.98 (app. quint, J = 6.3 Hz, 2H, CH_2) ppm. **^{13}C NMR** (125 MHz, DMSO-d_6) δ 189.5 (QC, CO), 173.5 (QC, C-NH_2), 168.1 (QC, C-N), 118.5 (QC, C-CO), 36.8 (CH_2, *C*H_2-C-N), 26.7 (CH_2, *C*H_2-CO), 22.5 (CH_2, CH_2) ppm. The NMR data match that previously reported.[5a]

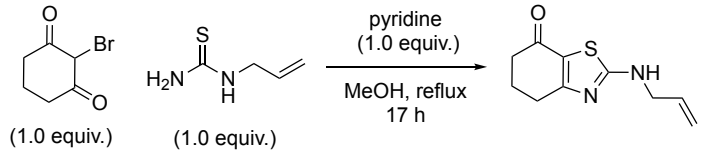
*Synthesis of 2-Amino-5,5-dimethyl-5,6-dihydrobenzo[d]thiazol-7(4H)-one (**2b**):*



A solution of 2-bromo-5,5-dimethylcyclohexane-1,3-dione (3.85 g, 17.57 mmol, 1.0 equiv.), thiourea (1.34 g, 17.60 mmol, 1.0 equiv.) and pyridine (5.7 mL, 70.62 mmol, 4.0 equiv.) in EtOH (20 mL) was heated at reflux for 18 hours. The solution was concentrated by half and then diluted with water and a saturated aqueous solution of $NaHCO_3$ added. The precipitate was filtered and washed with cold water, then MeCN, to leave the pure product as an off-white solid (1.45 g, 7.39 mmol, 42%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.83 (s, 2H, NH_2), 2.67 (s, 2H, CH_2-C-N), 2.39 (s, 2H, CH_2-CO), 1.12 (s, 6H, CH_3) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 190.8 (QC, CO), 173.2 (C-NH_2), 165.8 (QC, C-N), 120.6 (QC, C-CO), 51.4 (CH_2, CH_2-CO), 41.2 (CH_2, CH_2-N), 34.9 (QC, *C*$(CH_3)_2$), 28.5 (CH_3, 2×CH_3) ppm. The NMR data match that previously reported.[5b]

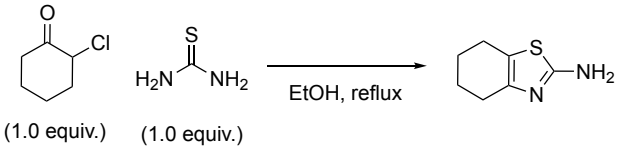
Synthesis of 2-(allylamino)-5,6-dihydrobenzo[d]thiazol-7(4H)-one:



A solution of 2-bromocyclohexane-1,3-dione (0.201 g, 1.05 mmol, 1.0 equiv.), *N*-allylthiourea (0.122 g, 1.05 mmol, 1.0 equiv.) and pyridine (85 μL, 1.05 mmol, 1.0 equiv.) in MeOH (10 mL) was heated at reflux for 17 hours. After removing the solvent *in vacuo*, the crude material was subjected to column chromatography ($MeOH/CH_2Cl_2$, 4:96) to give the pure product as a pale yellow solid (0.150 g, 0.72 mmol, 69%).

Mp 105–106 °C. **HRMS-ESI** (*m/z*): $[M+H]^+$ calcd for $C_{10}H_{13}N_2OS$, 209.0743; found, 209.0743. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3190 (br., w, NH), 3086 (br., w, $=CH_2$), 2941 (m, CH_2), 1638 (s), 1583 (s), 1521 (s), 1377 (s), 1187 (s), 991 (s), 534 (s). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.67 (br. s, 1H, NH), 5.91 – 5.83 (m, 1H, =CH), 5.32 (d, *J* = 17.1 Hz, 1H, $=CH_2$), 5.24 (d, *J* = 10.2 Hz, 1H, $=CH_2$), 3.93 (d, *J* = 5.1 Hz, 2H, CH_2-N), 2.75 (t, *J* = 6.1 Hz, 2H, CH_2-CO), 2.50 (t, *J* = 6.4 Hz, 2H, CH_2-C-N), 2.11 (app. quint, *J* = 6.2 Hz, 2H, CH_2) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 190.7 (QC, CO), 175.0 (QC, C-NH_2), 167.5 (QC, C-N), 132.0 (CH,=CH), 119.9 (QC, C-S), 118.1 (CH_2 =CH_2), 48.4 (CH_2, CH_2-N), 37.1 (CH_2, CH_2-CO), 27.3 (CH_2, CH_2-C-N), 22.8 (CH_2) ppm.

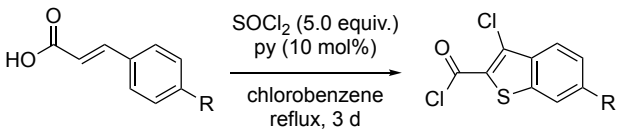
Synthesis of 4,5,6,7-tetrahydrobenzo[d]thiazol-2-amine:[6a]



A solution of 2-chlorocyclohexanone (1.02 g, 7.69 mmol, 1.0 equiv.) and thiourea (0.580 g, 7.62 mmol, 1.0 equiv.) in EtOH (10 mL) was heated at reflux until 2-chlorocyclohexanone could no longer be detected by TLC analysis (Rf = 0.74, EtOAc/hexane, 70:30). The solvent was removed *in vacuo* to leave the crude product as the hydrochloride salt. This was washed with Et_2O to remove unreacted 2-chlorocyclohexanone and agitated in aqueous NH_3 (2.0 M) to give the free base, which was filtered and washed with water to give the pure product as off-white crystals (1.03 g, 6.68 mmol, 87%).

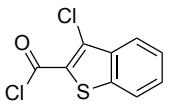
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.75 (br. s, 2H, NH_2), 2.53 – 2.45 (m, 4H, CH_2-C-S and CH_2-C-N), 1.75 (br. s, 4H, 2×CH_2) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.6 (QC, C-NH_2), 144.3 (QC, C-N), 117.4 (QC, C-S), 26.1 (CH_2), 23.3 (CH_2), 23.0 (CH_2), 22.7 (CH_2) ppm. The NMR data match that previously reported.[6b]

General procedure for the synthesis of 3-chlorobenzo[b]thiophene-2-carbonyl chloride and its 6-substituted derivatives:[7a]



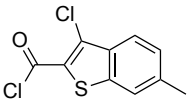
To a suspension of the appropriate cinnamic acid (1.0 equiv.) in chlorobenzene (typically approximately 1.0 M) was added thionyl chloride (5.0 equiv.), followed by pyridine (10 mol%), dropwise at room temperature. The reaction mixture was heated at reflux for 3 days before being filtered through a pad of celite and the filtrate concentrated *in vacuo*. The crude material was dissolved in hot hexane and any undissolved material filtered. The filtrate was left to cool to room temperature, allowing the pure product to recrystallise and be collected by filtration. After comparing the ^{1}H NMR spectra with literature data (if available), the reactive acyl chlorides were used promptly, as is commonly practiced in the literature.

*3-Chlorobenzo[b]thiophene-2-carbonyl chloride (**3b**):*



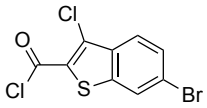
Yellow crystals, 45%. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.9 Hz, 1H, HetCH), 7.85 (d, *J* = 7.9 Hz, 1H, HetCH), 7.62 (app. t, *J* = 7.2 Hz, 1H, HetCH), 7.55 (app. t, *J* = 7.3 Hz, 1H, HetCH) ppm. The NMR data match that previously reported.[7b]

*3-Chloro-6-methylbenzo[b]thiophene-2-carbonyl chloride (**3c**):*



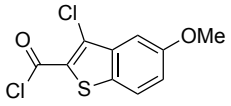
Yellow crystals, 46%. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.4 Hz, 1H, HetCH), 7.61 (s, 1H, HetCH), 7.35 (d, *J* = 8.4 Hz, 1H, HetCH), 2.53 (s, 3H, Me) ppm. The NMR data match that previously reported.[7d]

*6-Bromo-3-chlorobenzo[b]thiophene-2-carbonyl chloride (**3d**):*



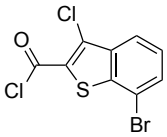
Yellow crystals, 41%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.03 (d, *J* = 1.2 Hz, 1H, HetCH), 7.88 (d, *J* = 8.8 Hz, 1H, HetCH), 7.66 (dd, *J* = 8.7, 1.5 Hz, 1H, HetCH) ppm. The NMR data match that previously reported.[7a]

*3-Chloro-5-methoxybenzo[b]thiophene-2-carbonyl chloride (**3e**):*



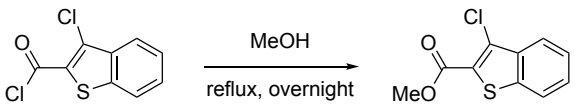
Purified via recrystallisation in CH_2Cl_2. Yellow crystals, 29%. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.9 Hz, 1H, HetCH), 7.34 (d, *J* = 2.1 Hz, 1H, HetCH), 7.27 (dd, *J* = 6.5, 2.1 Hz, 1H, HetCH), 3.94 (s, 3H, OMe) ppm. The NMR data match that previously reported.[7c]

*7-Bromo-3-chlorobenzo[b]thiophene-2-carbonyl chloride (**3f**):*



Purified via recrystallisation in heptane with minimal CH_2Cl_2. Pale yellow crystals, 7%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.2 Hz, 1H, HetCH), 7.77 (d, *J* = 7.6 Hz, 1H, HetCH), 7.45 (app. t, *J* = 7.9 Hz, 1H, HetCH) ppm.

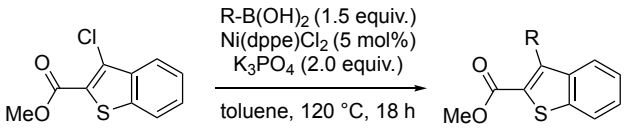
*Synthesis of methyl 3-chlorobenzo[b]thiophene-2-carboxylate (**3a**):*



A solution of 3-chlorobenzo[*b*]thiophene-2-carbonyl chloride (0.212 g, 0.92 mmol, 1.0 equiv.) was heated at reflux in MeOH overnight. After removing the excess MeOH *in vacuo*, the crude material was recrystallized in EtOH to give the pure product as pale yellow needles (0.196 g, 0.86 mmol, 93%).

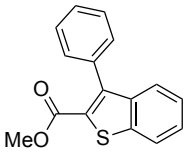
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.8 Hz, 1H, HetCH), 7.83 (d, *J* = 7.8 Hz, 1H, HetCH), 7.59 – 7.46 (m, 2H, HetCH), 3.97 (s, 3H, OMe) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ 161.7 (QC, CO), 138.6 (QC, HetC), 137.0 (QC, HetC), 128.2 (CH, HetCH), 127.5 (QC, HetC), 125.4 (CH, HetCH), 123.8 (CH, HetCH), 122.7 (CH, HetCH), 52.5 (CH_3, OMe) ppm. The NMR data match that previously reported.[8]

General procedure for the Ni(0)-catalysed synthesis of cross-coupled 3-arylbenzo[b]thiophene-2-carboxylates:[9]



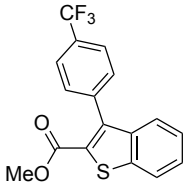
Methyl 3-chlorobenzo[*b*]thiophene-2-carboxylate (1.0 equiv.), the appropriate arylboronic acid (1.5 equiv.), Ni(dppe)Cl_2 (5 mol%) and K_3PO_4 (2.0 equiv.) were heated at 120 °C in toluene in a capped reaction vial for 18 hours. If methyl 3-chlorobenzo[*b*]thiophene-2-carboxylate could still be detected via TLC analysis (Rf = 0.28, EtOAc/hexane, 5:95) after this time, a further portion of arylboronic acid and Ni(dppe)Cl_2 was added and the reaction continued for a further 18 hours to consume starting material and enable purification. The reaction mixture was diluted with CH_2Cl_2 and filtered, before the solvents were removed *in vacuo*. The crude material was subjected to column chromatography (EtOAc/hexane, 5:95, unless otherwise specified) to give the pure product.

Methyl 3-phenylbenzo[b]thiophene-2-carboxylate:



White crystals, 80%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.1 Hz, 1H, HetCH), 7.74 – 7.26 (m, 9H, HetCH and ArCH), 3.79 (s, 3H, OMe) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ 162.9 (QC, CO), 144.2 (QC, HetC), 140.4 (QC, HetC), 140.0 (QC, HetC), 134.5 (QC, HetC), 129.6 (CH, 2×ArCH), 128.1 (CH, ArCH), 128.0 (CH, 2×ArCH), 127.8 (QC, ArC), 127.2 (CH, HetCH), 125.3 (CH, HetCH), 124.8 (CH, HetCH), 122.5 (CH, HetCH), 52.2 (CH_3, OMe) ppm. The NMR data match that previously reported.[9]

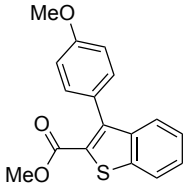
Methyl 3-(4-(trifluoromethyl)phenyl)benzo[b]thiophene-2-carboxylate:



A further portion of 4-(trifluoromethyl)phenylboronic acid (1.5 equiv.) and Ni(dppe)Cl_2 (2.5 mol%) was added after 18 hours to push the reaction to completion, however an inseparable mixture (10:90) of starting material and product was obtained after purification. Eluent: EtOAc/hexane (1:99). Pale yellow crystals, 70%. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.1 Hz, 1H, HetCH), 7.74 (d, *J* = 8.0 Hz, 2H, ArCH or HetCH), 7.51 (d, *J* = 8.0 Hz, 2H, ArCH or HetCH), 7.46 (d, *J* = 8.3 Hz, 2H, ArCH or HetCH), 7.35 (app. t, *J* = 7.6 Hz, 1H, HetCH), 3.77 (s, 3H, OMe) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$):

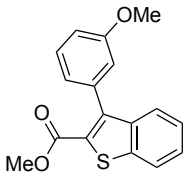
δ 162.6 (QC, CO), 142.3 (QC, HetC), 140.5 (QC, HetC), 139.5 (QC, HetC), 138.3 (QC, ArC), 130.13 (CH, 2×ArCH), 130.12 (q, J = 32.5 Hz, QC, *C*-CF_3), 128.5 (QC, HetC), 127.4 (CH, HetCH), 125.1 (CH, HetCH), 125.0 (q, J = 3.7 Hz, CH, 2×ArCH), 124.2 (q, J = 272.2 Hz, QC, CF_3), 124.1 (CH, HetCH), 122.6 (CH, HetCH), 52.2 (CH_3, OMe) ppm. The NMR data match that previously reported.[9]

Methyl 3-(4-methoxyphenyl)benzo[b]thiophene-2-carboxylate:



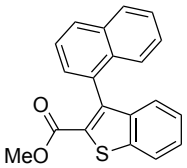
Eluent: EtOAc/hexane (10:90). White solid, 88%. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 2924 (w), 1719 (s, CO), 1500 (m), 1232 (vs), 1170 (vs), 759 (vs), 739 (vs). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.88 (d, J = 8.0 Hz, 1H, HetCH), 7.59 (d, J = 8.2 Hz, 1H, HetCH), 7.48 (app. t, J = 7.5 Hz, 1H, HetCH), 7.38 – 7.34 (m, 4H, HetCH and ArCH), 7.03 (d, J = 8.5 Hz, 2H, ArCH), 3.89 (s, 3H, OMe), 3.80 (s, 3H, OMe) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ 163.0 (QC, CO), 159.5 (QC, *C*-OMe), 144.1 (QC, HetC), 140.4 (QC, HetC), 140.2 (QC, HetC), 131.0 (CH, 2×ArCH), 127.2 (CH, HetCH), 126.5 (QC, ArC), 125.4 (CH, HetCH), 124.7 (CH, HetCH), 122.5 (CH, HetCH), 113.5 (CH, HetCH), 55.2 (CH_3, OMe), 52.1 (CH_3, OMe) ppm. The NMR data match that previously reported.[9]

Methyl 3-(3-methoxyphenyl)benzo[b]thiophene-2-carboxylate:



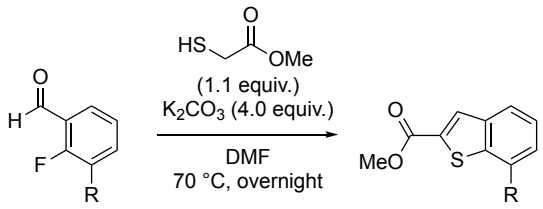
A further portion of 3-methoxyphenylboronic acid (0.5 equiv.) and Ni(dppe)Cl_2 (5 mol%) was added after 18 hours to push the reaction to completion. White solid, 84%. Mp 126 – 127 °C. **HRMS-ASAP** (*m*/z): $[M+H]^+$ calcd for $C_{17}H_{15}O_3S$, 299.0736, found, 299.0737. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 2944 (br., vw), 1723 (s, CO), 1226 (vs, OMe), 756 (s), 737 (s). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.89 (d, J = 8.1 Hz, 1H, HetCH), 7.58 (d, J = 8.2 Hz, 1H, HetCH), 7.48 (app. t, J = 7.9 Hz, 1H, ArCH or HetCH), 7.41 (app. t, J = 7.9 Hz, 1H, ArCH or HetCH), 7.36 (app. t, J = 7.9 Hz, 1H, ArCH or HetCH), 7.05 – 6.98 (m, 2H, ArCH), 6.96 (br. s, 1H, ArCH), 3.85 (s, 3H, OMe), 3.80 (s, 3H, OMe) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 162.8 (QC, CO), 159.2 (QC, *C*-OMe), 143.9 (QC, HetC), 140.3 (QC, HetC), 140.0 (QC, HetC), 135.8 (QC, HetC), 129.0 (CH, ArCH or HetCH), 127.9 (QC, ArC), 127.2 (CH, ArCH or HetCH), 125.3 (CH, ArCH or HetCH), 124.8 (CH, ArCH or HetCH), 122.4 (CH, ArCH or HetCH), 122.1 (CH, ArCH or HetCH), 115.2 (CH, ArCH), 113.6 (CH, ArCH), 55.2 (CH_3, OMe), 52.2 (CH_3, OMe) ppm.

Methyl 3-(naphthalen-1-yl)benzo[b]thiophene-2-carboxylate:



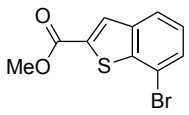
A further portion of 1-naphthylboronic acid (1.5 equiv.) and Ni(dppe)Cl_2 (5 mol%) was added after 18 hours to push the reaction to completion. Eluent: EtOAc/hexane (10:90). White solid, 79%. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 1721 (vs, CO), 1278 (m), 1243 (s), 776 (s), 756 (s). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.05 – 7.91 (m, 3H, ArCH or HetCH), 7.61 (app. t, *J* = 7.1 Hz, 1H, ArCH or HetCH), 7.54 – 7.43 (m, 3H, ArCH or HetCH), 7.40 (d, *J* = 8.4 Hz, 1H, ArCH or HetCH), 7.33 (app. t, *J* = 7.1 Hz, 1H, ArCH or HetCH), 7.30 – 7.23 (m, 2H, ArCH or HetCH), 3.65 (s, 3H, OMe) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 162.3 (QC, CO), 142.5 (QC, HetC), 140.6 (QC, HetC), 140.4 (HetC), 133.5 (QC, ArC or HetC), 132.6 (QC, ArC or HetC), 132.2 (QC, ArC or HetC), 129.5 (QC, ArC or HetC), 128.5 (CH, ArCH or HetCH), 128.3 (CH, ArCH or HetCH), 127.3 (CH, ArCH or HetCH), 127.2 (CH, ArCH or HetCH), 126.1 (CH, ArCH or HetCH), 125.9 (CH, ArCH or HetCH), 125.49 (CH, ArCH or HetCH), 125.47 (CH, ArCH or HetCH), 125.2 (CH, ArCH or HetCH), 124.8 (CH, ArCH or HetCH), 122.5 (CH, ArCH or HetCH), 52.2 (CH_3, OMe) ppm. The NMR data match that previously reported.[9]

General procedure for the synthesis of 7-substituted benzothiophenyl-2-methyl esters:[10a]



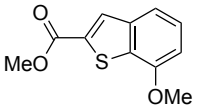
To a suspension of the appropriate 3-substituted-2-fluorobenzaldehyde in DMF (typically approximately 2.0 M) was added methyl thioglycolate (1.1 equiv.) and K_2CO_3 (4.0 equiv.) and the reaction mixture stirred vigorously at 70 °C overnight. After removing the solvent *in vacuo*, the crude material was washed with water and extracted with EtOAc. The organic layer was dried with sodium sulfate, filtered and concentrated *in vacuo* to give the pure product.

*Methyl 7-bromobenzo[b]thiophene-2-carboxylate (**3g**):*



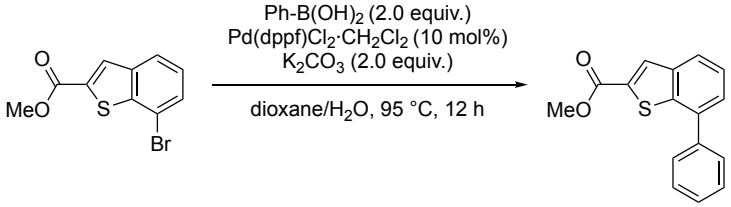
Beige crystals, 99%. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.13 (s, 1H, HetCH), 7.82 (d, *J* = 8.0 Hz, 1H, HetCH), 7.59 (d, *J* = 7.6 Hz, 1H, HetCH), 7.29 (app. t, *J* = 7.8 Hz, 1H, HetCH), 3.96 (s, 3H, OMe) ppm. The NMR data match that previously reported.[10a]

*Methyl 7-methoxybenzo[b]thiophene-2-carboxylate (**3h**):*



Red needles, 72%. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.05 (s, 1H, HetCH), 7.48 (dd, *J* = 8.0, 0.6 Hz, 1H, HetCH), 7.36 (app. t, *J* = 7.9 Hz, 1H, HetCH), 6.87 (d, *J* = 7.4 Hz, 1H, HetCH), 4.01 (s, 3H, OMe), 3.94 (s, 3H, OMe) ppm. The NMR data match that previously reported.[10b]

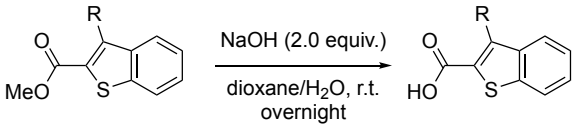
*Synthesis of methyl 7-phenylbenzo[b]thiophene-2-carboxylate (**3i**):*



Methyl 7-bromobenzo*[b]*thiophene-2-carboxylate (302 mg, 1.11 mmol, 1.0 equiv.), phenylboronic acid (268 mg, 2.20 mmol, 2.0 equiv.), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (91 mg, 0.11 mmol, 10 mol%) and K_2CO_3 (305 mg, 2.21 mmol, 2.0 equiv.) were heated at 95 °C in a mixture of dioxane/water (80:20, 6 mL). After 12 hours, the reaction mixture was filtered and the precipitate washed with EtOAc, followed by CH_2Cl_2. The solvents were removed *in vacuo* to leave the crude material, which was subjected to column chromatography (EtOAc/hexane, 10:90) to give the pure product as white crystals (187 mg, 0.70 mmol, 63%).

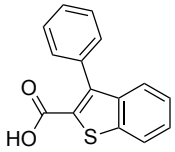
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (dd, *J* = 7.2, 1.9 Hz, 1H, HetCH), 7.73 – 7.70 (m, 2H, HetCH), 7.54 – 7.42 (m, 5H, ArCH), 3.94 (s, 3H, OMe) ppm. The NMR data match that previously reported.[10c]

General procedure for the basic hydrolysis of methyl benzo[b]thiophene-2-carboxylates to carboxylic acids:



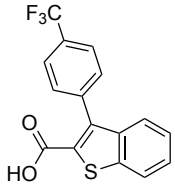
A solution of the methyl ester in dioxane (typically approximately 0.2 M) was stirred at room temperature with aqueous NaOH (2.0 equiv) in a capped vial overnight. If the methyl ester could still be detected via TLC analysis after this time, a further portion of aqueous NaOH was added and the reaction continued until the starting material could no longer be detected via TLC analysis. The reaction was quenched with aqueous HCl (3.0 equiv), then water. The product was extracted with ethyl acetate and the combined organic extracts washed with brine, before being dried with $MgSO_4$. The solvents were removed *in vacuo* to leave the pure carboxylic acid.

3-Phenylbenzo[b]thiophene-2-carboxylic acid:



White crystals, 95%. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.07 (d, J = 8.1 Hz, 1H, HetCH), 7.55 – 7.38 (m, 9H, ArCH and HetCH) ppm. **^{13}C NMR** (125 MHz, DMSO-d_6): δ 163.3 (QC, CO), 142.3 (QC, HetC), 139.7 (QC, HetC), 139.4 (QC, HetC), 134.2 (QC, ArC or HetC), 129.7 (CH, 2×ArCH), 128.0 (CH, 2×ArCH), 127.9 (CH, ArCH or HetCH), 127.2 (CH, ArCH or HetCH), 125.1 (CH, ArCH or HetCH), 124.6 (CH, ArCH or HetCH), 122.9 (CH, ArCH or HetCH) ppm. The NMR data match that previously reported.[9]

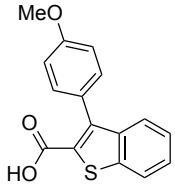
3-(4-(Trifluoromethyl)phenyl)benzo[b]thiophene-2-carboxylic acid:



A further portion of aqueous NaOH (2.0 equiv.) was required to consume the starting material. Crude material was subjected to column chromatography ($MeOH/CH_2Cl_2$, 10:90) to remove unreacted methyl 3-chlorobenzo[b]thiophene-2-carboxylate from the previous step. White crystals, 77%. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 2834 (br., w, OH), 1664 (s, CO), 1328 (vs), 1109 (vs). **^{1}H NMR** (500 MHz, DMSO-d_6): δ 13.36 (br. s, 1H, OH), 8.11 (d, J = 8.2 Hz, 1H, HetCH), 7.86 (d, J = 8.0 Hz, 2H, ArCH), 7.65 (d, J = 7.9 Hz, 2H, ArCH), 7.57 (app. t, J = 7.4 Hz, 1H, HetCH), 7.45 – 7.40 (m, 2H, HetCH) ppm. **^{13}C NMR** (100 MHz,

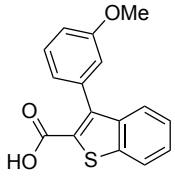
DMSO-d_6): δ 163.1 (QC, CO), 140.6 (QC, HetC), 139.5 (QC, HetC), 139.3 (QC, HetC), 138.8 (QC, ArC or HetC), 138.7 (QC, ArC or HetC), 130.7 (CH, 2×ArCH), 128.4 (q, J = 31.8 Hz, QC, C-CF_3), 127.5 (CH, HetCH), 125.5 (CH, HetCH), 125.3 (q, J = 272.1 Hz, QC, CF_3), 124.9 (q, J = 3.7 Hz, CH, 2×ArCH), 124.4 (CH, HetCH), 123.1 (CH, HetCH) ppm. The NMR data match that previously reported.[9]

3-(4-Methoxyphenyl)benzo[b]thiophene-2-carboxylic acid:



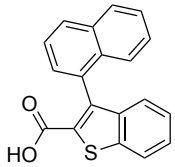
White crystals, 93%. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 2544 (br., w, OH), 1653 (s, CO), 1500 (s), 1289 (s), 1250 (s), 737 (vs). **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.06 (d, J = 8.1 Hz, 1H, HetCH), 7.53 (app. t, J = 7.5 Hz, 1H, HetCH), 7.47 (d, J = 8.0 Hz, 1H, HetCH), 7.41 (app. t, J = 7.5 Hz, 1H, HetCH), 7.34 (d, J = 8.5 Hz, 2H, ArCH), 7.05 (d, J = 8.5 Hz, 2H, ArCH), 3.83 (s, 3H, OMe) ppm. **^{13}C NMR** (125 MHz, DMSO-d_6): δ 163.4 (QC, CO), 159.0 (QC, C-OMe), 142.1 (QC, HetC), 139.9 (QC, HetC), 139.3 (QC, HetC), 131.0 (CH, 2×ArCH), 129.2 (QC, ArC), 127.2 (CH, HetCH), 126.1 (QC, HetC), 125.0 (CH, HetCH), 124.6 (CH, HetCH), 122.8 (CH, HetCH), 113.4 (CH, 2×ArCH), 55.1 (CH_3, OMe) ppm. The NMR data match that previously reported.[9]

3-(3-Methoxyphenyl)benzo[b]thiophene-2-carboxylic acid:



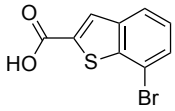
A further portion of aqueous NaOH (0.5 equiv.) was required to consume the starting material. White crystals, 97%. Mp 206 – 208 °C. **HRMS-ESI** (m/z): $[M+Na]^+$ calcd for $C_{16}H_{12}O_3SNa$, 307.0399; found, 307.0406. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 2972 (br., w, OH), 1684 (s, CO), 1242 (s), 1034 (s), 728 (vs). **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.07 (d, J = 8.1 Hz, 1H, HetCH), 7.54 (app. t, J = 7.4 Hz, 1H, ArCH or HetCH), 7.48 – 7.36 (m, 3H, ArCH and HetCH), 7.06 – 7.00 (m, 1H, ArCH or HetCH), 6.98 – 6.91 (m, 2H, ArCH), 3.78 (s, 3H, OMe) ppm. **^{13}C NMR** (125 MHz, DMSO-d_6): δ 163.2 (QC, CO), 158.8 (QC, C-OMe), 142.0 (QC, HetC), 139.7 (QC, HetC), 139.3 (QC, HetC), 135.6 (CH, ArCH or HetCH), 129.8 (QC, ArC), 129.0 (CH, ArCH or HetCH), 127.2 (QC, HetC), 125.1 (CH, ArCH or HetCH), 124.6 (CH, ArCH or HetCH), 122.8 (CH, ArCH or HetCH), 121.9 (CH, ArCH), 115.3 (CH, ArCH), 113.4 (CH, ArCH), 55.07 ppm.

3-(Naphthalen-1-yl)benzo[b]thiophene-2-carboxylic acid:



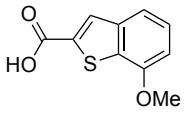
White crystals, 92%. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 2862 (br., w, OH), 1653 (vs, CO), 1286 (s), 735 (s). **^{1}H NMR** (500 MHz, DMSO-d_6): δ 13.08 (br. s, 1H, OH), 8.14 (d, J = 8.2 Hz, 1H, ArCH or HetCH), 8.04 – 8.02 (m, 2H, ArCH or HetCH), 7.63 (app. t, J = 7.6 Hz, 1H, ArCH or HetCH), 7.55 – 7.50 (m, 2H, ArCH or HetCH), 7.46 (d, J = 6.9 Hz, 1H, ArCH or HetCH), 7.37 (app. t, J = 7.6 Hz, 1H, ArCH or HetCH), 7.32 – 7.26 (m, 2H, ArCH or HetCH), 7.03 (d, J = 8.1 Hz, 1H, ArCH or HetCH) ppm. **^{13}C NMR** (125 MHz, DMSO-d_6): δ 163.1 (QC, CO), 140.5 (QC, HetC), 140.3 (QC, HetC), 139.5 (QC, HetC), 133.1 (QC, ArC or HetC), 132.5 (QC, ArC or HetC), 131.7 (QC, ArC or HetC), 131.4 (QC, ArC or HetC), 128.3 (CH, ArCH or HetCH), 128.1 (CH, ArCH or HetCH), 127.3 (CH, ArCH or HetCH), 127.2 (CH, ArCH or HetCH), 126.3 (CH, ArCH or HetCH), 125.9 (CH, ArCH or HetCH), 125.4 (CH, ArCH or HetCH), 125.2 (CH, ArCH or HetCH), 125.0 (CH, ArCH or HetCH), 124.6 (CH, ArCH or HetCH), 123.0 (CH, ArCH or HetCH) ppm. The NMR data match that previously reported.[9]

7-Bromobenzo[b]thiophene-2-carboxylic acid:



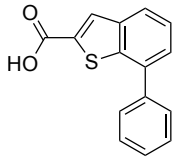
White solid, 98%. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 13.70 (br. s, 1H, OH), 8.26 (s, 1H, HetCH), 8.05 (dd, J = 8.1, 0.9 Hz, 1H, HetCH), 7.77 (dd, J = 7.7, 0.9 Hz, 1H, HetCH), 7.44 (app. t, J = 7.8 Hz, 1H, HetCH) ppm. The NMR data match that previously reported.[10a]

7-methoxybenzo[b]thiophene-2-carboxylic acid:



White solid, 98%. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 13.47 (br. s, 1H, OH), 8.09 (s, 1H, HetCH), 7.59 (dd, J = 8.1, 0.9 Hz, 1H, HetCH), 7.42 (app. t, J = 7.9 Hz, 1H, HetCH), 7.07 (dd, J = 8.0, 0.8 Hz, 1H, HetCH), 3.97 (s, 3H, OMe) ppm. The NMR data match that previously reported.[11]

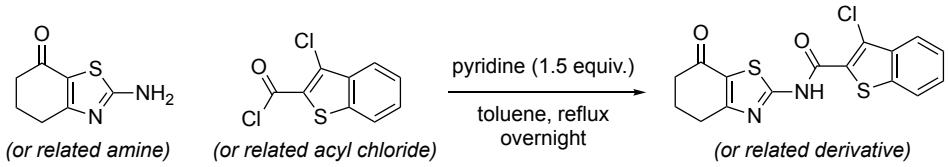
7-Phenylbenzo[b]thiophene-2-carboxylic acid:



White solid, yield not determined. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 13.50 (br. s, 1H, OH), 8.20 (s, 1H, HetCH), 8.03 (dd, J = 7.2, 1.9 Hz, 1H, HetCH), 7.74 – 7.71 (m, 2H, ArCH), 7.61 – 7.46 (m, 5H, HetCH and ArCH) ppm. The NMR data match that previously reported.[11]

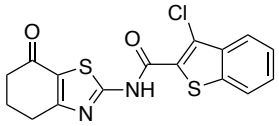
*3. Synthesis of Derivatives of WEHI-0086109 (**1**)*

*General procedure for the synthesis of WEHI-0086109 (**14a**) derivatives via a Schotten–Baumann Amidation:*



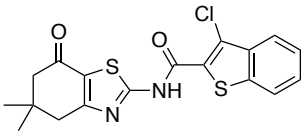
Where required, the appropriate acyl chloride was freshly prepared from the corresponding carboxylic acid. To a solution of the carboxylic acid in dioxane (typically approximately 0.04 M) was added thionyl chloride (5.0 equiv.) and the reaction mixture heated at reflux overnight, before the solvents and excess thionyl chloride were removed *in vacuo* to leave the acyl chloride, which was used immediately. A solution of the acyl chloride (1.0 equiv.), the appropriate benzothiazole amine fragment (1.0 equiv.) and pyridine (1.5 equiv.) in toluene (typically approximately 0.05 M with respect to the acyl chloride) was heated at reflux overnight, or until the starting materials could no longer be detected via TLC analysis. The solvent was removed *in vacuo* before the residue was washed with aqueous HCl (2.0 M) and extracted with CH_2Cl_2, before the organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. If required, the crude material was subjected to either column chromatography or recrystallisation (detailed below) to give the pure carboxamide. In some cases, a small analytical sample of high purity was obtained (detailed below) for the purpose of biological testing.

*3-Chloro-N-(7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzo[b]thiophene-2-carboxamide (**1**):*



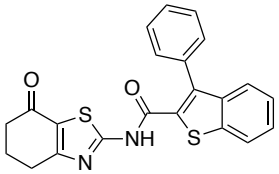
Yellow solid, > 99%. Mp 223 – 226 °C. **HRMS-ESI** (*m*/*z*): $[M+Na]^+$ calcd for $C_{16}H_{11}ClN_2O_2S_2Na$, 384.9843; found, 384.9839. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3366 (m, NH), 1662 (s, CO), 1654 (vs, CO-NH), 1537 (s), 1522 (s), 1374 (s), 1299 (s), 771 (s). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.48 (br. s, 1H, NH), 7.97 – 7.95 (m, 1H, HetCH), 7.91 – 7.89 (m, 1H, HetCH), 7.60 – 7.54 (m, 2H, HetCH), 2.97 (app. t, *J* = 6.2 Hz, 2H, CH_2-CO), 2.63 – 2.61 (m, 2H, CH_2-C-N), 2.23 (app. quint, *J* = 6.3 Hz, 2H, CH_2) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.5 (QC, CO), 163.6 (QC, C-N), 162.0 (C-NH), 158.2 (QC, CO-NH), 139.0 (QC, HetC), 136.6 (QC, HetC), 129.7 (QC, HetC), 128.6 (CH, HetCH), 126.2 (QC, HetCH), 126.0 (CH, HetCH), 123.7 (CH, HetCH), 123.0 (CH, HetCH), 121.6 (QC, HetC), 37.8 (CH_2, CH_2-C-N), 26.9 (CH_2, CH_2-CO), 23.0 (CH_2, CH_2) ppm. **HPLC**: t_R 8.86 min, 96% purity at 254 nm. Eluted using a concentration gradient of 0 – 100% solvent B in A over 15 minutes.

*3-Chloro-N-(5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzo[b]thiophene-2-carboxamide (**4**):*



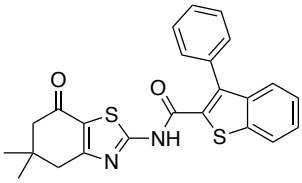
Purified via column chromatography (EtOAc/hexane, 30:70). Brown solid, 86%. An analytical sample was obtained via recrystallisation in CH_2Cl_2 layered with hexane and used for biological testing. Mp 178 – 179 °C. **HRMS-ESI** (*m*/*z*): $[M–H]^-$ calcd for $C_{18}H_{14}ClN_2O_2S_2$, 389.0191; found, 389.0179 **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3325 (vw, NH), 1658 (s, CO), 1543 (s), 1514 (s), 1366 (s), 1289 (s), 885 (m), 740 (s). **^{1}H NMR** (400 MHz, $CDCl_3$): 7.95 (dd, *J* = 7.0, 1.8 Hz, 1H, HetCH), 7.90 (dd, *J* = 6.9, 1.5 Hz, 1H, HetCH), 7.60 – 7.53 (m, 2H, HetCH), 2.80 (s, 2H, CH_2-CO), 2.47 (s, CH_2-C-N), 1.13 (s, 6H, CH_3) ppm. The signal arising from the NH proton could be detected at approximately 10.50 ppm, but was too broadened to report. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 192.1 (QC, CO), 162.3 (QC, C-N), 162.2 (QC, C-NH), 158.2 (QC, CO-NH), 139.0 (QC, HetC), 136.6 (QC, HetC), 129.7 (QC, HetC), 128.6 (CH, HetCH), 126.0 (CH, HetCH), 125.0 (QC, HetC), 123.7 (CH, HetCH), 123.0 (CH, HetCH), 121.6 (QC, HetC), 51.8 (CH_2, CH_2-C-N), 40.9 (CH_2, CH_2-CO), 35.1 (QC, $C(CH_3)_2$, 28.4 (CH_3, 2×CH_3) ppm. **HPLC**: t_R 8.40 min, 99% purity at 254 nm.

*N-(7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-3-phenylbenzo[b]thiophene-2-carboxamide (**5**):*



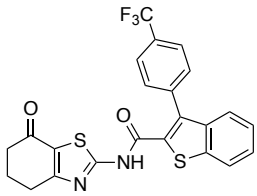
Purified via column chromatography (EtOAc/hexane, 50:50), off-white solid, 13%. Mp 247 – 250 °C. **HRMS-ESI** (*m*/*z*): $[M–H]^-$ calcd for $C_{22}H_{15}N_2O_2S_2$, 403.0580; found, 403.0568. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3343 (m, NH), 1661 (s, CO), 1528 (s), 1506 (vs), 1371 (s), 1287 (s), 1217 (s), 743 (s). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.1 Hz, 1H, HetCH), 7.67 – 7.64 (m, 3H, ArCH and HetCH), 7.53 – 7.48 (m, 4H, ArCH and HetCH), 7.39 (app. t, *J* = 7.5 Hz, 1H, ArCH or HetCH), 2.70 (t, *J* = 6.1 Hz, 2H, CH_2-CO), 2.52 (t, *J* = 6.2 Hz, 2H, CH_2-C-N), 2.05 (app. quint, *J* = 6.2 Hz, 2H, CH_2) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.5 (QC, CO), 163.6 (QC, C-N), 162.2 (QC, C-NH), 160.1 (QC, CO-NH), 140.6 (QC, HetC), 140.2 (QC, HetC), 140.0 (QC, HetC), 132.7 (QC, ArC or HetC), 131.9 (QC, ArC or HetC), 130.0 (CH, ArCH), 129.9 (CH, 2×ArCH), 129.7 (CH, 2×ArCH), 127.6 (CH, HetCH), 125.6 (QC, HetC), 125.3 (CH, HetCH), 125.2 (CH, HetCH), 122.7 (CH, HetCH), 37.7 (CH_2, CH_2-C-N), 26.7 (CH_2, CH_2-CO), 22.9 (CH_2, CH_2) ppm. **HPLC**: t_R 8.86 min, 96% purity at 254 nm.

*N-(5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-3-phenylbenzo[b]thiophene-2-carboxamide (**6**):*



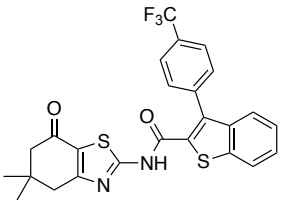
Synthesised with the addition of catalytic DMAP (10 mol%). Purified via recrystallisation in toluene. Yellow crystals, 58%. Mp 229 – 230 °C. **HRMS-ESI** (*m*/*z*): $[M–H]^-$ calcd for $C_{24}H_{19}N_2O_2S_2$, 431.0893; found, 431.0895. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3329 (w, NH), 1654 (s, CO), 1512 (s), 1370 (m), 1292 (m). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.41 (br. s, 1H, NH), 7.94 (d, *J* = 8.0 Hz, 1H, HetCH), 7.69 – 7.63 (m, 3H, ArCH and HetCH), 7.59 – 7.46 (m, 4H, ArCH and HetCH), 7.44 – 7.35 (m, 1H, ArCH or HetCH), 2.52 (s, 2H, CH_2-CO), 2.36 (s, 2H, CH_2-C-N), 0.99 (s, 6H, CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 192.1 (QC, CO), 162.5 (QC, C-N), 162.1 (QC, C-NH), 160.1 (QC, CO-NH), 140.6 (QC, HetC), 140.2 (QC, HetC), 140.1 (QC, HetC), 132.8 (QC, ArC or HetC), 131.9 (QC, ArC or HetC), 130.0 (CH, ArCH), 129.9 (CH, 2×ArCH), 129.7 (CH, 2×ArCH), 127.6 (CH, HetCH), 125.3 (CH, HetCH), 125.2 (CH, HetCH), 124.4 (QC, HetC), 122.7 (CH, HetCH), 51.7 (CH_2, CH_2-C-N), 40.7 (CH_2, CH_2-CO), 34.8 (QC, *C*(CH_3)$_2$), 28.3 (CH_3, 2×CH_3) ppm. **HPLC**: t_R 9.70 min, > 99% purity at 254 nm.

N-(7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-3-(4-(trifluoromethyl)phenyl)benzo[b]thiophene-2-carboxamide (7):



Purified via column chromatography (EtOAc/hexane, 50:50), off-white solid, 47%. Mp 271 – 272 °C. **HRMS-ESI** (*m*/*z*): $[M+H]^+$ calcd for $C_{23}H_{16}F_3N_2O_2S_2$, 473.0600; found, 473.0603. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3377 (vw, NH), 1643 (m, CO), 1490 (m), 1279 (s), 1162 (m), 1121 (s), 1066 (vs), 736 (m). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.02 (br. s, 1H, NH), 7.92 (d, *J* = 8.1 Hz, 1H, ArCH), 7.83 (d, *J* = 7.8 Hz, 2H, ArCH), 7.57 (d, *J* = 8.2 Hz, 2H, ArCH), 7.54 – 7.50 (m, 2H, ArCH), 7.43 (app. t, *J* = 7.5 Hz, 1H, ArCH), 2.60 (t, *J* = 5.9 Hz, 2H, CH_2-C-N), 2.49 (t, *J* = 6.3 Hz, 2H, CH_2-CO), 1.99 (app. quint, *J* = 6.1 Hz, 2H, CH_2) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.2 (QC, CO), 162.71 (QC, C-N or C-NH), 162.69 (QC, C-N or C-NH), 160.2 (QC, CO-NH), 140.2 (QC, HetC), 139.3 (QC, HetC), 139.0 (QC, HetC), 136.7 (QC, HetC), 131.9 (QC, ArC), 131.4 (q, *J* = 32.5 Hz, QC, *C*-CF_3), 130.3 (CH, 2×ArCH), 127.8 (CH, HetCH), 126.3 (q, *J* = 3.3 Hz, 2×*C*H-C-CF_3), 125.7 (CH, HetCH), 124.7 (CH, HetCH), 123.8 (q, *J* = 272.6 Hz, QC, CF_3), 122.8 (CH, HetCH), 125.6 (QC, HetC), 37.7 (CH_2, *C*H_2-CO), 26.4 (CH_2, *C*H_2-C-N), 22.8 (CH_2) ppm. **HPLC**: t_R 9.03 min, 97% purity at 254 nm.

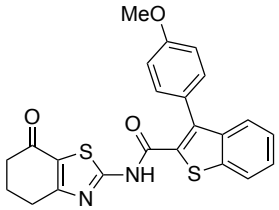
*N-(5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-3-(4-(trifluoromethyl)phenyl)benzo[b]thiophene-2-carboxamide (**8**):*



Purified via column chromatography (EtOAc/hexane, 30:70). Off-white solid, 82%. An analytical sample was obtained via recrystallisation in EtOAc layered with hexane and used for biological testing. Mp 228 – 229 °C. **HRMS-ESI** (*m*/*z*): $[M+H]^+$ calcd for $C_{25}H_{20}F_3N_2O_2S_2$, 501.0913; found, 501.0917. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3374 (m, NH), 1666 (vs, CO), 1513 (vs), 1328 (s), 1177 (s), 1065 (s), 751 (m). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.43 (br. s, 1H, NH), 7.94 (d, *J* = 8.2 Hz, 1H, ArCH or HetCH), 7.84 (d, *J* = 8.1 Hz, 2H, ArCH or HetCH), 7.58 (d, *J* = 8.1 Hz, 2H, ArCH or HetCH), 7.56 – 7.50 (m, 2H, ArCH or HetCH), 7.47 – 7.40 (m, 1H, ArCH or HetCH), 2.31 (s, 2H, CH_2-CO), 2.30 (s, 2H, CH_2-C-N), 0.87 (s, 6H, CH_3) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 191.9 (QC, CO), 162.9 (QC, C-NH), 161.5 (QC, C-N), 160.0 (QC, CO-NH), 140.2 (QC, ArC), 139.3 (QC, ArC), 139.2 (QC, ArC), 136.9 (QC, HetC), 131.6 (QC, ArC), 131.5 (q, *J* = 32.5 Hz, QC, *C*-CF_3) 130.4 (CH, 2×ArCH), 127.8 (CH, HetCH), 126.4 (q, *J* = 3.5 Hz, CH, 2×*C*H-C-CF_3), 125.8 (CH, HetCH), 124.8 (CH, HetCH), 124.4 (QC, S-*C*-CO),

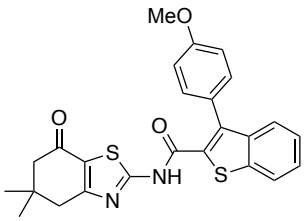
123.8 (q, J = 271.3 Hz, QC, CF_3), 122.8 (CH, HetCH), 51.7 (CH_2, CH$_2$-CO), 40.3 (CH$_2$-C-N), 34.8 (QC, C(CH$_3$)$_2$), 28.2 (CH$_3$, 2×CH$_3$) ppm. **HPLC**: t_R 10.00 min, 98% purity at 254 nm.

*3-(4-Methoxyphenyl)-N-(7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzo[b]thiophene-2-carboxamide (**9**):*



Purified via recrystallisation in MeOH with minimal CH_2Cl_2. Yellow solid, 49%. Mp 241 – 242 °C. **HRMS-ESI** (m/z): [M+Na]$^+$ calcd for $C_{23}H_{18}N_2O_3S_2Na$, 457.0651; found, 457.0677. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3337 (m, NH), 1663 (s, CO), 1654 (s, CO-NH), 1507 (s), 1288 (s), 748 (s). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.32 (br. s, 1H, NH), 7.91 (d, J = 8.2 Hz, 1H, HetCH), 7.51 – 7.48 (m, 2H, HetCH), 7.42 (d, J = 8.5 Hz, 2H, ArCH), 7.38 (app. t, J = 7.6 Hz, 1H, HetCH), 7.17 (d, J = 8.5 Hz, 2H, ArCH), 3.94 (s, 3H, OMe), 2.72 (t, J = 6.1 Hz, 2H, CH_2-CO), 2.51 (t, J = 6.4 Hz, 2H, CH_2-C-N), 2.05 (app. quint, J = 6.3 Hz, 2H, CH_2) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.4 (QC, CO), 163.7 (QC, C-N), 162.2 (QC, C-NH), 160.8 (QC, CO-NH or C-OMe), 160.2 (QC, CO-NH or C-OMe), 140.7 (QC, HetC), 140.3 (QC, HetC), 140.0 (QC, HetC), 131.8 (QC, ArC), 131.1 (CH, 2×ArCH), 127.5 (CH, HetCH), 125.7 (QC, HetC), 125.2 (CH, 2×HetCH), 124.4 (QC, HetC), 122.7 (CH, HetCH), 115.5 (CH, 2×ArCH), 55.5 (CH$_3$, OMe), 37.8 (CH_2, CH_2-C-N), 26.8 (CH_2, CH_2-CO), 23.0 (CH$_3$, 2×CH$_3$) ppm. **HPLC**: t_R 8.50 min, > 99% purity at 254 nm.

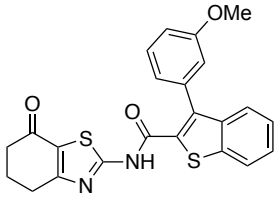
*N-(5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-3-(4-methoxyphenyl)benzo[b]thiophene-2-carboxamide (**10**):*



Purified via recrystallisation in MeOH/CH_2Cl_2. Yellow crystals, 35%. Mp 261 – 262 °C. **HRMS-ESI** (m/z): [M–H]$^-$ calcd for $C_{25}H_{22}N_2O_3S_2$, 461.0999; found, 461.0982. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3330 (m, NH), 1654 (s, CO), 1513 (s), 1369 (s), 1288 (vs), 749 (m). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.34 (br. s, 1H, NH), 7.93 (d, J = 8.3 Hz, 1H, HetCH), 7.52 – 7.50 (m, 2H, HetCH), 7.44 – 7.37 (m, 3H, ArCH and HetCH), 7.18 (d, J = 8.2 Hz, 2H, ArCH), 3.95 (s, 3H, OMe), 2.60 (s, 2H, CH_2-CO), 2.38 (s, 2H, CH_2-C-N), 1.04 (s, 6H, CH$_3$) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.1 (QC, CO), 162.5 (QC, C-N), 162.2 (QC, C-NH), 160.8 (QC, CO-NH or C-OMe), 160.1 (QC, CO-NH or C-OMe), 140.7 (QC, HetC), 140.4

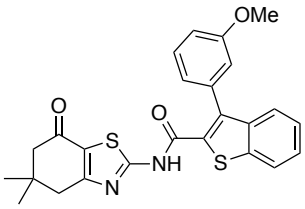
(QC, HetC), 140.0 (QC, HetC), 131.8 (QC, ArC), 131.1 (CH, 2×ArCH), 127.5 (CH, HetCH), 125.2 (CH, 2×HetCH and QC, HetC), 124.4 (QC, HetC), 122.7 (CH, HetCH), 115.5 (CH, 2×ArCH), 55.5 (CH_3, OMe), 51.8 (CH_2, CH_2-C-N), 40.8 (CH_2, CH_2-CO), 34.9 (QC, $C(CH_3)_2$), 28.3 (CH_3, 2×CH_3) ppm. **HPLC**: t_R 9.55 min, > 99% purity at 254 nm.

*3-(3-Methoxyphenyl)-N-(7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzo[b]thiophene-2-carboxamide (**11**):*



Purified via recrystallisation in MeOH with minimal CH_2Cl_2. Yellow crystals, 52%. Mp 233 – 234 °C. **HRMS-ESI** (*m*/*z*): $[M+H]^+$ calcd for $C_{23}H_{19}N_2O_3S_2$, 435.0837; found, 435.0852. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3336 (m, NH), 1654 (vs, CO), 1515 (vs), 1366 (s), 1345 (s), 1279 (s), 744 (vs). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.18 (br. s, 1H, NH), 7.93 (d, *J* = 8.1 Hz, 1H, HetCH), 7.59 (app. t, *J* = 7.9 Hz, 1H, ArCH or HetCH), 7.53 – 7.49 (m, 2H, ArCH or HetCH), 7.39 (app. t, *J* = 7.6 Hz, 1H, ArCH or HetCH), 7.18 (d, *J* = 8.1 Hz, 1H, ArCH or HetCH), 7.08 (d, *J* = 7.4 Hz, 1H, ArCH or HetCH), 7.02 (s, 1H, ArCH), 3.88 (s, 3H, OMe), 2.75 (t, *J* = 6.2 Hz, 2H, CH_2-CO), 2.53 (t, *J* = 6.5 Hz, 2H, CH_2-C-N), 2.08 (app. quint, *J* = 6.3 Hz, 2H, CH_2) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.5 (QC, CO), 163.8 (QC, C-N), 162.1 (QC, C-NH), 160.6 (QC, CO-NH or *C*-OMe), 159.9 (QC, CO-NH or *C*-OMe), 140.7 (QC, HetC), 140.1 (QC, HetC), 139.8 (QC, HetC), 134.0 (QC, ArC or HetC), 132.1 (QC, ArC or HetC), 131.2 (CH, ArCH or HetCH), 127.6 (CH, ArCH or HetCH), 125.7 (QC, HetC), 125.3 (CH, ArCH or HetCH), 125.2 (CH, HetCH), 122.6 (CH, ArCH or HetCH), 121.7 (CH, ArCH or HetCH), 116.0 (CH, ArCH or HetCH), 115.1 (CH, ArCH or HetCH), 55.5 (CH_3, OMe), 37.8 (CH_2, CH_2-C-N), 26.9 (CH_2, CH_2-CO), 23.0 (CH_2, CH_2) ppm. **HPLC**: t_R 8.57 min, > 99% purity at 254 nm.

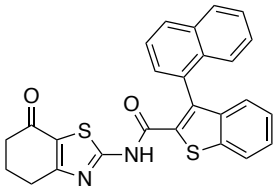
*N-(5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-3-(3-methoxyphenyl)benzo[b]thiophene-2-carboxamide (**12**):*



Purified via column chromatography (EtOAc/hexane, 30:70), off-white solid, 54%. An analytical sample was obtained via recrystallisation in CH_2Cl_2 layered with hexane and used for biological testing. Mp 182 – 184 °C. **HRMS-ESI** (*m*/*z*): $[M-H]^-$ calcd for $C_{25}H_{21}N_2O_3S_2$, 461.0999; found, 461.0963. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3316 (w, NH), 1653 (s, CO), 1508 (vs), 1369 (s), 1287 (s), 1225 (s), 1157 (s), 1032

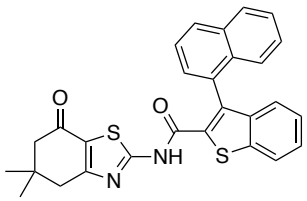
(s), 698 (s). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.18 (br. s, 1H, NH), 7.95 – 7.93 (m, 1H, HetCH), 7.59 (dd, *J* = 8.5, 7.4 Hz, 1H, ArCH or HetCH), 7.54 – 7.50 (m, 2H, ArCH or HetCH), 7.41 – 7.37 (m, 1H, ArCH or HetCH), 7.19 (ddd, *J* = 8.4, 2.6, 1.0 Hz, 1H, ArCH or HetCH), 7.09 (ddd, *J* = 7.5, 1.6, 1.0 Hz, 1H, ArCH or HetCH), 7.01 (dd, *J* = 2.6, 1.6 Hz, 1H, ArCH), 3.88 (s, 3H, OMe), 2.65 (s, 2H, CH_2-CO), 2.40 (s, 2H, CH_2-C-N), 1.06 (s, 6H, CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 192.1 (QC, CO), 162.33 (QC, C-N or C-NH), 162.30 (QC, C-N or C-NH), 160.6 (QC, CO-NH or *C*-OMe), 159.9 (QC, CO-NH or *C*-OMe), 140.7 (QC, HetC), 140.1 (QC, HetC), 139.8 (QC, HetC), 134.1 (QC, ArC or HetC), 132.2 (QC, ArC or HetC), 131.2 (CH, ArCH or HetCH), 127.6 (CH, ArCH or HetCH), 125.3 (CH, ArCH or HetCH), 125.2 (CH, ArCH or HetCH), 124.5 (QC, HetC), 122.7 (CH, ArCH or HetCH), 121.7 (CH, ArCH or HetCH), 115.9 (CH, ArCH or HetCH), 115.1 (CH, ArCH or HetCH), 55.5 (CH_3, OMe), 51.8 (CH_2, CH_2-C-N), 40.9 (CH_2, CH_2-CO), 34.9 (QC, $C(CH_3)_2$), 28.3 (CH_3, 2×CH_3) ppm. **HPLC**: t_R 9.57 min, 97% purity at 254 nm.

*3-(Naphthalen-1-yl)-N-(7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzo[b]thiophene-2-carboxamide (**13**):*



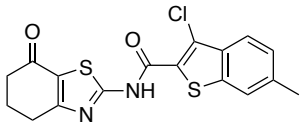
Purified via recrystallisation in MeCN. Off-white needles, 56%. Mp 246 – 248 °C. **HRMS-ESI** (*m*/*z*): $[M–H]^-$ calcd for $C_{26}H_{17}N_2O_2S_2$, 453.0737; found, 453.0718. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3337 (w, NH), 1648 (s, CO), 1507 (vs), 1369 (s), 1269 (s), 773 (s). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.75 (br. s, 1H, NH), 8.18 (dd, *J* = 8.3, 1.3 Hz, 1H, ArCH or HetCH), 8.08 – 7.97 (m, 2H, ArCH or HetCH), 7.76 (dd, *J* = 8.3, 6.9 Hz, 1H, ArCH or HetCH), 7.66 (dd, *J* = 7.0, 1.3 Hz, 1H, ArCH or HetCH), 7.58 (app. quint, *J* = 4.1 Hz, 1H, ArCH or HetCH), 7.52 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, ArCH or HetCH), 7.41 – 7.40 (m, 2H, ArCH or HetCH), 7.28 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H, ArCH or HetCH), 7.16 – 7.14 (m, 1H, ArCH or HetCH), 2.75 – 2.61 (m, 2H, CH_2-CO), 2.49 (dd, *J* = 7.6, 5.7 Hz, 2H, CH_2-C-N), 2.08 – 2.02 (m, 2H, CH_2) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 192.5 (QC, CO), 163.7 (QC, C-N), 161.7 (QC, C-NH), 159.7 (QC, CO-NH), 140.8 (QC, HetC), 140.7 (QC, HetC), 138.3 (QC, HetC), 134.1 (QC, ArC or HetC), 133.6 (QC, ArC or HetC), 131.88 (QC, ArC or HetC), 130.85 (CH, ArCH or HetCH), 130.1 (QC, ArC or HetC), 128.9 (CH, ArCH or HetCH), 128.3 (CH, ArCH or HetCH), 127.71 (CH, ArCH or HetCH), 127.67 (CH, ArCH or HetCH), 127.2 (CH, ArCH or HetCH), 125.9 (CH, ArCH or HetCH), 125.7 (QC, ArC or HetC), 125.4 (CH, ArCH or HetCH), 125.3 (CH, ArCH or HetCH), 125.2 (CH, ArCH or HetCH), 122.7 (CH, ArCH or HetCH), 37.7 (CH_2, CH_2-C-N), 26.9 (CH_2, CH_2-CO), 22.9 (CH_2, CH_2) ppm. **HPLC**: t_R 9.41 min, > 99% purity at 254 nm.

*N-(5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-3-(naphthalen-1-yl)benzo[b]thiophene-2-carboxamide (**14**):*



Purified via recrystallisation in MeCN. Pale brown crystals, 47%. Mp 264 – 265 °C. **HRMS-ESI** (*m*/*z*): $[M–H]^-$ calcd for $C_{28}H_{21}N_2O_2S_2$, 481.1050; found, 481.1039. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3310 (m, NH), 1658 (s, CO), 1512 (vs), 1366 (s), 1295 (s), 1224 (s), 784 (vs). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.92 (br. s, 1H, NH), 8.17 (d, *J* = 8.1 Hz, 1H, ArCH or HetCH), 8.05 – 7.99 (m, 2H, ArCH or HetCH), 7.77 – 7.73 (m, 1H, ArCH or HetCH), 7.65 (d, *J* = 6.7 Hz, 1H, ArCH or HetCH), 7.59 – 7.50 (m, 2H, ArCH or HetCH), 7.41 – 7.40 (m, 2H, ArCH or HetCH), 7.30 – 7.26 (m, 1H, ArCH or HetCH), 7.16 (d, *J* = 8.1 Hz, 1H, ArCH or HetCH), 2.55 (app. dd, *J* = 23.8, 17.1 Hz, 2H, CH_2-CO), 2.35 (s, 2H, CH_2-C-N)), 1.01 (d, *J* = 9.6 Hz, 6H, CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 192.1 (QC, CO), 162.2 (QC, C-N or C-NH), 162.0 (QC, C-N or C-NH), 159.7 (QC, CO-NH), 140.70 (QC, HetC), 140.66 (QC, HetC), 138.4 (QC, HetC), 134.1 (QC, ArC or HetC), 133.5 (QC, ArC or HetC), 131.9 (QC, ArC or HetC), 130.8 (CH, ArCH or HetCH), 130.1 (QC, ArC or HetC), 128.8 (CH, ArCH or HetCH), 128.2 (CH, ArCH or HetCH), 127.7 (CH, ArCH or HetCH), 127.6 (CH, ArCH or HetCH), 127.1 (CH, ArCH or HetCH), 125.8 (CH, ArCH or HetCH), 125.4 (CH, ArCH or HetCH), 125.3 (CH, ArCH or HetCH), 125.2 (CH, ArCH or HetCH), 124.4 (QC, ArC or HetC), 122.7 (CH, ArCH or HetCH), 51.7 (CH_2, CH_2-C-N), 40.8 (CH_2, CH_2-CO), 34.9 (QC, $C(CH_3)_2$), 28.3 (CH_3, CH_3), 28.2 (CH_3, CH_3) ppm. **HPLC**: t_R 10.43 min, > 99% purity at 254 nm.

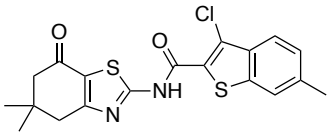
*3-chloro-6-methyl-N-(7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzo[b]thiophene-2-carboxamide (**17**):*



Yellow solid, 94%. An analytical sample was obtained via recrystallisation in CH_2Cl_2 layered with hexane and used for biological testing. Mp 226 – 227 °C. **HRMS-ESI** (*m*/*z*): $[M–H]^-$ calcd for $C_{17}H_{12}ClN_2O_2S_2$, 375.0034; found, 375.0019. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3345 (m, NH), 1641 (vs, CO), 1506 (s), 1366 (m), 1317 (m), 1271 (m), 896 (m), 808 (s), 608 (vs). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.40 (br. s, 1H, NH), 7.82 (d, *J* = 8.3 Hz, 1H, HetCH), 7.68 (s, 1H, HetCH), 7.36 (d, *J* = 8.3 Hz, 1H HetCH), 2.96 (t, *J* = 6.1 Hz, 2H, CH_2-CO), 2.62 (t, *J* = 6.6 Hz, 2H, CH_2-N), 2.53 (s, 3H, Me) 2.22 (app. quint, *J* = 6.3 Hz, 2H, CH_2) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.5 (QC, CO), 163.7 (QC, C-N), 162.0 (QC, C-NH), 158.3 (QC, CO-NH), 139.6 (QC, HetC), 139.4 (QC, HetC), 134.5 (QC, HetC), 128.5 (QC,

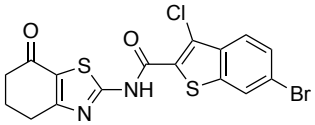
HetC), 128.0 (CH, HetCH), 126.2 (QC, HetC), 123.4 (CH, HetCH), 122.7 (CH, HetCH), 121.5 (QC, HetC), 37.8 (CH_2, CH_2-C-N), 27.0 (CH_2, CH_2-CO) 23.0 (CH_2, CH_2), 21.9 (CH_3, Me) ppm. **HPLC**: t_R 7.90 min, 97% purity at 254 nm.

*3-chloro-N-(5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-6-methylbenzo[b]thiophene-2-carboxamide (**18**):*



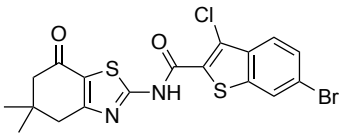
Yellow solid, 94%. An analytical sample was obtained via recrystallisation in CH_2Cl_2 layered with hexane and used for biological testing. Mp 219 – 220 °C. **HRMS-ESI** (*m*/*z*): $[M+H]^+$ calcd for $C_{19}H_{18}ClN_2O_2S_2$, 405.0493; found, 405.0508. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3370 (m, NH), 2953 (w), 1661 (s, CO), 1647 (s), 1514 (vs), 1362 (s), 1277 (s), 889 (s), 810 (s). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.4 Hz, 1H, HetCH), 7.69 (s, 1H, HetCH), 7.37 (dd, *J* = 8.4, 0.8 Hz, 1H, HetCH), 2.83 (s, 2H, CH_2, CH_2-CO), 2.53 (s, 3H, Me), 2.48 (s, 2H, CH_2-C-N), 1.15 (s, 6H, CH_3) ppm. The signal arising from the NH proton could be detected at approximately 10.50 ppm, but was too broadened to report. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.1 (QC, CO), 162.3 (QC, C-N or C-NH), 162.2 (QC, C-N or C-NH), 158.3 (QC, CO-NH), 139.6 (QC, HetC), 139.4 (QC, HetC), 134.5 (QC, HetC), 128.4 (QC, HetC), 128.0 (CH, HetCH), 124.9 (QC, HetC), 123.4 (CH, HetCH), 122.7 (CH, HetCH), 121.6 (QC, HetC), 51.8 (CH_2, CH_2-C-N), 41.0 (CH_2, CH_2-CO), 35.1 (QC, $C(CH_3)_2$), 28.4 (CH_3, 2×CH_3) , 21.9 (CH_3, Me) ppm. **HPLC**: t_R 9.14 min, 97% purity at 254 nm.

*6-bromo-3-chloro-N-(7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzo[b]thiophene-2-carboxamide (**19**):*



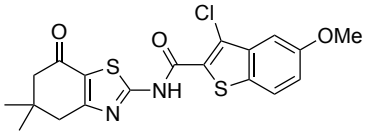
Purified via recrystallization in toluene.Yellow solid, 58%. Mp 256 – 257. **HRMS-ESI** (*m*/*z*): $[M–H]^–$ calcd for $C_{16}H_9BrClN_2O_2S_2$, 438.8983; found, 438.8987. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3355 (m, NH), 1650 (vs, CO), 1532 (s), 1308 (m), 809 (s), 602 (s). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.35 (br. s, 1H, NH), 8.06 (dd, *J* = 1.7, 0.5 Hz, 1H, HetCH), 7.80 (dd, *J* = 8.7, 0.6 Hz, 1H, HetCH), 7.66 (dd, *J* = 8.7, 1.7 Hz, 1H, HetCH), 2.97 (t, *J* = 6.2 Hz, 2H, CH_2-CO), 2.64 – 2.61 (m, 2H, CH_2-C-N), 2.23 (app. quint, *J* = 6.3 Hz, 2H, CH_2) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.5 (QC, CO), 163.5 (QC, C-N), 161.8 (QC, C-NH), 157.9 (QC, CO-NH), 140.1 (QC, HetC), 135.4 (QC, HetC), 130.2 (QC, HetC), 129.8 (CH, HetCH), 126.3 (QC, HetC), 125.6 (CH, HetCH), 124.8 (CH, HetCH), 123.4 (QC, HetC), 121.4 (QC, C-Br), 37.8 (CH_2, CH_2-CO), 26.9 (CH_2, CH_2-C-N), 23.0 (CH_2, CH_2) ppm. **HPLC**: t_R 8.26 min, > 99% purity at 254 nm.

*6-bromo-3-chloro-N-(5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzo[b]thiophene-2-carboxamide (**20**):*



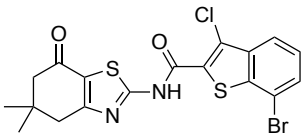
Purified via recrystallization in toluene. Yellow solid, 66%. Mp 199 – 200 °C. **HRMS-ESI** (*m*/*z*): $[M-H]^-$ calcd for $C_{18}H_{13}BrClN_2O_2S_2$, 466.9296; found, 466.9283. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3354 (m, NH), 1656 (vs, CO), 1538 (s), 1518 (s), 1363 (s), 608 (s). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.06 (d, *J* = 1.6 Hz, 1H, HetCH), 7.79 (d, *J* = 8.7 Hz, 1H, HetCH), 7.65 (dd, *J* = 8.7, 1.7 Hz, 1H, HetCH), 2.82 (s, 2H, CH_2-CO), 2.48 (s, 2H, CH_2-C-N), 1.15 (s, 6H, CH_3) ppm. The signal arising from the NH proton could be detected at approximately 10.40 ppm, but was too broadened to report. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.1 (QC, CO), 162.1 (QC, C-N or C-NH), 162.0 (QC, C-N or C-NH), 157.8 (QC, CO-NH), 140.1 (QC, HetC), 135.4 (QC, HetC), 135.4 (QC, HetC), 130.2 (QC, HetC), 129.8 (CH, HetCH), 125.6 (CH, HetCH), 125.1 (QC, HetC), 124.8 (CH, HetCH), 123.4 (QC, HetC), 121.3 (QC, C-Br), 51.8 (CH_2, CH_2-CO), 40.9 (CH_2, CH_2-C-N), 35.1 (QC, $C(CH_3)_2$), 28.4 (CH_3, 2×CH_3) ppm. **HPLC**: t_R 9.41 min, 98% purity at 254 nm.

*3-chloro-N-(5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-5-methoxybenzo[b]thiophene-2-carboxamide (**21**):*



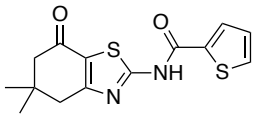
Synthesised with the addition of catalytic DMAP (10 mol%). Crude material extracted with EtOAc and subjected to additional wash with aqueous NaOH (1.0 M) before drying. Purified via recrystallisation in CH_2Cl_2 layered with hexane. Pale yellow solid, 41%. Mp 211 – 214. **HRMS-ESI** (*m*/*z*): $[M+H]^+$ calcd for $C_{19}H_{18}ClN_2O_3S_2$, 421.0442; found, 421.0461. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3359 (w, NH), 1666 (s, CO), 1506 (vs), 1361 (s), 1277 (s), 1209 (vs), 1022 (m), 896 (s), 828 (m), 740 (m). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.9 Hz, 1H, HetCH), 7.29 (s, 1H, HetCH), 7.22 (d, *J* = 8.8 Hz, 1H, HetCH), 3.94 (s, 3H, OMe), 2.82 (s, 2H, CH_2-CO), 2.48 (s, 2H, CH_2-C-N), 1.15 (s, 6H, CH_3) ppm. The signal arising from the NH proton could be detected at approximately 10.50 ppm, but was too broadened to report. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.1 (QC, CO), 162.3 (QC, C-N or C-NH), 162.2 (QC, C-N or C-NH), 158.8 (QC, *C*-OMe), 158.2 (QC, HetC), 137.7 (QC, HetC), 131.7 (QC, HetC), 130.5 (QC, HetC), 124.9 (QC, HetC), 123.9 (CH, HetCH), 120.7 (QC, HetCH), 120.2 (CH, HetCH), 104.1 (CH, HetCH), 55.7 (CH_3, OMe), 51.8 (CH_2, CH_2-C-N), 40.9 (CH_2, CH_2-CO), 35.1 (QC, $C(CH_3)_2$), 28.4 (CH_3, 2×CH_3) ppm. **HPLC**: t_R 8.31 min, 96% purity at 254 nm.

*7-bromo-3-chloro-N-(5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzo[b]thiophene-2-carboxamide (**22**):*



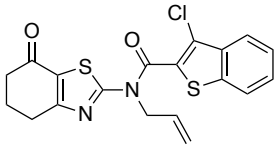
Purified via recrystallisation in MeOH with minimal CH_2Cl_2. Brown crystals, 50%. Mp 220 – 221 °C. **HRMS-ESI** (*m*/*z*): $[M–H]^-$ calcd for $C_{18}H_{13}BrClN_2O_2S_2$, 466.9296; found, 466.9276. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3354 (w, NH), 2957 (w), 1652 (vs, CO), 1514 (s), 1365 (s), 1280 (s), 888 (m). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.39 (br. s, 1H, NH), 7.93 (dd, *J* = 8.2, 0.9 Hz, 1H, HetCH), 7.73 (dd, *J* = 7.7, 0.9 Hz, 1H, HetCH), 7.45 (app. t, *J* = 7.9 Hz, 1H, HetCH), 2.83 (s, 2H, CH_2-CO), 2.49 (s, 2H, CH_2-C-N), 1.16 (s, 6H, CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 192.1 (QC, CO), 162.2 (QC, C-N or C-NH), 162.0 (C-N or C-NH), 158.0 (QC, CO-NH), 140.6 (QC, HetC), 137.4 (QC, HetC), 131.2 (CH, HetCH), 131.1 (QC, HetC), 127.3 (CH, HetCH), 125.0 (CH, HetCH), 122.8 (CH, HetCH), 121.8 (QC, HetC), 116.5 (CH, HetCH), 51.8 (CH_2, CH_2-C-N), 40.8 (CH_2, CH_2-CO), 35.0 (QC, $C(CH_3)_2$, 28.4 (CH_3, 2×CH_3) ppm. **HPLC**: t_R 9.63 min, 96% purity at 254 nm.

*N-(5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)thiophene-2-carboxamide (**24**):*



Purified via column chromatography (EtOAc/hexane, 40:60), pale yellow solid, 75%. Mp 254 – 256 °C. **HRMS-ESI** (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{15}N_2O_2S_2$, 307.0569; found, 307.0586. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3361 (vw, NH), 1653 (s, CO), 1533 (s), 1507 (s), 1363 (s), 1352 (s), 1275 (vs), 727 (vs). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.02 (br. s, 1H, NH), 7.76 (dd, *J* = 3.8, 1.2 Hz, 1H, HetCH), 7.69 (dd, *J* = 4.9, 1.2 Hz, 1H, HetCH), 7.19 (dd, *J* = 5.0, 3.8 Hz, 1H, HetCH), 2.74 (s, 2H, CH_2-CO), 2.47 (s, 2H, CH_2-N), 1.13 (s, 6H, CH_3) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.0 (QC, CO), 163.4 (QC, C-N), 161.8 (QC, C-NH), 158.9 (QC, CO-NH), 135.8 (QC, HetC), 133.4 (CH, HetCH), 130.6 (CH, HetCH), 128.4 (CH, HetCH), 124.5 (QC, HetC), 51.8 (CH_2, CH_2-C-N), 40.8 (CH_2, CH_2-CO), 35.1 (QC, $C(CH_3)_2$, 28.4 (CH_3, 2×CH_3) ppm. **HPLC**: t_R 5.97 min, > 99% purity at 280 nm.

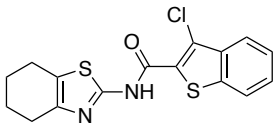
*N-allyl-3-chloro-N-(7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzo[b]thiophene-2-carboxamide (**25**):*



Synthesised using acetone in place of toluene. Purified via column chromatography (EtOAc/hexane, 40:60). Off-white crystals, 60%. An analytical sample was obtained via further column chromatography

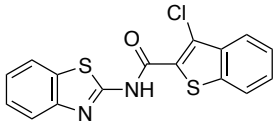
in MeOH/CH_2Cl_2 (2:98). Mp 127 – 129. **HRMS-ESI** (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{15}ClN_2O_2S_2$, 425.0156; found, 425.0167. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 1646 (vs, CO), 1523 (m), 1452 (m), 1369 (s), 1230 (s), 920 (m), 748 (vs). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.92 – 7.90 (m, 1H, HetCH), 7.87 – 7.86 (m, 1H, HetCH), 7.57 – 7.52 (m, 2H, HetCH), 5.93 – 5.86 (m, 1H, =CH), 5.14 (d, *J* = 10.4 Hz, 1H, =CH), 5.02 (d, *J* = 17.2 Hz, 1H, =CH), 4.96 (d, *J* = 5.7 Hz, 2H, CH_2-N), 2.97 (t, *J* = 6.1 Hz, 2H, CH_2-CO), 2.61 (t, *J* = 6.5 Hz, 2H, CH_2-C-N), 2.22 (app. quint, *J* = 6.3 Hz, 2H, CH_2) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 193.0 (QC, CO), 163.4 (QC, C-N, C-NH or CO-NH), 163.1 (QC, C-N, C-NH or CO-NH), 162.9 (QC, C-N, C-NH or CO-NH), 137.6 (CH, HetCH), 135.2 (CH, HetCH), 131.6 (CH, =CH), 127.34 (QC, HetC), 127.31 (CH, HetCH), 126.6 (QC, HetC), 125.8 (CH, HetCH), 122.9 (CH, HetCH), 122.8 (CH, HetCH), 121.6 (QC, HetC), 118.3 (CH_2, $=CH_2$), 51.3 (CH_2, CH_2-N), 37.9 (CH_2, CH_2-N), 27.1 (CH_2, CH_2-CO), 23.1 (CH_2, CH_2) ppm. **HPLC**: t_R 9.60 min, 98% purity at 254 nm.

*3-chloro-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzo[b]thiophene-2-carboxamide (**26**):*



Purified via recrystallization in EtOH. Orange crystals, 64%. An analytical sample was obtained via recrystallisation in $CHCl_3$ layered with hexane and used for biological testing. Mp 212 – 213 °C. **HRMS-ESI** (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{13}ClN_2OS_2$, 349.0231; found, 349.0248. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3381 (w, NH), 1646 (m), 1538 (m), 1507 (m), 1292 (s), 759 (s). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.92 – 7.88 (m, 1H, HetCH), 7.87 – 7.83 (m, 1H, HetCH), 7.56 – 7.49 (m, 2H, HetCH), 2.75 – 2.71 (br. m, 2H, CH_2-C-N), 2.71 – 2.66 (br. m, 2H, CH_2-C-S), 1.90 – 1.84 (br. m, 4H, CH_2) ppm. The signal arising from the NH proton could be detected at approximately 10.30 ppm, but was too broadened to report. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 158.2 (QC, C-NH), 154.7 (QC, CO-NH), 144.2 (QC, CH_2-*C*-N), 138.6 (QC, HetC), 136.8 (QC, HetC), 130.8 (QC, HetC), 128.0 (CH, HetCH), 125.7 (CH, HetCH), 123.9 (QC, CH_2-*C*-S), 123.5 (CH, HetCH), 122.9 (CH, HetCH), 120.8 (QC, HetC), 26.2 (CH_2, *C*H_2-C-N), 23.2 (CH_2, *C*H_2-C-S), 23.0 (CH_2, CH_2), 22.9 (CH_2, CH_2) ppm. **HPLC**: t_R 9.29 min, > 99% purity at 254 nm.

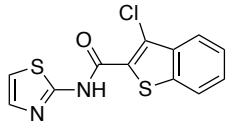
*N-(benzo[d]thiazol-2-yl)-3-chlorobenzo[b]thiophene-2-carboxamide (**27**):*



Synthesised using commercially available 2-aminobenzothiazole, using acetone in place of toluene. Purified via recrystallisation in dioxane. Pale yellow solid, 30%. Mp 257 – 258 °C (lit. 265 – 267 °C).[12] **HRMS-ESI** (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{10}ClN_2OS_2$, 344.9918; found, 344.9930. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3374 (m, NH), 1651 (w), 1527 (vs), 1275 (vs), 893 (m), 758 (s). **^{1}H NMR** (500 MHz, DMSO-d_6): δ 13.48 (br. s, 1H, NH), 8.12 (d, *J* = 7.6 Hz, 1H, HetCH), 7.96 (d, *J* = 7.6 Hz, 2H, HetCH), 7.64 – 7.58

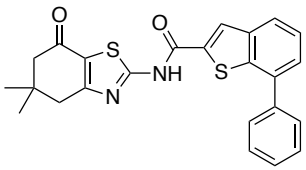
(m, 3H, HetCH), 7.49 (app. t, J = 7.5 Hz, 1H, HetCH), 7.35 (app. t, J = 7.5 Hz, 1H, HetCH) ppm. The mp, IR and ^{1}H NMR data match that previously reported, with the exception of the signals from the heteroaromatic protons region being reported as one multiplet in the literature.[12] **^{13}C NMR** (125 MHz, DMSO-d_6): δ 165.4 (br., QC, C-NH and CO-NH), 137.6 (QC, HetC), 136.7 (QC, HetC), 132.3 (br., QC, HetC), 128.1 (br., QC, HetC), 128.0 (CH, 2×HetCH), 127.0 (CH, HetCH), 125.0 (CH, HetCH), 123.9 (CH, HetCH), 123.4 (CH, HetCH), 122.8 (CH, HetCH), 122.7 (QC, HetC), 122.6 (CH, HetCH), 115.6 (br., QC, HetC) ppm. **HPLC**: t_R 9.10 min, 99% purity at 254 nm.

*3-chloro-N-(thiazol-2-yl)benzo[b]thiophene-2-carboxamide (**28**):*



Synthesised using commercially available 2-aminothiazole, using acetone in place of toluene. Purified via recrystallisation in EtOH. Pale yellow solid, 49%. Mp 200 – 201 °C. **HRMS-ESI** (*m*/*z*): $[M+H]^+$ calcd for $C_{12}H_8ClN_2OS_2$, 294.9761; found, 294.9771. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3382 (w, NH), 1647 (m, CO), 1534 (vs), 1316 (s), 1271 (m), 891 (m), 764 (s), 717 (s). **^{1}H NMR** (500 MHz, DMSO-d_6/$CDCl_3$, 95:5): δ 13.12 (br. s, 1H, NH), 8.10 (dd, J = 6.6, 1.9 Hz, 1H, HetCH), 7.93 (dd, J = 6.6, 2.3 Hz, 1H, HetCH), 7.62 – 7.56 (m, 2H, HetCH), 7.54 (d, J = 4.1 Hz, 1H, =CH-N), 7.21 (d, J = 4.1 Hz, 1H, =CH-S) ppm. **^{13}C NMR** (125 MHz, DMSO-d_6/$CDCl_3$, 95:5): δ 164.5 (br., QC, C-NH), 163.7 (br., QC, CO-NH), 137.3 (QC, HetC), 136.5 (QC, HetC), 132.2 (br., CH, CH-N), 129.8 (br., QC, HetC), 127.7 (CH, HetCH), 125.8 (CH, HetCH), 123.4 (CH, HetCH), 122.6 (CH, HetCH), 121.8 (QC, HetC), 112.5 (CH, CH-S) ppm. **HPLC**: t_R 7.26 min, 99% purity at 254 nm.

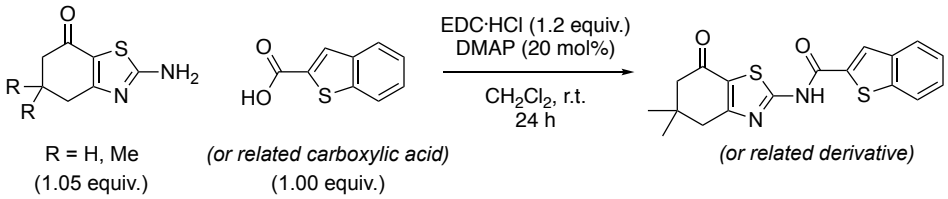
*N-(5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-7-phenylbenzo[b]thiophene-2-carboxamide (**31**):*



Off-white solid, 60%. An analytical sample was obtained by heating in MeOH/CH_2Cl_2 (50:50) and adding hexane dropwise to induce recrystallisation. This sample was used for biological testing. Mp 313 – 314 °C. **HRMS-ESI** (*m*/*z*): $[M–H]^-$ calcd for $C_{24}H_{19}N_2OS_2$, 431.0893; found, 431.0894. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3248 (w, NH), 1664 (m), 1632 (s, CO), 1536 (m), 1506 (s), 1377 (s), 1286 (vs), 1204 (m), 752 (m), 697 (vs). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.82 (br. s, 1H, NH), 8.10 (s, 1H, HetCH), 7.90 (d, J = 7.4 Hz, 1H, HetCH), 7.71 (d, J = 7.1 Hz, 2H, HetCH), 7.58 – 7.45 (m, 5H, ArCH), 2.77 (s, 2H, CH_2-CO), 2.47 (s, 2H, CH_2-C-N), 1.13 (s, 6H, CH_3) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.1 (QC, CO), 163.1 (QC, C-N), 161.9 (QC, C-NH), 159.5 (QC, HetC), 141.1 (QC, HetC), 139.5 (QC, HetC or

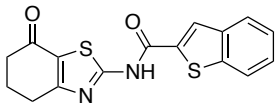
ArC), 139.4 (QC, HetC or ArC), 137.3 (QC, HetC or ArC), 135.2 (QC, HetC), 129.1 (CH, 2×ArCH), 128.58 (CH, HetCH or ArCH), 128.55 (CH, HetCH or ArCH), 128.0 (CH, 2×ArCH), 127.3 (CH, HetCH), 126.3 (CH, HetCH), 124.7 (CH, HetCH), 124.6 (QC, HetC), 51.8 (CH_2, CH_2-CO), 40.8 (CH_2, CH_2-C-N), 35.1 (QC, $C(CH_3)_2$, 28.4 (CH_3, 2×CH_3) ppm. **HPLC**: t_R 9.22 min, > 99% purity at 280 nm.

*General procedure for the synthesis of WEHI-0086109 (**1**) derivatives via EDC Coupling:*



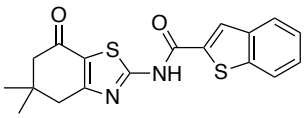
A suspension of the benzothiophenyl carboxylic acid (1.00 equiv.), the appropriate thiazole amine fragment (1.05 equiv.) and DMAP (20 mol%) in CH_2Cl_2 (0.05 M with respect to the carboxylic acid) was stirred at room temperature. To this was added EDC·HCl (1.2 equiv.) and the reaction mixture stirred at room temperature under a nitrogen atmosphere. After 24 hours, the reaction mixture was cooled to 0 °C and quenched with aqueous HCl (1.0 M). The precipitated product was collected by filtration and washed with cold water, followed by cold CH_2Cl_2, and dried under vacuum.

*N-(7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzo[b]thiophene-2-carboxamide:(**15**):*



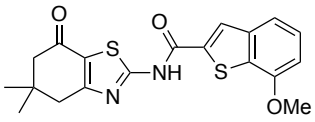
Synthesised using commercially available benzothiophene-2-carboxylic acid. Off-white solid, 42%. Mp 264 – 265 °C. **HRMS-ESI** (*m*/*z*): $[M+Na]^+$ calcd for $C_{16}H_{12}N_2O_2S_2Na$, 351.0232; found, 351.0251. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3241 (w, NH), 1648 (s, CO), 1540 (s), 1375 (s), 1284 (vs), 1206 (s), 1189 (s), 719 (vs). **^{1}H NMR** (500 MHz, DMSO-d_6): δ 13.50 (br. s, 1H, NH), 8.60 (br. s, 1H, HetCH), 8.09 (d, J = 8.1 Hz, 1H, HetCH), 8.01 (d, J = 7.9 Hz, 1H, HetCH), 7.51 (app. dt, J = 26.2, 7.4 Hz, 2H, HetCH), 2.91 (br. t, J = 6.2 Hz, 2H, CH_2-CO), 2.52 (br. t, J = 6.2 Hz, 2H, CH_2-C-N), 2.12 (br. app. quint, J = 6.2 Hz, 2H, CH_2) ppm. **^{13}C NMR** (125 MHz, DMSO-d_6): δ 192.0 (QC, CO), 163.9 (br, QC, C-N or C-NH), 163.3 (br, QC, C-N or C-NH), 161.0 (br, QC, CO-NH), 141.2 (QC, HetC), 138.9 (QC, HetC), 136.6 (br, QC, HetC), 128.6 (CH, HetCH), 127.3 (CH, HetCH), 126.0 (CH, HetCH), 125.3 (CH, HetCH), 123.5 (br, QC, HetC), 123.0 (CH, HetCH), 37.2 (CH_2, CH_2-C-N), 26.1 (br, CH_2, CH_2-O), 22.6 (CH_2, CH_2) ppm. **HPLC**: t_R 6.37 min, 99% purity at 254 nm.

*N-(5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzo[b]thiophene-2-carboxamide (**16**):*



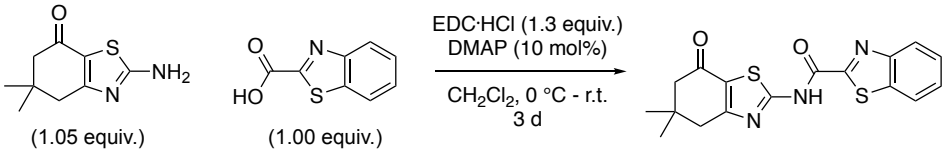
Synthesised using commercially available benzothiophene-2-carboxylic acid. White solid, 55%. Mp 292 – 293 °C. **HRMS-ESI** (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{16}N_2O_2S_2Na$, 379.0545; found, 379.0551. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3237 (w, NH), 1664 (s), 1635 (vs, CO), 1536 (s), 1289 (s), 1207 (s), 879 (m), 719 (s). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 13.51 (br. s, 1H, NH), 8.60 (br. s, 1H, HetCH), 8.09 (d, J = 7.9 Hz, 1H, HetCH), 8.02 (d, J = 7.6 Hz, 1H, HetCH), 7.56 – 7.47 (m, 2H, HetCH), 2.83 (s, 2H, CH_2-CO), 2.44 (s, 2H, CH_2-C-N), 1.08 (s, 6H, CH_3) ppm. **^{13}C NMR** (125 MHz, DMSO-d_6): δ 191.6 (QC, CO), 163.4 (br, C-N or C-NH), 162.6 (br, C-N or C-NH, 160.8 (br, CO-NH), 141.2 (QC, HetC), 138.9 (QC, HetC), 136.5 (br, QC, HetC), 128.6 (CH, HetCH), 127.3 (CH, HetCH), 126.0 (CH, HetCH), 125.3 (CH, HetCH), 123.0 (CH, HetCH), 122.4 (br, QC, HetC), 51.1 (CH_2, CH_2-C-N), 34.7 (QC, $C(CH_3)_2$, 27.8 (CH_3, 2×CH_3) ppm. The signal arising from the CH_2-CO carbon is obscured by the residual solvent peak, but was determined via an HSQC experiment to appear at approximately 40.2 ppm. **HPLC**: t_R 7.48 min, > 99% purity at 254 nm.

*N-(5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-7-methoxybenzo[b]thiophene-2-carboxamide (**30**):*



Off-white solid, 75%. Mp 305 – 309 °C (with decomp.). **HRMS-ESI** (*m*/*z*): $[M–H]^-$ calcd for $C_{19}H_{17}N_2O_3S_2$, 385.0686; found, 385.0698. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3228 (w, NH), 1716 (m), 1639 (m), 1542 (m), 1301 (s), 1272 (s), 1098 (vs), 712 (vs). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 13.48 (br. s, 1H, NH), 8.58 (br. s, 1H, HetCH), 7.60 (d, J = 7.9 Hz, 1H, HetCH), 7.45 (app. t, J = 7.9 Hz, 1H, HetCH), 7.11 (d, J = 7.8 Hz, 1H, HetCH), 3.99 (s, 3H, OMe), 2.83 (s, 2H, CH_2-CO), 2.44 (s, 2H, CH_2-C-N), 1.08 (s, 6H, CH_3) ppm. **^{13}C NMR** (125 MHz, DMSO-d_6): δ 191.7 (QC, CO), 163.6 (br., QC, C-N), 162.3 (br., QC, C-NH), 161.1 (br., QC, CO-NH), 153.9 (QC, HetC), 140.5 (QC, HetC), 136.9 (br., QC, HetC), 130.0 (QC, HetC), 129.0 (CH, HetCH), 127.0 (CH, HetCH), 122.3 (br., QC, HetC), 118.3 (CH, HetCH), 107.2 (CH, HetCH), 55.9 (CH_3, OMe), 51.1 (CH_2, CH_2-C-N), 34.8 (QC, $C(CH_3)_2$) 27.9 (CH_3, 2×CH_3) ppm. The signal arising from the CH_2-CO carbon is obscured by the residual solvent peak, but was determined via an HSQC experiment to appear at approximately 40.0 ppm. **HPLC**: t_R 7.59 min, 99% purity at 254 nm.

*Synthesis of N-(5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzo[d]thiazole-2-carboxamide (**23**):*



(1.05 equiv.) (1.00 equiv.)

The required carboxylic acid was prepared from commercially available ethyl benzothiazole-2-carboxylate using the procedure reported by Mecinović.[13] A suspension of the carboxylic acid (80.5 mg, 0.45 mmol, 1.00 equiv.), the amine (92.5 mg, 0.47 mmol, 1.05 equiv.) and DMAP (6.5 mg, 0.05 mmol, 10 mol%) in CH_2Cl_2 (5 mL) was cooled to 0 °C with stirring. To this was added EDC·HCl (110.1 mg, 0.57 mmol, 1.30 equiv.) and the reaction mixture warmed to room temperature to stir under a nitrogen atmosphere. After 3 days, the reaction mixture was diluted with water and the organic layer extracted with CH_2Cl_2 before being dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was subjected to column chromatography (MeOH/CH_2Cl_2, 2:98) to give the pure product as off-white crystals (100.5 mg, 0.28 mmol, 62%).

Mp 216 – 217 °C. **HRMS-ESI** (*m/z*): $[M+Na]^+$ calcd for $C_{17}H_{15}N_3O_2S_2Na$, 380.0498; found, 380.0517. **FTIR** $\bar{\nu}_{max}$ (cm^{-1}): 3360 (vw, NH), 1653 (CO), 1506 (vs), 1369 (vs), 1287 (s), 1037 (m), 893 (s), 759 (s). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.74 (br. s, 1H), 8.15 – 8.13 (m, 1H, HetCH), 8.04 – 8.02 (m, 1H, HetCH), 7.64 – 7.55 (m, 2H, HetCH), 2.85 (s, 2H, CH_2-CO), 2.50 (s, 2H, CH_2-C-N), 1.16 (s, 6H, CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 192.1 (QC, CO), 162.5 (QC, CH_2-*C*-N), 161.9 (QC, C-NH), 160.0 (QC, CO-NH), 157.5 (QC, CO-*C*=N), 152.5 (QC, HetC), 137.7 (QC, HetC), 127.8 (CH, HetCH), 127.5 (CH, HetCH), 125.1 (QC, CH_2-CO-*C*-S), 125.0 (CH, HetCH), 122.6 (CH, HetCH), 51.8 (CH_2, CH_2-C-N), 41.0 (CH_2, CH_2-CO), 35.1 (QC, $C(CH_3)_2$), 28.4 (CH_3, 2×CH_3) ppm. **HPLC**: t_R 7.46 min, > 99% purity at 254 nm.

*4. Screening of Derivatives of WEHI-0086109 (**1**) Against T. brucei and Mammalian Cells*

Assay protocol for T. b. brucei and HEK293 screening:

Compound activity against *T.b. brucei* Strain 427 was assessed in an resazurin-based viability assay, modified from an assay described by Sykes and Avery.[2] Briefly, 1200 parasites/mL of logarithmic phase *T .b. brucei* parasites were added to a 384-well microtiter plate (BD biosciences) in 55 µL of HMI-9 media containing10% FCS and incubated for 24 hours at 37 °C/5% CO_2. Serial compound concentrations were prepared in DMEM media and 5 µL added to assay plates to give final concentrations ranging from 83.34 to 0.04 µM. Plates were incubated for 48 hours at 37 °C/5% CO_2. After this time, 10 µL of 0.49 mM resazurin (Sigma Aldrich) prepared in HMI-9 media containing 10% FCS was added to assay plates and incubated for a further 2 hours at 37 °C/5% CO_2,followed by 22

hours at room temperature. Assay plates were read at 535 nm excitation/590 nm emission on an Envision® multiplate reader (PerkinElmer, Massachusetts, USA). Data was analysed and IC_{50} values calculated using the software GraphPad Prism 5. Pentamidine and diminazene were used as controls.

For the HEK293 cytotoxicity assay, 55 µL of DMEM media with10% FCS (Gibco) containing 7.27×10^4 cells/mL of confluent HEK293 cells was added to each well of a 384-well microtiter plate (BD Biosciences) and incubated for 24 hours at 37 °C/5% CO_2. Serial compound concentrations were prepared in DMEM and 5 µL of this dilution subsequently added to assay plates to give final compound concentrations ranging from 83.34 to 0.04 µM. Plates were incubated for 48 hours at 37 °C/5% CO_2. After this time, 10 µL of 0.49 mM resazurin (Sigma Aldrich) prepared in DMEM media containing 10% FCS was added to assay plates and incubated for a further 2 hours at 37 °C/5% CO_2, followed by 22 hours at room temperature. Assay plates were read at 535 nm excitation/590 nm emission on an Envision® multiplate reader (PerkinElmer, Massachusetts, USA). Data was analysed and IC_{50} values calculated using the software GraphPad Prism 5. Puromycin was used as a control.

Assay protocol for T. b. rhodesiense and L6 screening:

The stock of *T. b. rhodesiense STIB900* was isolated in 1982 from a human patient in Tanzania and, after several mouse passages, cloned and adapted to axenic culture conditions.[14] Minimum Essential Medium (MEM, 50 µl) supplemented with 25 mM HEPES, 1g/L additional glucose, 1% MEM non-essential amino acids (100×), 0.2 mM 2-mercaptoethanol, 1mM Na-pyruvate and 15% heat inactivated horse serum was added to each well of a 96-well microtiter plate. Serial drug dilutions of eleven 3-fold dilution steps covering a range from 100 to 0.002 µg/mL were prepared. Then 4×10^3 bloodstream forms of *T. b. rhodesiense* STIB 900 in 50 µL was added to each well and the plate incubated at 37 °C under a 5 % CO_2 atmosphere for 70 hours. After this time, 10 µl Alamar Blue (resazurin, 12.5 mg in 100 mL double-distilled water) was then added to each well and incubation continued for a further 2–4 hours.[15] The plates were then read with a Spectramax Gemini XS microplate fluorometer (Molecular Devices Cooperation, Sunnyvale, CA, USA) using an excitation wavelength of 536 nm and an emission wavelength of 588 nm. Data were analysed with the graphic program Softmax Pro (Molecular Devices Cooperation, Sunnyvale, CA, USA), which calculated IC_{50} values by linear regression[16] and 4-parameter logistic regression from the sigmoidal dose inhibition curves. Melarsoprol (Arsobal Sanofi-Aventis, received from WHO) was used as control.

The *in vitro* L6 cytotoxicity assays were performed in 96-well microtiter plates, each well containing 100 µl of RPMI 1640 medium supplemented with 1% L-glutamine (200 mM) and 10% fetal bovine serum, and 4000 L6 cells (a primary cell line derived from rat skeletal myoblasts)[17] Serial drug dilutions of eleven 3-fold dilution steps covering a range from 100 to 0.002 µg/mL were prepared. After 70 hours of incubation the plates were inspected under an inverted microscope to assure growth of the controls

and sterile conditions. Alamar Blue (10µl) was then added to each well and the plates incubated for another 2 hours. The plates were then read with a Spectramax Gemini XS microplate fluorometer (Molecular Devices Cooperation, Sunnyvale, CA, USA) using an excitation wavelength of 536 nm and an emission wavelength of 588 nm. The IC_{50} values were calculated by linear regression[16] and 4-parameter logistic regression from the sigmoidal dose inhibition curves using SoftmaxPro software (Molecular Devices Cooperation, Sunnyvale, CA, USA). Podophyllotoxin (Sigma P4405) was used as control.

4. References

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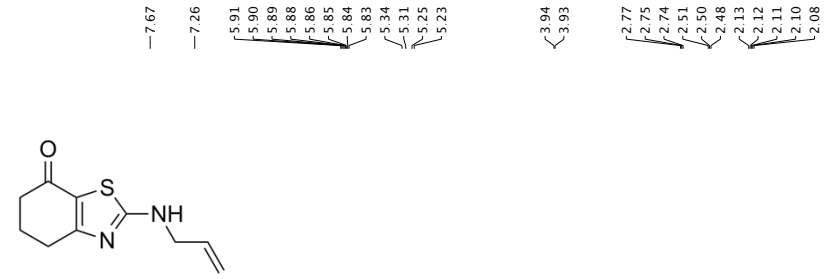
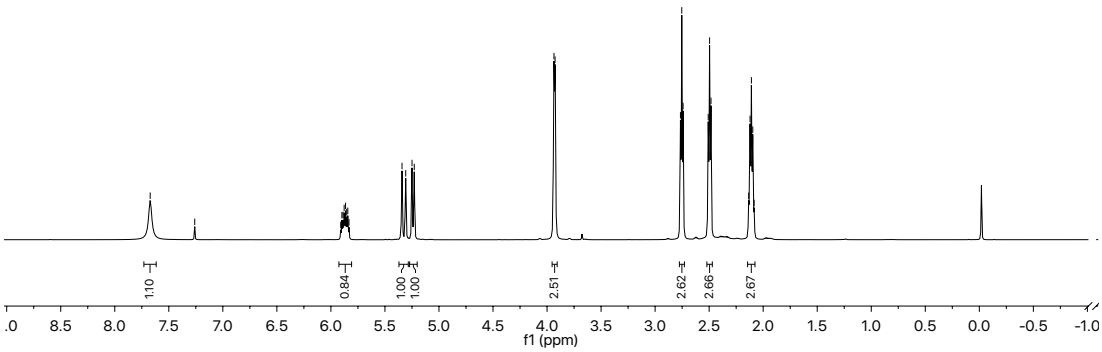
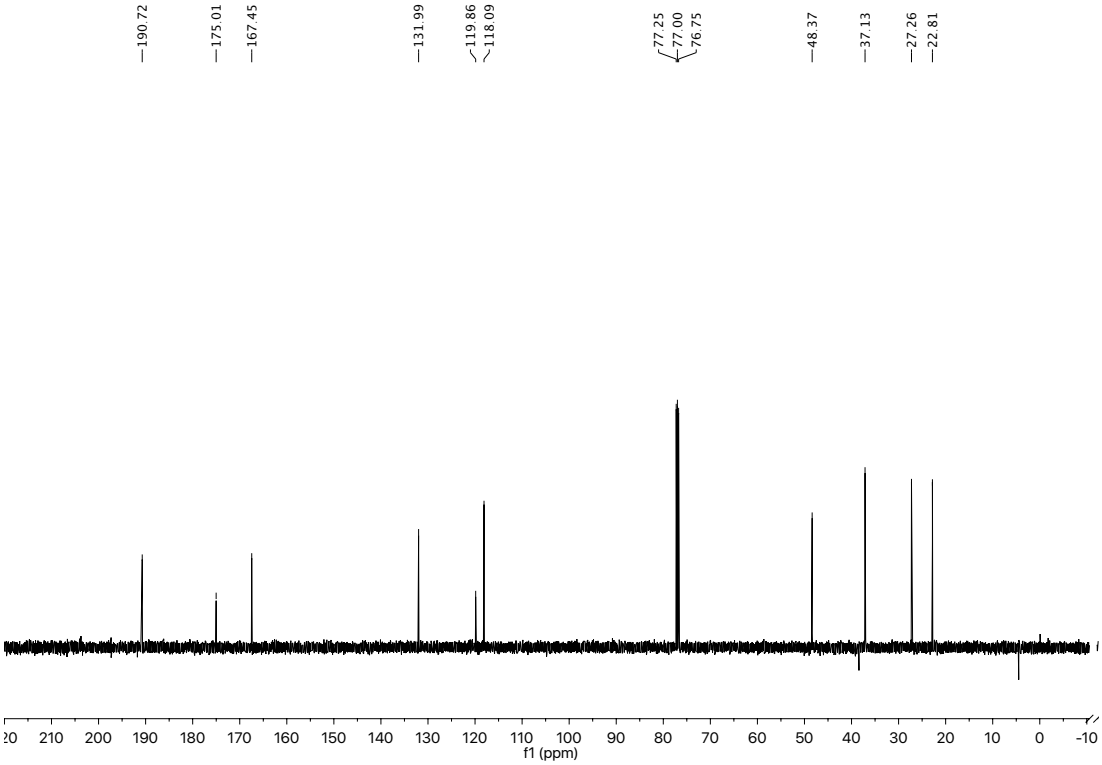
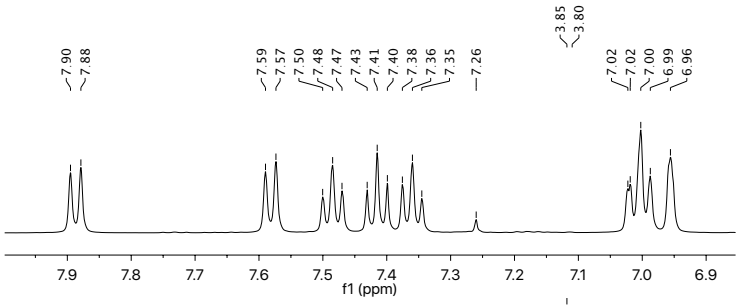
6. NMR Spectra for Novel Compounds





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7.35
7.26
3.85
3.80
7.02
7.02
7.00
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6.96
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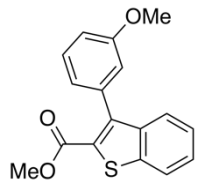
f1 (ppm)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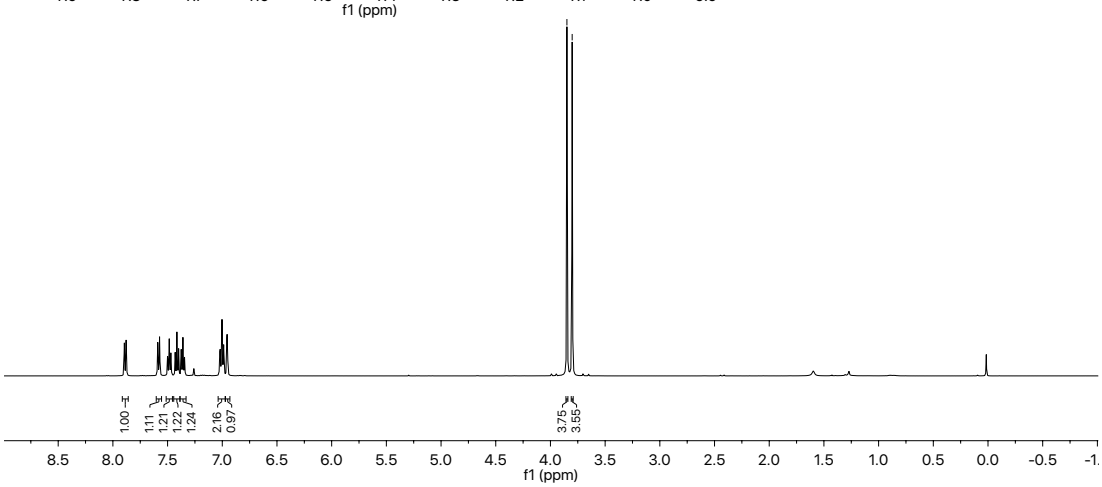
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2.16
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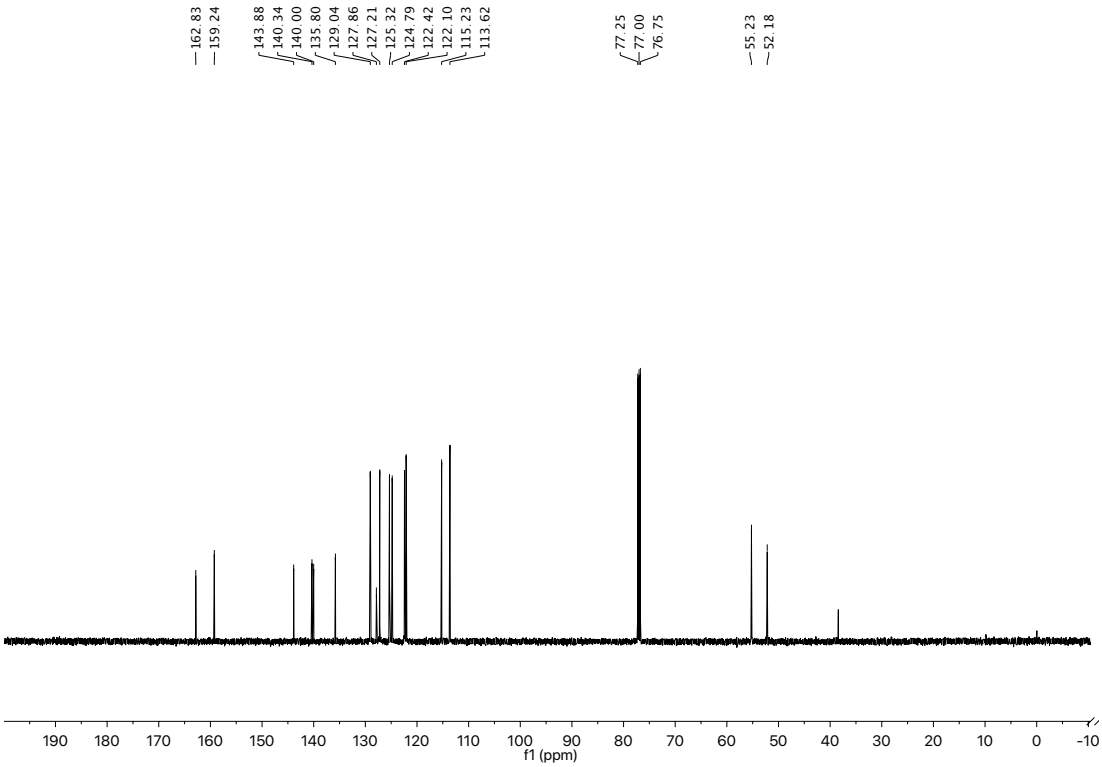
f1 (ppm)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122.10
115.23
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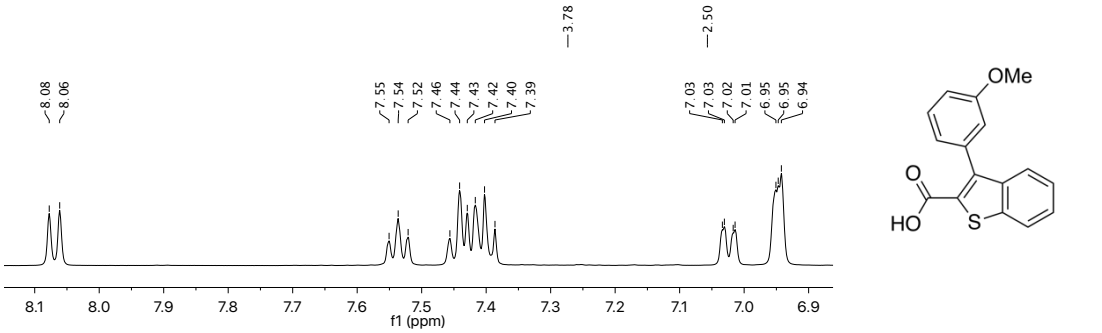
f1 (ppm)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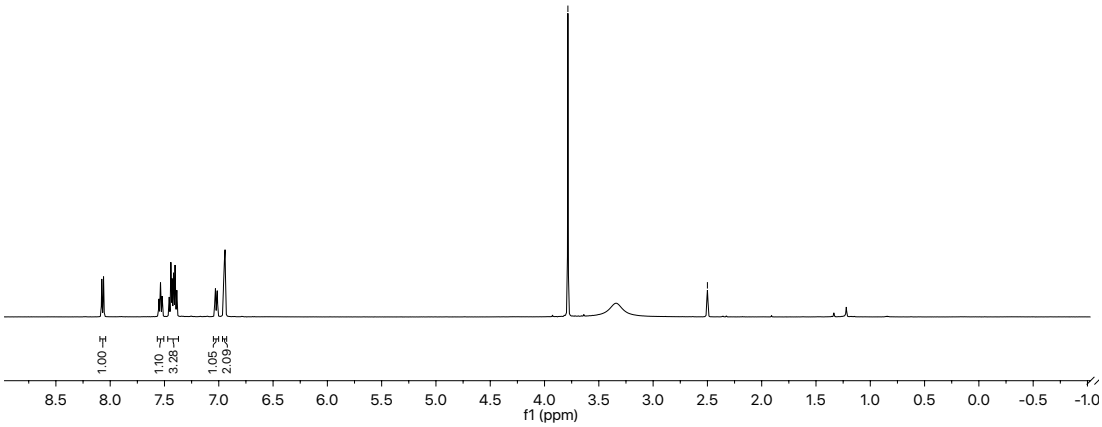
OMe
O
HO
S
f1 (ppm)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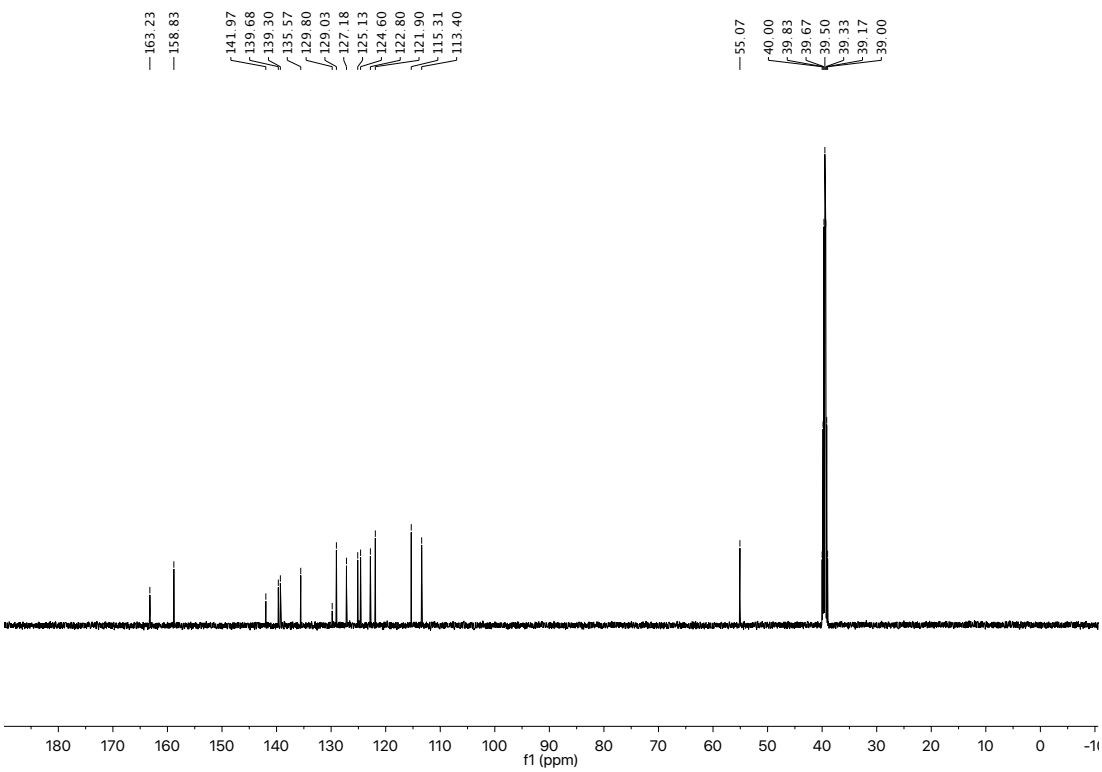
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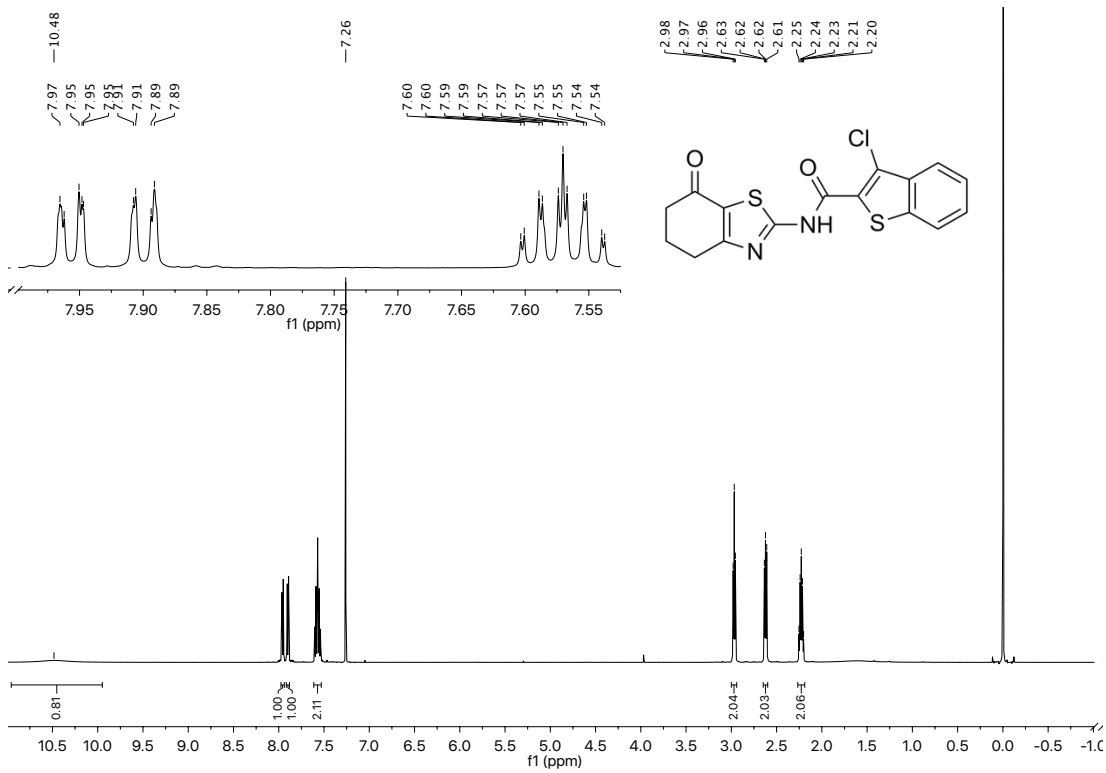
f1 (ppm)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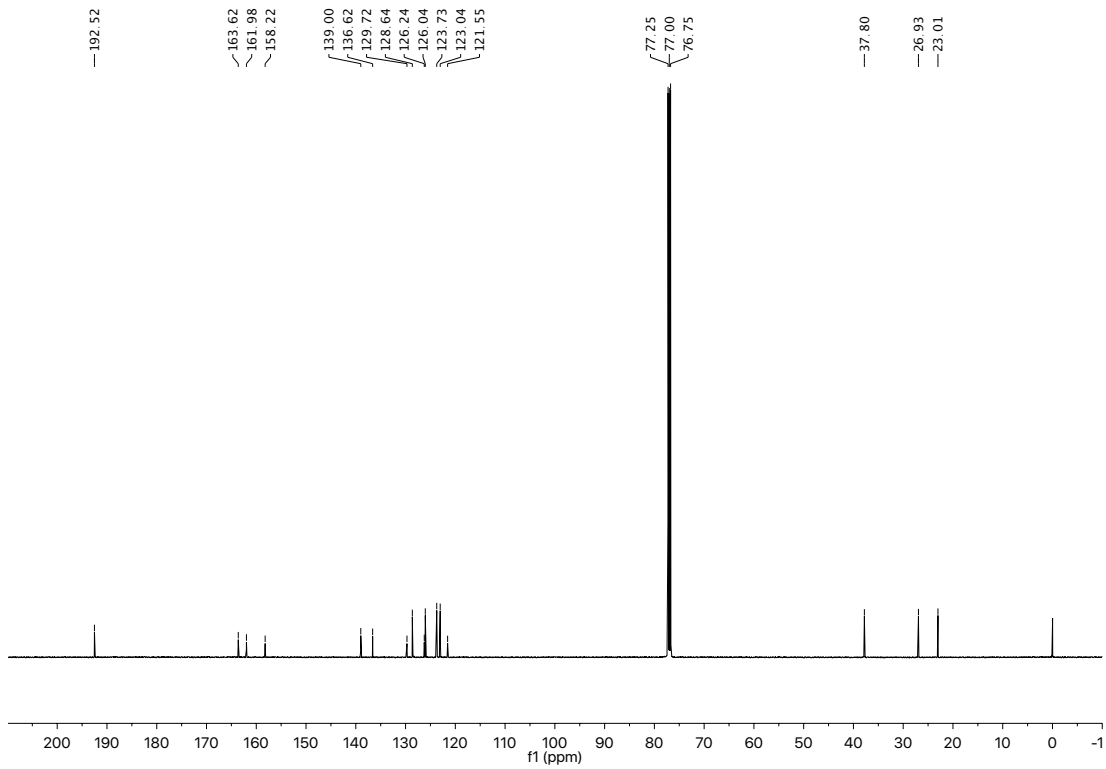
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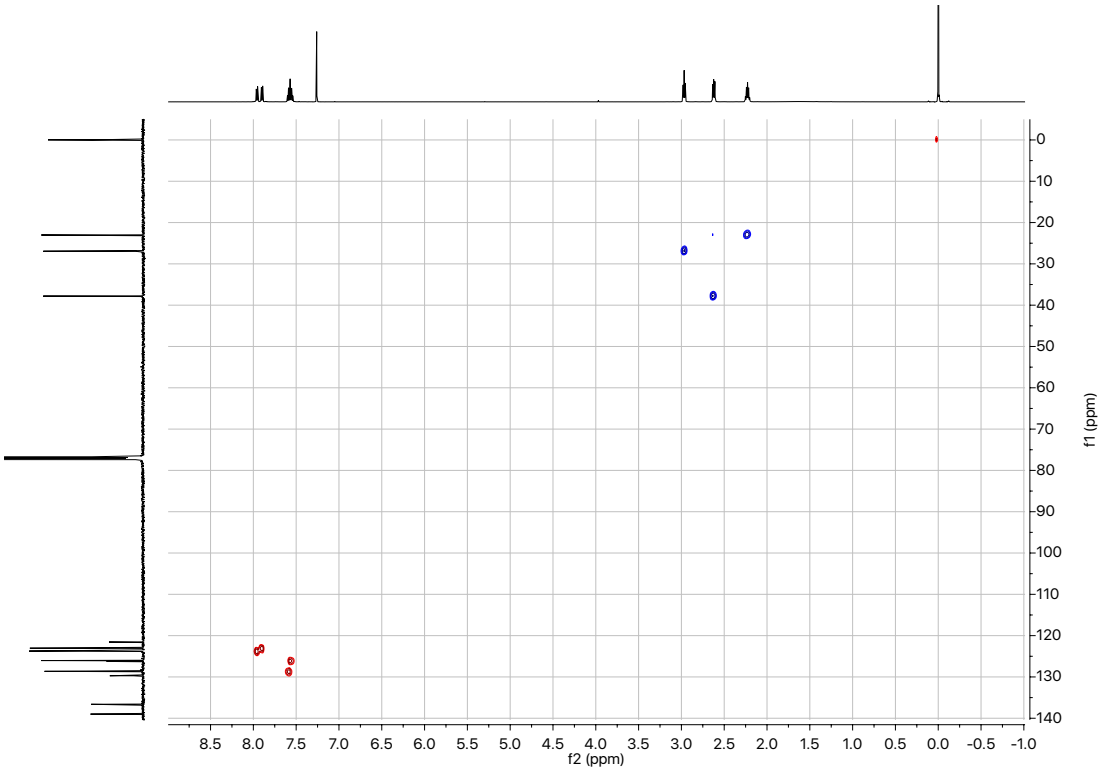
f1 (ppm)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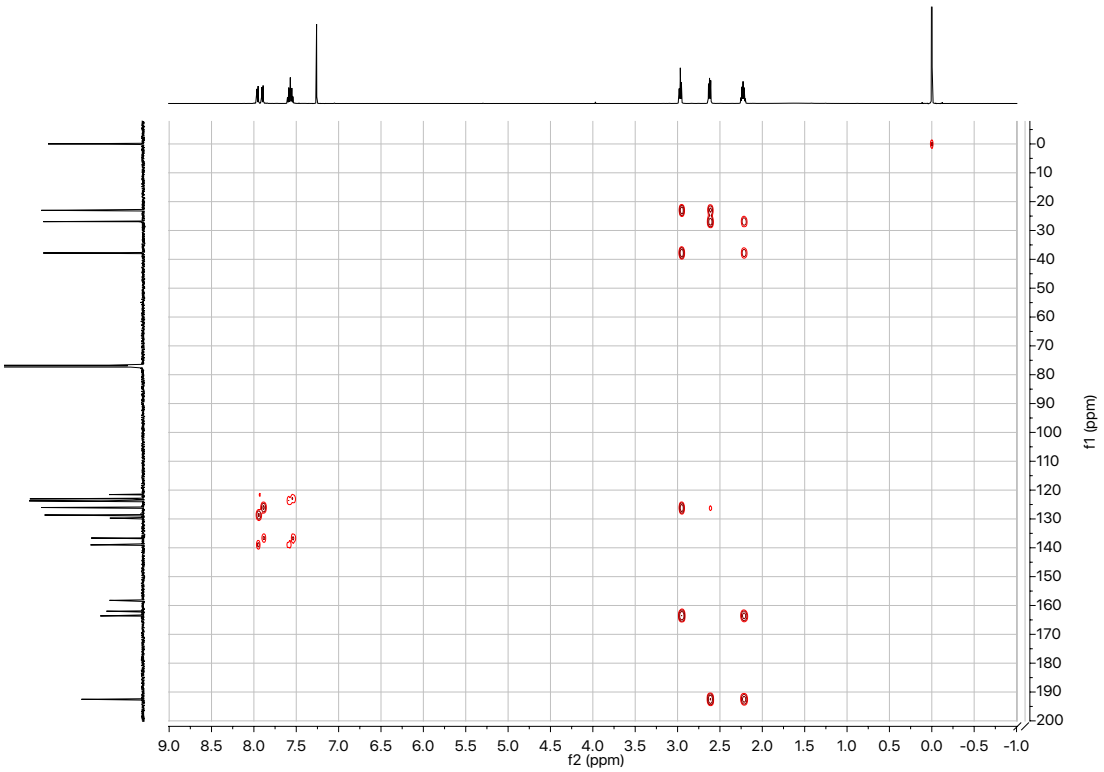
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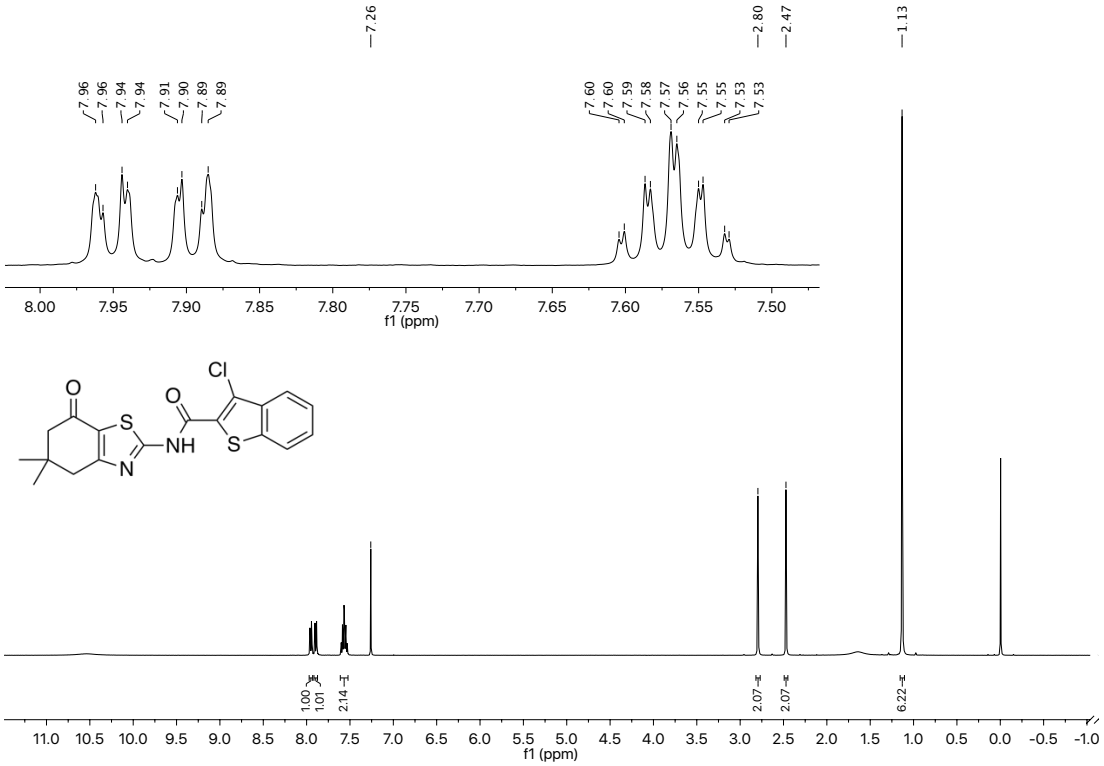
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7.53
7.53
f1 (ppm)
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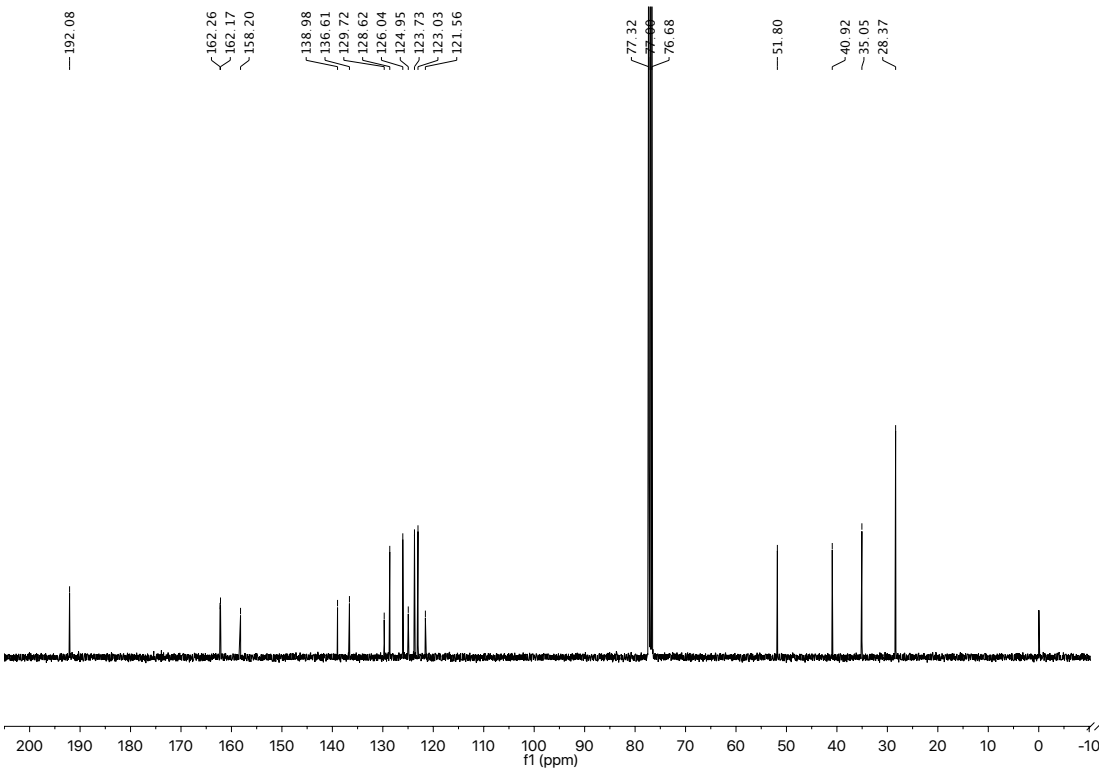
6.22
f1 (ppm)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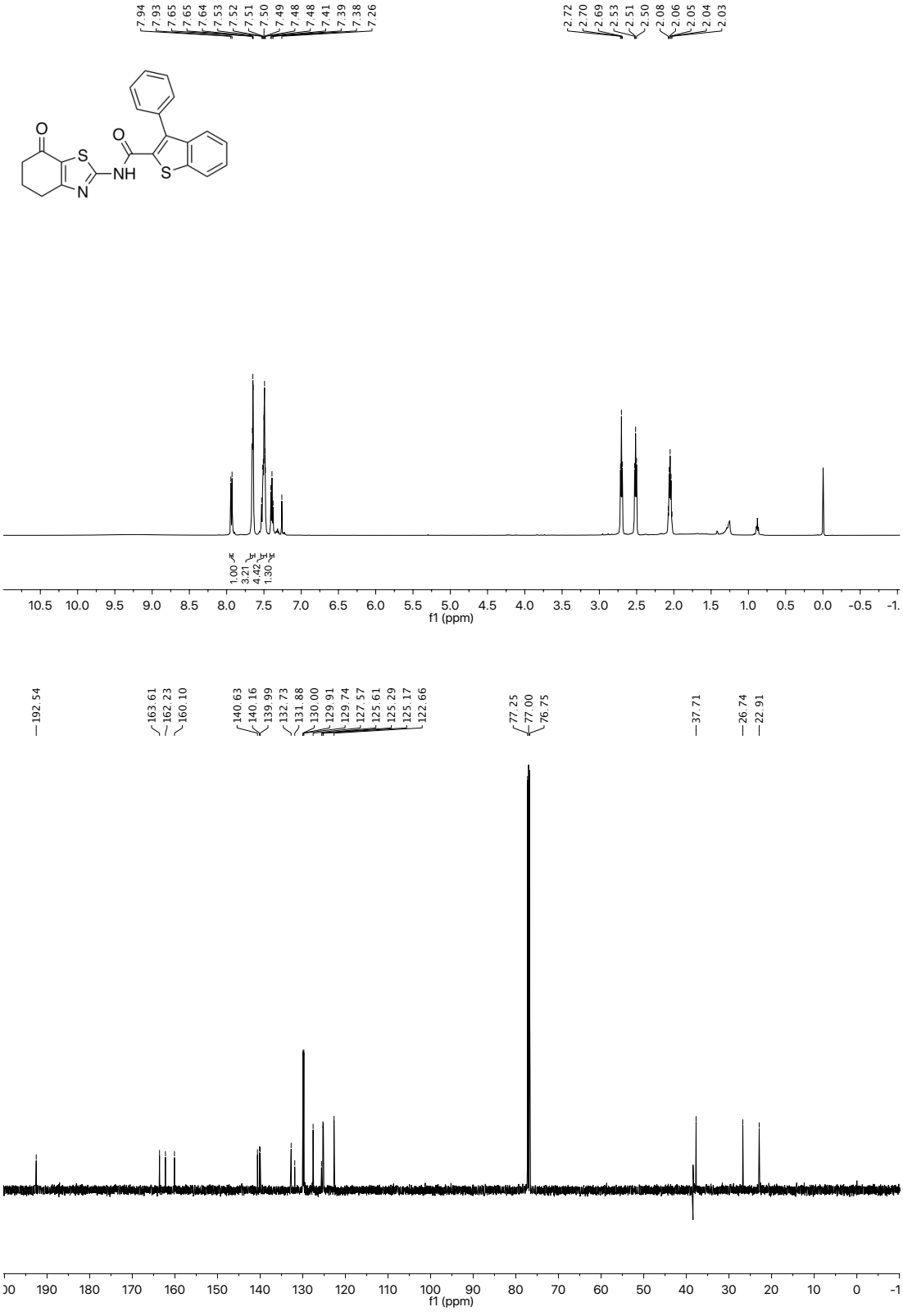
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2.05
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2.03
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f1 (ppm)
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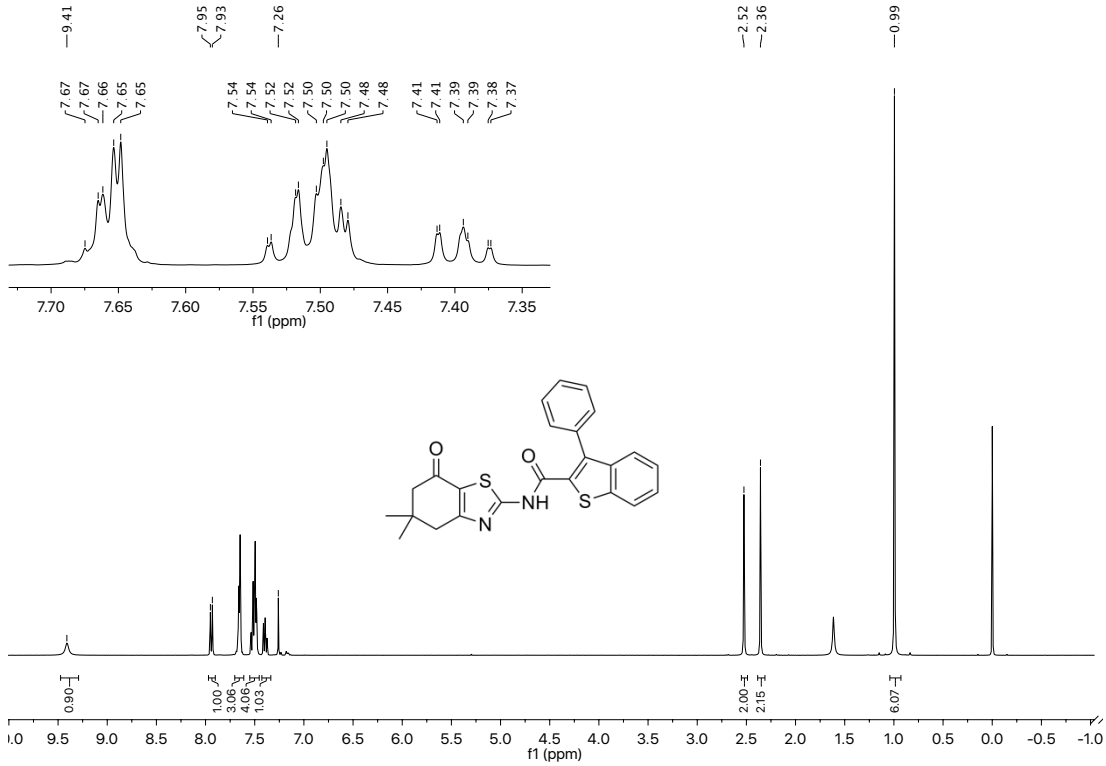
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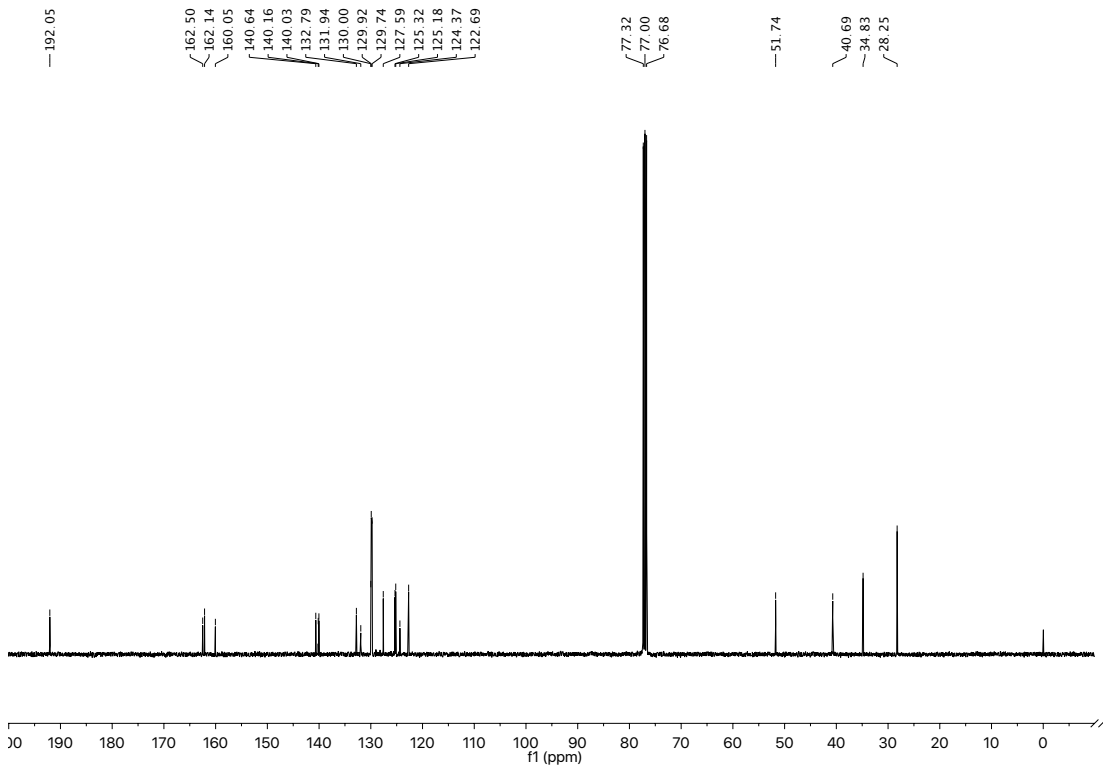
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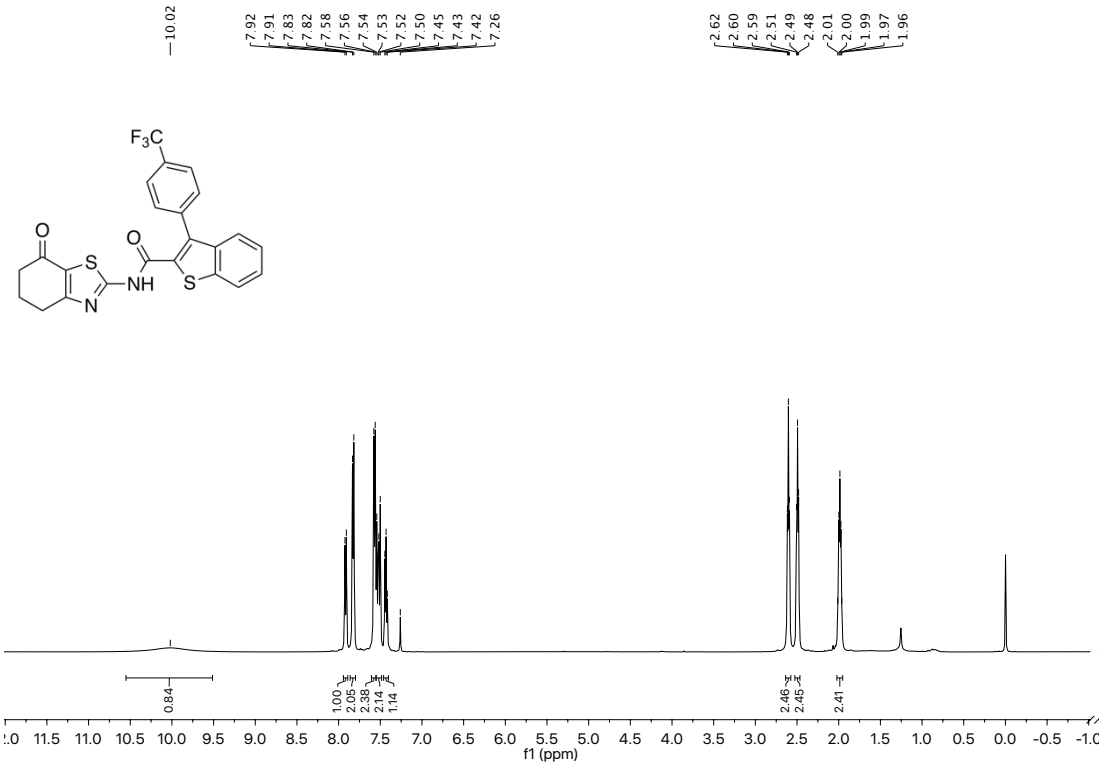
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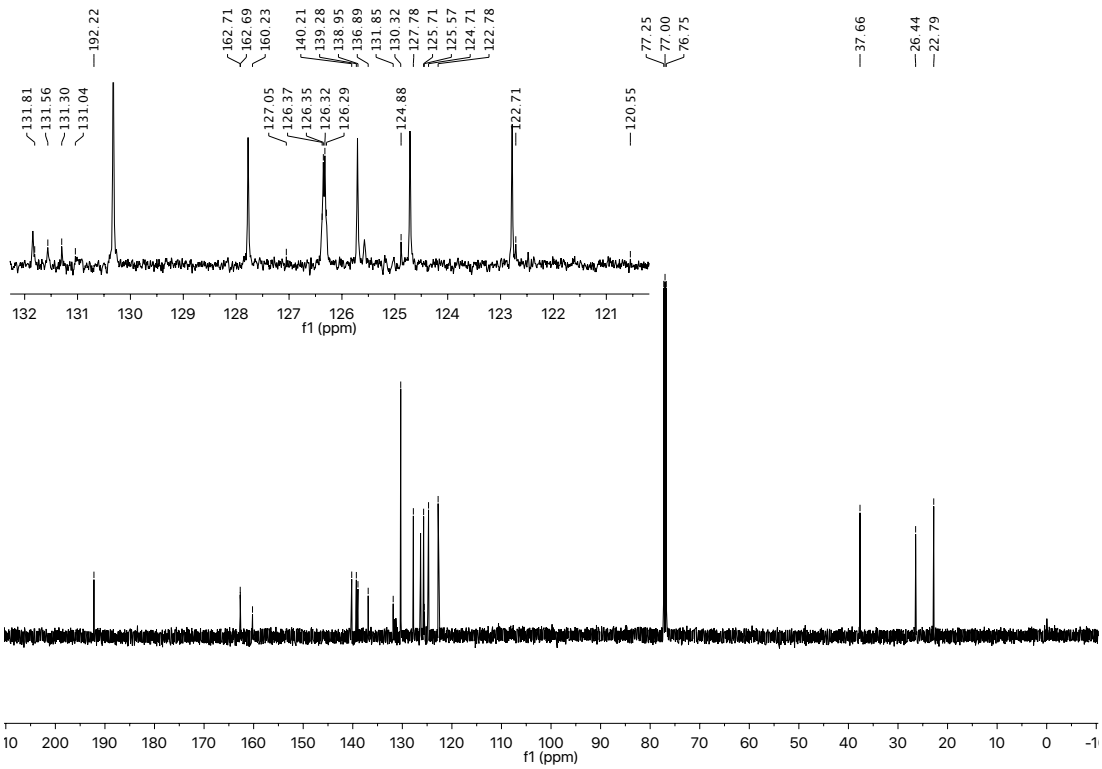
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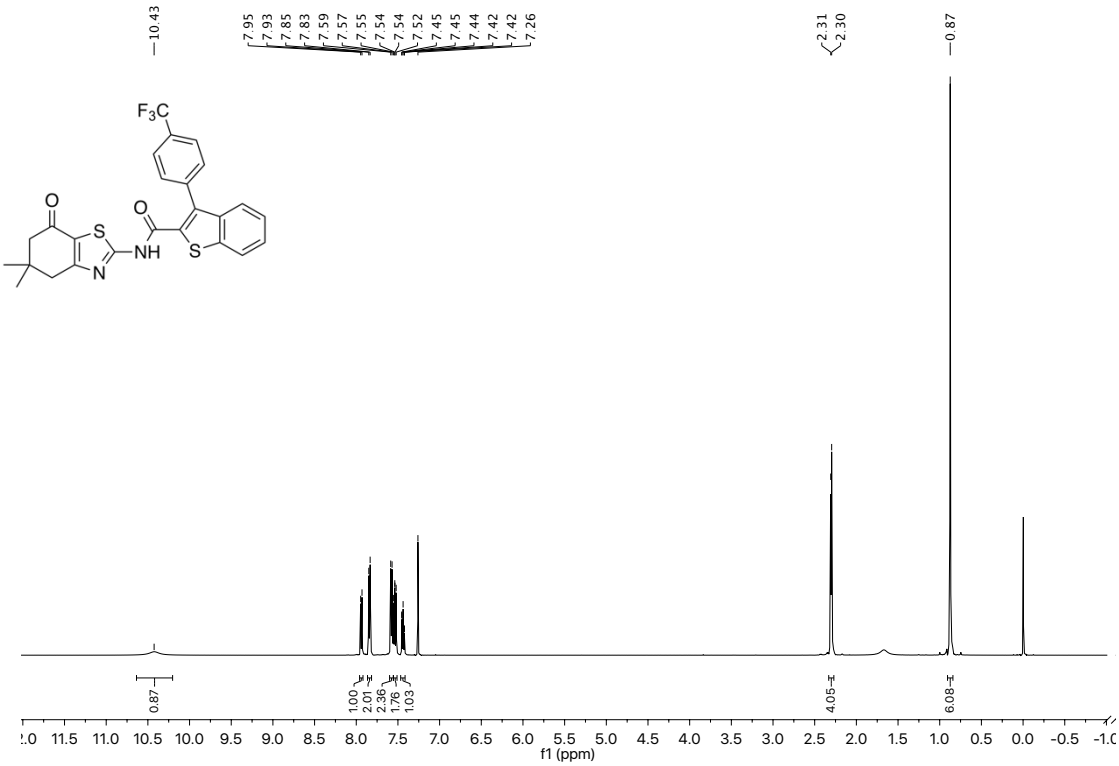
f1 (ppm)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7.93
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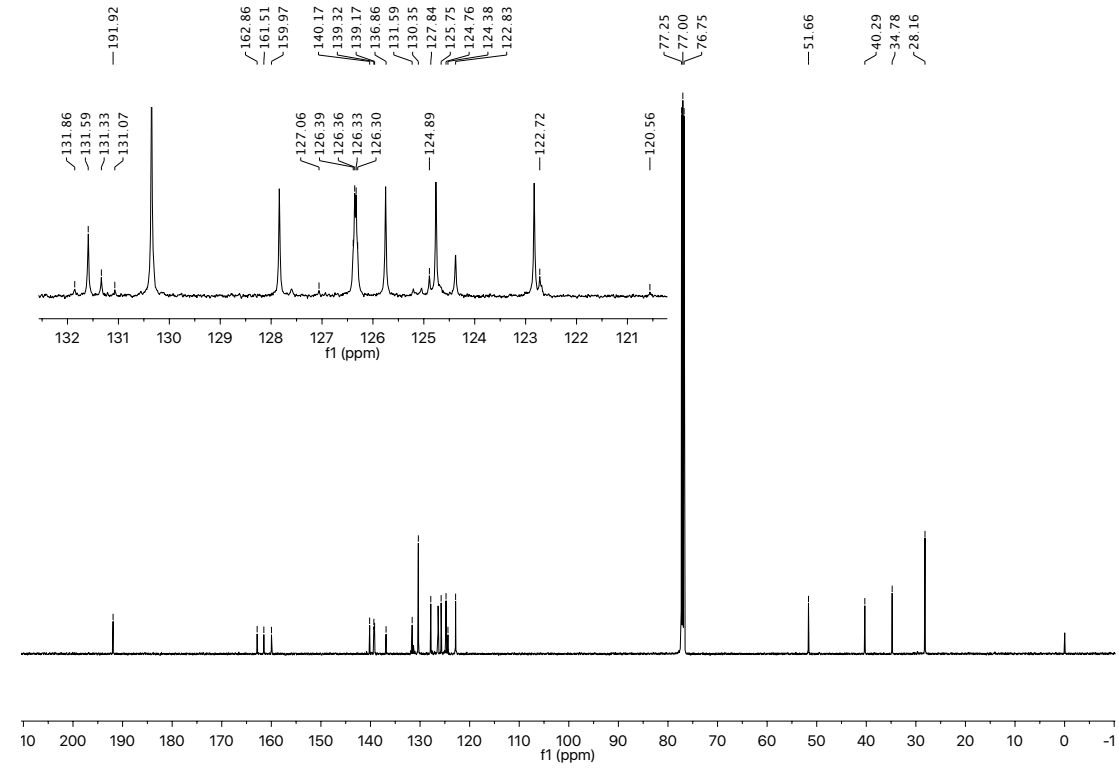
7.59
7.57
7.55
7.54
7.54
7.52
7.45
7.45
7.44
7.42
7.42
7.26
2.31
2.30
0.87
F3C
O
O
S
NH
S
N
0.87
1.00
2.01
2.36
1.76
1.03
4.05
6.08
f1 (ppm)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139.32
139.17
136.86
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130.35
127.84
125.75
124.76
124.38
122.83
77.25
77.00
76.75
51.66
40.29
34.78
28.16
131.86
131.59
131.33
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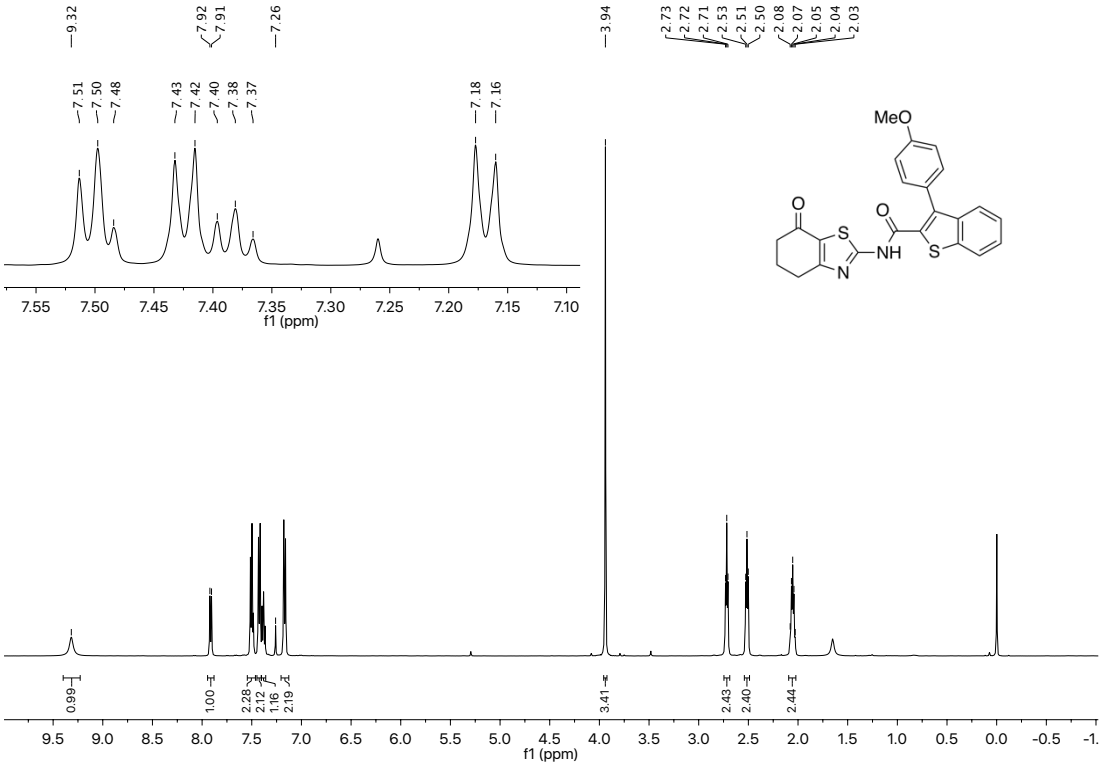
126.39
126.36
126.33
126.30
124.89
122.72
120.56
f1 (ppm)
f1 (ppm)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7.26
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2.73
2.72
2.71
2.53
2.51
2.50
2.08
2.07
2.05
2.04
2.03
7.51
7.50
7.48
7.43
7.42
7.40
7.38
7.37
7.18
7.16
MeO
O
O
S
NH
S
N
f1 (ppm)
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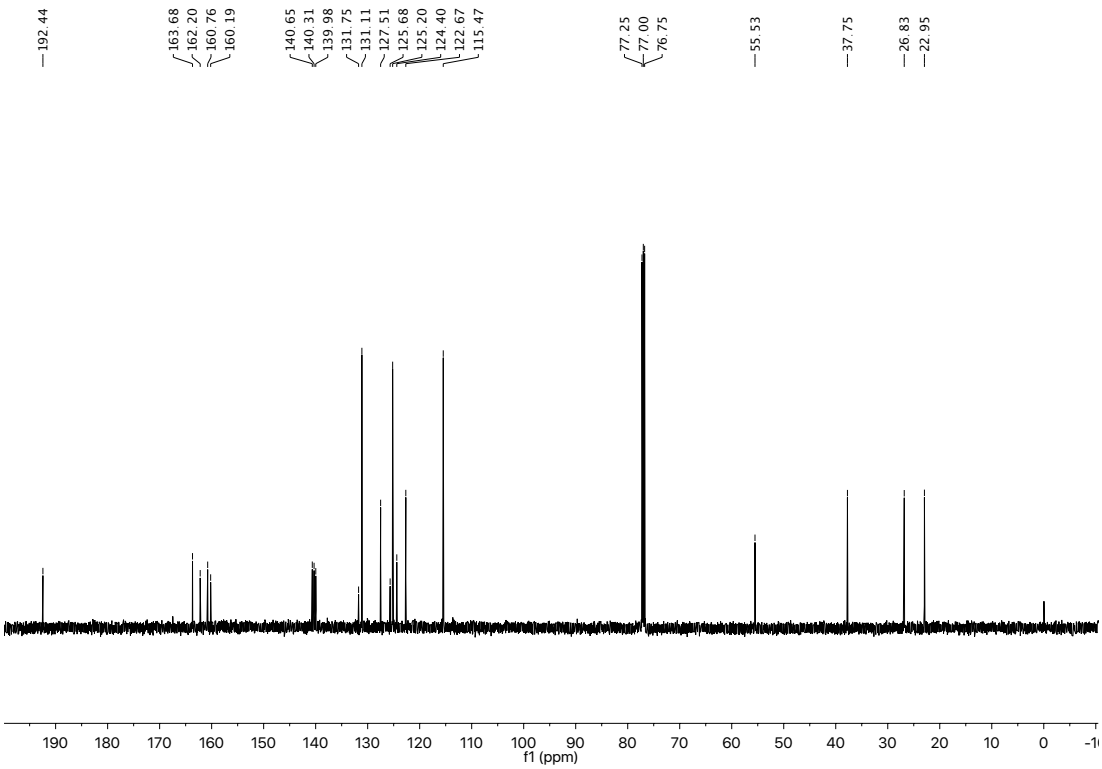
1.00
2.28
2.12
1.16
2.19
3.41
2.43
2.40
2.44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140.65
140.31
139.98
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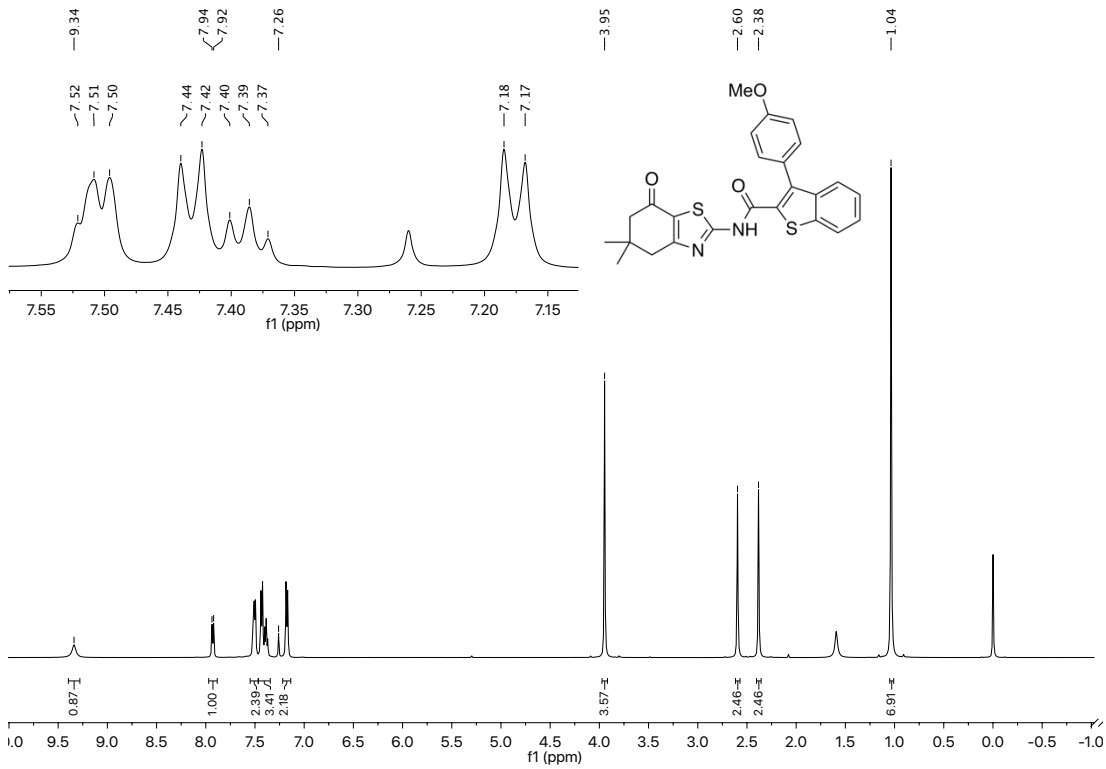
131.11
127.51
125.68
125.20
124.40
122.67
115.47
77.25
77.00
76.75
55.53
37.75
26.83
22.95
f1 (ppm)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7.26
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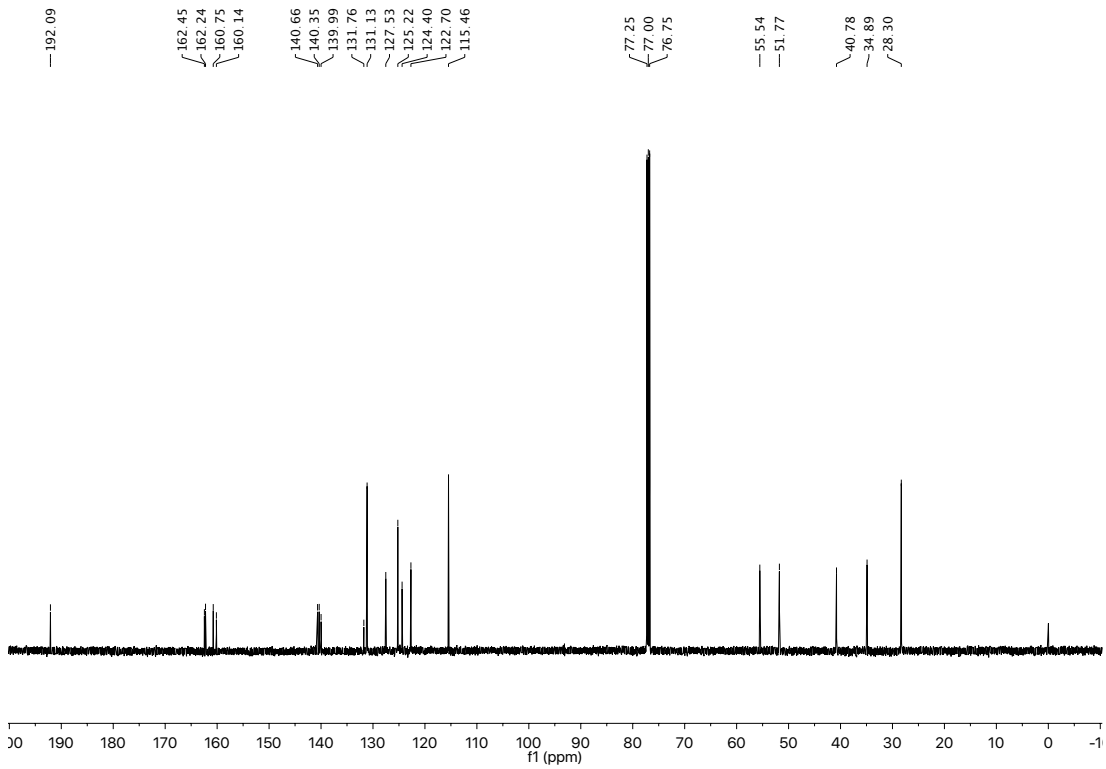
2.60
2.38
1.04
7.52
7.51
7.50
7.44
7.42
7.40
7.39
7.37
7.18
7.17
MeO
O
S
N
O
NH
S
f1 (ppm)
0.87
1.00
2.39
3.41
2.18
3.57
2.46
2.46
6.91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139.99
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131.13
127.53
125.22
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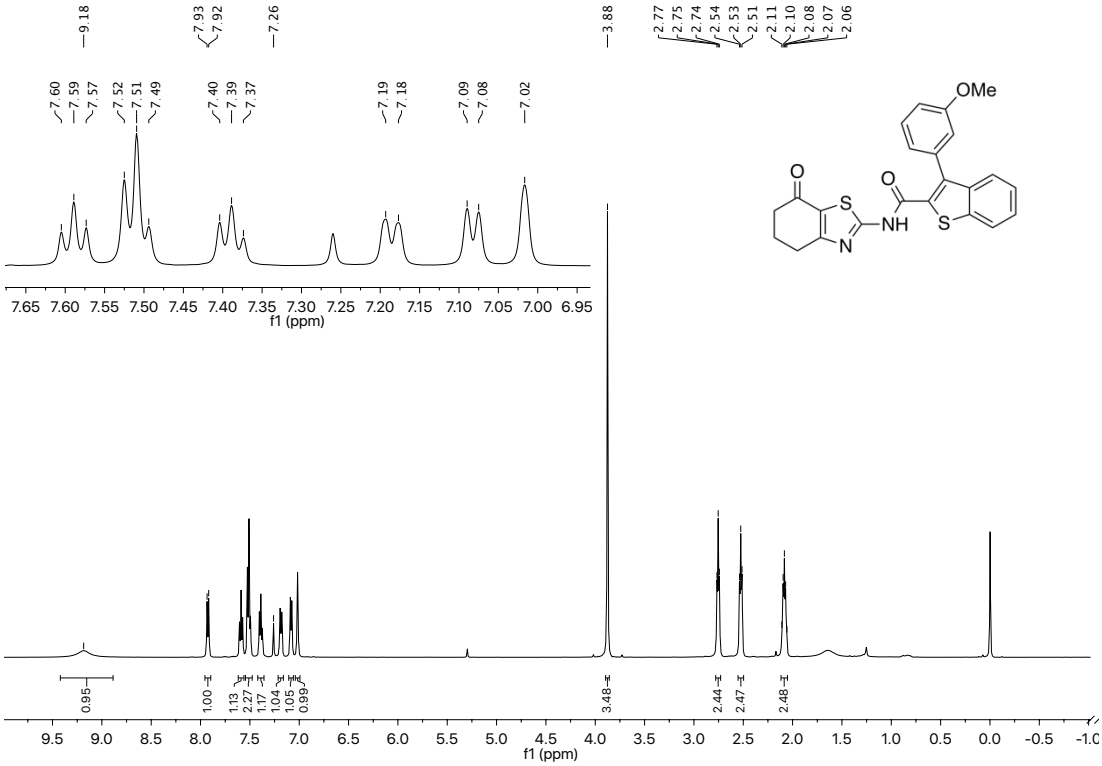
77.25
77.00
76.75
55.54
51.77
40.78
34.89
28.30
f1 (ppm)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7.26
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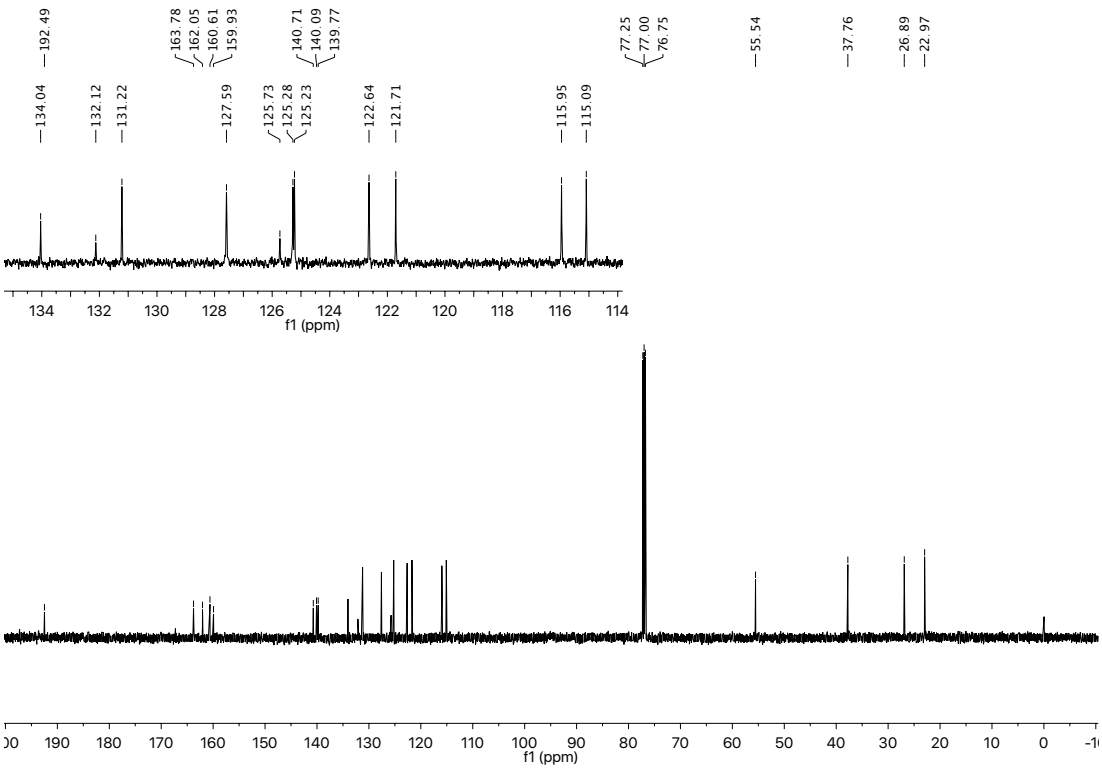
2.74
2.54
2.53
2.51
2.11
2.10
2.08
2.07
2.06
7.60
7.59
7.57
7.52
7.51
7.49
7.40
7.39
7.37
7.19
7.18
7.09
7.08
7.02
OMe
O
S
NH
N
O
S
f1 (ppm)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77.25
77.00
76.75
55.54
37.76
26.89
22.97
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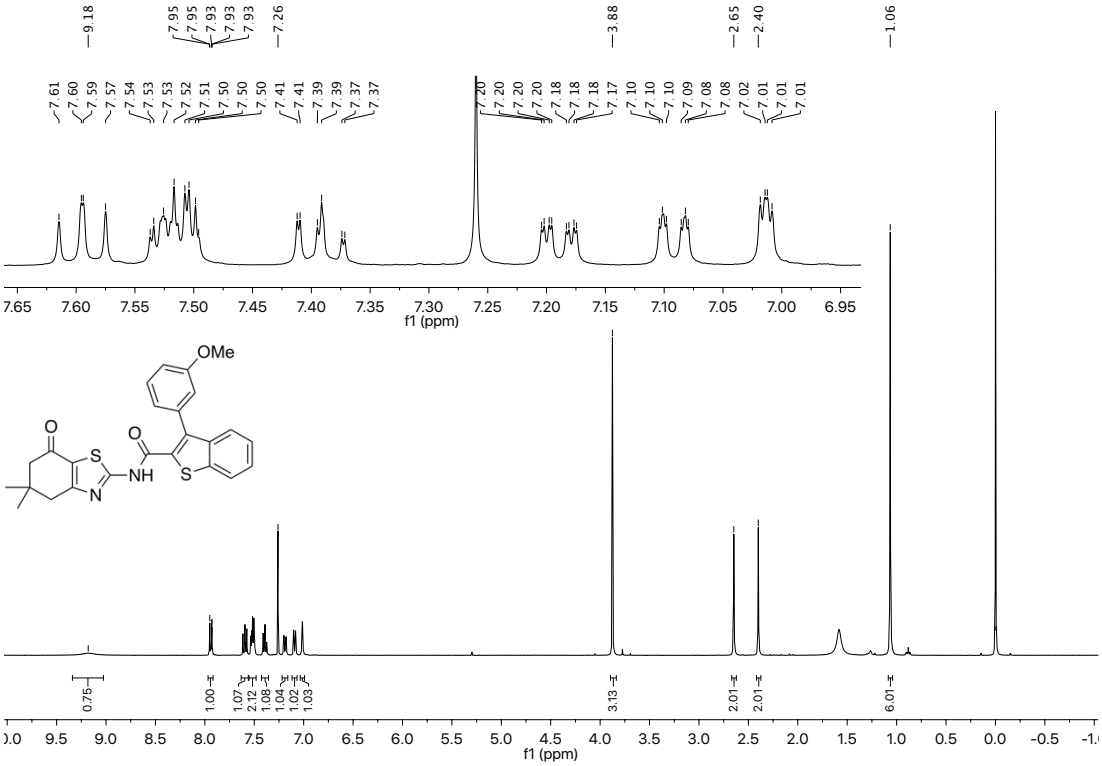
132.12
131.22
127.59
125.73
125.28
125.23
122.64
121.71
115.95
115.09
f1 (ppm)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7.93
7.26
3.88
2.65
2.40
1.06
7.61
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7.59
7.57
7.54
7.53
7.53
7.52
7.51
7.50
7.50
7.50
7.41
7.41
7.39
7.39
7.37
7.37
7.20
7.20
7.20
7.20
7.18
7.18
7.18
7.17
7.10
7.10
7.10
7.09
7.08
7.08
7.02
7.01
7.01
7.01
OMe
O
S
NH
N
O
S
0.75
1.00
1.07
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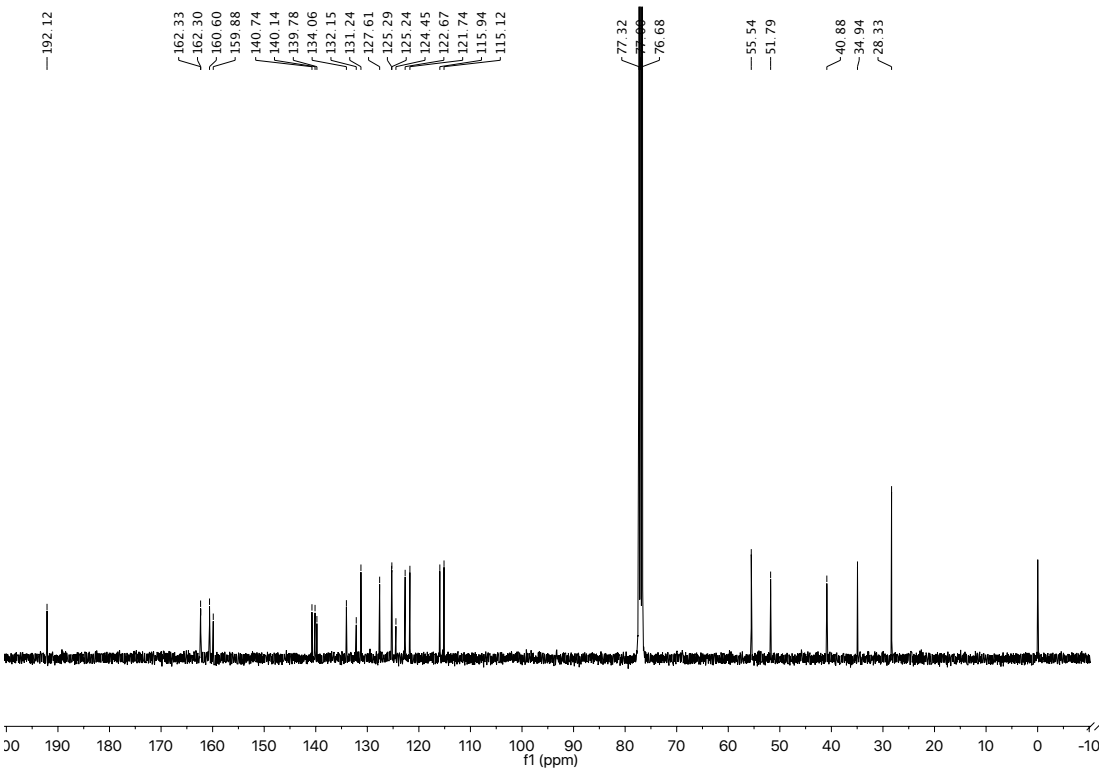
1.08
1.04
1.02
1.03
3.13
2.01
2.01
6.01
f1 (ppm)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139.78
134.06
132.15
131.24
127.61
125.29
125.24
124.45
122.67
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115.94
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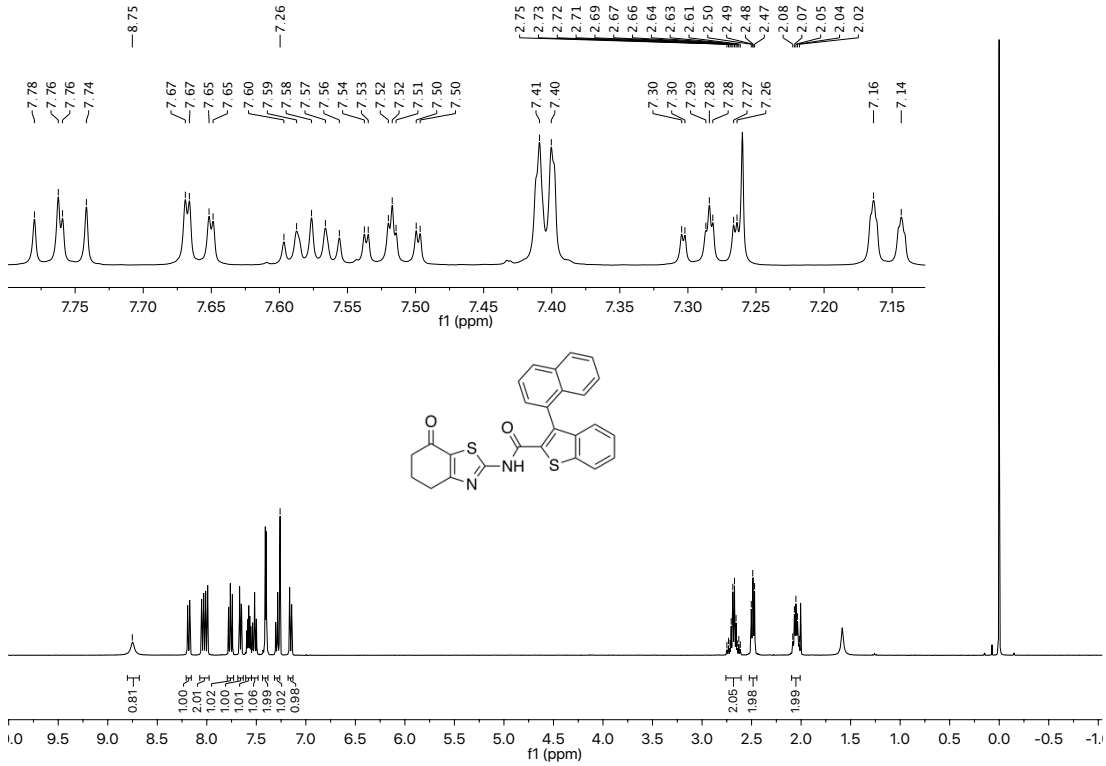
77.32
77.00
76.68
55.54
51.79
40.88
34.94
28.33
f1 (ppm)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7.26
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2.72
2.71
2.69
2.67
2.66
2.64
2.63
2.61
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2.49
2.48
2.47
2.08
2.07
2.05
2.04
2.02
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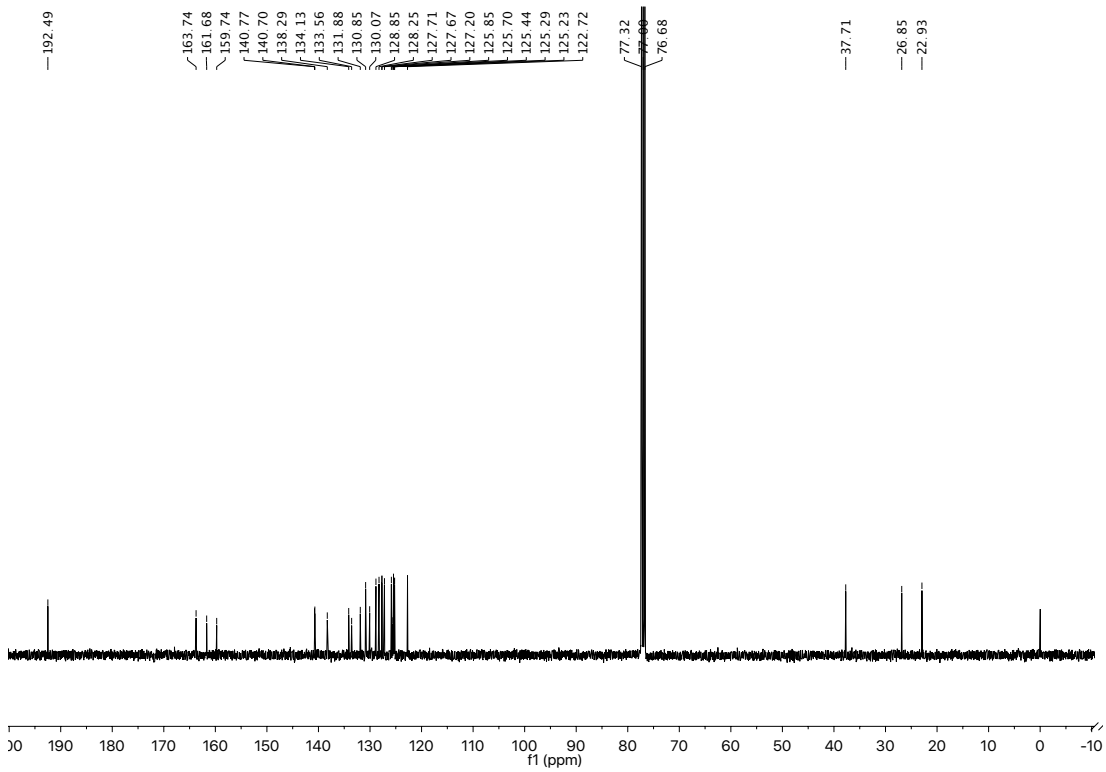
7.76
7.74
7.67
7.67
7.65
7.65
7.60
7.59
7.58
7.57
7.56
7.54
7.53
7.52
7.52
7.51
7.50
7.50
7.41
7.40
7.30
7.30
7.29
7.28
7.28
7.27
7.26
7.16
7.14
f1 (ppm)
O
O
S
NH
S
N
0.81
1.00
2.01
1.02
1.00
1.01
1.06
1.99
1.02
0.98
2.05
1.98
1.99
f1 (ppm)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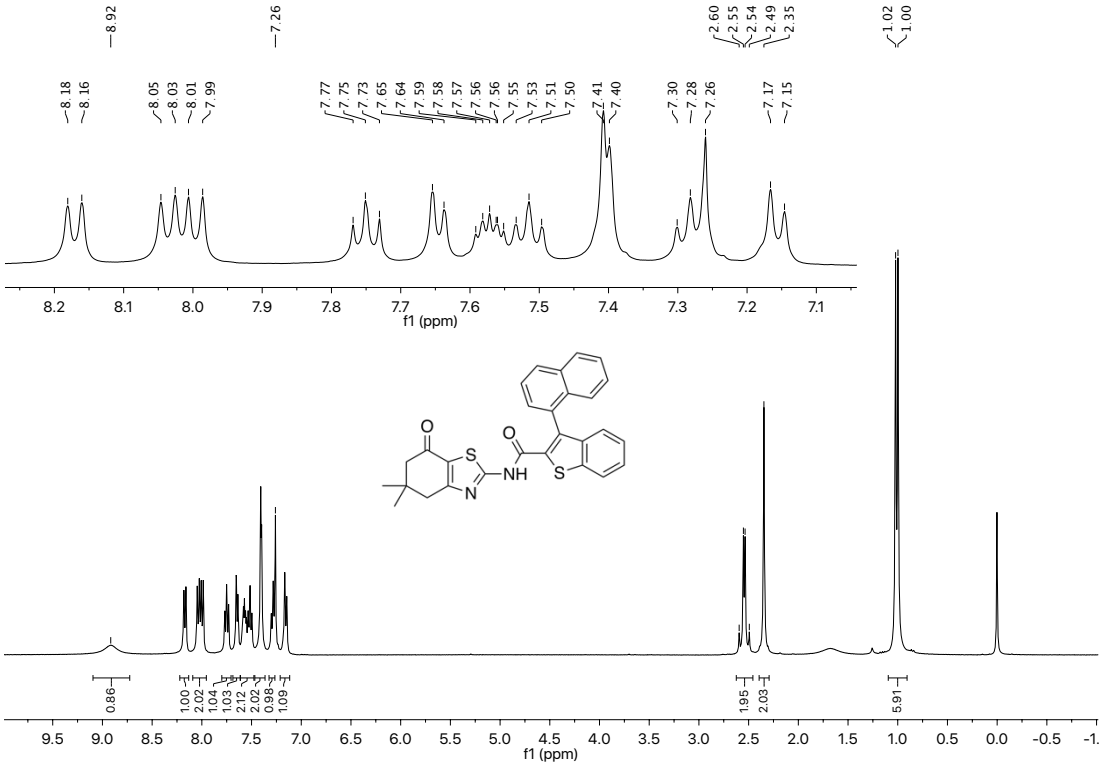
138.29
134.13
133.56
131.88
130.85
130.07
128.85
128.25
127.71
127.67
127.20
125.85
125.70
125.44
125.29
125.23
122.72
77.32
77.00
76.68
37.71
26.85
22.93
f1 (ppm)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7.26
2.60
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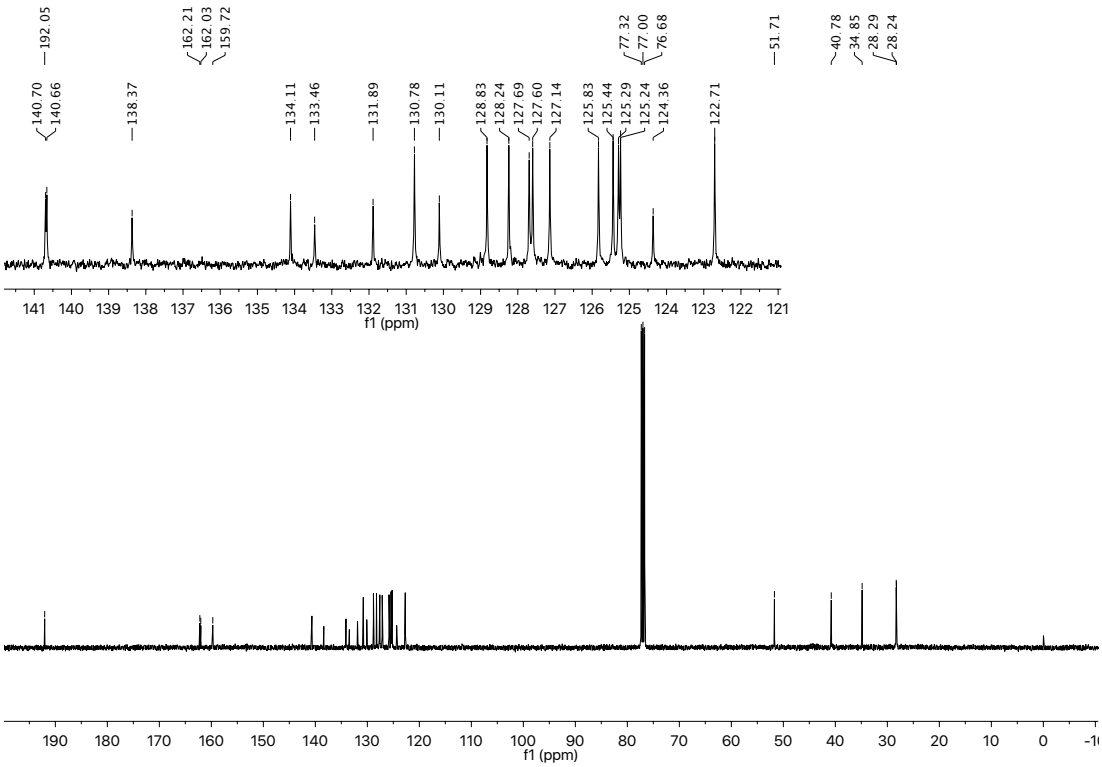
2.54
2.49
2.35
1.02
1.00
8.18
8.16
8.05
8.03
8.01
7.99
7.77
7.75
7.73
7.65
7.64
7.59
7.58
7.57
7.56
7.56
7.55
7.53
7.51
7.50
7.41
7.40
7.30
7.28
7.26
7.17
7.15
f1 (ppm)
O
S
NH
N
S
O
0.86
1.00
2.02
1.04
1.03
2.12
2.02
0.98
1.09
1.95
2.03
5.91
f1 (ppm)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162.03
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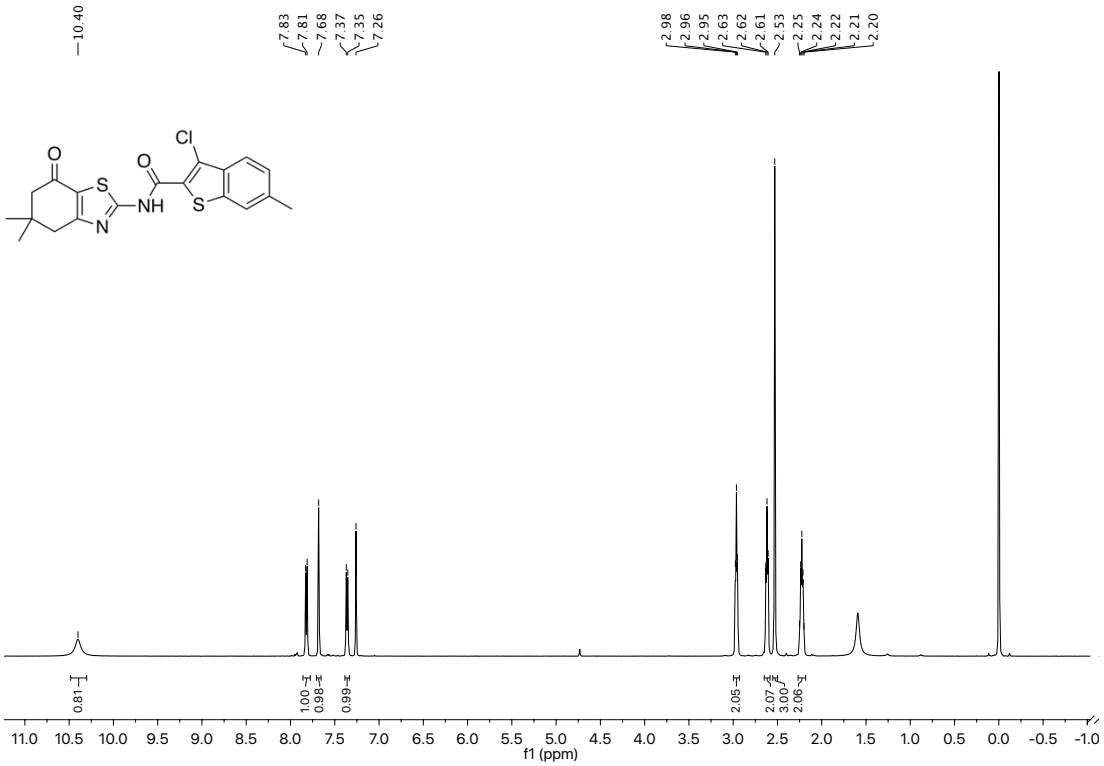
77.32
77.00
76.68
51.71
40.78
34.85
28.29
28.24
140.70
140.66
138.37
134.11
133.46
131.89
130.78
130.11
128.83
128.24
127.69
127.60
127.14
125.83
125.44
125.29
125.24
124.36
122.71
f1 (ppm)
f1 (ppm)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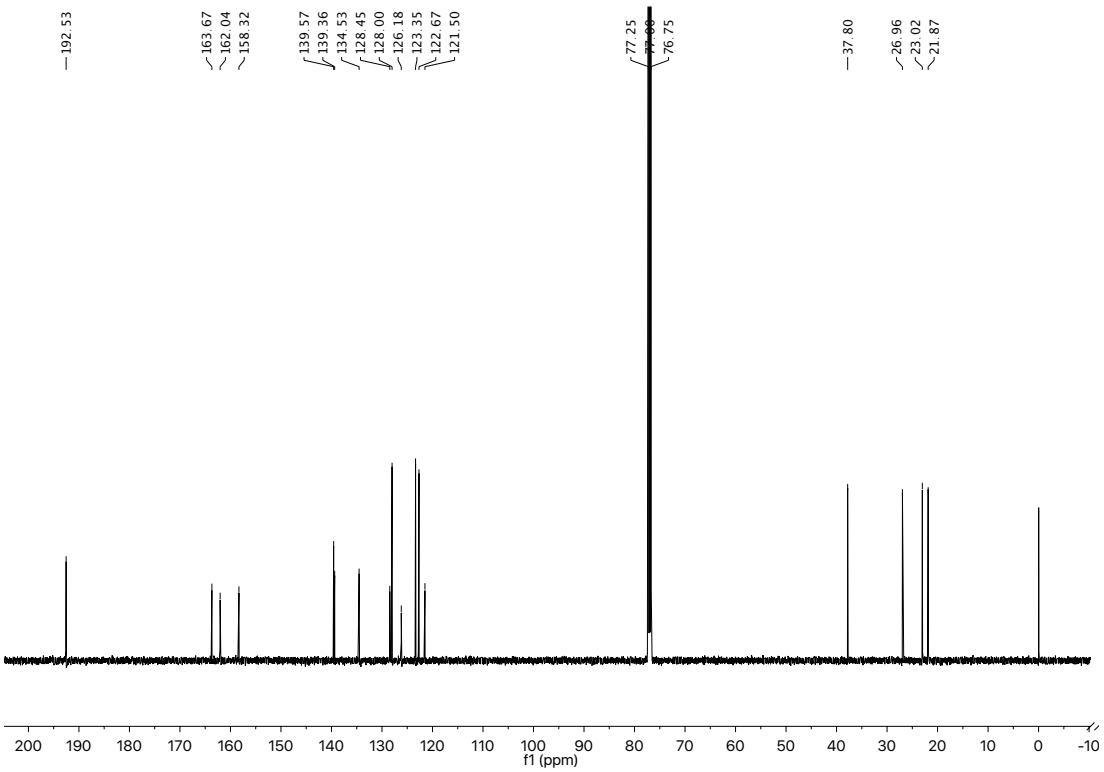
7.26
2.98
2.96
2.95
2.63
2.62
2.61
2.53
2.25
2.24
2.22
2.21
2.20
O
O
Cl
S
NH
S
N
0.81
1.00
0.98
0.99
2.05
2.07
3.00
2.06
f1 (ppm)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128.45
128.00
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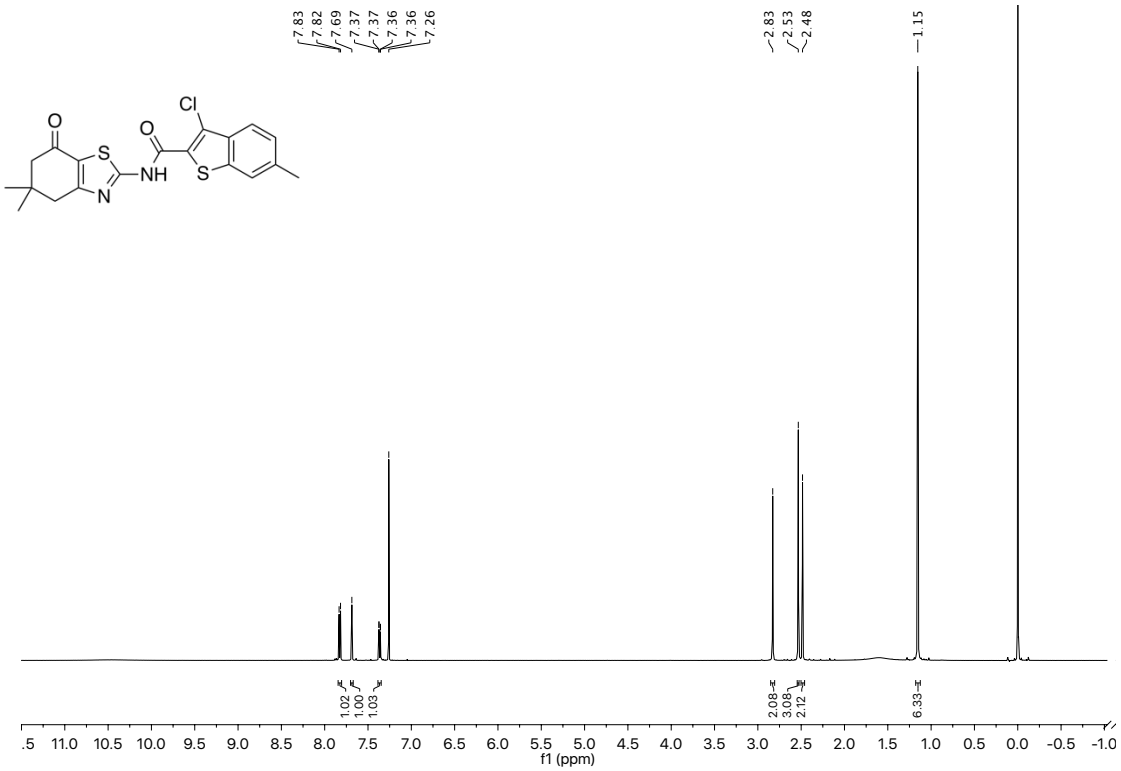
121.50
77.25
77.00
76.75
37.80
26.96
23.02
21.87
f1 (ppm)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7.82
7.69
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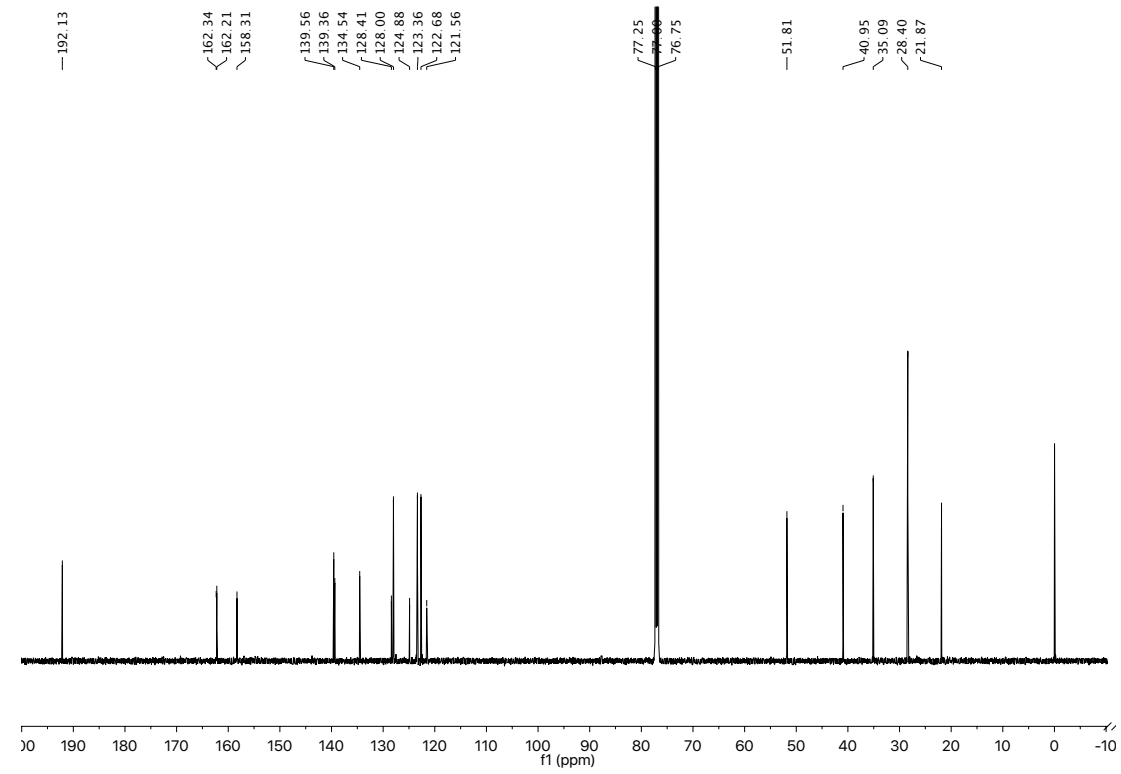
7.37
7.36
7.36
7.26
2.83
2.53
2.48
1.15
O
S
NH
N
O
Cl
S
1.02
1.00
1.03
2.08
3.08
2.12
6.33
f1 (ppm)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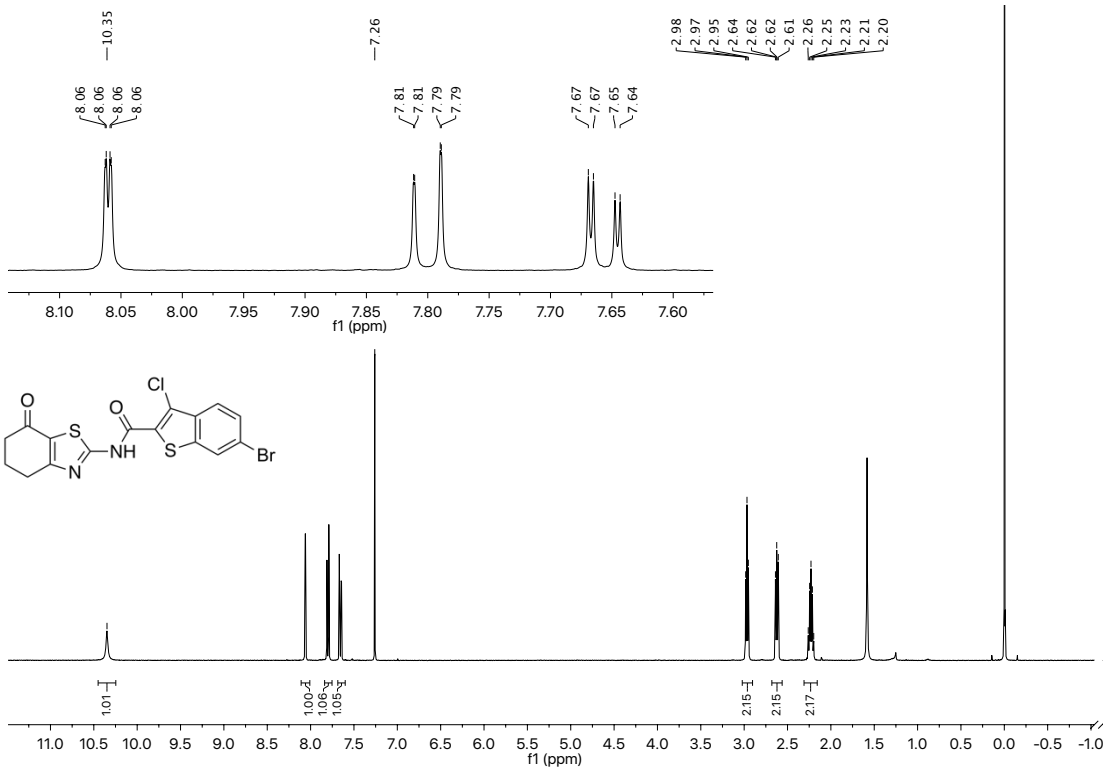
40.95
35.09
28.40
21.87
f1 (ppm)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8.06
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8.06
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7.81
7.79
7.79
7.67
7.67
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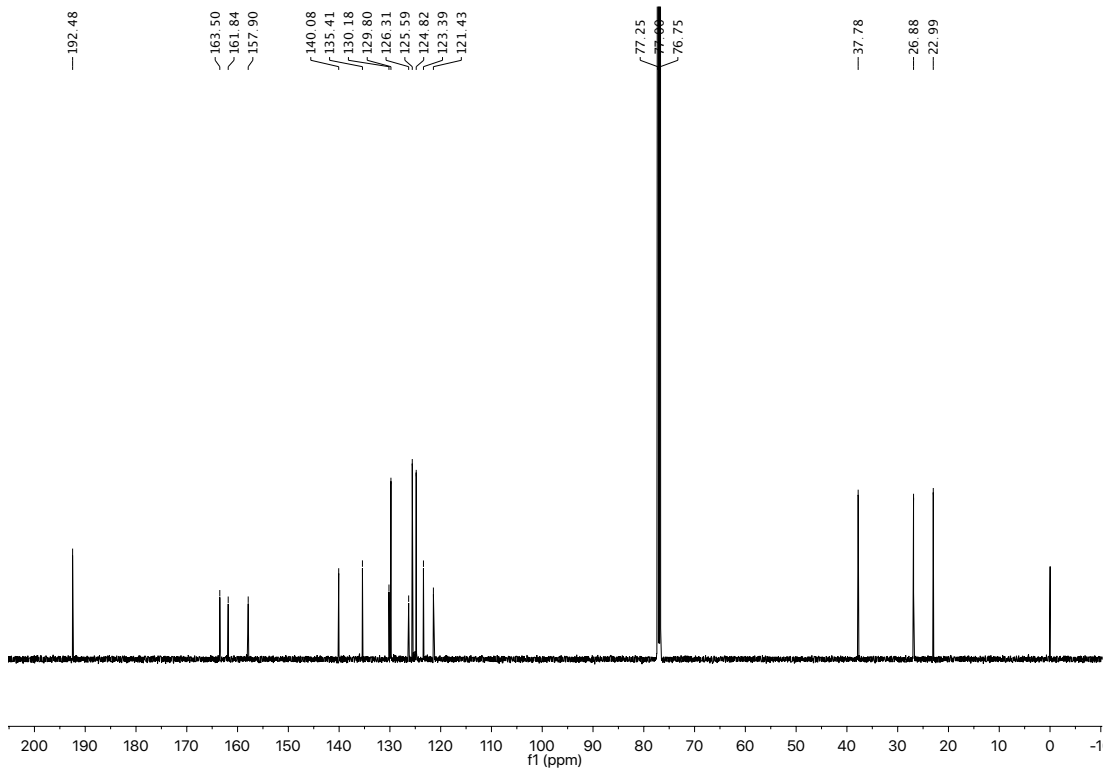
2.97
2.95
2.64
2.62
2.62
2.61
2.26
2.25
2.23
2.21
2.20
f1 (ppm)
Cl
O
O
S
NH
S
N
Br
1.01
1.00
1.06
1.05
2.15
2.15
2.17
f1 (ppm)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135.41
130.18
129.80
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123.39
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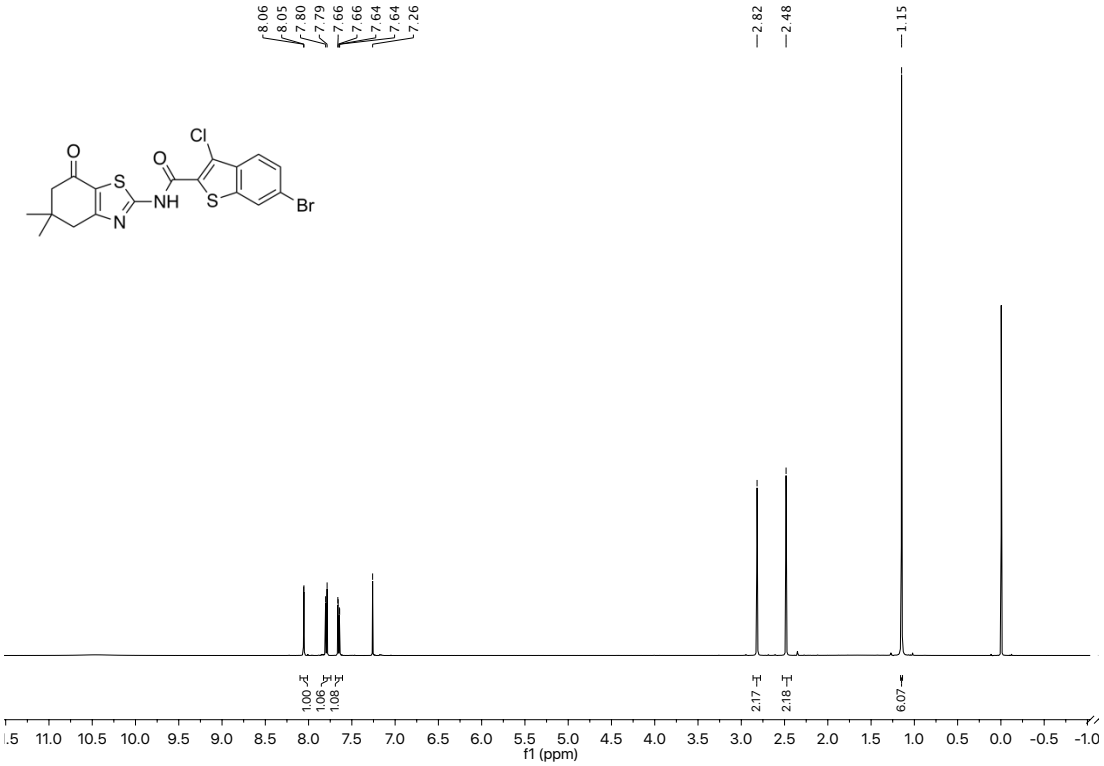
77.25
77.00
76.75
37.78
26.88
22.99
f1 (ppm)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8.05
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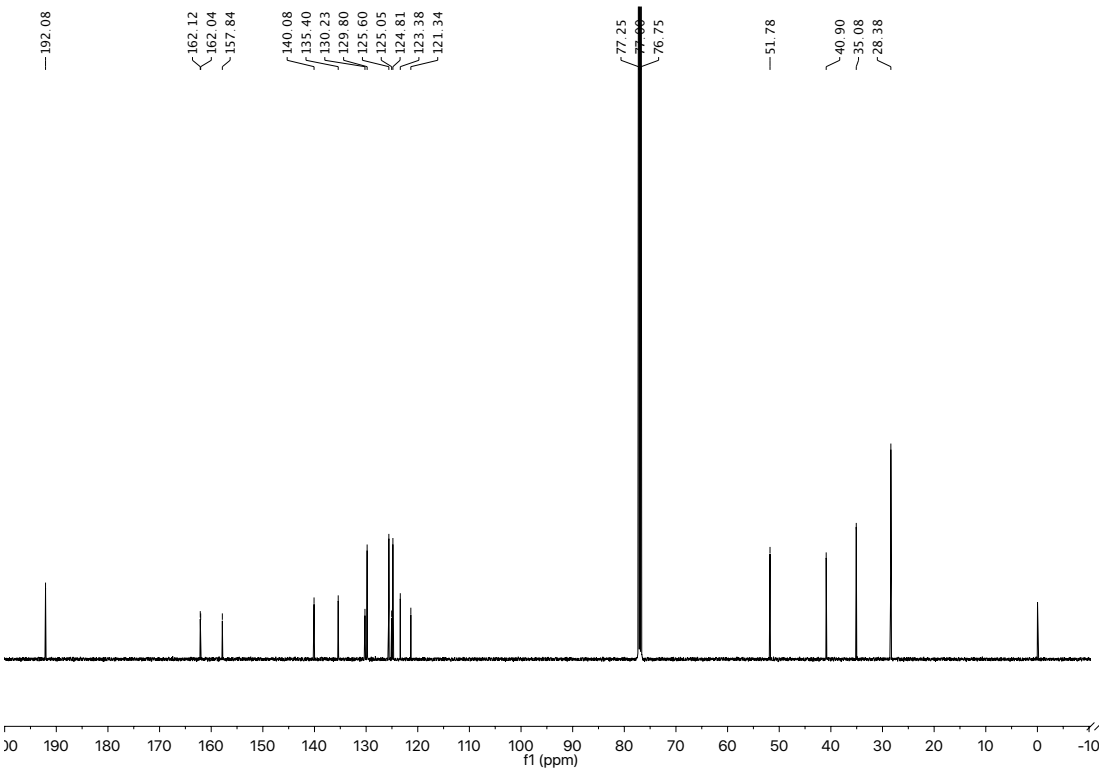
7.79
7.66
7.66
7.64
7.64
7.26
2.82
2.48
1.15
O
S
NH
N
O
Cl
S
Br
1.00
1.06
1.08
2.17
2.18
6.07
f1 (ppm)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135.40
130.23
129.80
125.60
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124.81
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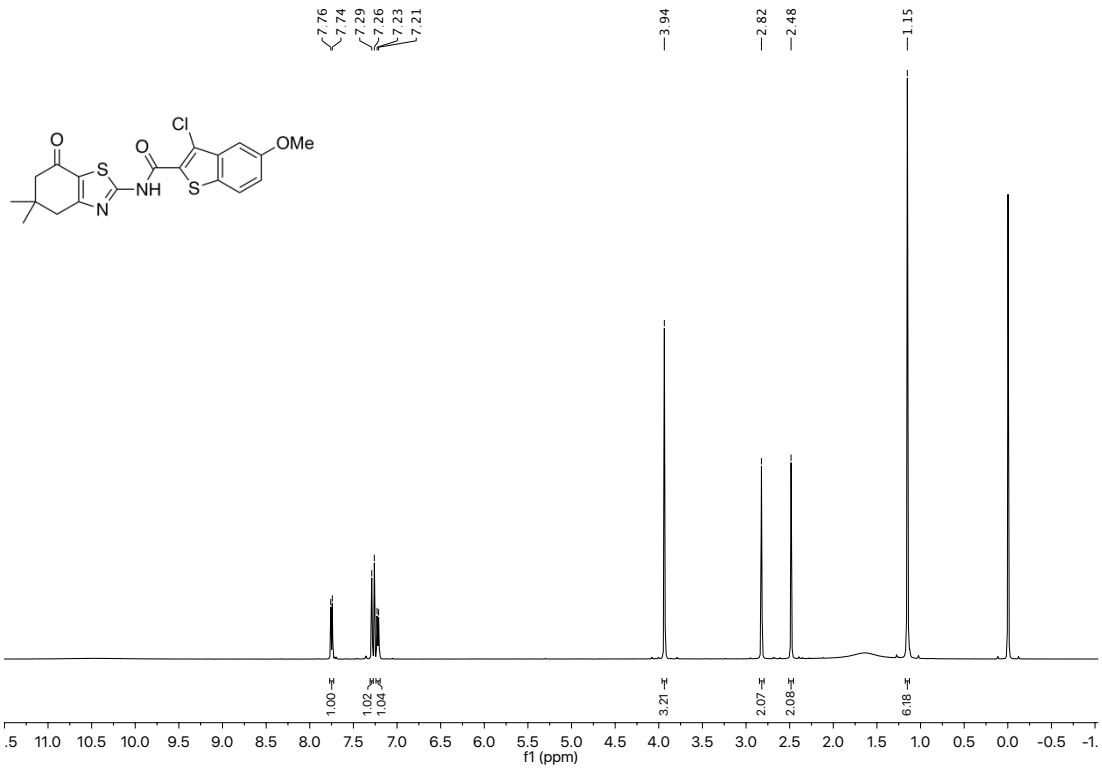
77.25
77.00
76.75
51.78
40.90
35.08
28.38
f1 (ppm)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7.74
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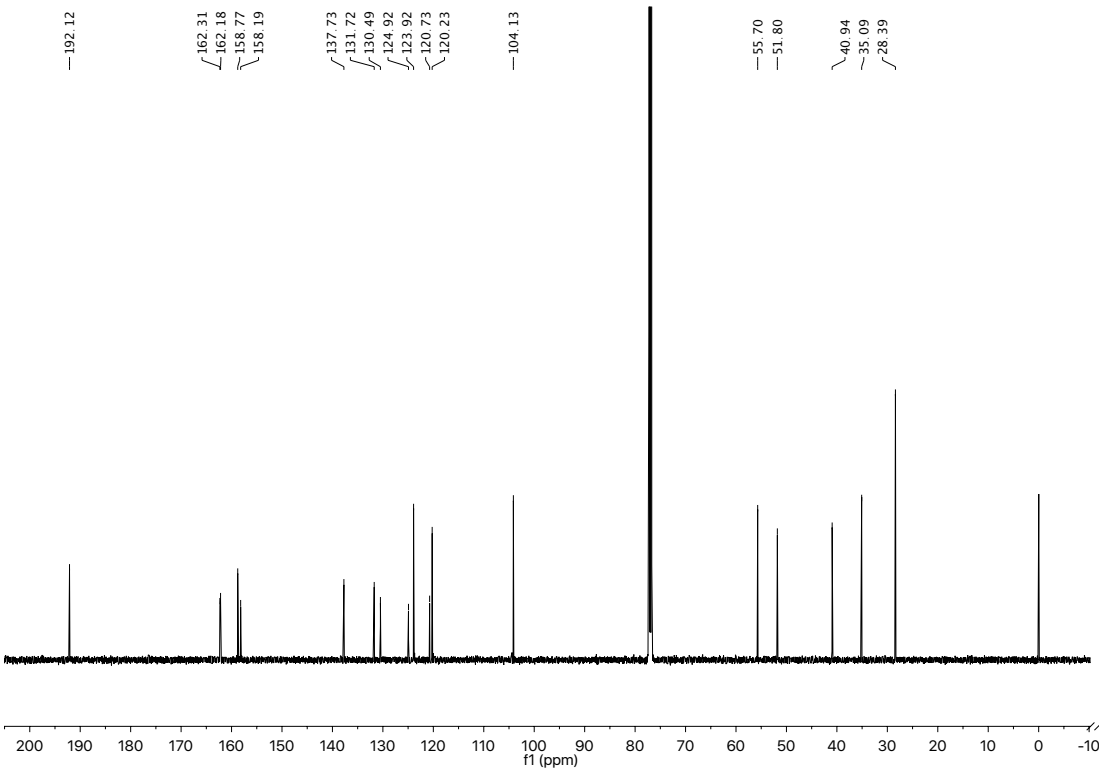
7.26
7.23
7.21
3.94
2.82
2.48
1.15
Cl
OMe
O
O
S
NH
S
N
1.00
1.02
1.04
3.21
2.07
2.08
6.18
f1 (ppm)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137.73
131.72
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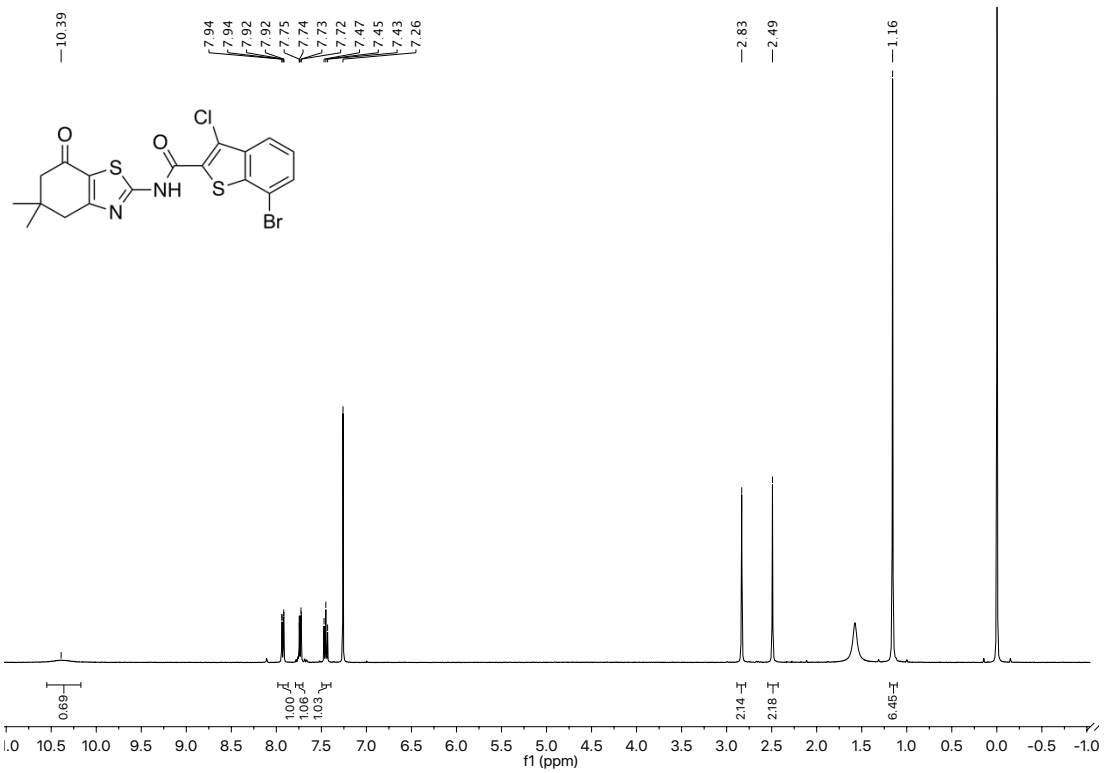
120.73
120.23
104.13
55.70
51.80
40.94
35.09
28.39
f1 (ppm)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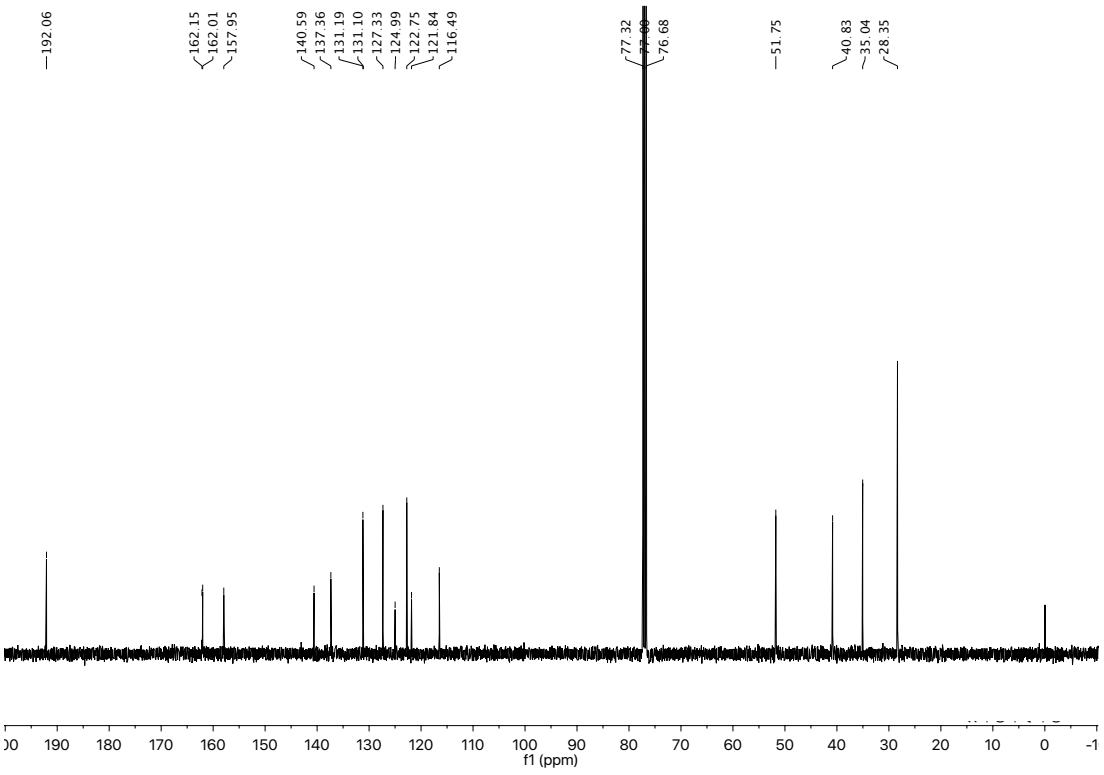
7.94
7.92
7.92
7.75
7.74
7.73
7.72
7.47
7.45
7.43
7.26
2.83
2.49
1.16
O
S
N
NH
O
Cl
S
Br
0.69
1.00
1.06
1.03
2.14
2.18
6.45
f1 (ppm)


192.06
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157.95
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137.36
131.19
131.10
127.33
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122.75
121.84
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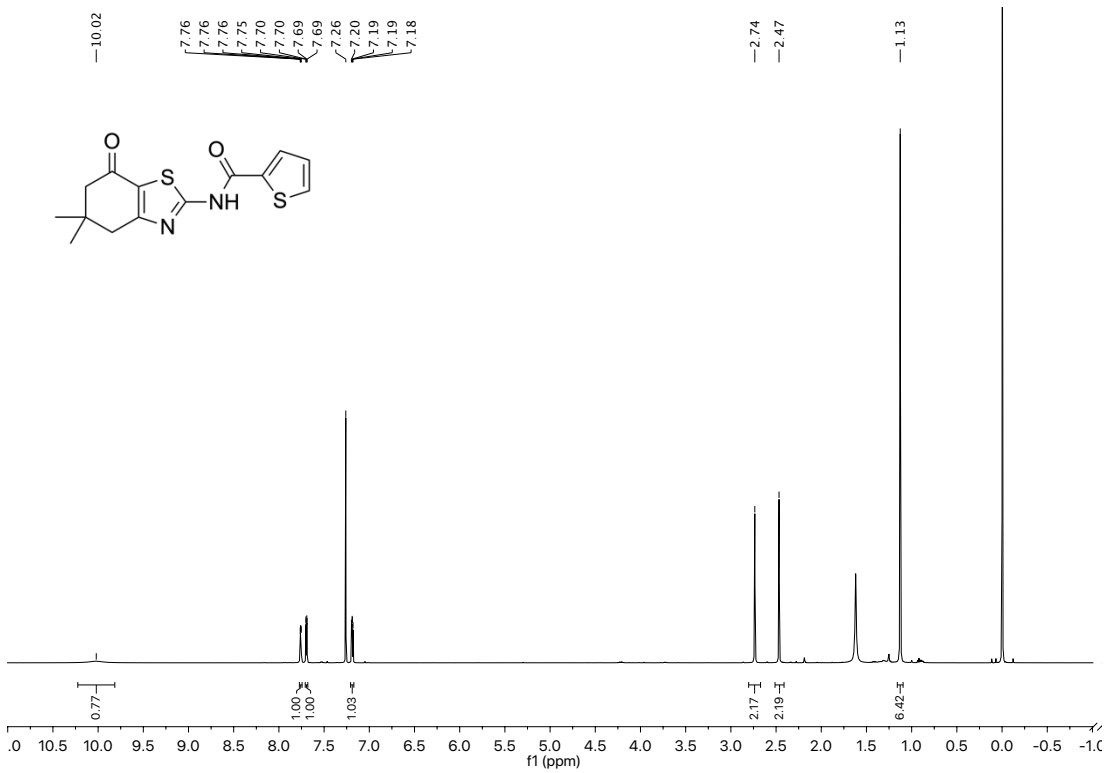
51.75
40.83
35.04
28.35
f1 (ppm)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7.76
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7.70
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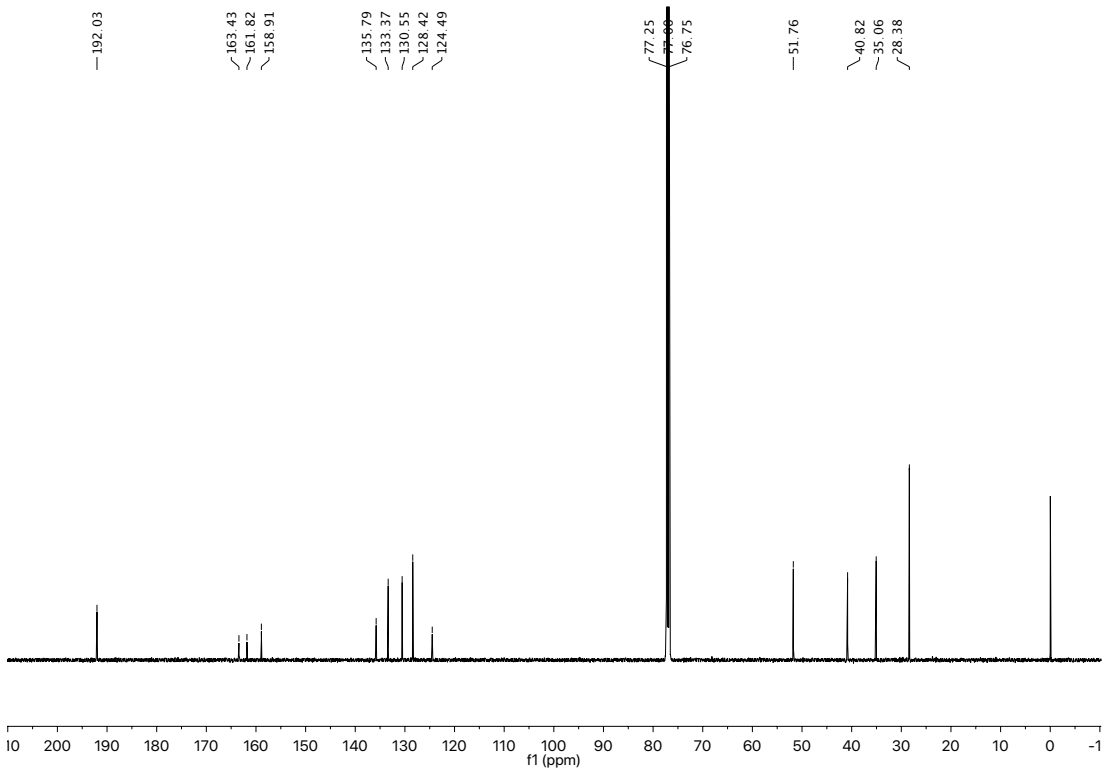
7.26
7.20
7.19
7.19
7.18
2.74
2.47
1.13
O
O
S
NH
S
N
0.77
1.00
1.00
1.03
2.17
2.19
6.42
f1 (ppm)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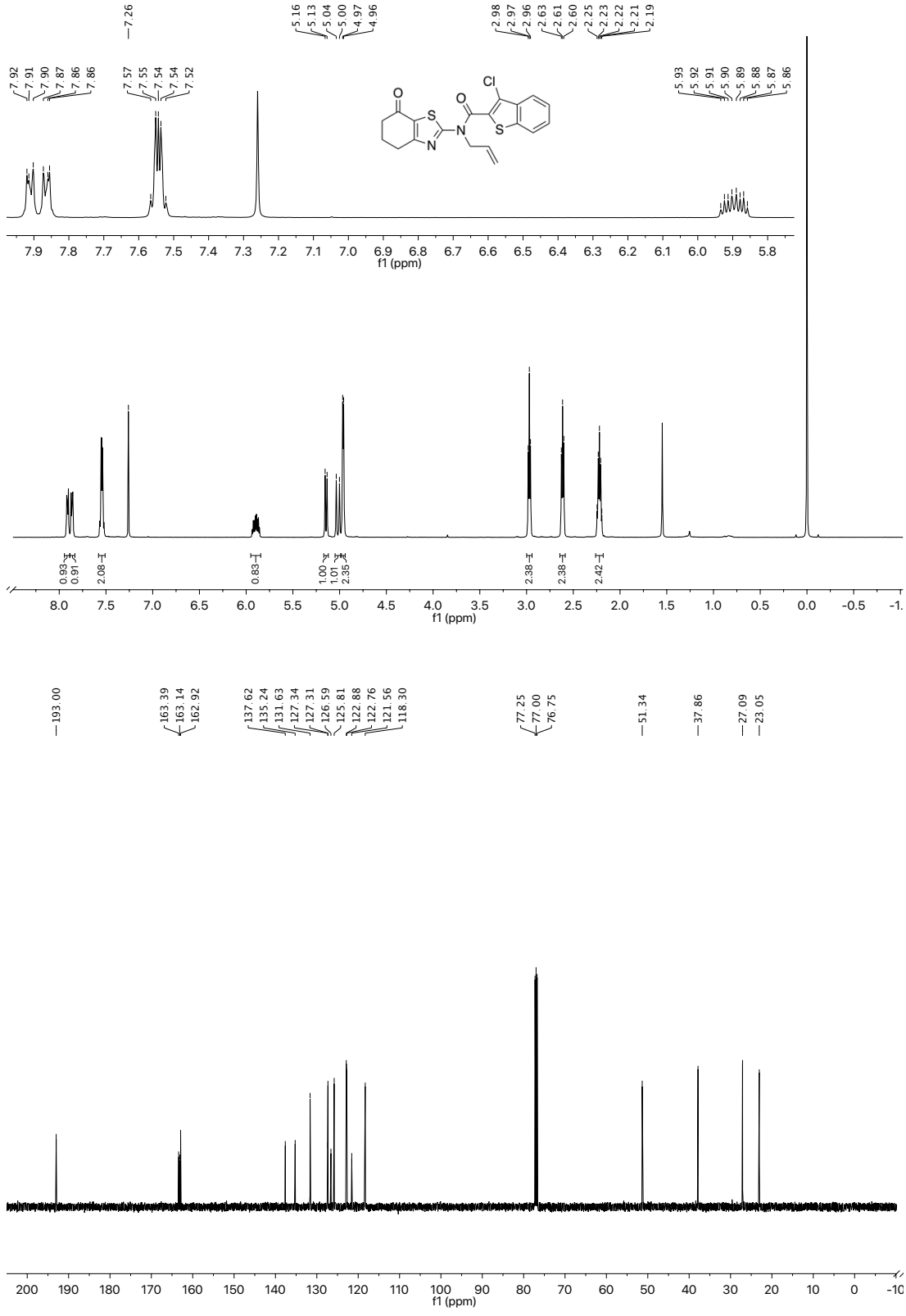
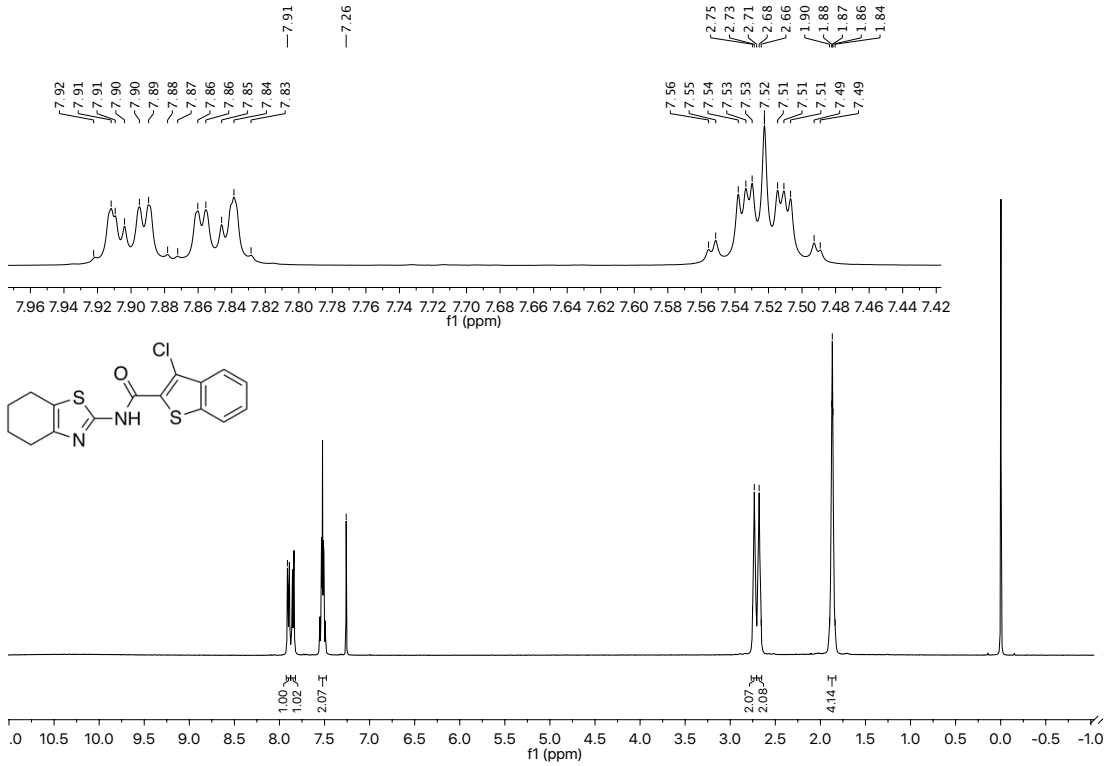
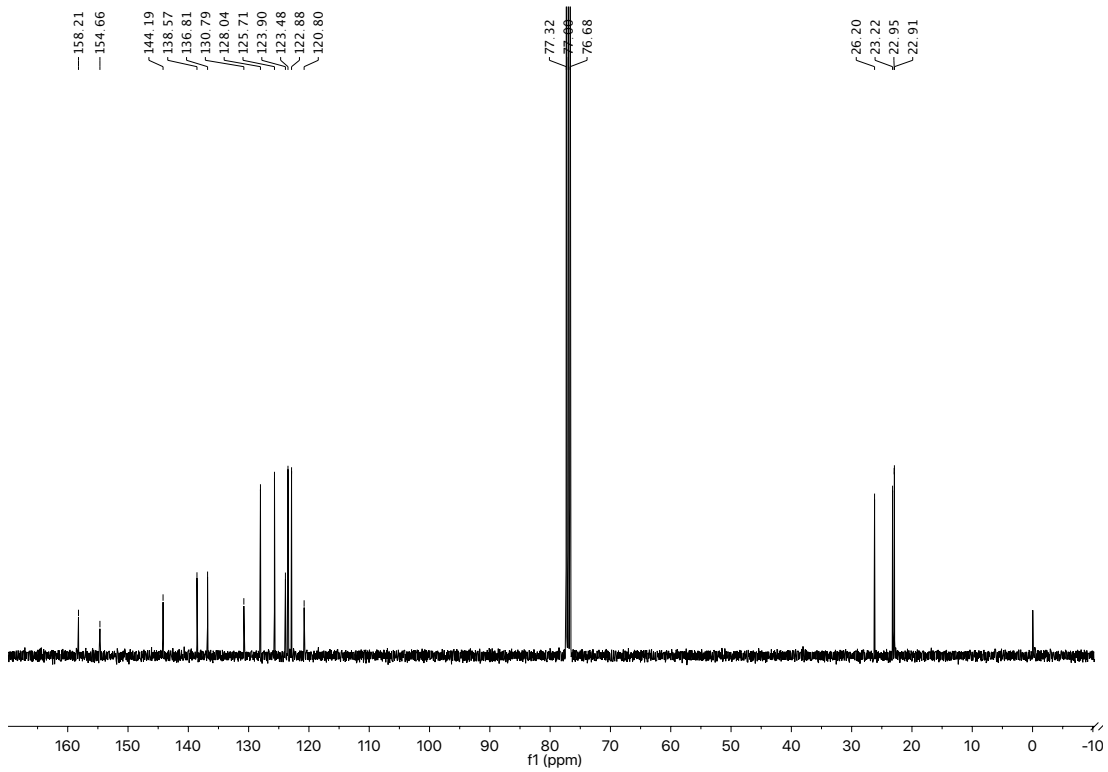
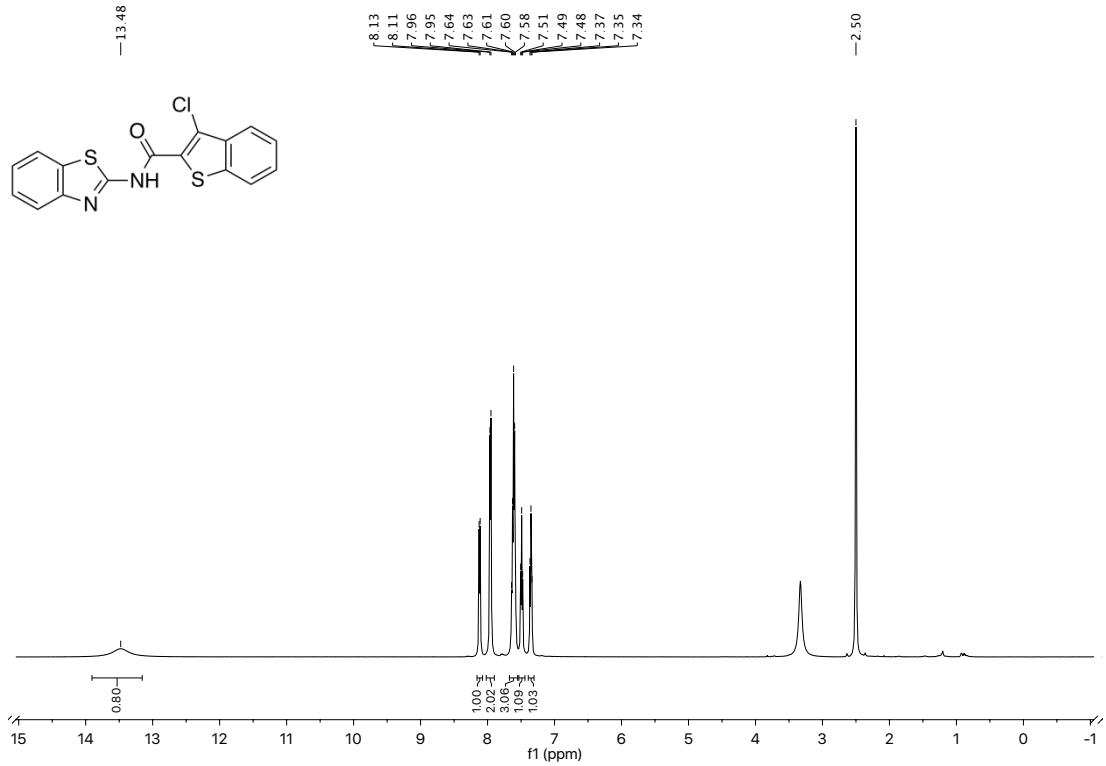
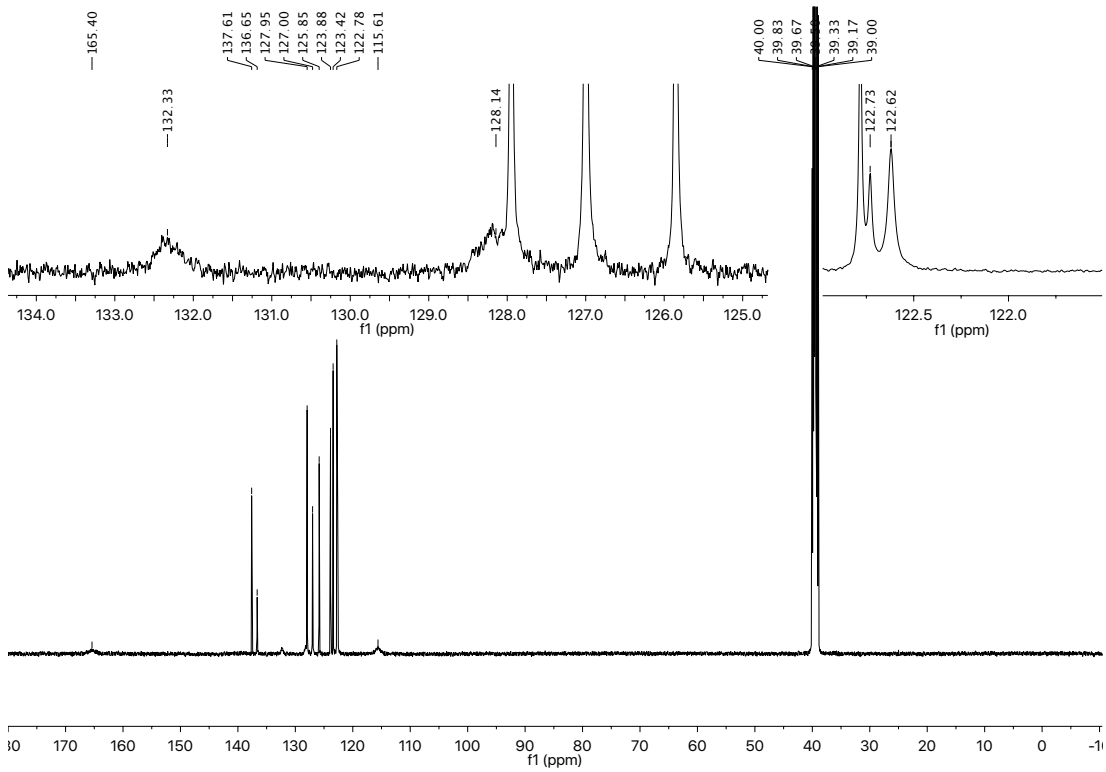
133.37
130.55
128.42
124.49
77.25
76.75
51.76
40.82
35.06
28.38
f1 (ppm)

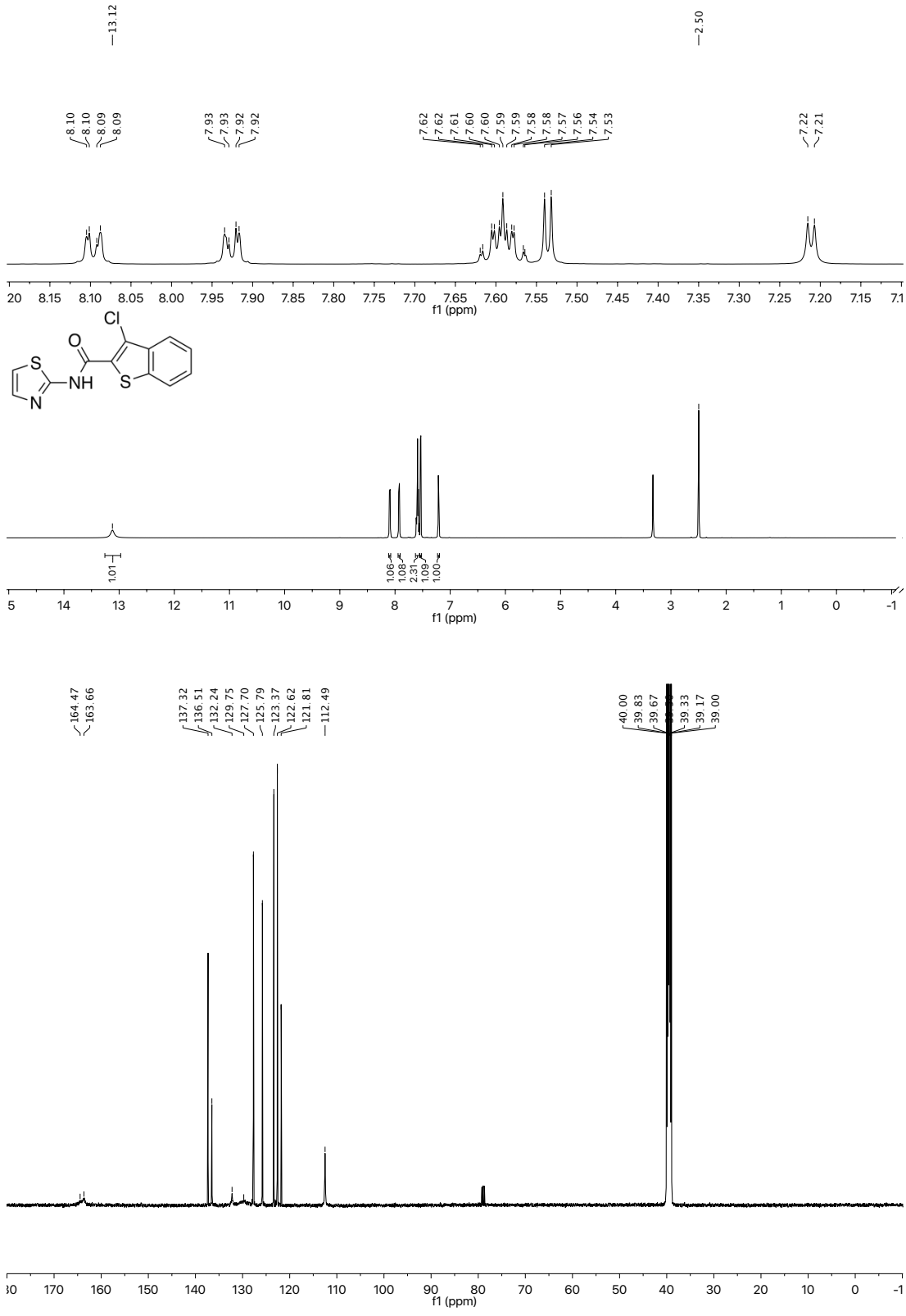

7.92
7.91
7.90
7.87
7.86
7.86
7.57
7.55
7.54
7.54
7.52
7.26
5.16
5.13
5.04
5.00
4.97
4.96
2.98
2.97
2.96
2.63
2.61
2.60
2.25
2.23
2.22
2.21
2.19
5.93
5.92
5.91
5.90
5.89
5.88
5.87
5.86
Cl
O
O
S
N
N
S
f1 (ppm)
0.93
0.91
2.08
0.83
1.00
1.01
2.35
2.38
2.38
2.42
f1 (ppm)
193.00
163.39
163.14
162.92
137.62
135.24
131.63
127.34
127.31
126.59
125.81
122.88
122.76
121.56
118.30
77.25
77.00
76.75
51.34
37.86
27.09
23.05
f1 (ppm)

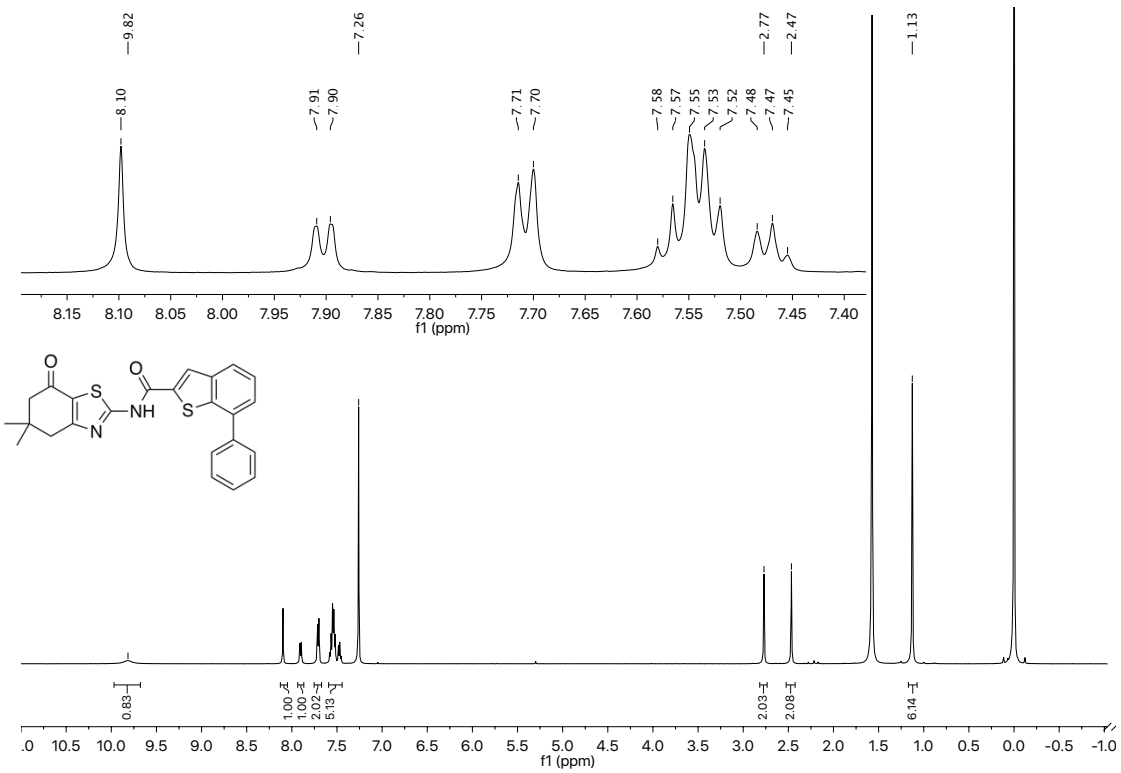

7.91
7.26
2.75
2.73
2.71
2.68
2.66
1.90
1.88
1.87
1.86
1.84
7.92
7.91
7.91
7.90
7.90
7.89
7.88
7.87
7.86
7.86
7.85
7.84
7.83
7.56
7.55
7.54
7.53
7.53
7.52
7.51
7.51
7.51
7.49
7.49
7.96 7.94 7.92 7.90 7.88 7.86 7.84 7.82 7.80 7.78 7.76 7.74 7.72 7.70 7.68 7.66 7.64 7.62 7.60 7.58 7.56 7.54 7.52 7.50 7.48 7.46 7.44 7.42
f1 (ppm)
Cl
O
S
NH
S
N
1.00
1.02
2.07
2.07
2.08
4.14
.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

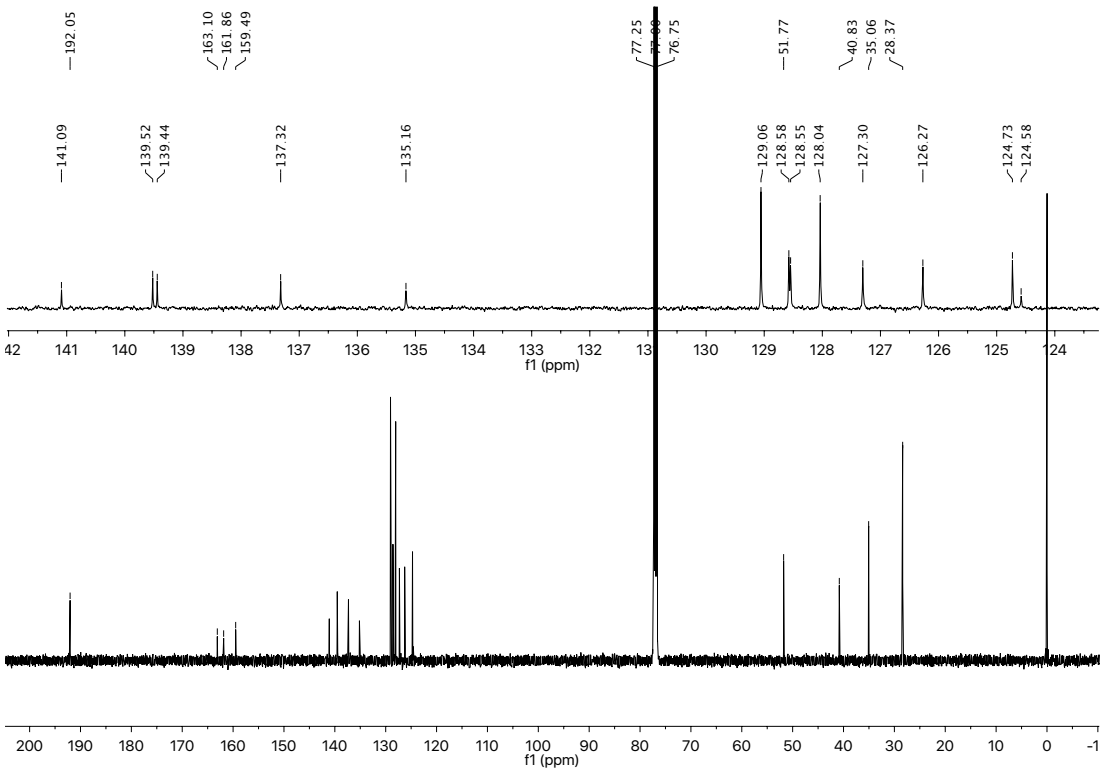

158.21
154.66
144.19
138.57
136.81
130.79
128.04
125.71
123.90
123.48
122.88
120.80
77.32
77.00
76.68
26.20
23.22
22.95
22.91
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

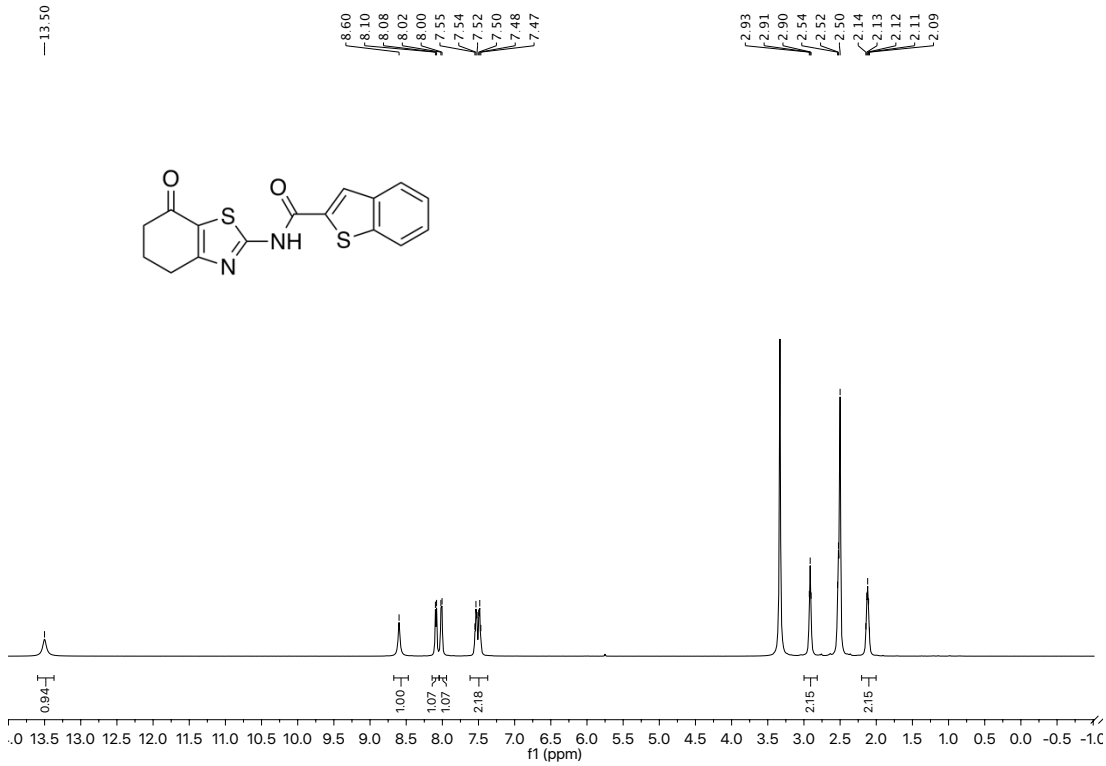

13.48
8.13
8.11
7.96
7.95
7.64
7.63
7.61
7.60
7.58
7.51
7.49
7.48
7.37
7.35
7.34
2.50
Cl
O
S
NH
S
N
0.80
1.00
2.02
3.06
1.09
1.03
f1 (ppm)

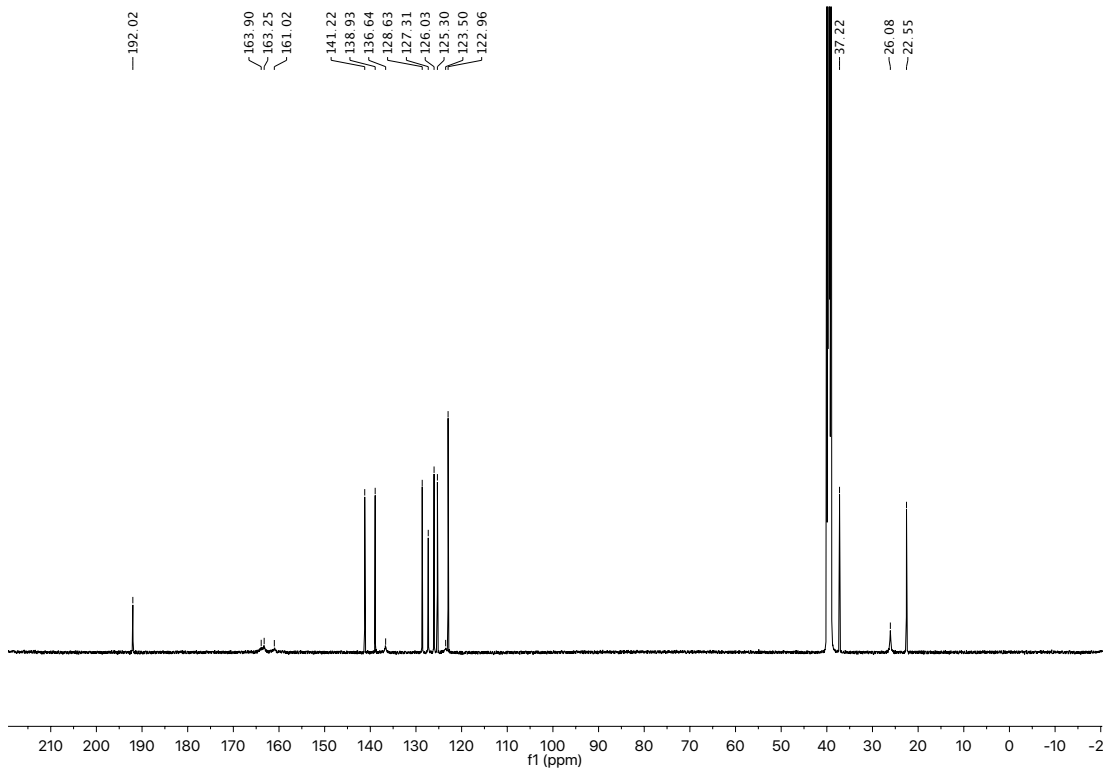

165.40
137.61
136.65
127.95
127.00
125.85
123.88
123.42
122.78
115.61
132.33
128.14
40.00
39.83
39.67
39.33
39.17
39.00
122.73
122.62
f1 (ppm)
f1 (ppm)
f1 (ppm)

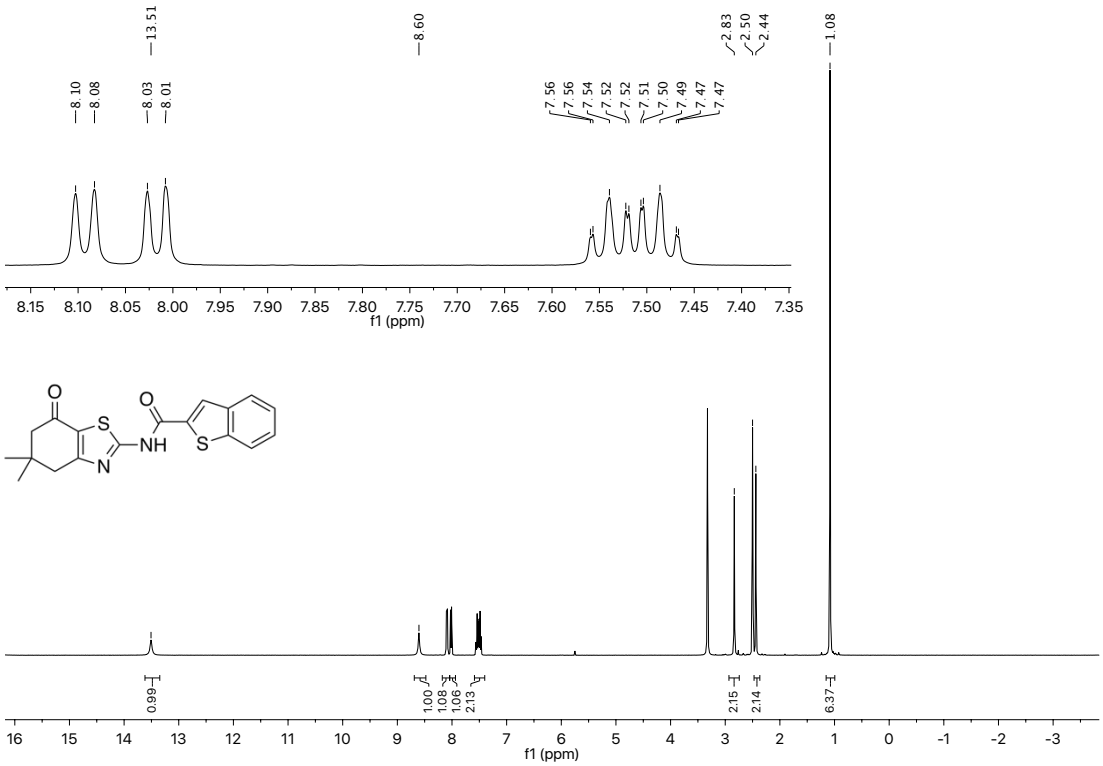

13.12
2.50
8.10
8.10
8.09
8.09
7.93
7.93
7.92
7.92
7.62
7.62
7.61
7.60
7.60
7.59
7.59
7.58
7.58
7.57
7.56
7.54
7.53
7.22
7.21
f1 (ppm)
Cl
O
S
NH
S
N
1.01
1.06
1.08
2.31
1.09
1.00
f1 (ppm)
164.47
163.66
137.32
136.51
132.24
129.75
127.70
125.79
123.37
122.62
121.81
112.49
40.00
39.83
39.67
39.33
39.17
39.00
f1 (ppm)

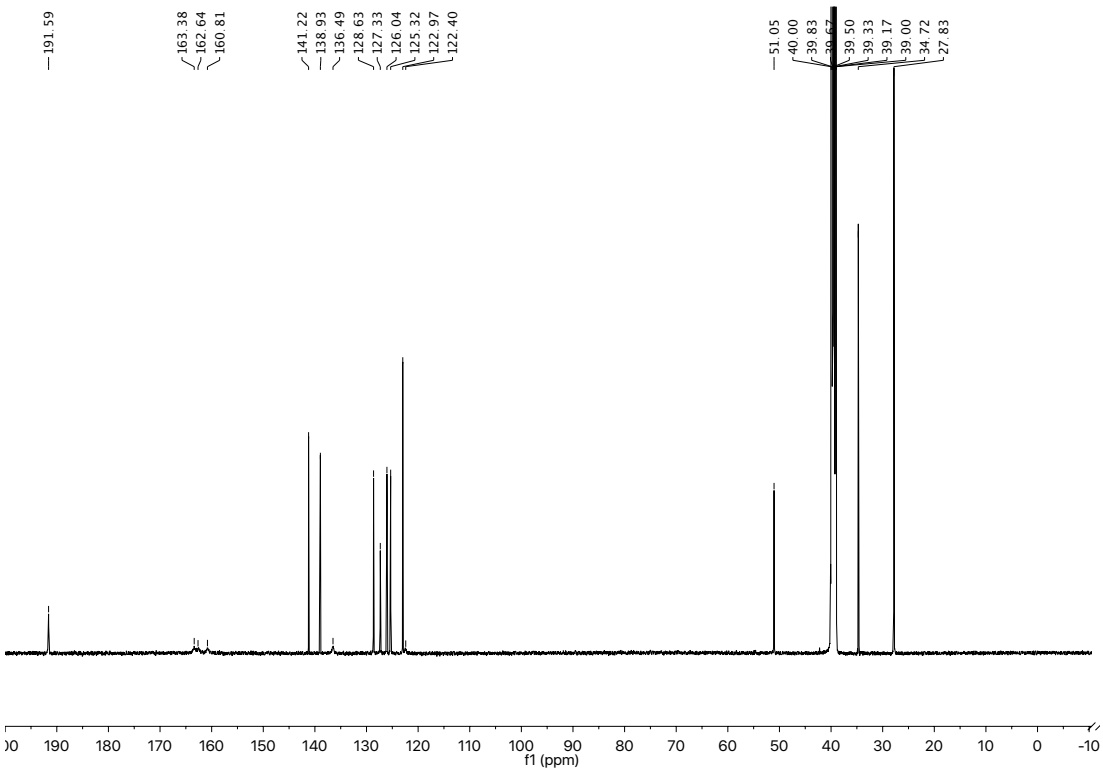

9.82
8.10
7.91
7.90
7.71
7.70
7.58
7.57
7.55
7.53
7.52
7.48
7.47
7.45
7.26
2.77
2.47
1.13
f1 (ppm)
O
S
N
NH
O
S
0.83
1.00
1.00
2.02
5.13
2.03
2.08
6.14

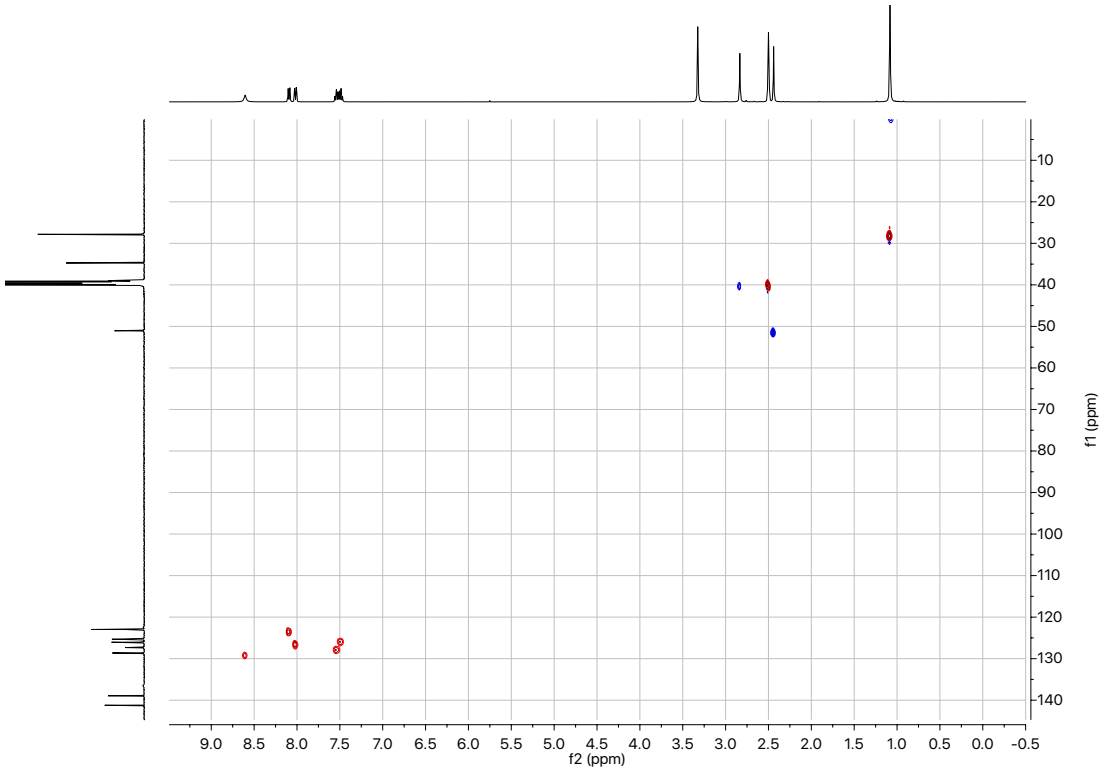

192.05
163.10
161.86
159.49
141.09
139.52
139.44
137.32
135.16
77.25
77.00
76.75
51.77
40.83
35.06
28.37
129.06
128.58
128.55
128.04
127.30
126.27
124.73
124.58
f1 (ppm)

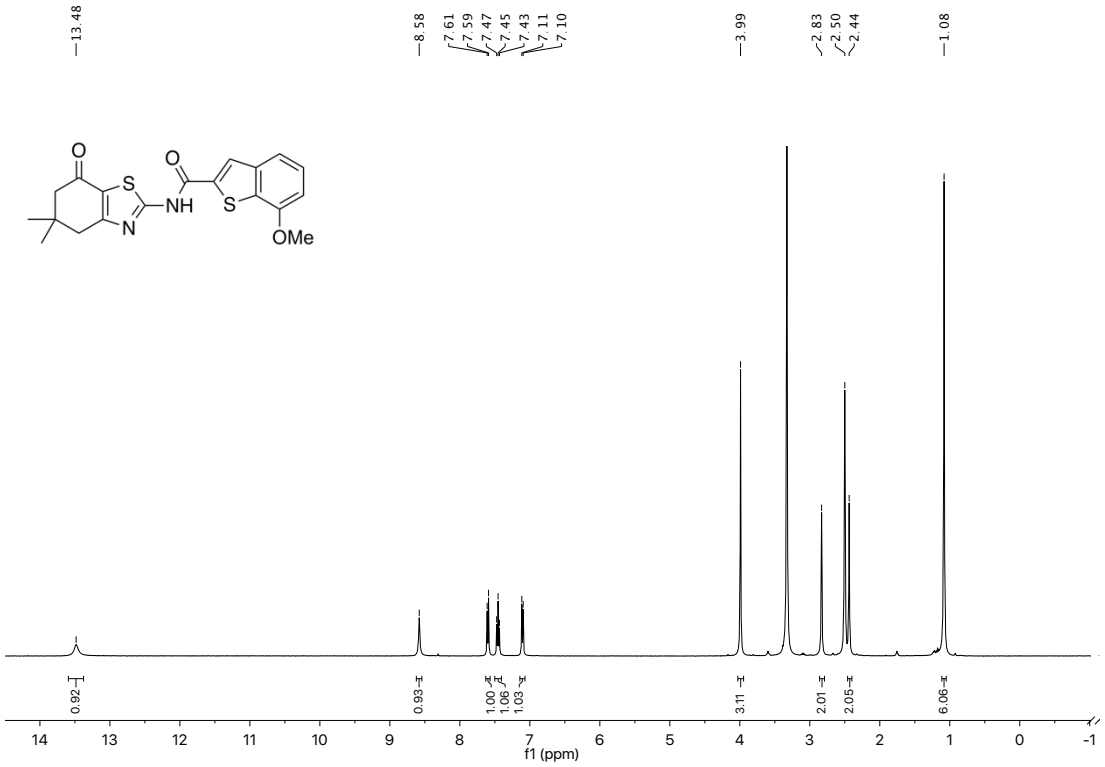

13.50
8.60
8.10
8.08
8.02
8.00
7.55
7.54
7.52
7.50
7.48
7.47
2.93
2.91
2.90
2.54
2.52
2.50
2.14
2.13
2.12
2.11
2.09
O
S
NH
N
O
S
0.94
1.00
1.07
1.07
2.18
2.15
2.15
f1 (ppm)

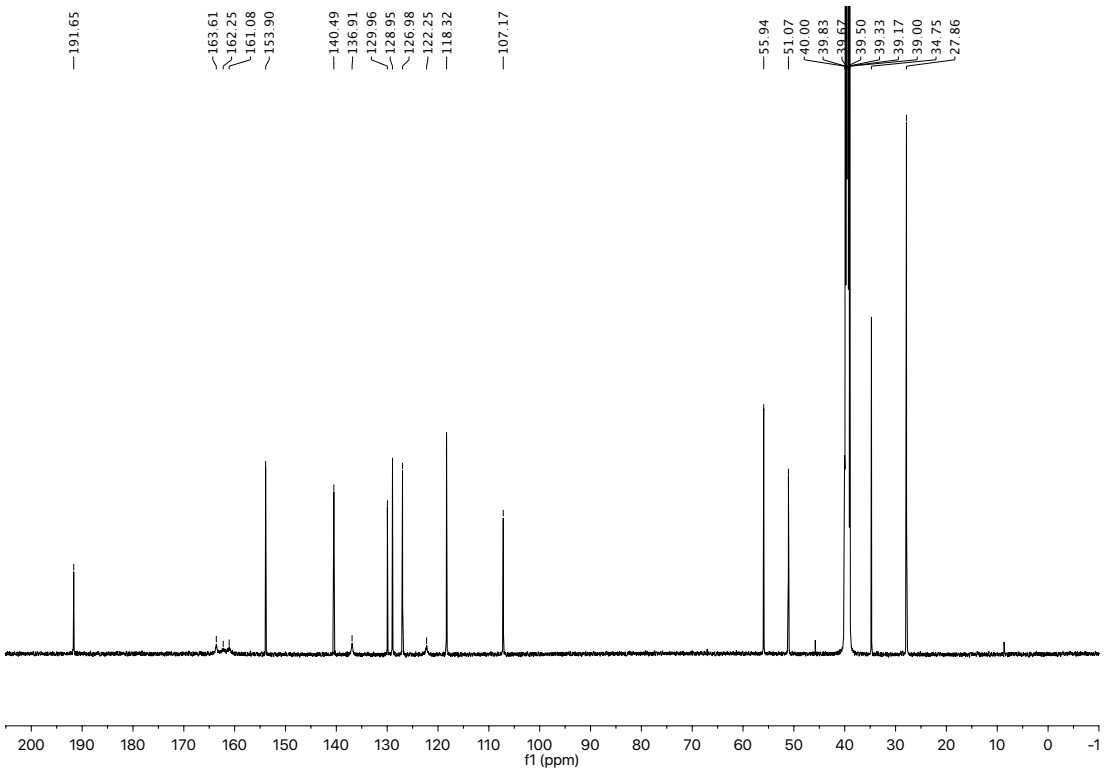

192.02
163.90
163.25
161.02
141.22
138.93
136.64
128.63
127.31
126.03
125.30
123.50
122.96
37.22
26.08
22.55
f1 (ppm)

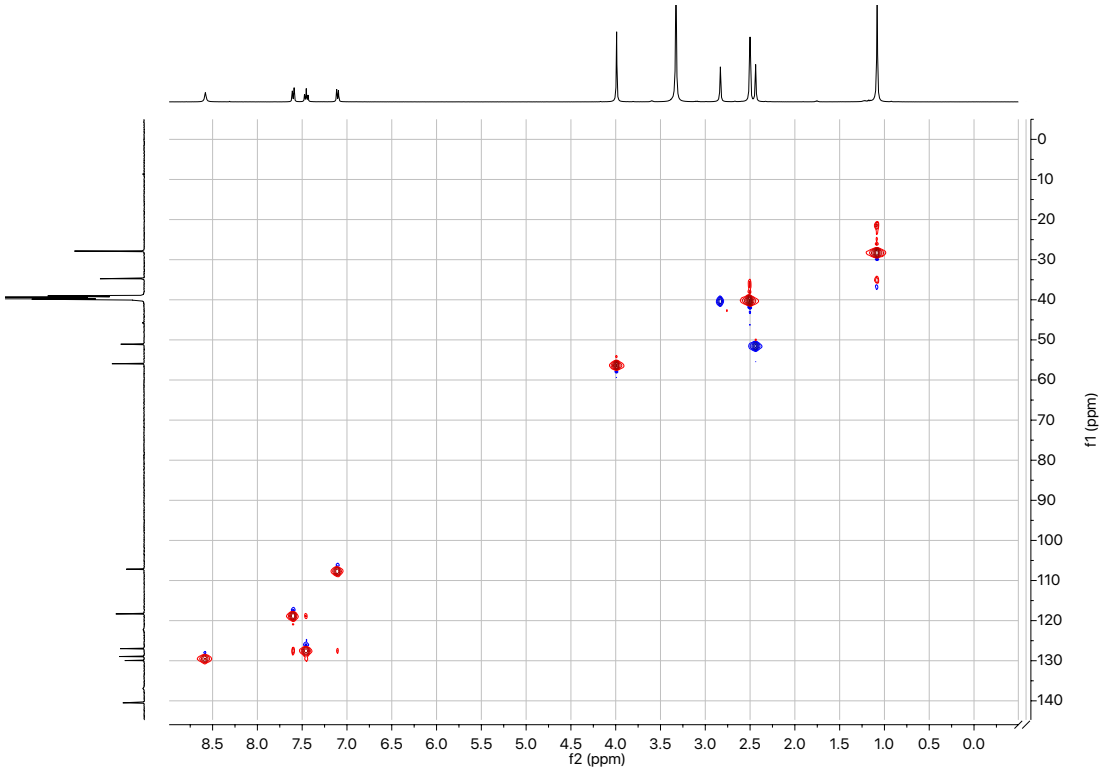

8.10
8.08
8.03
8.01
13.51
8.60
7.56
7.56
7.54
7.52
7.52
7.51
7.50
7.49
7.47
7.47
2.83
2.50
2.44
1.08
f1 (ppm)
O
S
NH
N
O
S
0.99
1.00
1.08
1.06
2.13
2.15
2.14
6.37
f1 (ppm)

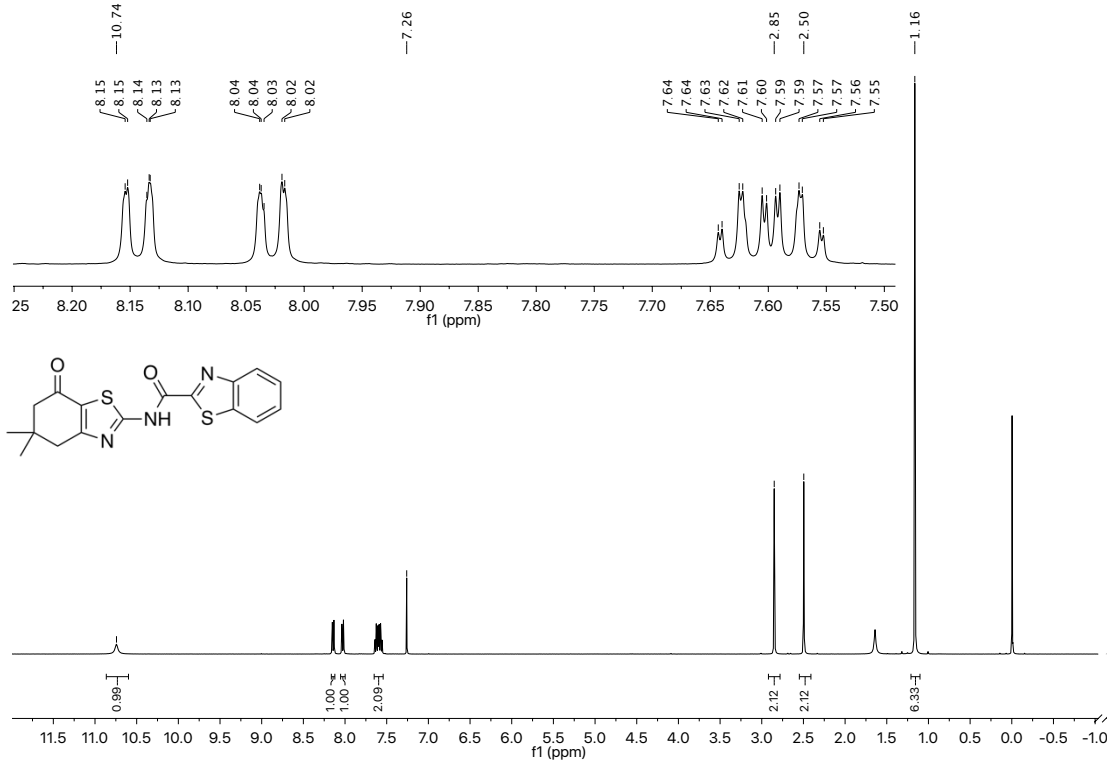

191.59
163.38
162.64
160.81
141.22
138.93
136.49
128.63
127.33
126.04
125.32
122.97
122.40
51.05
40.00
39.83
39.67
39.50
39.33
39.17
39.00
34.72
27.83
f1 (ppm)

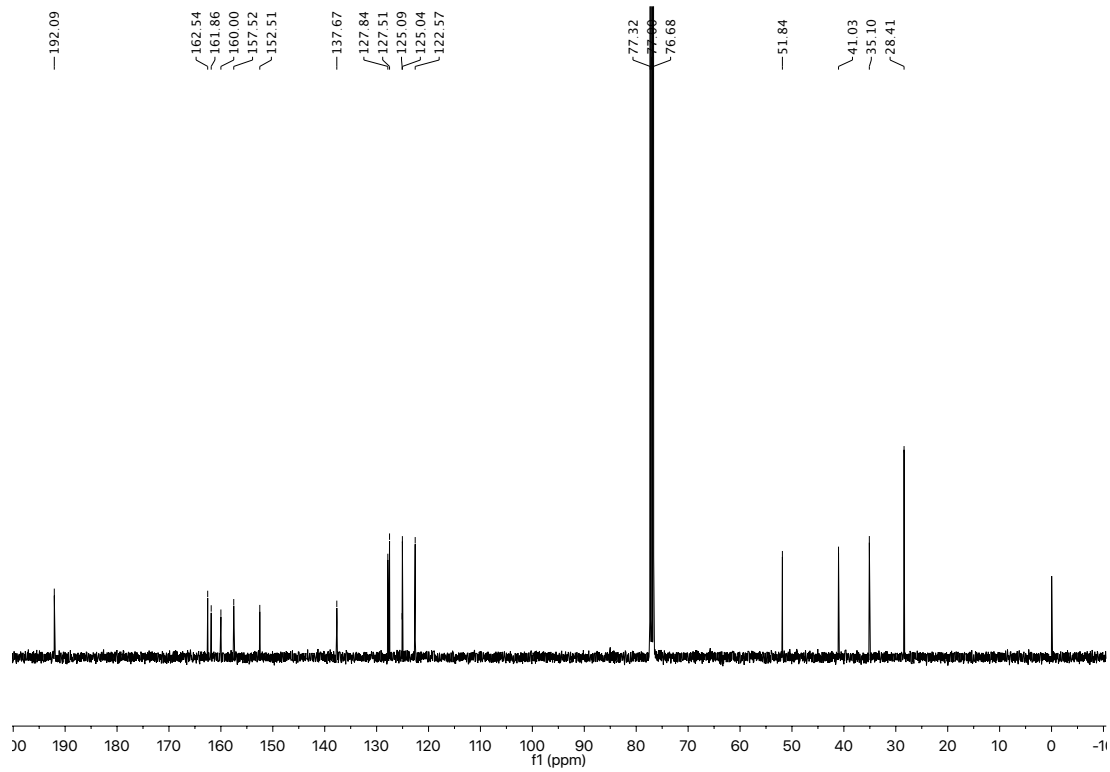

10
20
30
40
50
60
70
80
90
100
110
120
130
140
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f2 (ppm)


13.48
8.58
7.61
7.59
7.47
7.45
7.43
7.11
7.10
3.99
2.83
2.50
2.44
1.08
O
S
NH
O
S
N
OMe
0.92
0.93
1.00
1.06
1.03
3.11
2.01
2.05
6.06
f1 (ppm)


191.65
163.61
162.25
161.08
153.90
140.49
136.91
129.96
128.95
126.98
122.25
118.32
107.17
55.94
51.07
40.00
39.83
39.67
39.50
39.33
39.17
39.00
34.75
27.86
f1 (ppm)


0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
f1 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)


10.74
8.15
8.15
8.14
8.13
8.13
8.04
8.04
8.03
8.02
8.02
7.26
7.64
7.64
7.63
7.62
7.61
7.60
7.59
7.59
7.57
7.57
7.56
7.55
2.85
2.50
1.16
f1 (ppm)
0.99
1.00
1.00
2.09
2.12
2.12
6.33


192.09
162.54
161.86
160.00
157.52
152.51
137.67
127.84
127.51
125.09
125.04
122.57
77.32
77.00
76.68
51.84
41.03
35.10
28.41
f1 (ppm)