Electronic supplementary information for An efficient, "green" synthesis of dihydrothiophene ureidoformamides by domino reactions of 1,3-thiazolidinedione under catalyst-free conditions

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Contents

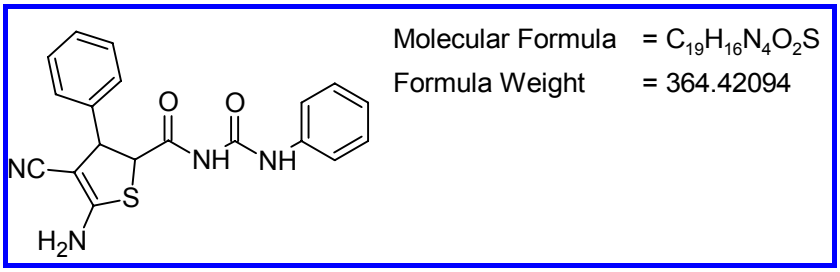
Experimental

All chemical reagents were obtained from commercial suppliers and used without further purification. Analytical thin-layer chromatography were performed on glass plates precoated with silica gel impregnated with a fluorescent indicator (254 nm), and the plates were visualized by exposure to ultraviolet light. All melting points were uncorrected. Mass spectra were taken on a Finnigan TSQ Quantum－MS instrument in the electrospray ionization (ESI) mode. ^{1}H NMR, ^{13}C NMR, COSY, HSQC and HMBC spectra were recorded on a AVANCE 500 Bruker spectrometer operating at 500 MHz and 125 MHz in DMSO-d_6, respectively, and chemical shifts were reported in ppm. Elemental analyses were performed on a Yanagimoto MT3CHN recorder.

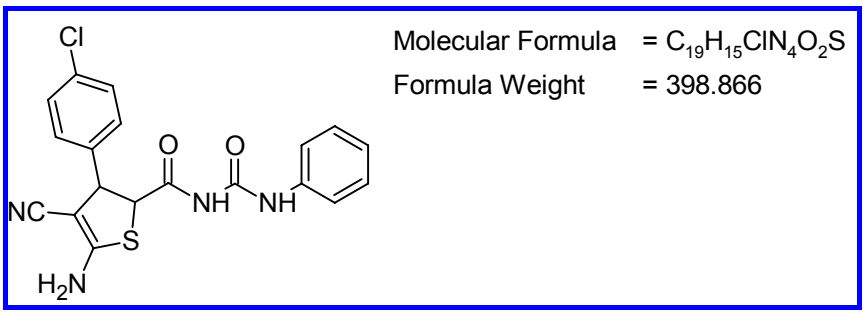
General Procedure for the Preparation of Dihydrothiophene Ureidoformamides from Aldehyde, Malononitrile, 1,3-Thiazolidinedione and Amine

A mixture of aldehyde (2.0 mmol) and malononitrile (2.2 mmol) in PEG 400/H_2O (4.0 ml, v/v =1:1) was stirred at 80℃ for 10 min. Then amine (2.0 mmol) and 1,3-thiazolidinedione (2.0 mmol) were added and the reaction was stirred at the same temperature for several hours monitored by TLC. After the reaction completed, water (10ml) was added to the mixture, and the precipitated was separated by filtration and washed with water. The crude product was recrystallized or washed with a mixture of ethanol and n-hexane to give the pure product.

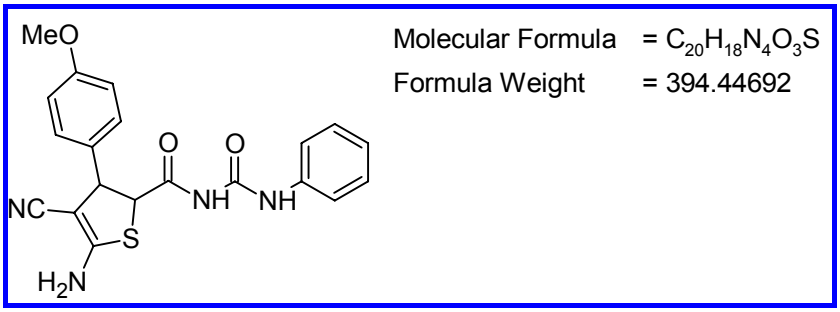
Characterization Data



5-amino-4-cyano-3-phenyl-N-(phenylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide **5a**; mp: 242-244℃(lit. 244-246℃)[1]; white solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 4.20 (s, 1H), 4.62 (s, 1H), 7.09-7.12 (m, 1H), 7.26 (s, 2H), 7.30-7.41 (m, 7H), 7.55 (d, 2H, J=7.5Hz), 10.29 (br, 1H), 10.77 (br, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 51.94, 55.78, 70.82, 118.70, 120.25, 124.30, 127.59, 128.01, 129.23, 129.42, 137.91, 141.98, 151.05, 162.20, 172.84. MS (ESI) *m*/*z*: 363 $(M-H)^-$. Anal. Calcd for $C_{19}H_{16}N_4O_2S$: C, 62.62; H, 4.43; N, 15.37%, Found: C, 62.31; H, 4.53; N, 15.56%.

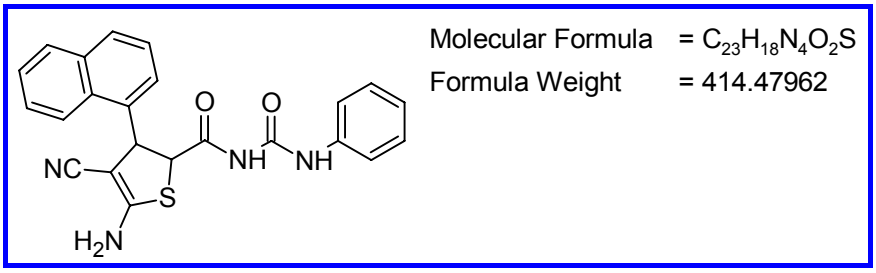


5-amino-3-(4-chlorophenyl)-4-cyano-N-(phenylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide **5b**; mp: 247-249℃(lit. 248-250℃)[1]; white solid, ^{1}H NMR (500MHz, DMSO-d_6): δ = 4.17 (s, 1H), 4.62 (s, 1H), 7.09-7.12 (m, 1H), 7.31-7.39 (m, 5H), 7.46 (d, 2H, J=8.0Hz), 7.55 (d, 2H, J=8.0Hz), 10.28 (br, 1H), 10.77 (br, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 51.27, 55.65, 70.46, 118.57, 120.24, 124.30, 129.19, 129.42, 129.54, 132.59, 137.90, 140.93, 151.06, 162.49, 172.70. MS (ESI) *m*/*z*: 397 $(M-H)^-$. Anal. Calcd for $C_{19}H_{15}ClN_4O_2S$: C, 57.21; H, 3.79; N, 14.05%, Found: C, 57.38; H, 4.03; N, 13.96%.

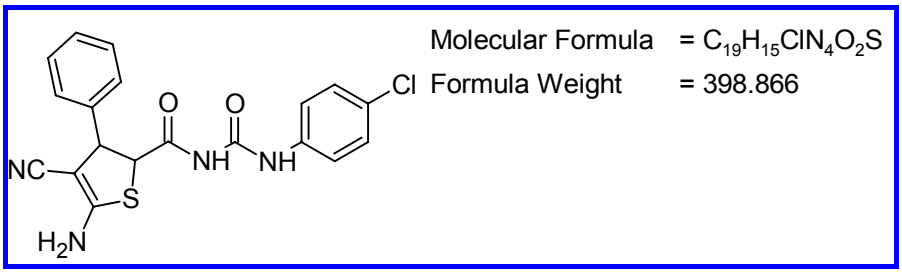


5-amino-4-cyano-3-(4-methoxyphenyl)-N-(phenylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide **5c**; mp 216-218℃(lit. 217-219℃)[1]; light yellow solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 3.75 (s, 3H), 4.16 (s, 1H), 4.58 (d, 1H, J=2.0Hz), 6.95 (d, 2H, J=8.5Hz), 7.09-7.12 (m, 1H), 7.22 (s, 2H), 7.26 (d, 2H, J=8.5Hz), 7.33-7.36 (m,

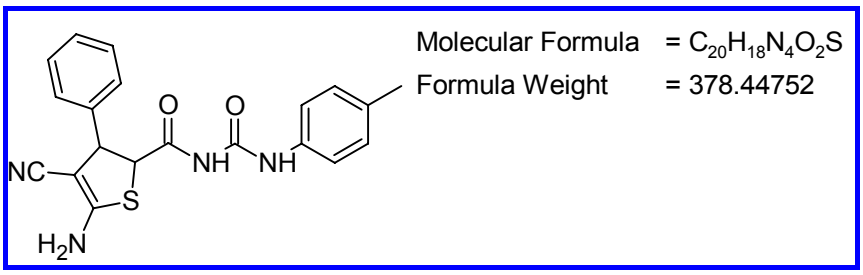
2H), 7.56 (d, 2H, J=8.0Hz), 10.30 (s, 1H), 10.78 (s, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 51.43, 55.56, 56.03, 71.18, 114.58, 118.74, 120.25, 124.30, 128.72, 129.41, 133.75, 137.90, 151.04, 159.18, 161.89, 172.89. MS (ESI) *m*/*z*: 393 $(M-H)^-$. Anal. Calcd for $C_{20}H_{18}N_4O_3S$: C, 60.90; H, 4.60; N, 14.20%, Found: C, 60.78; H, 4.83; N, 13.96%.



5-amino-4-cyano-3-(naphthalen-1-yl)-N-(phenylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide **5d**; mp: 236-238℃; white solid, ^{1}H NMR (500MHz, DMSO-d_6): δ = 4.15 (s, 1H), 5.46 (s, 1H), 7.10-7.13 (m, 1H), 7.34-7.40 (m, 4H), 7.47 (d, 1H, J=7.0Hz), 7.57-7.66 (m, 5H), 7.91-7.95 (m, 2H), 8.03 (d, 1H, J=8.0Hz). ^{13}C NMR (125MHz, DMSO-d_6): δ = 55.10, 69.25, 118.64, 120.31, 122.87, 124.35, 124.94, 126.08, 126.44, 127.48, 128.72, 129.42, 129.60, 130.84, 134.38, 136.40, 137.91, 150.97, 162.80, 172.88. MS (ESI) *m*/*z*: 413 $(M-H)^-$. Anal. Calcd for $C_{23}H_{18}N_4O_2S$: C, 66.65; H, 4.38; N, 13.52%, Found: C, 66.68; H, 4.29; N, 13.74%.

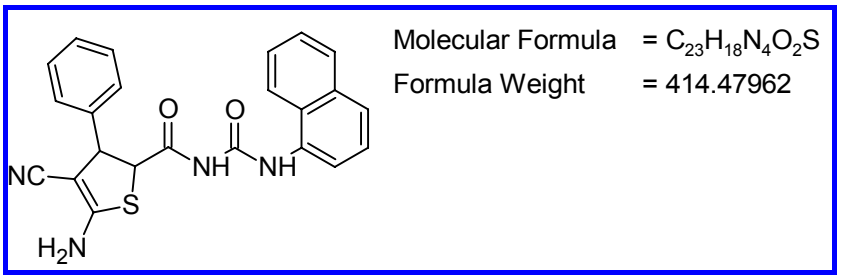


5-amino-N-(4-chlorophenylcarbamoyl)-4-cyano-3-phenyl-2,3-dihydrothiophene-2-carboxamide **5e**; mp: 244-246℃(lit. 246-247℃)[1]; white solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 4.19 (s, 1H), 4.61 (s, 1H), 7.25 (s, 2H), 7.31-7.40 (m, 7H), 7.60 (d, 2H, J=8.0Hz), 10.31 (br, 1H), 10.81 (br, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 51.94, 55.77, 70.83, 118.67, 121.96, 127.58, 127.99, 128.01, 129.24, 136.94, 141.95, 151.08, 162.19, 172.76. MS (ESI) *m*/*z*: 397 $(M-H)^-$. Anal. Calcd for $C_{19}H_{15}ClN_4O_2S$: C, 57.21; H, 3.79; N, 14.05%, Found: C, 56.98; H, 4.01; N, 13.89%.

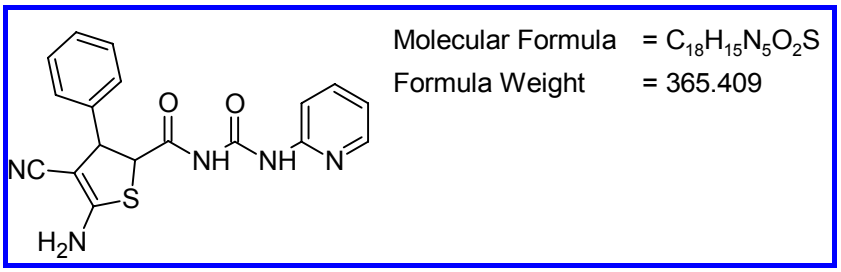


5-amino-4-cyano-3-phenyl-N-(p-tolylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide **5f**; mp: >250℃(lit. >250℃)[1]; white solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 2.27 (s, 3H), 4.19 (s, 1H), 4.61 (d, 1H, J=2.0Hz), 7.14 (d, 2H, J=8.5Hz), 7.24 (s, 2H),

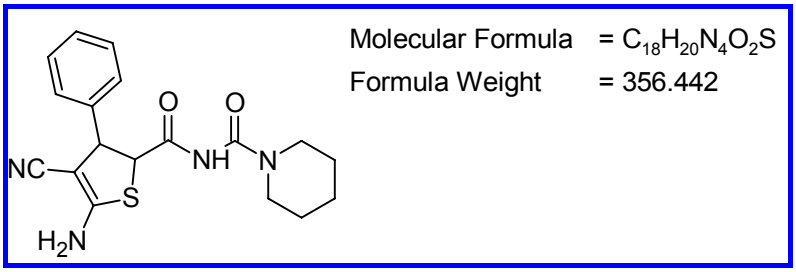
7.31-7.35 (m, 3H), 7.38-7.44 (m, 4H), 10.21 (br, 1H), 10.73 (br, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 20.86, 51.99, 55.77, 70.85, 118.68, 120.25, 127.59, 128.00, 129.23, 133.33, 135.35, 141.99, 150.99, 162.20, 172.79. MS (ESI) *m*/*z*: 377 $(M-H)^-$. Anal. Calcd for $C_{20}H_{18}N_4O_2S$: C, 63.47; H, 4.79; N, 14.80%, Found: C, 63.45; H, 4.90; N, 14.76%.



5-amino-4-cyano-N-(1-naphthylcarbamoyl)-3-phenyl-2,3-dihydrothiophene-2-carbox amide **5g**; mp: 230-232℃; white solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 4.28 (s, 1H), 4.71 (s, 1H), 7.30-7.34 (m, 3H), 7.40-7.43 (m, 4H), 7.51-7.54 (m, 1H), 7.59-7.62 (m, 1H), 7.70-7.73 (m, 1H), 7.76 (d, 1H, J=8.0Hz), 7.99-8.01 (m, 2H), 8.09 (d, 1H, J=6.5Hz), 11.01 (br, 2H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 52.03, 55.81, 70.93, 118.63, 118.76, 120.87, 125.03, 126.04, 126.28, 126.74, 127.21, 127.61, 128.03, 129.15, 129.25, 132.87, 134.09, 142.10, 151.51, 162.24, 173.60. MS (ESI) *m*/*z*: 413 $(M-H)^-$. Anal. Calcd for $C_{23}H_{18}N_4O_2S$: C, 66.65; H, 4.38; N, 13.52%, Found: C, 66.71; H, 4.48; N, 13.77%.

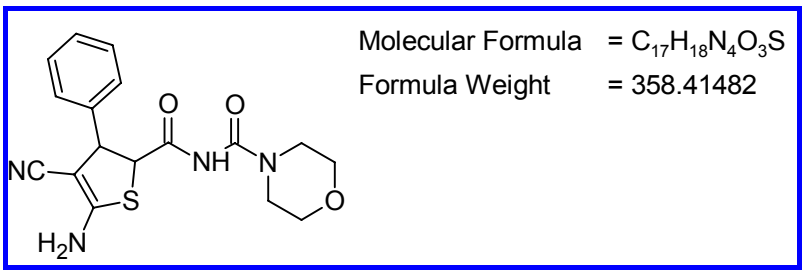


5-amino-4-cyano-3-phenyl-N-(pyridin-2-ylcarbamoyl)-2,3-dihydrothiophene-2-carbo xamide **5h**; mp: 202-204℃; White solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 4.26 (s, 1H), 4.63 (s, 1H), 7.13-7.16 (m, 1H), 7.25 (s, 2H), 7.30-7.41 (m, 5H), 7.80-7.83 (m, 1H), 7.91 (s, 1H), 8.33 (d, 1H, J=4.0Hz), 10.62 (br, 1H), 10.98 (br, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 51.84, 56.03, 70.82, 113.53, 118.68, 120.20, 127.60, 128.01, 129.22, 139.07, 142.00, 148.69, 150.89, 151.26, 162.08, 172.92. MS (ESI) *m*/*z*: 364 $(M-H)^-$. Anal. Calcd for $C_{18}H_{15}N_5O_2S$: C, 59.16; H, 4.14; N, 19.17%, Found: C, 59.29; H, 4.43; N, 18.88%.

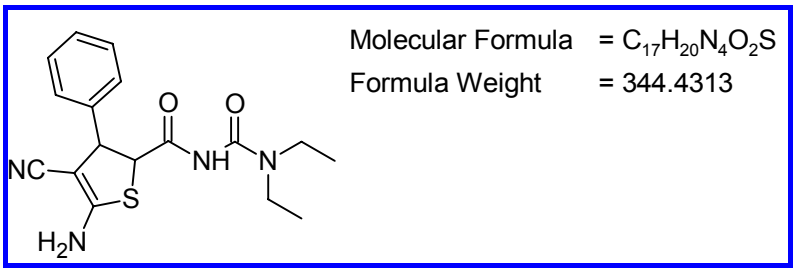


N-[(5-amino-4-cyano-3-phenyl-2,3-dihydrothiophen-2-yl)carbonyl]piperidine-1-carb

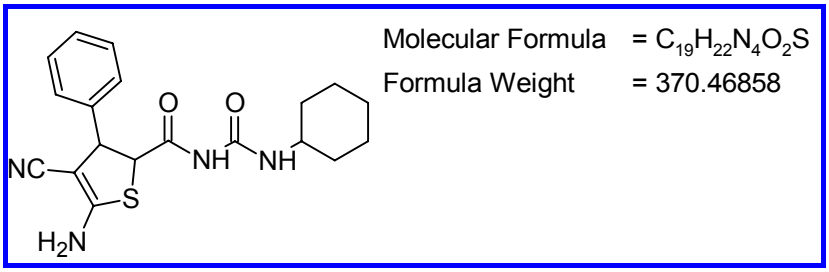
oxamide **6a**; mp 220-222℃(lit. 220-222℃)[2]; white solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 1.45 (d, 4H, J=5.0Hz), 1.52-1.54 (m, 2H), 3.30-3.33 (m, 4H), 4.43 (s, 1H), 4.61 (d, 1H, J=2.5Hz), 7.12 (s, 2H), 7.30-7.39 (m, 5H), 10.00 (s, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 24.20, 25.87, 45.64, 51.58, 56.17, 71.18, 118.86, 127.48, 127.87, 129.23, 142.75, 152.50, 162.25, 171.31. MS (ESI) *m/z*: 355 $(M-H)^-$. Anal. Calcd for $C_{18}H_{20}N_4O_2S$: C, 60.65; H, 5.66; N, 15.72%, Found: C, 60.49; H, 5.47; N, 15.68%.



N-[(5-amino-4-cyano-3-phenyl-2,3-dihydrothiophen-2-yl)carbonyl]morpholine-4-car boxamide **6b**; mp: 216-218℃; white solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 3.35 (d, 4H, J=5.5Hz), 3.54-3.56 (m, 4H), 4.42 (s, 1H), 4.60 (d, 1H, J=2.5Hz), 7.12 (s, 2H), 7.28-7.31 (m, 3H), 7.36-7.39 (m, 2H), 10.09 (s, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 45.13 51.48, 56.13, 66.30, 71.24, 118.88, 127.49, 127.88, 129.23, 142.75, 152.85, 162.20, 171.40. MS (ESI) *m/z*: 357 $(M-H)^-$. Anal. Calcd for $C_{17}H_{18}N_4O_3S$: C, 56.97; H, 5.06; N, 15.63%, Found: C, 57.06; H, 5.28; N, 15.44%.

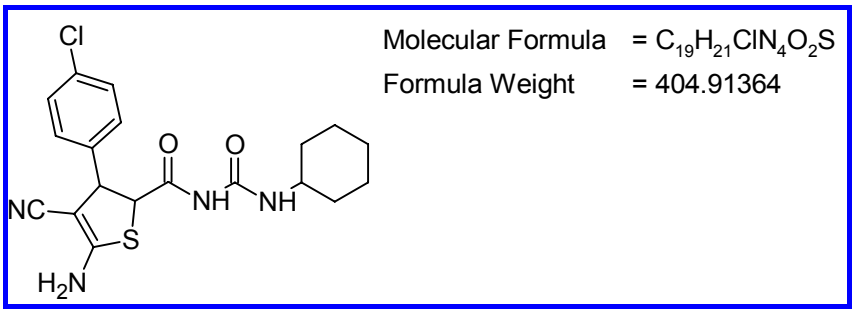


5-amino-4-cyano-N-(diethylcarbamoyl)-3-phenyl-2,3-dihydrothiophene-2-carboxami de **6c**; mp: 174-176℃(lit. 174-177℃)[2]; white solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 1.01-1.04 (m, 6H), 3.25-3.26 (m, 4H), 4.50 (s, 1H), 4.30 (d, 1H, J=9.5Hz), 7.12 (s, 2H), 7.30-7.39 (m, 5H), 9.81 (s, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 13.95, 41.60, 51.37, 56.43, 71.11, 118.89, 127.47, 127.86, 129.24, 142.78, 152.73, 162.27, 171.45. MS (ESI) *m/z*: 343 $(M-H)^-$. Anal. Calcd for $C_{17}H_{20}N_4O_2S$: C, 59.28; H, 5.85; N, 16.27%, Found: C, 59.16; H, 5.79; N, 16.43%.

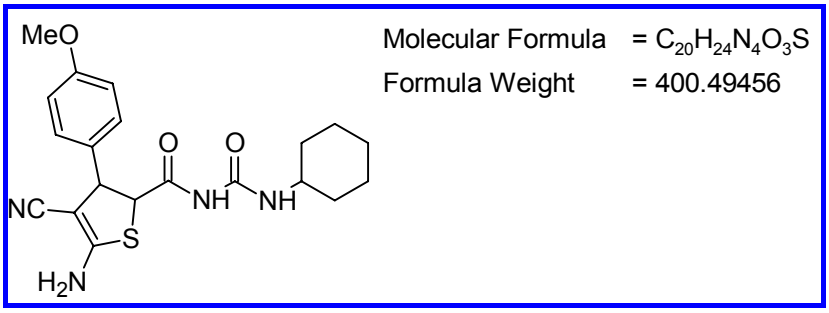


5-amino-4-cyano-N-(cyclohexylcarbamoyl)-3-phenyl-2,3-dihydrothiophene-2-carbox amide **6d**; mp: 228-230℃; white solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 1.25-1.35

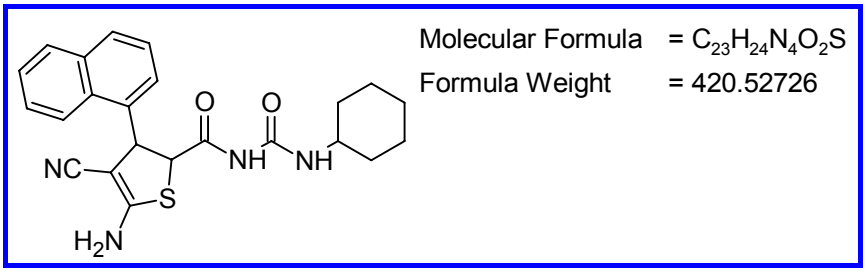
(m, 5H), 1.54 (d, 1H, J=12Hz), 1.64 (d, 2H, J=8.0Hz), 1.81 (d, 2H, J=5.0Hz), 3.56 (s, 1H), 4.08 (s, 1H), 4.55 (d, 1H, J=2.0Hz), 7.20 (s, 2H), 7.29-7.39 (m, 5H), 8.17 (s, 1H), 10.43 (s, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 24.62, 25.51, 32.70, 48.33, 51.99, 55.66, 70.89, 118. 64, 127.57, 127.96, 129.20, 141.99, 152.46, 162.19, 172.40. MS (ESI) *m*/*z*: 369 $(M-H)^-$. Anal. Calcd for $C_{19}H_{22}N_4O_2S$: C, 61.60; H, 5.99; N, 15.12%, Found: C, 61.37; H, 5.83; N, 15.40%.



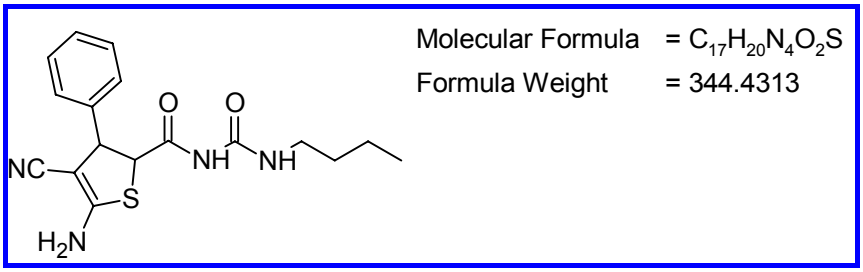
5-amino-3-(4-chlorophenyl)-4-cyano-N-(cyclohexylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide **6e**; mp: 240-242℃; white solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 1.19-1.32 (m, 5H), 1.52 (s, 1H), 1.63 (s, 2H), 1.80 (s, 2H), 3.55 (s, 1H), 4.03 (s, 1H), 4.55 (s, 1H), 7.26 (s, 2H), 7.34 (d, 2H, J=7.5Hz), 7.44 (d, 2H, J=8.0Hz), 8.16 (s, 1H), 10.44 (s, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 24.62, 25.49, 32.70, 48.49, 51.20, 55.51, 70.51, 118.52, 129.15, 129.52, 132.54, 140.95, 152.47, 162.47, 172.27. MS (ESI) *m*/*z*: 403 $(M-H)^-$. Anal. Calcd for $C_{19}H_{21}ClN_4O_2S$: C, 56.36; H, 5.23; N, 13.84%, Found: C, 56.44; H, 5.09; N, 13.68%.



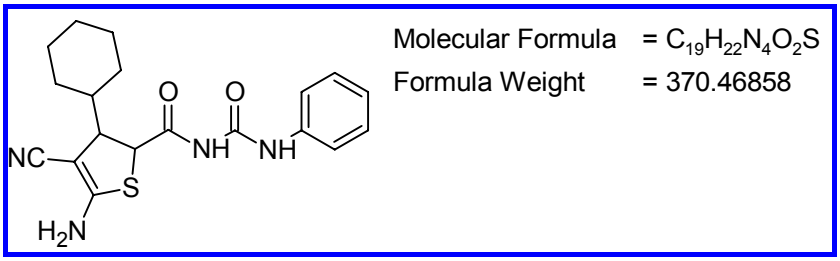
5-amino-4-cyano-N-(cyclohexylcarbamoyl)-3-(4-methoxyphenyl)-2,3-dihydrothiophene-2-carboxamide **6f**; mp: 224-226℃; white solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 1.19-1.35 (m, 5H), 1.53 (d, 1H, J=12.5Hz), 1.63 (s, 2H), 1.80 (d, 2H, J=5Hz), 3.55 (s, 1H), 3.75 (s, 3H), 4.01 (s, 1H), 4.50 (d, 1H, J=2.0Hz), 6.93 (d, 2H, J=8.5Hz), 7.17-7.22 (m, 4H), 8.17 (s, 1H), 10.44 (s, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 24.63, 25.49, 48.31, 51.40, 55.57, 55.88, 71.19, 114.56, 118.70, 128.69, 133.77, 152.45, 159.13, 161.85, 172.44. MS (ESI) *m*/*z*: 399 $(M-H)^-$. Anal. Calcd for $C_{20}H_{24}N_4O_3S$: C, 59.98; H, 6.04; N, 13.99%, Found: C, 60.02; H, 5.99; N, 13.87%.



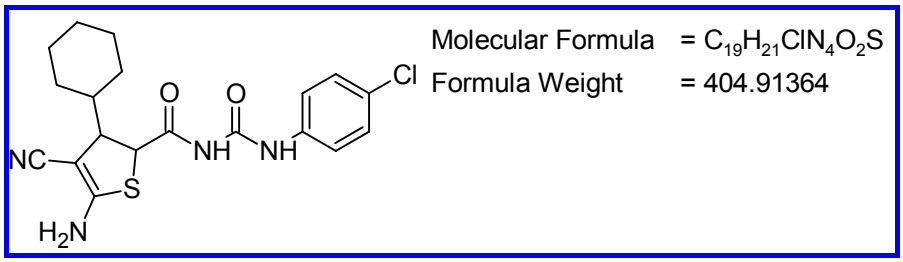
5-amino-4-cyano-N-(cyclohexylcarbamoyl)-3-(naphthalen-1-yl)-2,3-dihydrothiophene -2-carboxamide **6g**; mp: 238-240℃; white solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 1.22-1.31 (m, 5H), 1.54 (s, 1H), 1.67 (s, 2H), 1.85 (s, 2H), 3.57 (s, 1H), 4.04 (s, 1H), 5.39 (s, 1H), 7.36 (s, 2H), 7.44 (d, 1H, J=7.0Hz), 7.58-7.63 (m, 3H), 7.84 (d, 1H, J=7.0Hz), 7.93 (d, 1H, J=7.5Hz), 8.02 (d, 1H, J=7.5Hz), 8.19 (s, 1H), 10.47 (s, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 24.69, 25.51, 32.69, 48.52, 55.05, 69.26, 118.61, 122.73, 124.93, 126.06, 126.41, 127.41, 128.67, 129.60, 130.84, 134.37, 136.41, 152.37, 162.81, 172.54. MS (ESI) *m*/*z*: 419 (M-H)$^-$. Anal. Calcd for $C_{23}H_{24}N_4O_2S$: C, 65.69; H, 5.75; N, 13.32%, Found: C, 65.44; H, 5.68; N, 13.53%.



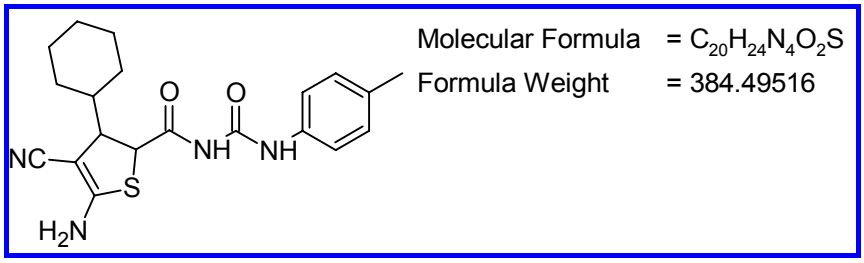
5-amino-N-(butylcarbamoyl)-4-cyano-3-(naphthalen-1-yl)-2,3-dihydrothiophene-2-ca rboxamide **6h**; mp: 228-230℃; white solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 0.88-0.91 (s, 3H), 1.26-1.34 (m, 2H), 1.43-1.48 (m, 2H), 3.16 (d, 2H, J=6.5Hz), 4.10 (s, 1H), 4.56 (d, 1H, J=2.5Hz), 7.20 (s, 2H), 7.29-7.32 (m, 3H), 7.37-7.40 (m, 2H), 8.20 (br, 1H), 10.40 (s, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 14.06, 19.97, 31.67, 39.15, 52.10, 55.66, 70.82, 118.65, 127.57, 127.97, 129.21, 141.99, 153.30, 162.19, 172.08. MS (ESI) *m*/*z*: 343 (M-H)$^-$. Anal. Calcd for $C_{17}H_{20}N_4O_2S$: C, 59.28; H, 5.85; N, 16.27%, Found: C, 59.22; H, 5.69; N, 16.34%.



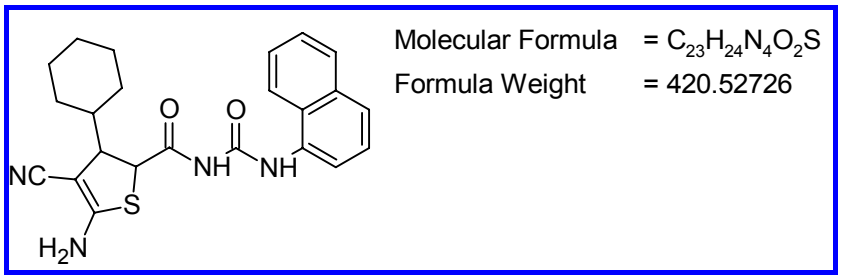
5-amino-4-cyano-3-cyclohexyl-N-(phenylcarbamoyl)-2,3-dihydrothiophene-2-carboxa mide **7a**; mp: 226-228℃; white solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 1.08-1.24 (m, 5H), 1.52 (s, 1H), 1.64-1.75 (m, 5H), 3.30 (d, 1H, J=13.5Hz), 4.20 (s, 1H), 6.99 (s, 2H), 7.08-7.11 (m, 1H), 7.32-7.35 (m, 2H), 7.54 (d, 2H, J=8.0Hz), 10.23 (s, 1H), 10.72 (s, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 26.25, 26.36, 26.47, 29.30, 29.57, 42.31, 50.41, 52.81, 68.73, 119.36, 120.25, 124.28, 129.39, 137.88, 151.05, 161.83, 173.61. MS (ESI) *m*/*z*: 369 (M-H)$^-$. Anal. Calcd for $C_{19}H_{22}N_4O_2S$: C, 61.60; H, 5.99; N, 15.12%, Found: C, 61.42; H, 5.88; N, 15.31%.



5-amino-N-(4-chlorophenylcarbamoyl)-4-cyano-3-cyclohexyl-2,3-dihydrothiophene-2-carboxamide **7b**; mp: 220-222℃; white solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 1.16-1.24 (m, 5H), 1.52 (s, 1H), 1.63-1.74 (m, 5H), 3.28 (d, 1H, J=2.5Hz), 4.19 (s, 1H), 6.99 (s, 2H), 7.38 (d, 2H, J=8.5Hz), 7.59 (s, 2H, J=8.5Hz), 10.28 (s, 1H), 10.78 (s, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 26.24, 26.35, 26.47, 29.32, 29.52, 42.30, 50.41, 52.77, 68.67, 119.37, 121.96, 127.95, 129.22, 136.91, 151.10, 161.84, 173.52. MS (ESI) *m*/*z*: 403 $(M-H)^-$. Anal. Calcd for $C_{19}H_{21}ClN_4O_2S$: C, 56.36; H, 5.23; N, 13.84%, Found: C, 56.40; H, 5.37; N, 13.81%.

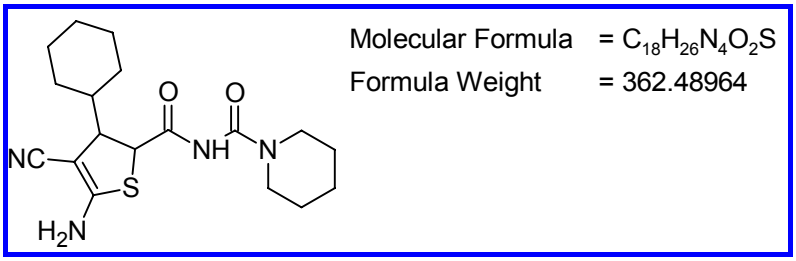


5-amino-4-cyano-3-cyclohexyl-N-(p-tolylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide **7c**; mp: 216-218℃; white solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 1.14-1.23 (m, 5H), 1.52 (s, 1H), 1.67-1.74 (m, 5H), 2.26 (s, 3H), 3.29 (s, 1H), 4.20 (s, 1H), 6.98 (s, 2H), 7.13 (d, 2H, J=7.0Hz), 7.41 (d, 2H, J=7.0Hz), 10.17 (s, 1H), 10.70 (s, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 20.85, 26.25, 26.36, 26.47, 29.27, 29.57, 42.29, 50.80, 52.37, 52.80, 68.70, 119.37, 120.23, 133.30, 135.32, 151.00, 161.84, 173.57. MS (ESI) *m*/*z*: 383 $(M-H)^-$. Anal. Calcd for $C_{20}H_{24}N_4O_2S$: C, 62.48; H, 6.29; N, 14.57%, Found: C, 62.37; H, 6.36; N, 14.82%.

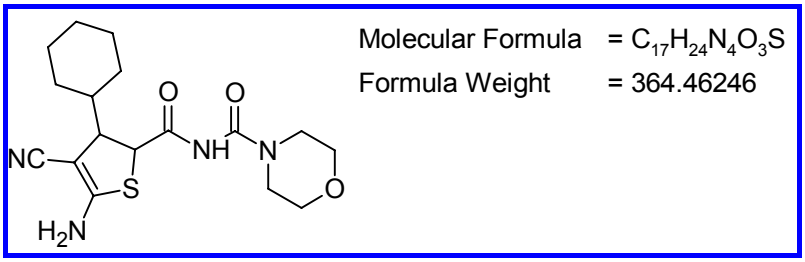


5-amino-4-cyano-3-cyclohexyl-N-(naphthalen-1-ylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide **7d**; mp: 208-210℃; white solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 1.14-1.25 (m, 5H), 1.56 (s, 1H), 1.65 (d, 1H, J=11.0Hz), 1.74 (s, 4H), 3.38 (d, 1H, J=2.5Hz), 4.28 (s, 1H), 7.05 (s, 2H), 7.50-7.54 (m, 1H), 7.57-7.60 (m, 1H), 7.66-7.70 (m, 1H), 7.74 (d, 1H, J=8.5Hz), 7.95-7.99 (m, 2H), 8.10 (d, 1H, J=7.5Hz), 11.00 (br, 2H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 26.28, 26.40, 26.50, 29.30, 29.50, 42.50, 50.51, 52.92, 68.68, 118.51, 119.46, 120.80, 124.97, 125.95, 126.26, 126.71, 127.19,

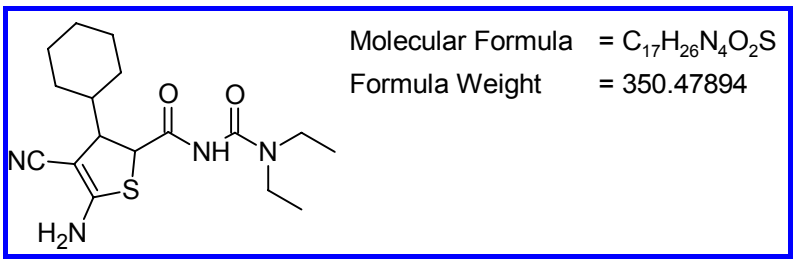
129.13, 132.85, 134.06, 151.50, 161.94, 174.39. MS (ESI) *m/z*: 419 $(M-H)^-$. Anal. Calcd for $C_{23}H_{24}N_4O_2S$: C, 65.69; H, 5.75; N, 13.32%, Found: C, 65.77; H, 6.03; N, 13.62%.



N-(5-amino-4-cyano-3-cyclohexyl-2,3-dihydrothiophene-2-carbonyl)piperidine-1-carboxamide **7e**; mp: 200-202℃; white solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 1.07-1.18 (m, 6H), 1.47-1.72 (m, 13H), 3.34 (s, 3H), 4.40 (s, 1H), 6.86 (s, 2H), 9.92 (s, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 24.24, 25.92, 26.27, 26.38, 26.49, 29.28, 29.71, 42.38, 45.58, 50.59, 51.92, 68.89, 119.56, 152.57, 161.99, 172.01. MS (ESI) *m/z*: 361 $(M-H)^-$. Anal. Calcd for $C_{18}H_{26}N_4O_2S$: C, 59.64; H, 7.23; N, 15.46%, Found: C, 59.74; H, 7.01; N, 15.65%.

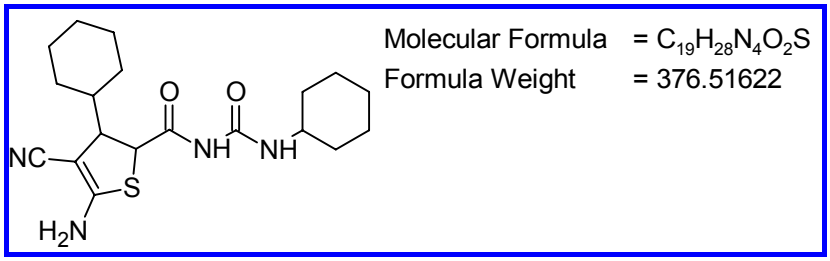


N-(5-amino-4-cyano-3-cyclohexyl-2,3-dihydrothiophene-2-carbonyl)morpholine-4-carboxamide **7f**; mp: 194-196℃; white solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 1.13-1.23 (m, 5H), 1.47 (s, 1H), 1.65-1.73 (m, 5H), 3.32 (d, 1H, J=2.5Hz), 3.37 (s, 4H), 3.57 (s, 4H), 4.39 (s, 1H), 6.87 (s, 2H), 10.01 (s, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 26.26, 26.38, 26.48, 29.35, 29.64, 42.45, 45.10, 50.70, 51.86, 66.34, 68.89, 119.57, 152.88, 161.96, 172.03. MS (ESI) *m/z*: 363 $(M-H)^-$. Anal. Calcd for $C_{17}H_{24}N_4O_3S$: C, 56.02; H, 6.64; N, 15.37%, Found: C, 56.14; H, 7.02; N, 15.18%.

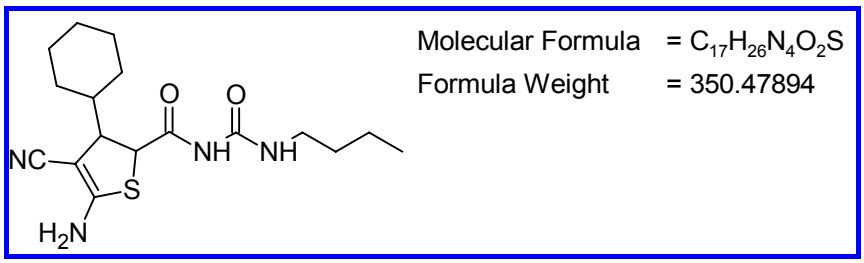


5-amino-4-cyano-3-cyclohexyl-N-(diethylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide **7g**; mp: 192-194℃; white solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 1.00-1.23 (m, 11H), 1.47 (br, 1H), 1.65-1.73 (m, 5H), 3.27-3.34 (m, 5H), 4.48 (s, 1H), 6.861 (s, 2H), 9.74 (s, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 13.98, 26.26, 26.36, 26.49, 29.31, 29.77, 41.62, 42.34, 50.79, 51.80, 68.89, 119.59, 152.81, 162.00, 172.40. MS (ESI) *m/z*: 349 $(M-H)^-$. Anal. Calcd for $C_{17}H_{26}N_4O_2S$: C, 58.26; H, 7.48; N, 15.99%,

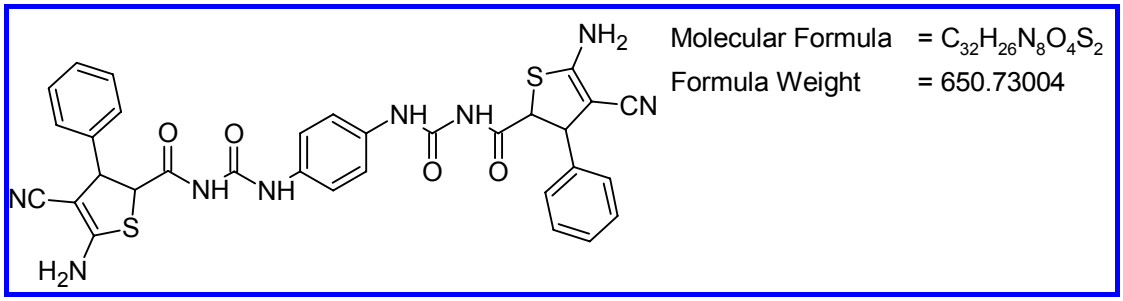
Found: C, 58.14; H, 7.20; N, 15.92%.



N-(5-amino-4-cyano-3-cyclohexyl-2,3-dihydrothiophene-2-carbonyl)piperidine-1-car boxamide **7h**; mp: 224-226℃; white solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 1.01-1.34 (m, 10H), 1.48-1.54 (m, 2H), 1.64-1.80 (m, 9H), 3.21 (s, 1H), 3.54 (s, 1H), 4.09 (s, 1H), 6.94 (s, 2H), 8.13 (s, 1H), 10.39 (s, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 19.01, 24.60, 25.59, 26.25, 26.34, 26.47, 29.20, 29.59, 32.66, 42.22, 48.28, 50.18, 52.82, 56.49, 68.76, 119.32, 152.49, 161.82, 173.25. MS (ESI) *m*/*z*: 375 $(M-H)^-$. Anal. Calcd for $C_{19}H_{28}N_4O_2S$: C, 60.61; H, 7.50; N, 14.88%, Found: C, 60.59; H, 7.26; N, 14.94%.

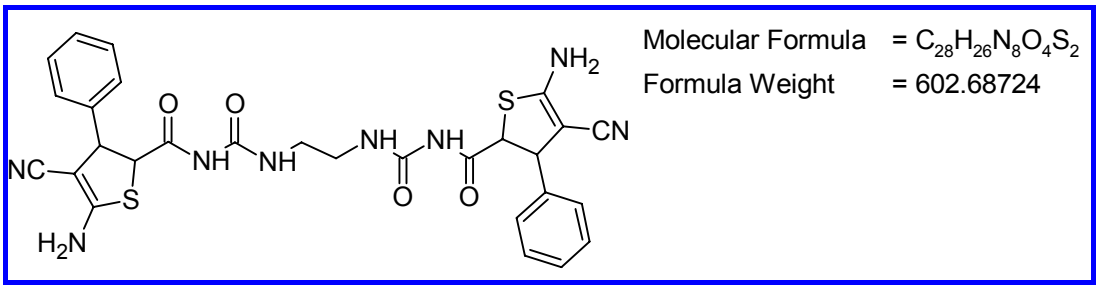


5-amino-N-(butylcarbamoyl)-4-cyano-3-cyclohexyl-2,3-dihydrothiophene-2-carboxa mide **7i**; mp: 198-200℃; white solid; ^{1}H NMR (500MHz, DMSO-d_6): δ = 0.86-0.89 (t, 3H), 1.03-1.31 (m, 10H), 1.41-1.48 (m, 3H), 1.63-1.73 (m, 5H), 3.15 (d, 2H, J=6.5Hz) 3.23 (s, 1H), 4.10 (s, 1H), 6.93 (s, 2H), 8.16 (s, 1H), 10.36 (s, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 14.03, 19.96, 26.27, 26.35, 26.47, 29.11, 29.63, 31.66, 39.11, 42.14, 50.10, 52.86, 68.74, 119.31, 153.35, 161.79, 172.96. MS (ESI) *m*/*z*: 349 $(M-H)^-$. Anal. Calcd for $C_{17}H_{26}N_4O_2S$: C, 58.26; H, 7.48; N, 15.99%, Found: C, 58.19; H, 7.64; N, 16.12%.

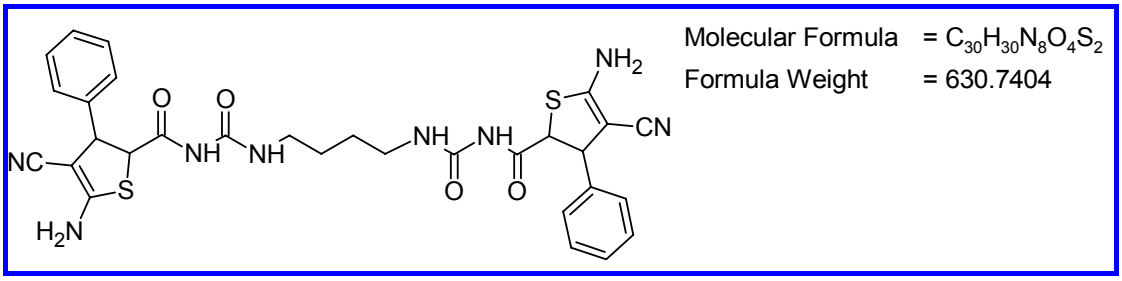


N,N'-(1,4-phenylenebis(azanediyl))bis(oxomethylene)bis(5-amino-4-cyano-3-phenyl-2 ,3-dihydrothiophene-2-carboxamide) **8a**; mp: 230-232℃; light brown solid, ^{1}H NMR (500MHz, DMSO-d_6): δ = 4.18 (s, 2H), 4.61 (s, 2H), 7.25 (br, 4H), 7.34-7.40 (m, 10H), 7.52 (br, 4H), 10.26 (br, 2H), 10.77 (br, 2H). ^{13}C NMR (125MHz, DMSO-d_6): δ =51.96, 55.77, 70.82, 118.69, 120.90, 127.59, 128.01, 129.23, 133.83, 141.98, 151.04,

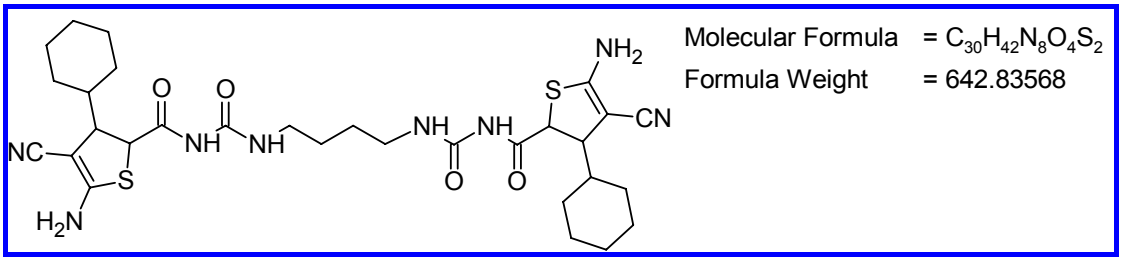
162.21, 172.75. MS (ESI) *m/z*: 649 $(M-H)^-$. Anal. Calcd for $C_{32}H_{26}N_8O_4S_2$: C, 59.06; H, 4.03; N, 17.22%, Found: C, 59.09; H, 4.27; N, 16.97%.



N,N'-(ethane-1,2-diylbis(azanediyl))bis(oxomethylene)bis(5-amino-4-cyano-3-phenyl-2,3-dihydrothiophene-2-carboxamide) **8b**; mp: 206-208℃; light brown solid, ^{1}H NMR (500MHz, DMSO-d_6): δ = 3.32 (s, 4H), 4.09 (s, 2H), 4.56 (s, 2H), 7.22 (s, 4H), 7.30-7.37 (m, 6H), 7.39 (d, 4H, J=7.5Hz), 8.33 (s, 2H), 10.47 (br, 2H). ^{13}C NMR (125MHz, DMSO-d_6): δ =39.62, 52.08, 55.67, 70.75, 118.71, 127.58, 127.99, 129.23, 141.95, 153.67, 162.24, 171.83. MS (ESI) *m/z*: 601 $(M-H)^-$. MS (ESI) *m/z*: 649 $(M-H)^-$. Anal. Calcd for $C_{28}H_{26}N_8O_4S_2$: C, 55.80; H, 4.35; N, 18.59%, Found: C, 55.59; H, 4.19; N, 18.47%.

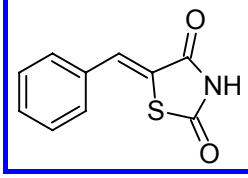


N,N'-(butane-1,4-diylbis(azanediyl))bis(oxomethylene)bis(5-amino-4-cyano-3-phenyl-2,3-dihydrothiophene-2-carboxamide) **8c**; mp: 238-240℃; brown solid, ^{1}H NMR (500MHz, DMSO-d_6): δ = 1.47 (s, 4H), 3.18 (s, 4H), 4.09 (s, 2H), 4.57 (s, 2H), 7.22 (s, 4H), 7.31 (d, 6H, J=7.0Hz), 7.37-7.40 (m, 4H), 8.25 (s, 2H), 9.82 (br, 2H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 27.13, 39.20, 52.06, 55.68, 70.25, 70.79, 118.70, 127.59, 127.98, 129.22, 141.97, 153.36, 162.25, 172.03. MS (ESI) *m/z*: 629 $(M-H)^-$. Anal. Calcd for $C_{30}H_{30}N_8O_4S_2$: C, 57.13; H, 4.79; N, 17.77%, Found: C, 56.89; H, 4.77; N, 17.65%.



N,N'-(butane-1,4-diylbis(azanediyl))bis(oxomethylene)bis(5-amino-4-cyano-3-cyclohexyl-2,3-dihydrothiophene-2-carboxamide) **8d**; mp: 210-212℃; brown solid, ^{1}H NMR (500MHz, DMSO-d_6): δ = 1.06-1.21 (m, 10H), 1.44 (s, 6H), 1.63-1.71 (m, 10H), 3.15 (s, 4H), 3.23 (s, 2H), 4.10 (s, 2H), 6.94 (s, 4H), 8.19 (s, 2H), 10.35 (br, 2H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 26.26, 26.35, 26.47, 27.09, 27.90, 29.13, 29.62, 39.16,

42.14, 50.14, 52.83, 68.77, 119.34, 153.40, 161.83, 172.87. MS (ESI) *m*/*z*: 641 $(M-H)^-$. Anal. Calcd for $C_{30}H_{42}N_8O_4S_2$: C, 56.05; H, 6.59; N, 17.43%, Found: C, 56.13; H, 6.72; N, 17.66%.



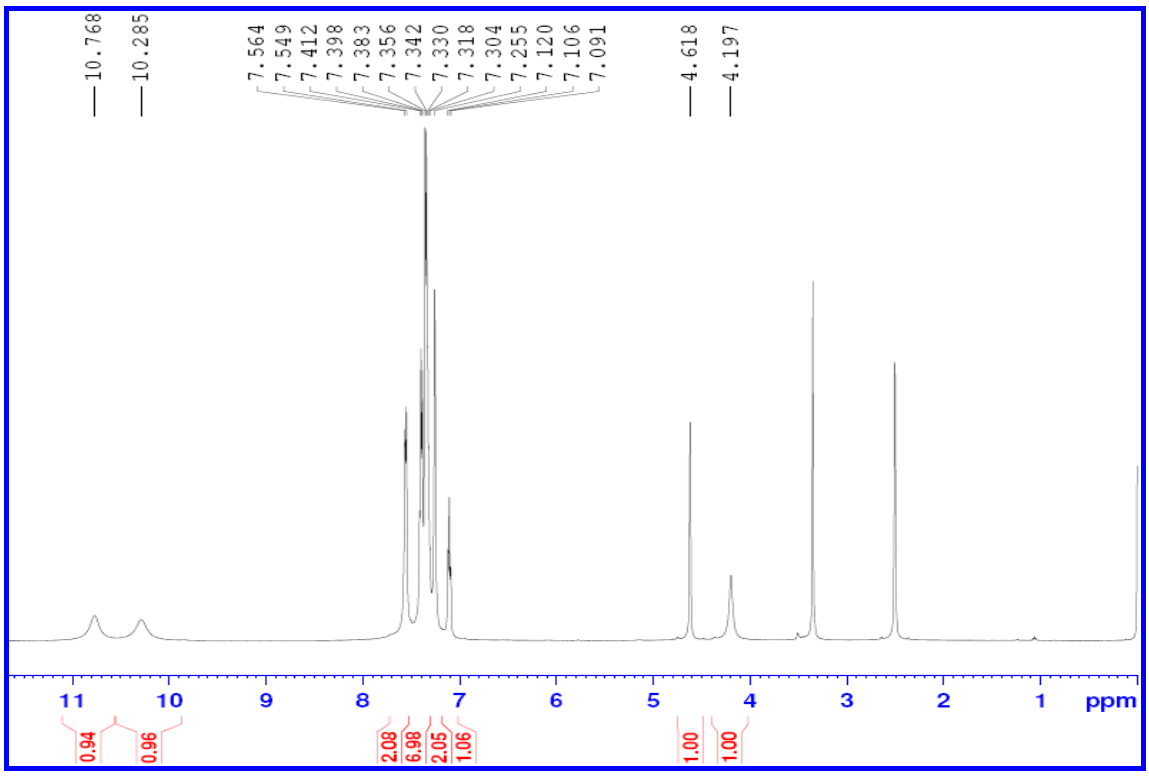
Molecular Formula = $C_{10}H_7NO_2S$
Formula Weight = 205.23308

5-benzylidenethiazolidine-2,4-dione **10a**; mp: 238-240℃; white solid, ^{1}H NMR (500MHz, DMSO-d_6): δ = 7.46-7.48 (m, 1H), 7.51-7.54 (m, 2H), 7.58 (d, 2H, J=7.5Hz), 7.78 (s, 1H), 12.63 (s, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ = 124.05, 129.78, 130.47, 130.87, 132.23, 133.51, 167.81, 168.35. MS (ESI) *m*/*z*: 204 $(M-H)^-$. Anal. Calcd for $C_{10}H_7NO_2S$: C, 58.52; H, 3.44; N, 6.82%, Found: C, 58.23; H, 3.71; N, 6.68%.

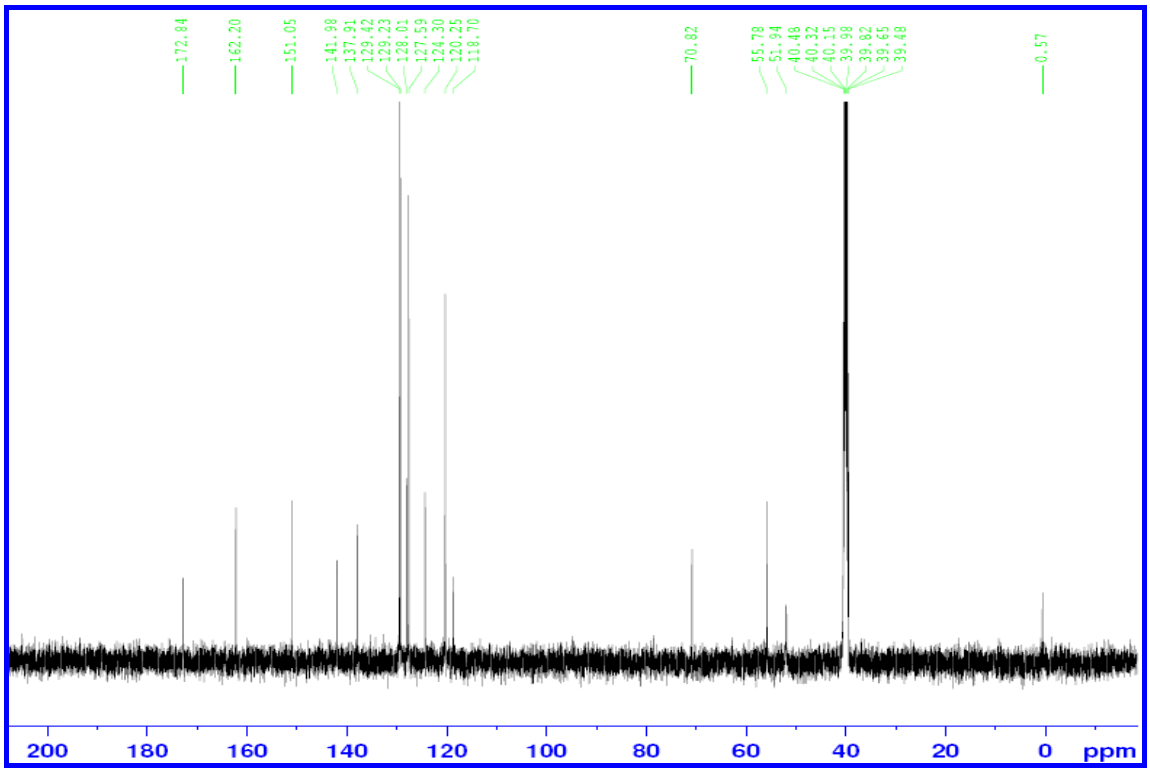
(1) J. Sun, E. Y. Xia, L. L. Zhang and C. G. Yan, *Eur. J. Org. Chem.*, **2009**, 5247.

(2) J. Sun, L. L. Zhang, E. Y. Xia and C. G. Yan, *J. Org. Chem.*, 2009, **74**, 3398.

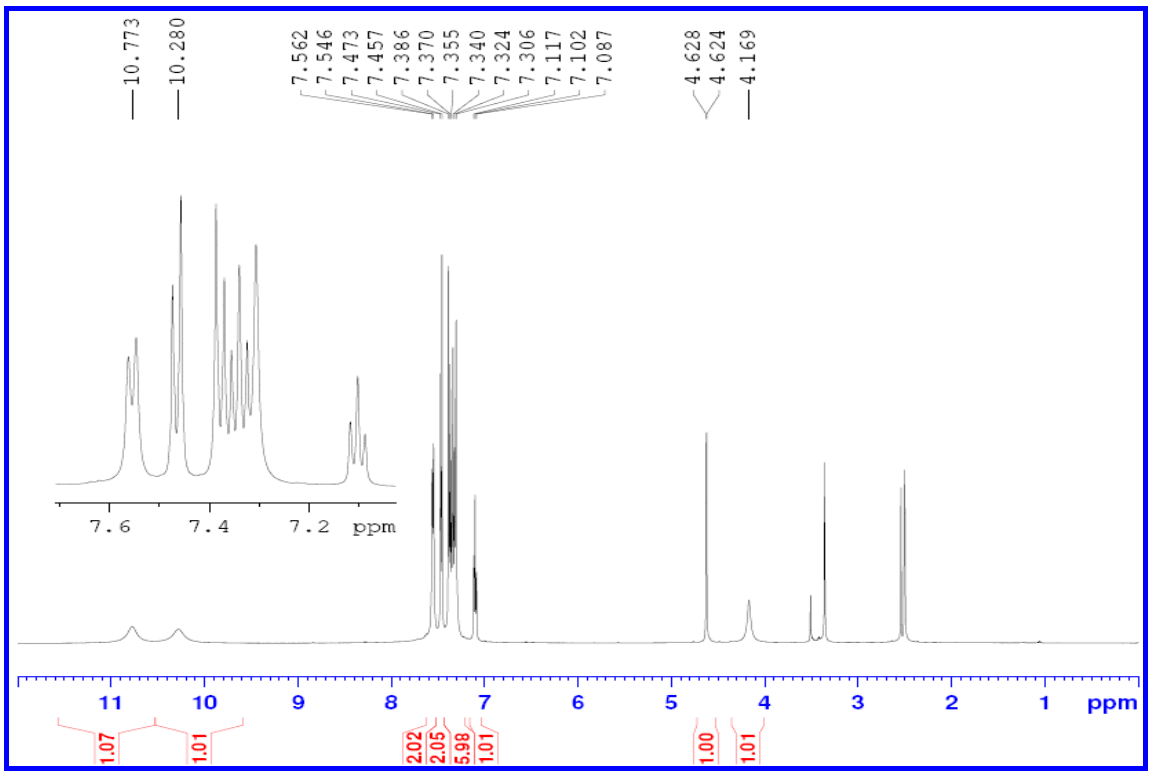
Copies of NMR Spectra



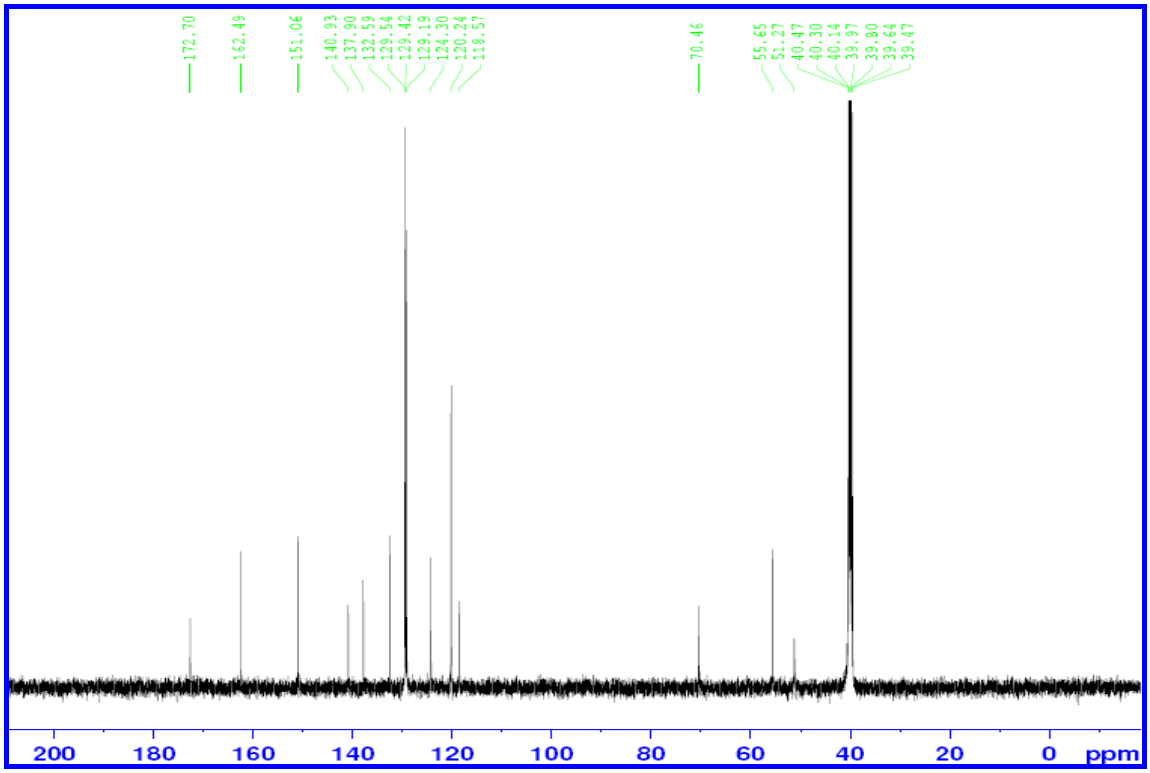
^{1}H NMR (500MHz, DMSO-d_6) of Compound **5a**



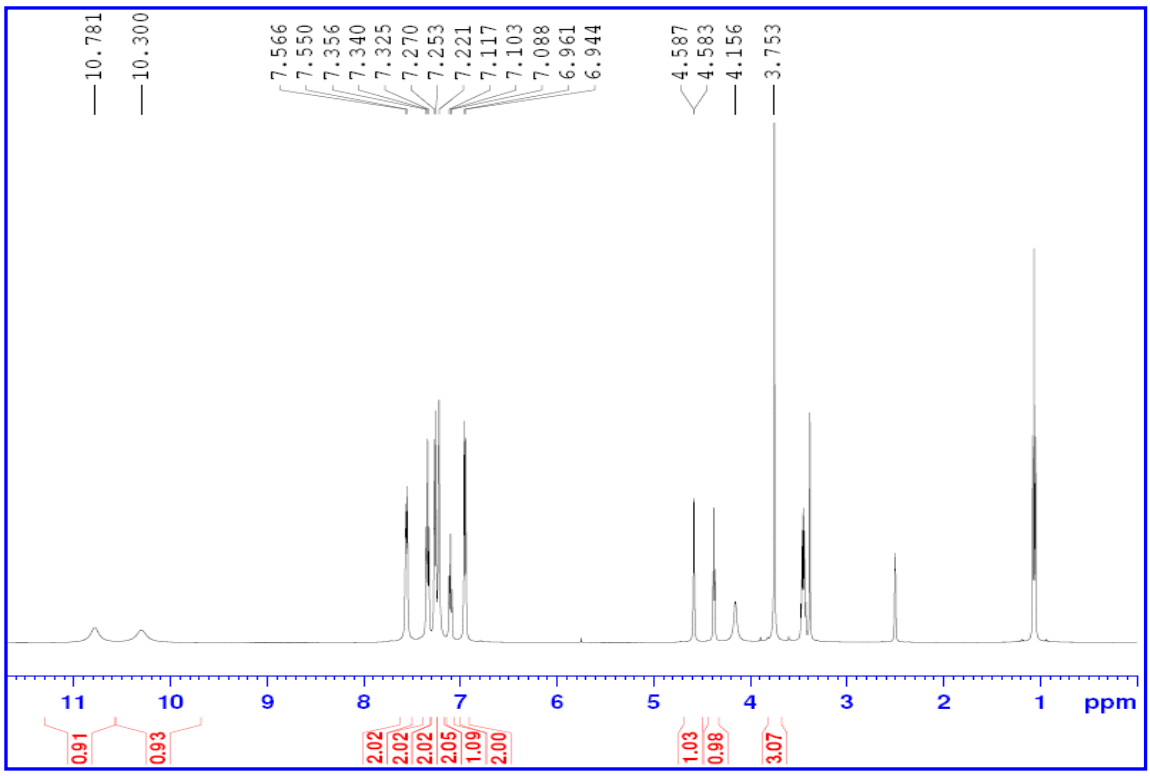
^{13}C NMR (125MHz, DMSO-d_6) of Compound **5a**



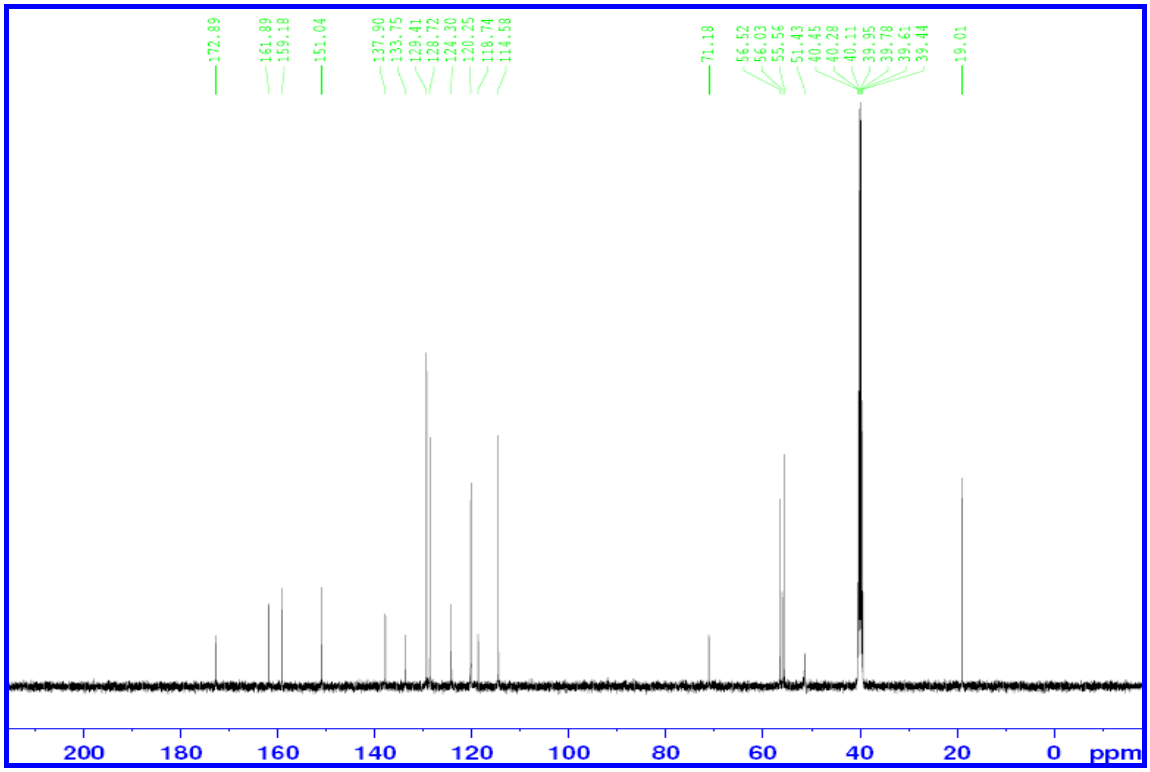
^{1}H NMR (500MHz, DMSO-d_6) of Compound **5b**



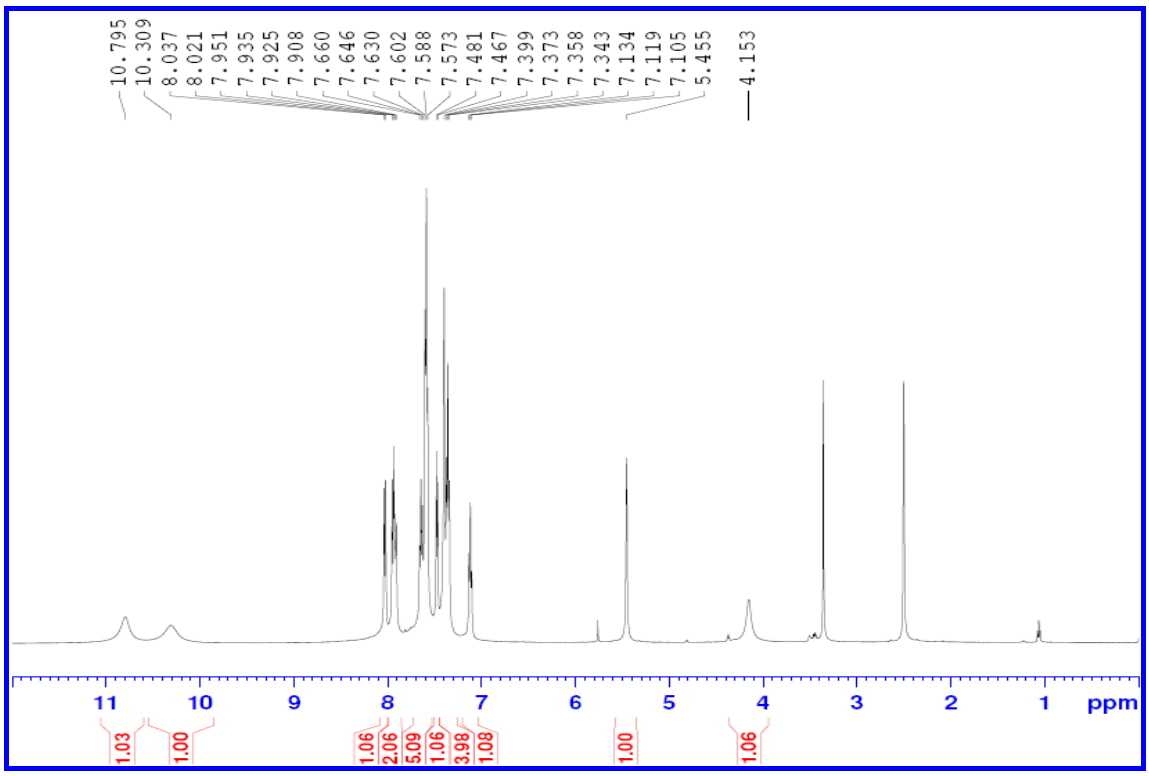
^{13}C NMR (125MHz, DMSO-d_6) of Compound **5b**



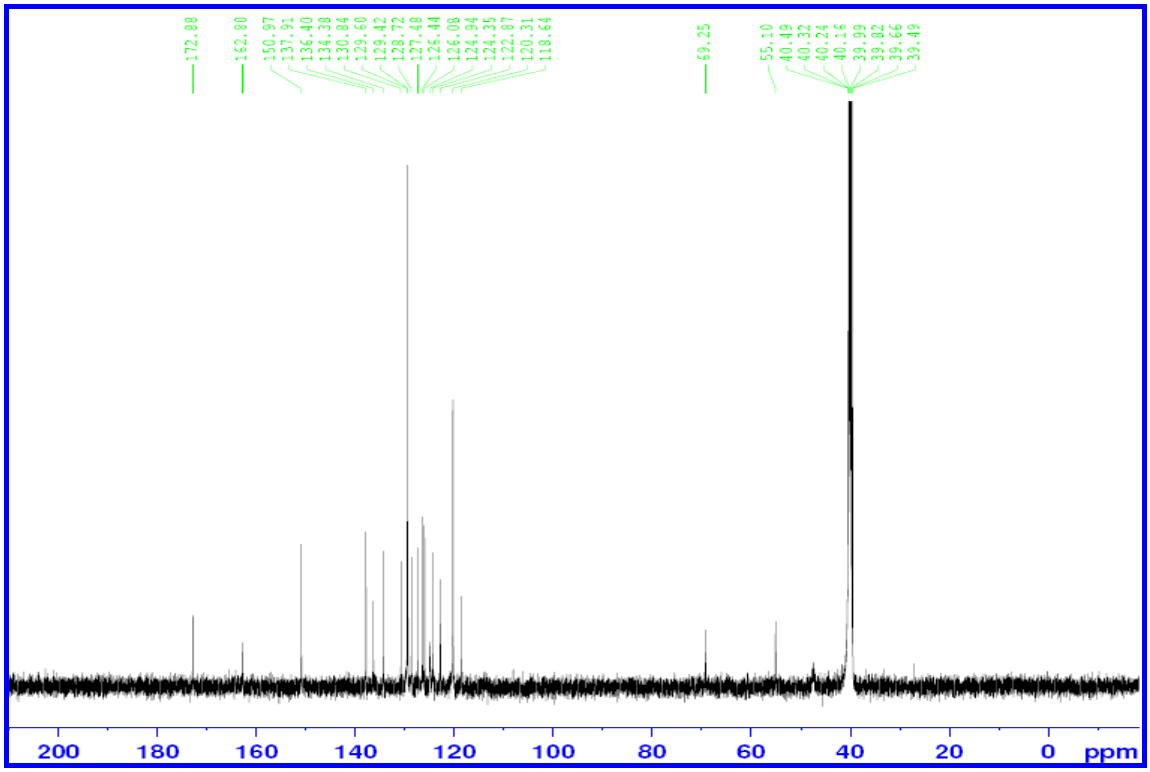
^{1}H NMR (500MHz, DMSO-d_6) of Compound **5c**



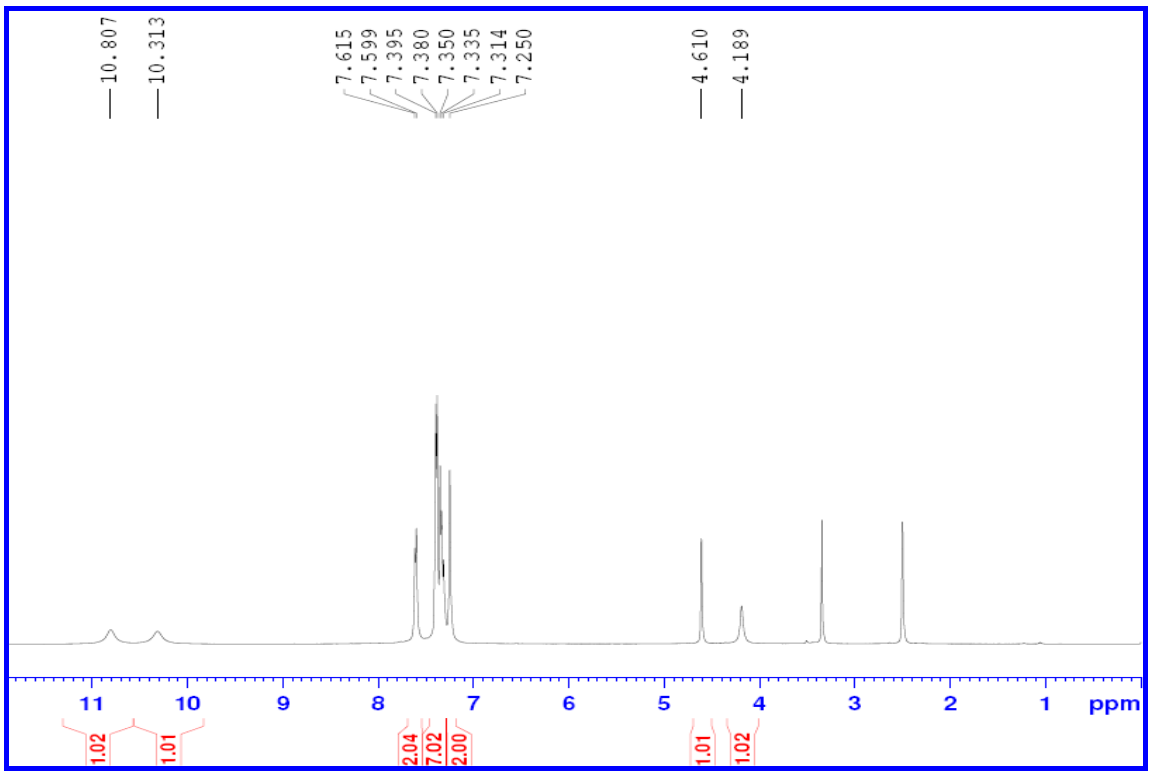
^{13}C NMR (125MHz, DMSO-d_6) of Compound **5c**



^{1}H NMR (500MHz, DMSO-d_6) of Compound **5d**



^{13}C NMR (125MHz, DMSO-d_6) of Compound **5d**



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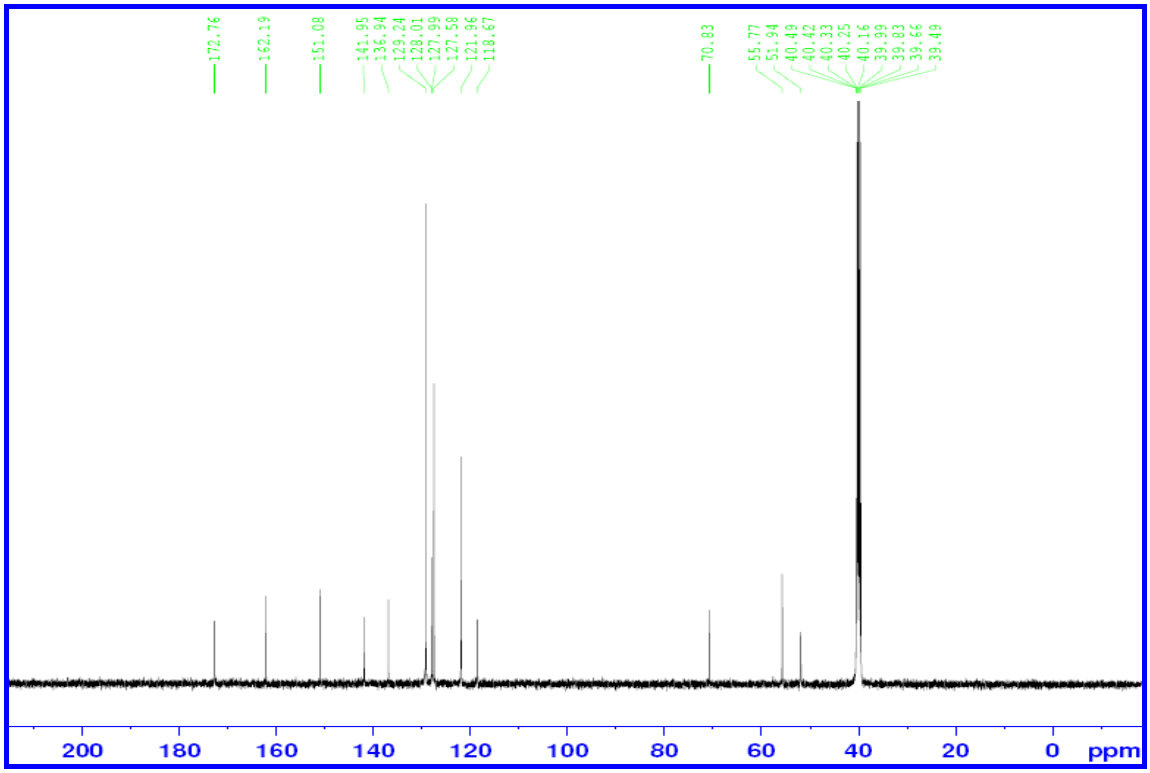

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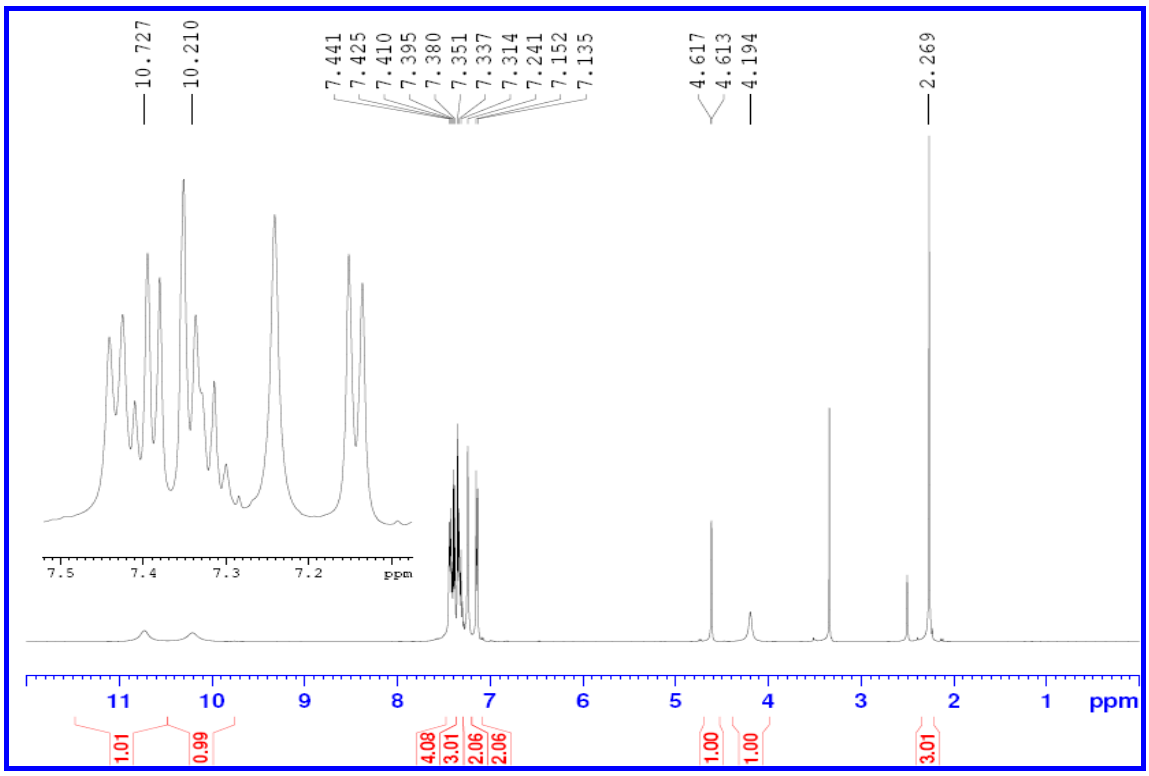

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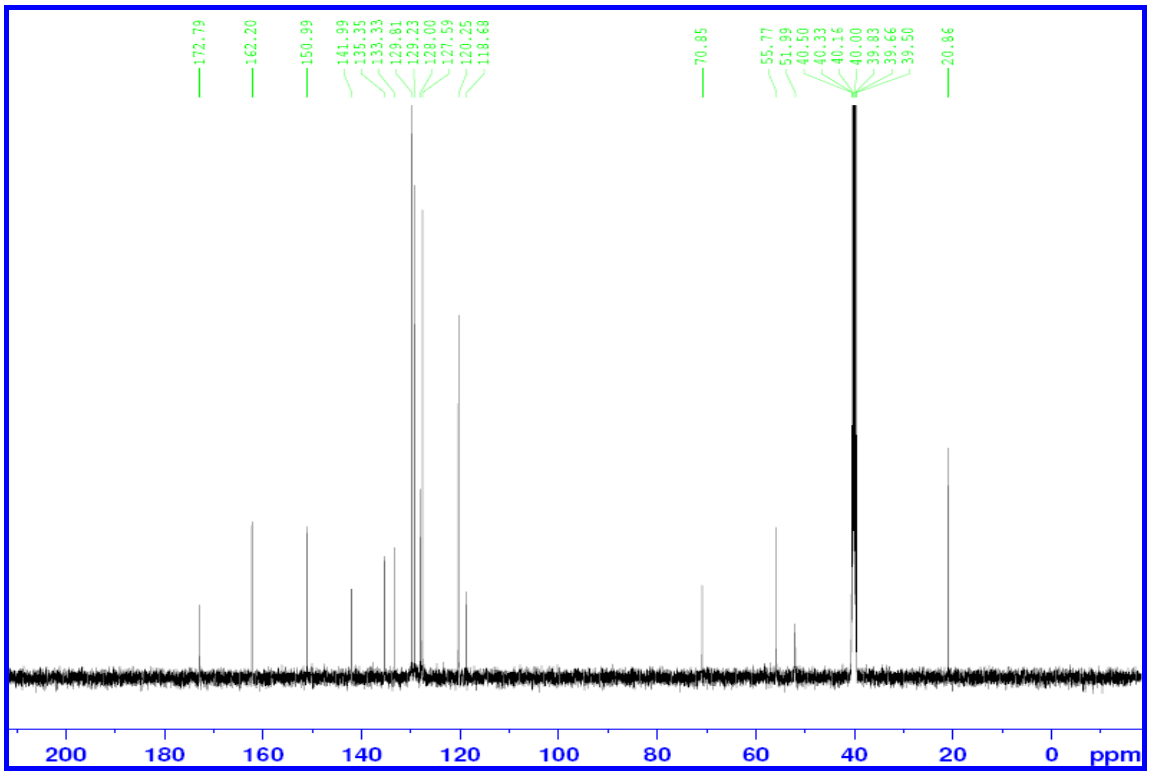

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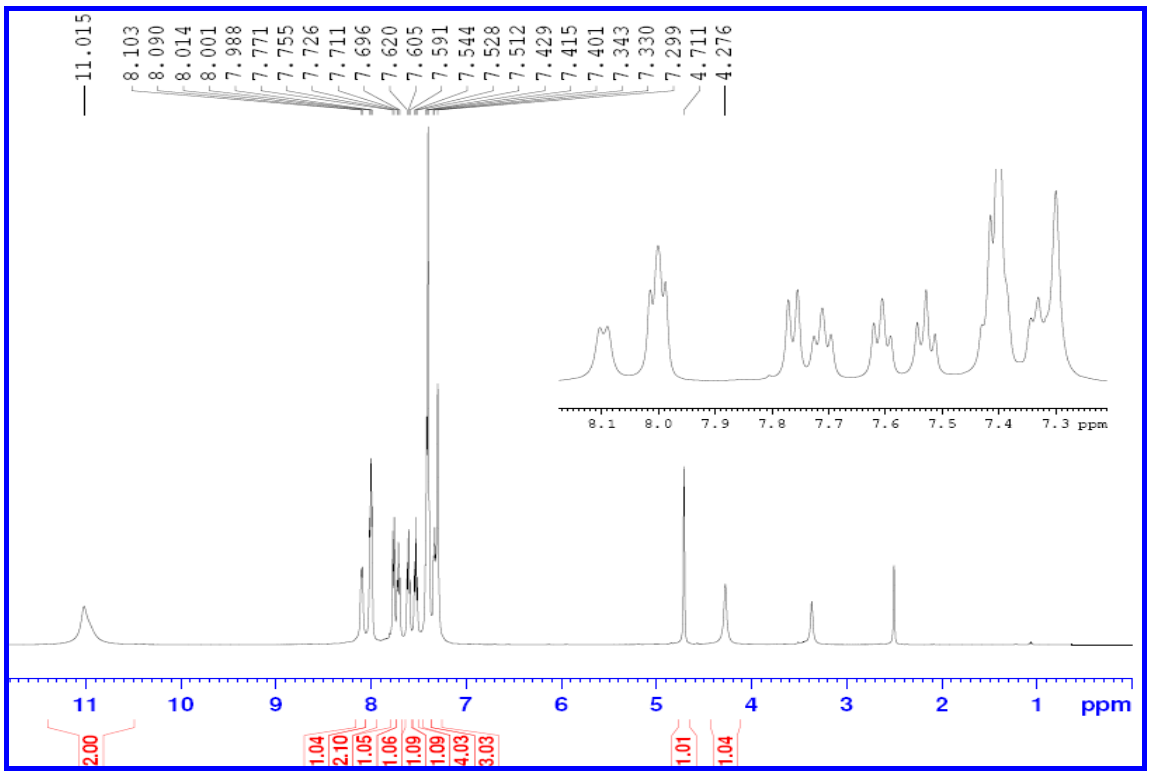

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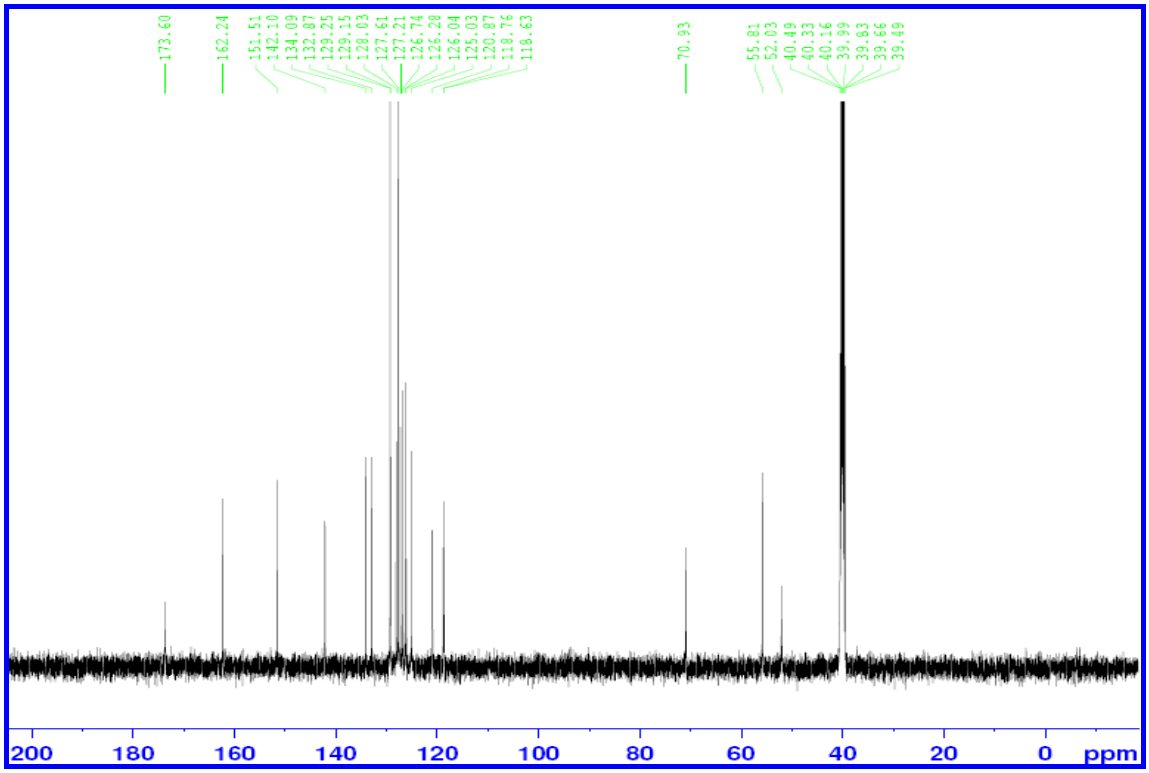

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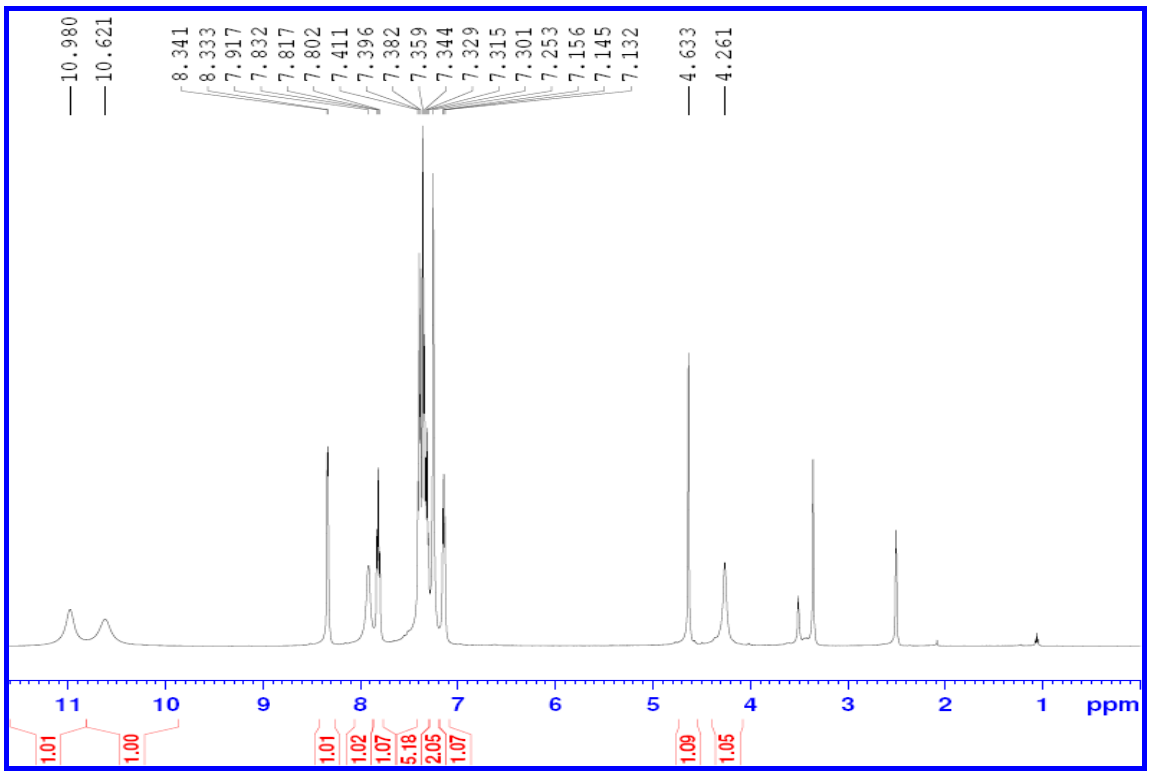

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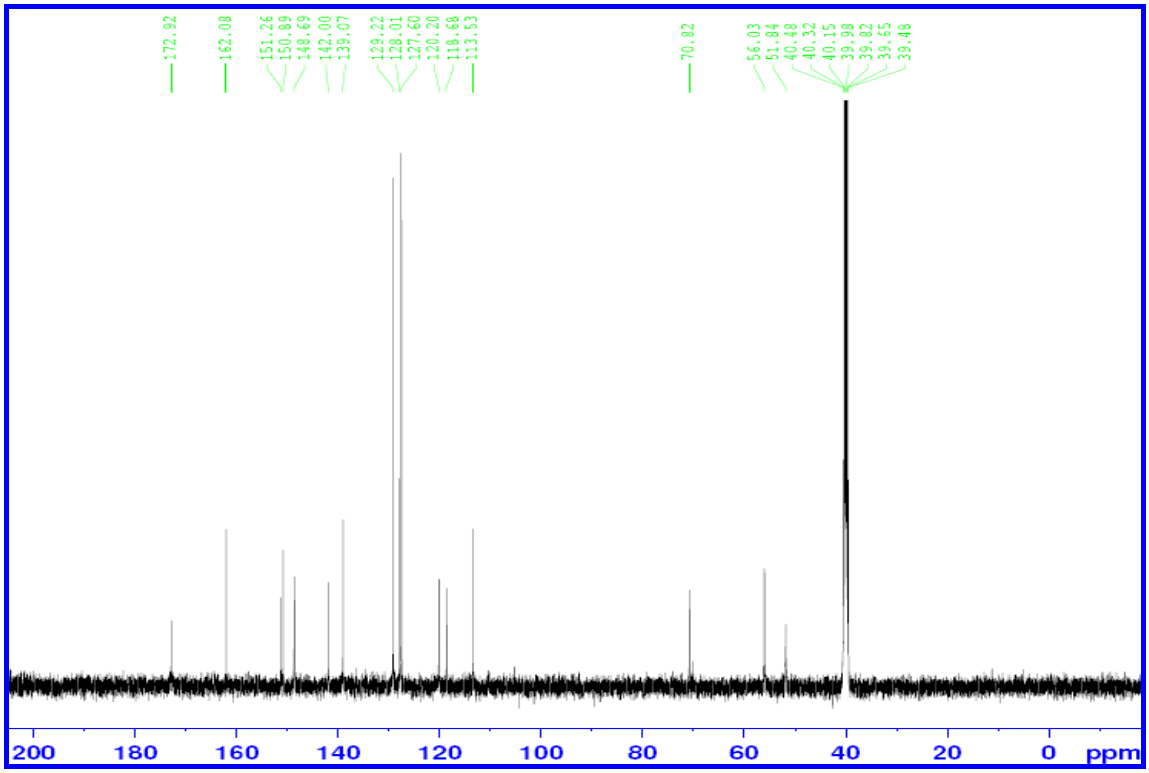

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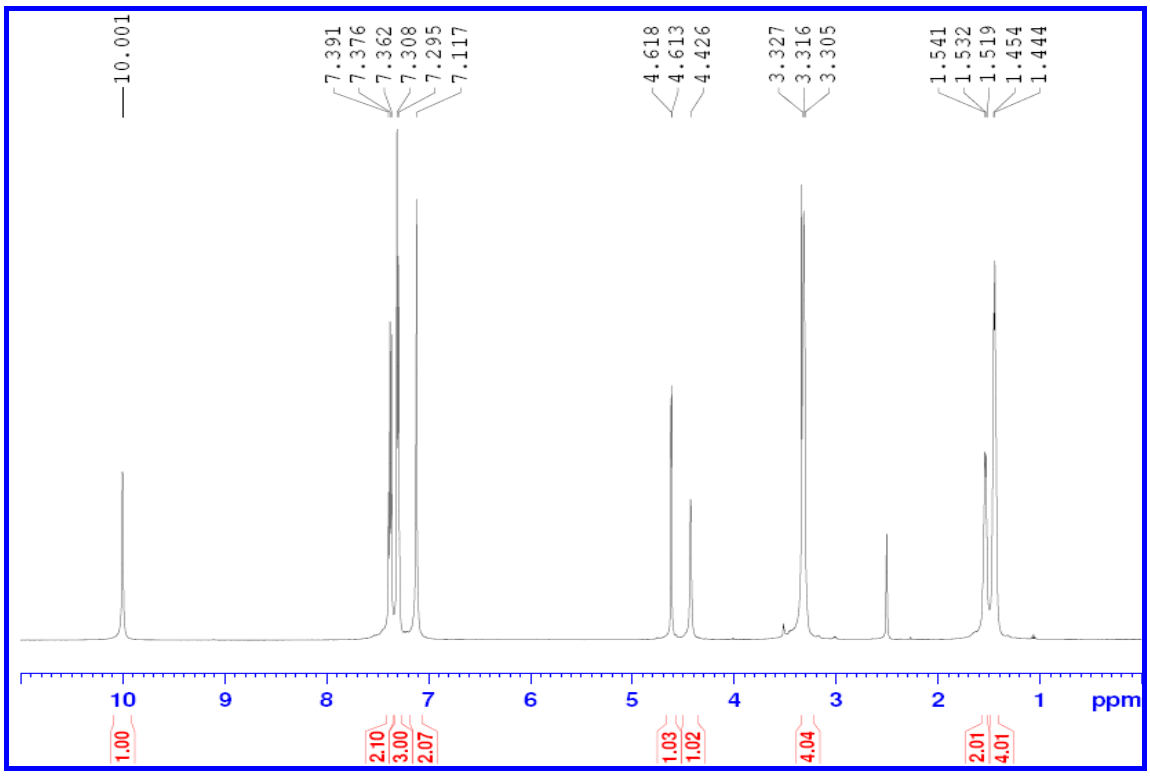
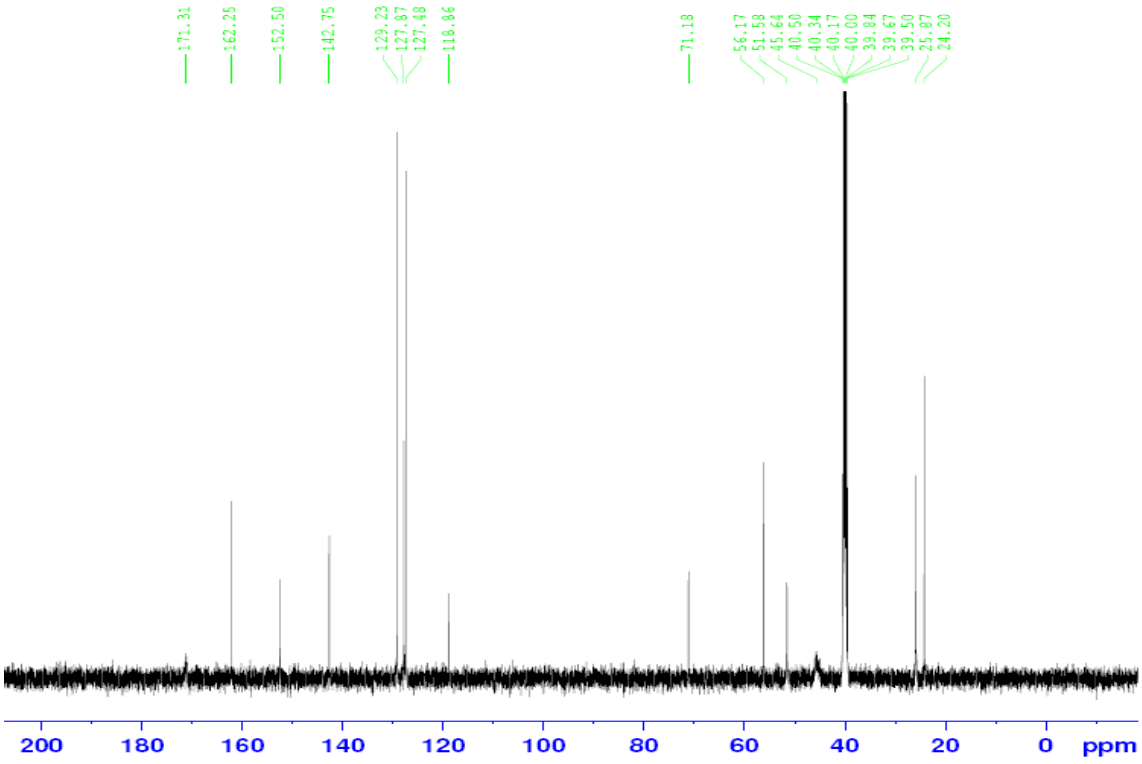


^{1}H NMR (500MHz, DMSO-d_6) of Compound **6a**



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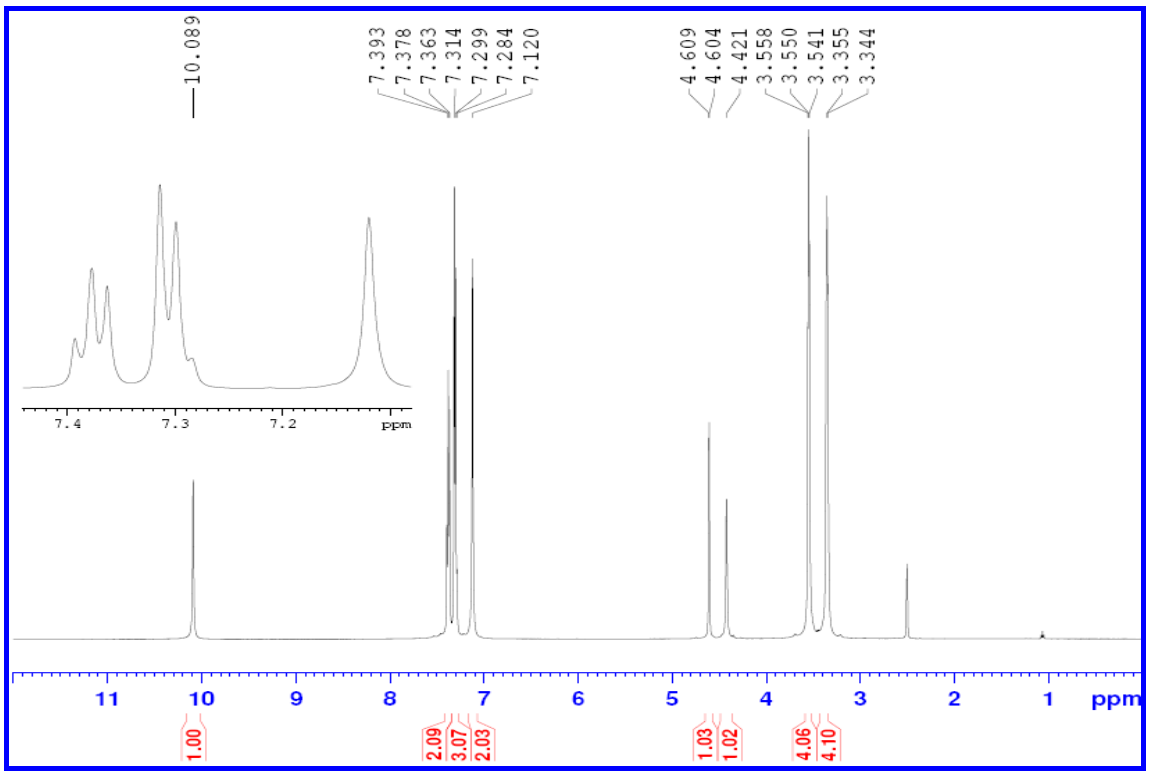

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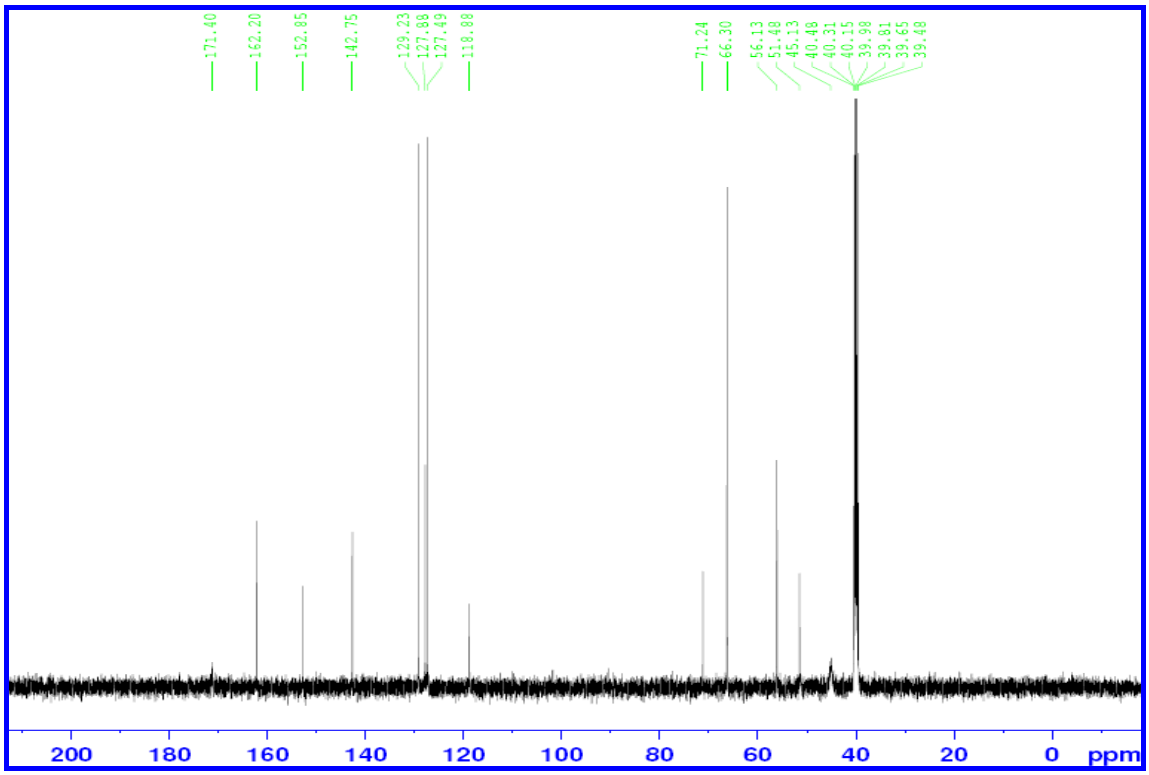

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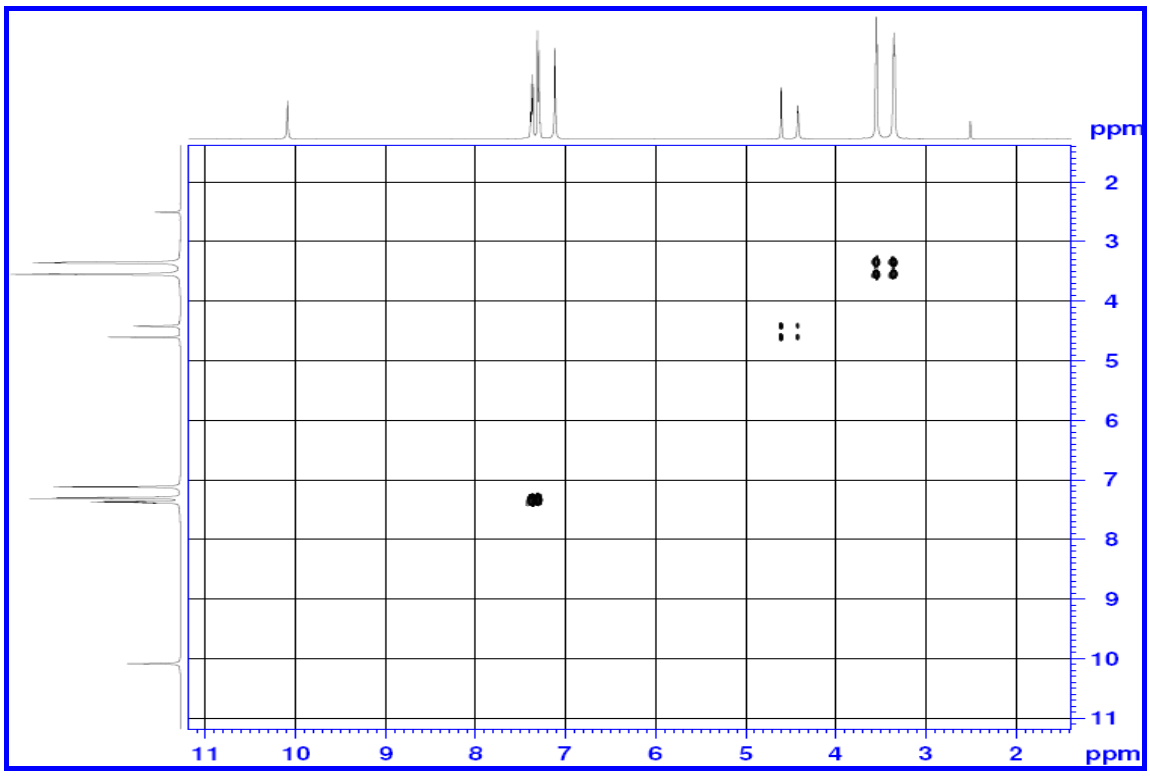
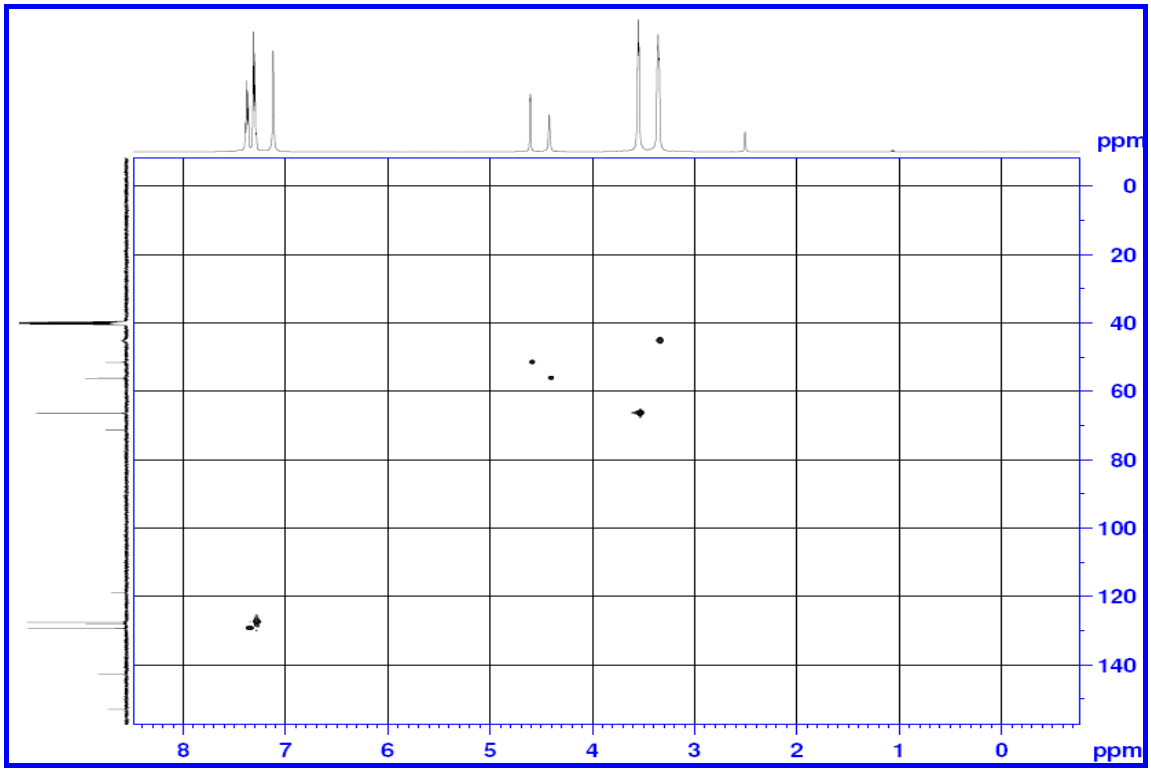
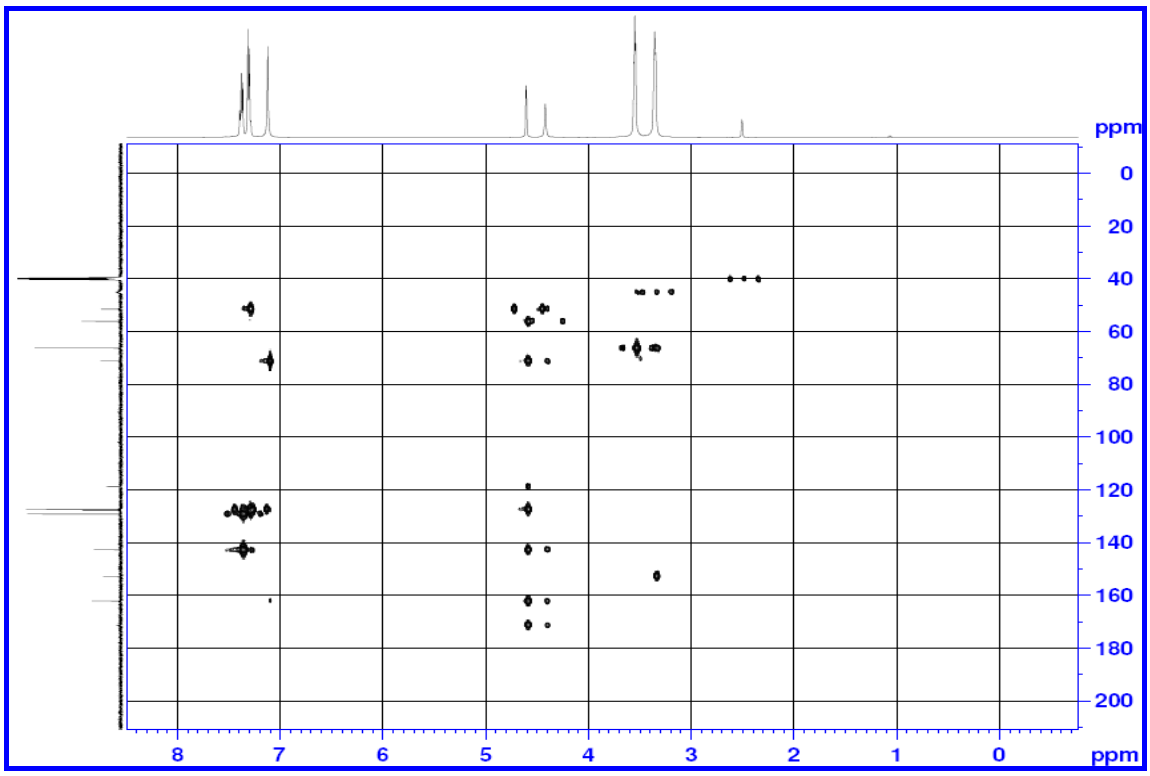


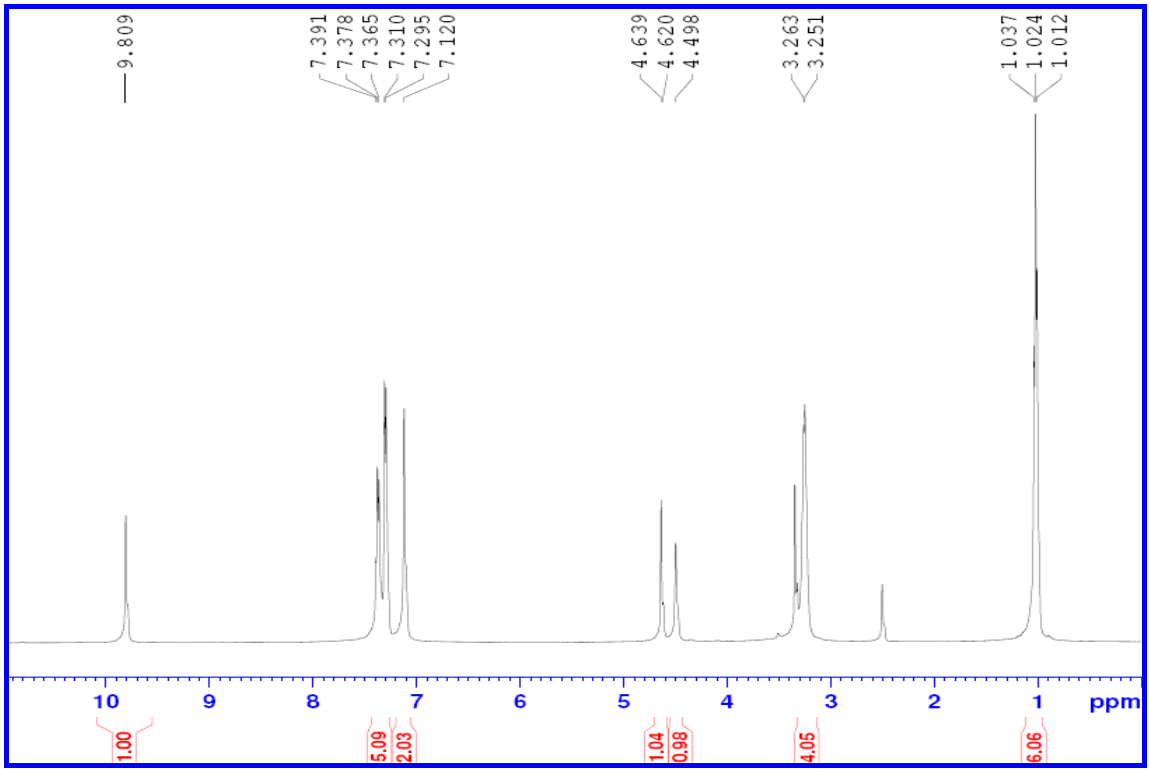
COSY (500MHz, DMSO-d_6) of Compound **6b**



HSQC (500MHz, DMSO-d_6) of Compound **6b**



HMBC (500MHz, DMSO-d_6) of Compound **6b**



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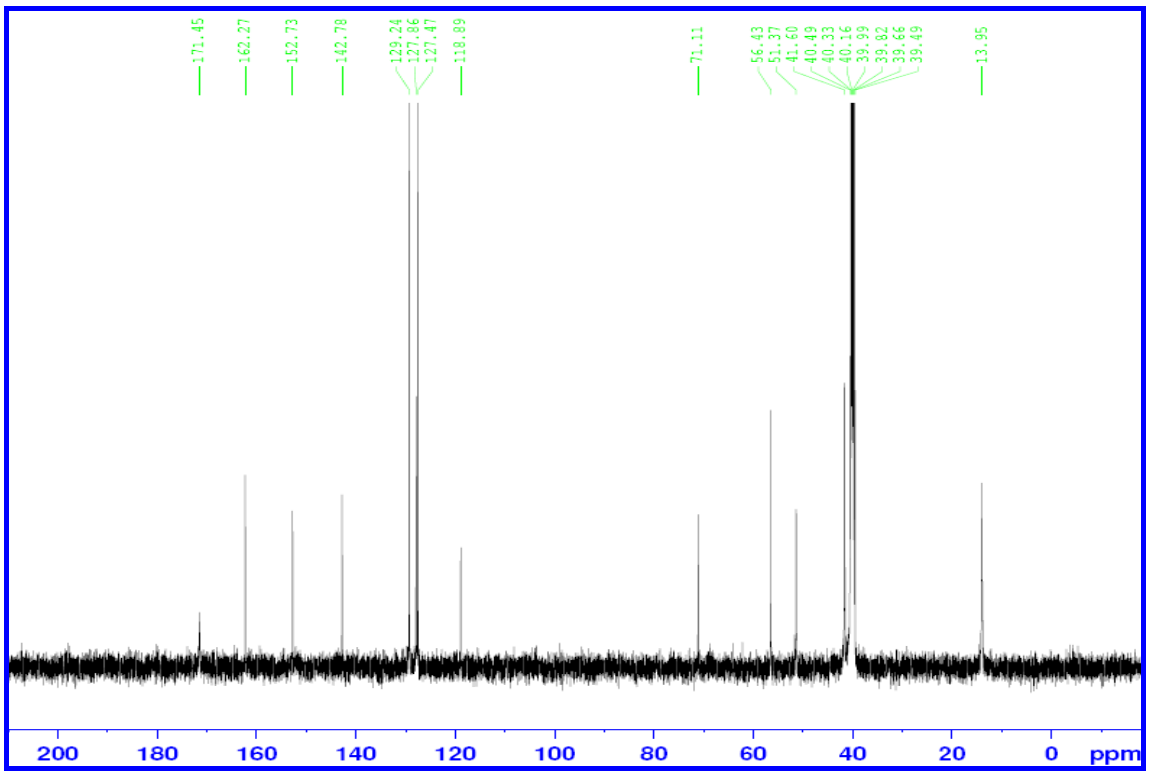
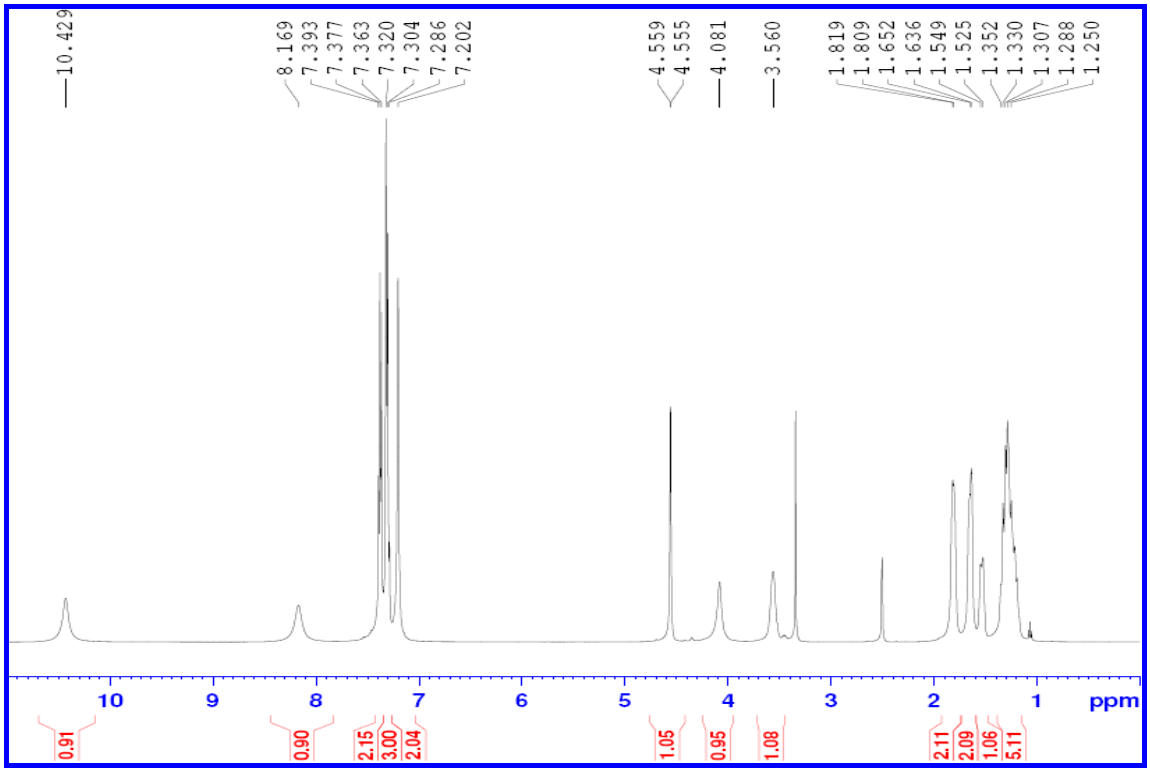


^{13}C NMR (125MHz, DMSO-d_6) of Compound **6c**



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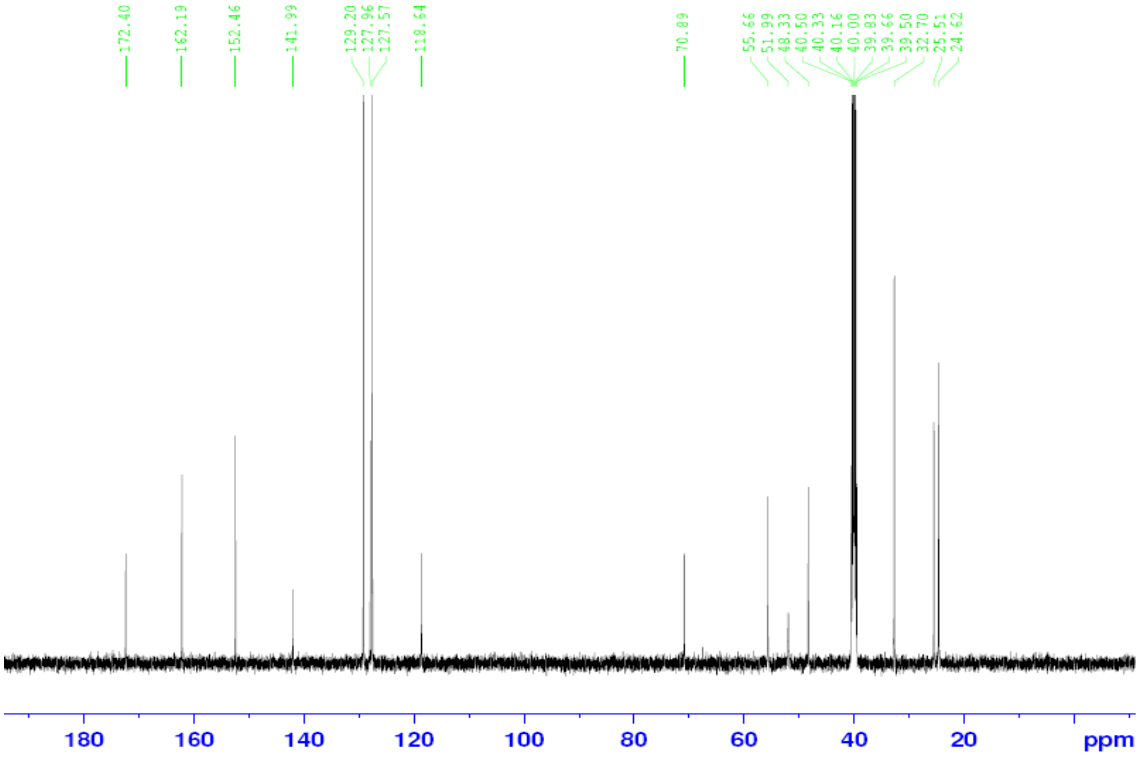

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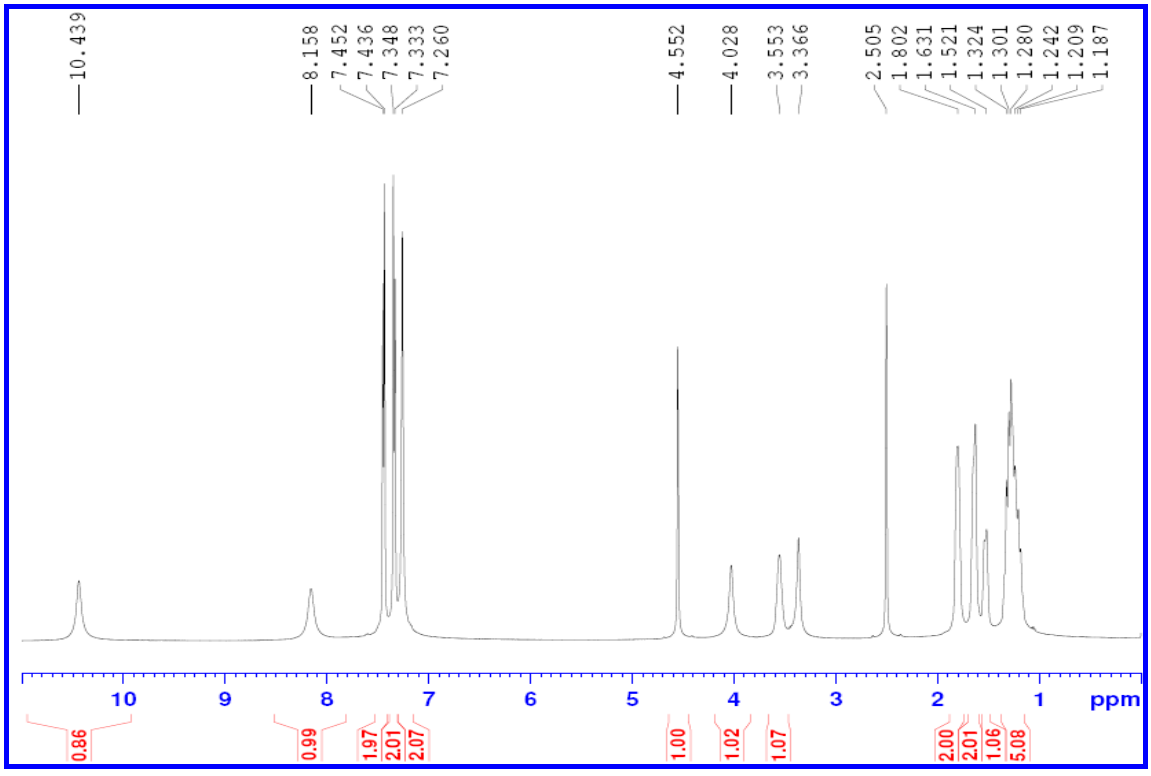

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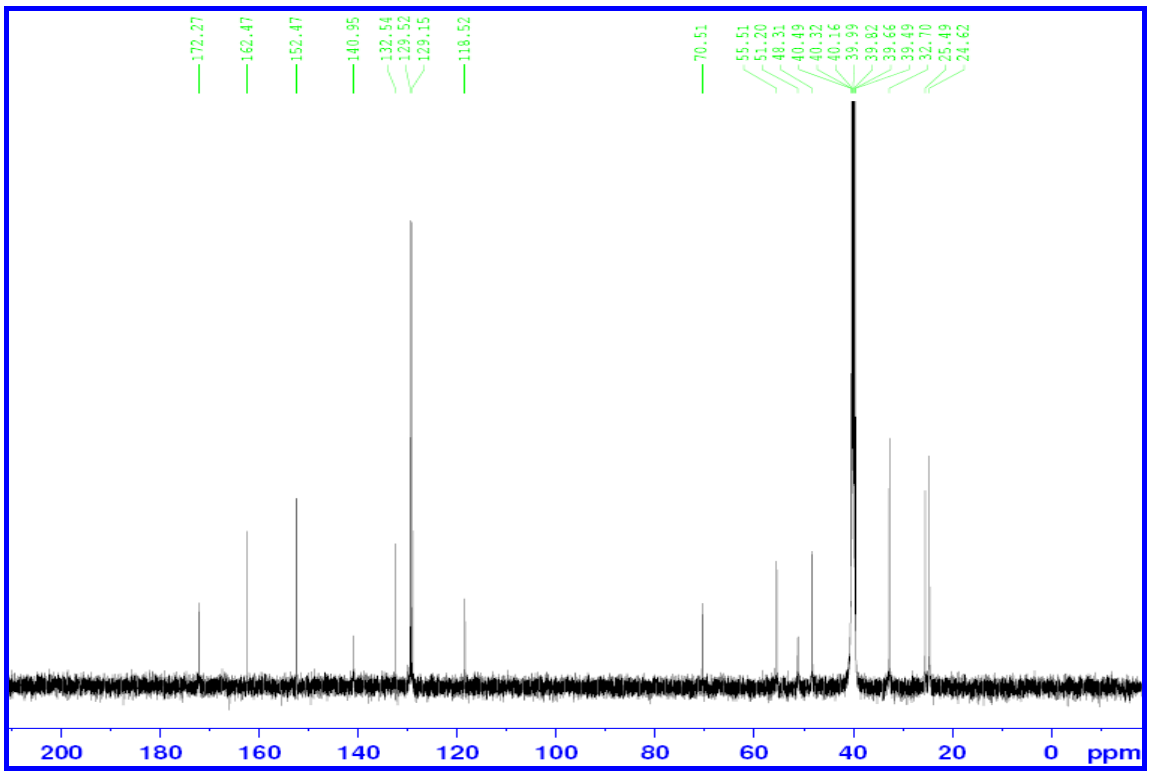

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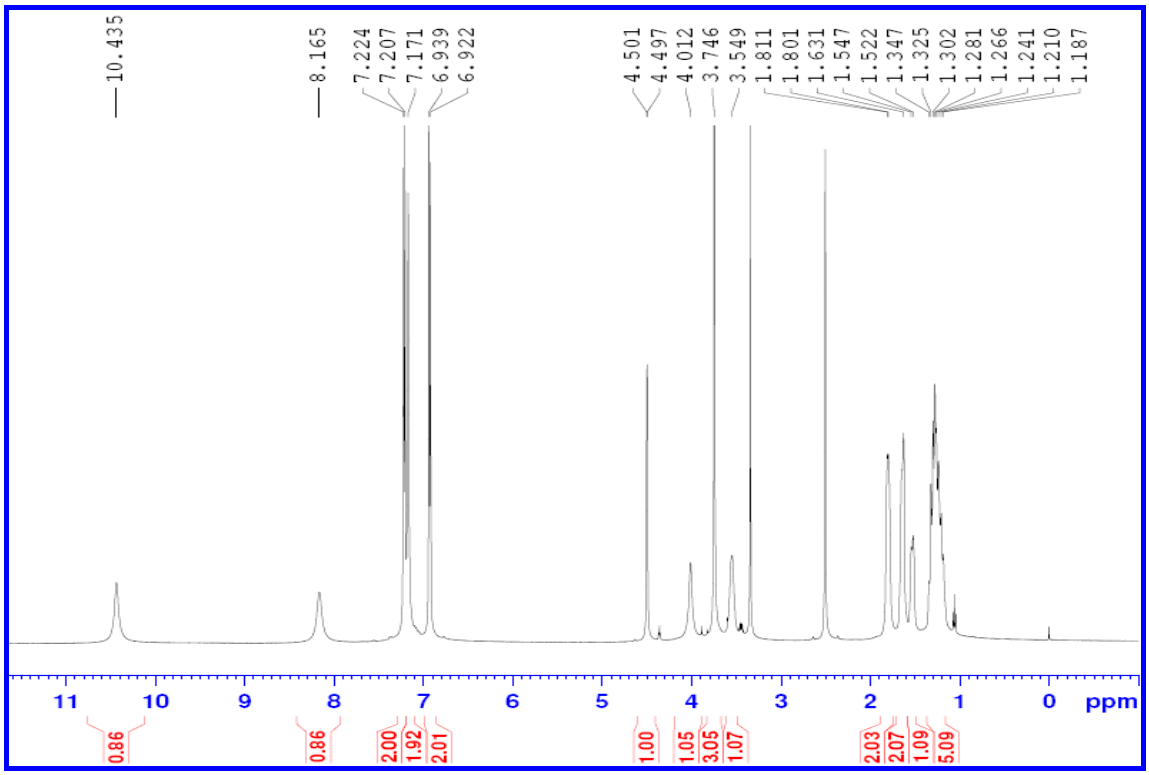

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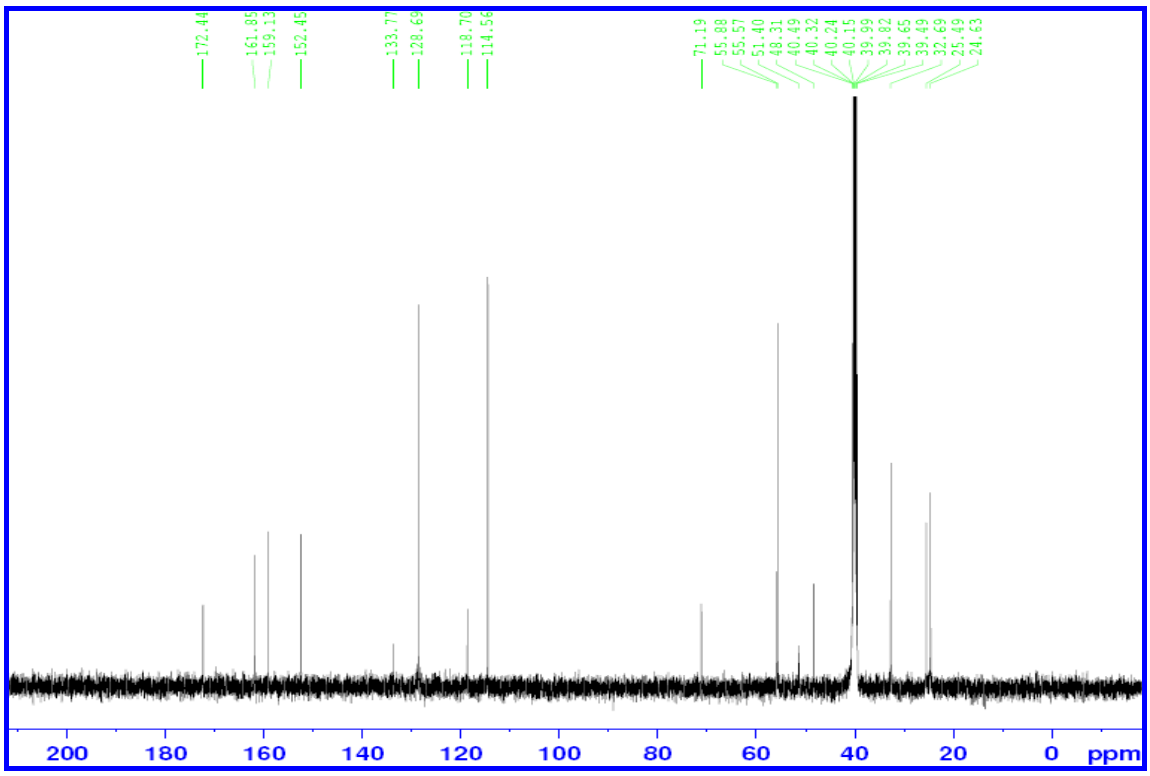

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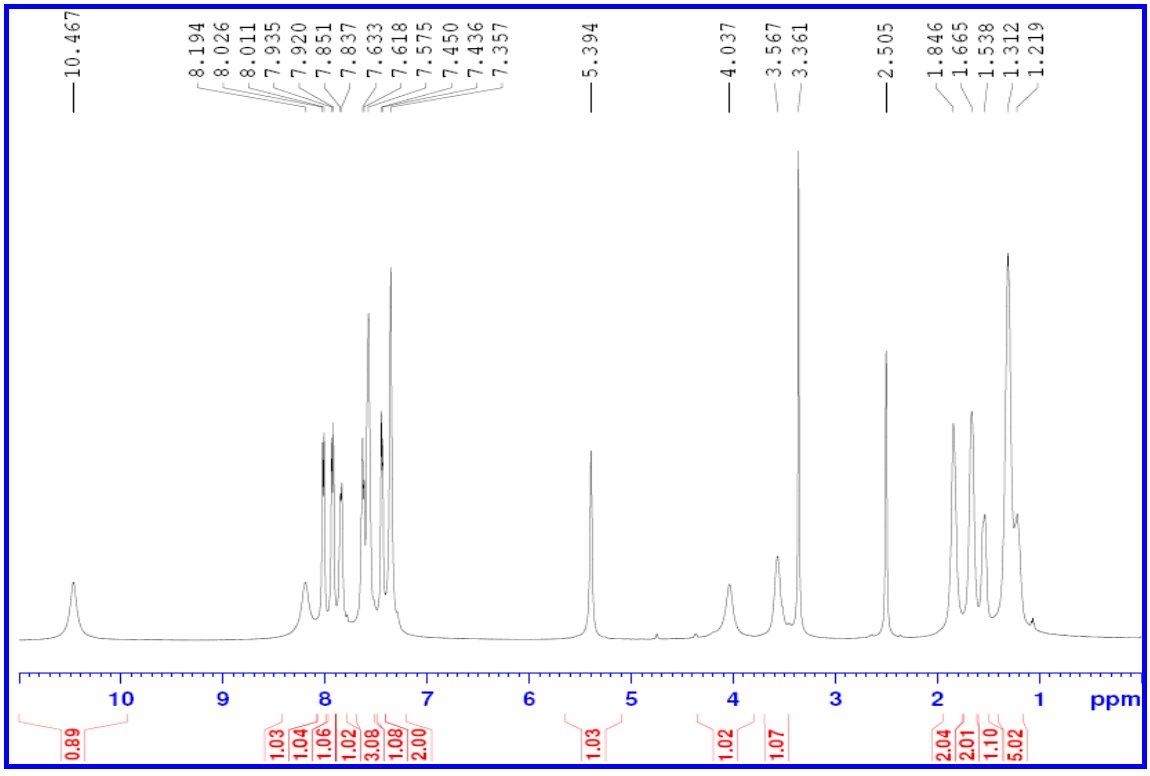

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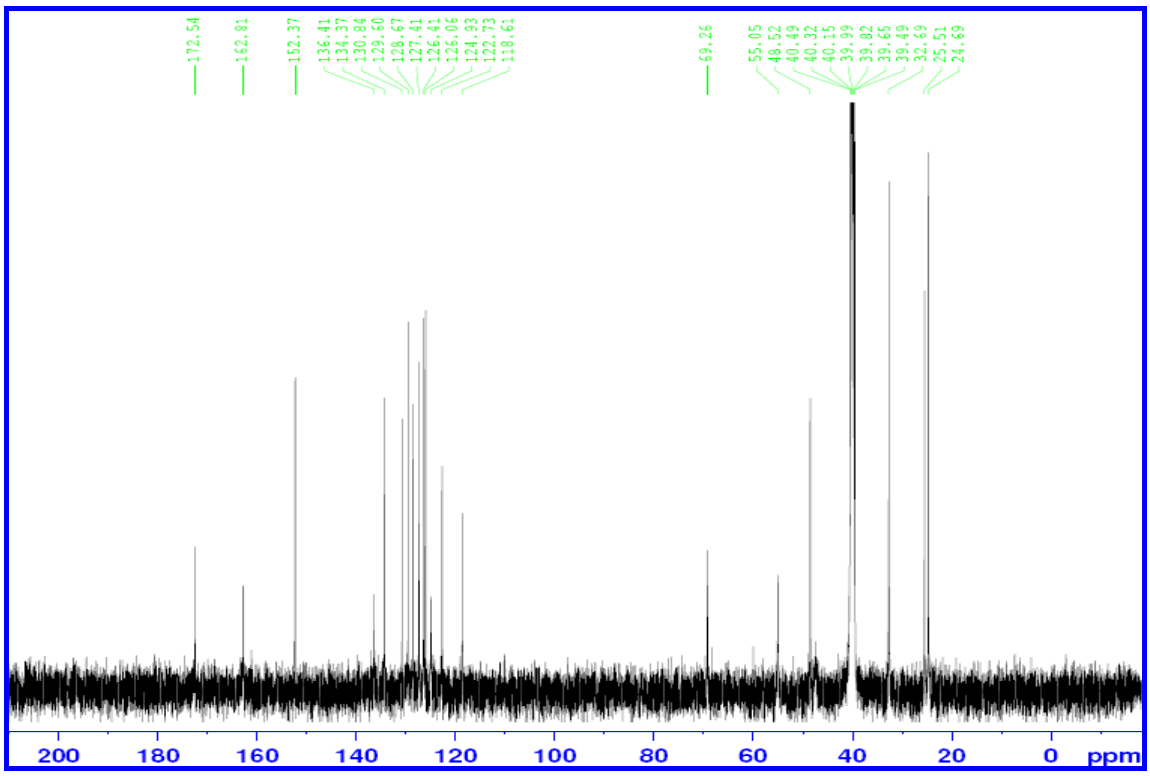

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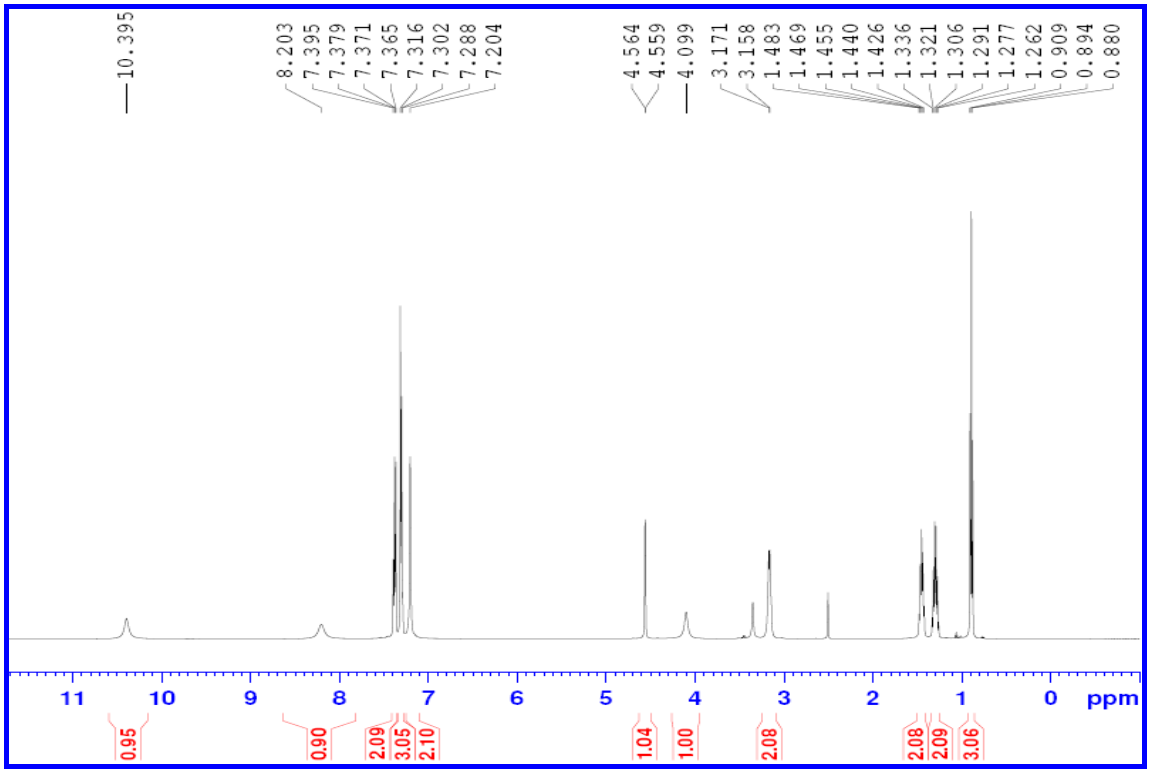

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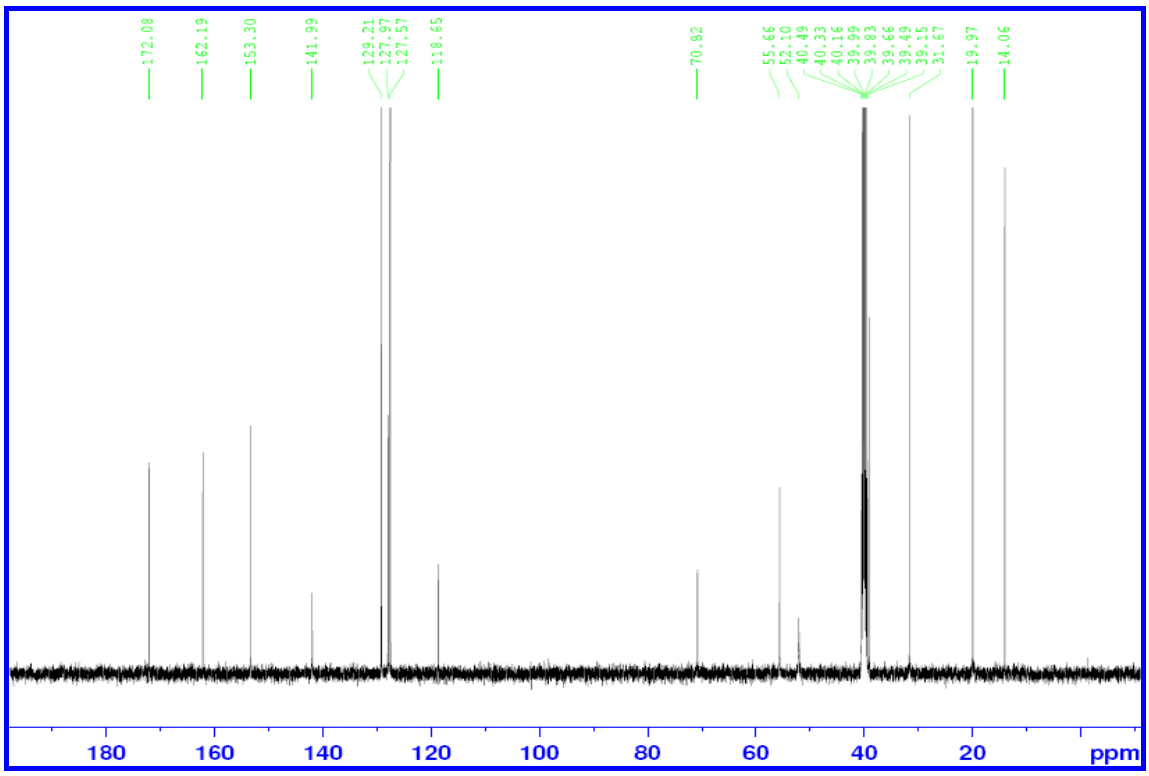

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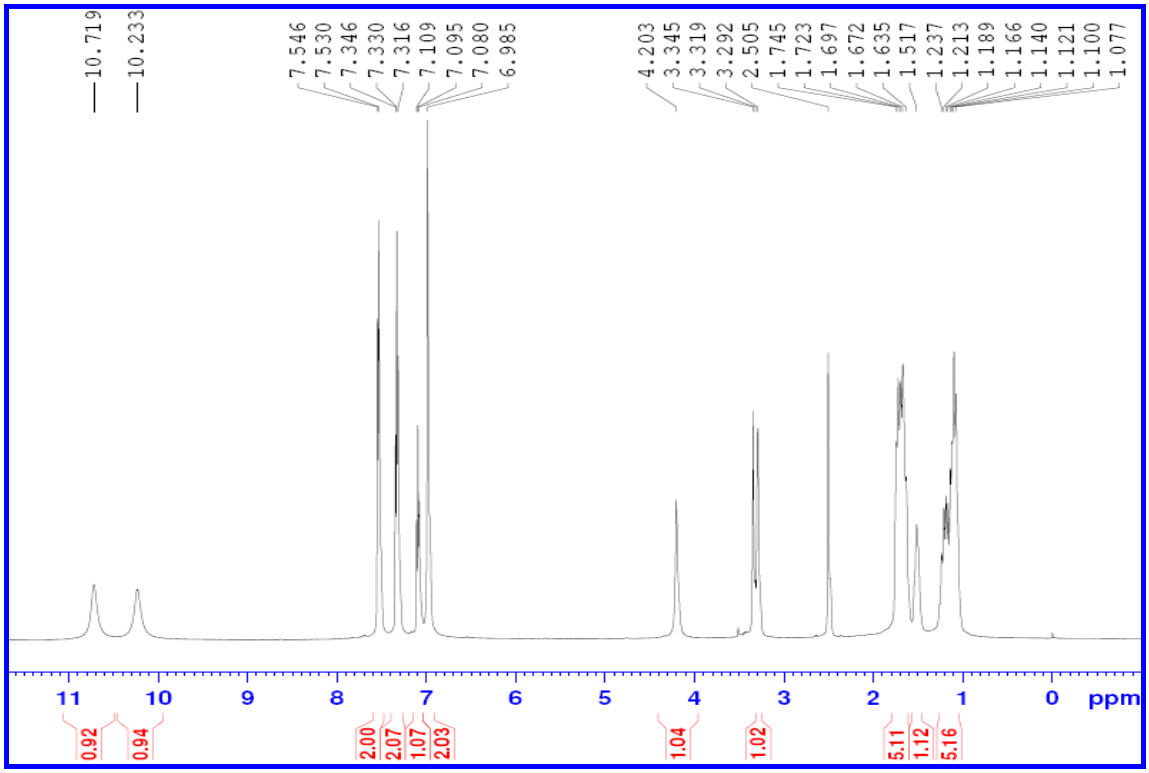

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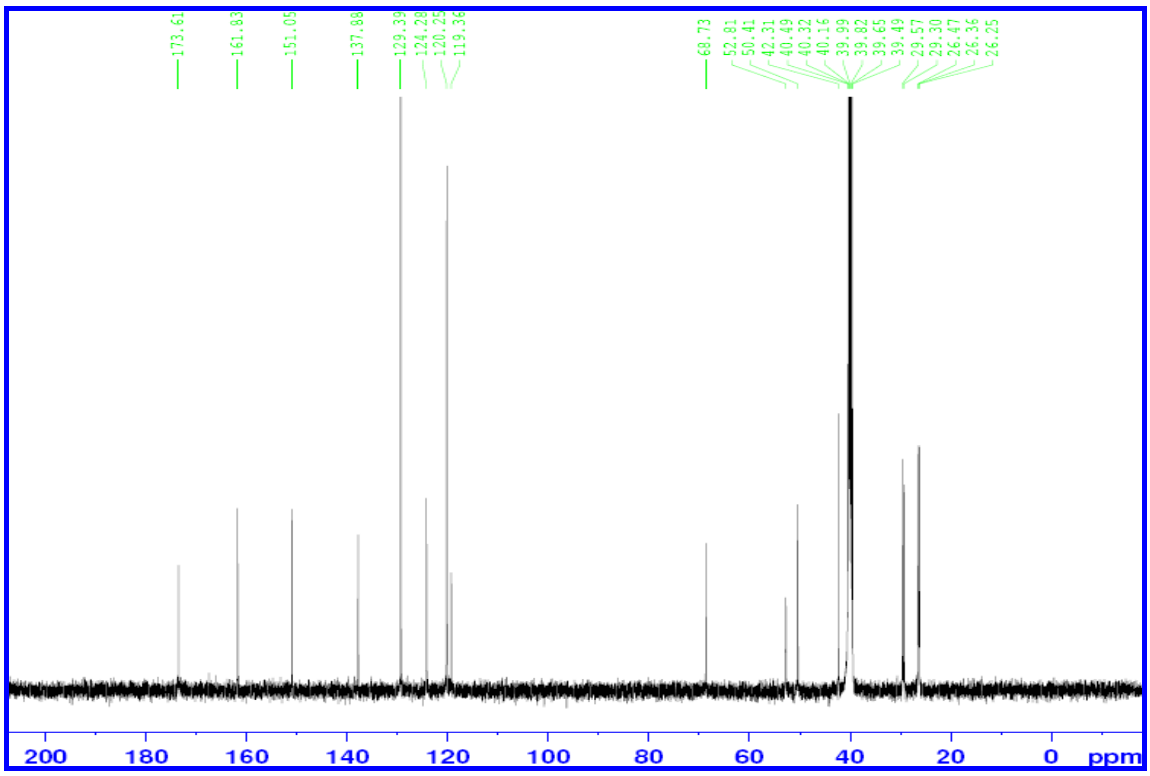

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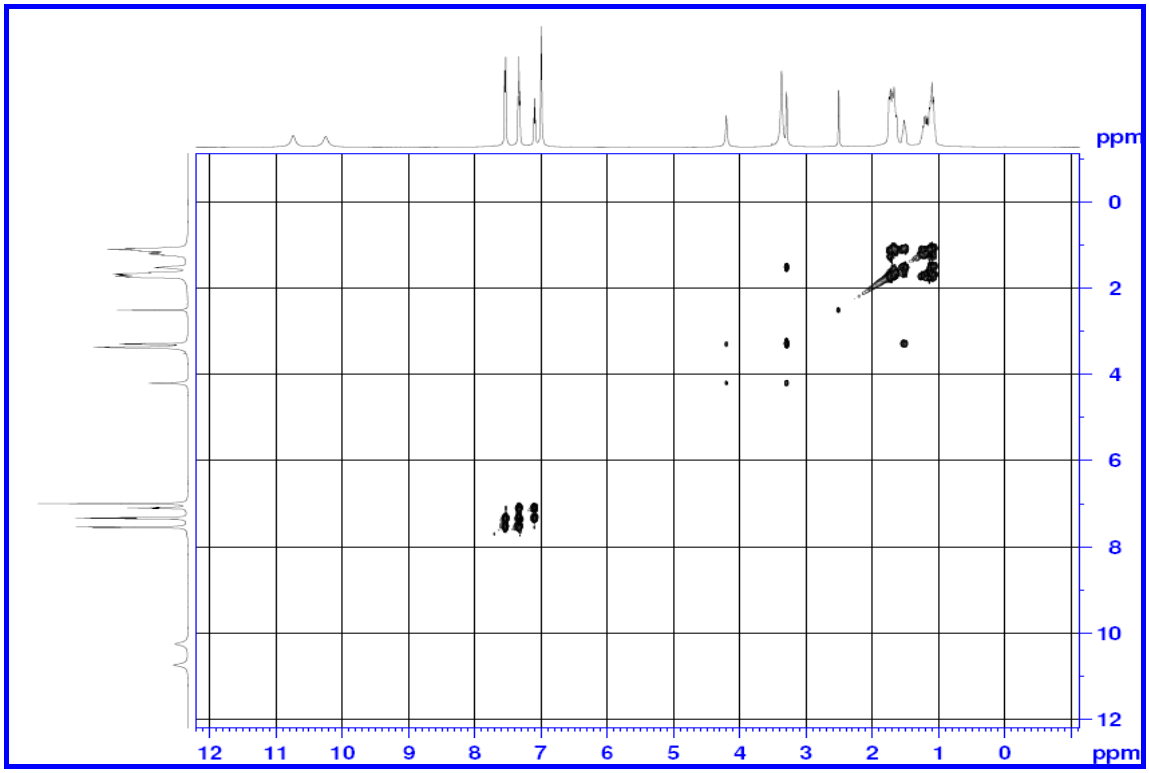
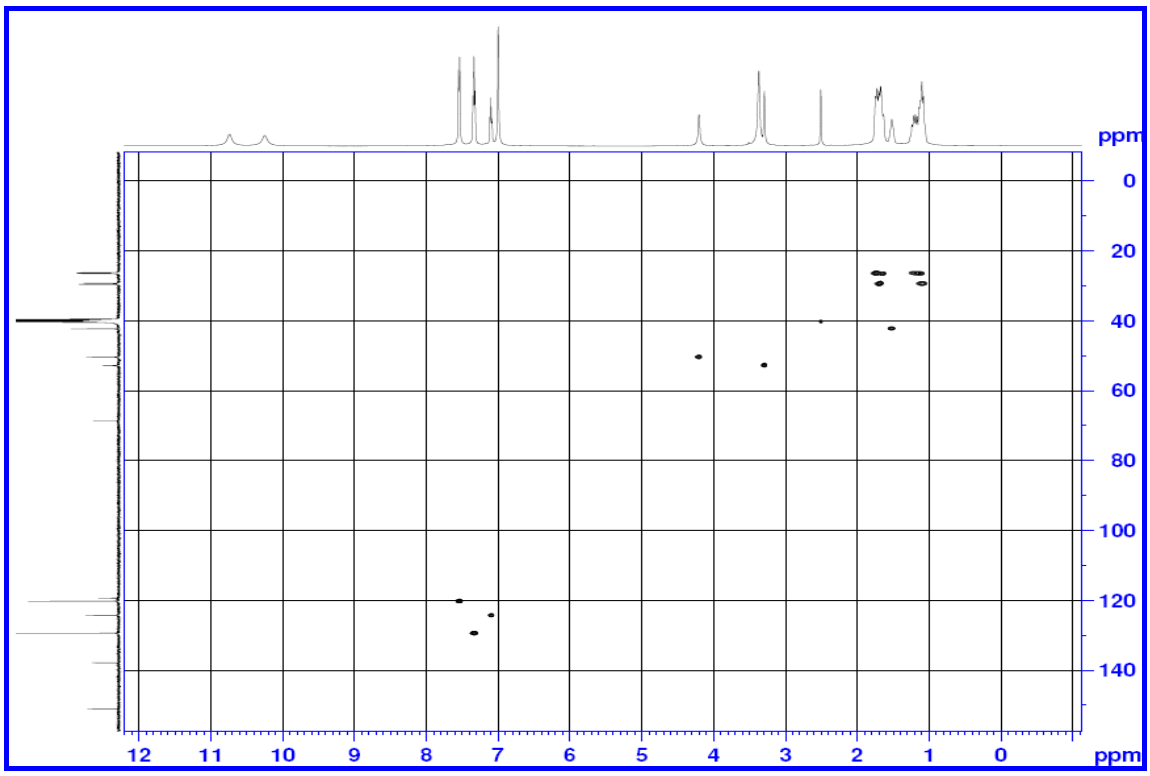
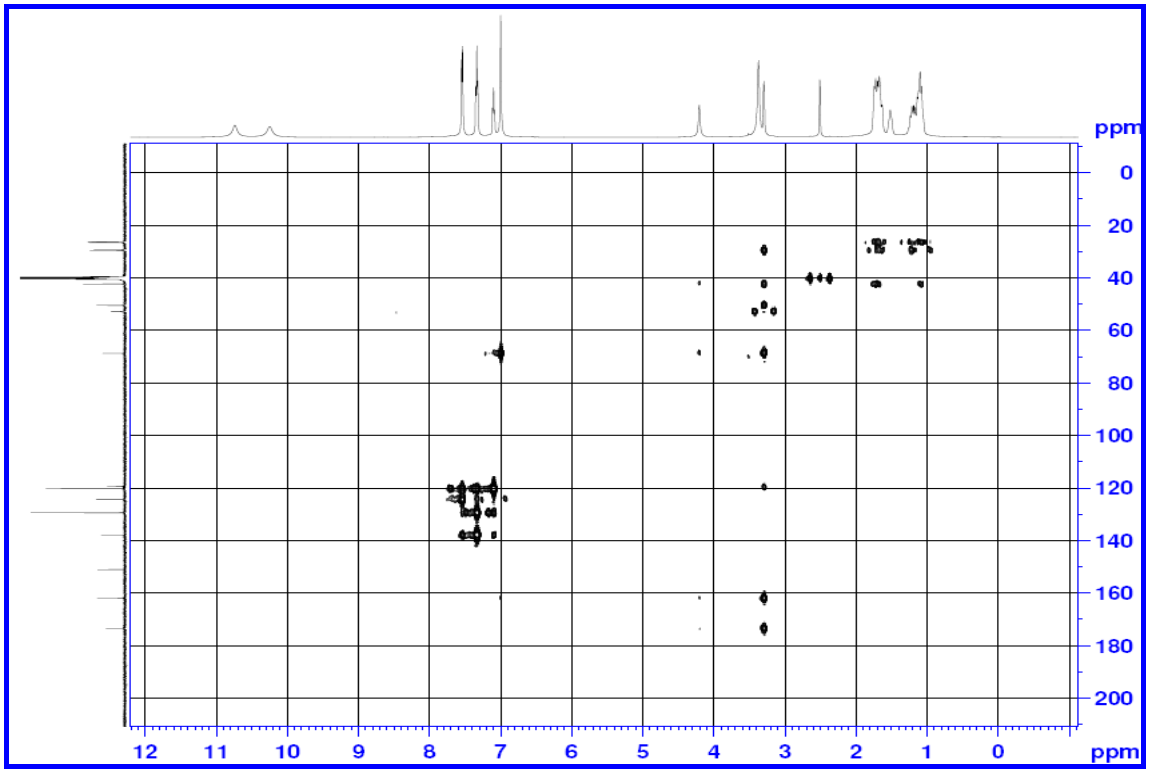


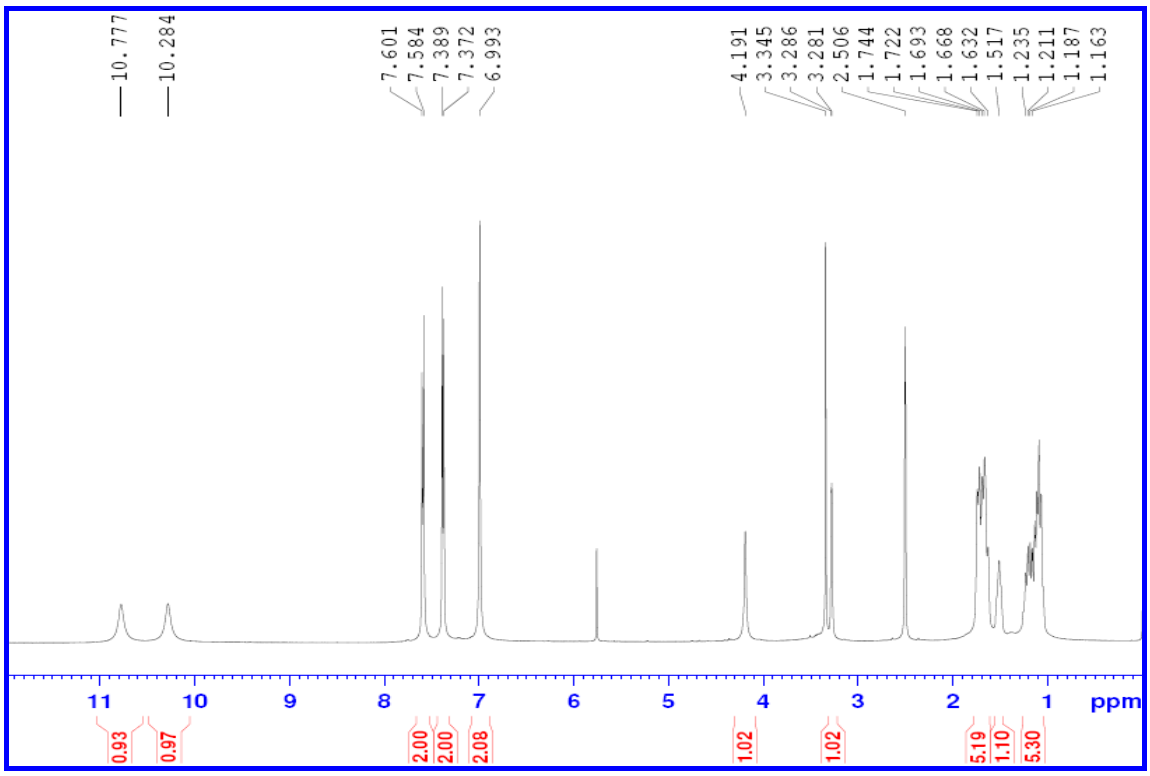
COSY (500MHz, DMSO-d_6) of Compound **7a**



HSQC (500MHz, DMSO-d_6) of Compound **7a**



HMBC (500MHz, DMSO-d_6) of Compound **7a**



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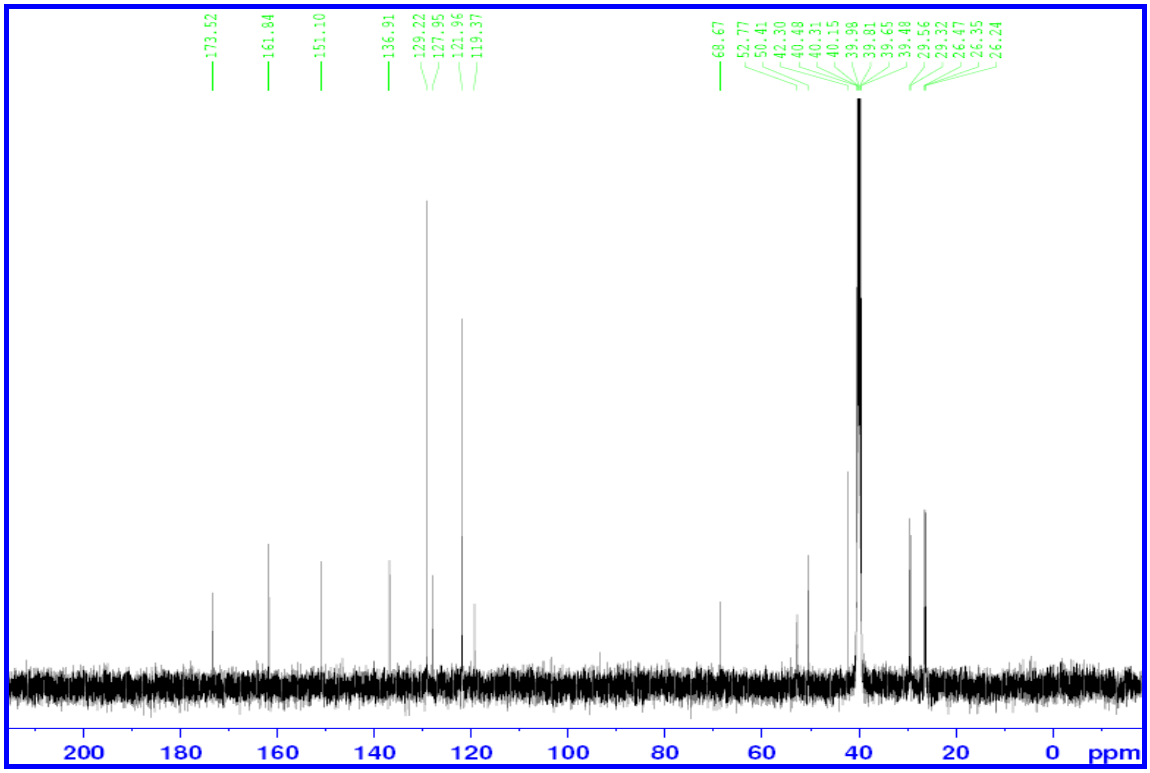

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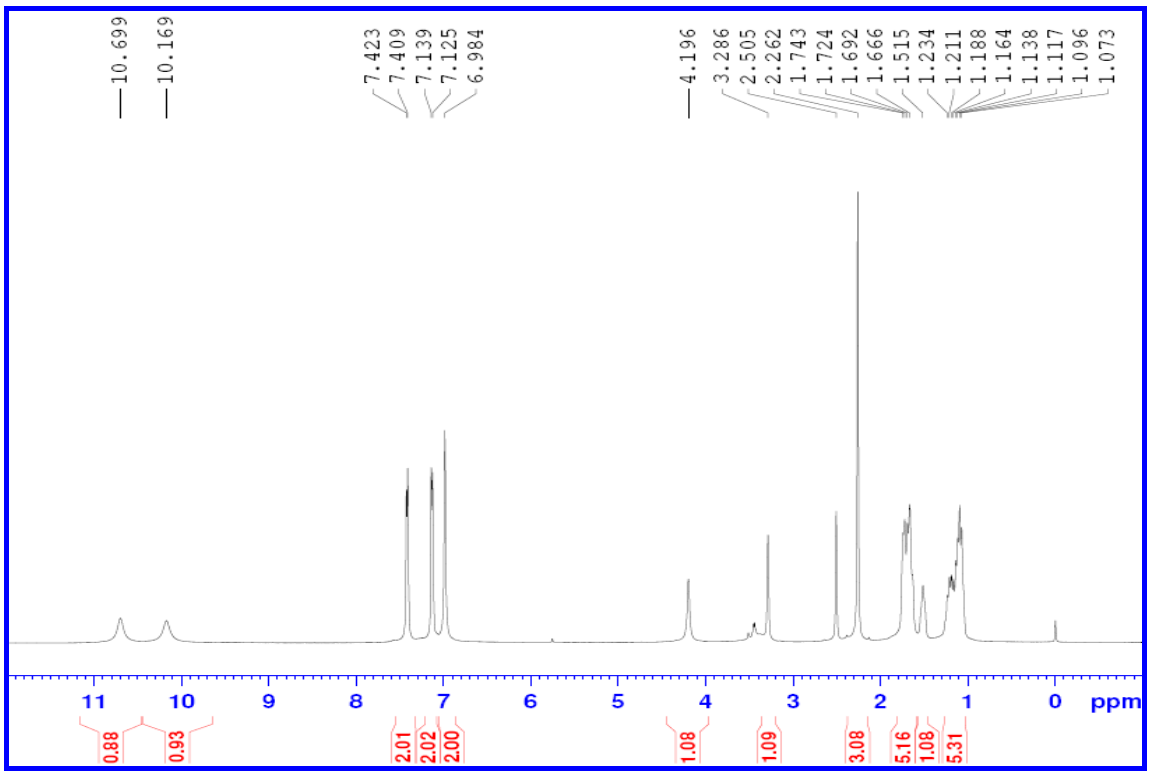

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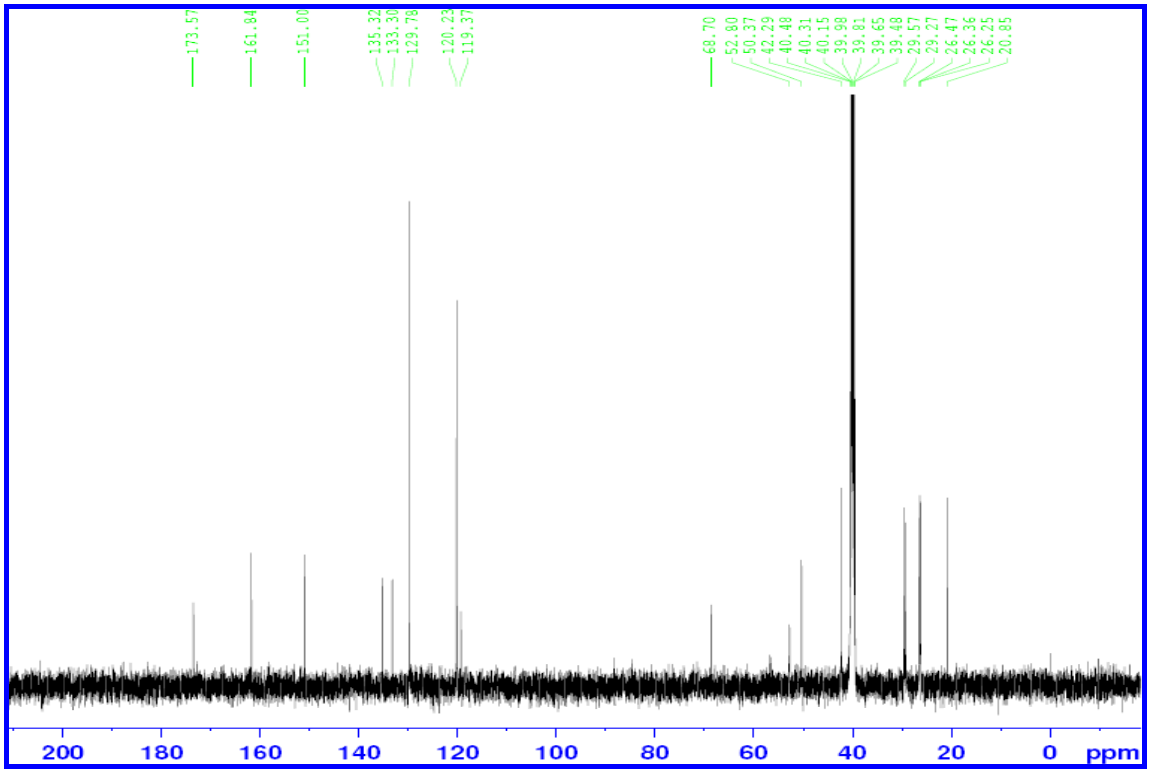

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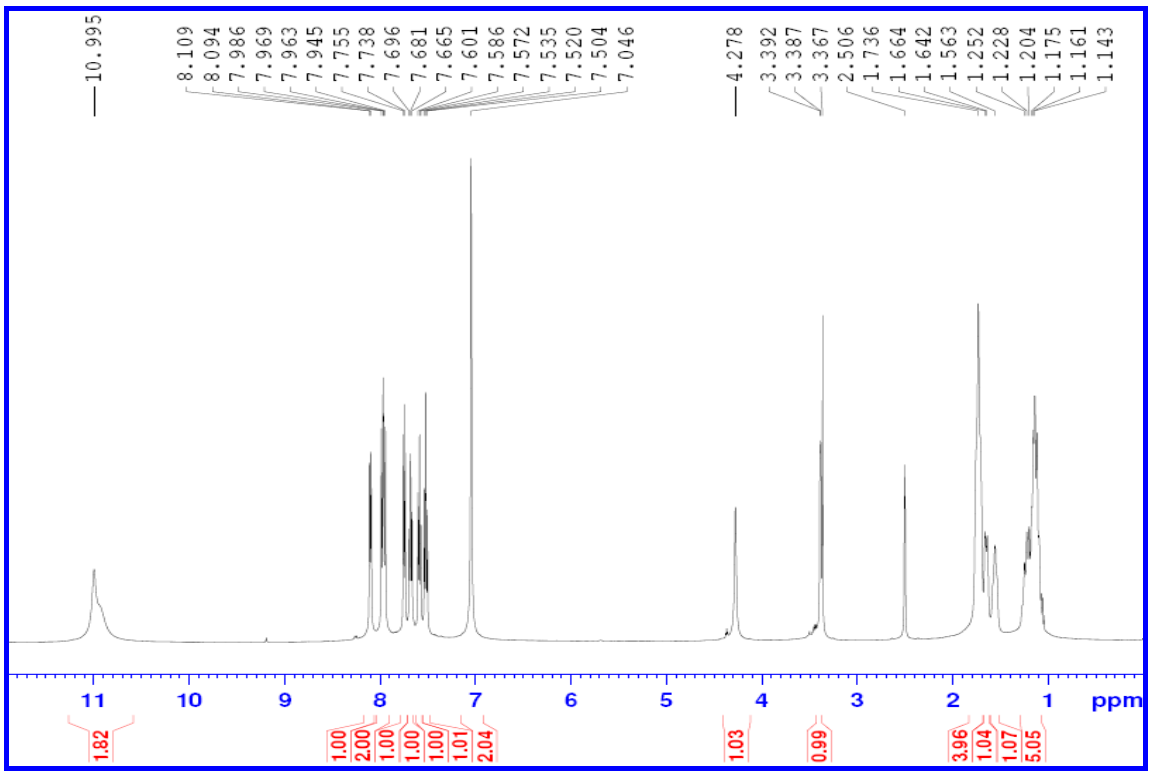

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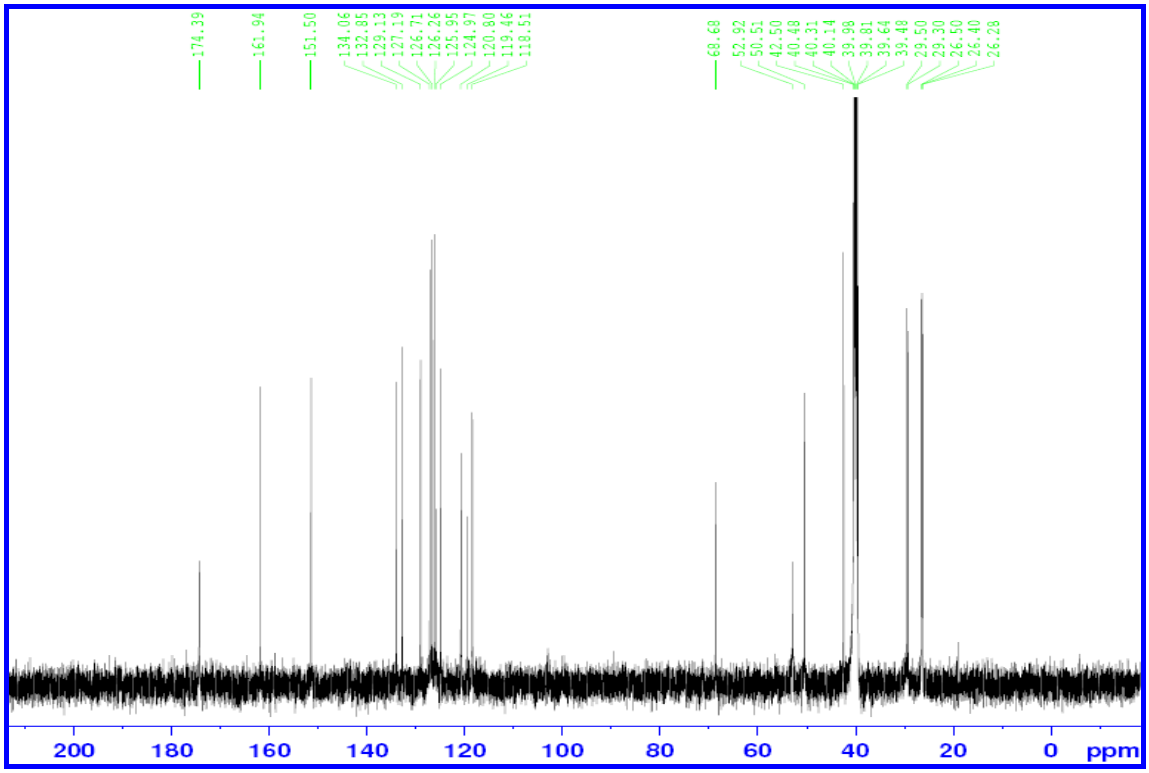

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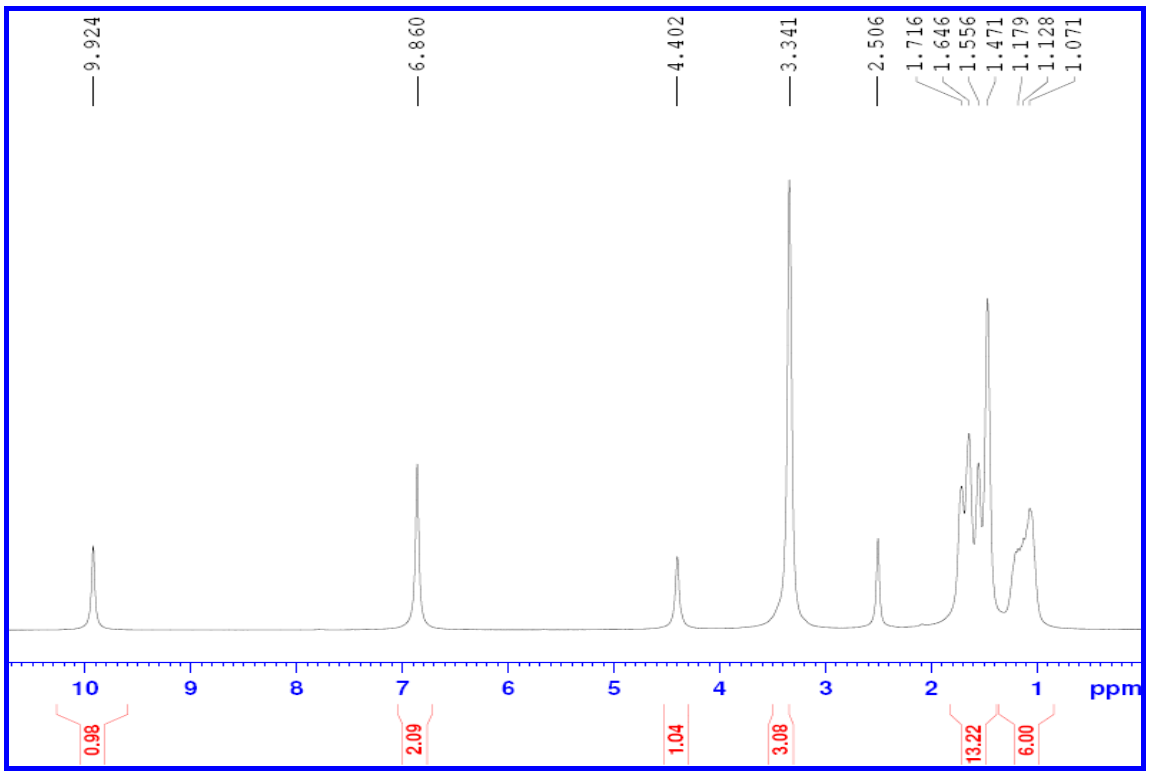

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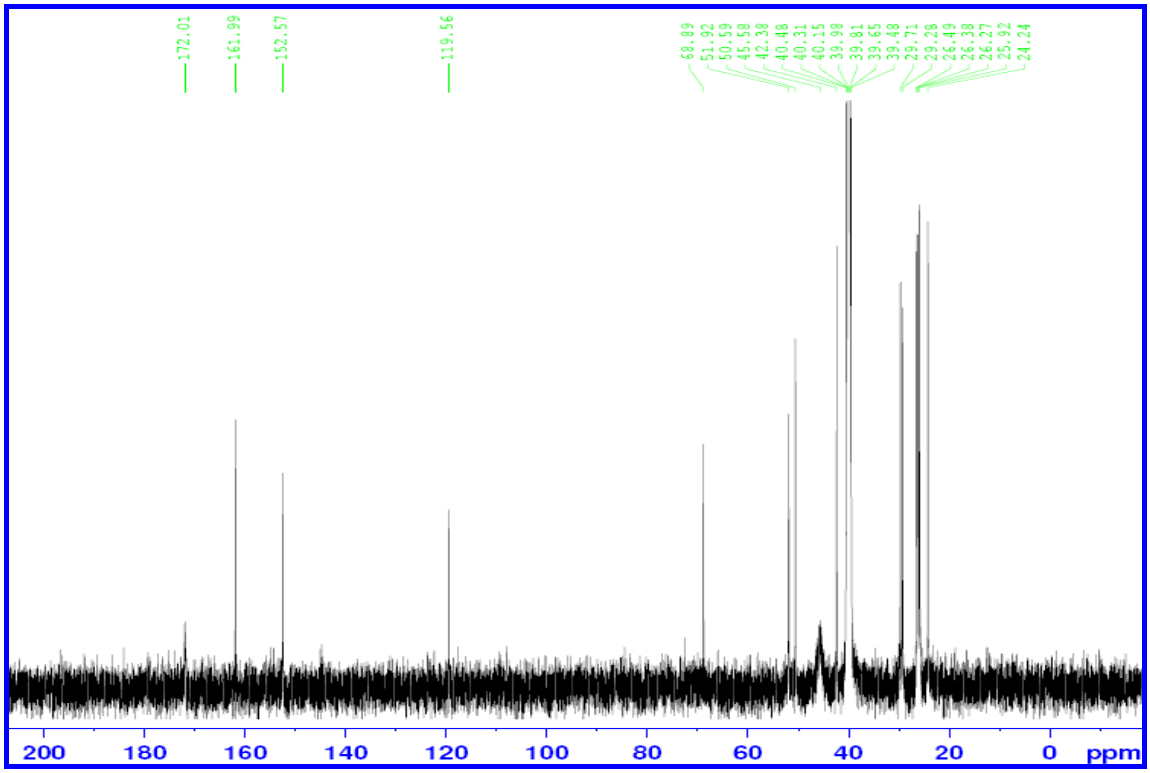

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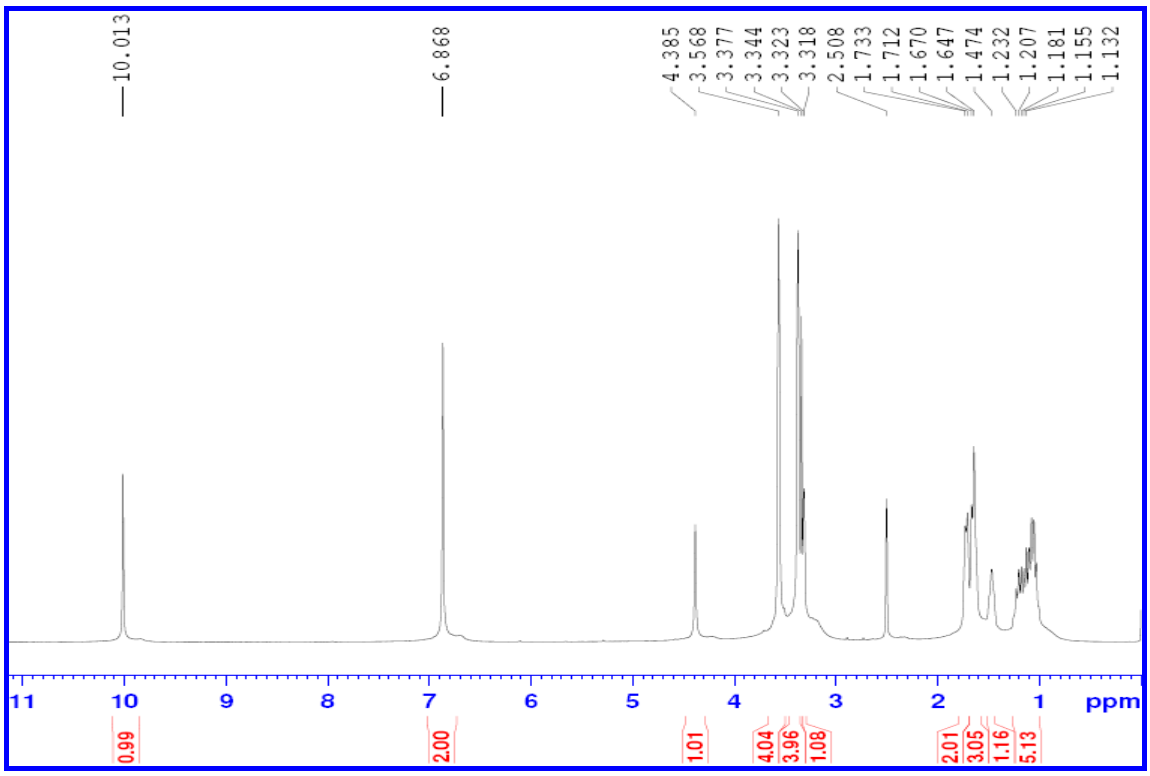

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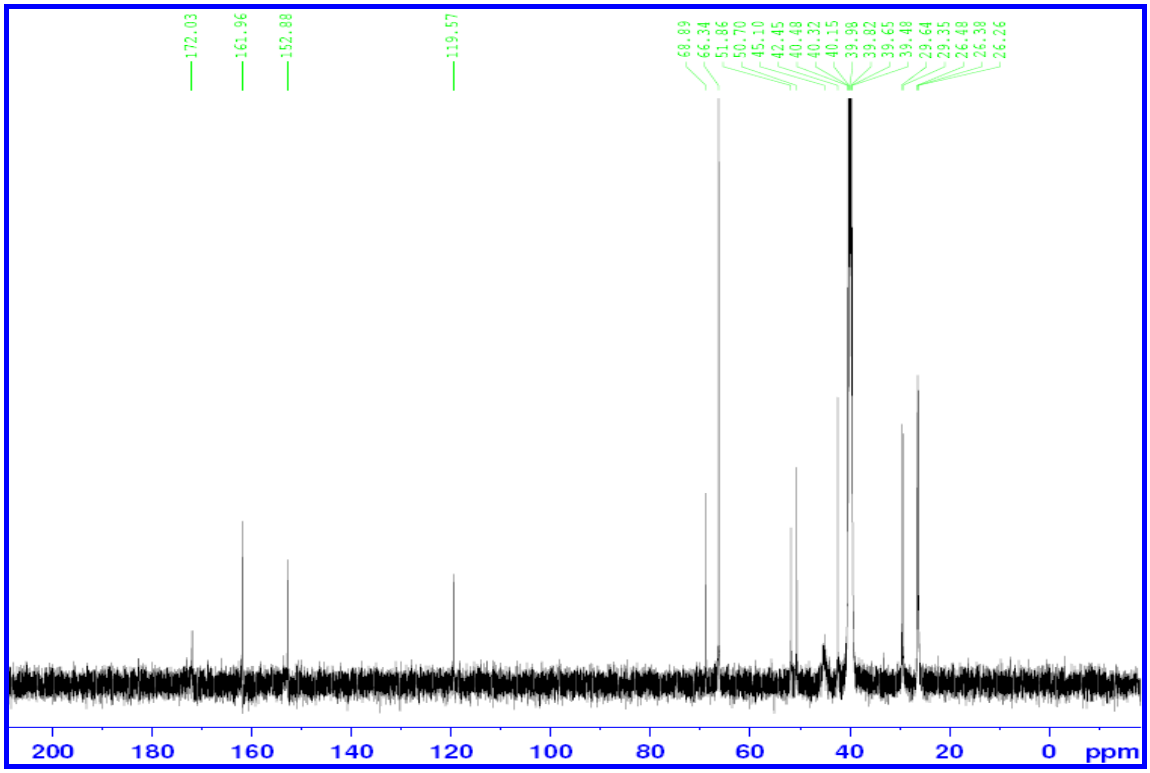

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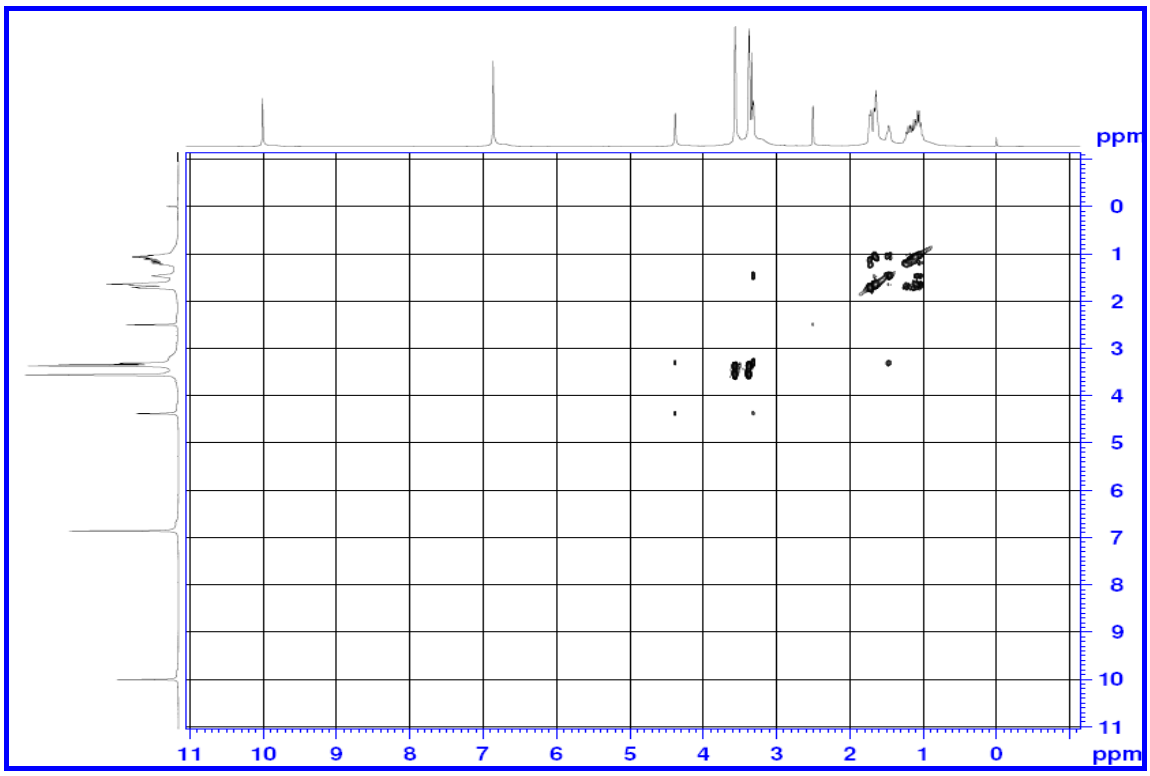
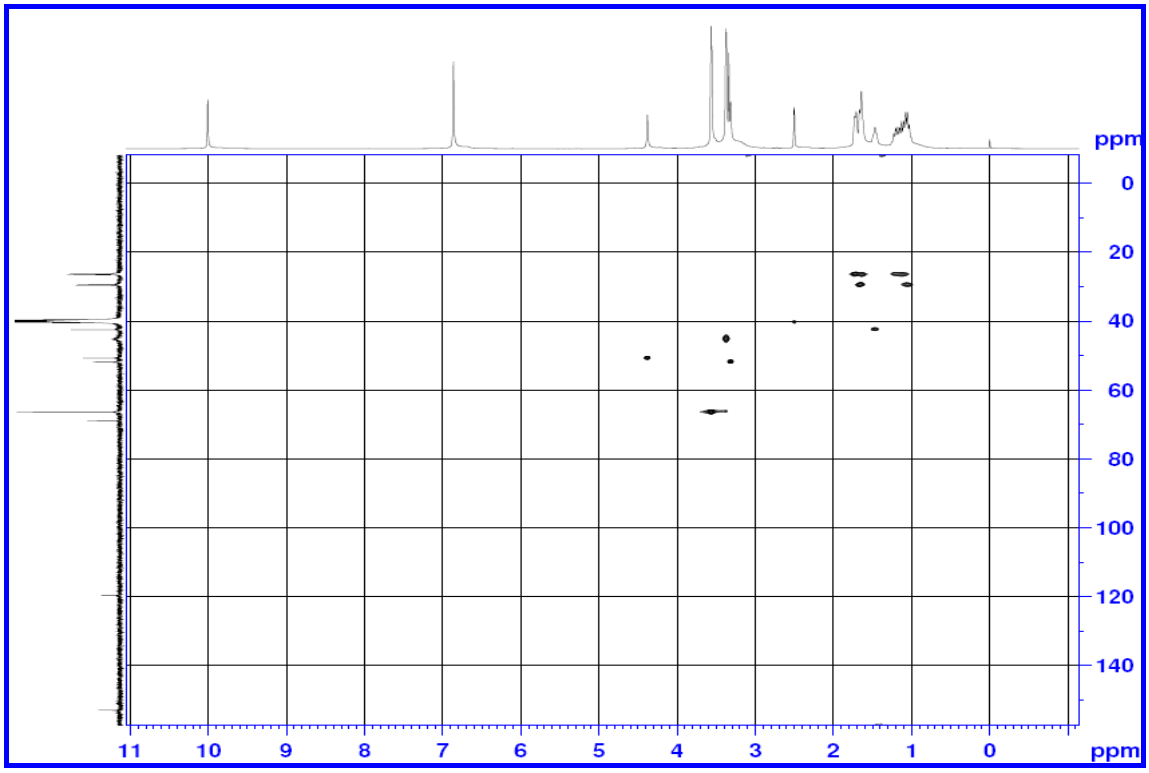


COSY (500MHz, DMSO-d_6) of Compound **7f**



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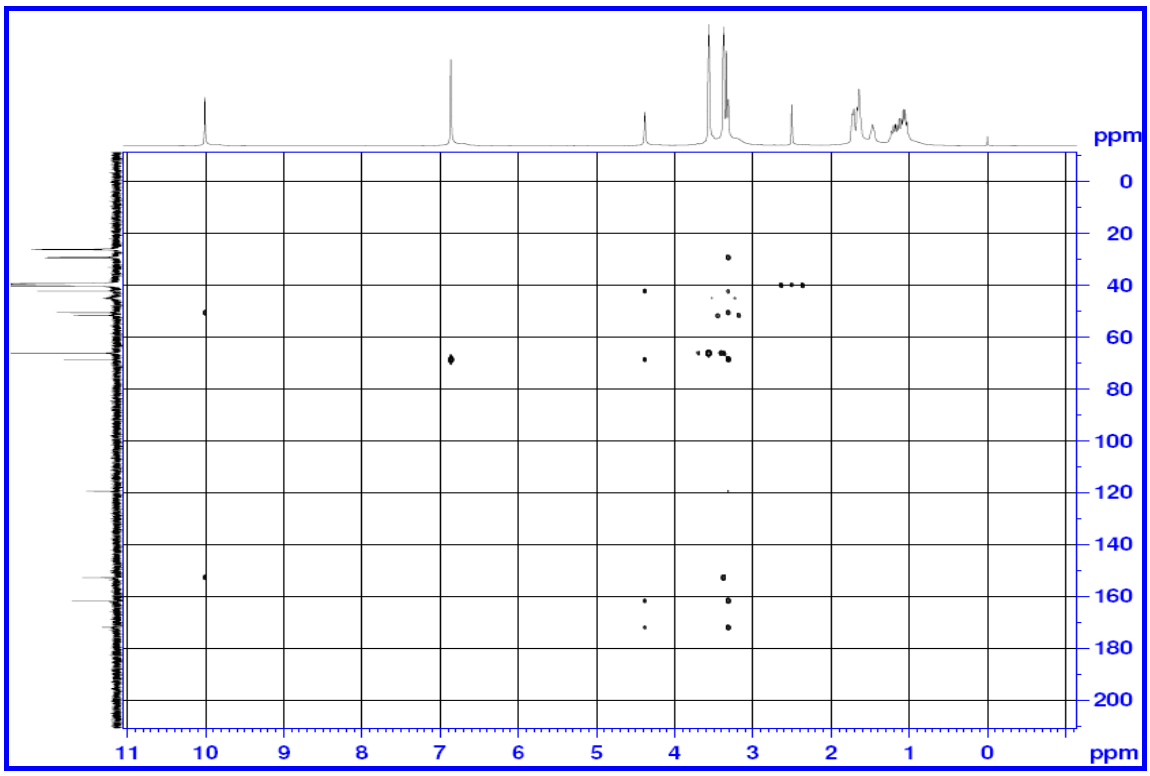

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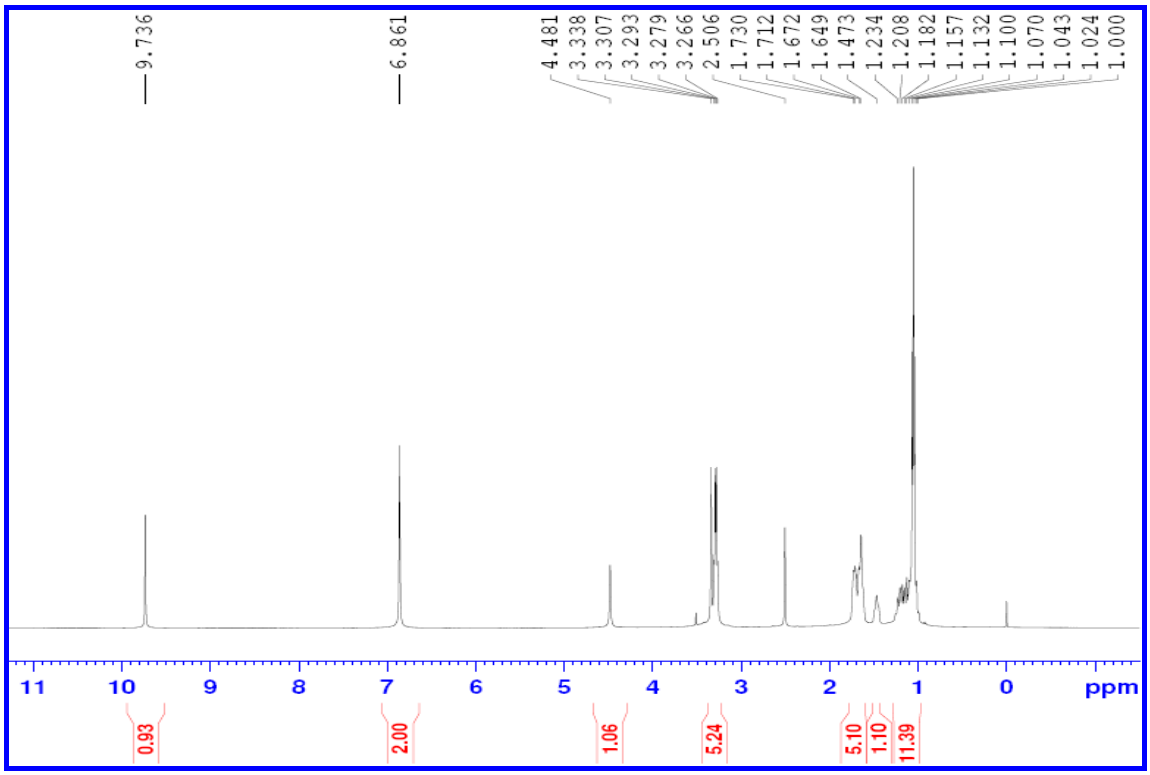

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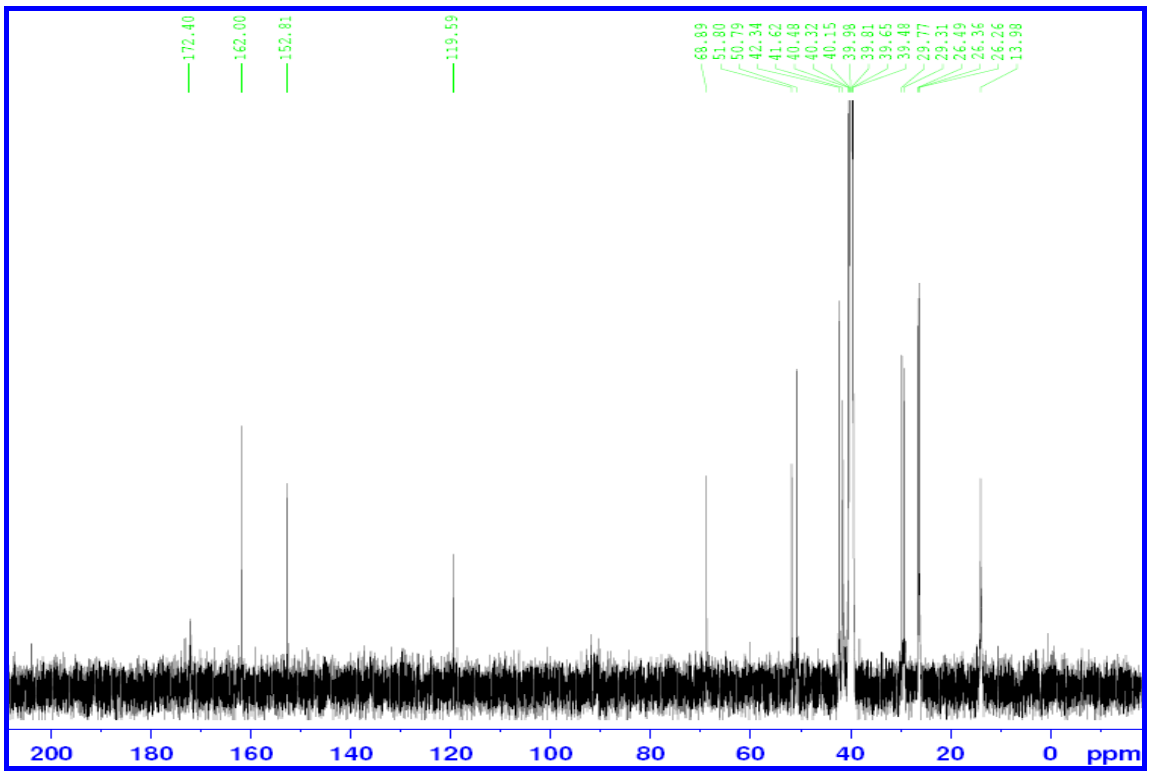

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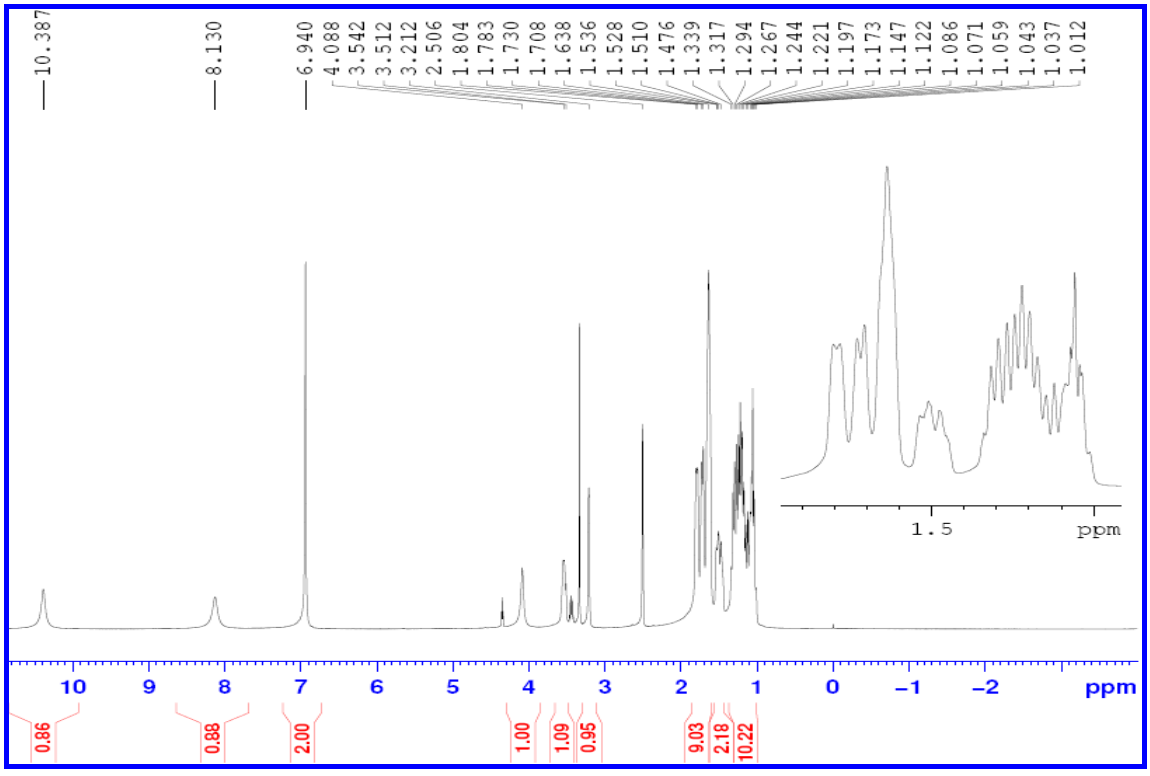

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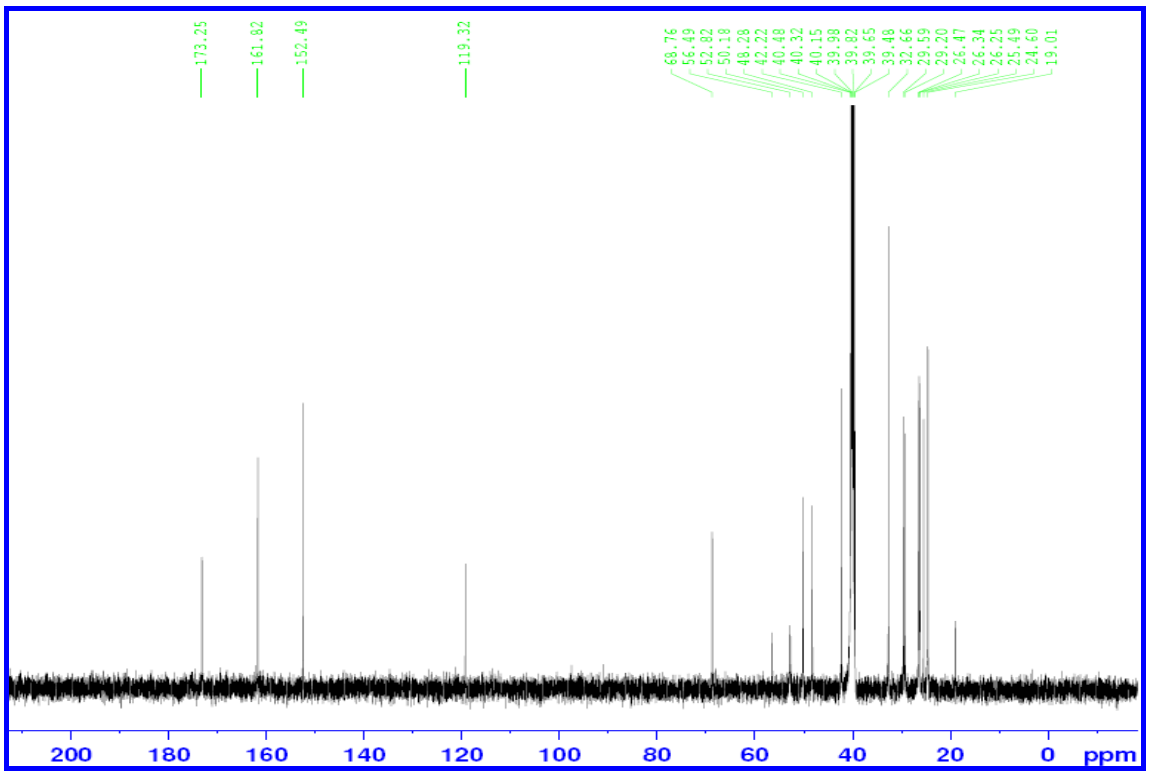

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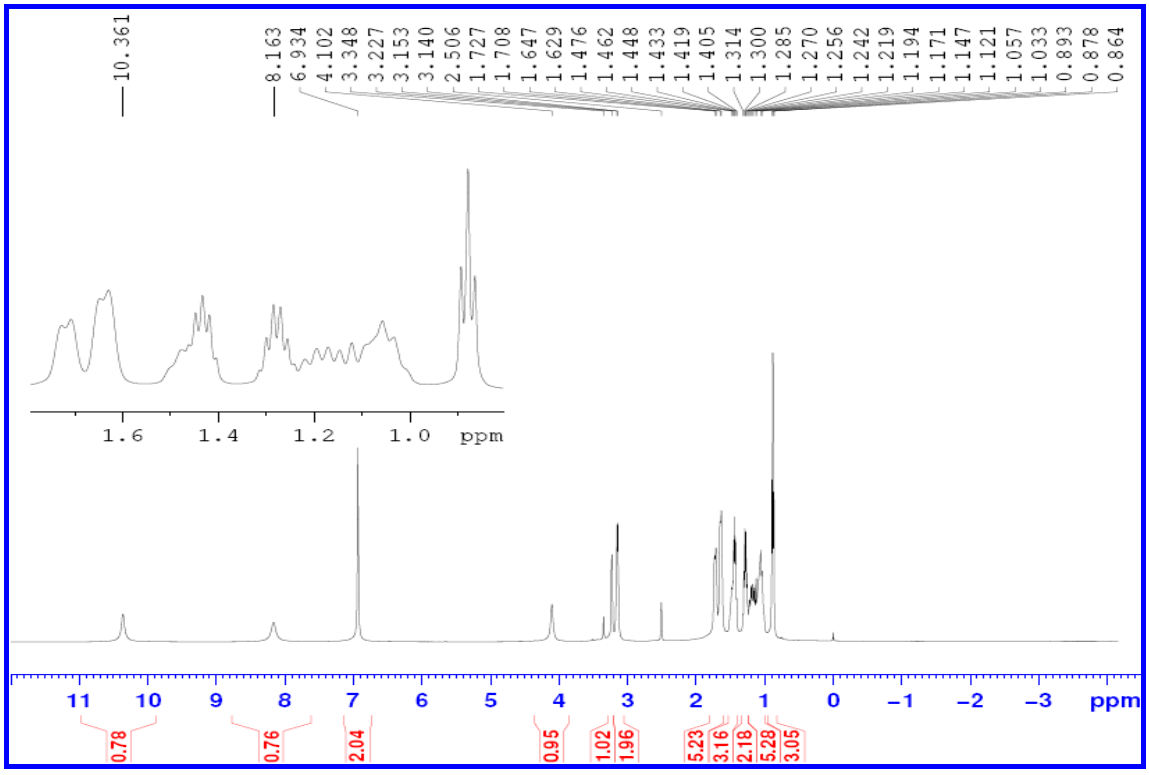

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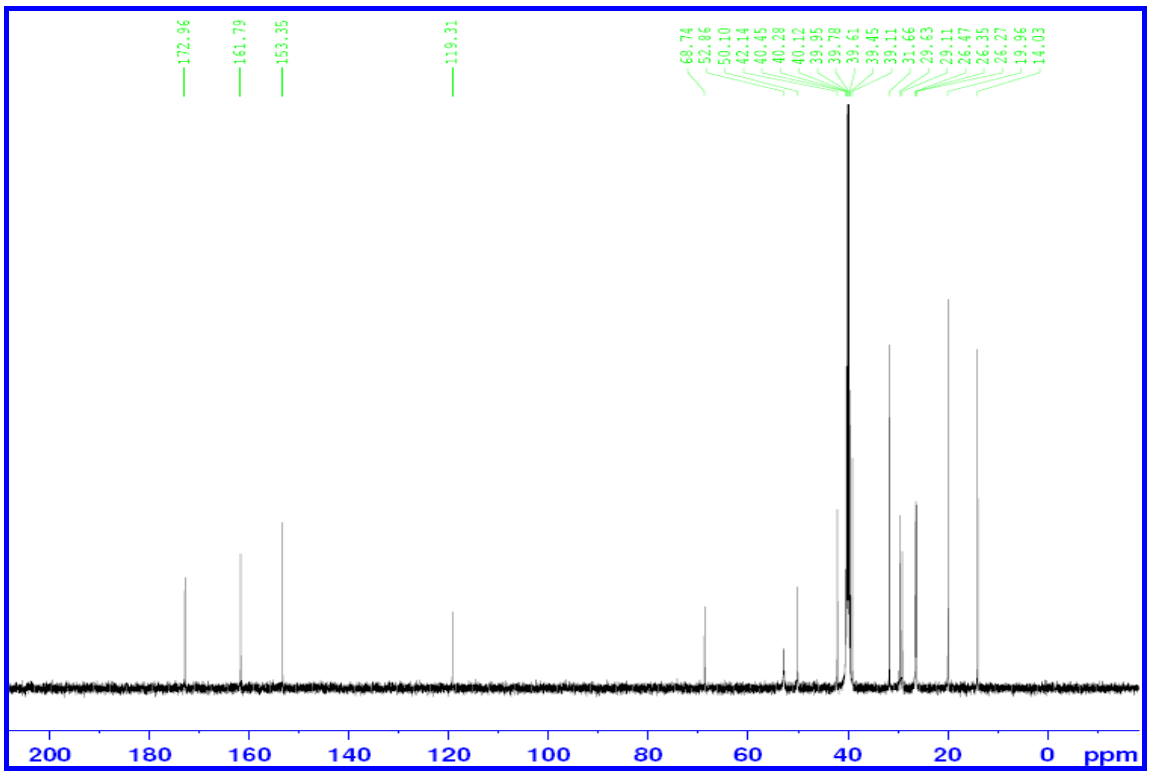

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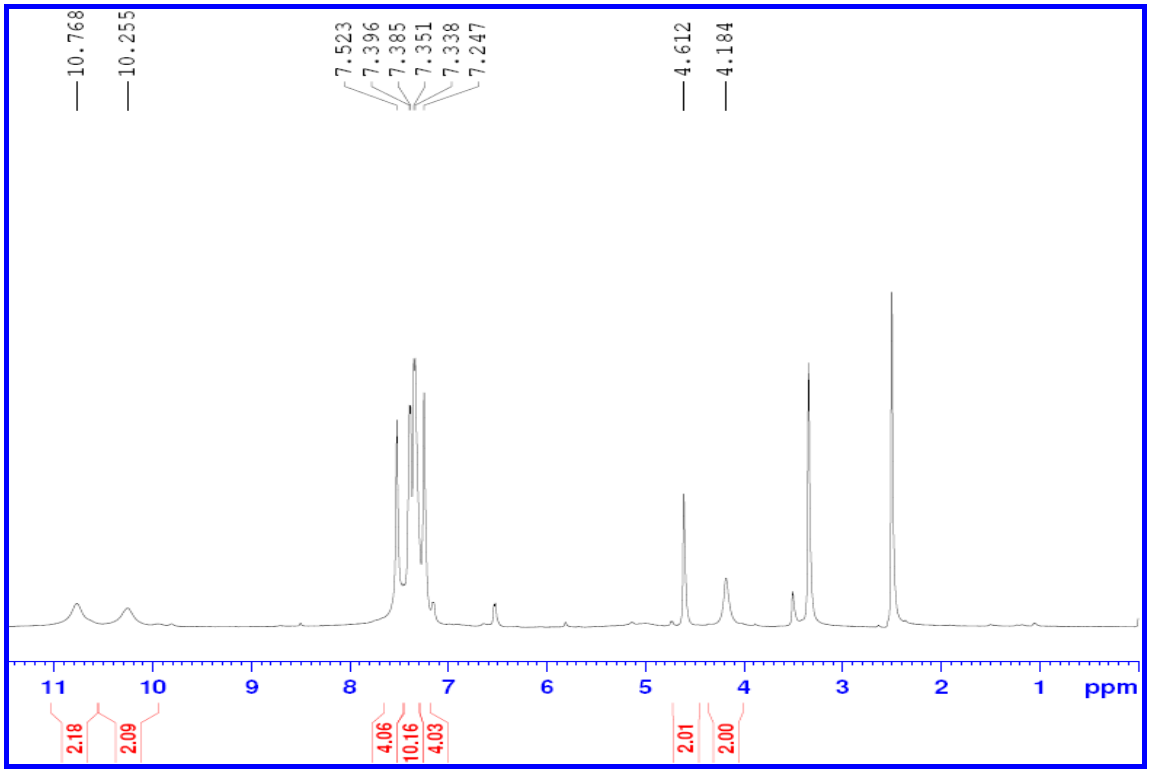

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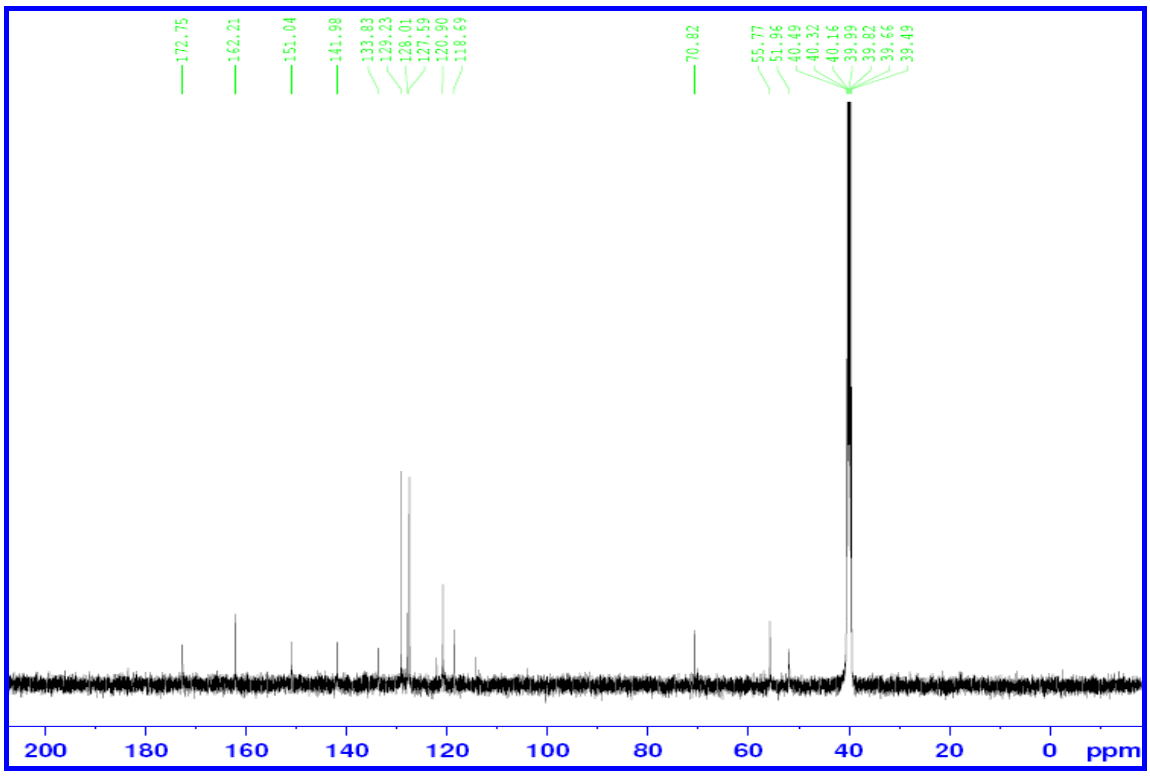
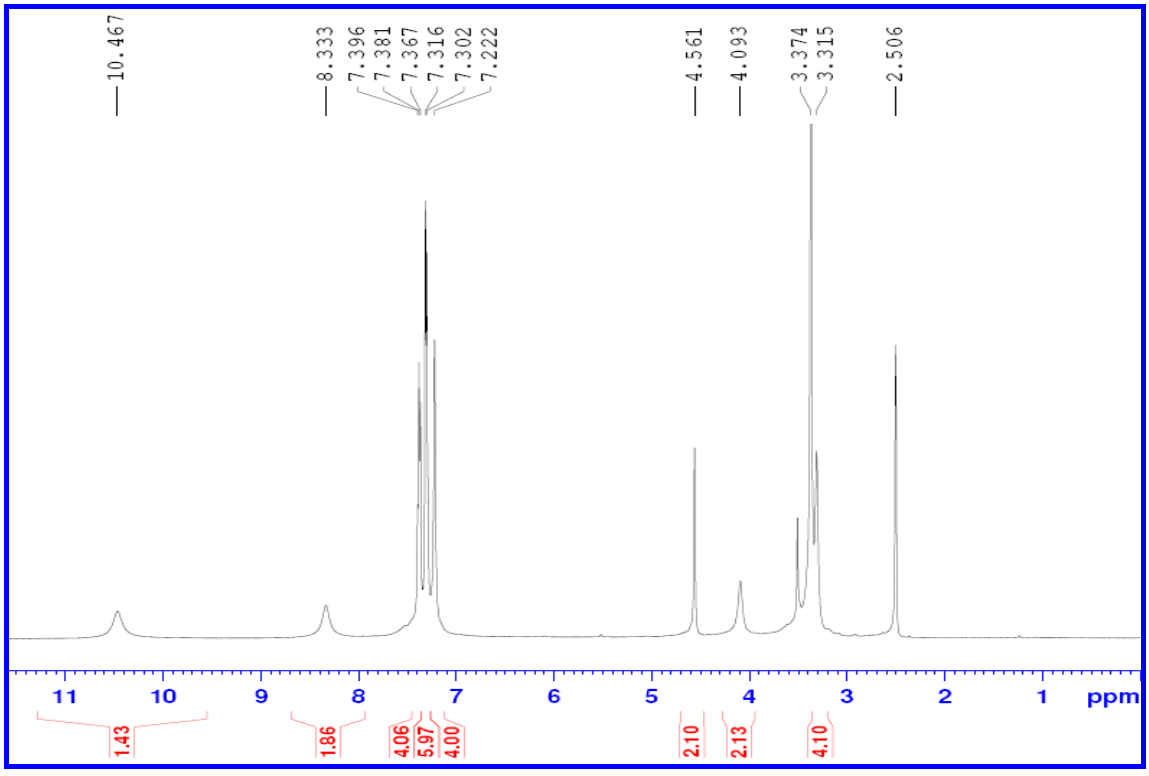
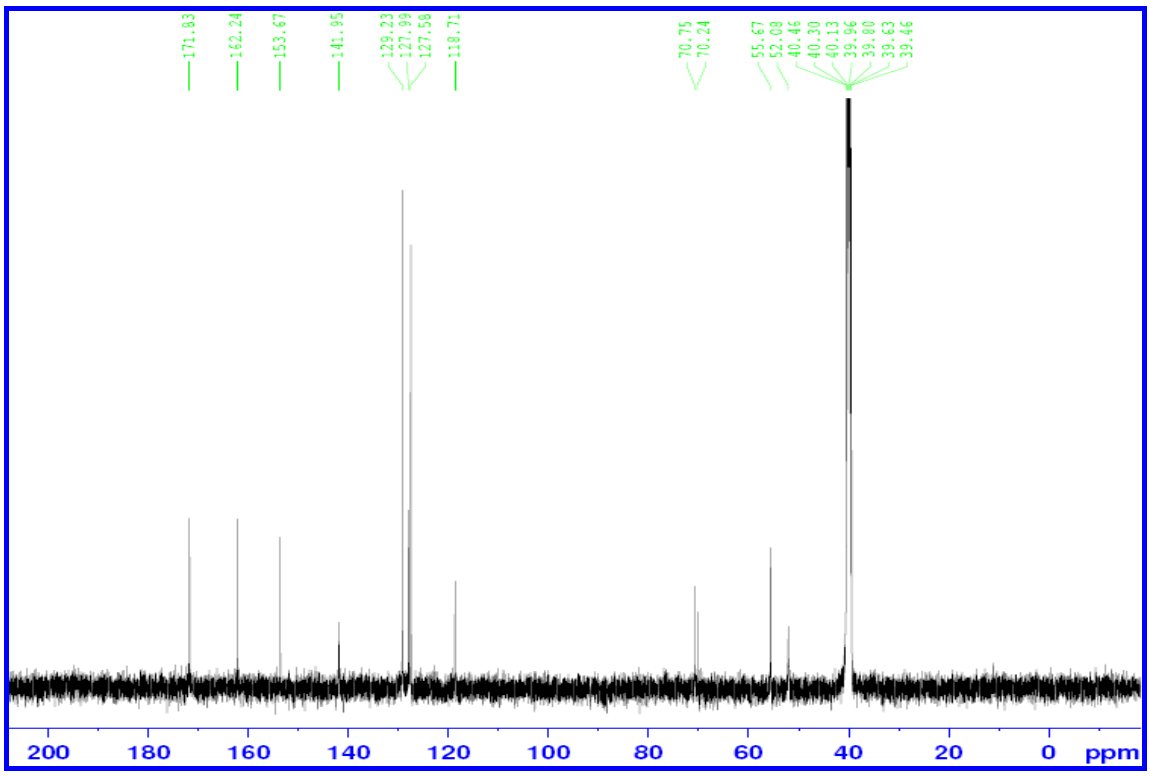


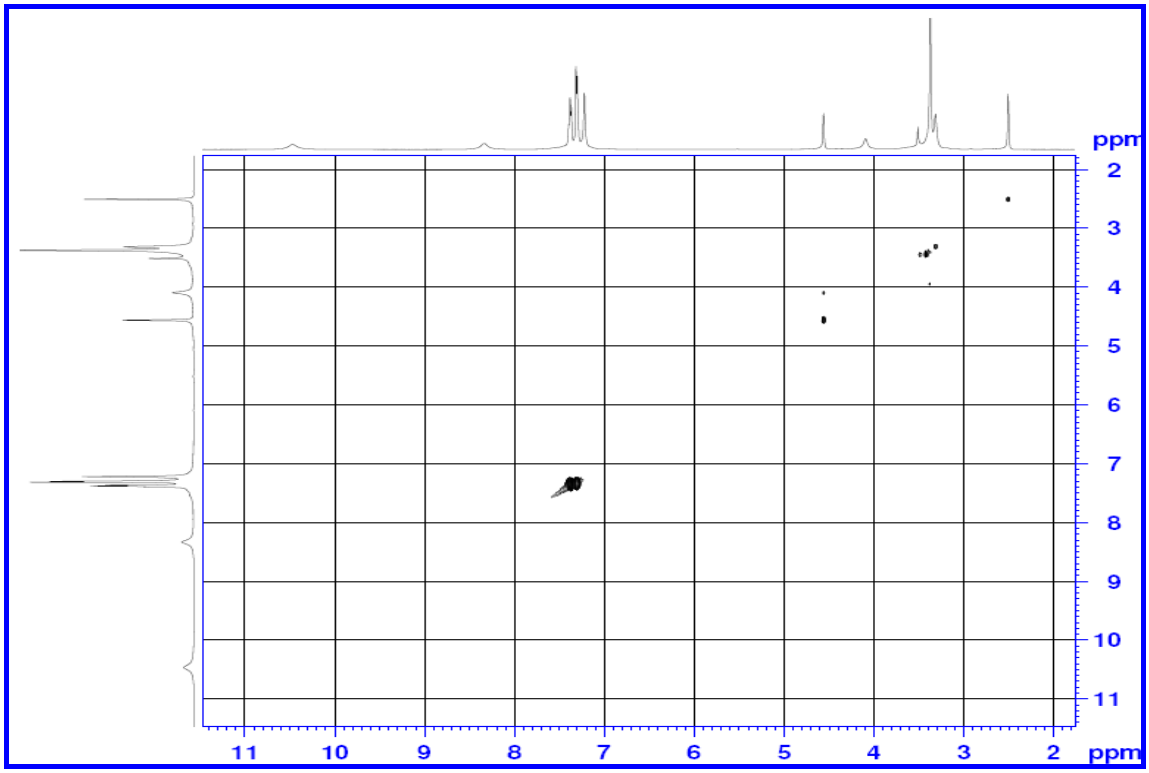
^{13}C NMR (125MHz, DMSO-d_6) of Compound **8a**



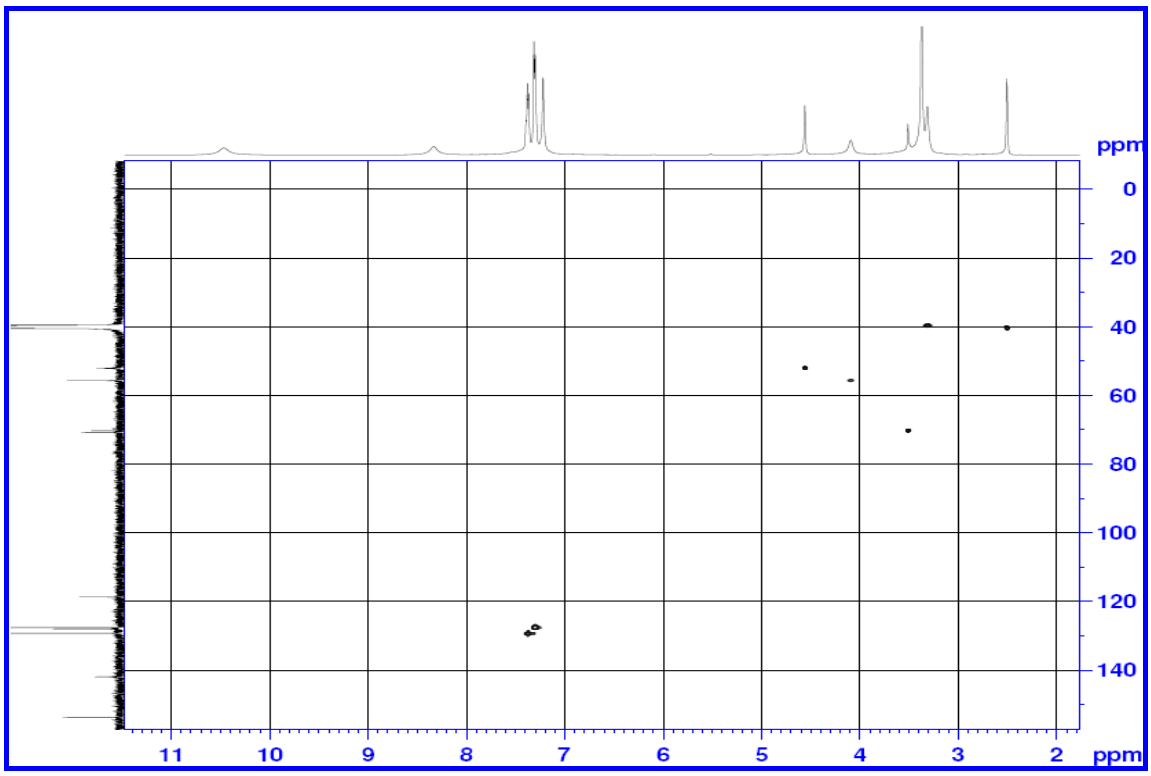
^{1}H NMR (500MHz, DMSO-d_6) of Compound **8b**



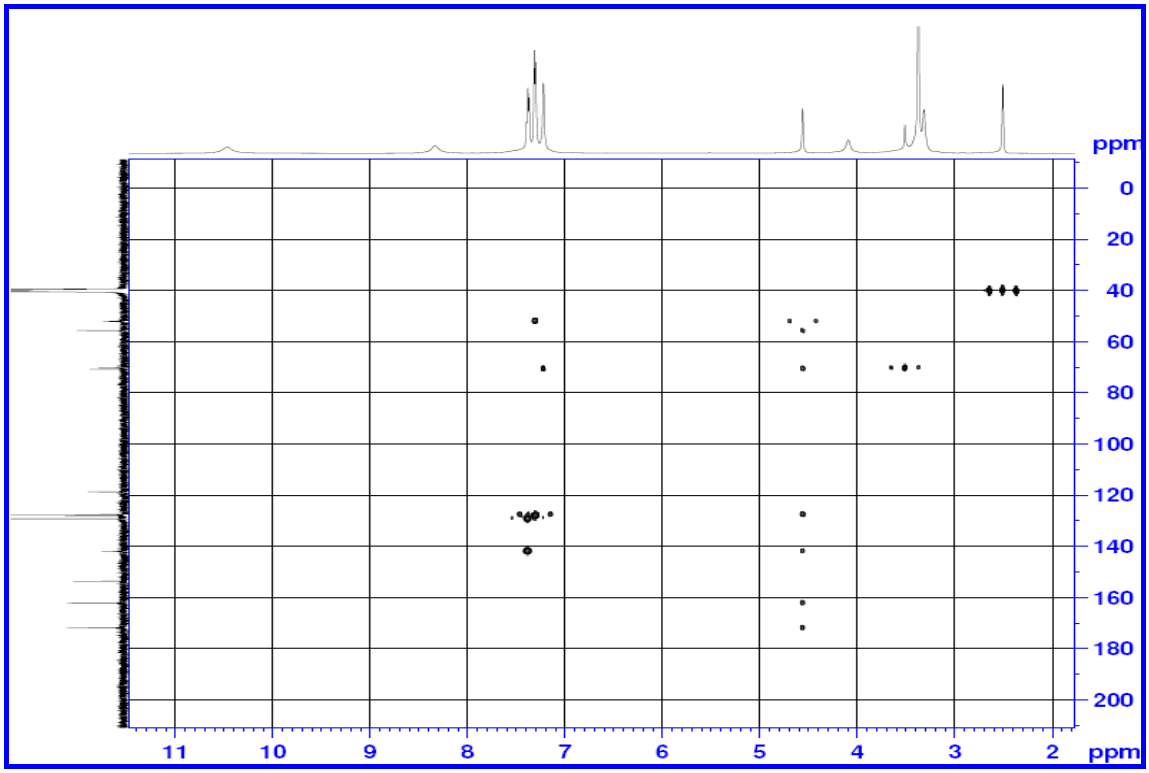
^{13}C NMR (125MHz, DMSO-d_6) of Compound **8b**



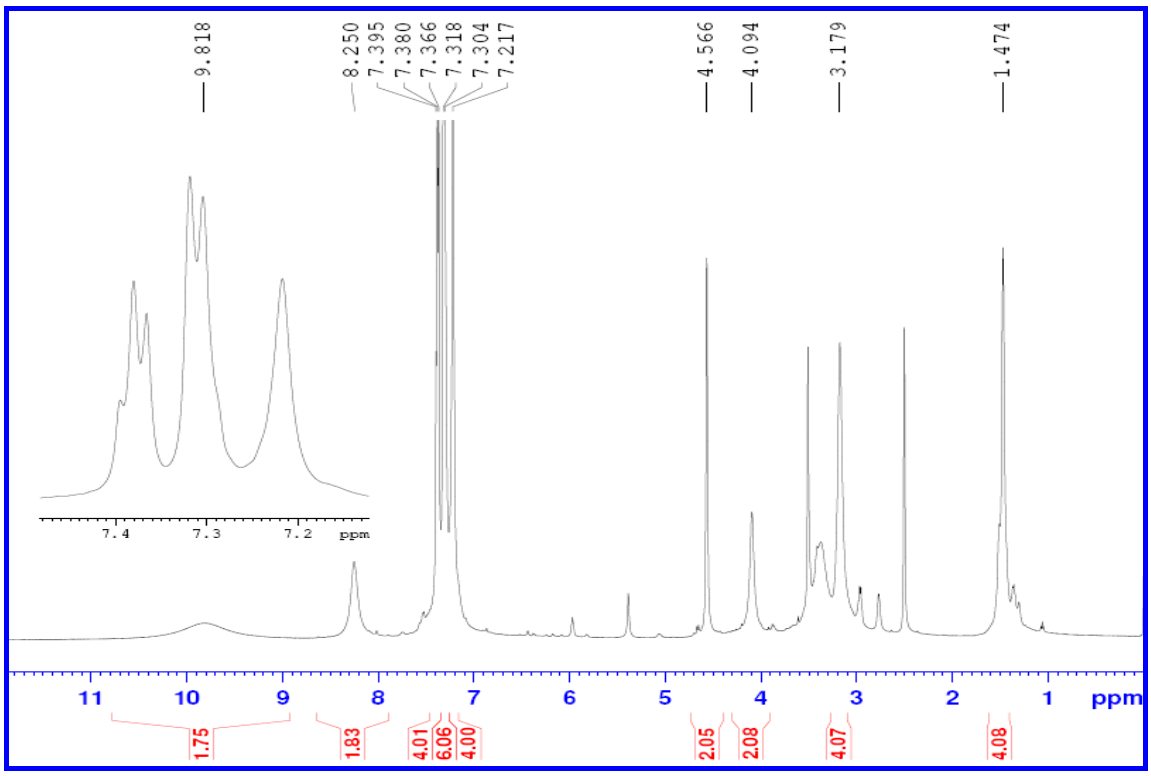
COSY (500MHz, DMSO-d_6) of Compound **8b**



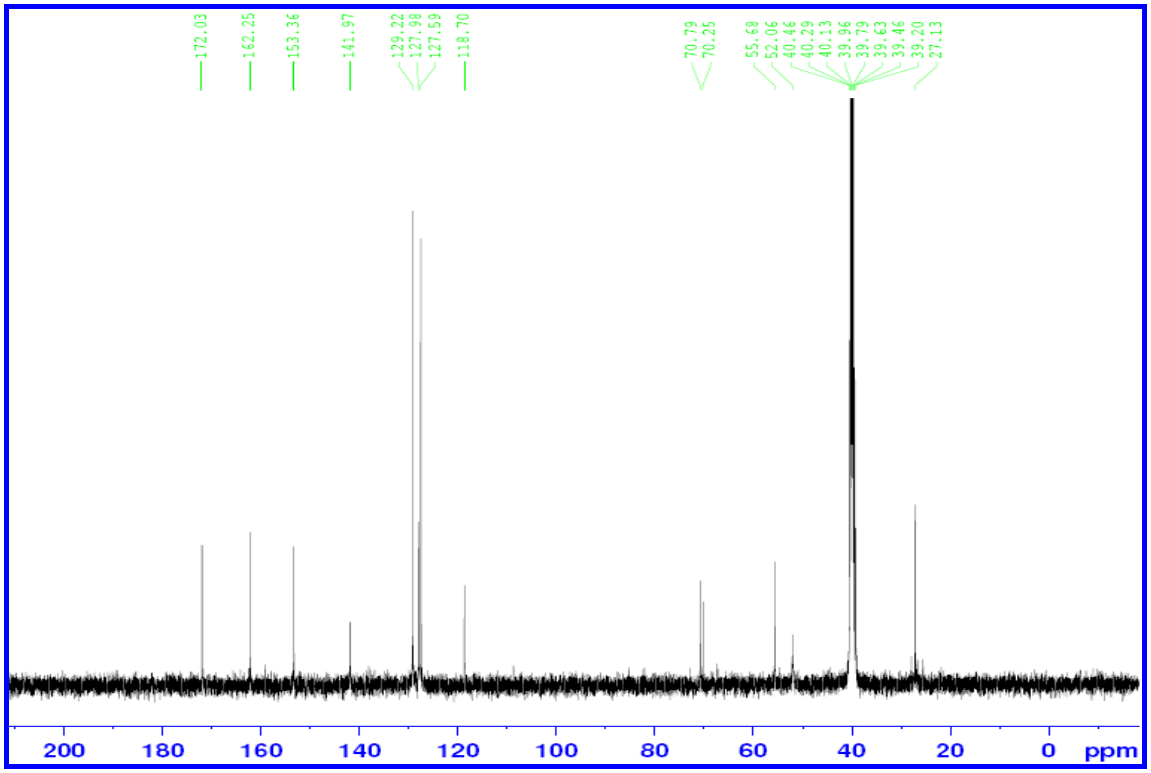
HSQC (500MHz, DMSO-d_6) of Compound **8b**



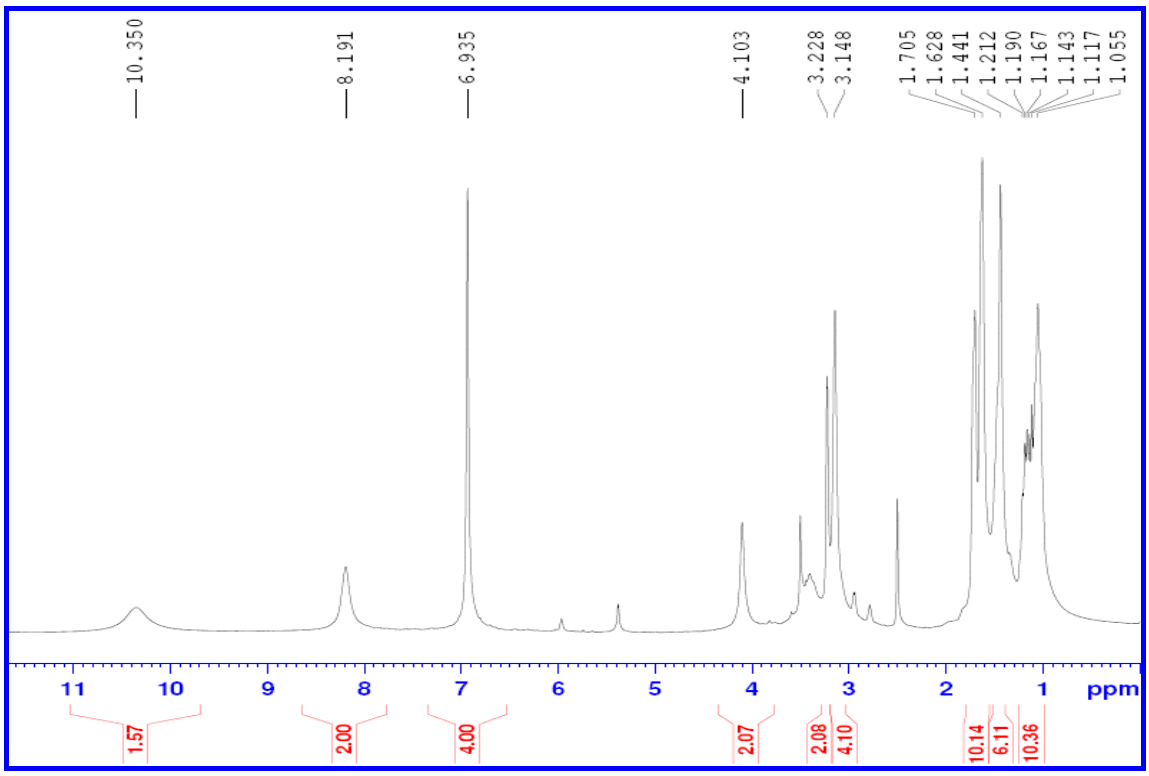
HMBC (500MHz, DMSO-d_6) of Compound **8b**



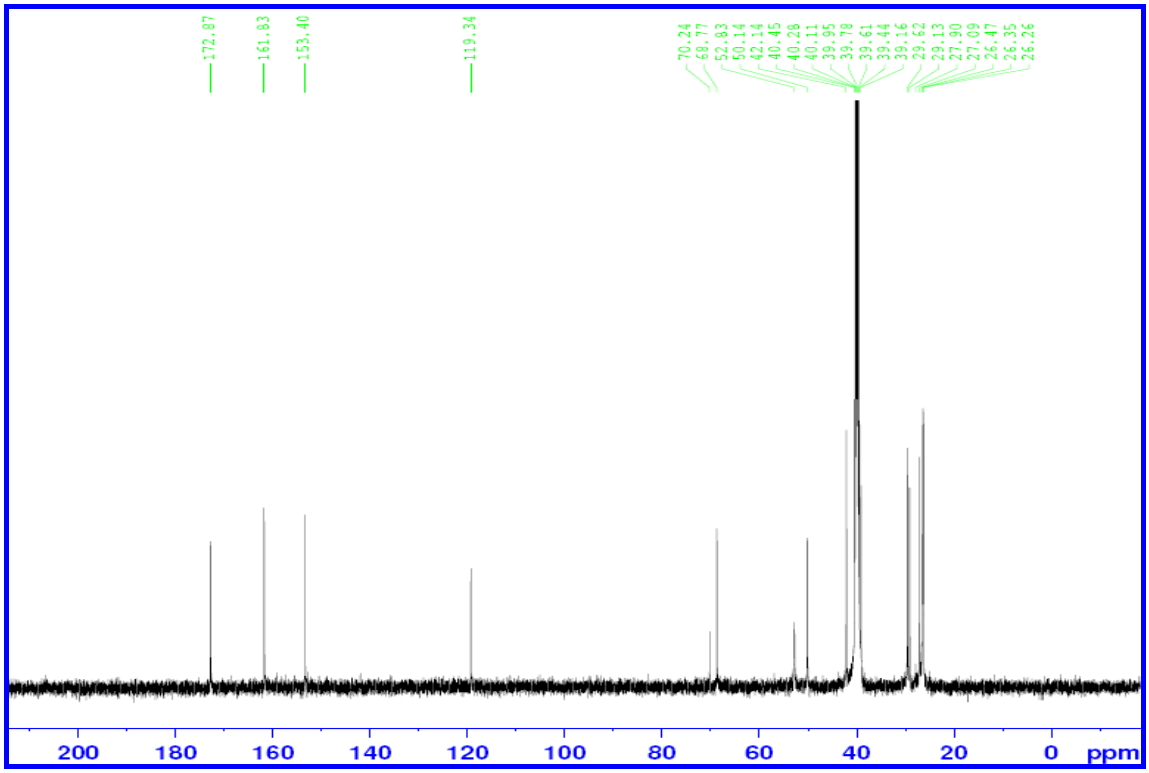
^{1}H NMR (500MHz, DMSO-d_6) of Compound **8c**



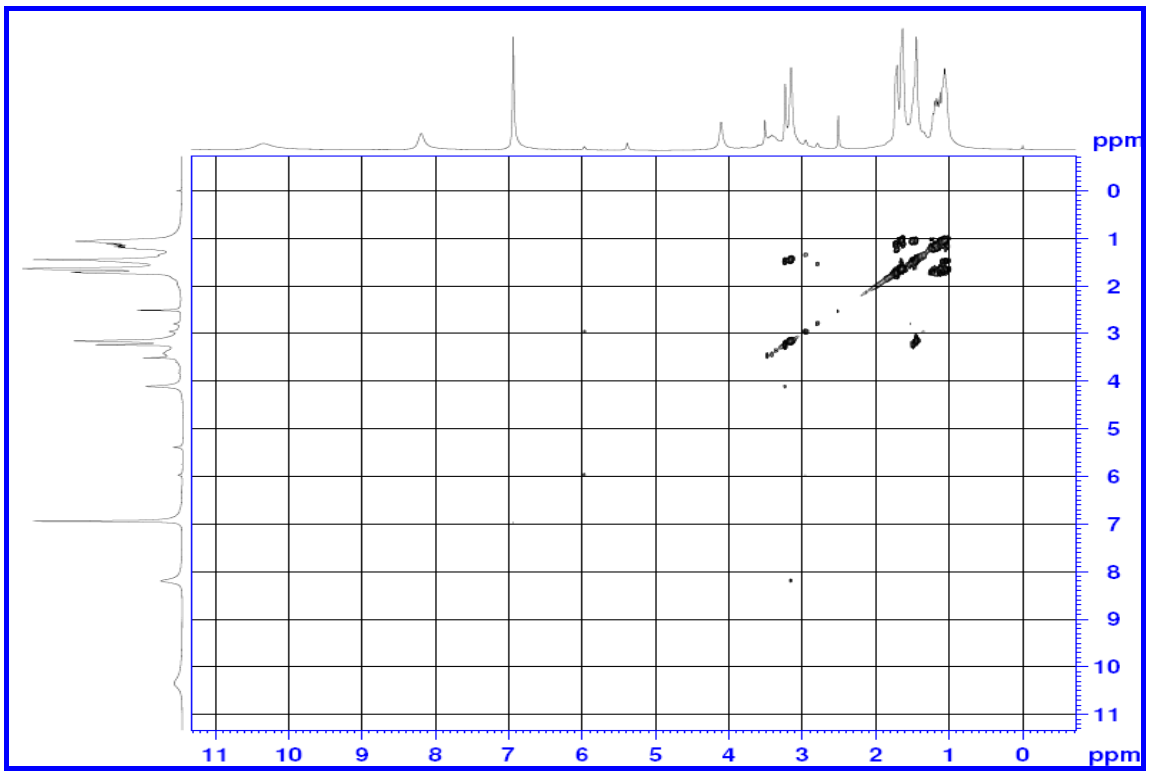
^{13}C NMR (125MHz, DMSO-d_6) of Compound **8c**



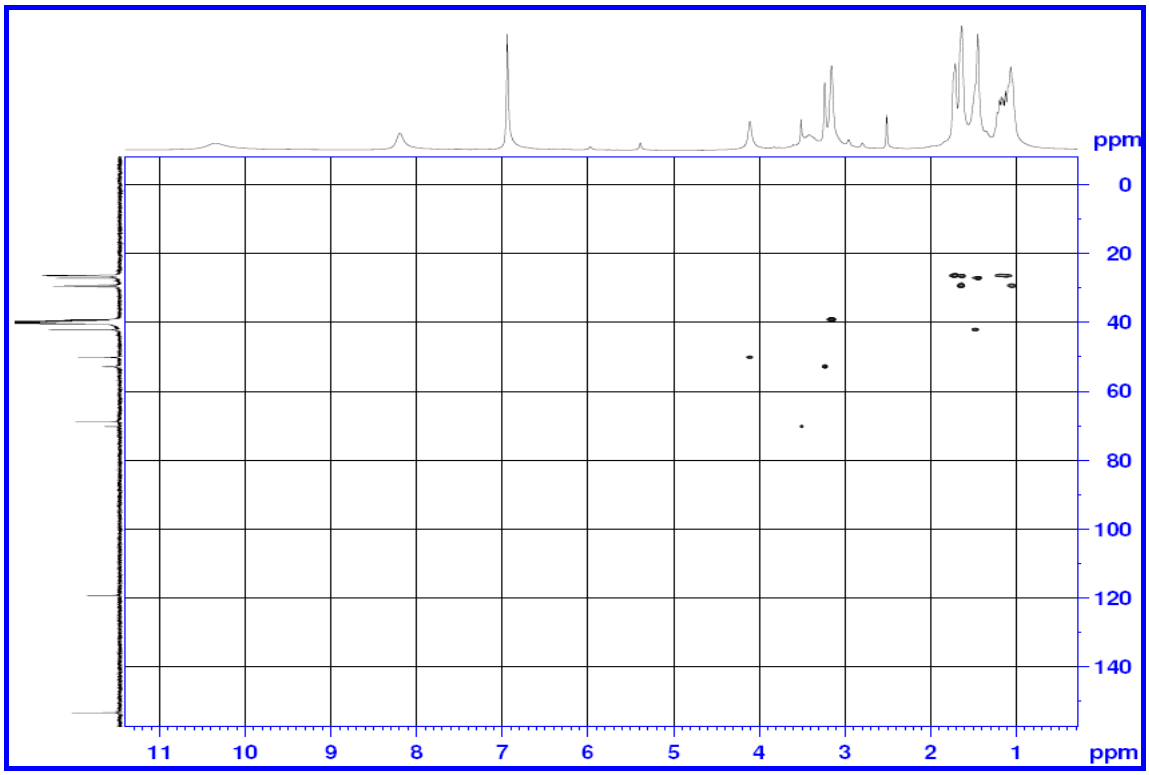
^{1}H NMR (500MHz, DMSO-d_6) of Compound **8d**



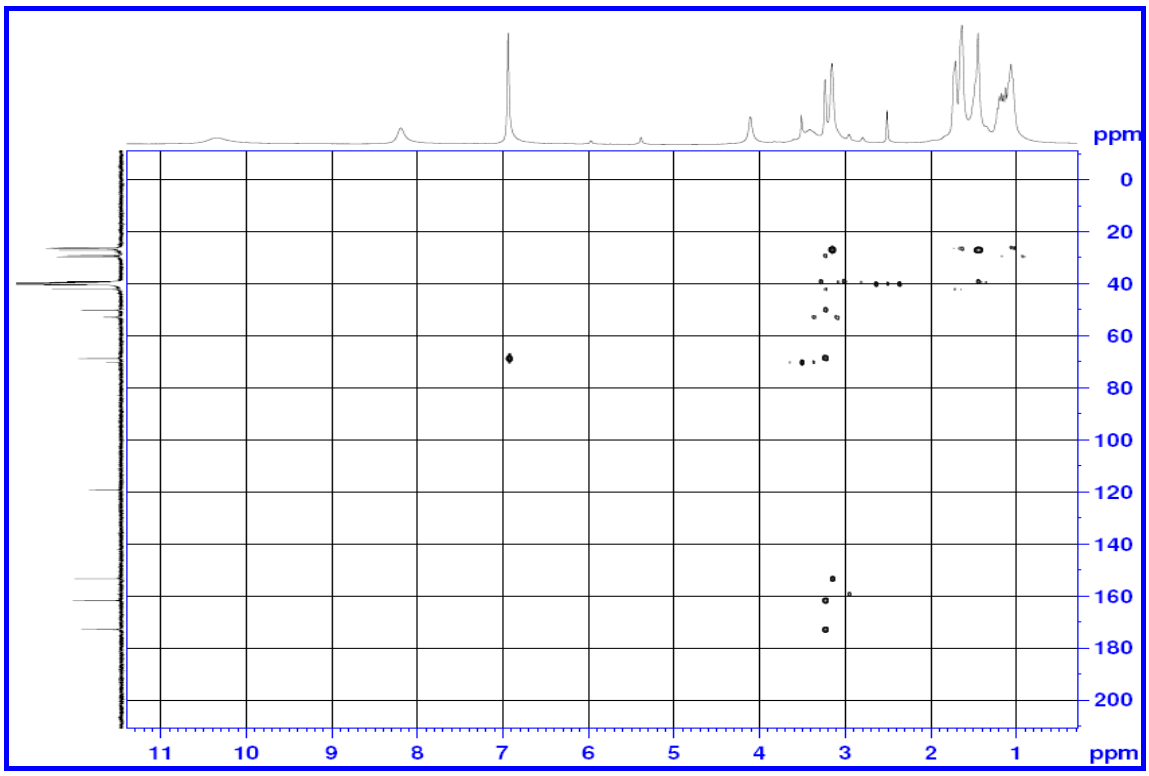
^{13}C NMR (125MHz, DMSO-d_6) of Compound **8d**



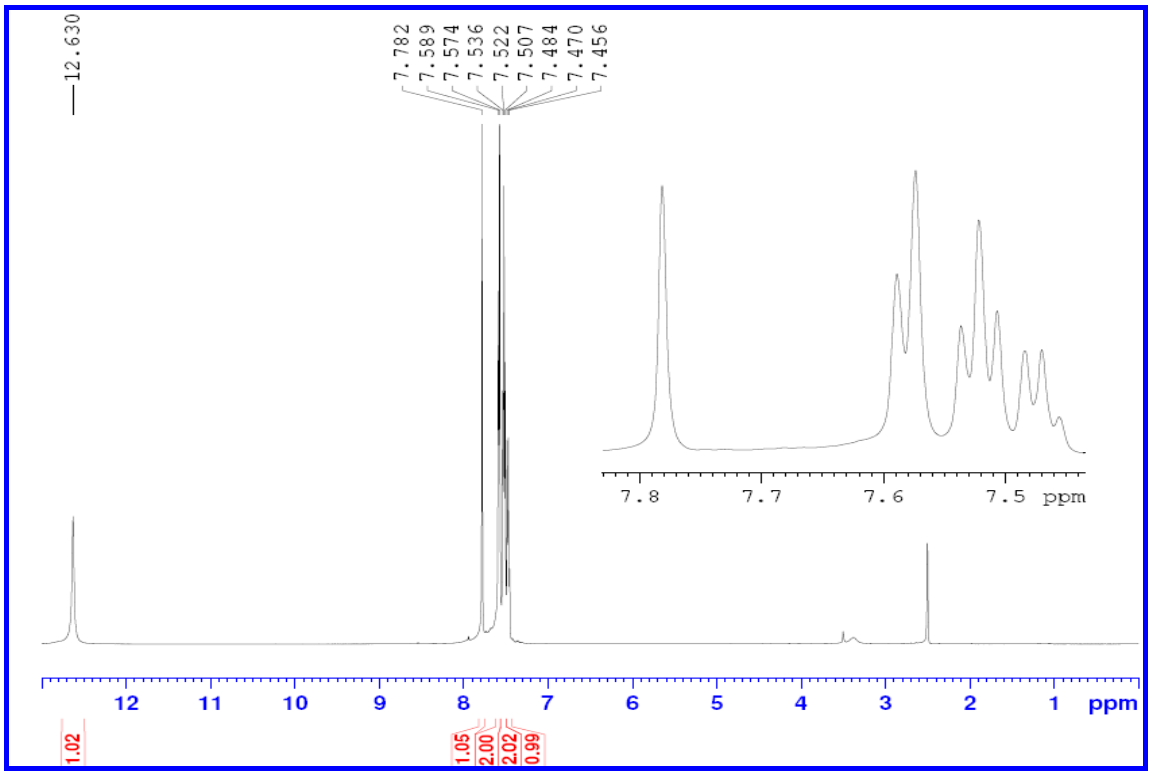
COSY (500MHz, DMSO-d_6) of Compound **8d**



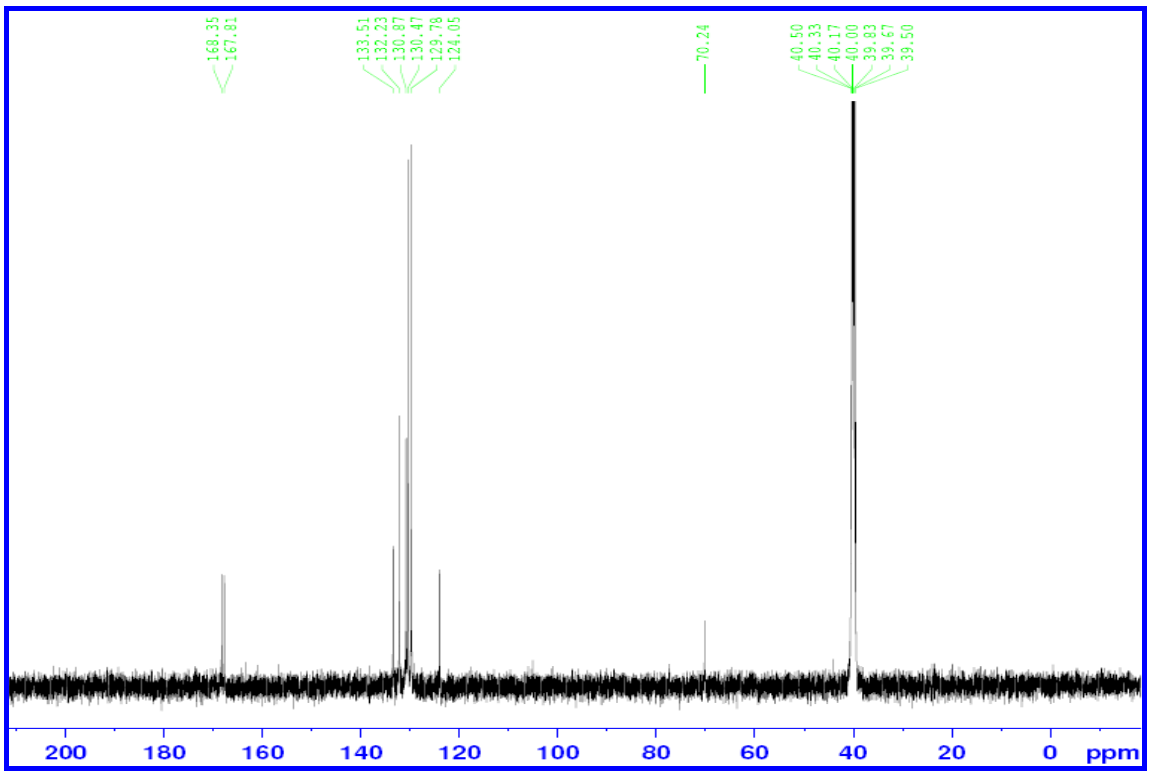
HSQC (500MHz, DMSO-d_6) of Compound **8d**



HMBC (500MHz, DMSO-d_6) of Compound **8d**



^{1}H NMR (500MHz, DMSO-d_6) of Compound **10**



^{13}C NMR (125MHz, DMSO-d_6) of Compound **10**