Supporting Information

Rational design, synthesis, molecular docking and DFT studies of novel melatonin and isatin based azole derivatives.

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1. General Information

All the solvents and reagents (analytical grade) were purchased from commercial suppliers and used for synthesis without further purification. Optimization of reactions was monitored using silica gel precoated thin layer chromatographic (TLC) plates. Melting points were determined on a Buchi instrument (M-560) and were uncorrected. Infra-red spectra were recorded using KBr disks on SHIMADZU IR Affinity 1S spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in deuterated DMSO-d_6 on JEOL, ECX-400P Spectrometer USA at 400 MHz and 100 MHz respectively. Chemical shifts, coupling constants, and absorption frequency values have been expressed in terms of δ (ppm), J (Hz), and v (cm^{-1}), respectively. The abbreviations have been used in the spectral data as singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublet (dd), and multiplet (m). Mass spectrometry measurements were obtained on 6530 Accurate-Mass Q-TOF LC/MS spectrometer.

2. Experimental section

2.1 General procedure for the synthesis of propargylated melatonin 2. The reaction is carried out by using 1 mmol of melatonin and 1 mmol of NaH in DMF at 0 °C, and the reaction mixture was stirred for 30 minutes. Now propargyl bromide was added dropwise to the reaction mixture. The reaction was kept at room temperature for 50 minutes, and TLC was used to observe the progress of the reaction. After completion of the reaction, the reaction mixture was poured into 30 mL of ice-cold water and then extracted with ethyl acetate (3×30 mL). The extract was dried over anhydrous Na_2SO_4 and concentrated to afford product 2 in excellent yield.

2.2 General method for the synthesis of compounds 7a-d and 8a-d.

To a stirred solution of N-propargylated melatonin 2 (1 mmol) and isatin azides 5a-d or 6a-d (1 mmol) in t-BuOH-H2O (8:2), sodium ascorbate (0.4 mmol) and CuSO4.5H2O (0.2 mmol) was added as catalysts and heat for 12-18 mins at 45 °C. the progress of reaction was observed by TLC. The resulting reaction mixture was poured onto 50 mL ice cold water and then extracted with ethylacetoacetate (3 × 30 mL). The combined extracts were washed with brine solution, dried over anhydrous Na2SO4, filtered and then concentrated at reduced pressure under vacuum resulting in the isolation of the crude product. The crude product was further purified via silica gel chromatography (100-200 mesh size) to give desired product 7a-d, and 8a-d, in excellent yields.

Characterization data of 7a-d and 8a-d

N-(2-(1-((1-(2-(2,3-dioxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-5-yl) methyl)-5-methoxy-1H- indol-3-yl) ethyl) acetamide (7a)

Red solid; Yield 87 %; mp:141-143^{o}C IR (KBr, cm^{-1}) 1732, 1609, 1228, 788, 465 ^{1}H NMR 400 MHz, DMSO) δ 8.04 (s, 1H), 7.95 (t, *J* = 4.5 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 7.13 – 6.96 (m, 3H), 6.76 (dd, *J* = 16.3, 9.2 Hz, 2H), 5.26 (s, 2H), 4.59 (t, *J* = 5.3 Hz, 2H), 4.08 (t, *J* = 5.2 Hz, 2H), 3.76 (s, 3H), 3.27 (dd, *J* = 13.3, 6.6 Hz, 2H), 2.74 (t, *J* = 7.3 Hz, 2H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 183.38 (s), 169.52 (s), 158.55 (s), 153.77 (s), 150.64 (s), 144.33 (s), 138.51 (s), 131.62 (s), 128.63 (s), 126.86 (s), 124.93 (s), 124.45 (s), 123.71 (s), 117.74 (s), 111.95 (s), 111.61 (s), 111.14 (s), 110.58 (s), 101.05 (s), 55.87 (s), 47.38 (s), 41.20 (s), 25.65 (s), 23.18 (s). HRMS data: calcd. mass (M+H)$^{+}$, 486.2016, found, 487.2084.

N-(2-(1-((1-(2-(5-bromo-2,3-dioxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-5-yl)methyl)-5-methoxy-1H-indol-3-yl)ethyl)acetamide (7b)

orange solid; Yield 86 %; mp:133-135^{o}C IR (KBr, cm^{-1}) 1734, 1614, 1228, 783, 465 ^{1}H NMR (400 MHz,) δ 8.04 (s, 1H), 7.96 (t, *J* = 5.6 Hz, 1H), 7.68 (d, *J* = 2.1 Hz, 1H), 7.49 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 7.09 (s, 1H), 7.03 (t, *J* = 2.9 Hz, 1H), 6.74 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.69 (d, *J* = 8.5 Hz, 1H), 5.28 (s, 2H), 4.57 (t, *J* = 5.7 Hz, 2H), 4.07 (t, *J* = 5.7 Hz, 2H), 3.76 (s, 3H), 3.27 (dd, *J* = 13.4, 7.4 Hz, 2H), 2.77 – 2.71 (m, 2H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, DMSO-D6) δ 182.20 (s), 169.56 (s), 158.22 (s), 153.78 (s), 149.60 (s), 144.47 (s), 140.16 (s), 131.61 (s), 128.67 (s), 127.26 (s), 126.97 (s), 124.50 (s), 119.53 (s), 115.55 (s), 112.77 (s), 112.00 (s), 111.67 (s), 111.18 (s), 101.09 (s), 55.89 (s), 47.45 (s), 41.28 (s), 25.73 (s), 23.24 (s). HRMS data: calcd. mass (M+H)$^{+}$, 564.1115, found, 565.1185.

N-(2-(1-((1-(2-(5-chloro-2,3-dioxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-5-yl)methyl)-5-methoxy-1H-indol-3-yl)ethyl)acetamide(7c)

Brick red Solid; Yield 88 %; mp:138-140^{o}C IR (KBr, cm^{-1}) 1741, 1613, 1229, 787, 472 ^{1}H NMR (400 MHz, DMSO) δ 8.04 (s, 1H), 7.95 (t, *J* = 5.6 Hz, 1H), 7.57 (d, *J* = 2.2 Hz, 1H), 7.39 – 7.29 (m, 2H), 7.09 (s, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.74 (dd, *J* = 8.7, 5.6 Hz, 2H), 5.27 (s, 2H), 4.58 (t, *J* = 5.7 Hz, 2H), 4.08 (t, *J* = 5.7 Hz, 2H), 3.76 (s, 3H), 3.28 (dd, *J* = 14.2, 6.5 Hz, 2H), 2.77 – 2.72 (m, 2H), 1.80 (s, 3H) ^{13}C NMR (100 MHz, DMSO) δ 182.29 (s), 169.51 (s), 158.33 (s), 153.74 (s), 149.17 (s), 144.40 (s), 137.30 (s), 131.56 (s), 128.62 (s), 127.95 (s), 126.90 (s), 124.45 (s), 119.09 (s), 112.28 (s), 111.95 (s), 111.59 (s), 111.12 (s), 101.06 (s), 55.84 (s), 47.40 (s), 41.21 (s), 25.65 (s), 23.17 (s). HRMS data: calcd. mass (M+H)$^{+}$, 520.1638, found, 521.1708.

N-(2-(1-((1-(2-(5-fluoro-2,3-dioxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-5-yl)methyl)-5-methoxy-1H-indol-3-yl)ethyl)acetamide (7d)

crimson red solid; Yield 85 %; mp:131-133^{o}C IR (KBr, cm^{-1}) 1735, 1616, 1225, 786, 467 ^{1}H NMR (400 MHz, DMSO) δ 8.04 (s, 1H), 7.96 (t, *J* = 5.6 Hz, 1H), 7.42 (dd, *J* = 7.0, 2.7 Hz, 1H), 7.32 (d, *J* = 8.9 Hz, 1H), 7.20 (dd, *J* = 10.3, 7.7 Hz, 1H), 7.08 (s, 1H), 7.03 (d, *J* = 2.3 Hz, 1H), 6.78 – 6.69 (m, 2H), 5.27 (s, 2H), 4.58 (t, *J* = 5.6 Hz, 2H), 4.08 (t, *J* = 5.6 Hz, 2H), 3.76 (s, 3H), 3.27 (dd, *J* = 13.8, 6.8 Hz, 2H), 2.74 (t, *J* = 7.5 Hz, 2H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 182.78 (s), 169.52 (s), 160.02 (s), 158.59 (s), 157.62 (s), 153.74 (s), 150.19 (s), 146.85 (s), 144.37 (s), 131.55 (s), 128.61 (s), 126.88 (s), 124.49 (s), 124.26 (s), 118.59 (d, *J* = 7.2 Hz), 116.10 (s), 111.81 (dd, *J* = 30.2, 13.0 Hz), 111.12 (s), 101.02 (s), 55.82 (s), 47.37 (s), 41.19 (s), 25.63 (s), 23.17 (s). HRMS data: calcd. mass (M+H)$^{+}$, 504.192, found, 505.2021.

(Z)-N-(2-(1-((1-(2-(3-(hydroxyimino)-2-oxoindolin-1-yl) ethyl)-1H-1,2,3-triazol-5-yl) methyl)-5-methoxy-1H-indol-3-yl) ethyl) acetamide (8a)

Yellow Solid; Yield 85 %; mp:182-184^{o}C IR (KBr, cm^{-1}) 3285, 1725, 1224, 780, 485 ^{1}H NMR (400 MHz, DMSO) δ 13.43 (s, 1H), 7.98 (s, 1H), 7.94 (dd, *J* = 10.2, 6.3 Hz, 2H), 7.31 (d, *J* = 8.9 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.07 – 6.99 (m, 3H), 6.79 – 6.70 (m, 2H), 5.26 (s, 2H), 4.59 (t, *J* = 5.6 Hz, 2H), 4.11 (t, *J* = 5.6 Hz, 2H), 3.76 (s, 3H), 3.28 (dd, *J* = 14.1, 6.6 Hz, 2H), 2.75 (t, *J* = 7.5 Hz, 2H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 169.56 (s), 163.52 (s), 153.78 (s), 144.23 (s), 143.71 (s), 143.02 (s), 132.25 (s), 131.67 (s), 128.65 (s), 127.31 (s), 126.88 (s), 124.24 (s), 123.07 (s), 115.60 (s), 111.94 (s), 111.59 (s), 111.14 (s), 109.04 (s), 101.10 (s), 55.90 (s), 47.55 (s), 41.21 (s), 25.63 (s), 23.17 (s). HRMS data: calcd. mass $(M+H)^{+}$,501.2134, found, 502.2208.

(Z)-N-(2-(1-((1-(2-(5-bromo-3-(hydroxyimino)-2-oxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-5-yl)methyl)-5-methoxy-1H-indol-3-yl)ethyl)acetamide (8b)

Yellow solid; Yield 84 %; mp:181-183^{o}C IR (KBr, cm^{-1}) 3285, 1725, 1228, 783, 485 ^{1}H NMR (400 MHz, DMSO) δ 13.79 (s, 1H), 8.03 (d, *J* = 2.0 Hz, 1H), 8.00 (s, 1H), 7.96 (t, *J* = 5.7 Hz, 1H), 7.31 (d, *J* = 8.9 Hz, 1H), 7.25 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.10 (s, 1H), 7.03 (d, *J* = 2.3 Hz, 1H), 6.75 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.65 (d, *J* = 8.5 Hz, 1H), 5.27 (s, 2H), 4.58 (t, *J* = 5.4 Hz, 2H), 4.10 (t, *J* = 5.4 Hz, 2H), 3.76 (s, 3H), 3.30 – 3.25 (m, 2H), 2.75 (t, *J* = 7.5 Hz, 2H), 1.80 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 169.55 (s), 163.05 (s), 153.74 (s), 144.33 (s), 142.81 (s), 142.15 (s), 134.38 (s), 131.58 (s), 129.22 (s), 128.64 (s), 126.94 (s), 124.23 (s), 117.10 (s), 114.52 (s), 111.92 (s), 111.59 (s), 111.10 (d, *J* = 5.6 Hz), 101.07 (s), 55.85 (s), 47.53 (s), 41.20 (s), 25.65 (s), 23.18 (s) HRMS data: calcd. mass $(M+H)^{+}$,579.1254, found, 580.1328.

(Z)-N-(2-(1-((1-(2-(5-chloro-3-(hydroxyimino)-2-oxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-5-yl)methyl)-5-methoxy-1H-indol-3-yl)ethyl)acetamide(8c)

Yellow Solid; Yield 84 %; mp:185-187^{o}C IR (KBr, cm^{-1}) 3282, 1726, 1222, 773, 486 ^{1}H NMR (400 MHz, DMSO) δ 13.77 (s, 1H), 8.00 (s, 1H), 7.93 (t, J = 5.6 Hz, 1H), 7.90 (d, J = 2.2 Hz, 1H), 7.31 (d, J = 8.9 Hz, 1H), 7.14 (dd, J = 8.5, 2.2 Hz, 1H), 7.09 (s, 1H), 7.04 (d, J = 2.3 Hz, 1H), 6.75 (dd, J = 8.8, 2.4 Hz, 1H), 6.70 (d, J = 8.5 Hz, 1H), 5.27 (s, 2H), 4.58 (t, J = 5.5 Hz, 2H), 4.11 (t, J = 5.5 Hz, 2H), 3.76 (s, 3H), 3.30 – 3.25 (m, 2H), 2.75 (t, J = 7.5 Hz, 2H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 169.57 (s), 163.16 (s), 153.77 (s), 144.33 (s), 142.94 (s), 141.79 (s), 131.61 (d, J = 2.5 Hz), 128.66 (s), 126.90 (d, J = 6.5 Hz), 126.56 (s), 124.22 (s), 116.67 (s), 111.96 (s), 111.59 (s), 111.11 (s), 110.58 (s), 101.14 (s), 55.88 (s), 47.53 (s), 41.21 (s), 25.64 (s), 23.17 (s).HRMS data: calcd. mass (M+H)$^{+}$, 535.1735, found, 536.1768.

(Z)-N-(2-(1-((1-(2-(5-fluoro-3-(hydroxyimino)-2-oxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-5-yl)methyl)-5-methoxy-1H-indol-3-yl)ethyl)acetamide(8d)

Yellow Solid; Yield 84 %; mp:180-182^{o}C IR (KBr, cm^{-1}) 3282, 1726, 1225, 781, 486 ^{1}H NMR (400 MHz, DMSO) δ 13.74 (s, 1H), 7.99 (s, 1H), 7.96 (t, J = 5.7 Hz, 1H), 7.70 (d, J = 8.2 Hz, 1H), 7.31 (d, J = 8.9 Hz, 1H), 7.09 (s, 1H), 7.03 (s, 1H), 6.98 (t, J = 9.1 Hz, 1H), 6.76 – 6.69 (m, 2H), 5.26 (s, 2H), 4.58 (t, J = 5.5 Hz, 2H), 4.11 (t, J = 5.5 Hz, 2H), 3.76 (s, 3H), 3.28 (t, J = 10.4 Hz, 2H), 2.74 (t, J = 7.4 Hz, 2H), 1.80 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 169.56 (s), 163.36 (s), 159.48 (s), 157.11 (s), 153.75 (s), 144.29 (s), 143.40 (s), 139.32 (s), 131.59 (s), 128.62 (s), 126.90 (s), 124.26 (s), 118.49 (s), 118.26 (s), 116.02 (d, J = 9.5 Hz), 114.38 (s), 114.12 (s), 111.91 (s), 111.56 (s), 111.13 (s), 110.08 (d, J = 8.2 Hz), 101.04 (s), 55.84 (s), 47.50 (s), 41.18 (s), 25.62 (s), 23.17 (s). HRMS data: calcd. mass (M+H)$^{+}$,519.2068, found, 520.2141.

NMR-Spectra

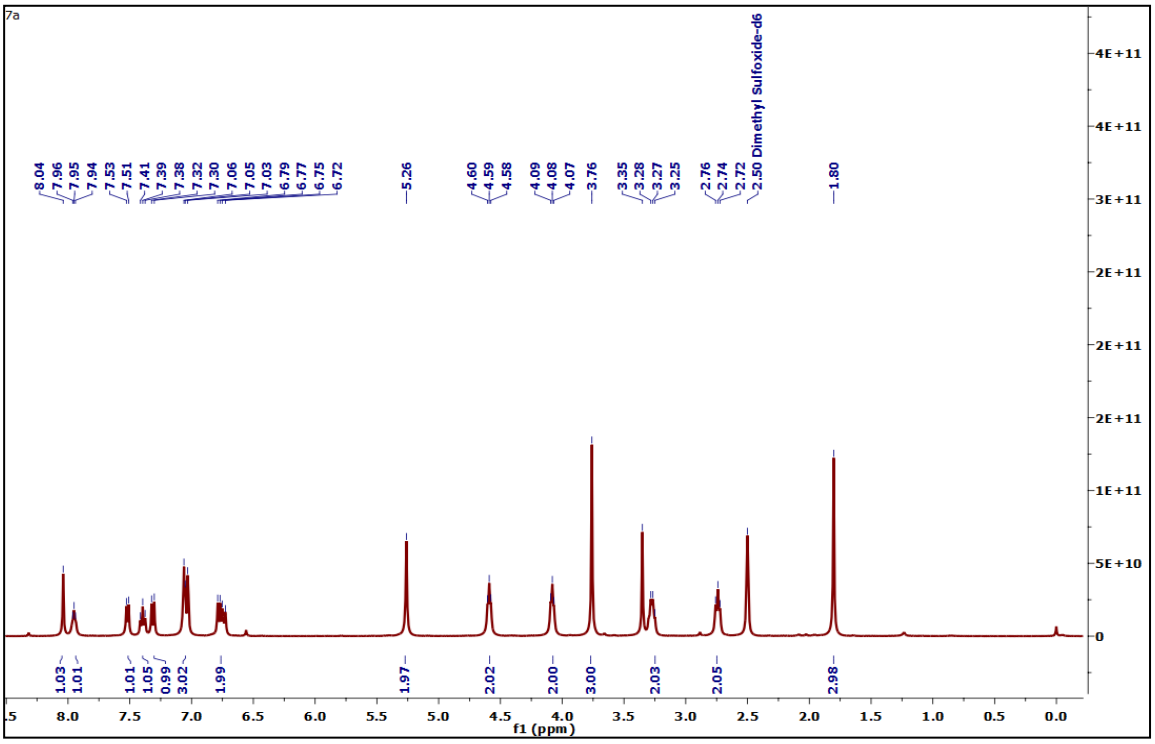

Figure 1. ^{1}H NMR spectrum of compound 7a (400 MHz, DMSO-d6).

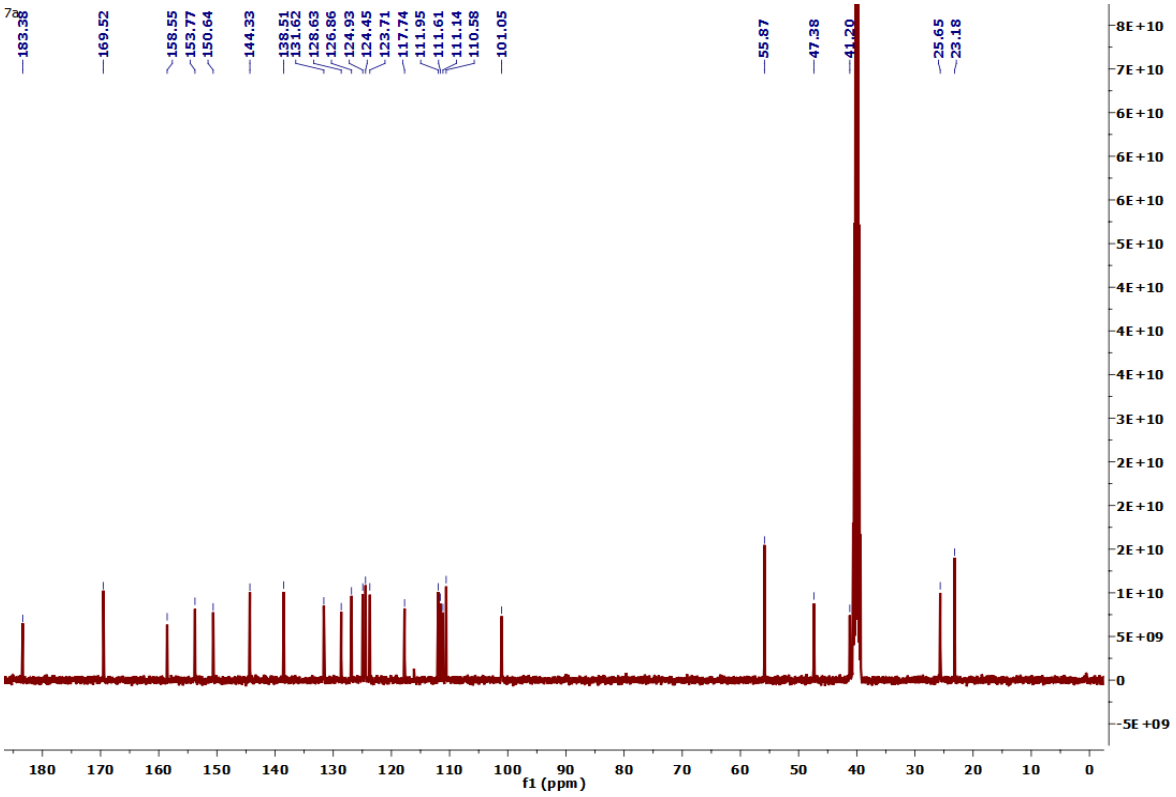

Figure 2.^{13}C NMR spectrum of compound 7a (100 MHz, DMSO-d6)

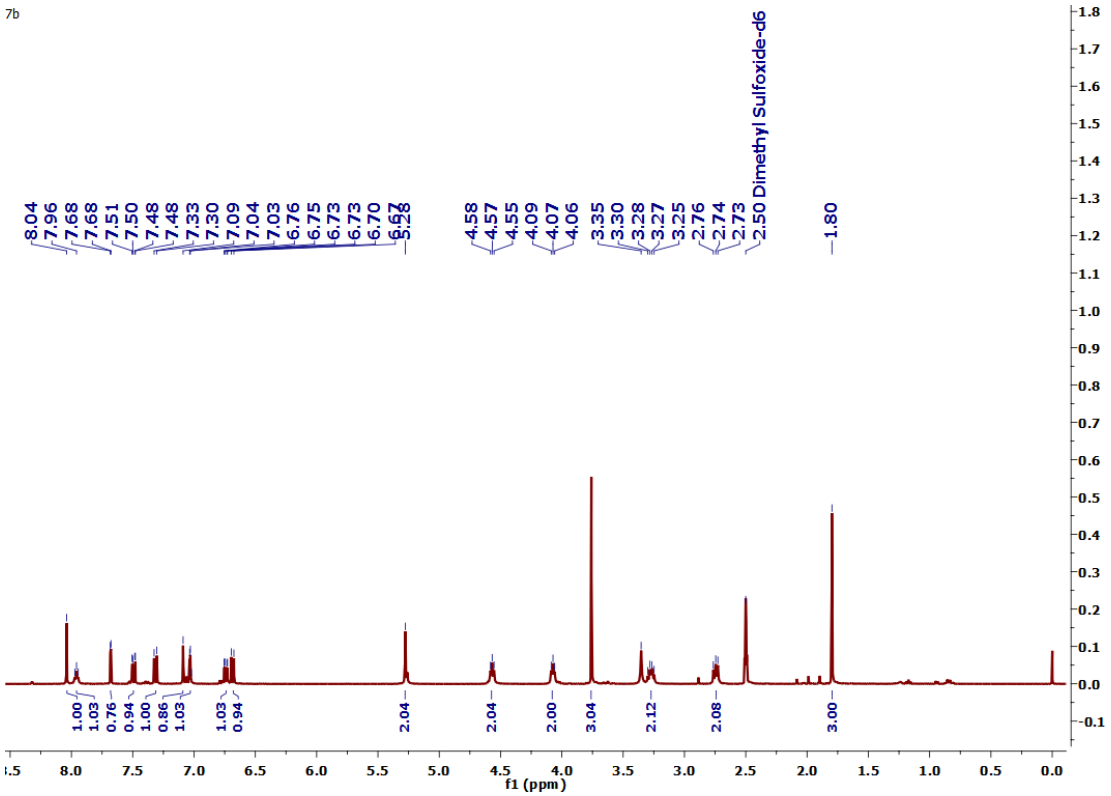

Figure 3. ^{1}H NMR spectrum of compound 7b (400 MHz, DMSO-d6).

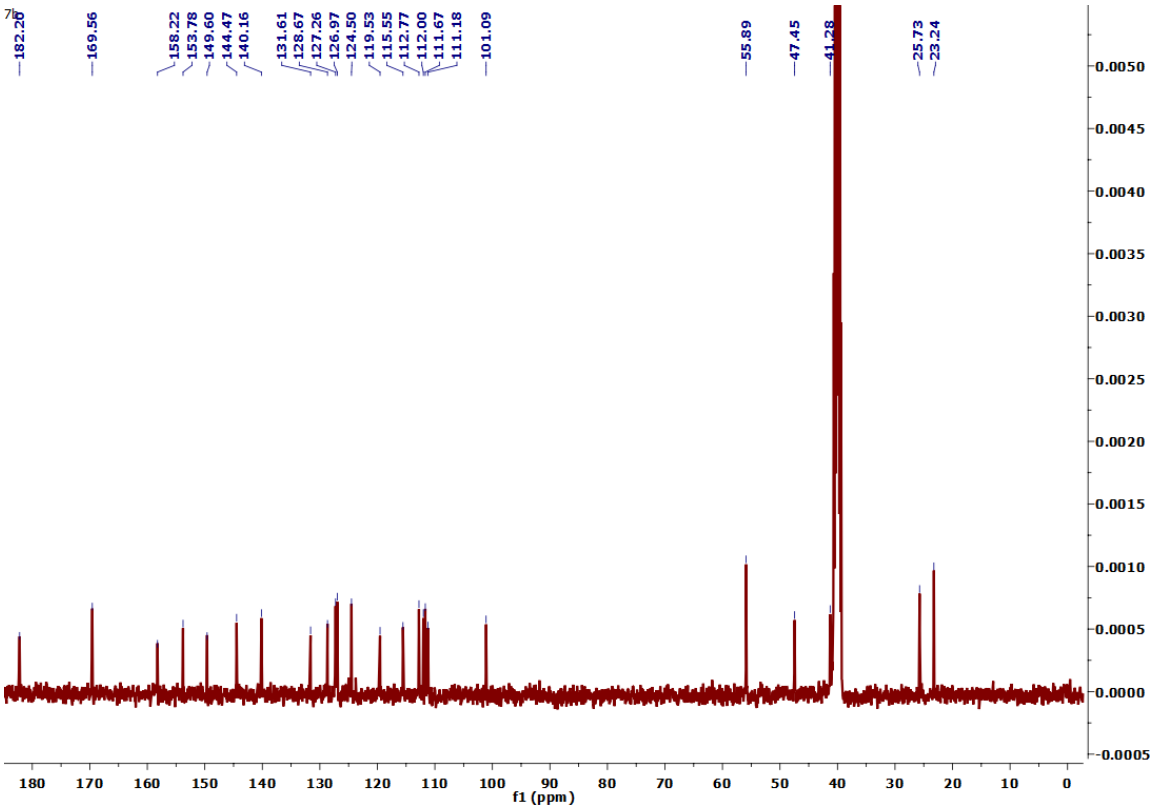

Figure 4.^{13}C NMR spectrum of compound 7b (100 MHz, DMSO-d6)

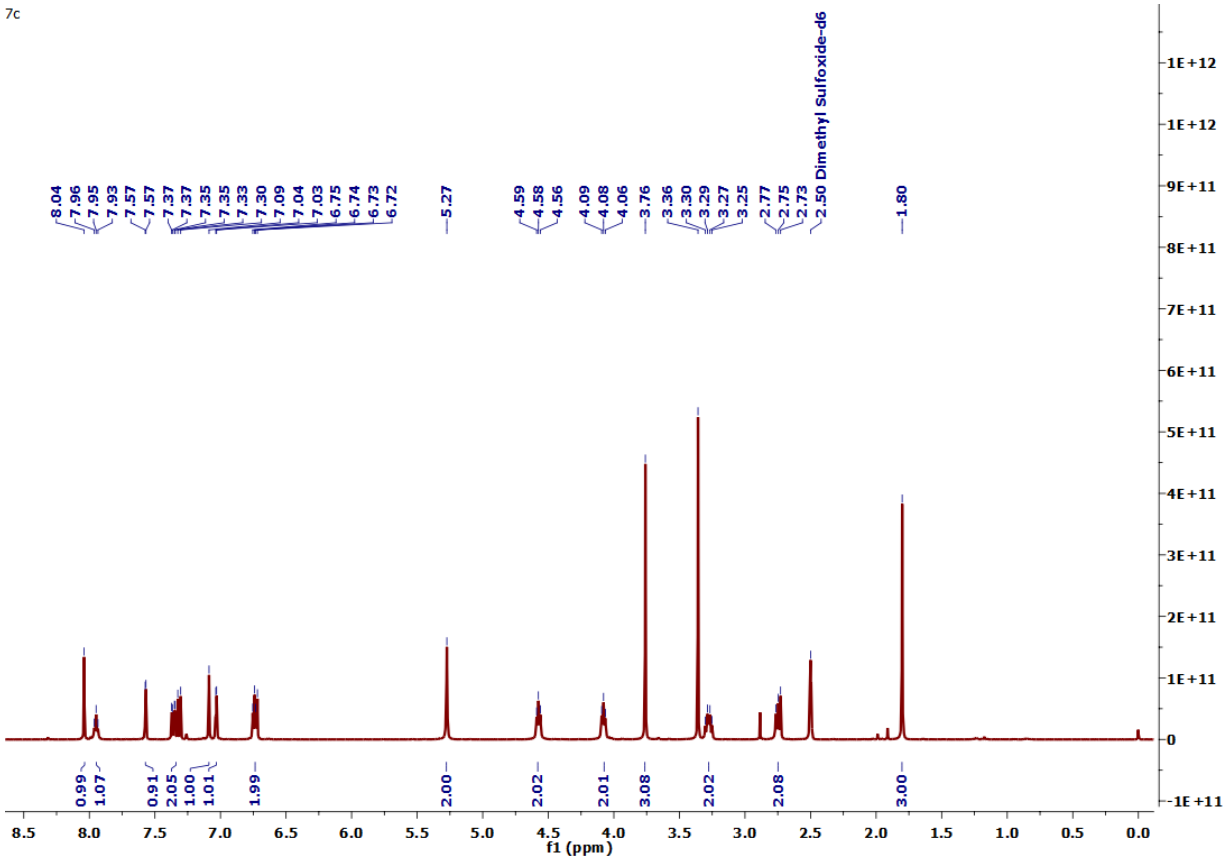

Figure 5. ^{1}H NMR spectrum of compound 7c (400 MHz, DMSO-d6).

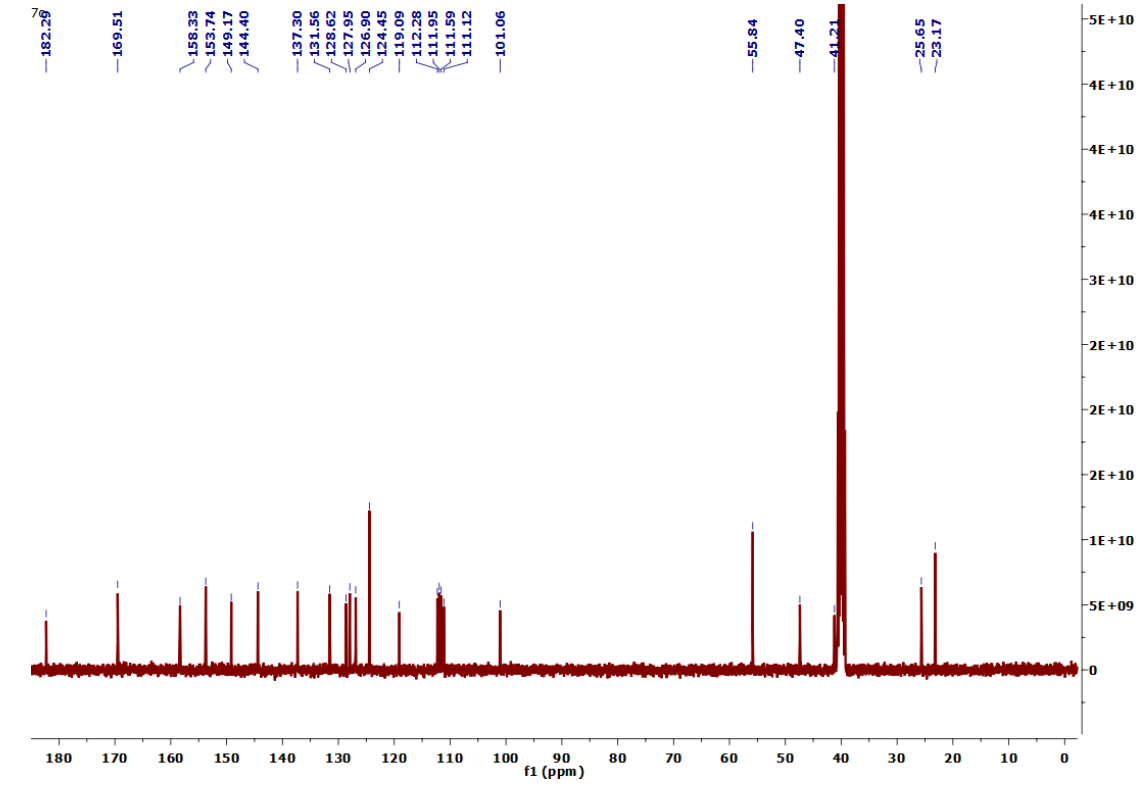

Figure 6.^{13}C NMR spectrum of compound 7c (100 MHz, DMSO-d6)

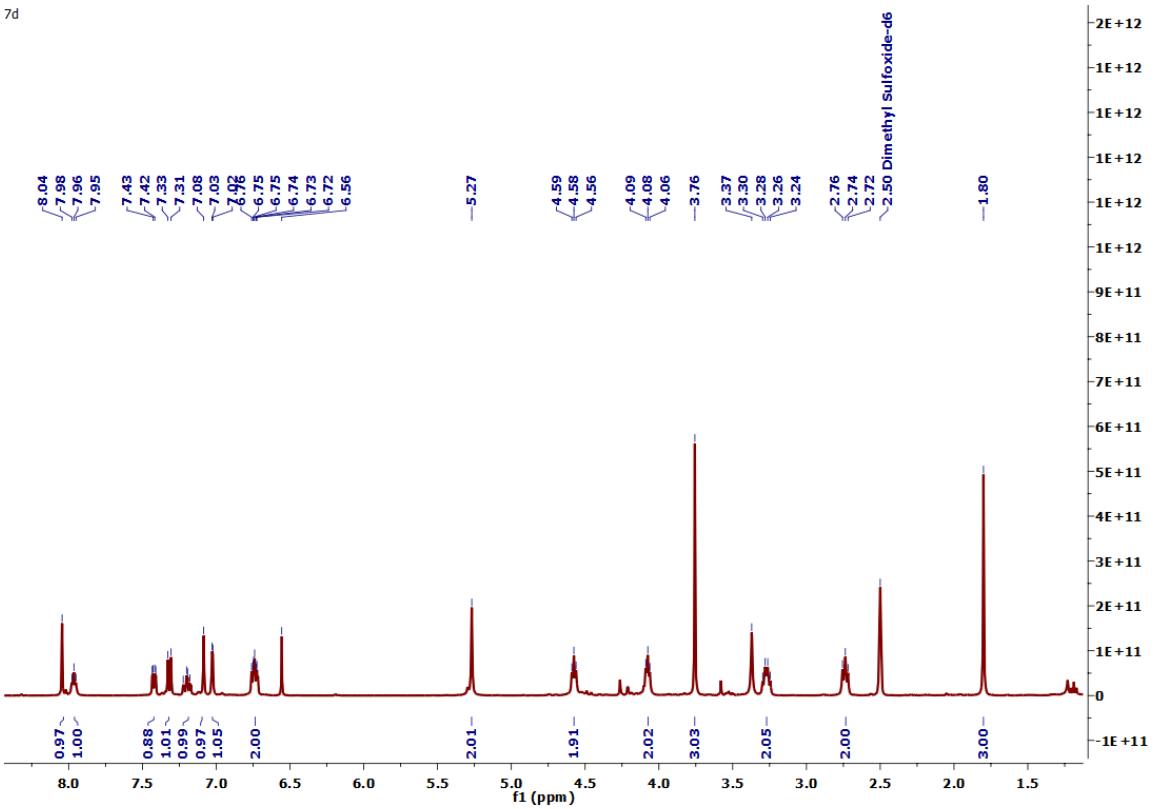

Figure 7. ^{1}H NMR spectrum of compound 7d (400 MHz, DMSO-d6).

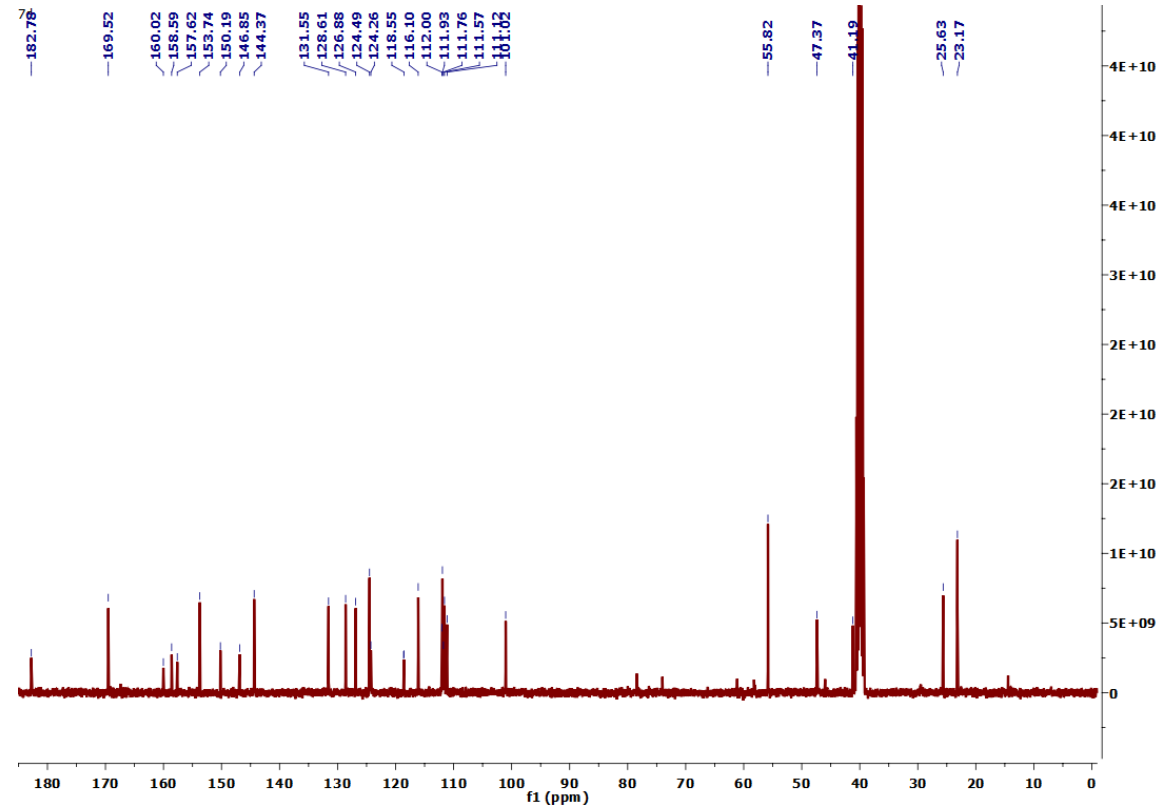

Figure 8.^{13}C NMR spectrum of compound 7d (100 MHz, DMSO-d6)

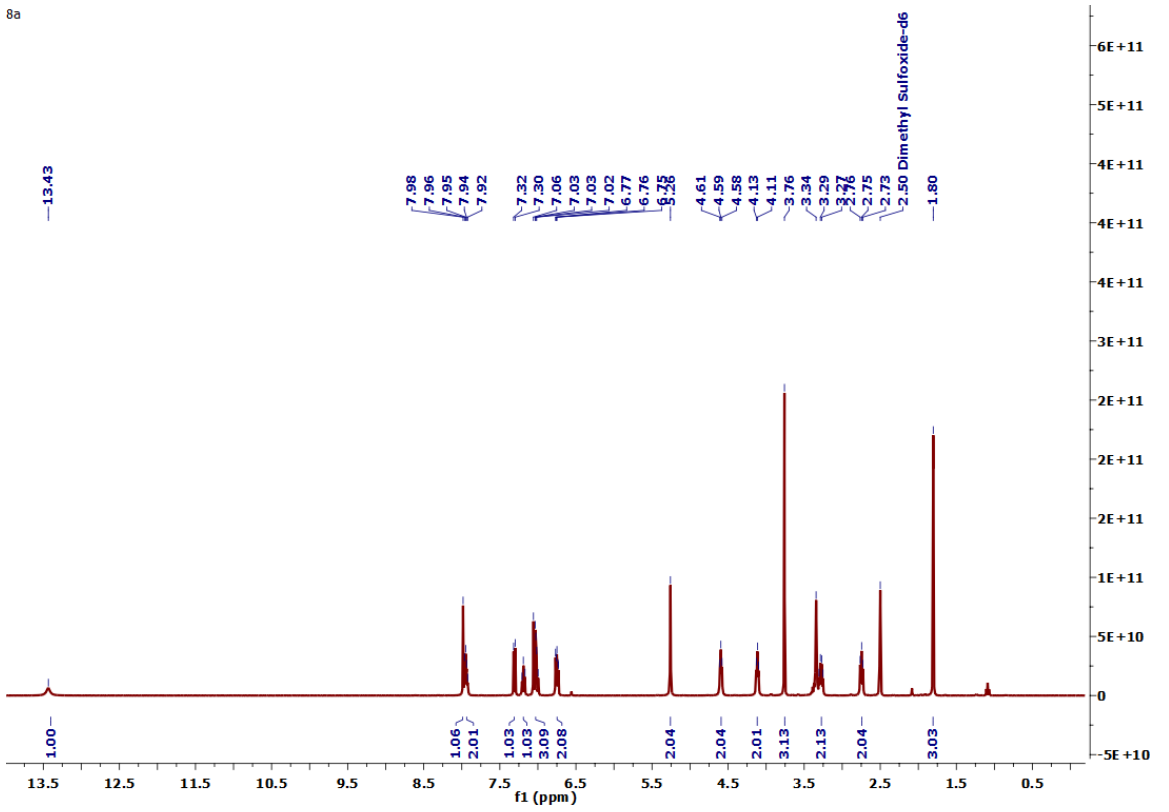

Figure 9. ^{1}H NMR spectrum of compound 8a (400 MHz, DMSO-d6).

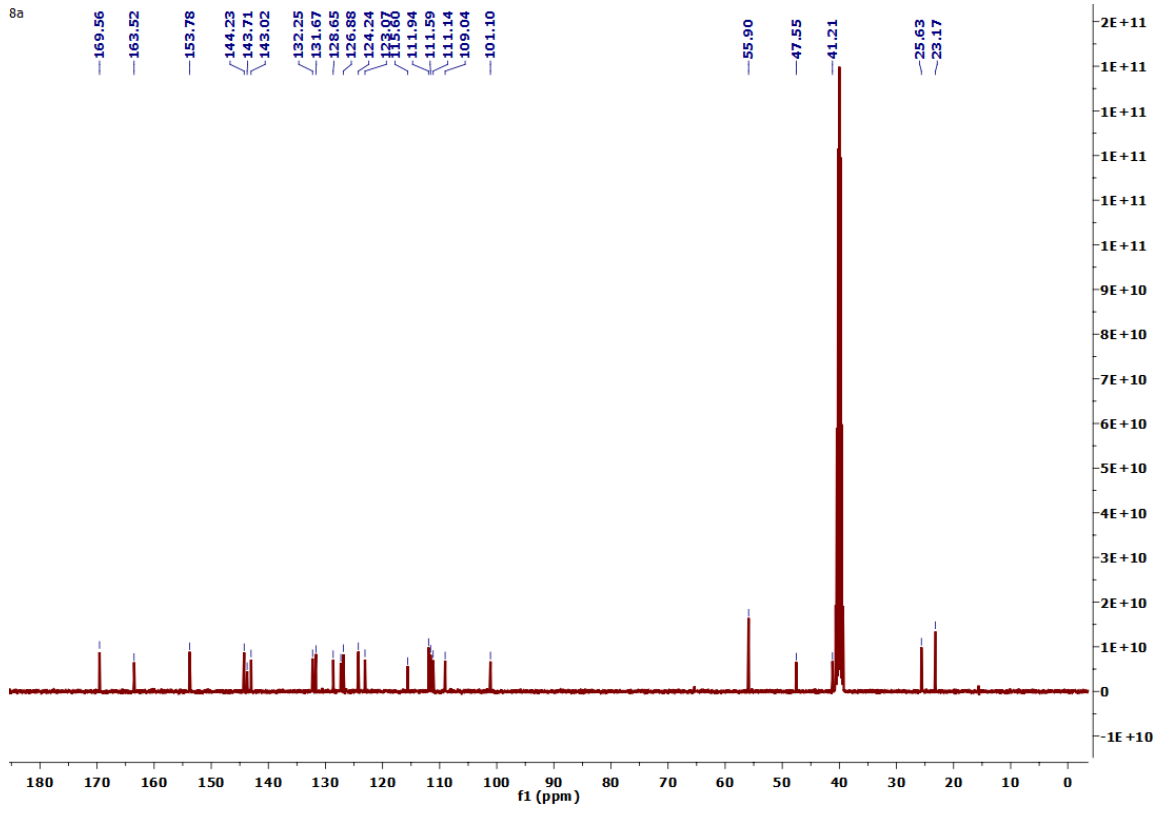

Figure 10.^{13}C NMR spectrum of compound 8a (100 MHz, DMSO-d6)

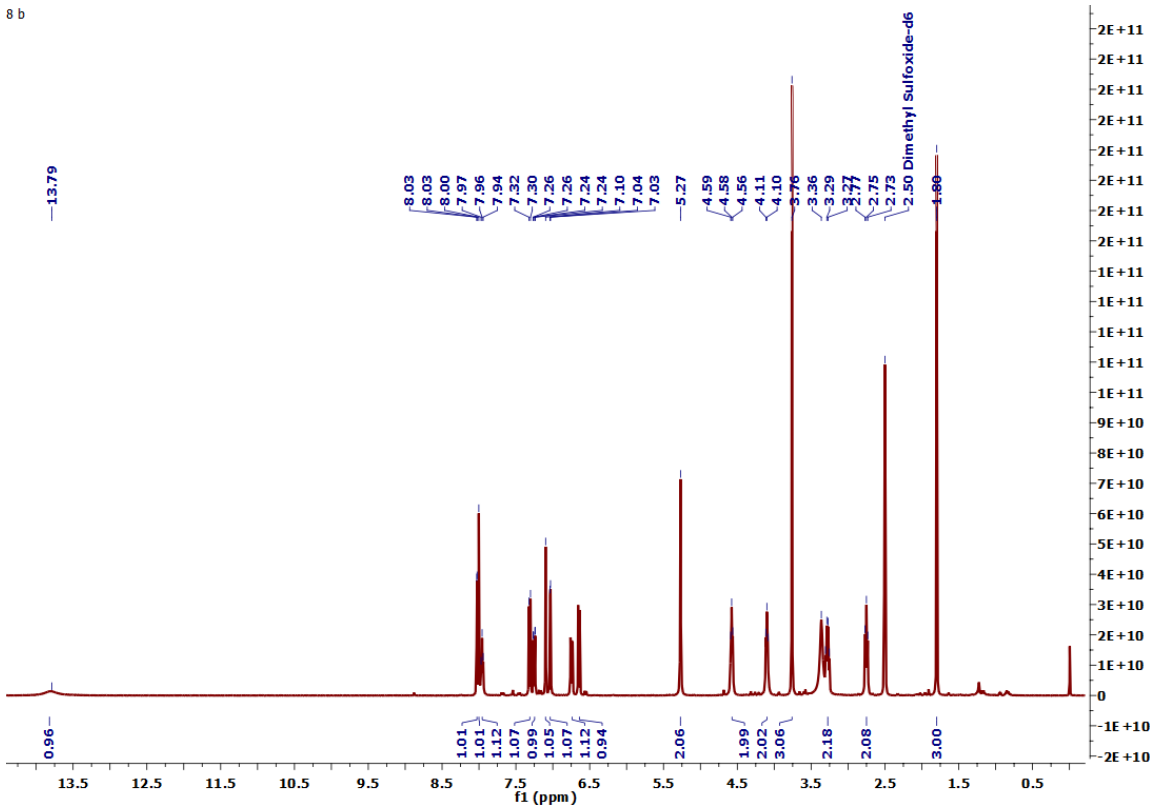

Figure 11. ^{1}H NMR spectrum of compound 8b (400 MHz, DMSO-d6).

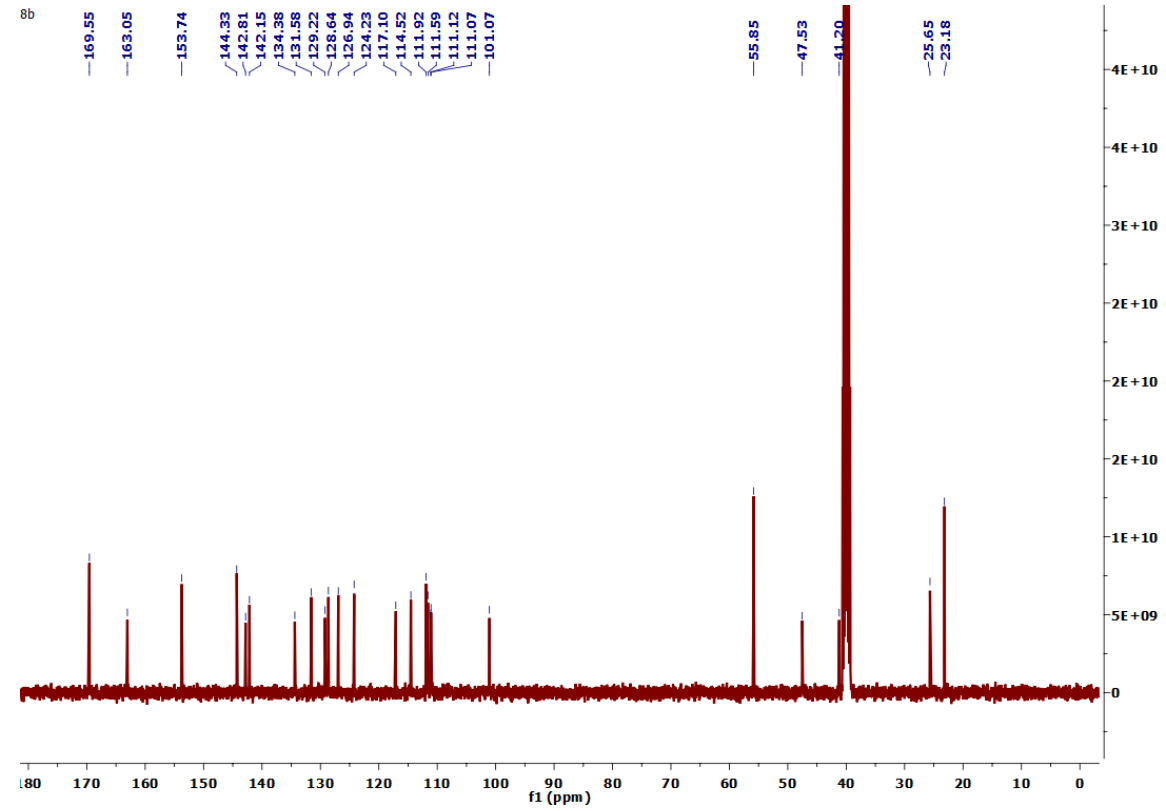

Figure 12.^{13}C NMR spectrum of compound 8b (100 MHz, DMSO-d6)

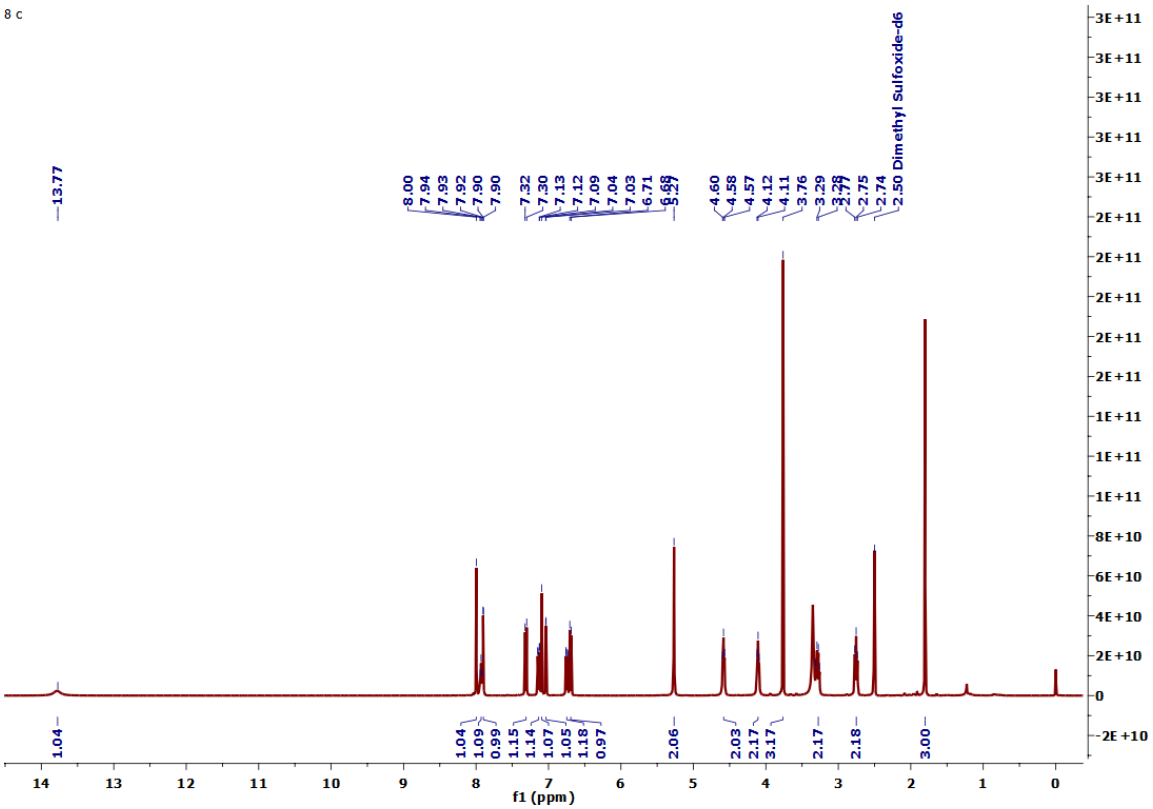

Figure 13. ^{1}H NMR spectrum of compound 8c (400 MHz, DMSO-d6).

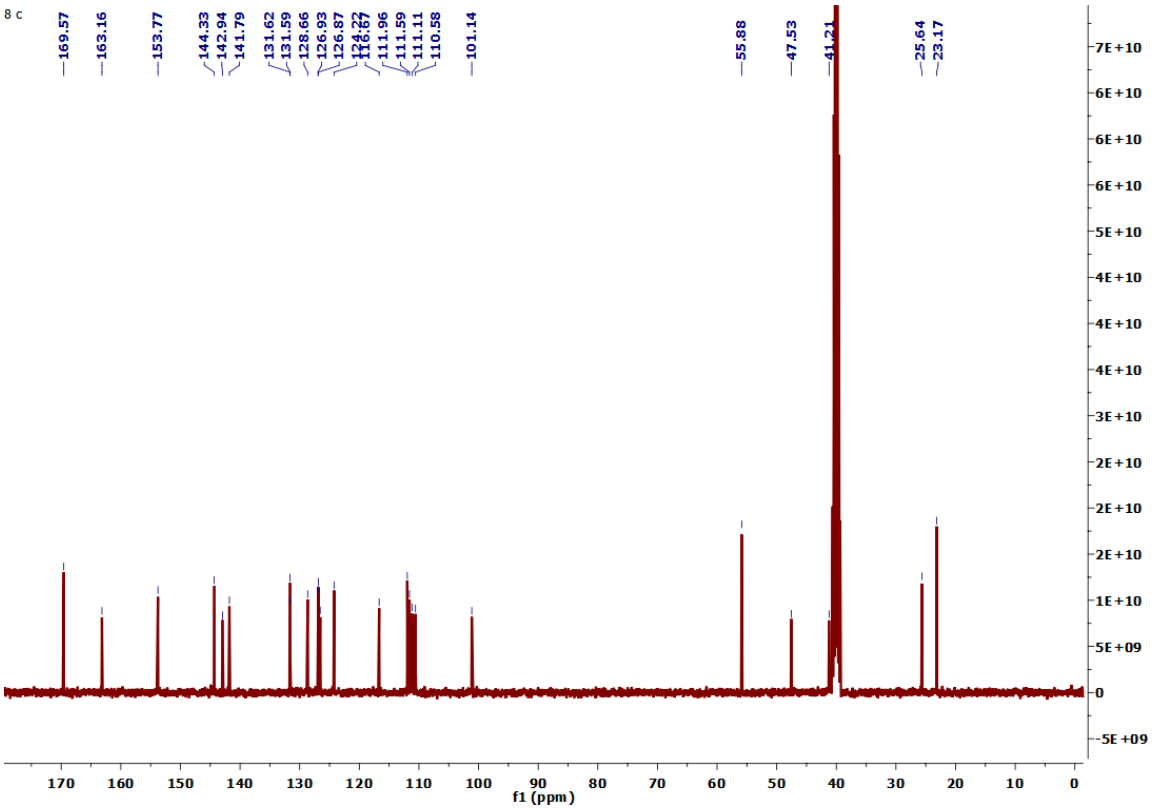

Figure 14.^{13}C NMR spectrum of compound 8c (100 MHz, DMSO-d6)

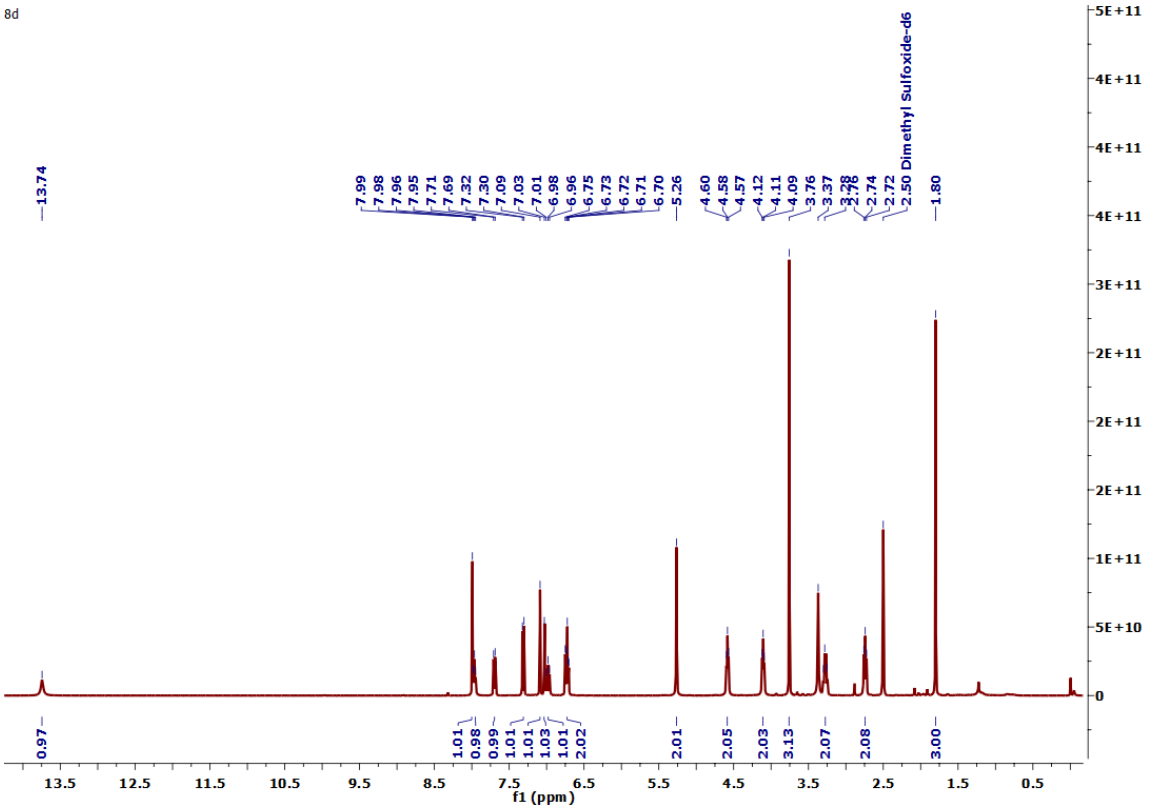

Figure 15. ^{1}H NMR spectrum of compound 8d (400 MHz, DMSO-d6).

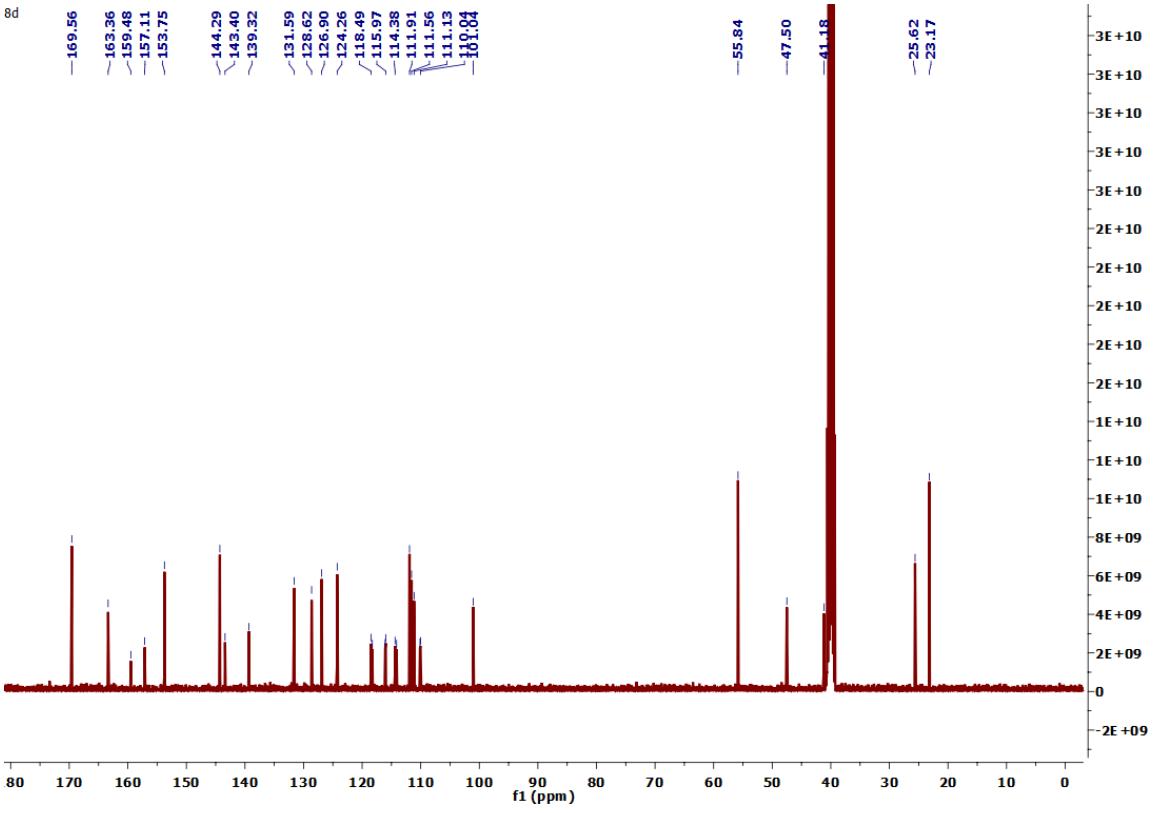

Figure 16.^{13}C NMR spectrum of compound 8d (100 MHz, DMSO-d6)

IR-Spectra

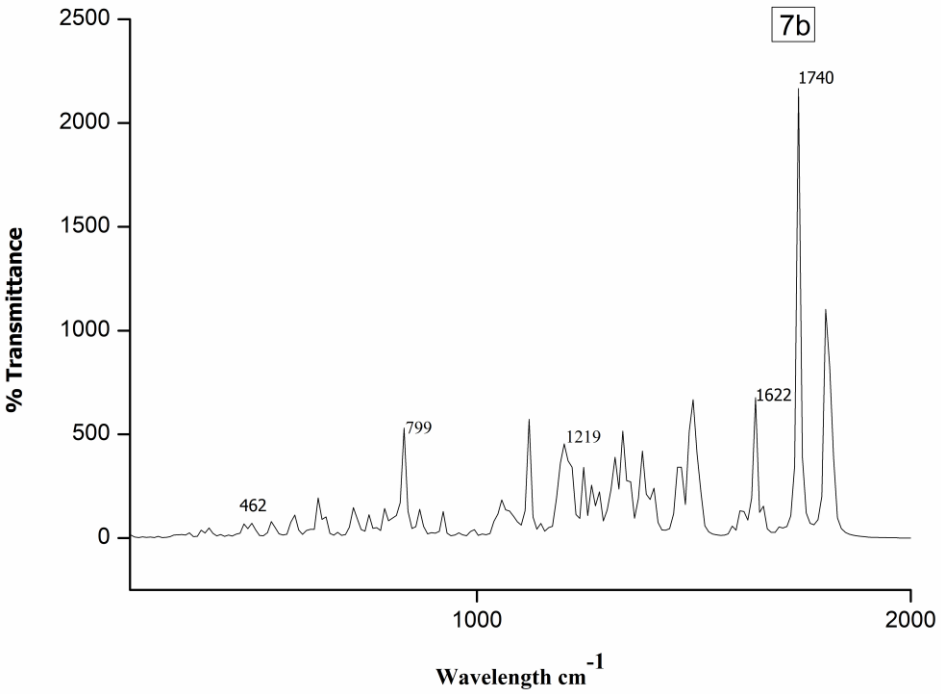

Figure 17. Theoretically studied vibrational frequency spectra of 7b.

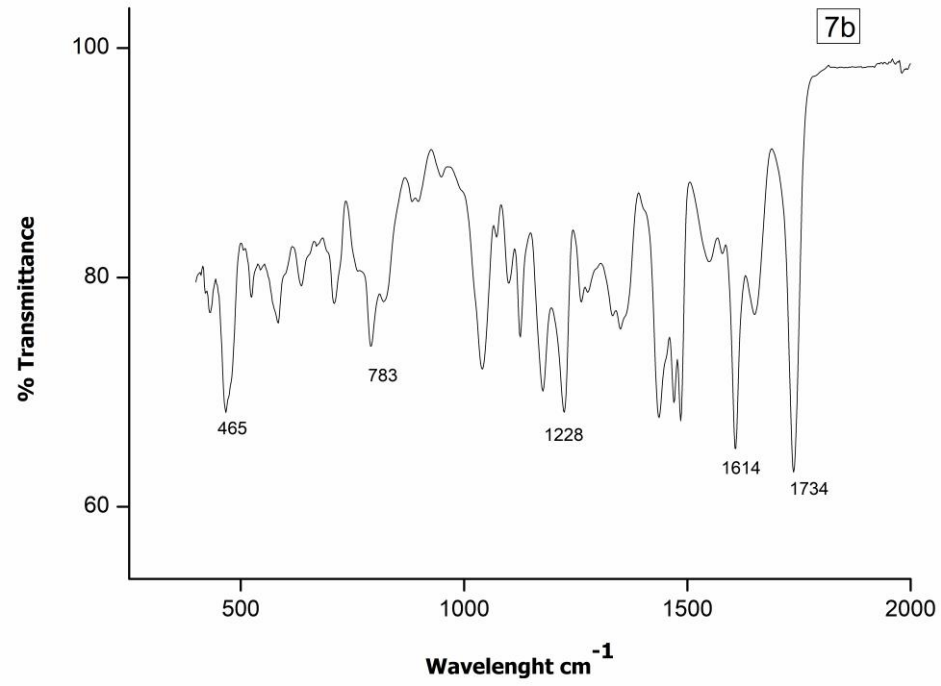

Figure 18. Experimental vibrational frequency spectra of 7b.

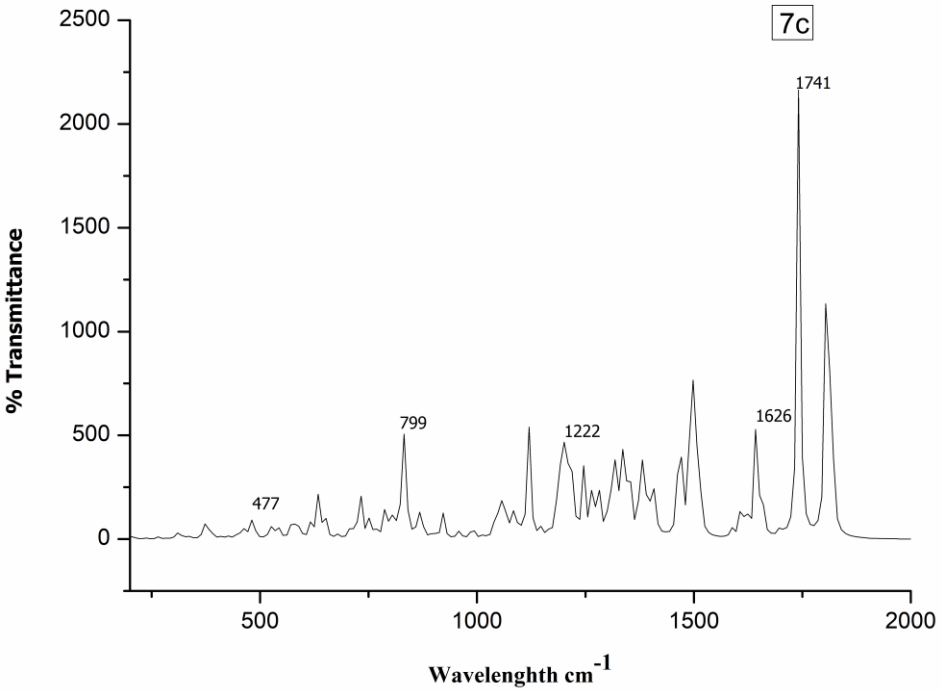

Figure 19. Theoretically studied vibrational frequency spectra of 7c.

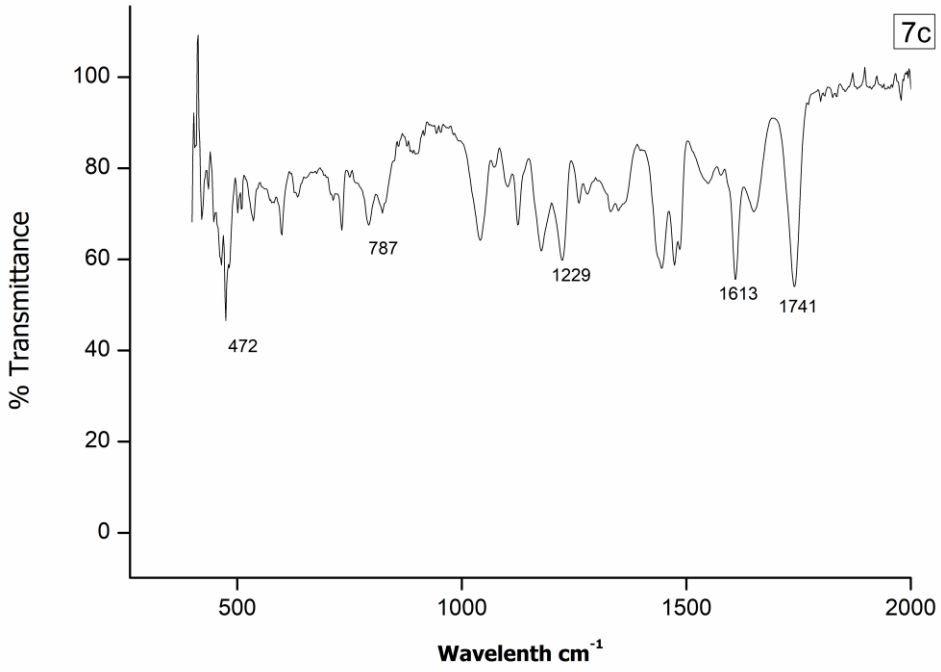

Figure 20. Experimental vibrational frequency spectra of 7c.

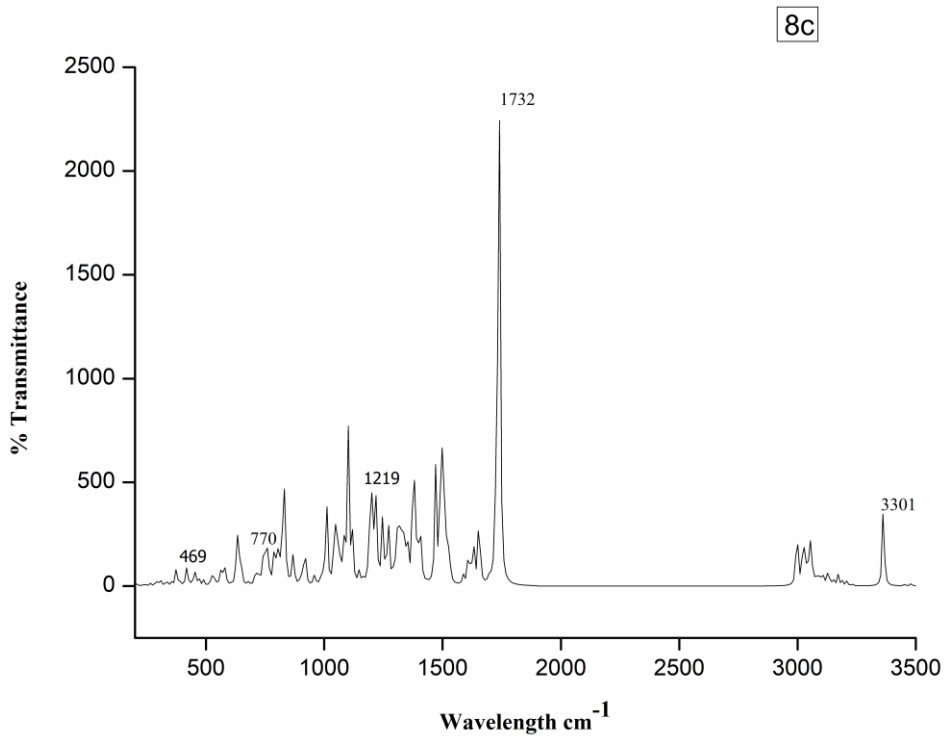

Figure 21. Theoretically studied vibrational frequency spectra of 8c.

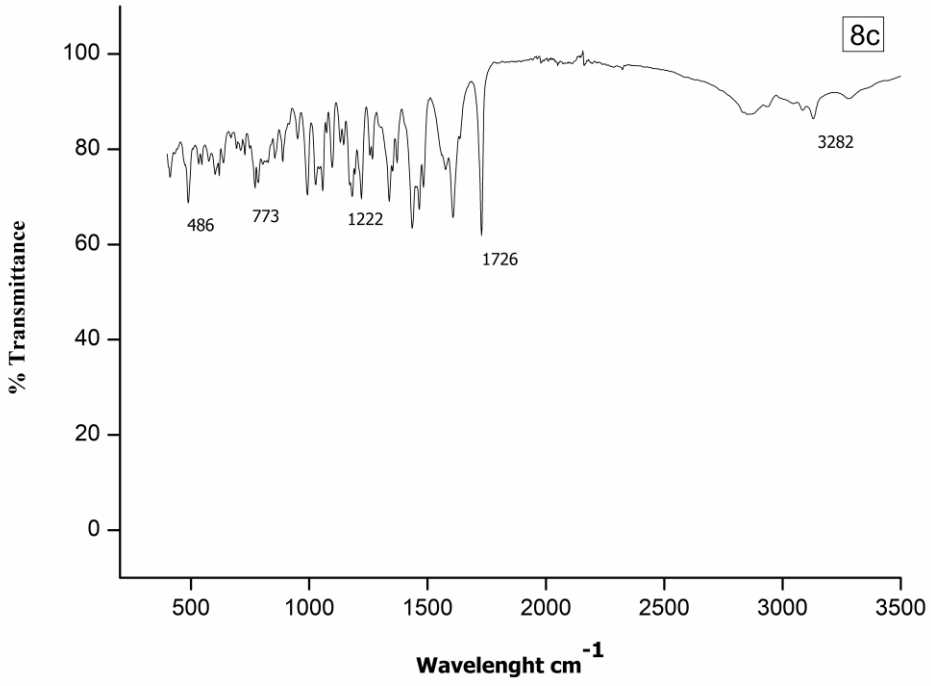

Figure 22. Experimental vibrational frequency spectra of 8c.