SUPPLEMENTARY DATA

Novel functionalized melamine-based nitroheterocycles: synthesis and activity against trypanosomatid parasites

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Synthesis of 2-amino-4,6-dichloro-[1,3,5]-triazine (2)

Cyanuric chloride (**1**, 2.5g 99%, 13.5 mmol) was dissolved in acetone (19 mL) and poured into 20 mL of ice-water (HPLC grade) to form a very fine suspension. Ammonium hydroxide solution (27 mL 1N, 27 mmol) was added dropwise carefully maintaining the temperature between 0 °C and 5 °C. The mixture was stirred 30 mins at 0 °C and additional 30 mins at room temperature. The precipitate was filtered off, washed with cold water (4 x 15 mL) and dried over P_2O_5 under high vacuum giving **2** (1.588 g, 71%) as a white solid; mp 223-225 °C; δ_H(300 MHz; DMSO-d_6) 8.59 (2 H, br s, N*H*$_2$); δ_C(75 MHz; DMSO-d_6) 167.3 (*C*Cl), 169.5 (*C*NH$_2$); *m/z* (ES$^+$) 165.7 ((M+H)$^+$, 60%)

N^2-propyl-2,4-diamino-6-chloro-[1,3,5]-triazine (3c)

2-amino-4,6-dichloro-triazine (500 mg, 3.03 mmol) was dissolved in acetone (6 mL) and poured into 6 mL of water to form a very fine suspension. A solution of propylamine (182.7 mg 98%, d=0.71, 0.26 mL, 3.03 mmol) was added followed by the addition of NaOH 2N (1.5 mL, 3.6 mmol) and maintaining the temperature on the range 0 °C/5 °C. The mixture was left stirring for 1 h at 0 °C and overnight at room temperature. The precipitate was filtered off, washed with water (2x15 mL) and dried over P_2O_5 giving **3c** (431mg, 76%) as a white solid; mp 156-158 °C; δ_H(300 MHz; DMSO-d_6) 0.89 (3 H, t, *J* 7.39, CH$_2$C*H*$_3$), 1.48 (2 H, m, C*H*$_2$CH$_3$), 3.15 (2 H, m, C*H*$_2$NH), 6.96-7.82 (3 H, 3m, ,–N*H*-,-N*H*$_2$); δ_C(75 MHz; DMSO-d_6) 8.6 (CH$_2$*C*H$_3^*$), 8.7 (CH$_2$*C*H$_3$), 22.3 (*C*H$_2$CH$_3$), 22.6 (*C**H$_2$CH$_3$), 42.2 (*C*H$_2$NH), 42.3 (*C**H$_2$NH), 165.9 (*C*Cl), 166.1 (*C**Cl), 166.8 (*C**NH$_2$), 167.3 (*C**NH$_2$), 168.4 (*C*NH), 169.1 (*C**NH); *m/z* (ES$^+$) 188.1 ((M+H)$^+$, 100%).

N^2-butyl-2,4-diamino-6-chloro-[1,3,5]-triazine (3d)

2-amino-4,6-dichloro-triazine (500 mg, 3.03 mmol) was dissolved in acetone (6 mL) and poured into 6 mL of water to form a very fine suspension. A solution of butylamine (222.7 mg 99.5%, d=0.74, 0.3 mL, 3.03 mmol) was added followed by the addition of NaOH 2N (1.5 mL, 3.6 mmol) carefully maintaining the temperature on the range 0 °C/5 °C. The mixture was left stirring for 1 h at 0 °C and overnight at room temperature. The precipitate was filtered off, washed with water (2x15 mL) and dried over P_2O_5 giving **3d** (577 mg, 94%) as a pure white solid; mp 133-135 °C; δ_H(300 MHz; DMSO-d_6) 0.87 (3 H, t, *J* 7.27, CH$_2$C*H*$_3$), 1.29 (2 H, sextet, *J* 7.27, C*H*$_2$CH$_3$), 1.45 (2 H, quintuplet, *J* 7.27, NHCH$_2$C*H*$_2$), 3.15 (2 H, m, NHC*H*$_2$), 6.98-7.79 (3 H, 3m, ,N*H*-,-N*H*$_2$); δ_C(75 MHz; DMSO-d_6) 14.0 (*C*H$_3$), 19.8 (*C**H$_2$CH$_3$), 19.9 (*C*H$_2$CH$_3$), 31.1 (NHCH$_2$*C*H$_2$), 31.5 (NHCH$_2$*C**H$_2$), 40.1 (NH*C**H$_2$), 41.2 (NH*C**H$_2$), 165.9 (*C*Cl), 166.1 (*C**Cl), 166.8 (*C**NH$_2$), 167.3 (*C*NH$_2$), 168.4 (*C*NH), 169.1 (*C**NH; *m/z* (EI) 202.1 (M$^+$, 100%).

2-N-[3-(t-butyl-diphenylsilyl)-oxy]-ethylamine (3e*)

Imidazole (8.86 g 98%, 127.68 mmol), *tert*-butyl-chlorodiphenyl-silane (TBDPS) (16.53 g 98%, d=1.568, 10.54 mL, 58.93 mmol) were mixed together and dissolved in anhydrous DMF (20 mL) and ethanolamine (3 g, 49.11 mmol) was added dropwise to the solution with stirring and under nitrogen. The mixture was left stirring at room temperature overnight until complete reaction. The solvent was removed under vacuum and the crude oil was purified by flash chromatography eluting with DCM / MeOH/NH$_4$OH (100:0:0 to 98:2:2) to give a pure product **3e** (7.6 g, 52%) as a yellow oil; δ_H(300 MHz; CDCl$_3$) 1.07 (9 H, s, CC*H*$_3$), 1.70 (2 H, br s, N*H*$_2$), 2.81 (2 H, t, *J* 5.32, C*H*$_2$NH$_2$), 3.68 (2 H, t, *J* 5.32, OC*H*$_2$), 7.41 (6 H, m, ArC*H*), 7.69 (4 H, m, ArC*H*); δ_C(75 MHz; CDCl$_3$) 19.7 (*C*CH$_3$), 27.3 (C*C*H$_3$),

44.7 (CH_2NH_2), 66.6 (OCH_2), 128.1 (Ar*C*), 134.1 (Ar*C*), 135.9 (Ar*C*); *m/z* (ES^+) 314.1 [$(M+H)^+$, 100%)], 598.9 [$(2M+H)^+$, 50%].

2-N-{[3-(*t*-butyl-diphenylsilyl)-oxy]-ethyl}-6-chloro-(2,4-diamino)-[1,3,5]-triazine (3e)

2-amino-4,6-dichloro-triazine (270 mg, 1.64 mmol) was dissolved in acetone (3.5 mL) and poured into 5 mL of water to form a very fine suspension. 3-[(*t*-butyl-diphenylsilyl)-oxy]-ethylamine was dissolved in water (1.5 mL) and was added dropwise to the suspension followed by the addition of NaOH 2N (0.9 mL, 1.8 mmol). The temperature during the addition was maintained on the range 0 °C/5 °C. The mixture was left stirring for 30 mins at 0 °C and for further 1.30 h at room temperature. The precipitate was filtered off, washed with MeOH and dried over P_2O_5 giving **3e** (245 mg, 35%) as a white pure solid; mp: 95-97 °C; δ_H(300 MHz; DMSO-d_6) 0.98 (9 H, s, CC*H*$_3$), 3.46 (2 H, t, *J* 5.59, C*H*$_2$NH), 3.71 (2 H, m, *J* 5.59, C*H*$_2$O), 7.10-7.80 (3 H, 3m, -N*H*-, -N*H*$_2$), 7.42 (6 H, m, Ar*H*), 7.61 (4 H, m, Ar*H*); δ_C(75 MHz; DMSO-d_6) 19.1 (*C*CH$_3$), 26.59 (C*C*H$_3$), 42.5 (*C**H$_2$NH), 42.6 (*C*H$_2$NH), 62.3 (*C*H$_2$O), 62.6 (*C**H$_2$O), 128.2 (Ar*C*H), 130.1 (Ar*C*H), 133.4 (Ar*C*H), 135.4 (Ar*C*H), 166.3 (*C*Cl), 166.5 (*C**Cl), 166.9 (*C**NH$_2$), 167.0 (*C*NH$_2$), 168.5 (*C*NH).

2-N-[3-(t-butyl-diphenylsilyl)-oxy]-propylamine (3f*)

3-Amino-1-propanol (1.2 g, 97%, 15.4 mmol) was dissolved in anhydrous pyridine (7mL) and TBDP chloride (5.11 g 98%, d= 1.074, 4.75 mL, 18.58 mmol) was slowly added to the solution. The mixture was stirred overnight at room temperature and under nitrogen. The mixture was then concentrated under reduced pressure and the crude oil was purified by flash chromatography eluting with DCM/MeOH (100:0 to 90:10) to give **3f** (4.1 g, 84%) as a pure product; mp 119-120 °C; δ_H(500 MHz; $CDCl_3$) 1.08 (9 H, s, CC*H*$_3$), 2.05 (2 H, m, CH$_2$C*H*$_2$CH$_2$), 3.22 (2 H, t, *J* 7.52, -C*H*$_2$NH$_2$), 3.77 (2 H, t, *J* 5.42, C*H*$_2$O), 7.41 (6 H, m, Ar*H*), 7.69 (m, 4H, Ar*H*); δ_C(125 MHz; $CDCl_3$) 19.2 (*C*CH$_3$), 26.9 (C*C*H$_3$), 30.6 (CH$_2$*C*H$_2$CH$_2$), 30.0 (*C*H$_2$NH), 61.2 (*C*H$_2$O), 127.8 (*Ar*H), 129.8 (*Ar*H), 133.1 (*Ar*H), 135.5 (*Ar*H); *m/z* (CI^+) 314.1 ($(M+H)^+$, 100%).

2-N-{[3-(*t*-butyl-diphenylsilyl)-oxy]-propyl}-6-chloro-(2,4-diamino)-[1,3,5]-triazine (3f)

2-amino-4,6-dichloro-triazine (500 mg, 3.03 mmol) was dissolved in acetone (8 mL) and poured into 10 mL of water to form a very fine suspension. 3-[(*t*-butyl-diphenylsilyl)-oxy]-propylamine was dissolved in water (2 mL) and was added dropwise to the suspension followed by the addition of NaOH 2N (1.5 mL, 3.6 mmol). The temperature during the addition was maintained on the range 0°C/5°C. The mixture was left stirring for 30 mins at 0°C and then left stirring overnight at room temperature. The precipitate was filtered off, washed with water and dried over P_2O_5 giving **3f** (604 mg, 45%) as a white solid; mp 132-134 °C; δ_H(500 MHz; DMSO-d_6) 0.99 (9 H, s, CC*H*$_3$), 1.77 (2 H, m, CH$_2$C*H*$_2$CH$_2$), 3.34 (2 H, m, C*H*$_2$NH$_2$), 3.70 (2 H, m, C*H*$_2$O), 7.00-7.53 (2 H, 3m, CN*H*$_2$), 7.43 (6 H, m, Ar*H*), 7.61 (4 H, m, Ar*H*), 8.57 (m, 1H, N*H*); δ_C(125 MHz; DMSO-d_6) 18.7 (*C*CH$_3$), 26.5 (C*C**H$_3$), 26.6 (C*C*H$_3$), 31.3 (CH$_2$*C*H$_2$CH$_2$), 31.8 (CH$_2$*C**H$_2$CH$_2$), 36.9 (*C**H$_2$NH), 37.1 (*C*H$_2$NH), 61.1 (*C**H$_2$O), 61.3 (*C*H$_2$O), 127.5 (*Ar*H), 127.8 (*Ar*H), 129.1 (*Ar*H), 129.7 (*Ar*H), 133.2 (*Ar*H), 134.4 (Ar*C**H) 134.9 (*Ar*H), 165.6(*C*Cl), 166.4 (*C**Cl), 166.9 (*C**NH$_2$), 168.0 (*C*NH$_2$), 169.2 (*C*NH); *m/z* (CI^+) 442.3 ($(M+H)^+$, 70%), 444.3 ($(M+H+^{37}Cl)^+$, 25%).

N^2-hydroxypropy-6-chloro-2,4-diamino-[1,3,5]-triazine (3g)

2-amino-4,6-dichloro-[1,3,5]-triazine (1.5 g, 9.09 mmol) was dissolved in DMF (20 mL) at -20 °C and 3-amino-propanol (690 mg 99%, d= 0.986, 0.69 mL, 9.09 mmol) was added dropwise to the solution maintaining the temperature around -20 °C. DIPEA (Diisopropylethylamine) (1.76g 99.5%, d=0.742,

2.38mL, 13.6 mmol) was added dropwise to the previous mixture at -20°C. The temperature was left rise to room temperature and the reaction was left stirring for 2 h. The solvent was removed under vacuum and the oil obtained was washed with DCM to give a lumpy white solid which was ground by using a pestle and mortar. The solid was dissolved in the minimum amount of DMF and then added dropwise DCM with stirring to get a fine precipitate. The fine white solid was filtered off, washed with DCM and dried under high vacuum at 40°C giving **3g** (1.68 g, 91%) as a white solid; δ_H(500 MHz; DMSO-d_6) 1.60 (2 H, quintuplet, *J* 6.46, $CH_2CH_2CH_2$), 3.25 (2 H, quintuplet, *J* 6.46, CH_2NH), 3.43 (2 H, t, *J* 6.46, CH_2OH), 4.40 (1 H, br s, OH), 7.07-7.28 (2 H, br m, NH_2), 7.55-769 (1 H, 2 x t, *J* 5.50, -N*H*-); δ_C(125 MHz; DMSO-d_6) 31.9 ($CH_2CH_2CH_2$), 32.2 ($CH_2C^*H_2CH_2$), 37.4 (CH_2NH), 37.5 (C^*H_2NH), 58.3 (CH_2OH), 58.4 (C^*H_2OH), 165.5 (*C*Cl), 166.9 (*C*NH-), 167.9 (CNH_2).

3-(4-amino-6-chloro-1,3,5-triazin-2-yl amino) propanoic acid (3h)

4,6-dichloro-1,3,5-triazin-2-amine (**2**, 1.01g, 6 mmol) dissolved in EtOH (80ml) was added portion wise to water (60ml) at 2 ^oC and the resultant suspension was left to cool untill the temperature returned to 2^oC. Beta alanine (542 mg, 6 mmol) in water (10 mL) and $NaHCO_3$ (1.01 g, 12 mmol) in water (10ml) were added dropwise over approx 10 mins at a rate maintaining the temperature at 2 ^oC. The resultant mix was stirred at 2 ^oC for a further 2 mins and then at room temperature for 90 mins whereupon the solution became clear. TLC analysis (RP C18 plates, 1:1 MeCN:H_2O) showed the triazine starting material still present. Reaction left to stir at room temperature overnight, TLC analysis showed unchanged. Further aliquots of beta alanine (250mg in water, 1 mL) and $NaHCO_3$ (250 mg in water 1ml) were added and the reaction mixture was stirred at 40 ^oC for 30 mins whereupon tlc analysis showed complete loss of triazine starting material. The pH was adjusted to pH = 2 (conc HCl dropwise) and the mixture was reduced in vacuum to remove the ethanol only and yield a white precipitate. The precipitate was stood at room temperature for 30 mins and then filtered under vacuum, air dried for 15 mins and then dried in a drying pistol (P_2O_5) at high vacuum (1 h) to yield the **3h** (0.974 g, 75%) as a fine white solid; δ_H(300 MHz; DMSO-d_6) 2.5 (2 H, m, CH_2), 3.4 (2 H, m, CH_2), 7.3 (2 H, s, NH_2), 7.7 (1 H, br m, 1H, N*H*-), 12.2 (1H, br s, -CO_2H); δ_C(75 MHz; DMSO-d_6) 33.3 (CH_2), 36.3 (CH_2), 165.5 (triazine *C*), 166.9 (triazine *C*), 168.1 (triazine *C*), 172.7 (*C*=O); *m/z* (ES^+) 218 $(M + H)^+$, 240 $(M + Na)^+$; *m/z* 240.0264 ($[M+Na]^+$ $C_6H_8N_5O_2ClNa$ requires 240.0256).

4-(4-amino-6-chloro-1,3,5-triazin-2-yl amino) butanoic acid (3i)

4, 6-dichloro-1, 3, 5-triazin-2-amine (**2**, 553 mg, 3.3 mmol) was dissolved in EtOH (40mL) and Water (40mL) and stirred at 2°C. 4-Aminobutyric acid (458 mg, 4.4 mmol) in Water (10mL), was added dropwise to the reaction mixture at a rate maintaining the temperature at 2°C. $NaHCO_3$ (835 mg, 9.9 mmol) in Water (10 mL) was also added at a rate maintaining the temperature at 2°C. The resulting mixture was stirred at room temperature for 60 mins and then at 35°C for 2h. The pH was adjusted to 2 (conc HCl dropwise), and the suspension left to cool down to room temperature. The precipitate was filtered under vacuum, washed with Water (10mL), air dried 10 mins, and then dried in a drying pistol at 30°C over P_2O_5 at high vacuum for 3h to yield **3i** (607 mg, 78%) as a fine white solid. mp 201-203°C (Found: C, 36.0; H, 4.4; N, 29.7; Cl, 15.1 $C_7H_{10}N_5O_2Cl{*}0.2H_2O$ Requires C, 35.7 H, 4.5; N, 29.8; Cl, 15.1 %); δ_H(500 MHz; DMSO-d_6) 1.71 (2 H, m, CH_2), 2.25 (2 H, t, *J* 7.0, CH_2), 3.20 (2 H, m, CH_2), 7.20 (2 H, m, NH_2), 7.70 (1 H, t, *J* 5.2, N*H*),12.09 (1 H, br s, CO_2H); δ_C(125 MHz; DMSO-d_6) 24.0 and 24.4 (CH_2) 30.9 and 31.0 (CH_2), 39.4 and 39.6 (CH_2), 165.6, 165.7, 166.4, 166.9, 168.0 and 168.7 (triazine *C*), 174.2 (*C*=O); *m/z* (ES^+) 232 ($(M+H)^+$, 100%). 232.0598 ($M+H^+$ $C_7H_{11}N_5O_2Cl^+$ Requires 232.0596).

6-(4-amino-6-chloro-1,3,5-triazin-2-yl amino) hexanoic acid (3j)

4, 6-dichloro-1, 3, 5-triazin-2-amine (**2**, 210 mg, 1.3 mmol) was dissolved in EtOH (15mL) and Water (15mL) and stirred at 2°C. 6-Amino caproic acid (348 mg, 2.6 mmol) in Water (5mL), was added dropwise to the reaction mixture at a rate maintaining the temperature at 2°C. $NaHCO_3$ (461 mg, 5.5 mmol) in Water (7mL) was also added at a rate maintaining the temperature at 2°C. The resulting mixture was stirred at room temperature for 60 mins and a further 2h at 35°C. The pH was adjusted to 2 (conc HCl dropwise), and the suspension left to cool down to room temperature. The precipitate was filtered under vacuum, washed with Water (10mL), air dried 10 mins, and then dried in a drying pistol at 30°C over P_2O_5 at high vacuum to yield **3j** (292 mg, 88%). mp 171-173°C (Found: C, 41.3; H, 5.3; N, 26.3; Cl, 15.5 $C_9H_{14}N_5O_2Cl$*0.13HCl Requires C, 40.9 H, 5.4; N, 26.5; Cl, 15.2 %); δ_H(500 MHz; DMSO-d_6) 1.27 (2 H, m, CH_2), 1.48 (4H, m, 2 CH_2), 2.20 (2 H, t, *J* 7.3, CH_2), 3.18 (2 H, m, CH_2), 7.05-7.3 (2 H, br s, NH_2), 7.60-7.80 (1 H, t, *J* 5.6, N*H*),12.02 (1 H, br s, CO_2H); δ_C(125 MHz; DMSO-d_6) 24.2 and 28.4 (2 *C*H_2), 25.9 (*C*H_2), 33.6 (*C*H_2), 39.7 (*C*H_2), 165.5, 166.9, 168.0 and 165.7, 166.4, 168.0 (triazine *C*), 174.5 (*C*=O); *m/z* (ES^+) 260 ($(M+H)^+$, 100%). 260.0909 ($M+H^+$ $C_9H_{15}N_5O_2Cl^+$ Requires 260.0909).

4,6-diamino-[1,3,5]-triazin-2-yl-hydrazine (4a)

Hydrazine hydrate (4.32g, 4.2 mL, 86.4 mmol) was added dropwise to a suspension of 2,4-diamino-6-chloro-[1,3,5]-triazine (2.5g, 17.7 mmol) in water (20 mL). The mixture was stirred overnight at 85 °C and then stopped. The white solid was filtered off and washed with 300 mL of water. The solid was then dried under high vacuum to give **4a** (1.78g, 72%); mp 271-272 °C; δ_H(300MHz; DMSO-d_6) 4.09 (2 H, br s, -NH_2), 6.19 (4 H, br s, 2 x NH_2), 7.72 (1 H, br s, N*H*-); δ_C(75MHz; DMSO-d_6) 167.2 (triazine-*C*), 168.8 (triazine-*C*); *m/z* (ES^+) 141.8 [$(M+H)^+$,30%], 163.9 [$(M+Na)^+$, 15%].

N^4-isopropyl-4,6-diamino-[1,3,5]-triazin-2-yl-hydrazine (4b)

N^2-isopropyl-2,4-diamino-6-chloro-[1,3,5]-triazine (750 mg, 3.99 mmol) was dissolved in EtOH (9mL) and hydrazine hydrate (599 mg, d=1.03, 0.58 mL, 8.67 mmol) was added dropwise into the suspension at room temperature. The mixture was left stirring overnight at 85 °C. The solvent was removed under vacuum until the formation of white crystals. The solid was filtered off and washed with cold EtOH and dried over high vacuum giving 180 mg of pure product. The remaining solution was concentrated under high vacuum and EtOAc was added until the precipitation of further product. The solid was filtered off and dried over high vacuum giving **4b** (356 mg, 49%) as a white solid; mp 106-107 °C; δ_H(300 MHz; D_2O) 1.04 (6 H, d, *J* 6.40, $CH(CH_3)_2$), 3.85 (1 H, septuplet, *J* 6.40, C*H*CH_3); δ_C(75MHz; D_2O) 22.2 ($CH(CH_3)_2$), 42.5 (*C*$H(CH_3)_2$), 164.6 (triazine-*C*); *m/z* (EI^+): m/z 183.0 (M^+, 20%).

N^4-n-propyl-4,6-diamino-[1,3,5]-triazin-2-yl-hydrazine (4c)

N^2-propyl-2,4-diamino-6-chloro-[1,3,5]-triazine (409 mg, 2.17 mmol) was suspended in water (8mL) and hydrazine hydrate (343.04 mg, d=1.03, 0.52 mL, 10.85 mmol) was added dropwise into the suspension at room temperature. The mixture was left stirring overnight at 85 °C. The precipitate was filtered and dried under high vacuum giving **4c** (282 mg, 71%) as a white solid; mp: 109-111 °C; δ_H(300 MHz; DMSO-d_6) δ 0.85 (3 H, t, *J* 7.33, CH_2CH_3), 1.47 (2 H, m, -CH_2-), 3.14 (2 H, m, CH_2NH-), 4.56 (2 H, br s, NHNH_2), 6.94-7.85 (3 H, 3m, -N*H*-, NH_2); δ_C(75 MHz; DMSO-d_6) 8.7 (CH_2CH_3), 22.9 (*C*H_2), 23.0 (*C*$^*H_2$), 41.9 (*C*H_2NH), 42.0 (*C*$^*H_2$NH), 166.2 (triazine-*C*), 166.7 (triazine-*C*), 168.5 (triazine-*C*); *m/z* (EI^+) 183.1 (M^+, 40%).

N^4-n-butyl-4,6-diamino-[1,3,5]-triazin-2-yl-hydrazine (4d)

N^2-butyl-2,4-diamino-6-chloro-[1,3,5]-triazine (552 mg, 2.74 mmol) was suspended in water (10mL) and hydrazine hydrate (685.6 mg, d=1.03, 0.66 mL, 13.7 mmol) was added dropwise into the suspension at room temperature. The mixture was left stirring overnight at 85 °C. The precipitate was filtered and dried under high vacuum giving **4d** (281 mg, 52%) as a white pure solid; mp 114-117 °C; δ_H(300 MHz, DMSO-d_6) 0.86 (3 H, t, *J* 6.99, CH_2CH_3), 1.28 (2 H, sextet, 2H, *J* 6.99, CH_2CH_3), 1.43 (2 H, m, $CH_2CH_2CH_2$), 3.18 (m, 2H, CH_2NH), 4.29 (2 H, br s, NH_2), 6.95-7.93 (3 H, 3m, 2-N*H*-, NH_2). δ_C(75 MHz, DMSO-d_6) 14.2 (-CH_3), 19.9 (-CH_2CH_3), 31.9 ($CH_2CH_2CH_2$-), 39.9 (CH_2NH-), 166.2 (triazine-*C*), 168.4 (triazine-*C*); *m/z* (CI^+) 198.2 ($(M+H)^+$, 40%).

2N-{[3-(*t*-butyl-diphenylsilyl)-oxy]-ethyl}-(4,6-diamino)-[1,3,5]-triazin-2-yl-hydrazine (4e)

2N-{[3-(*t*-butyl-diphenylsilyl)-oxy]-ethyl}-6-chloro-(2,4-diamino)-[1,3,5] -triazine (235 mg, 0.55 mmol) was suspended in water (3.5 mL) and hydrazine hydrate (138 mg, d=1.03, 0.13 mL, 2.75 mmol) was added dropwise to the suspension. The mixture was left stirring overnight at 75 °C. The product was then filtered, washed with water and dried under high vacuum over P_2O_5 giving **4e** (220 mg, 86%) as a white solid; mp: 80-82 °C; δ_H(300 MHz, DMSO-d_6) 0.96 (9 H, s, CCH_3), 3.45 (2 H, m, CH_2NH), 3.71 (2 H, m, -CH_2O-), 6.20-7.20 (3 H, 3m, -N*H*-, -NH_2), 7.43 (6 H, m, Ar*H*), 7.62 (4 H, m, Ar*H*), 7.69 (1 H, m, -N*H*-); δ_C(75 MHz, DMSO-d_6) 19.1 (CCH_3), 26.9 (CC^*H_3), 27.0 (CCH_3), 42.4 (CH_2NH-), 42.6 (C^*H_2-NH-), 62.3 (-CH_2-O-), 62.6 (-C^*H_2O-), 128.1 (ArC^*H), 128.2 (Ar*C*H), 130.1 (Ar*C*H), 133.4 (Ar*C*), 135.4 (Ar*C*H), 166.2 (triazine-*C*); *m/z* (ES^+) 424.1 ($(M+H)^+$, 100%).

2N-{[3-(*t*-butyl-diphenylsilyl)-oxy]-propyl}- (4,6-diamino)-[1,3,5]-triazin-2-yl-hydrazine (4f)

2N-{[3-(*t*-butyl-diphenylsilyl)-oxy]-propyl}-6-chloro-(2,4-diamino)-[1,3,5] -triazine (550 mg, 1.24 mmol) was suspended in EtOH (7 mL) and hydrazine hydrate (186.2 mg, d=1.03, 0.18 mL, 3.72mmol) was added dropwise to the suspension. The mixture was left stirring overnight at 75 °C. The product was then filtered, washed with EtOH and water and dried under high vacuum over P_2O_5 giving **4f** (281 mg, 52%) as a white solid; mp 234-237 °C; δ_H(500 MHz, DMSO-d_6) 0.99 (9 H, s, $C(CH_3)_3$), 1.77 (2 H, quintuplet, *J* 6.30, $CH_2CH_2CH_2$), 3.35 (2 H, m, -CH_2NH-), 3.70 (2 H, t, *J* 6.30, -CH_2O-), 4.08 (2 H, br s, NH_2), 5.98-6.57 (3 H, 3m, N*H*-, NH_2), 7.44 (6 H, m, Ar*H*), 7.62 (4 H, m, Ar*H*), 7.69 (1 H, m, N*H*-); δ_C(125 MHz, DMSO-d_6) 18.7 (CCH_3), 26.5 (CC^*H_3), 26.6 (CCH_3), 32.2 ($CH_2CH_2CH_2$), 36.9 (CH_2NH-), 61.7 (CH_2O-), 127.5 (ArC^*H), 127.8 (Ar*C*H), 129.1 (ArC^*H), 129.7 (Ar*C*H), 133.3 (Ar*C*), 134.4 (ArC^*H) 135.0 (Ar*C*H), 167.9 (triazine-*C*); *m/z* (CI^+): 438.4 ($(M+H)^+$, 40%).

N^4-hydroxypropyl-4,6-diamino-[1,3,5]-triazin-2-yl-hydrazine (4g)

N^2-hydroxypropyl-6-chloro-2,4-diamino-[1,3,5]-triazine (400 mg, 1.96 mmol) was dissolved in DMF (6 mL) and hydrazine hydrate (196.2 mg, d=1.03, 0.19 mL, 3.92 mmol) was added dropwise to the solution at room temperature and with stirring. The mixture was left stirring for 3 h at 85 °C and then left cooling down to room temperature. The solution was concentrated under vacuum and the white solid was washed with cold water and dried under high vacuum giving 390 mg of crude solid. The crude product was used for the preparation of the corresponding hydrazone. δ_H(500 MHz, D_2O) 1.75 (2 H, m, $CH_2CH_2CH_2$), 3.05 (2 H, br s, NH_2), 3.36 (2 H, m, -CH_2NH-), 3.60 (2 H, m, CH_2OH), 8.0 (1 H. br m, N*H*-, D-exchange); δ_C(125 MHz, D_2O) 31.4 ($CH_2CH_2CH_2$-), 37.2 (CH_2NH-), 37.3 (C^*H_2NH-), 59.0 (-CH_2-OH), 59.1 (-C^*H_2OH), 162.4 (triazine-*C*), 162.7 (triazine-*C*), 168.9 (triazine-*C*); *m/z* (ES^+): 200.1 ($(M+H)^+$, 50%).

3-(4-amino-6-hydrazinyl-1,3,5-triazin-2-yl amino) propanoic acid (4h)

Hydrazine hydrate (0.1ml, 3.2 mmol) was added to starting material **3h** (200mg, 0.9 mmol) dissolved in EtOH (2 mL) and resultant mixture stirred at 75 ^{o}C overnight. Tlc analysis (RP C18 plates, 1:1 MeCN:H_2O) showed the triazine starting material (Rf = 0.9) still present. A further aliquot of hydrazine hydrate (0.1ml, 3.2 mmol) was added and the reaction was stirred at 75 ^{o}C for a further 90 mins whereupon tlc analysis showed complete loss of triazine starting material. The reaction was cooled to room temperature, filtered, washed with EtOH (3 x 15ml) and air dried 10 mins to yield the crude title compound **4h** (0.235g) as a fine white solid; δ_H(300 MHz, DMSO-d_6/DCl) 2.5 (2 H, m, CH_2), 3.4 (2 H, m, CH_2); δ_C(75 MHz, DMSO-d_6) 32.9 (*C*H_2), 36.3 (*C*H_2), 156.2 (triazine-*C*), 162 (triazine-*C*), 172.3 (*C*=O); *m/z* 214 $(M+H)^+$.

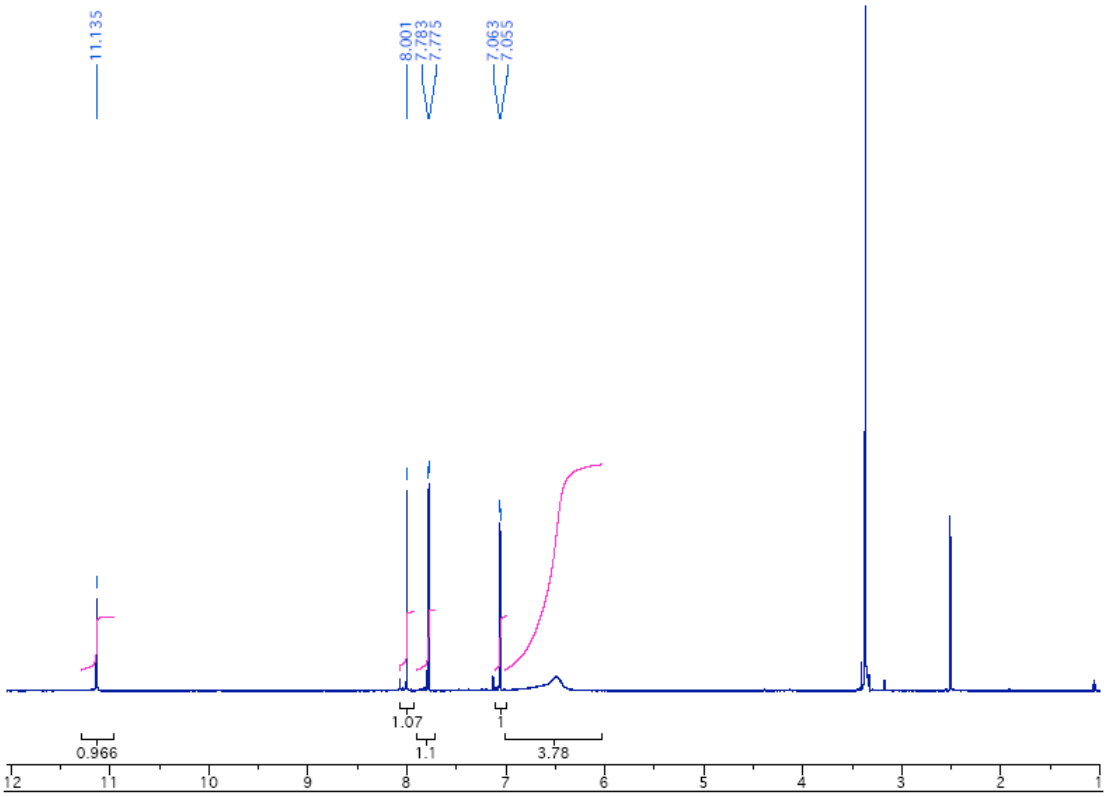
4-(4-amino-6-hydrazinyl-1,3,5-triazin-2-yl amino) butanoic acid (4i)

Hydrazine hydrate (0.1mL, 2.0 mmol) was added slowly to starting material **3i** (180 mg, 0.78 mmol) dissolved in EtOH (5mL) and the resulting mixture stirred for 5h at 75°C. The reaction was left to cool to room temperature, filtered, washed with EtOH (20mL) and dried under high vacuum to yield **4i** (162 mg, 92%). mp 195-197°C (Found: C, 35.6; H, 5.8; N, 41.8. $C_7H_{13}N_7O_2$*0.4H_2O Requires C, 35.9 H, 5.9; N, 41.8 %); δ_H(500 MHz; DMSO-d_6) 1.51 (2 H, qt, *J* 7.1, CH_2), 1.95 (2H, t, *J* 7.3, CH_2), 3.00 (2 H, m,, CH_2), 6.04, 6.46 and 7.44 (6 H, 3 br s, 2 NH_2 and N*H*); δ_C(125 MHz; DMSO-d_6) 25.4 (*C*H_2) 32.0 (*C*H_2), 39.7 (*C*H_2), 165.8, 168.0, 168.0 (triazine *C*), 175.9 (*C*=O); *m/z* (ES^+) 228 ($(M+H)^+$, 100%). 28.1202 ($M+H^+$ $C_7H_{14}N_7O_2^+$ Requires 228.1203).$^+$

6-(4-amino-6-hydrazinyl-1,3,5-triazin-2-yl amino) hexanoic acid (4j)

Hydrazine hydrate (0.05ml, 1.0 mmol) was added to starting material **3j** (150mg, 0.57 mmol) dissolved in EtOH (2 mL) and resultant mixture was stirred at 65 ^{o}C for 5 h. The reaction mixture was left to cool to room temperature, filtered, washed with EtOH (3 x 5ml) and air dried 10 mins to yield the title compound **4j** (149 mg, 100%) as a fine white solid; mp 166-169°C (Found: C, 41.6; H, 6.7; N, 37.3 $C_9H_{17}N_5O_2$*0.3H_2O Requires C, 41.5 H, 6.8; N, 37.6 %); δ_H(500 MHz; DMSO-d_6) 1.12 (2 H, qt, *J* 7.5, CH_2), 1.33 (4H, m, 2 CH_2), 1.97 (2 H, t, *J* 7.3, CH_2), 3.05 (2 H, m, CH_2), 6.07, 6.54 and 7.50 (6 H, 3 br s, 2 NH_2 and N*H*); δ_C(125 MHz; DMSO-d_6) 24.8 and 29.2 (2 *C*H_2), 26.2 (*C*H_2), 34.9 (*C*H_2), 39.6 (*C*H_2), 165.8, 166.5 and 168.1 (triazine *C*), 175.5 (*C*=O); *m/z* (ES^+) 256 ($(M+H)^+$, 100%). 256.1506 ($M+H^+$ $C_9H_{18}N_7O_2^+$ Requires 256.1517)

Compound 5a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7.775
7.063
7.055
0.966
1.07
1.1
1
3.78
12
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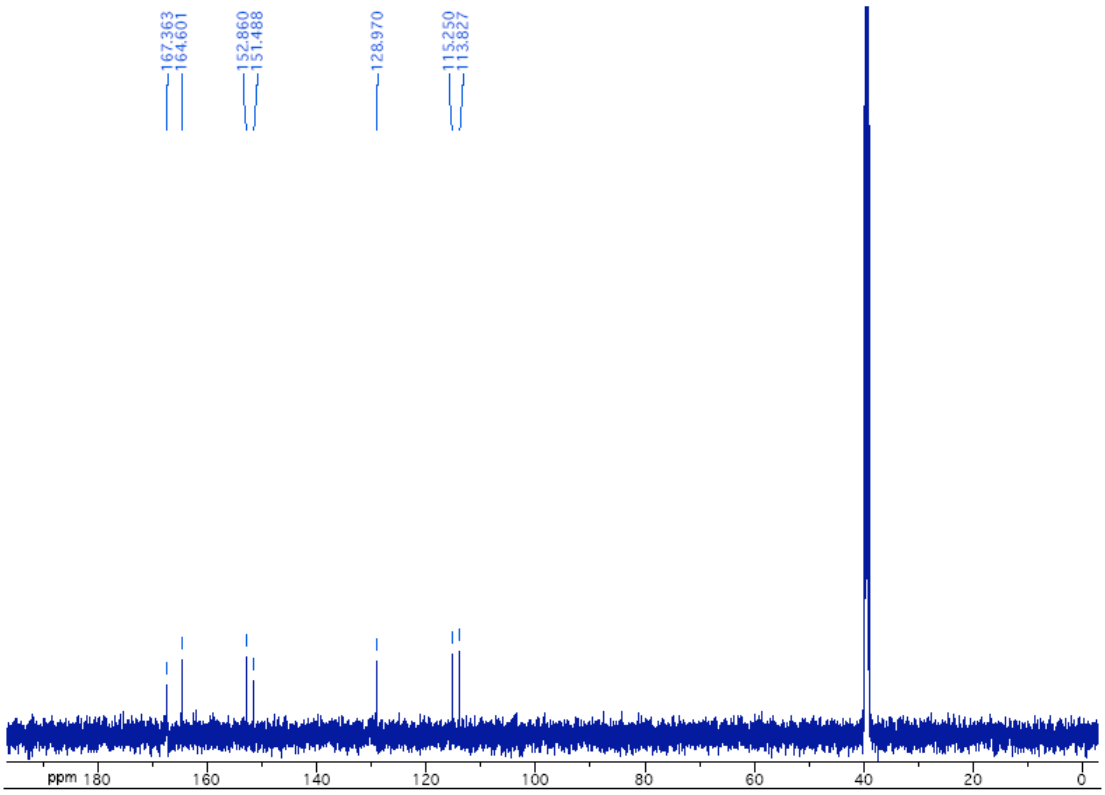
10
9
8
7
6
5
4
3
2
1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164.601
152.860
151.488
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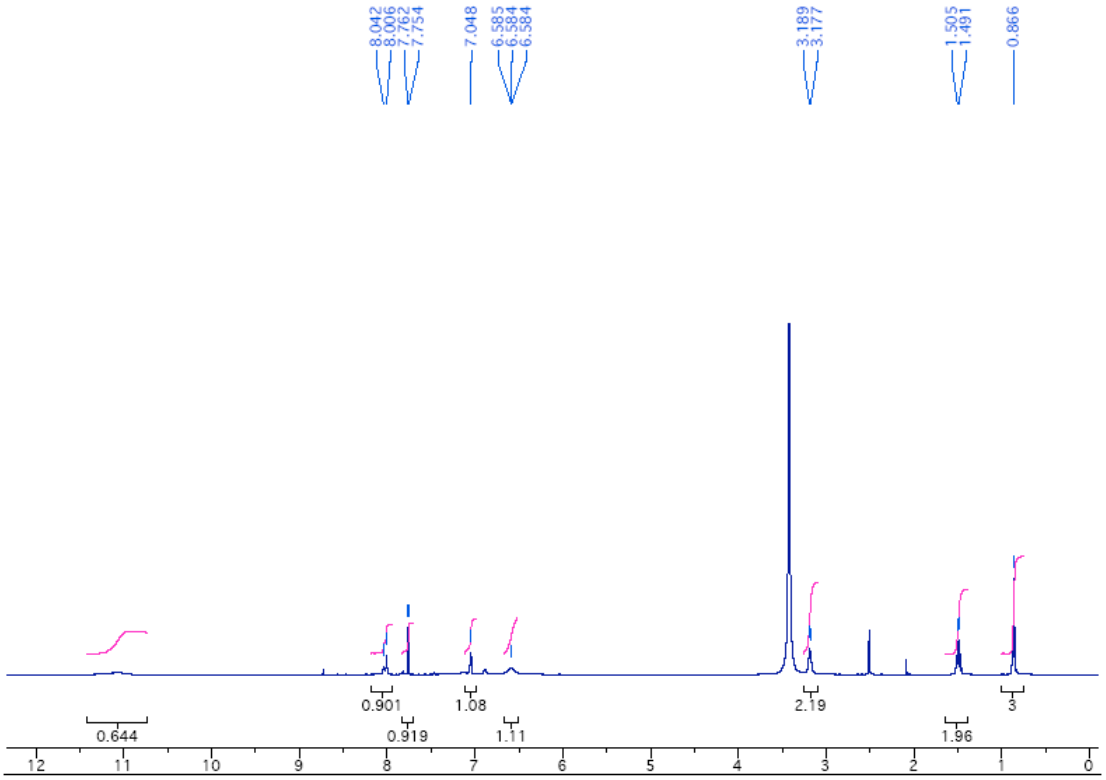
115.250
113.827
ppm 180
160
140
120
100
80
60
40
20
0

Compound 5b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7.762
7.754
7.048
6.585
6.584
6.584
6.584
3.189
3.177
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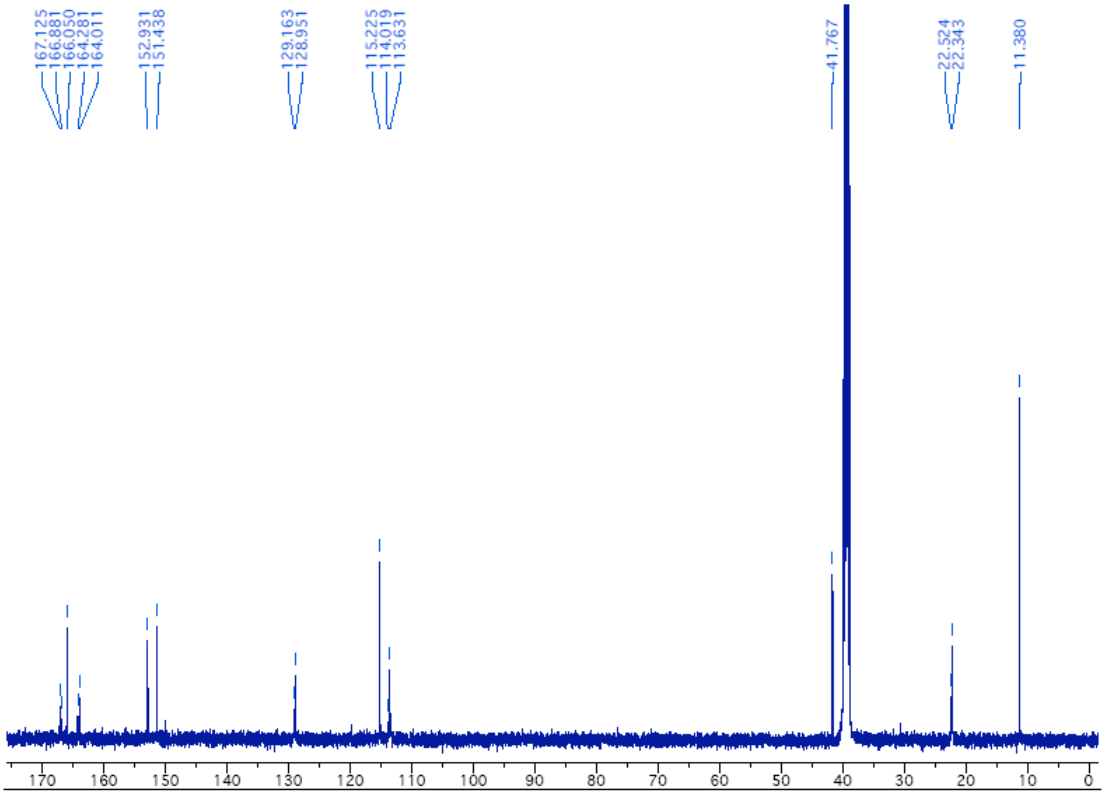
1.491
0.866
0.644
0.901
0.919
1.08
1.11
2.19
1.96
3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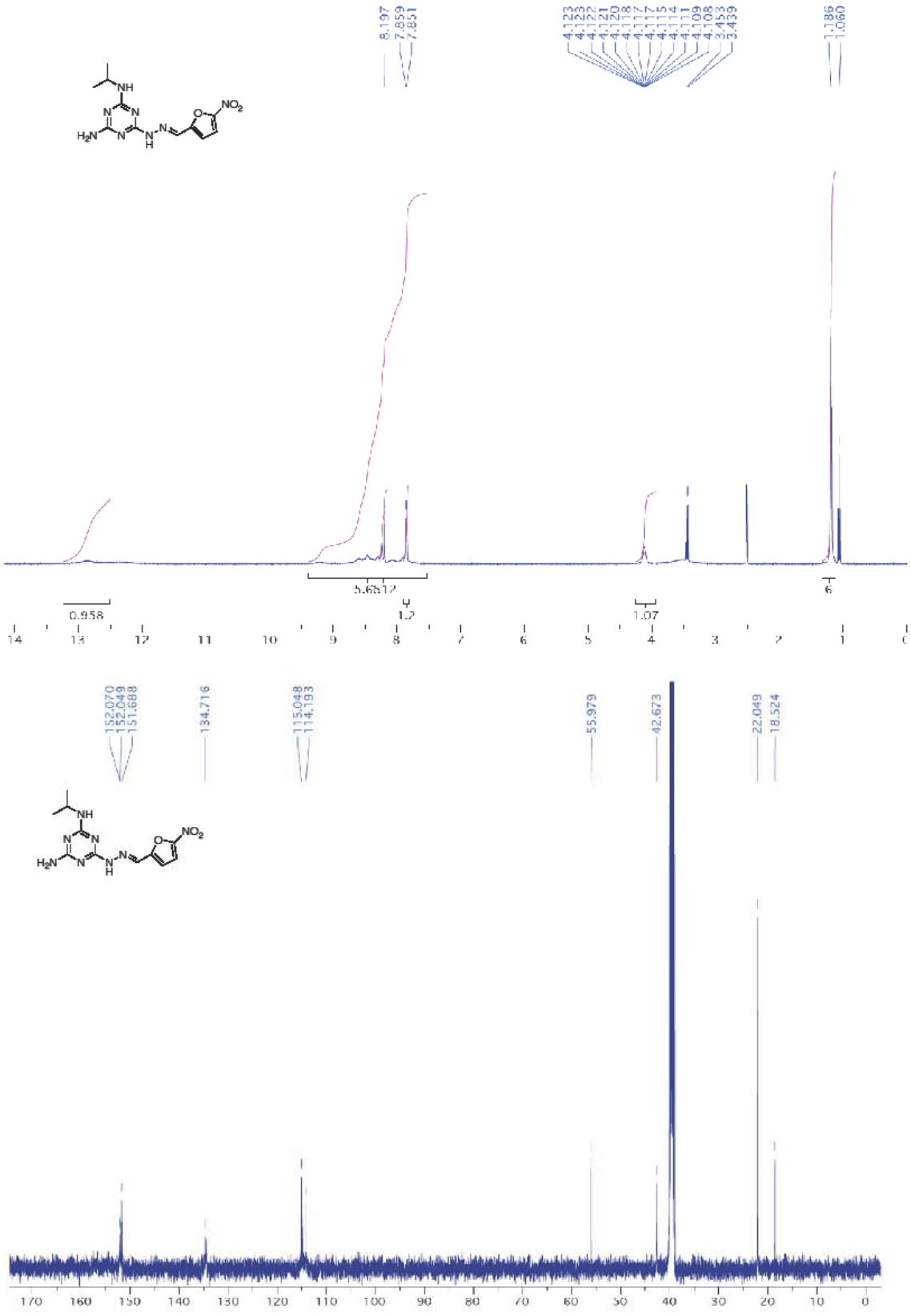
166.881
166.050
164.281
164.011
152.931
151.438
129.163
128.951
115.225
114.619
114.013
113.631
41.767
22.524
22.343
11.380

Compound 5c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7.859
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4.122
4.121
4.120
4.118
4.117
4.117
4.115
4.114
4.111
4.109
4.108
3.453
3.439
1.186
1.060
0.958
5.6817
1.2
1.07
6
152.070
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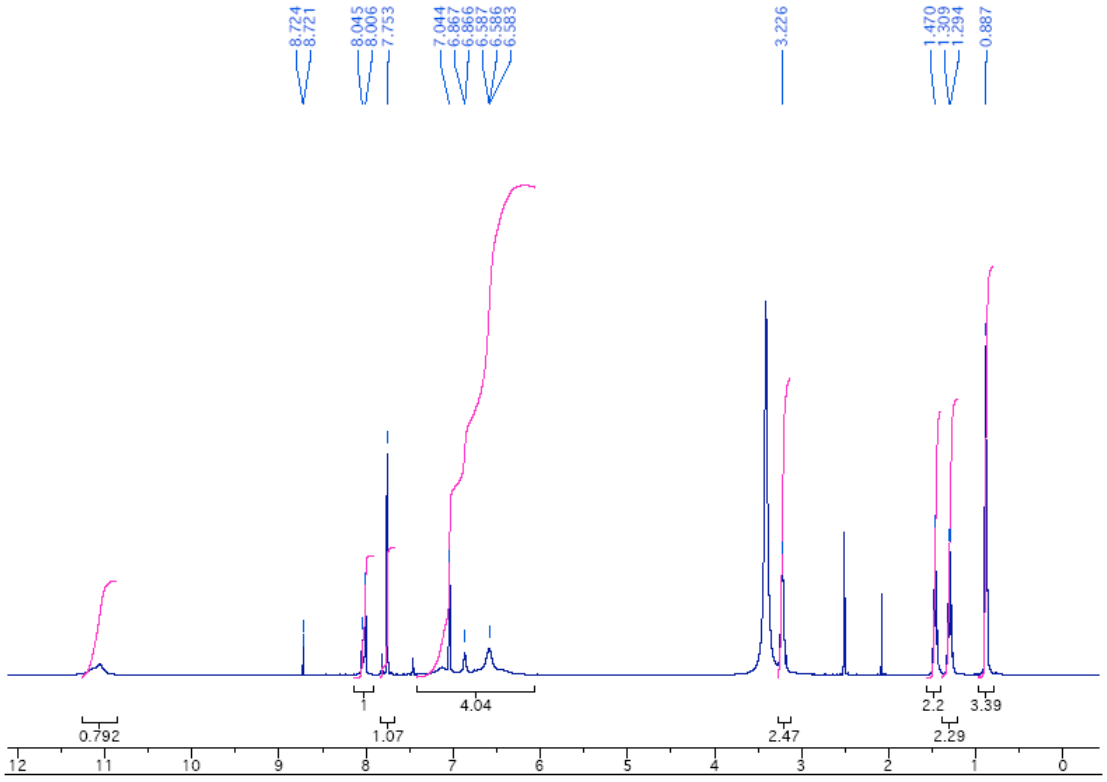
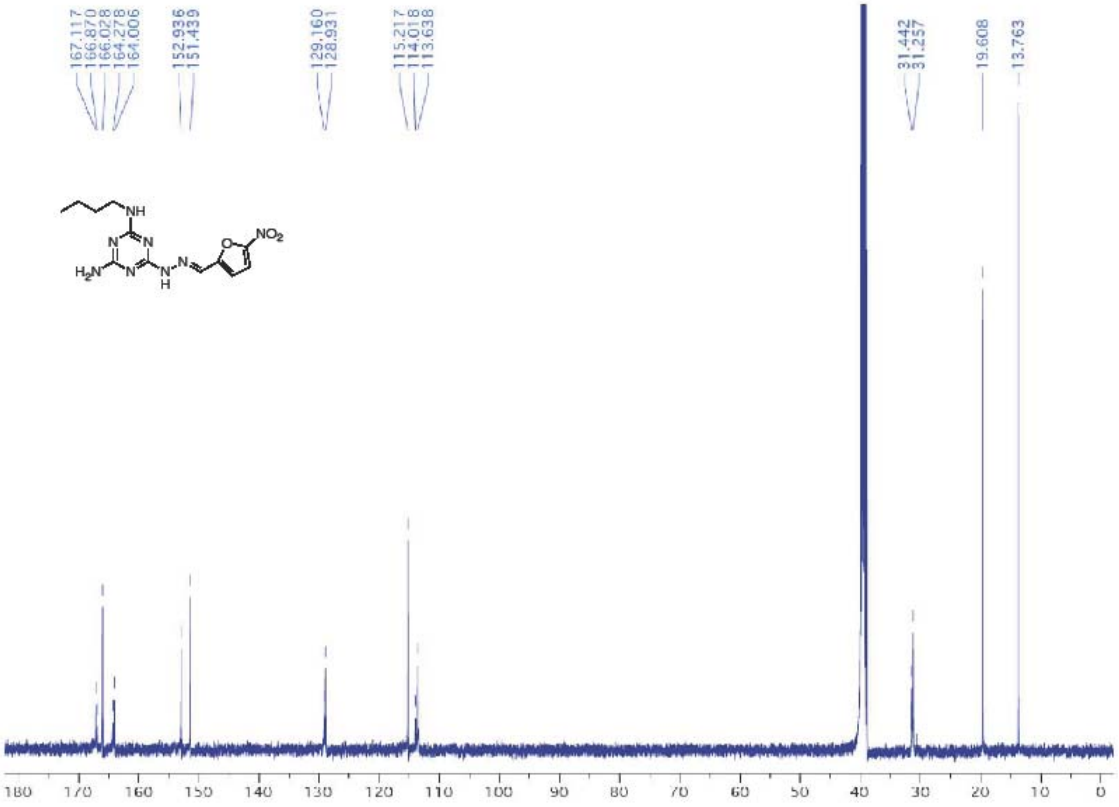
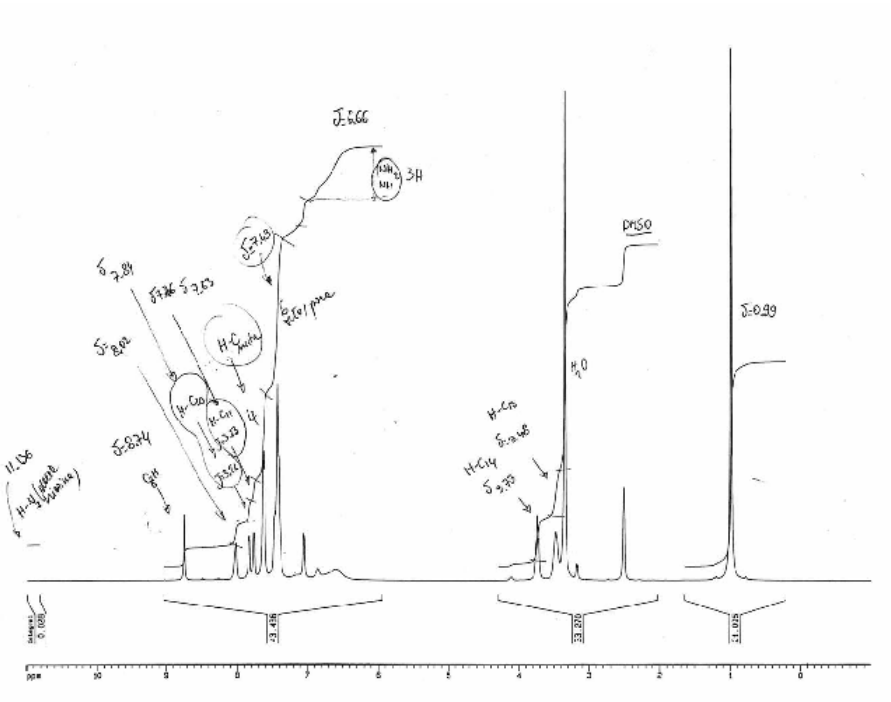
151.688
134.716
115.048
114.793
55.979
42.673
22.049
18.524

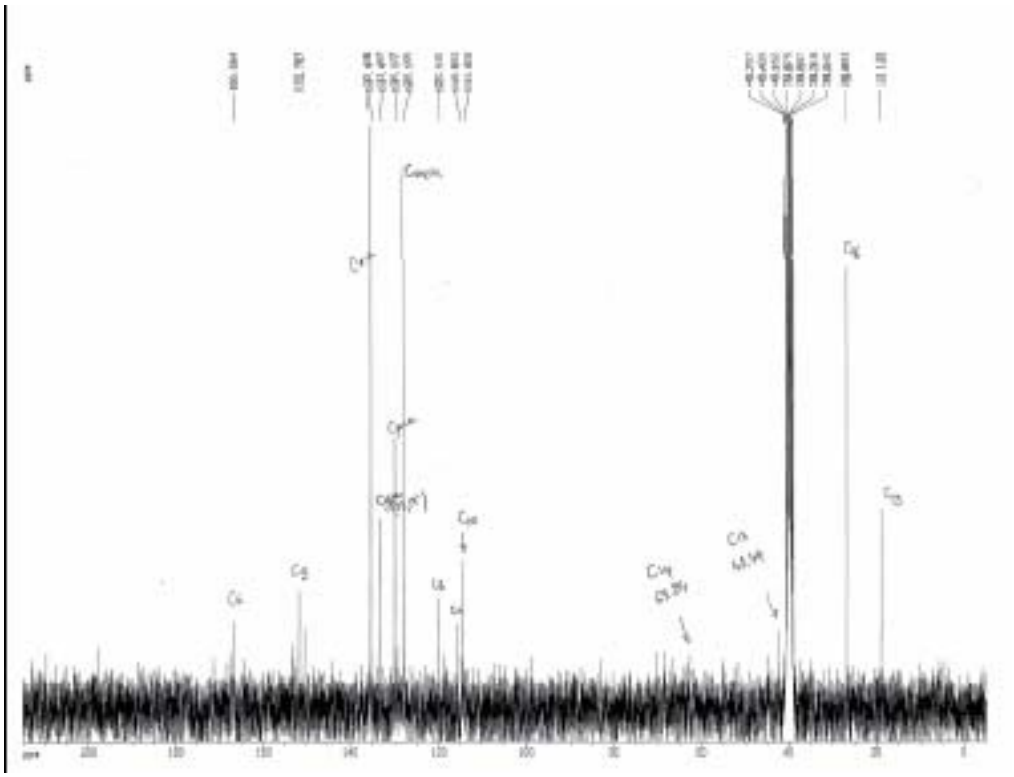
Compound 5d


8.724
8.721
8.045
8.006
7.753
7.044
6.867
6.866
6.587
6.586
6.583
3.226
1.470
1.309
1.294
0.887
0.792
1
1.07
4.04
2.47
2.2
2.29
3.39

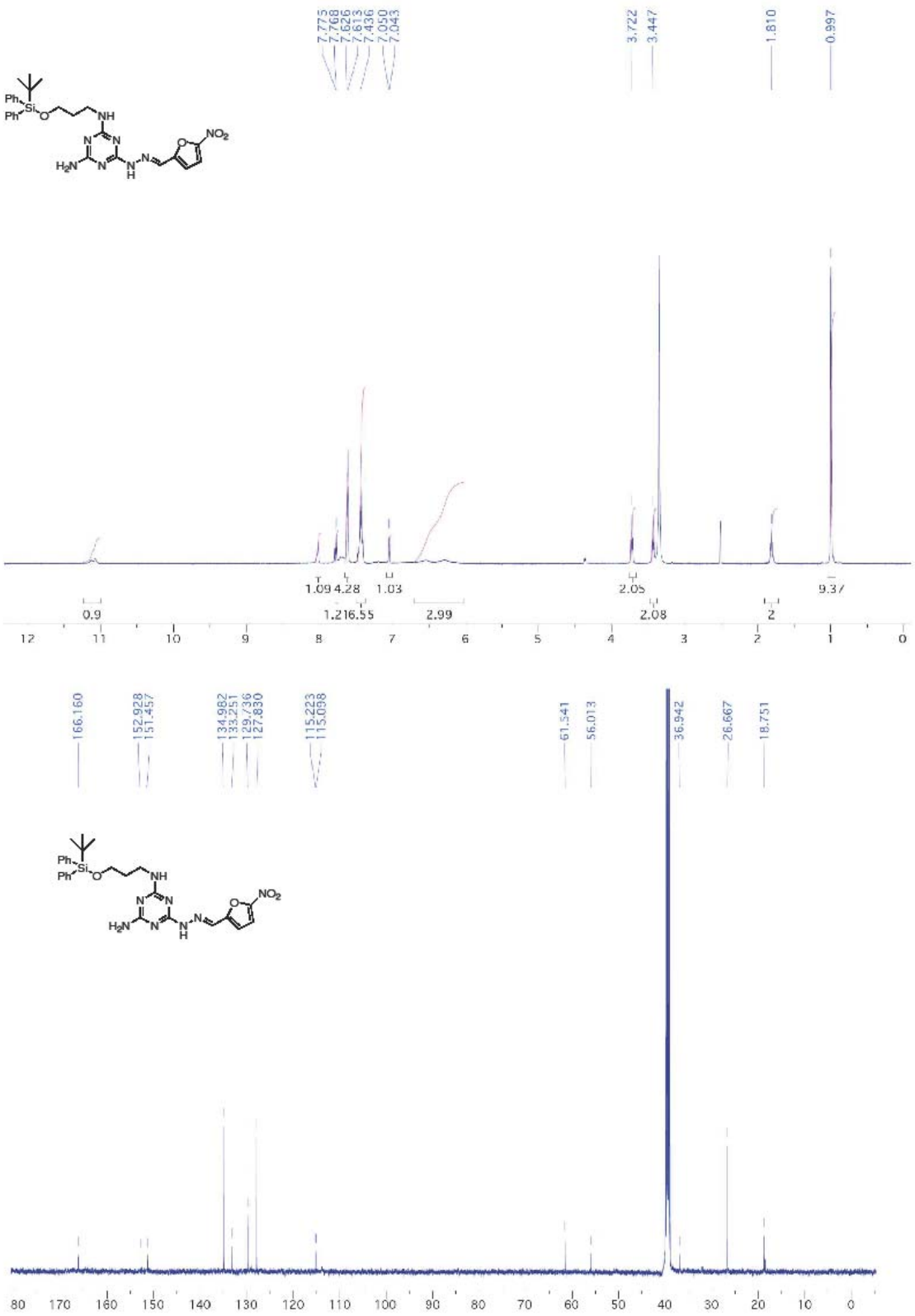

167.117
166.870
166.028
164.278
164.006
152.936
151.439
129.160
128.931
115.217
114.018
113.638
31.442
31.257
19.608
13.763
NH
N
N
H2N
N
N
H
O
NO2

Compound 5e





Compound 5f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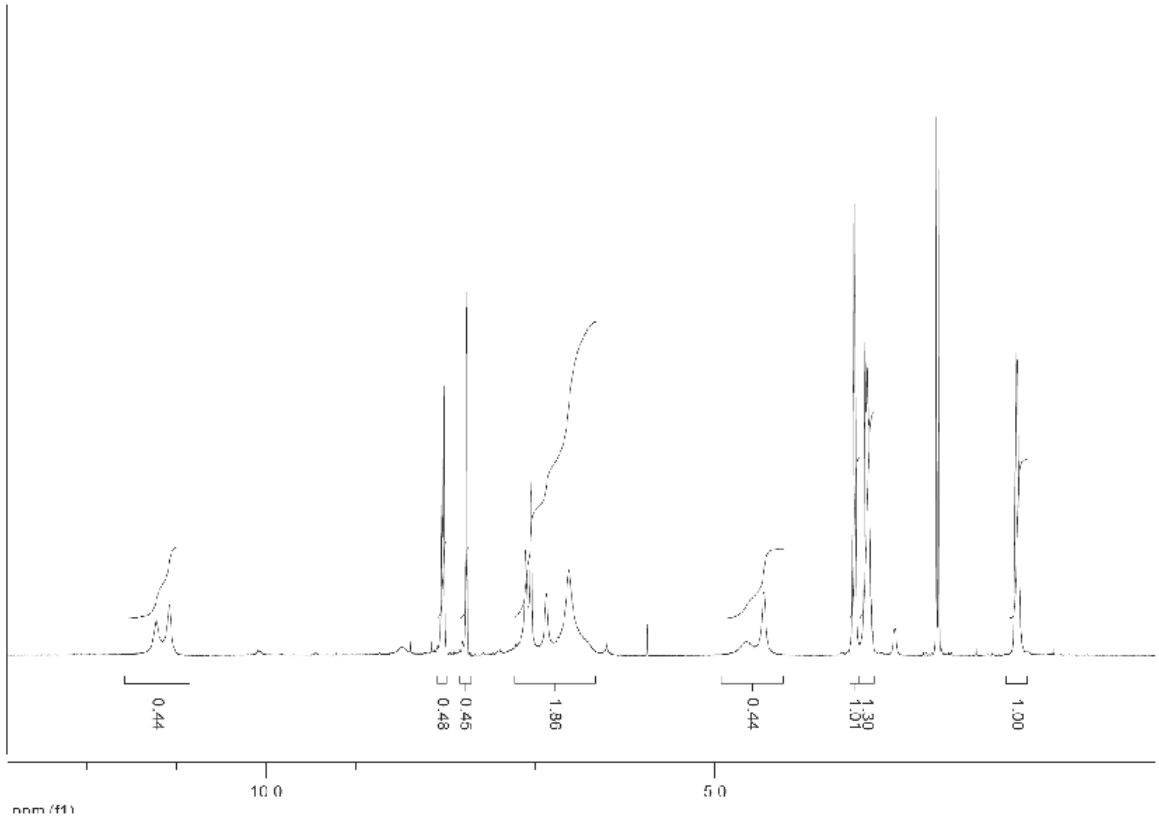
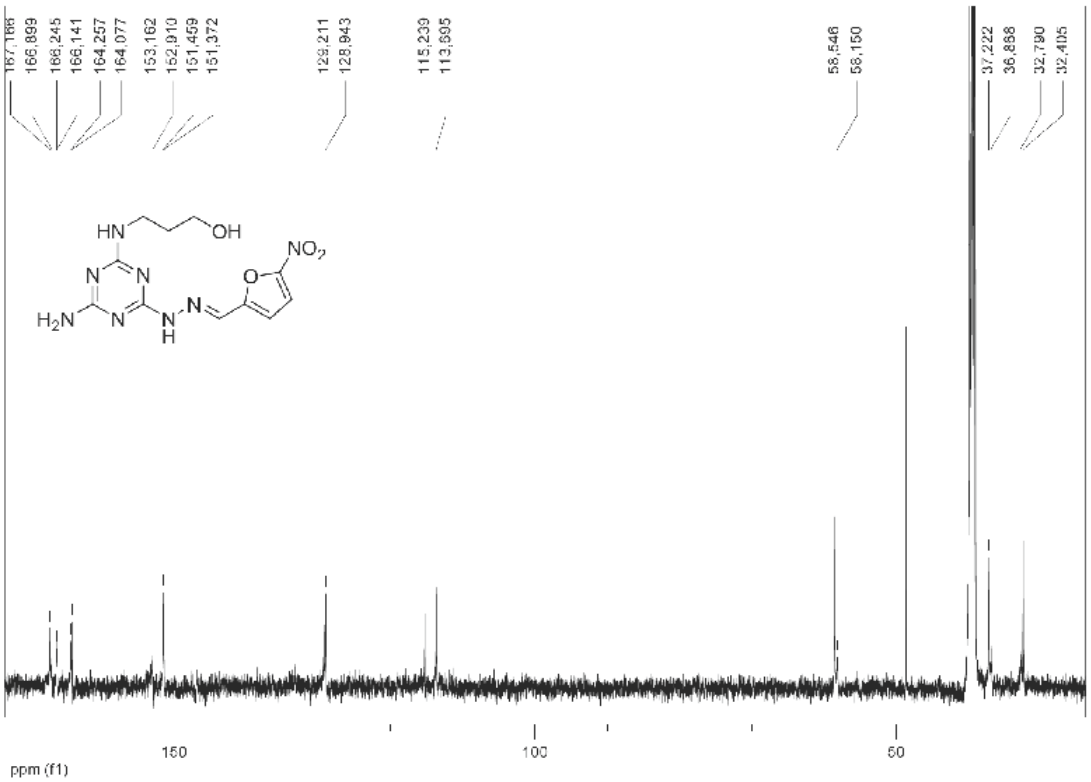
7.768
7.626
7.613
7.436
7.050
7.043
3.722
3.447
1.810
0.997
1.09
4.28
1.03
2.05
9.37
0.9
1.21
6.55
2.99
2.08
2
166.160
152.928
151.457
134.982
133.251
129.736
127.830
115.223
115.058
61.541
56.013
36.942
26.667
18.751

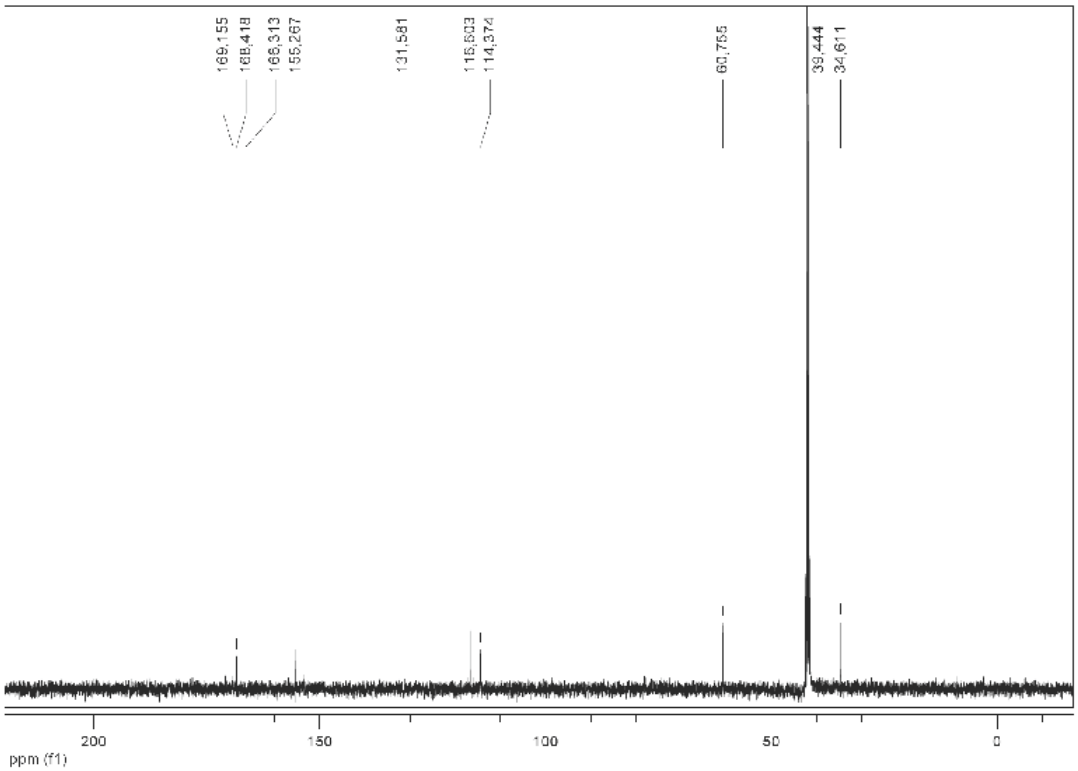
Compound 5g



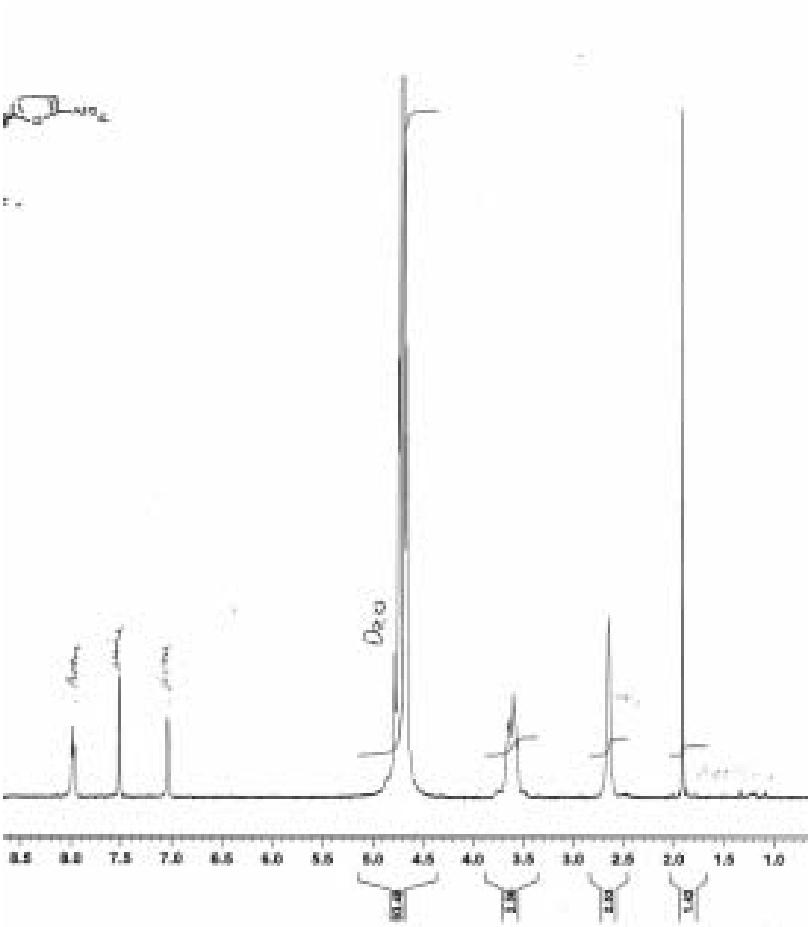
Room Temperature

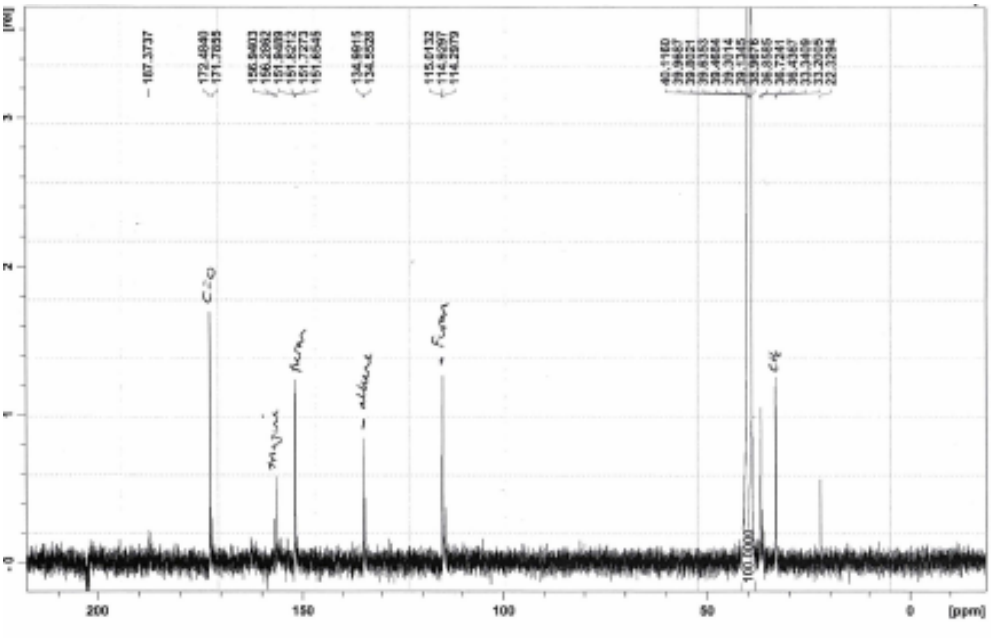


100ºC

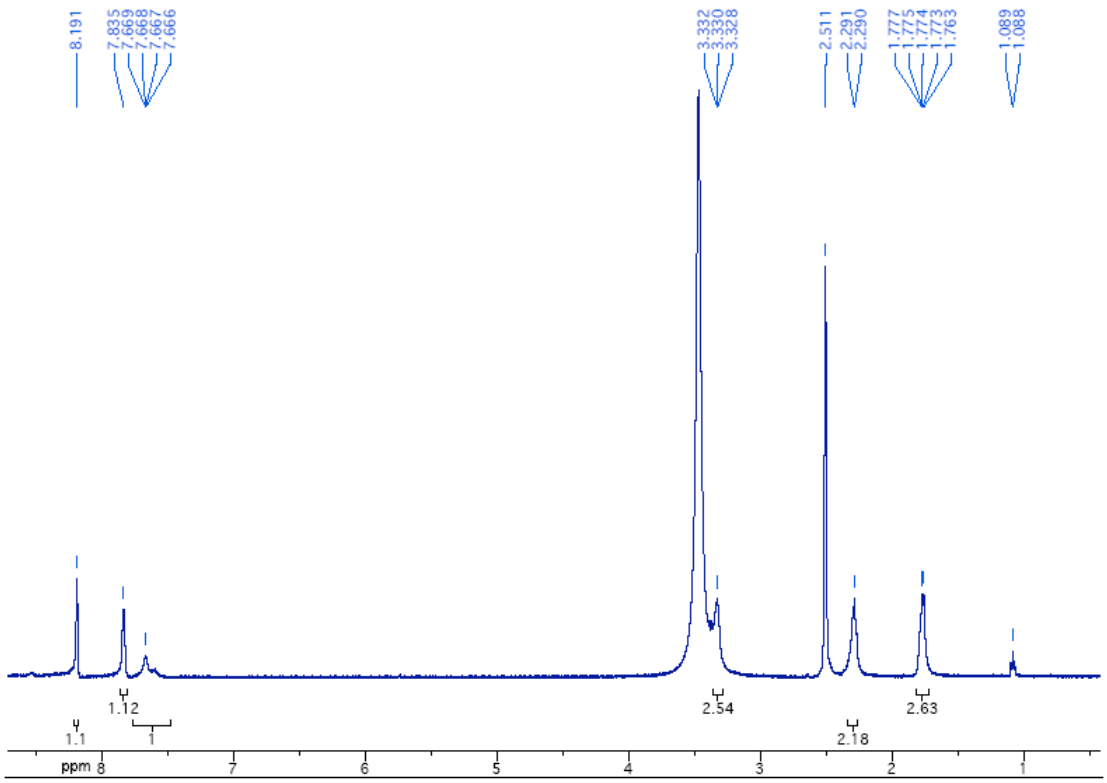


Compound 5h





Compound 5i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7.669
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7.666
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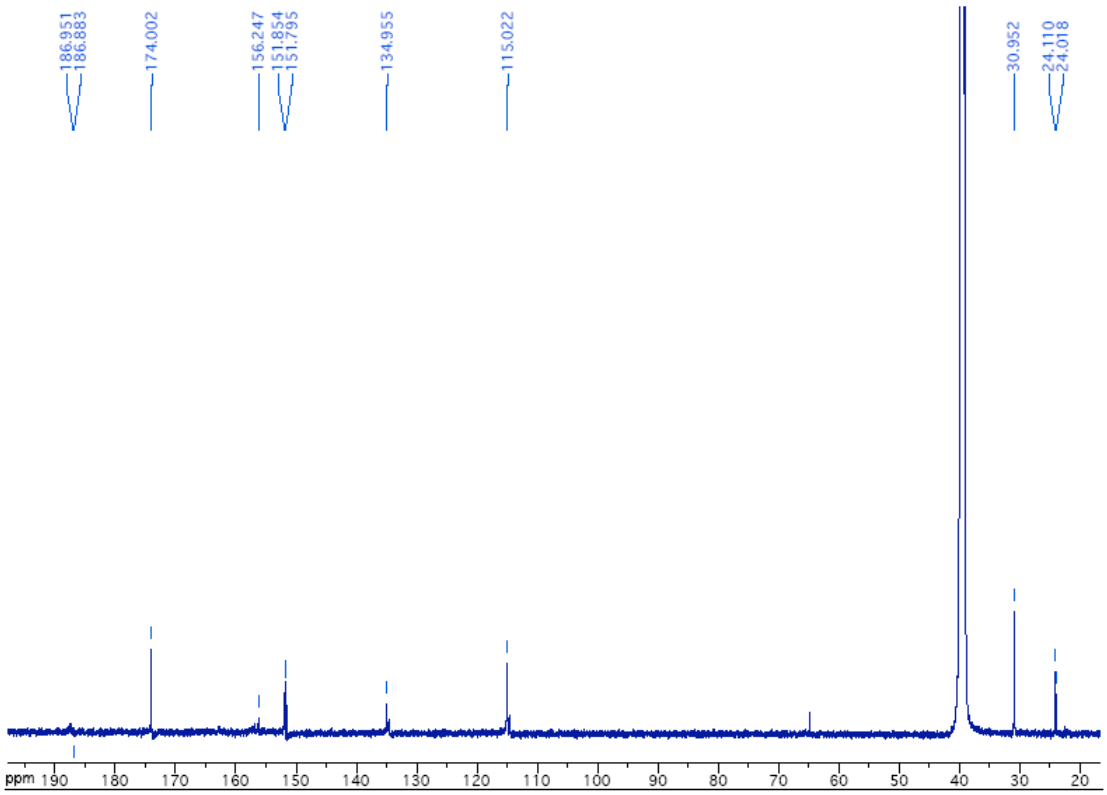
3.330
3.328
2.511
2.291
2.290
1.777
1.775
1.774
1.773
1.763
1.089
1.088
1.12
1.1
1
2.54
2.18
2.63
ppm 8
7
6
5
4
3
2
1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151.795
134.955
115.022
30.952
24.110
24.018
ppm 190
180
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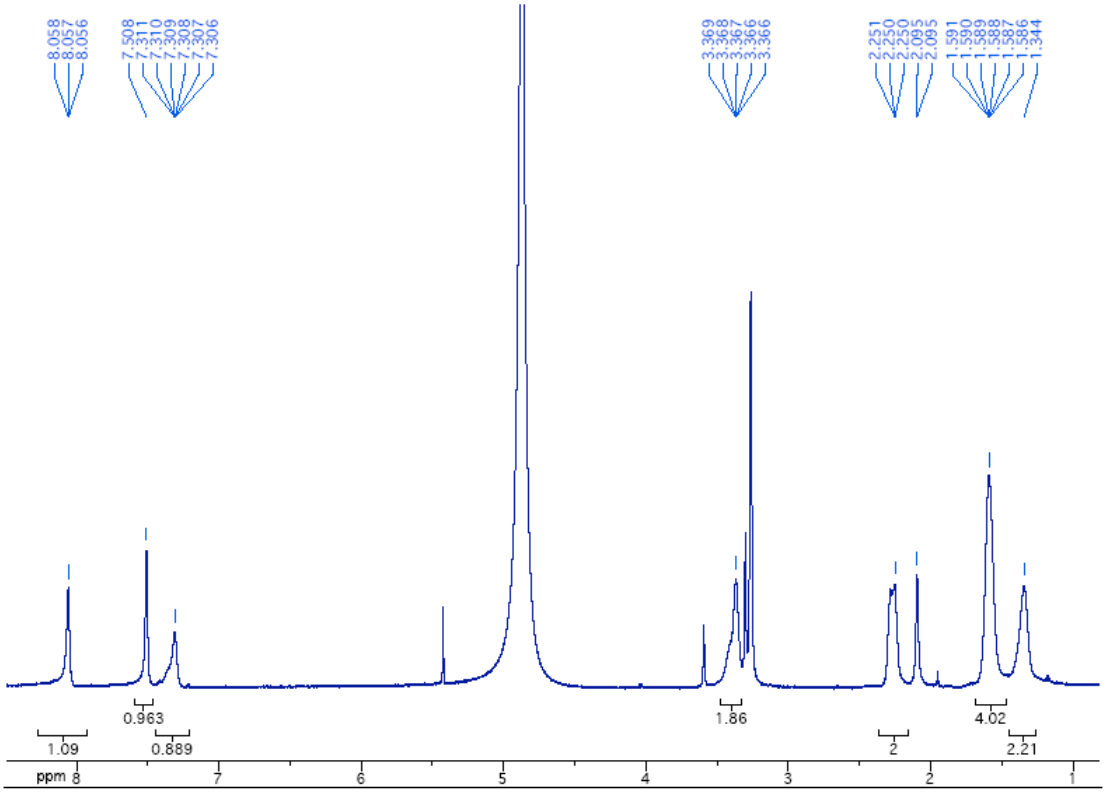
150
140
130
120
110
100
90
80
70
60
50
40
30
20

Compound 5j


8.058
8.057
8.056
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7.311
7.310
7.309
7.308
7.307
7.306
3.369
3.368
3.367
3.366
3.366
2.251
2.250
2.250
2.095
2.095
1.591
1.590
1.589
1.588
1.587
1.586
1.344
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1.86
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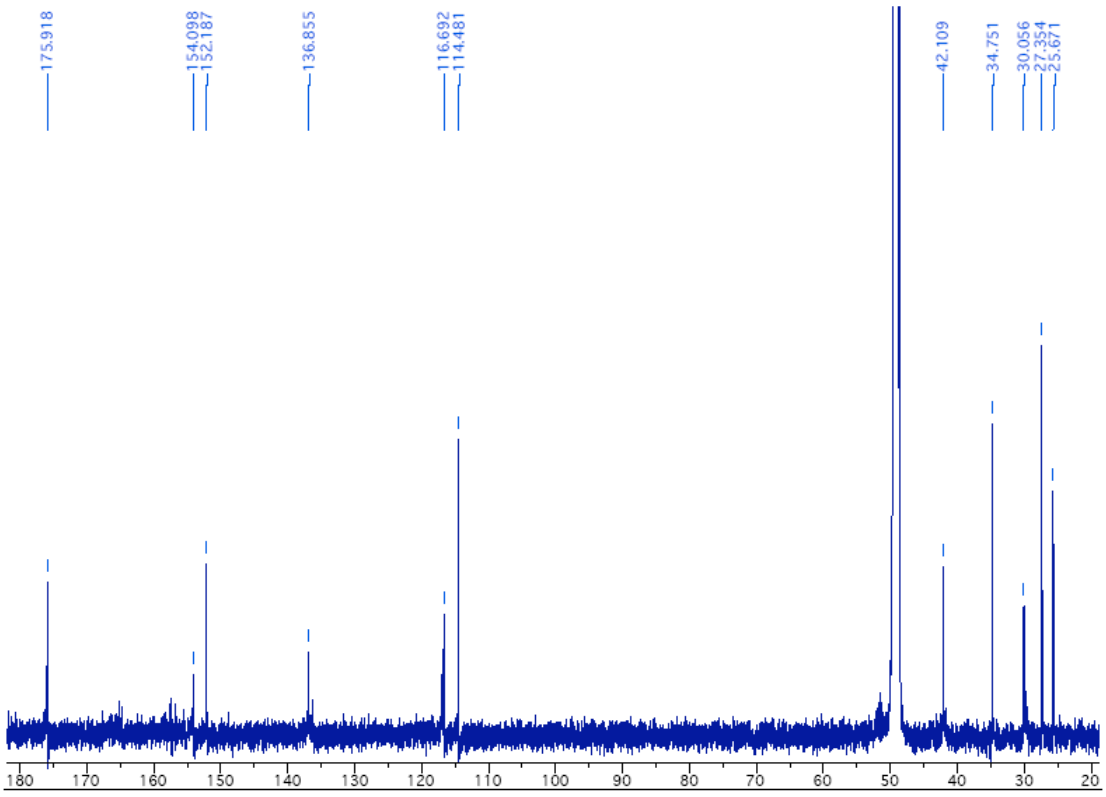
0.889
2
2.21
ppm


175.918
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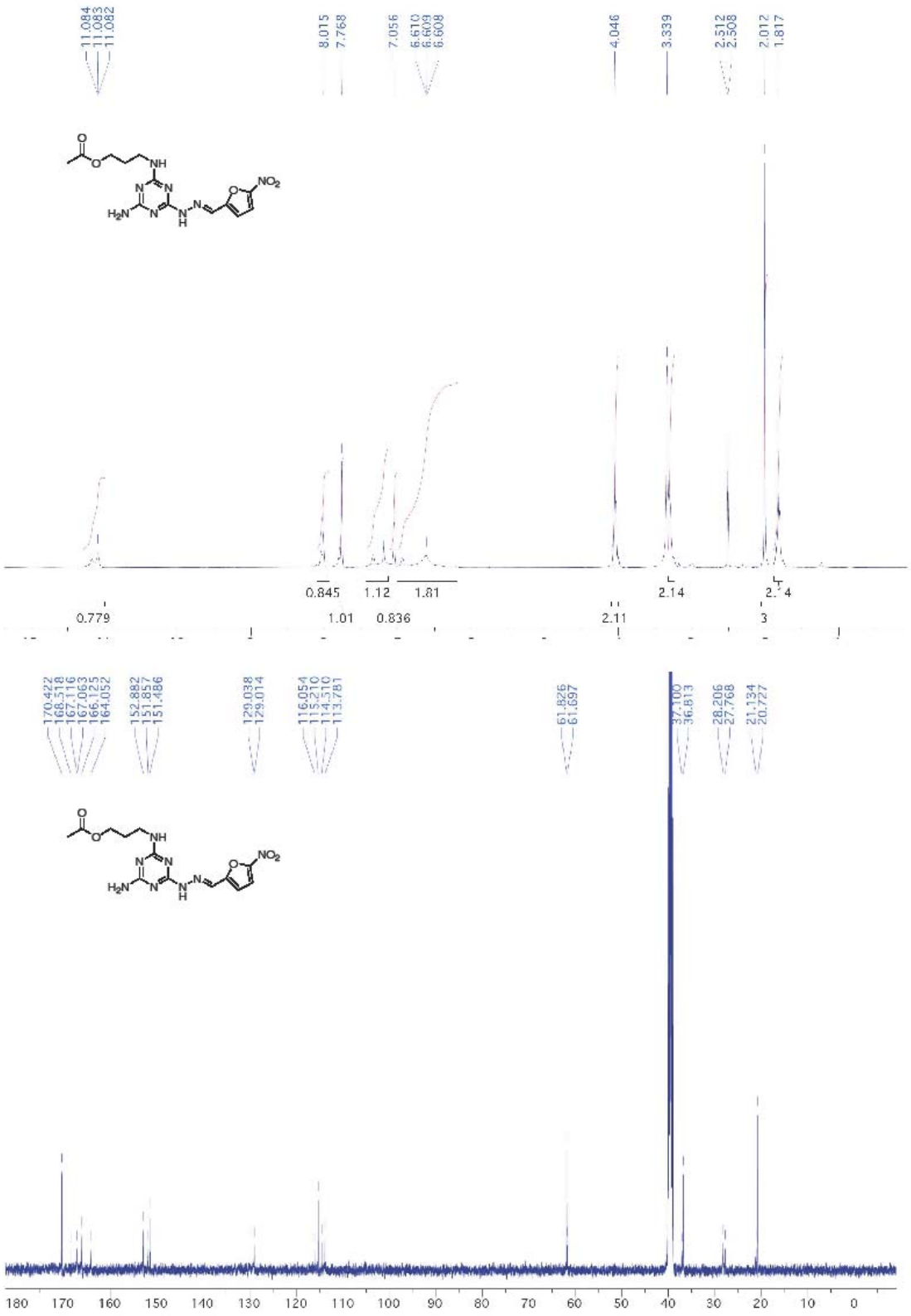
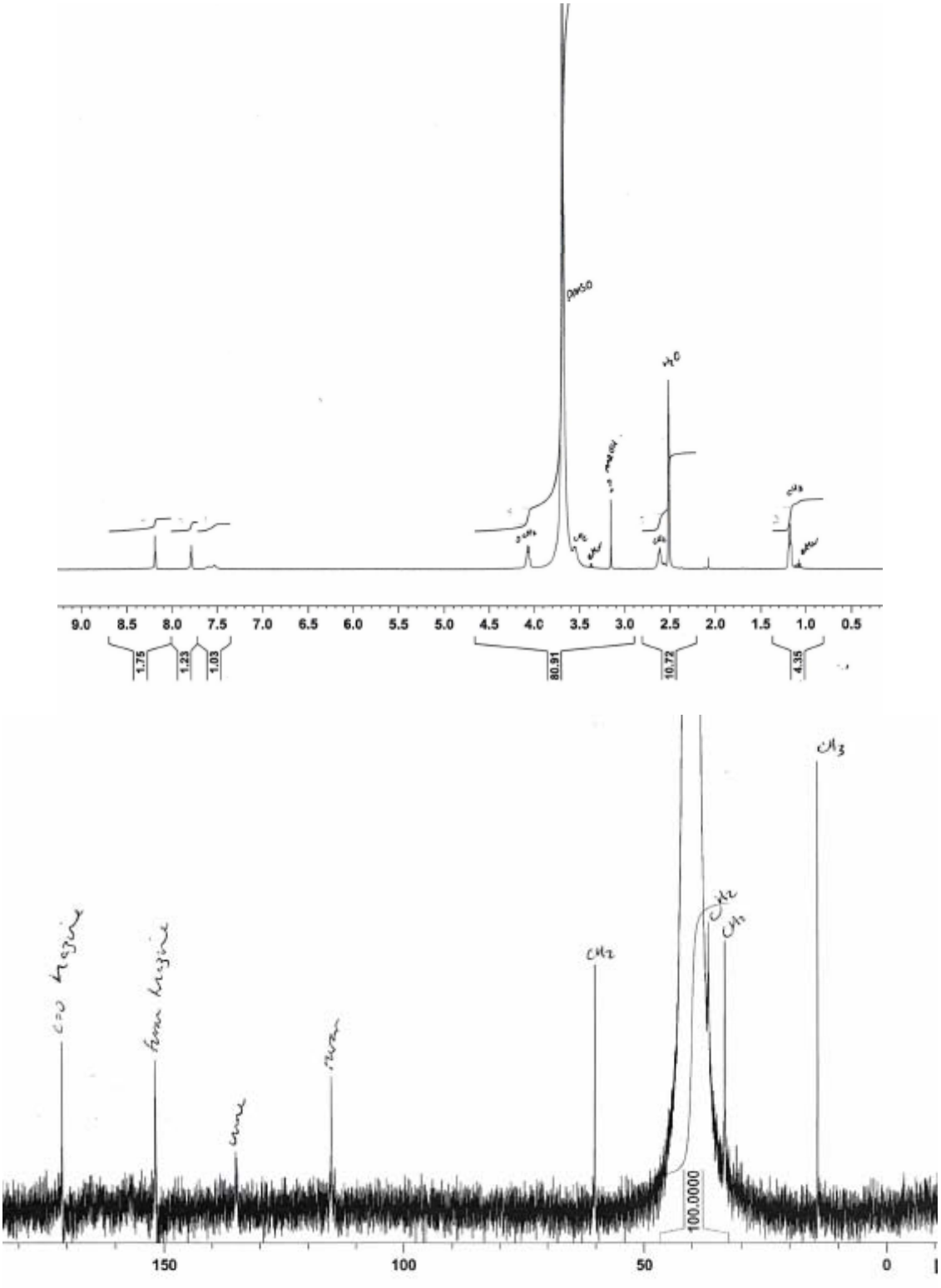
116.692
114.481
42.109
34.751
30.056
27.354
25.671

Compound 6a


11.084
11.083
11.082
8.015
7.768
7.056
6.610
6.609
6.608
4.046
3.339
2.512
2.508
2.012
1.817
0.845
1.12
1.81
2.14
0.779
1.01
0.836
2.11
3
170.422
168.318
167.116
167.063
166.125
164.052
152.882
151.857
151.486
129.038
129.014
116.054
115.210
114.510
113.781
61.826
61.697
37.100
36.813
28.206
27.768
21.134
20.727
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Compound 6b


DMSO
H2O
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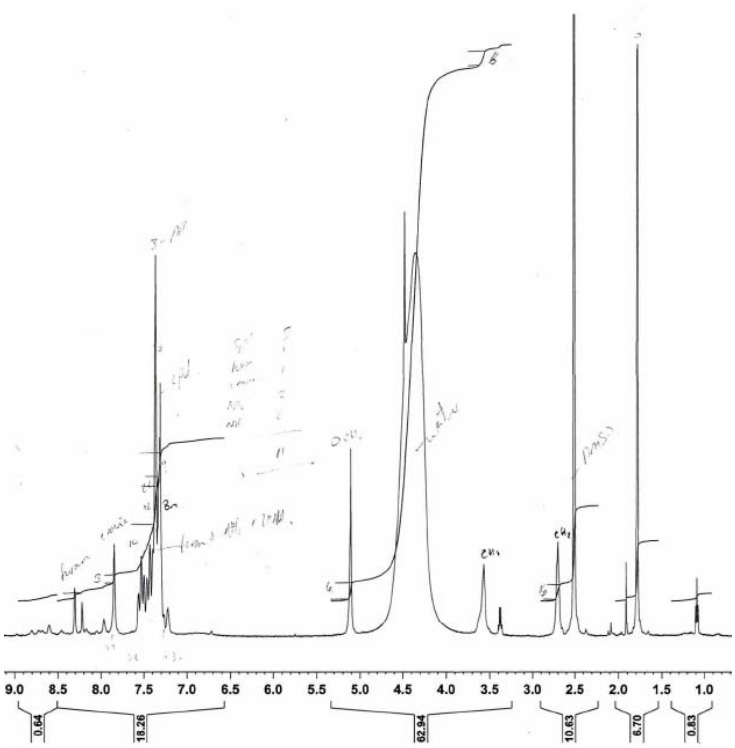
1.75
1.23
1.03
80.91
10.72
4.35
150
100
50
0
100.0000

Compound 6c


9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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19.26
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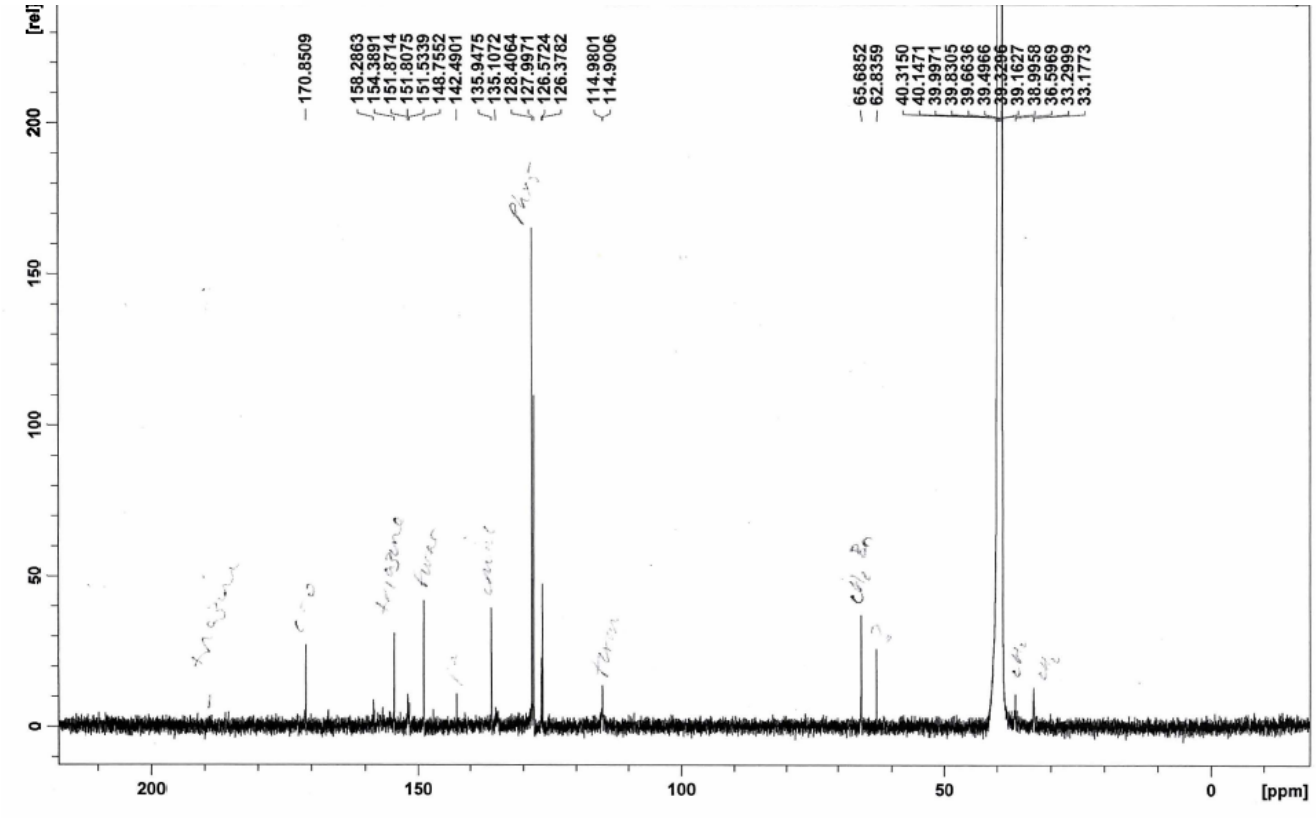
10.83
6.70
0.83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127.9971
126.5724
126.3782
114.9801
114.9006
65.6852
62.8359
40.3150
40.1471
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36.5969
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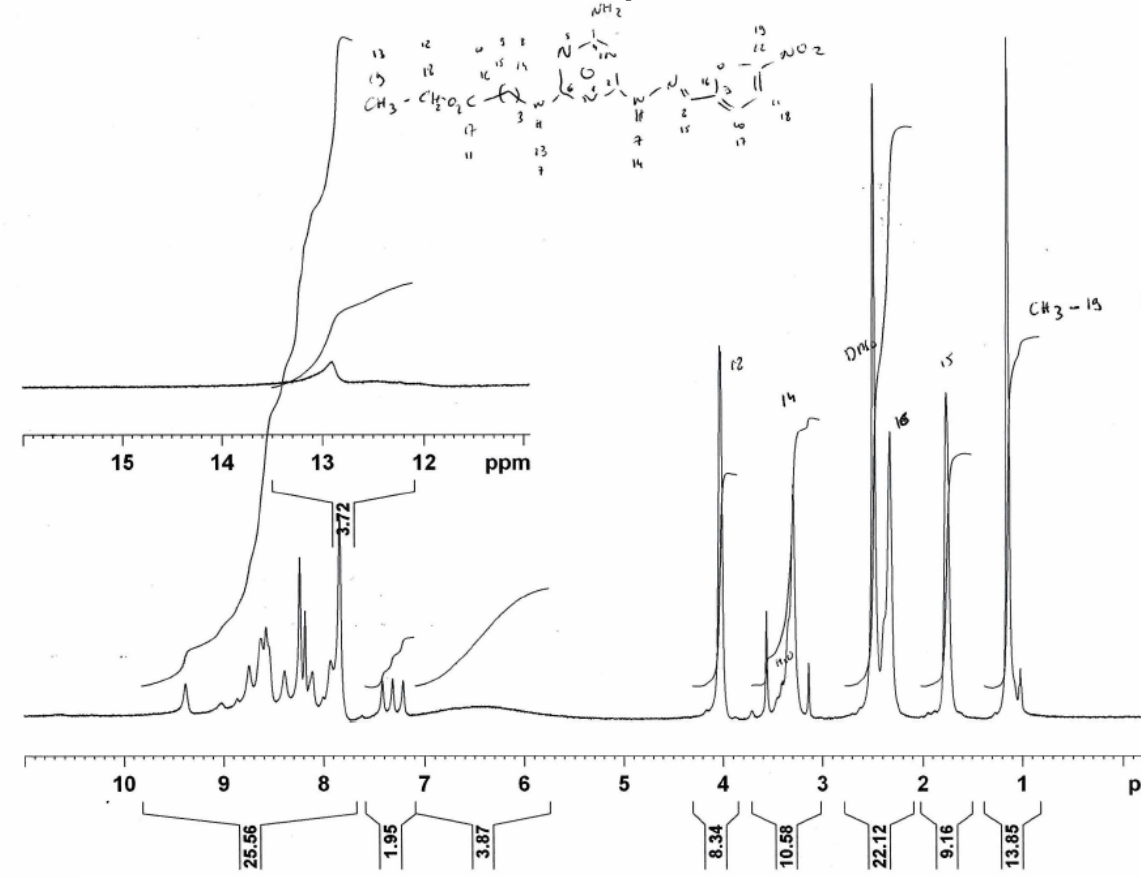
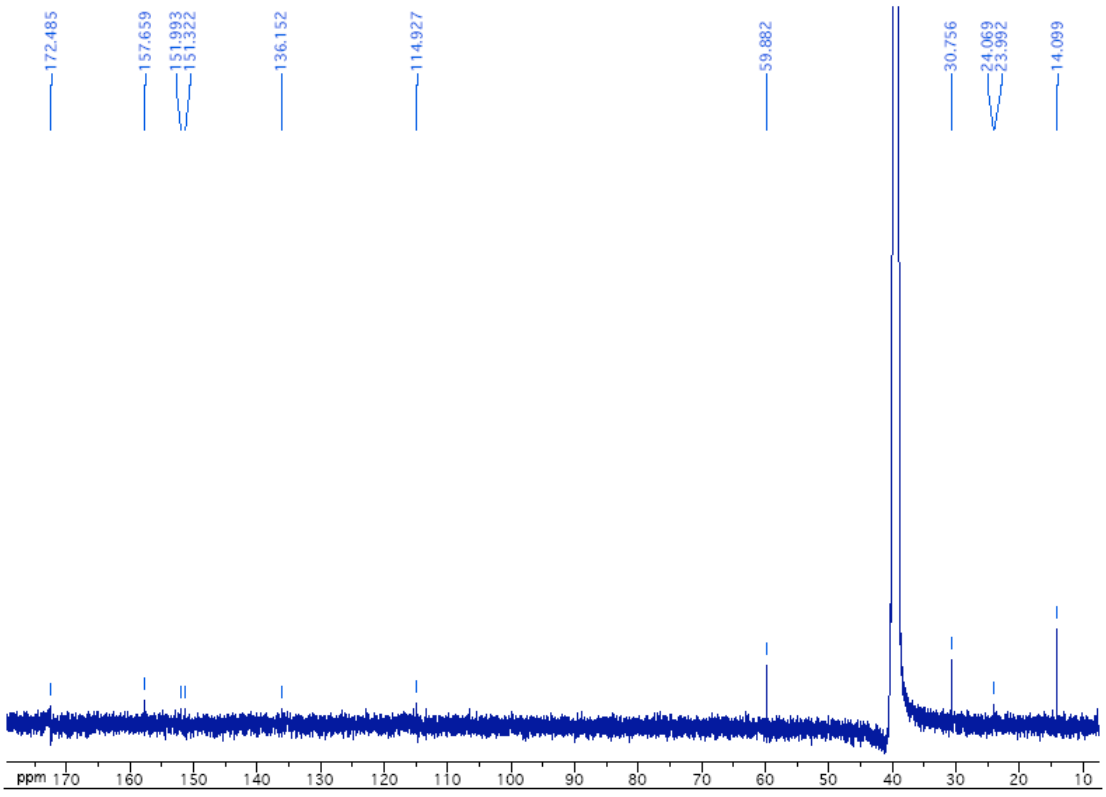
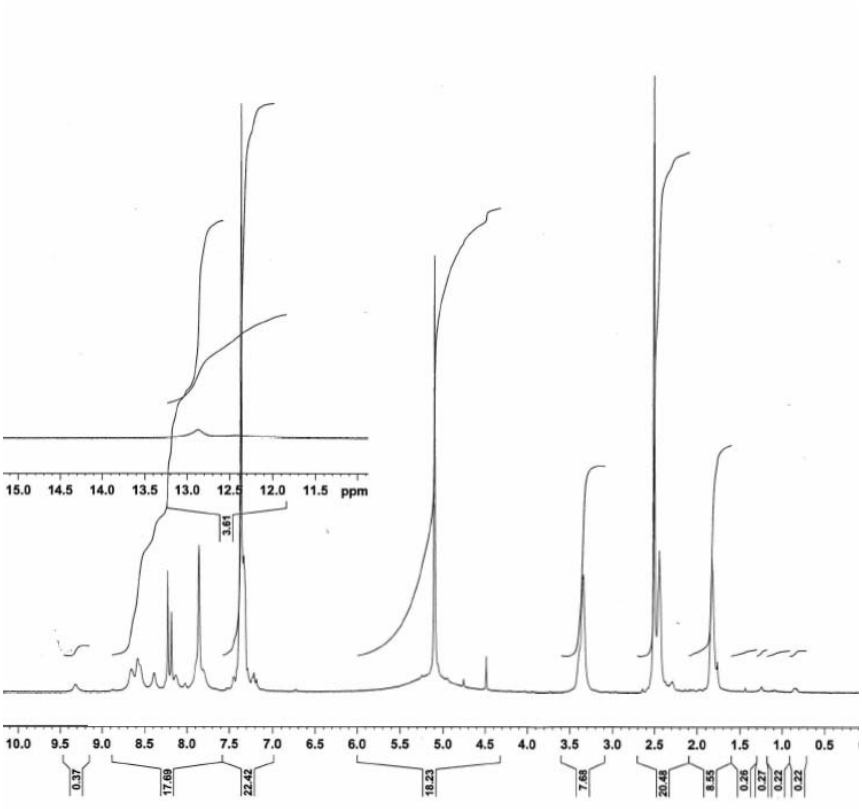
33.1773

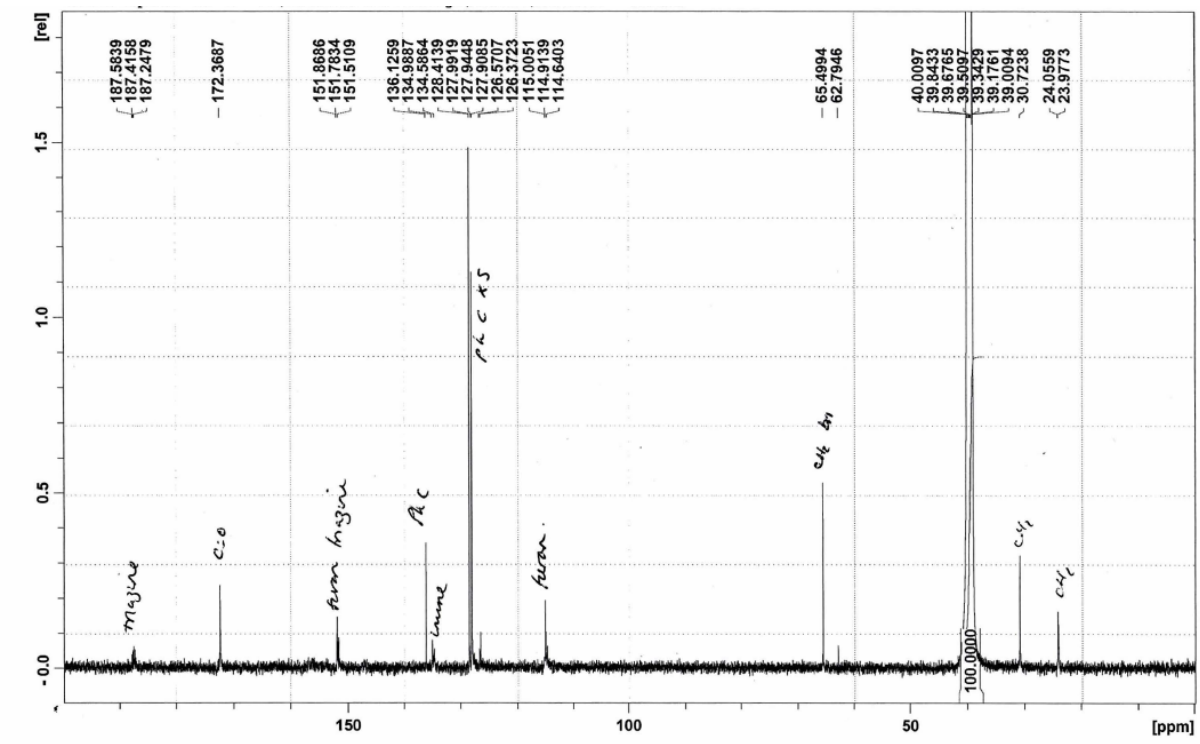
Compound 6d


15
14
13
12
ppm
3.72
10
9
8
7
6
5
4
3
2
1
p
25.56
1.95
3.87
8.34
10.58
22.12
9.16
13.85
DMSO
CH3 - 19

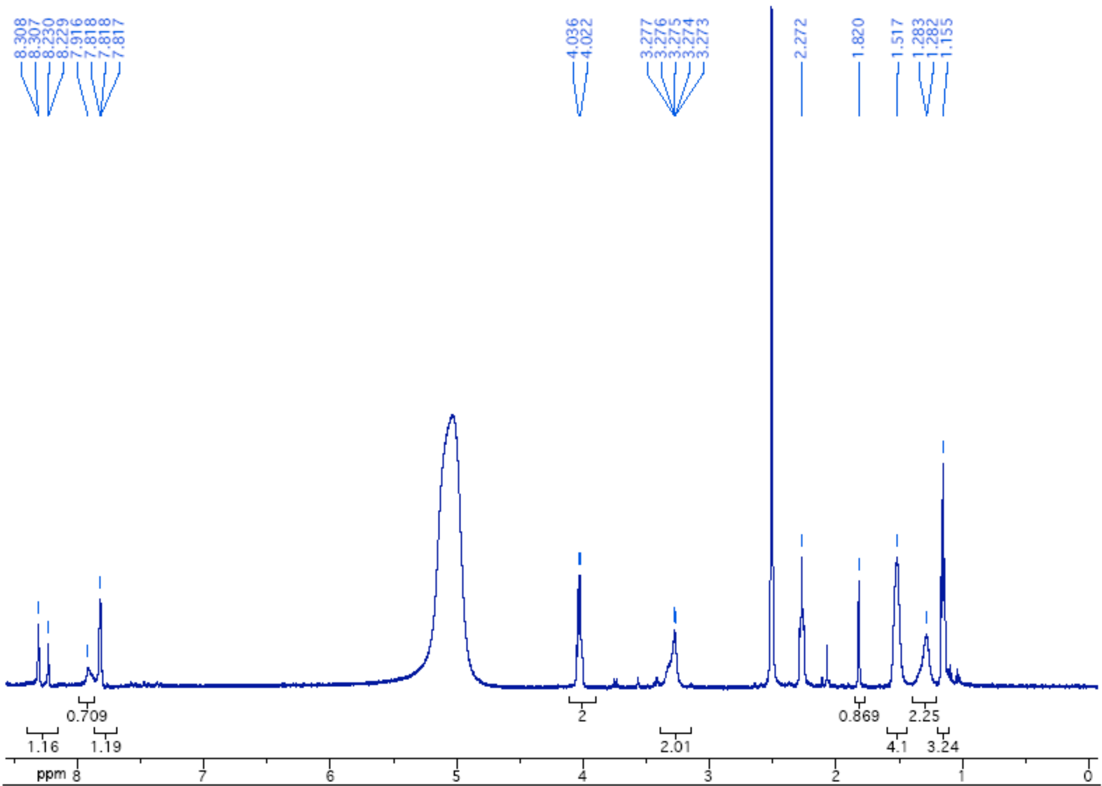

172.485
157.659
151.993
151.322
136.152
114.927
59.882
30.756
24.069
23.992
14.099
ppm
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

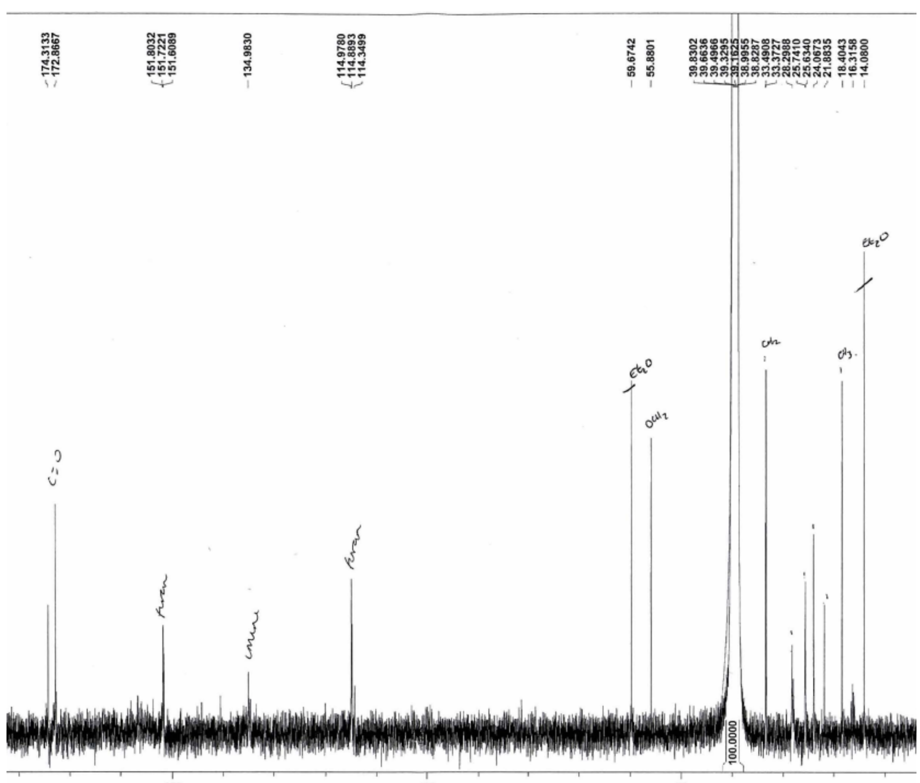
Compound 6e


15.0 14.5 14.0 13.5 13.0 12.5 12.0 11.5 ppm
3.61
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
0.37
17.69
22.42
18.23
7.68
20.48
8.55
0.26
0.27
0.22
0.22

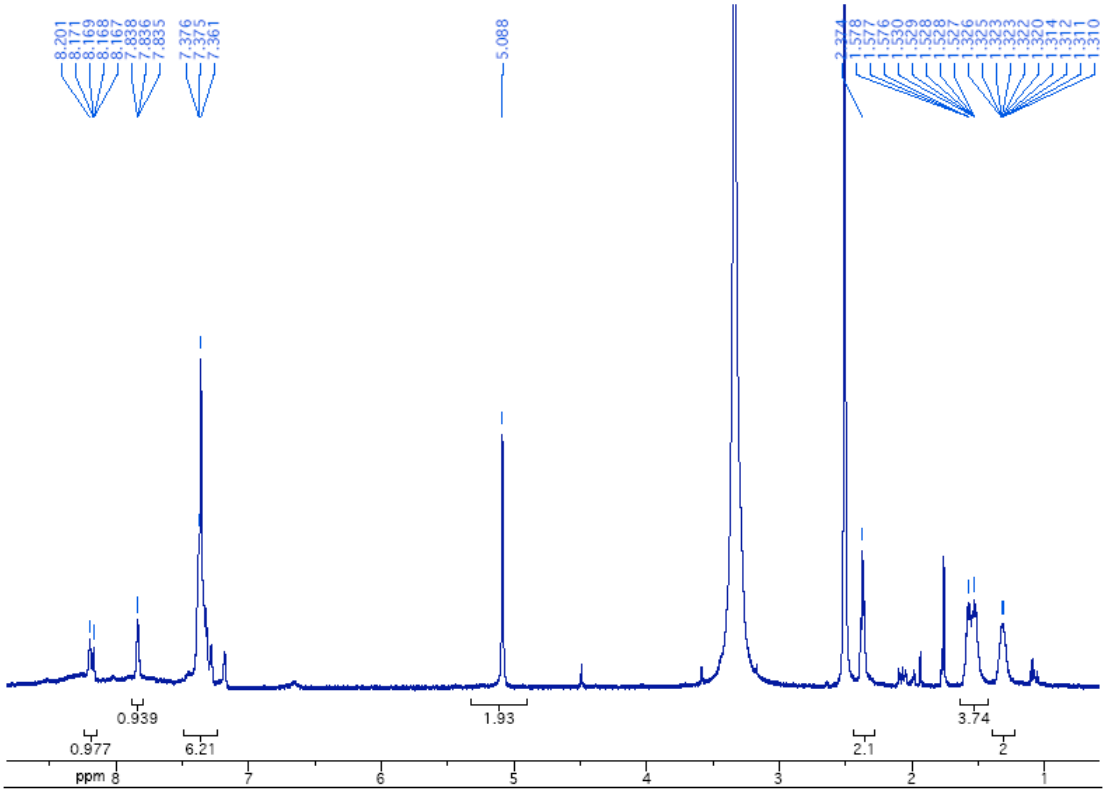

[rel]
187.5839
187.4158
187.2479
172.3687
151.8686
151.7834
151.5109
136.1259
134.9887
134.5864
128.4139
127.9919
127.9448
127.9085
126.5707
126.3723
115.0051
114.9139
114.6403
65.4994
62.7946
40.0097
39.8433
39.6765
39.5097
39.3429
39.1761
39.0094
30.7238
24.0559
23.9773
100.0000
150
100
50
[ppm]

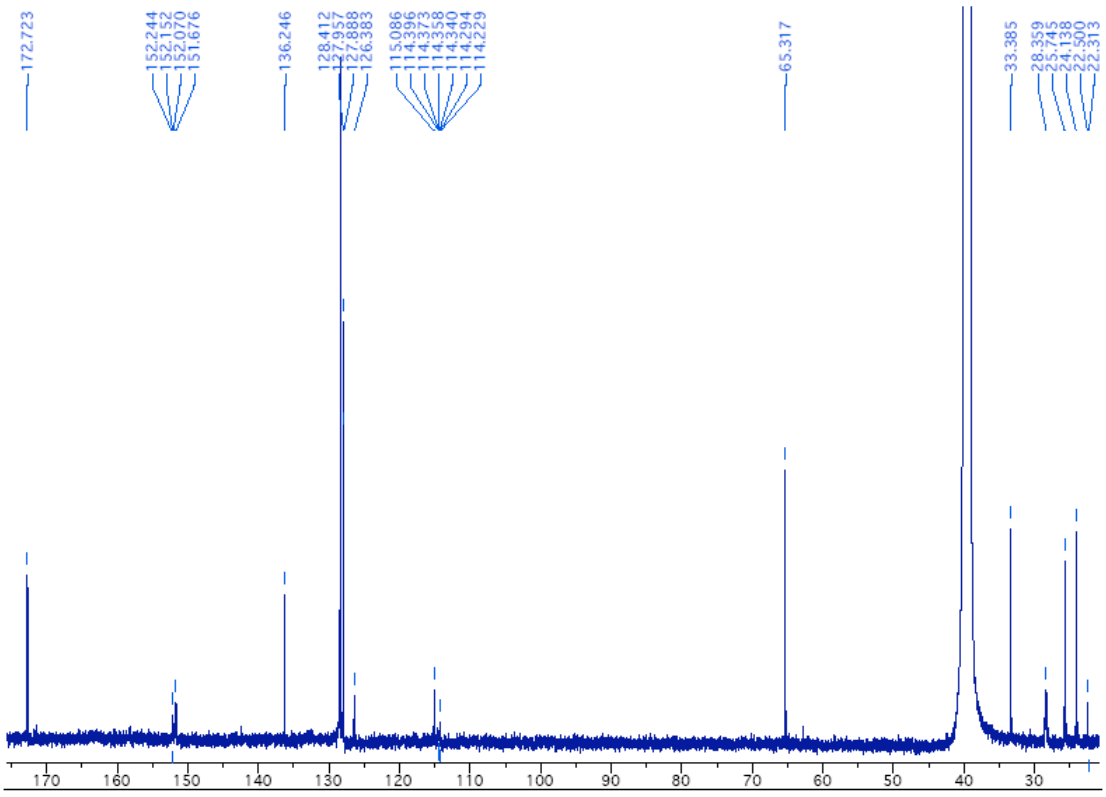
Compound 6f


8.308
8.307
8.230
8.229
7.916
7.818
7.818
7.817
4.036
4.022
3.277
3.276
3.275
3.274
3.273
2.272
1.820
1.517
1.283
1.282
1.155
0.709
1.16
1.19
2
2.01
0.869
4.1
2.25
3.24
ppm

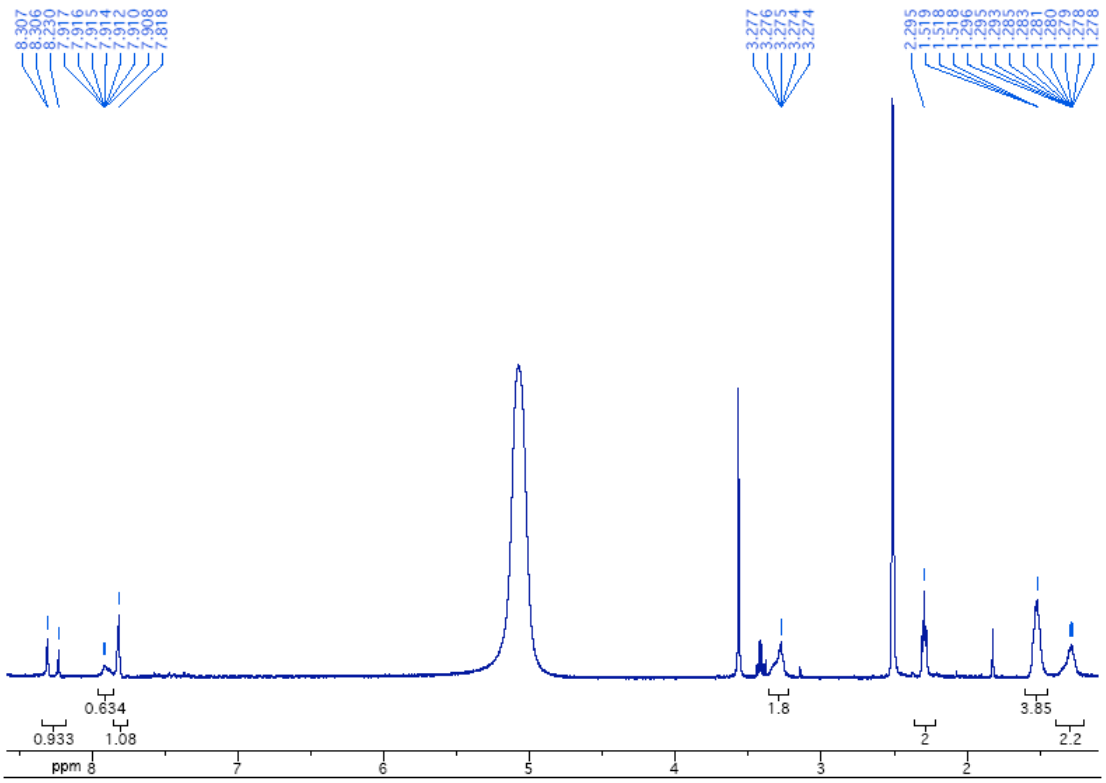

174.3133
172.8667
151.8032
151.7221
151.6089
134.9830
114.9780
114.8893
114.3499
59.6742
55.8801
100.0000
150
100
50

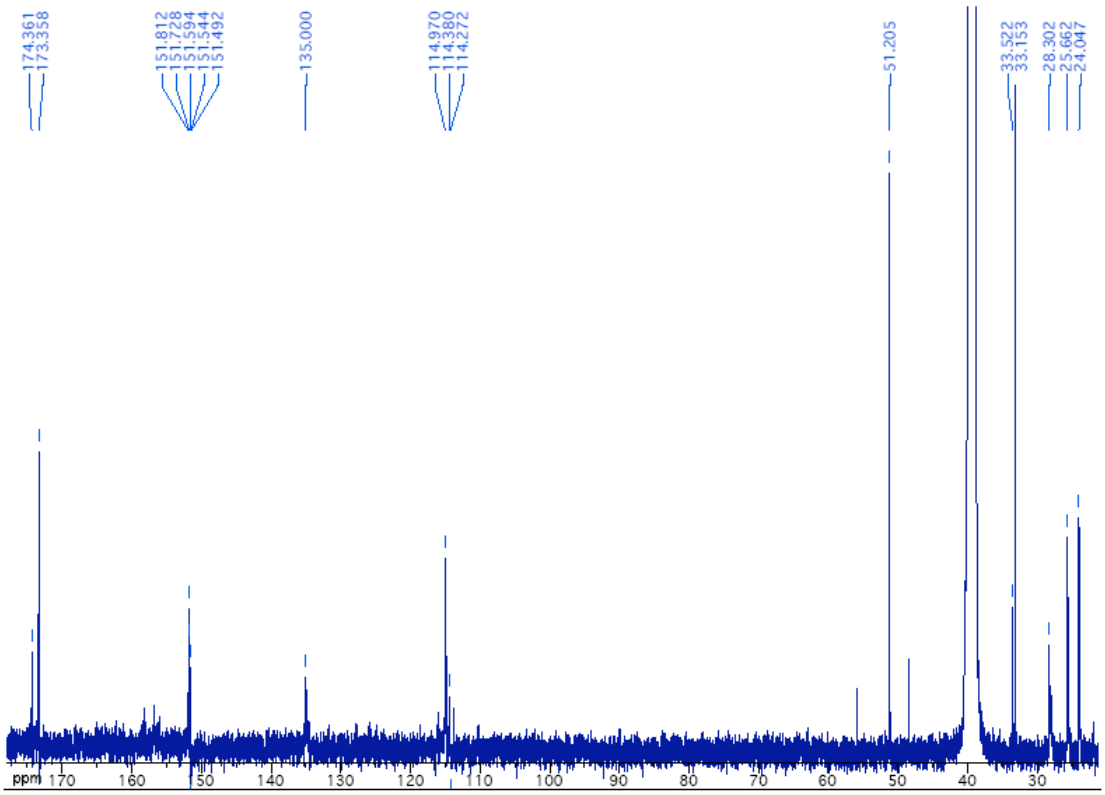
Compound 6g


8.201
8.171
8.169
8.168
8.167
7.838
7.836
7.835
7.376
7.375
7.361
5.088
2.374
1.578
1.577
1.576
1.530
1.529
1.528
1.527
1.326
1.325
1.323
1.322
1.320
1.314
1.312
1.311
1.310
0.939
1.93
3.74
0.977
6.21
2.1
2
ppm 8
7
6
5
4
3
2
1

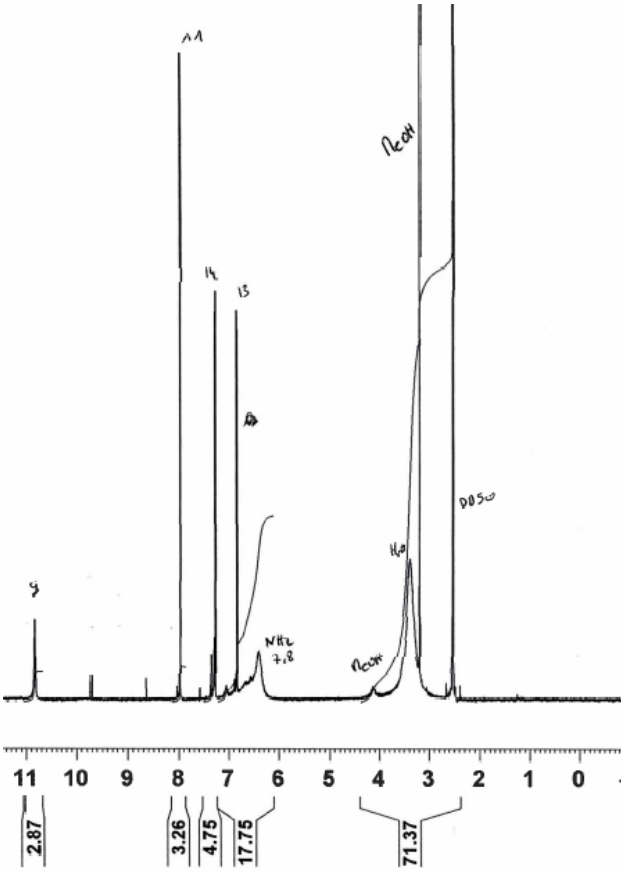

172.723
152.244
152.152
152.070
151.676
136.246
128.412
127.936
127.838
126.383
115.086
114.396
114.373
114.358
114.340
114.294
114.229
65.317
33.385
28.359
25.745
24.138
22.500
22.313
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30

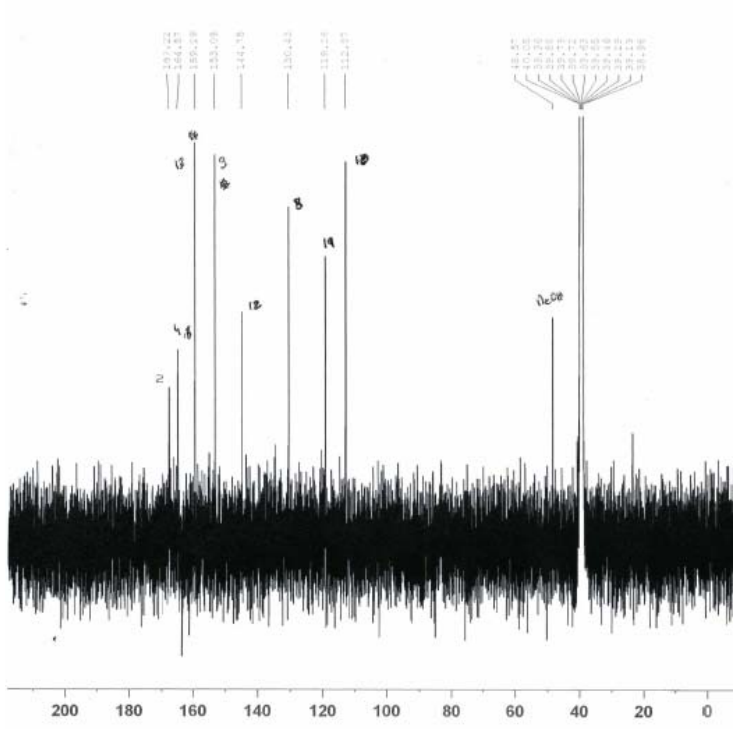
Compound 6h


8.307
8.306
8.290
8.289
7.917
7.916
7.915
7.914
7.912
7.910
7.908
7.818
3.277
3.276
3.275
3.274
3.274
2.295
1.519
1.518
1.518
1.296
1.295
1.293
1.285
1.283
1.281
1.280
1.279
1.278
1.278
0.634
1.8
3.85
0.933
1.08
2
2.2
ppm 8
7
6
5
4
3
2

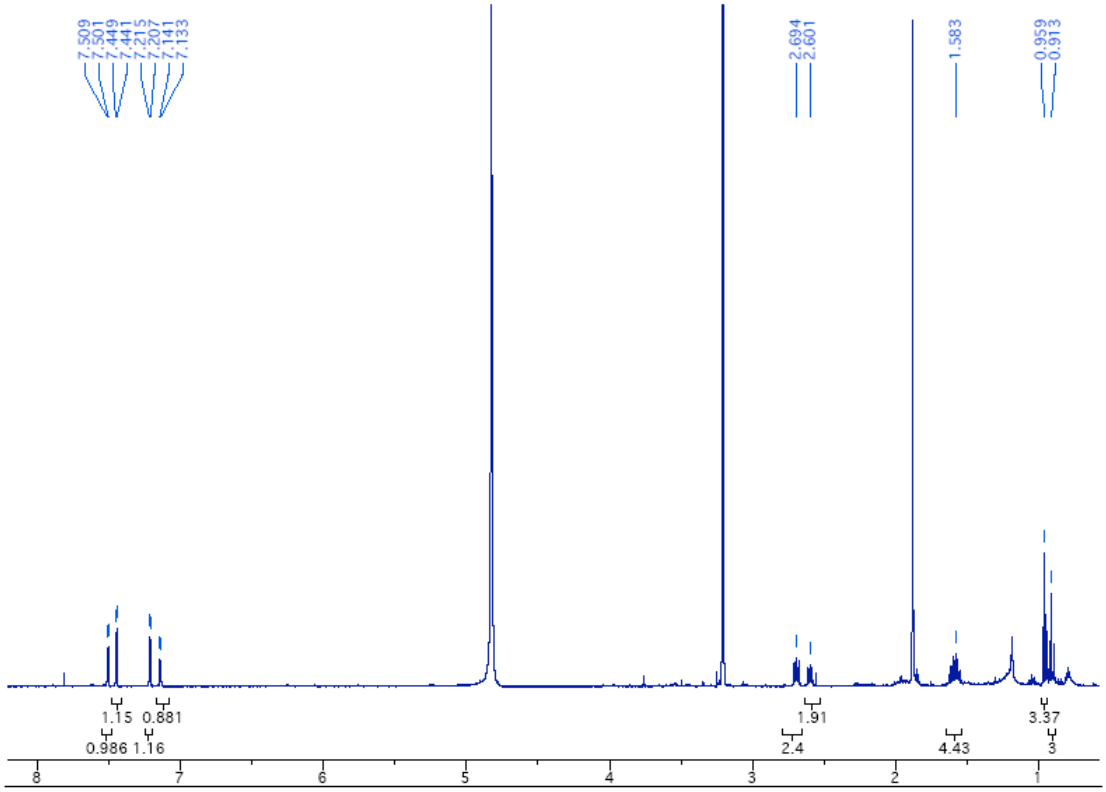

174.361
173.358
151.812
151.728
151.644
151.544
151.492
135.000
114.970
114.380
114.272
51.205
33.522
33.153
28.302
25.662
24.047
ppm 170
160
150
140
130
120
110
100
90
80
70
60
50
40
30

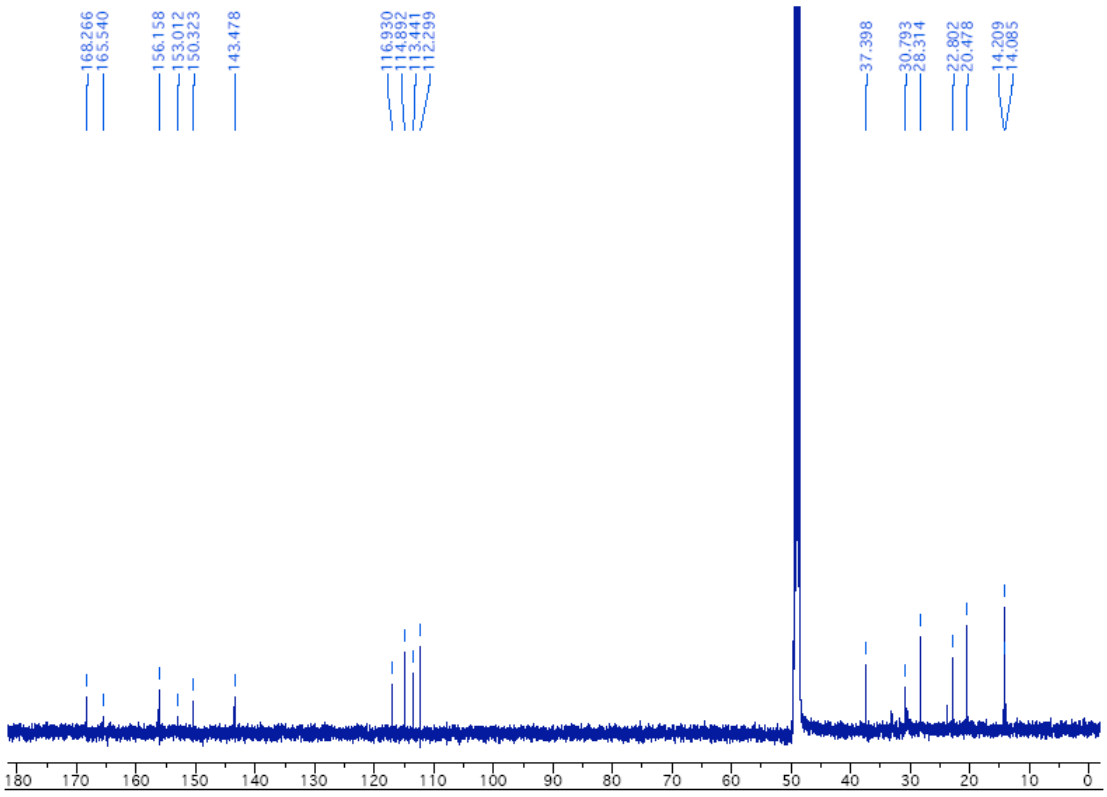
Compound 9a


11
14
13
NH2
7.8
MeOH
MeOH
DMSO
H2O
11 10 9 8 7 6 5 4 3 2 1 0
2.87
3.26
4.75
17.75
71.37

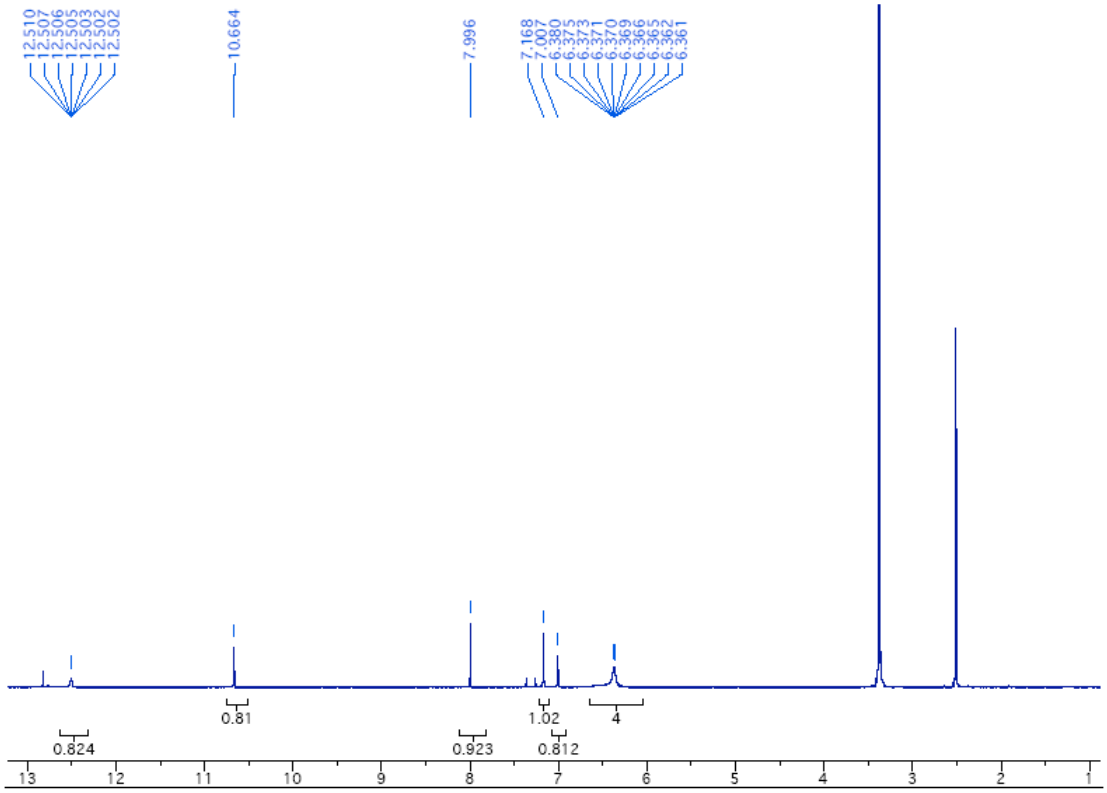

200 180 160 140 120 100 80 60 40 20 0

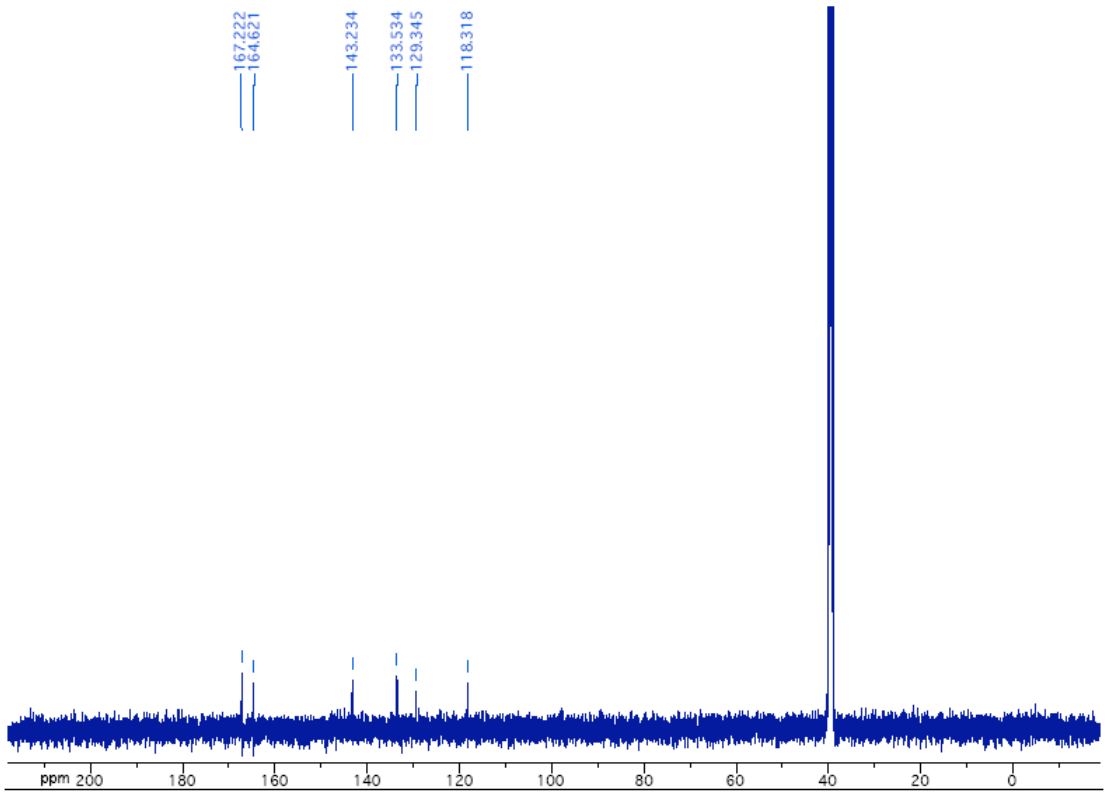
Compound 9d


7.509
7.501
7.449
7.441
7.215
7.207
7.141
7.133
2.694
2.601
1.583
0.959
0.913
1.15
0.881
0.986
1.16
1.91
2.4
4.43
3.37
3
8
7
6
5
4
3
2
1

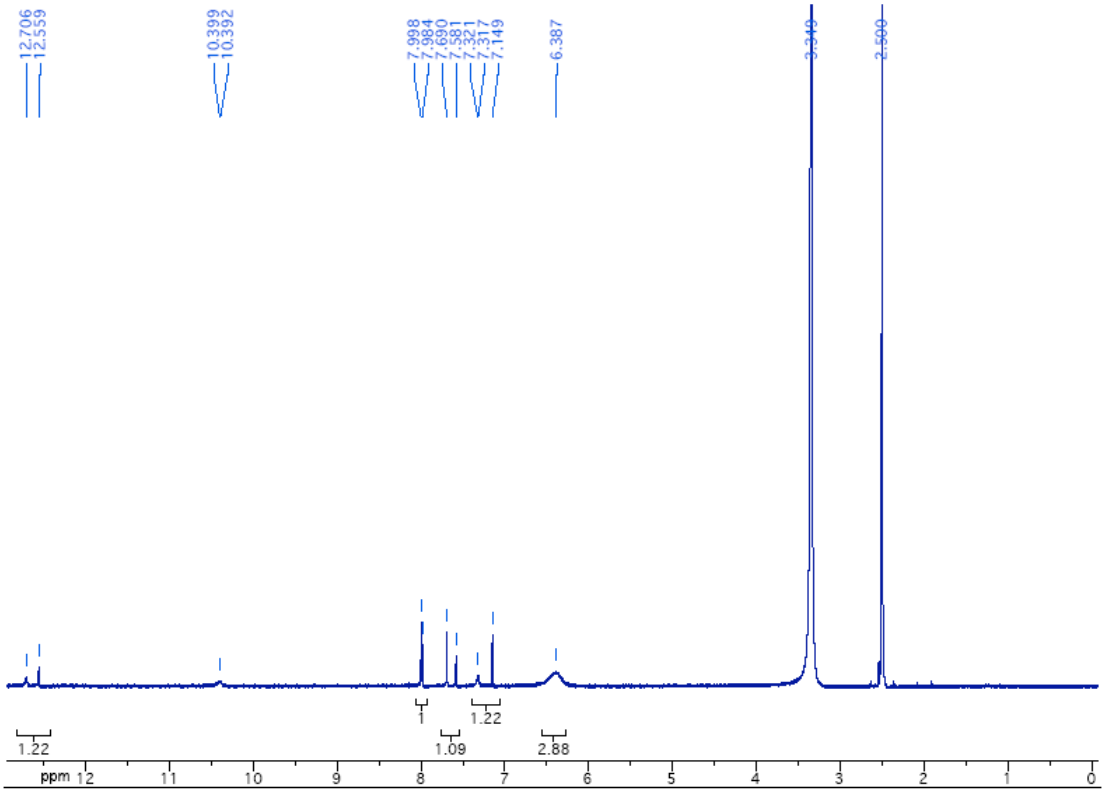

168.266
165.540
156.158
153.012
150.323
143.478
116.930
114.892
113.441
112.299
37.398
30.793
28.314
22.802
20.478
14.209
14.085
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Compound 9e


12.510
12.507
12.506
12.505
12.503
12.502
12.502
10.664
7.996
7.168
7.007
6.380
6.375
6.373
6.371
6.370
6.369
6.366
6.365
6.362
6.361
0.824
0.81
0.923
1.02
0.812
4
13
12
11
10
9
8
7
6
5
4
3
2
1


167.222
164.621
143.234
133.534
129.345
118.318
ppm 200
180
160
140
120
100
80
60
40
20
0

Compound 9f


12.706
12.559
10.399
10.392
7.998
7.994
7.690
7.680
7.331
7.327
7.317
7.149
6.387
3.340
2.500
1
1.22
1.22
1.09
2.88
ppm 12
11
10
9
8
7
6
5
4
3
2
1
0