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Electronic Supporting Information

A sustainable strategy for the synthesis of bis-2-iminothiazolidin-4-ones utilizing novel series of asymmetrically substituted bis-thioureas as viable precursors

Wael Abdelgayed Ahmed Arafa*[a,b] and Hamada Mohamed Ibrahim[b]

[a]Chemistry Department, College of Science, Jouf University, P.O. Box 72341, Sakaka, Aljouf, Kingdom of Saudi Arabia

[b]Chemistry Department, Faculty of Science, Fayoum University P.O. Box 63514, Fayoum City, Egypt

E-mail:waa00@fayoum.edu.eg

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Experiments

General procedure for the synthesis of bis-thioureas (3a–d).

Isothiocyanates (**1a**, **b**, 0.5 mmol) and diamines (**2a**, **b**, 1.0 mmol) were mixed in a 25 mL round-bottomed flask. The reaction mixture was sonicated in the water bath (23 ^{o}C) of an ultrasonic cleaner, for 5 min as indicated in Table 1. After completion of the reaction (the reaction was monitored by TLC, silica gel; DCM:petroleum ether = 5:2 V/V), the reaction mixture was triturated with 2 mL chilled EtOH, and the precipitate was filtered, affording the crude product, which was purified by recrystallization from EtOH (95–97%).

1,1'-((1*R*,4*R*)-Cyclohexane-1,4-diyl)bis(3-benzylthiourea) (**3a**), colorless solid, m.p. 229–231 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.65 (b, 2H, 2NH), 7.35-7.21 (m, 12H, 2NH + Ar-H), 4.66 (d, J = 5.1, 4H, 2CH_2), 3.92 (b, 2H, cyclohexyl-H), 1.95–1.93 (m, 4H, cyclohexyl-H), 1.27–1.21 (m, 4H, cyclohexyl-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 181.4, 139.2, 127.9, 127.4, 126.4, 51.5, 47.0, 30.5; IR (KBr, cm^{-1}): 3265, 3221 (NH), 1573 (C=C), 1262 (C=S); MS *m/z* (%): 412 (0.4), 321 (24.2), 248 (12.8), 165 (57.4), 91 (100); Anal. Calcd for $C_{22}H_{28}N_4S_2$: C, 64.04; H, 6.84; N, 13.58%; Found: C, 64.09; H, 6.79; N, 13.62%.

1,1'-((1*R*,4*R*)-Cyclohexane-1,4-diyl)bis(3-allylthiourea) (**3b**), pale yellow solid, m.p. 330–332 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.33 (b, 2H, 2NH), 7.27–7.25 (d, 2H, 2NH), 5.90–5.77 (m, 2H, CH_2=C*H*), 5.16–5.04 (m, 4H, CH_2=CH), 4.03 (b, 4H, CH_2–N), 3.91 (b, 2H, cyclohexyl-H), 1.92–1.90 (m, 4H, cyclohexyl-H), 1.25–1.19 (m, 4H, cyclohexyl-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 181.1, 135.1, 115.3, 51.4, 45.7, 30.8; IR (KBr, cm^{-1}): 3237, 3211 (NH), 1569 (C=C), 1260 (C=S); MS *m/z* (%): 312 (0.1),

300 (0.2), 256 (40.4), 198 (26.9), 117 (33.4), 96 (49.7), 58 (100); Anal. Calcd for $C_{14}H_{24}N_4S_2$: C, 53.81; H, 7.74; N, 17.93%; Found: C, 53.77; H, 7.80; N, 17.85%.

1,1'-(1,4-Phenylenebis(methylene))bis(3-benzylthiourea) (**3c**), light yellow solid, m.p. 166–167 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.89 (b, 4H, 4NH), 7.35–7.23 (m, 14H, Ar-H), 4.66 (b, 8H, $4CH_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 181.5, 139.2, 137.8, 128.2, 127.3, 127.2, 126.8, 47.0, 46.8; IR (KBr, cm^{-1}): 3271, 3232 (NH), 1562 (C=C), 1250 (C=S); MS *m/z* (%): 434 (0.6), 343 (21.6), 252 (58.3), 104 (23.5), 91 (100); Anal. Calcd for $C_{24}H_{26}N_4S_2$: C, 66.33; H, 6.03; N, 12.89%; Found: C, 66.42; H, 5.95; N, 12.79%.

1,1'-(1,4-Phenylenebis(methylene))bis(3-allylthiourea) (**3d**), yellow solid, m.p. 176–178 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.80 (b, 2H, 2NH), 7.55 (b, 2H, 2NH), 7.23 (s, 4H, Ar-H), 5.89–5.80 (m, 2H, CH_2=C*H*), 5.17–5.05 (m, 4H, CH_2=CH), 4.63 (d, *J* = 5.0 Hz, 4H, $2CH_2$), 4.06 (b, 4H, CH_2–N); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 181.2, 137.8, 135.0, 127.1, 115.3, 46.7, 45.8; IR (KBr, cm^{-1}): 3267, 3224 (NH), 1562 (C=C), 1259 (C=S); MS *m/z* (%): 334(0.3), 279 (1.6), 262 (31.4), 99 (43.6), 91 (88.7), 56 (100); Anal. Calcd for $C_{16}H_{22}N_4S_2$: C, 57.45; H, 6.63; N, 16.75%; Found: C, 57.51; H, 6.57; N, 16.83%.

General methods for the synthesis of derivatives 5–7.

Method A:

To a solution of 1 mmol of bis-thioureas **3a**–**d** and 10 mL of deionized water in a 50 mL round-bottom flask was added dropwise at room temperature 2 mmol of dialkyl acetylenedicarboxylate (DAADs, **4a**, **b**) with continuous stirring. After the complete addition of DAADs, the reaction mixture was sonicated for 10 min (TLC, DCM:MeOH = 9:1 V/V); during the reaction, a solid appears in the solution. After completion of the

reaction, excess solvent was removed by filtration and the residue recrystallized from ethanol, affording the desired product as colorless to light yellow crystals.

Method B

Isothiocyanates (**1a**, **b**, 0.5 mmol) were added dropwisely to diamines (**2a**, **b**, 1.0 mmol) under ultrasonic irradiation for 5 min. To the resulted residue, 10 mL of water was added followed by dropwisely addition of 2 mmol of dialkyl acetylenedicarboxylate (DAADs, **4a**, **b**) at room temperature. After the complete addition of DAADs, the reaction mixture was sonicated for 10 min (TLC, DCM:MeOH = 9:1 V/V); during the reaction, a solid appears in the solution. After completion of the reaction, excess solvent was removed by filtration and the residue recrystallized from ethanol, affording the desired product as colorless to light yellow crystals (88–92%).

Dimethyl 2,2'-((2*Z*,2'*Z*)-((1*R*,4*R*)-cyclohexane-1,4-diyl)bis(2-(benzylimino)-4-oxothiazolidin-3-yl-5-ylidene))(2*Z*,2'*Z*)-diacetate (5a), colorless solid, m.p. 193–195 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.33–7.28 (m, 10H, Ar-H), 6.77 (s, 2H, =C*H*), 4.92 (s, 4H, 2CH_2), 3.77 (s, 8H, cyclohexyl-H + 2OCH_3), 1.81–1.79 (m, 4H, cyclohexyl-H), 1.56 (b, 4H, cyclohexyl-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 166.2, 165.7, 157.4, 140.4, 139.1, 130.7, 128.0, 127.5, 126.4, 52.1, 52.0, 47.2, 30.7; IR (KBr, cm^{-1}): 1716 (C=O), 1689 (C=O), 1651 (C=N), 1624 (C=C); MS *m/z* (%): 632 (2.8), 601 (1.2), 514 (20.6), 298 (14.7), 216 (51.2), 91 (100); Anal. Calcd for $C_{32}H_{32}N_4O_6S_2$: C, 60.74; H, 5.10; N, 8.85%; Found: C, 60.65; H, 5.19; N, 8.80%.

Diethyl 2,2'-((2*Z*,2'*Z*)-((1*R*,4*R*)-cyclohexane-1,4-diyl)bis(2-(benzylimino)-4-oxothiazolidin-3-yl-5-ylidene))(2*Z*,2'*Z*)-diacetate (5b), light yellow solid, m.p. 183–185 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.33–7.26 (m, 10H, Ar-H), 6.74 (s, 2H, =C*H*), 4.92 (s, 4H, 2CH_2), 4.24 (q, *J* = 7.12 Hz, 4H, 2OCH_2), 3.37 (s, 2H, cyclohexyl-H), 1.81–1.79 (m, 4H, cyclohexyl-H), 1.57-1.55 (m, 4H, cyclohexyl-H) 1.25 (t, *J* = 7.12 Hz,

6H, $2CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 166.0, 165.9, 157.3, 139.4, 138.0, 133.7, 128.0, 127.4, 126.3, 62.2, 52.4, 47.8, 30.4, 14.3; IR (KBr, cm^{-1}): 1717 (C=O), 1688 (C=O), 1650 (C=N), 1622 (C=C); MS *m/z* (%): 660 (0.2), 587 (1.9), 494 (29.2), 298 (27.5), 126 (85.1), 106 (100); Anal. Calcd for $C_{34}H_{36}N_4O_6S_2$: C, 61.80; H, 5.49; N, 8.48%; Found C, 61.89; H, 5.42; N, 8.54%.

Dimethyl 2,2'-((2*Z*,2'*Z*)-((1*R*,4*R*)-cyclohexane-1,4-diyl)bis(2-(allylimino)-4-oxothiazolidin-3-yl-5-ylidene))(2*Z*,2'*Z*)-diacetate (5c), light yellow solid, m.p. 197–198 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 6.77 (s, 2H, =C*H*), 5.99–5.87 (m, 2H, CH_2=C*H*), 5.18–5.05 (m, 4H, CH_2=CH), 4.34–4.32 (m, 4H, CH_2–N), 4.15 (b, 2H, cyclohexyl-H), 3.79 (s, 6H, $2OCH_3$), 1.89–1.45 (m, 8H, cyclohexyl-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 166.4, 165.9, 158.6, 139.8, 135.2, 131.9, 115.5, 52.1, 52.0, 45.8, 30.9; IR (KBr, cm^{-1}): 1719 (C=O), 1689 (C=O), 1656 (C=N), 1620 (C=C); MS *m/z* (%): 501 (M-CH_3O, 1.6), 414 (2.6), 374 (3.7), 263 (31.7), 112 (54.8), 69 (100); Anal. Calcd for $C_{24}H_{28}N_4O_6S_2$: C, 54.12; H, 5.30; N, 10.52%; Found C, 54.06; H, 5.38; N, 10.59%.

Diethyl 2,2'-((2*Z*,2'*Z*)-((1*R*,4*R*)-cyclohexane-1,4-diyl)bis(2-(allylimino)-4-oxothiazolidin-3-yl-5-ylidene))(2*Z*,2'*Z*)-diacetate (5d), light yellow solid, m.p. 203–205 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 6.79 (s, 2H, =C*H*), 5.97–5.89 (m, 2H, CH_2=C*H*), 5.16–5.04 (m, 4H, CH_2=CH), 4.35–4.33 (m, 4H, CH_2–N), 4.13 (b, 2H, cyclohexyl-H), 4.27 (q, *J* = 7.1 Hz, 4H, $2CH_2$), 1.88–1.46 (m, 8H, cyclohexyl-H) 1.33 (t, *J* = 7.2 Hz, 6H, $2CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 166.7, 165.8, 158.3, 138.6, 135.3, 133.6, 115.4, 62.1, 51.8, 45.8, 31.0, 14.3; IR (KBr, cm^{-1}): 1720 (C=O), 1686 (C=O), 1651 (C=N), 1617 (C=C); MS *m/z* (%): 560 (0.8), 454 (0.5), 381 (1.6), 283 (0.9), 186 (23.5), 101 (85.7), 88 (100); Anal. Calcd for $C_{26}H_{32}N_4O_6S_2$: C, 55.70; H, 5.75; N, 9.99%; Found C, 55.63; H, 5.81; N, 10.14%.

Dimethyl 2,2'-((2*E*,2'*E*)-((1,4-phenylenebis(methylene))bis(azanylylidene))bis(3-benzyl-4-oxothiazolidine-2,5-diylidene))(2*Z*,2'*Z*)-diacetate (6a) + **methyl (*Z*)-2-((*Z*)-2-(benzylimino)-3-(4-(((2*E*,5*Z*)-2-(benzylimino)-5-(2-methoxy-2-oxoethylidene)-4-oxothiazolidin-3-yl)methyl)benzyl)-4-oxothiazolidin-5-ylidene)acetate (7a)**, light yellow solid, m.p. 195–199 °C; (Regioisomeric Mixture); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.29–7.18 (m, 14H, Ar-H), 6.80 (s, 1H, =C*H*), 6.79 (s, 1H, =C*H*), 4.98–4.95 (m, 4H, CH_2), 4.64–4.61 (m, 4H, CH_2), 3.78 (s, 6H, 2OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 166.8, 166.1, 158.5, 140.2, 139.2, 137.9, 137.8, 131.9, 127.9, 127.8, 127.4, 127.3, 127.2, 126.4, 126.3, 52.5, 47.4, 47.3, 47.0, 46.9; IR (KBr, cm^{-1}): 1716 (C=O), 1697 (C=O), 1647 (C=N), 1608 (C=C); MS *m/z* (%): 654 (1.6), 623 (0.8), 552 (29.4), 479 (47.1), 350 (37.2), 295 (23.7), 91 (74.8), 104 (100); Anal. Calcd for $C_{34}H_{30}N_4O_6S_2$: C, 62.37; H, 4.62; N, 8.56%; Found C, 62.43; H, 4.56; N, 8.62%.

Diethyl 2,2'-((2*E*,2'*E*)-((1,4-phenylenebis(methylene))bis(azanylylidene))bis(3-benzyl-4-oxothiazolidine-2,5-diylidene))(2*Z*,2'*Z*)-diacetate (6b) + **ethyl (*Z*)-2-((*Z*)-2-(benzylimino)-3-(4-(((2*E*,5*Z*)-2-(benzylimino)-5-(2-ethoxy-2-oxoethylidene)-4-oxothiazolidin-3-yl)methyl)benzyl)-4-oxothiazolidin-5-ylidene)acetate (7b)**, colorless solid, m.p. 144–146 °C; (Regioisomeric Mixture); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.31-7.18 (m, 14H, Ar-H), 6.78 (s, 1H, =C*H*), 6.77 (s, 1H, =C*H*), 4.98–4.85 (m, 4H, CH_2), 4.65–4.62 (m, 4H, CH_2), 4.24 (q, *J* = 7.08 Hz, 4H, O$CH_2$$CH_3$), 1.26 (t, *J* = 7.08 Hz, 6H, OCH_2CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 166.9,, 166.5, 159.8, 139.3, 139.0, 137.5, 134.1, 128.0, 127.9, 127.8, 127.6, 127.5, 126.4, 126.3, 61.7, 47.9, 44.7, 14.1; IR (KBr, cm^{-1}): 1720 (C=O), 1695 (C=O), 1644 (C=N), 1611 (C=C); MS *m/z* (%): 683 (M + H, 0.7), 513 (0.5), 309 (0.2), 205 (58.2), 106 (89.4), 91 (100); Anal. Calcd for $C_{36}H_{34}N_4O_6S_2$: C, 63.33; H, 5.02; N, 8.21%; Found C, 63.40; H, 4.97; N, 8.14%.

Dimethyl 2,2'-((2*E*,2'*E*)-((1,4-phenylenebis(methylene))bis(azanylylidene))bis(3-allyl-4-oxothiazolidine-2,5-diylidene))(2*Z*,2'*Z*)-diacetate (6c) + **methyl (*Z*)-2-((*Z*)-2-

(allylimino)-3-(4-(((2*E*,5*Z*)-2-(allylimino)-5-(2-methoxy-2-oxoethylidene)-4-oxothiazolidin-3-yl)methyl)benzyl)-4-oxothiazolidin-5-ylidene)acetate (7c), colorless solid, m.p. 185–187 °C; (Regioisomeric Mixture); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.30–7.25 (m, 4H, Ar-H), 6.78 (s, 1H, =C*H*), 6.77 (s, 1H, =C*H*), 5.99–5.78 (m, 2H, C*H*=CH$_2$), 5.17–5.10 (m, 4H, CH_2=CH), 4.94–4.92 (d, 2H, Ar-CH_2), 4.64–4.61 (d, 2H, Ar-CH_2), 4.41–4.39 (m, 2H, N-CH_2CH=CH$_2$), 4.08–4.06 (m, 2H, N-CH_2CH=CH$_2$), 3.78 (d, 6H, 2OCH$_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.0, 166.1, 158.4, 138.0, 137.5, 135.5, 131.3, 127.8, 127.7, 127.5, 127.4, 120.6, 117.2, 115.6, 115.1, 114.9, 53.7, 52.5, 44.4; IR (KBr, cm^{-1}): 1712 (C=O), 1697 (C=O), 1647 (C=N), 1604 (C=C); MS *m/z* (%): 554 (0.3), 413 (2.8), 245 (46.8), 92 (95.4), 90 (100); Anal. Calcd for $C_{26}H_{26}N_4O_6S_2$: C, 56.30; H, 4.73; N, 10.10%; Found C, 56.39; H, 4.68; N, 10.21%.

Diethyl 2,2'-((2*E*,2'*E*)-((1,4-phenylenebis(methylene))bis(azanylylidene))bis(3-allyl-4-oxothiazolidine-2,5-diylidene))(2*Z*,2'*Z*)-diacetate (6d) + ethyl (*Z*)-2-((*Z*)-2-(allylimino)-3-(4-(((2*E*,5*Z*)-2-(allylimino)-5-(2-ethoxy-2-oxoethylidene)-4-oxothiazolidin-3-yl)methyl)benzyl)-4-oxothiazolidin-5-ylidene)acetate (7d), light yellow solid, m.p. 185–187 °C; (Regioisomeric Mixture); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.29–7.24 (m, 4H, Ar-H), 6.75 (s, 1H, =C*H*), 6.74 (s, 1H, =C*H*), 5.99–5.79 (m, 2H, C*H*=CH$_2$), 5.16–5.09 (m, 4H, CH_2=CH), 4.94–4.91 (d, 2H, Ar-CH_2), 4.63–4.60 (d, 2H, Ar-CH_2), 4.40–4.37 (m, 2H, N-CH_2CH=CH$_2$), 4.27–4.20 (m, 4H, OCH_2CH$_3$), 4.07–4.05 (m, 2H, N-CH_2CH=CH$_2$), 1.28–1.23 (m, 6H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 166.8, 166.1, 159.8, 138.6, 137.7, 135.7, 135.5, 132.6, 127.6, 127.5, 115.8, 115.6, 61.5, 47.9, 45.6, 45.4, 14.2; IR (KBr, cm^{-1}): 1717 (C=O), 1689 (C=O), 1655 (C=N), 1602 (C=C); MS *m/z* (%): 553 (M – C_2H_5O, 1.3), 412 (4.9), 245 (67.2), 90 (100); Anal. Calcd for $C_{28}H_{30}N_4O_6S_2$: C, 57.72; H, 5.19; N, 9.62%; Found: C, 57.79; H, 5.08; N, 9.57%.

General procedures for the preparation of compounds 8–10.

Method A: from ethyl chloroacetate:

The appropriate bis-thioureas **3a**–**d** (1 mmol), ethyl chloroacetate (2 mmol) and sodium acetate (0.16 g, 2 mmol) were irradiated under ultrasonic in ethanol (25 mL) at 90 ^{o}C for 30 min (TLC, DCM:MeOH = 9:1 V/V). The resulting solid was filtered, dried and recrystallized from ethanol containing few drops of dioxane to afford the corresponding bis-thiazolidine derivatives **8**–**10**.

Method B: from chloroacetyl chloride:

To bis-thioureas **3a**–**d** (1 mmol) in a 10 mL round bottom flask was added chloroacetyl chloride (1.2 mmol) drop wise under ultrasonic irradiation. After complete addition of chloroacetylchloride, acetonitrile (5 mL) was added to the reaction mixture and stirred was continued for 5 min (TLC, DCM:MeOH = 9:1 V/V). The resulting solid was filtered, dried and recrystallized from ethanol containing few drops of dioxane to afford the corresponding bis-thiazolidine derivatives **8**–**10** (93-88%).

(2*Z*,2'*Z*)-3,3'-((1*R*,4*R*)-Cyclohexane-1,4-diyl)bis(2-(benzylimino)thiazolidin-4-one) (8a), light yellow solid, m.p. 219–221^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.33–7.22 (m, 10H, Ar-H), 4.77 (s, 4H, CH_2, CH_2Ph), 4.04 (s, 4H, thiazole-CH_2), 3.20–3.16 (m, 2H, chclohexane), 1.76–1.74 (m, 4H, chclohexane), 1.45–1.39 (m, 4H, chclohexane); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 171.3, 153.1, 138.9, 128.1, 127.5, 126.9, 53.9, 52.0, 32.1, 30.8; IR (KBr, cm^{-1}): 1716 (C=O), 1639 (C=N), 1581 (C=C); MS *m/z* (%): 492 (31.6), 419 (34.9), 287 (2.9), 205 (34.8), 106 (69.3), 81 (100); Anal. Calcd for $C_{26}H_{28}N_4O_2S_2$: C, 63.39; H, 5.73; N, 11.37%; Found: C, 63.43; H, 5.69; N, 11.42%.

(2*Z*,2'*Z*)-3,3'-((1*R*,4*R*)-Cyclohexane-1,4-diyl)bis(2-(allylimino)thiazolidin-4-one) (8b), light yellow solid, m.p. 157–159 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 5.82–5.73 (m, 2H, CH_2CH=CH_2), 5.11–5.05 (m, 4H, CH_2CH=CH_2), 4.19 (d, J = 3.7 Hz, 4H, CH_2CH=CH_2), 4.02 (s, 4H, thiazole-CH_2), 3.18–3.13 (m, 2H, chclohexane), 1.78–1.76

(m, 4H, chclohexane), 1.46–1.40 (m, 4H, chclohexane); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 171.3, 153.0, 131.7, 116.7, 54.0, 43.9, 32.1, 30.9; IR (KBr, cm^{-1}): 1720 (C=O), 1635 (C=N), 1596 (C=C); MS *m/z* (%): 392 (12.6), 284 (25..8),184 (73.2), 101 (73.9), 74 (100); Anal. Calcd for $C_{18}H_{24}N_4O_2S_2$: C, 55.08; H, 6.16; N, 14.27%; Found: C, 54.96; H, 6.22; N, 14.35%.

(2*Z*,2'*Z*)-2,2'-((1,4-Phenylenebis(methylene))bis(azanylylidene))bis(3-benzylthiazolidin-4-one) (9a) + (2*Z*,2'*Z*)-3,3'-(1,4-phenylenebis(methylene))bis(2-(benzylimino)thiazolidin-4-one) (10a), light yellow solid, m.p. 165–167 ^{o}C; (Regioisomeric Mixture); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.31–7.13 (m, 14H, ArH), 4.84–4.82 (m, 4H, CH_2), 4.45–4.42 (m, 4H, CH_2), 4.12–4.10 (m, 4H, thiazole-CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 171.2, 153.1, 139.8, 137.9, 128.0, 127.7, 127.6, 126.5, 126.4, 54.2, 54.1, 49.1, 32.3; IR (KBr, cm^{-1}): 1717 (C=O), 1630 (C=N), 1604 (C=C); MS *m/z* (%): 515 (M + H, 1.3), 514 (12.8), 324 (17.9), 233 (85.2), 205 (23.8), 134 (27.9), 104 (11.5), 91 (100); Anal. Calcd for $C_{28}H_{26}N_4O_2S_2$: C, 65.35; H, 5.09; N, 10.89%; Found: C, 65.41; H, 4.98; N, 10.79%.

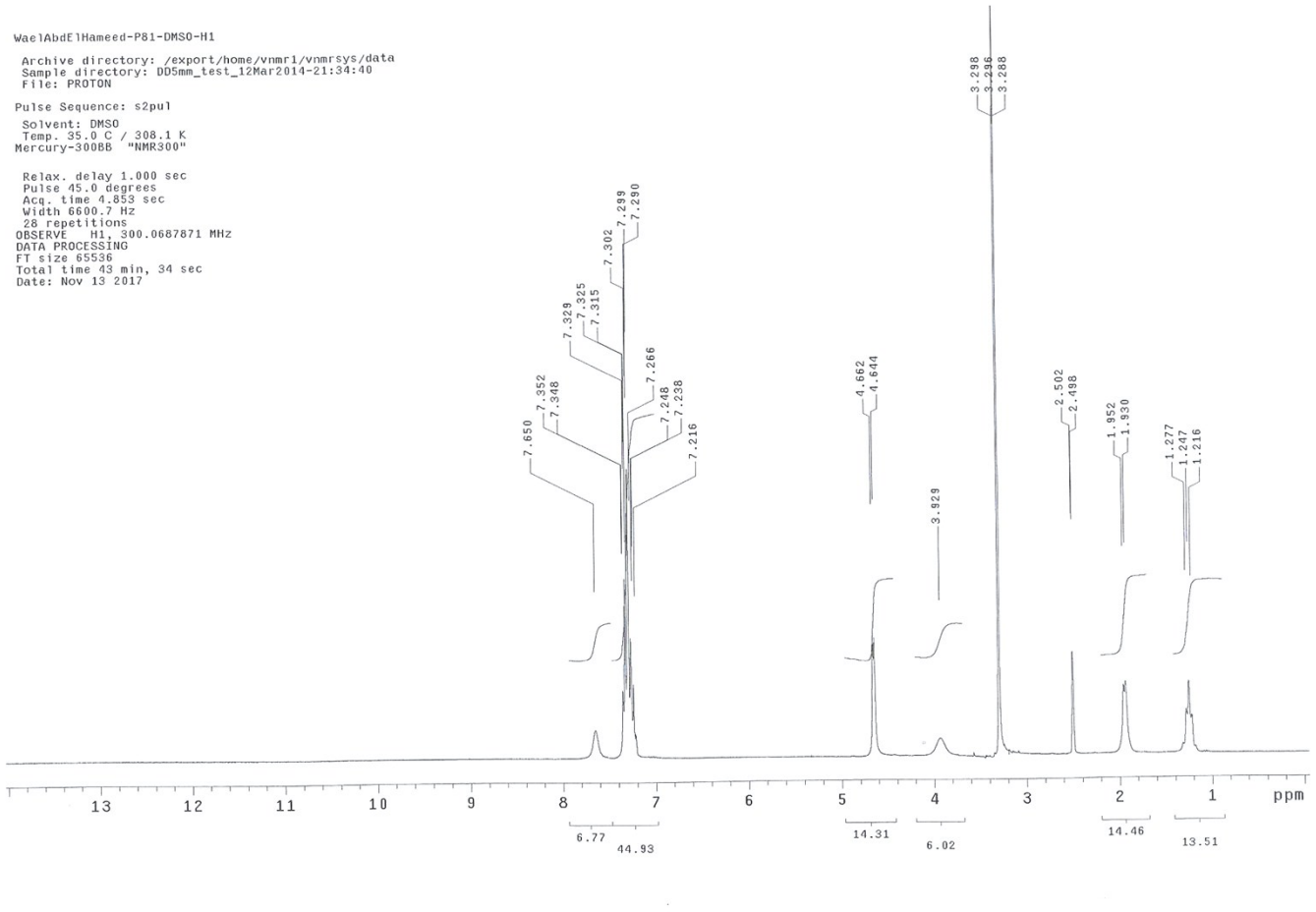
(2*Z*,2'*Z*)-2,2'-((1,4-phenylenebis(methylene))bis(azanylylidene))bis(3-allylthiazolidin-4-one) (9b) + (2*Z*,2'*Z*)-3,3'-(1,4-phenylenebis(methylene))bis(2-(allylimino)thiazolidin-4-one) (10b), yellow solid, m.p. 124–126 ^{o}C; (Regioisomeric Mixture); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.25 (m, 4H, Ar-H), 5.80–5.71 (m, 2H, CH_2C*H*=CH_2), 5.15–5.10 (m, 4H, CH_2CH=CH_2), 4.43–4.42 (m, 4H, CH_2), 4.26-4.25 (m, 4H, CH_2CH=CH_2), 4.07 (s, 4H, thiazole-CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 171.2, 153.0, 137.7, 131.6, 127.4, 127.0, 120.4, 116.6, 114.9, 54.1, 54.0, 43.9, 32.2; IR (KBr, cm^{-1}): 1717 (C=O), 1634 (C=N), 1591 (C=C); MS *m/z* (%): 414 (1.2), 332 (23.8), 304 (11.8), 205 (46.2), 105 (87.9), 91 (100); Anal. Calcd for $C_{20}H_{22}N_4O_2S_2$: C, 57.95; H, 5.35; N, 13.52%; Found: C, 58.04; H, 5.29; N, 13.48%.

Synthesis of derivatives 11a, b

A one-pot three component mixture of the appropriate bis-thioureas **3a, b** (1 mmol), ethyl chloroacetate (2 mmol), 4-chlorobenzaldehyde (2 mmol) and sodium acetate (5 mmol) were mixed in ethanol (15 mL). The reaction mixture was sonicated at 90 °C for 30 min (TLC, DCM:MeOH = 8:2 V/V). The resulting residue was filtered and recrystallized from dioxane to afford the corresponding bis-thiazolidine derivatives **11a, b** in 86–90% yield.

(2*Z*,2'*Z*,5'*E*)-3,3'-((1*R*,4*R*)-Cyclohexane-1,4-diyl)bis(2-(benzylimino)-5-((*E*)-4-chlorobenzylidene)thiazolidin-4-one) (11a), yellow solid, m.p. 322–325 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.82 (s, 1H, C*H*=C), 7.71–7.63 (m, 8H, Ar-H), 7.39–7.26 (m, 10H, Ar-H), 4.74 (s, 4H, CH_2, CH_2Ph), 3.23–3.19 (m, 2H, chclohexane), 1.77–1.75 (m, 4H, chclohexane), 1.44–1.40 (m, 4H, chclohexane); IR (KBr, cm^{-1}): 1719 (C=O), 1637 (C=N), 1608 (C=C); MS *m/z* (%): 625 (M – C_6H_4Cl, 1.3), 521 (12.7), 306 (1.9), 125 (100); Anal. Calcd for $C_{40}H_{34}Cl_2N_4O_2S_2$: C, 65.12; H, 4.65; N, 7.59%; Found: C, 65.07; H, 4.70; N, 7.49%.

(2*Z*,2'*Z*,5'*E*)-3,3'-((1*R*,4*R*)-Cyclohexane-1,4-diyl)bis(2-(allylimino)-5-((*E*)-4-chlorobenzylidene)thiazolidin-4-one) (11b), yellow solid, m.p. 302–304 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.80 (s, 1H, C*H*=C), 7.75–7.69 (m, 8H, Ar-H), 5.80–5.72 (m, 2H, CH_2C*H*=CH_2), 5.12–5.07 (m, 4H, CH_2CH=CH_2), 4.21 (m, 4H, CH_2CH=CH_2), 3.17–3.14 (m, 2H, chclohexane), 1.78–1.75 (m, 4H, chclohexane), 1.47–1.41 (m, 4H, chclohexane); IR (KBr, cm^{-1}): 1712 (C=O), 1641 (C=N), 1611 (C=C); MS *m/z* (%): 636 (0.9), 512 (26.2), 374 (12.6), 125 (100); Anal. Calcd for $C_{32}H_{30}Cl_2N_4O_2S_2$: C, 60.28; H, 4.74; N, 8.79%; Found: C, 60.32; H, 4.69; N, 8.68%.


WaelAbdElHameed-P81-DMSO-H1
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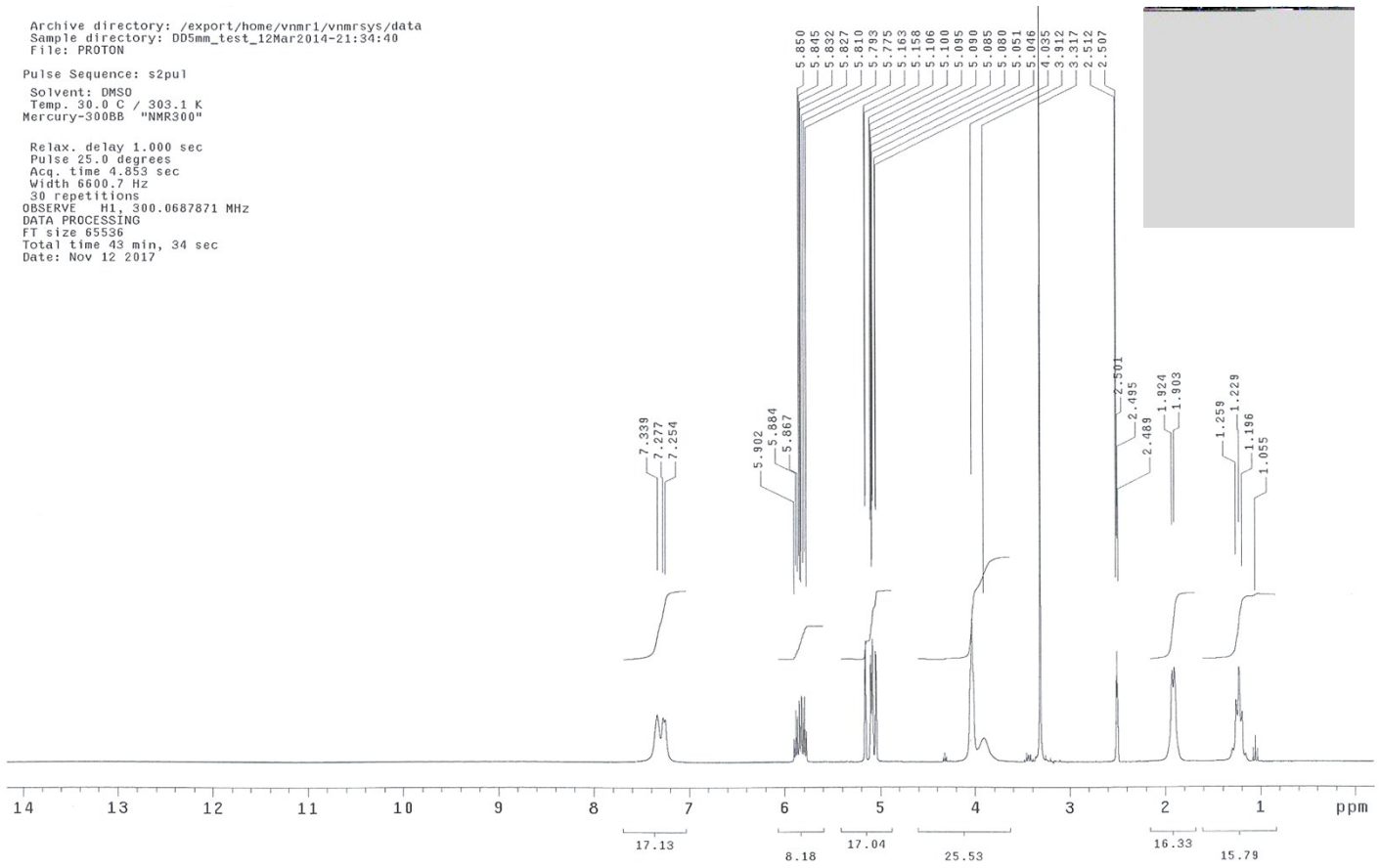
Solvent: DMSO
Temp. 35.0 C / 308.1 K
Mercury-300BB "NMR300"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 4.853 sec
Width 6600.7 Hz
28 repetitions
OBSERVE H1, 300.0687871 MHz
DATA PROCESSING
FT size 65536
Total time 43 min, 34 sec
Date: Nov 13 2017
7.650
7.352
7.348
7.329
7.325
7.315
7.302
7.299
7.290
7.266
7.248
7.238
7.216
4.662
4.644
3.929
3.298
3.296
3.288
2.502
2.498
1.952
1.930
1.277
1.247
1.216
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
6.77
44.93
14.31
6.02
14.46
13.51

^{1}H NMR of **3a**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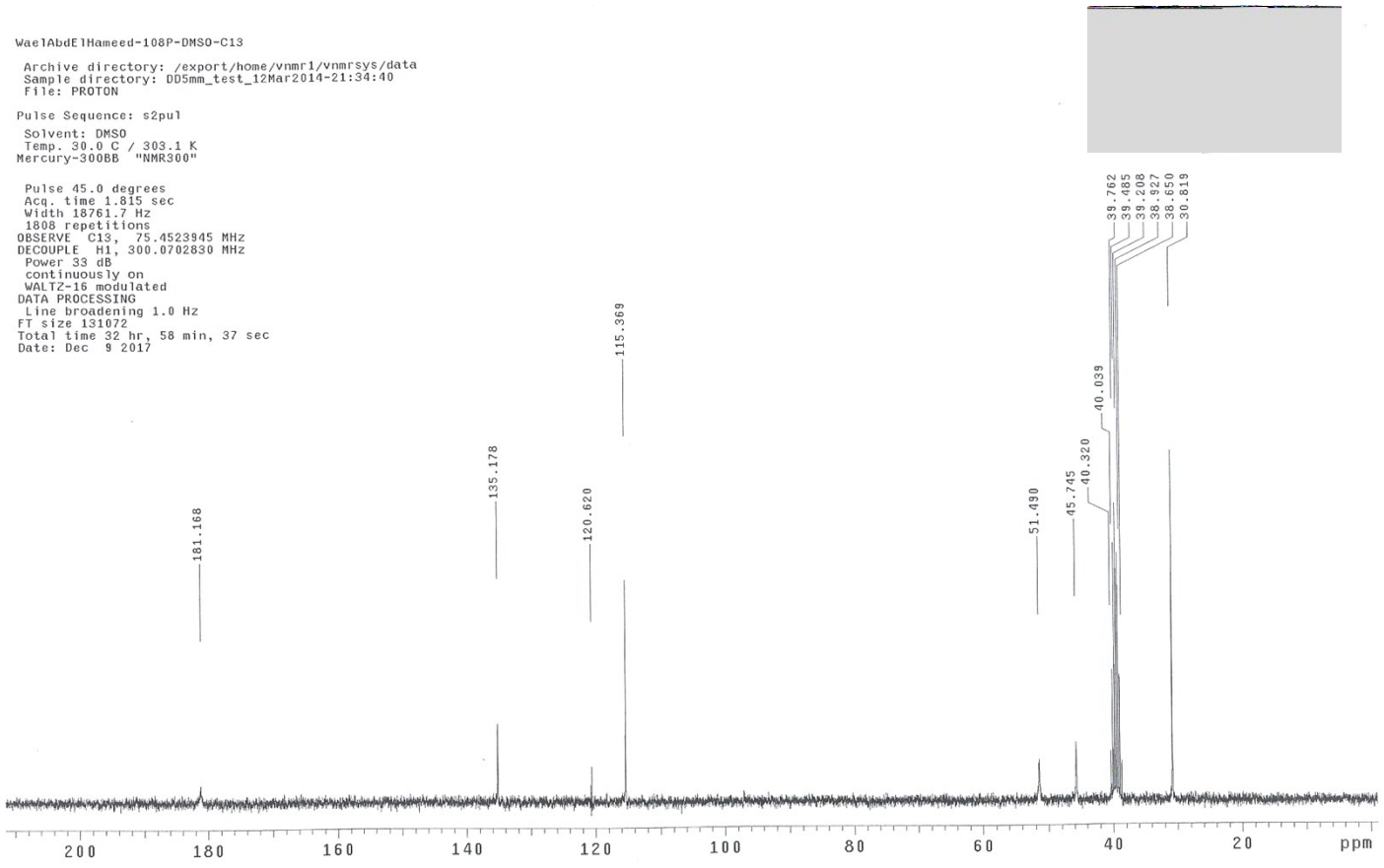
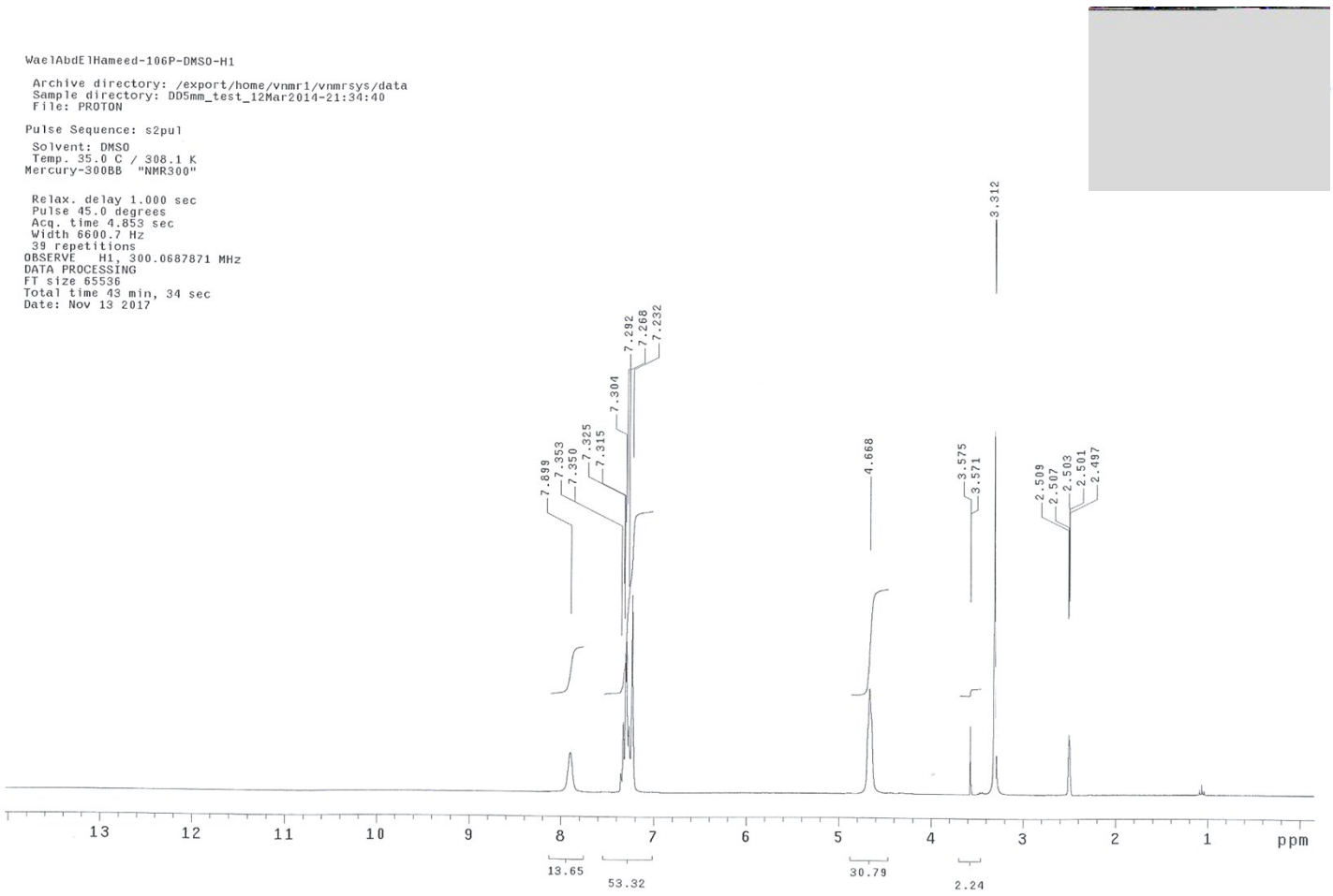
File: PROTON
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 30.0 C / 303.1 K
Mercury-300BB "NMR300"
Relax. delay 1.000 sec
Pulse 25.0 degrees
Acq. time 4.853 sec
Width 6600.7 Hz
30 repetitions
OBSERVE H1, 300.0687871 MHz
DATA PROCESSING
FT size 65536
Total time 43 min, 34 sec
Date: Nov 12 2017
5.850
5.845
5.832
5.827
5.810
5.793
5.775
5.163
5.158
5.106
5.100
5.095
5.090
5.085
5.080
5.051
5.046
4.035
3.912
3.317
2.512
2.507
2.501
2.495
2.489
1.924
1.903
1.259
1.229
1.196
1.055
7.339
7.277
7.254
5.902
5.884
5.867
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
17.13
8.18
17.04
25.53
16.33
15.79

^{1}H NMR of **3b**


WaelAbdElHameed-108P-DMSO-C13
Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory: DD5mm_test_12Mar2014-21:34:40
File: PROTON
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 30.0 C / 303.1 K
Mercury-300BB "NMR300"
Pulse 45.0 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
1808 repetitions
OBSERVE C13, 75.4523945 MHz
DECOUPLE H1, 300.0702830 MHz
Power 33 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 32 hr, 58 min, 37 sec
Date: Dec 9 2017
181.168
135.178
120.620
115.369
51.490
45.745
40.320
40.039
39.762
39.485
39.208
38.927
38.650
30.819
200
180
160
140
120
100
80
60
40
20
ppm

^{13}C NMR of **3b**


WaelAbdElHameed-106P-DMSO-H1
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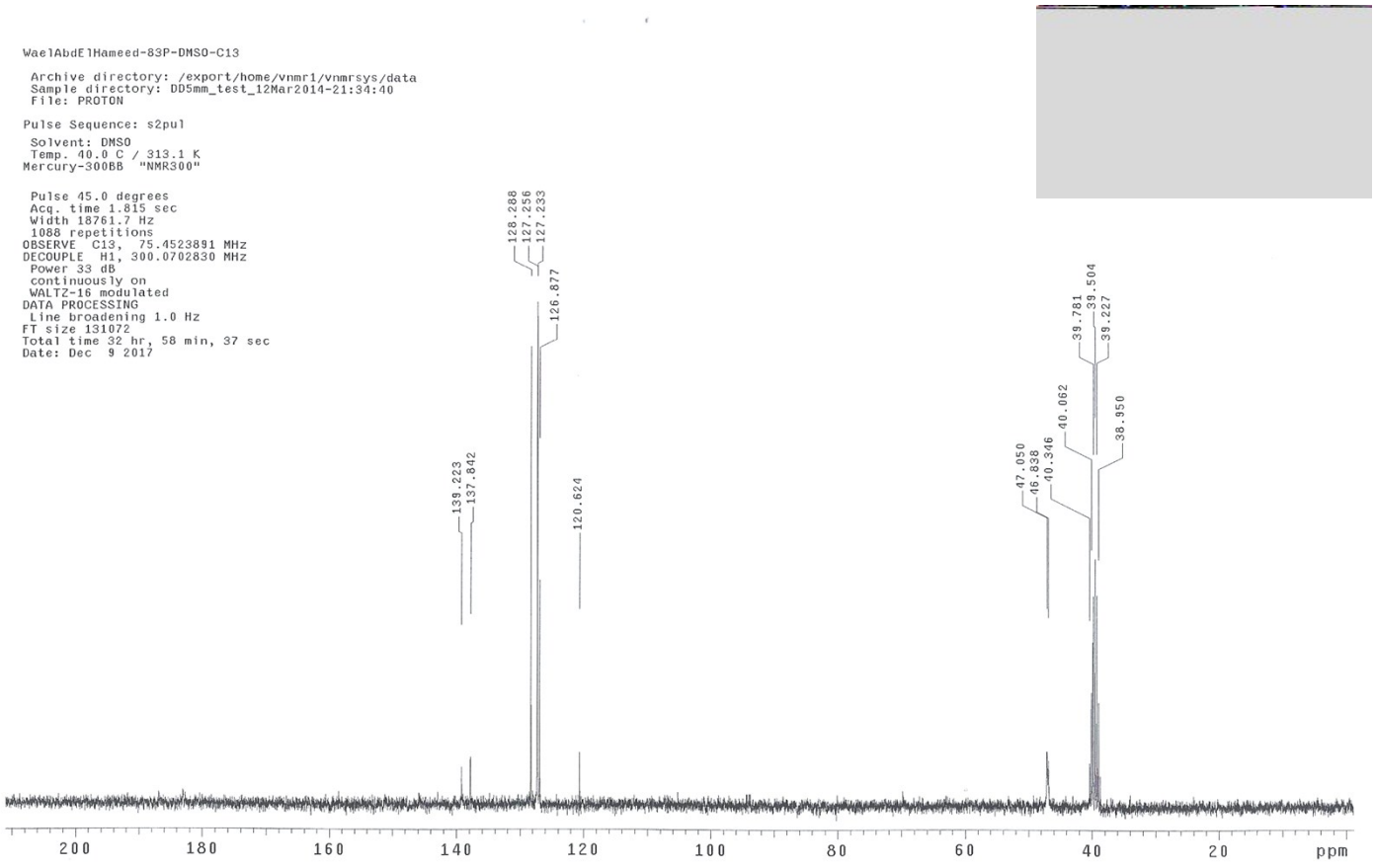
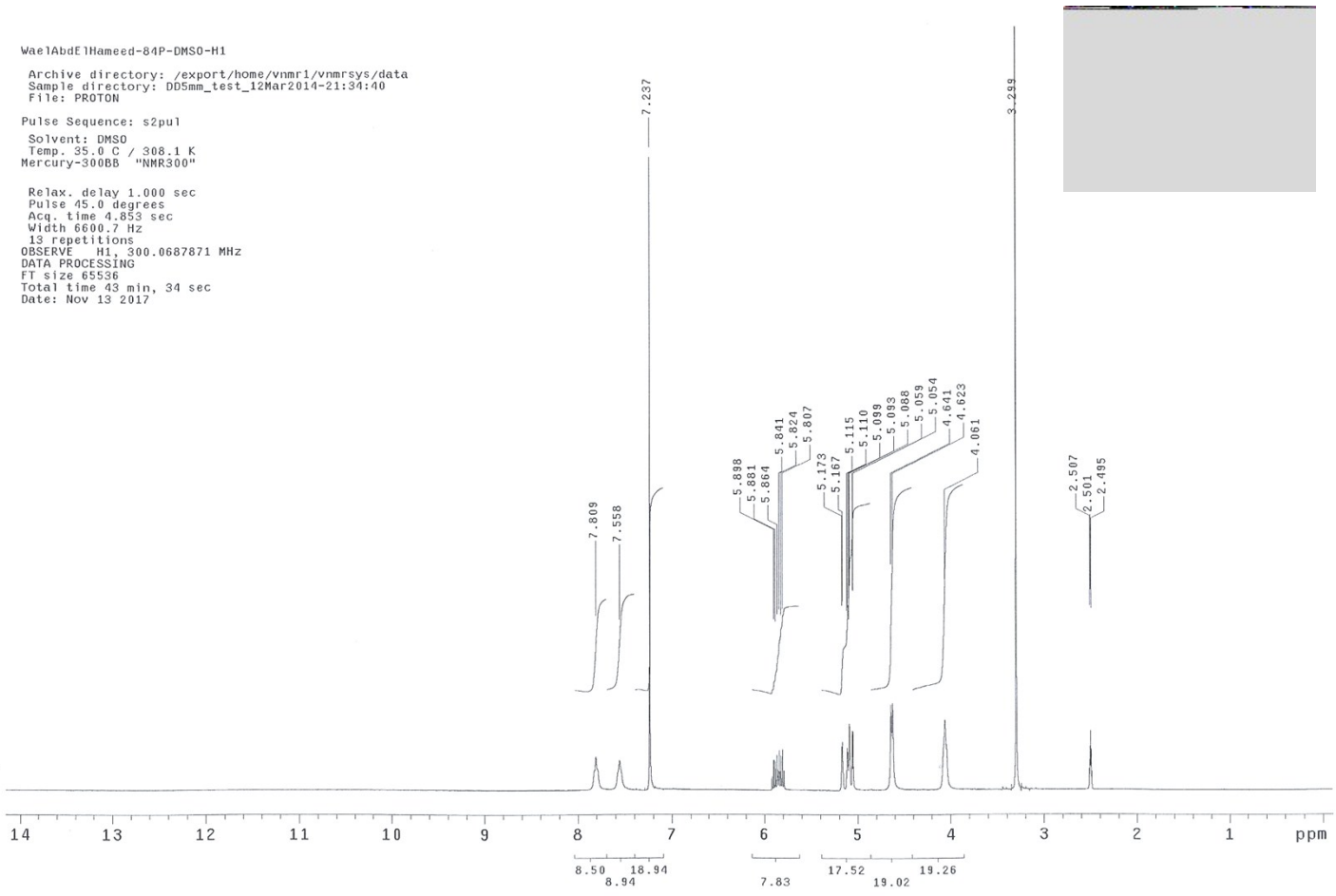
Sample directory: DD5mm_test_12Mar2014-21:34:40
File: PROTON
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 35.0 C / 308.1 K
Mercury-300BB "NMR300"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 4.853 sec
Width 6600.7 Hz
39 repetitions
OBSERVE H1, 300.0687871 MHz
DATA PROCESSING
FT size 65536
Total time 43 min, 34 sec
Date: Nov 13 2017
7.899
7.353
7.350
7.325
7.315
7.304
7.292
7.268
7.232
4.668
3.575
3.571
3.312
2.509
2.507
2.503
2.501
2.497
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
13.65
53.32
30.79
2.24

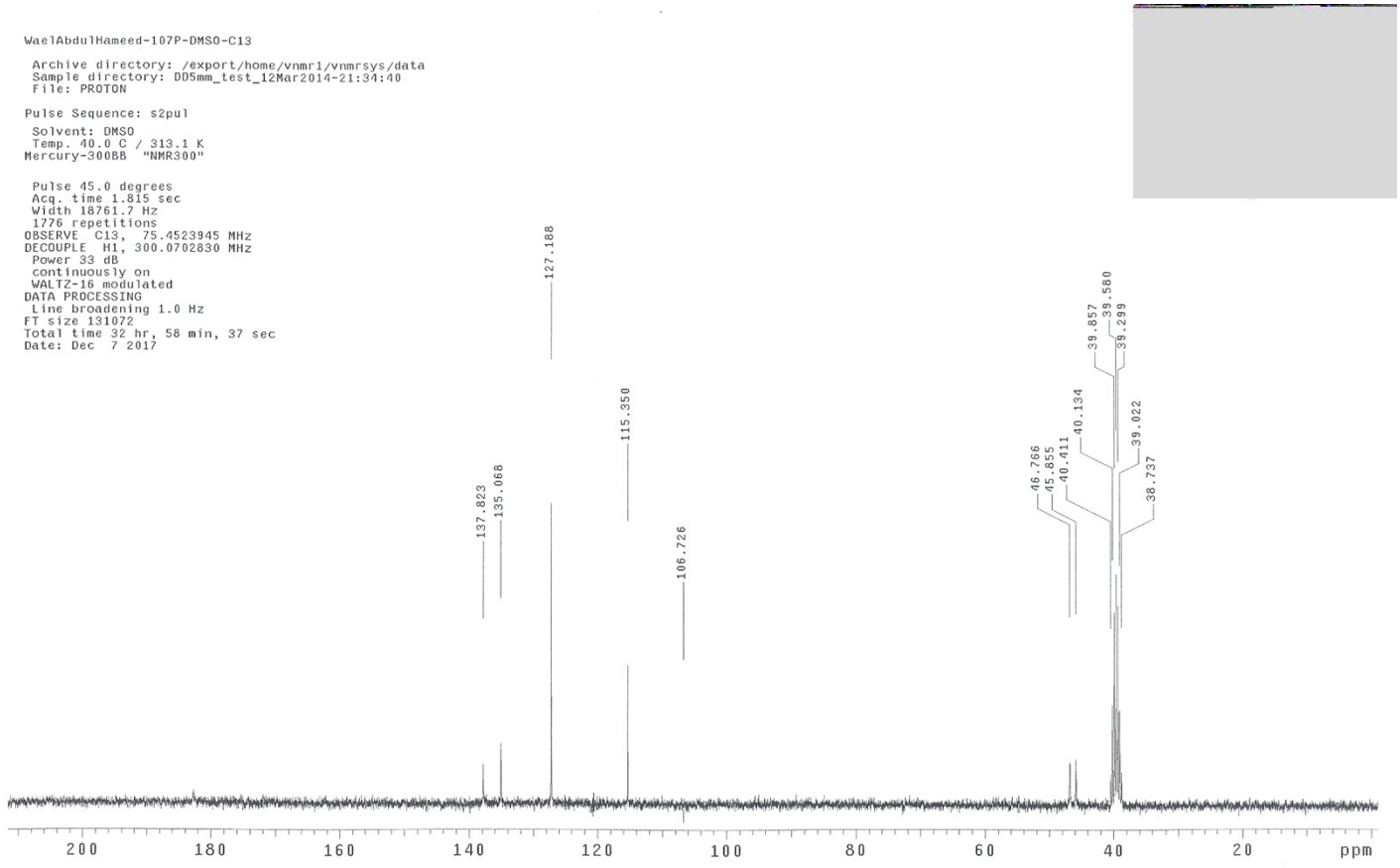
^{1}H NMR of **3c**


WaelAbdElHameed-83P-DMSO-C13
Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory: DD5mm_test_12Mar2014-21:34:40
File: PROTON
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 40.0 C / 313.1 K
Mercury-300BB "NMR300"
Pulse 45.0 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
1088 repetitions
OBSERVE C13, 75.4523891 MHz
DECOUPLE H1, 300.0702830 MHz
Power 33 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 32 hr, 58 min, 37 sec
Date: Dec 9 2017
128.288
127.256
127.233
126.877
139.223
137.842
120.624
47.050
46.838
40.346
40.062
39.781
39.504
39.227
38.950
200
180
160
140
120
100
80
60
40
20
ppm

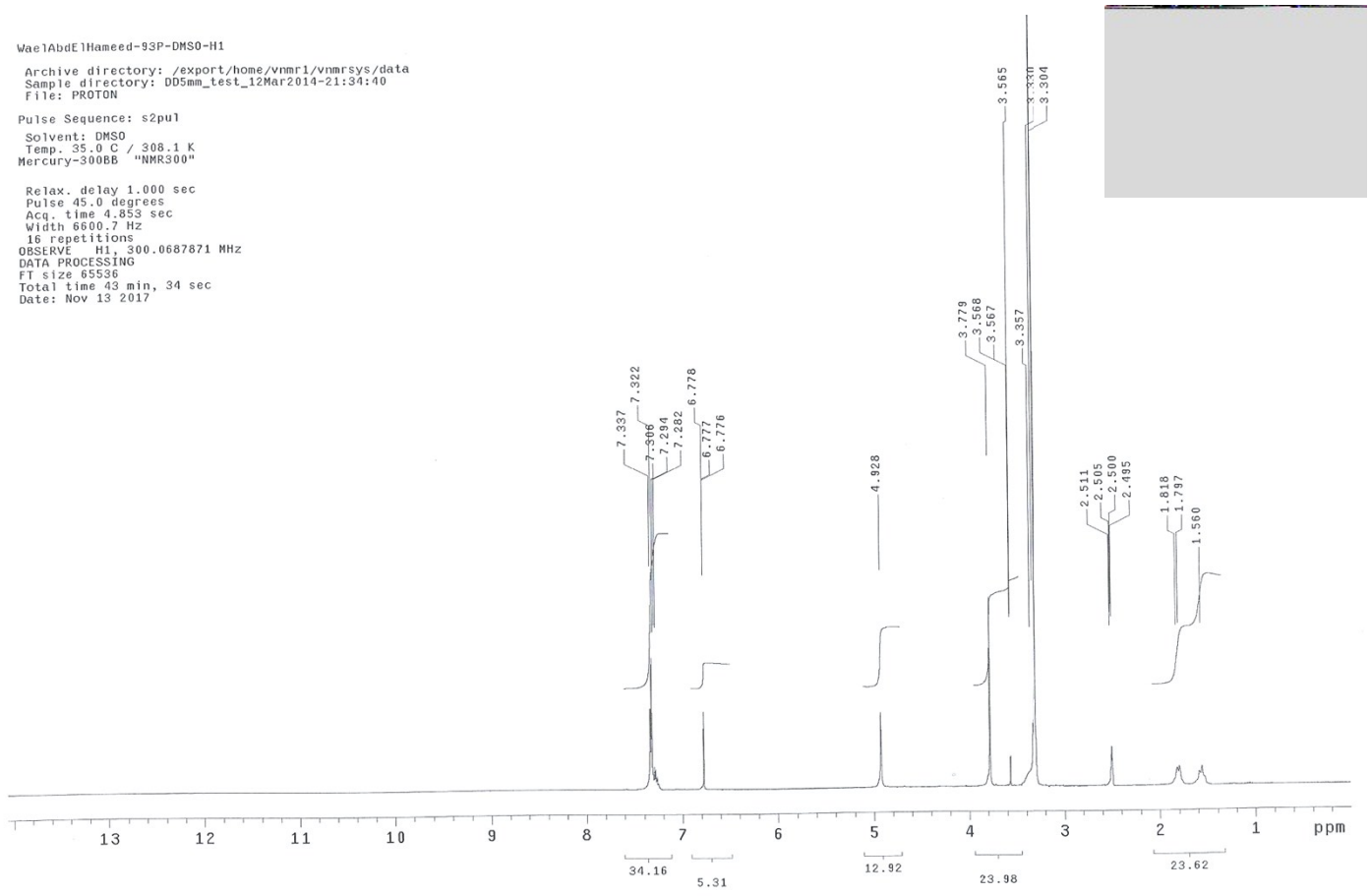
^{13}C NMR of **3c**


WaelAbdElHameed-84P-DMSO-H1
Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory: DD5mm_test_12Mar2014-21:34:40
File: PROTON
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 35.0 C / 308.1 K
Mercury-300BB "NMR300"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 4.853 sec
Width 6600.7 Hz
13 repetitions
OBSERVE H1, 300.0687871 MHz
DATA PROCESSING
FT size 65536
Total time 43 min, 34 sec
Date: Nov 13 2017
7.809
7.558
7.237
5.898
5.881
5.864
5.841
5.824
5.807
5.173
5.167
5.115
5.110
5.099
5.093
5.088
5.059
5.054
4.641
4.623
4.061
3.299
2.507
2.501
2.495
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
8.50
18.94
8.94
7.83
17.52
19.26
19.02

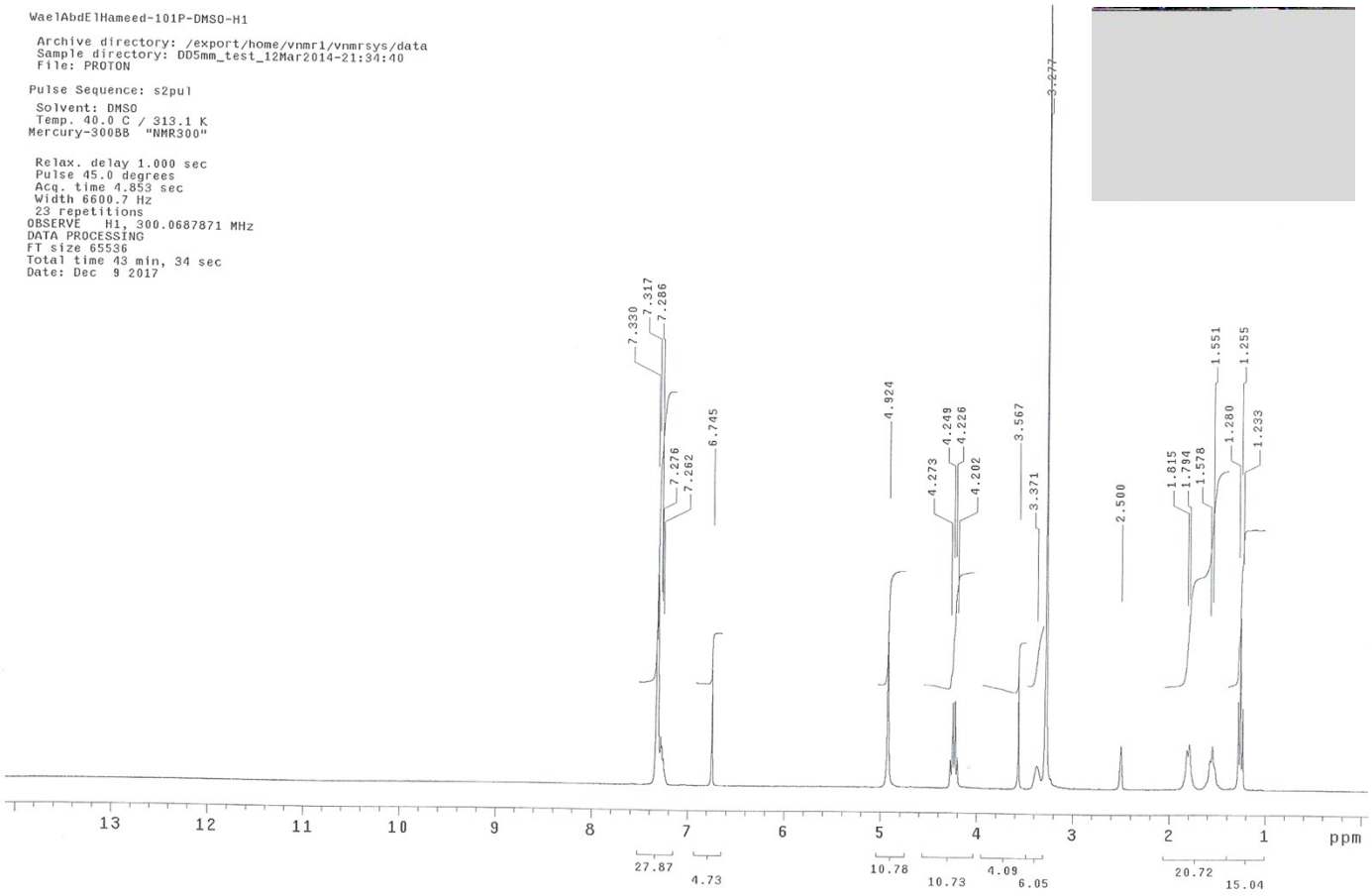
^{1}H NMR of **3d**


WaelAbdulHameed-107P-DMSO-C13
Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory: DD5mm_test_12Mar2014-21:34:40
File: PROTON
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 40.0 C / 313.1 K
Mercury-300BB "NMR300"
Pulse 45.0 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
1776 repetitions
OBSERVE C13, 75.4523945 MHz
DECOUPLE H1, 300.0702830 MHz
Power 33 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 32 hr, 58 min, 37 sec
Date: Dec 7 2017
137.823
135.068
127.188
115.350
106.726
46.766
45.855
40.411
40.134
39.857
39.580
39.299
39.022
38.737
200
180
160
140
120
100
80
60
40
20
ppm

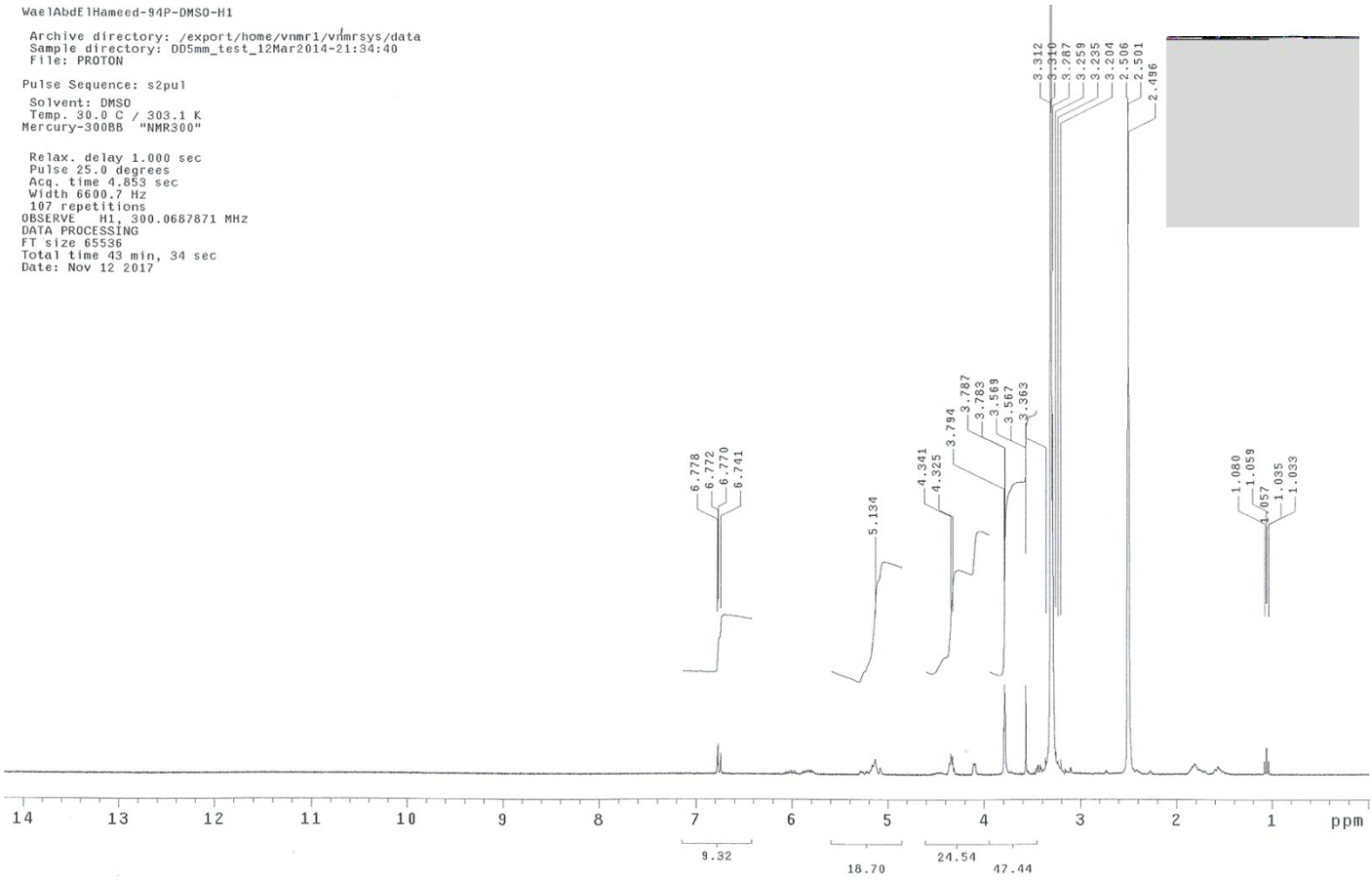
^{13}C NMR of **3d**


WaelAbdElHameed-93P-DMSO-H1
Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory: DD5mm_test_12Mar2014-21:34:40
File: PROTON
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 35.0 C / 308.1 K
Mercury-300BB "NMR300"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 4.853 sec
Width 6600.7 Hz
16 repetitions
OBSERVE H1, 300.0687871 MHz
DATA PROCESSING
FT size 65536
Total time 43 min, 34 sec
Date: Nov 13 2017
7.337
7.322
7.306
7.294
7.282
6.778
6.777
6.776
4.928
3.779
3.568
3.567
3.565
3.357
3.330
3.304
2.511
2.505
2.500
2.495
1.818
1.797
1.560
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
34.16
5.31
12.92
23.98
23.62

^{1}H NMR of **5a**


WaelAbdElHameed-101P-DMSO-H1
Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory: DD5mm_test_12Mar2014-21:34:40
File: PROTON
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 40.0 C / 313.1 K
Mercury-300BB "NMR300"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 4.853 sec
Width 6600.7 Hz
23 repetitions
OBSERVE H1, 300.0687871 MHz
DATA PROCESSING
FT size 65536
Total time 43 min, 34 sec
Date: Dec 9 2017
7.330
7.317
7.286
7.276
7.262
6.745
4.924
4.273
4.249
4.226
4.202
3.567
3.371
3.277
2.500
1.815
1.794
1.578
1.551
1.280
1.255
1.233
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
27.87
4.73
10.78
10.73
4.09
6.05
20.72
15.04

^{1}H NMR of **5b**


WaelAbdElHameed-94P-DMSO-H1
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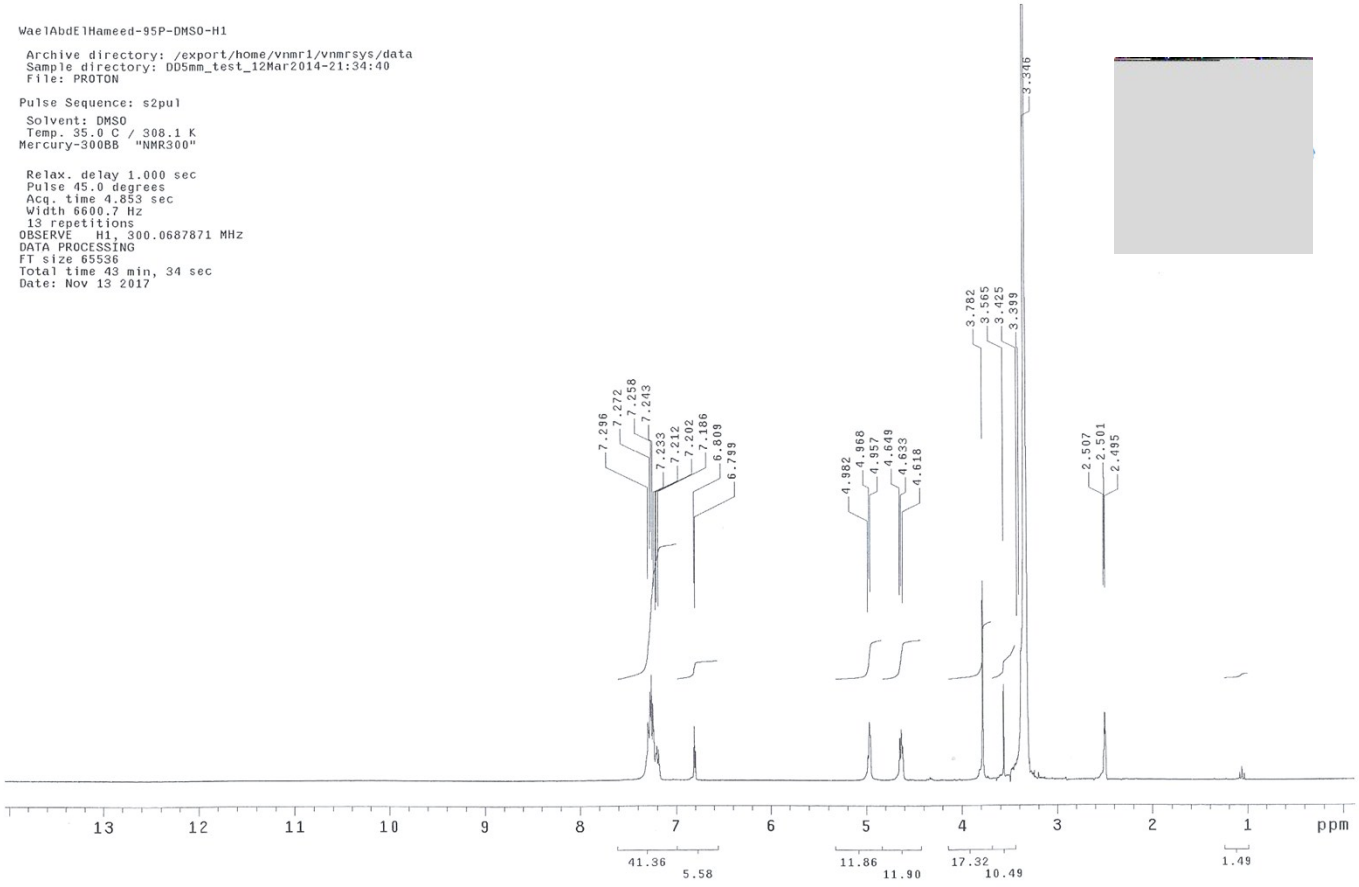
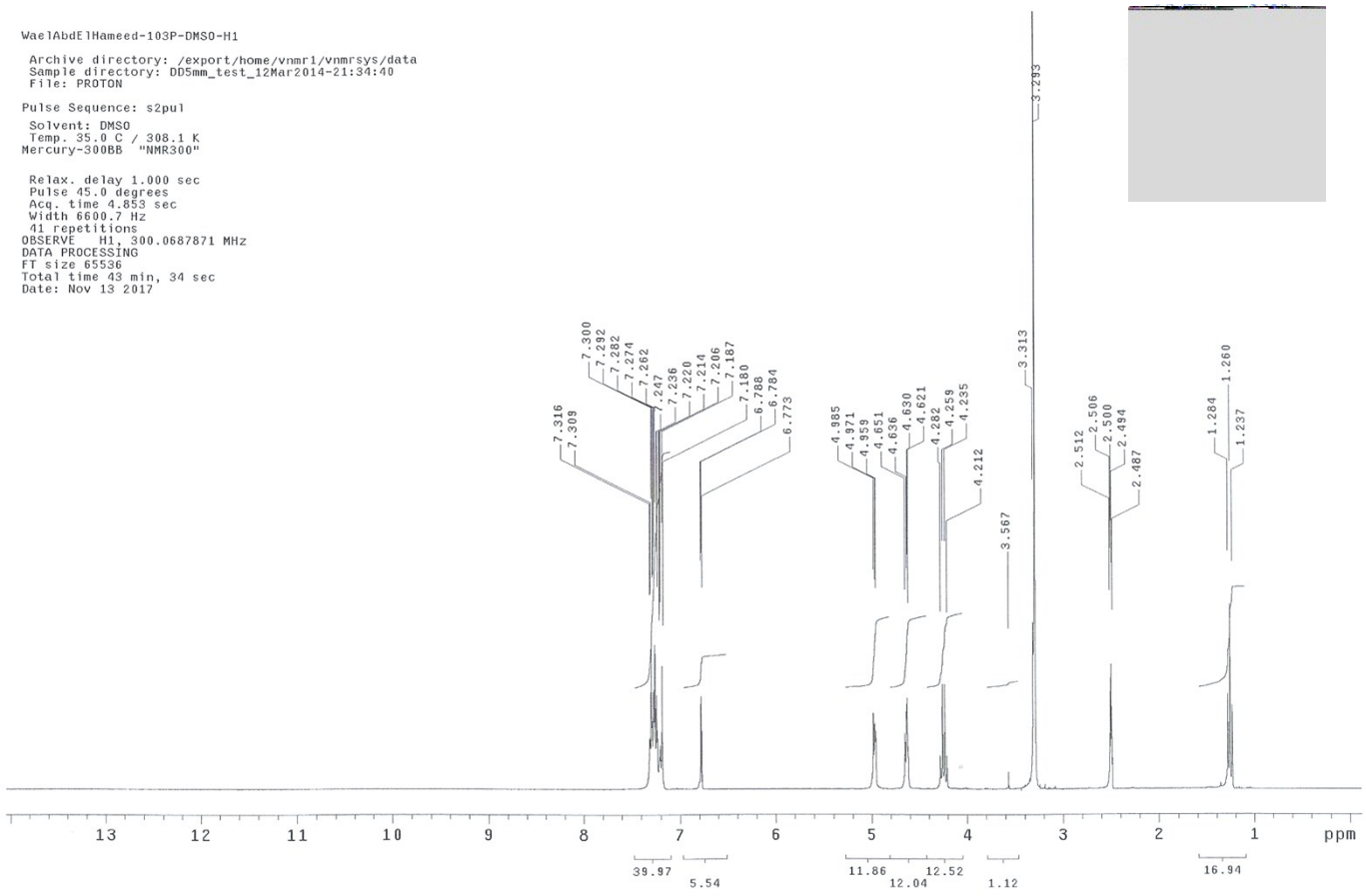
Sample directory: DD5mm_test_12Mar2014-21:34:40
File: PROTON
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 30.0 C / 303.1 K
Mercury-300BB "NMR300"
Relax. delay 1.000 sec
Pulse 25.0 degrees
Acq. time 4.853 sec
Width 6600.7 Hz
107 repetitions
OBSERVE H1, 300.0687871 MHz
DATA PROCESSING
FT size 65536
Total time 43 min, 34 sec
Date: Nov 12 2017
3.312
3.310
3.267
3.259
3.235
3.204
2.506
2.501
2.496
6.778
6.772
6.770
6.741
5.134
4.341
4.325
3.794
3.787
3.783
3.569
3.567
3.363
1.080
1.059
1.057
1.035
1.033
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
9.32
18.70
24.54
47.44

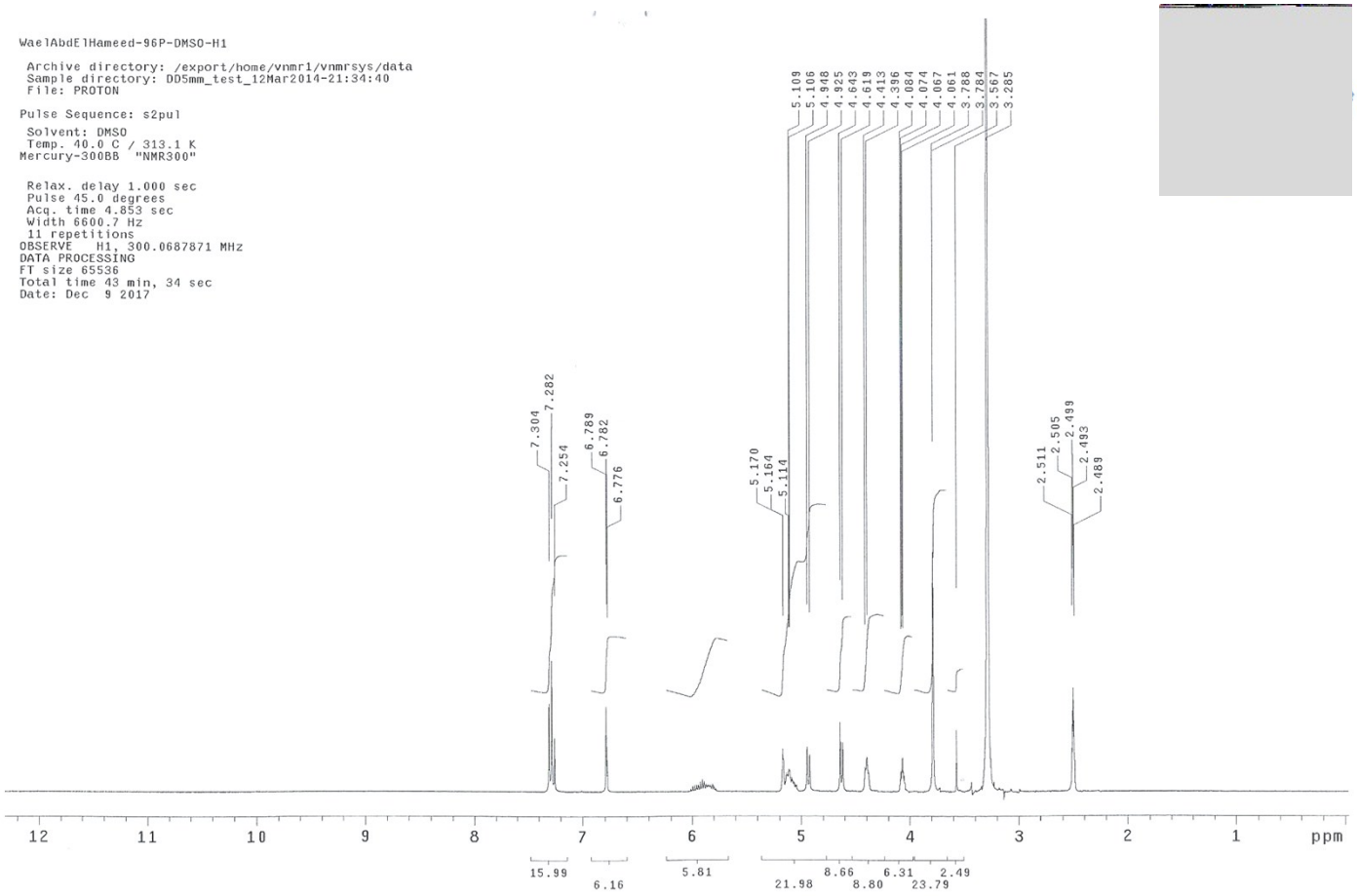
^{1}H NMR of **5c**



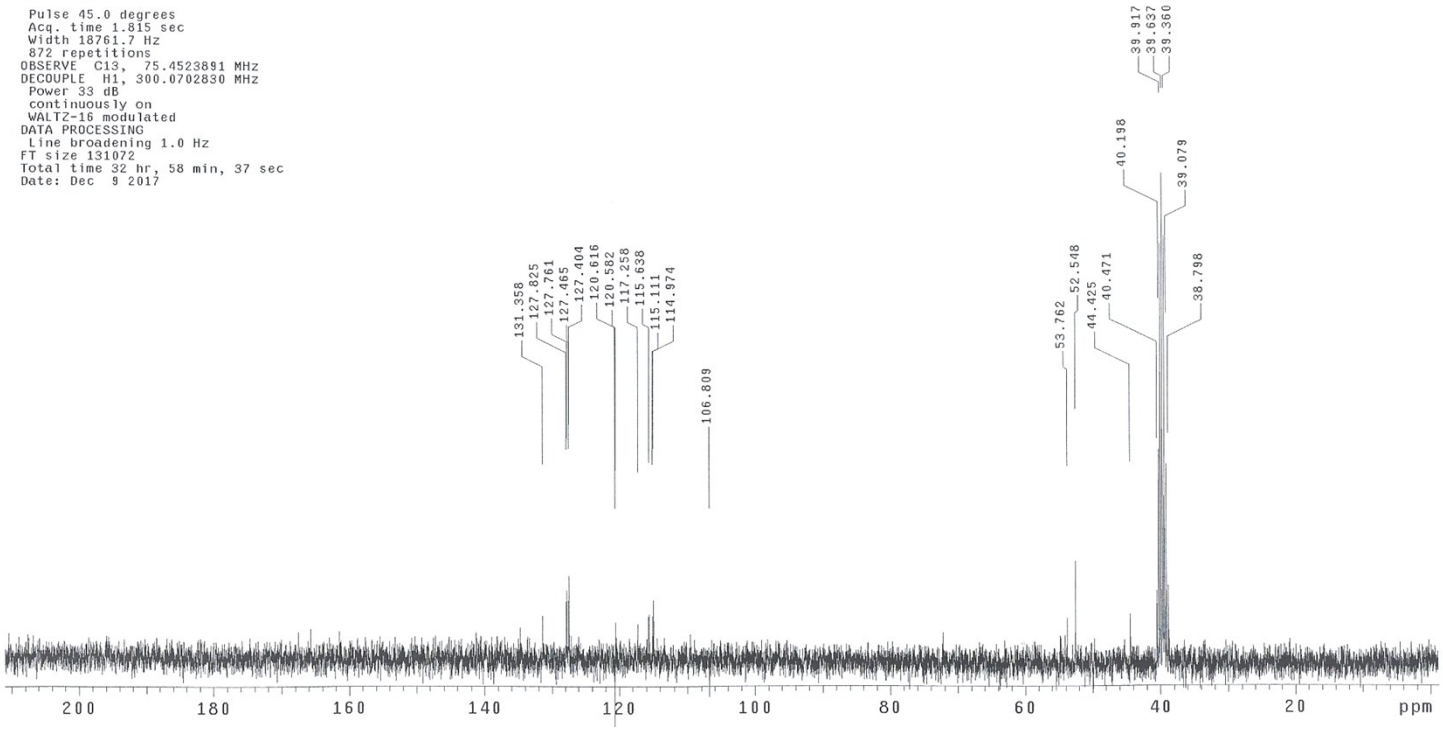
^{1}H NMR of **6a + 7a**



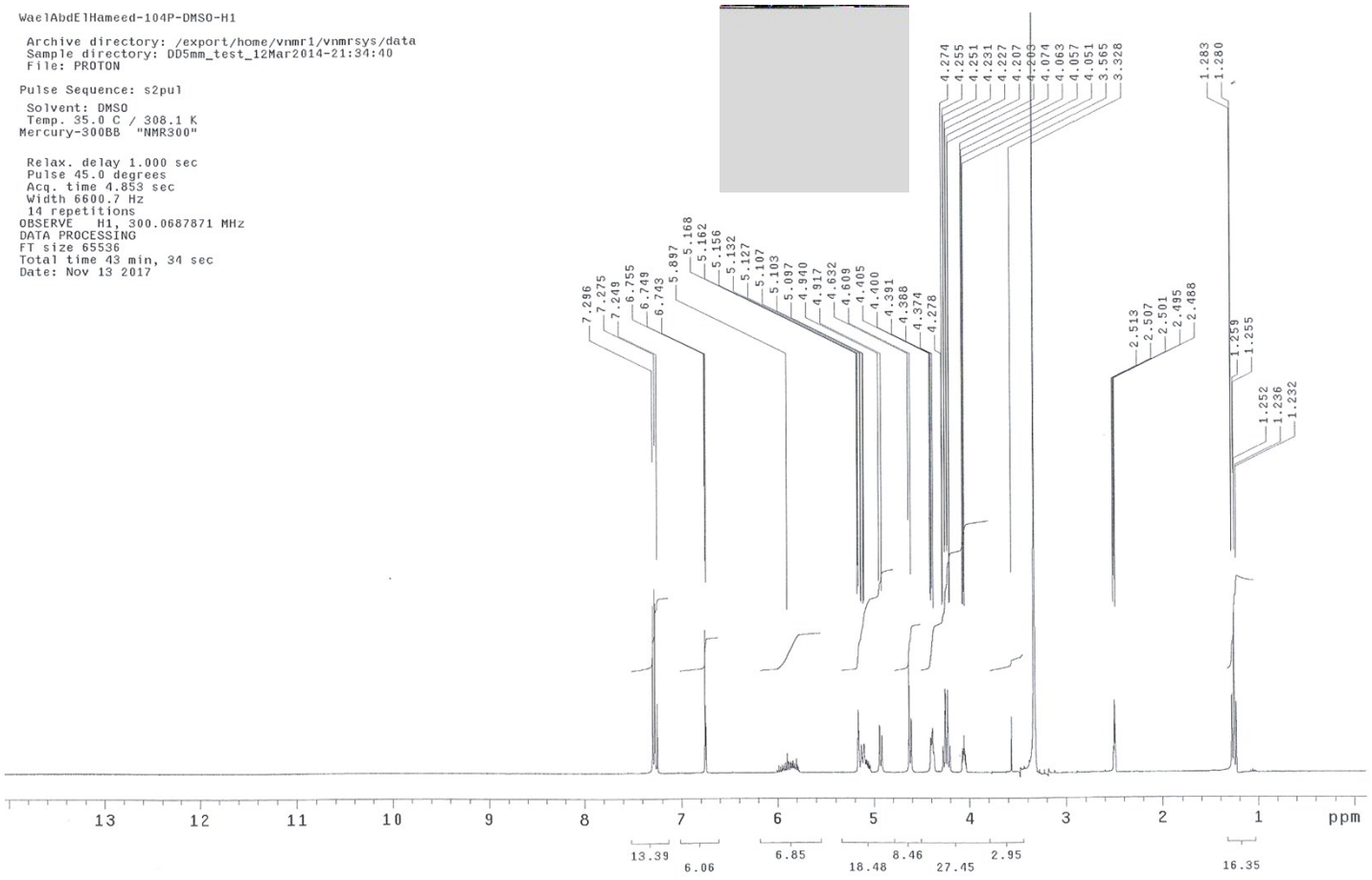
^{1}H NMR of **6b + 7b**



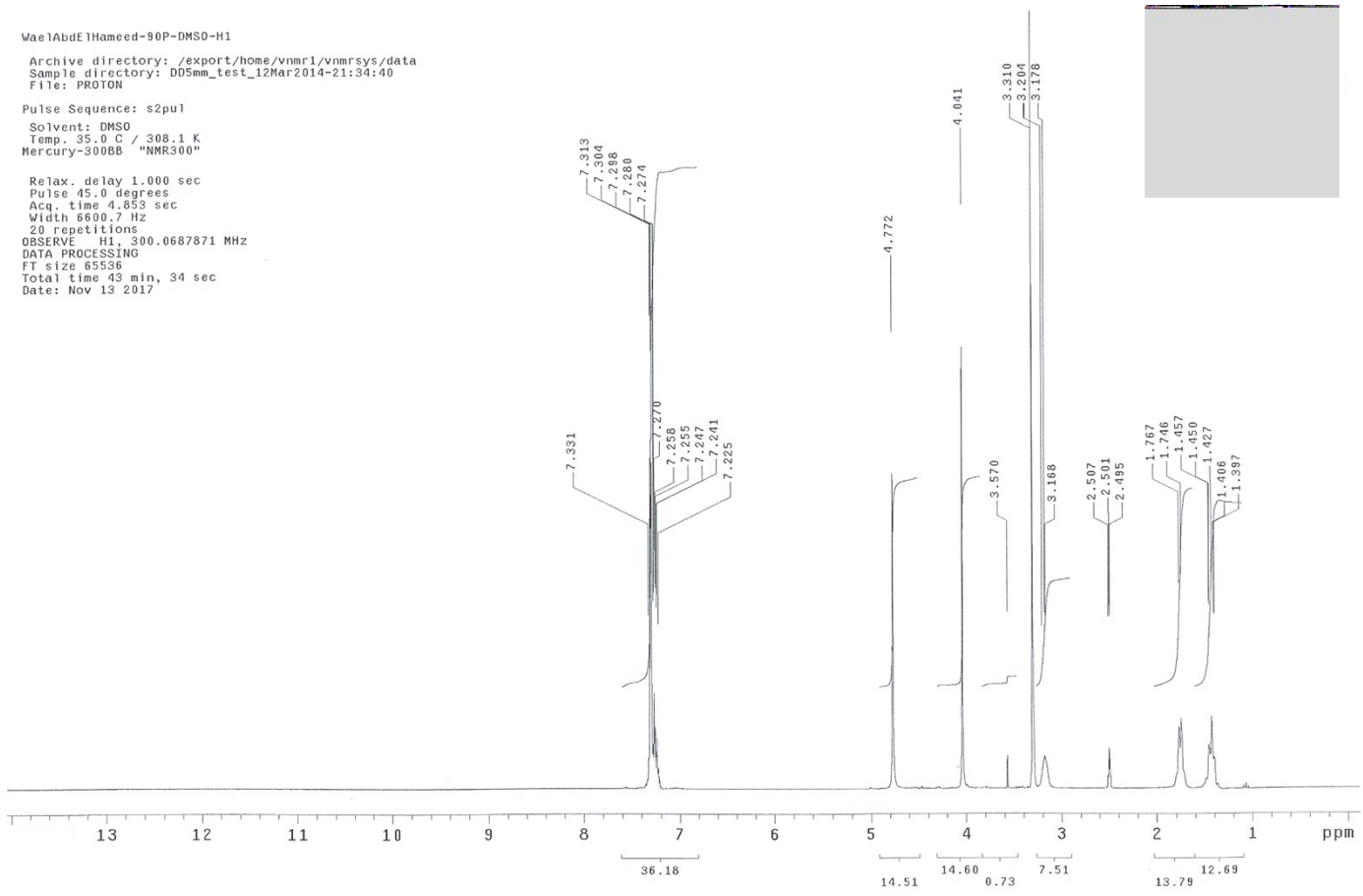
^{1}H NMR of **6c + 7c**



^{13}C NMR of **6c** + **7c**



^{1}H NMR of **6d + 7d**


WaelAbdElHameed-90P-DMSO-H1
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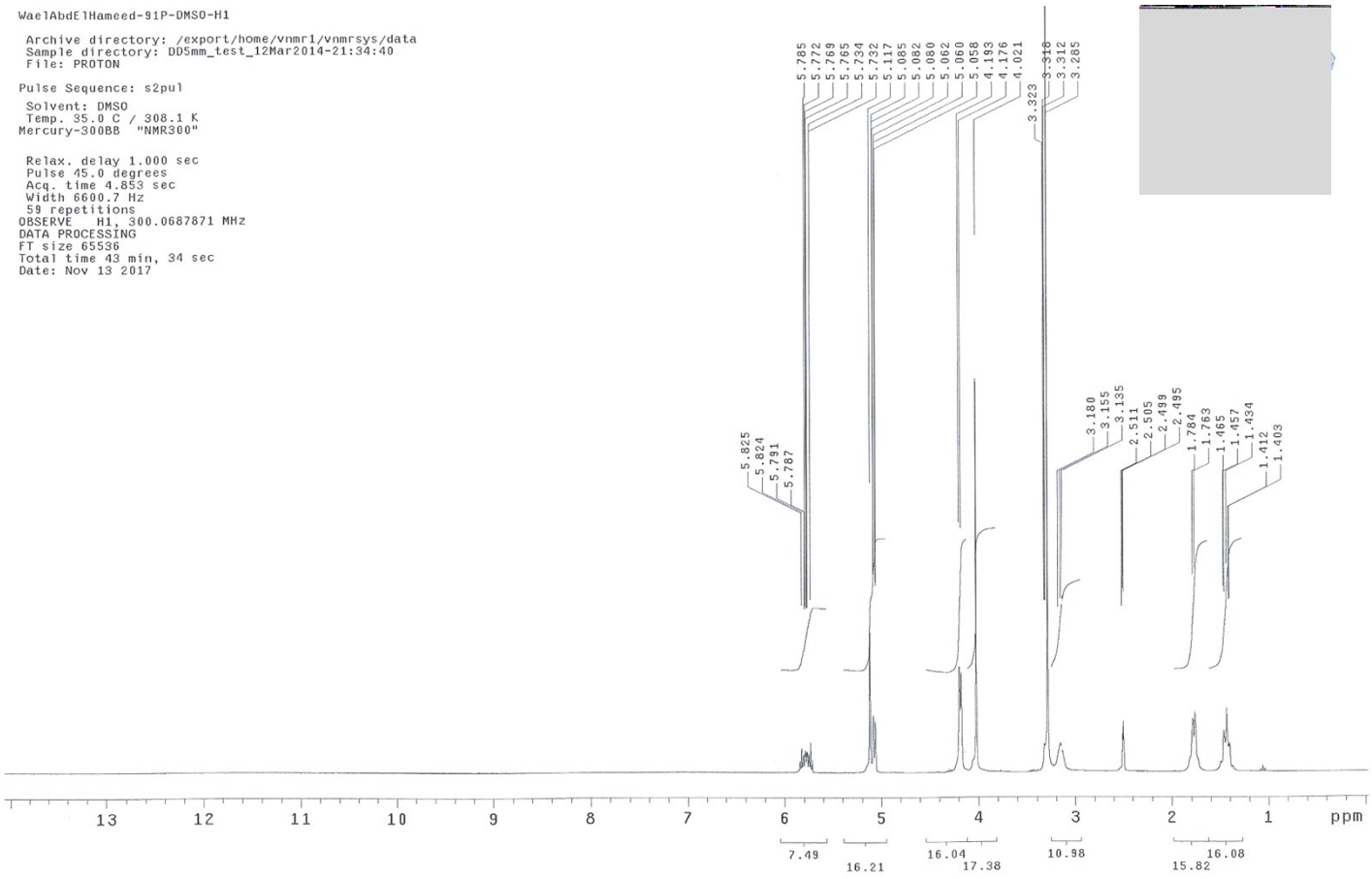
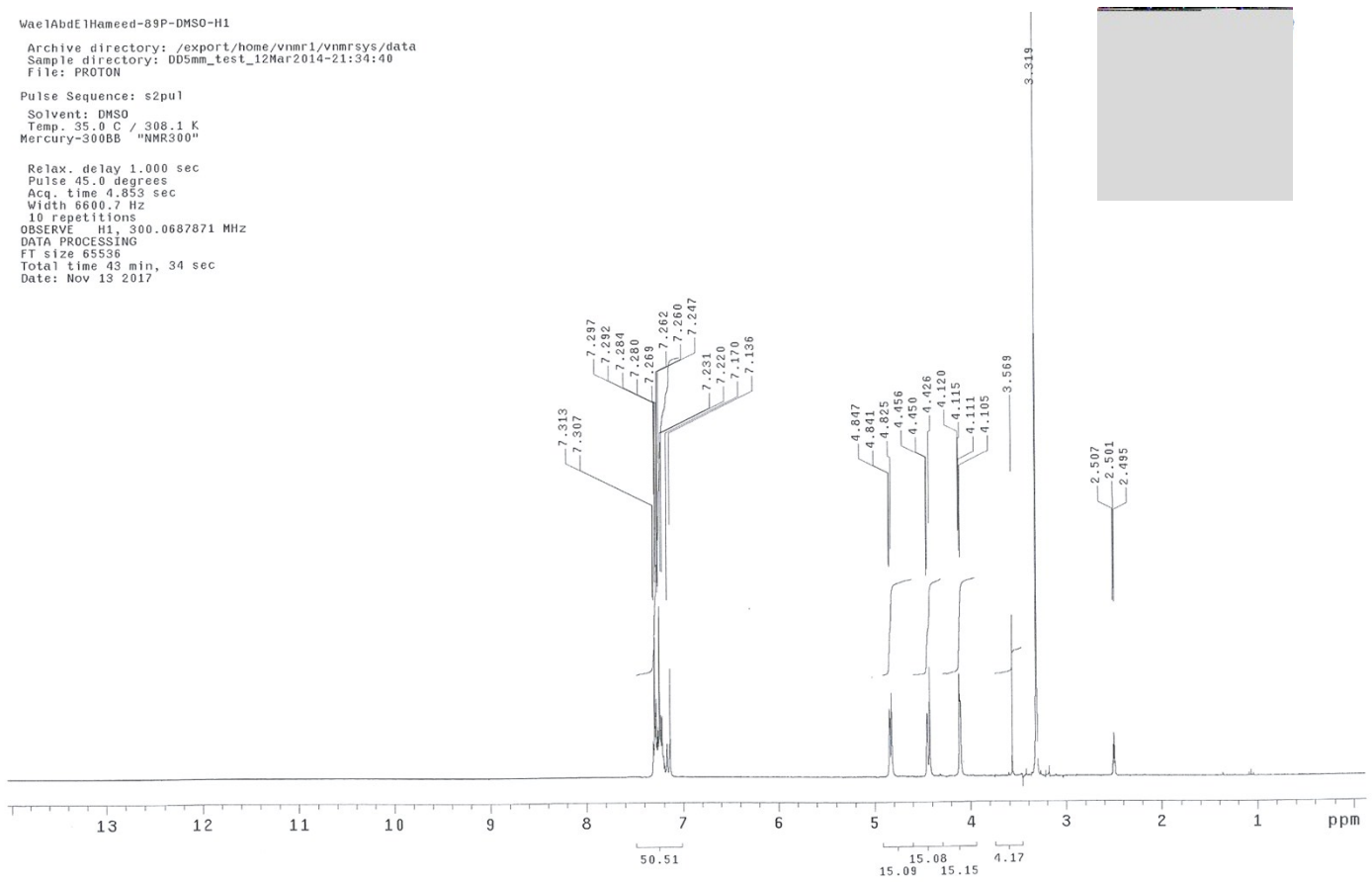
Sample directory: DD5mm_test_12Mar2014-21:34:40
File: PROTON
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 35.0 C / 308.1 K
Mercury-300BB "NMR300"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 4.853 sec
Width 6600.7 Hz
20 repetitions
OBSERVE H1, 300.0687871 MHz
DATA PROCESSING
FT size 65536
Total time 43 min, 34 sec
Date: Nov 13 2017
7.331
7.313
7.304
7.288
7.280
7.274
7.270
7.258
7.255
7.247
7.241
7.225
4.772
4.041
3.570
3.310
3.204
3.178
3.168
2.507
2.501
2.495
1.767
1.746
1.457
1.450
1.427
1.406
1.397
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
36.18
14.51
14.60
0.73
7.51
13.79
12.69

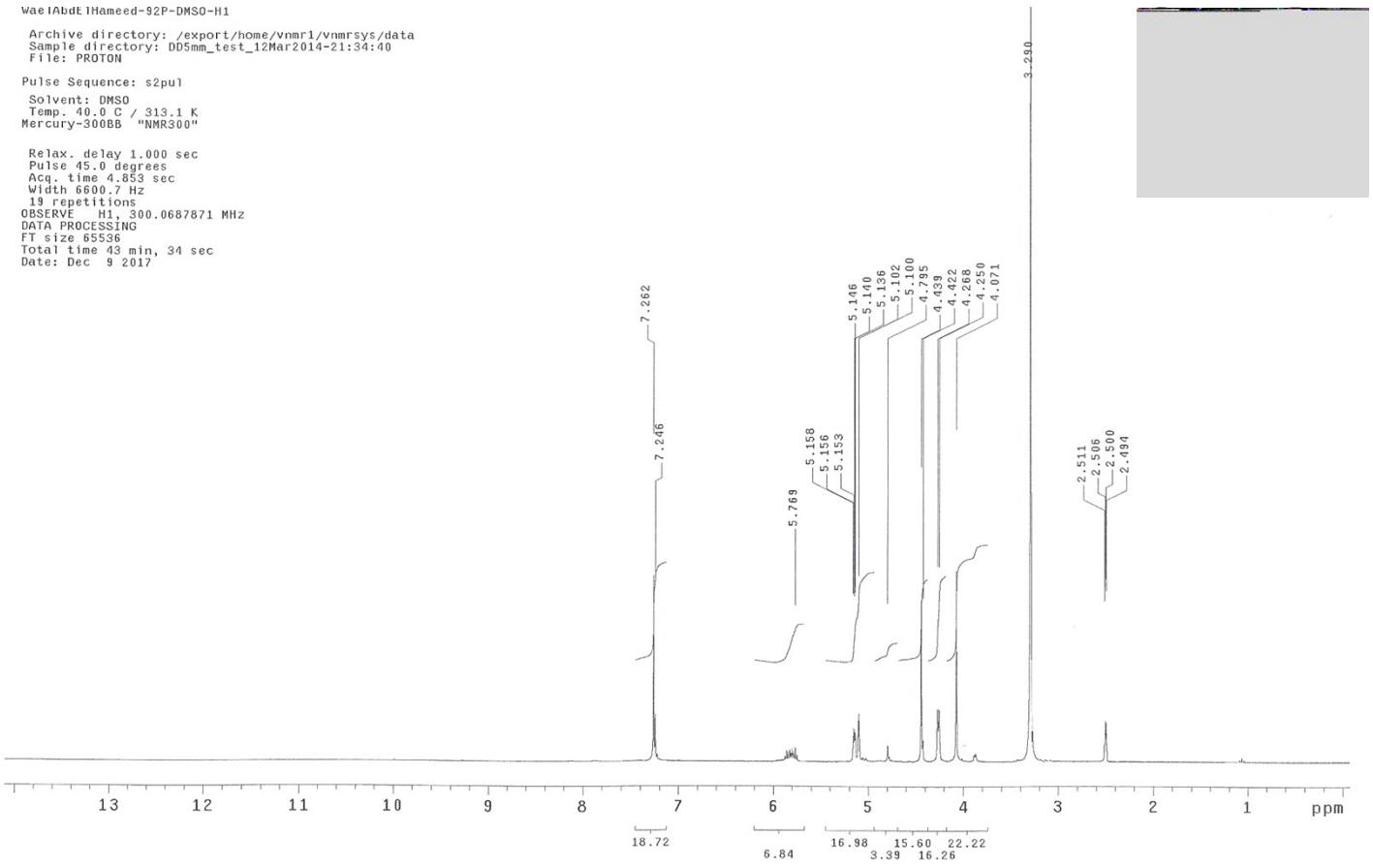
^{1}H NMR of **8a**


WaelAbdElHameed-91P-DMSO-H1
Archive directory: /export/home/vnmr1/vnmrsys/data
Sample directory: DD5mm_test_12Mar2014-21:34:40
File: PROTON
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 35.0 C / 308.1 K
Mercury-300BB "NMR300"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 4.853 sec
Width 6600.7 Hz
59 repetitions
OBSERVE H1, 300.0687871 MHz
DATA PROCESSING
FT size 65536
Total time 43 min, 34 sec
Date: Nov 13 2017
5.825
5.824
5.791
5.787
5.785
5.772
5.769
5.765
5.734
5.732
5.117
5.085
5.082
5.080
5.062
5.060
5.058
4.193
4.176
4.021
3.323
3.318
3.312
3.285
3.180
3.155
3.135
2.511
2.505
2.499
2.495
1.784
1.763
1.465
1.457
1.434
1.412
1.403
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
7.49
16.21
16.04
17.38
10.98
16.08
15.82

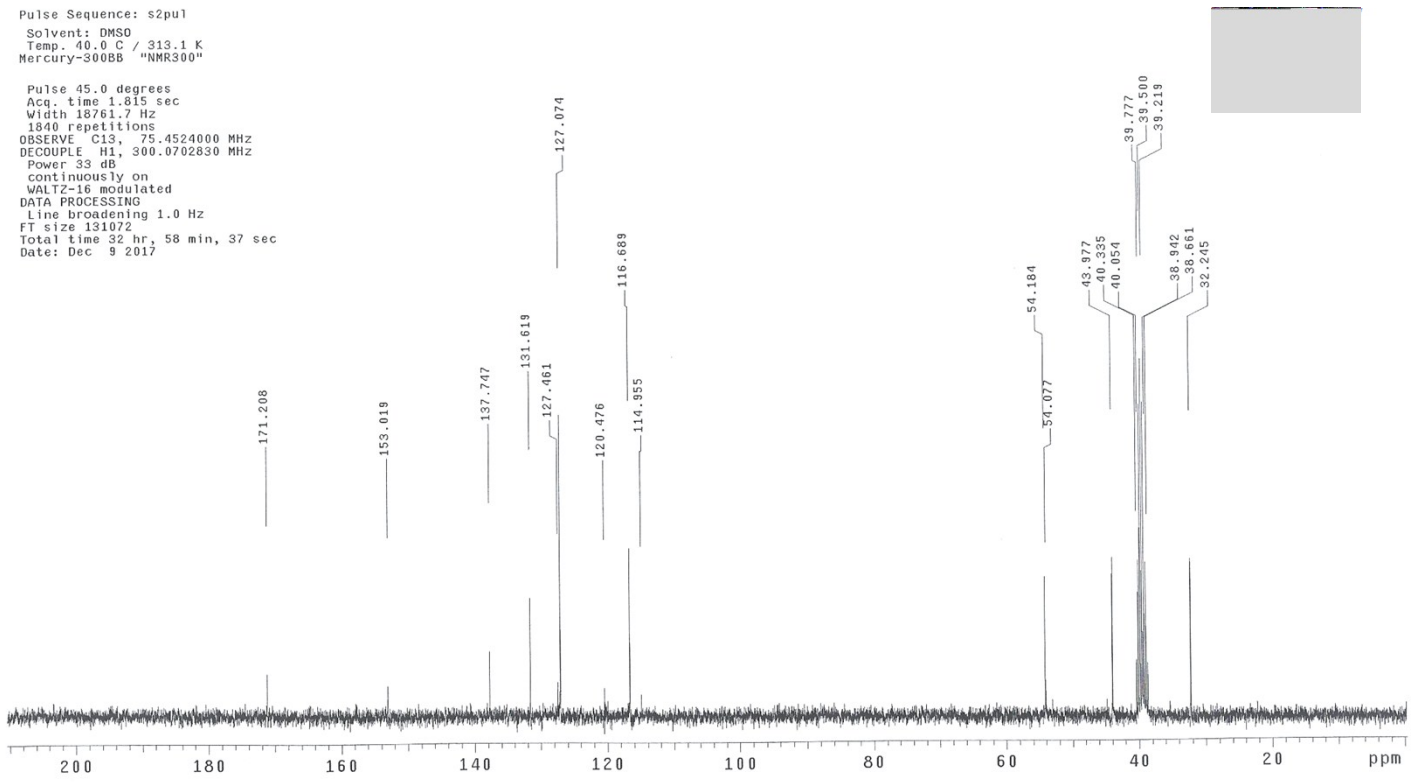
^{1}H NMR of **8b**



^{1}H NMR of **9a** + **10a**



^{1}H NMR of **9b + 10b**



^{13}C NMR of **9b** + **10b**

Green Metrics Calculations[1,2]

$$\textbf{\% Atomic Efficiency (AE)} = \frac{\text{Mol Wt. of desired product}}{\text{Mol Wt. of all reagents}} \times 100$$

$$\textbf{\% Carbon Efficiency (CE)} = \frac{\text{Mass of carbon in product}}{\text{Totall mass of carbon in the reactants}} \times 100$$

$$\textbf{Reaction Mass Efficiency (RME)} = \frac{\text{Mass of the isolated product}}{\text{Total mass of reactants used in the reaction}} \times 100$$

$$\textbf{E-Factor (EF)} = \frac{\text{Mass of the total waste}}{\text{Mass of the crude product}}$$

$$\textbf{Process Mass Intensity (PMI)} = \frac{\text{Total mass used in process}}{\text{Mass of product}}$$

References

1. D. Curzons, D. J. C. Constable, D. N. Mortimer and V. L. Cunningham, *Green Chem.*, 2001, **3**, 1-6.
2. C. Jimenez-Gonzalez, D. J. C. Constable and C. S. Ponder, *Chem. Soc. Rev.*, 2012, **41**, 1485-1498.