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Efficient S-Acylation of Thiourea

Supporting Information

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S1. General Information:

Acetonitrile (HPLC grade) was used as obtained from commercial sources without purification. Acid chloride starting materials were either purchased commercially or prepared from commercially available carboxylic acids by treating them with oxalyl chloride (3.00 eq.) and 3 drops DMF in DCM (0.1 M) for 48 hours according to standard procedures. NSAID acid chloride derivatives were prepared as per the procedure of Biancalana *et al.*¹

Melting points were obtained on a uni-melt Thomas Hoover Capillary melting point apparatus and stand uncorrected. IR spectra were recorded on Perkin-Elmer FT-IR Paragon 1000 spectrophotometer. Solid samples were dispersed in KBr and recorded as pressed discs. HRMS were recorded on a Waters LCT Premier ToF LC-MS instrument in ESI mode using 50% acetonitrile-water containing 0.1% formic acid as eluent; samples were made up in acetonitrile or methanol.

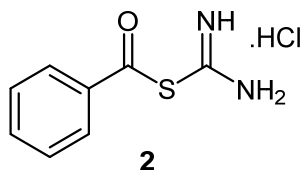
¹H and ¹³C NMR spectra were obtained in DMSO-d₆ using TMS as an internal standard at 25 °C and were recorded on Bruker Advance 600, 400 or 300 spectrometers respectively. All spectra were obtained in University College Cork. Chemical shifts are expressed as parts per million (ppm) relative to TMS. Coupling constants (J) are expressed in hertz (Hz). Splitting patterns in ¹H NMR spectra are designated as s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), t (triplet), dt (doublet of triplets), td (triplet of doublets), q (quartet), quint. (quintet), sext. (sextet) sept. (septet), and m (multiplet i.e. signals which were not cleanly resolved into any of the preceding designations).

Note: In some cases, the isothiuronium carbon (N=CH-N) was not observed by ¹³C NMR. In the case of compound (**2**), extending the relaxation delay (D1 Parameter) from 1.00 s to 4.00 s allowed for enhancement of this signal at 161 ppm. This was not conducted routinely on other samples. As the NH₂=C-NH₂ protons appear to rapidly exchange at room temperature, the resulting broadening of the signal causes it to integrate for fewer than four protons.²

S2. General Procedure:

To a stirred solution of thiourea (78 mg, 1.00 mmol, 1.00 eq.) in acetonitrile (10 mL) at 50 °C was added a solution of the required acid chloride (1.00 mmol, 1.00 eq.) in acetonitrile (10 mL) dropwise. The resulting thick suspension was allowed to stir at this temperature for a further hour to ensure complete reaction. More acetonitrile was added to aid stirring if the suspension was too thick. After an hour, the reaction mixture was cooled on ice and then vacuum filtered. The cake was washed with ethyl acetate (2 x 10 mL) affording the products. The products were obtained quantitatively unless otherwise stated.

S3.1. S-Benzoyl Isothiuronium Chloride (**2**)³

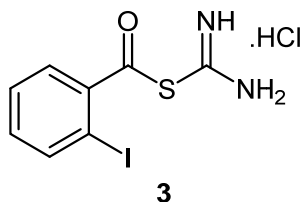


Isolated according to the general procedure as a colourless solid (180 mg, 1.00 mmol, 100%)

Melting Point (MeCN) = 135-136 °C (Lit: 169-170 °C)^{3b}

¹H NMR (400 MHz, DMSO-d₆): 7.49 (2H, t, *J* = 8.01 Hz, *m*-ArCH), 7.61 (1H, t, *J* = 8.01 Hz, *p*-ArCH), 7.94 (2H, d, *J* = 8.01 Hz, *o*-ArCH). 9.78 (4H, bs, NH₂=C-NH₂). ¹³C NMR (100 MHz, DMSO-d₆): 128.5, 129.2, 130.7, 132.8, 161.5, 167.3. IR (KBr, cm⁻¹): 3328, 3125, 3006, 2743, 1670, 1434, 1202, 875. HRMS (ESI⁺): Mass calc'd for C₈H₉NOS⁺ = 181.0430; Found = 181.0436. Anal. Calc'd for C₈H₉NOCIS = C (44.34%), H (4.19%), N (12.93%); Found = C (44.21%), H (4.21%), N (13.01%)

S3.2. S-(2-Iodobenzoyl) Isothiuronium Chloride (**3**)

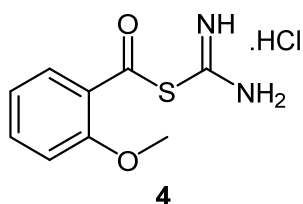


Isolated according to the general procedure as a pale yellow solid (304 mg, 1.00 mmol, 100%)

Melting Point (MeCN) = 190-192 °C.

¹H NMR (400 MHz, DMSO-d₆): 7.23 (1H, td, *J* = 8.11 Hz, 1.87 Hz, ArC(4)H), 7.46-7.50 (1H, m, ArC(5)H), 7.70 (1H, dd, *J* = 8.11 Hz, 1.87 Hz, ArC(3)H), 7.98 (1H, d, *J* = 8.11 Hz, ArC(6)H). ¹³C NMR (100 MHz, DMSO-d₆): 94.1, 128.1, 130.0, 132.4, 136.9, 161.3, 168.1. IR (KBr, cm⁻¹): 3328, 3183, 3024, 2791, 1756, 1679, 1575, 1430, 1289, 1192, 1020, 871, 774, 723, 681. HRMS (ESI⁺): Mass calc'd for C₈H₈IN₂OS⁺ = 306.9397; Found = 306.9390. Anal. Calc'd for C₈H₈ClIN₂OS = C (31.29%), H (2.63%); N (9.12%); Found = C (31.33%), H (2.48%); N (9.54%).

S3.3. *S*(2-Methoxybenzoyl) Isothiuronium Chloride (4)

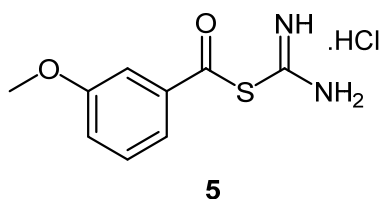


Isolated according to the general procedure as a colourless solid (210 mg, 1.00 mmol, 100%)

Melting Point (MeCN) = 169-171 °C.

^1H (400 MHz, DMSO- d_6): 3.81 (3H, s, OCH_3), 6.99 (1H, t, $J = 8.51$ Hz, ArC(4)H), 7.11 (1H, d, $J = 8.51$ Hz, ArC(3)H), 7.49 (1H, td, $J = 8.47$ Hz, 1.91 Hz, ArC(5)H), 7.63 (1H, dd, $J = 8.47$ Hz, 1.91 Hz, ArC(6)H). 9.86-9.92 (4H, bd, $\text{NH}_2=\text{C}-\text{NH}_2$). ^{13}C NMR (100 MHz, DMSO- d_6): 55.6, 112.3, 120.0, 121.2, 130.6, 133.0, 158.0, 167.3. IR (KBr, cm^{-1}): 3328, 3128, 2989, 1697, 166, 1592, 1483, 1430, 1291, 1251, 1195, 1160, 1016, 889, 726. HRMS (ESI $^+$): Mass calc'd for $\text{C}_9\text{H}_{11}\text{N}_2\text{O}_2\text{S}^+ = 211.0536$; Found = 211.0536. Anal. Calc'd for $\text{C}_9\text{H}_{11}\text{N}_2\text{O}_2\text{ClS} = \text{C}$ (44.00%), H (4.10%), N (11.40); Found = C (44.38%), H (4.24%), N (11.71%).

S3.4. *S*(3-Methoxybenzoyl) Isothiuronium Chloride (5)

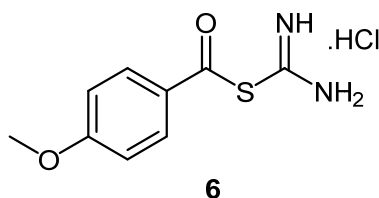


Isolated according to the general procedure as a colourless solid (209 mg, 1.00 mmol, 100%)

Melting Point (MeCN) = 166-168 °C.

^1H NMR (400 MHz, DMSO- d_6): 3.80 (3H, s, OCH_3), 7.19 (1H, dd, $J = 8.15$ Hz, 1.83 Hz, ArC(2)H), 7.39-7.44 (2H, m, overlapping ArC(6)H and ArC(3)H), 7.53 (1H, d, $J = 8.15$ Hz, ArC(4)H), 9.62 (4H, bs, $\text{NH}_2=\text{C}-\text{NH}_2$). ^{13}C NMR (100 MHz, DMSO- d_6): 55.2, 113.8, 118.9, 121.5, 129.7, 132.1, 159.2, 167.1. IR (KBr, cm^{-1}): 3329, 3281, 3163, 3085, 2954, 2836, 1697, 1609, 1583, 1526, 1470, 1420, 1311, 1293, 1267, 1051, 755. HRMS (ESI $^+$): Mass calc'd for $\text{C}_9\text{H}_{11}\text{N}_2\text{O}_2\text{S}^+ = 211.0536$; Found = 211.0528. Anal. Calc'd for $\text{C}_9\text{H}_{11}\text{N}_2\text{O}_2\text{ClS} = \text{C}$ (44.00%), H (4.10%), N (11.40); Found = C (44.31%), H (4.18%), N (11.71%).

S3.5. *S*(4-Methoxybenzoyl) Isothiuronium Chloride (6)



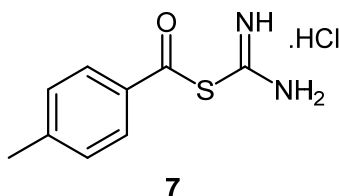
Isolated according to the general procedure as a colourless solid (209 mg, 1.00 mmol, 100%)

Melting Point (MeCN) = 167-169 °C

^1H NMR (400 MHz, DMSO- d_6): 3.82 (3H, s, OCH_3), 6.99-7.03 (2H, m, ArC(3 and 5)H), 7.87-7.9 (2H, m, ArC(2+6)H), 9.72 (4H, bs, $\text{NH}_2=\text{C}-\text{NH}_2$). ^{13}C NMR (100 MHz, DMSO- d_6): 55.4, 113.7, 122.9, 131.3,

161.6, 162.8, 167.0. IR (KBr, cm^{-1}): 3329, 3281, 3163, 3025, 2954, 2836, 1697, 1602, 1583, 1526, 1470, 1420, 1311, 1293, 1270, 1220, 1051, 879, 706. HRMS (ESI^+): Mass calc'd for $\text{C}_9\text{H}_{11}\text{N}_2\text{O}_2\text{S}^+ = 211.0536$; Found = 211.0537. Anal. Calc'd for $\text{C}_9\text{H}_{11}\text{N}_2\text{O}_2\text{ClS} = \text{C}$ (44.00%), H (4.10%), N (11.40); Found = C (44.58%), H (4.01%), N (11.36%).

S.3.6. *S*(4-Methylbenzoyl) Isothiuronium Chloride (7)

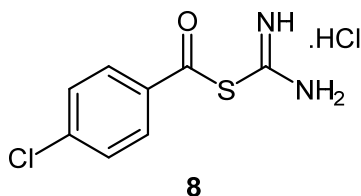


Isolated according to the general procedure as a colourless solid (196 mg, 1.00 mmol, 100%)

Melting Point (MeCN) = 138-139 °C.

^1H NMR (400 MHz, DMSO-d_6): 7.29 (2H, d, $J = 8.11$ Hz, ArC(3+5)H), 7.83 (2H, d, $J = 8.11$ Hz, ArC(2+6)H), 9.71 (4H, bs, $\text{NH}_2=\text{C}-\text{NH}_2$). ^{13}C NMR (100 MHz, DMSO-d_6): 21.1, 128.0, 129.1, 129.3, 143.0, 167.2. IR (KBr, cm^{-1}): 3328, 3161, 3006, 1672, 1606, 1447, 1408, 1210, 1179, 879, 787, 684, 547. HRMS (ESI^+): Mass calc'd for $\text{C}_9\text{H}_{11}\text{N}_2\text{OS}^+ = 195.0587$; Found = 195.0589. Anal. Calc'd for $\text{C}_9\text{H}_{11}\text{ClN}_2\text{OS} = \text{C}$ (46.85%) H (4.81%), N (12.14%); Found = C (46.99%), H (5.01%), N (12.11%).

S.3.7. *S*(4-Chlorobenzoyl) Isothiuronium Chloride (8)

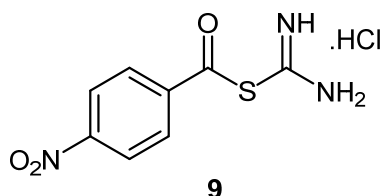


Isolated according to the general procedure as a colourless solid (214 mg, 1.00 mmol, 100%)

Melting Point (MeCN): 181-183 °C.

^1H NMR (400 MHz, DMSO-d_6): 7.55-7.57 (2H, m, ArC(3+5)H), 7.92-7.95 (2H, m, ArC(2+6)H), 9.79 (4H, bs, $\text{NH}_2=\text{C}-\text{NH}_2$). ^{13}C (100 MHz, DMSO-d_6): 128.7, 129.6, 131.1, 137.7, 166.4. IR (KBr, cm^{-1}): 3328, 3187, 3015, 1668, 1584, 1483, 1439, 1399, 1205, 1179, 1091, 884, 739. HRMS (ESI^+): Mass calc'd for $\text{C}_8\text{H}_8\text{ClN}_2\text{OS}^+ = 215.0040$; Found = 215.0044. Anal. Calc'd for $\text{C}_8\text{H}_7\text{Cl}_2\text{N}_2\text{OS} = \text{C}$ (38.42%), H (2.82%), N (11.20%); Found = C (38.72%), H (3.01%), N (11.30%).

S.3.8. *S*(4-Nitrobenzoyl) Isothiuronium Chloride (9)

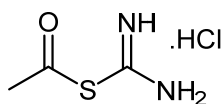


Isolated according to the general procedure as a yellow solid (227 mg, 1.00 mmol, 100%)

Melting Point (MeCN): 161 °C (Decomposition).

^1H NMR (400 MHz, DMSO- d_6): 8.16-8.18 (2H, m, Ar(C3+5)H), 8.32-8.34 (2H, m, Ar(C2+6)H), 9.36 (NH₂=C-NH₂). ^{13}C NMR (100 MHz, DMSO- d_6): 122.1, 129.1, 134.6, 148.4, 164.1. IR (KBr, cm^{-1}): 3328, 352, 2936, 1662, 1584, 1536, 1409, 1361, 1319, 1192, 948, 849, 744, 547. HRMS (ESI⁺): Mass calc'd for C₈H₈N₃O₃S⁺ = 226.0281; Found = 226.0299. Anal. Calc'd for C₈H₈ClN₃O₃S = C (36.72%), H (3.08%), N (16.06%)

S.3.9. S-(Acetyl) Isothiuronium Chloride (11)³



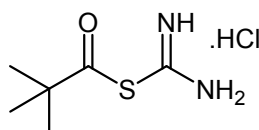
11

Isolated according to the general procedure as a colourless solid (120 mg, 1.00 mmol, 100%)

Melting Point (MeCN): 94-96 °C (Lit: 107-108 °C)⁴

^1H NMR (400 MHz, DMSO- d_6): 1.91 (3H, s, CH₃), 9.57 (4H, bs, NH₂=C-NH₂). ^{13}C NMR (100 MHz, DMSO- d_6): 21.0, 172.0. IR (KBr, cm^{-1}): 3328, 3275, 3194, 3089, 1747, 1658, 1583, 1409, 1102, 706, 541. HRMS (ESI⁺): Mass calc'd for C₃H₇N₂OS⁺ = 119.0279; Found = 119.0274. Anal. Calc'd for C₃H₇N₂OClS = C (23.31%), H (4.56%), N (18.12%); Found = C (23.33%), H (4.61%), N (18.21%).

S.3.10. S-(Pivaloyl) Isothiuronium Chloride (12)



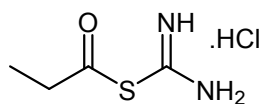
12

Isolated according to the general procedure as a colourless solid (161 mg, 1.00 mmol, 1.00 eq.)

Melting Point (MeCN): 140-142 °C

^1H NMR (400 MHz, DMSO- d_6): 1.11 (9H, s, C(CH₃)), 9.42 (4H, bs, NH₂=C-NH₂). ^{13}C NMR (100 MHz, DMSO- d_6): 27.0, 37.7, 179.3. IR (KBr, cm^{-1}): 3328, 3275, 3175, 3016, 1747, 1660, 1594, 1434, 925, 708, 541. HRMS (ESI⁺): Mass calc'd for C₆H₁₃N₂OS = 161.0749; Found = 161.0735. Anal. Calc'd for C₆H₁₃N₂OClOS = C (36.64%), H (6.66%), N (14.24%); Found = C (36.88%), H (7.01%), N (14.59%).

S.3.11. S-(Propanoyl) Isothiuronium Chloride (13)⁴



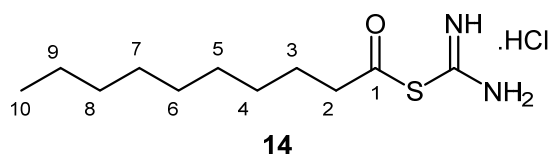
13

Isolated according to the general procedure as a colourless solid (132 mg, 1.00 mmol, 100%)

Melting Point (MeCN): 121-125 °C (Lit: 95-100 °C)⁴

^1H NMR (400 MHz, DMSO- d_6): 0.96 (3H, t, J = 7.48 Hz, CH₂CH₃), 2.19 (4H, q, J = 7.48 Hz, CH₂CH₃), 8.48 (4H, bs, NH₂=C-NH₂). ^{13}C NMR (100 MHz, DMSO- d_6): 9.00, 26.9, 161.9, 175.1. IR (KBr, cm^{-1}): 3328, 3275, 3194, 3089, 1750, 1659, 1583, 1409, 1102, 706. HRMS (ESI⁺): Mass calc'd for C₄H₉N₂OS⁺ = 133.0430; Found = 133.0421.

S.3.12. S-(Decanoyl) Isothiuronium Chloride (14)

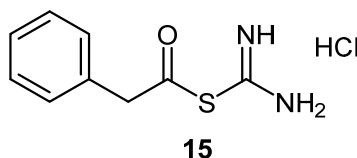


Isolated according to the general procedure as a waxy colourless solid (232 mg, 1.00 mmol, 100%)

Melting Point (MeCN): 115-117 °C

^1H NMR (400 MHz, DMSO- d_6): 0.86 (3H, t, J = 7.51 Hz, $\text{CH}_3(10)$), 1.24 (12H, m, $\text{CH}_2(9-4)$), 1.46-1.50 (2H, m, $\text{CH}_2(3)$), 2.18 (2H, t, J = 7.88 Hz, $\text{CH}_2(2)$), 9.18 (4H, bs, $\text{NH}_2=\text{C}-\text{NH}_2$). ^{13}C NMR (100 MHz, DMSO- d_6): 13.9, 22.1, 24.5, 28.5, 28.6, 28.7, 31.2, 33.6, 174.5. IR (KBr, cm^{-1}): 3385, 3261, 3175, 3031, 2822, 2859, 1748, 1676, 1427, 732. HRMS (ESI $^+$): Mass calc'd for $\text{C}_{11}\text{H}_{23}\text{N}_2\text{OS}$ = 231.1531; Found = 231.1536. Anal. Calc'd for $\text{C}_{11}\text{H}_{23}\text{N}_2\text{OCIS}$ = C (49.52%), H (8.69%), N (10.50%); Found = C (49.18%), H (8.75%), N (10.71%).

S.3.13. S-(Phenylacetyl) Isothiuronium Chloride (15)

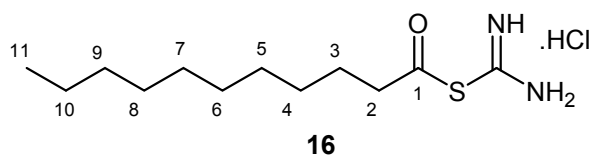


Isolated according to the general procedure as an off-white solid (195 mg, 1.00 mmol, 100%)

Melting Point (MeCN): 81-83 °C

^1H NMR (400 MHz, DMSO- d_6): 3.56 (2H, s, CH_2), 7.24-7.32 (5H, m, overlapping ArC(2,3,4,5,6)H), 9.50 (4H, bs, $\text{NH}_2=\text{C}-\text{NH}_2$). ^{13}C NMR (100 MHz, DMSO- d_6): 40.7, 126.5, 128.2, 129.3, 135.0, 172.6. IR (KBr, cm^{-1}): 3385, 3276, 3192, 3083, 2748, 1710, 1662, 1583, 1403, 1227, 1022, 703. HRMS (ESI $^+$): Mass calc'd for $\text{C}_9\text{H}_{11}\text{N}_2\text{OS}^+$ = 195.0592; Found = 195.0583. Anal. Calc'd for $\text{C}_9\text{H}_{11}\text{N}_2\text{OCIS}$ = C (55.65%), H (5.19%), N (14.42%); Found = C (55.01%), H (5.34%), N (14.84%).

S.3.14. S-(Undecanoyl) Isothiuronium Chloride (16)



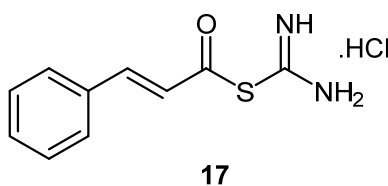
Isolated according to the general procedure as a waxy white solid (246 mg, 1.00 mmol, 100%)

Melting Point (MeCN): 122-124 °C

^1H NMR (400 MHz, DMSO- d_6): 0.85 (3H, t, J = 7.55 Hz, $\text{CH}_3(11)$), 1.24 (14H, m, $\text{CH}_2(10-4)$), 1.47 (2H, m, $\text{CH}_2(3)$), 2.18 (2H, t, J = 7.88 Hz, $\text{CH}_2(2)$), 9.56 (bs, $\text{NH}_2=\text{C}-\text{NH}_2$). ^{13}C NMR (100 MHz, DMSO- d_6): 13.9, 22.1, 24.5, 28.5, 28.6, 28.7, 28.88, 28.92, 31.26, 33.62, 174.45. HRMS (ESI $^+$): Mass calc'd for $\text{C}_{12}\text{H}_{25}\text{N}_2\text{OS}^+$ = 245.1682; Found = 245.1691. Anal. Calc'd for $\text{C}_{12}\text{H}_{25}\text{N}_2\text{OCIS}$ = C (51.32%), H (8.97%), N (9.97%); Found = C (51.44%) H (9.04%) N (10.14%).

-

S.3.15. S-(Cinnamoyl) Isothiuronium Chloride (17)

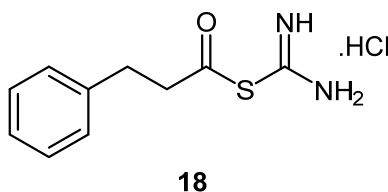


Isolated according to the general procedure as an off-white solid (207 mg, 1.00 mmol, 100%)

Melting Point (MeCN): 148-149 °C

^1H NMR (400 MHz, DMSO- d_6): 6.54 (1H, d, J = 17.56 Hz, α -CH), 7.41-7.70 (6H, m, overlapping ArC(2, 3, 4, 5, 6 and β -CH), 9.55 (4H, bs, $\text{NH}_2=\text{C}-\text{NH}_2$). ^{13}C NMR (100 MHz, DMSO- d_6): 119.2, 128.2, 128.9, 130.2, 134.2, 143.9, 167.5. IR (KBr, cm^{-1}): 3385, 3266, 2984, 2734, 1716, 166, 1611, 1422 1329, 1043, 752, 725. HRMS (ESI $^+$): Mass calc'd for $\text{C}_{10}\text{H}_{11}\text{N}_2\text{OS}^+$ = 207.0592; Found = 207.0585. Anal. Calc'd for $\text{C}_{10}\text{H}_{11}\text{N}_2\text{OCIS}$ = C (49.48%), H (4.57%), N (11.54%); Found = C (50.01%), H (4.91%), N (4.88%).

S.3.16. S-(Dihydrocinnamoyl) Isothiuronium Chloride (18)

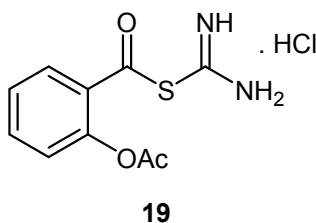


Isolated according to the general procedure as an off-white solid (208 mg, 1.00 mmol, 100%)

Melting Point (MeCN): 84-87 °C

^1H NMR (400 MHz, DMSO- d_6): 2.52 (2H, partially overlapping with DMSO residual peak, PhCH_2CH_2), 2.81 (2H, t, J = 6.83 Hz, PhCH_2CH_2), 7.17-7.26 (5H, m, ArC(2, 3, 4, 5 and 6)H), 9.77 (bs, $\text{NH}_2=\text{C}-\text{NH}_2$). ^{13}C NMR (100 MHz, DMSO- d_6): 29.2, 34.1, 116.9, 124.8, 127.06, 127.13, 139.7, 160.5, 172.6. IR (KBr, cm^{-1}): 3385, 3262, 3191, 3037, 2733, 1714, 1699, 1663, 1588, 1500, 1425, 1223, 963, 708, 699. HRMS (ESI $^+$): Mass calc'd for $\text{C}_{10}\text{H}_{13}\text{N}_2\text{OS}^+$ = 209.0755; Found = 209.0749. Anal. Calc'd for $\text{C}_{10}\text{H}_{13}\text{N}_2\text{OCIS}$ = C (49.08%), H (5.35%), N (11.45%); Found = C (49.38%), H (5.55%), N (11.74%).

S.3.17. Aspirin Analogue (19)



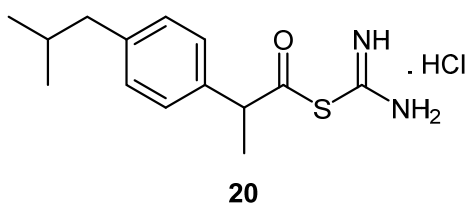
Isolated according to the general procedure as a colourless solid (239 mg, 1.00 mmol, 100%)

Melting Point (MeCN) = 97-99 °C

^1H NMR (400 MHz, DMSO- d_6): 2.24 (3H, s, CH_3), 7.20 (1H, d, J = 8.14 Hz, ArC(3)H), 7.38 (1H, t, J = 8.14 Hz, ArC(4)H), 7.64 (1H, td, J = 8.14 Hz, 1.33 Hz, ArC(5)H), 7.92 (1H, dd, J = 8.14 Hz, 1.33 Hz, ArC(6)H). ^{13}C NMR (100 MHz, DMSO- d_6): 20.8, 123.7, 124.0, 126.0, 131.3, 133.8, 161.4, 165.6, 169.2. IR (KBr, cm^{-1}): 3283, 3193, 3012, 1751, 1635, 1598, 1429, 1404, 1370, 1204, 1186, 1155, 857, 666, 651, 634.

HRMS (ESI⁺): Mass calc'd for C₁₀H₁₁N₂O₃S⁺ = 239.0485; Found = 239.0488. Anal. Calc'd = C (43.72%) H (4.04%) N (10.20%); Found = C (44.02%) H (4.19%) N (10.36%).

S.3.18. Ibuprofen Analogue (20)

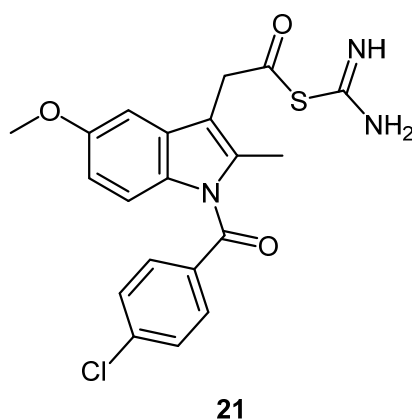


Isolated according to the general procedure as a waxy colourless solid (264 mg, 1.00 mmol, 100%)

Melting Point (MeCN): 131-133 °C

¹H NMR (400 MHz, DMSO-d₆): 0.84 (6H, d, *J* = 7.54 Hz, (CH₃)₂CH), 1.33 (3H, d, *J* = 7.88 Hz, CH₃CH), 1.79 (1H, sept., *J* = 7.54 Hz, (CH₃)CH), 2.40 (2H, d, *J* = 7.55 Hz, CH₂), 3.62 (1H, q, *J* = 7.88 Hz, CH₃CH). ¹³C NMR (100 MHz, DMSO-d₆): 18.5, 22.1, 29.6, 44.18, 44.24, 127.1, 128.9, 138.4, 139.5, 161.71, 175.4. IR (KBr, cm⁻¹): 3385, 3241, 2953, 1746, 1736, 1643, 1421, 925, 912, 729, 711, 695, 535, 469. HRMS (ESI⁺): Mass calc'd for C₁₄H₂₁N₂O₃S⁺ = 265.1369; Found = 265.1377. Anal. Calc'd for C₁₄H₂₁N₂O₃S = C (55.89%), H (7.04%), N (9.31%); Found = C (55.63%) H (6.95%) N (9.44%).

S.3.19. Indomethacin Analogue (21)

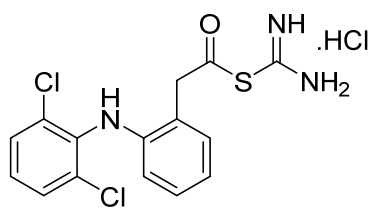


Isolated according to the general procedure as a brown solid (417 mg, 1.00 mmol, 100%)

Melting Point (MeCN): 168-171 °C

¹H NMR (400 MHz, DMSO-d₆): 2.22 (3H, s, ArCH₃), 3.67 (2H, s, CH₂), 3.76 (3H, s, OCH₃), 6.72 (1H, dd, *J* = 8.18 Hz, 1.33 Hz, C(6)H), 6.92 (1H, d, *J* = 8.18 Hz, C(7)H), 7.05 (1H, d, *J* = 1.33 Hz, C(4)H). 7.64-7.70 (4H, m, Ar(2', 3', 5' and 6')H). ¹³C NMR (100 MHz, DMSO-d₆): 13.2, 29.5, 55.4, 101.7, 111.3, 113.4, 114.6, 116.5, 129.0, 130.2, 130.71, 131.1, 134.1, 135.1, 137.6, 155.5, 167.8, 172.0. IR (KBr, cm⁻¹): 3332, 3312, 2952, 1727, 1687, 1657, 1482, 1308, 1227, 1047, 792. HRMS (ESI⁺): Mass calc'd for C₂₀H₁₉ClN₃O₃S⁺ = 416.0830; Found 416.0851. Anal. Calc'd for C₂₀H₁₉Cl₂N₃O₃S = C (53.10%) H (4.23%) N (9.29%); Found = C (53.33%) H(4.29%) N (9.45%).

S.3.20. Diclofenac Analogue (22)



22

Isolated according to the general procedure as a colourless solid (354 mg, 1.00 mmol, 100%)

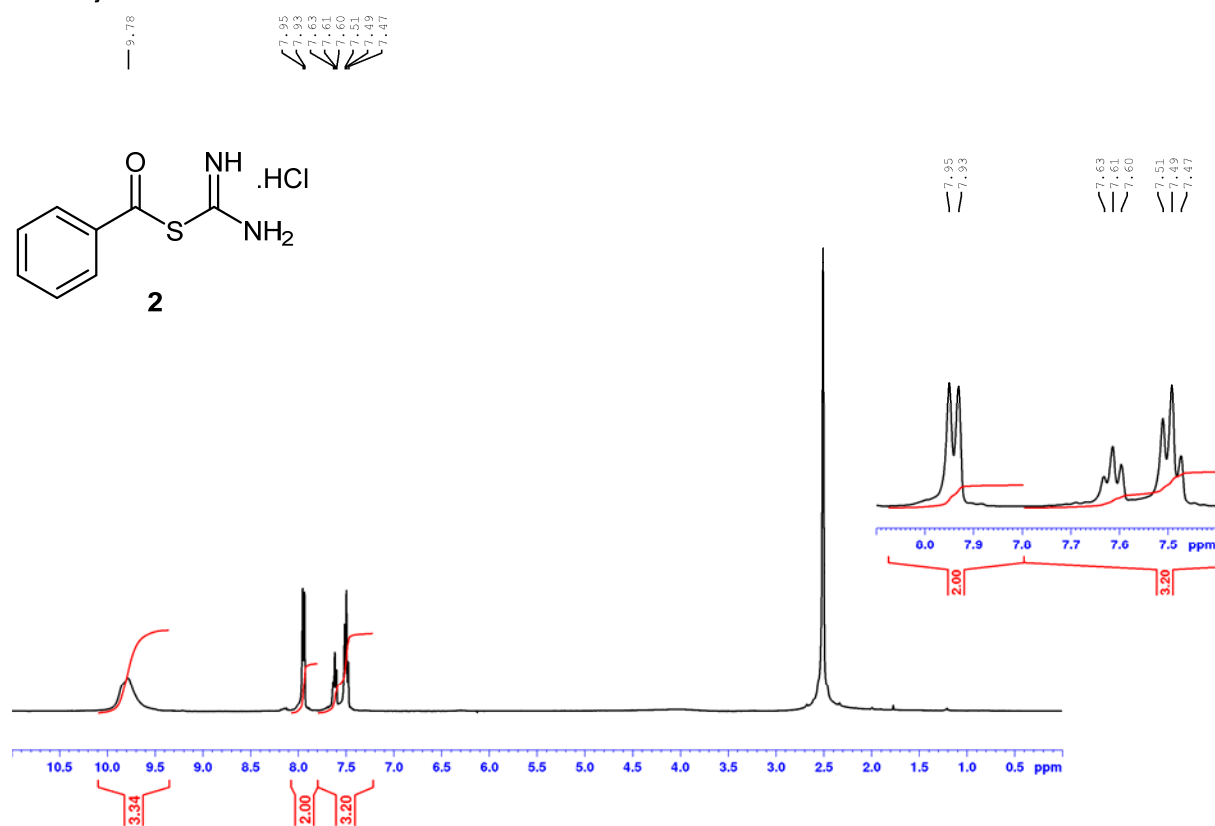
Melting Point (MeCN): 190-192 °C

^1H NMR (400 MHz, DMSO- d_6): 3.72 (2H, s, CH_2), 6.30 (1H, d, $J = 8.14$ Hz, ArH), 6.86 (1H, t, $J = 7.95$ Hz, ArH), 7.06 (1H, t, $J = 7.95$ Hz, ArH), 7.16-7.22 (2H, m, 2xArH), 7.32 (1H, s, ArH), 7.51 (1H, s, ArH), 7.53 (1H, s, ArH). ^{13}C NMR (100 MHz, DMSO- d_6): 37.9, 115.9, 120.7, 124.0, 125.5, 127.5, 129.1, 129.9, 130.8, 137.1, 142.6, 173.4. IR (KBr, cm^{-1}): 3338, 3311, 3244, 2952, 1729, 1687, 1659, 1482, 1311, 1227, 1047, 792. HRMS (ESI $^+$): Mass calc'd for $\text{C}_{15}\text{H}_{14}\text{Cl}_2\text{N}_3\text{OS}^+$ = 354.0230; Found 354.0239. Anal. Calc'd for $\text{C}_{15}\text{H}_{14}\text{Cl}_3\text{N}_3\text{OS}$ = C (43.11%) H (3.6%) N (10.76%); Found = C (43.81%) H (3.81%) N (10.91%).

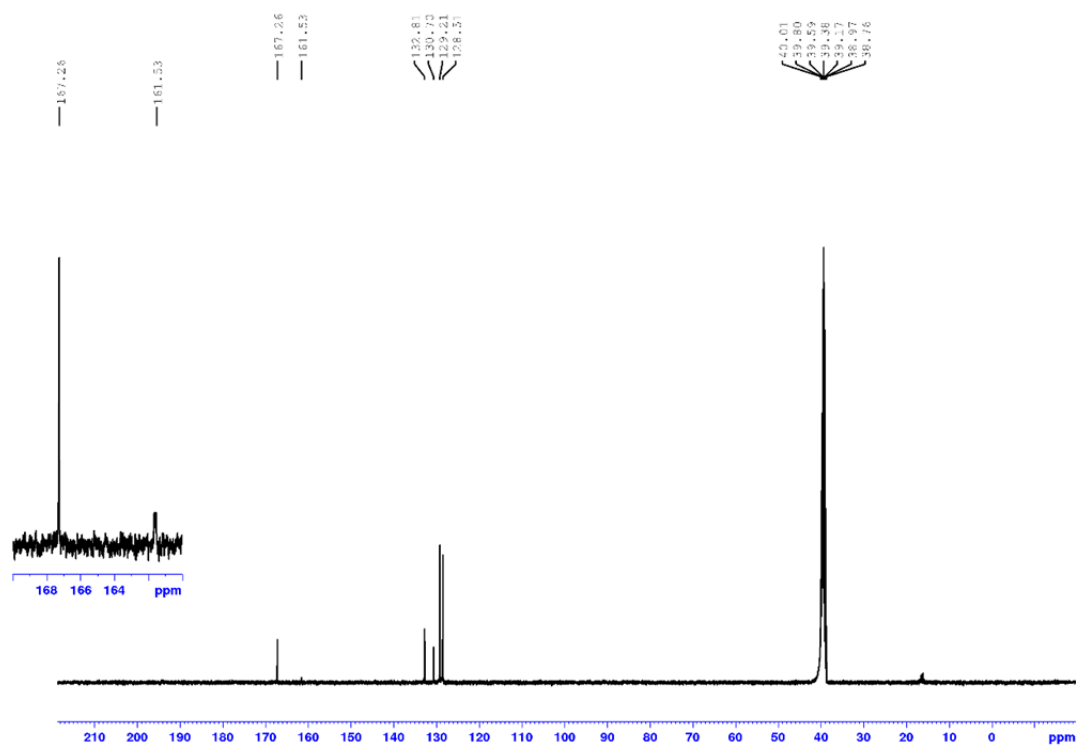
S.4. ^1H and ^{13}C NMR spectra for 2-21

S.4.1. S-(Benzoyl) Isothiuronium Chloride (2)

S-Benzoyl Isothiuronium Chloride

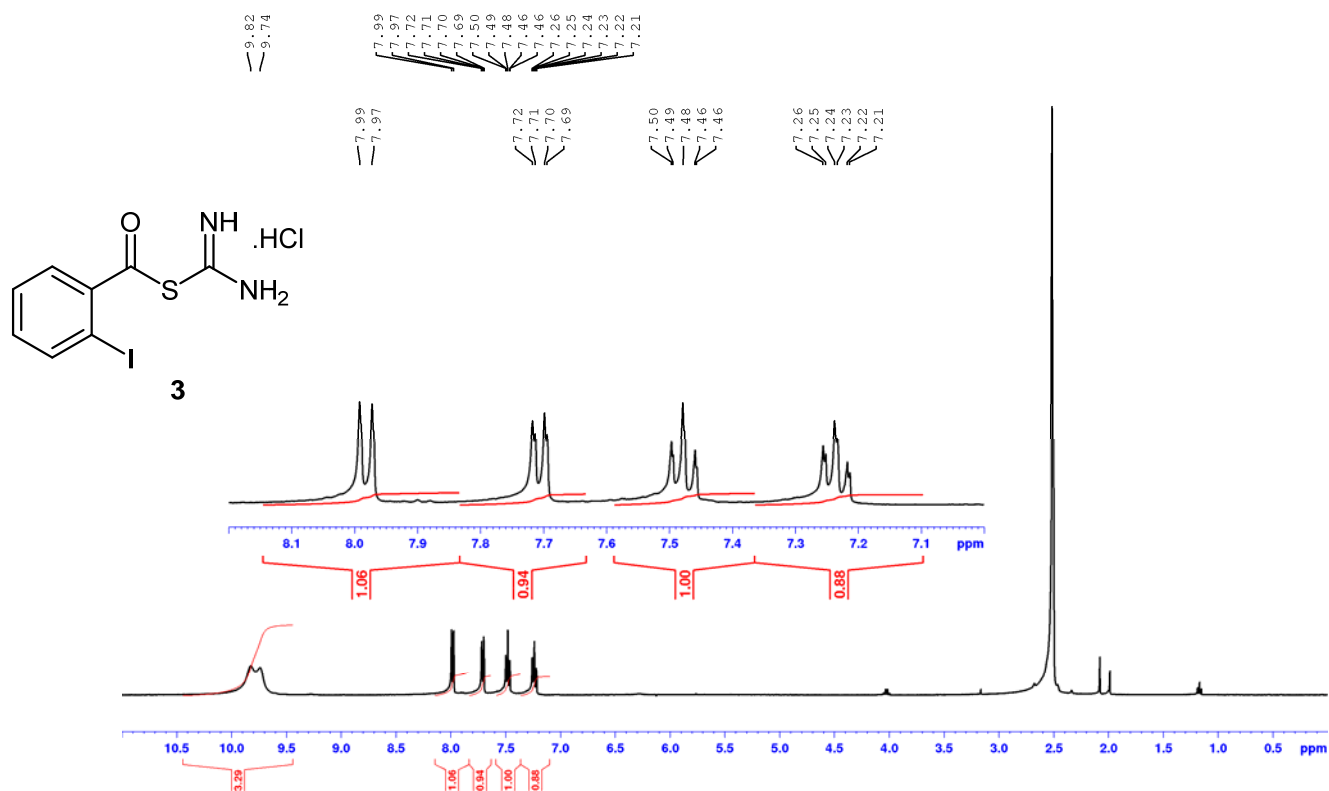


S-Benzoyl Isothiuronium Chloride (D1 Parameter = 4.0 seconds)

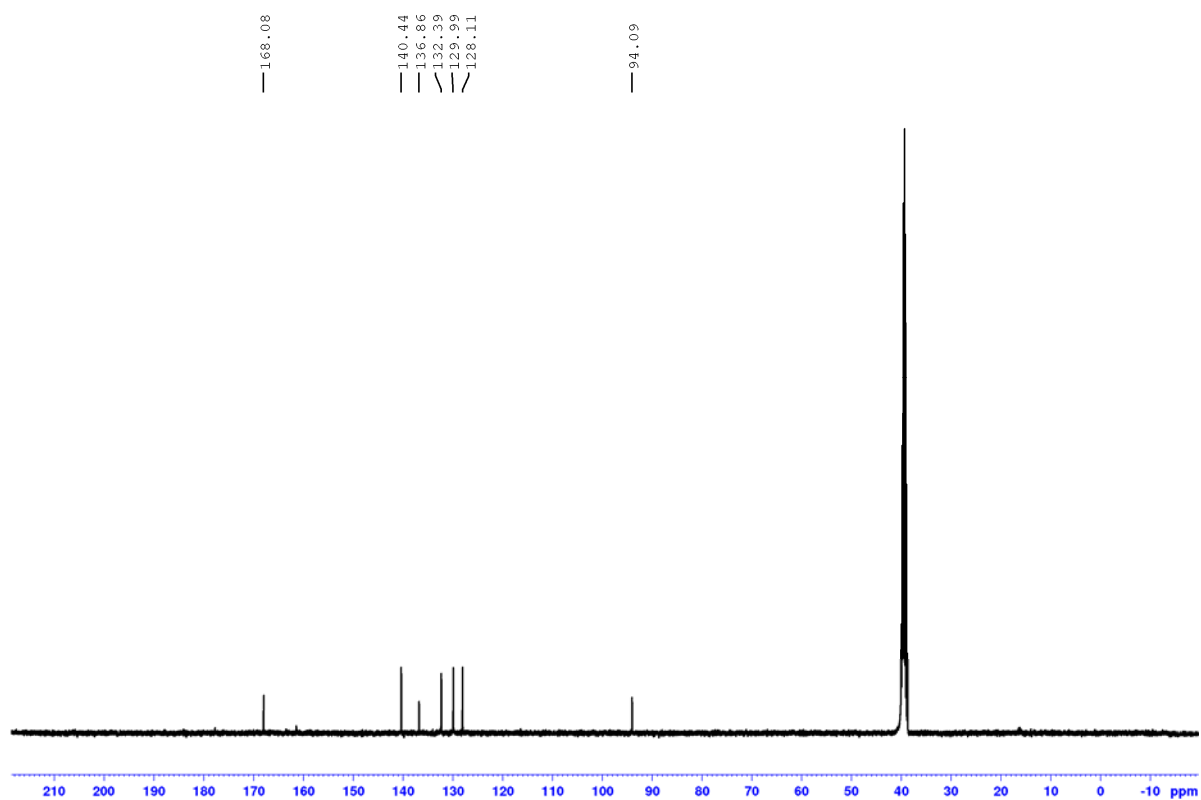


S4.2. S-(2-Iodobenzoyl) Isothiuronium Chloride (3)

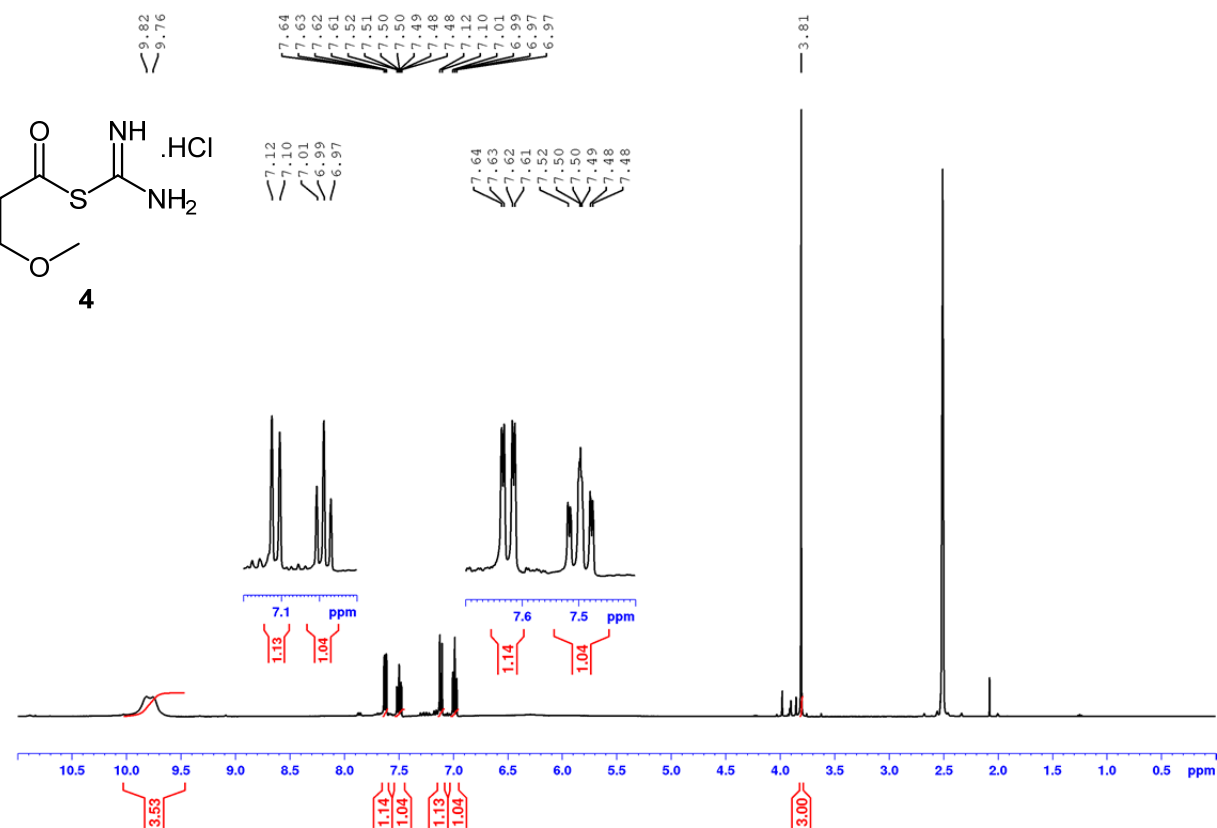
S-(2-Iodobenzoyl) Isothiuronium Chloride



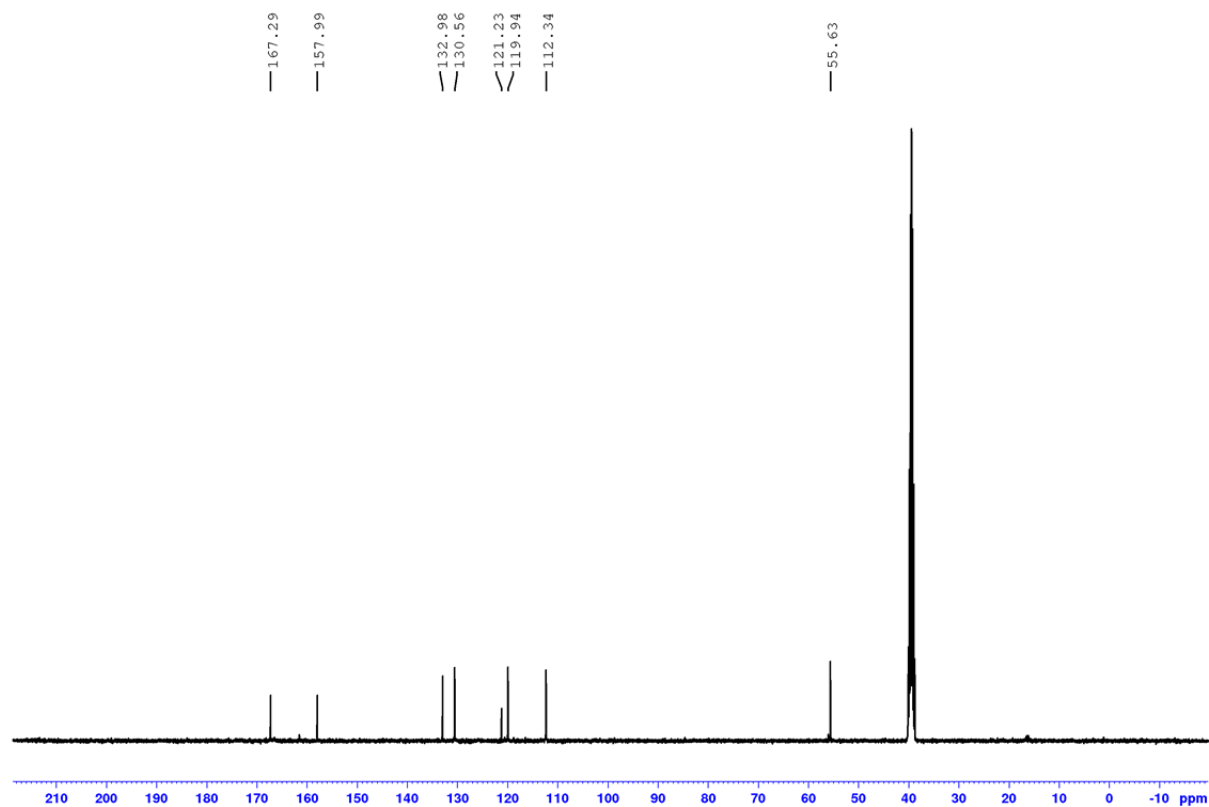
S-(2-Iodobenzoyl) Isothiuronium Chloride



S-(2-Methoxybenzoyl) Isothiouronium Chloride

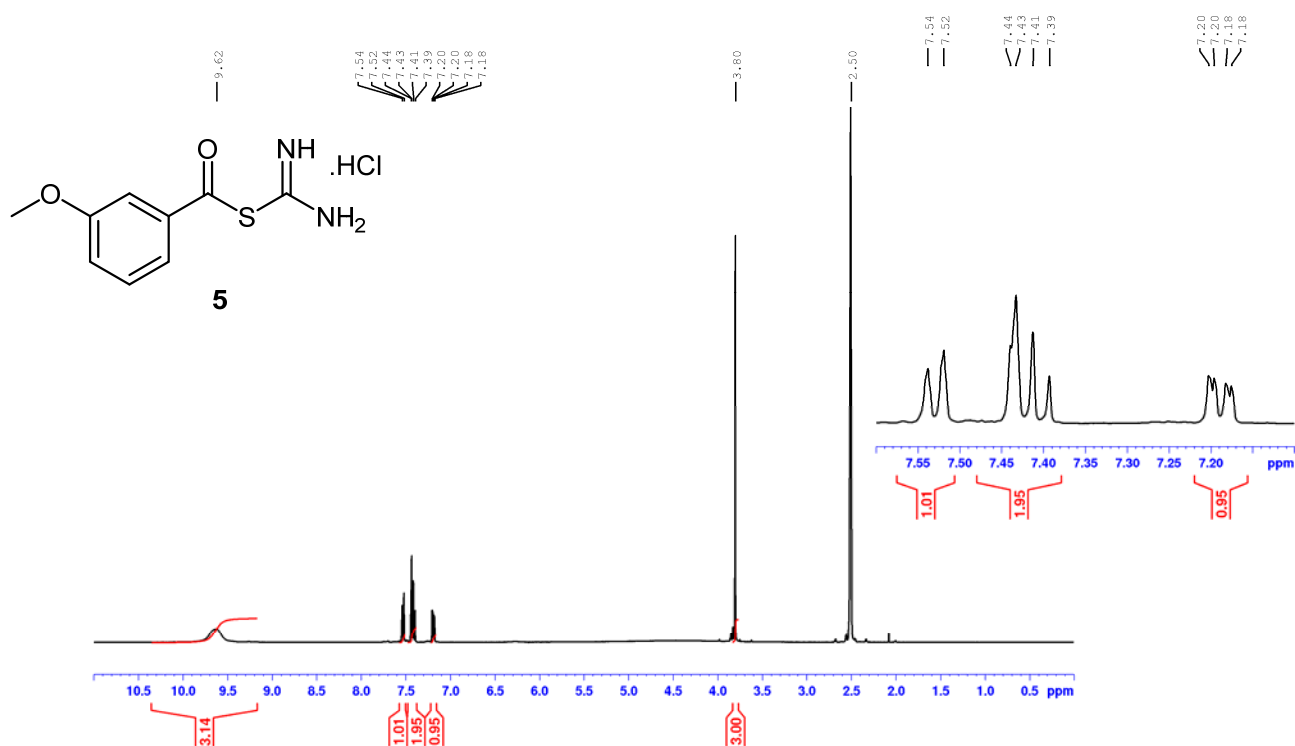


S-(2-Methoxybenzoyl) Isothiouronium Chloride

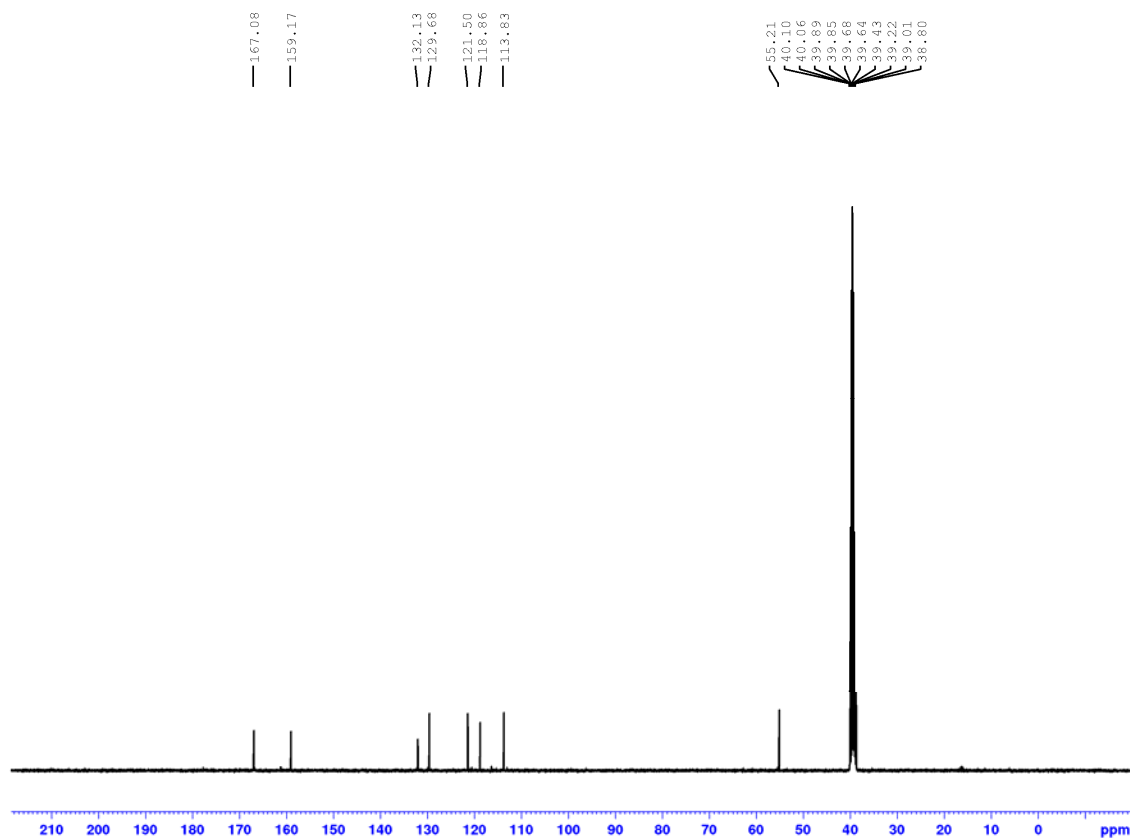


S.4.4. S-(3-Methoxybenzoyl) Isothiuronium Chloride (5)

S-(3-Methoxybenzoyl) Isothiuronium Chloride

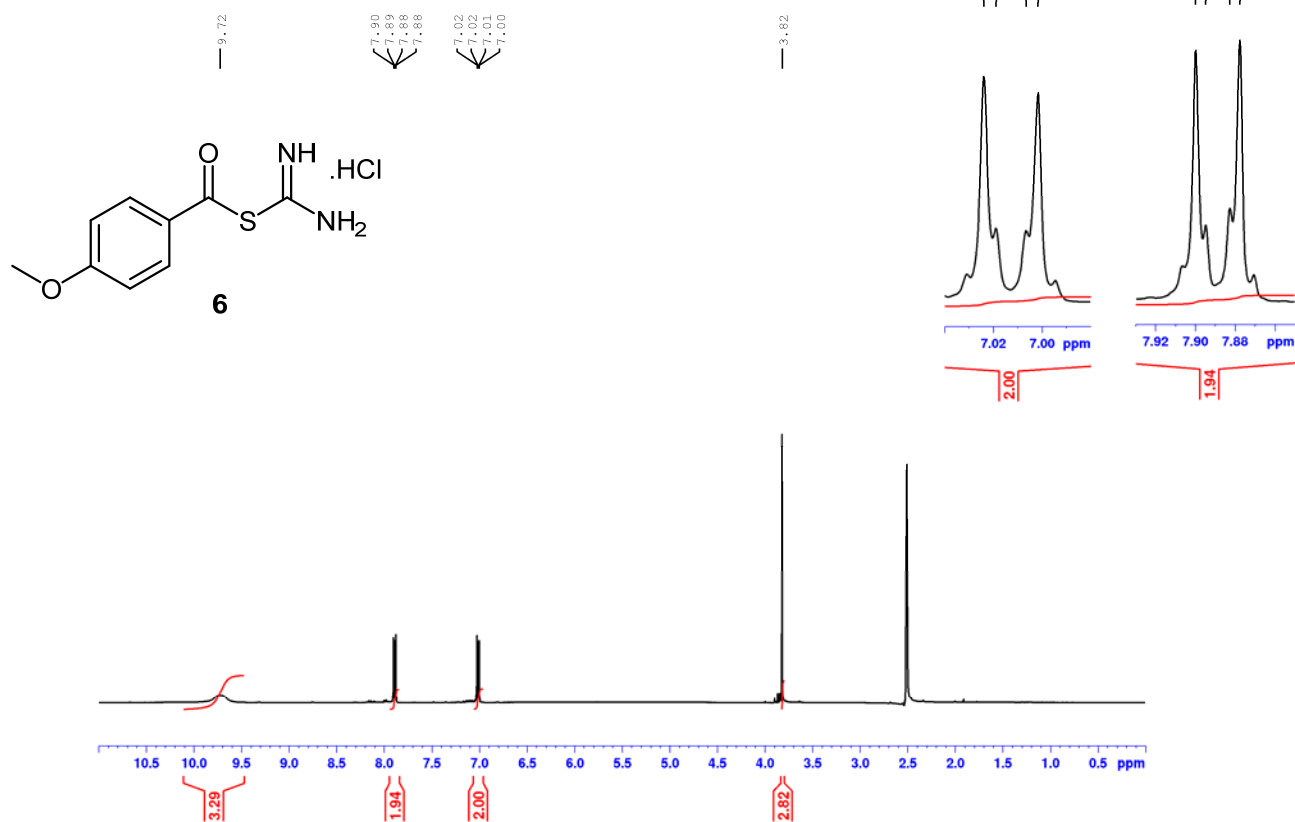


S-(3-methoxybenzoyl) Isothiuronium Chloride

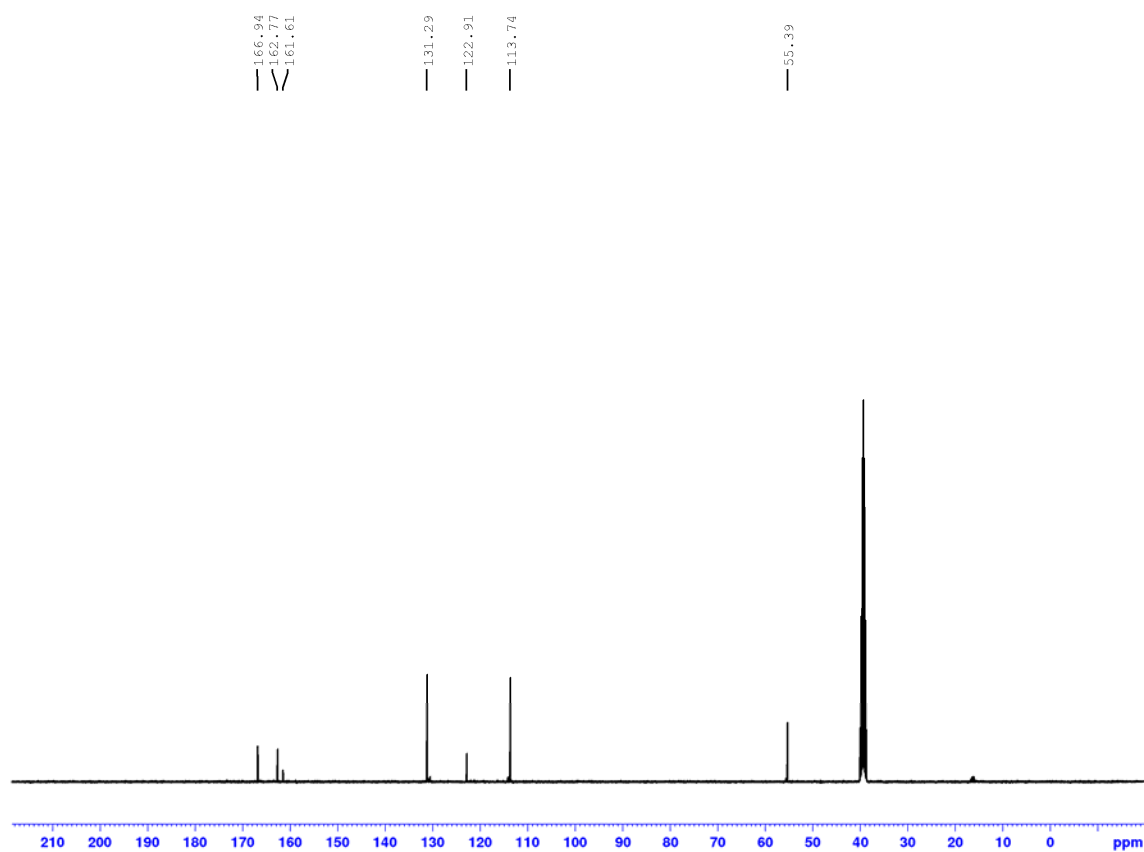


S.4.5. S-(4-Methoxybenzoyl) Isothiuronium Chloride (6)

S-(4-Methoxybenzoyl) Isothiuronium Chloride

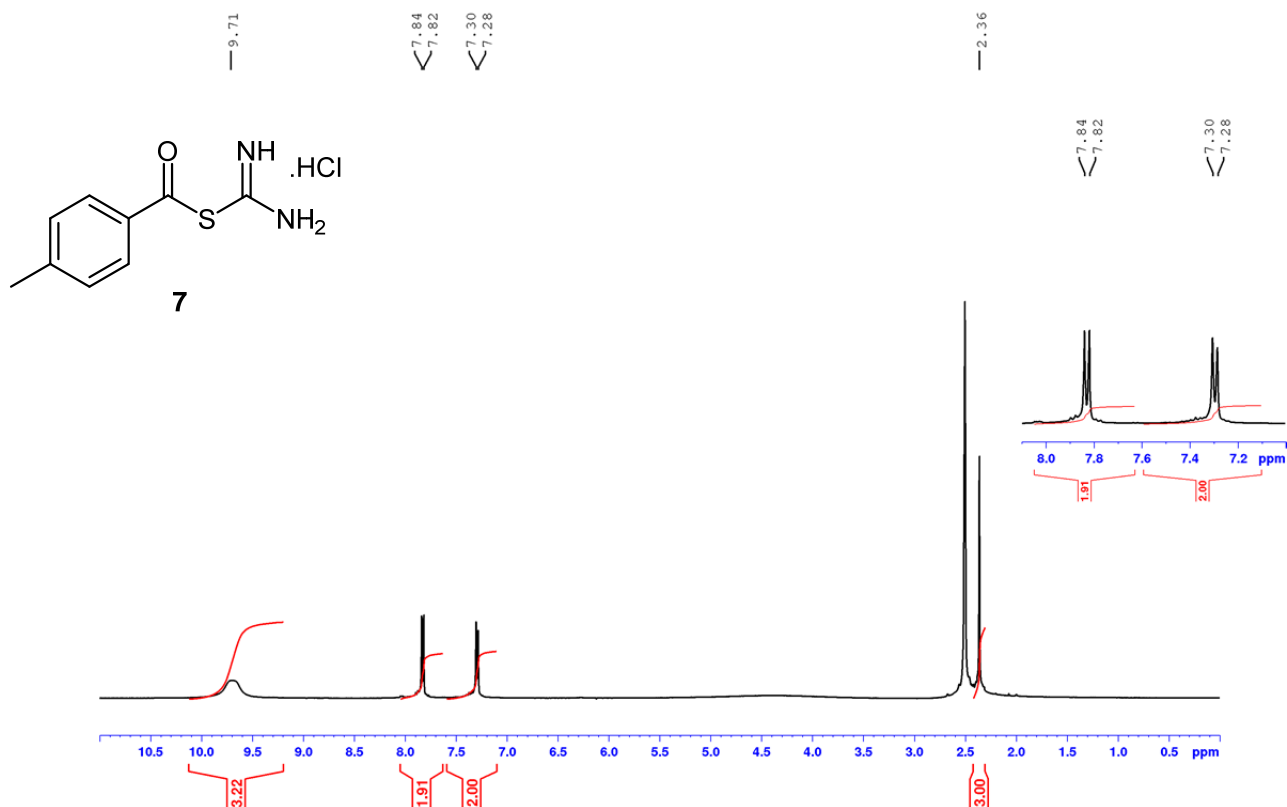


S-(4-Methoxybenzoyl) Isothiuronium Chloride

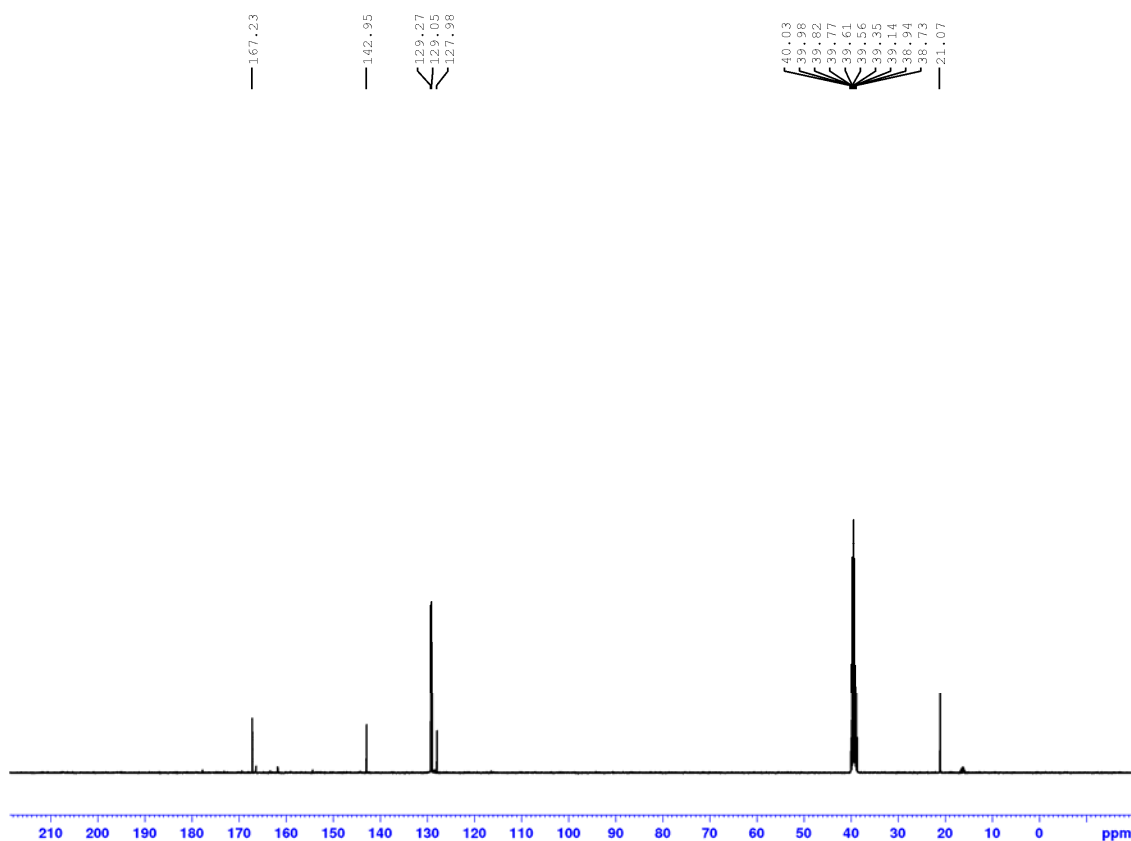


S.4.6. S-(4-Methylbenzoyl) Isothiuronium Chloride (7)

S-(4-Methylbenzoyl) Isothiuronium Chloride

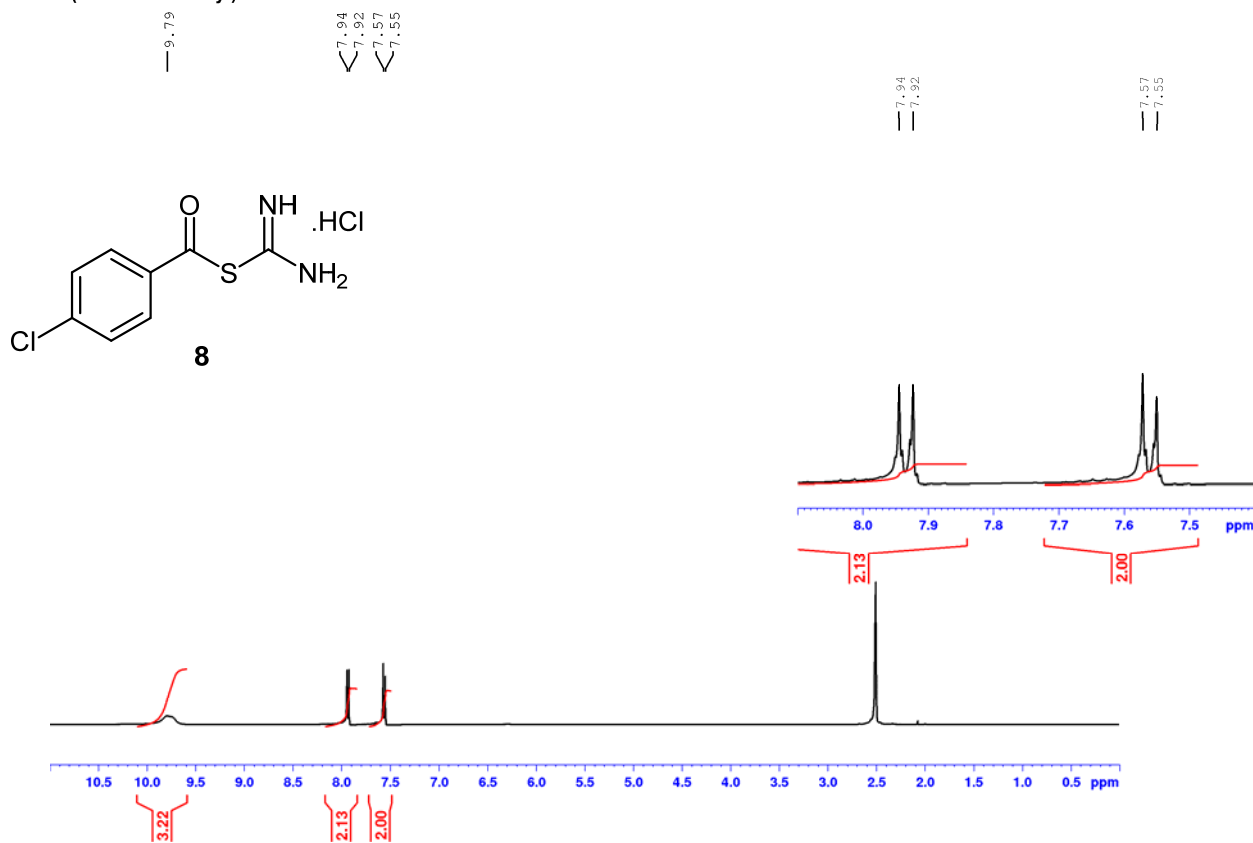


S-(4-Methylbenzoyl) Isothiuronium Chloride

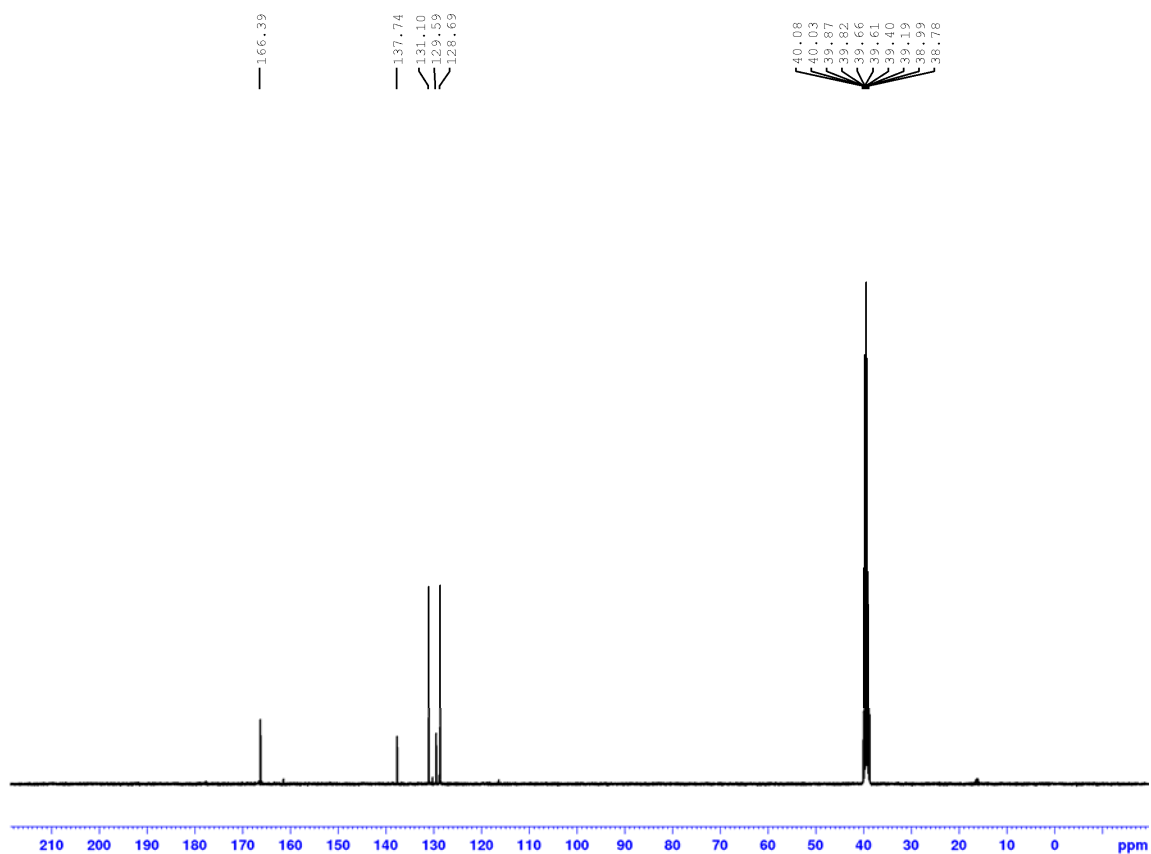


S.4.7. S(4-Chlorobenzoyl) Isothiuronium Chloride (8)

S-(4-chlorobenzoyl) isothiuronium Chloride

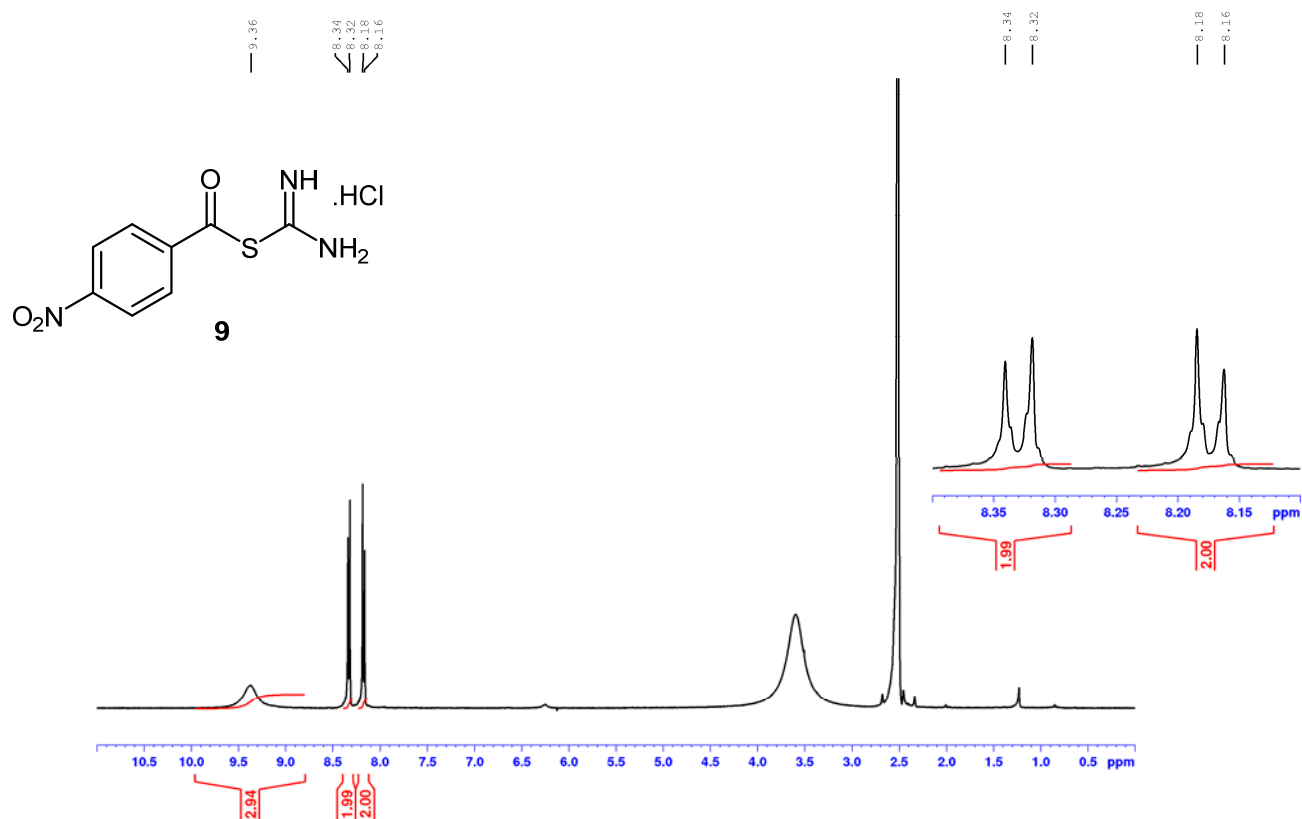


S-(4-Chlorobenzoyl) Isothiuronium Chloride

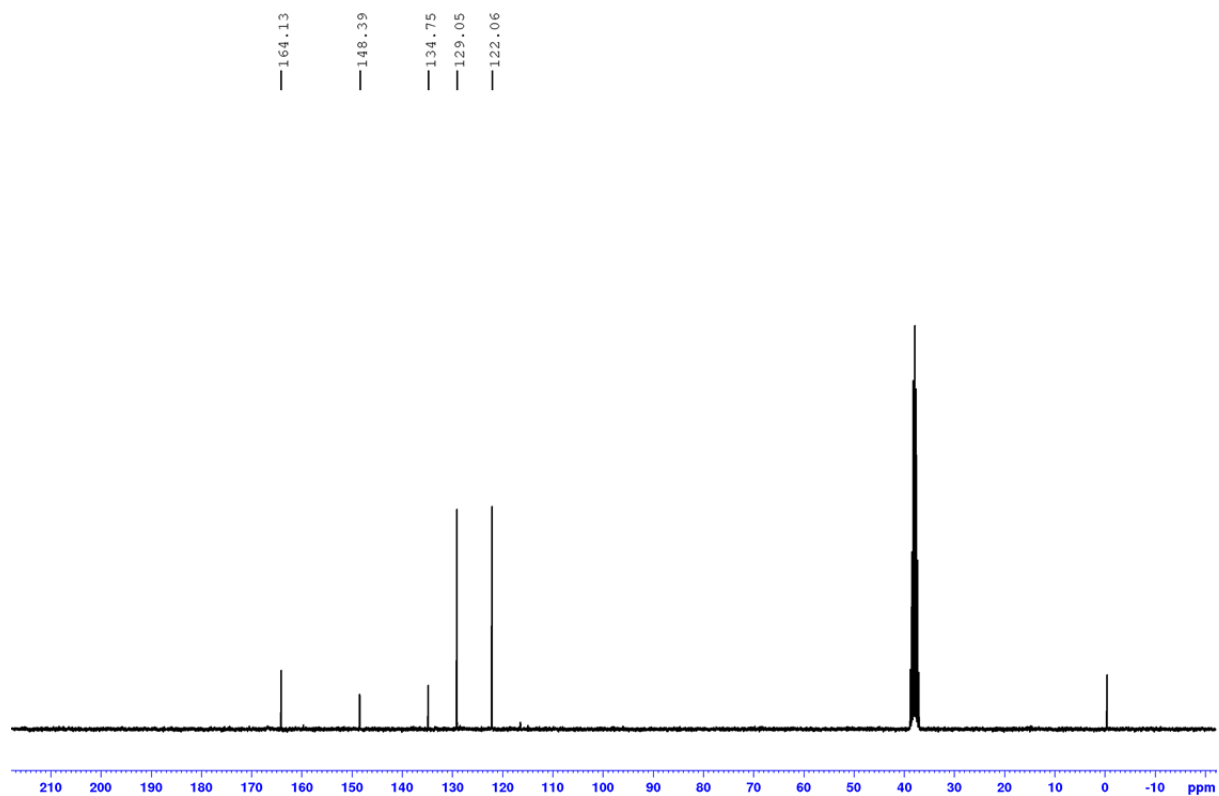


S.4.8. S(4-Nitrobenzoyl) Isothiuronium Chloride (9)

S-(4-Nitrobenzoyl) Isothiuronium Chloride

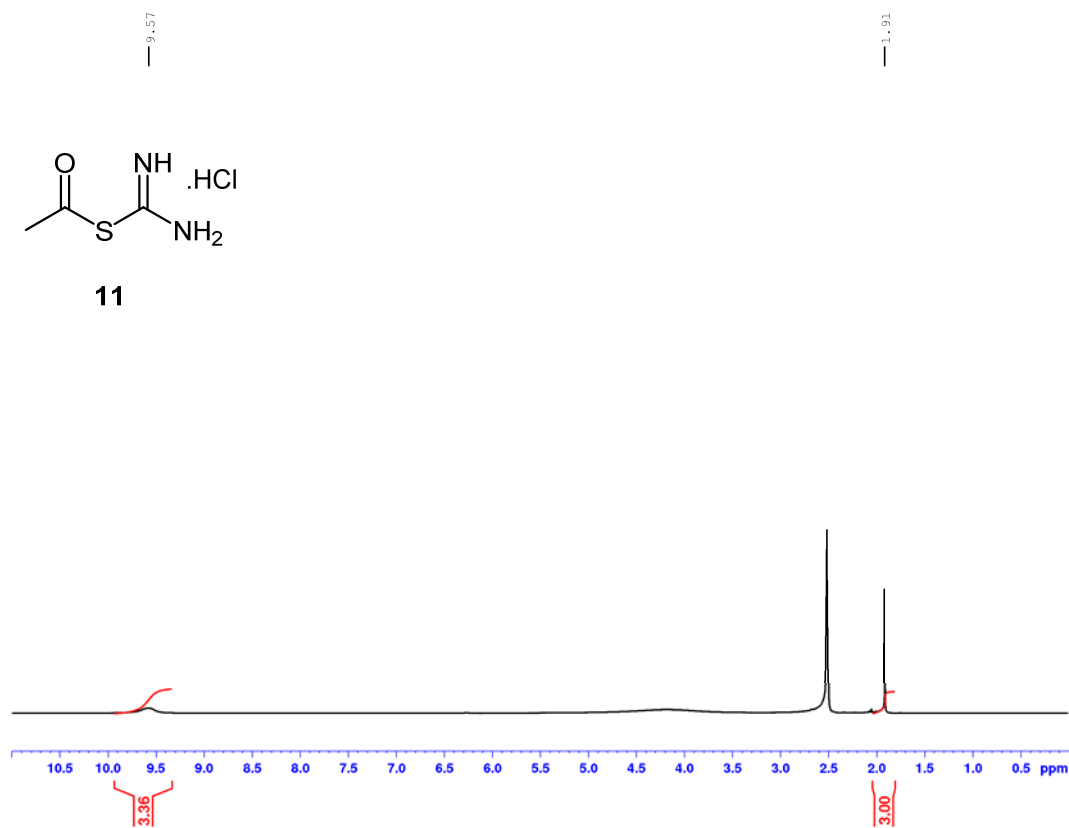
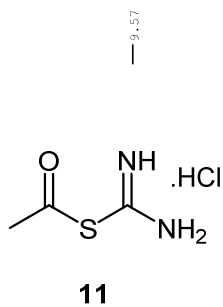


S-(4-Nitrobenzoyl) Isothiuronium Chloride

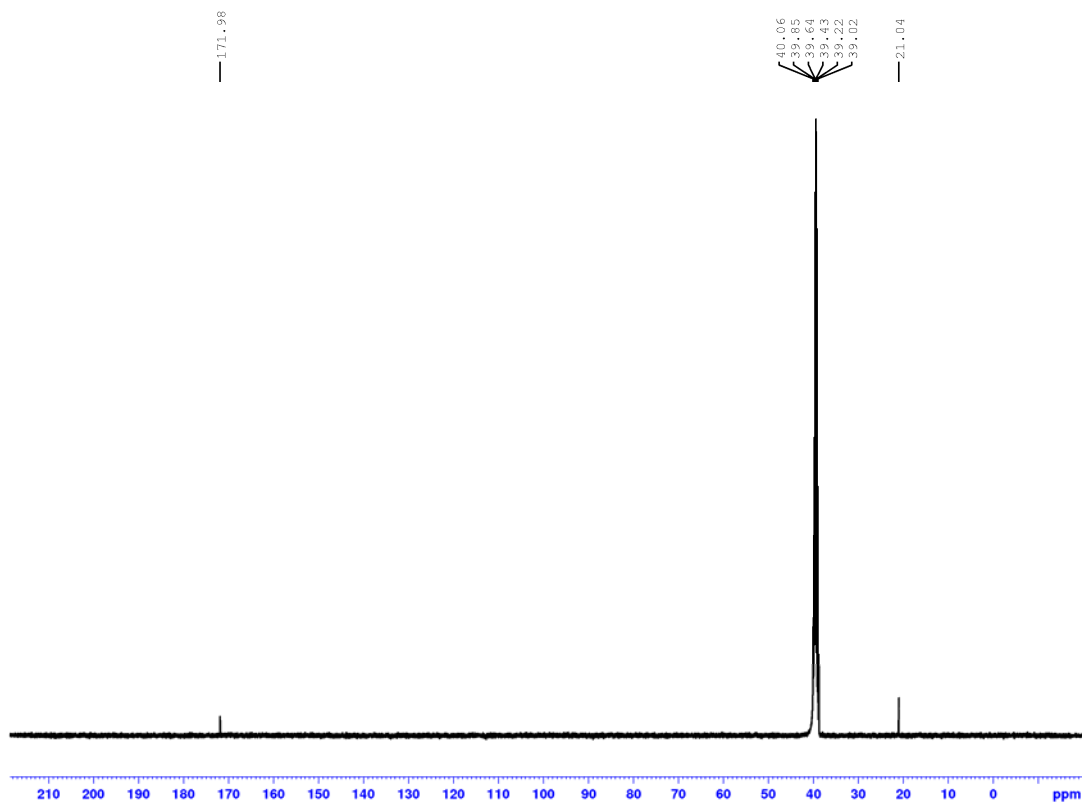


S.4.9. S-(Acetyl) Isothiuronium Chloride (11)

S-Acetyl Isothiuronium Chloride

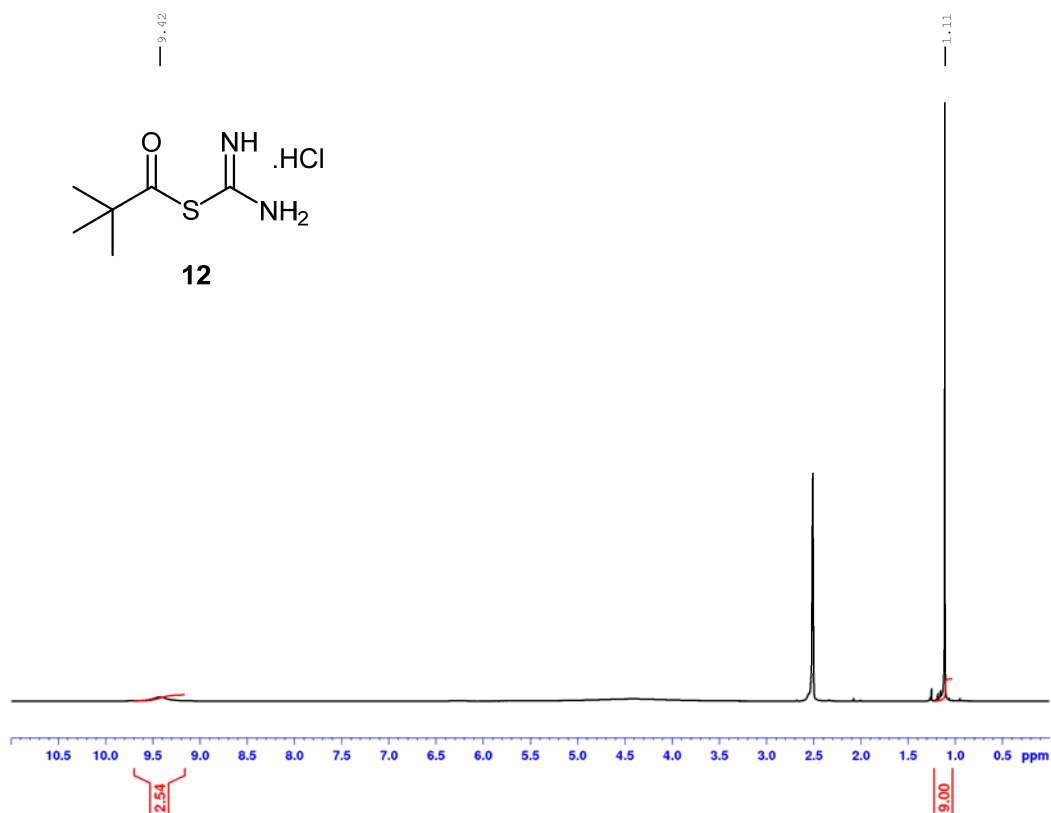


S-Acetyl Isothiuronium chloride

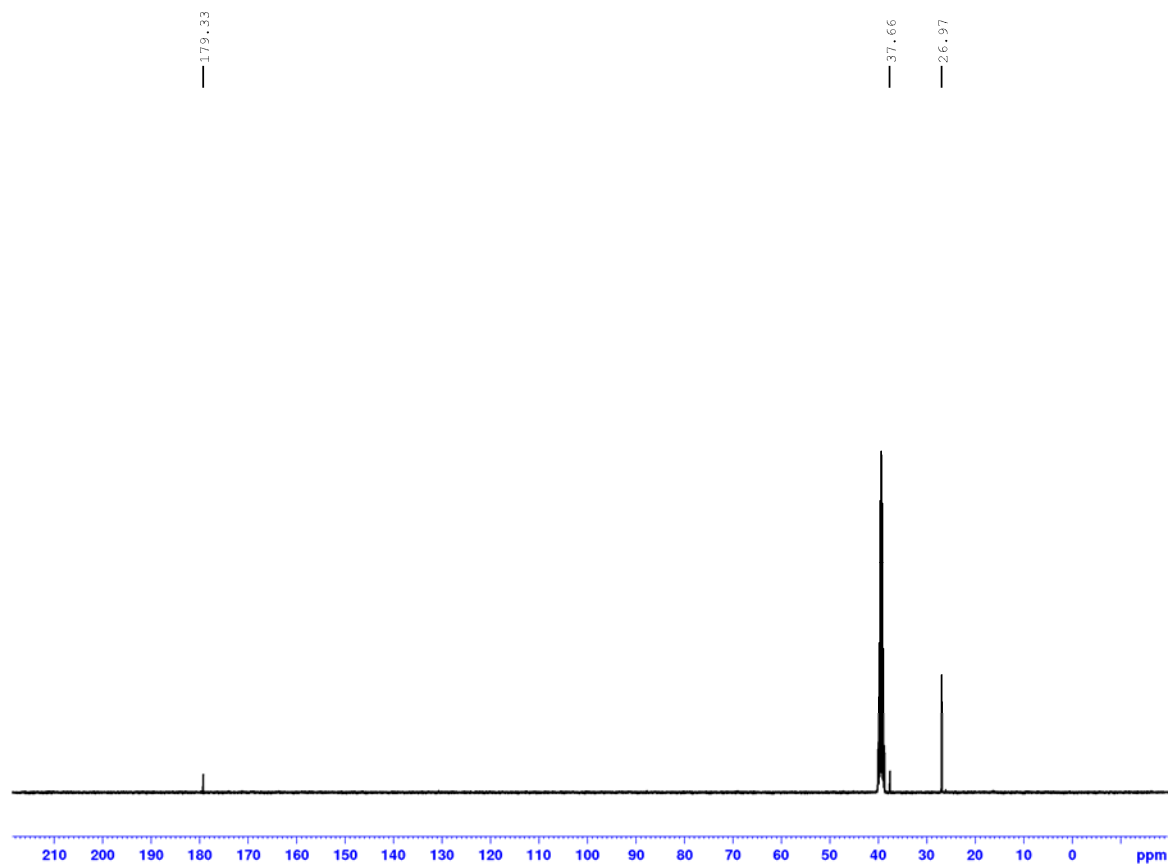


S.4.10 S-(Pivaloyl) Isothiuronium Chloride (12)

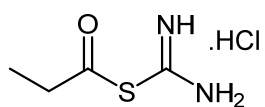
S-(2,2-dimethylacetyl) Isothiuronium Chloride



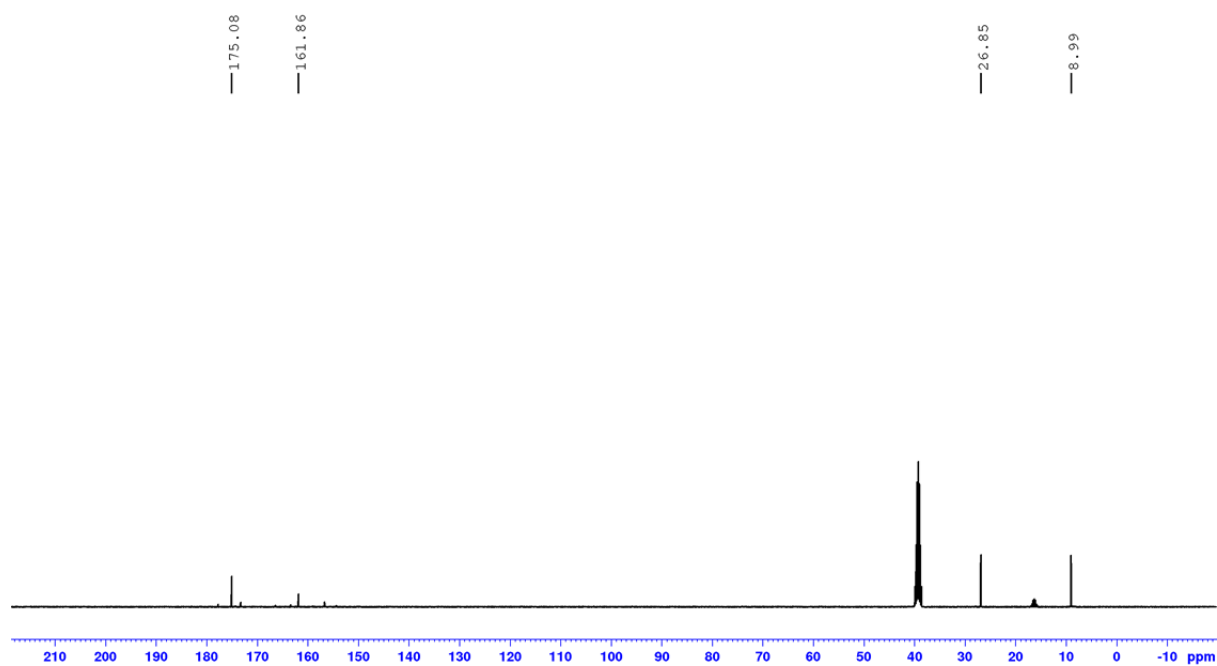
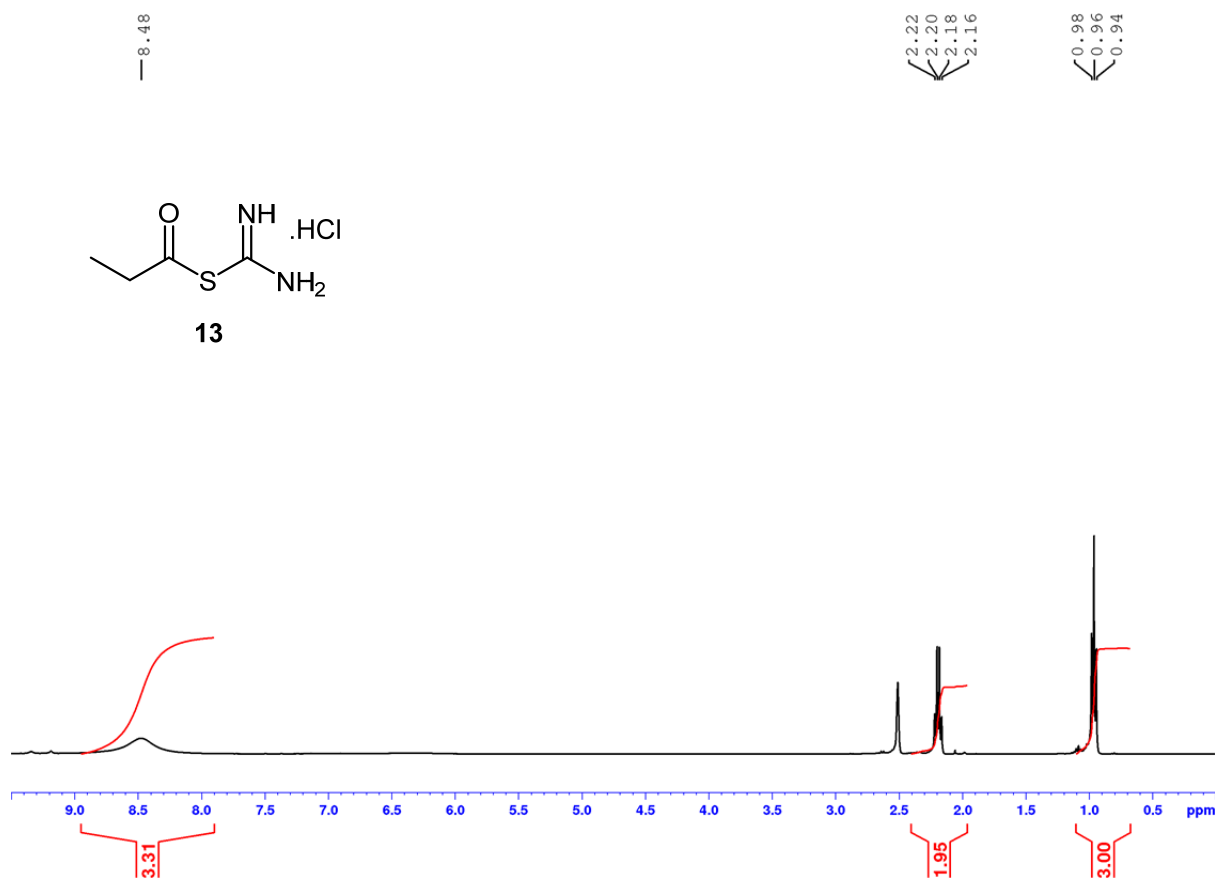
S-(2,2-dimethylacetyl) Isothiuronium Chloride



S.4.11. S-Propanoyl Isothiuronium Chloride (13)

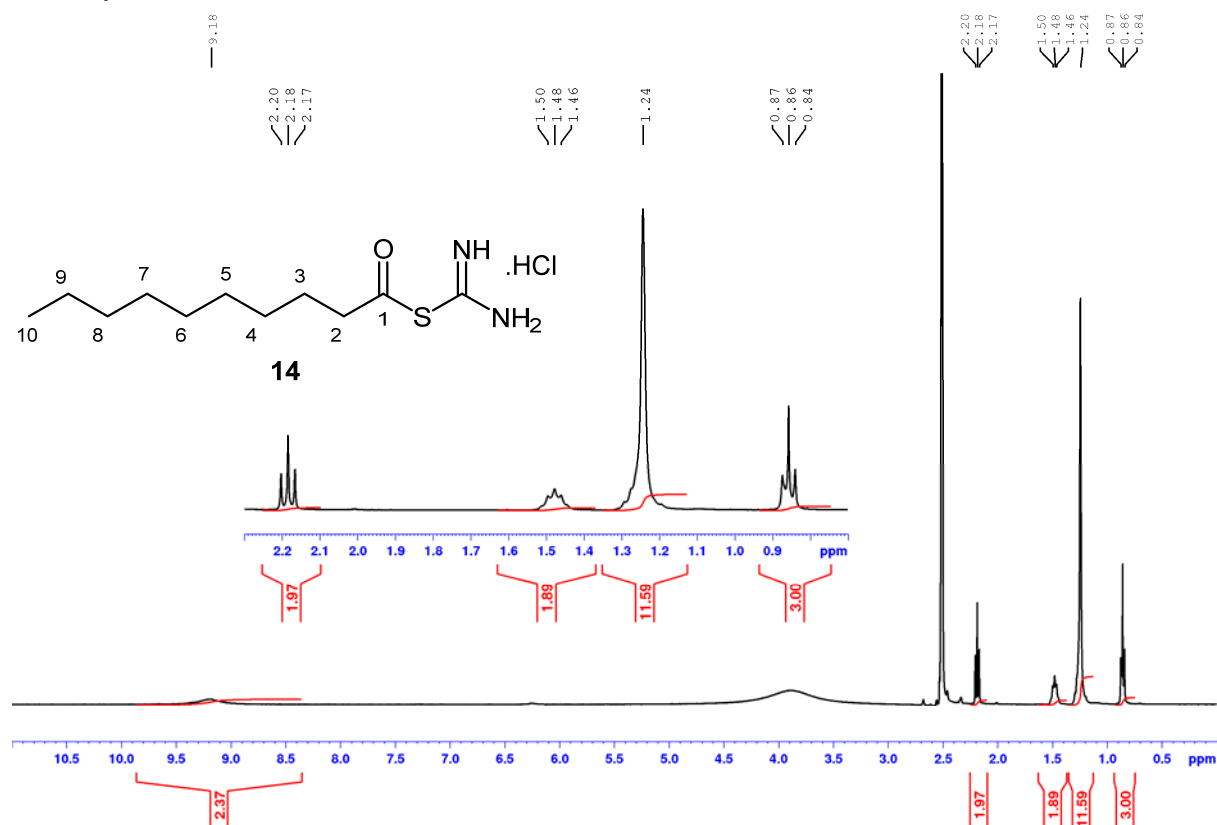


13

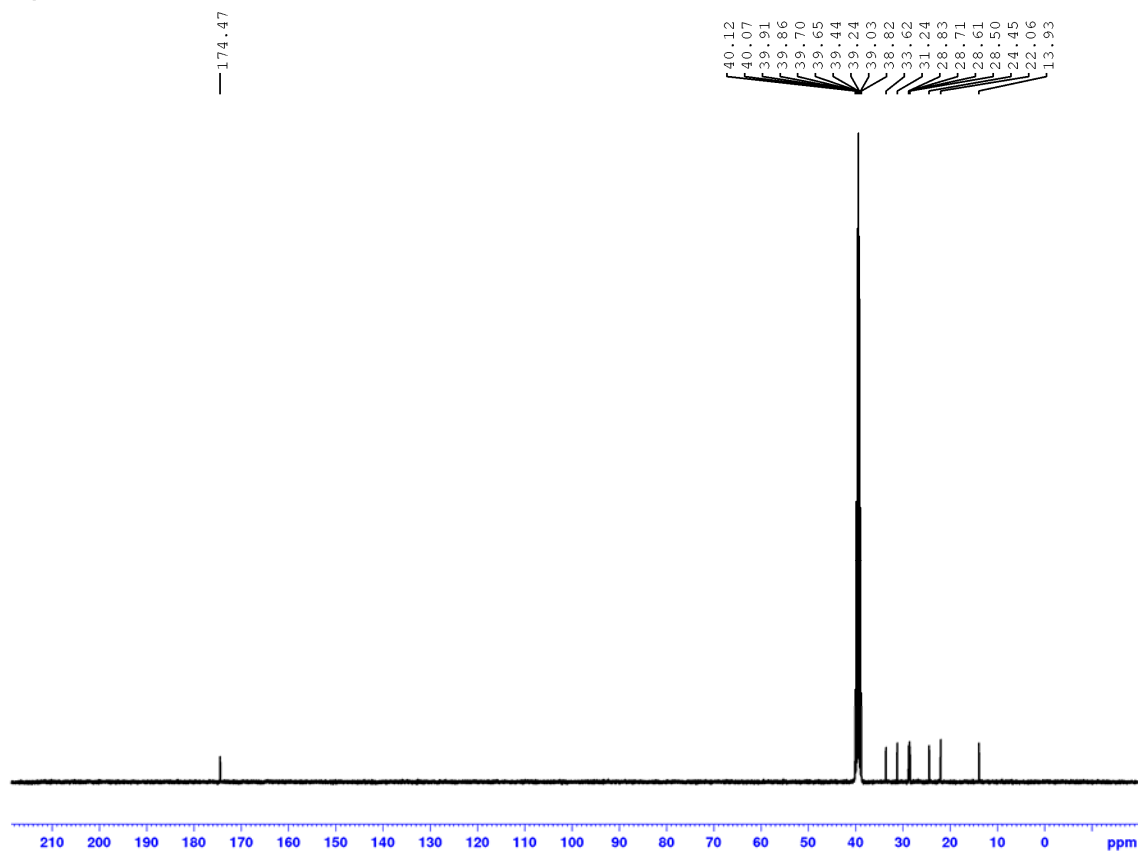


S.4.12. S-Decanoyl Isothiuronium Chloride (14)

S-Decanoyl Isothiuronium Chloride

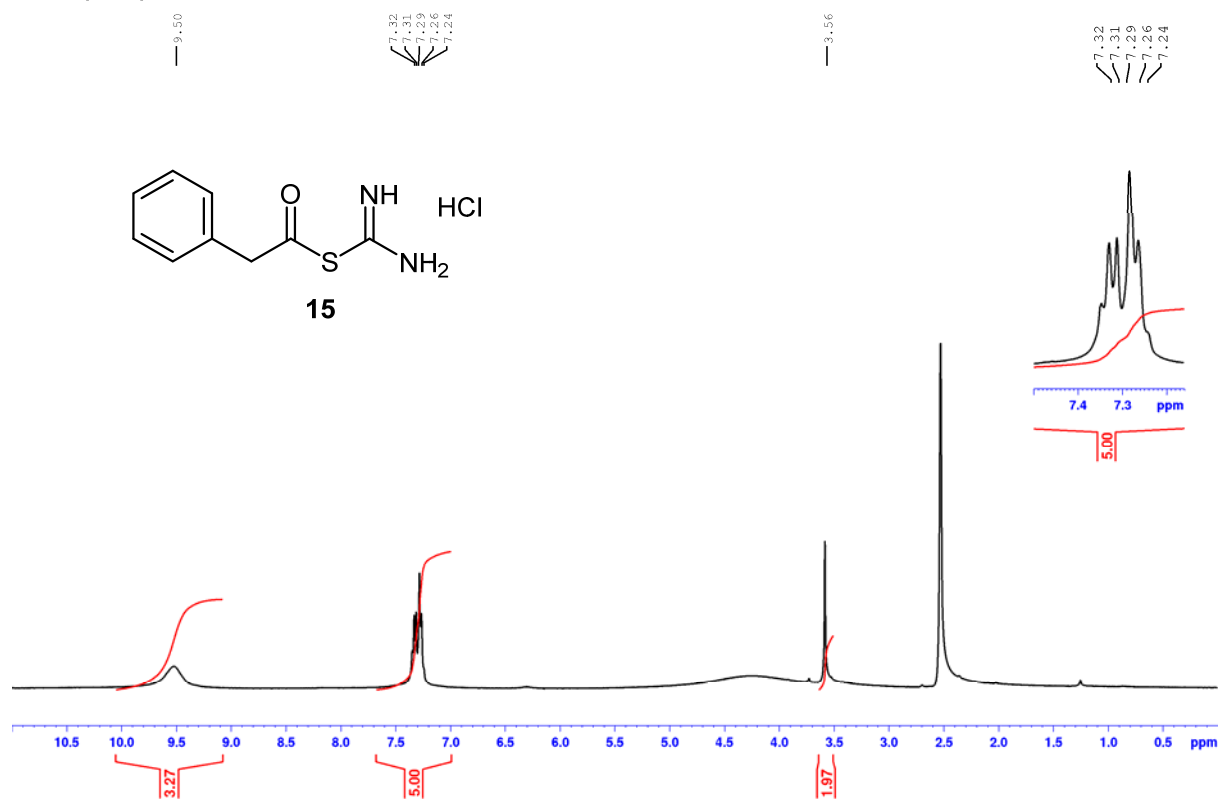


S-Decanoyl Isothiuronium Chloride

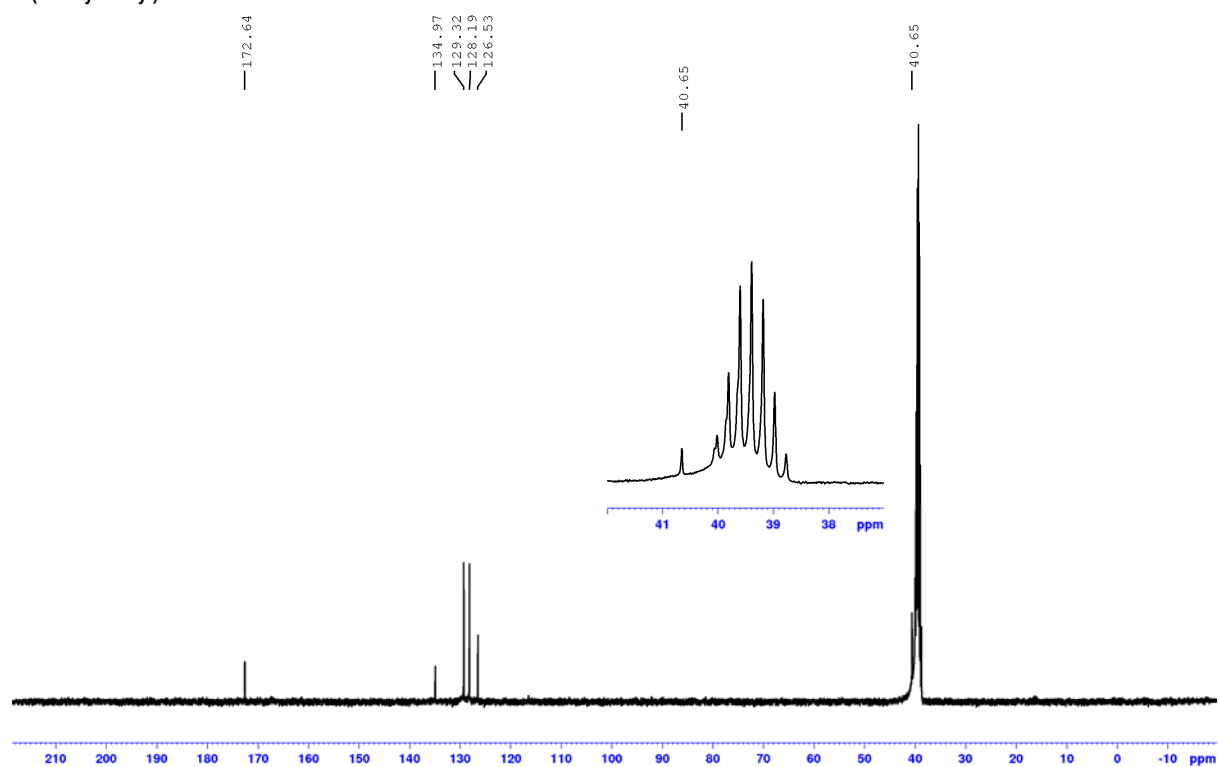


S.4.13. S-(Phenylacetyl) Isothiuronium Chloride (15)

S-(Phenylacetyl) Isothiuronium Chloride

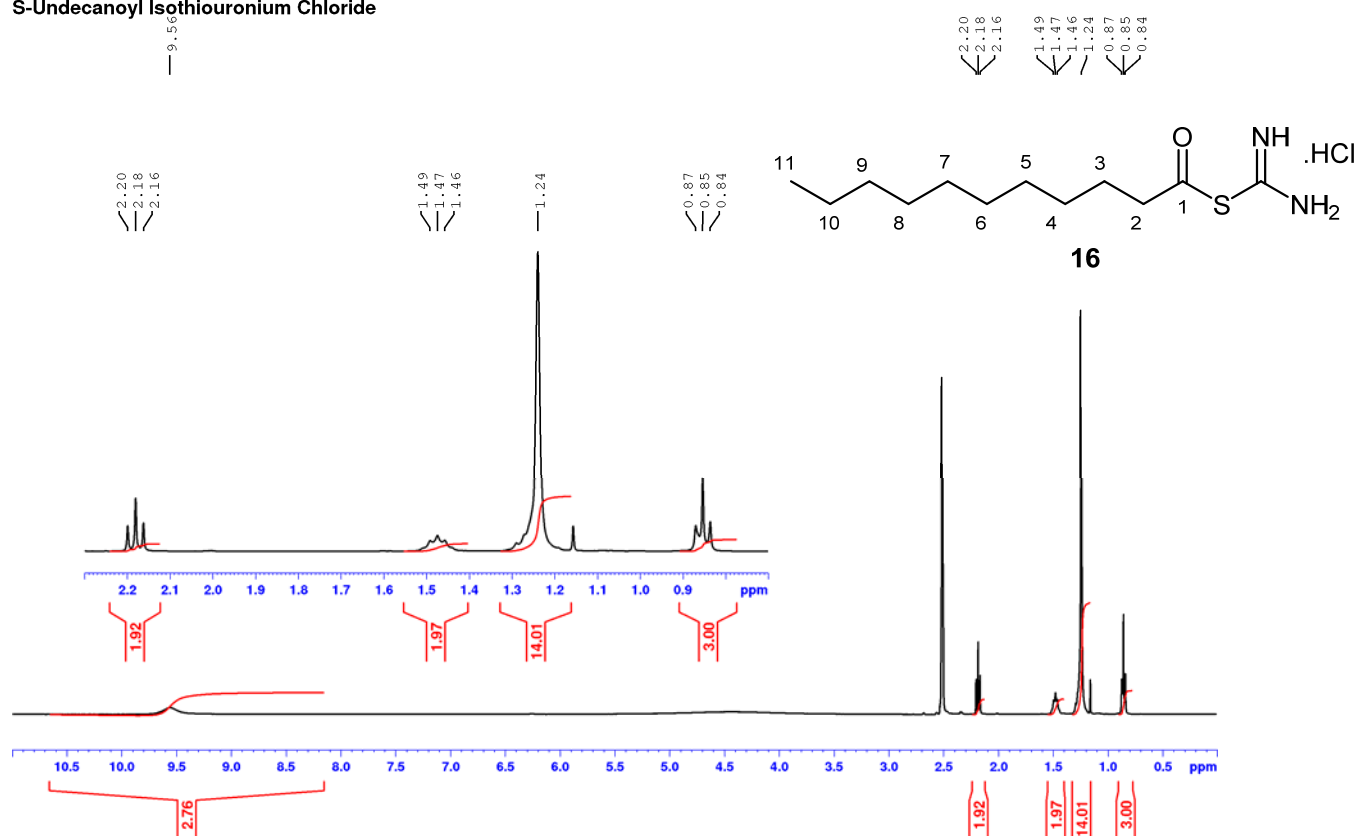


S-(Phenylacetyl) Isothiuronium Chloride

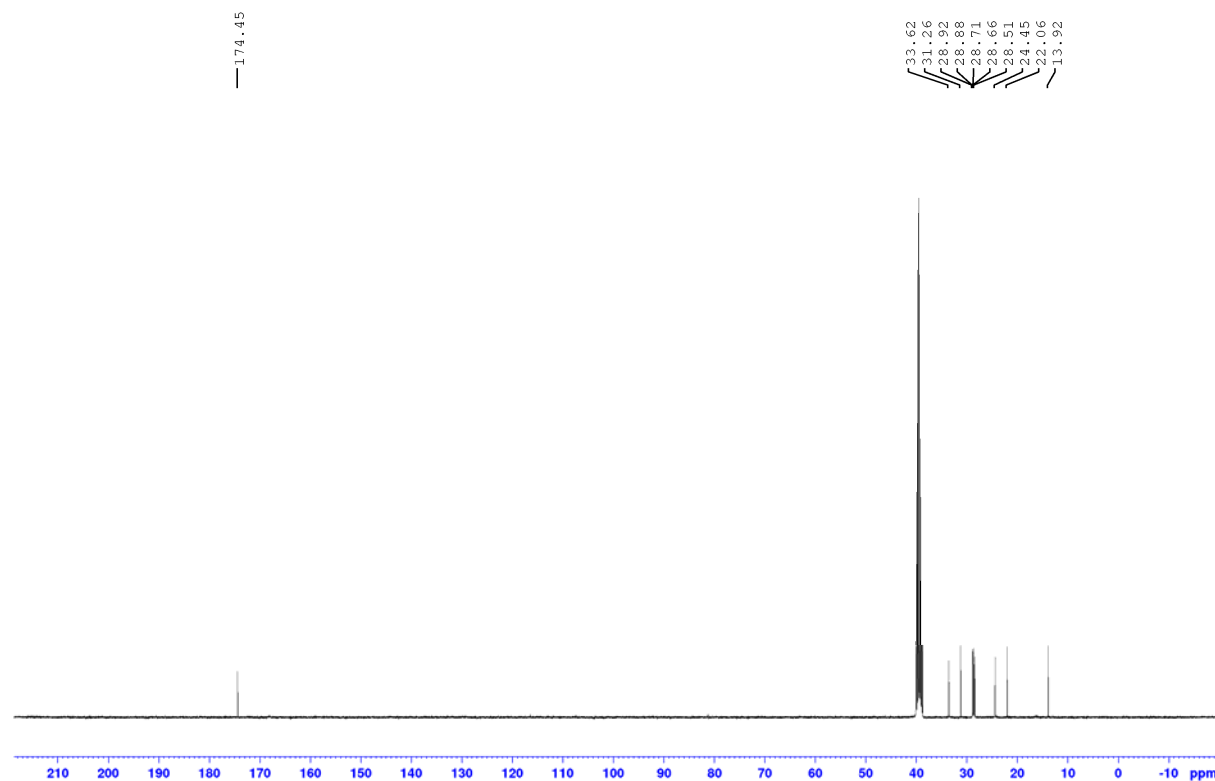


S.4.14. S-Undecanoyl Isothiuronium Chloride (16)

S-Undecanoyl Isothiuronium Chloride

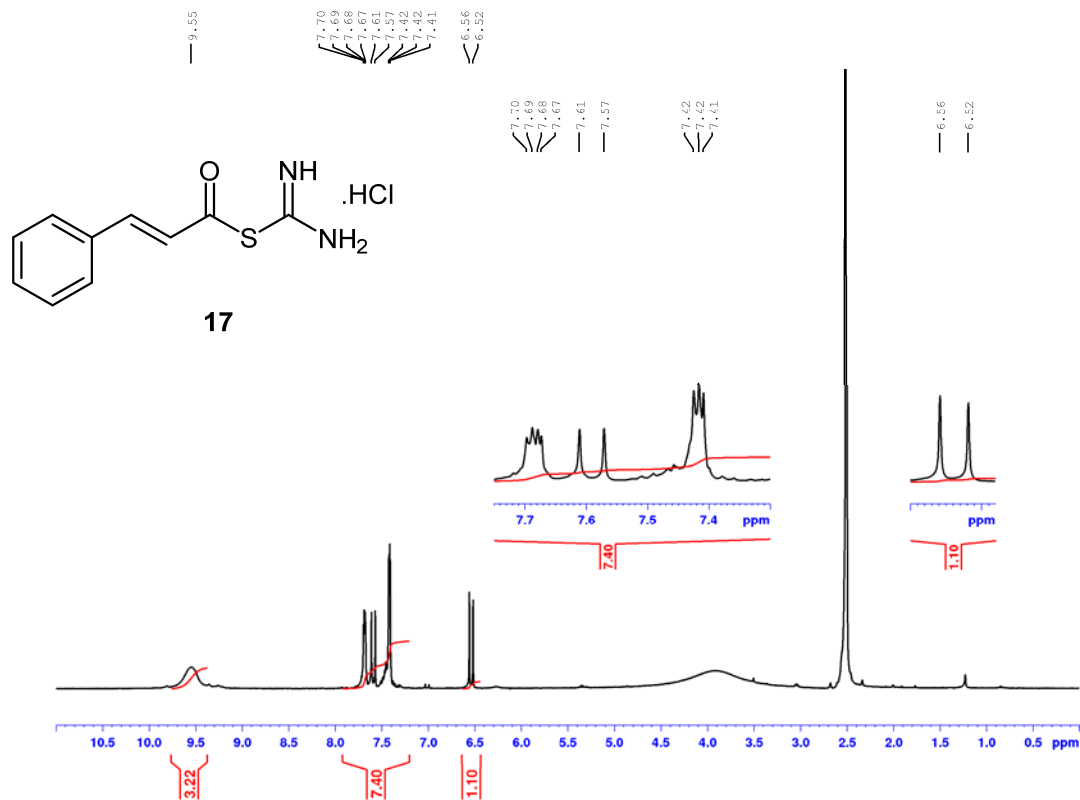


S-Undecanoyl Isothiuronium Chloride

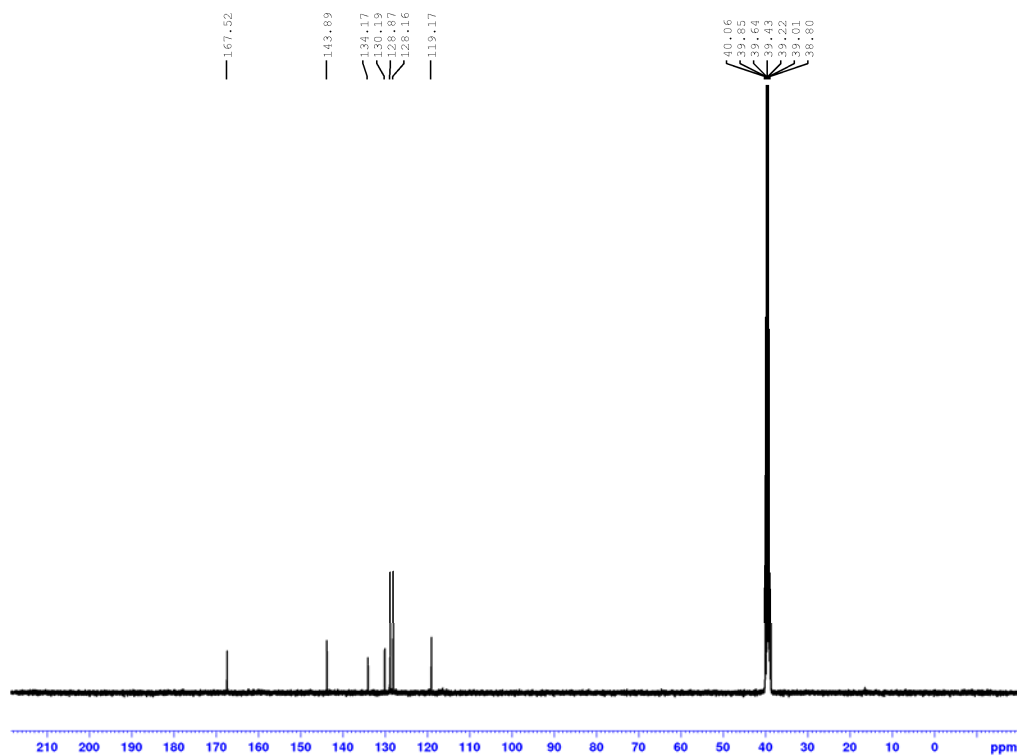


S.4.15. S-(Cinnamoyl) Isothiuronium Chloride (17)

S-Cinnamoyl Isothiuronium Chloride

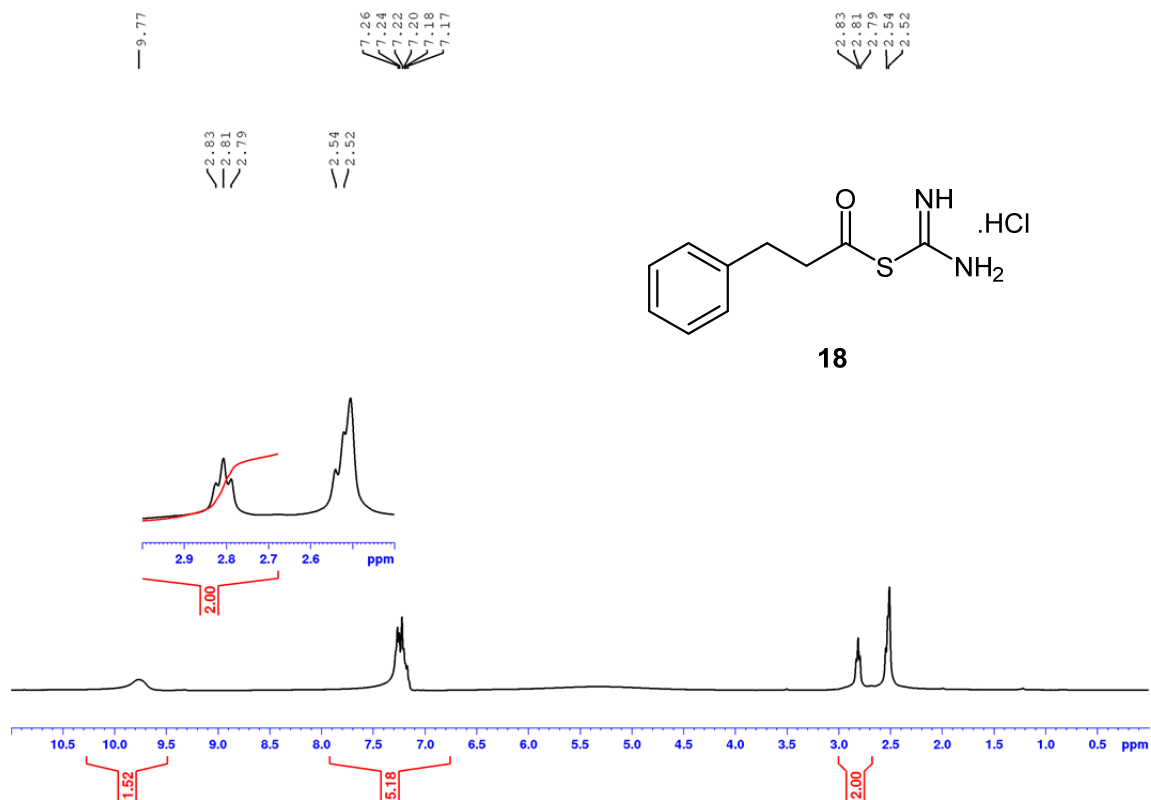


S-Cinnamoyl Isothiuronium Chloride

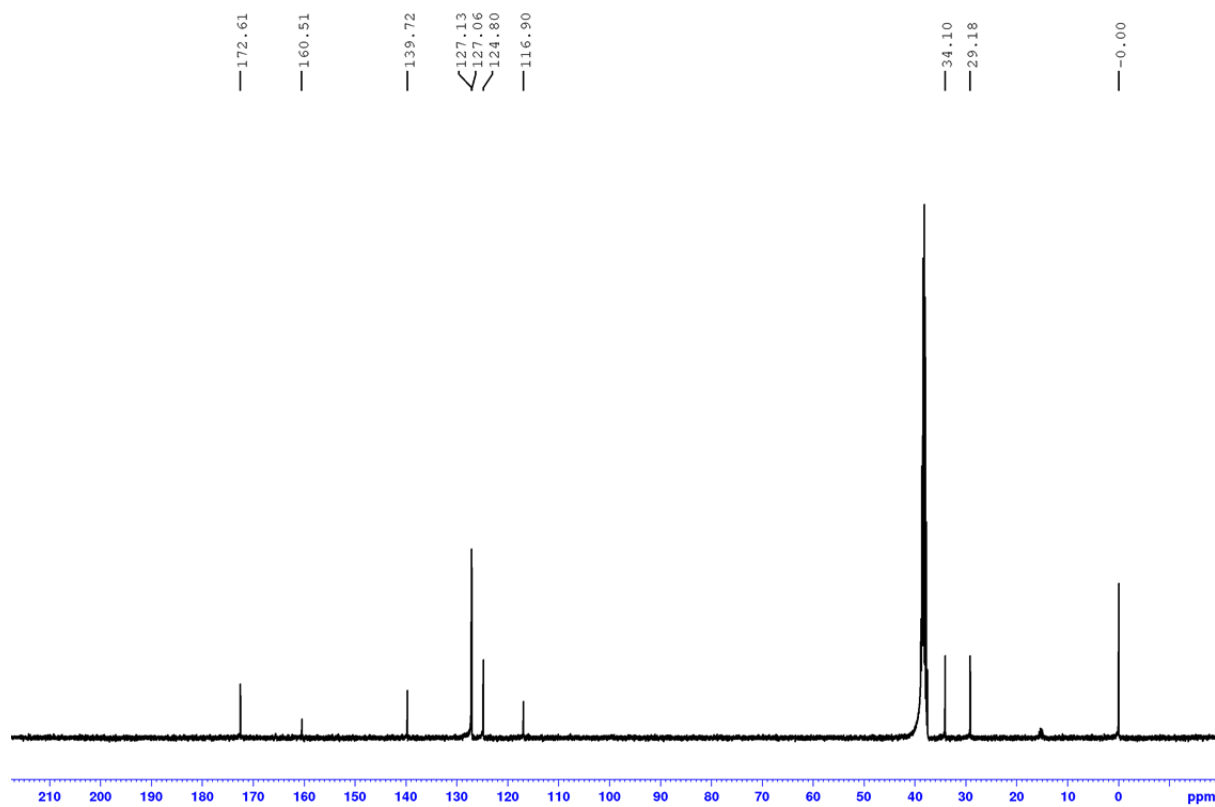


S.4.16 S-(Dihydrocinanmoyl) Isothiuronium Chloride (18)

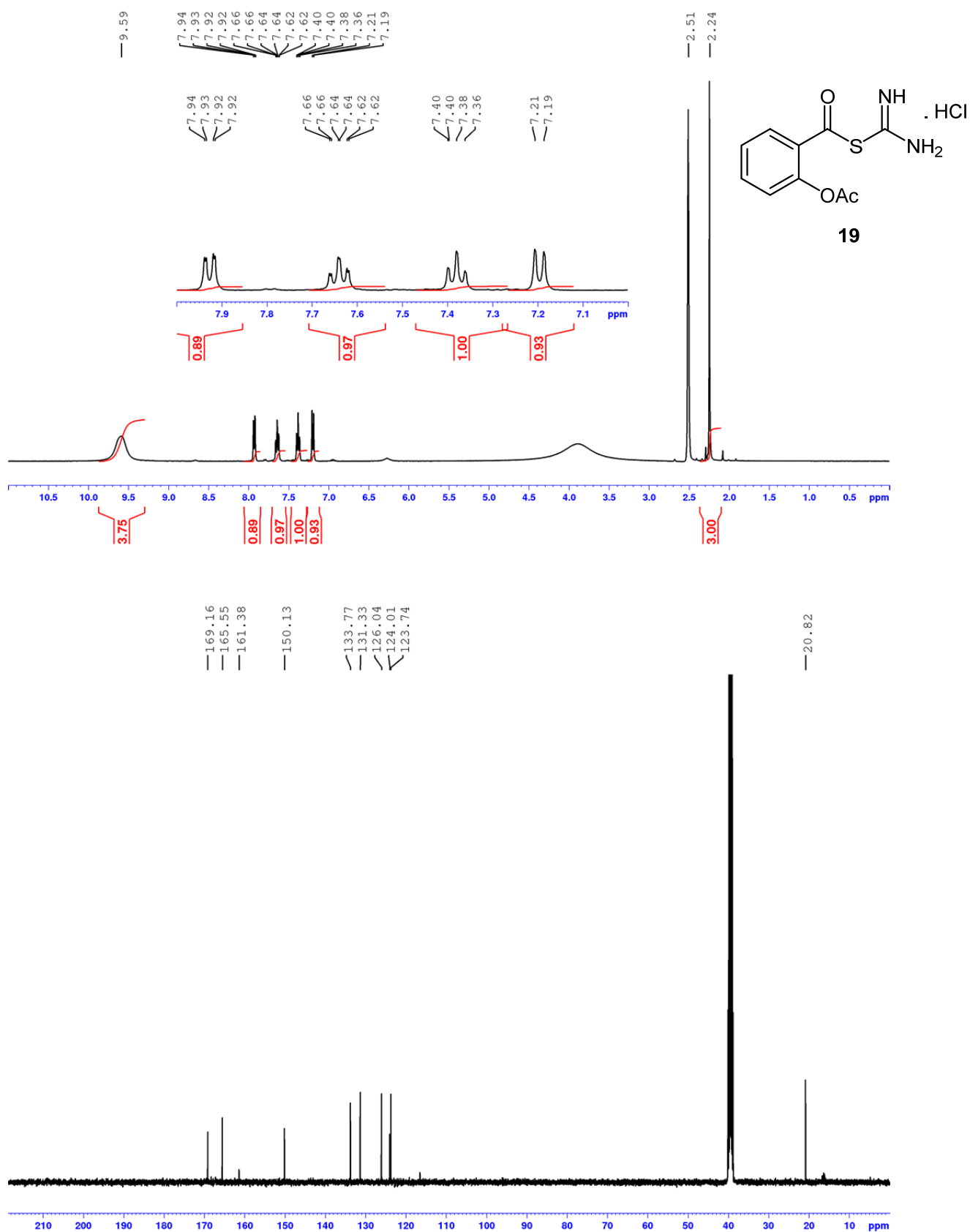
S-(Dihydrocinnamoyl) Isothiuronium Chloride



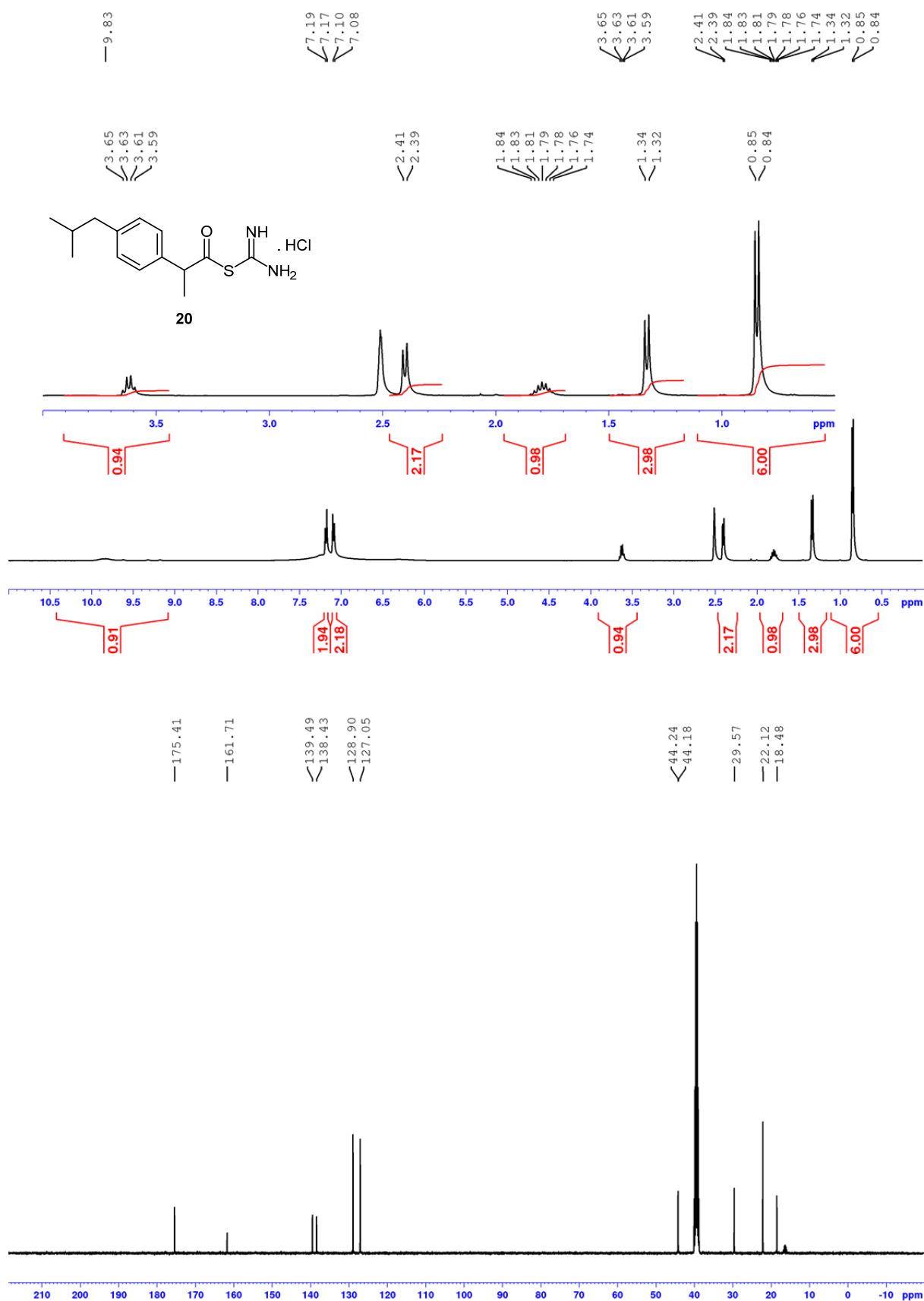
S-(Dihydrocinnamoyl) Isothiuronium Chloride



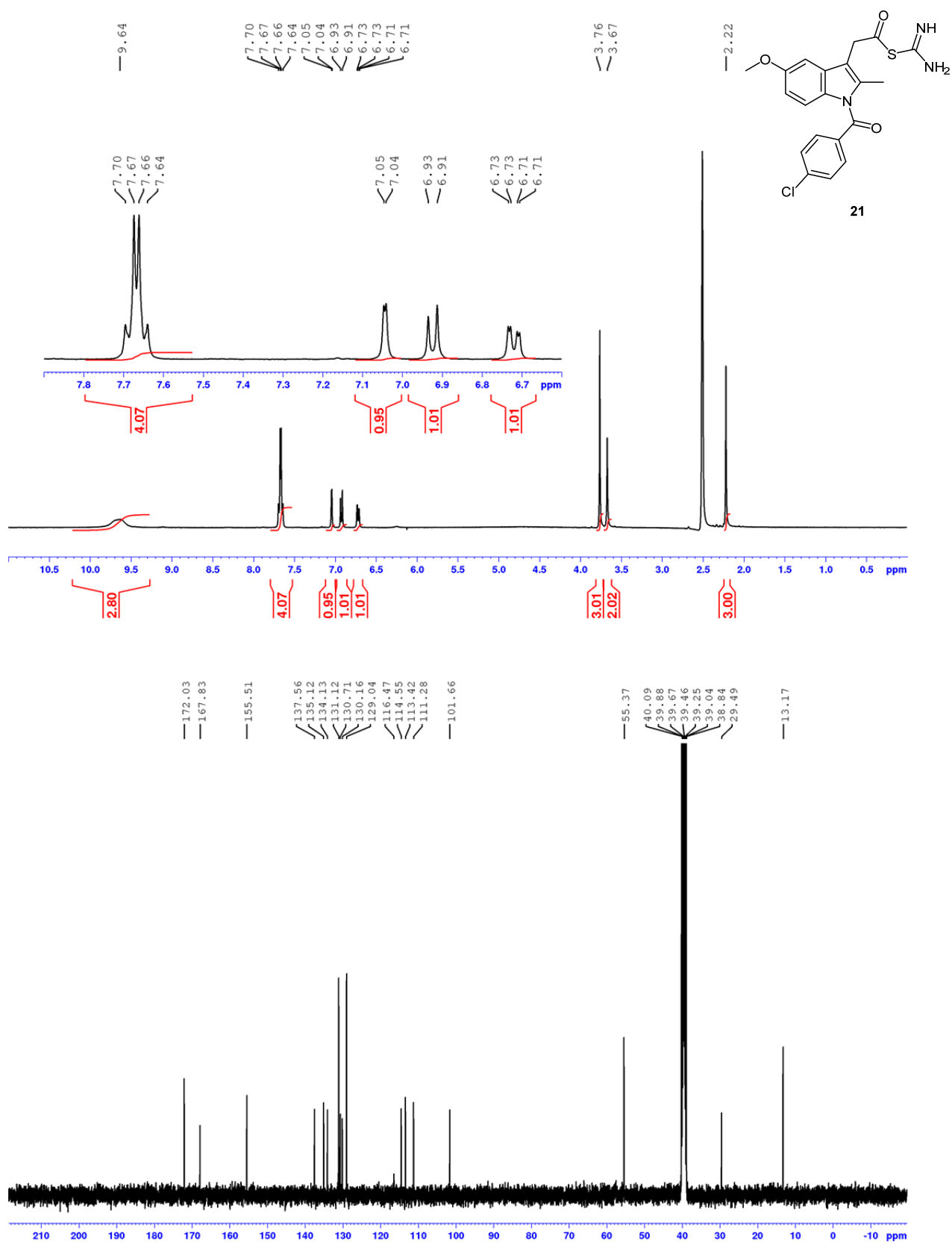
S.4.17 Aspirin Analogue (19)



S.4.18 – Ibuprofen Analogue (20)

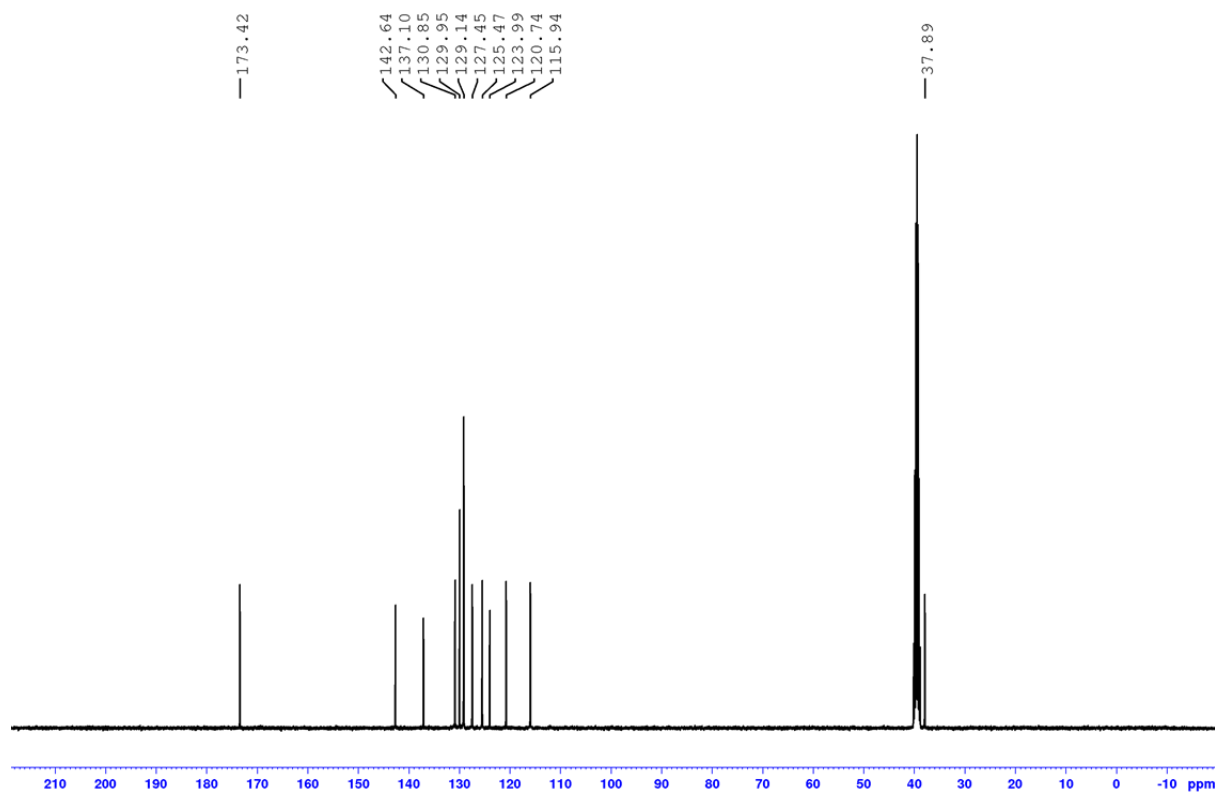
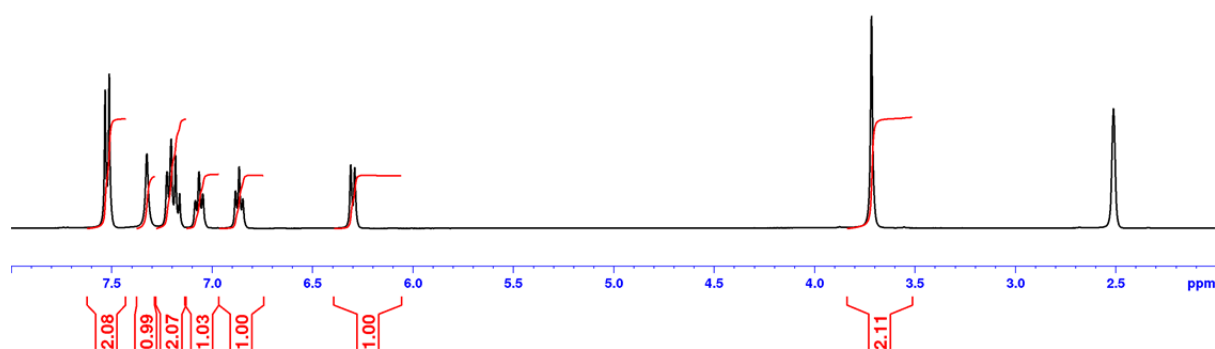
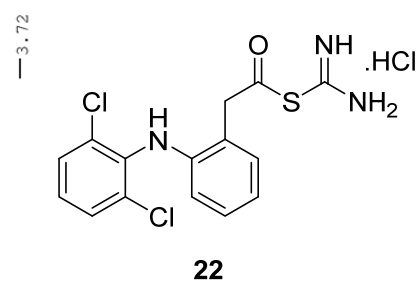


S.4.19 – Indomethacin Analogue (21)



S.4.20 – Diclofenac Analogue (22)

7.53
7.51
7.32
7.22
7.20
7.18
7.16
7.08
7.06
7.05
6.88
6.86
6.85
6.31
6.29



Crystallographic data for compound (5)

Bond precision: C-C = 0.0034 Angstrom Wavelength=0.71073

Cell: a=6.3248(12) b=17.819(3) c=10.2503(16)

alpha=90 beta=103.617(6) gamma=90

Temperature: 300 K

	Calculated	Reported
Volume	1122.8(3)	1122.8(4)
Space group	P 21/c	P 1 21/c 1
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C ₉ H ₁₁ N ₂ O ₂ SCl	C ₉ H ₁₁ N ₂ O ₂ SCl
Sum formula	C ₉ H ₁₁ ClN ₂ O ₂ S	C ₉ H ₁₁ ClN ₂ O ₂ S
Mr	246.71	246.71
Dx,g (cm⁻³)	1.459	1.460
Z	4	4
Mu (mm⁻¹)	0.508	0.508
F(000)	512.0	512.0
F(000')	513.27	----
h,k,l max	7, 21, 12	7, 21, 12
Nref	2128	2111
Tmin, Tmax	0.841, 0.912	0.760, 0.910
Tmin'	0.822	

Correction method = # Reported T Limits: T_{min} = 0.760 T_{max} = 0.910

Data completeness = 0.992 Theta(max)= 25.670

R(reflections) = 0.0406(1620) wR2(reflections) = 0.1060(2111)

S = 1.068 Npar= 153

References

1. Biancalana, L.; Batchelor, L. K.; De Palo, A.; Zacchini, S.; Pampaloni, G.; Dyson, P. J.; Marchetti, F., *Dalton Transactions* **2017**, 46 (36), 12001-12004.
2. Spera, S.; Ikura, M.; Bax, A., *Journal of Biomolecular NMR* **1991**, 1 (2), 155-165.
3. aDixon, A. E.; Taylor, J., *Journal of the Chemical Society, Transactions* **1920**, 117 (0), 720-728;
bDixon, A. E.; Hawthorne, J., *Journal of the Chemical Society, Transactions* **1907**, 91 (0), 122-146.
4. Leitch, L. C.; Baker, B. E.; Brickman, L., *Canadian Journal of Research* **1945**, 23b (4), 139-157.