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Thieme

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.

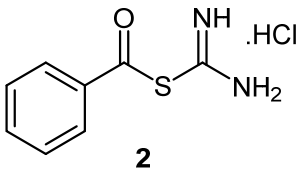
^{1}H and ^{13}C NMR spectra were obtained in DMSO-d_6 using TMS as an internal standard at 25 ^{o}C and were recorded on Brucker Advance 600, 400 or 300 spectrometers respectively. All spectra were obtained in University College Cork. Chemical shifts are expressed as parts per million (ppm) relative to TMS. Coupling constants (J) are expressed in hertz (Hz). Splitting patterns in ^{1}H 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 isothiouronium carbon (N=**C**H-N) was not observed by ^{13}C 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 NH_2=C-NH_2 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 ^{o}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 Isothiouronium Chloride (2)[3]



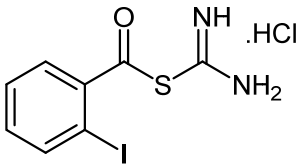
2

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

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

^{1}H NMR (400 MHz, DMSO-d_6): 7.49 (2H, t, *J* = 8.01 Hz, *m*-ArC**H**), 7.61 (1H, t, *J* = 8.01 Hz, *p*-ArC**H**), 7.94 (2H, d, *J* = 8.01 Hz, *o*-ArC**H**). 9.78 (4H, bs, N**H$_2$**=C-N**H$_2$**). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_8H_9NOS^{+}$ = 181.0430; Found = 181.0436. Anal. Calc'd for C_8H_9NOClS = C (44.34%), H (4.19%), N (12.93%); Found = C (44.21%), H (4.21%), N (13.01%)

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



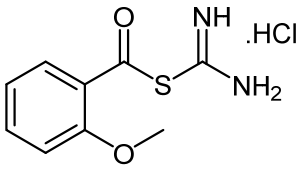
3

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

Melting Point (MeCN) = 190-192 ^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): 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**). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_8H_8IN_2OS^{+}$= 306.9397; Found = 306.9390. Anal. Calc'd for $C_8H_8ClIN_2OS$ = C (31.29%), H (2.63%); N (9.12%); Found = C (31.33%), H (2.48%); N (9.54%).

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



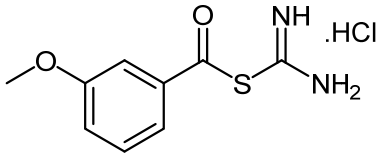
4

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

Melting Point (MeCN) = 169-171 ^{o}C.

^{1}H (400 MHz, DMSO-d_6): 3.81 (3H, s, OC**H$_3$**), 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, N**H$_2$**=C-N**H$_2$**) ^{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 $C_9H_{11}N_2O_2S^{+}$ = 211.0536; Found = 211.0536. Anal. Calc'd for $C_9H_{11}N_2O_2ClS$ = C (44.00%), H (4.10%), N (11.40); Found = C (44.38%), H (4.24%), N (11.71%).

S.3.4. *S*(3-Methoxybenzoyl) Isothiouronium Chloride (5)



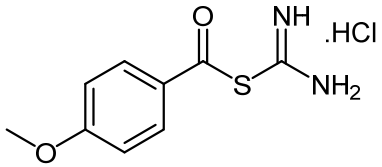
5

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

Melting Point (MeCN) = 166-168 ^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): 3.80 (3H, s, OC**H$_3$**), 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, N**H$_2$**=C-N**H$_2$**). ^{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 $C_9H_{11}N_2O_2S^{+}$ = 211.0536; Found = 211.0528. Anal. Calc'd for $C_9H_{11}N_2O_2ClS$ = C (44.00%), H (4.10%), N (11.40); Found = C (44.31%), H (4.18%), N (11.71%).

S.3.5. *S*(4-Methoxybenzoyl) Isothiouronium Chloride (6)



6

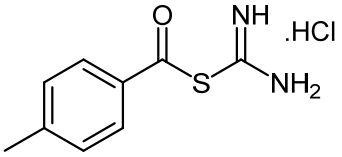
Isolated according to the general procedure as a colourless solid (209 mg, 1.00 mmol, 100%)

Melting Point (MeCN) = 167-169 ^{o}C

^{1}H NMR (400 MHz, DMSO-d_6): 3.82 (3H, s, OC**H$_3$**), 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, N**H$_2$**=C-N**H$_2$**). ^{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 $C_9H_{11}N_2O_2S^+$ = 211.0536; Found = 211.0537. Anal. Calc'd for $C_9H_{11}N_2O_2ClS$ = 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) Isothiouronium Chloride (7)



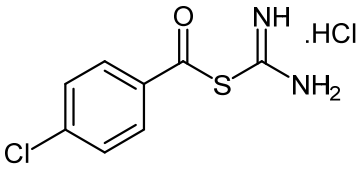
7

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

Melting Point (MeCN) = 138-139 ^oC.

^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, N**H**$_2$=C-N**H**$_2$). ^{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 $C_9H_{11}N_2OS^+$ = 195.0587; Found = 195.0589. Anal. Calc'd for $C_9H_{11}ClN_2OS$ = 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) Isothiouronium Chloride (8)



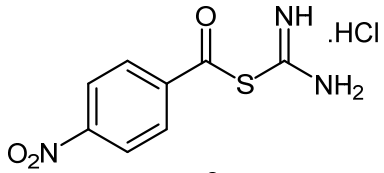
8

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

Melting Point (MeCN): 181-183 ^oC.

^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, N**H**$_2$=C-N**H**$_2$). ^{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 $C_8H_8ClN_2OS^+$ = 215.0040; Found = 215.0044. Anal. Calc'd for $C_8H_7Cl_2N_2OS$ = 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) Isothiouronium Chloride (9)



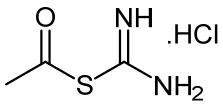
9

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

Melting Point (MeCN): 161 ^oC (Decomposition).

^{1}H 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 (NH_2=C-NH_2). ^{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 $C_8H_8N_3O_3S^+$ = 226.0281; Found = 226.0299. Anal. Calc'd for $C_8H_8ClN_3O_3S$ = C (36.72%), H (3.08%), N (16.06%)

S.3.9. *S*-(Acetyl) Isothiouronium Chloride (11)[3]



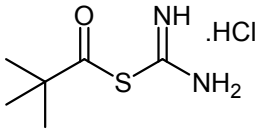
11

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

Melting Point (MeCN): 94-96 ^{o}C (Lit: 107-108 ^{o}C)[4]

^{1}H NMR (400 MHz, DMSO-d_6): 1.91 (3H, s, C**H**$_3$), 9.57 (4H, bs, N**H**$_2$=C-N**H**$_2$). ^{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 $C_3H_7N_2OS^+$ = 119.0279; Found = 119.0274. Anal. Calc'd for $C_3H_7N_2OClS$ = C (23.31%), H (4.56%), N (18.12%); Found = C (23.33%), H (4.61%), N (18.21%).

S.3.10. *S*-(Pivaloyl) Isothiouronium Chloride (12)



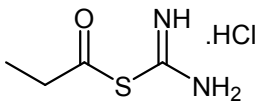
12

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

Melting Point (MeCN): 140-142 ^{o}C

^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (9H, s, C(C**H**$_3$)), 9.42 (4H, bs, N**H**$_2$=C-N**H**$_2$). ^{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 $C_6H_{13}N_2OS$ = 161.0749; Found = 161.0735. Anal. Calc'd for $C_6H_{13}N_2ClOS$ = C (36.64%), H (6.66%), N (14.24%); Found = C (36.88%), H (7.01%), N (14.59%).

S.3.11. *S*-(Propanoyl) Isothiouronium Chloride (13)[4]



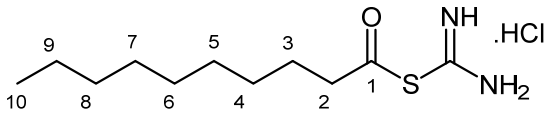
13

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

Melting Point (MeCN): 121-125 ^{o}C (Lit: 95-100 ^{o}C)[4]

^{1}H NMR (400 MHz, DMSO-d_6): 0.96 (3H, t, *J* = 7.48 Hz, CH_2C**H**$_3$), 2.19 (4H, q, *J* = 7.48 Hz, C**H**$_2$$CH_3$), 8.48 (4H, bs, N**H**$_2$=C-N**H**$_2$). ^{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 $C_4H_9N_2OS^+$ = 133.0430; Found = 133.0421.

S.3.12. *S*-(Decanoyl) Isothiouronium Chloride (14)



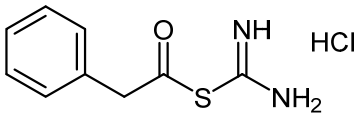
14

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

Melting Point (MeCN): 115-117 ^{o}C

^{1}H NMR (400 MHz, DMSO-d_6): 0.86 (3H, t, *J* = 7.51 Hz, C**H$_3$**(10)), 1.24 (12H, m, C**H$_2$**(9-4)), 1.46-1.50 (2H, m, C**H$_2$**(3)), 2.18 (2H, t, *J* = 7.88 Hz, C**H$_2$**(2)), 9.18 (4H, bs, N**H$_2$**=C-N**H$_2$**). ^{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 $C_{11}H_{23}N_2OS$ = 231.1531; Found = 231.1536. Anal. Calc'd for $C_{11}H_{23}N_2OClS$ = C (49.52%), H (8.69%), N (10.50%); Found = C (49.18%), H (8.75%), N (10.71%).

S.3.13. *S*-(Phenylacetyl) Isothiouronium Chloride (15)



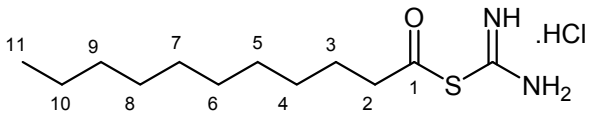
15

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

Melting Point (MeCN): 81-83 ^{o}C

^{1}H NMR (400 MHz, DMSO-d_6): 3.56 (2H, s, C**H$_2$**), 7.24-7.32 (5H, m, overlapping ArC(2,3,4,5,6)**H**), 9.50 (4H, bs, N**H$_2$**=C-N**H$_2$**). ^{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 $C_9H_{11}N_2OS^{+}$ = 195.0592; Found = 195.0583. Anal. Calc'd for $C_9H_{11}N_2OClS$ = C (55.65%), H (5.19%), N (14.42%); Found = C (55.01%), H (5.34%), N (14.84%).

S.3.14. *S*-(Undecanoyl) Isothiouronium Chloride (16)



16

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

Melting Point (MeCN): 122-124 ^{o}C

^{1}H NMR (400 MHz, DMSO-d_6): 0.85 (3H, t, *J* = 7.55 Hz, C**H$_3$**(11)), 1.24 (14H, m, C**H$_2$**(10-4)), 1.47 (2H, m, C**H$_2$**(3)), 2.18 (2H, t, *J* = 7.88 Hz, C**H$_2$**(2)) 9.56 (bs, N**H$_2$**=C-N**H$_2$**). ^{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 $C_{12}H_{25}N_2OS^{+}$ = 245.1682; Found = 245.1691. Anal. Calc'd for $C_{12}H_{25}N_2OClS$ = C (51.32%), H (8.97%), N (9.97%); Found = C (51.44%) H (9.04%) N (10.14%).

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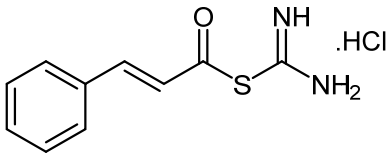
S.3.15. *S*-(Cinnamoyl) Isothiouronium Chloride (17)



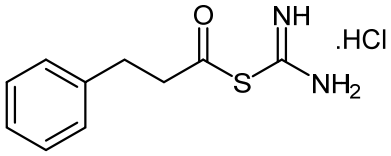
17

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

Melting Point (MeCN): 148-149 ^{o}C

^{1}H NMR (400 MHz, DMSO-d_6): 6.54 (1H, d, *J* = 17.56 Hz, α-C**H**), 7.41-7.70 (6H, m, overlapping ArC(2, 3, 4, 5, 6 and β-C**H**), 9.55 (4H, bs, N**H$_2$**=C-N**H$_2$**). ^{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 $C_{10}H_{11}N_2OS^{+}$ = 207.0592; Found = 207.0585. Anal. Calc'd for $C_{10}H_{11}N_2OClS$ = C (49.48%), H (4.57%), N (11.54%); Found = C (50.01%), H (4.91%), N (4.88%).

S.3.16. *S*-(Dihydrocinnamoyl) Isothiouronium Chloride (18)



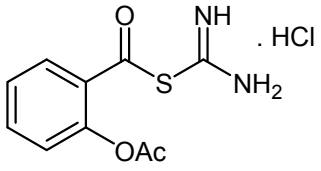
18

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

Melting Point (MeCN): 84-87 ^{o}C

^{1}H NMR (400 MHz, DMSO-d_6): 2.52 (2H, partially overlapping with DMSO residual peak, PhCH$_2$C**H$_2$**), 2.81 (2H, t, *J* = 6.83 Hz, PhC**H$_2$**CH$_2$), 7.17-7.26 (5H, m, ArC(2, 3, 4, 5 and 6)**H**), 9.77 (bs, N**H$_2$**=C-N**H$_2$**). ^{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 $C_{10}H_{13}N_2OS^{+}$ = 209.0755; Found = 209.0749. Anal. Calc'd for $C_{10}H_{13}N_2OClS$ = 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)



19

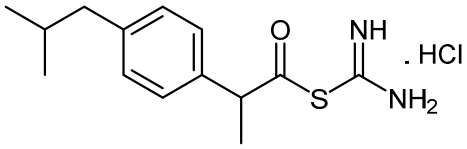
Isolated according to the general procedure as a colourless solid (239 mg, 1.00 mmol, 100%)

Melting Point (MeCN) = 97-99 ^{o}C

^{1}H NMR (400 MHz, DMSO-d_6): 2.24 (3H, s, C**H$_3$**), 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 $C_{10}H_{11}N_2O_3S^+$= 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)



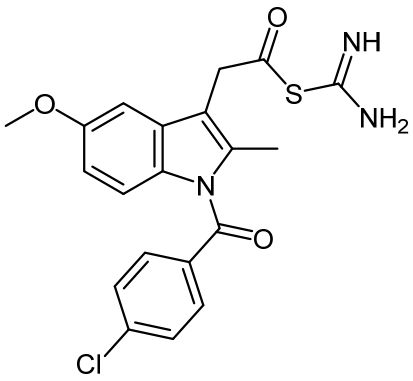
20

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

Melting Point (MeCN): 131-133 ^oC

^1H NMR (400 MHz, DMSO-d_6): 0.84 (6H, d, *J* = 7.54 Hz, (C**H**$_3$)$_2$CH), 1.33 (3H, d, *J* = 7.88 Hz, C**H**$_3$CH), 1.79 (1H, sept., *J* = 7.54 Hz, (CH_3)C**H**), 2.40 (2H, d, *J* = 7.55 Hz, C**H**$_2$), 3.62 (1H, q, *J* = 7.88 Hz, CH_3C**H**). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{14}H_{21}N_2OS^+$ = 265.1369; Found = 265.1377. Anal. Calc'd for $C_{14}H_{21}N_2OClS$ = 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)



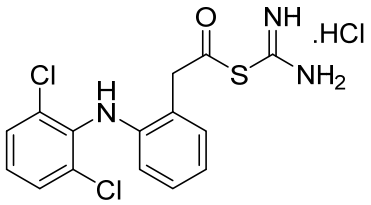
21

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

Melting Point (MeCN): 168-171 ^oC

^1H NMR (400 MHz, DMSO-d_6): 2.22 (3H, s, ArC**H**$_3$), 3.67 (2H, s, C**H**$_2$), 3.76 (3H, s, OC**H**$_3$), 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**). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{20}H_{19}ClN_3O_3S^+$ = 416.0830; Found 416.0851. Anal. Calc'd for $C_{20}H_{19}Cl_2N_3O_3S$ = 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%)

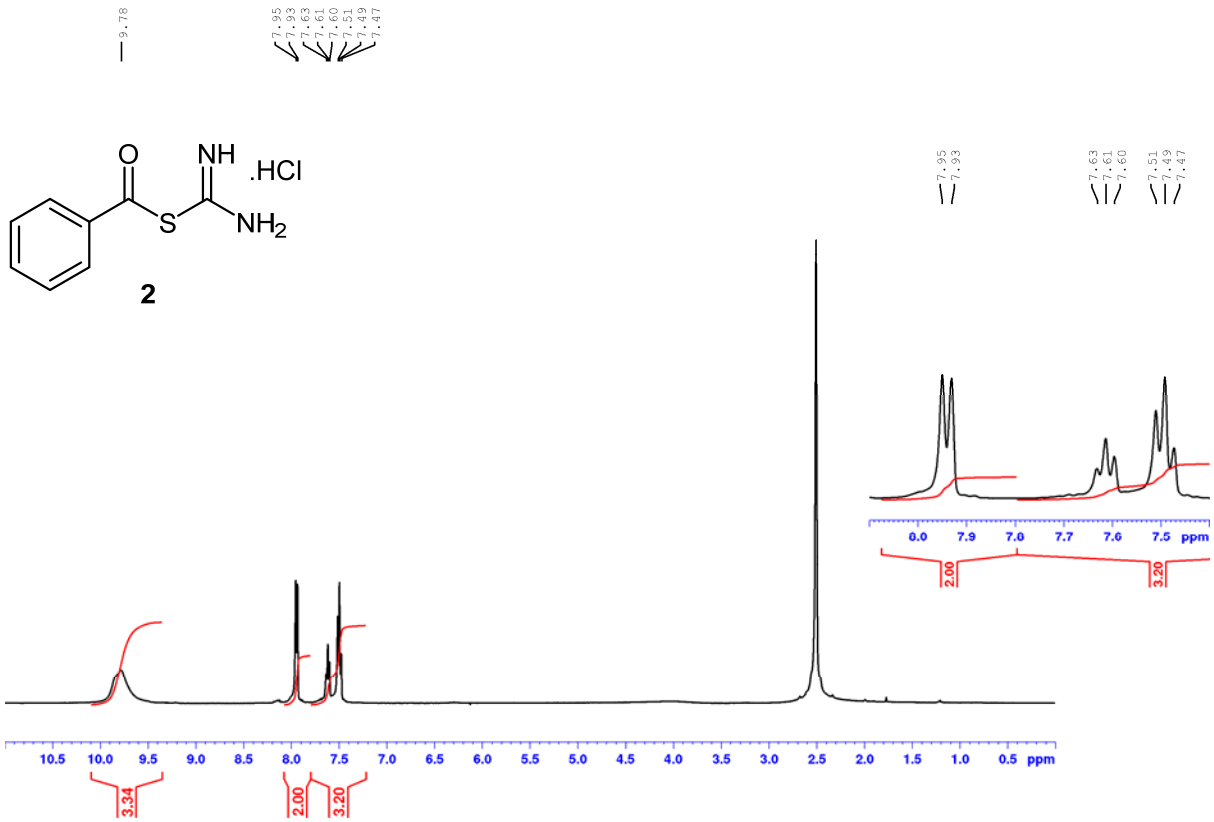
Melting Point (MeCN): 190-192 ^{o}C

^{1}H NMR (400 MHz, DMSO-d_6): 3.72 (2H, s, C**H$_2$**), 6.30 (1H, d, *J* = 8.14 Hz, Ar**H**), 6.86 (1H, t, *J* = 7.95 Hz, Ar**H**), 7.06 (1H, t, *J* = 7.95 Hz, Ar**H**), 7.16-7.22 (2H, m, 2xAr**H**), 7.32 (1H, s, Ar**H**), 7.51 (1H, s, Ar**H**), 7.53 (1H, s, Ar**H**). ^{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 $C_{15}H_{14}Cl_2N_3OS^{+}$ = 354.0230; Found 354.0239. Anal. Calc'd for $C_{15}H_{14}Cl_3N_3OS$ = C (43.11%) H (3.6%) N (10.76%); Found = C (43.81%) H (3.81%) N (10.91%).

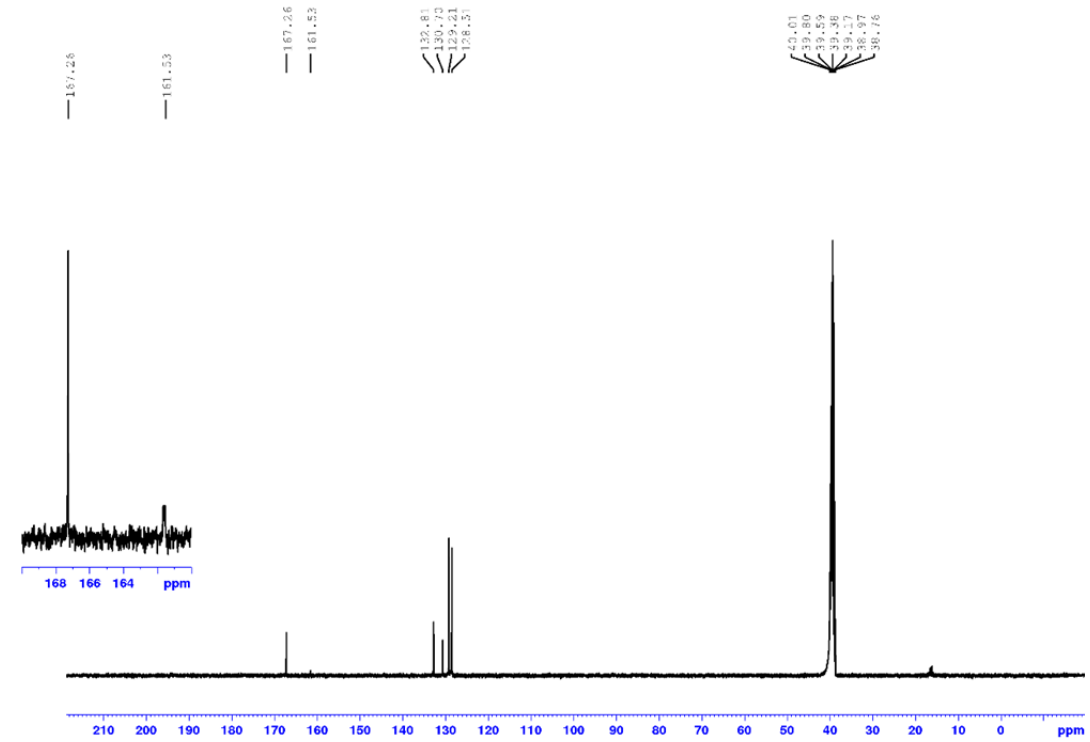
S.4. ^{1}H and ^{13}C NMR spectra for 2-21

S.4.1. *S*-(Benzoyl) Isothiouronium Chloride (2)

S-Benzoyl Isothiouronium Chloride

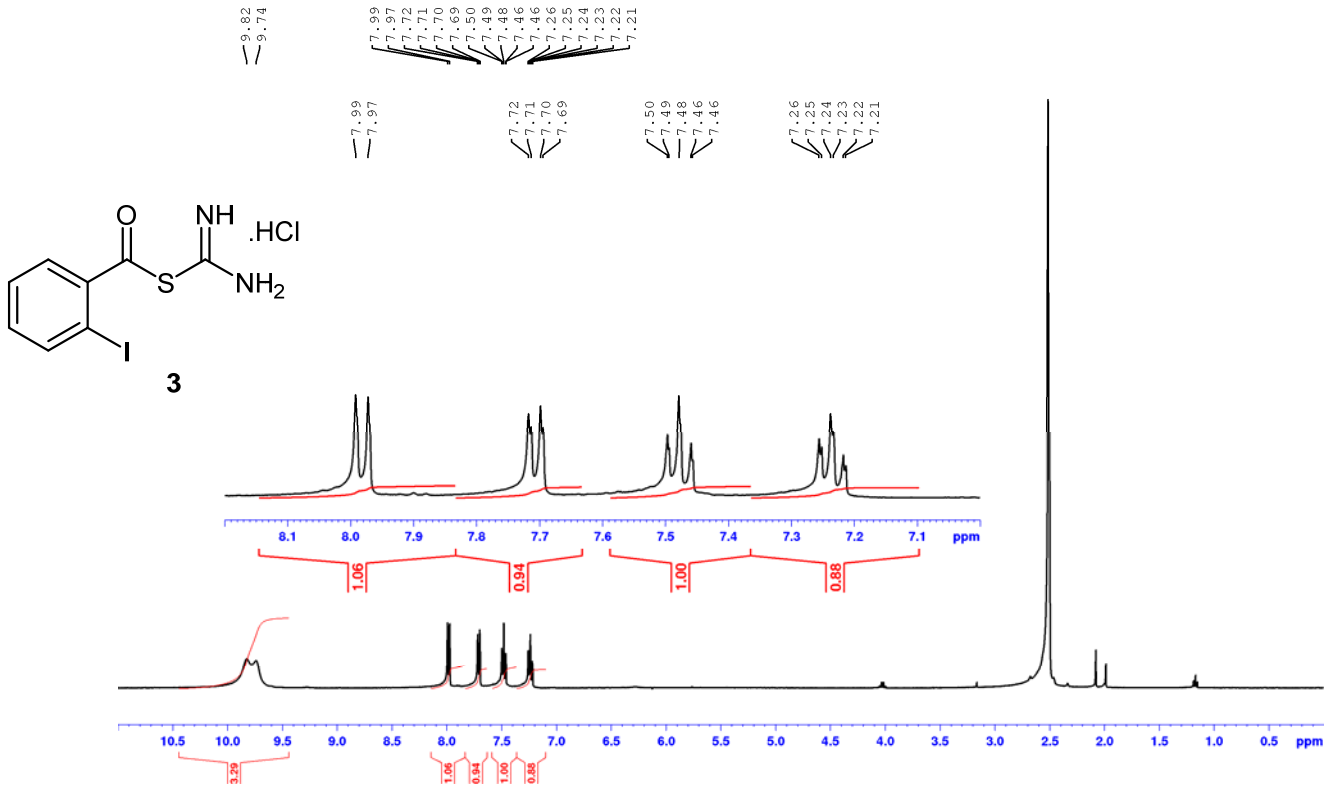


S-Benzoyl Isothiouronium Chloride (D1 Parameter = 4.0 seconds)

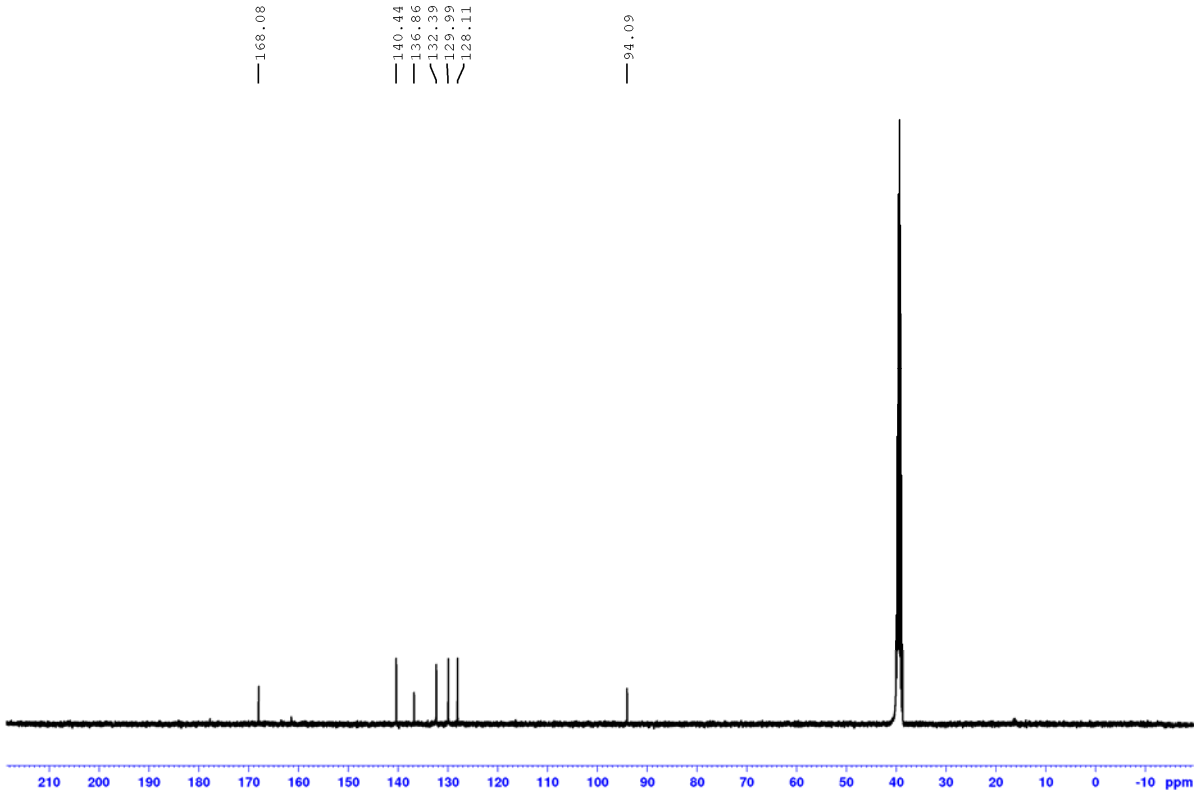


S4.2. *S*-(2-Iodobenzoyl) Isothiouronium Chloride (3)

S-(2-Iodobenzoyl) Isothiouronium Chloride

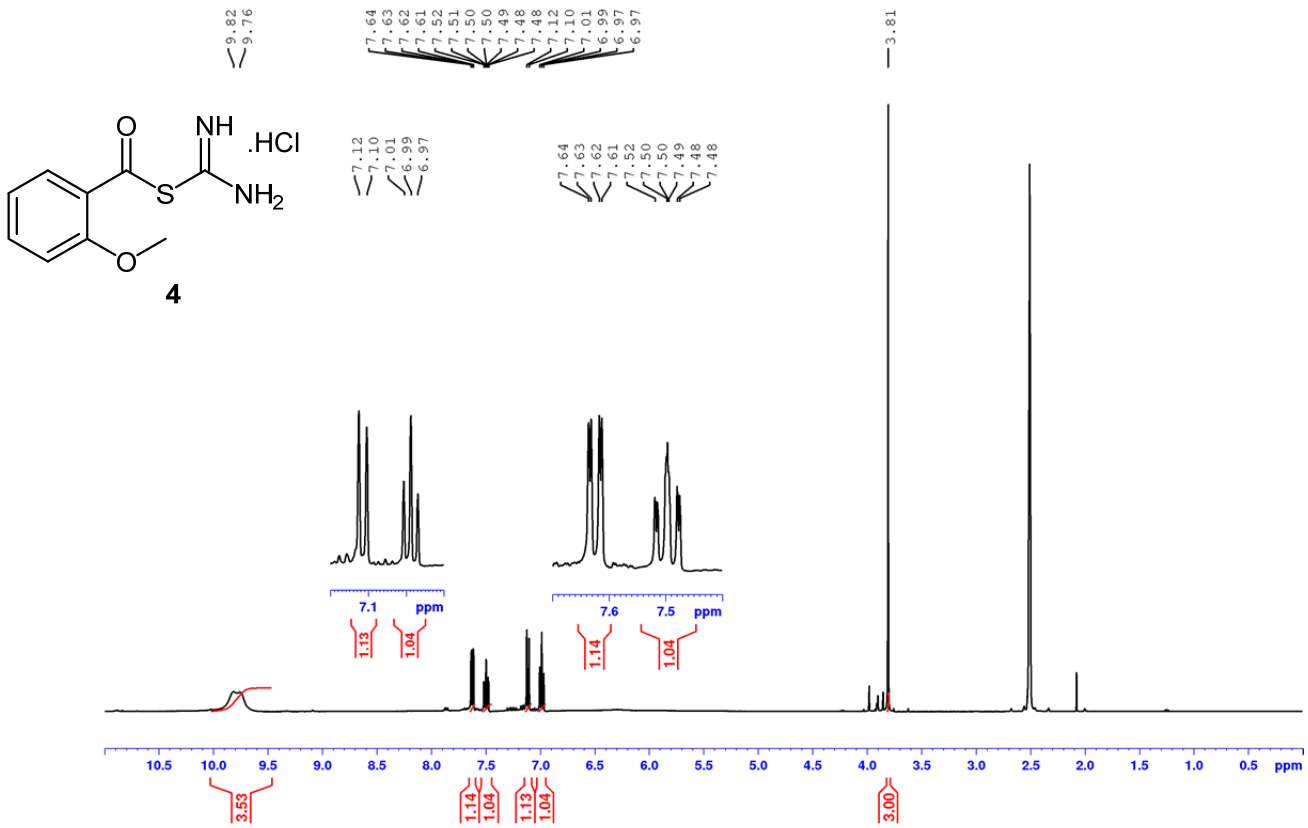


S-(2-Iodobenzoyl) Isothiouronium Chloride

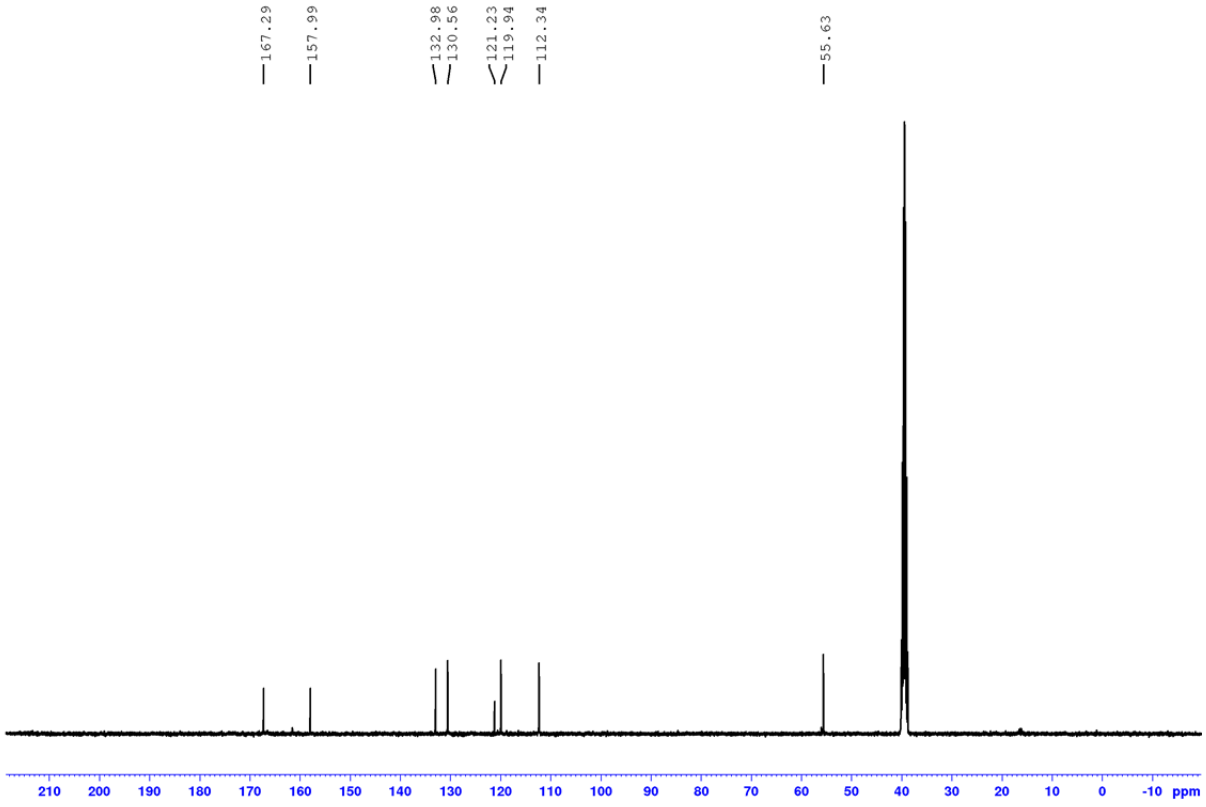


S.4.3. *S*(2-Methoxybenzoyl) Isothiouronium Chloride (4)

S-(2-Methoxybenzoyl) Isothiouronium Chloride

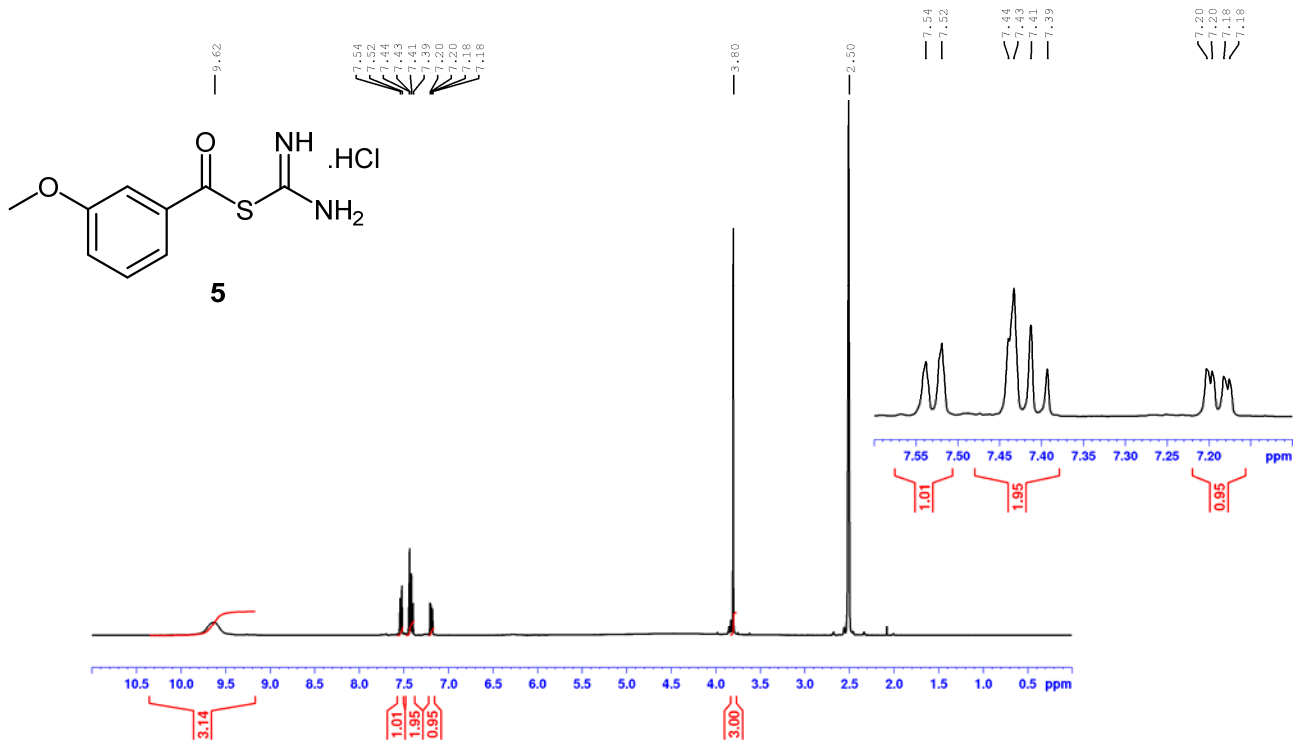


S-(2-Methoxybenzoyl) Isothiouronium Chloride

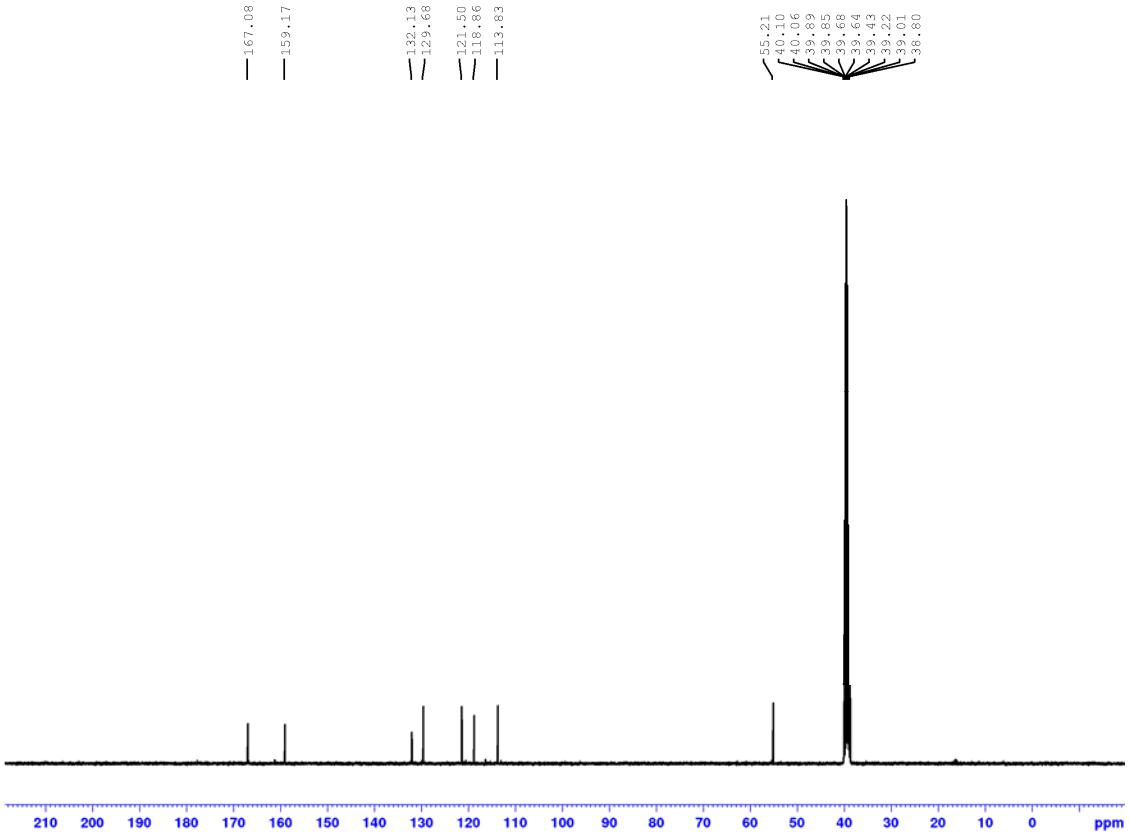


S.4.4. *S*(3-Methoxybenzoyl) Isothiouronium Chloride (5)

S-(3-Methoxybenzoyl) Isothiouronium Chloride

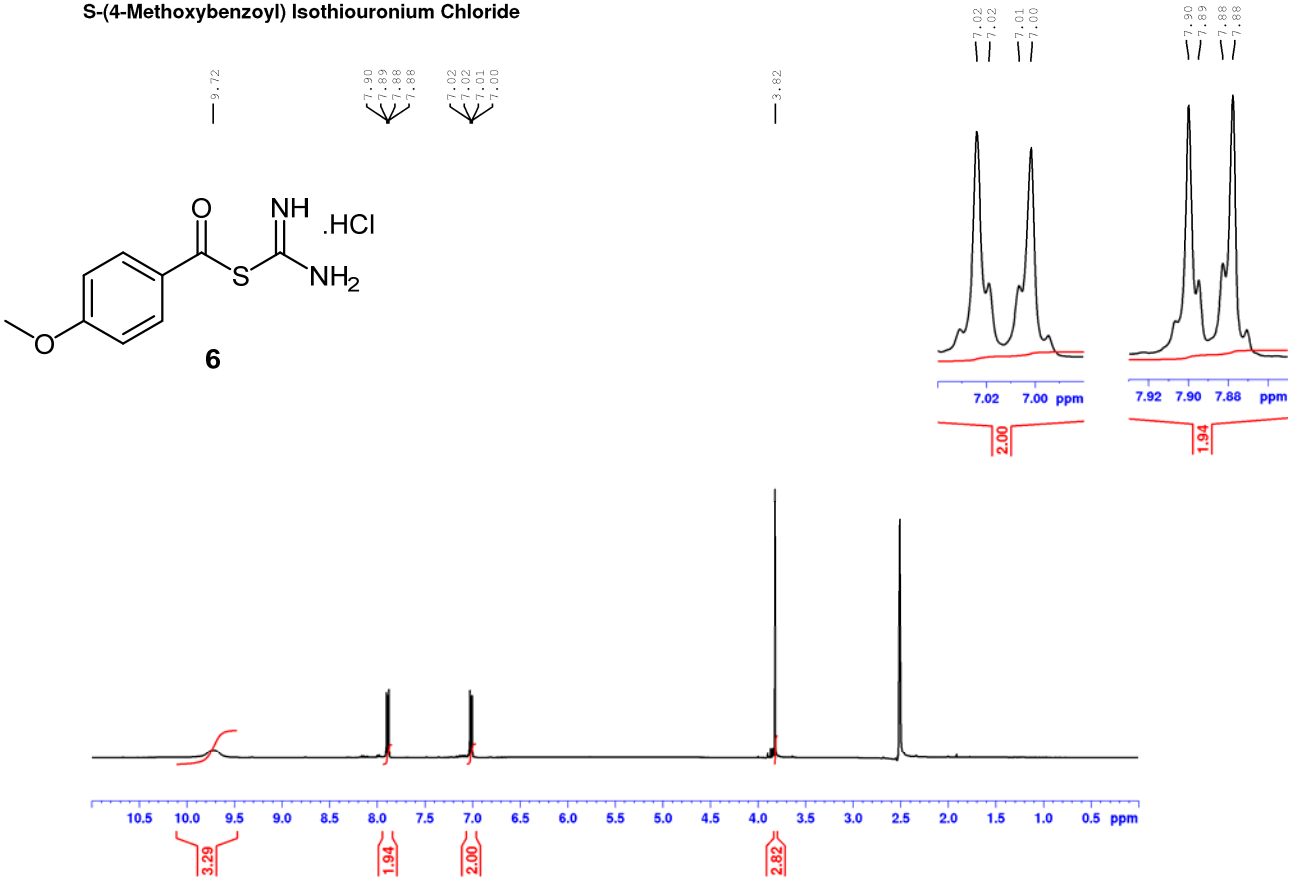


S-(3-methoxybenzoyl) Isothiouronium Chloride

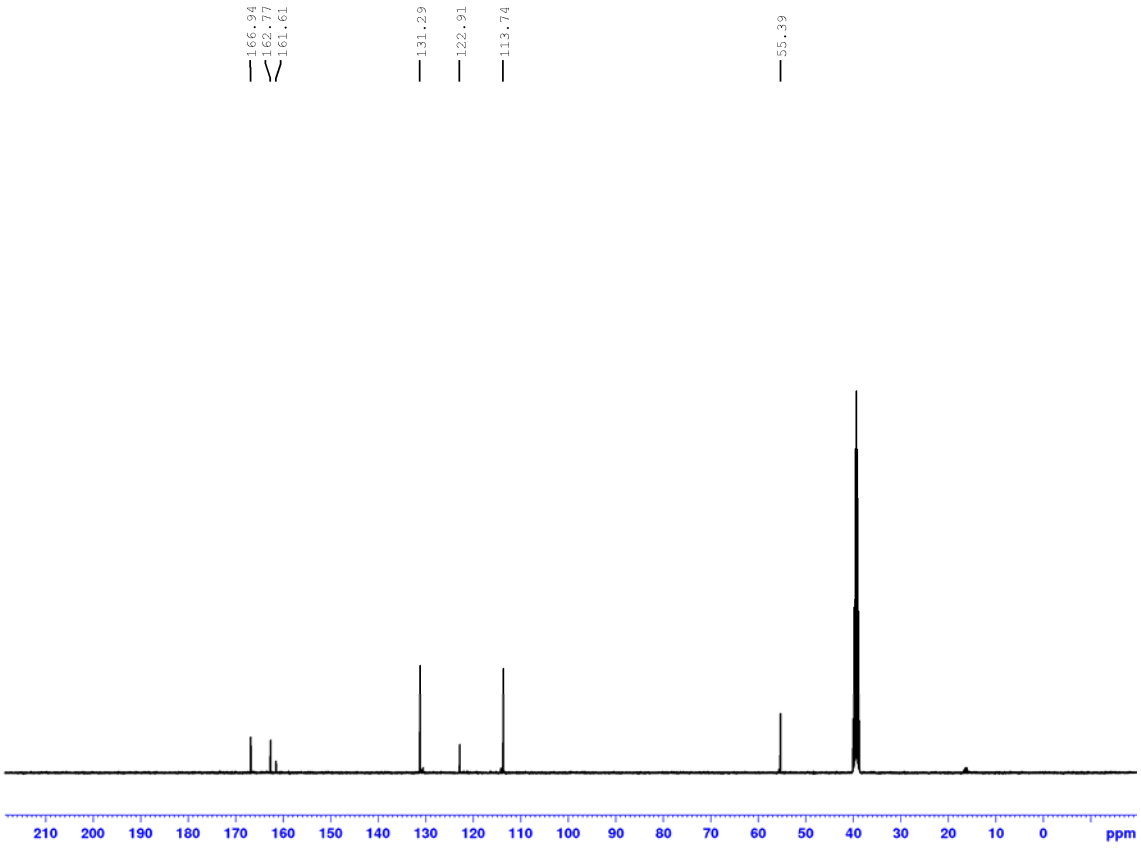


S.4.5. *S*(4-Methoxybenzoyl) Isothiouronium Chloride (6)

S-(4-Methoxybenzoyl) Isothiouronium Chloride

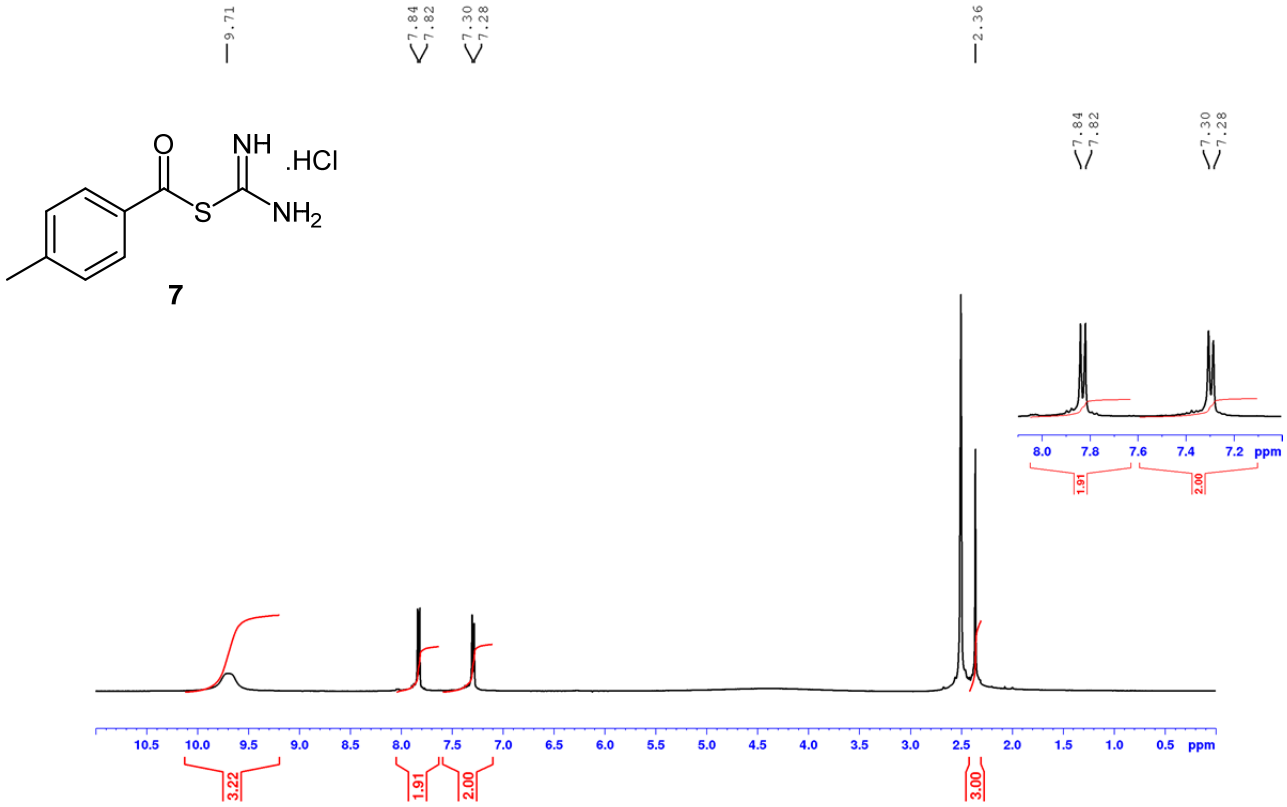


S-(4-Methoxybenzoyl) Isothiouronium Chloride

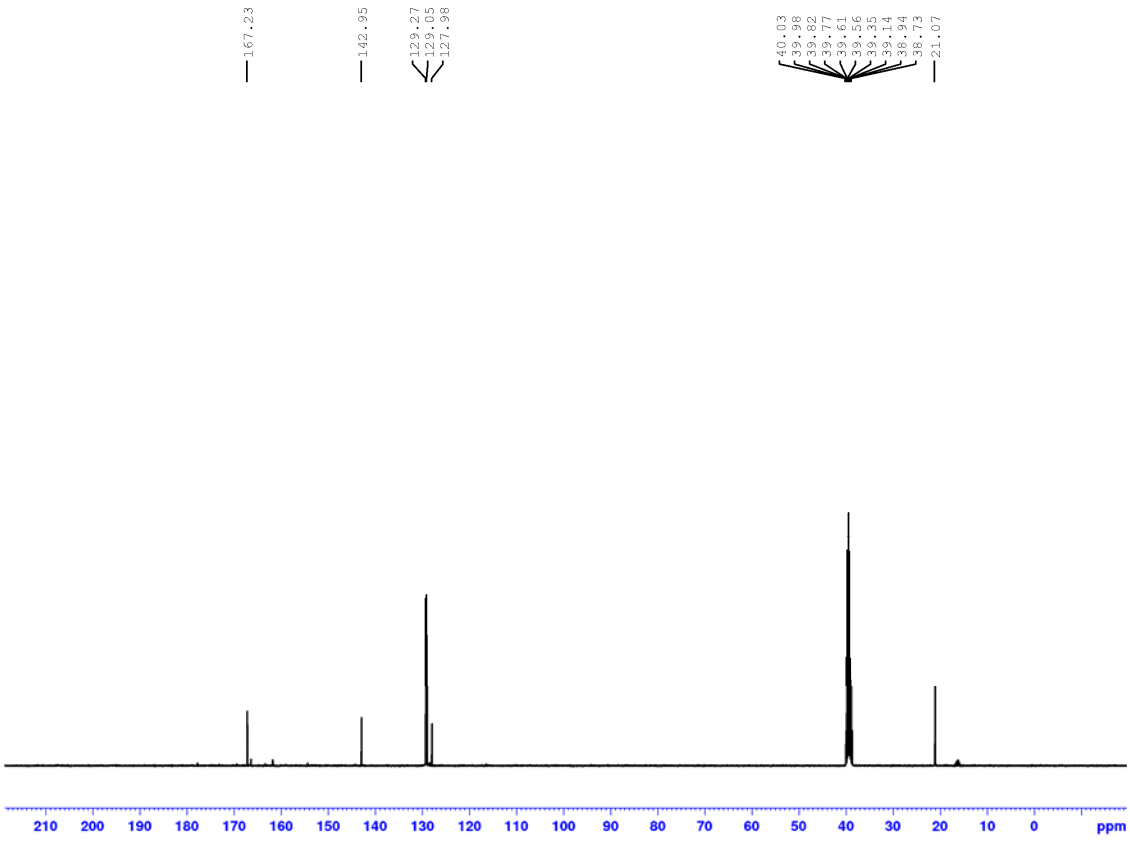


S.4.6. *S*(4-Methylbenzoyl) Isothiouronium Chloride (7)

S-(4-Methylbenzoyl) Isothiouronium Chloride

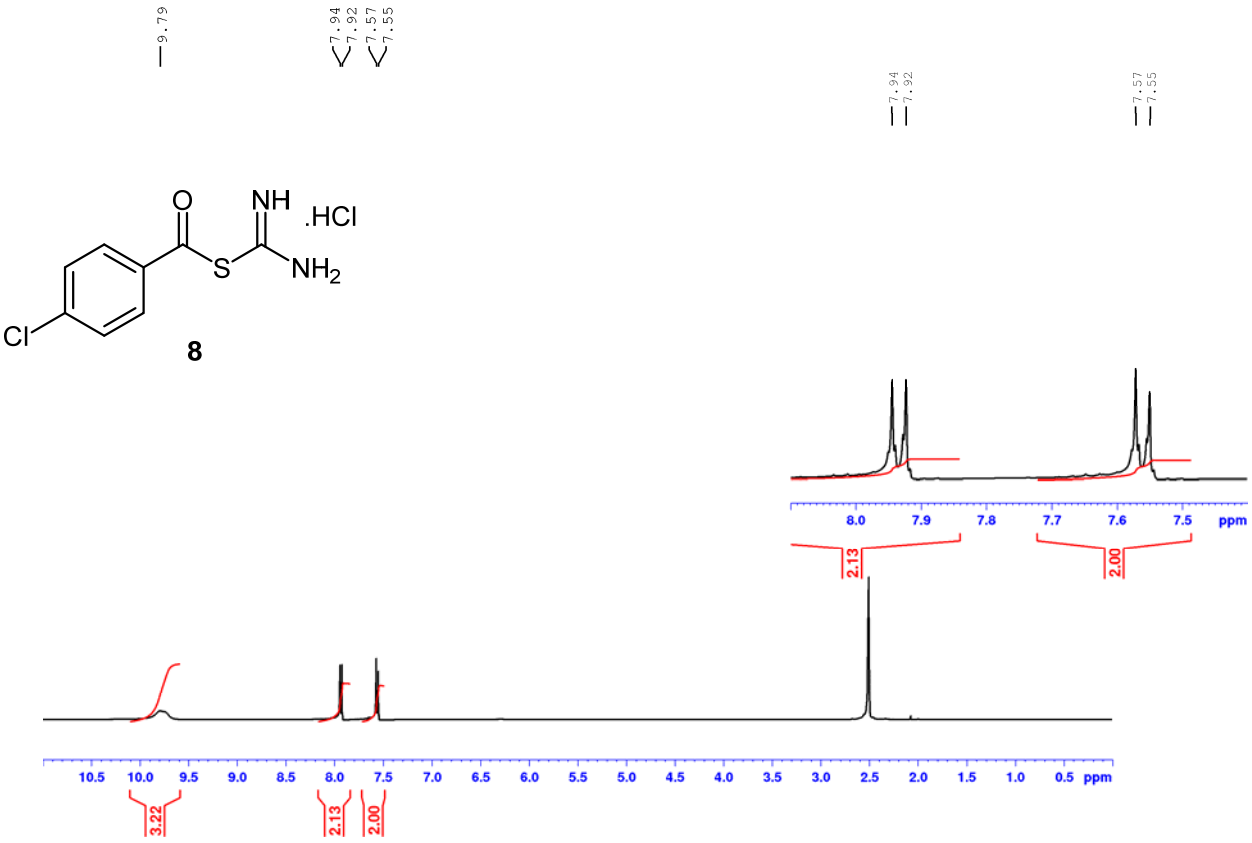


S-(4-Methylbenzoyl) Isothiouronium Chloride

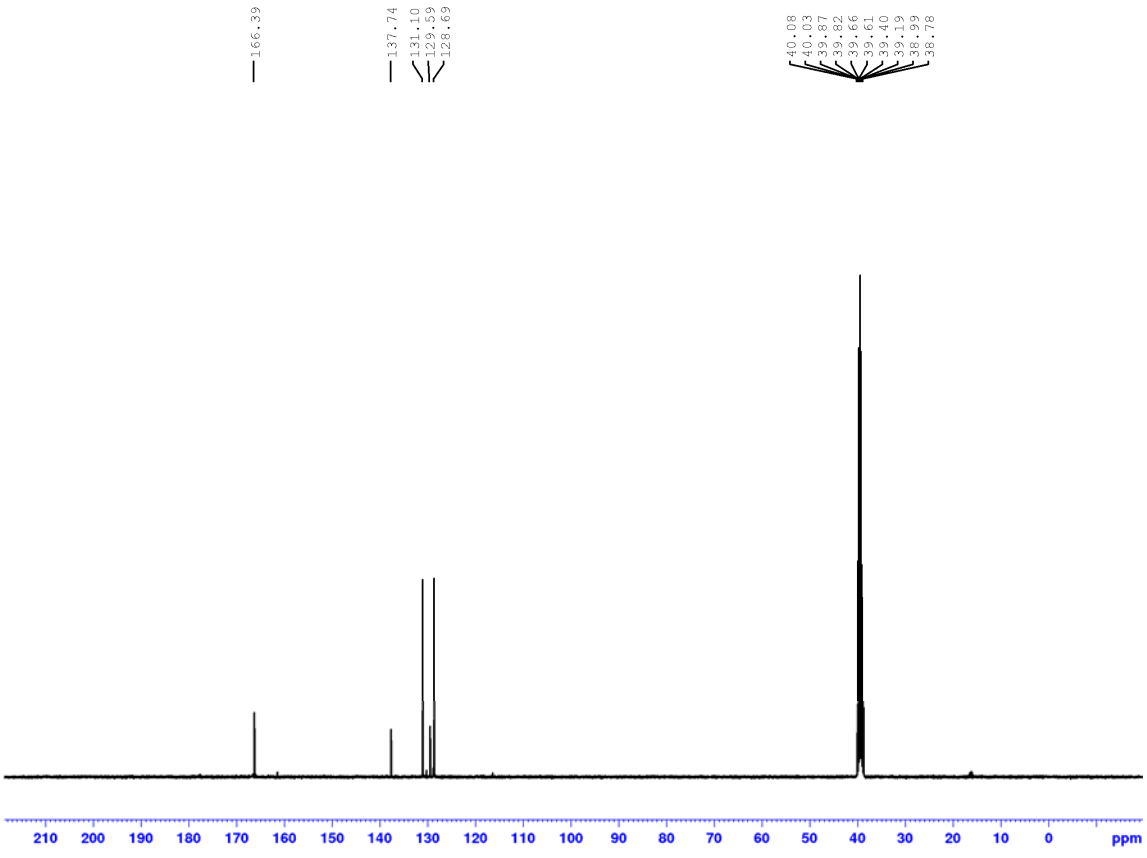


S.4.7. *S*(4-Chlorobenzoyl) Isothiouronium Chloride (8)

S-(4-chlorobenzoyl) isothiouronium Chloride

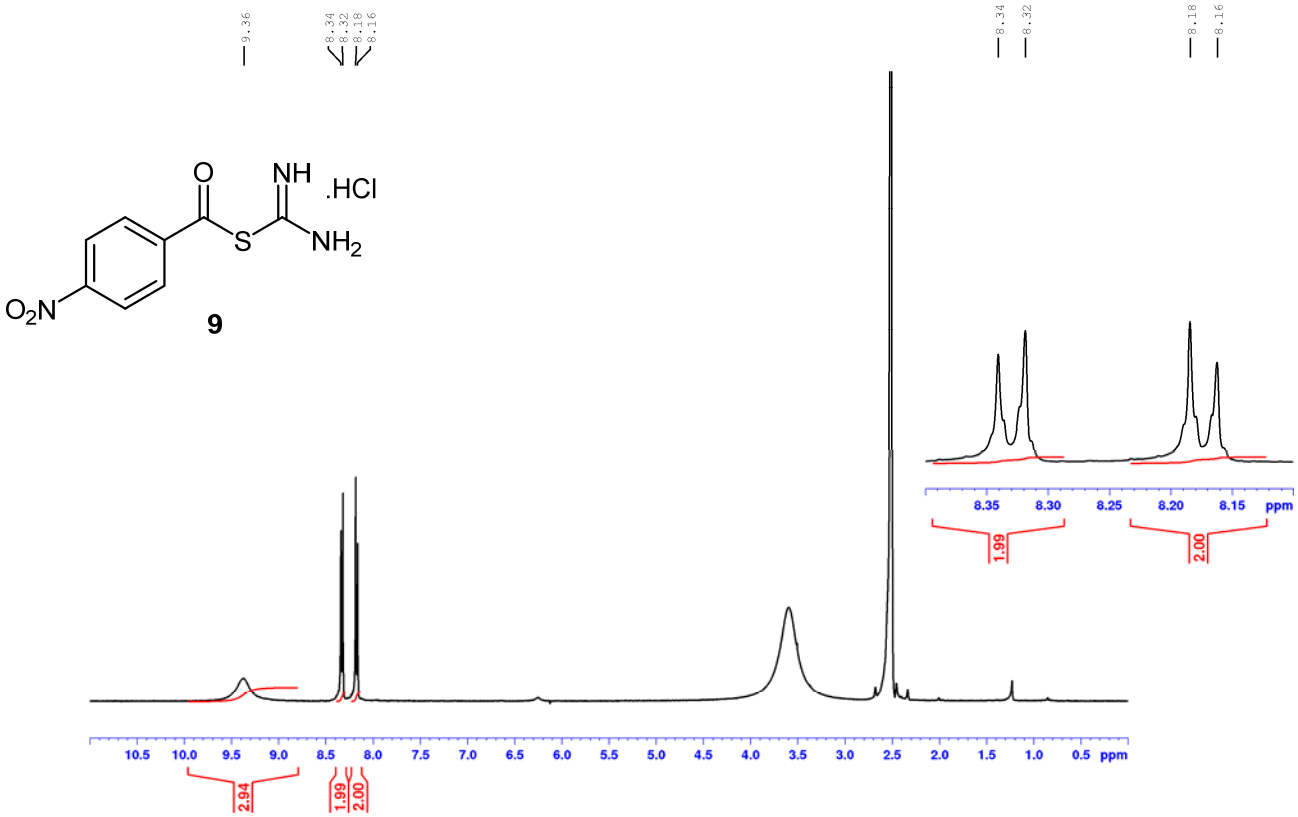


S-(4-Chlorobenzoyl) Isothiouronium Chloride

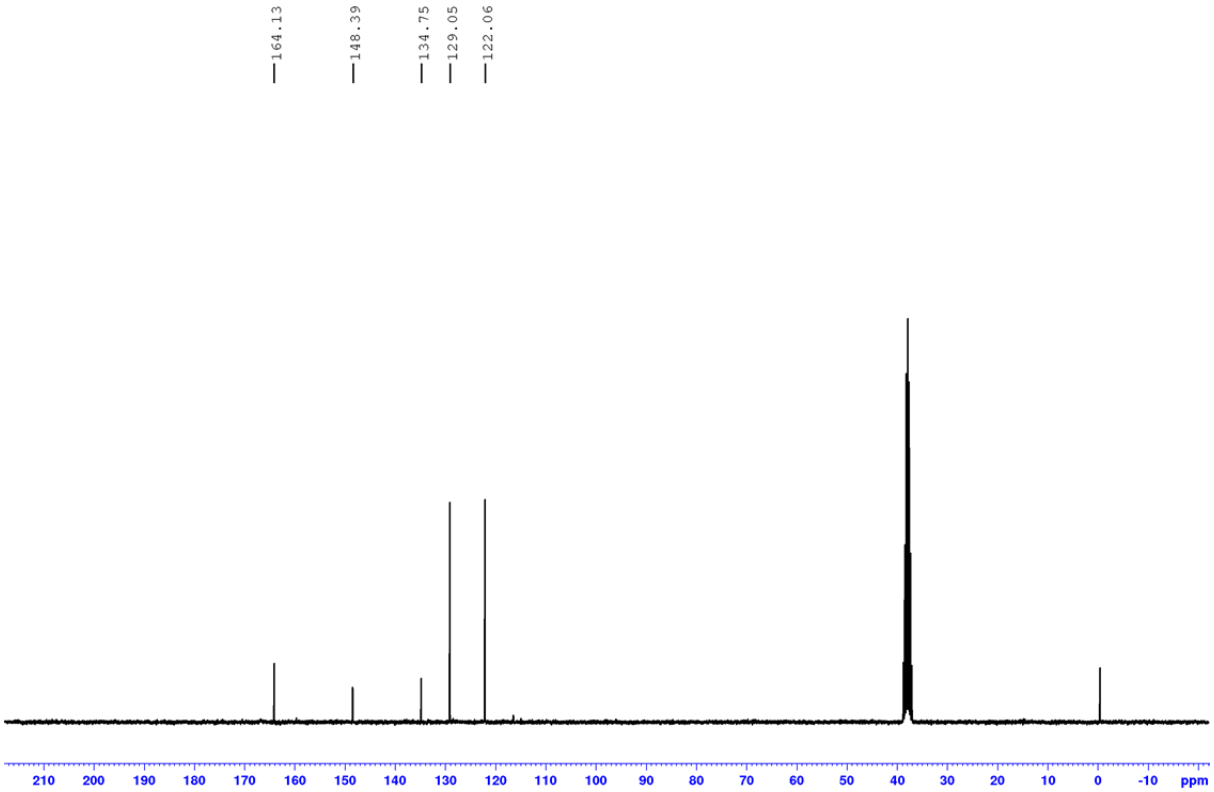


S.4.8. *S*(4-Nitrobenzoyl) Isothiouronium Chloride (9)

S-(4-Nitrobenzoyl) Isothiouronium Chloride

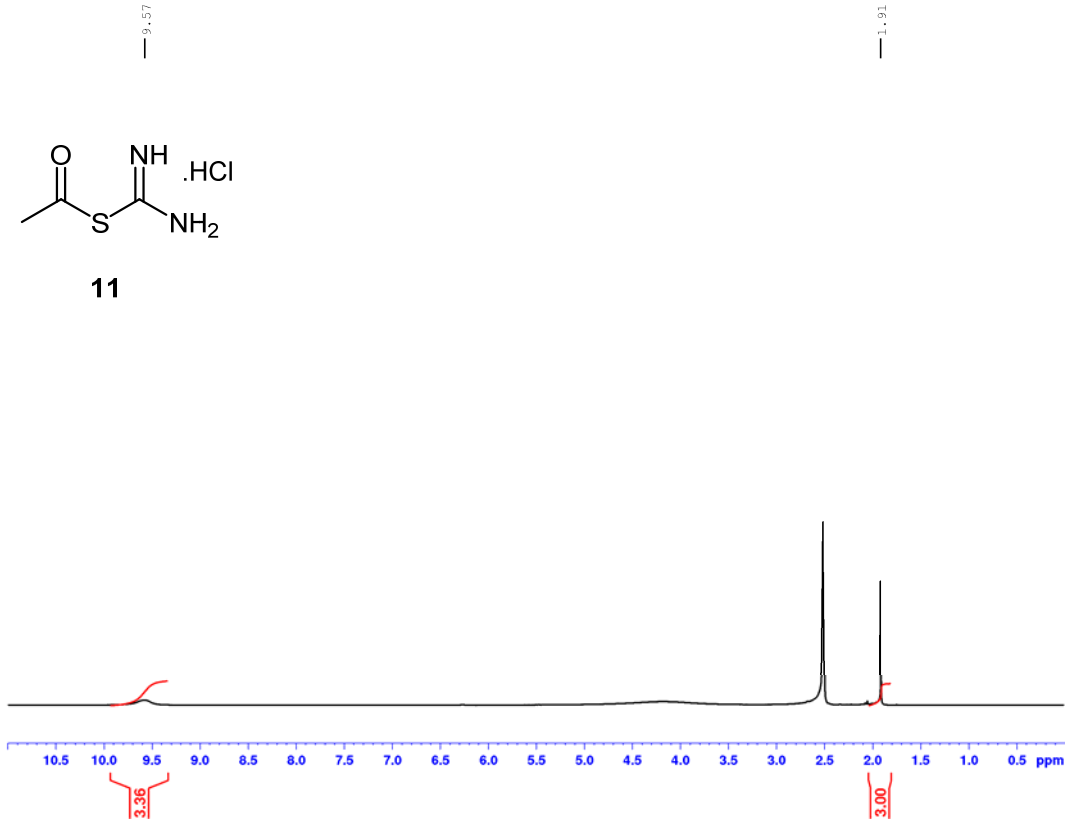


S-(4-Nitrobenzoyl) Isothiouronium Chloride



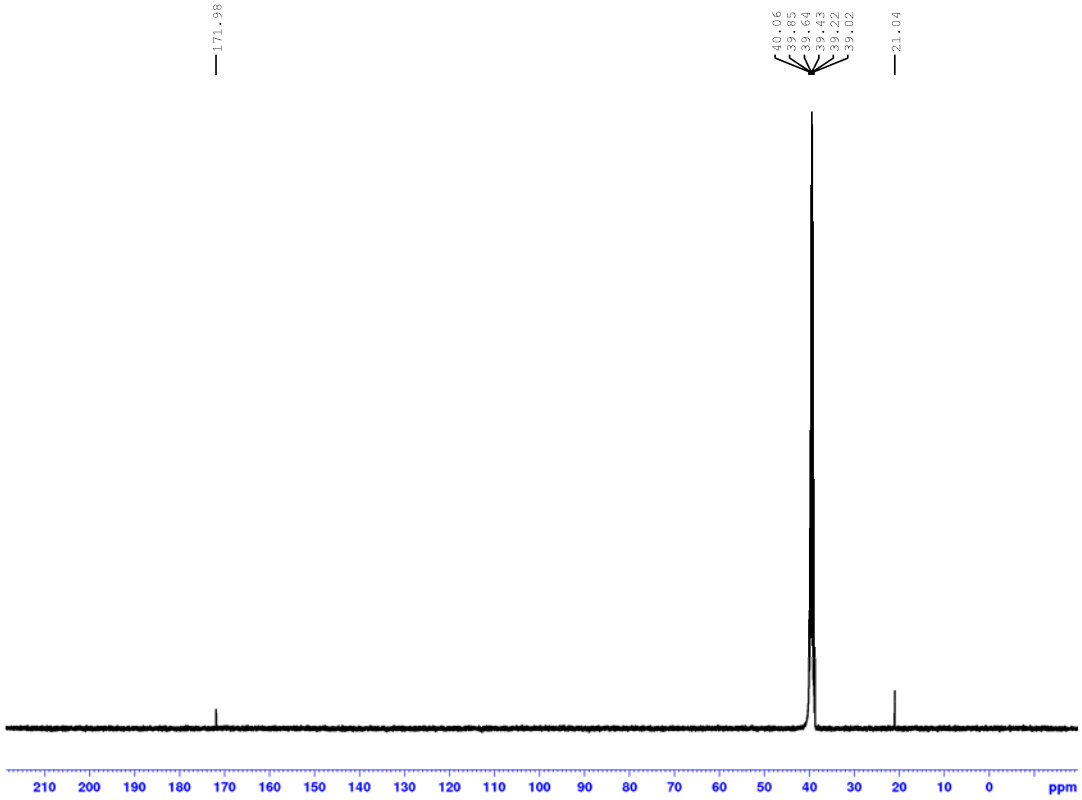
S.4.9. *S*-(Acetyl) Isothiouronium Chloride (11)

S-Acetyl Isothiouronium Chloride



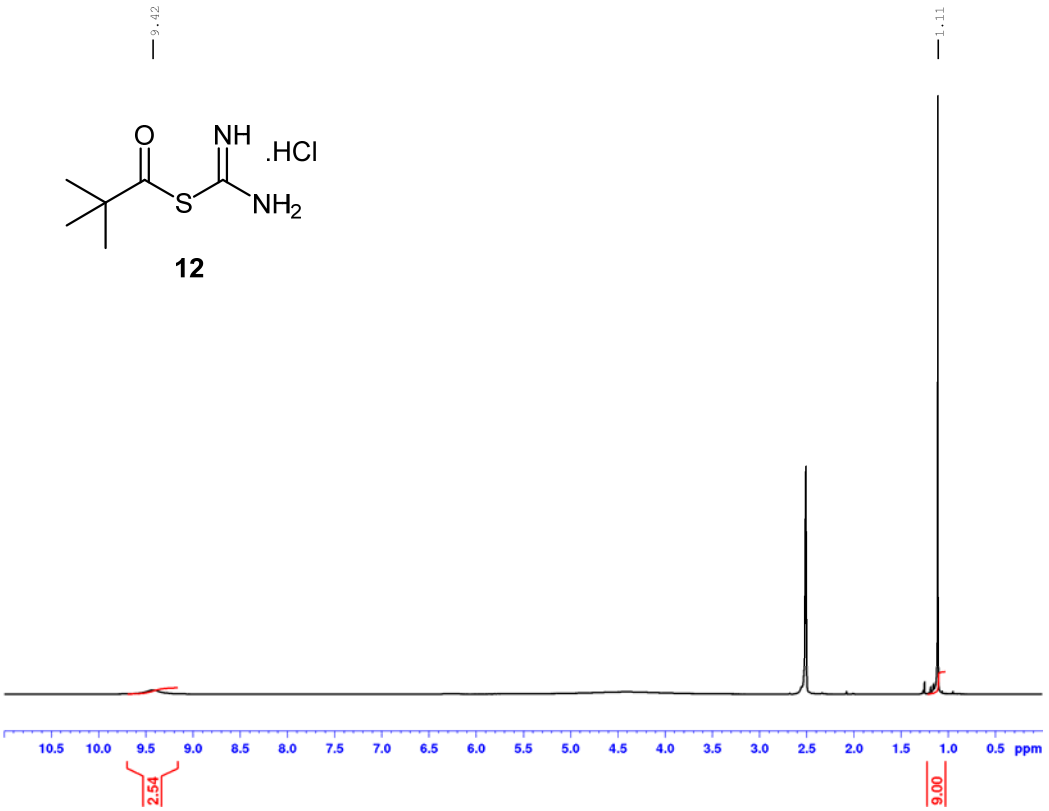
11

S-Acetyl Isothiouronium chloride

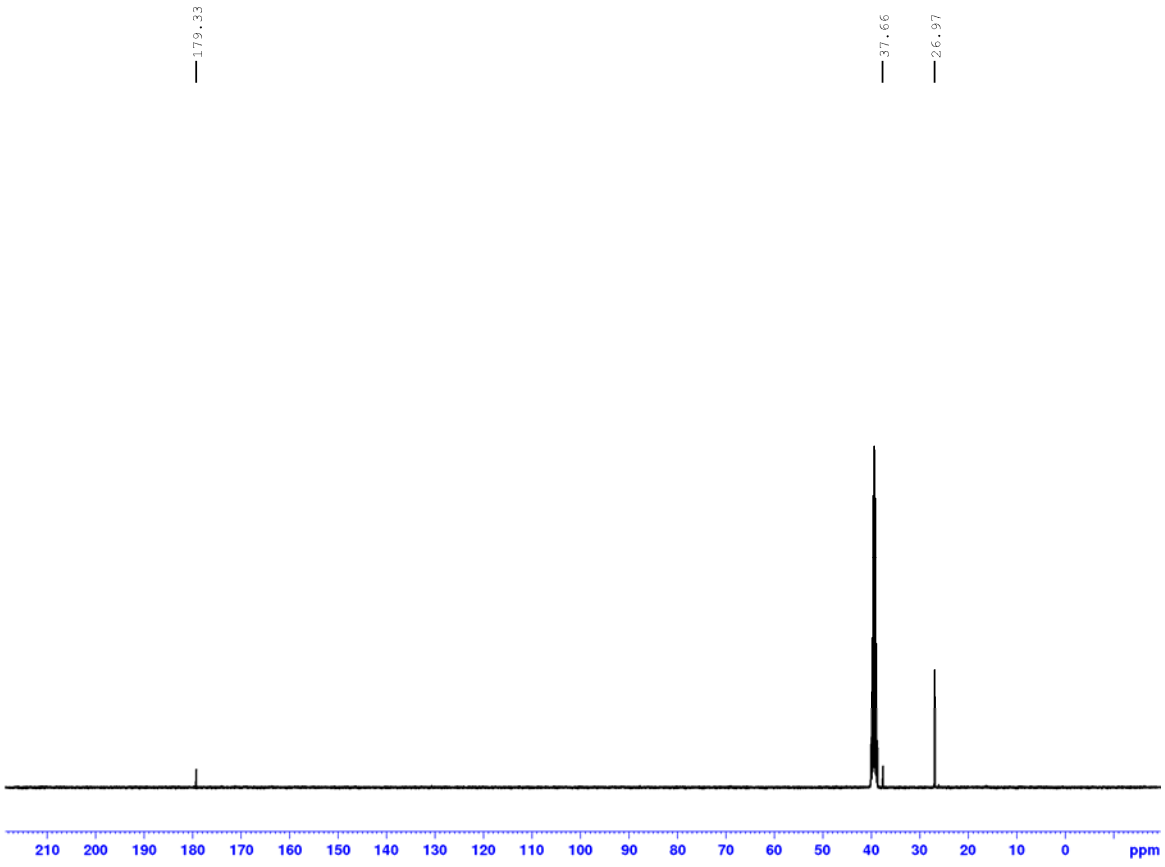


S.4.10 *S*-(Pivaloyl) Isothiouronium Chloride (12)

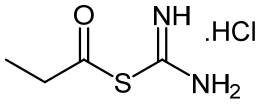
S-(2,2-dimethyacetyl) Isothiouronium Chloride



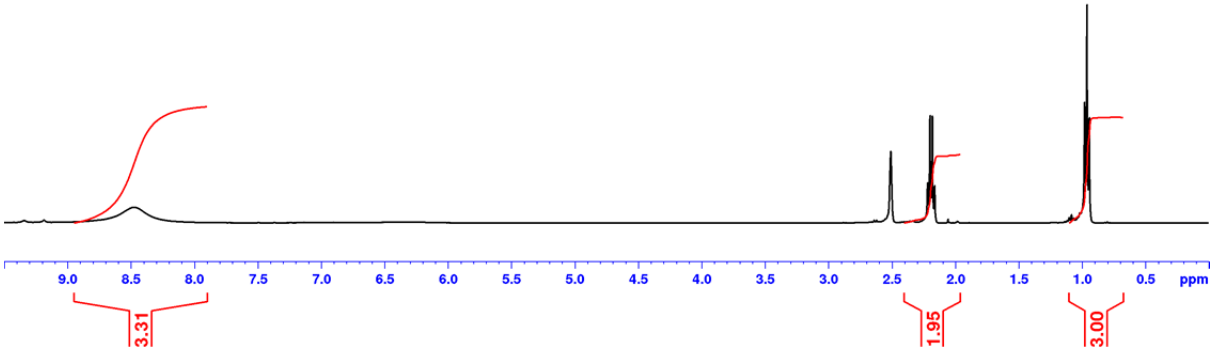
S-(2,2-dimethylacetyl) Isothiouronium Chloride

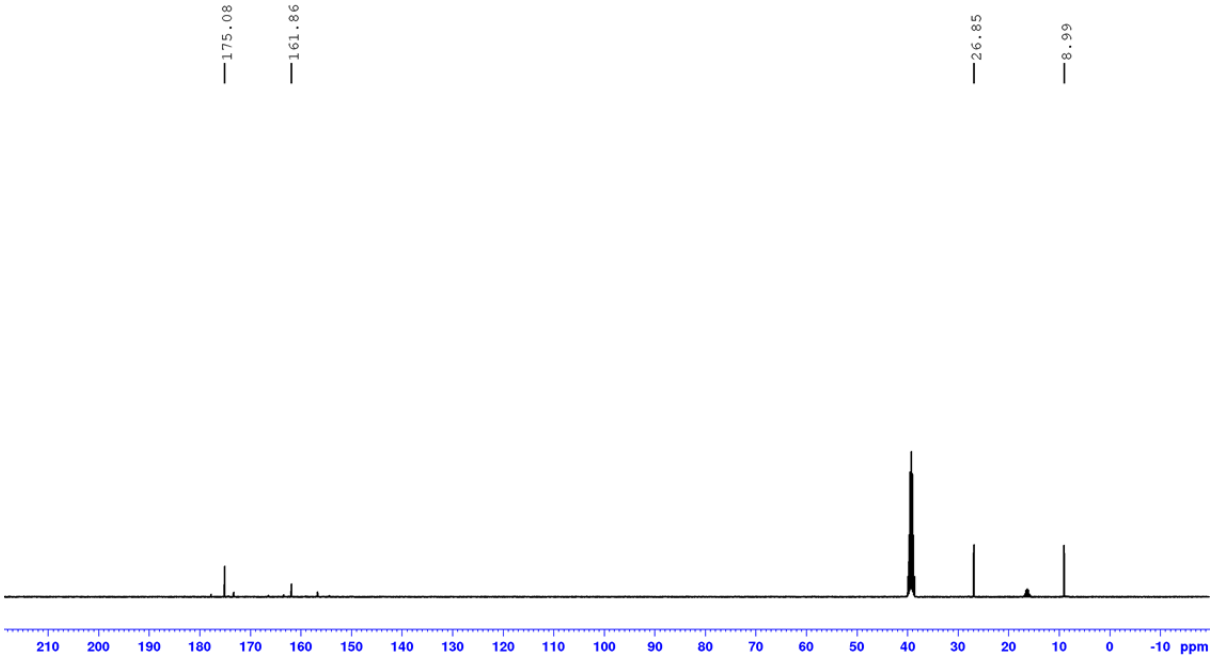


S.4.11. *S*-Propanoyl Isothiouronium Chloride (13)



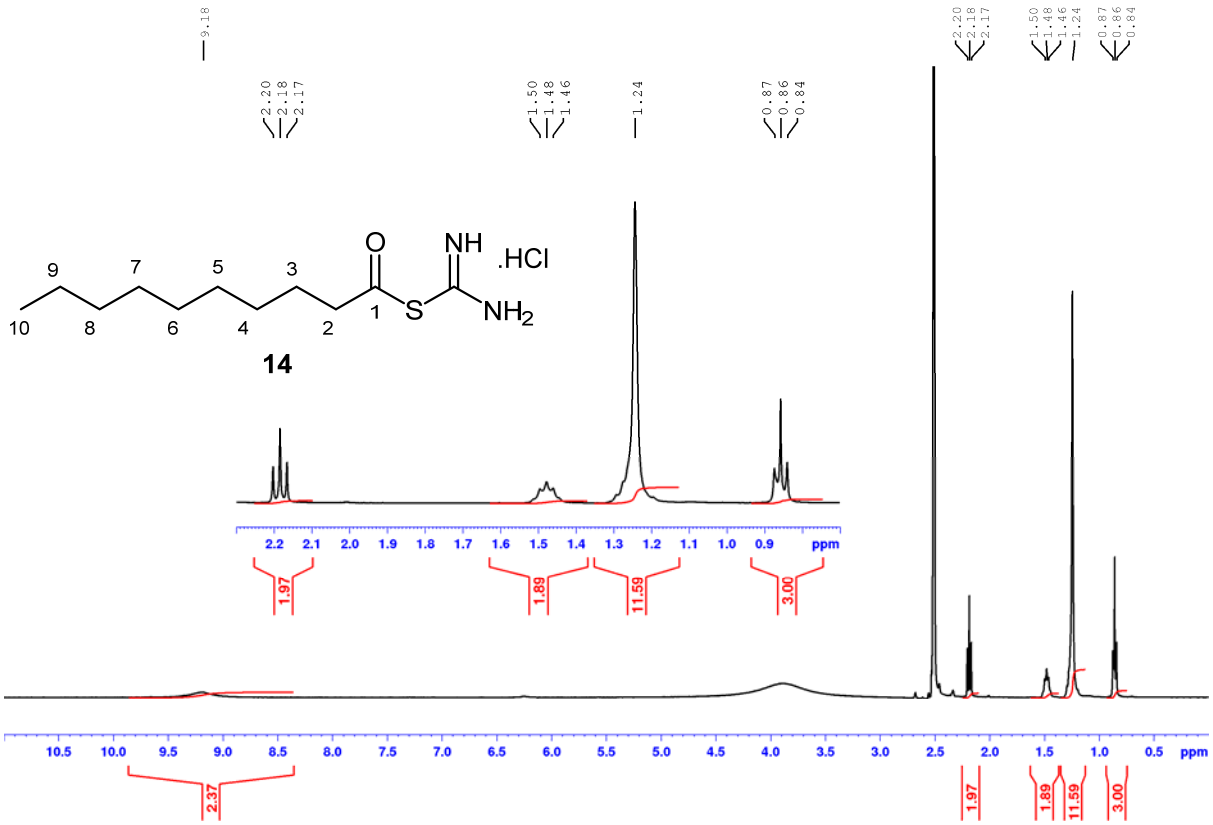
13



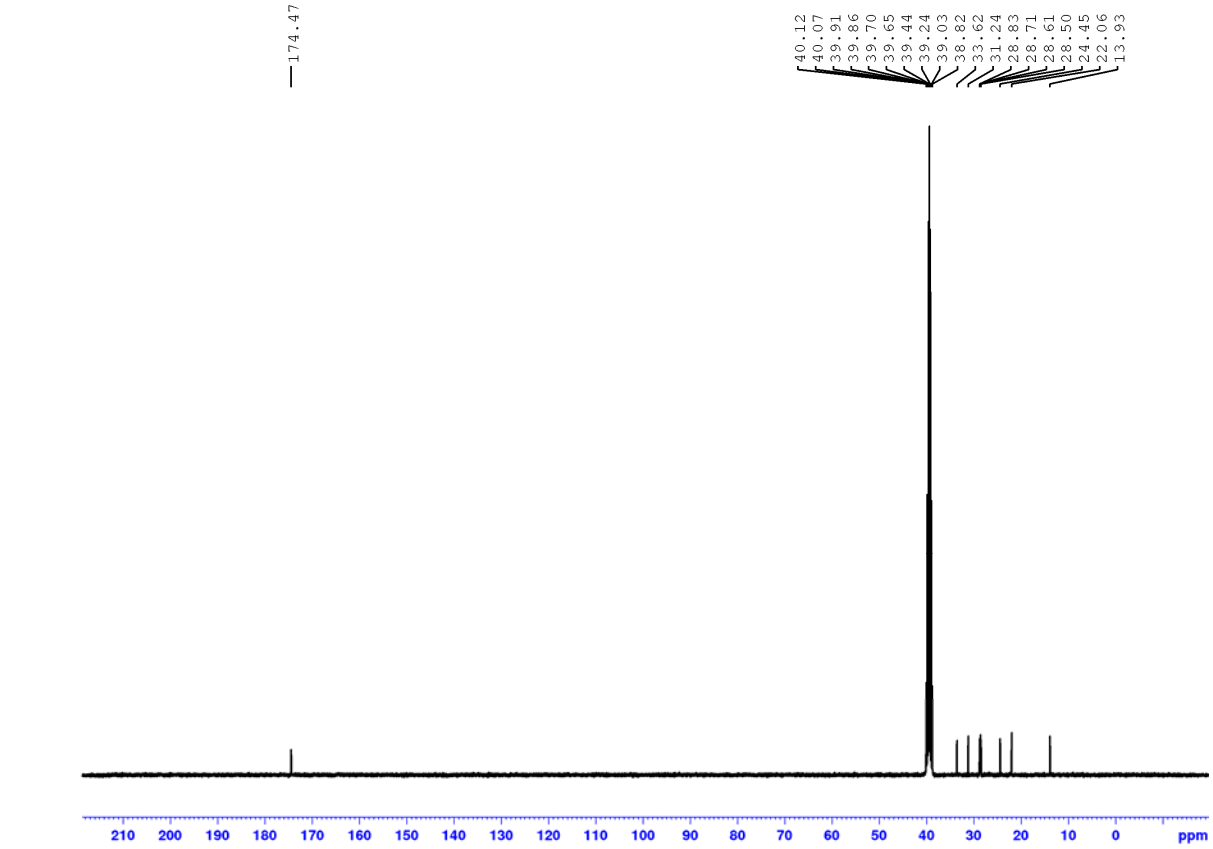


S.4.12. *S*-Decanoyl Isothiouronium Chloride (14)

S-Decanoyl Isothiouronium Chloride

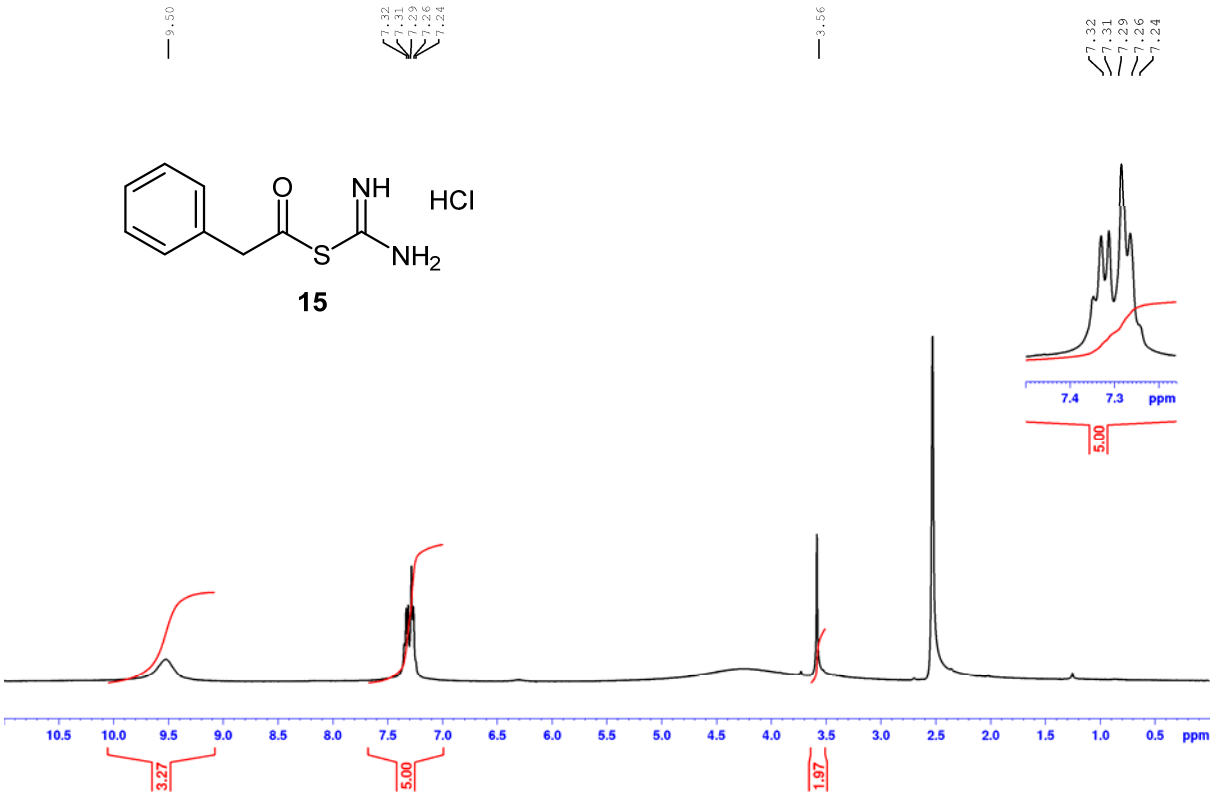


S-Decanoyl Isothiouronium Chloride

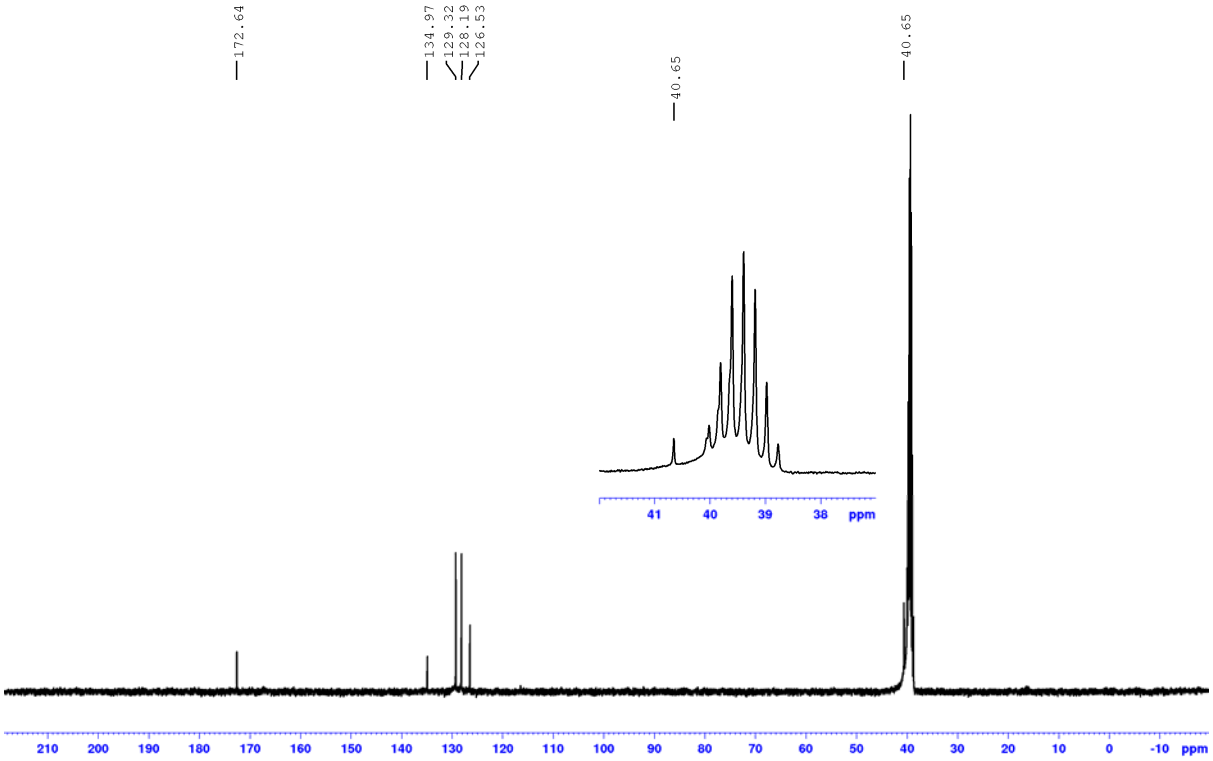


S.4.13. *S*-(Phenylacetyl) Isothiouronium Chloride (15)

S-(Phenylacetyl) Isothiouronium Chloride

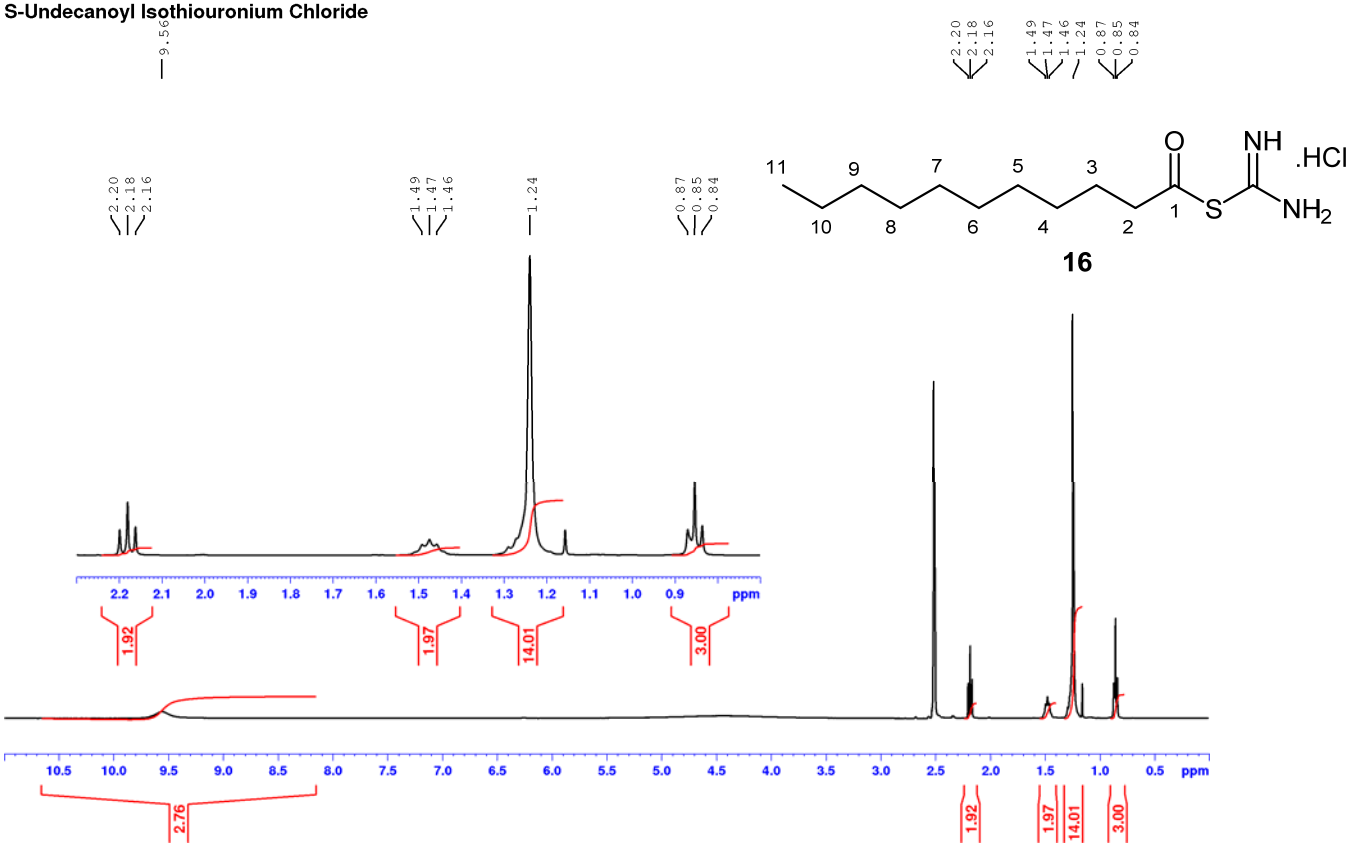


S-(Phenylacetyl) Isothiouronium Chloride

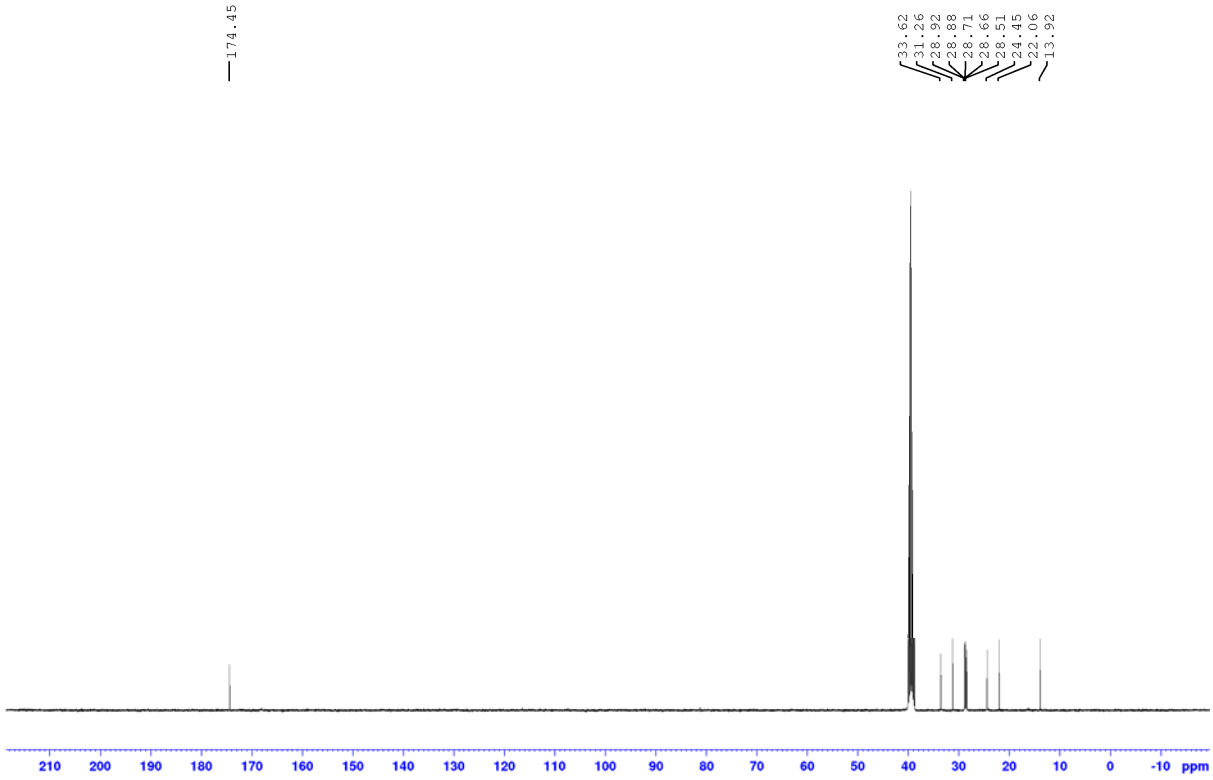


S.4.14. *S*-Undecanoyl Isothiouronium Chloride (16)

S-Undecanoyl Isothiouronium Chloride

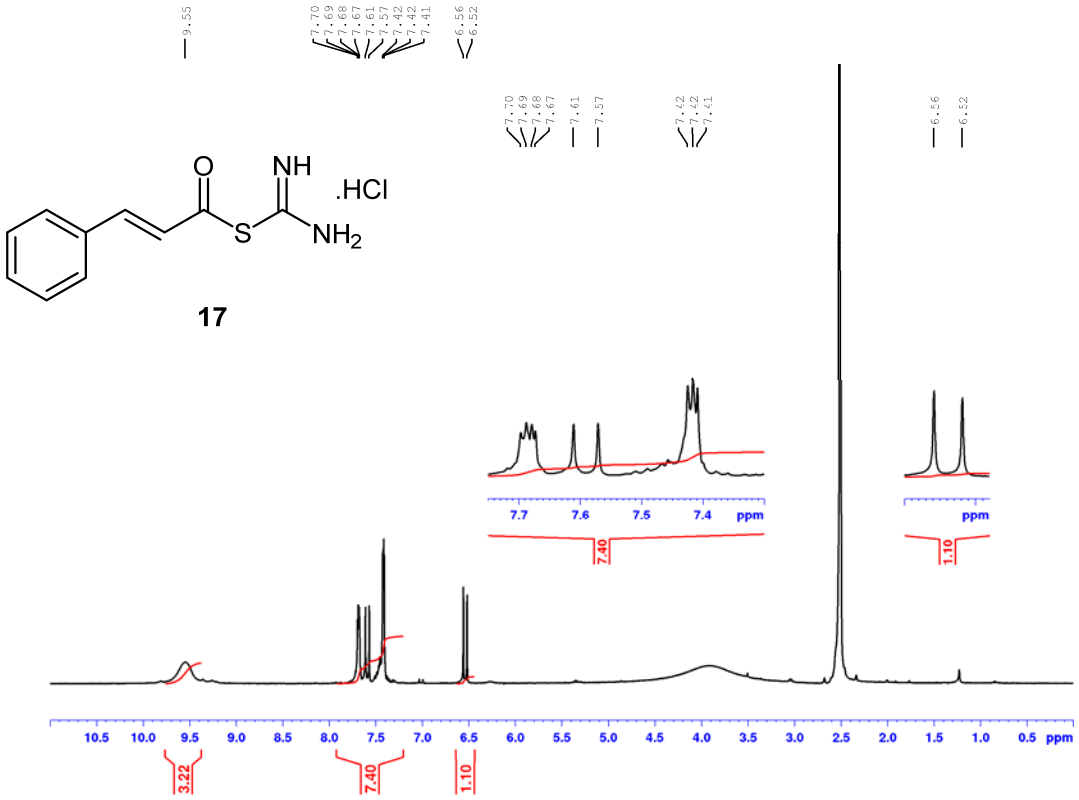


S-Undecanoyl Isothiouronium Chloride

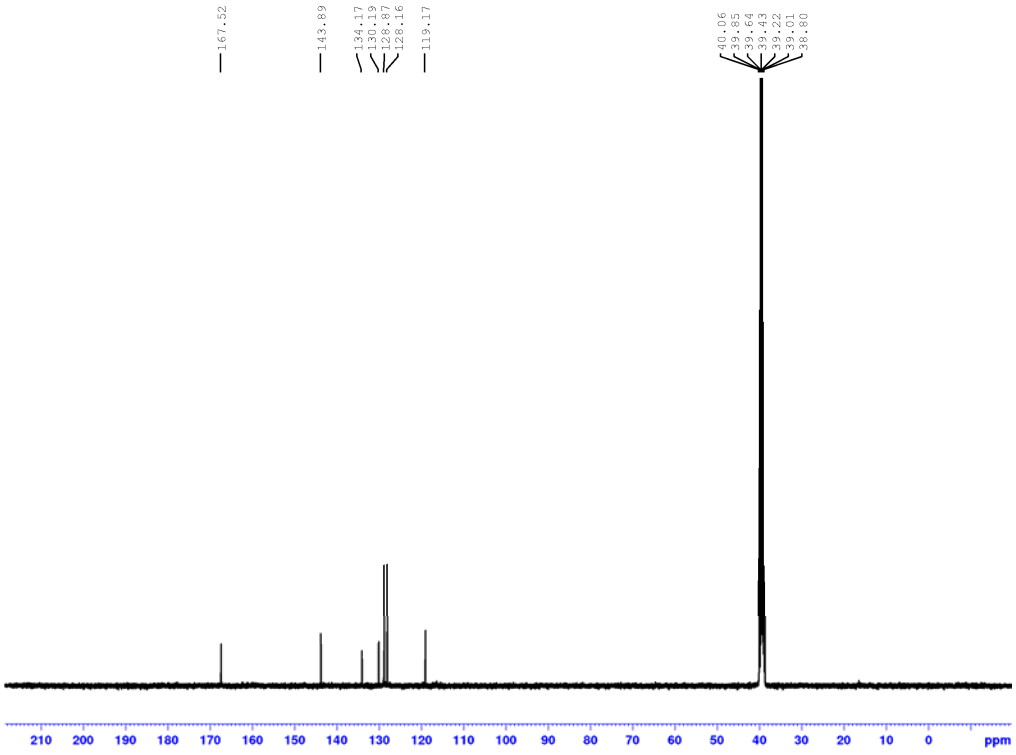


S.4.15. *S*-(Cinnamoyl) Isothiouronium Chloride (17)

S-Cinnamoyl Isothiouronium Chloride

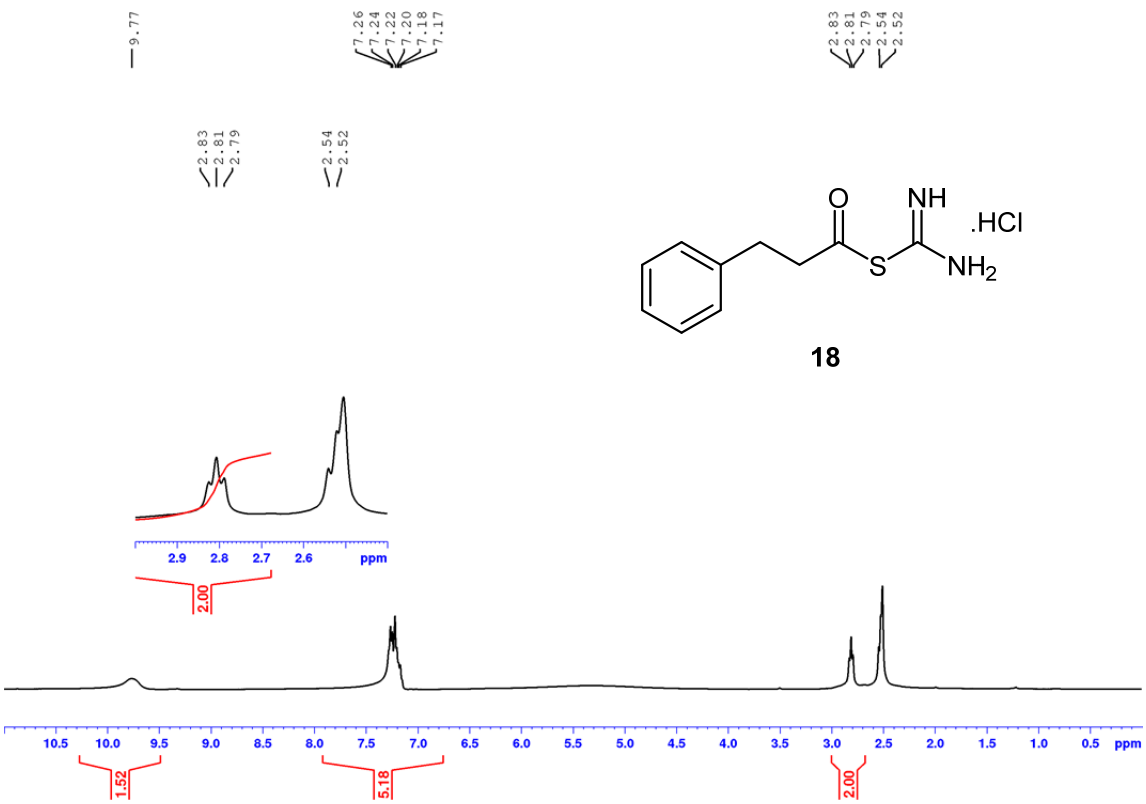


S-Cinnamoyl Isothiouronium Chloride

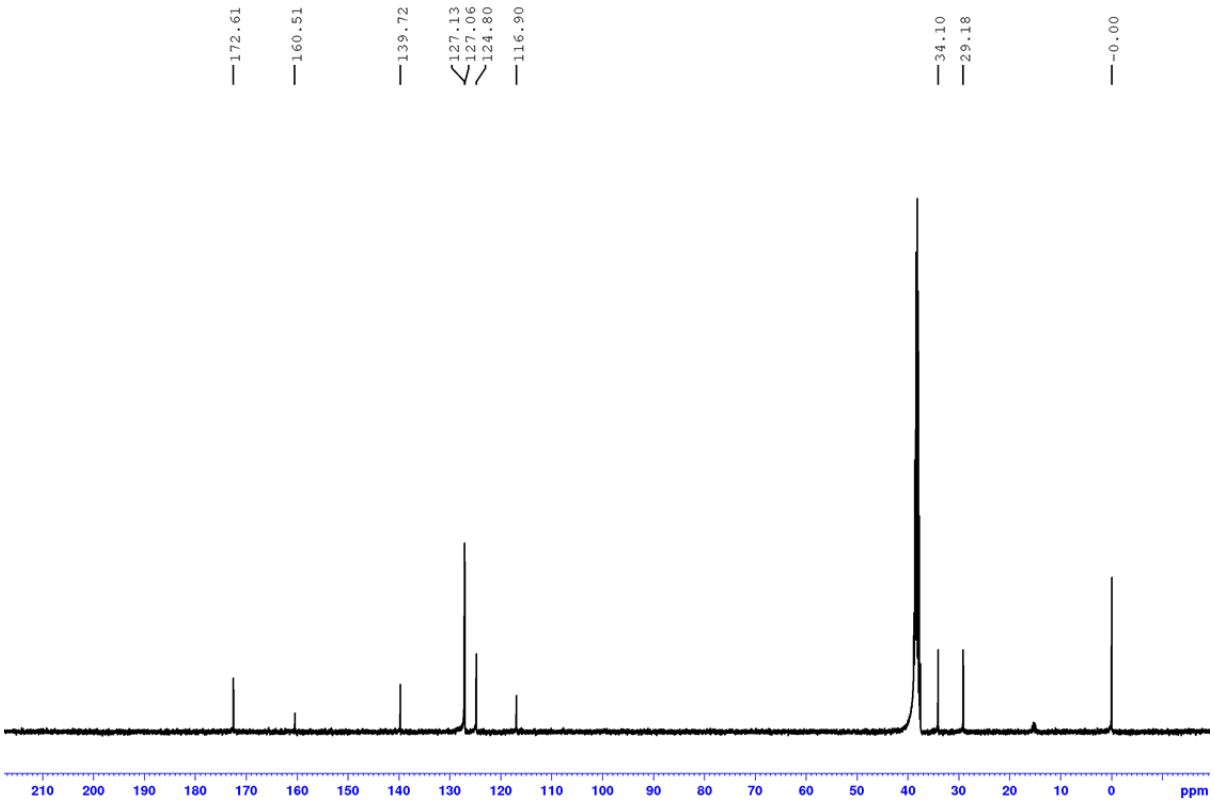


S.4.16 *S*-(Dihydrocinanmoyl) Isothiouronium Chloride (18)

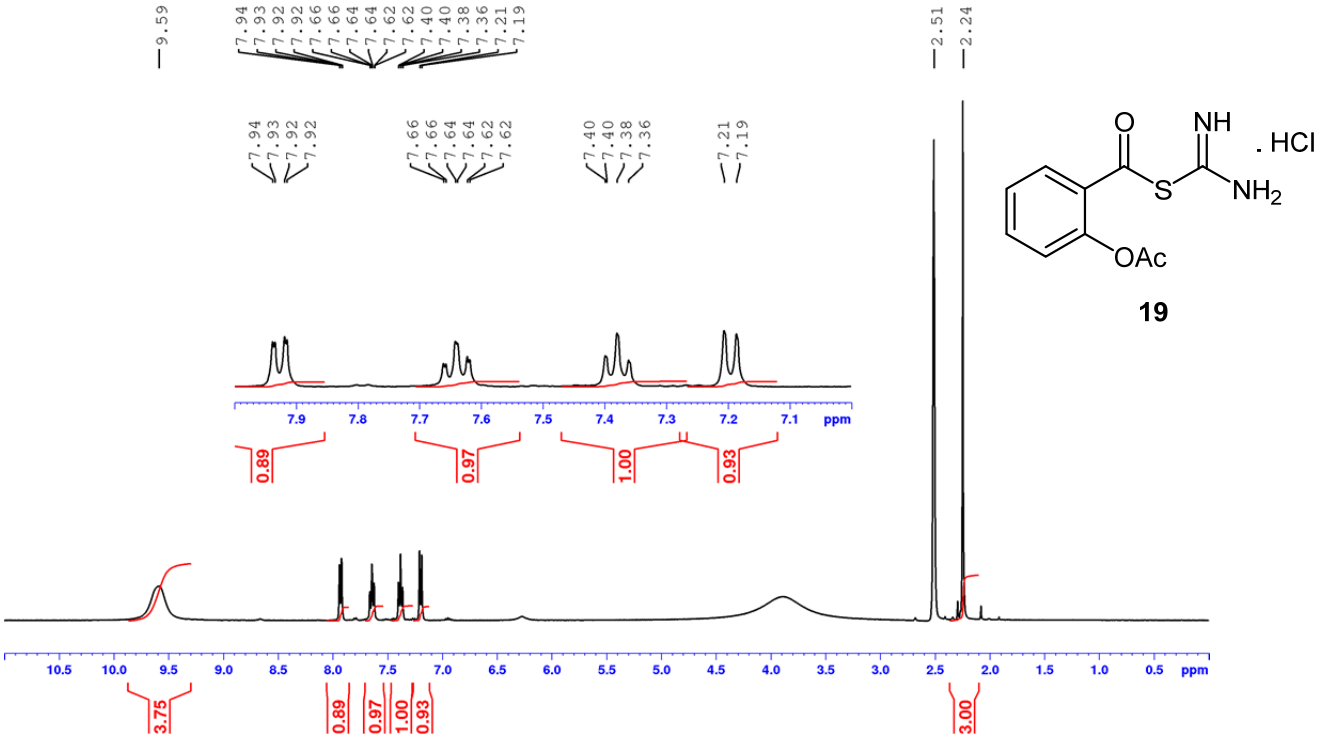
S-(Dihydrocinnamoyl) Isothiouronium Chloride

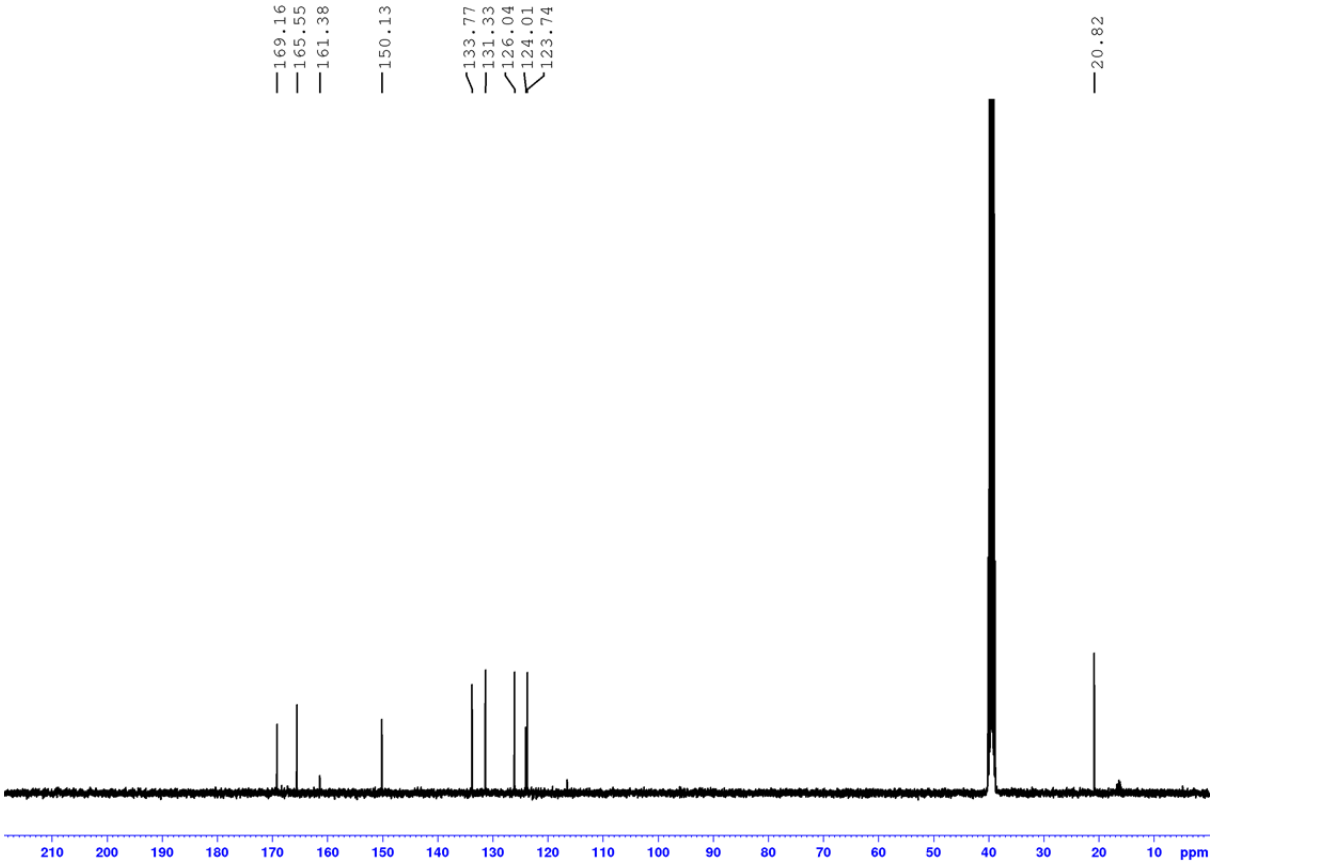


S-(Dihydrocinnamoyl) Isothiouronium Chloride

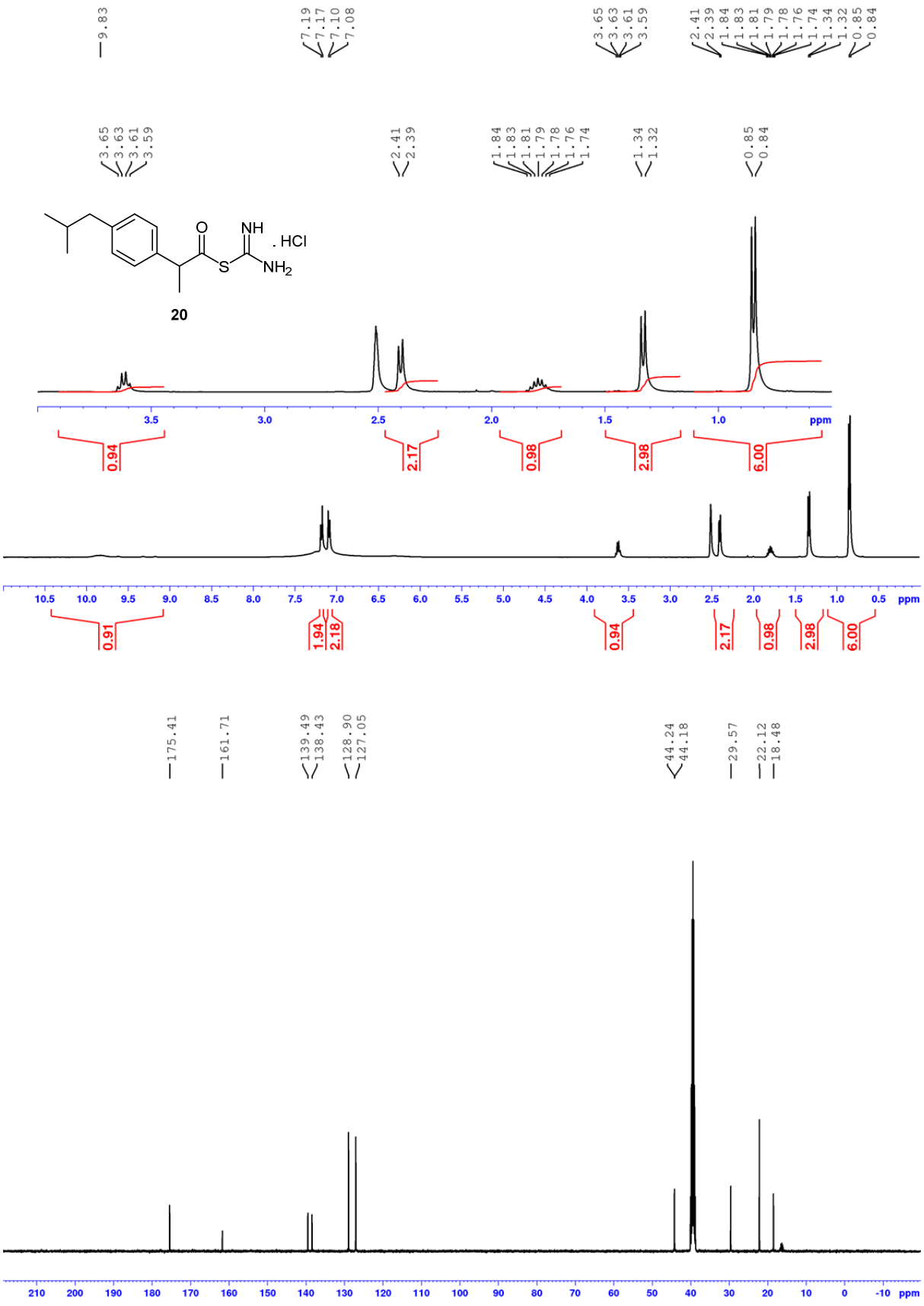


S.4.17 Aspirin Analogue (19)

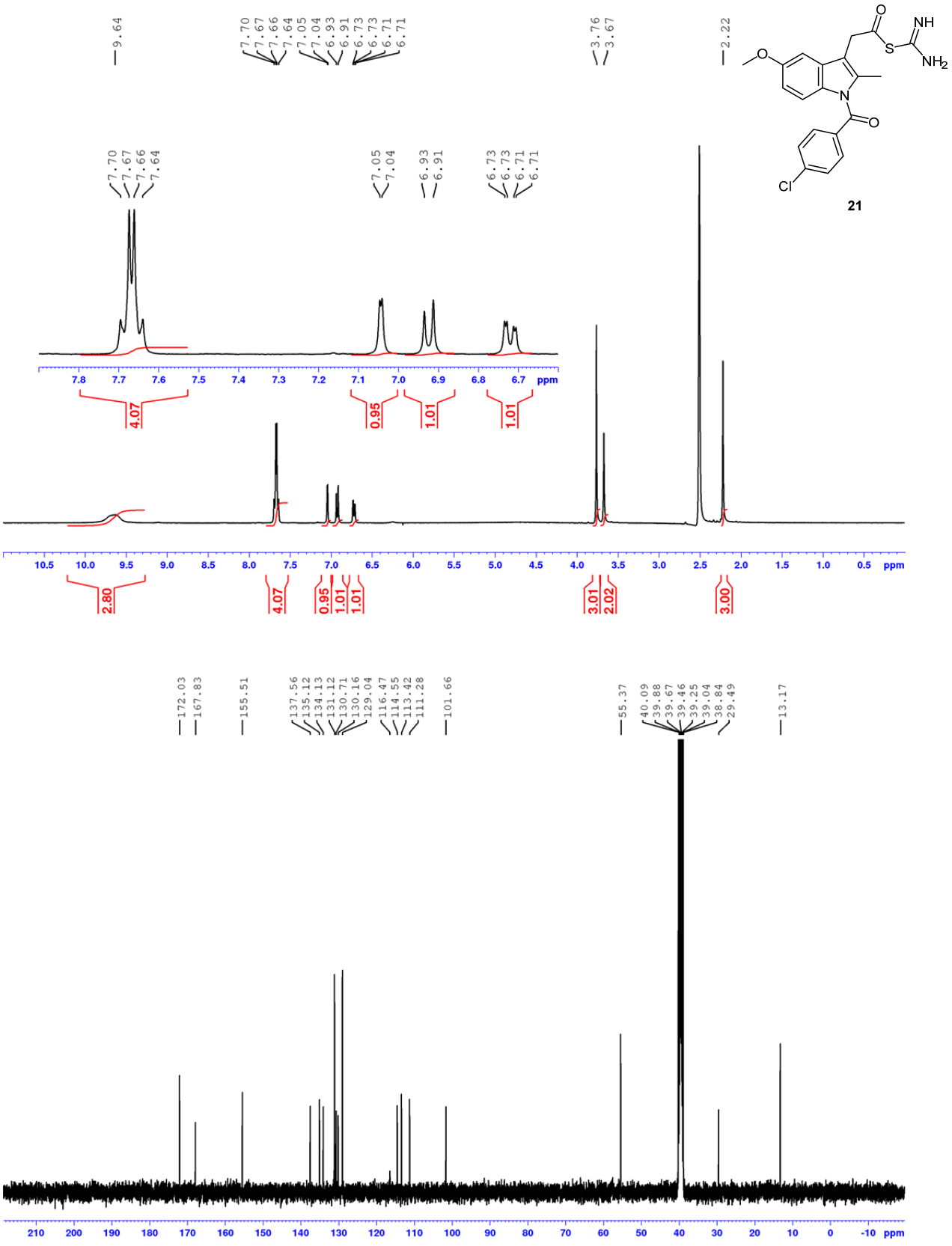




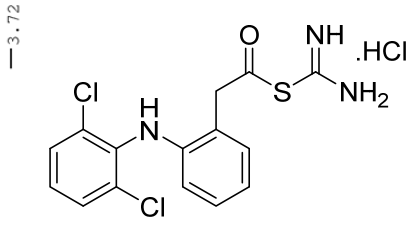
S.4.18 – Ibuprofen Analogue (20)



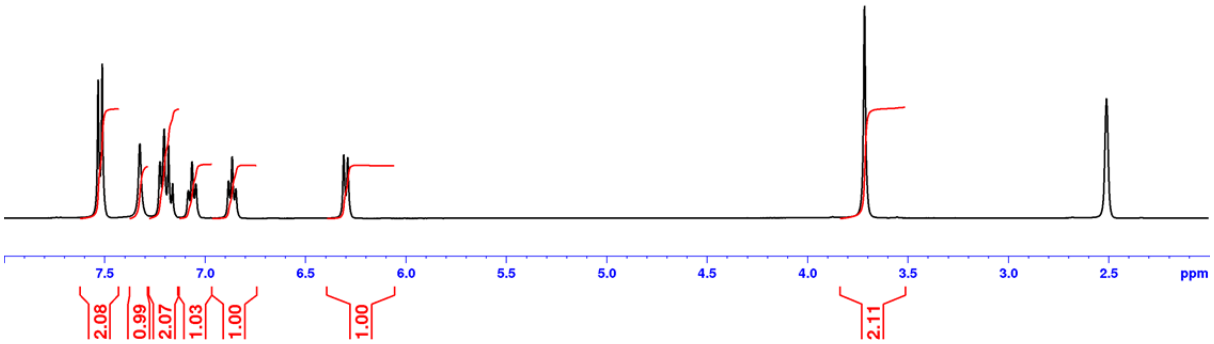
S.4.19 – Indomethacin Analogue (21)

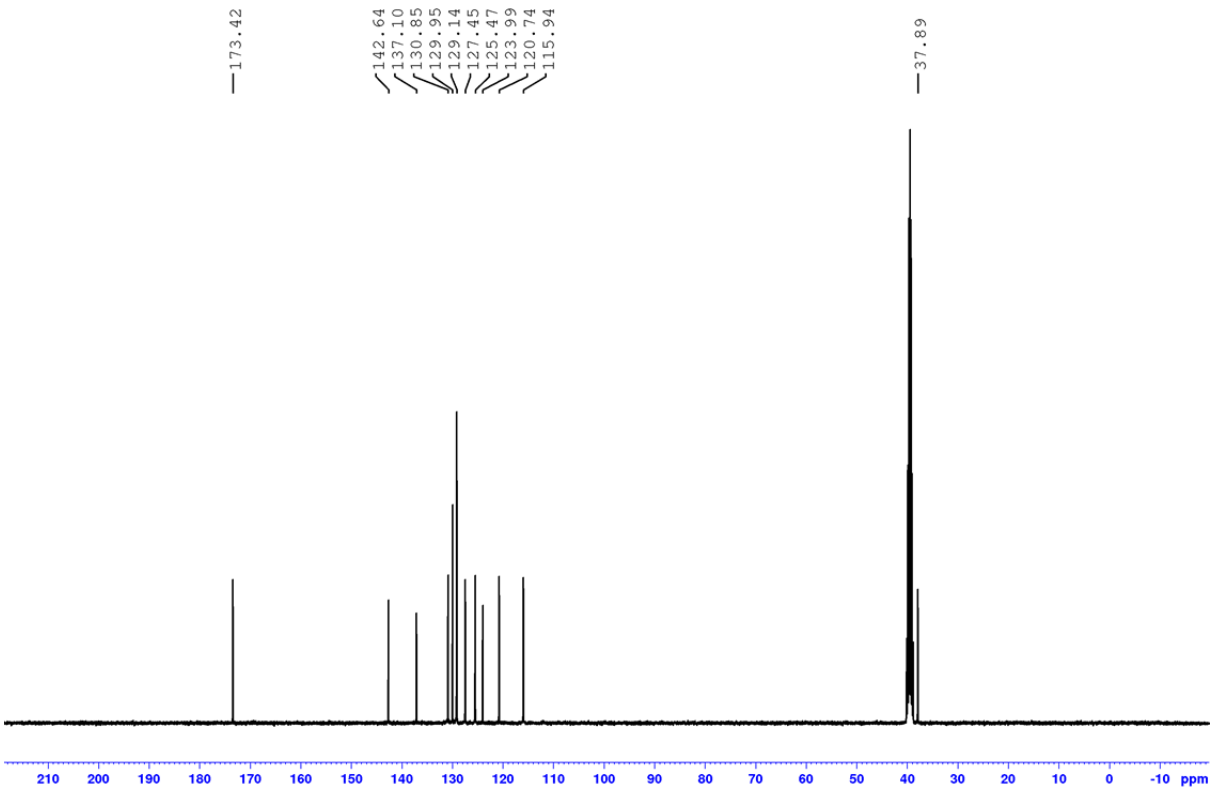


S.4.20 – Diclofenac Analogue (22)



22





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	$C_9H_{11}N_2O_2SCl$	$C_9H_{11}N_2O_2SCl$
Sum formula	$C_9H_{11}ClN_2O_2S$	$C_9H_{11}ClN_2O_2S$
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

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4. Leitch, L. C.; Baker, B. E.; Brickman, L., *Canadian Journal of Research* **1945**, *23b* (4), 139-157.