Chapter 2

Novel quinoline derivatives containing substituted oxadiazole-5(4*H*)-thione as an anticancer agent

2.1 Introduction

Quinoline is a structurally important moiety in medicinal chemistry because of the vast spectrum of pharmacological activities that it possesses including anti-inflammatory,[47] antihypertensive,[48] inhibition of PDGF-RTK tyrosine kinase,[49] anticancer (**1-5**, **Figure 1**),[50-52] anti-malarial,[53,54] and antibacterial.[55,56] They are also regarded as products with outstanding anti-TB15 performance indications. The USFDA has approved Bed aquiline clinically important drug for the management of MDR-TB.[57] Conversely, the 1,2,4-oxadiazole nucleus is widely acknowledged as an active pharmacophore with varied biological potential.[58] It attracted researchers for the creation of novel therapeutic drugs and highlighted the significance of the nucleus.[59] A literature study supported the notion of utilizing piperazine as a spacer between the quinoline and 1,2,4-oxadiazole nuclei. A range of piperazine-based benzothiazinone-piperazine derivatives and nitrofuranyl methyl piperazines serve as anti-tuberculosis medicines.[60]

Bioisosteres are chemical groups or molecules that are often employed as reagents for one another during synthesizing new drugs because of similar activity. The concept is that for the improvement of efficacy or selectivity or pharmacokinetic profile of a drug or to achieve biological activity certain group in a molecule is replaced by Bioisosteres.[61] These kind of analogues are supported by many research finding to be efficient in certain neoplastic diseases.[62] In order to serve as two distinct pharmacophores, a hybrid molecule must have two or more structural domains with discrete biological and dual activity.[63,64]

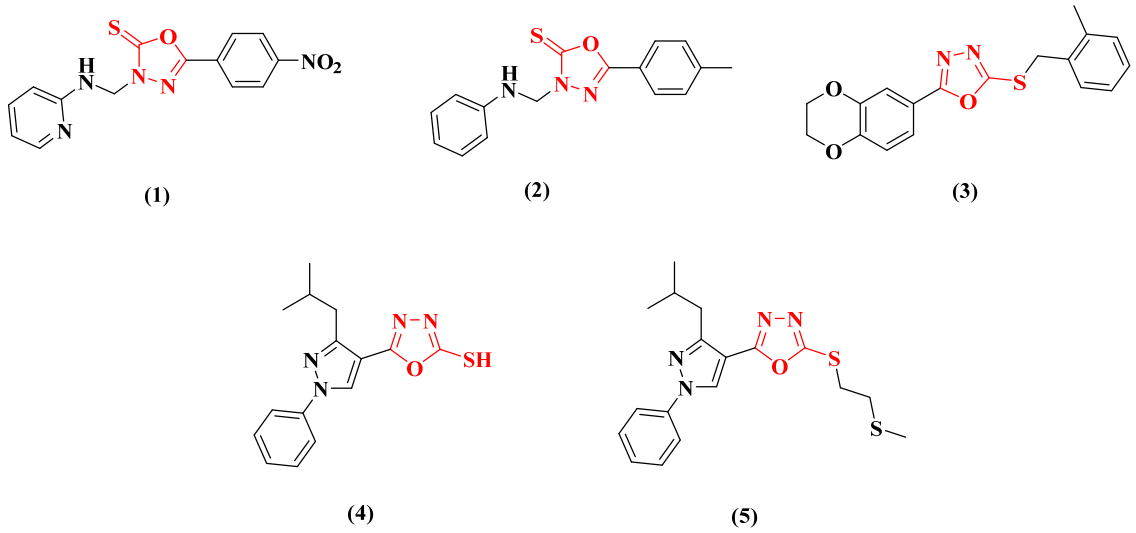
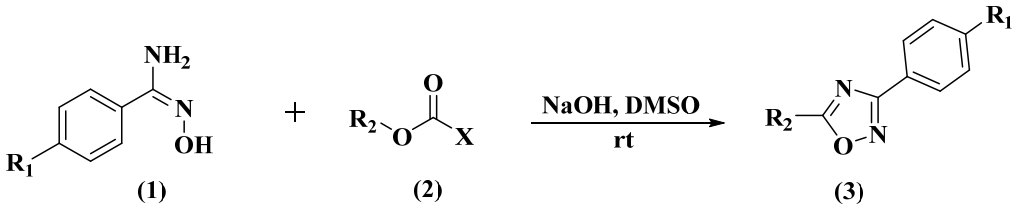


Figure 1: Bio-active oxadiazole moieties.

2.1.1 Synthetic methodologies for the substituted quinoline and oxadiazole framework and its biological significance

In 2017, Baykov et al. published a paper detailing the first one-pot synthetic technique for the 3,5-disubstituted-1,2,4-oxadiazoles (**3**) at room temperature utilizing amidoximes (**1**) and carboxylic acid methyl or ethyl esters (**2**) in a superbase medium of NaOH/DMSO (**Figure 2.1**).[65]

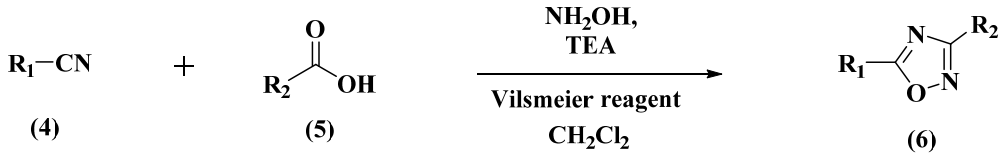


Where R_1 = H, OMe, Me , R_2 = Me, Et

Figure 2.1

Zarei M. proposed an innovative one-pot synthesis method for 3,5-disubstituted-1,2,4-oxadiazoles (**6**) from nitriles (**4**), which were transformed into 1,2,4-oxadiazoles **6** through a reaction with hydroxylamine hydrochloride, triethylamine, followed by carboxylic acids (**5**)

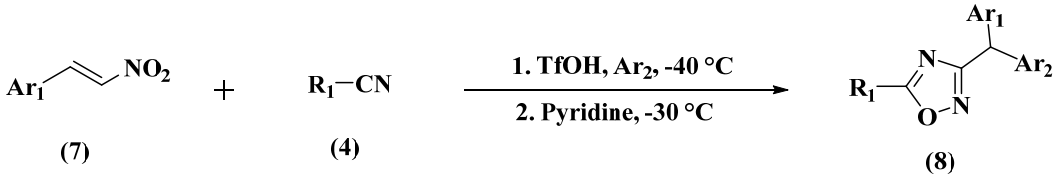
and Vilsmeier reagent in CH_2Cl_2. The combination was rinsed with a saturated $NaHCO_3$ solution and subsequently crystallized from ethanol to provide pure products (**Figure 2.2**).[66]



Where R_1 = Ph, Me, 2-thiophenyl, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$, 4-MeC_6H_4
R_2 = H, Me, Et, Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4

Figure 2.2

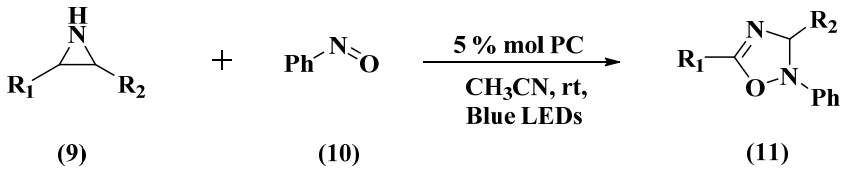
Golushko A. et al. devised an innovative synthesis approach for 1,2,4-oxadiazoles (**8**) via a simultaneous reaction of nitroalkenes (**7**) with arenes and nitriles **4** in the presence of TfOH. Notwithstanding the high yields (about 90% in most instances) and brief reaction time (10 minutes), the application of a superacid necessitates resilient starting materials, which may pose a significant constraint (**Figure 2.3**).[67]



Where, Ar_1 = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-BrC_6H_4
Ar_2 = Ph, 2,6-xylidine, 2,3 xylidine

Figure 2.3

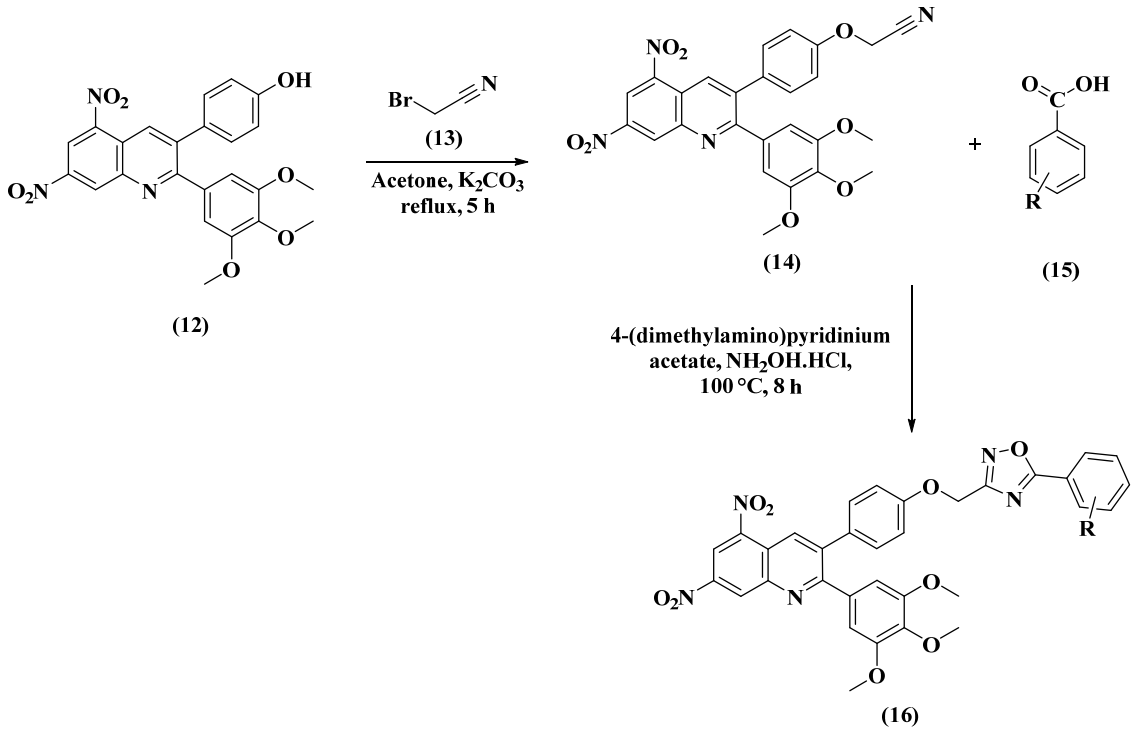
In 2019, Cai B. et al. conducted a study on the [3+2]-cycloaddition reaction of disubstituted-1*H*-aziridines (**9**) with nitroso arenes (**10**) under blue LEDs and in the presence of the organic dye photo redox catalyst 9-mesityl-10-methylacridinium perchlorate (PC), leading to the synthesis of 2,3,5-trisubstituted-1,2,4-oxadiazoles (**11**).[68] This synthetic approach offered an environment friendly and effective way for the production of 1,2,4-oxadiazole (**Figure 2.4**).



Where, R_1 = Bu, Ph, 4-MeC_6H_4, 2-C_4H_4S
R_2 = Ph, 4-ClC_6H_4, 2-FC_6H_4

Figure 2.4

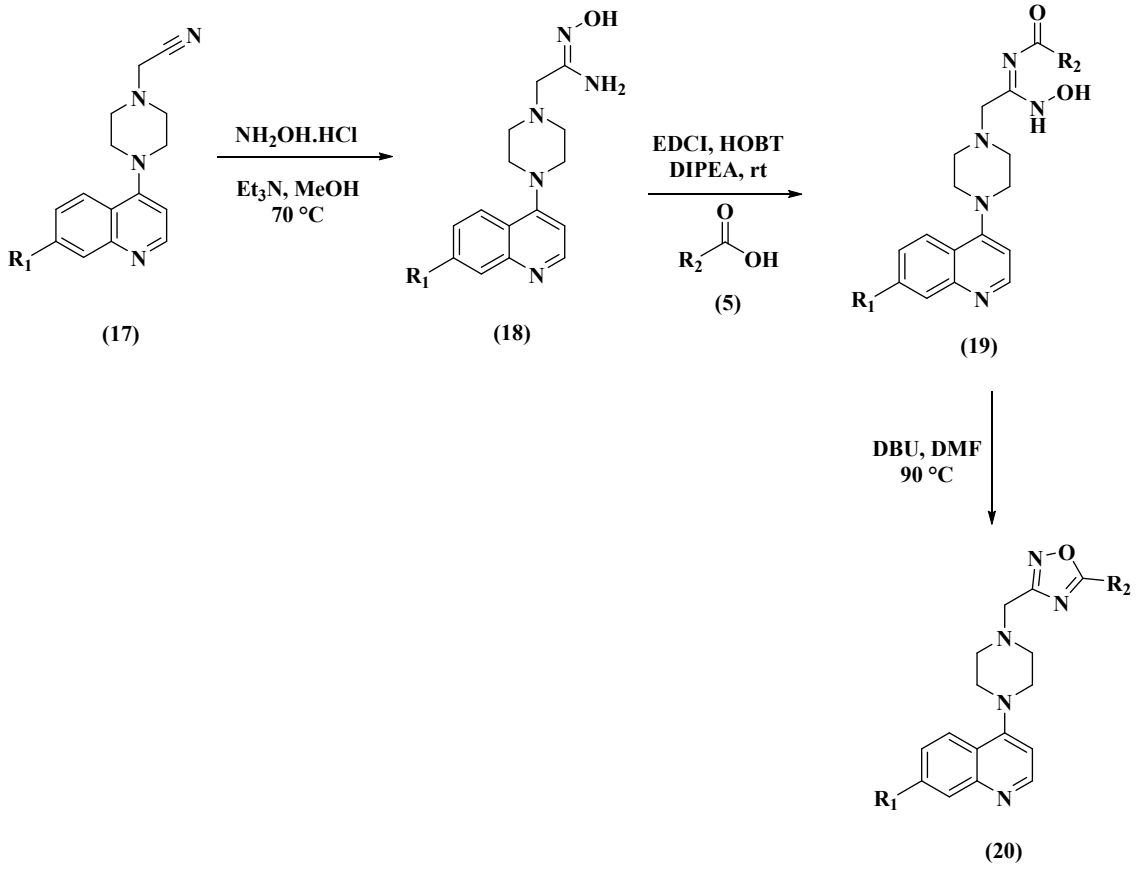
Compound **12** was subsequently refluxed with 2-bromoacetonitrile (**13**) in the presence of K_2CO_3 in anhydrous acetone for a duration of 5 h, yielding pure intermediate **14**. Ultimately, compound **14** was subjected to treatment with different substituted aromatic carboxylic acids (**15**) in the presence of 4-(dimethylamino)pyridinium acetate catalyst and $NH_2OH{\cdot}HCl$ at 100 °C for 8 h, resulting in the formation of pure compounds **16**. All compounds goes under the anti-cancer screening and they shows excellent activity compared with etoposide (**Figure 2.5**).[69]



Where R = H, 4-CH_3, 4-OCH_3, 4-Cl, 4-Br, 2-CH_3

Figure 2.5

Twenty-one novel compounds including a hybrid of substituted quinoline and 1,2,4-oxadiazole were synthesized using the synthetic techniques outlined in the **figure 2.6**. Compound **17** was efficiently transformed into the corresponding hydroxy-acetamidine **18** by treatment with hydroxylamine in the presence of an appropriate base. The quinoline amide derivatives **19** was synthesized through acid-amine coupling of **18** with carboxylic acids **5** in the presence of EDCI and HOBt, with favourable results. The target compounds, specifically quinoline containing a 1,2,4-oxadiazole moiety, designated as **20**, were synthesized in high yield from their precursors by heating with DBU at 90 °C. All derivatives were assessed for *in vitro* evaluation of their antitubercular potential against Mtb WT H37Rv. The 7-chloro quinoline derivative **20** was found to be promising with MIC value of 0.5 µg/ml and some derivatives were also remarkable with MIC value of 0.25 µg/ml. These compounds were found to be orally bioavailable and highly effective. Altogether, these results indicate that most derivatives **20** were promising lead compounds for the development of a novel chemical class of antitubercular drugs.[70]



(17) (18) (5) (19) (20)

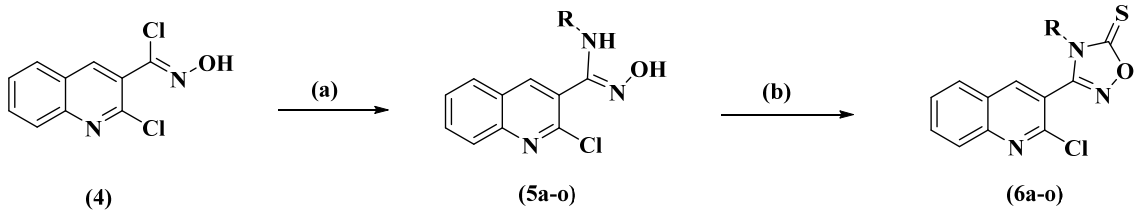
Where R_1 = Cl, 4-C_5H_4N, 3-C_5H_4N, 3,5-FC_6H_3
R_2 = Ph, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4

Figure 2.6

2.2 Results and Discussion

2.2.1 Chemistry

The synthesis of quinoline derivatives containing substituted 1,2,4-oxadiazole-5(4*H*)-thione **(6a-o)** as a potent anticancer agent is portrayed in scheme-1. Compounds **5a-o** which were already synthesized previously in chapter-1 were treated with KOH and carbon disulfide using methanol as a solvent in an ice bath, followed by stirring at 80 °C to yield the 1,2,4-oxadiazole-5(4*H*)-thione derivatives **(6a-o)**.[71] Newly synthesized novel compounds **6a-o** were evaluated for anti-cancer activity at NIH, USA.

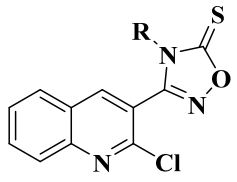


(4) (5a-o) (6a-o)

Reaction condition: a) THF/H_2O, Substituted amine, $NaHCO_3$, 60 °C, 4 h; b) CS_2, KOH, MeOH, 80 °C, 12 h;

Scheme 1: Synthesis of the quinoline containing oxadiazole derivatives.

Table 1: Physicochemical characteristics of the novel quinoline containing oxadiazole derivatives **6a-o**.



Compound	R	Molecular Weight	Molecular Formula	Yield (%)	Melting Point (°C)
6a	4-OCH_3-C_6H_4-	370.30	$C_{18}H_{12}ClN_3O_2S$	90	190-192
6b	C_6H_5-	340.20	$C_{17}H_{10}ClN_3OS$	84	197-199
6c	4-Br-C_6H_4-	419.20	$C_{17}H_9BrClN_3OS$	96	220-222
6d	4-CH_3-C_6H_4-	353.80	$C_{18}H_{12}ClN_3OS$	92	198-200

6e	4-Cl-C_6H_4-	374.20	$C_{17}H_9Cl_2N_3OS$	85	213-215
6f	2-OCH_3-C_6H_4-	370.30	$C_{18}H_{12}ClN_3O_2S$	92	187-189
6g	2-$C_{10}H_8$-	390.17	$C_{21}H_{12}ClN_3OS$	80	205-207
6h	4-F-C_6H_4-	358.21	$C_{17}H_9ClFN_3OS$	83	224-226
6i	3-Cl-C_6H_4-	374.20	$C_{17}H_9Cl_2N_3OS$	83	214-216
6j	1-$C_{10}H_8$-	390.17	$C_{21}H_{12}ClN_3OS$	78	204-206
6k	2,4-CH_3-C_6H_3-	368.20	$C_{19}H_{14}ClN_3OS$	87	180-182
6l	2,6-CH_3-C_6H_3-	368.20	$C_{19}H_{14}ClN_3OS$	86	184-186
6m	2,3-CH_3-C_6H_3-	368.20	$C_{19}H_{14}ClN_3OS$	84	183-185
6n	2-CH_3-C_6H_4-	353.80	$C_{18}H_{12}ClN_3OS$	91	195-197
6o	2,5-CH_3-C_6H_3-	368.20	$C_{19}H_{14}ClN_3OS$	90	180-182

2.3 Biological Activity

The evaluation of newly synthesized indole derivatives for anticancer efficacy included several human cancer cell lines, such as CNS cancer, non-small cell lung cancer, ovarian cancer, renal cancer, melanoma, colon cancer, prostate cancer, breast cancer, and leukemia. The cell lines were subsequently divided to enhance screening efficiency. The NCI utilized 60 unique sub-cell lines to evaluate a single medication for improved antitumor efficacy.[46]

Compound **6a** (sample no: **843432-2303OS10**) showed its biological impact by inhibiting the cells' growth in Ovarian Cancer Cell Line: NCI/ADR-RES and in renal cancer cell line: RXF 393.

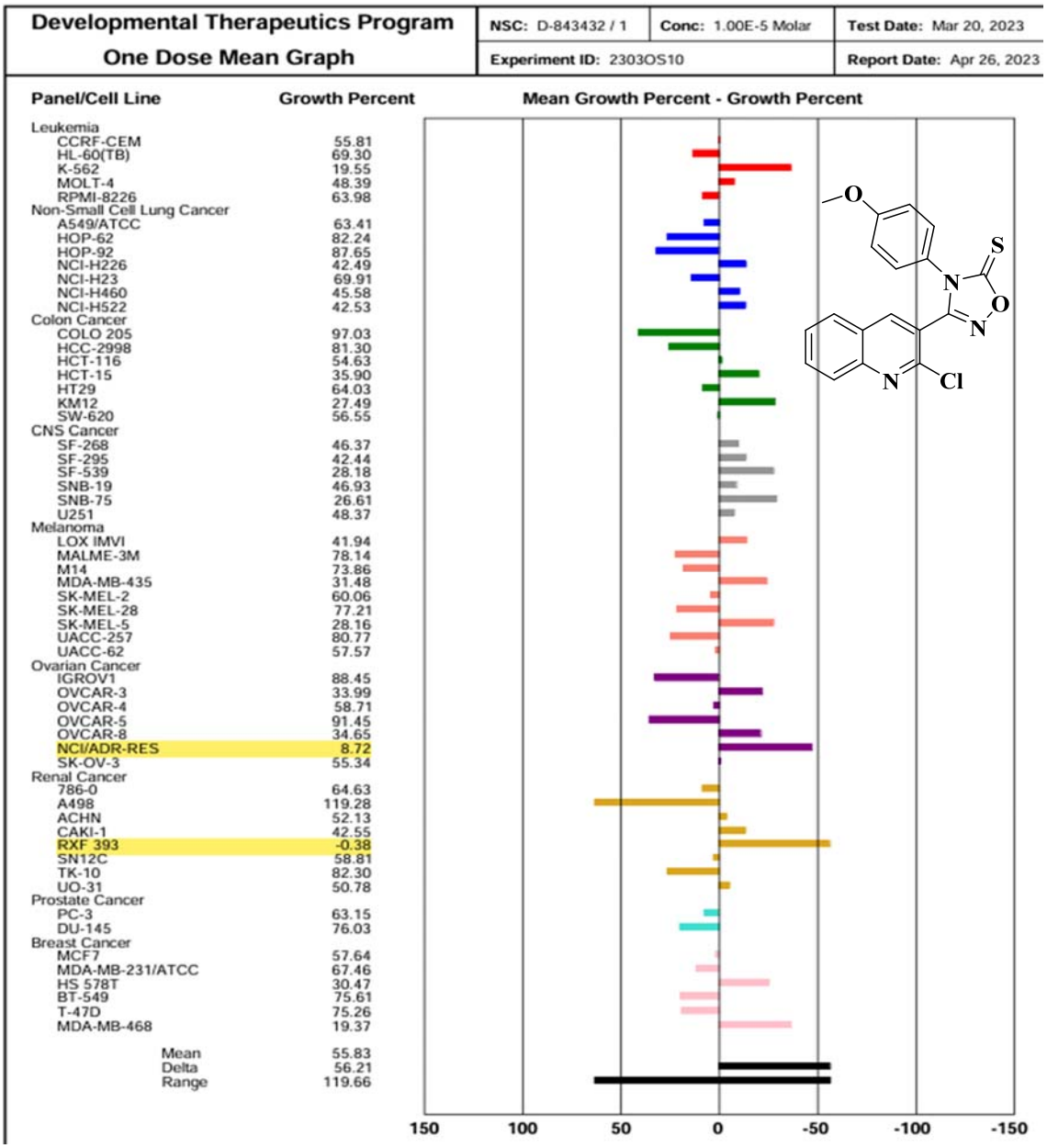


Figure 1. Anti-cancer activity of molecule **6a** as a mean graph plot of GI_{50} values against NCI-60 cell line panels.

Compound **6c** (sample **849434-2310OS97**) showed its biological impact by inhibiting the cells' growth in leukemia cell line: HL-60(TB) and K-562, in Melanoma cell line: MDA-MB-435 and at last, in Ovarian Cancer Cell Line: NCI/ADR-RES.

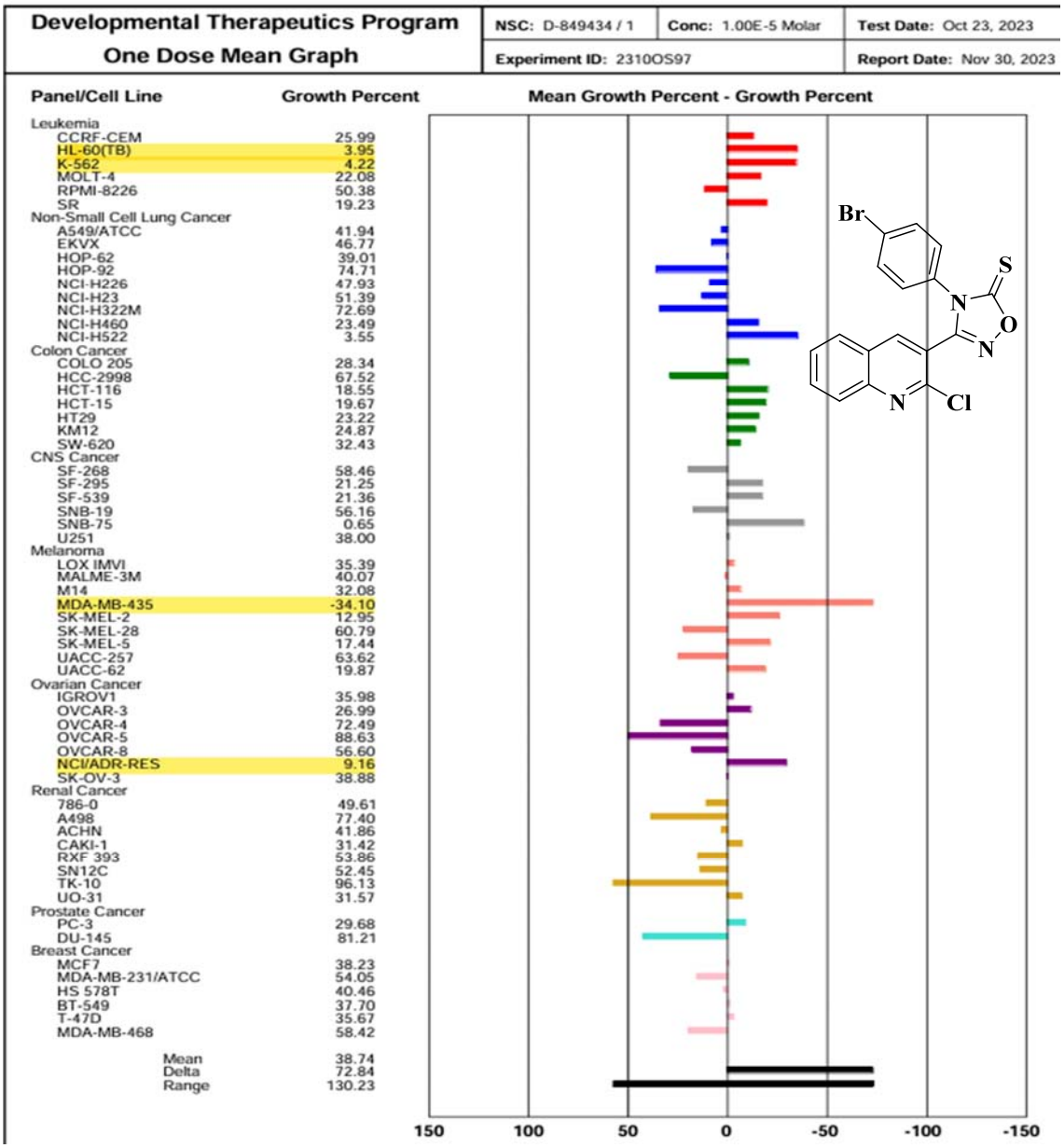


Figure 2. Anti-cancer activity of molecule **6c** as a mean graph plot of GI_{50} values against NCI-60 cell line panels.

2.4 Conclusion

A range of hybrid quinoline derivatives with substituted oxadiazole-5(4*H*)-thione was synthesized. The newly synthesized compounds were confirmed using ^{1}H NMR, ^{13}C NMR, and mass spectrometry analytical methods. The National Cancer Institute (NCI) chose synthesized compounds **6a-o** for *in vitro* anticancer assessment. The primary *in vitro* anticancer study entailed the administration of a single dose to all NCI-60 cell lines corresponding to nine tumor subpanels: breast, CNS, ovarian, prostate, renal, colon, lung, melanoma, and leukemia. Compounds **6a** and **6c** shown significant anti-cancer action.

2.5 Experimental Section

2.5.1 Chemistry

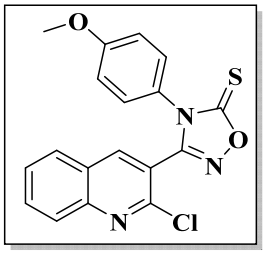
The open-capillary method was used to determine all the melting points on an electrothermal device, and the results are uncorrected. Compounds were detected in thin-layer chromatography with UV light at 254 nm, 365 nm and/or with iodine vapour on precoated silica gel 60 F254 (Merck). IR spectra were recorded using Shimadzu FTIR spectrometer with ATR method. A Bruker AVANCE III (400 MHz) spectrometer was used to capture ^{1}H and ^{13}C NMR spectra in DMSO-d_6 or $CDCl_3$ using tetramethylsilane (TMS) as an internal standard, and chemical shifts are represented in ppm downfield. Shimadzu GCMS QP2010 Ultra mass spectrometer was used to record mass spectra utilising a direct intake probe. All reagents purchased from Sigma-Aldrich, Alfa Aesar, Loba Chemie, Molychem, and Sisco Research Laboratories Pvt. Ltd. (SRL) and used without further purification.

General procedure for the synthesis of compound (6a-p):

KOH (2 mmol) and CS_2 (3 mmol) were added to a solution of compound **5a** (1 mmol) in methanol (10 mL) in an ice bath for 30 min, followed the reaction was heated at 80 °C for 12 h with stirring. After completion of the reaction (monitored by TLC), the reaction mixture was poured onto ice cold water and the formed precipitate was collected by filtration with suction, washed with water, and dried. The obtained residue was slurry washed with diethyl ether to give the title compound which are analytically pure.

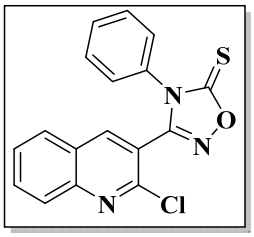
By using the same general synthetic procedure for **6a-p**, the following compounds were prepared:

3-(2-Chloroquinolin-3-yl)-4-(4-methoxyphenyl)-1,2,4-oxadiazole-5(4*H*)-thione (6a):



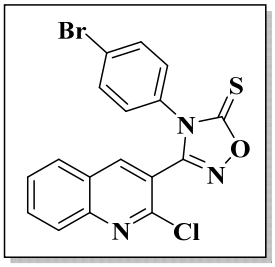
Compound **6a** was prepared from **5a** (0.2 gm, 0.61 mmol), KOH (0.07 gm, 1.22 mmol) and CS_2 (0.14 gm, 1.83 mmol) in methanol (10 mL). A white solid (90% yield); mp: 190-192 °C. ^{1}H NMR (400 MHz, DMSO-d_6) ^{1}H NMR (400 MHz, DMSO) δppm: 9.19 (s, 1H, Ar-H), 8.24 (d, J = 8.3, 1.4 Hz, 1H, Ar-H), 8.05 (d, J = 8.5 Hz, 1H, Ar-H), 7.93 (t, J = 1.7 Hz, 1H, Ar-H), 7.71 – 7.61 (m, 3H, 3 × Ar-H), 7.02 (d, J = 9.0 Hz, 2H, 2 × Ar-H), 3.77 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, DMSO) δppm: 165.13, 154.54, 154.31, 147.61, 133.63, 133.44, 132.06, 129.72, 127.74, 125.06, 124.63, 119.31, 114.39, 110.67, 55.26. Mass spectrum: 370.3 *m/z*.

3-(2-Chloroquinolin-3-yl)-4-phenyl-1,2,4-oxadiazole-5(4*H*)-thione (6b):



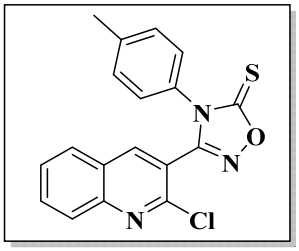
Compound **6b** was prepared from **5b** (0.2 gm, 0.67 mmol), KOH (0.07 gm, 1.34 mmol) and CS_2 (0.15 gm, 2.01 mmol) in methanol (10 mL). A white solid (84% yield); mp: 197-199 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.29 (s, 1H, Ar-H), 8.0 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.91 – 7.78 (m, 2H, 2 × Ar-H), 7.64 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.33 – 7.22 (m, 5H, 5 × Ar-H). ^{13}C NMR (101 MHz, $CDCl_3$) δppm: 176.87, 152.48, 148.02, 147.22, 140.92, 133.28, 132.41, 129.57, 128.62, 128.14, 128.04, 127.60, 127.33, 125.75, 124.31. Mass spectrum: 340.20 *m/z*.

4-(4-Bromophenyl)-3-(2-chloroquinolin-3-yl)-1,2,4-oxadiazole-5(4*H*)-thione (6c):



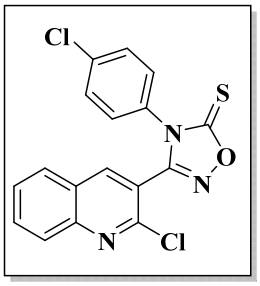
Compound **6c** was prepared from **5c** (0.2 gm, 0.53 mmol), KOH (0.06 gm, 1.06 mmol) and CS_2 (0.12 gm, 1.59 mmol) in methanol (10 mL). A white solid (96% yield); mp: 220-222 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.32 (s, 1H, Ar-H), 8.03 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.92 – 7.82 (m, 2H, 2 × Ar-H), 7.68 (t, *J* = 7.0 Hz, 1H, Ar-H), 7.46 (d, *J* = 8.8 Hz, 2H, 2 × Ar-H), 7.11 (d, *J* = 8.8 Hz, 2H, 2 × Ar-H). ^{13}C NMR (101 MHz, DMSO) δppm: 176.23, 152.67, 147.75, 146.55, 143.27, 133.46, 132.93, 132.87, 130.74, 129.31, 128.98, 128.33, 125.97, 123.90, 123.37. Mass spectrum: 419.20 *m/z*.

3-(2-Chloroquinolin-3-yl)-4-(p-tolyl)-1,2,4-oxadiazole-5(4*H*)-thione (6d):



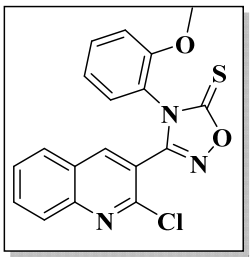
Compound **6d** was prepared from **5d** (0.2 gm, 0.64 mmol), KOH (0.20 gm, 1.28 mmol) and CS_2 (0.12 gm, 1.92 mmol) in methanol (10 mL). A white solid (92% yield); mp: 198-200 °C. ^{1}H NMR (400 MHz, DMSO) ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.53 (s, 1H), 8.15 (d, *J* = 8.6 Hz, 1H), 7.98 (d, *J* = 8.6 Hz, 1H), 7.86 (t, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 7.7 Hz, 2H), 4.80 (s, 1H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δppm: 165.55, 155.01, 148.07, 139.78, 138.11, 134.30, 132.60, 131.03, 130.25, 129.99, 128.34, 128.22, 125.58, 125.12, 118.33, 111.10, 21.03, 20.84. Mass spectrum: 353.80 *m/z*.

4-(4-Chlorophenyl)-3-(2-chloroquinolin-3-yl)-1,2,4-oxadiazole-5(4*H*)-thione (6e):



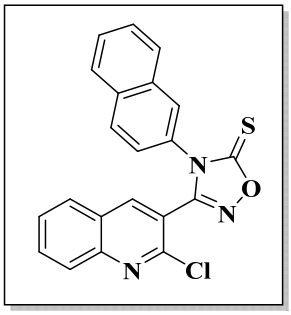
Compound **6e** was prepared from **5e** (0.2 gm, 0.60 mmol), KOH (0.07 gm, 1.2 mmol) and CS_2 (0.15 gm, 1.3 mmol) in methanol (10 mL). A white solid (85% yield); mp: 213-215 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.32 (s, 1H, Ar-H), 8.03 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.88 (t, *J* = 7.5 Hz, 2H, 2 × Ar-H), 7.68 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.29 (d, *J* = 3.1 Hz, 2H, 2 × Ar-H), 7.17 (d, *J* = 6.4 Hz, 2H, 2 × Ar-H).^{13}C NMR (101 MHz, $CDCl_3$) δppm: 176.60, 152.15, 148.14, 146.94, 140.99, 135.70, 132.79, 132.61, 131.71, 129.86, 129.66, 128.85, 128.70, 128.31, 128.06, 125.77, 124.02. Mass spectrum: 374.2 *m/z*.

3-(2-Chloroquinolin-3-yl)-4-(2-methoxyphenyl)-1,2,4-oxadiazole-5(4*H*)-thione (6f):



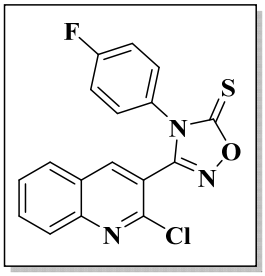
Compound **6f** was prepared from **5f** (0.2 gm, 0.61 mmol), KOH (0.07 gm, 1.22 mmol) and CS_2 (0.14 gm, 1.83 mmol) in methanol (10 mL). A white solid (92% yield); mp: 187-199 °C. ^{1}H NMR (400 MHz, DMSO) δppm: 8.74 (s, 1H, Ar-H), 8.07 (d, *J* = 8.3 Hz, 1H, Ar-H), 8.03 – 7.86 (m, 2H, 2 × Ar-H), 7.73 (t, *J* = 8.2 Hz, 1H, Ar-H), 7.51 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.32 (t, *J* = 7.0 Hz, 1H, Ar-H), 7.12 – 6.93 (m, 2H, 2 × Ar-H), 3.67 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, DMSO) δppm: 175.56, 153.67, 153.13, 147.07, 146.45, 141.79, 132.77, 131.74, 129.96, 128.52, 128.30, 127.72, 125.30, 123.12, 121.11, 120.62, 112.35, 55.66. Mass spectrum: 370.30 *m/z*.

3-(2-Chloroquinolin-3-yl)-4-(naphthalen-2-yl)-1,2,4-oxadiazole-5(4*H*)-thione (6g):



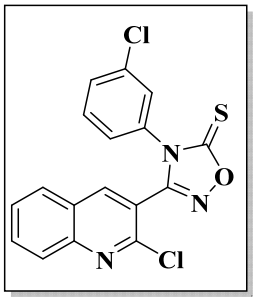
Compound **6g** was prepared from **5g** (0.2 gm, 0.57 mmol), KOH (0.06 gm, 1.14 mmol) and CS_2 (0.13 gm, 1.71 mmol) in methanol (10 mL). A white solid (80% yield); mp: 205-207 °C. ^{1}H NMR (400 MHz, DMSO) δppm: 9.05 (s, 1H, Ar-H), 8.11 (d, *J* = 8.2 Hz, 1H, Ar-H), 8.01 (q, *J* = 7.1, 6.7 Hz, 3H, 3 × Ar-H), 7.92 (d, *J* = 6.1 Hz, 2H, 2 × Ar-H), 7.76 (d, *J* = 7.2 Hz, 2H, 2 × Ar-H), 7.76 – 7.56 (m, 2H, 2 × Ar-H), 7.50 (t, *J* = 7.9 Hz, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO) δppm: 147.45, 142.73, 134.02, 133.38, 131.10, 129.89, 128.97, 128.35, 128.26, 128.18, 127.50, 125.84, 125.56, 123.55, 122.66. Mass: 390.17 *m/z*.

3-(2-Chloroquinolin-3-yl)-4-(4-fluorophenyl)-1,2,4-oxadiazole-5(4*H*)-thione (6h):



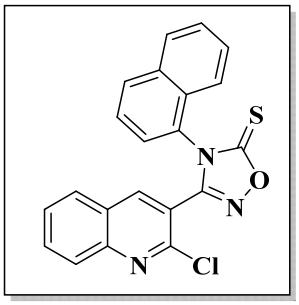
Compound **6h** was prepared from **5h** (0.2 gm, 0.63 mmol), KOH (0.08 gm, 1.26 mmol) and CS_2 (0.15 gm, 1.89 mmol) in methanol (10 mL). A white solid (83% yield); mp: 214-216 °C. ^{1}H NMR (400 MHz, DMSO) δppm: 9.00 (s, 1H, Ar-H), 8.21 (d, *J* = 8.2 Hz, 1H, Ar-H), 8.00 (d, *J* = 5.9 Hz, 2H, 2 × Ar-H), 7.81 (t, *J* = 5.9 Hz, 1H, Ar-H), 7.51 (dd, *J* = 8.8, 4.8 Hz, 2H, 2 × Ar-H), 7.28 (t, *J* = 8.6 Hz, 2H, 2 × Ar-H). ^{13}C NMR (101 MHz, DMSO) δppm: 163.71, 157.58, 156.28, 148.36, 146.62, 144.57, 134.07, 129.91, 129.81, 129.62, 129.20, 128.41, 127.79, 125.89, 117.20, 117.02, 116.97. Mass spectrum: 358.21 *m/z*.

4-(3-Chlorophenyl)-3-(2-chloroquinolin-3-yl)-1,2,4-oxadiazole-5(4*H*)-thione (6i):



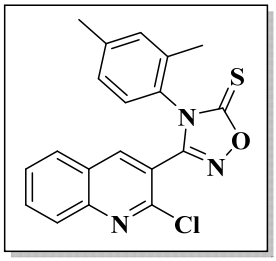
Compound **6i** was prepared from **5i** (0.2 gm, 0.60 mmol), KOH (0.07 gm, 1.2 mmol) and CS_2 (0.15 gm, 1.3 mmol) in methanol (10 mL). A white solid (83% yield); mp: 214-216 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.53 (s, 1H, Ar-H), 8.08 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.99 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.93 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.74 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.39 – 7.24 (m, 3H, 3 × Ar-H), 7.06 (d, *J* = 8.0 Hz, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO) δppm: 148.55, 147.26, 146.55, 142.50, 141.90, 139.59, 133.24, 132.29, 132.00, 130.40, 128.92, 128.72, 128.13, 126.95, 126.80, 126.58, 121.52, 120.09, 118.54, 117.46, 116.64. Mass spectrum: 374.20 *m/z*.

3-(2-Chloroquinolin-3-yl)-4-(naphthalen-1-yl)-1,2,4-oxadiazole-5(4*H*)-thione (6j):



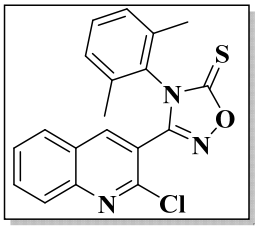
Compound **6j** was prepared from **5j** (0.2 gm, 0.57 mmol), KOH (0.06 gm, 1.14 mmol) and CS_2 (0.13 gm, 1.71 mmol) in methanol (10 mL). A white solid (78% yield); mp: 204-206 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.35 (s, 1H, Ar-H), 7.97 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.94 – 7.77 (m, 5H, 5 × Ar-H), 7.70 – 7.53 (m, 3H, 3 × Ar-H), 7.47 – 7.40 (m, 2H, 2 × Ar-H). ^{13}C NMR (101 MHz, $CDCl_3$) δppm: 166.85, 156.84, 148.47, 147.34, 141.89, 134.40, 133.04, 131.23, 129.23, 128.82, 128.58, 128.34, 128.19, 128.06, 127.23, 127.00, 126.78, 125.39, 125.09, 121.62, 117.20. Mass spectrum: 390.19 *m/z*.

3-(2-Chloroquinolin-3-yl)-4-(2,4-dimethylphenyl)-1,2,4-oxadiazole-5(4*H*)-thione (6k) :



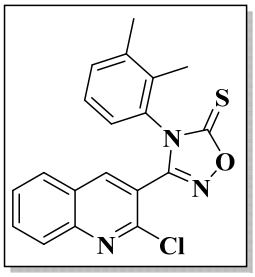
Compound **6k** was prepared from **5k** (0.2 gm, 0.61 mmol), KOH (0.07 gm, 1.22 mmol) and CS_2 (gm, 1.63 mmol) in methanol (10 mL). A white solid (97% yield); mp: 180-182 °C. ^{1}H NMR (400 MHz, DMSO) δppm: 9.05 (s, 1H, Ar-H), 8.18 (d, *J* = 8.2 Hz, 1H, Ar-H), 8.04 – 7.94 (m, 2H, 2 × Ar-H), 7.82-7.78 (m, 1H, Ar-H), 7.21 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.17 (s, 1H, Ar-H), 6.94 (d, *J* = 8.2, 1H, Ar-H), 2.27 (s, 3H, CH_3), 2.20 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δppm: 166.32, 155.74, 148.30, 134.64, 134.56, 132.12, 132.00, 131.68, 129.54, 129.06, 128.56, 127.81, 127.69, 125.18, 124.78, 122.28, 109.80, 20.88, 17.80. Mass spectrum: 368.20 *m/z*.

3-(2-Chloroquinolin-3-yl)-4-(2,6-dimethylphenyl)-1,2,4-oxadiazole-5(4*H*)-thione (6l):



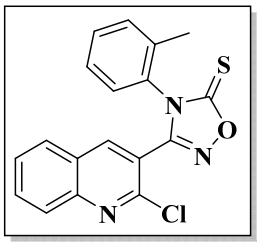
Compound **6l** was prepared from **5l** (0.2 gm, 0.61 mmol), KOH (0.07 gm, 1.22 mmol) and CS_2 (gm, 1.63 mmol) in methanol (10 mL). A white solid (86% yield); mp: 184-186 °C. ^{1}H NMR (400 MHz, DMSO) δppm: 8.73 (s, 1H, Ar-H), 8.12 (d, *J* = 8.2 Hz, 1H, Ar-H), 8.05 – 7.94 (m, 2H, 2 × Ar-H), 7.77 (t, *J* = 1.9 Hz, 1H, Ar-H), 7.28 (t, *J* = 15.1 Hz, 1H, Ar-H), 7.17 (d, *J* = 7.6 Hz, 2H, 2 × Ar-H), 2.21 (s, 6H, CH_3). ^{13}C NMR (101 MHz, DMSO) δppm: 156.62, 147.99, 136.43, 135.74, 134.07, 132.54, 130.19, 128.70, 128.22, 127.22, 125.54, 125.06, 110.46, 18.52, 18.14. Mass: 368.20 *m/z*.

3-(2-Chloroquinolin-3-yl)-4-(2,3-dimethylphenyl)-1,2,4-oxadiazole-5(4*H*)-thione (6m):



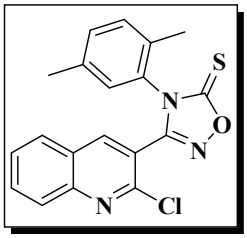
Compound **6m** was prepared from **5m** (0.2 gm, 0.61 mmol), KOH (0.07 gm, 1.22 mmol) and CS_2 (gm, 1.63 mmol) in methanol (10 mL). A white solid (84% yield); mp: 183-185 °C. ^{1}H NMR (400 MHz, DMSO) δppm: 9.03 (s, 1H, Ar-H), 8.18 (d, *J* = 8.2 Hz, 1H, Ar-H), 8.03 – 7.94 (m, 2H, 2 × Ar-H), 7.85 – 7.75 (m, 1H, Ar-H), 7.20 (t, *J* = 7.5 Hz, 2H, 2 × Ar-H), 7.04 (t, *J* = 7.8 Hz, 1H, Ar-H), 2.24 (s, 3H, CH_3), 2.18 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO) δppm: 166.09, 156.28, 148.00, 135.56, 134.56, 133.84, 132.57, 132.24, 131.77, 130.74, 130.22, 128.22, 127.39, 125.56, 125.08, 123.33, 110.83, 20.93, 18.37. Mass spectrum: 353.80 *m/z*.

3-(2-Chloroquinolin-3-yl)-4-(o-tolyl)-1,2,4-oxadiazole-5(4*H*)-thione (6n):



Compound **6n** was prepared from **5n** (0.2 gm, 0.64 mmol), KOH (0.20 gm, 1.28 mmol) and CS_2 (0.12 gm, 1.92 mmol) in methanol (10 mL). A white solid (91% yield); mp: 195-197 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.17 (s, 1H, Ar-H), 8.00 (d, *J* = 9.4 Hz, 1H, Ar-H), 7.85 – 7.80 (m, 2H, 2 × Ar-H), 7.63 (t, *J* = 6.9 Hz, 1H, Ar-H), 7.24 (dd, *J* = 6.4, 1.6 Hz, 2H, 2 × Ar-H), 7.13 (t, *J* = 2.4 Hz, 1H, Ar-H), 2.34 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δppm: 176.42, 152.45, 147.92, 147.39, 140.54, 136.13, 132.42, 132.26, 131.66, 130.21, 128.59, 128.44, 128.11, 127.97, 127.07, 125.58, 124.04, 18.08. Mass spectrum: 354.17 *m/z*.

3-(2-Chloroquinolin-3-yl)-4-(2,5-dimethylphenyl)-1,2,4-oxadiazole-5(4*H*)-thione (6o):



Compound **6o** was prepared from **5o** (0.2 gm, 0.61 mmol), KOH (0.07 gm, 1.22 mmol) and CS_2 (gm, 1.63 mmol) in methanol (10 mL). A white solid (90% yield); mp: 180-182 °C. ^{1}H NMR (400 MHz, DMSO) δppm: 9.04 (s, 1H, Ar-H), 8.18 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.99 (m, 2H, 2 × Ar-H), 7.84 – 7.76 (m, 1H, Ar-H), 7.24 (s, 1H, Ar-H), 7.21 (d, *J* = 6.4 Hz, 1H, Ar-H), 7.13 (d, *J* = 7.8 Hz, 1H, Ar-H), 2.24 (s, 3H, CH_3), 2.10 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO) δppm: 157.36, 156.68, 148.21, 146.66, 144.54, 139.26, 135.12, 134.10, 131.92, 129.84, 129.52, 129.23, 128.36, 126.69, 126.46, 125.81, 66.82, 20.25, 14.85. Mass spectrum: 368.20 *m/z*.

2.6 Spectral data

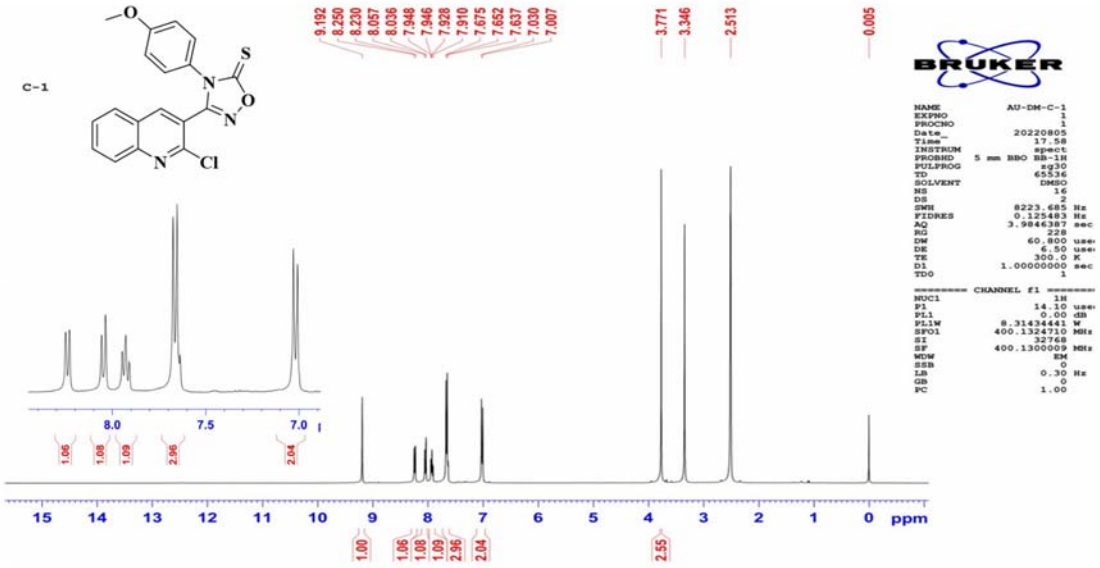


Figure 1: ^{1}H NMR of compound **6a**

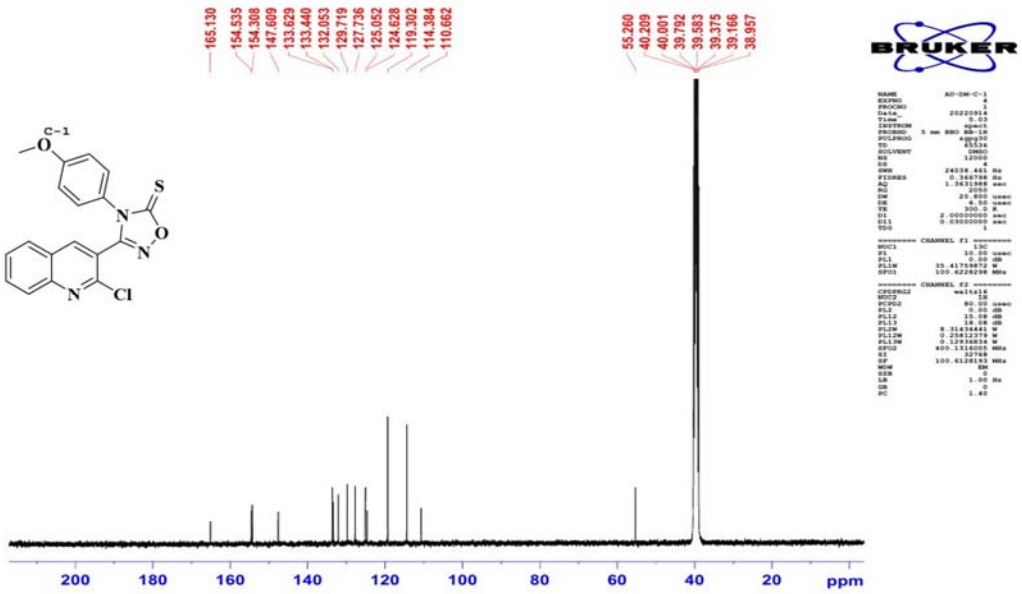


Figure 2: ^{13}C NMR of compound **6a**

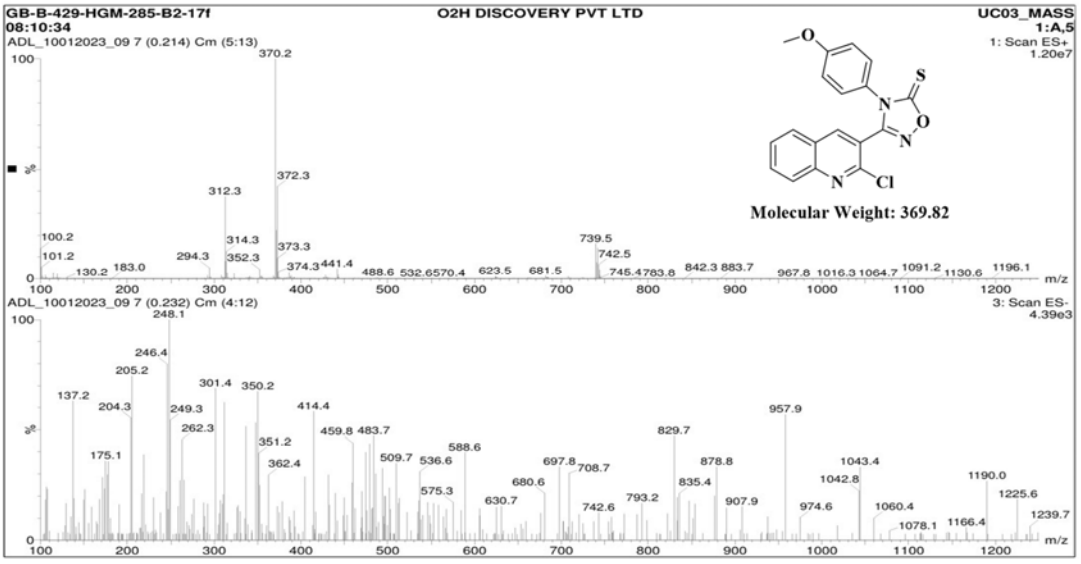


Figure 3: LCMS of compound **6a**

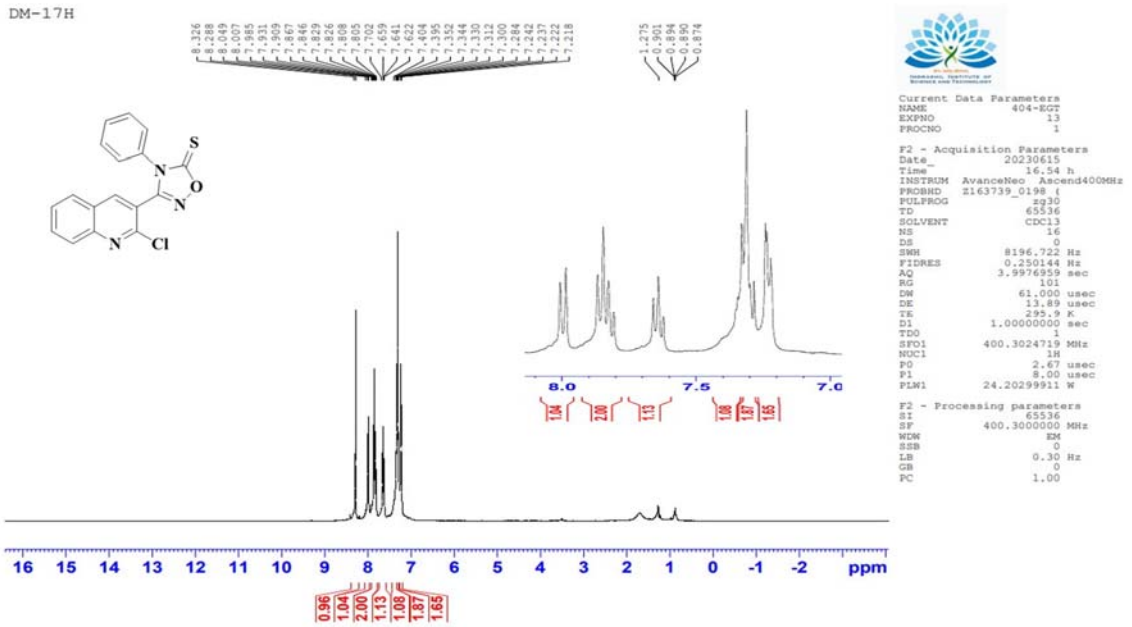


Figure 4: ^{1}H NMR of compound **6b**

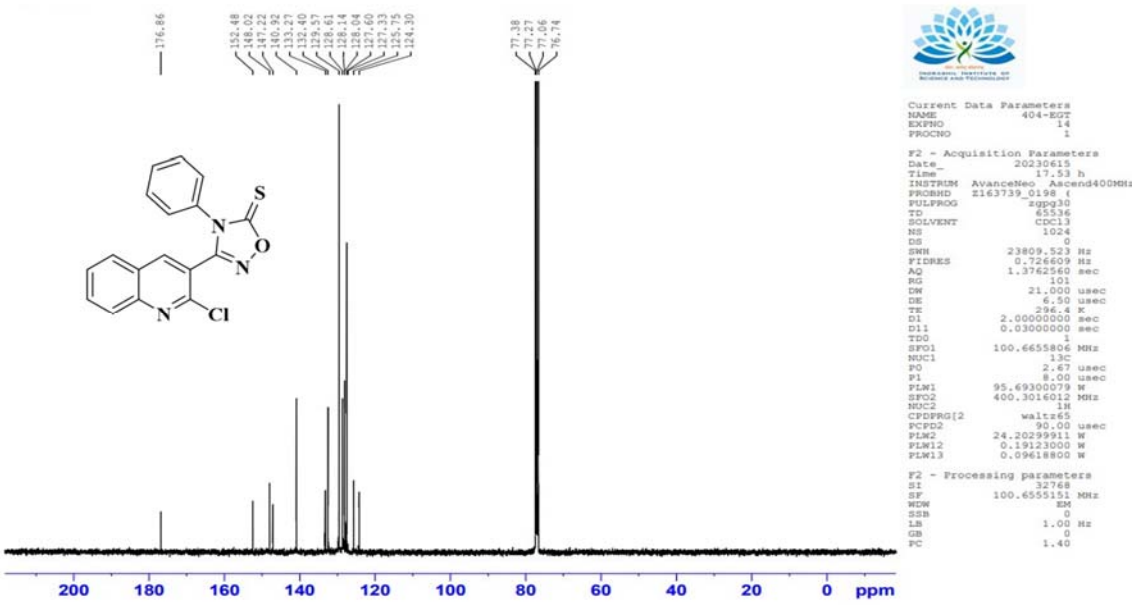


Figure 5: ^{13}C NMR of compound **6b**

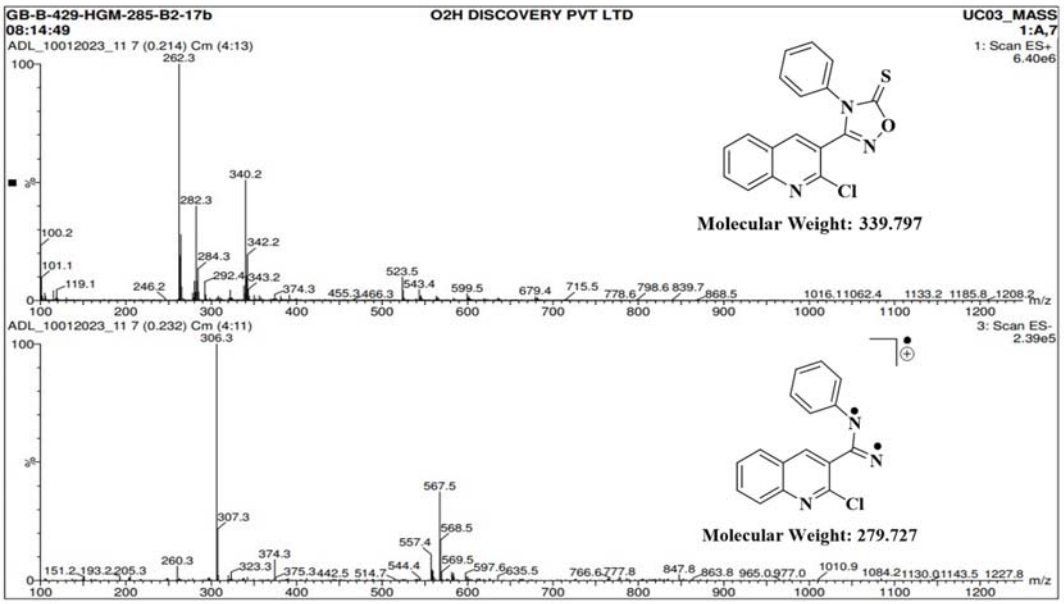


Figure 6: Mass spectrum of compound **6b**

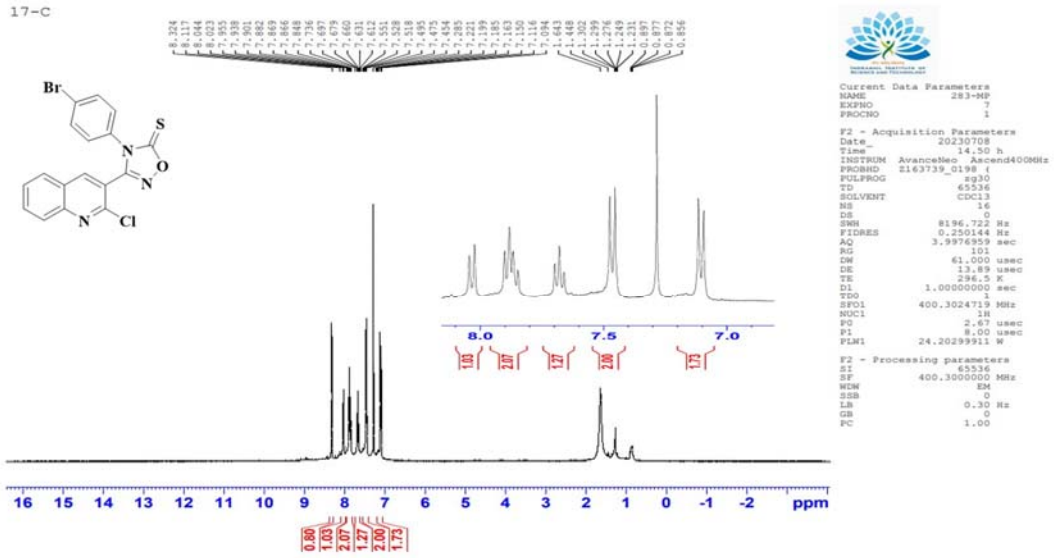


Figure 7: [1]H NMR of compound **6c**

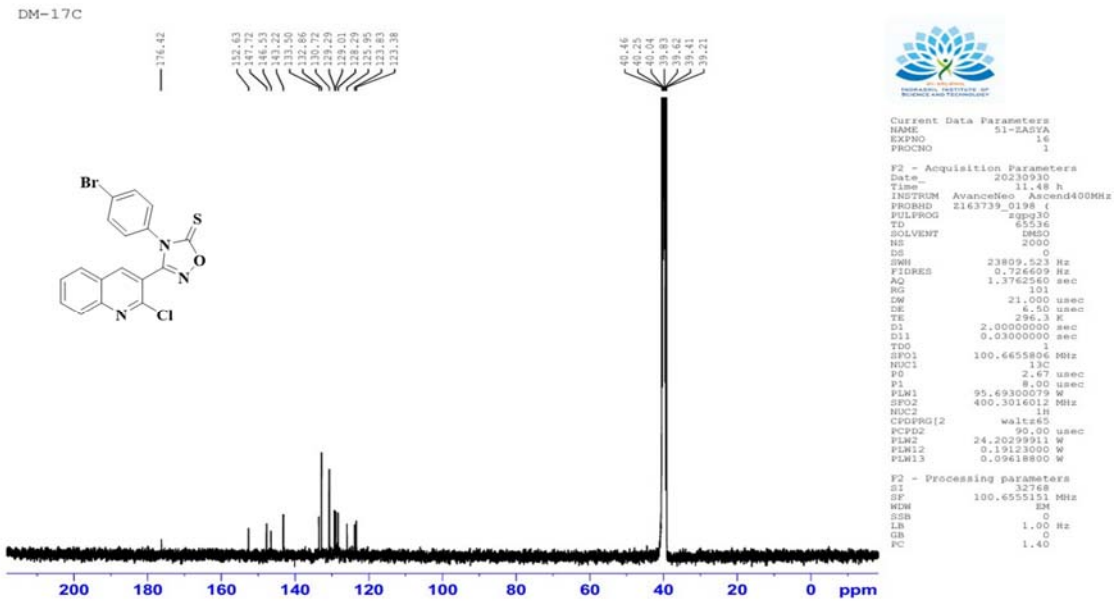


Figure 8: ^{13}C NMR of compound **6c**

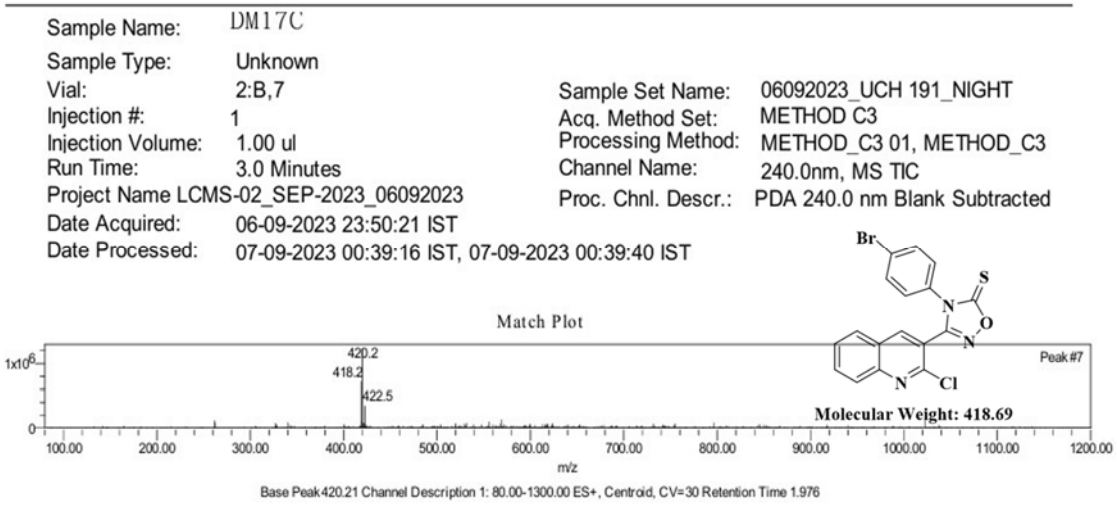


Figure 9: Mass spectrum of compound **6c**

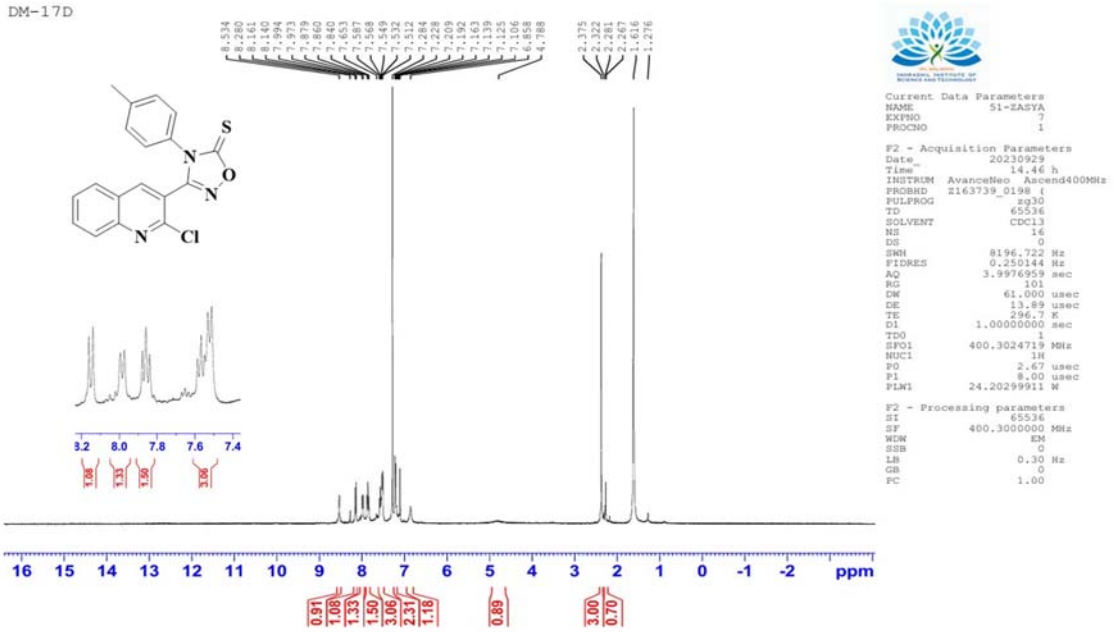


Figure 10: ^{1}H NMR of compound **6d**

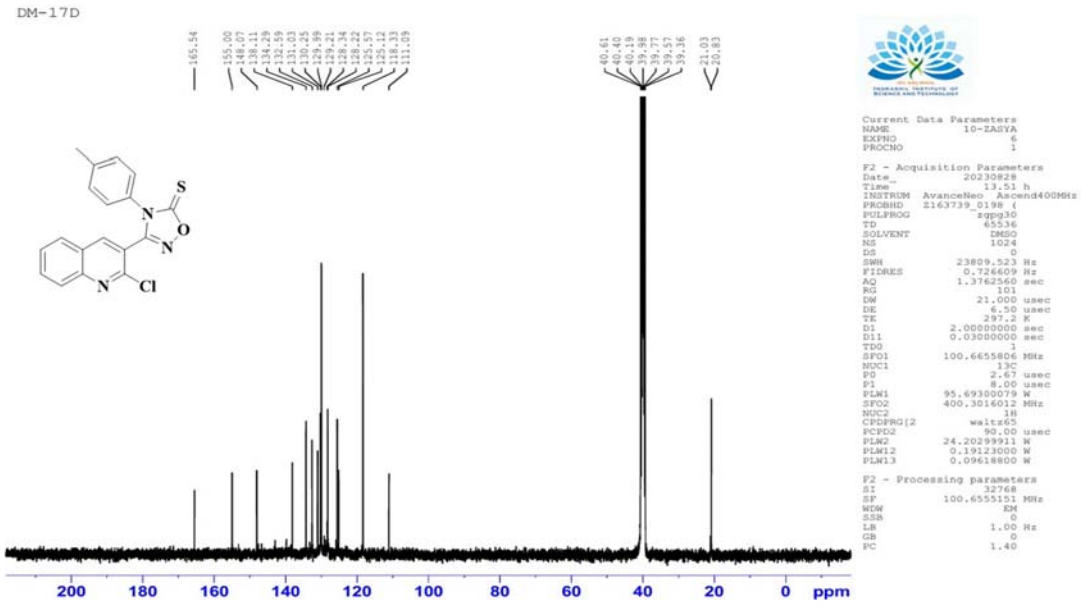


Figure 11: ^{13}C NMR of compound **6d**

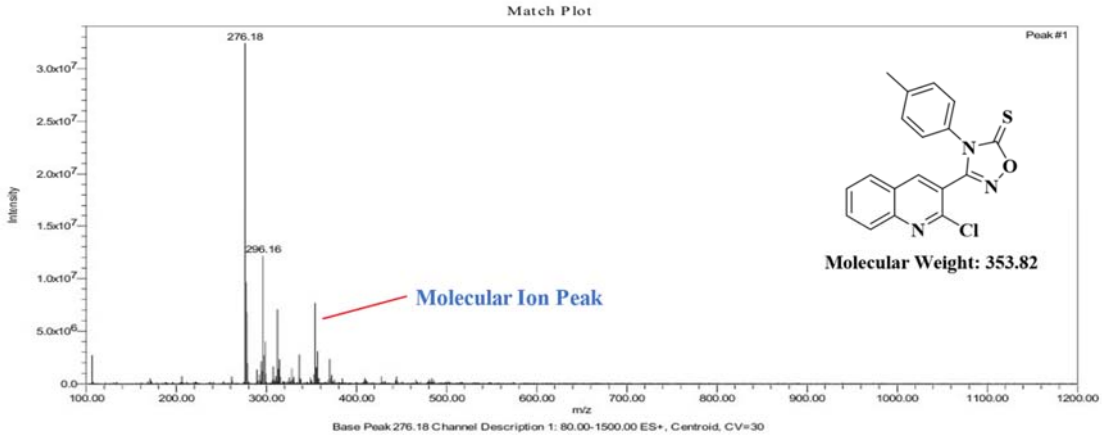


Figure 12: Mass of compound **6d**

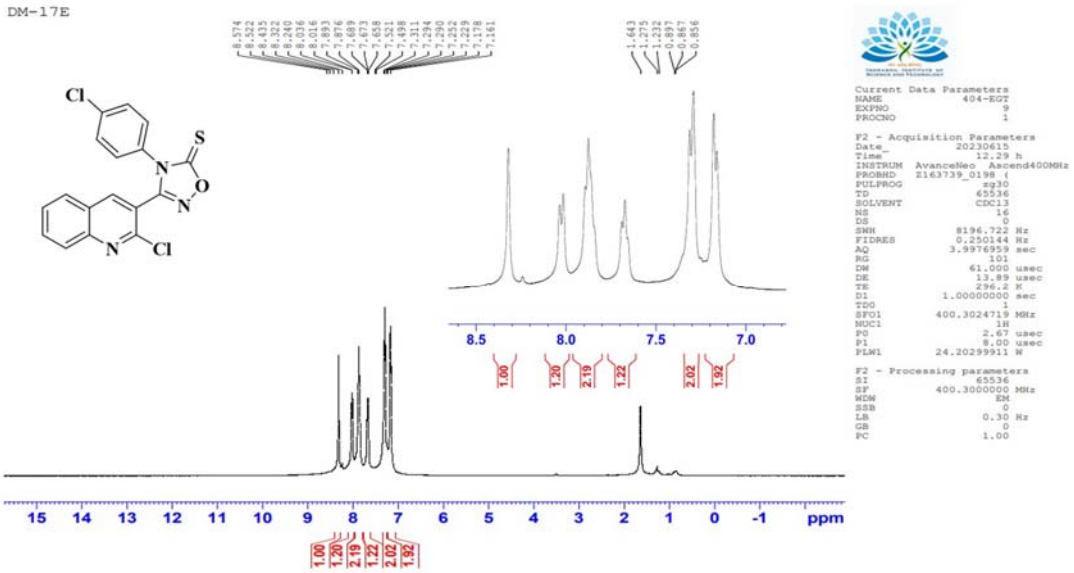


Figure 13: ^{1}H NMR of compound **6e**

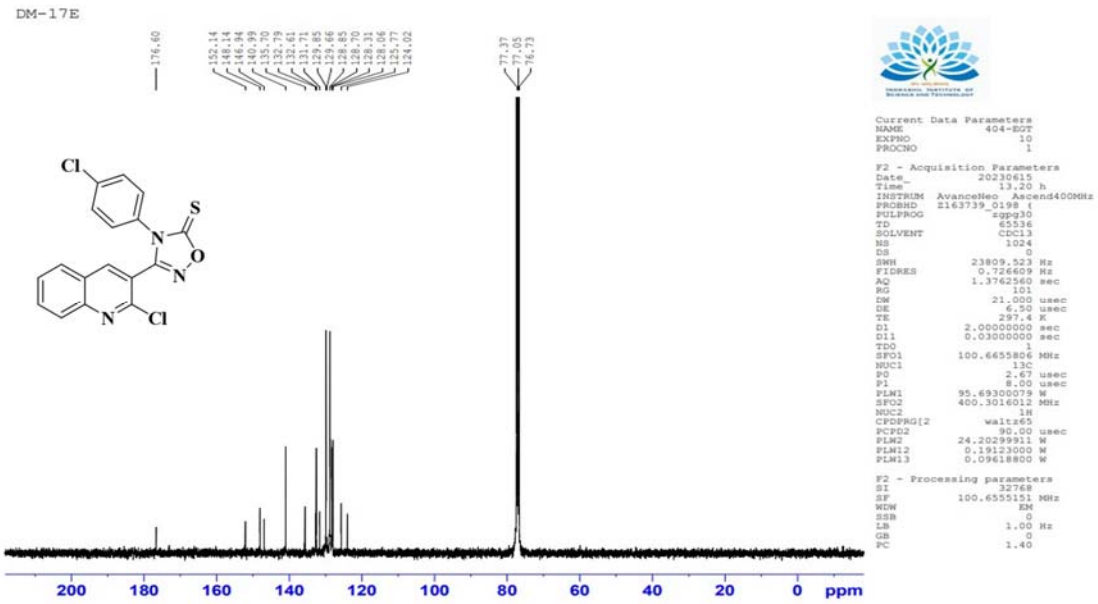


Figure 14: ^{13}C NMR of compound **6e**

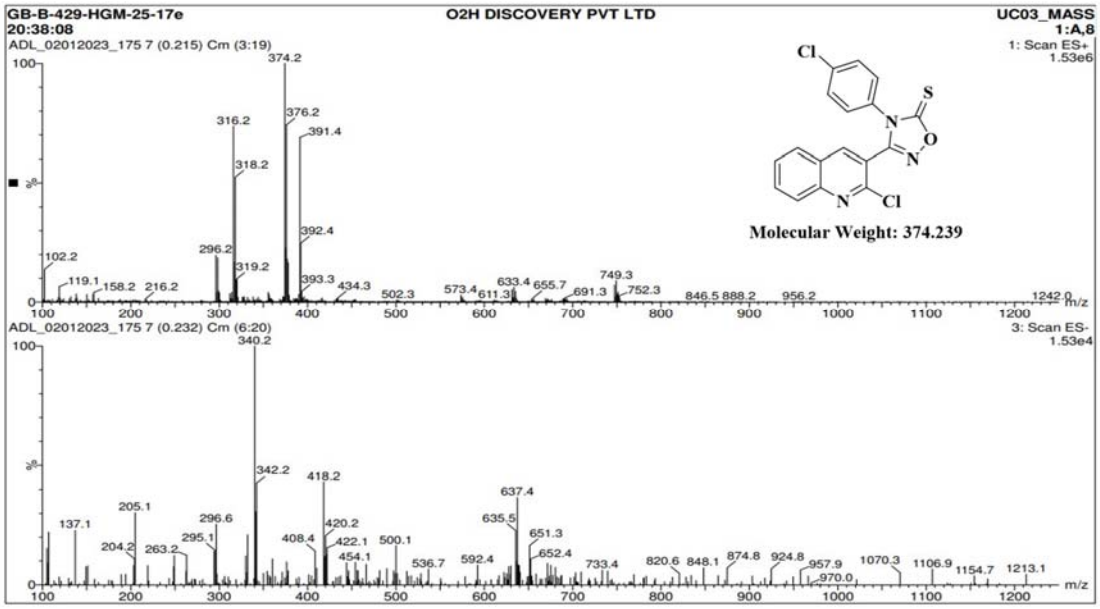


Figure 15: Mass of compound **6e**

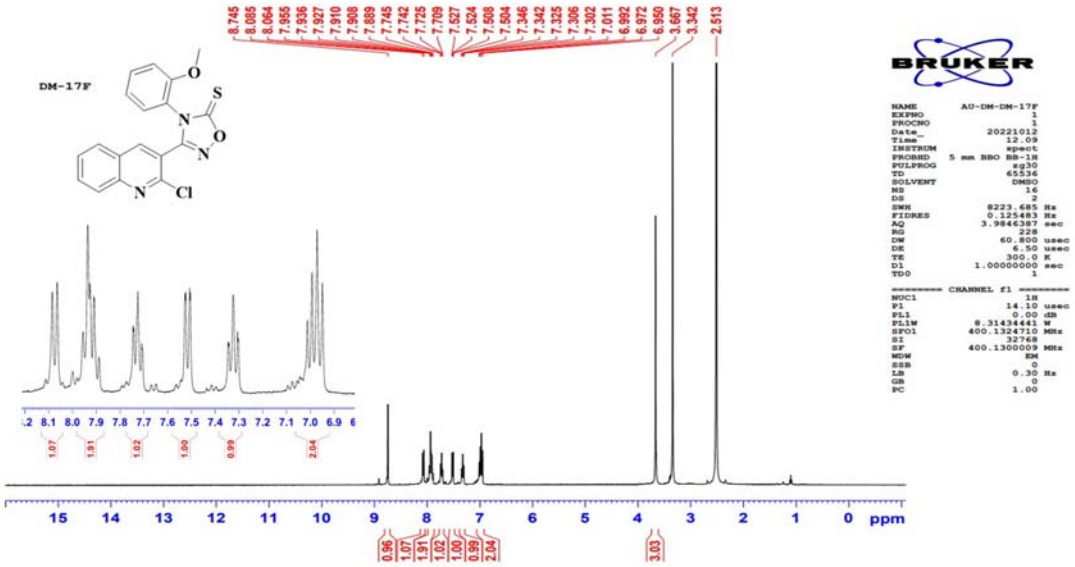


Figure 16: ^{1}H NMR of compound **6f**

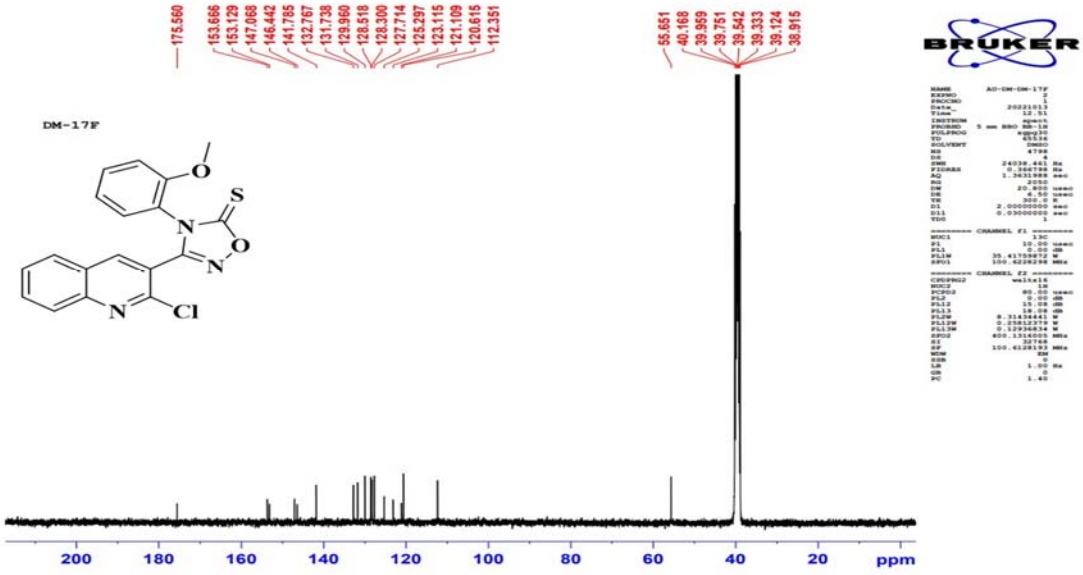


Figure 17: ^{13}C NMR of compound **6f**

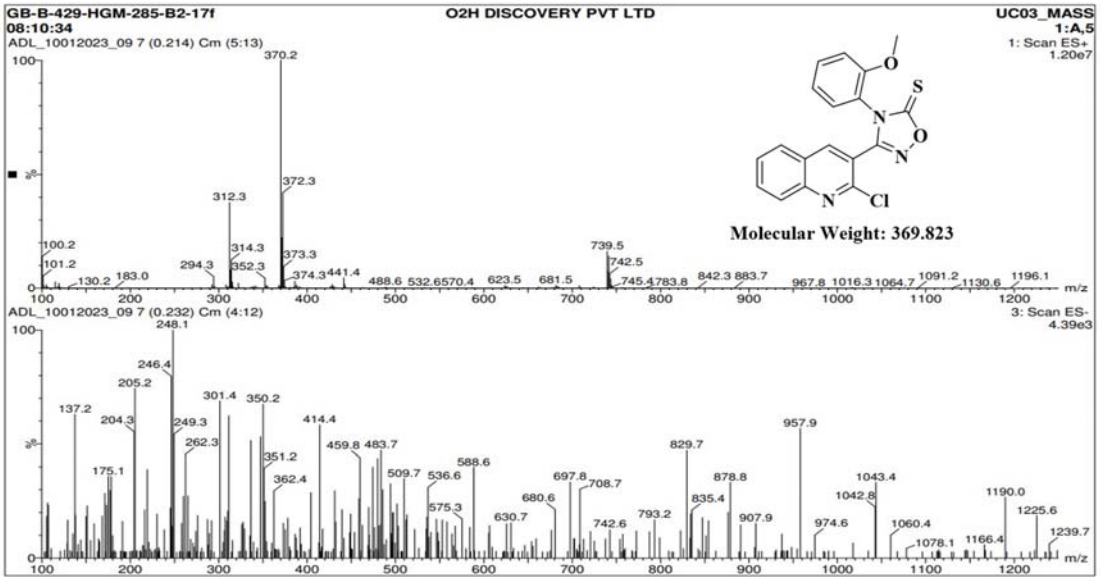


Figure 18: Mass spectrum of compound **6f**

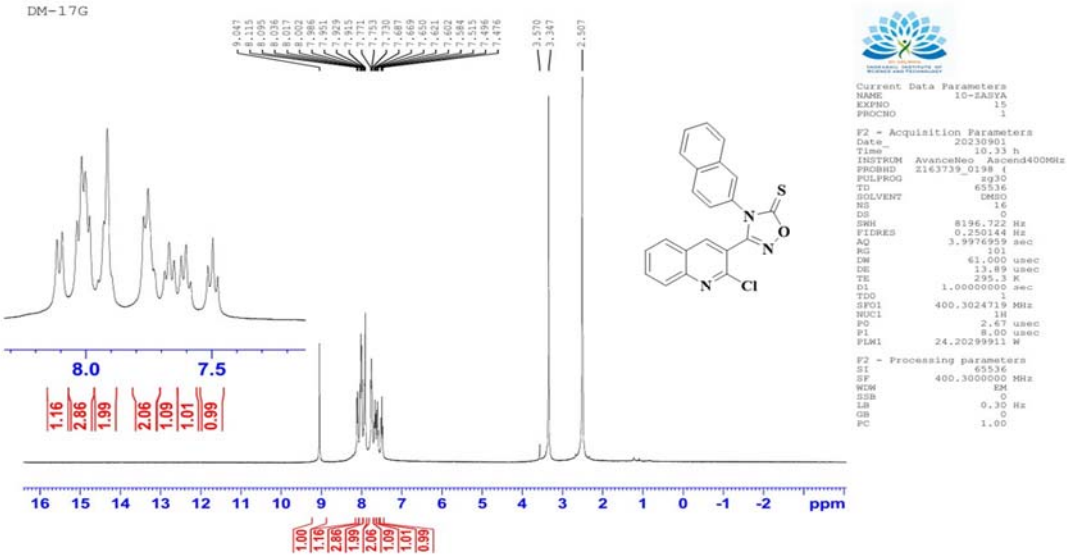


Figure 19: ^{1}H NMR of compound **6g**

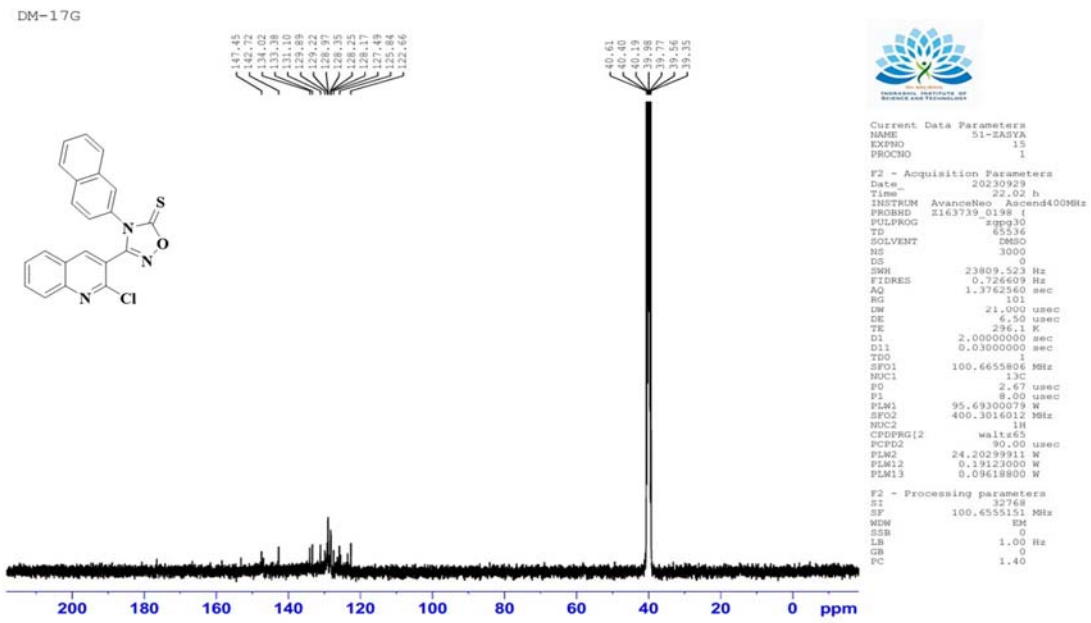


Figure 20: ^{13}C NMR of compound **6g**

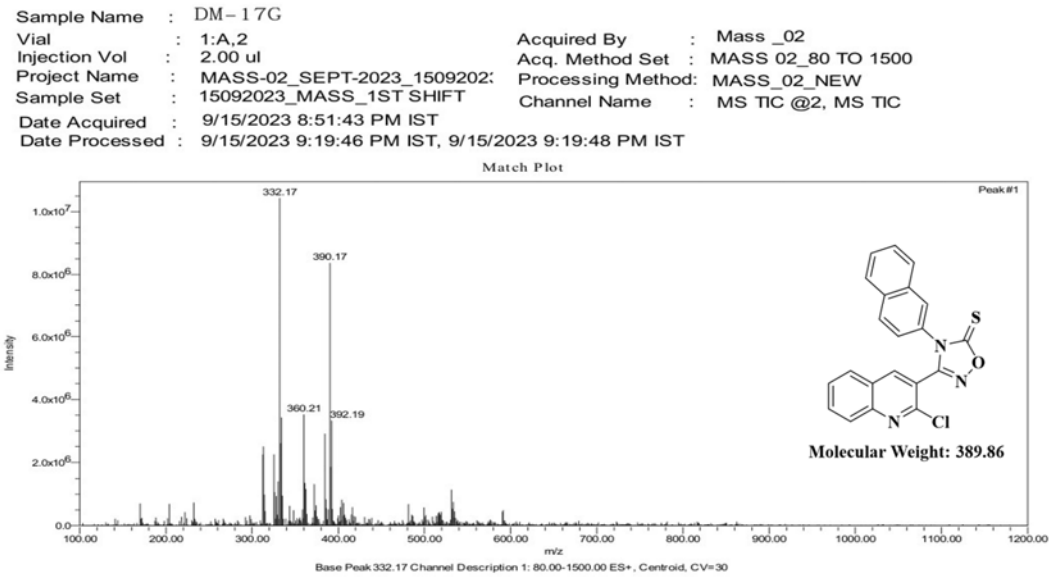


Figure 21: Mass spectrum of compound **6g**

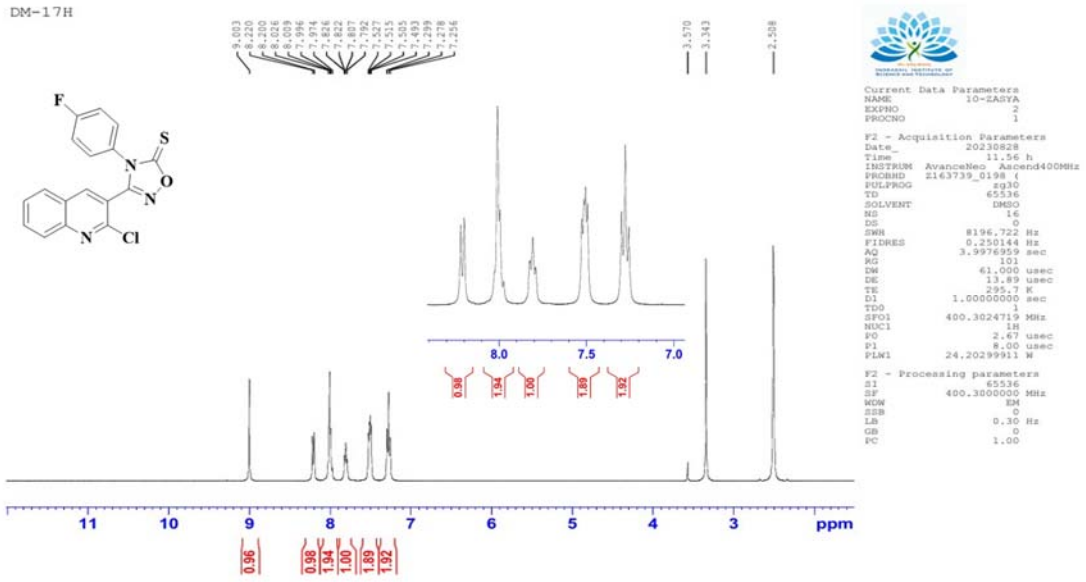


Figure 22: ^{1}H NMR of compound **6h**

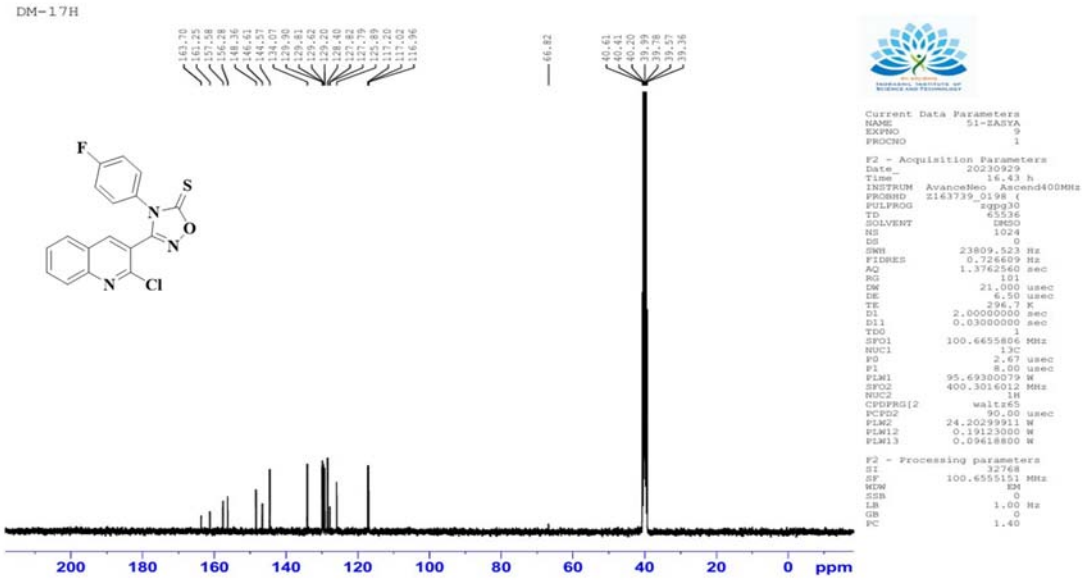


Figure 23: ^{13}C NMR of compound **6h**

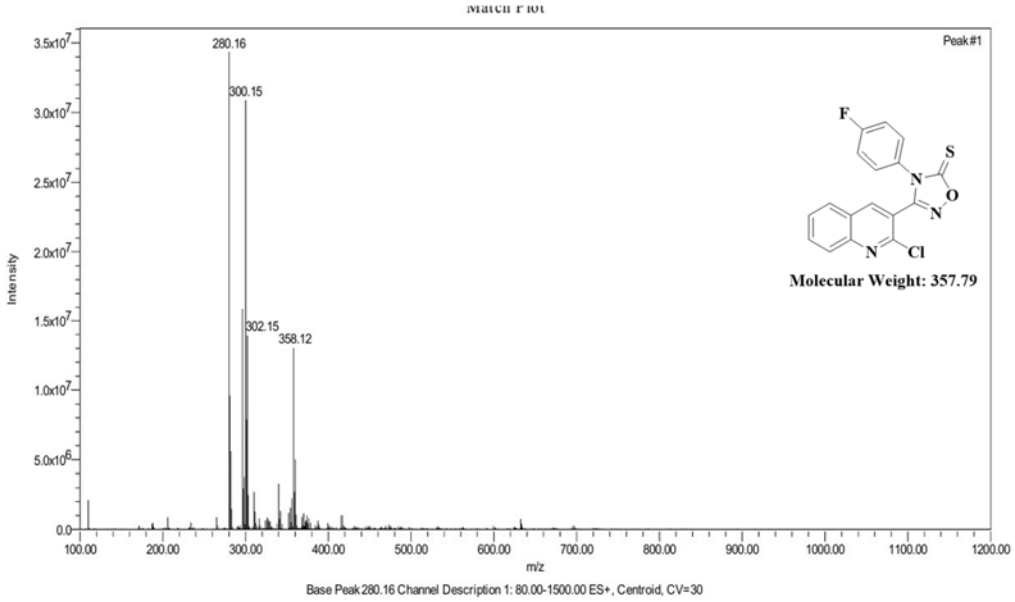


Figure 24: Mass spectrum of compound **6h**

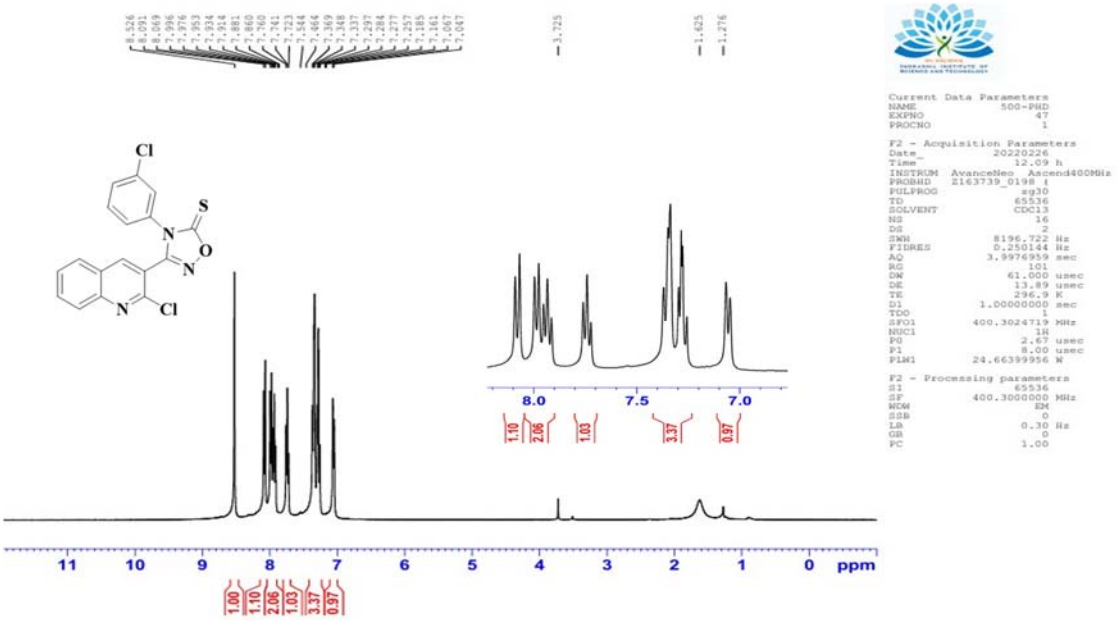


Figure 25: ^{1}H NMR of compound **6i**

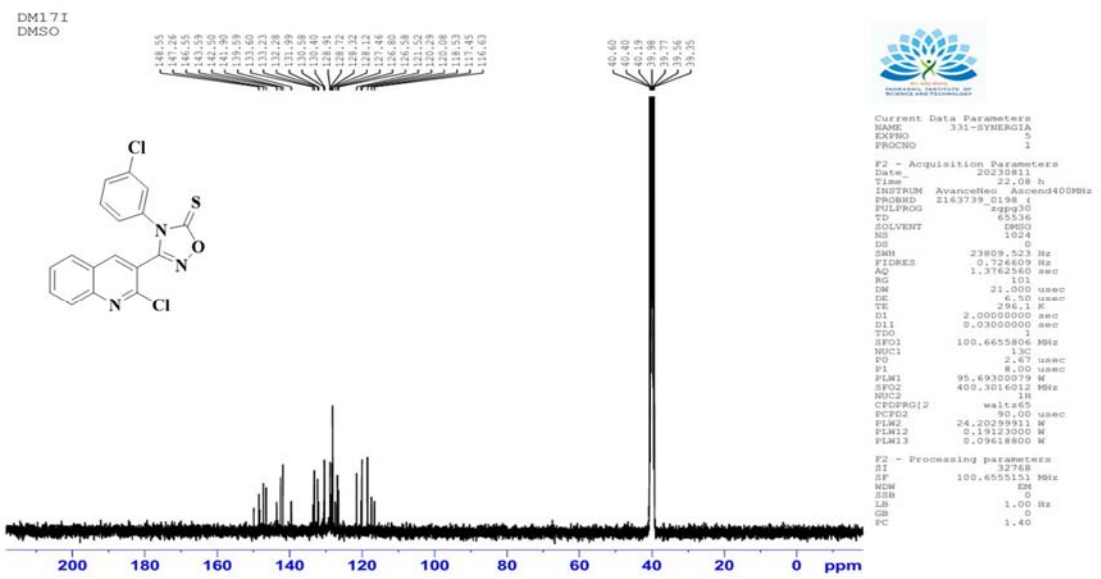


Figure 26: ^{13}C NMR of compound **6i**

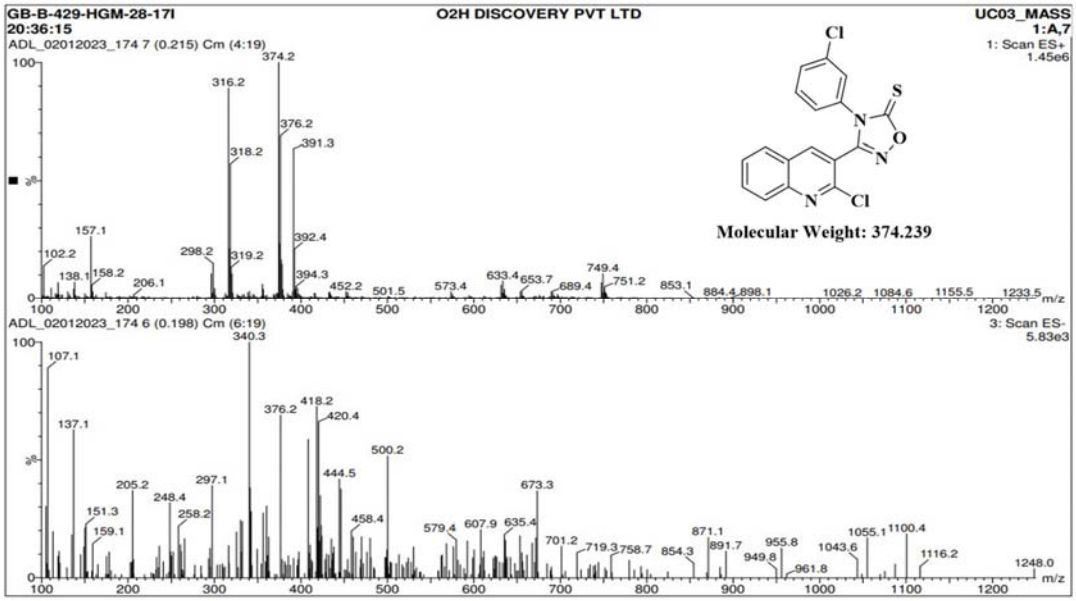


Figure 27: Mass spectrum of compound **6i**

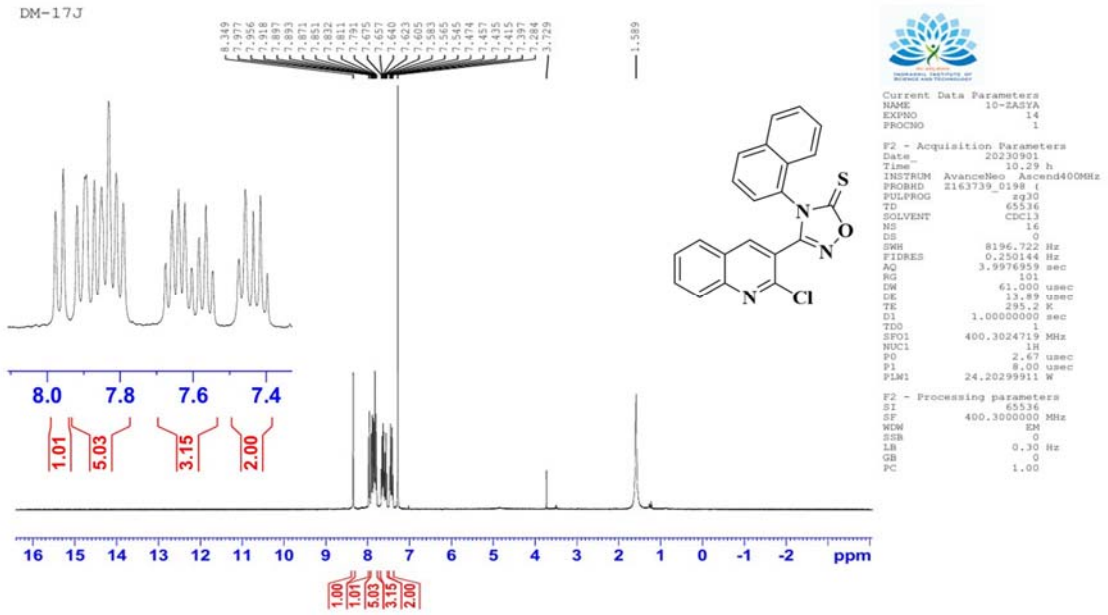


Figure 28: ^{1}H NMR of compound **6j**

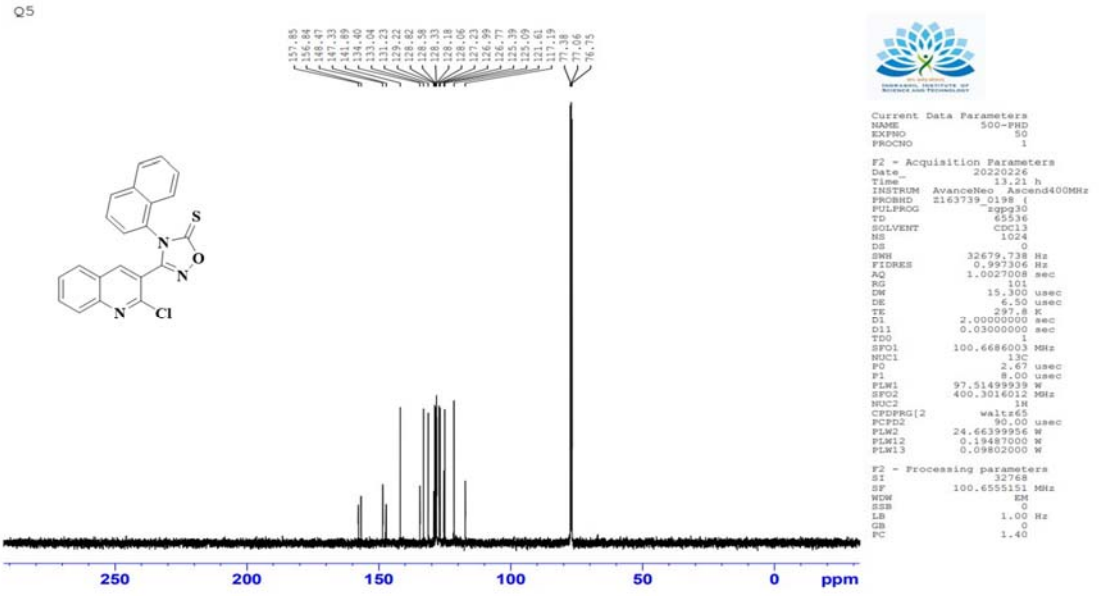


Figure 29: ^{13}C NMR of compound **6j**

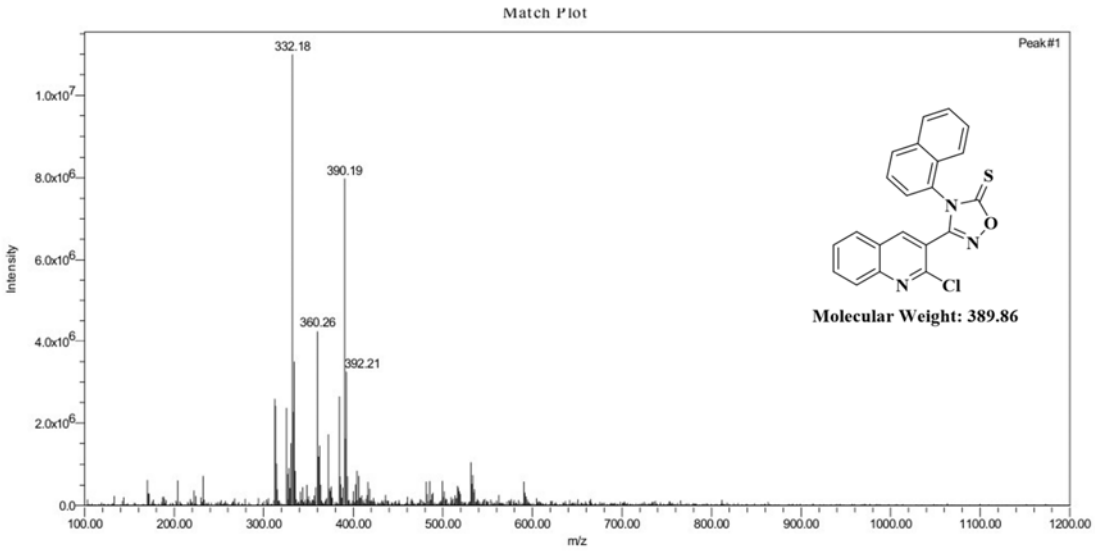


Figure 30: Mass spectrum of compound **6j**

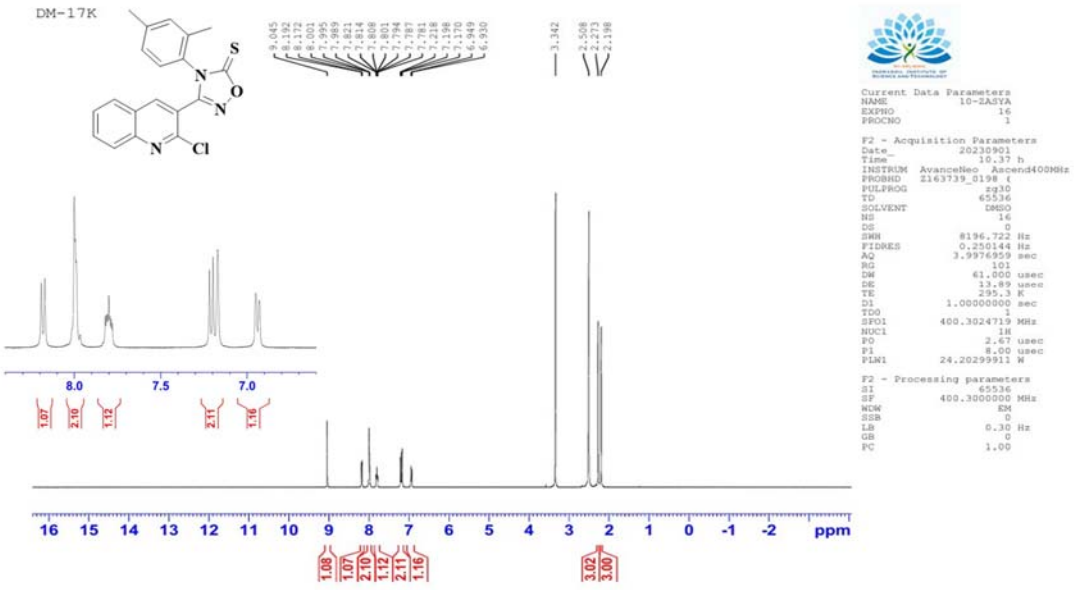


Figure 31: ^{1}H NMR of compound **6k**

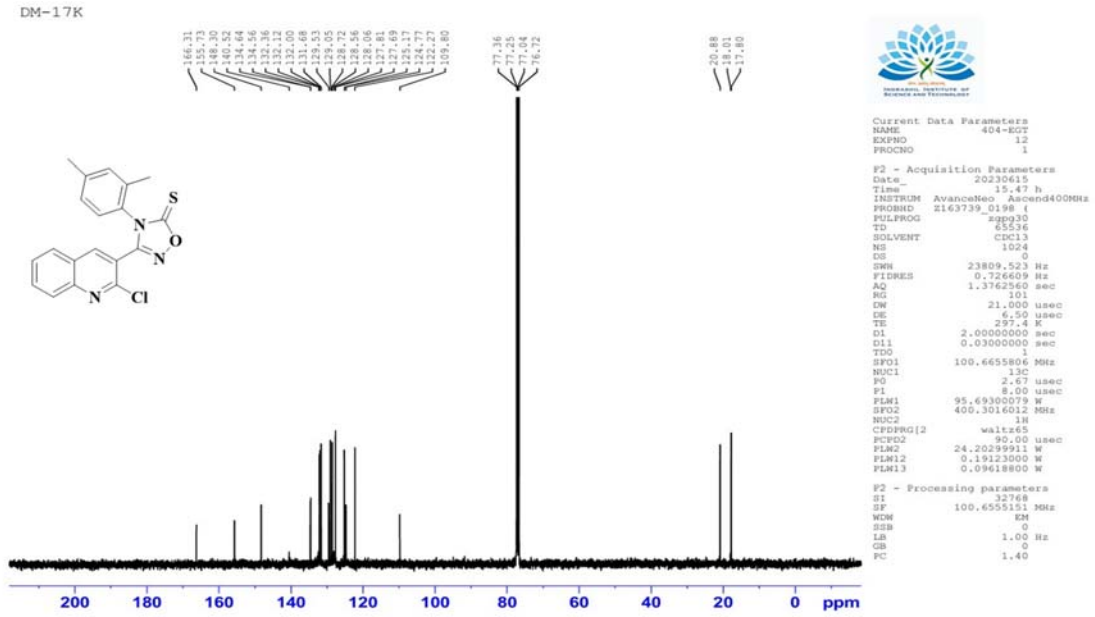


Figure 32: ^{13}C NMR of compound **6k**

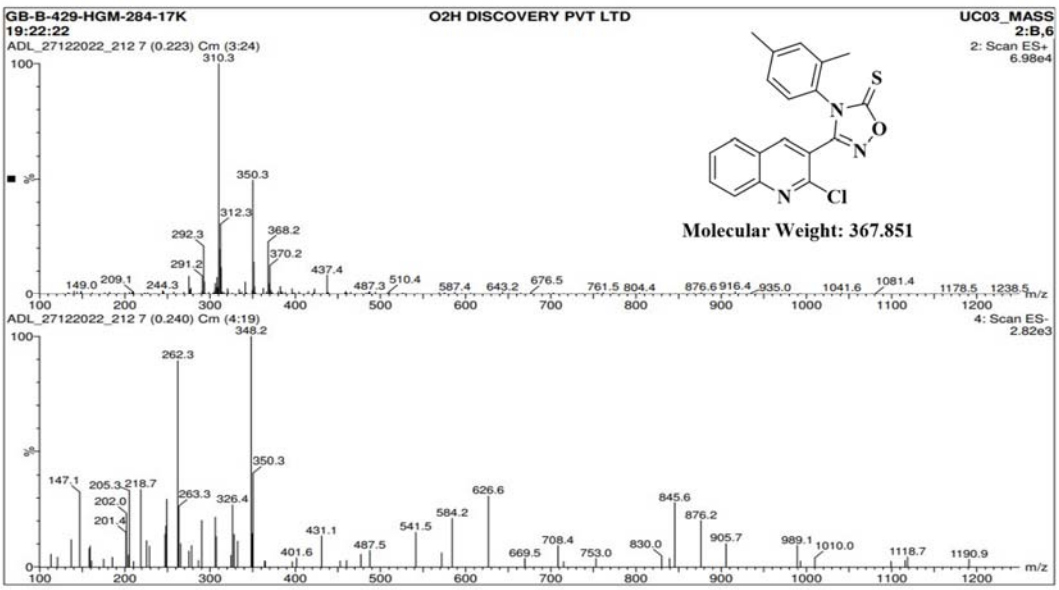


Figure 33: Mass spectrum of compound **6k**

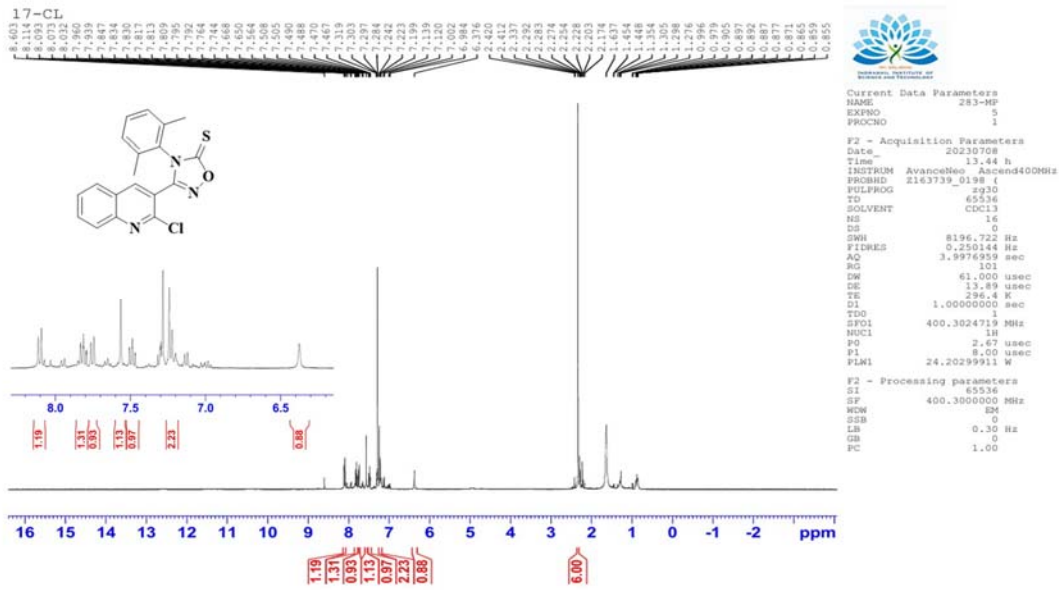


Figure 34: ^{1}H NMR of compound **6l**

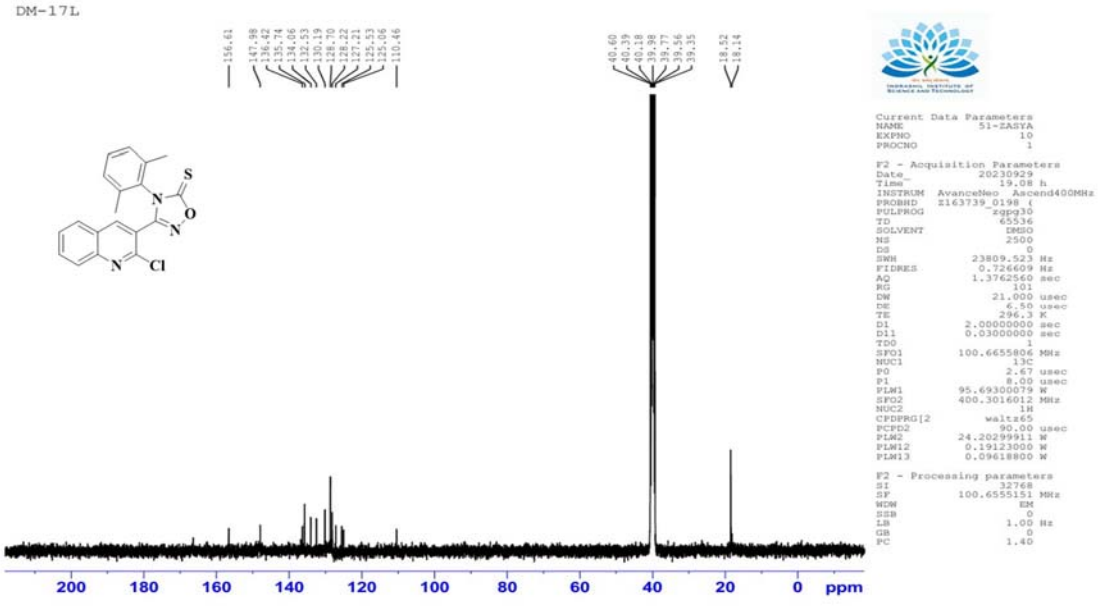


Figure 35: ^{13}C NMR of compound **6l**

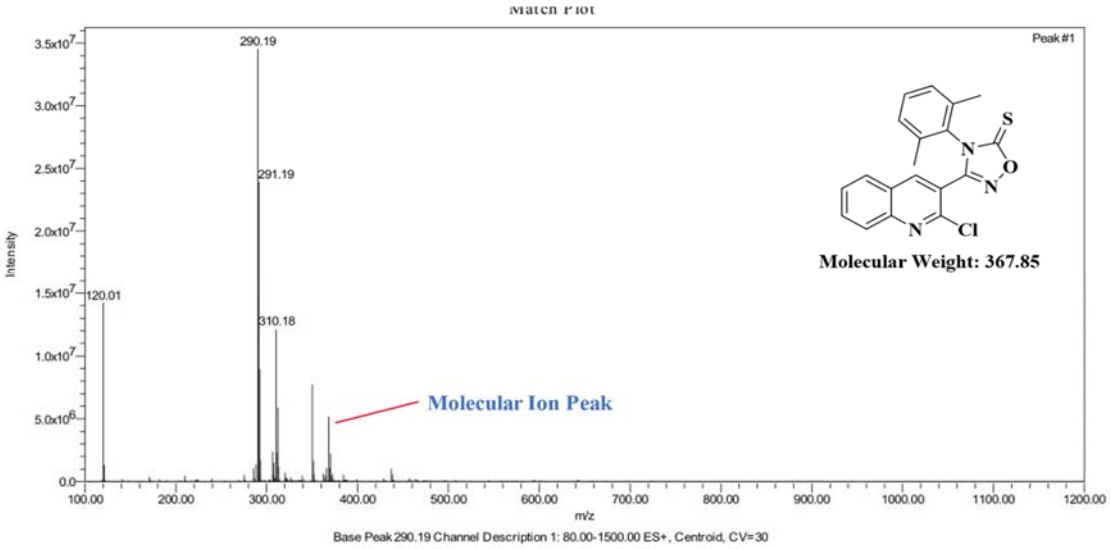


Figure 36: Mass spectrum of compound **6l**

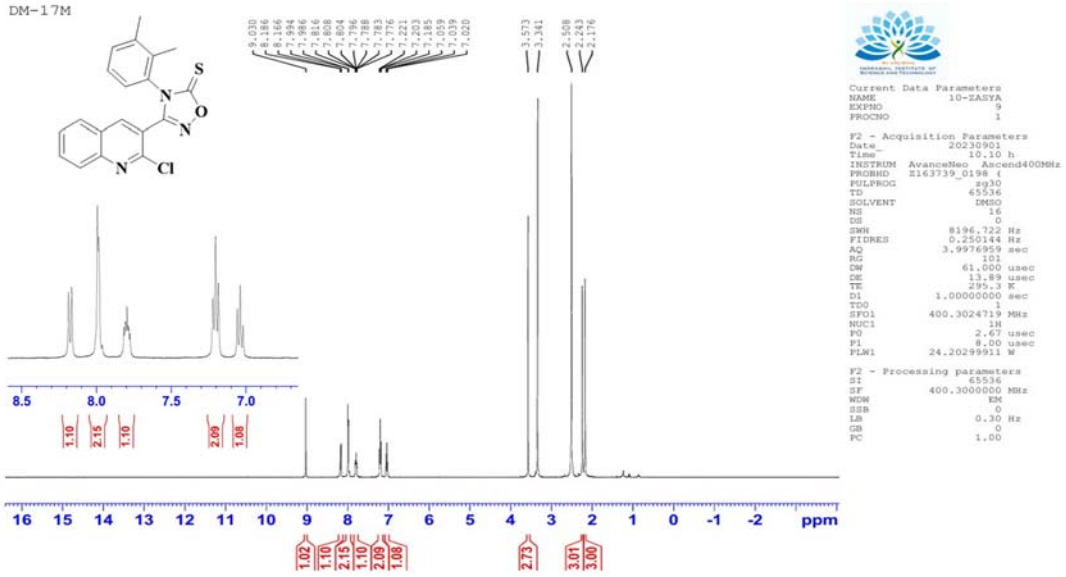


Figure 37: ^{1}H NMR of compound **6m**

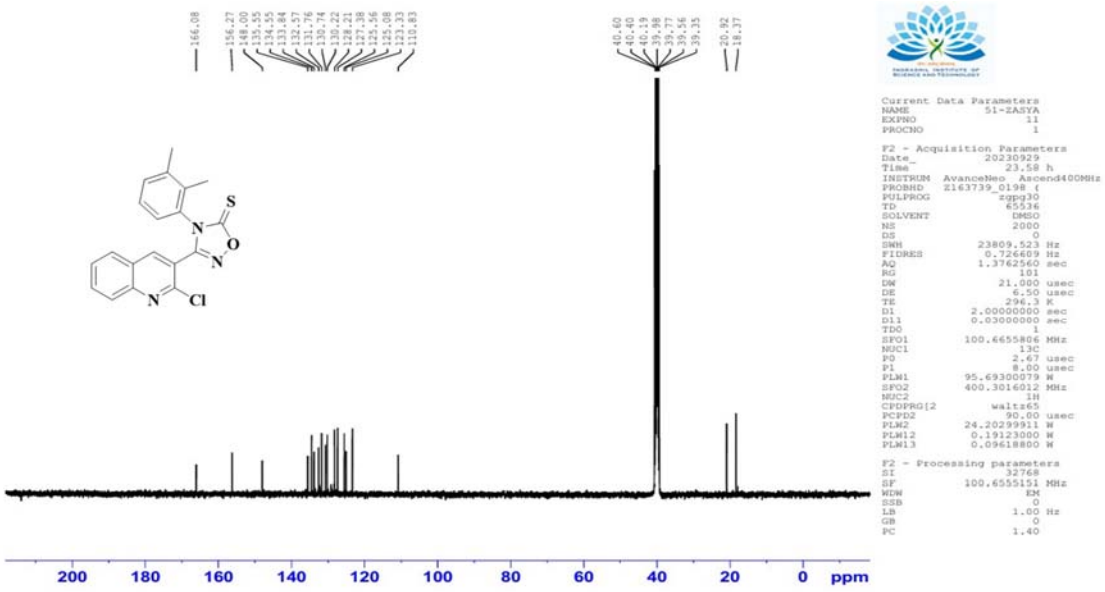


Figure 38: ^{13}C NMR of compound **6m**

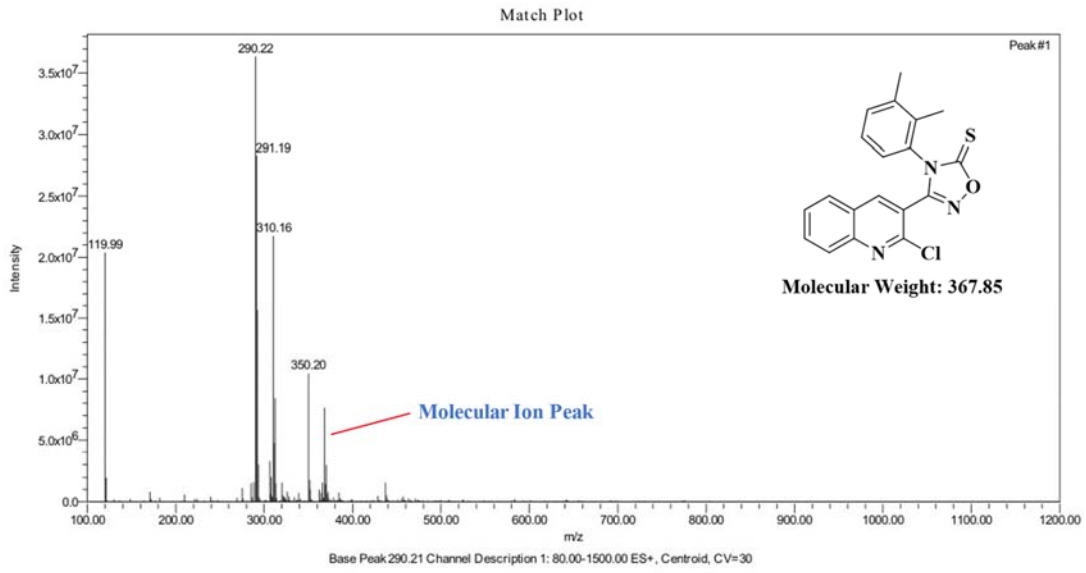


Figure 39: Mass spectrum of compound **6m**

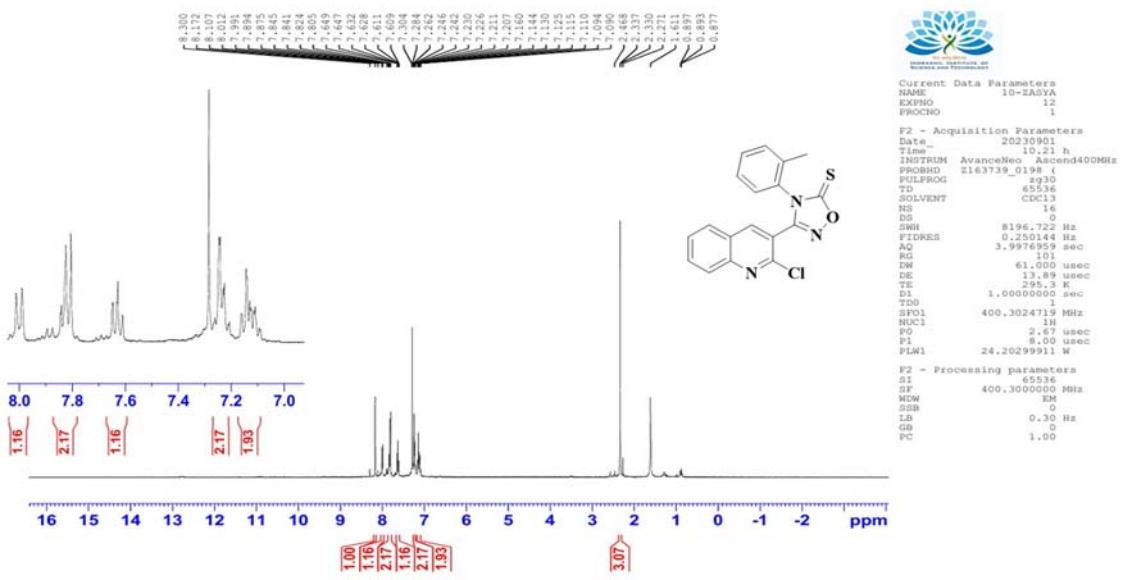


Figure 40: [1]H NMR of compound **6n**

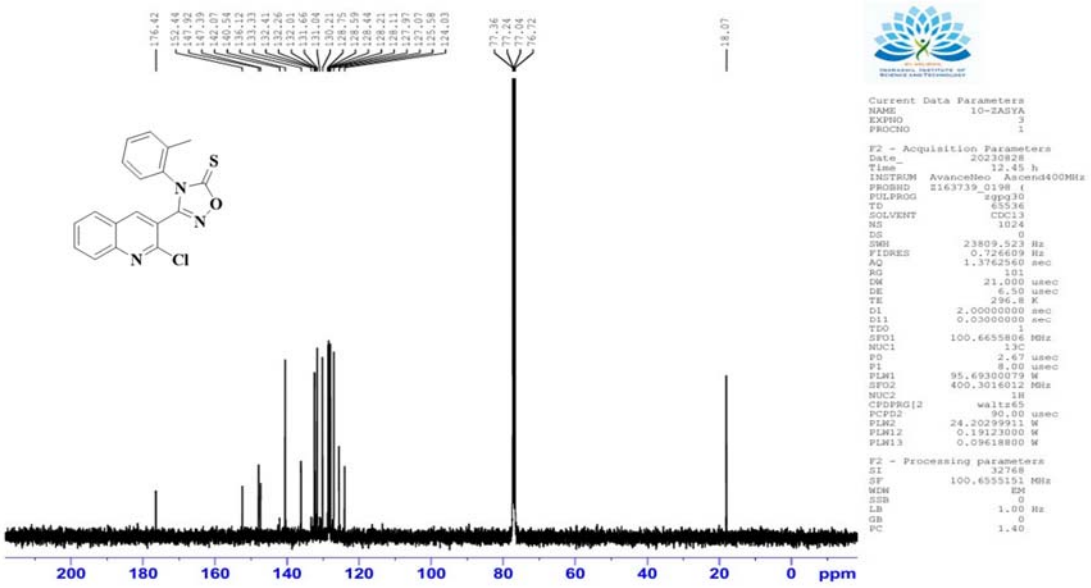


Figure 41: [13]C NMR of compound **6n**

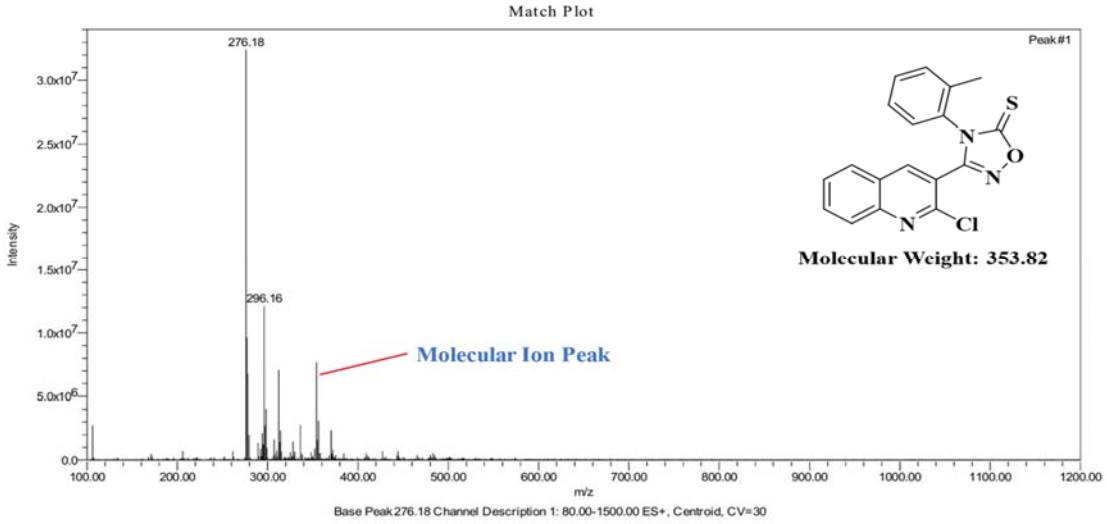


Figure 42: Mass spectrum of compound **6n**

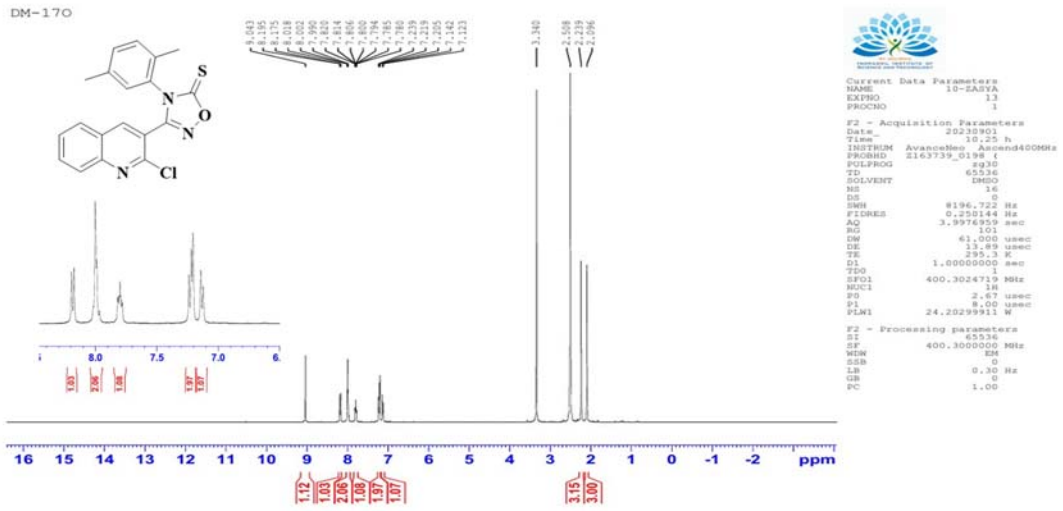


Figure 43: ^{1}H NMR of compound **6o**

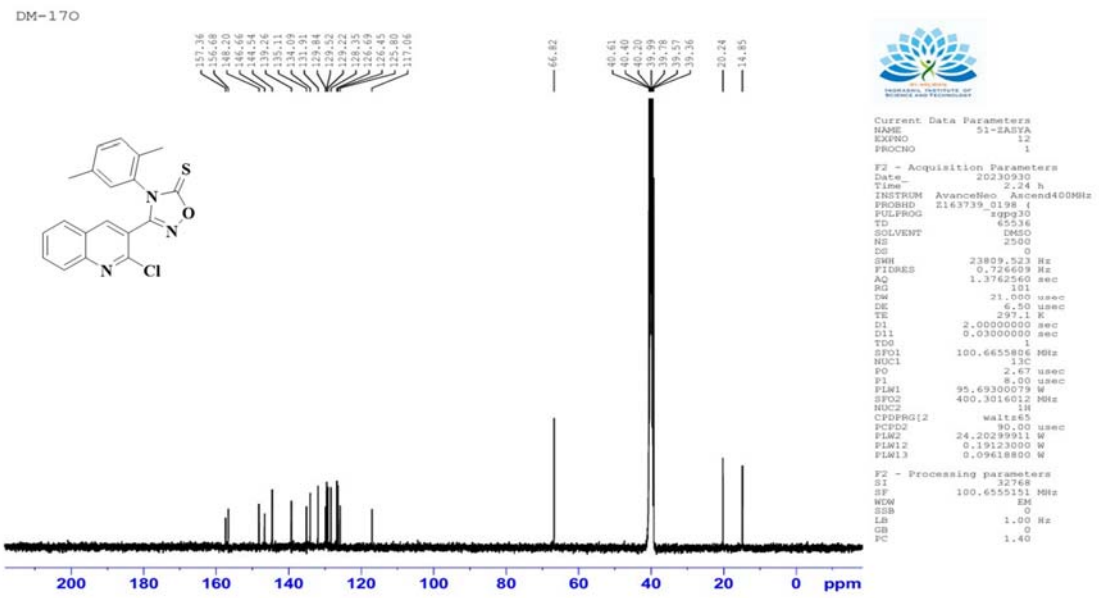


Figure 44: ^{13}C NMR of compound **6o**

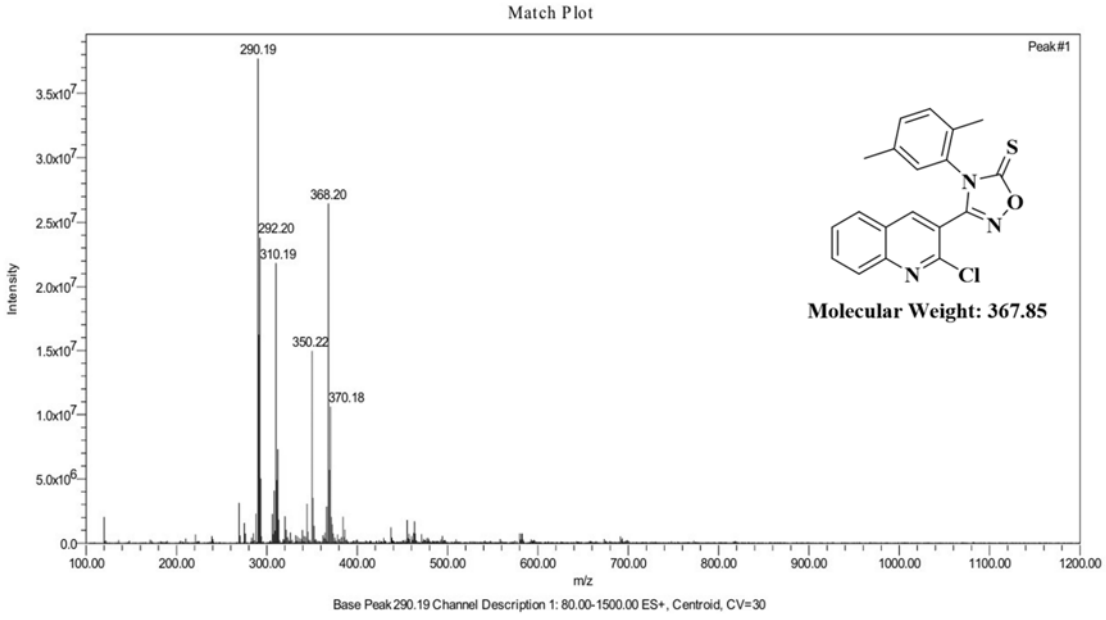


Figure 45: Mass spectrum of compound **6o**